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Frozen elephant trunk surgery in aortic dissection

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Frozen elephant trunk surgery in aortic dissection

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Editorial: Frozen elephant trunk surgery in aortic dissection

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KEYWORDS

frozen elephant trunk, FET, aortic arch, aortic dissection, TEVAR, hybrid, circulatory arrest, hypothermia

Editorial on the Research Topic
Frozen elephant trunk surgery in aortic dissection

Introduction

The aortic dissection (AD) is a potentially fatal disease, with up to 1% per hour death rate reported in the first several hours before surgery for type A dissection (1). The surgical treatment remains a highly complex procedure with a high risk of postoperative morbidity and mortality (2). However, in the past decades we have seen a progressive and steady evolution: until the 1980s the treatment involved the ascending aorta and aortic arch replacement followed by a thoraco-abdominal aortic replacement, with extremely high hospital and inter-procedure mortality. Subsequently, in 1983 the elephant trunk (ET) surgery was introduced by Borst et al. in order to facilitate the two-stage open technique for the surgical treatment of the descending aorta, avoiding the need of aortic cross-clamp (3). The introduction of endovascular technologies represented a fundamental turning point: the "conventional" trunk was replaced by a rigid stent graft in the mid-1990s to introduce a "one-step procedure" or to facilitate the realization of a two-stage hybrid treatment: this evolution gave birth to the frozen elephant trunk (FET) technique (4, 5). The techniques of cerebral perfusion and hypothermia have changed as well: we witnessed the evolution from deep hypothermic circulatory arrest, electrocerebral inactivity and no cerebral perfusion to mild hypothermia or normothermia and antegrade unilateral or bilateral selective cerebral perfusion: this contributed in reducing the rate of postoperative neurological and hypothermia-related complications (6–10). Today the evolution continues, not only by improving the techniques in cerebral, spinal and visceral protection but also by implementing the best advancements in minimally invasive and trans-catheter procedures: it is the case of partial sternotomy, hybrid (surgical and percutaneous) and completely trans-catheter replacement of the dissected aortic arch (11). This Topic and its collection of articles discuss some of the best advances in the field of FET surgery for various types of AD (Table 1).

Papers presentation

In their paper, Moula et al. conducted a metanalysis which aimed to investigate the differences in intrahospital outcomes of ET vs. FET. Twenty-one published articles between 2008 and 2021 with 3,153 patients were included. ET was associated with higher early mortality but lower incidence of SCI compared to FET. However, when studies published in the last 5 years were analyzed, no significant differences were found between ET and FET.

According to the position paper of Vascular domain of the EACTS, FET should be considered not only in type A AD with a primary entry in the distal aortic arch or in the proximal half of the descending aorta, but also in patients with complicated acute type B AD when primary TEVAR is not feasible (12). With this in mind, Luo et al. described their experience of early and long-term follow-up for chronic type B and type non-A non-B AD using the FET technique in 79 patients operated from 2009 to 2019. The operation mortality rate was 5.1%, SCI occurred in 3.8% and stroke in 2.5%. At a median follow-up time of 53 months, overall survival rates were 96.2, 92.3, 88.0, 79.8, and 76.2% at 1/2, 1, 3, 5, and 7 years, respectively. Fang et al. described their experience with FET in patients presenting with a type A AD following thoracic endovascular aortic repair (TEVAR). They divided the patients in 2 groups: the group of retrograde AD (stent-induced AD) and the one with an antegrade AD (entry tear in the ascending aorta, unrelated with the distal stent). All patients underwent total arch replacement and FET. No significant differences in the incidence of post-operative complications or mortality were noted between the two groups. In their paper, Liu P. et al. shared their experience with the en bloc arch reconstruction (island technique) with FET surgery for acute type A AD. With a hospital mortality rate of 9.8%, a stroke rate of 4.9% and a 3-year actuarial survival rate of 70.2%, they concluded that this technique appears to be feasible and effective with good early clinical follow-up results.

Aortic arch replacement generally contemplates a relatively long circulatory arrest (CA). This implies the use of cerebral perfusion/protection techniques during the CA on one side, and the establishment of moderate or deep hypothermia to protect all the other vital organs on the other side. Multiple postoperative complications are related, directly or indirectly, to hypothermia and CA: thrombocytopenia and deficiency of coagulation factors (thus causing a major risk of postoperative bleeding), alteration of the functions of the liver, kidneys, brain, pancreas, intestine and smooth muscles. Permanent neurological damage has been observed in 3 to 12% of patients when using circulatory arrest in deep hypothermia (13). Consequently, each effort to reduce CA and increase the core body temperature that permits a safely performed procedure is of outmost importance. To this purpose, Sénage et al. have described their technique: by placing two surgical sealing tourniquets around the aortic arch with the stent graft already deployed, the distal suture can be performed on a perfused aorta in normothermia and just a few minutes (4.5 ± 2.8 min) of CA (10). On the other hand, Wang et al. have described another way of dramatically reducing the CA: the aortic balloon occlusion (ABO) technique. Immediately after the stent-graft deployment, the sheathed aortic balloon is deployed inside the stent-graft. Once the balloon is fixed, lower body perfusion can be restarted through the femoral artery cannula, allowing a CA time of 6.3 ± 5.7 min and a mean nasopharyngeal temperature of 27.4°C. After propensity score matching of the ABO group and the conventional group, the first had significantly lower 30-days mortality, significantly fewer postoperative renal and hepatic injury, lower postoperative wake-up time, reduced chest tube output, lower red blood cell transfusion volume and no fatal events. In the particular subgroup of acute type A AD with lower body malperfusion, Tong et al. found no difference in perioperative outcomes between conventional and ABO in FET technique. According to the authors, the immediate true lumen perfusion in ABO technique may relive malperfusion only in dynamic obstruction, while it would have no effect on static malperfusion. This may explain to some extent the findings of the paper.

ASCP has allowed to gradually increase core body temperature during CA, but if it is carried out by using only one main arterial line, bifurcated with that of the systemic perfusion, brain flow is determined by peripheric and cerebral vascular resistance. This poses the risk of increased or inconstant cerebral flow which may result in neurologic injury. With this in mind, Liu Y. et al. shared their experience with a separate pump-controlled ASCP: even though no significant differences were found between separate pump and single pump flow, authors concluded that it is a safe and feasible procedure that may avoid cerebral flow inhomogeneity and potential cerebral injury.

Various papers have shared their insight on single-Center short and long-term results after FET. Liang et al. found that postoperative hepatic dysfunction after FET was associated with increased early mortality and morbidity, but not with late death in midterm follow-up. Chivasso et al. reported their single-Center experience with the FET technique: 30-days- and in-hospital mortality were 10.6 and 13.6%, respectively. Stroke occurred in 4.5% of patients. In total of 3.0% experienced spinal cord ischemia. Moreover, the authors found that left ventricular ejection fraction, peripheral vascular disease, coronary malperfusion, lower limbs malperfusion, and cardiopulmonary bypass time were independent predictors of long-term mortality. Wisniewski et al. evaluated the early and mid-term results after FET procedure for AD or aortic aneurysm in their Center, finding an overall in-hospital mortality of 12.5%, permanent neurological dysfunction and spinal cord injury (SCI) rates of 9.7 and 5.5%, respectively. At a mean follow-up of 26 ± 20 months, the mortality rate was 9.7%. Tan, Jubouri et al. have studied long-term outcomes of 931 cases of Thoraflex^{TM} Hybrid implantation for aortic arch dissection, aneurysm, and penetrating atherosclerotic ulcer, finding that 30-day mortality was 0.6%, overall mortality was 1.5% while freedom from adverse events at 84 months was 95%.

Sheng et al. developed a preoperative nomogram and risk calculator for postoperative hypoxemia and related clinical outcomes after FET. Hypoxemia was frequent following acute AD surgery (24.2%) and was related to poorer clinical outcomes. Five independent risk factors for severe hypoxemia development were identified: older age, smoking history, renal insufficiency, higher body mass index, and white blood cell count. Lin et al. developed a nomogram model to predict postoperative 30-day mortality in acute type A AD patients receiving total aortic arch replacement with FET technique, by analyzing clinical data on 1,156 consecutive patients. Left ventricular end-diastolic diameter <45 mm, estimated glomerular filtration rate <50 ml/min/1.73 m^2, persistent abdominal pain, radiological celiac trunk malperfusion, concomitant coronary artery bypass grafting and cardiopulmonary bypass time >4 h were found to be independent predictors of the 30-day mortality.

TABLE 1 Summary of the collection of the articles.

Authors	Title	Keywords	Summary
Moula et al.	The evolution of arch surgery: Frozen elephant trunk or conventional elephant trunk?	• Frozen elephant trunk • Conventional elephant trunk • Evolution	In a metanalysis of 21 published articles between 2008 and 2021, ET was associated with higher early mortality but lower incidence of SCI compared to FET. No significant difference was found between ET and FET when only studies conducted in the last 5 years were included.
Luo et al.	Early and Long-Term Follow-Up for Chronic Type B and Type Non-A Non-B Aortic Dissection Using the Frozen Elephant Trunk Technique	• Type B aortic dissection • Type Non-A-Non-B aortic dissection • Follow-up	In 79 patients of Type B or Non-A-non-B AD operated from 2009 to 2019, the operation mortality rate was 5.1%. SCI occurred in 3.8% and stroke in 2.5%. At a median follow-up time of 53 months, overall survival rates were 96.2, 92.3, 88.0, 79.8, and 76.2% at 1/2, 1, 3, 5 and 7 years, respectively.
Fang et al.	Surgical Repair of Two Kinds of Type A Aortic Dissection After Thoracic Endovascular Aortic Repair	• Antegrade aortic dissection • Retrograde aortic dissection • TEVAR	The authors studied patients with AD post TEVAR which underwent FET surgery and divided them in two groups: retrograde AD (stent-induced AD) and antegrade AD (entry tear in the ascending aorta, unrelated with the distal stent). No significant differences in the incidence of post-operative complications or mortality were noted between the two groups.
Liu P. et al.	En Bloc Arch Reconstruction With the Frozen Elephant Trunk Technique for Acute Type A Aortic Dissection	• En bloc arch reconstruction • Island technique	In the authors' experience, with a hospital mortality rate of 9.8%, a stroke rate of 4.9% and a 3-year actuarial survival rate of 70.2%, the "island technique" appears to be feasible and effective with good early clinical follow-up results.
Wang et al.	Improvement of Clinical Outcomes of Total Aortic Arch Replacement and Frozen Elephant Trunk Surgery With Aortic Balloon Occlusion	• Aortic balloon occlusion • Circulatory arrest • Hypothermia	Aortic balloon occlusion technique can be safely performed in higher body temperatures (27.4°C) by significantly reducing circulatory arrest time (6.3 ± 5.7 min). In the authors' experience, it was associated with a lower 30-days mortality, fewer postoperative renal and hepatic injury, lower postoperative wake-up time, reduced chest tube output, lower red blood cell transfusion volume and no fatal events.
Tong et al.	Aortic Balloon Occlusion Technique Does Not Improve Peri-Operative Outcomes for Acute Type A Acute Aortic Dissection Patients With Lower Body Malperfusion	• Aortic balloon occlusion • Malperfusion	In patients presenting with acute type A AD and lower body malperfusion, the aortic balloon occlusion technique doesn't improve perioperative outcomes, which result similar to those of the conventional FET.
Liu Y. et al.	Efficacy of pump-controlled selective antegrade cerebral perfusion in total arch replacement: A propensity-matched analysis	• Selective antegrade cerebral perfusion • Pump-controlled cerebral perfusion • Single pump conjoint systemic and cerebral perfusion	The separate pump-controlled SACP may avoid cerebral flow inhomogeneity and potential cerebral injury during aortic arch surgery. However, when compared with a single pump flow for conjoint systemic and cerebral perfusion, no significant differences in perioperative neurological outcomes were found.
Liang et al.	Postoperative Hepatic Dysfunction After Frozen Elephant Trunk for Type A Aortic Dissection	• Hepatic dysfunction • Type A aortic dissection	Postoperative hepatic dysfunction after FET was associated with increased early mortality and morbidity, but not with late death in midterm follow-up.
Chivasso et al.	Systematic total arch replacement with thoraflex hybrid graft in acute type A aortic dissection: A single centre experience	• Postoperative outcomes • Type A aortic dissection • Frozen elephant trunk	The authors report a 30-days- and in-hospital mortality of 10.6 and 13.6%, respectively. The stroke and SCI rates were 4.5% and 3.0% respectively. LVEF, peripheral vascular disease, coronary malperfusion, lower limbs malperfusion, and CPB time were independent predictors of long-term mortality.
Wisniewski et al.	Single-Center Experience With the Thoraflex™ Hybrid Prosthesis: Indications, Implantation Technique and Results	• Postoperative outcomes • Frozen elephant trunk • Thoraflex™ Hybrid Prosthesis	The overall in-hospital mortality after FET for AD or aortic aneurysm was 12.5%. Permanent neurological dysfunction and SCI rates were 9.7 and 5.5%, respectively. At a mean follow-up of 26 ± 20 months, the mortality rate was 9.7%.
Tan, Jubouri et al.	What Is the Long-Term Clinical Efficacy of the Thoraflex™ Hybrid Prosthesis for Aortic Arch Repair?	• Long-term outcomes • Frozen elephant trunk • Thoraflex™ Hybrid Prosthesis	The authors describe the long-term outcomes of 931 cases of Thoraflex™ Hybrid implantation for aortic arch dissection, aneurysm, and penetrating atherosclerotic ulcer, finding that 30-day mortality was 0.6%, overall mortality was 1.5% while freedom from adverse events at 84 months was 95%.
Sheng et al.	Preoperative Nomogram and Risk Calculator for Postoperative Hypoxemia and Related Clinical Outcomes Following Stanford Type A Acute Aortic Dissection Surgery	• Nomogram • Risk calculator • Postoperative hypoxemia	Hypoxemia is frequent following acute AD surgery (24.2%) and is related to poorer clinical outcomes. Five independent risk factors for severe hypoxemia development were identified: older age, smoking history, renal insufficiency, higher body mass index, and white blood cell count.

(Continued)

TABLE 1 (Continued)

Authors	Title	Keywords	Summary
Lin et al.	Prediction Nomogram for Postoperative 30-Day Mortality in Acute Type A Aortic Dissection Patients Receiving Total Aortic Arch Replacement With Frozen Elephant Trunk Technique	• Nomogram • Risk calculator • Postoperative 30-days mortality	LVEDD <45 mm, GFR <50 ml/min/1.73 m^2, persistent abdominal pain, radiological celiac trunk malperfusion, concomitant CABG and CPB time >4 h were found to be independent predictors of the 30-day mortality in acute type A AD patients receiving total aortic arch replacement with FET technique.
Berger et al.	Distal Aortic Failure Following the Frozen Elephant Trunk Procedure for Aortic Dissection	• Distal aortic failure • Distal aortic reintervention • Distal stent graft-induced new entries • Frozen elephant trunk	Distal aortic failure assesses the treatment success of proximal aortic procedures with FET. The authors found that the incidence and risk for distal aortic failure following FET is very high (47.3%), especially in patients with more acute and more extensive aortic dissections or larger preoperative descending aortic diameters. They concluded that regular follow-up after FET is mandatory, since frequently FET is not a "single-step procedure".
Jubouri et al.	Incidence of Distal Stent Graft Induced New Entry vs. Aortic Remodeling Associated With Frozen Elephant Trunk	• Distal stent graft-induced new entries • Aortic remodeling • Frozen elephant trunk	In this literature review, the authors conclude that (I) excessive oversizing of the stent-graft may induce dSINE; (II) a longer length of the stent-graft may promote false lumen thrombosis and aortic remodeling.
Walter et al.	Postoperative In-Stent Thrombus Formation Following Frozen Elephant Trunk Total Arch Repair	• Distal stent thrombosis • Frozen elephant trunk	In the authors' experience, distal stent thrombosis was a rare (6%), but highly relevant clinical event: distal embolization occurred in 21% of the patients with in-stent thrombosis, causing one in-hospital death by severe visceral ischemia. Female sex and aortic aneurysm were significant predictors for thrombus development. All patients received therapeutic anticoagulation, while overstenting with a stent-in-FET was the treatment in 11% of patients.
Kayali et al.	Kinking of Frozen Elephant Trunk Hybrid Prostheses: Incidence, Mechanism, and Management	• Distal stent kinking • Frozen elephant trunk	In this review, distal stent kinking after FET was found to be a rare (0-8%) but critical complication as it may result in intraluminal thrombosis and multi-organ embolism. The authors discuss the mechanism of the stent-graft kinking and the therapeutical and operative management of this life-threatening condition.
Yang et al.	Both J- and L-shaped upper hemisternotomy approaches are suitable for total arch replacement with frozen elephant trunk in patients with Type A dissection	• Minimally invasive • Upper hemisternotomy • Frozen elephant trunk	The authors retrospectively analyze their experience with FET performed by means of a minimally invasive access. They concluded that both J-shaped or L-shaped partial upper sternotomy are a feasible and safe option for FET surgery, in order to offer all the benefits of minimally invasive cardiac surgery.
Singh et al.	RELAY^{TM} Branched–International Results of Vessel Patency and Reintervention	• Percutaneous • Aortic arch TEVAR • RELAY^{TM} Branched endoprosthesis • Multicentric study	In this retrospective multicentric investigation of aortic arch TEVAR operation using the RELAY^{TM} single-, double-, and triple-branched endoprostheses, technical success was achieved in 99.3% of cases. The 30-days mortality was 2.7% while the 30-days reintervention rate was 5.4%. Over a 24 months period, target vessel patency was maintained in 80.2% of patients, reintervention rate was 20.8% while no patient died.
Tan, Surkhi et al.	Does endovascular duration impact clinical outcomes in aortic arch repair? The RELAY^{TM} branched international stance	• Percutaneous • Endovascular time • Aortic arch TEVAR • RELAY^{TM} Branched endoprosthesis	Longer endovascular operative duration of the RELAY^{TM} branched endoprosthesis was associated with a lower likelihood of reintervention at 30 days, 6-, and 12 months and a greater likelihood of target vessel patency at 6- and 24 months. The prolonged endovascular duration may be the product of more extensive aortic arch repair.
Li et al.	Comparison of Prognosis Between Hybrid Debranching Surgery and Total Open Arch Replacement With Frozen Elephant Trunk for Type A Acute Aortic Syndrome Patients	• Debranching • Hybrid • Frozen elephant trunk	After a propensity score match analysis between patients having hybrid versus FET surgery, authors concluded that hybrid surgery could reduce aortic cross-clamp time and intraoperative hemorrhage. However, hybrid surgery was associated with increased incidence of permanent neurological complications, especially post-operative cerebral infarction.

FET: Frozen elephant trunk, ET: Elephant trunk, SCI: Spinal cord injury, AD: Aortic dissection, TEVAR: Thoracic endovascular aortic repair, SACP: Selective antegrade cerebral perfusion, LVEF: Left ventricular ejection fraction, CPB: Cardiopulmonary bypass, LVEDD: Left ventricular end-diastolic diameter, GFR: Glomerular filtration rate, CABG: Coronary artery bypass grafting, dSINE: Distal stent graft-induced new entries.

It has been demonstrated that the FET technique induces a precocious thrombosis of the false lumen in more than 90% of patients, followed by shrinkage and positive progressive remodeling over time (12, 14). This is why FET is frequently viewed as single stage procedure for pathologies involving the aortic arch. However, growing evidence is confirming that subsequent aortic reintervention after FET, regardless of the underlying aortic disease, is frequently needed. In order to assess the treatment success of proximal aortic procedures with FET, Berger et al. coined a new term: distal aortic failure. It was defined as: (I) distal aortic reintervention, (II) aortic diameter dilatation to ≥6 cm or growth of >5 mm within 6 months, (III) occurrence of a distal

stent graft-induced new entries (dSINE) and (IV) aortic-related death. The authors found that the incidence and risk for distal aortic failure following the FET technique is very high (47.3%), especially in patients with more acute and more extensive aortic dissections or larger preoperative descending aortic diameters. The authors concluded therefore that regular follow-up after FET is mandatory. Jubouri et al. reviewed the incidence of dSINE and the rate of aortic remodeling after FET as a significant indicator of patient's prognosis. These two factors are closely interconnected, as the onset of a dSINE ensures a continuous perfusion of the false lumen and consequently a progressive increase of aortic diameter, impacting negatively on aortic remodeling. The authors concluded that (I) excessive oversizing of the stent-graft may induce dSINE; (II) a longer length of the stent-graft may promote false lumen thrombosis and aortic remodeling. However, other authors have expressed concerns that a longer stent-graft length may increase the risk of SCI due to a major cover of the spinal cord (15). More studies are needed to fully explore the correlation between dSINE, aortic remodeling, the length and graft size of the stent-graft. Walter et al. investigated the occurrence and clinical consequence of postoperative in-stent thrombosis following FET. In their experience, it was a rare (6%), but highly relevant clinical event: distal embolization occurred in 21% of the patients with in-stent thrombosis, causing one in-hospital death by severe visceral ischemia. Female sex and aortic aneurysm were significant predictors for thrombus development. All patients received therapeutic anticoagulation, while over stenting with a stent-in-FET was the treatment in 11% of patients. Kayali et al. reviewed the incidence and clinical consequences of stent-graft kinking after FET. It was found to be a rare (0–8% in the literature) but critical complication as it may result in intraluminal thrombosis and multi-organ embolism. In their paper, the authors discuss the mechanism of the stent-graft kinking and the therapeutical and operative management of this life-threatening condition.

Finally, several authors have discussed the implementation of the best advancements in minimally invasive, trans-catheter and hybrid procedures in aortic arch surgery. Yang et al. retrospectively analyzed their experience with FET performed by means of a minimally invasive access. They concluded that both J-shaped or L-shaped partial upper sternotomy are a feasible and safe option for FET surgery, in order to offer all the benefits of minimally invasive surgery. Singh et al. presented a retrospective European multicentric investigation of aortic arch TEVAR operation using the RELAY^{TM} single-, double-, and triple-branched endoprostheses. Technical success was achieved in 99.3% of cases. The 30-days mortality was 2.7% while the 30-days reintervention rate was 5.4%. Over a 24 months period, target vessel patency was maintained in 80.2% of patients, while reintervention rate was 20.8%. No patient died during the follow-up. The authors concluded that the RELAY^{TM} branched endoprosthesis show great promise as a new therapeutic aortic arch TEVAR for patients that may not be suitable for open surgical repair. Tan, Surkhi et al. found that longer endovascular operative duration of the RELAY^{TM} branched endoprosthesis was associated with a lower likelihood of reintervention at 30 days, 6-, and 12 months and a greater likelihood of target vessel patency at 6- and 24 months. As the authors explained, this is likely an indirect correlation, as the prolonged endovascular duration may be the product of more extensive aortic arch repair. Li et al. studied the impact of a hybrid (traditional and trans-catheter) aortic arch treatment in acute type-A AD. Briefly, the authors firstly performed the open part with the reimplantation of the supra-aortic vessels to a prosthesis connected to the ascending aorta. A four-branch prosthetic graft was used whenever an ascending aorta replacement was needed. Next, the endovascular treatment part was performed and the stent-graft was released in the four-branched prosthetic graft or in the straight prosthetic graft. After a propensity score match analysis between patients having hybrid surgery vs. FET, authors found that hybrid surgery could reduce aortic cross-clamp time and intraoperative blood loss. However, hybrid surgery was associated with increased incidence of permanent neurological complications, especially post-operative cerebral infarction.

Conclusion

In conclusion, this Topic collects some of the best and actuarial advancements in the field of the frozen elephant trunk surgery in aortic dissection. The evolution of the surgical treatment will surely pursue in order to further improve postoperative and follow-up outcomes in patients presenting with this potentially life-threatening condition.

Author contributions

BC drafted the manuscript writing. All authors contributed substantially to the conception or design of the work. All authors contributed to the validation and final approval.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Improvement of Clinical Outcomes of Total Aortic Arch Replacement and Frozen Elephant Trunk Surgery With Aortic Balloon Occlusion

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Background: Total aortic arch replacement (TAR) with frozen elephant trunk (FET) surgery provides improved long-term results, but the surgery itself is associated with higher risks compared with isolated proximal reconstructions. We applied an aortic balloon occlusion (ABO) technique to reduce the circulatory arrest (CA) time and improve other clinical outcomes.

Methods: All patients who underwent TAR with FET surgery (130 with ABO technique, 230 with the conventional approach) in Fuwai Hospital from August 2017 to February 2019 were reviewed in this retrospective observational cohort study. Intra- and early-postoperative results and clinical characteristics were analyzed.

Results: After 1:1 propensity score matching (130 cases in each group), the 30-day mortality of the ABO group and the conventional group were 4.6% and 10.8% ($p = 0.063$), respectively. Although the reduction in complications was not statistically significant, the complication rate in the ABO group was relatively low, having fewer cases of postoperative renal (23.1 vs. 38.5%, $p = 0.007$) and hepatic (12.3 vs. 30.0%, $p < 0.001$) injury, lower postoperative wake-up time (15.2 ± 23.6 h vs. 20.1 ± 26.5 h, respectively, $p < 0.001$), reduced chest tube output (176.03 ± 143.73 ml vs. 213.29 ± 130.12 ml, respectively, $p = 0.003$), lower red blood cell transfusion volume (4.98 ± 6.53 u vs. 7.28 ± 10.41 u, respectively, $p = 0.008$), and no fatal events.

Conclusions: The ABO technique is a simple method that can reduce the CA time and improve the recovery stage following TAR with FET surgery. The technique represents a practical strategy to treat patients with high operative risks due to its lower complication rate compared with the conventional approach.

Keywords: aortic dissection, total aortic arch replacement, frozen elephant trunk, hypothermic circulatory arrest, aortic balloon occlusion technique

INTRODUCTION

Total aortic arch replacement (TAR) with frozen elephant trunk (FET) surgery is considered the most reliable method in treating type A aortic dissection (AD) in our hospital (1–3). Currently, we routinely perform TAR with FET with a lower average circulatory arrest (CA) time (17 min) with a target temperature of 26°C in non-complicated cases; this has improved postoperative results compared with the past decades. This new technique used in TAR with FET surgery can reduce the lower body CA time to 5 min on average (4). The target lowest temperature for CA has now been raised to 28°C. This study was aimed to investigate the merits of our new technique by comparing the clinical endpoints according to the International Aortic Arch Surgery Study Group (IAASSG) (5). The laboratory test results were examined to further discuss the advantages of this new technique.

METHODS

Study Design and Patient Population

The study was approved by the institutional ethics committee of Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, and Peking Union Medical College (Approval No. 2018-1069), and individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All data sets were represented by routine parameters from our institution that did not constitute an additional burden to the patients. The study included consecutive patients who underwent TAR with FET surgery in Fuwai Hospital from August 2017 to February 2019. A total of 130 patients underwent TAR with FET surgery via the balloon occlusion technique, while 230 patients received regular TAR with FET procedure.

Surgical Technique of ABO Technique

A four-branched graft (Terumo; Vascutek Limited, Renfrewshire, UK) was trimmed, and the 40M All AD aortic balloon (Coda Balloon Catheter; Cook Incorporated, Bloomington, IN, USA) was inserted into an 18F Gore sheath (W.L. Gore & Associates, Inc., Flagstaff, AZ, USA), which had already been inserted into the graft. Arterial cannulation was performed through the right axillary and femoral arteries with a bifurcated arterial line from one central perfusion. Cardiopulmonary bypass (CPB) was stopped at 28°C which was the target nasopharyngeal temperature. After clamping the proximal innominate artery, the anterograde selective cerebral perfusion (ASCP) was obtained at a rate of 5–10 ml/kg/min through the right axillary artery cannula. After the Cronus stent elephant trunk (diameter: 26 or 28 mm; length: 100 or 120 mm; Cronus, MicroPort Endovascular Shanghai Co., Ltd., Shanghai, China) was released in the true lumen of the descending thoracic aorta (DTA).

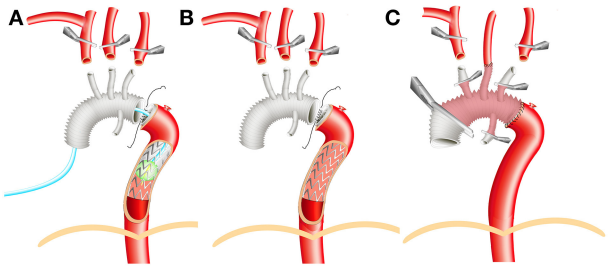

FIGURE 1 | Illustration of surgical technique. **(A)** Aortic balloon occlusion. **(B)** Conventional total aortic arch replacement (TAR) with frozen elephant trunk (FET). **(C)** Aortic reconstruction before rewarming.

The sheathed aortic balloon was deployed into the stent-graft, acknowledging that any part the balloon could be constricted by the solid metal stent. The balloon was inflated via injection of 40 ml saline to compress the stent-graft. Once the balloon was fixed, lower body perfusion was restarted through the right femoral artery cannula along with ASCP through the right axillary artery cannula. The CPB flow restarted and gradually increased to 50% of the total flow. The lower body CA was 6.3 ± 5.7 min (**Figure 1A**). During conventional TAR with FET surgery, lower body CA is required until distal anastomosis (suture of the wall of the DTA, the proximal wall of the stent-graft, and the distal wall of trifurcated graft) is completed, before CPB can be restarted and gradually increased to 50% of the total flow (**Figure 1B**).

For DeBakey type III patients, with an ascending aortic aneurysm and/or intracardiac diseases (such as aortic valve regurgitation or atrial septal defect), it is possible to treat all diseases during a one-stage operation by performing TAR with FET surgery. The treatment of AD in the DTA and/or left subclavian artery is more effective in the long term compared with thoracic endovascular aortic repair. The chronicity of AD and the aortic pathology of the patients were recorded in the patient records. After matching, both the aortic pathology and chronicity classifications of AD indicated that the conventional group was more, or at least as likely to be, reasonable as the conventional group before matching. The left common carotid artery was anastomosed first, and then perfusion through both carotid arteries could be realized. The rewarming process was subsequently started (**Figure 1C**).

Data Collection and Statistical Analysis

Major complications and clinical endpoints were recorded according to the consensus statement from the IAASSG (5). Specifically, postoperative acute kidney injury (AKI) was defined as a serum creatinine (Scr) volume over 1.5 times that of the normal value (<133 μmol/L). Liver injury was defined as transaminase concentrations 1.5 times greater than those of the corresponding upper range of their normal values [alanine transaminase (ALT) <40 U/L, aspartate transaminase

Abbreviations: ABO, aortic balloon occlusion; TAR, total arch replacement; FET, frozen elephant trunk; CA, circulatory arrest; RBC, red blood cell; AD, aortic dissection; IAASSG, international aortic arch surgery study group; CPB, cardiopulmonary bypass; ASCP, anterograde selective cerebral perfusion; DTA, descending thoracic aorta; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

(AST) <55 U/L] for more than 48 h. The clinical examinations were all collected preoperatively. In addition, continuous renal replacement therapy (CRRT) is indicated when the patient has a urine volume <0.5 ml/(h-kg) for more than 6 h or a pH <7.2 and residual base <-8 mmol/L or serum potassium >6.0 mmol/L or a 2- to 2.9-fold increase in serum creatinine value from baseline levels.

Following the surgical procedure, data regarding patient transfer to the intensive care unit (ICU) was collected. (0), twice on postoperative days 1 to 3 (1, 1.5, 2, 2.5, 3), mid-time point of ICU if the patient stayed in ICU more than 4 days (Mid), the last examination before transferred out from ICU (ICU), the first examination after transfer out from ICU to ward (Ward), and the last examination before discharge (Discharge). These items were considered as both time-matched comparisons during the first three postoperative days and event-matched comparisons obliterating time (preoperative, transfer out of ICU, and fully recovered discharge values) to achieve maximum power. Categorical variables were compared using the χ^2 test. Continuous variables were presented as mean ± SD; ALT and AST were presented as mean ± SEM. All parameters related to time also included the median (M) and interquartile range. A normality test between the two groups was performed on the continuous variables. If the variable satisfied the normality test (Shapiro–Wilk test), the statistical analysis was evaluated with a *t*-test. If the variable failed the Shapiro–Wilk test, it was evaluated by the Mann–Whitney *U*-test. Clinical data were depicted in the figures to show the characteristics of the trends of perioperative alteration between the two groups. Due to fluctuating values, no statistical analyses could be performed to compare differences between time points and multiple comparison corrections to obtain *p*-values. According to the basic characteristics of comparison groups, once there are significant differences of potential confounding variables found between groups, propensity score matching will be conducted to control the confounding factors and reduce the risk of potential biases. The propensity score will be generated through a multivariable logistic regression analysis model and be applied to create 1:1 matching pairs of the conservative group and the innovative group. A nearest neighbor matching algorithm without a caliper method will be used. All the statistical analysis in the study will be performed using SPSS software (version 22.0; IBM-SPSS Inc., Armonk, NY, USA).

RESULTS

Baseline Characteristics and Early Outcomes

The baseline demographic and clinical characteristics of the patients are listed in **Table 1**. Several differences are evident: the aortic balloon occlusion (ABO) group is associated with older age, less cardiac surgery history, and inconsistently distributed CPB time, all of which were included in the propensity score matching. The matched cohorts consisted of mostly male patients, aged 49.9 ± 12.2 and 49.6 ± 10.0 years, respectively ($p = 0.547$). The most common aortic pathology type present in both cohorts was the AD in the acute stage (<72 h). All patients had similar smoking, cardiovascular disease, and cerebrovascular event histories. There were no statistically significant differences between patients having aortic arch lesions with a proximal extension to the aortic root (43.1 vs. 42.3%, $p = 0.827$) or distal extension to iliac arteries (59.4 vs. 63.4%, $p = 0.513$) in the ABO group and the conventional group, respectively. In addition to TAR with FET operations, the concomitant root operations and coronary artery bypass grafts were performed according to the related indications in a similar proportion in both groups. Duration of lower body CA and ASCP time was significantly lower in the ABO group compared with the conventional group (1 ± 4.2 min and 6.3 ± 5.7 min, $p < 0.001$, respectively), whereas the nasal temperature was greater (25.5 ± 1.0°C and 27.4 ± 1.1°C, respectively) during CA.

After propensity score matching, the 30-day mortality of the ABO group and the conventional group was 4.6 and 10.8% ($p = 0.063$), respectively. Although the 30-day mortality of the ABO group was lower in the ABO group, the difference was not statistically significant. The ICU stay time was similar in both groups, 119.9 ± 106.3 h vs. 131.1 ± 150.0 h ($p = 0.415$), as was the postoperative in-hospital stay time, 11.8 ± 5.4 days vs. 12.3 ± 6.7 days ($p = 0.900$). The incidence of stroke (3.1 vs. 4.6%, $p = 0.519$), temporal paraplegia (2.3 vs. 5.4%, $p = 0.197$), and delirium (3.1 vs. 7.7%, $p = 0.099$) were also similar in the ABO group compared with the conventional group, respectively.

Renal System Results

Volumes of Scr and urine, and CRRT were found to be the most common and therefore reliable parameters to evaluate the postoperative AKI. Patients with oliguria or anuria who underwent CRRT had the worse prognosis. Scr was a key indicator when evaluating the underlying AKI incidence. The ABO technique significantly reduced the incidence of postoperative AKI (23.1 vs. 38.5%, $p = 0.007$) and CRRT (7.7 vs. 16.2%, $p = 0.037$) in the ABO group compared with the conventional group, respectively.

To further investigate the in-hospital recovery course of renal function and explore the benefits of ABO technique, we examined the patients' blood examination results. Scr value reflects whether postoperative renal function recovery is good or poor. Blood urea nitrogen values were similar in pattern to those of Scr; however, the blood urea nitrogen peak appeared later. Uric acid (UA) was also recorded from the renal function examination, and it tended to decrease. The decrease in postoperative UA levels may also reflect renal function recovery (**Figure 2**).

Postoperative Bleeding

The operation time after CPB was significantly shorter in the ABO group than the conventional group (128.8 ± 54.3 min vs. 167.6 ± 73.1 min, $p < 0.001$). The propensity-matched comparisons showed that the ABO group had a lower operative time and lower volumes of red blood cell (RBC) and platelet transfusions.

RBC transfusion is necessary when a patient's hemoglobin concentration is below 80 g/L following cardiac surgery (6). More than 50% of patients received at least one 1

TABLE 1 | Preoperative and operative details.

Variables	Aortic balloon occlusion (*N* = 130)	Conventional before matching (*N* = 230)	*P*	Conventional after matching (*N* = 130)	*P*
Age	49.84 ± 12.21	48.00 ± 10.27	0.087	49.63 ± 9.97	0.547
Male	99 (76.15)	173 (75.22)	0.843	103 (79.23)	0.551
Smoke history	74 (56.92)	130 (56.52)	0.941	76 (58.46)	0.802
Mild	5 (3.85)	6 (2.61)	0.806	6 (4.62)	0.935
Heavy	69 (53.08)	124 (53.91)		70 (53.85)	
Chronic obstructive pulmonary disease	6 (4.62)	2 (0.87)	0.021	2 (1.54)	0.151
Cardiac surgery history	2 (1.54)	15 (6.52)	0.032	3 (2.31)	0.652
Coronary artery disease history	13 (10.00)	24 (10.43)	0.896	14 (10.77)	0.839
Myocardial infarction history[1]	1 (0.77)	6 (2.61)	0.225	4 (3.08)	0.176
Cerebrovascular accident[2]	11 (8.46)	23 (10.00)	0.632	12 (9.23)	0.827
Marfan syndrome	6 (4.62)	22 (9.57)	0.092	7 (5.38)	0.776
Time of onset (d)	86.04 ± 401.33 2.83 (1.23–11.90)	51.26 ± 259.97 2.52 (1.07–9.06)	0.373	53.27 ± 261.73 2.72 (1.01–10.62)	0.336
Classification based on chronicity *N* (%)					
Acute, <7 d (h)	50.47 ± 37.92 35.25 (23.48–66.88) 87 (66.92)	51.96 ± 42.41 38.32 (22.48–69.56) 168 (73.04)	0.228 (0.220)	48.62 ± 37.11 31.83 (19.62–69.70) 93 (71.54)	0.432 (0.420)
Subacute, 7–30 d (d)	15.10 ± 5.54 14.07 (10.40–19.11) 23 (17.69)	14.28 ± 5.71 12.28 (9.4–17.58) 20 (8.70)	0.638 (0.011)	14.06 ± 5.94 12.23 (10.01–16.56) 13 (10.00)	0.017 (0.073)
Chronic, >30 d (d)	556.21 ± 933.51 160 (54.5–372.5) 20 (15.38)	265.21 ± 565.71 97 (40–213) 42 (18.26)	0.161 (0.488)	271.46 ± 565.79 84.5 (35.75–223.25) 24 (18.46)	0.013 (0.508)
Aortic pathology					
Aneurysm	7 (5.38)	9 (3.91)	0.515	7 (5.83)	1
Aortic dissection	123 (94.62)	221 (96.09)		123 (94.62)	
Aortic dissection classification[3]	*N* (N/123)	*N* (N/221)		*N* (N/123)	
Stanford type A (DeBakey I&II)	105 (85.37)	208 (94.12)	0.007	119 (91.54)	0.002
Stanford type B (DeBakey III)	7 (5.69)	4 (1.81)	0.050	0 (0)	0.007
Stanford type NANB	11 (8.94)	9 (4.04)	0.064	4 (3.25)	0.062
Aortic dissection involvement	*N* (N/123)	*N* (N/221)		*N* (N/123)	
Root	53 (43.09)	93 (42.08)	0.856	55 (42.31)	0.797
Ascending	105 (85.37)	208 (94.12)	0.007	119 (91.54)	0.002
Arch	123 (100)	221 (100)	1	123 (100)	1
Total/proximal	116 (94.31)	217 (98.19)	0.050	123 (100)	0.007
Left subclavian artery or distal	7 (5.69)	4 (1.81)		0 (0)	
Thoracic descending	115 (93.50)	207 (93.67)	0.951	116 (94.31)	0.790
Total abdominal	84 (68.29)	143 (64.17)		84 (68.29)	1
Iliac	73 (59.35)	135 (61.09)	0.752	78 (63.41)	0.513
Aortic diameter on CT					
Ascending aorta	45.81 ± 9.96	47.53 ± 12.21	0.274	45.85 ± 11.60	0.736
Descending aorta	31.26 ± 6.38	34.03 ± 9.44	0.100	32.84 ± 7.06	0.492
Branch aortic dissection involvement	*N* (N/123)	*N* (N/221)		*N* (N/123)	
Coronary (total)	26 (21.14)	56 (25.34)	0.381	32 (26.02)	0.367
Left coronary artery	11 (8.94)	20 (9.05)	0.974	11 (8.94)	1
Left coronary artery only	1 (0.77)	4 (1.74)	0.450	3 (2.31)	0.314
Right coronary artery	25 (20.33)	52 (23.53)	0.494	29 (23.58)	0.538
Right coronary artery only	15 (11.54)	36 (15.65)	0.282	21 (16.15)	0.281
Coronary (Both)	10 (7.69)	16 (6.96)	0.796	8 (6.15)	0.625
Left renal artery involvement	60 (48.78)	110 (49.77)	0.860	67 (54.47)	0.372
Left renal artery evidence of stenosis	22 (17.89)	44 (19.91)	0.648	24 (19.51)	0.744

(Continued)

TABLE 1 | Continued

Variables	Aortic balloon occlusion ($N = 130$)	Conventional before matching ($N = 230$)	*P*	Conventional after matching ($N = 130$)	*P*
Right renal artery involvement	38 (30.89)	71 (32.13)	0.814	41 (33.33)	0.682
Right renal artery evidence of stenosis	17 (13.82)	27 (12.22)	0.669	14 (11.38)	0.564
Aortic root operation					
None	41 (31.54)	96 (41.74)		53 (40.77)	
Repair or plasty	53 (40.77)	68 (29.57)		44 (33.85)	
Bentall	27 (20.77)	52 (22.61)	0.158	25 (19.23)	0.388
Wheat	8 (6.15)	10 (4.35)		5 (3.85)	
David	1 (0.77)	4 (1.74)		3 (2.31)	
Concomitant coronary artery bypass graft (CABG)	18 (13.85)	30 (13.04)	0.830	16 (12.31)	0.713
Planned CABG	18 (13.85)	25 (10.87)	<0.001	14 (10.77)	<0.001
Salvage CABG	0 (0)	5 (2.17)		2 (1.54)	
Operation time	396.95 ± 85.42 379 (337–430)	409.76 ± 118.77 395 (330–463)	0.445	402.64 ± 113.06 394 (321–458)	0.872
Cardiopulmonary bypass time	185.20 ± 56.99 175 (148–201)	188.57 ± 89.25 162 (141–209)	0.152	188.12 ± 74.35 159 (141–211)	0.245
Clamp time	119.34 ± 36.25 114 (94–143)	113.05 ± 39.53 109 (89–131)	0.034	112.95 ± 38.75 107.5 (85–132.25)	0.073
Cooling time	20.90 ± 7.26 20 (16–24)	30.33 ± 9.78 29 (23–36)	<0.001	30.52 ± 10.03 29 (23–36)	<0.001
Circulatory arrest duration	6.33 ± 5.74 5 (3–7)	17.24 ± 4.36 17 (14–20)	<0.001	17.09 ± 4.18 17 (14.75–19)	<0.001
Antegrade selective cerebral perfusion time	39.88 ± 14.51 37 (31–47)	33.28 ± 10.01 32 (26–38)	<0.001	33.38 ± 10.92 32 (26–39)	<0.001
Rewarming time	53.64 ± 17.51 53 (45–62)	65.58 ± 19.52 63 (53–74)	<0.001	65.98 ± 19.60 64 (54–74.5)	<0.001
Post cardiopulmonary bypass time	128.78 ± 54.29 119 (98–137)	166.10 ± 66.00 157 (123–199)	<0.001	167.55 ± 73.08 156 (126–199)	<0.001
The temperature when the circulatory arrest was commenced (°C)					
Nasopharyngeal	27.41 ± 1.06	25.37 ± 1.34	<0.001	25.45 ± 0.96	<0.001
Rectal	29.00 ± 1.91	28.46 ± 2.55	0.015	28.61 ± 2.53	<0.001

Continuous variables are expressed as mean ± standard deviation and compared by Mann-Whitney U-test except for age, which is normally distributed and compared by Student's t-test. Categorical variables are expressed as number (%) and compared using the χ^2 test.

[1]*Myocardial infarction history is included in patients with coronary artery disease history. This is the old history and is not associated with the onset of aortic dissection, which may involve coronary arteries and may cause new myocardial ischemia/infarction.*

[2]*Cerebrovascular accident includes stroke history and transient ischemic attack history.*

[3]*Stanford type A (DeBakey I) is defined as ascending aortic arch involvement and distal beyond, Stanford type B (DeBakey II) as involving from the left subclavian artery or distal beyond, and the rest as none-type A-none-type B (NANB) Stanford type, which is dissection involved in the proximal aortic arch, but not ascending aorta. There were no DeBakey III patients.*

unit transfusion of RBC during their in-hospital stay (**Figure 3A**). Plasma and platelet transfusions were used mostly intraoperative to avoid bleeding and decrease the thoracic drainage output. Platelet level dropped drastically after the operation, especially in the conventional group, which may be caused by blood loss and/or heparin-induced thrombocytopenia (**Table 2**). In addition, compared with the ABO group, more patients in the conventional group required a platelet transfusion (13.9 vs. 26.9%, respectively, $p = 0.009$). Platelet levels showed an obvious increase after postoperative day 3, and no further platelet transfusions were necessary (**Figure 3B**).

Respiratory System and Inflammation

After transfer to the ICU, patients frequently regained consciousness before the mechanical ventilation was withdrawn. The incidence of lung infection was lower in the ABO group compared with the conventional group (2.3 vs. 8.5%, respectively, $p = 0.028$). The postoperative wake-up time was much shorter in the ABO group compared with the conventional group, at 15.2 ± 23.6 h vs. 20.1 ± 26.5 h, respectively ($p < 0.001$), which may be because the superior central nervous system was well-protected via the ABO technique to a certain extent. The mechanical ventilation support time was 34.1 ± 41.0 h and 48.9 ± 87.8 h ($p = 0.133$). The ABO group had short mechanical ventilation support time, 8.5% vs. 21.5% ($p = 0.003$) in the ABO group compared with the conventional group, respectively. The leukocyte counts revealed both neutrophil and total leukocyte counts were higher in the conventional group during the initial postoperative period (**Figure 4**). The neutrophil and total leukocyte counts dropped to preoperative levels before discharge, suggesting a favorable recovery during the in-hospital stay.

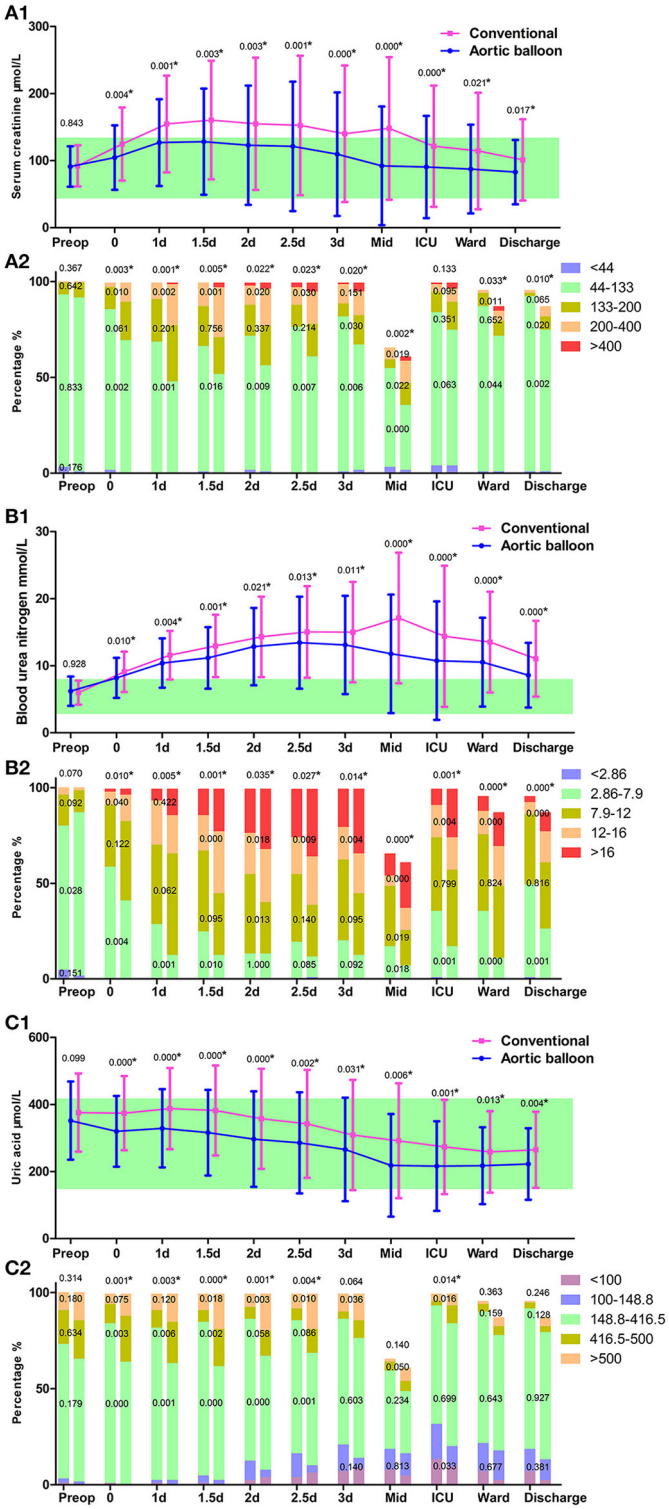

FIGURE 2 | Renal function. **(A1)** The trajectory of serum creatinine (Scr). **(A2)** Scr grading in the column. **(B1)** The trajectory of blood urea nitrogen (BUN). **(B2)** BUN grading in the column. **(C1)** The trajectory of uric acid (UA). **(C2)** UA grading in the column. Data points are represented by mean with standard deviation bars. The green band represents the referred normal range of the examination. The *P*-value of the continuous variable is represented above the standard deviation bar, which is calculated by Student's t-test (normally distributed) or Mann-Whitney U test (non-normally distributed) with no multiple comparison correction to the *P*-value. The *P*-value of the categorical variable is represented in the graded column to represent for each grade, or above the grade to represent a total, which is calculated by χ^2 test. $^*P < 0.05$.

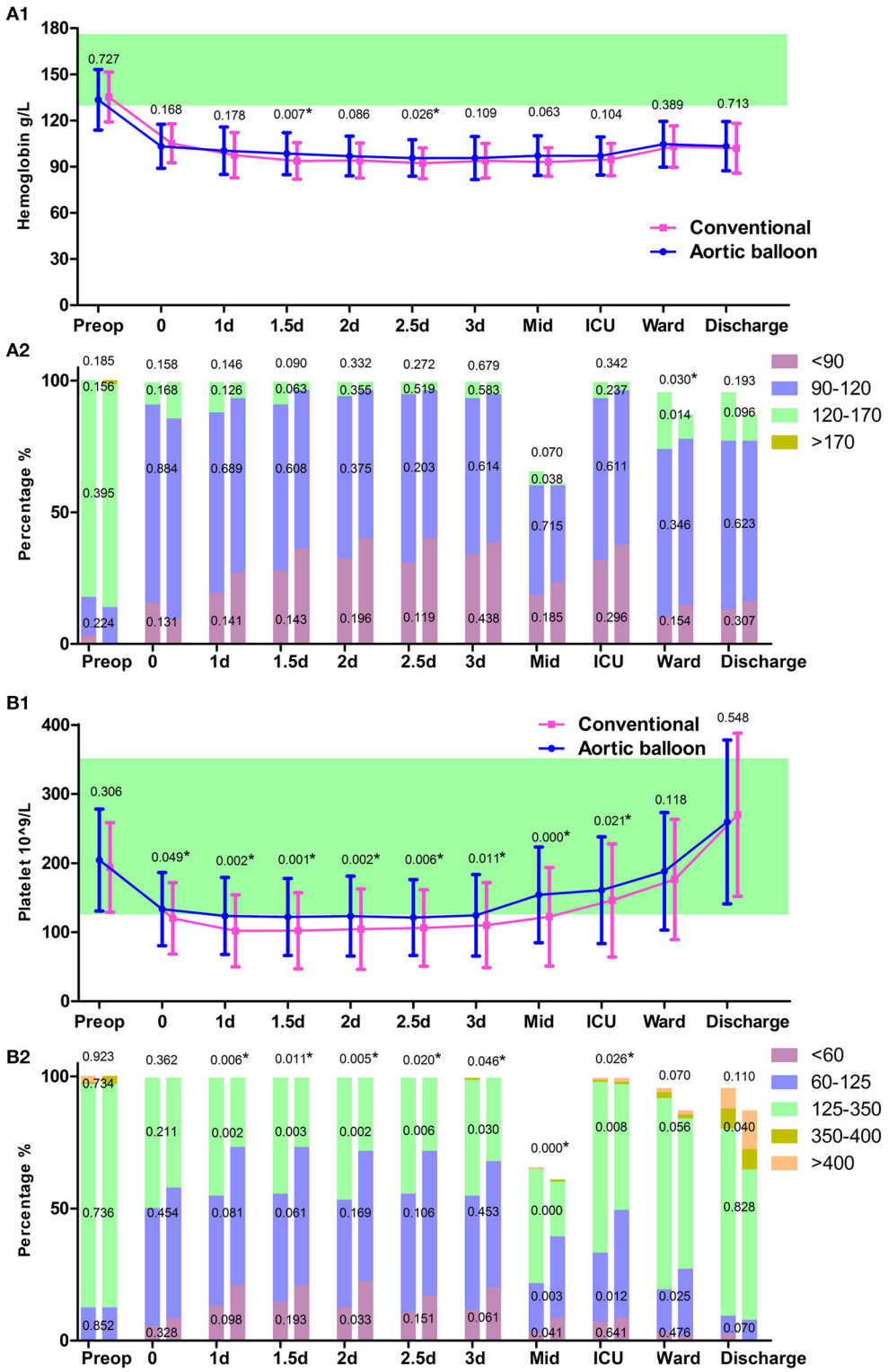

FIGURE 3 | Blood routine test. **(A1)** The trajectory of hemoglobin. **(A1)** hemoglobin grading in the column. **(B1)** The trajectory of platelet count. **(B2)** Platelet count grading in the column. Data points are represented by mean with standard deviation bars. *$P < 0.05$.

TABLE 2 | The early outcomes.

Variables	Aortic balloon occlusion (*N* = 130)	Conventional before matching (*N* = 230)	*P*	Conventional after matching (*N* = 130)	*P*
30-day mortality	6 (4.62)	18 (7.83)	0.241	15 (10.77)	0.063
Wake-up time (h)	15.16 ± 23.56 8.12 (4.92–13.80)	20.07 ± 26.49 11.75 (7.80–19.02)	<0.001	23.52 ± 32.71 11.92 (7.85–22.32)	<0.001
Mechanical ventilation (h)	34.13 ± 40.97 18.67 (13.30–36.87)	46.74 ± 106.69 21.48 (13.47–46.97)	0.217	48.93 ± 87.83 21.70 (13.52–55.23)	0.133
Prolonged mechanical ventilation (>72 h)	11 (8.46)	42 (18.26)	0.012	28 (21.54)	0.003
ICU stay (h)	119.90 ± 106.32 90.53 (59.33–132.75)	119.69 ± 123.36 86.38 (58.67–134.15)	0.380	131.14 ± 150.00 86.38 (44.32–136.58)	0.415
Postoperative in-hospital stay (d)	11.80 ± 5.35 11 (8–14)	12.42 ± 6.03 11 (9–14)	0.321	12.34 ± 6.70 10 (8–14)	0.900
Acute kidney injury	30 (23.08)	82 (35.65)	0.013	50 (38.46)	0.007
Continuous renal replacement therapy	10 (7.69)	23 (10.00)	0.466	21 (16.15)	0.037
Stroke	4 (3.08)	9 (3.91)	0.683	6 (4.62)	0.519
Temporal paraplegia	3 (2.31)	10 (4.35)	0.319	7 (5.38)	0.197
Delirium	4 (3.08)	15 (6.25)	0.160	10 (7.69)	0.099
Hepatic injury	16 (12.31)	64 (27.83)	0.001	39 (30.00)	<0.001
Acute pancreatitis	6 (4.62)	22 (9.57)	0.091	13 (10.00)	0.095
Severe lung infection	3 (2.31)	18 (7.83)	0.032	11 (8.46)	0.028
Re-exploration for post-operative bleeding	7 (5.38)	9 (3.91)	0.515	8 (6.15)	0.790
Left recurrent nerve injury	4 (3.08)	1 (0.008)	0.040	1 (0.004)	0.176
Total chest tube drainage of 0–3 postoperative day (ml)					
Operation day	429.15 ± 585.05	403.21 ± 264.47	0.760	432.72 ± 309.23	0.484
Postoperative day 1	321.47 ± 201.07	381.23 ± 213.73	0.001	375.35 ± 218.95	0.006
Postoperative day 2	211.34 ± 192.45	269.51 ± 179.42	<0.001	259.13 ± 175.19	0.001
Postoperative day 3	176.03 ± 143.73	223.86 ± 148.50	<0.001	213.29 ± 130.12	0.003
Prothrombine X (IU) usage	1144.26 ± 293.47 122 (93.85)	1303.51 ± 401.08 228 (99.13)	<0.001 (0.003)	1321.19 ± 381.82 119 (91.54)	<0.001 (0.475)
Novoseven (mg) usage	2.11 ± 0.56 83 (63.85)	2.23 ± 0.64 147 (63.91)	0.084 (0.990)	2.12 ± 0.66 78 (60.00)	0.863 (0.523)
Transfusion requirement (average per patients and percentage of usage)					
Red blood cell (u) total	4.98 ± 6.53 83 (63.85)	6.47 ± 8.51 174 (75.65)	0.042 (0.017)	7.28 ± 10.41 99 (76.15)	0.008 (0.030)
Operative	2.06 ± 3.15 55 (42.31)	3.02 ± 4.53 117 (50.87)	0.090 (0.118)	3.64 ± 5.19 74 (56.92)	0.009 (0.018)
Postoperative	2.92 ± 4.50 65 (50.00)	3.45 ± 6.18 132 (57.39)	0.351 (0.176)	4.17 ± 7.55 80 (61.54)	0.101 (0.061)
Plasma (ml) total	488.37 ± 573.32 82 (63.08)	614.78 ± 833.55 141 (61.30)	0.397 (0.739)	725.58 ± 992.81 86 (66.15)	0.120 (0.604)
Operative	302.33 ± 399.31 71 (54.62)	367.83 ± 432.13 124 (53.91)	0.292 (0.898)	400.00 ± 445.11 77 (59.23)	0.089 (0.452)
Postoperative	186.05 ± 354.60 42 (32.31)	246.96 ± 576.29 73 (31.74)	0.887 (0.912)	325.58 ± 716.36 47 (36.15)	0.337 (0.513)
Platelets (u) total	1.16 ± 0.99 102 (78.46)	1.40 ± 1.53 189 (82.17)	0.245 (0.390)	1.62 ± 1.84 112 (86.15)	0.049 (0.104)
Operative	0.86 ± 0.66 93 (71.54)	0.92 ± 0.90 172 (74.78)	0.675 (0.502)	0.95 ± 0.99 99 (76.15)	0.595 (0.397)
Postoperative	0.29 ± 0.84 18 (13.85)	0.48 ± 1.28 51 (22.17)	0.078 (0.054)	0.68 ± 1.62 35 (26.92)	0.015 (0.009)

Continuous variables are expressed as mean ± standard deviation and compared by the Mann-Whitney U-test. Categorical variables are expressed as number (%) and compared using the χ^2 test.

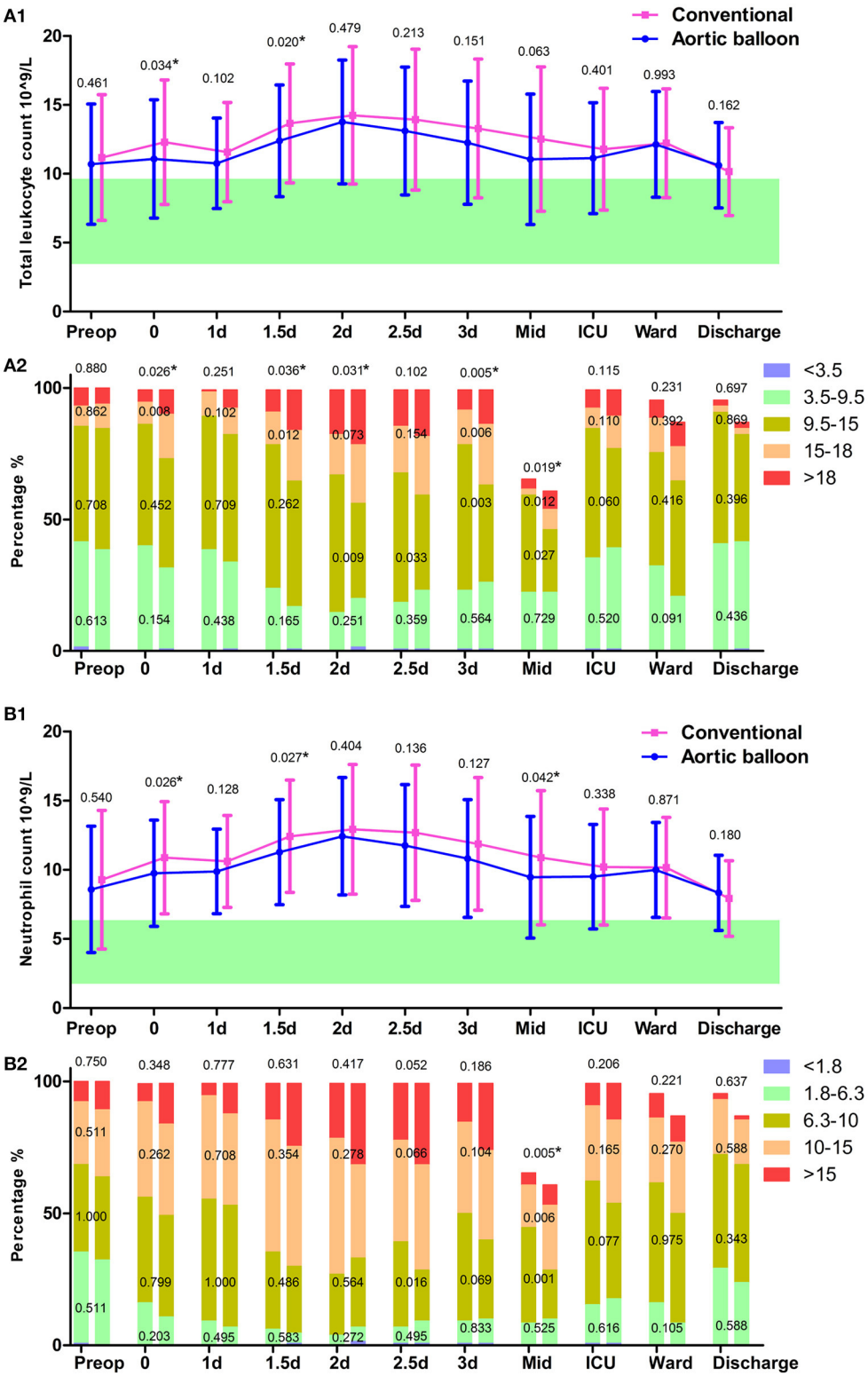

FIGURE 4 | Leukocyte test. **(A1)** The trajectory of total leukocyte count. **(A2)** Total leukocyte count grading in the column. **(B1)** The trajectory of neutrophil count. **(B2)** Neutrophil count grading in the column. Data points are represented by mean with standard deviation bars. *$P < 0.05$.

Hepatic System Results

Hepatic complications were reflected by postoperative transaminase, and the ABO group had a lower incidence of hepatic injury (12.3 vs. 30.0%, $p < 0.001$) than the conventional group. The average level of ALT progressively increased in the ABO group during the in-hospital stay, and the conventional group rapidly increased in the first three postoperative days and fell to a similar level to that of the ABO group. Both groups had a sharp growth in average levels of AST during the ICU stay, and these gradually recovered to normal levels after patients were transferred back to the ward (**Figure 5**). The tendency of ALT and AST, therefore, played an important role in indicating hepatic injury.

DISCUSSION

In our institution, TAR with FET is the standard method to treat AD and other complexed aortic arch diseases (2); it is a safe and effective strategy (7) with promising long-term outcomes (3). Recently, the ABO technique was applied to TAR with FET. Its use consistently shortened the lower body CA time and raised the target nadir temperature, improving organ protection during the operation. Due to the complexity of postoperative complications, multi-system real-time surveillance is required during the ICU stay (8). This study investigated the effects of the ABO technique on the clinical outcomes, through continuous monitoring of patients' blood examination results during the in-hospital stay.

Renal injury was defined by Scr increase or urine output decrease. In our results, all oliguria and anuria received CRRT treatment, and AKI was graded by Scr level. Scr levels in both groups rose during the stay in the ICU but had recovered to preoperative levels before discharge. The postoperative Scr levels in the ABO group were consistently lower than that in the conventional group. The ABO technique may improve blood perfusion in the kidneys. Increasing the CA temperature alone cannot provide renal protective effects if CA time is not shortened (9).

Over the past few decades, transfusions in our hospital have greatly improved. Significant improvements have been achieved using the ABO technique, with a reduction in RBC, plasma, and platelet transfusion volumes, as well as reduced bleeding control times and thoracic drainage output. This benefit may be due to an improved postoperative coagulation function strategy, which may also be related to the use of the ABO technique. A previous study found that a decrease in patients' postoperative platelet counts was associated with the severity of AKI (10). A rebound in the number of platelets was also observed in the current study, as indicated by the persistent platelet activation and aggregation in the initial postoperative period (10). The postoperative platelet count may increase to such a high level that anti-platelet therapy could be actively proposed following a suitable evaluation. Moreover, the FET procedure was considered as a risk factor that may increase the incidence of spinal cord ischemia (11). Thus, anti-platelet therapy and dynamic assessment of limb movement should be considered in patients with high postoperative platelet counts to reduce the risk of thrombi.

The hepatic function was also significantly improved by the ABO technique; the AST was significantly higher in the conventional group and the ALT increased steadily during the in-hospital stay and exceeded the AST level before discharge. Previous studies highlight how AST is more sensitive than ALT in predicting postoperative hepatic injury (12–14). In our investigation, the AST level was high during the initial postoperative period, although it returned to normal levels following transfer out of the ICU. This demonstrates that AST was a more sensitive indicator to evaluate the hepatic injury suffered from the CPB procedure, while ALT was more strongly associated with drug-induced hepatic injury. Although ALT levels increased during the in-hospital stay in line with drug usage, most cases did not need specific hepatoprotective treatment (15).

The ABO technique significantly shortened the postoperative wake-up time, which may provide an improved protective effect on the central nervous system, although this hypothesis needs further investigation. In addition, the subsequent mechanical ventilation support time was shortened, and the pulmonary infection rate was also low.

This study has several limitations. First, this is a retrospective study and we only presented the data within a short period, mainly because the technique was only invented in August 2017, although this makes the standard of ICU care included in the study as uniform as possible. Second, as a historical comparison, the influence of increasing team experience may also create potential bias. Third, propensity score matching is well-performed but could not adjust differences for every indicator analyzed in this study, and results of some comparisons may have been impacted. In addition, as for this new technique we introduced, it is not suitable for the following situations: where both femoral arteries are not suitable for cannulation; the DTA has formed a large aneurysm at the suture level of the trifurcated graft; or where Cronus stents have been implanted. There is still space for improvement of the new technique and we will continue our study in the future.

CONCLUSIONS

We systematically introduced a new ABO technique, based on the primary clinical outcomes, and this new method is not inferior to the traditional approach. Furthermore, some improved clinical outcomes were seen in the ABO group. Although there were no significant statistical differences between the two groups, in some respects, the clinical outcomes of the ABO group were improved compared with those of the conventional group. However, the sample size of the current study is small. We hope to enroll more patients to further investigate the value in the clinical application of this new technique.

The ABO technique may serve as an important operative method that improves the blood perfusion of organs and the recovery process during the in-hospital stay. However, the aortic balloon occlusion technique cannot be seen as a perfect technique that avoids all complications. We believe that continuous perfusion via the ABO technique is crucial in diminishing

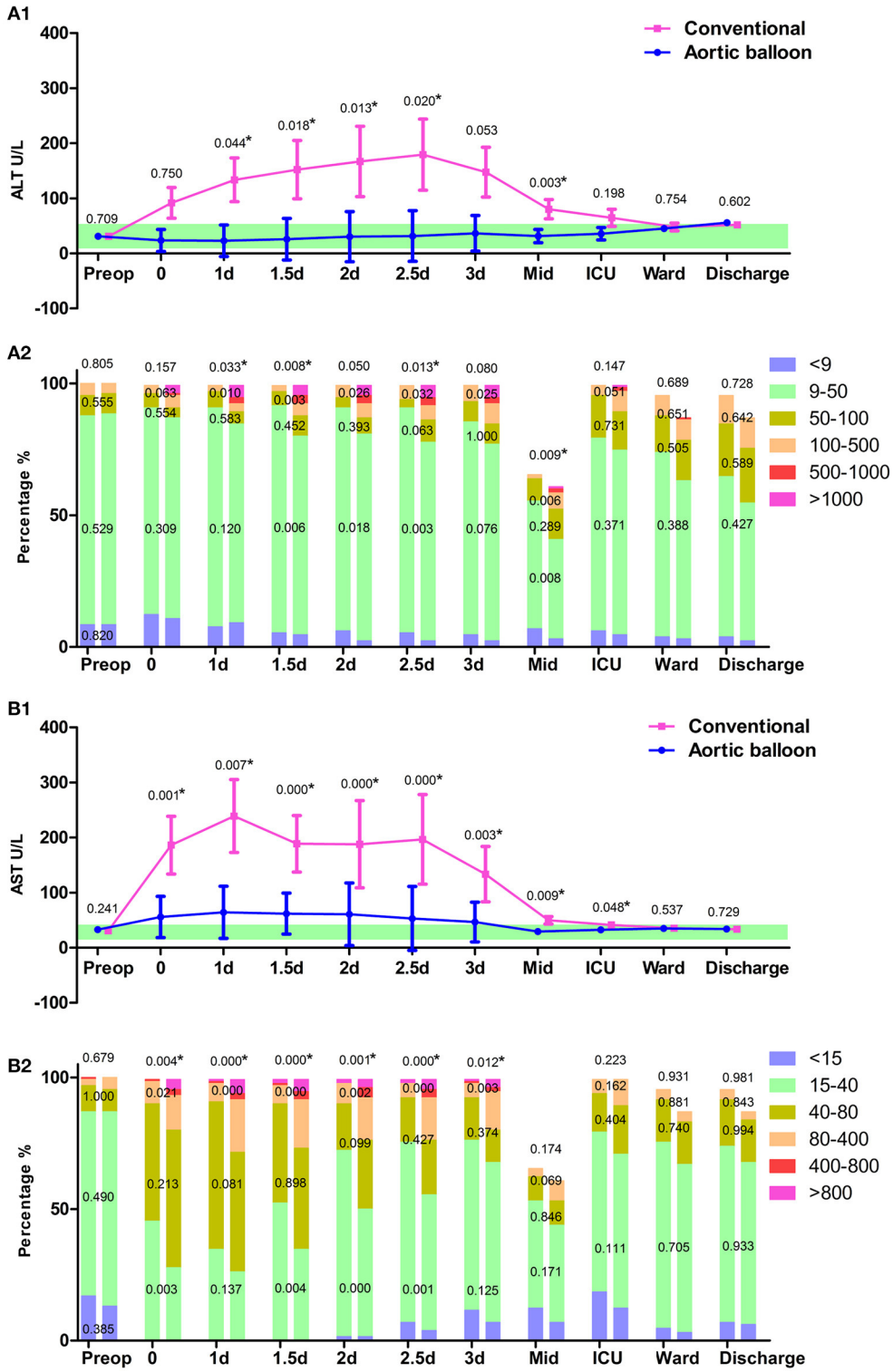

FIGURE 5 | Hepatic function. **(A1)** The trajectory of alanine transaminase (ALT). **(A2)** ALT grading in the column. **(B1)** The trajectory of aspartate transaminase (AST). **(B2)** AST grading in the column. Data points are represented by mean with a standard error of mean bars. *$P < 0.05$.

operative injury rates in high-risk patients. Therefore, using this new technique in TAR–FET may encourage cardiac surgeons to aim for improved clinical outcomes in this complex group of patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences, and Peking Union Medical College (No: 2018-1069). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LW and XS: conception and design. ZC: administrative support. YL and SL: provision of study materials or patients. LW: collection and assembly of data. LW and JL: data analysis and interpretation. LW, ZC, YL, JL, HG, SL, and XS: article writing and final approval of article. All authors contributed to the article and approved the submitted version.

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Comparison of Prognosis Between Hybrid Debranching Surgery and Total Open Arch Replacement With Frozen Elephant Trunk for Type A Acute Aortic Syndrome Patients

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Background: It is unclear whether the total arch replacement (TAR) combined with frozen elephant trunk (FET) implantation and hybrid debranching surgery have a difference in the prognosis of patients with type A acute aortic syndrome (AAS). We attempted to compare the short-term and long-term prognosis of total arch replacement (TAR) combined with frozen elephant trunk (FET) implantation and hybrid debranching surgery in patients with type A acute aortic syndrome (AAS).

Methods: From January 2014 to September 2020, a total of 518 patients who underwent TAR with FET surgery and 31 patients who underwent hybrid surgery were included. We analyzed the post-operative mortality and morbidity of complications of the two surgical methods, and we determined 67 patients for subgroup analysis through a 1:2 propensity score match (PSM). We identified risk factors for patient mortality and post-operative neurological complications through multivariate regression analysis.

Results: Compared with the TAR with FET group, hybrid surgery could reduce aortic cross-clamp time, reduce intraoperative blood loss and prevent some patients from cardiopulmonary bypass. There was no significant difference in 30-day mortality between the TAR with FET group and the hybrid surgery group (10.6 vs. 9.7%). However, hybrid surgery had increased the incidence of permanent neurological complications in patients (95%CI: 4.7–35.7%, $P = 0.001$), especially post-operative cerebral infarction ($P < 0.001$). During the average follow-up period of 31.6 months, there was no significant difference in the 1-year survival rate and 3-year survival rate between the TAR with FET group and the hybrid surgery group ($P = 0.811$), but hybrid surgery increased the incidence of long-term neurological complications ($P < 0.001$). In multivariate regression analysis, surgical methods were not a risk factor for post-operative deaths, but hybrid surgery was a risk factor for post-operative neurological complications ($P < 0.001$).

Conclusions: Hybrid surgery is an acceptable treatment for AAS, and its post-operative mortality is similar to FET. But hybrid surgery may increase the risk of permanent neurological complications after surgery, and this risk must be carefully considered when choosing hybrid surgery.

Keywords: acute aortic syndrome, frozen elephant trunk, hybrid aortic arch repair, debranching, prognosis

INTRODUCTION

Acute aortic syndrome (AAS) is a life-threatening disease. AAS includes aortic dissection (AD), intramural aortic hematoma, and penetrating atherosclerotic aortic ulcer (PAU), which have similar pathophysiological changes, clinical features, and treatment strategies (1). Stanford type-A AAS usually requires emergency treatment, especially when the lesion involves the aortic arch. If not treated, the mortality of acute type A AD can reach 50% within 48 h (2), and surgical treatment has obvious advantages over conservative treatment (3).

The treatment of type-A AAS involving the aortic arch usually includes open thoracic aortic surgery and hybrid surgery. Among open thoracic aortic surgeries, total arch replacement (TAR) combined with frozen elephant trunk (FET) implantation is a surgical method with good therapeutic effects (4), but it usually requires the use of prosthetic graft to replace the aortic arch, which is a complicated surgical technique and requires hypothermic circulatory arrest (HCA). Hybrid surgery is a new option for type-A AAS patients involving the aortic arch (5, 6). It reduces surgical trauma and does not require HCA. Hybrid surgery is a treatment method that combines surgery with interventional therapy. In interventional therapy, thoracic endovascular aortic repair (TEVAR) is a good strategy for the treatment of type-B AAS (7). However, when the lesion involves the ascending aorta and the aortic arch, TEVAR cannot be used because it affects the blood supply to the branches of the aortic arch (8). Hybrid debranching surgery can transfer the branch vessels of the aortic arch to the normal part of the ascending aorta or prosthetic graft to expand the proximal anchoring area, and then complete aortic repair through TEVAR (9). However, the safety and effectiveness of this treatment method are still uncertain (10). As the effectiveness and safety of surgical treatment have been widely recognized, surgical treatment is still the first choice for AAS involving the ascending aorta and aortic arch (2). It is necessary to analyze the prognosis of hybrid debranching surgery and open thoracic aortic surgery to analyze its safety and effectiveness.

It is not yet clear whether there is a difference between TAR with FET and hybrid debranching surgery in the prognosis of type-A AAS patients. The main purpose of this study is to compare the short-term prognosis and the long-term prognosis differences between TAR with FET and hybrid debranching surgery for type-A AAS patients with lesions involving the aortic arch, so as to provide evidence for surgeons in the selection of surgical options.

MATERIALS AND METHODS

Participants

From the aortic disease database jointly maintained by nine medical centers in China, data on a total of 549 Stanford type-A AAS patients who underwent hybrid surgery or TAR with FET between January 1, 2014 and September 30, 2020 were collected. The ethics committee of Beijing Anzhen Hospital approved this multicenter retrospective cohort study. Patients' written informed consent was dropped due to the retrospective nature of the study. We collected demographics, surgical information, and perioperative clinical data. All patients were diagnosed as Stanford Type A AAS by experienced imaging specialists and cardiovascular surgeons through aortic computed tomography angiography (CTA), and all patients were judged by the aortic surgery team to have indications for aortic repair. Patients with missing surgical data and previous TEVAR were excluded from the study. The surgery was performed by the surgical team of the medical center at the time of the patient's admission. Surgeons were more inclined to choose hybrid surgery for older patients, but the operation method still depended on the preference of the surgeon and the requirements of the patient.

Total Arch Replacement Combined With Frozen Elephant Trunk Implantation

We have previously described the process of TAR with FET in detail (4). In short, all patients received intravenous anesthesia and tracheal intubation. The venous cannula was inserted into the right atrium, and the arterial cannulas were inserted into the right axillary artery and right femoral artery to establish cardiopulmonary bypass. The aortic root repair method was determined according to the extent of the lesion, and the aortic valve replacement and ascending aortic replacement surgery were performed first. In addition, the decision to perform coronary artery bypass graft was based on whether the disease involved the coronary arteries. When the nasopharyngeal temperature dropped below 28°C, the circulatory arrest began. The selective cerebral perfusion was performed through the right axillary artery. The stent graft was placed in the descending aorta under direct vision. The four-branch prosthetic graft was used to replace the total aortic arch, and the circulation was restored after the distal end of the four-branch prosthetic graft was anastomosed. Subsequently, the left common carotid artery, innominate artery, and left subclavian artery were reconstructed in sequence, and the body temperature was gradually restored and the cardiopulmonary bypass was terminated (**Figure 1A**).

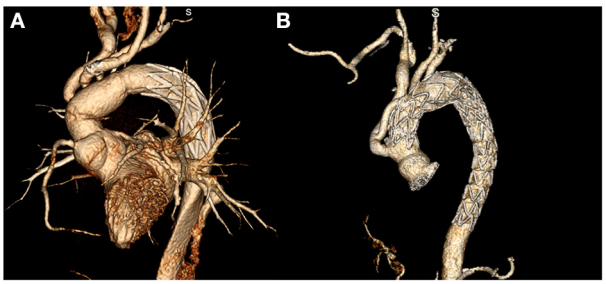

FIGURE 1 | Post-operative aortic CTA reconstruction images of patients with acute aortic syndrome treated with total arch replacement combined with frozen elephant trunk implantation **(A)** and hybrid debranching surgery **(B)**.

Hybrid Surgery

The entire hybrid surgery was performed in the hybrid operating room equipped with a floor mounted angiography C-arm system. All patients underwent intravenous anesthesia, tracheal intubation, and median sternotomy. The open repair surgery part of the hybrid surgery was completed first. Whether to repair the ascending aorta was determined according to the extent of the lesion. For patients with lesions involving the ascending aorta, the right axillary artery and femoral artery were selected for arterial cannulation, and the right atrium was selected for venous cannulation, and then cardiopulmonary bypass was established. The right axillary artery was used to supply blood to the brain during innominate artery surgery for brain protection. After the ascending aorta was cross clamped, the ascending aorta was cut longitudinally, and cold blood cardioplegia was perfused through the opening of coronary artery. After that, surgeon checked the diseased condition of the aortic root and decided whether to repair the aortic valve, whether to perform Bentall surgery or Wheat surgery. After completing the repair of the aortic root, the four-branch prosthetic graft was anastomosed end-to-end with the proximal aorta, and the proximal end of the innominate artery and the artery between the innominate artery and the left common carotid artery was clamped. After the rectal temperature drops to 28°C, surgeon removed the clamp of the ascending aorta and continued to clamp the innominate artery and the artery between the innominate artery and the left common carotid artery, and then completed the anastomosis of the four-branch prosthetic graft with the distal aorta without circulatory arrest. Subsequently, the left common carotid artery, innominate artery, and left subclavian artery were anastomosed end-to-end with the four-branch prosthetic graft in turn, and then the body temperature was restored and the cardiopulmonary bypass was stopped.

For AAS patients whose lesions only involve the aortic arch but not the ascending aorta, because there was no need to repair the ascending aorta, the procedure did not include cardiopulmonary bypass. The ascending aorta was clamped by the lateral wall clamp, and the Y-shaped artificial aortic vessel was anastomosed end-to-side with the lateral wall of the aorta. Then the innominate artery was cut and clamped, and the stump of the innominate artery was sutured. The distal end of the innominate artery was anastomosed end-to-end with the branch of the Y-shaped prosthetic graft, and the blood supply of the innominate artery was restored after de-airing. Next, using the same method, the left common carotid artery and the left subclavian artery were anastomosed end-to-end with the same branch of the Y-shaped prosthetic graft. In addition, a straight prosthetic graft was wrapped around the ascending aorta and used as a proximal anchoring area during endovascular treatment.

Next, the endovascular treatment part of hybrid surgery was performed. The femoral artery was used as the entry site for endovascular treatment. The stiff guide wire was advanced to the ascending aorta, and the stent graft was placed along the guide wire. The stent graft was released in the four-branch prosthetic graft or the straight prosthetic graft. If the secondary tear was found in the distal aorta or the first stent graft was insufficient to cover the diseased descending aorta, then the second stent graft was used for treatment. After the endovascular treatment was completed, the sternum was sutured and the incision was closed (**Figure 1B**).

Follow-Up and Definition

All patients in this study were followed up by telephone or online communication. The follow-up information mainly included the patient's survival status, death time, cause of death, adverse cardiovascular events, neurological function status, and other organ complications. Among them, adverse cardiovascular events were defined as recurrence of AAS or reoperation due to cardiovascular disease.

In this study, emergency surgery referred to surgery performed within 24 h after admission. Permanent neurological complications referred to the obvious abnormal changes found in the brain computed tomography or magnetic resonance imaging or the patient's permanent neurological deficits, mainly including cerebral infarction, cerebral hemorrhage or hemiplegia. Transient neurological complication referred to the brain computed tomography or magnetic resonance imaging without obvious abnormal changes, the patient had transient neurological deficit, and the neurological function has been cured when discharged from the hospital. In the long-term follow-up, neurological complications refer to the symptoms of neurological ischemia or neurological deficits in patients, including dizziness, paraplegia, or inability to walk. New-onset neurological complications refer to patients who did not develop permanent neurological complications during hospitalization, but neurological complications occurred during long-term follow-up.

Statistical Analysis

The description of the data and basic statistical analysis were performed using R 4.0.4. Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as frequencies (n) with percentages (%). Statistical analysis of continuous variables was performed using Student's t-test or Mann-Whitney U-test, while categorical variables were analyzed using the chi-square test and Fisher's exact test. Kaplan-Meier test was used to analyze the

survival rate of patients. In addition, propensity score matching (PSM) completed using R 4.0.4 was used to obtain patients in the FET group and hybrid surgery group with similar baselines, the variables used included all pre-operative demographic variables, type of AAS, previous non-cardiac surgery, diabetes, emergency surgery, and aortic valve surgery. The matching ratio of the patient was 1:2, and the matching method was nearest neighbor matching with the caliper size set to 0.1 standard deviation. Due to the higher loss of follow-up rate of patients in the FET group, all patients in the FET group who were lost to follow-up were not included in the PSM. In all statistical analyses, p-value < 0.05 were considered statistically significant, and all statistical tests used a two-sided test.

RESULTS

Baseline Characteristics

The study included a total of 549 patients, including 518 patients underwent TAR with FET and 31 patients underwent hybrid surgery. The basic characteristics and pre-operative data of the patients were listed in **Table 1**. The basic characteristics of the two groups of patients were similar. However, for patients who were older or had been onset for more than 14 days, surgeons were more inclined to choose hybrid surgery. Therefore, the patients who underwent hybrid surgery were older, and fewer patients had the onset within 14 days. The AAS types of patients with the two surgical methods were also different. All PAU patients were treated with hybrid surgery. In comparison, the proportion of AD patients in the patients with hybrid surgery was relatively small (90.3 vs. 99.0%). This may be related to the slow onset of PAU patients and the longer time to prepare for hybrid surgery. In addition, patients who underwent hybrid surgery had shorter heights and more patients had a history of non-cardiac surgery, which may be related to the patient's old age.

PSM was used in the study to eliminate bias caused by different baseline characteristics. A total of 67 patients were identified through PSM, of which 44 patients underwent TAR with FET and 23 patients underwent hybrid surgery. The basic characteristics and pre-operative data of these patients were listed in **Table 1**. There was no significant difference in the baseline characteristics of patients who underwent the two types of surgery.

Surgical Data

The surgical data were listed in **Table 2**. All operations were successfully treated, and no endoleaks were found in the CT examination after the operation, and no caudal migration of the endograft occurred. Compared with patients who underwent hybrid surgery, most patients who underwent TAR with FET were emergency surgery, and there were significantly more patients who had surgery involving the aortic valve or ascending aorta. Among the patients who underwent hybrid surgery, 38.7% of the patients required cardiopulmonary bypass for the operation. Compared with TAR with FET, there was no significant difference in the cardiopulmonary bypass time of these hybrid surgery patients, but the aortic cross-clamp time was significantly reduced, and all hybrid surgery patients did not undergo circulatory arrest. Hybrid surgery reduced intraoperative blood loss but had no significant effect on the operative duration. In the PSM cohort, the difference between the two groups of patients was similar to the overall cohort.

Early Outcomes

The short-term prognosis was listed in **Table 3**. In the overall cohort, there was no significant difference in the 30-day mortality rate and the mortality rate during hospitalization for the two types of surgery, which indicated that the two types of surgery had no effect on the patient's mortality in the short term. Similarly, the two surgical methods had no significant effect on the ventilation time, ICU stays, and hospitalization days. We analyzed the cause of the patient's death during hospitalization. Among patients who underwent TAR with FET, the main causes of death included multiple organ failure ($n = 21$), heart failure ($n = 11$), malignant arrhythmia ($n = 4$), septic shock ($n = 3$), and cerebral hemorrhage ($n = 2$). Among the patients who underwent hybrid surgery, the main causes of death included heart failure ($n = 2$) and cerebral infarction ($n = 1$).

The analysis of short-term post-operative complications found that hybrid surgery increased the incidence of post-operative complications, especially permanent neurological complications (25.8 vs. 5.6%, 95%CI: 4.7–35.7%, $P = 0.001$). Among them, the incidence of cerebral infarction in hybrid surgery patients increased significantly (22.6 vs. 2.3%, $p < 0.001$). But there is no significant difference between the two surgical methods for other complications. In the PSM cohort, the short-term prognosis results were similar to the overall cohort.

Mid- and Long-Term Outcomes

As of November 2020, excluding 44 patients who died during hospitalization, we had successfully followed up 388 patients, of which 363 cases (76.1%) underwent TAR with FET and 25 cases (89.3%) underwent hybrid surgery. The average follow-up time was 31.6 months (range between 2 and 82 months). Due to the relatively high rate of loss to follow-up in the FET group, we compared the pre-operative and intraoperative data and short-term prognosis of patients who were lost to follow-up and those who were not lost to follow-up (**Supplementary Table 1**), and we found that the pre-operative and intraoperative characteristics and short-term prognosis of these two groups of patients were not significantly different.

In the overall cohort, there was no significant difference in the long-term mortality of the two surgical methods (Log-rank $p = 0.811$). The 1-year survival rate of FET group was 80.4%, the 3-year survival rate was 77.8%, the 1-year survival rate of the hybrid surgery group was 84.3%, and the 3-year survival rate was 79.1% (**Figure 2A**). In the PSM cohort, there was no significant difference in the long-term mortality of the two surgical methods (**Figure 2B**).

The follow-up results were listed in **Table 4**, excluding patients who died during the follow-up. In the overall cohort, patients in the hybrid surgery group had more post-operative complications, especially neurological complications. Compared with patients in the FET group, significantly more patients in the hybrid surgery group had dizziness, inability to walk, and hoarseness. The higher incidence of neurological complications in hybrid

TABLE 1 | Demographic and pre-operative data.

	Overall			Propensity score matched		
	TAR with FET	**Hybrid surgery**	***P*-value**	**TAR with FET**	**Hybrid surgery**	***P*-value**
Number of patients (%)	518	31		44	23	
Gender, female (%)	101 (19.5%)	8 (25.8%)	0.446	11 (25.0%)	6 (26.1%)	0.923
Age (years)	48.9 ± 10.8	58.8 ± 11.7	< 0.001	55.8 ± 9.6	57.2 ± 12.9	0.656
Information on admission						
Within 14 days after onset (%)	429 (82.8%)	18 (58.1%)	0.001	33 (75.0%)	15 (65.2%)	0.399
Pulse (beats/min)	80.2 ± 12.4	81.1 ± 14.6	0.709	79.3 ± 13.2	83.0 ± 15.8	0.314
Systolic pressure (mmHg)	130.5 (30.0)	130.0 (26.0)	0.448	139.0 (40.0)	130.0 (27.0)	0.254
Diastolic pressure (mmHg)	80.0 (19.0)	75.0 (24.0)	0.149	80.0 (20.0)	75.0 (24.0)	0.135
Height (cm)	171.2 ± 7.8	167.7 ± 7.9	0.016	170.1 ± 7.3	168.4 ± 7.9	0.386
Weight (kg)	75.0 ± 13.2	70.3 ± 11.8	0.056	73.2 ± 12.3	71.7 ± 12.9	0.661
Body mass index (kg/m^2)	25.5 ± 3.8	24.9 ± 3.4	0.411	25.1 ± 3.1	25.3 ± 3.9	0.854
Type of acute aortic syndrome			< 0.001			0.636
Aortic dissection (%)	513 (99.0%)	28 (90.3%)		43 (97.7%)	22 (95.7%)	
Intramural aortic hematoma (%)	5 (1.0%)	1 (3.2%)		1 (2.3%)	1 (4.3%)	
Penetrating atherosclerotic aortic ulcer (%)	0 (0.0%)	2 (6.5%)		0 (0.0%)	0 (0.0%)	
Medical history						
Hypertension (%)	393 (75.9%)	21 (67.7%)	0.279	36 (81.8%)	16 (69.6%)	0.253
Coronary artery disease (%)	32 (6.2%)	4 (12.9%)	0.138	7 (15.9%)	3 (13.0%)	1.000
Diabetes (%)	25 (4.8%)	4 (12.9%)	0.074	2 (4.5%)	1 (4.3%)	1.000
Chronic respiratory disease (%)	13 (2.5%)	1 (3.2%)	0.564	1 (2.3%)	1 (4.3%)	1.000
Renal insufficiency (%)	22 (4.2%)	3 (9.7%)	0.161	7 (15.9%)	3 (13.0%)	1.000
Previous cerebrovascular disease (%)	21 (4.1%)	2 (6.5%)	0.379	3 (6.8%)	0 (0.0%)	0.546
With other chronic diseases (%)	5 (1.0%)	1 (3.2%)	0.297	1 (2.3%)	0 (0.0%)	1.000
Smoking history (%)	212 (40.9%)	16 (51.6%)	0.241	21 (47.7%)	12 (52.2%)	0.730
Previous cardiac surgery (%)	24 (4.6%)	1 (3.2%)	1.000	5 (11.4%)	1 (4.3%)	0.656
Previous non-cardiac surgery (%)	85 (16.4%)	10 (32.3%)	0.023	8 (18.2%)	6 (26.1%)	0.532
Echocardiographic results						
Left ventricular ejection fraction (%)	61.0 (8.0)	62.5 (9.5)	0.076	64.0 (7.8)	63.0 (8.0)	0.634
Pre-operative laboratory examination results						
Absolute value of erythrocyte (10^{12}/L)	4.46 ± 1.63	4.15 ± 0.65	0.325	4.32 ± 0.73	4.18 ± 0.69	0.453
Absolute value of leukocyte (10^9/L)	11.5 ± 5.1	10.1 ± 4.6	0.154	10.5 ± 4.7	10.8 ± 5.0	0.810
Platelet (10^9/L)	186.6 ± 86.1	213.7 ± 89.3	0.112	178.8 ± 85.1	209.4 ± 76.0	0.174
Hemoglobin (g/L)	133.3 ± 22.3	128.6 ± 19.4	0.282	128.6 ± 21.7	129.5 ± 20.8	0.876
Creatinine (μmol/L)	85.5 (43.6)	82.0 (34.0)	0.806	91.2 (80.7)	92.7 (38.1)	0.817
eGFR (ml/min/1.73 m^2)	88.5 (42.7)	88.2 (38.9)	0.296	76.7 (57.0)	81.2 (54.8)	0.690
INR	1.09 (0.15)	1.05 (0.19)	0.294	1.07 (0.19)	1.09 (0.20)	0.881
APTT (s)	32.3 (7.3)	29.2 (6.7)	0.013	33.6 (7.0)	30.2 (7.8)	0.093
Albumin (g/mL)	38.7 ± 18.0	40.7 ± 11.0	0.584	37.3 ± 5.8	40.9 ± 10.9	0.192
Fasting blood glucose (mmol/L)	7.30 ± 2.56	6.70 ± 2.06	0.426	6.97 ± 2.59	6.58 ± 2.14	0.674

eGFR, Estimated Glomerular Filtration Rate; INR, International Normalized Ratio; APTT, activated partial thromboplastin time. The categorical variables in the table are presented by the number of cases (with percentage) and the continuous variables are expressed by the median (with interquartile range) or mean (with standard deviation).

surgery patients also increased the rate of rehospitalization. Among the hybrid surgery patients who were re-hospitalized after the operation, 50.0% of the patients were hospitalized for neurological complications. Other reasons for rehospitalization included infection (25.0%) and respiratory failure (25.0%). However, the main reasons for the rehospitalization of TAR with FET patients were coronary heart disease (60.0%) and abdominal aortic aneurysm repair (40.0%). In addition, the proportion of patients in the hybrid surgery group who needed to be hospitalized again increased significantly. At the same time, we analyzed the incidence of new neurological complications. The incidence of new-onset neurological complications in the hybrid surgery group was significantly increased, but most of the new-onset neurological complications were dizziness, and there was no significant difference in the incidence of new-onset paraplegia and inability to walk. In the PSM cohort, the long-term prognosis of the two surgical methods was similar to that of the overall cohort, but there was no significant difference in the

TABLE 2 | Intraoperative variables.

	Overall			Propensity score matched		
	TAR with FET ($n = 518$)	**Hybrid surgery ($n = 31$)**	***P*-value**	**TAR with FET ($n = 44$)**	**Hybrid surgery ($n = 23$)**	***P*-value**
Emergency surgery (%)	301 (58.1%)	8 (25.8%)	< 0.001	13 (29.5%)	7 (30.4%)	0.940
Concomitant surgery						
Surgery involves aortic valve (%)	269 (51.9%)	3 (9.7%)	< 0.001	6 (13.6%)	2 (8.7%)	0.705
Surgery involves mitral valve (%)	16 (3.1%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	-
Bentall surgery (%)	165 (31.9%)	0 (0.0%)	< 0.001	3 (6.8%)	0 (0.0%)	0.546
Cabrol, Wheat or David surgery (%)	73 (14.1%)	1 (3.2%)	0.104	3 (6.8%)	0 (0.0%)	0.546
Ascending aorta replacement surgery (%)	502 (96.9%)	12 (38.7%)	< 0.001	43 (97.7%)	8 (34.8%)	< 0.001
CABG (%)	31 (6.0%)	1 (3.2%)	1.000	1 (2.3%)	0 (0.0%)	1.000
Surgery with cardiopulmonary bypass (%)	518 (100.0%)	12 (38.7%)	< 0.001	44 (100.0%)	8 (34.8%)	< 0.001
Cardiopulmonary bypass time (min)	206.0 (71.0)	158.0 (89.3)	0.100	204.5 (67.0)	149.0 (22.0)	0.241
Aortic cross-clamp time (min)	112.0 (53.0)	70.0 (41.0)	0.021	117.0 (54.0)	71.0 (13.0)	0.041
Circulatory arrest time (min)	24.0 (11.0)	0.0 (0.0)	0.001	23.0 (15.0)	0.0 (0.0)	< 0.001
Operative duration (hours)	7.16 (2.17)	7.25 (3.25)	0.812	7.04 (2.23)	7.00 (3.75)	0.754
Proximal diameter of stent graft (mm)	-	34.0 (5.0)	-	-	34.0 (3.5)	-
Length of stent graft (mm)	-	200.0 (0.0)	-	-	200.0 (0.0)	-
Intraoperative blood loss (ml)	2350.0 (2440.0)	700.0 (500.0)	< 0.001	1860.0 (2150.0)	800.0 (900.0)	< 0.001

CABG, Coronary Artery Bypass Graft. The categorical variables in the table are presented by the number of cases (with percentage) and the continuous variables are expressed by the median (with interquartile range).

incidence of unable to walk, hoarseness, new-onset neurological complications and re-hospitalization between the two groups.

We used logistic regression analysis and Cox regression analysis to explore whether the two surgical methods are independent risk factors for short-term mortality, long-term mortality, and neurological complications (**Table 5**). We found that the surgical method was not the independent risk factor for post-operative mortality during hospitalization and long-term mortality. Risk factors for mortality during post-operative hospitalization included coronary heart disease, while protective factors included ascending aortic replacement surgery, higher left ventricular ejection fraction, and higher pre-operative platelets. Risk factors for long-term mortality after surgery included previous cerebrovascular disease, previous cardiac surgery, emergency surgery, and surgery combined with coronary artery bypass graft. However, hybrid surgery was an independent risk factor for permanent post-operative neurological complications (OR = 5.304, 95%CI: 2.120–13.271, $p < 0.001$) and long-term post-operative neurological complications (OR = 5.791, 95%CI: 2.087–16.067, $p < 0.001$). In addition, the risk factors for permanent neurological complications after surgery also included diabetes, and the risk factors for long-term neurological complications after surgery also included coronary heart disease. This indicated that hybrid surgery can lead to an increased risk of short-term and long-term neurological complications.

DISCUSSION

AAS is a high-mortality aortic disease, and its post-operative mortality is about 10–26% (11–13). The treatment of AAS is still a challenge for cardiovascular surgeons (12). Although AAS disease can be treated by a variety of surgical methods, the choice of surgical methods still needs further research (14). Different surgical methods may have differences in the cure effect of the disease, the incidence of complications, and post-operative mortality, which may affect the patient's re-admission, poor quality of life, or death after surgery. The current surgical methods for Type A AAS involving the aortic arch mainly include TAR with FET or elephant trunk and hybrid surgery (8). At present, TAR with FET or hybrid surgery is often used to treat type A AAS in Asia, but there are few studies comparing TAR with FET or hybrid surgery (15–17). Therefore, whether hybrid surgery is more advantageous than FET requires further research.

TAR with FET has been widely used for a long time, and long-term studies in multiple centers have shown that its treatment effect is better, the mortality rate is relatively low, and the prognosis is relatively good (18, 19). FET can maintain distal perfusion by covering the tears of the descending aorta and expanding the true lumen, which can reduce post-operative and long-term aortic events and reduce mortality. In our study, we found that the mortality rate of TAR with FET is similar to the previous report. However, FET requires hypothermic circulatory arrest and complex surgery in the aortic arch, which is generally considered to increase the risk of serious complications after TAR with FET surgery (20, 21).

Hybrid surgery has attracted attention because it does not require hypothermic circulatory arrest and can avoid cardiopulmonary bypass and myocardial ischemia according to the condition (22). In our research, we found that even for patients who require cardiopulmonary bypass for ascending

TABLE 3 | Short-term Prognosis.

	Overall			Propensity score matched		
	TAR with FET (*n* = 518)	**Hybrid surgery (*n* = 31)**	***P*-value**	**TAR with FET (*n* = 44)**	**Hybrid surgery (*n* = 23)**	***P*-value**
Ventilation time (hours)	39.0 (86.5)	41.0 (104.0)	0.724	70.0 (119.5)	43.0 (105.5)	0.461
ICU stays (days)	3.29 (5.42)	5.00 (8.46)	0.205	4.71 (7.50)	5.00 (8.46)	0.966
Hospitalization days (days)	18.0 (15.0)	21.0 (15.0)	0.181	22.0 (19.8)	21.0 (18.0)	0.737
Post-operative complications (%)	99 (19.1%)	11 (35.5%)	0.027	11 (25.0%)	9 (39.1%)	0.230
Permanent neurological complications (%)	29 (5.6%)	8 (25.8%)	0.001	1 (2.3%)	6 (26.1%)	0.005
Cerebral infarction (%)	12 (2.3%)	7 (22.6%)	< 0.001	0 (0.0%)	5 (21.7%)	0.003
Cerebral hemorrhage (%)	9 (1.7%)	1 (3.2%)	0.444	1 (2.3%)	1 (4.3%)	1.000
Hemiplegia (%)	8 (1.5%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	-
Transient neurological complications (%)	10 (1.9%)	0 (0.0%)	1.000	1 (2.3%)	0 (0.0%)	1.000
Acute renal failure (%)	76 (14.7%)	5 (16.1%)	0.795	8 (18.2%)	4 (17.4%)	1.000
Permanent hemodialysis (%)	8 (1.5%)	1 (3.2%)	0.410	0 (0.0%)	1 (4.3%)	0.343
Acute liver failure (%)	16 (3.1%)	1 (3.2%)	1.000	1 (2.3%)	0 (0.0%)	1.000
Low cardiac output syndrome (%)	21 (4.1%)	0 (0.0%)	0.623	1 (2.3%)	0 (0.0%)	1.000
Pulmonary infection (%)	58 (11.2%)	1 (3.2%)	0.235	4 (9.1%)	1 (4.3%)	0.653
Tracheostomy (%)	18 (3.5%)	1 (3.2%)	1.000	4 (9.1%)	1 (4.3%)	0.653
Reoperation (%)	38 (7.3%)	0 (0.0%)	0.156	6 (13.6%)	0 (0.0%)	0.087
Reoperation for bleeding (%)	22 (4.2%)	0 (0.0%)	0.628	3 (6.8%)	0 (0.0%)	0.546
30-day mortality (%)	55 (10.6%)	3 (9.7%)	1.000	7 (15.9%)	3 (13.0%)	1.000
In-hospital mortality (%)	41 (7.9%)	3 (9.7%)	0.730	7 (15.9%)	3 (13.0%)	1.000

ICU, Intensive Care Unit. The categorical variables in the table are presented by the number of cases (with percentage) and the continuous variables are expressed by the median (with interquartile range).

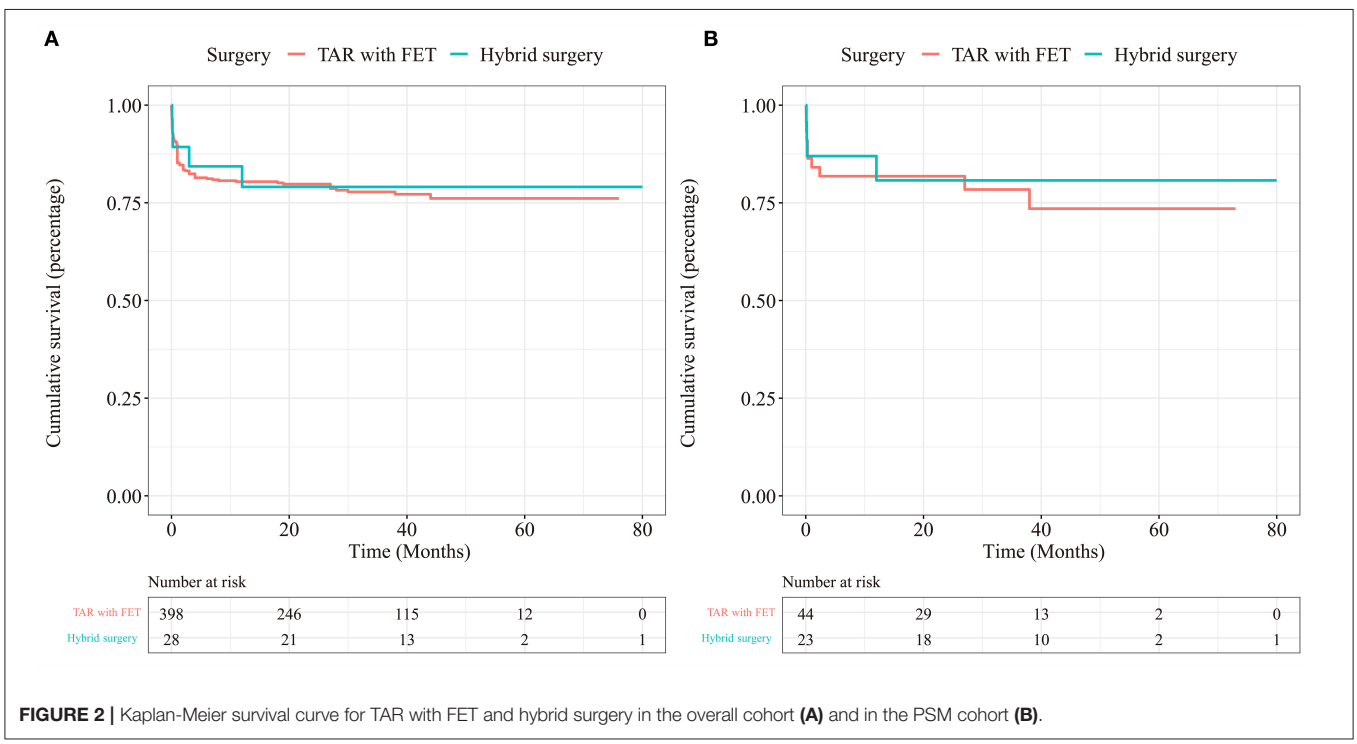

FIGURE 2 | Kaplan-Meier survival curve for TAR with FET and hybrid surgery in the overall cohort **(A)** and in the PSM cohort **(B)**.

aorta repair, hybrid surgery can still shorten the aortic cross-clamp time to reduce myocardial ischemia, and it also reduces intraoperative blood loss. Because of this advantage, hybrid surgery is usually applied to older patients in the hope

TABLE 4 | Mid- and long-term prognosis and follow-up results.

	Overall			Propensity score matched		
	TAR with FET (n = 311)	**Hybrid surgery (n = 23)**	***P*-value**	**TAR with FET (n = 37)**	**Hybrid surgery (n = 20)**	***P*-value**
Renal insufficiency (%)	10 (3.2%)	1 (4.3%)	0.549	0 (0.0%)	1 (5.0%)	0.351
Liver insufficiency (%)	3 (1.0%)	1 (4.3%)	0.249	1 (2.7%)	1 (5.0%)	1.000
Neurological complications (%)	53 (17.0%)	12 (52.2%)	< 0.001	3 (8.1%)	9 (45.0%)	0.002
Dizziness (%)	28 (9.0%)	8 (34.8%)	0.001	3 (8.1%)	7 (35.0%)	0.024
Paraplegia (%)	8 (2.6%)	1 (4.3%)	0.478	0 (0.0%)	1 (5.0%)	0.351
Unable to walk (%)	9 (2.9%)	4 (17.4%)	0.008	0 (0.0%)	2 (10.0%)	0.119
New-onset neurological complication (%)	49 (15.8%)	8 (34.8%)	0.038	3 (8.1%)	6 (30.0%)	0.054
Dizziness (%)	28 (9.0%)	7 (30.4%)	0.005	3 (8.1%)	6 (30.0%)	0.054
Paraplegia (%)	5 (1.6%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	-
Unable to walk (%)	4 (1.3%)	1 (4.3%)	0.302	0 (0.0%)	0 (0.0%)	-
Hoarseness (%)	44 (14.1%)	8 (34.8%)	0.015	7 (18.9%)	5 (25.0%)	0.736
Limb ischemia (%)	22 (7.1%)	1 (4.3%)	1.000	2 (5.4%)	1 (5.0%)	1.000
Recurrence of cardiovascular disease (%)	0 (0.0%)	1 (4.3%)	0.070	0 (0.0%)	1 (5.0%)	0.357
Re-hospitalization (%)	5 (1.6%)	4 (17.4%)	0.002	1 (2.7%)	3 (15.0%)	0.119
Reoperation (%)	5 (1.6%)	0 (0.0%)	1.000	1 (2.7%)	0 (0.0%)	1.000

The categorical variables in the table are presented by the number of cases (with percentage).

TABLE 5 | Multivariate regression results of post-operative mortality and neurological complications.

Characteristics	B	*P*-value	OR value	OR 95%CI
Short-term prognosis				
Permanent neurological complications				
Hybrid surgery	1.668	< 0.001	5.304	2.120–13.271
Diabetes	1.145	0.042	3.141	1.043–9.458
Mortality during hospitalization				
Coronary artery disease	1.219	0.042	3.384	1.048–10.930
Ascending aorta replacement surgery	−2.189	0.001	0.112	0.030–0.425
LVEF (%)	−0.052	0.046	0.949	0.902–0.999
Platelet (10^9/L)	−0.010	0.007	0.990	0.982–0.997
Long-term prognosis				
Neurological complications				
Hybrid surgery	1.756	< 0.001	5.791	2.087–16.067
Coronary artery disease	1.315	0.044	3.723	1.033–13.416
All-cause mortality	**B**	***P*-value**	**HR value**	**HR 95%CI**
Previous cerebrovascular disease	1.574	< 0.001	4.825	2.382–9.775
Previous cardiac surgery	0.925	0.024	2.522	1.127–5.644
Emergency surgery	1.016	< 0.001	2.761	1.652–4.615
Combined CABG surgery	1.094	< 0.001	2.985	1.565–5.692

LVEF, Left Ventricular Ejection Fraction; CABG, Coronary Artery Bypass Graft; OR, Odds Ratio; HR, Hazard Ratio. The variables considered in the multivariate regression analysis included surgery method, gender, age, onset within 14 days, BMI, hypertension, coronary artery disease, diabetes, chronic respiratory disease, renal insufficiency, previous cerebrovascular disease, smoking history, previous cardiac surgery, LVEF, absolute value of erythrocyte, absolute value of leukocyte, platelets, emergency surgery, ascending aorta replacement surgery, CABG, cardiopulmonary bypass time, aortic cross-clamp time.

of reducing surgical trauma and surgical risk. However, whether hybrid surgery has advantages over TAR with FET in terms of post-operative mortality and complication rate is still uncertain.

In this study, we compared the results of 518 TAR with FET patients and 31 hybrid surgery patients, and used PSM and multivariate regression analysis to control for confounding factors. The post-operative mortality of surgery is an important indicator for evaluating surgical methods. In our study, it was found that the short-term 30-day mortality rate and the long-term 1- and 3-year mortality rates of the two surgical methods were similar. In the recent studies of hybrid surgery, it was found that the in-hospital mortality rate of hybrid surgery for

type A aortic dissection is about 6.0–9.2% (23, 24), which is similar to the mortality rate of FET surgery. In addition, in the multivariate regression analysis of this study, the surgical method is not an independent predictor of short-term and long-term post-operative mortality. Therefore, hybrid surgery may have post-operative mortality similar to FET, and it will not increase the patient's risk of death.

Permanent neurological complications after surgery will affect the patient's quality of life and increase the risk of rehospitalization. An observational study comparing open surgery and hybrid surgery conducted by Preventza etale found that the risk of neurological events after hybrid surgery is increased (16). Earlier, Benedetto etale synthesized and analyzed four observational studies (15). The results of their studies suggest that hybrid surgery may increase the incidence of permanent neurological deficits after surgery. However, there was no statistically significant difference in the incidence of neurological events between the two surgical methods in the above research results ($P > 0.05$). Permanent neurological complications after hybrid surgery are considered to be related to aortic atherosclerosis. The surgical operation in the aortic arch and the delivery and release of stents may cause the rupture of atherosclerotic plaques and cause permanent neurological complications (8, 25, 26). In addition, 61.3% of the hybrid surgery patients in this study did not undergo cardiopulmonary bypass during the operation. In these patients, the ascending aorta was clamped by the lateral wall clamp so as to be anastomosed with the prosthetic graft. Side-clamping of the ascending aorta may cause the atherosclerotic plaque of the ascending aorta to rupture and cause neurological complications (27). In this study, we found that whether in the overall cohort or in the PSM cohort, hybrid surgery can increase the occurrence of permanent neurological complications during hospitalization. Hybrid surgery is an independent risk factor for permanent neurological complications (OR = 5.304, $p < 0.001$), and it also increases the occurrence of long-term neurological complications. The incidence of neurological complications reported in this study is higher than that in previous studies. The possible reason is that patients with hybrid surgery have higher diabetes and coronary heart disease, which are all related to atherosclerosis. However, the relationship between permanent neurological complications after hybrid surgery and atherosclerosis still needs further research.

This study has some limitations. First, the inherent flaws of retrospective research are the main limitation of this research. Second, in this study, the number of patients in the hybrid surgery group was small, and a larger amount of data was needed to reduce bias. Third, there is a difference between the baselines of the two groups of patients. Although we use PSM to avoid the impact of the baseline difference, due to the small caliper value set during the PSM process, it is impossible to find a sufficient number of corresponding cases. This may affect the analysis results of the PSM cohort. Fourth, there were fewer patients with a follow-up period of more than 4 years in this study, which may affect the results of survival analysis for more than 4 years. Finally, this multi-center study did not conduct a complete imaging follow-up, so imaging differences between the two groups of patients were not analyzed.

In summary, as a long-term use and approved surgical method, TAR with FET has acceptable short-term and long-term prognosis. Hybrid surgery has the advantages of avoiding hypothermic circulatory arrest, reducing the time of aortic cross-clamp and reducing intraoperative bleeding. Its short-term and long-term mortality are similar to TAR with FET. However, hybrid surgery may increase the risk of permanent neurological complications after surgery. More research is needed to confirm the impact of hybrid surgery on post-operative permanent neurological complications. When choosing hybrid surgery to treat AAS, the risk of post-operative neurological complications must be carefully considered.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Beijing Anzhen Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MG designed the research. JL, LL, and MW analyzed the data and wrote the paper. HL, LS, YL, RF, ZZ, CZ, and HZ were responsible for data collection. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.689507/full#supplementary-material

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Early and Long-Term Follow-Up for Chronic Type B and Type Non-A Non-B Aortic Dissection Using the Frozen Elephant Trunk Technique

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Background: This study aimed to evaluate the early and long-term outcomes of a single center using a frozen elephant trunk (FET) procedure for chronic type B or non-A non-B aortic dissection.

Methods: From February 2009 to December 2019, 79 patients diagnosed with chronic type B or non-A non-B aortic dissection who underwent the FET procedure were included in the present study. We analyzed operation mortality and early and long-term outcomes, including complications, survival and interventions.

Results: The operation mortality rate was 5.1% (4/79). Spinal cord injury occurred in 3.8% (3/79), stroke in 2.5% (2/79), and acute renal failure in 5.1% (4/79). The median follow-up time was 53 months. The overall survival rates were 96.2, 92.3, 88.0, 79.8, and 76.2% at 1/2, 1, 3, 5 and 7 years, respectively. Moreover, 79.3% of patients did not require distal aortic reintervention at 7 years. The overall survival in the subacute group was superior to that in the chronic group ($P = 0.047$).

Conclusion: The FET technique is a safe and feasible approach for treating chronic type B and non-A non-B aortic dissection in patients who have contraindications for primary endovascular aortic repair. The technique combines the advantages of both open surgical repair and endovascular intervention, providing comparable early and long-term follow-up outcomes and freedom from reintervention.

Keywords: non-A non-B aortic dissection, chronic type B aortic dissection, frozen elephant trunk technique, total arch replacement, long term outcomes

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INTRODUCTION

According to current expert consensus, patients with uncomplicated type B aortic dissection (AD) are suggested for medical treatment and periodic clinical and imaging surveillance. Surgical repair and interventional treatment are considered options for complicated type B or non-A non-B AD (1–3). Recently, thoracic endovascular aortic repair (TEVAR) has been recommended as the first-line treatment for complicated type B or non-A non-B AD because of its lower morbidity and mortality (4). However, TEVAR may not be feasible for patients who have an unfavorable aortic

anatomy, a lack of a sufficient proximal landing zone, a high risk of retrograde type A aortic dissection (RTAAD) and/or concomitant with a proximal aortic lesion.

The frozen elephant trunk (FET) procedure may be an alternative treatment for these kinds of patients, according to the recent recommendations published by the European Society for Vascular Surgery and the European Association for Cardio-Thoracic Surgery (5, 6). The FET procedure combines the advantages of open surgery and endovascular treatment, by which total arch replacement (TAR) and descending aortic dissection repair (7, 8) can be performed simultaneously. The FET procedure can eliminate the risk of type Ia endoleak and RTAAD, benefit the thrombosis of false lumen, enable positive aortic remodeling and improve prognosis (9). However, there have been few reports on the outcomes of chronic type B or non-A non-B AD using the FET procedure, and the long-term outcomes, in particular, have not been reported (10).

Therefore, we retrospectively reviewed the experience in our center on the treatment of complicated type B or non-A non-B aortic dissection using the FET procedure according to the most recent published recommendations (5, 6). This study was conducted in accordance with the rules and checklist of the STROBE statement.

PATIENTS AND METHODS

This study was performed in accordance with the Declaration of Helsinki (2013). The Ethics Committees of Beijing Anzhen Hospital, Capital Medical University, approved this retrospective study (2020100X).

Patients

From February 2009 to December 2019, 79 consecutive patients diagnosed with chronic type B or non-A non-B aortic dissection underwent open surgical repair using TAR combined with FET under hypothermic cardiopulmonary bypass (CPB) and antegrade selective cerebral perfusion (ASCP) via median sternotomy in Beijing Anzhen Hospital. Computed tomographic angiography (CTA) and echocardiography were performed to evaluate and confirm the diagnosis preoperatively.

According to the definition of the STROAGE guidelines, there were 60 subacute dissections (75.9%, 14–90 days from the appearance of symptoms) and 19 chronic dissections (24.1%, >90 days) (11). The mean age was 45.0 ± 13.1 years, and 54 patients were male (68.4%). Hypertension was the most frequent risk factor in this cohort, which was observed in 49 patients (62.0%). Marfan syndrome was noted in 14 (17.7%), along with coronary artery disease in 5 (6.3%), chronic heart failure in 1 (1.3%), respiratory disease and prior cerebrovascular accident in 2 each (2.5%) and chronic kidney disease in 1 (1.3%). Sixty-two patients (78.5%) had ascending/root aortic aneurysms, aortic arch aneurysms in 9 cases (11.5%), severe aortic valve regurgitation in 23 cases (29.5%) and severe mitral valve regurgitation in 3 cases (3.8%). Four patients had undergone a previous aortic procedure, including the Bentall procedure in 3 (3.8%), mitral valvuloplasty in 1 (1.3%), ascending aortic replacement in 1 (1.3%) and abdominal aortic replacement in 1 (1.3%). More detailed parameters are presented in **Table 1**.

Surgical Technique

The detailed surgical technique of TAR combined with FET was described previously (12, 13). Island technique arch reconstruction was performed when there was no involvement of the brachiocephalic trunk and the left common carotid artery. Detailed procedures were described previously (14, 15).

The length of the stented graft (MicroPort Medical Co Ltd, Shanghai, China) was 10 cm, the diameter was 24–30 mm, and the graft had 3 and 1-cm stent-free vascular grafts for sutures in the proximal and distal edges, respectively. The size of the stented graft was determined according to the diameter of the proximal descending aorta of healthy individuals matched for age, sex, and height. The diameter of the stented graft was larger than the true lumen but slightly smaller than the entire chosen aorta.

Briefly, after a median sternotomy, the brachiocephalic vessels and the transverse arch were dissected and exposed. The left sternocleidomastoid muscle and other cervical muscle groups were partially transected if necessary. The left subclavian artery (LSCA) and the left common carotid artery (LCCA) were carefully separated and exposed, and care was taken to avoid injury to the thoracic duct; then, the thoracic duct was ligated if necessary.

Right axillary artery cannulation was used for CPB and ASCP. Cooling was initiated when CPB was established. Cold hyperkalemic cardioplegic solution was used for cardiac arrest. Then, valvular repair or replacement and proximal aortic operations were performed during the cooling phase. When the nasopharyngeal temperature was under 25°C, circulatory arrest was performed. Unilateral ASCP was initiated with a flow rate of 5–10 $mL \cdot kg^{-1} \cdot min^{-1}$ by the right axillary artery. Unilateral ASCP was considered to be adequate for cerebral circulation in the left hemisphere when the left radial artery pressure was 20 mmHg and there was recurrent bleeding through the LCCA; otherwise, bilateral ASCP was performed.

The anterior wall of the aortic arch was incised up to the origin of the LCCA, and the incision was performed ∼0.5 cm distal to the origin of the IA and the LCCA. No dissection of the innominate artery (IA) or the LCCA was confirmed intraoperatively. The stented graft was inserted into the true lumen of the descending aorta and deployed. The stent-free vascular graft was pulled and trimmed to a semioval shape to match the aortic arch wall containing the IA and the LCCA. A running suture was performed within the stent-free vascular graft between the LSCA and the LCCA using 4-0 Prolene, and the inner suture was performed counterclockwise while the outer suture was performed clockwise. Thus, the residual aortic wall and the stent-free vascular graft formed a circular opening. Finally, the distal end of the ascending aortic graft was anastomosed to the circular opening using open distal anastomosis. After anastomosis, the CPB gradually resumed to normal flow, and rewarming was started. The left subclavian artery was transected 0.5–1.0 cm distal to the origin, and the proximal segment was sutured using 5-0 Prolene. The LSCA was anastomosed to the LCCA in an end-to-side fashion (**Figure 1**).

TABLE 1 | Preoperative parameters and comorbidities.

Variables	Total (n = 79)	Subacute (n = 60)	Chronic (n = 19)	P-value
Time from onset to surgery (d)	33 (21–81)	26.5 (20–37)	270 (132–790)	
Type B AD	32 (40.5)	21 (35.0)	11 (57.9)	0.076
Non-A non-B AD	47 (59.5)	39 (65.0)	8 (42.1)	0.076
Male	54 (68.4)	41 (68.3)	11 (68.4)	0.994
Age (y)	45.0 ± 13.1	45.8 ± 12.6	42.1 ± 14.3	0.275
Smoking	30 (38.0)	25 (41.7)	5 (26.3)	0.230
Comorbidities				
Hypertension	49 (62.0)	36 (60.0)	13 (68.4)	0.510
Marfan syndrome	14 (17.7)	8 (13.3)	6 (31.6)	0.141
Coronary artery disease	5 (6.3)	4 (6.7)	1 (5.3)	0.827
Chronic heart failure	1 (1.3)	1 (1.7)	0	0.759
Prior cerebrovascular accident	2 (2.5)	2 (3.3)	0	0.574
COPD	2 (2.5)	1 (1.7)	1 (5.3)	0.426
Chronic kidney disease	1 (1.3)	0	1 (5.3)	0.241
Gout	1 (1.3)	0	1 (5.3)	0.241
Proximal lesion				
Aortic arch aneurysm	9 (11.5)	4 (6.8)	5 (26.3)	0.163
Aortic root/ascending aneurysm	62 (78.5)	45 (75.0)	17 (89.5)	0.219
Type A IMH	6 (7.6)	5 (8.3)	1 (5.3)	0.648
Severe AR	23 (29.5)	17 (28.8)	6 (31.6)	0.818
Severe MR	3 (3.8)	3 (5.1)	0	0.427
Crawford type I aneurysm	2 (2.6)	2 (3.4)	0	0.570

IQR, interquartile range; SD, standard deviation; IMH, intramural hematoma; AR, aortic regurgitation; MR, mitral regurgitation; COPD, chronic obstructive pulmonary disease.

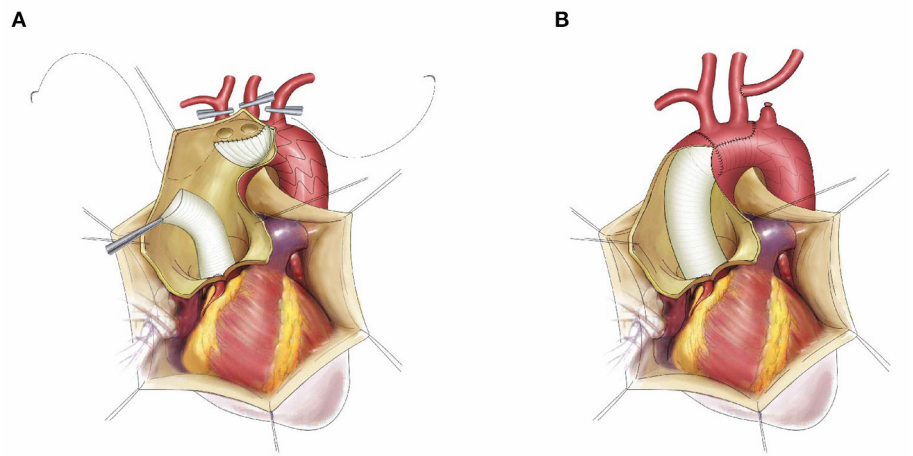

FIGURE 1 | The schematic diagram of frozen elephant trunk with "island technique" and left subclavian aorta to left common carotid artery transposition. The stented graft was inserted into the true lumen of descending aorta, the stent-free vascular graft was trimmed to a semi-oval shape containing the innominate artery and left common carotid artery, then the inner suture was performed counterclockwise while the outer suture was performed clockwise **(A)**; The final result after suture, left subclavian aorta to left common carotid artery transposition **(B)**.

Study Endpoints and Follow-Up

The primary study endpoints were operation death and late death. Overall in-hospital mortality was defined as death within 30 days after surgery and hospital death. Late mortality was defined as all-cause death beyond 30 days after surgery during follow-up. Secondary endpoints included distal aortic reoperations and complications. Distal aortic reoperation referred to any reinterventions, including open surgeries or endovascular interventions on the distal aorta. Complications included stroke, endoleak, limb ischemia and spinal cord injury.

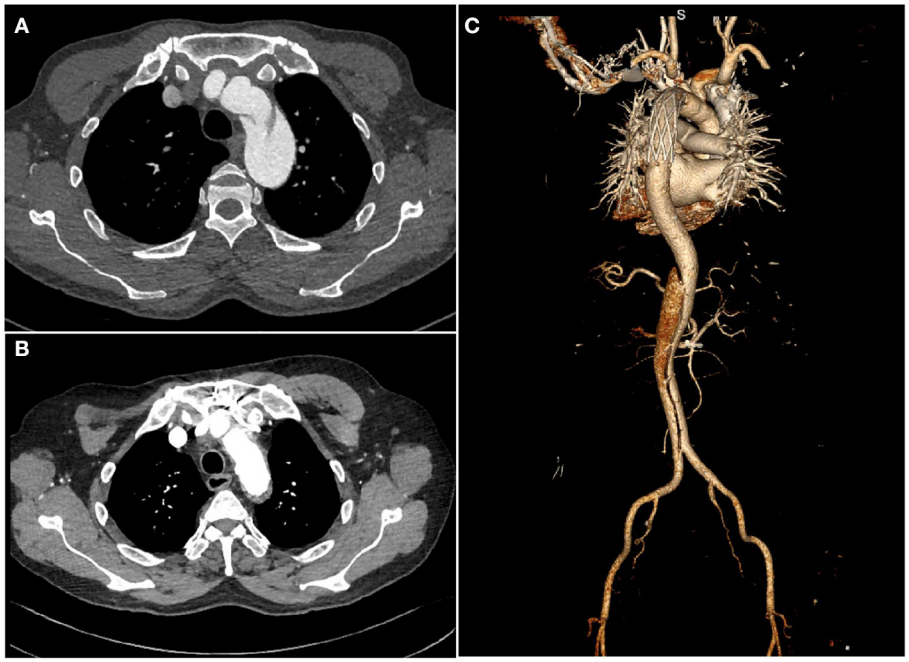

FIGURE 2 | Computed tomography images of a patient with chronic type B dissection with aortic arch involvement **(A)** preoperatively **(B,C)**, postoperatively.

All discharged patients were followed up regularly through clinic visits, phone calls, emails or letters. All survivors were recommended to undergo periodic CTA scans of the entire aorta (**Figure 2**).

Statistical Analysis

All analyses in the study were performed using SPSS software version 25.0 (IBM Corporation, Chicago, USA) and GraphPad Prism for Windows 8.0 (La Jolla, CA, USA.). Continuous variables are summarized as the mean ± standard deviation (SD) or median with interquartile range (IQR) according to their normality and were compared using Student's *t*-test or the Mann-Whitney U test. Categorical variables are expressed as numbers (percentage) and were compared using the Pearson χ^2 test or Fisher's exact test. Survival analysis and freedom from distal aortic reoperation were estimated using the Kaplan-Meier method. Competing risk analysis was performed based on the methods described by Blackstone et al. (16). A 2-sided significance level with a $P < 0.05$ was considered statistically significant.

RESULTS

Surgical Data

All patients underwent elective surgery and completed it successfully. Most patients (59.5%) underwent "island technique" aortic arch branch anastomosis (**Table 2**). Approximately half of the patients (54.4%) required the Bentall procedure, 23 patients (29.1%) underwent ascending aortic replacement, and 3 patients (3.8%) underwent the David procedure. Other concomitant procedures included mitral valve repair in 3 patients (3.8%) and coronary artery bypass grafting in 5 patients (6.3%). Extra anatomic bypass occurred in 4 cases (5.1%), including ascending aorta-femoral aorta bypass in 2 patients (2.8%), axillary artery-axillary artery bypass in 1 patient and ascending aorta-axillary artery bypass in 1 patient (1.4%).

The median CPB and aortic cross-clamp times were 167 (151–191) min and 89 (75–119) min, respectively (**Table 2**). The mean rectal temperature and circulatory arrest time were 25.3 ± 2.0°C and 25 ± 7 mins, respectively, and the median nasopharyngeal temperature was 23.6 (22.1–24.3)°C.

Morbidity and Mortality

The early postoperative results are presented in **Table 3**. Four patients (5.1%) died within 30 days. Two patients died of stroke; 1 patient suffered from heart failure and renal failure postoperatively, and it was difficult to maintain their blood pressure. The patient eventually died; 1 patient suffered from respiratory failure, renal failure and intestinal bleeding, his family members requested transfer to a local hospital, and the patient eventually died.

Reoperation for bleeding occurred in 5 patients (6.3%). Two patients (2.5%) required TEVAR because of intimal tears distal to the FET and poor reopening in the distal part of the FET. Two patients (2.5%) required resternotomy because of acute cardiac tamponade. Four patients (5.1%) experienced renal failure and needed continuous renal replacement therapy (CRRT). Spinal cord injury occurred in 3 patients (3.8%), including two cases of paraparesis and one of paraplegia. Poor wound healing occurred in 2 patients (2.5%). There was no recurrent laryngeal nerve

TABLE 2 | Intraoperative data.

Variables	Total ($n = 79$)	Subacute ($n = 60$)	Chronic ($n = 19$)	*P*-value
Aortic cross-clamp time (min)	89 (75–119)	89 (72–115)	100 (83–124)	0.233
Rectal temperature (°C)	25.3 ± 2.0	25.2 ± 2.0	25.7 ± 1.7	0.376
Nasopharyngeal temperature (°C)	23.7 (22.3–24.4)	23.7 (22.2–24.4)	23.9 (22.3–24.4)	0.528
Circulatory arrest time (min)	25 ± 7	24.8 ± 7.6	26.5 ± 5.8	0.385
Cardiopulmonary bypass time (min)	167 (151–191)	167 (150–191)	167 (155–200)	0.705
Concomitant procedures				
Proximal procedures				
Bentall procedure	43 (54.4)	30 (50.0)	13 (68.4)	0.160
David procedure	3 (3.8)	2 (3.3)	1 (5.3)	0.567
Ascending aortic replacement	23 (29.1)	20 (33.3)	3 (15.8)	0.142
MV repair	3 (3.8)	2 (3.3)	1 (5.3)	0.567
CABG	5 (6.3)	4 (6.7)	1 (5.3)	0.823
Aortic arch branches				
Island technique	47 (59.5)	37 (61.7)	10 (52.6)	0.484
Separate	32 (40.5)	23 (38.3)	9 (47.4)	0.484
Extra-anatomic bypass	4 (5.1)	3 (5.0)	1 (5.3)	0.675

IQR, interquartile range; SD, standard deviation; MV, mitral value; CABG, coronary artery bypass grafting.

TABLE 3 | Postoperative results.

Variables	Total ($n = 79$)	Subacute ($n = 60$)	Chronic ($n = 19$)	*P*-value
Operation death, n (%)	4 (5.1)	3 (5.0)	1 (5.3)	0.675
ICU stay ≤ 3 d, n (%)	66 (83.5)	50 (83.3)	16 (82.4)	0.928
Mechanical ventilation (h), median (IQR)	16.3 (12.0–19.5)	15.5 (11.8–18.9)	17.4 (14.7–31.7)	0.130
Spinal cord injury, n (%)	3 (3.8)	2 (3.3)	1 (5.3)	0.567
Stroke, n (%)	2 (2.5)	1 (1.7)	1 (5.3)	0.426
Acute renal failure, n (%)	4 (5.1)	3 (5.0)	1 (5.3)	0.567
Low cardiac output syndrome, n (%)	1 (1.3)	1 (1.7)	0	0.759
Pulmonary complication, n (%)	2 (2.5)	1 (1.7)	1 (5.3)	0.426
Poor wound healing, n (%)	2 (2.5)	1 (1.7)	1 (5.3)	0.426
Injury to recurrent nerves	0	0	0	–
Limb ischemia	0	0	0	–
Reoperation				
Reoperation for bleeding, n (%)	5 (6.3)	4 (6.7)	1 (5.3)	0.823
TEVAR, n (%)	2 (2.5)	1 (1.7)	1 (5.3)	0.426
Drainage of pericardial sac, n (%)	2 (2.5)	2 (3.3)	0	0.574

ICU, intensive care unit; IQR, interquartile range.

injury case. The median time of mechanical ventilation was 16.3 (12.0–19.5) h. Most patients (83.5%) stayed in the intensive care unit within 72 h. The detailed parameters are presented in **Table 3**.

Follow-Up

Among the 75 patients, 66 patients (88.0%) completed the follow-up. The median follow-up time was 53 months [range 3–144 months; 95% confidence interval (CI) 37.88–67.12]. A total of 10 patients died during the follow-up period, with causes that included aortic-related events ($n = 5$), cerebral hemorrhage ($n = 2$) and sudden death ($n = 3$) for unknown reasons. The overall survival rates were 96.2% (95% CI, 88.7–98.8%), 92.3% (95% CI, 83.7–96.5%), 88.0% (95% CI, 78.1–93.6%), 79.8% (95% CI, 65.8–88.6%) and 76.2% (95% CI, 60.5–86.3%) at 1/2, 1, 3, 5, and 7 years, respectively (**Figure 3A**). The overall survival rate of patients in the subacute group was higher than that in the chronic group ($P = 0.0467$) (**Figure 3B**). The freedom from distal operation rates were 97.3% (95% CI, 89.8–99.3%), 97.3% (95% CI, 89.8–99.3%), 87.8% (95% CI, 75.9–94.1%), 84.3% (95% CI, 66.9–92.2%) and 79.3% (95% CI, 61.3–89.7%) at 1/2, 1, 3, 5, and 7 years, respectively (**Figure 4**).

In the competing risk analysis, the incidence rates of distal aortic reintervention at 7 years were 13 and 24% for late mortality

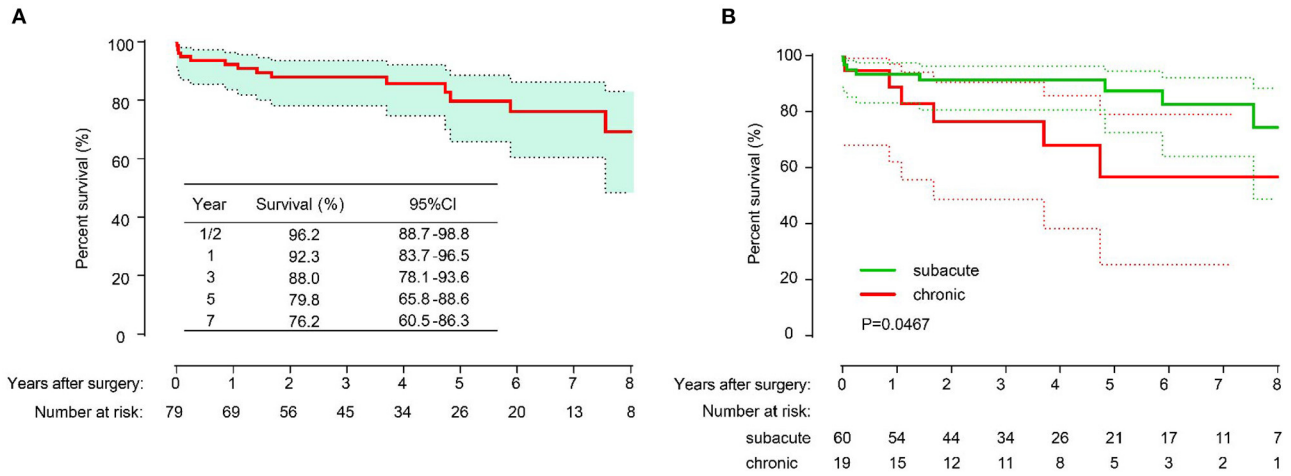

FIGURE 3 | The long-term overall survival of all patients **(A)**; Freedom from distal aortic reoperation of all patients **(B)**.

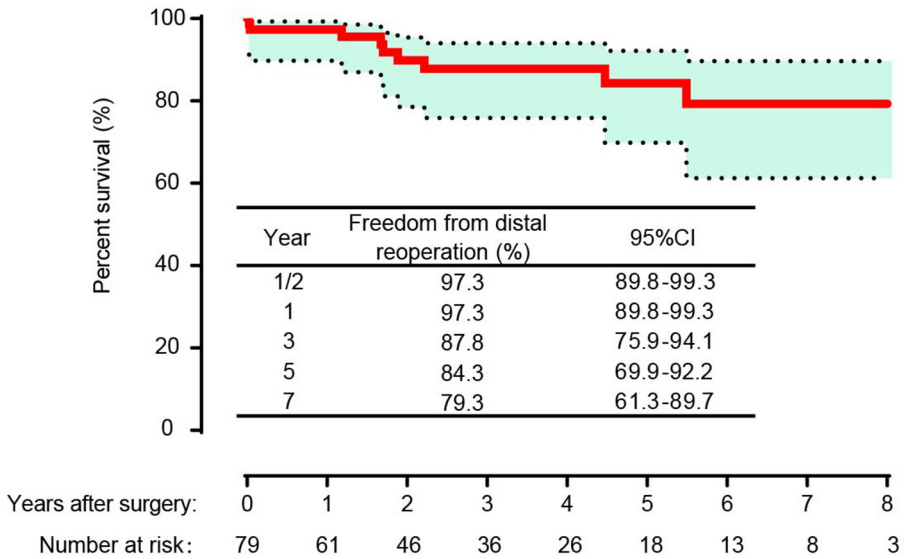

FIGURE 4 | Survival in patients with subacute and chronic type B aortic dissection and compared with the log-rank test.

and 64% for survival without distal aortic reoperation (**Figure 5**). A total of 11 patients underwent distal aortic intervention during the follow-up period. Thoracoabdominal aortic aneurysm repair was performed in 8 patients. TEVAR was performed in two patients for residual dissection and anastomotic leak. One patient underwent EVAR due to an abdominal aortic aneurysm.

DISCUSSION

The FET procedure is an attractive method for patients with complicated chronic type B or non-A non-B AD who are unfit for TEVAR. The early and long-term outcomes after the FET procedure are favorable.

In current recommendations, TEVAR is considered to be the optimal treatment for complicated type B AD. However, careful evaluation should be performed to determine whether there are enough proximal landing zones and favorable aortic anatomy. Open surgery may be the optimal option for patients with complicated chronic type B AD concomitant with aortic arch aneurysms or proximal aortic lesions. In patients diagnosed with non-A non-B AD with LCCA involvement only, LSCA to LCCA transposition or bypass should be performed, followed by TEVAR (17), and the outcomes are also satisfactory. However, in cases with aortic arch entry or LSCA to LCCA transposition that does not provide a sufficient proximal landing zone, double transposition or total arch rerouting should be considered,

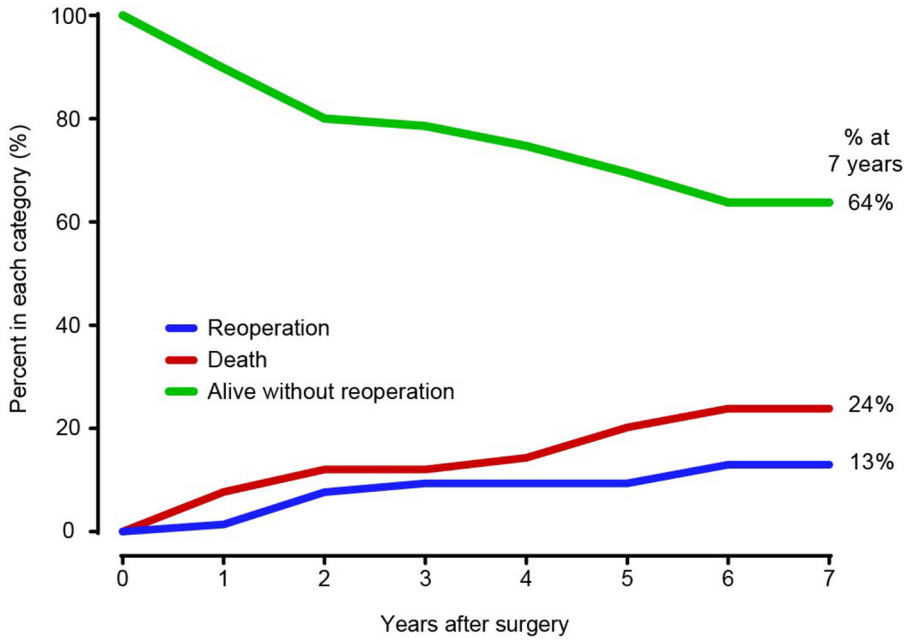

FIGURE 5 | Competing risks of death and distal aortic reintervention.

but it would also increase the risk of RTAAD (18, 19). According to previous reports, the high-risk factors for RTAAD include ascending aorta >38 mm, bicuspid aortic valve, arch abnormalities and extensive ascending aortic length (5). For such patients, total arch replacement combined with FET implantation was performed in our center. In this study cohort, most patients (78.5%) had concomitant root/ascending aortic aneurysms, and some had aortic arch aneurysms or valvular lesions. Therefore, our center adopted open surgery to perform the FET procedure, and proximal aortic or valvular lesions were treated.

We recommend that the FET procedure be performed if the patients have type B or non-A non-B AD concomitant with the following conditions (20): (i) aortic root or ascending aorta aneurysm; (ii) left common carotid artery dissection involvement or aortic arch aneurysm; (iii) proximal aortic lesion with coronary artery disease or aortic valve disease; (iv) contraindication for TEVAR; and (v) a high risk of RTAAD. The FET procedure for treating type B or non-A non-B AD unfit for TEVAR has some advantages (21). The greatest characteristic was that it combined the advantages of open surgical repair and interventional techniques. First, aortic arch replacement, descending aortic dissection repair and proximal aortic lesion repair can be performed through a median sternotomy in one stage. Second, FET implantation can enlarge the true lumen, promote aortic remodeling and potentially avoid secondary thoracic and abdominal aortic replacement. Third, the FET has extra suture margins at both ends, and anastomosis can be performed for patients who need thoracic and abdominal aortic replacement. Fourth, FET provides a landing zone for secondary TEVAR for those who develop distal stent graft-induced new entry.

The overall in-hospital mortality was 5.1%, which was acceptable for complicated chronic type B or non-A non-B AD, suggesting that the FET procedure is a safe and feasible technique. The overall in-hospital mortality was comparable or superior to those in previous reports (21–24). Takagi et al. (22) reported that the overall in-hospital mortality of chronic type B AD was 3%. Nozdrzykowski et al. (23) reported a single-center experience with 15 patients diagnosed with chronic type B AD who underwent open surgery, and the overall in-hospital mortality was 13.4%. Recently, Weiss et al. (24) reported a retrospective multicenter experience with 57 patients, and the overall in-hospital mortality was 14%. Interestingly, the overall survival rate in the subacute group was superior to that in the chronic group ($P = 0.047$), which contrasted with a previous report (24). Weiss et al. (24) showed that the overall survival rates between acute and chronic AD were not significantly different ($P = 0.65$). Recently, our center also reported experience with chronic type A aortic dissection, and the survival rate showed a distinction between the subacute and chronic groups, although there was no significant difference ($P = 0.107$) (25). The possible explanation may be that chronic B-type dissection itself is often accompanied by dilatation of the descending aorta, which predisposes patients to aortic events. However, this result still needs to be verified objectively, and large-scale studies should be conducted.

Paraplegia remains the most severe complication in aortic surgery because it has serious impacts on the quality of life of patients. In this study, the incidence of spinal cord injury, including paraplegia and paraparesis, was 3.8%, which was similar to the results reported by Weiss et al. (4.0%) (24). Moreover, Preventza et al. (26) found that the incidence of

spinal cord injury was 4.7% in a meta-analysis of more than 3,000 patients. Minimizing the circulatory arrest time and FET length above T8 are the key factors in reducing the incidence of spinal cord injury. Furthermore, for high-risk patients, cerebrospinal fluid drainage and neuromonitoring should be performed (27). The incidence of stroke was 2.5%, but all patients with stroke died within 30 days. The results of the meta-analysis indicated that the incidence of stroke was 4.9–6.5% in patients who underwent the FET procedure (28, 29). The presence of bovine aortic arch, preoperative cardiopulmonary resuscitation, aortic valve insufficiency (moderate and severe) and dissection of the common carotid artery were risk factors for postoperative stroke (30, 31). In our study cohort, the incidence of stroke was low compared to those in previous reports (28, 29), which might be due to the small amount of common carotid artery dissection involvement and careful brain protection. Most patients underwent "island technique" arch reconstruction, which preserved autologous vessels and might also have a protective effect on postoperative stroke. However, stroke remains the most devastating complication and warrants further brain protection, including moderate or deep hypothermia, ASCP, cerebral oxygen saturation monitoring and slowing of the rewarming speed (32). Postoperative acute kidney failure is the most common complication following dissection surgery. Minimizing the circulatory arrest time, CPB time and operation time are the key factors to prevent acute kidney failure. For patients with acute renal failure after surgery, early CRRT is recommended, which can partially reverse renal function. The renal resistive index may be helpful for decision-making and improving the prognosis of patients with acute kidney failure (33).

In this series, the overall survival rates and rates of freedom from distal aortic reoperation were 92.3, 79.8, 76.2, and 97.3, 84.3, 79.3% at 1, 5, and 7 years, respectively. There was no cerebral infarction or paraplegia reported. The early and long-term results of this technique for patients with chronic type B or non-A non-B AD were acceptable, which indicates that the FET procedure is a safe and effective approach for such patients. The competing analysis showed that the need for distal aortic reintervention was 13.0% at 7 years, which was comparable with the result reported by Charchyan et al. (20). The authors showed that the cumulative incidence rates of aortic reintervention were 5.6% at 0.5 years and 11.1% at 4 years. Moreover, Weiss et al. (24) showed that 16% of patients with complicated type B aortic dissection required secondary aortic reinterventions at 3 years. In our cohort, it is worth noting that most of the patients who needed reintervention required thoracoabdominal aortic replacement in the follow-up. Moreover, most of the patients (7/8) who required thoracoabdominal aortic replacement had Marfan syndrome, which reminded us of the importance of clinical surveillance and imaging, especially in cases of Marfan syndrome.

LIMITATIONS

There are several limitations to the current study. The present study is a retrospective cohort study, which has inherent selection bias. Moreover, it is a single-center study with a small sample size. Studies with larger groups of patients and multiple center trials should be conducted.

CONCLUSION

The FET procedure is a safe and effective approach for treating complicated chronic type B or non-A non-B AD in patients in whom TEVAR is infeasible. This technique combines the advantages of open surgical techniques and endovascular intervention, allowing simultaneous proximal aortic and aortic arch repair and stabilization of the descending aorta. The early and long-term outcomes were acceptable for such patients. The overall survival rate in the subacute group showed superior outcomes compared with the chronic group, but the results should be objectively understood.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committees of Beijing Anzhen Hospital, Capital Medical University (2020100X). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CL contributed to the conception, data collection, analysis, and drafted the manuscript. RQ, YZ, and SC contributed to the analysis. HL, RG, and YG contributed to the data collection. LS contributed to the conception and writing editing. JZ contributed to the conception, design, acquisition of work, and critically revised the manuscript. All authors approved the submitted version.

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En Bloc Arch Reconstruction With the Frozen Elephant Trunk Technique for Acute Type a Aortic Dissection

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Objective: The study objective was to evaluate the effect of en bloc arch reconstruction with frozen elephant trunk (FET) technique for acute type A aortic dissection.

Methods: 41 patients with acute Stanford type A dissection underwent en bloc arch reconstruction combined with FET implantation between April 2018 and August 2020. The mean age of the patients was 46 ± 13 years, and 9 patients were female. One patient had Marfan syndrome. Six patients had pericardial tamponade, 9 had pleural effusion, 5 had transient cerebral ischemic attack, and 3 had chronic kidney disease.

Results: The hospital mortality rate was 9.8% (4 patients). 2 (4.9%) patients had stroke, 23 (56.1%) had acute kidney injury, and 5 (12.2%) had renal failure requiring hemodialysis. During follow-up, the rate of complete false lumen thrombosis was 91.6% (33/36) around the FET, 69.4% (25/36) at the diaphragmatic level, and 27.8% (10/36) at the superior mesenteric artery level. The true lumen diameter at the same three levels of the descending aorta increased significantly while the false lumen diameter reduced at the two levels: pulmonary bifurcation and the diaphragm. The 1-, 2-and 3-year actuarial survival rates were 90.2% [95% confidence interval (CI), 81.2–99.2], 84.2% (95% CI, 70.1–98.3) and 70.2% (95% CI, 42.2–98), respectively.

Conclusions: In patients with acute type A dissection, en bloc arch reconstruction with FET technique appeared to be feasible and effective with early clinical follow-up results. Future studies including a large sample size and long-term follow-up are required to evaluate the efficacy.

Keywords: acute type a aortic dissection, en bloc technique, total arch replacement, frozen elephant trunk, open aortic arch repair

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INTRODUCTION

Acute type A aortic dissection is a life-threatening cardiovascular disease which remains a challenging procedure in cardiac surgery. Traditional open replacement of the aortic arch requires deep hypothermia circulatory arrest and replacement of the supra-aortic vessels with special consideration for cerebral protection (1). The frozen elephant trunk (FET) technique, combining conventional open surgery with endovascular repair, has been played an important role in treatment of such extensive aortic pathologies (2). Several approaches to arch replacement, such as the separate grafts, hybrid, en bloc (island), and branched stent graft techniques have been

applied (3–5). Several reports showed the safety and feasibility of the FET technique with en bloc arch reconstruction for aortic arch disease (5–8). However, a limited number of case studies have reported the treatment of acute aortic A dissection. The aim of this study is to review our experience with the en bloc arch reconstruction and the FET technique for acute type A dissection.

MATERIALS AND METHODS

Patients

From April 2018 to August 2020, en bloc arch reconstruction with FET implantation was performed on 41 consecutive patients with acute Stanford type A dissection involving the descending aorta. All diagnoses were confirmed by echocardiography, computed tomography angiography (CTA), and/or magnetic resonance imaging.

The mean age of the 32 (78%) men and 9 (22%) women was 46 ± 13 years (range, 14–69 years). Six (16.4%) patients had pericardial tamponade and 9 (22%) had pleural effusion. Transient cerebral ischemic attack was present in 5 (12.2%) patients, chronic kidney disease in 3 (7.3%), renal failure requiring hemodialysis in 1 (2.4%), lower extremity ischemia in 2 (4.9%), severe aortic regurgitation in 19 (46.3%), myocardial ischemia in 6 (14.6%) patients and classic Marfan syndrome in one patient. 33 (80.5%) patients had hypertension without effective control. The primary tear site was located in the ascending aorta, aortic arch and proximal descending thoracic aorta in 30 patients, 5 patients and 4 patients, respectively, and an entry tear was not detected in 2 patients. The details of the preoperative patient characteristics are listed in **Table 1**. This study was performed in compliance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2020-KY-0310-002), and informed consent from the patients was not needed due to the retrospective nature of this study.

TABLE 1 | Preoperative and presentation characteristics.

Variables	All patients ($n = 41$)
Male gender	32 (78%)
Age (years)	
Mean ± SD	46 ± 13
Median (range)	46 (14–69)
BMI	
Mean ± SD	26.9 ± 3.1
Median (range)	26.6 (22.0–35.5)
Chest, back or abdominal pain	37 (90.2%)
Pericardial tamponade	6 (14.6%)
Pleural effusion	9 (22%)
Atrial fibrillation	7 (17.1%)
Lower extremity ischemia	2 (4.9%)
Renal failure requiring hemodialysis	1 (2.4%)
Transient cerebral ischemic attack	5 (12.2%)
Myocardial ischemia	6 (14.6%)
Chronic kidney disease	3 (7.3%)
Hypertension	33 (80.5%)
Diabetes mellitus	2 (4.9%)
Hyperlipidemia	9 (22%)
Smoking	16 (39%)
Pneumonia	9 (22%)
Alcoholism	9 (22%)
Aortic rupture	0
Cardiopulmonary resuscitation	0
Marfan syndrome	1 (2.4%)
Primary tear site	
Ascending aorta	30 (73.2%)
Transverse arch	5 (12.2%)
Proximal descending thoracic aorta	4 (9.8%)
Unknown	2 (4.9%)
Aortic regurgitation	
None	9 (22%)
Mild	8 (19.5%)
Moderate	5 (12.2%)
Severe	19 (46.3%)
LV function	
Good (EF≥60%)	33 (80.5%)
Medium (EF 30∼60%)	8 (19.5%)
Maximal ascending aortic diameter (cm)	
Mean ± SD	5.1 ± 0.9
Median (range)	5.0 (3.4–7.2)
History of CBV event	3 (7.3%)
History of coronary artery disease	2 (4.9%)
Previous cardiac surgery	1 (2.4%)

SD, Standard deviation; BMI, body Mass Index; CBV, cerebrovascular; LV, left ventricular; EF, ejection fraction; Categorical values are n (%).

Surgical Procedure

After the induction of general anesthesia, vascular cannulation in the left radial artery and dorsalis pedis artery was performed for continuous monitoring of arterial pressure. Cerebral perfusion was monitored throughout the procedure by near-infrared spectroscopy. Using conventional median sternotomy, the aortic arch and brachiocephalic vessels were dissected and exposed (**Figure 1A**). The cardiopulmonary bypass (CPB) was based on the right axillary artery and the femoral artery cannulation, and the right axillary artery was used for antegrade cerebral perfusion (ACP). Venous drainage was obtained with two-stage cannula in the right atrium. The left-heart venting catheter was inserted through the right superior pulmonary vein to prevent ventricular distension. When the patient was cooled to 32°C, the ascending aorta was clamped just proximal to the innominate artery. The proximal ascending aorta was longitudinally opened and cardioplegic solution was directly administrated via the coronary ostia for myocardia protection. The decision for reimplantation of the aortic valve, supra-commissural ascending aortic replacement or composite aortic root replacement was made after careful inspection

Abbreviations: FET, frozen elephant trunk; CTA, computed tomography angiography; CPB, cardiopulmonary bypass; ACP, antegrade cerebral perfusion; AKI, acute kidney injury.

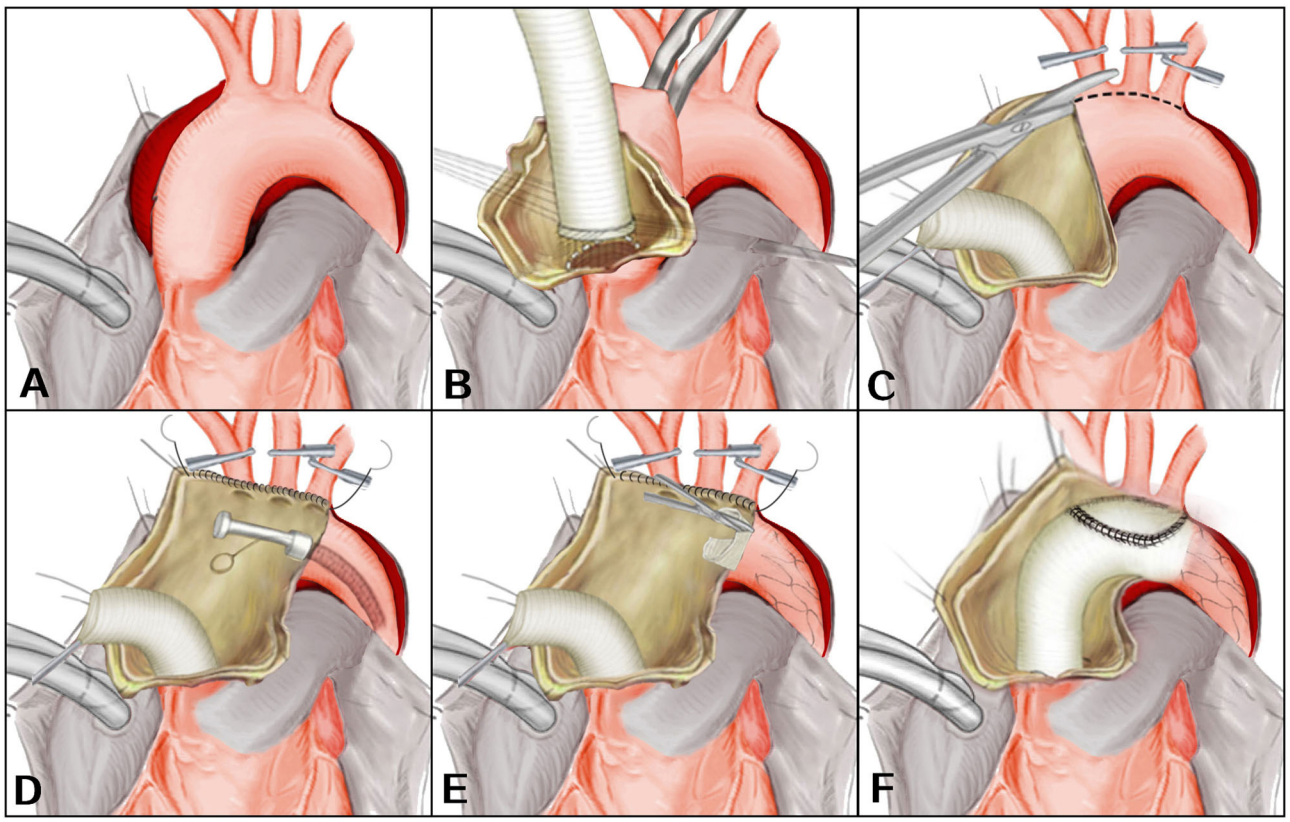

FIGURE 1 | (A–F) En bloc reconstruction with the frozen elephant trunk technique. Revised from Jun-Ming Zhu, MD.

of the morphological appearance of the cusps and root geometry (**Figure 1B**). During this period, the body temperature was continuously decreased. The brachiocephalic vessels were clamped when the proximal procedure was accomplished and the nasopharyngeal temperature reached 28°C. The circulatory arrest was instituted, and ACP was started at ∼5 to 10 ml/kg per min.

After the ascending aorta was unclamped and opened, an incision was made on the anterior wall of the aortic arch longitudinally up to the origin of the descending aorta (**Figure 1C**). The arch vessels were excised as a unit from the superior surface of the dissected aortic arch and the separated layers of the aortic patch were reunited using continuous suture. A FET (Cronus, Microport Medical, Shanghai, China) was inserted anterogradely into the true lumen of proximal descending aorta. The proximal edge of the metallic stent (not the stent-free sewing edge) was located between the origin of the left subclavian artery and the descending aorta (**Figure 1D**). The stent-free sewing edge was pulled and trimmed to avoid blocking the origin of brachiocephalic arteries (**Figure 1E**). An opening corresponding to the size of the aortic patch surrounding the brachiocephalic arteries was made into the aortic graft which was anastomosed to the aortic root. The distal end of the aortic graft was anastomosed to the descending aorta containing the trimmed stent-free sewing edge. Then the aortic graft where an opening was made was anastomosed to the aortic patch (**Figure 1F**). CPB was gradually resumed to its normal flow, and rewarming was begun after the anastomosis was accomplished. A bovine pericardial patch and the remaining native aorta were sutured around the ascending aortic graft to control bleeding.

Statistical Analysis and Follow-Up Methods

Continuous variables are expressed as the mean ± standard deviation and median (range), and categorical variables are presented as absolute values and percentages. Paired *t*-test were used to compare continuous variables. The Kaplan-Meier method was used to assess the cumulative survival rates. All statistical analyses were performed using SPSS 19 (SPSS Inc., Chicago, IL, USA). All statistical tests were 2-sided and *P*-value of <0.05 was considered statistically significant. Follow-up CTA was routinely performed before discharge, at 3, 6, and 12 months and annually thereafter.

RESULTS

From April 2018 to August 2020, 41 patients with acute Stanford type A dissection received total arch replacement using en bloc arch reconstruction and the FET technique at the first

TABLE 2 | Surgical data.

Variables	Mean ±SD (range)/*n* (%)
Time of surgery (min)	
Mean ± SD	446 ± 46
Median (range)	456 (367–561)
Cardiopulmonary bypass time (min)	
Mean ± SD	263 ± 44
Median (range)	276 (172–335)
Aortic cross-clamp time (min)	
Mean ± SD	158 ± 38
Median (range)	158 (87–213)
Antegrade cerebral perfusion time (min)	
Mean ± SD	44 ± 10
Median (range)	42 (20–71)
Aortic root procedure	
Bentall procedure	8 (19.5%)
Aortic valve reconstruction	11 (26.8%)
Supra-coronary aortic replacement	22 (53.7%)
Mitral valve repair	0
Coronary artery bypass graft	1 (2.4%)
Diameter of FET	
26 mm	31 (75.6%)
28 mm	10 (24.4%)
Distal landing zone	
T6	15 (36.6%)
T7	26 (63.4%)

SD, Standard deviation.

affiliated hospital of Zhengzhou University. Surgery time was 367–561 min (mean, 446 ± 46); CPB time was 172–335 min (means, 263 ± 44); aortic cross-clamp time was 87–213 min (means, 158 ± 38); and ACP time was 20–71 min (means, 44 ± 10). Concomitant procedures included the Bentall procedure in 8 patients, aortic valve reconstruction in 11 patients, supra-coronary aortic replacement in 22 patients, and coronary artery bypass graft in 1 patient. The operative data are summarized in **Table 2**.

The postoperative hospital stay was 4 - 28 days, and the length of the intensive care unit stay was 1–8 days. The ventilation was required for a media 21 h after operation (range 7–243 h). In-hospital mortality was 9.8% (4 patients). The causes of death included low output syndrome (2 patients), multiple-organ failure (1 patient), and intractable hemorrhage (1 patient). Stroke was observed in 2 (4.9%) patients who recovered before hospital discharge. Paraplegia was observed in 1 (4.2%) patient and pneumonia was observed in 4 (9.8%) patients. Acute kidney injury (AKI) which was defined according to the RIFLE criteria was observed in 23 (56.1%) patients (9), and five patients presented with renal failure requiring hemodialysis. Two patients presented with tracheostomy and two patients required mediastinal re-exploration for hemorrhage and sternal dehiscence, respectively. **Table 3** lists the major postoperative outcomes of this study.

TABLE 3 | Postoperative outcomes.

Event	Mean ± SD (range)/*n* (%)
Length of ICU stay (days)	
Mean ± SD	2.5 ± 1.7
Median (range)	2 (1–8)
Ventilation (h)	
Mean ± SD	37 ± 47
Median (range)	21 (7–243)
Postoperative hospital stay (days)	
Mean ± SD	14 ± 4.5
Median (range)	14 (4–28)
Pneumonia	4 (9.8%)
Acute kidney injury	23 (56.1%)
Renal failure requiring hemodialysis	5 (12.2%)
Tracheostomy	2 (4.9%)
Reoperation for bleeding	1 (2.4%)
Reoperation for sternal dehiscence	1 (2.4%)
Stroke	2 (4.9%)
Paraplegia	1 (2.4%)
In-hospital mortality	4 (9.8%)

SD, Standard deviation; ICU, intensive care unit; Acute kidney injury was defined according to the RIFLE criteria.

Images

Thirty-six patients underwent postoperative imaging with computed tomography which showed the enlargement of the true lumen, induction of thrombosis of the false lumen, and shrinkage of the aorta during follow-up. Preoperative and postoperative computed tomography angiography images are shown in **Figures 2**, **3**. With regard to the final follow-up CTA, complete thrombus formation of the false lumen around the FET was observed in 91.6% of patients (33/36), at the diaphragmatic level in 69.4% of patients (25/36), and the superior mesenteric artery level in 27.8% of patients (10/36). The supra-aortic vessels were patent in 100% of patients (36/36) without stenosis. The true lumen diameter of the dissected aorta increased significantly from 10.7 ± 4.9 mm to 23.1 ± 8.9 mm at the pulmonary bifurcation level ($P < 0.001$), from 10.5 ± 4.4 mm to 17.5 ± 7.0 mm at the level of the diaphragm ($P < 0.001$), and from 9.6 ± 3.9 mm to 9.9 ± 4.0 mm at the superior mesenteric artery level ($P < 0.001$). The false lumen diameter of the dissected aorta decreased significantly from 14.8 ± 6.6 mm to 3.0 ± 1.7 mm at the pulmonary bifurcation level ($P < 0.001$), and from 12.4 ± 5.0 mm to 6.5 ± 3.2 mm at the diaphragm level ($P < 0.001$). At the superior mesenteric artery level the average diameter of false lumen did not significantly change from 10.7 ± 4.2 mm to 10.5 ± 4.1 mm ($P = 0.06$) (**Table 4**).

Follow-Up

One patient was lost during the follow-up. There were 2 late deaths during a mean of follow-up 13 ± 10 months (range, 1–37 months). One patient died of unknown causes 14 months after surgery, and the other patient died of lung cancer 29 months after surgery. Severe complications during follow-up were not

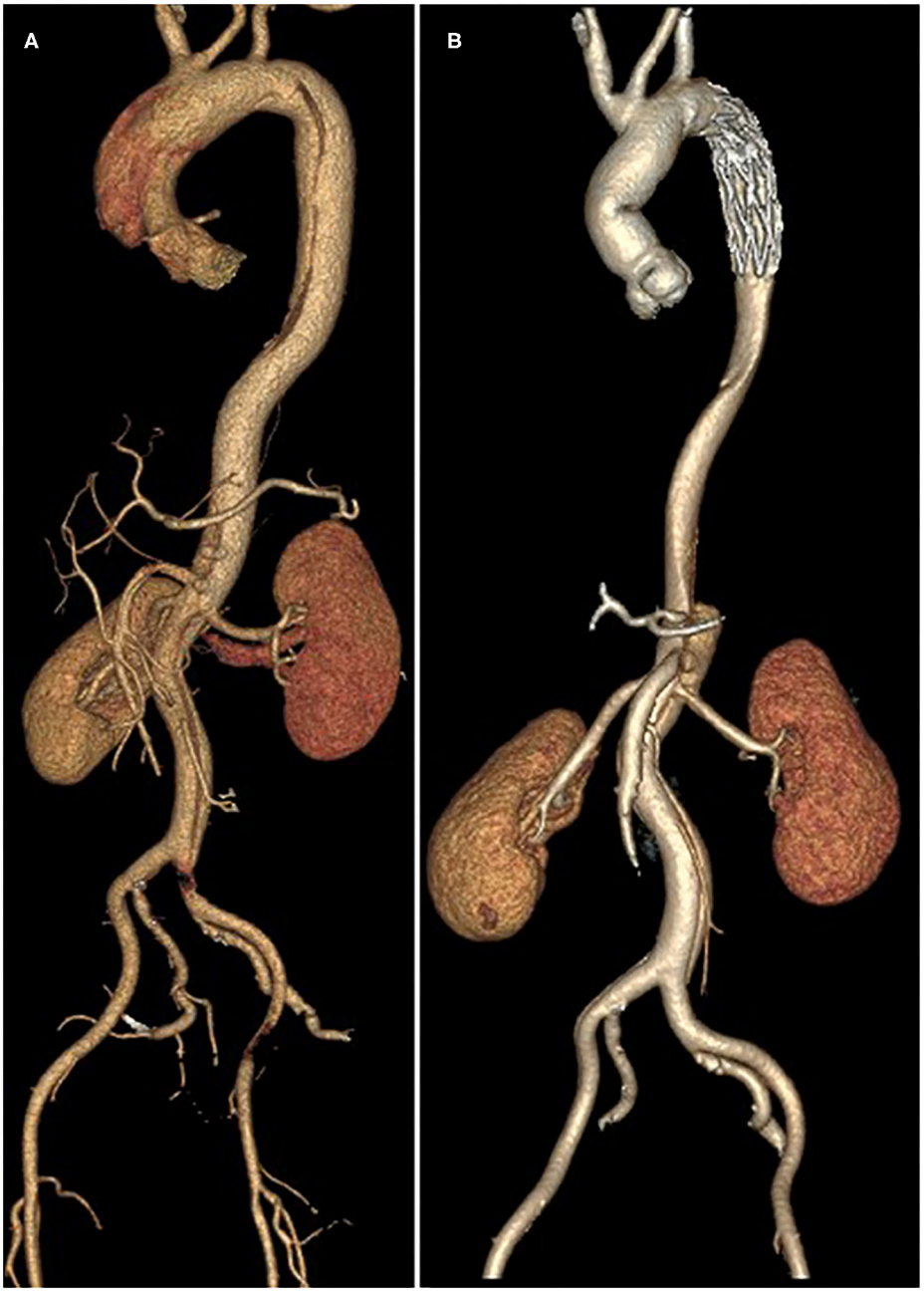

FIGURE 2 | Preoperative **(A)** and postoperative **(B)** computed tomography angiography reconstruction.

observed. Kaplan–Meier analysis estimated that the actuarial survival rates at 1-, 2-and 3-year were 90.2% [95% confidence interval (CI), 81.2–99.2], 84.2% (95% CI, 70.1–98.3) and 70.2% (95% CI, 42.2–98), respectively (**Figure 4**).

DISCUSSION

In our present study, we reported our experience with the en bloc arch replacement combined with the FET technique in patients with acute type A dissection. Treatment of extensive diseased aorta involving the aortic arch and the descending aorta is a surgical challenge, and management of the dissected aortic arch is likely one of the most impelling. Some authors suggest only an ascending aortic replacement with or without proximal arch replacement to reduce postoperative mortality and morbidity rate (10), while other authors more aggressively support a total arch replacement by using of elephant trunk process to improve short- and long-term prognosis after operation (11, 12). The

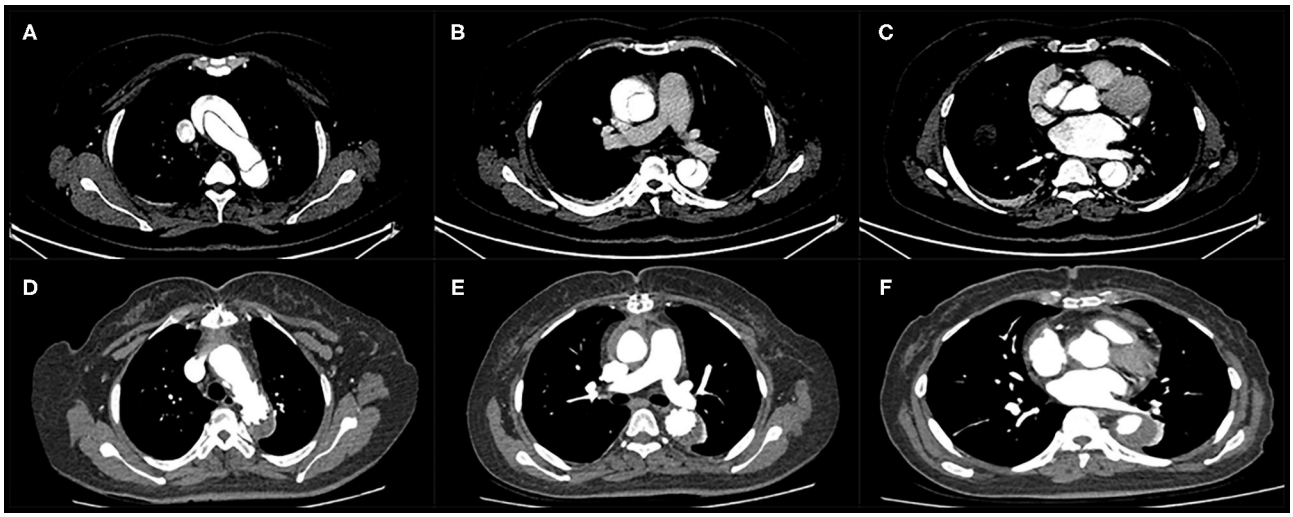

FIGURE 3 | Computed tomography angiography of a patient with acute type A dissection before surgery **(A–C)** and during follow-up **(D–F)**. Thrombus formation in the false lumen was observed around the stented graft and distal to the edge of the stented graft.

TABLE 4 | Comparison preoperative and follow-up diameters (mm ± SD).

Aortic level	Preoperative	Follow-up	*P*-value
True lumen diameter			
Pulmonary bifurcation	10.7 ± 4.9	23.1 ± 8.9	<0.001
Diaphragm	10.5 ± 4.4	17.5 ± 7.0	<0.001
Superior mesenteric artery	9.6 ± 3.9	9.9 ± 4.0	<0.001
False lumen diameter			
Pulmonary bifurcation	14.8 ± 6.6	3.0 ± 1.7	<0.001
Diaphragm	12.4 ± 5.0	6.5 ± 3.2	<0.001
Superior mesenteric artery	10.7 ± 4.2	10.5 ± 4.1	0.06

SD, Standard deviation.

question of whether such an aggressive technique should be used in acute type A aortic dissection is still controversial. We described our technique for total aortic arch replacement: the main aortic graft was anastomosed to the supra-arch vessels in an island fashion. The technique needed to finish all the anastomoses before myocardial and lower body perfusion can be restored, namely proximal and distal anastomoses as well as an island reimplantation of the supra-aortic branches, so the CPB time and especially the myocardial ischemic time are potentially long. A disadvantage of this method may be leave behind the potentially diseased aortic wall on the area of the greater curvature. Patients with connective tissue disorders may be required for reoperation in the future because of the continued degeneration of the leaving native aortic tissue. There are only limited experiences with en bloc arch reconstruction combined with the FET technique in patients with connective tissue disorders in that there is only one patient with Marfan syndrome in this study. During the follow-up period, the evidence of progression of the aortic disease was not observed, but this does not give a clear indication on the prognosis of connective tissue disorders. In the meanwhile, to control the bleeding at the distal anastomosis or the posterior part of the island is technically demanding when the CPB has been resumed. For surgeon, bleeding from the anastomotic location maybe the most dreadful complication during aortic surgery due to the fragile aortic wall. The essential advantages of the en bloc arch reconstruction lie in only one anastomosis to be performed for the aortic arch vessels and long-term patency by virtue of the preservation of the native supra-aortic arteries. At present there are different methods for aortic arch reconstruction for acute type A aorticdissection, such as the *en bloc* (island) technique, the branched graft technique and the hybrid technique. Shrestha M and colleagues showed that the en bloc technique and the branched graft technique could achieve similar results for total aortic replacement (5), which was consistent with Schoenhoff et al. (13). Zhang et al. reported that compared with branched graft technique, hybrid aortic arch technique is a viable alternative treatment for patients with DeBakey type I aortic dissection (3). Li and his colleges compared the outcomes of the modified en bloc technique and the branched graft technique for acute type A aortic dissection and found that the modified en bloc technique was superior to the branched graft technique (7). In this series involving 41 patients undergoing island-technique for arch reconstruction with FET technique, the hospital mortality rate was 9.8%; Stroke and paraplegia rates were 4.9 and 2.4%, respectively. Re-thoracotomy due to bleeding occurred in 1 patient. The results can be considered satisfactory with regard to both mortality and morbidity in accord with other reports in view of the pathologic background of the disease and the complex surgical procedures (14, 15).

Nowadays, there is still no agreement on the optimal way to provide brain protection during acute type A aortic dissection surgery and it is more complex with the presence of possible arch vessels dissection and brain damage due to insufficient blood supply. Retrograde cerebral perfusion with oxygenated blood through the superior vena cava is less popular (16), the

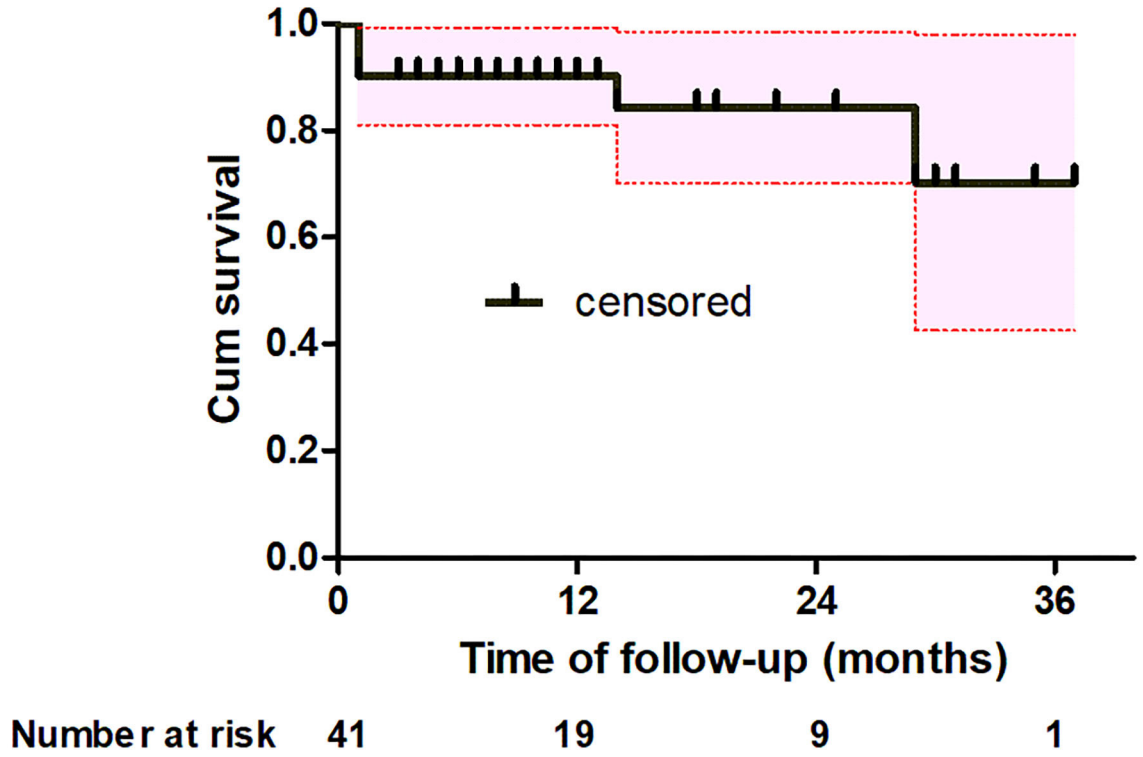

FIGURE 4 | Kaplan-Meier analysis shows estimate of the actuarial survival (black solid line) for all patients with the 95% confidence interval (red dotted line).

application of ACP has strongly increased at many centers worldwide in recent years (17). Sufficient cerebral perfusion is considered mandatory during circulatory arrest, and the circle of Willis was abnormal in about 40–68% of patients with diseases of the aortic arch (18, 19). However, sufficient collaterals could be achieved and there was no clinical impact of abnormalities of the circle of Willis (18, 19). Several reports have showed that ACP can maintain nearly normal cerebral metabolism, relieve cerebral edema, reduce intracranial pressure and metabolic acidosis in animal models (20, 21), and the use of ACP can provide a mortality benefit in patients with acute type A dissection (22). Even though the technical details of ACP are still discussed, the management of temperature protocol and safe time limits for cerebral perfusion are yet to be defined. A report from El-Sayed Ahmad et al. found that more than 60 min of selective ACP and moderate-to-mild systemic hypothermic circulatory arrest can safely be applied to patients with acute type A dissection (23). A meta-analysis revealed that using bilateral perfusion during aortic surgery resulted in superior operative outcomes compared to using unilateral perfusion if circulatory arrest was prolonged (24). Several studies have shown that ACP in combination with warmer circulatory arrest temperatures can be safely and decrease the incidence of permanent neurologic deficit and other poor clinical outcomes (15, 25). In the present series mean duration of ACP was 44 ± 10 min and core temperature was routinely cool to 28°C. The stroke rate was 4.9% and consistent with the stroke rate of 5% shown by De Bartolomeo et al. (2).

The ideal cannulation strategy in acute type A aortic dissection is another controversial topic, and each cannulation strategy has own advantages and drawbacks during CPB. In previous studies, axillary artery cannulation or femoral artery cannulation has been widely used and well-discussed (26–30). Axillary artery cannulation can avoid the disadvantages of retrograde perfusion, provide anterograde selective cerebral perfusion and achieved better neurological outcomes (26, 27, 30). The disadvantages of axillary artery cannulation are more time-consuming, greater technical demand and insufficient flow, which may affect the perfusion of organs (28). Femoral artery cannulation can be easily and safely performed. However, retrograde perfusion through the femoral artery might increase the risk for systemic malperfusion because of thrombus embolization and false lumen pressurization (29). Kreibich, M et al. reported because of quick and easy establishment of CPB central ascending aortic cannulation could be used as another option in patients with acute type A aortic dissection (31). Suenaga, E et al. found that 46 patients with acute type A aortic dissection underwent transapical aortic cannulation and gained acceptable early and mid-term outcomes (32). In our center, axillary artery and femoral artery cannulation were used to establish CPB in order to provide better systemic perfusion for acute type A aortic dissection repair. Huang et al. analyzed 327 patients who underwent surgical repair for type A aortic dissection using axillary artery in combination with femoral artery cannulation and showed relatively low incidences of early mortality (3.06%)

and permanent neurologic dysfunction (0.92%) (33). The reason might be that the study consisted of different pathophysiological conditions, namely both acute and chronical cases. In a cohort of 476 patients with acute type A aortic dissection, the incidences of malperfusion-relation complications and in-hospital mortality were 18.1 and 13.5% in combined axillary artery and femoral artery cannulation group (34), which was similar to our study.

AKI is a common complication after aortic surgery which is more likely associated with high mortality. In present study, we observed that 23 patients presented AKI and five patients required continuous renal replacement therapy because of renal failure after operation, which is in accordance with the results reported by Li et al. (35). Open total aortic arch replacement is a complicated operation that includes the application of hypothermic circulatory arrest which can potentially lead to severe renal ischemic-reperfusion injury. Although the moderate hypothermic circulatory arrest has shortened the duration of CPB, the CPB duration is much longer compared with other cardiac surgeries and adds to the risk of AKI. Several studies had demonstrated that CPB duration was a predictor of AKI in patients undergoing cardiac and vascular surgery (36, 37). The potential mechanism was not clear, but one may speculate that CPB was associated with significant hemolysis which was related to the development of AKI after surgery. Another explanation is that cardiac surgery using CPB induces a systemic inflammatory response syndrome that may lead to tissue injury. Lannemyr et al. found that at the beginning of CPB renal tubular cell injury was detected with a peak biomarker increased early after the CPB in cardiac surgery (38). The renal ischemia—reperfusion injury may be the most important pathophysiologic processes which can cause acute renal failure. This means that the risk of renal tubular injury can be minimized by avoiding deep hypothermia and decreasing the CPB duration. Other risk factors of developing AKI underwent aortic arch surgery, which did have been found were older age, obesity, preoperative hypertension, chronic renal disease, emergency surgery, a higher number of red blood cell transfusion, and renal malperfusion due to the dissection itself or cardiac tamponade (35, 36, 39). As a result, emergency aortic surgery was strongly related to the development of postoperative AKI and might be known as a risk factor for AKI. In this series renal blood flow was restored after operation and one-fourth of our renal malperfusion patients did not develop postoperative AKI.

Postoperative patency and thrombosis of the false lumen is another important focus after acute type A aortic dissection repair. The FET technique is a useful way to seal the primary entry tear in the proximal descending aorta, reduce pressure in the false lumen to prevent its dilatation, and limit the risk of distal aortic reintervention (11, 12, 40). However, owing to continued false lumen perfusion through distal entry tears complete thrombosis of the false lumen does not always be achieved through the use of the FET technique. A meta-analysis indicated that compared with complete thrombosis, a residual patent lumen after repair of Stanford type A dissection is a significant independent predictor of long-term mortality and aortic events, and partial false lumen thrombosis is not associated with the long-term mortality (41). Increasing pressure in the false lumen can lead to the dilation of the aorta which increases wall tension and adds the risk of aneurysm expansion and rupture. Because of this, the second-stage repair may be needed after the primary operation. In our series, no patients received aortic reintervention during the follow-up period. The distal landing zone of the FET prosthesis was located at T6-T7 and paraplegia was observed in one patient in this study. Coverage of numerous potentially critical intercostal arteries by the stent graft is believed to pose an increased risk for paraplegia (42). Using FET the intercostal arteries below the T8 level could not be occluded in the present study. One potential explanation is that intercostal arteries arising from the thrombosis of false lumen and insufficient collateral circulation resulted in spinal cord ischemia. This paper describes our experience of applying the FET technique and the island process for arch vessel reimplantation for acute type A dissection. During the follow-up period complete false lumen thrombosis was observed in 91.6%, 69.4 and 27.8% of the patients at the pulmonary bifurcation level, the diaphragmatic level and the superior mesenteric artery level, respectively. The true lumen diameter significantly increased the false lumen diameter showed shrinkage at the same three levels of the descending aorta.

STUDY LIMITATIONS

This study has several limitations: including small size sample, limited follow-up period, no comparative group and retrospective review of a single center's experiences.

CONCLUSIONS

The present retrospective study indicated that en bloc arch reconstruction with the FET procedure is feasible and effective for acute type A dissection. Early clinical follow-up results displayed that this procedure can be safely performed without reoperation. Further studies involving larger numbers of patients with a longer follow-up period are required.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (2020-KY-0310-002). The need for individual patient consent was waived due to the retrospective nature of the analysis.

AUTHOR CONTRIBUTIONS

PL and BW conceived the research question, conceived and designed the analysis. CL, HX, GZ, and FS undertook

data collection and conducted the study. HZ and XY drafted the manuscript. All authors reviewed the results, commented on the manuscript, and approved the final manuscript.

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Postoperative Hepatic Dysfunction After Frozen Elephant Trunk for Type A Aortic Dissection

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Background: This study was aimed to investigate the incidence, risk factors, and outcomes of patients with postoperative hepatic dysfunction (PHD) after frozen elephant trunk (FET) for type A aortic dissection (TAAD).

Method: A retrospective study was performed with 492 patients who underwent FET for TAAD between 2015 and 2019. Independent risk factors for PHD were determined by multivariate mixed-effect logistic analysis with surgeon-specific factor as a random effect.

Results: The incidence of PHD was 25.4% ($n = 125$) in our cohort. Patients with PHD presented higher early mortality (10.4 vs. 1.1%, $p < 0.001$), rates of acute kidney injury (42.4 vs. 12.8%, $p < 0.001$), and newly required dialysis (23.2 vs. 3.0%, $p < 0.001$) compared with those without PHD. Moreover, with the median follow-up period of 41.3 months, the survival curve was worse in patients with PHD compared with no PHD group (log-rank $p < 0.001$), whereas it was similar after excluding patients who died within 30 days (log-rank $p = 0.761$). Multivariable analyses suggested that PHD was predicted by preoperative aspartate transferase [odds ratio (OR), 1.057; 95% confidence intervals (CI), 1.036–1.079; $p < 0.001$], celiac trunk malperfusion (OR, 3.121; 95% CI, 1.008–9.662; $p = 0.048$), and cardiopulmonary bypass time (OR, 1.014; 95% CI, 1.005–1.023; $p = 0.003$). Retrograde perfusion (OR, 0.474; 95% CI, 0.268–0.837; $p = 0.010$) was associated with a reduced risk of PHD. Celiac trunk malperfusion was an independent predictor for PHD but not associated with early mortality and midterm survival.

Conclusions: PHD was associated with increased early mortality and morbidity, but not with late death in midterm survival. PHD was predicted by preoperative aspartate transferase, celiac trunk malperfusion, and cardiopulmonary bypass (CPB) time, and retrograde perfusion was associated with a reduced risk of PHD.

Keywords: aortic dissection, frozen elephant trunk, hepatic dysfunction, malperfusion, risk factors

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INTRODUCTION

Type A aortic dissection (TAAD) remains a great challenge to cardiovascular surgeons, which is a life-threatening condition with the reported 30-day mortality of 15–30% (1, 2). Total arch replacement with frozen elephant trunk (FET) can prevent the residual downstream dissection and simplify the second-stage procedure with an ideal landing zone for further endovascular operation,

which is well-recommended for the treatment of aortic dissection (3, 4). Despite contemporary advances in surgical techniques, the high incidence of early morbidity still raised concerns over the risks of visceral malperfusion, and postoperative hepatic dysfunction (PHD) has been suggested to be associated with increased mortality (5, 6). The incidence and clinical outcomes of PHD after aortic dissection repair varied in terms of different definitions and patients recruited, which is hardily achieved to analyze with limited cases available. Besides, the TAAD can be complicated by extensive tear and branch artery malperfusion, such as celiac trunk malperfusion, and there have been few studies focusing on its effects after FET procedure. The goal of this study was to determine the effects of PHD on early and midterm outcomes, and evaluate the association between preoperative celiac trunk malperfusion and PHD.

MATERIALS AND METHODS

The data used in the cohort were approved by the Ethics Committee of Fuwai Hospital, with individual informed consent waived. A retrospective chart review was performed with patients who underwent FET for TAAD from January 2015 to December 2019 at our institute. The exclusion criteria were as follows: (1) aortic diseases other than TAAD, such as type B aortic dissection, aortic aneurysm, ulcer, and hematoma; (2) patients with history of heart surgery, Marfan syndrome, connective tissue disease, chronic renal failure, or severe congenital heart disease; and (3) patients with preoperative critical situation, intraoperative death, or missing data of perioperative hepatic enzymes values (details in **Supplementary Figure S1**). After all, a total of 492 patients were available for analyses and were divided into two groups depending on the presence of PHD: 125 patients in the PHD group and 367 patients in the no PHD group.

The primary aim of the study was to compare early clinical outcomes and midterm survival between the PHD and no PHD groups, and to determine the independent effect of the variables of interest (as shown in **Supplementary Table S1**) on the incidence of PHD and early mortality. In addition, a subgroup analysis was performed for the effect of celiac trunk malperfusion on PHD and survival.

PHD was defined as elevated hepatic transaminase by 1.5 times the upper range of normal within 48 h postoperatively (normal range for aspartate transferase, 0–40 IU/L; for alanine transferase, 0–50 IU/L) according to the International Aortic Arch Surgery Study Group (7). Last available preoperative hepatic transaminase before surgery was used as a baseline value. Death within 30 days of surgery was considered early mortality. Preoperative organ malperfusion was diagnosed based on clinical manifestations and laboratory tests, with CT angiography evidence confirmed (see **Appendix E1** for more details). Acute kidney injury was defined as increase serum creatinine $\geq$1.5 times the baseline or a new requirement for dialysis within 48 h after surgery. We assessed the dissection-related anatomical information including tear extension, branch artery involvement, and branch artery malperfusion based on CT angiography. Dissection involvement referred to vessels that originated from false lumen or combined with intimal tear or malperfusion; branch artery malperfusion was defined as vessels with limited or no flow CT-enhanced signal (**Figure 1**). Acute dissection was referred to onset within 14 days, and emergency surgery was defined as operation performed within 24 h after hospital arrival. Retrograde perfusion was referred to performing cardiopulmonary bypass (CPB) with cannulation site of the femoral artery, including double arterial cannulation (8). We collated clinical data retrospectively from laboratory reports, radiological examination reports, and medical charts, follow-up data were obtained by telephone interview or clinic visits.

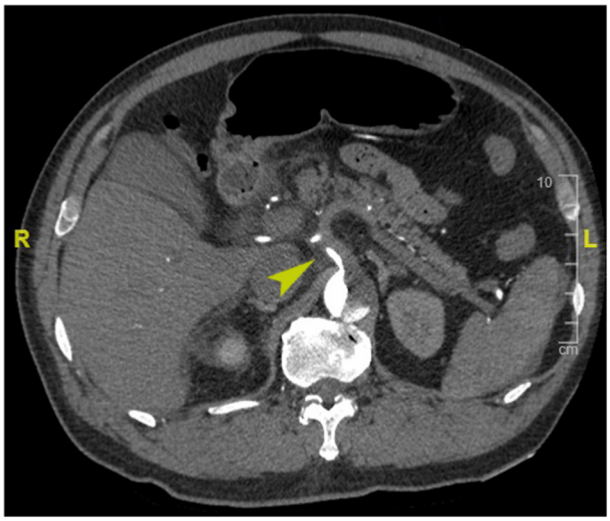

FIGURE 1 | Enhanced computed tomography angiography image of a representative case of preoperative celiac trunk malperfusion (arrowhead).

Surgical Technique

The details of surgical approach have been described in the previous study (9). Briefly, FET procedure was performed under hypothermic circulatory arrest, and arterial cannulation for CPB was instituted at different sites according to the status of the patient (right axillary artery, femoral artery, innominate artery, and double arterial cannulation). When the nasopharyngeal temperature was dropped to 20–25°C, the aortic arch was transected between the left subclavian artery and left common carotid artery. Antegrade cerebral perfusion for brain protection through the right axillary artery was established in all patients, with a flow rate of 5–10 ml/kg/min. Aortic root repair was performed during cooling if needed. After blocking the three branch vessels of the arch, the stented FET graft (Cronus, MicroPort Endovascular Shanghai Co., Ltd., China) was implanted into the true lumen of the descending aorta with hypothermic circulatory arrest, and subsequently, we anastomosed the four-branched graft (Terumo, Vascutek Limited, Renfrewshire, UK) end-to-end with the distal aortic arch and FET graft. Restoring circulation was performed through the femoral artery (in femoral and double arterial cannulation) or the perfusion branch of the

four-branched graft (in other cannulations). After reperfusion, the reconstruction of the left common carotid artery was performed first. CPB flow was returned to normal rate and rewarming was started, followed by reconstructions of the ascending aorta, left subclavian artery, and innominate artery, respectively.

Statistical Analyses

All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided *p*-value of ≤0.05 was considered statistically significant. The continuous variables of normal distribution were summarized as mean ± standard deviation and analyzed by one-way analysis of variance; those of non-normal distribution were expressed as median with interquartile range (IQR) and analyzed by the Kruskal–Wallis test. The Pearson's χ^2-test or Fisher's exact test was used to compare categorical variables that were reported as frequencies with percentages.

The multivariable mixed-effect logistic regression was applied to analyze the risk factors of PHD and early mortality by glmmTMB package with surgeon-specific factor as a random effect. Between 2015 and 2020, 11 aortic surgeons performed 492 FET procedures, and 5 out of 11 surgeons completed <20 surgeries, which were calculated as one group. Clinically important variables with a value of $p < 0.10$ in univariate logistic regression were included in the multivariate logistic regression (**Supplementary Table S2**). The Kaplan–Meier method and log-rank test were constructed to analyze the survival rates; the multivariable Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) in survival function, which was applied to analyze the effect of PHD and celiac trunk malperfusion on overall survival, following variables with $p < 0.10$ on the univariate Cox analysis.

RESULTS

Patient Characteristics

As shown in **Table 1**, the average age of patients who underwent FET was 47 ± 9 years, and 81.1% were male in our cohort. Most patients were in the presentation of acute stage (85.6%), and the dissection extension was commonly down to the iliac artery (67.7%). The percentage of acute stage (92.8 vs. 83.1%, $p = 0.012$), emergency surgery (90.4 vs. 74.4%, $p < 0.001$), preoperative liver transaminases ($p < 0.001$), and creatinine ($p < 0.001$) were higher in the PHD group compared with the no PHD group. Patients with PHD presented greater proportions of organ malperfusion (37.6 vs. 17.4%, $p < 0.001$), and the differences in ejection fraction ($p = 0.009$) and direct bilirubin ($p = 0.003$) were statistically significant but not clinically significant. In addition, significantly higher proportion of the celiac trunk (9.6 vs. 3.8%, $p = 0.023$), superior mesenteric artery (12.0 vs. 5.2%, $p = 0.017$), and iliac artery malperfusion (15.2 vs. 8.2%, $p = 0.036$) were shown in the PHD group. Otherwise, there was no significant difference identified in other preoperative characteristics between the two groups.

TABLE 1 | Preoperative characteristics.

Variables	All ($n = 492$)	PHD ($n = 125$)	No PHD ($n = 367$)	*p*-value
Age (years), mean ± SD	47 ± 9	47 ± 10	47 ± 9	0.982
Male	399 (81.1)	105 (84.0)	294 (80.1)	0.408
BMI (kg/m^2), mean ± SD	26.4 ± 4.0	27.0 ± 4.1	26.2 ± 4.0	0.057
BSA (m^2), mean ± SD	2.01 ± 0.20	2.04 ± 0.20	2.01 ± 0.20	0.120
Acute stage	421 (85.6)	116 (92.8)	305 (83.1)	0.012
Emergency surgery	387 (78.7)	113 (90.4)	274 (74.7)	<0.001
Hypertension	398 (80.9)	105 (84.0)	293 (79.8)	0.373
Coronary artery disease	43 (8.7)	12 (9.6)	31 (8.4)	0.833
Diabetes	16 (3.3)	3 (2.4)	13 (3.5)	0.741
COPD	5 (1.0)	0 (0.0)	5 (1.4)	0.426
Cerebrovascular accident	20 (4.1)	7 (5.6)	13 (3.5)	0.457
Smoking	216 (43.9)	57 (45.6)	159 (43.3)	0.735
NYHA grade ≥III	34 (6.9)	7 (5.6)	27 (7.4)	0.642
Ejection fraction, median (IQR)	60 (60–63)	60 (59–62)	60 (60–63)	0.009
Moderate to severe AI	52 (10.6)	15 (12.0)	37 (10.1)	0.664
Laboratory tests, median (IQR)				
ALT (IU/L)	21 (14–35)	24 (16–52)	20 (14–32)	0.005
AST (IU/L)	23 (17–32)	31 (20–54)	21 (17–28)	<0.001
SCr (μmol/L)	88 (73–115)	101 (80–132)	85 (70–107)	<0.001
Total bilirubin	19 (14–24)	19 (14–25)	19 (14–24)	0.931
Direct bilirubin	4 (3–6)	4 (3–7)	4 (3–5)	0.003
PT-INR	1.10 (1.06–1.18)	1.11 (1.06–1.19)	1.10 (1.06–1.17)	0.572
Albumin	39.8 (36.4–42.9)	40.6 (37.1–43.3)	39.4 (36.1–42.6)	0.054
ALT/AST ≥100 IU/L	31 (6.3)	20 (16.0)	11 (3.0)	<0.001
Organ malperfusion	111 (22.6)	47 (37.6)	64 (17.4)	<0.001
Myocardial	32 (6.5)	13 (10.4)	19 (5.2)	0.066
Cerebral	21 (4.3)	4 (3.2)	17 (4.6)	0.669
Visceral	28 (5.7)	20 (16.0)	8 (2.2)	<0.001
Renal	28 (5.7)	12 (9.6)	16 (4.4)	0.050
Peripheral	38 (7.7)	16 (12.8)	22 (6.0)	0.023
Dissection extension				
Aortic arch	54 (11.0)	12 (9.6)	42 (11.4)	0.686
Thoraco-abdominal aorta	106 (21.5)	24 (19.2)	82 (22.3)	0.540
One iliac artery	158 (32.1)	40 (32.0)	118 (32.2)	1.000
Both iliac artery	175 (35.6)	49 (39.2)	126 (34.3)	0.382
Vessel involvement				
Celiac trunk	195 (39.6)	51 (40.8)	144 (39.2)	0.839
Superior mesenteric artery	99 (20.1)	33 (26.4)	66 (18.0)	0.058

(Continued)

TABLE 1 | Continued

Variables	All ($n = 492$)	PHD ($n = 125$)	No PHD ($n = 367$)	*p*-value
Renal artery	333 (67.7)	89 (71.2)	244 (66.5)	0.388
Iliac artery	333 (67.7)	89 (71.2)	244 (66.5)	0.388
Malperfusion				
Celiac trunk	26 (5.3)	12 (9.6)	14 (3.8)	0.023
SMA	34 (6.9)	15 (12.0)	19 (5.2)	0.017
Celiac trunk/SMA	54 (11.0)	23 (18.4)	31 (8.4)	0.004
Renal artery	60 (12.2)	21 (16.8)	39 (10.6)	0.096
Iliac artery	49 (10.0)	19 (15.2)	30 (8.2)	0.036

Data are presented as n (%) unless otherwise stated.
AI, aortic insufficiency; ALT, alanine transferase; AST, aspartate transferase; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; IQR, interquartile range; NYHA, New York Heart Association; PHD, postoperative hepatic dysfunction; PT, Prothrombin time; SCr, serum creatinine; SD, standard deviation; SMA, superior mesenteric artery.

Operative Characteristics

In this cohort, 14.2% had concomitant coronary artery bypass graft procedure and retrograde perfusion was accessed in 53.9% (**Table 2**). Among patients undergoing FET for aortic dissection, median circulatory arrest time was 16 min (IQR, 14–19 min), and median lowest nasopharyngeal and bladder temperature on bypass were 24.1°C (IQR, 22.4–25.0°C), and 26.1°C (IQR, 24.7–27.5°C), respectively. Patients with PHD had more percentage of concomitant coronary artery bypass graft procedure (24.8 vs. 10.6%, $p < 0.001$). Longer total surgery time (439 vs. 365 min, $p < 0.001$), CPB time (183 vs. 159 min, $p < 0.001$), cross-clamping time (115 vs. 98 min, $p < 0.001$), and circulatory arrest time (17 vs. 16 min, $p = 0.035$) were found in the PHD group. Moreover, higher nasopharyngeal temperature ($p = 0.019$) was observed in patients with PHD, and the differences in intraoperative red blood cell transfusions ($p < 0.001$) and fresh-frozen plasma ($p < 0.001$) were statistically significant but not clinically significant.

Early Adverse Events

The overall early mortality in our cohort was 3.5% ($n = 17$), including 13 patients in the PHD group and 4 patients in the no PHD group (10.4 vs. 1.1%, $p < 0.001$, **Table 2**). The percentages of paraplegia (12.0 vs. 4.9%, $p = 0.001$), newly required dialysis (23.2 vs. 3.0%, $p < 0.001$), and intra-aortic balloon pump support (2.4 vs. 0.0%, $p = 0.021$) were higher in the PHD group. Furthermore, patients with PHD were more likely to be combined with acute kidney dysfunction vs. those without PHD (42.4 vs. 12.8%, $p < 0.001$). There was no difference in terms of stroke ($p = 0.309$), reintubation ($p = 0.762$), and reoperation of bleeding ($p = 0.866$). The postoperative in-hospital stay ($p < 0.001$), intensive care unit stay ($p < 0.001$), and ventilation time ($p < 0.001$) were longer for patients with PHD.

Overall Survival

Complete follow-up was available for 453 out of 492 patients (92.1%) with a median duration of 41.3 (IQR 25.2–56.4) months, during which 18 patients died in the PHD group and 21 in the no PHD group. The Kaplan–Meier estimated cumulative survival

TABLE 2 | Intraoperative details and early outcomes.

Variables	All ($n = 492$)	PHD ($n = 125$)	No PHD ($n = 367$)	*p*-value
Concomitant procedure, *n* (%)				
CABG	70 (14.2)	31 (24.8)	39 (10.6)	<0.001
Bentall procedure	119 (24.2)	34 (27.2)	85 (23.2)	0.430
David procedure	8 (1.6)	3 (2.4)	5 (1.4)	0.702
Wheat procedure	7 (1.4)	2 (1.6)	5 (1.4)	1.000
Aortic valve replacement	3 (0.6)	1 (0.8)	2 (0.5)	1.000
Ascending-femoral bypass	26 (5.3)	7 (5.6)	19 (5.2)	1.000
Retrograde perfusion, *n* (%)	265 (53.9)	63 (50.4)	202 (55.0)	0.427
Operative duration (min), median (IQR)				
Total surgery time	375 (317–455)	439 (355–525)	365 (311–431)	<0.001
Cardiopulmonary bypass	167 (140–202)	183 (160–253)	159 (135–193)	<0.001
Cross-clamp	100 (80–126)	115 (88–140)	98 (77–119)	<0.001
Circulatory arrest	16 (14–19)	17 (15–20)	16 (14–19)	0.035
Intraoperative transfusion, median (IQR)				
Red blood cells (U)	0 (0–0)	0 (0–4)	0 (0–0)	<0.001
Fresh-frozen plasma (ml)	400 (0–600)	400 (0–800)	400 (0–600)	<0.001
Platelet (U)	1 (1–1.25)	1 (1–1)	1 (1–2)	0.809
Lowest temperature (°C), median (IQR)				
Nasopharyngeal	24.1 (22.4–25.0)	24.5 (23.5–25.0)	24.0 (22.2–24.9)	0.019
Bladder	26.1 (24.7–27.5)	26.0 (24.8–27.8)	26.1 (24.6–27.4)	0.511
Early adverse events, *n* (%)				
In-hospital mortality	9 (1.8)	6 (4.8)	3 (0.8)	0.013
Early mortality	17 (3.5)	13 (10.4)	4 (1.1)	<0.001
Stroke	15 (3.0)	6 (4.8)	9 (2.5)	0.309
Paraplegia	33 (6.7)	15 (12.0)	18 (4.9)	0.011
Newly required dialysis	40 (8.1)	29 (23.2)	11 (3.0)	<0.001
Reintubation	12 (2.4)	4 (3.2)	8 (2.2)	0.762
Reoperation of bleeding	23 (4.7)	5 (4.0)	18 (4.9)	0.866
IABP support	3 (0.6)	3 (2.4)	0 (0.0)	0.021
Laboratory tests, median (IQR)				
ALT (IU/L)	28 (19–56)	133 (70–418)	23 (17–31)	<0.001
AST (IU/L)	57 (41–98)	215 (138–570)	47 (38–61)	<0.001
SCr (μmol/L)	148 (110–229)	232 (147–356)	134 (105–194)	<0.001
Hepatic dysfunction, *n* (%)	125 (25.4)	125 (100.0)	0 (0.0)	<0.001
Acute kidney dysfunction, *n* (%)	100 (20.3)	53 (42.4)	47 (12.8)	<0.001
Postoperative hospital stay (days), median (IQR)	12 (10–16)	13 (10–17)	12 (9–15)	0.029
ICU stay (h), median (IQR)	88 (45–136)	111 (67–201)	85 (43–118)	<0.001
Ventilation time (h), median (IQR)	21 (14–47)	35 (16–78)	20 (13–42)	<0.001

ALT, alanine transferase; AST, aspartate transferase; CABG, coronary artery bypass graft; IABP, intra-aortic balloon pump; ICU, intensive care unit; IQR, interquartile range; PHD, postoperative hepatic dysfunction, SCr, serum creatinine.

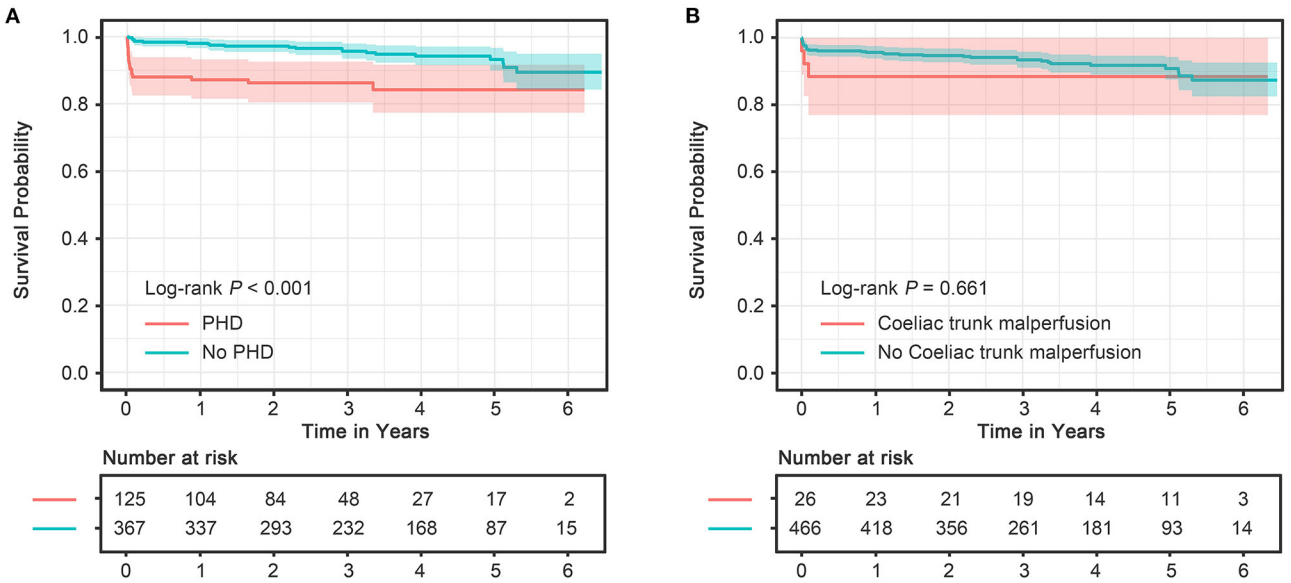

FIGURE 2 | (A) Kaplan–Meier method estimating midterm survival of patients with and without PHD. **(B)** Kaplan–Meier method estimating midterm survival of patients with and without celiac trunk malperfusion. CI, confidence interval; HR, hazard ratio; PHD, postoperative hepatic dysfunction.

rates at 3 and 5 years were 86.3 and 84.2%, respectively, in the PHD group, and 95.7 and 93.2%, respectively, in the no PHD group. The survival curve showed that patients with PHD were associated with worse midterm survival compared with patients without PHD (**Figure 2A**, log-rank $p < 0.001$), whereas similar survival curves (**Supplementary Figure S2**, log-rank $p = 0.761$) were observed after excluding patients that died within 30 days. The multivariate Cox proportional hazards analysis revealed that longer total surgery time predicted late death in the overall survivors (**Table 4**).

Logistic Regression Analyses

The results of the multivariable mix-effect logistic regression are presented in **Table 3** and **Supplementary Table S2**. Among the variables of interest, significant independent risk factors on PHD were found for preoperative aspartate transferase [Odd ratio (OR), 1.057; 95% CI, 1.036–1.079; $p < 0.001$], CPB time (OR, 1.014; 95% CI, 1.005–1.023; $p = 0.003$), celiac trunk malperfusion (OR, 3.121; 95% CI, 1.008–9.662; $p = 0.048$), early mortality for any organ malperfusion (OR, 3.571; 95% CI, 1.041–12.245; $p = 0.043$), and total surgery time (OR, 1.006; 95% CI, 1.002–1.010; $p = 0.004$). The retrograde perfusion had significantly reduced risk of PHD compared with single antegrade perfusion (OR, 0.474; 95% CI, 0.268–0.837; $p = 0.010$).

Subgroup Analysis

Of the 492 patients with aortic dissection, 26 patients (5.3%) had celiac trunk malperfusion in our cohort. Of those, the incidence of PHD (46.2 vs. 24.2%, $p = 0.023$) was much higher than those without celiac trunk malperfusion (**Figure 3**). Moreover, higher rates of early mortality (11.5 vs. 3.0%, $p = 0.077$) and postoperative acute kidney injury (42.3 vs. 19.1%, $p = 0.009$) were observed in celiac trunk malperfusion group. As shown in **Tables 3**, **4**, preoperative celiac trunk malperfusion was an independent predictor for PHD but not associated with early mortality (OR, 3.274; 95% CI, 0.512–20.947; $p = 0.211$) and late death in midterm survival (HR, 1.125; 95% CI, 0.313–4.048; $p = 0.857$). No significant difference was found in the survival curve of overall survival between patients with and without celiac trunk malperfusion (**Figure 2B**, log-rank $p = 0.661$).

TABLE 3 | The multivariable mixed effect logistic regressions.

Variables	OR	95% CI	*p*-value
Postoperative hepatic dysfunction			
Preoperative AST	1.057	1.036–1.079	<0.001
Retrograde perfusion	0.474	0.268–0.837	0.010
CPB time	1.014	1.005–1.023	0.003
Celiac trunk malperfusion	3.121	1.008–9.662	0.048
Early mortality			
Any organ malperfusion	3.571	1.041–12.245	0.043
Celiac trunk malperfusion	3.274	0.512–20.947	0.211
Total surgery time	1.006	1.002–1.010	0.004

The regressions were adjusted by surgeon-specific factors as a random effect.
AST, aspartate transferase; CI, confidence interval; CPB, cardiopulmonary bypass; OR, odds ratio.

TABLE 4 | The multivariable Cox proportional hazards analysis for midterm survival.

Variables	HR	95% CI	*p*-value
Celiac trunk malperfusion	1.125	0.313–4.048	0.857
Total surgery time	1.003	1.001–1.006	0.021

CI, confidence interval; HR, hazard ratio.

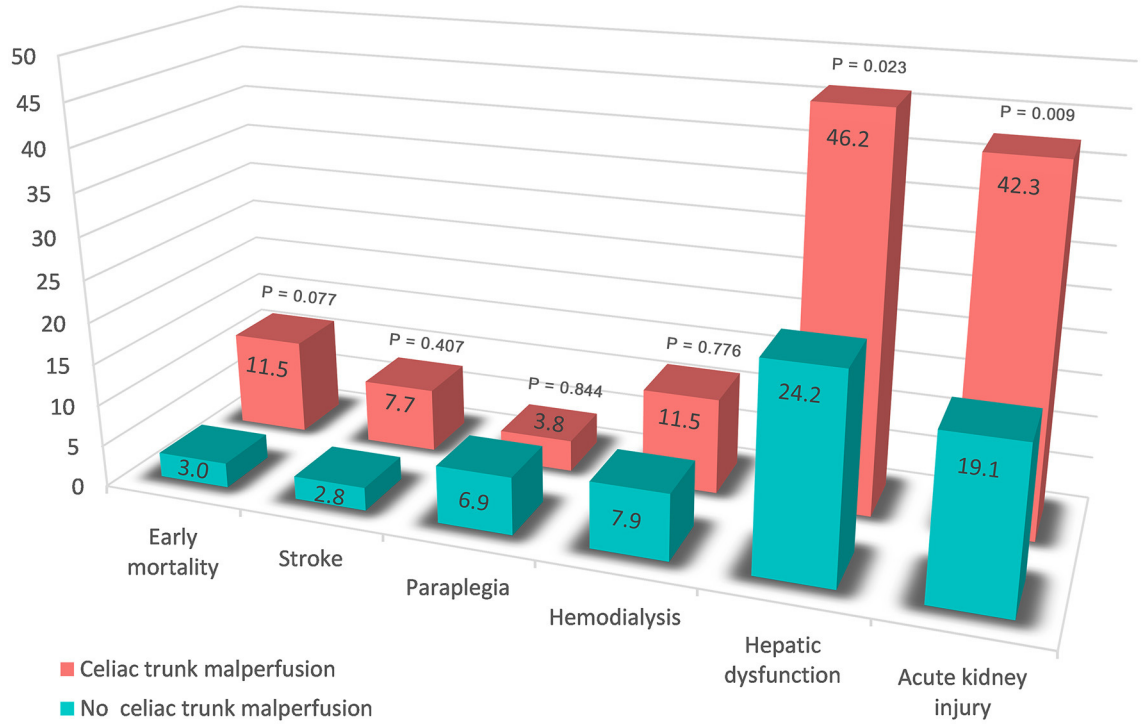

FIGURE 3 | Early outcomes in the patients with and without preoperative celiac trunk malperfusion.

DISCUSSION

In the present cohort, PHD after FET for TAAD was observed in 25.4%, and our analyses demonstrated that PHD was a severe complication associated with increased early mortality and morbidity, but not with late death in midterm survival. Preoperative celiac trunk malperfusion was an independent predictor for PHD but not associated with early mortality and midterm survival. Additionally, PHD was predicted by preoperative aspartate transferase and CPB time, and retrograde perfusion was associated with reduced risk of PHD.

Perioperative mortality in patients with aortic disease was affected by several risk factors, and PHD is one of the major factors for poor postoperative prognosis. The rate of PHD after aortic dissection repair ranged from 1.6 to 60.9% (6, 10, 11), and the differences of cohort design and definitions for hepatic dysfunction resulted in such discrepancy of incidence. While our results are in line with the findings that PHD was associated with early mortality and poor outcomes in overall survival. Also, several adverse events more frequently occurred in the PHD group. We have noticed that patients with PHD were more commonly combined with acute kidney dysfunction and the requirement of new dialysis, and similar results were reported elsewhere (6, 10, 12). The celiac trunk and renal arteries are so close that their hemodynamics might interact if a local dissection occurs. It has been reported that the preoperative renal malperfusion was an independent predictor of postoperative visceral malperfusion, and a mutual relationship might be shown between different types of malperfusion (13). Similarly, malperfusion of downstream branch arteries might suggest a narrowing true lumen combined with poor perfusion for spinal segmental arteries, and more lower extremities malperfusion and longer cross-clamp duration might also explain the higher rate of paraplegia in the PHD group.

Preoperative malperfusion of acute TAAD repair continues to be a predictor of early mortality and worse survival, and preoperative visceral malperfusion was reported to be associated with early PHD (13, 14). Clinical manifestation at presentation of organ malperfusion might lag the laboratory test and angiography imaging demonstration. Elevation of hepatic transferases or bilirubin levels reminded the presentation of preoperative liver disease, which was an independent risk factor of PHD that we found in the present cohort. On the other hand, concern about the increased risk of ischemic organ injury has been attached to dissection involvement and malperfusion in branch arteries, whereas a scarcity of data was found regarding this question. Aortic dissection often involves the arterial branches of downstream organs resulting in insufficient blood supply. Specifically, dissection involvement of the celiac trunk and mesenteric artery might cause visceral ischemia due to hypovolemia with poor collaterals, dynamic occlusion, or embolization. Also, thrombosis from progressive stenosis, such as malperfusion of the lower limb, might lead to various visceral system complications.

Our results supported the above view that celiac trunk malperfusion was associated with PHD. Subgroup analysis also suggested that patients with celiac trunk malperfusion had a trend toward higher early morality rate (**Figure 3**) but not associated with worse midterm survival (**Figure 2B**), which might be related to the reperfusion time of branch vessels after surgery.

Several studies have demonstrated that CPB was associated with liver damage after aortic dissection repair (6, 10, 15). The influence of longer CPB on liver function might come from the following aspects: hypothermia, hypoxia, hemolysis, and inflammatory reaction. It has been reported that 20–25% of the blood volume in liver arteries was decreased during CPB (16), and hence, a prolonged CPB duration can induce a critical reduction of perfusion and liver damage with alterations of hepatic enzymes (17). Meanwhile, longer CPB can lead to more hemolysis, resulting in increased free hemoglobin, acceleration of the immediate release of free cyanide (18), and production of endogenous substances. The subsequent disorders of the coagulation system and inflammatory action weakens the immune response, following the possibility of multi-organ dysfunction (15), especially in the liver, kidney, lung, and other organs. This could be one of the reasons why patients with PHD were more commonly gathered with acute kidney dysfunction and the newly required dialysis in our cohort. Pacini et al. (19) have found that CPB $>$ 180 min was independently related to liver dysfunction after aortic arch surgery, and there was a similar trend of increasing risk of PHD when CPB time exceeded the median value (167 min) in our analysis (**Supplementary Figure S3**).

Interestingly, retrograde perfusion predicted a lower risk of PHD compared with single antegrade perfusion. It has been reported that femoral cannulation, which offers the benefit of time-saving and rapidly instituting, is preferred for hemodynamically unstable patients during aortic disease repair (20). The protection of retrograde perfusion for PHD might be explained by short-distance, adequate, and faster perfusion for visceral arteries retrogradely through femoral access especially for those combined with true lumen narrowing of downstream (21). Otherwise, double arterial cannulation could be effective for both prevention and management of intraoperative malperfusion (8), and whether it played a role in this result needs further study.

Limitation

The present study has certain limitations. Analyses were exploratory in nature, and this study was observational and retrospective, which was subject to selective bias. Our conclusions were limited by its execution as a single institution experience and a relatively small sample of patients. Moreover, PHD after aortic dissection repair did not have a universally accepted definition. Although some researchers used the Model for End-Stage Liver Disease score to estimate liver function, its feasibility and accuracy need to be questioned due to warfarin administration and hemodynamic changes in aortic dissection (10, 22). Besides, the dissection-related information of liver arteries was not ascertained, which might more directly derive the interplay between branch arterial malperfusion and PHD.

CONCLUSIONS

In patients undergoing total arch replacement with FET, PHD was associated with increased early mortality and morbidity, but not with the late death in midterm survival. Higher rates of acute kidney injury and newly required dialysis occurred in the PHD group. Preoperative celiac trunk malperfusion was an independent predictor for PHD but not associated with early mortality and midterm survival. Moreover, PHD was predicted by preoperative aspartate transferase and CPB time, and retrograde perfusion was associated with a reduced risk of PHD.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions. data were not allowed to be made public according to the policy of our institute. Requests to access these datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fuwai Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SL and XS: overall responsibility. SL, YL, and BZ: conception and design. XS: obtained funding and final approval of the article. SL: statistical analysis and writing the article. HG, XQ, and XS: critical revision of the article. SL, YL, BZ, and YD: data collection. SL, BZ, and YD: analysis and interpretation. HG, XQ, and XS: project administration and resources. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.739606/full#supplementary-material

Supplementary Figure 1 | Consolidated Standards of Reporting Trials diagram. PCI, Percutaneous Coronary Intervention; TEVAR, Thoracic Endovascular Aortic Repair.

Supplementary Figure 2 | Kaplan-Meier method estimating midterm survival of patients with and without PHD after excluding patients who died within 30 days.

CI, confidence interval; HR, hazard ratio; PHD, postoperative hepatic dysfunction; SMA, superior mesenteric artery.

Supplementary Figure 3 | Restricted cubic splines visualizing the relationship between cardiopulmonary bypass duration and PHD on the multivariable logistic model (*P* for non-linearity = 0.178). PHD, postoperative hepatic dysfunction.

Appendix E1 | Definition of organ malperfusion.

Supplementary Table 1 | Variables considered in multivariable analyses.

Supplementary Table 2 | Details of the multivariable mixed effect logistic regressions.

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What Is the Long-Term Clinical Efficacy of the Thoraflex™ Hybrid Prosthesis for Aortic Arch Repair?

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Background: The widespread adoption of the frozen elephant trunk (FET) technique for total arch reconstruction (TAR) in aortic arch aneurysm and dissection has led to the development of numerous commercial single-piece FET devices, each with its own unique design features. One such device, Thoraflex™ Hybrid (Terumo Aortic, Glasgow, Scotland), has enjoyed widespread use since its introduction. We present and appraisal of its long-term clinical efficacy, based on international data.

Materials and Methods: Pre-, intra-, and postoperative data associated with Thoraflex™ Hybrid implantations for aortic arch dissection, aneurysm, and penetrating atherosclerotic ulcer (PAU) up to April 2019 was gathered and is presented herein. Follow-up data at discharge, 3-, 6-, 12-, 24-, 36-, 48-, 60-, 72-, and 84- months post-implantation are included.

Results: Data associated with 931 cases of Thoraflex™ Hybrid implantation are included. Mean age at implantation was 63 ± 12 years. 55% of patients included were male. Aortic dissection accounted for 48% ($n = 464$) of cases. Mean cardiopulmonary bypass and circulatory arrest durations were 202 +72 and 69 ± 50 min, respectively. 30-day mortality was 0.6% ($n = 6$), while overall mortality was 14 (1.5%). Freedom from adverse events at 84 months was 95% ($n = 869$). Postoperative complications included neurological deficit, multi-organ failure, cardiorespiratory compromise, and infection.

Discussion: Thoraflex™ Hybrid's unique design is advantageous in comparison to market alternatives. Our data is consistent with that reported in literature and suggests Thoraflex™ Hybrid is associated with favourable rates of mortality and morbidity.

Conclusion: Thoraflex™ Hybrid remains a central player in the aortic arch prosthesis market. Its use it widespread and is associated with favourable design features and clinical outcomes relative to market alternatives.

Keywords: frozen elephant trunk (FET), Thoraflex™, aortic arch, dissection (TAAD), aneurysm

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INTRODUCTION

The surgical management of aortic arch and thoracic aortic diseases is invariably complex, and often associated with high rates of mortality and morbidity. The frozen elephant trunk (FET) technique evolved from the conventional elephant trunk (cET) technique pioneered by Borst et al. and allows for the single-stage repair of the aortic arch and proximal descending thoracic aorta (DTA) (1). The FET technique has enjoyed widespread adoption in part due to its benefits and surgical straightforwardness relative to the cET technique (2). Total arch reconstruction (TAR) with FET has been reported to attenuate the risk of proximal endoleak and stent migration while promoting distal aortic remodelling (3). The stented (or "frozen") distal graft introduced anterograde into the distal arch or proximal DTA, combined with aortic arch revascularisation using a surgical polyester graft, offers a single-stage hybrid approach, eliminating both the need for a second procedure and associated interstage mortality (4). Commercially available FET devices provide a single-piece hybrid prosthesis for total arch reconstruction (TAR), negating the need for off-label implantation of commercial thoracic endovascular aortic repair (TEVAR) grafts antegrade through the aortic arch—a method described as being suboptimal and technically awkward, as well as being associated with stent migration, unstable proximal fixation, and type 1A endoleak (4).

The Thoraflex™ Hybrid prosthesis (Terumo Aortic, Glasgow, Scotland) has enjoyed particularly widespread international use, even prior to gaining FDA breakthrough device approval in April 2020 (5). Its innovative and intuitive design has propelled it to the forefront of the aortic arch device market, alongside other established arch devices such as the E-Vita™ family (CryoLife Inc., Kennesaw, GA, USA), Cronus™ (MicroPort Medical, Shanghai, China), and Frozenix™ (Japan Lifeline, Tokyo, Japan). Recent evidence suggests that Thoraflex Hybrid™ is particularly effective in acute type A aortic dissection (ATAAD), and may be associated with lower rates of postoperative complications than E-Vita™ Open (6).

The emergence of and competition between various prominent aortic arch devices necessitates an evidence-based appreciation of each device's benefits, drawbacks, and associated risks. We seek to review and analyse available evidence to evaluate the overall performance of Thoraflex Hybrid™ on the international level, with a view of facilitating informed clinical decision-making on device choice for TAR with FET. The international long-term clinical efficacy of Thoraflex Hybrid™ is evaluated in terms of design features, pre- intra- and postoperative data, and an evaluation of clinical outcomes, namely: mortality, aortic remodelling, neurological outcomes, coagulopathic complications, end-organ compromise, and reintervention rate. The analysis of outcomes associated with Thoraflex Hybrid™ is contextualised and evaluated against those associated with other aortic arch devices.

MATERIALS AND METHODS

Baseline characteristics, intraoperative metrics, and postoperative follow-up data were gathered from various aortic centres internationally and are collated below. An appraisal of these data provides an appreciation of the international performance of Thoraflex Hybrid™. Our analysis of clinical outcomes is augmented and contextualised in subsequent sections.

RESULTS

Baseline Characteristics

Nine hundred thirty-one patients were implanted with Thoraflex™ Hybrid as of April 2019. The baseline demographics, indications for implantation, and relevant medical history of these 931 individuals are summarised in **Table 1**. Mean age at the time of prosthesis implantation was 63 ± 12 years. 55% (n = 512) of patients treated were male. Male and female patients were on average 59 ± 13 years and 67 ± 9 years old, respectively. Aortic dissection was the predominant indication for aortic repair (n = 464, 48%), of which 158 patients presented with ATAAD (35%) and 79 with acute TBAD (18%). 419 (45%) patients presented with aortic aneurysm, while 48 (5%) presented with penetrating atherosclerotic ulcer (PAU). 41 (4%) patients were known to be comorbid with Marfan syndrome, with an average age of 41 ± 13 years, and the youngest was 23 years old. Patients were predominantly classified as ASA grade III or IV (n = 503, 54%; and n = 205, 22%, respectively).

Intraoperative Data

Intraoperative data on all 931 patients are summarised in **Table 2**. Average CPB, aortic cross-clamp, circulatory arrest, and ACP times were 202 ±7 2, 145 ± 63, 69 ± 50, and 90 ± 44 min, respectively. Thoraflex™ deployment time was on average 3 ± 3 min. The majority of patients (n = 512 [55%]) underwent concomitant procedures, including aortic valve resuspension, coronary artery bypass grafting, and Bentall procedure.

Follow-Up Data

Follow-up data from each centre were obtained. Follow-up points were set at discharge, 3-, 6-, 12-, 24-, 36-, 48-, 60-, 72-, and 84- months post-implantation. **Tables 3–5** summarise post-implantation mortality and complication rates. Overall, 30-day mortality was 0.8% 7 (n = 7), while freedom from adverse events at discharge and at 3, 6, and 12 months was 96% (n = 891), 96% (n = 890), and 95% (n = 887), respectively. 21% (n = 3) of all 14 postoperative mortalities across the 84-month follow-up duration were attributed specifically to the device used for aortic repair (Thoraflex Hybrid™), while 79% (n = 11) other mortalities across the 84-month follow-up period were procedure-related nor not device-related. Freedom from adverse events remained at 94% (n = 869) up to 84 months post-implantation. Analysis of post-implantation complications

TABLE 1 | Summarised baseline demographic characteristics, indications for use of Thoraflex™, and relevant past medical history.

Baseline characteristics, indications, medical history			
	Variable		**Value**
$n = 931$	Age (years)		63 ± 12
	Male		512 (55%)
	Female		419 (45%)
	Height (cm)		172 ± 11
	Weight (kg)		81 ± 15
	ASA grade	I	28 (3%)
		II	130 (14%)
		III	503 (54%)
		IV	205 (22%)
		V	65 (7%)
	Indication		**Value**
$n = 931$	Aneurysm		419 (45%)
	PAU		48 (5%)
	Dissection		464 (50%)
		Acute Type A	158 (35%)
		Acute Type B	79 (18%)
		Acute (unspecified)	28 (6%)
		Chronic Type A	112 (24%)
		Chronic Type B	70 (15%)
		Chronic (unspecified)	19 (4%)
	Pre-existing condition		**Value**
$n = 376$	Previous surgery		179 (19%)
	Aortic valve insufficiency		102 (11%)
	Marfan syndrome		41 (4%)
	Myocardial infarction		20 (2%)
	Cerebral aneurysms		5 (0.5%)
	CVA		5 (0.5%)
	Paresis/Paraplegia		14 (2%)
	TIA		10 (1%)

TABLE 2 | Summary of intraoperative data of all 931 patients implanted with Thoraflex™.

Intraoperative data		
Variable		**Value**
$n = 931$	CPB time (min)	202 ± 72
	AXC time (min)	145 ± 63
	HCA time (min)	69 ± 50
	ACP time (min)	90 ± 44
	Time to deploy Thoraflex™ Hybrid graft (min)	3 ± 3
	Total duration of operation (min)	329 ± 112
	Lowest core temperature (°C)	24 ± 3
	Concomitant surgery (n)	512 (55%)

and overall mortality rates facilitates and evaluation of the international performance of Thoraflex Hybrid™; these are discussed in subsequent sections.

DISCUSSION

Thoraflex™ Hybrid Design Features

The unique design features of Thoraflex Hybrid™ undoubtedly play a central role in influencing its usability and efficacy in aortic stabilisation and long-term positive remodelling. Several key design features of the device set it apart from market alternatives and improve the ease and safety of its deployment in straightforward but also in challenging anatomies.

Conventional TEVAR grafts were not designed for anterograde introduction into the DTA for TAR—hence such an off-label approach is associated with unstable fixation, migration, and endoleak (4). The proximal sewn graft of Thoraflex Hybrid™, combined with the distal anastomosis cuff, eliminates the risk of endoleak, and stent migration. Stable fixation is augmented by the unique nitinol ringed stent—its geometric configuration allows the stent to conform along the curvature of the native arch and proximal DTA, through most anatomical angulations (4).

The plexus of 4 arch branches originating from the market-leading Gelweave woven polyester graft represent a key advantage over devices such as the E-Vita™ family and Cronus™ (7). Three of the four branches facilitate supra-aortic vessel reimplantation during TAR without the need for the island technique. This is especially advantageous in patients with Marfan syndrome, atherosclerotic aortic arch, and in those with a greater distance between the origins of each arch vessel (8). The adjustable length of each arch branch may also simplify challenging LSA anastomoses, and indeed the availability of a fourth branch allows reconfiguration of arch implantation to improve LSA reimplantation (7, 8). Chu et al. notes that preoperative left carotid-LSA bypass or transposition remains an option in especially challenging cases (4).

Furthermore, the inclusion of the fourth arch branch (a feature unique to Thoraflex Hybrid™) allows lower body perfusion to be restored immediately after distal anastomosis. This may greatly reduce the duration for which the viscera, spinal cord, and lower limbs are exposed to circulatory arrest, and thereby mitigate the risk of ischaemic complications (8, 9).

Thoraflex Hybrid™ is available in a wide range of diameters—the proximal graft and distal stented portions may be configured with different diameters with either a 100 or 150 mm stent length (10). This facilitates a greater level of anatomic similarity with the native aorta, and arguably represents the closest option to readily available custom-made FET grafts. Finally, the Thoraflex Hybrid™ graft is impregnated with gelatine to ensure blood-tightness, preventing catastrophic post-implantation graft oozing, or leakage (11).

Mortality

TAR with FET, especially in the acute setting, remains associated with high mortality and morbidity rates (12). This is unsurprising considering the haemodynamic significance and anatomical positioning of the aortic arch and DTA, as well as the surgical and anaesthetic complexity of TAR. As of January 2020, over 30,000 hybrid arch FET prostheses have been implanted, and early mortality has ranged from 1.8 to 17.2% across various

TABLE 3 | Summary of event-free survival rates at pre-set follow-up points.

Freedom from adverse events										
Follow-up point (Months)	**Discharge (*n* = 931)**	**3 (*n* = 925)**	**6 (*n* = 925)**	**12 (*n* = 924)**	**24 (*n* = 924)**	**36 (*n* = 924)**	**48 (*n* = 924)**	**60 (*n* = 924)**	**72 (*n* = 924)**	**84 (*n* = 924)**
Event-free survival n (%)	894 (96%)	891 (96%)	890 (95%)	887 (95%)	886 (95%)	882 (95%)	873 (94%)	869 (94%)	869 (94%)	869 (94%)

TABLE 4 | Summary of 30-day mortality causes.

30-day mortality causes		
Postoperative day	**Cause of death**	**Nature**
0	Multi-organ failure	Procedure related
1	Bleeding, biventricular heart failure	Procedure related
1	Left ventricular dysfunction	Not device related
14	Multi-organ failure	Procedure related
15	Acute Respiratory Distress Syndrome (ARDS)	Procedure related
24	Haemodynamic shock	Procedure related
223	Respiratory failure	Device related
284	Multi-organ failure	Procedure related
316	Bleeding, biventricular heart failure	Procedure related
563	Bleeding, biventricular heart failure	Procedure related
744	Multi-organ failure	Procedure related
812	Respiratory failure	Device related
882	Respiratory failure	Device related
952	Multi-organ failure	Procedure related

commercial and non-commercial device configurations (13). International data on the performance of Thoraflex Hybrid™ in terms of mortality are encouragingly positive. As noted in **Tables 3**, **4**, our series featured a 1.5% ($n = 14$) 30-day mortality rate and a 7-year survival rate of 99% ($n = 924$). It is worth noting that only 3 of all deaths highlighted herein have been attributed to the implanted device; all other deaths and adverse events were procedure-related but not- device related. The causes of mortality following TAR with FET are multi-factorial, and include neurological injury, disease progression, end-organ damage, and intraoperative haemorrhage. This is unsurprising given the invasive and radical nature of TAR, as well as the need for CPB, HCA, and adjunctive cerebral perfusion. The 3 device-related mortalities included herein resulted from postoperative respiratory failure, one of which was secondary to spinal cord injury.

Chu et al., in their retrospective Canadian multi-centre study, reported an overall 30-day and in-hospital mortality rate of 5% for TAR with Thoraflex Hybrid™. 30-day, 12-month, and 24-month survival rates were 95, 95, and 90%, respectively. Their cohort spanned 9 different centres, and included acute dissection, acute rupture, chronic dissection, and aneurysm of the aortic arch and DTA. 30% of cases included were emergent salvage procedures, and all cases were conducted under moderate HCA with ACP (4). More recently, Soknes et al. note that from December 2014—December 2019, 34 patients were treated at their Oslo centre with Thoraflex Hybrid™, with an 8.8% 30-day mortality rate. There were 4 further mortalities during follow up (on average, 32.4 ± 19.4 months). One-year survival was 88%, while 3-year survival was 75%. Notably, all early mortalities in this cohort were attributable to stroke or spinal cord ischaemia (SCI) (14). Further, Shrestha et al. (7) report on the first 100 patients treated with Thoraflex Hybrid™ at their Bologna centre reported a 7% 30-day and in-hospital mortality rate, with acute dissection ($n = 37$) being the predominant indication (chronic dissection: $n = 31$; aortic aneurysm: $n = 31$) (7). Interestingly, Di Bartolomeo et al. reported a 0% mortality rate associated with TAR using Thoraflex Hybrid™ at their Bologna centre, though out of their 10-patient cohort, none were acute cases (15). Reports from various international centres on the performance of Thoraflex Hybrid™ reveal varied results yet are consistent with the present series in highlighting that FET with Thoraflex Hybrid™ is associated with relatively favourable mortality and event-free survival rates, especially over a longer-term tenure across complex patient anatomy treatment.

How does Thoraflex Hybrid™ perform against market competitors? In their multi-centre report on TAR with FET, Berger et al. compared outcomes associated with implantation of Thoraflex Hybrid™ (55 patients, Bad Krozingen, Germany and Salzburg, Austria) and E-Vita™ Open (33 patients, Vienna, Austria) for acute aortic dissection. Their findings demonstrated that Thoraflex Hybrid™ was associated with an 11% in-hospital mortality rate, compared to 12% in E-Vita™ Open (16). Ma et al. note that the in-hospital mortality rates associated with E-Vita™ when implanted for acute dissection, chronic dissection, and aortic aneurysm were 18, 17, and 12%, respectively. In contrast, Thoraflex Hybrid™ was associated with an early mortality rate of 6% at one Hannover centre. Notably, Song et al. reported 0 in-hospital mortalities in 16 patients treated with Cronus™ for ATAAD in Xiamen, China, between February 2018 and August 2019; while Charchyan et al. more recently reported that though the difference in mortality rates between Thoraflex Hybrid™ and E-Vita™ for non-acute DeBakey type I aortic dissection were insignificant, Thoraflex Hybrid™ was associated with improved morbidity rates and freedom from dSINE (17, 18).

Having contextualised the cohort of patients in this international appraisal of performance standards of Thoraflex™ Hybrid for arch repair, it remains clear that the prosthesis is associated with significantly lower rates of mortality relative to market counterparts.

TABLE 5 | Summary of all postoperative adverse events ($n = 59$).

Summary of postoperative adverse events		
Post-operative day	**Adverse event**	**Device related?**
0–30 days postoperative		
0	Respiratory insufficiency	Not device related
0	Percardial effusion	Not device related
0	Bleeding, immediate rethoracotomy, death	Procedure related
0	Paraplegia	Procedure related
0	Bleeding, pericardial tamponade	Procedure related
0	Drainage of haematoma	Procedure related
0	Haematoma	Procedure related
0	Hoarseness	Procedure related
0	Acute on chronic renal failure	Not device related
0	Acute renal failure	Not device related
0	Acute renal failure	Not device related
0	Bleeding	Not device related
1	Multi-organ failure; sepsis; rhabdomyolysis; death	Procedure related
1	Paraplegia	Not device related
1	Paraparesis	Not device related
1	Pneumothorax	Procedure related
1	Bacterial pneumonia	Not device related
1	Left ventricular dysfunction	Not device related
1	Respiratory insufficiency	Not device related
1	Right ventricular failure	Procedure related
1	Radialis nerve paralysis	Procedure related
1	Infection	Not device related
2	Pneumonia	Not device related
2	Infection	Procedure related
2	Bilateral vocal cord paresis	Procedure related
2	Psychiatric distoriation	Not device related
6	Renal failure; Liver failure; haemodynamic instability and shock	Procedure related
7	Recurrent TIAs	Procedure related
7	Occlusion of left subclavian artery with subclavian steal syndrome	Procedure related
8	Infection	Procedure related
9	Atrial Fibrillation	Not Device Related
9	Suspicion of microembolism in lower arm	Procedure related
11	Fever, infection	Procedure related
11	Sternal instability	Not device related
12	Sepsis, Mediastinitis, Pleural empyema	Procedure related
22	Multi-organ failure	Not device related
26	Thoracic and epigastric pain	Not device related
30 days–3 months postoperative		
36	Haemothorax (right side)	Procedure related
41	Hospitalisation because of sternal pain	Not device related
43	Weakness of the left arm	Procedure related
3–6 months postoperative		
150	Endoleak (persistent type Ib)	Not device related
6–12 months postoperative		
248	Hospitalisation because of sternal pain	Not device related
283	Haematothorax (right side)	Procedure related
341	Weakness of the left arm	Procedure related
12–24 months postoperative		
398	Stroke	Procedure related
24–36 months postoperative		
514	Acute on chronic renal failure	Procedure related
889	Hematoma	Procedure related
36–48 months postoperative		
1,118	Paraplegia	Not device related
1,298	Stroke	Not device related
1,319	Recurrent TIAs	Not device related
1,338	Bacterial pneumonia	Not device related
48–60 months postoperative		
1,512	Acute on chronic renal failure	Not device related
1,583	Stroke	Procedure related
1,622	Pneumothorax	Procedure related
1,662	Hematoma	Not device related
1,669	Stroke	Not device related
1,703	Paraplegia	Not device related
1,710	Paraplegia	Not device related
1,771	Recurrent TIAs	Not device related
1,801	Pericardial Effusion	Not device related
60–84 months postoperative		
1,918	Infection	Procedure related
2,024	Stroke	Not device related
2,421	Fever, infection	Procedure related
2,501	Acute renal failure	Not device related

Aortic Remodelling

Aortic remodelling is a key metric by which the success or failure of aortic repair can be gauged: positive remodelling refers to post-FET implantation thrombosis and elimination of the FL, whereas negative remodelling indicates FL or aneurysmal expansion. Remodelling of the aorta post-intervention (open, endovascular, or hybrid) is often quantified in terms of the TL to total aortic diameter ratio, TL to FL diameter ratio, or the presence of FL thrombosis at the level of the stent graft or distal thereto. Aortic remodelling has also been identified as a predictor of yearly aortic growth rates; Fattouch et al. emphasise that patients with persisting FL patency exhibit greater rates of aortic growth than those with FL thrombosis (2.8 ± 0.4 mm vs. 1.1 ± 0.2 mm, respectively) (19). This effect is thought to be especially pronounced around the proximal DTA due to the greater haemodynamic shear stress exerted thereon as a result of its convexity. Indeed, Sakaguchi et al. have identified an aortic

diameter >35 mm as being a risk factor for persistent FL patency (20). Follow-up imaging to determine the extent of postoperative aortic remodelling was unavailable in the present series.

However, Shrestha et al. Hannover group reported a significant increase in both the TL diameter and stable aortic diameter around the Thoraflex Hybrid™ stent graft in all patients with acute aortic dissection included in their study. This effect was noted to have remained stable throughout follow up, and a 100% rate of positive aortic remodelling was achieved within 24 months. TL diameter between the distal end of the Thoraflex Hybrid™ stent and the diaphragm was also improved. Similar results were seen in patients with chronic aortic dissection treated with Thoraflex Hybrid™, wherein a decrease in total aortic diameter—driven by FL obliteration—was observed (7). Yet, Shrestha et al. note that though positive aortic remodelling was evident in patients with thoracic aortic aneurysms, the effect was comparatively less pronounced (7). Similarly, in their recent report on aortic remodelling in 25 patients (8 acute, 13 chronic aortic dissection) treated with Thoraflex Hyrbid™ FET in Birmingham, UK, Mehanna et al. report a promising increase in TL to total aortic diameter ratio during the follow up period, form 0.31 pre-intervention to 0.40 during follow-up ($P = 0.031$). This was accompanied by a decrease in the FL to total aortic diameter ratio during the same period: 0.66–0.54 ($P = 0.024$) (21). No significant difference in aortic remodelling was reported between cases of acute and chronic dissection—suggesting that Thoraflex Hybrid™ is efficacious in inducing positive remodelling regardless of surgical acuity (21).

Interestingly, in their multicentre (in Germany and Austria) comparison of Thoraflex Hybrid™ against E-Vita™ Open, Berger et al. note that patients treated with E-Vita™ Open exhibited more extensive FL thrombosis in the perigraft space relative to Thoraflex Hybrid™ patients (95 vs. 74%, respectively), and that Thoraflex Hybrid™ patients were more likely to require secondary TEVAR ($P = 0.003$) (16). Yet, the authors note that their results are inconsistent with other findings and is likely due to the Thoraflex Hybrid™ grafts used in the study being consistently shorter than the E-Vita™ Open grafts (Thoraflex Hybrid™ and E-Vita™ Open grafts were exclusively used in their 100 and 130 mm configurations, respectively, to attenuate the risk of spinal cord injury) (16). Thoraflex Hybrid™ grafts were also implanted more frequently at Zones 2 and 1 than E-Vita™ Open grafts—proximalising further the distal landing zone ($P < 0.001$). This resulted in shorter coverage of the DTA. Further, at 6 and 12 months post-intervention, FL thrombosis around the coeliac trunk was significantly better in patients treated with Thoraflex Hybrid™ than E-Vita™ Open: 19 vs. 14% and 37 vs. 30%, respectively (16).

A group from Vienna also highlighted that in their series of 27 patients treated for acute thoracic aortic dissection with E-Vita™ Open, FL patency at the level of the diaphragm and coeliac trunk in 52 and 78% of cases, respectively (22). Thoraflex Hybrid™ can therefore be associated with strong rates of positive aortic remodelling, arguably to a greater extent than that other market players. Positive remodelling in patients with Thoraflex Hybrid™ can be augmented by strategic graft sizing, taking proximal anastomosis zone, patient height, and other anatomic factors into account.

In addition to positive and negative remodelling, it is worth considering the risk of in-stent thrombosis associated with Thoraflex Hybrid™. The stent-graft portion of all FET prostheses is designed to seal off any dissection tears within descending aortic intima, however, intraluminal clots causing TL narrowing or downstream malperfusion effect may develop (23). The incidence of in-stent thrombosis is rare irrespective of FET prosthesis used and is sparsely reported in literature. The underlying pathology behind this rare phenomenon has yet to be determined. While reporting their early-to-midterm postoperative results with Frozenix™ deployment at Zone 0 for TAR in patients with ATAAD, Yamamoto et al. highlight that 3 (3%) patients required secondary TEVAR due to TL thrombosis (23). Further, Yoshitake et al. evaluated 426 patients who underwent aortic repair for ATAAD over 11 years. Amongst the patients undergoing FET ($n = 139$), secondary TEVAR was needed in 8 (5.8%) cases due to TL stenosis (24). Finally, Kandola et al. reported only 1 (3%) case of in-stent thrombosis within their population of 36 single-stage FET cases (25). It is crucial to emphasise that there has hitherto been no published evidence suggesting any incidence of in-stent thrombosis following implantation of Thoraflex Hybrid™.

Neurological Complications

Neurological complications are among the most common and debilitating adverse events associated with aortic arch surgery. This is unsurprising given the necessity for intraoperative circulatory arrest, and the propensity for aortic grafts to occlude branches of the DTA that supply the spinal cord. As a result, cerebral (postoperative stroke, transient ischaemic attack [TIA], cognitive deficit, etc.) and spinal cord manifestations (paraplegia, spinal deficit etc.) may result (9). The pathogenesis of aortic surgery-induced neurological injury is varied and complex; attributing neurological complications to the chosen aortic device, cerebral perfusion technique, device sizing, CPB/HCA duration, or device positioning is therefore challenging.

1.9% ($n = 18$) of patients in the present series suffered postoperative neurological injury. One patient who suffered postoperative paraplegia attributed to spinal cord injury subsequently died on postoperative day 23. This case was attributed to the use of Thoraflex Hybrid™. Seventeen further neurological adverse events were reported across the 84-month follow-up period, including paraplegia, paraparesis, recurrent TIA, cerebral infarct, and recurrent laryngeal nerve (RLN) palsy. None of these subsequent events were attributed to the use of Thoraflex Hybrid™, rather, were described as not device related or procedure related.

Di Bartolomeo et al. Bologna group report similarly promising findings in their experience with Thoraflex Hybrid™ implantation for residual type A dissection, chronic type B dissection, and degenerative aortic arch aneurysm (15). Out of 10 patients treated, zero cases of paraplegia, paraparesis, or major neurological deficit were reported. One patient suffered a postoperative TIA. Similar Thoraflex Hybrid™ case series in Hannover and Munich reported postoperative stroke rates of 10

and 5%, respectively. The Munich group also noted that 13% of patients suffered postoperative phrenic nerve injury (8). Shrestha et al. also noted that 7% ($n = 7$) of patients treated with Thoraflex Hybrid™ (7).

In their Canadian multi-centre analysis of early outcomes following Thoraflex Hybrid™ TAR ($n = 40$), Chu et al. report overall stroke and temporary neurological deficit rates of 5 and 3%, respectively. 5% ($n = 2$) patients suffered transient spinal cord ischaemia, and 15% ($n = 6$) suffered postoperative delirium but had returned to baseline prior to discharge. No cases of permanent paraplegia were reported (4). These findings suggest that Thoraflex Hybrid™ may be associated with significantly improved neurological outcomes relative to market counterparts: Leontyev et al. Leipzig group reported a 19.6% rate of new postoperative paraplegia and a 11.8% postoperative stroke rate following TAR with E-Vita™ Open (26). Our extensive international study over 84 months highlights the long term efficacy of Thoraflex™ Hybrid, with very low rates of neurological complications in comparison.

Though it is challenging to attribute the discrepancy in rates of neurological complications to aortic device alone, it is worth noting that Thoraflex Hybrid's™ unique design—which includes a 4th arch branch to enable early lower body perfusion after distal anastomosis—may help to reduce the risk of spinal cord (and end-organ) ischaemia by reducing the duration of HCA needed (8, 9). Indeed, HCA duration (as well as minimum core temperature and stent graft length) have been identified as predictors of SCI risk, and interestingly, Berger et al. multicentre investigation reported at patients implanted with Thoraflex Hybrid™ underwent substantially shorter HCA durations than those treated with E-Vita™ Open (51 min [41–59], vs. 60 min [51–69], $P = 0.007$) (9, 16). Shrestha et al. highlight that their patients implanted with Thoraflex Hybrid™ underwent HCA for a median of 47 min (36–61) (7).

Extent of DTA coverage by the Thoraflex Hybrid™ stent-graft may also be a determinant of SCI risk (27). Decreased occlusion of the intercostal vessels when shorter stent-grafts are used, or proximalisation of arch repair to Zone 1 or 0 may therefore protect against SCI (28). Yamamoto et al. suggest selective LSA perfusion during HCA as a way to improve intraoperative spinal cord perfusion via collateral vasculature to further mitigate this risk (23).

Further, it is thought that rapid FL thrombosis in patients with chronic aortic dissection potentiates SCI due to the tendency for aortic branches to be supplied by the patent FL. Limiting Thoraflex™ Hybrid stent graft length to 100 mm (assuming a Zone 2 or 3 anastomosis), minimum cooling temperatures of 25°C, and preoperative CSF drainage in elective cases may help to attenuate the risk of spinal cord complications (7).

Coagulopathy and Reintervention

Coagulopathic complications refer to adverse events involving (or potentiated by) excessive intra- or postoperative bleeding. Frequently, postoperative bleeding necessitates reintervention—a common feature of the postoperative course in aortic surgery. Unfortunately, this further exposes patients to the risks associated with surgery, anaesthesia, and hospitalisation.

In the present series, there were 10 reports of haemodynamic complications within postoperative day 30, 4 of which resulted in death. There were also 2 reports of haemothorax (days 36 and 283 postoperative), and 1 report of persistent type 1b endoleak (identified on day 150 postoperative); though it is unclear what proportion of these patients required reintervention. The Bologna and Hannover groups reported that 20% ($n = 2$) and 13% of their series required reoperation for bleeding, respectively (8). In contrast, the Munich group reported zero bleeding-related complications (8). Shrestha et al. noted that 10% of their cohort underwent rethoracotomy for bleeding (7).

Kreibich et al. report a 33% reintervention rate post-FET; 69% of which involved TEVAR, 20% required open thoracoabdominal aortic aneurysm repair, and 11% required hybrid reintervention (29). Their study identified aortic diameter enlargement, graft endoleak, and dSINE as the most common indications for reoperation—accounting for 44, 23, and 11% of reinterventions, respectively. They emphasise that dSINE formation is particularly dangerous as its onset is typically asymptomatic but potentiates rapid negative remodelling (29). It is likely that prosthesis sizing plays a key role in potentiating endoleak and dSINE formation. The Canadian group reported a 3% ($n = 1$) reintervention rate for bleeding with Thoraflex Hybrid™, and 2 (5%) cases of post-arch repair formation of TBAD—one of which required secondary TEVAR in addition to medical therapy. The authors argue that both instances of postoperative TBAD would have been avoided with less aggressive sizing strategies (4).

It is worth highlighting 2 cases of spontaneous unexpected Thoraflex Hybrid™ stent-graft leakage reported by Kreibich et al., during second-stage thoracoabdominal aortic repair. Upon clamping of distal stented descending aorta, leakage was noted around the proximal untouched stent-graft. Both cases did not exhibit pre-existing stent-graft leaks on imaging (30). In the first case, re-exploration revealed that the stent-graft had become folded while *in situ*. The authors suggest that their unfolding of the Thoraflex Hybrid™ stent-graft lead to disruption of the newly formed neo-intima and neo-adventitia, disrupting tissue incorporation, and causing leakage (30). In the second case, macropores were noted around the stent graft (which eventually required resection and replacement), which the authors suggest may have been an iatrogenic result of aortic cross-clamping during the second stage (30). It should be emphasised therefore that both reports of Thoraflex™ Hybrid prosthesis leakage were very unlikely to be caused by the prosthesis itself, indeed our international study of 931 patients did not demonstrate a tendency toward graft leakage to any effect.

A recent systematic review by Bashir et al. including 6,313 patients treated with Thoraflex Hybrid™, E-Vita™, Frozenix™, and Cronus™ found that publications detailing coagulopathic events following Thoraflex Hybrid™ and Frozenix™ implantation were associated with the least degree of heterogeneity compared to the 3 market alternatives ($I^2 = 0.01\%$, $I^2 = 53.95\%$, $I^2 = 0.01\%$, and $I^2 = 54.41\%$, respectively) (31). Furthermore, while Thoraflex Hybrid™ has hitherto not been associated with major prosthesis-caused coagulopathic events, several recent reports by Ho et al. and Czerny et al. have revealed

that E-Vita™ Open NEO has a propensity for catastrophic oozing from the arch graft portion (32, 33). This is likely due to a lack of gelatine impregnation, leaving the graft permeable to blood (11). Pre-implantation priming of the graft with BioGlue (CryoLife, Kennesaw, GA, USA) has been suggested as a strategy to mitigate the risk of graft oozing, however, the suitability and safety of this is highly questionable (11, 32).

End-Organ Ischaemia

Systemic complications and end-organ damage are omnipresent risks in almost all major surgical procedures, but these are especially pertinent in aortic arch surgery due to the use of HCA and changes to end-organ blood supply following aortic stenting and remodelling. Indeed, this is reflected by the risk of SCI, cerebral ischaemia, and renal injury associated with aortic arch surgery.

Our series includes a total of 37 reports of postoperative complications including multi-organ failure ($n = 8$), cardiorespiratory complications ($n = 27$), renal injury ($n = 7$), and infection ($n = 13$) over the 84-month follow-up period. None of these reports have been associated directly with the use of Thoraflex™ Hybrid; rather, it is likely that these have resulted from procedure-related or hospital-related factors (especially infection). Cardiac complications from aortic arch surgery are varied—it is likely that the use of cardioplegia, circulatory arrest, anaesthesia, and possible iatrogenic occlusion of the coronary sinus may give rise to cardiac events such as myocardial infarct (MI), ventricular dysfunction, pericardial effusion, and new-onset arrhythmias (e.g., atrial fibrillation [AF]). New-onset arrhythmia was reported in 0.1% ($n = 1$) patient included in our series, ventricular dysfunction in 0.6% ($n = 6$), and pericardial effusion in 0.2% ($n = 2$). A further 0.6% ($0n = 6$) patients suffered respiratory failure. 3% ($n = 1$) patient in the Canadian series suffered a postoperative MI, while 25% ($n = 10$) developed new AF, although the patient cohort is significantly limited (4).

Postoperative renal injury—a common complication of many interventions—tends to result from hypoperfusion of the kidneys due to HCA or renal artery occlusion following stenting or aortic remodelling. A total of 0.7% ($n = 7$). patients included in our series suffered postoperative renal injury. Chu et al. found that 3% ($n = 1$) of patients in the Canadian study also suffered renal failure requiring dialysis, while 14% (n = 14) of patients in Shrestha et al. series suffered acute kidney injury (AKI) requiring dialysis (8 patients were discharged on dialysis) (4, 7). Notably, zero instances of renal injury were reported by the Hannover group, while 2 patients in the Munich study required permanent dialysis (8). One patient from the Bologna group suffered renal injury requiring temporary dialysis (8). In contrast, Leontyev et al. highlight that 25.5% ($n = 13$) suffered renal failure post-implantation of E-Vita™ Open, while Song et al's. report zero instances of AKI following implantation with Cronus™ (18, 26).

Because downstream pathology is not uncommon in patients undergoing TAR with FET, is it crucial that surgeons assess the presence of distal re-entry tears downstream. Surgical planning around the presence of distal re-entry tears may minimise the risk of FL thrombosis-induced end-organ perfusion, especially in cases of chronic TBAD (7). Interestingly, the development of custom-made branched or fenestrated endovascular aneurysm repair (EVAR) grafts may pave the way toward mitigating visceral perfusion in endovascular and open aortic repair.

CONCLUSION

Having appraised the design, reported outcomes, and published literature concerning the international clinical efficacy of Thoraflex Hybrid™ as an FET graft, it is clear that the device is associated with excellent usability, favourable mortality and aortic remodelling rates, as well as relatively low rates of postoperative complications. The risk-benefit profile of Thoraflex Hybrid™ is all the more favourable when viewed in the context of available market alternatives and off-brand FET techniques.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for this study with human participants, in accordance with the local legislation and institutional requirements.

AUTHOR CONTRIBUTIONS

ST, MJ, and MB were involved in the drafting of the manuscript. MB and IM were involved in reviewing and providing feedback on the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Incidence of Distal Stent Graft Induced New Entry vs. Aortic Remodeling Associated With Frozen Elephant Trunk

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Background: The introduction of the frozen elephant trunk (FET) technique for total arch replacement (TAR) has revolutionized the field of aortivascular surgery by allowing hybrid repair of complex aortic pathologies in a single step through combining an open surgical approach with an endovascular one. FET has been associated with favorable aortic remodeling, however, its is also associated with development of distal stent graft induced new entry (dSINE) tears postoperatively. The rate of aortic remodeling and the incidence of dSINE have been linked together, in addition, there seems to be a relationship between these two variables and FET insetion length as well as graft size.

Aims: The scope of this review is to highlight the rate of aortic remodeling as well the incidence of dSINE associated with different FET devices available commercially. This review also aimed to investigate the relationship between aortic remodeling, dSINE, FET insertion length and FET graft size.

Methods: We conducted a comprehensive literature search using multiple electronic databases including PubMed, Ovid, Scopus and Embase in order to collate all research evidence on the above mentioned variables.

Results: Thoraflex^{TM} Hybrid Plexus seems to yield optimum aortic remodeling by promoting maximum false thrombosis as well true lumen expansion. Thoraflex Hybrid^{TM} is also associated with the lowest incidence of dSINE post-FET relative to the other FET devices on the market. Aortic remodeling and dSINE do influence each other and are both linked with FET graft length and size.

Conclusion: The FET technique for TAR shows excellent aortic remodeling but is associated with a considerable risk of dSINE development. However, Thoraflex^{TM} Hybrid

has demonstrated itself to be the superior FET device on the aortic arch prostheses market. Since aortic remodeling, dSINE, FET insertion length and stent graft size are all interconnect, the choice of FET device length and size must be made with great care for optimum results.

Keywords: aortic dissection, aortic aneurysm, aortic surgery, frozen elephant trunk, total arch replacement

INTRODUCTION

The frozen elephant trunk (FET) technique for total arch replacement (TAR) was introduced in 2003 and has been in use to treat a wide range of complex aortic pathologies (1). This marked an evolution from the two-stage elephant trunk (ET) procedure which involved replacing the ascending aorta and arch with a graft, followed by placement of an "elephant trunk" prosthetic that extended into the descending aorta. The conventional ET impeded full aortic remodeling and potentially caused injury to the aortic intima, thus negatively influencing clinical outcomes. Therefore, necessitating a second surgical intervention to either extend the graft or attach it to the relative aortic segment (2). Hence, FET ameliorated the two-stage procedure through innovation and permitted combined open surgical replacement of the aortic arch along with endovascular intervention in the descending aorta during a single operation in hybrid theaters.

The FET procedure has been associated with favorable aortic remodeling outcomes (3, 4). Aortic remodeling, however, has had a multitude of definitions across the literature. Different studies have calculated this significant prognostic tool in varying ways; however, it is essentially a late effect characterized by the occlusion of the primary entry tear site subsequently promoting false lumen thrombosis. This led to a decrease in false lumen (FL) diameter and a re-expansion of the true lumen (TL) (5). It is well-established within the literature that aortic remodeling has proved to be an accurate prognostic tool for patients (6). Additionally, aortic remodeling has been linked to improved survival rates and form an overall good measure of clinical success (7). Failure of false lumen thrombosis has been linked to aneurysm dilatation, rupture of the thoracic aorta, and higher reintervention rates (8).

One of the noted complications of FET is development of distal stent graft induced new entry (dSINE) tears, typically due to the use of endovascular manipulation as well as stent graft and distal TL size mismatch. The choice of FET devices as well as its size and length has shown to be linked with the incidence of dSINE. Evidence in the literature also suggest that there is an inverse relationship between dSINE and the rate of aortic remodeling distally (9).

This review aimed to highlight the incidence of distal stent graft induced new entry (dSINE) as well as the rate of aortic remodeling associated with TAR with FET. Another scope of this review was to assess the efficacy of the Thoraflex^{TM} Hybrid device in achieving optimal remodeling and dSINE outcomes. Finally, we investigated the relationship between aortic remodeling, dSINE, and FET graft length and size.

AORTIC REMODELING

The revolutionary FET procedure is well-established in the literature with excellent aortic remodeling, including favorable FL thrombosis rates and significant positive changes in TL and FL diameters (3, 4). A 2019 study on total arch replacement reported that using the FET technique proved to have a high rate of TL expansion and FL thrombosis at the level of bronchial carina, in addition to the descending aorta. It was also thought that FET reduced the sequalae of vascular complications resulting from failed aortic remodeling (3). These results are also not expected to differ between acute and chronic aortic dissection presentations (10). In a meta-analyis that included 1,279 patients, FL thrombosis was achieved in 96.8% of patients (95% CI, 90.7–98.9%) (11). Similarly, these findings were supported in a review by Di Bartolomeo et al. (12), where complete or partial FL thrombosis was expected in 90% of patients. This figure is incomparable to conservative management, wherein FL thrombosis occurred in between 33.3 and 77.8% of patients (12). Unfortunately, these promising results have not been seen to the same extent at the level of the abdominal aorta and further management has been recommended for this subset (10).

The Thoraflex^{TM} Hybrid Plexus (THP^{TM}) (Terumo Aortic, Inchinnan, Scotland, UK) device has been designed with a special interrupted pattern, which is thought to protect the aortic wall from the substantial forces of blood flow to achieve excellent aortic remodeling (13). Mehanna et al. (13), who investigated aortic remodeling following FET with THP^{TM}, carried out Spearman rank correlation tests to assess the correlation of their results. Aortic remodeling ratios, prior to and following the procedure, had a moderately positive correlation. This was calculated as 0.566 and 0.582 for TL expansion and FL diameter decrease, respectively, with p values of 0.006 and 0.004, respectively, indicating strong statistical significance. A significant expansion of the TL ratio was seen using Thoraflex^{TM} Hybrid post-operatively, with a median increase from 0.31 to 0.4 mm ($p = 0.042$). This trend matched the significant FL ratio decrease from 0.66 to 0.54 mm ($p = 0.02$). The study included a total on 20 patients out of whom 8 were acute and 12 were chronic, with no significant difference found when comparing aortic remodeling in both groups ($p = 0.26$). The authors stressed that Thoraflex^{TM} Hybrid is the optimal FET device as it is the safest to use due to its interrupted pattern as mentioned earlier (13).

In the previous studies described, the authors used a Computed Tomography (CT) scan to assess the aortic remodeling diameters. In a 2021 study by Usai et al. (14), volume measurements were used instead to overcome the 2D

view limitations of CT images, allowing the authors to gauge a more accurate measure of lumen patency using the Thoraflex™ Hybrid device. Here, surfaces and volumes were measured using CT angiography prior to and following FET, in addition to 12- and 24-month follow-up. The mean true lumen (in cm^3) prior to the FET was 77.03 cm^3 ($\pm$ 47.96 cm^3). At discharge, this mean increased by 10.96 cm^3. This growth was sustained and the TL measurements 12 and 24 months after were 113.83 and 133.84 cm^3, respectively. This long-term analysis of TL volumetric expansion evidenced a statistically significant growth even after 2 years of the FET procedure ($p = 0.047$). Similarly, the mean FL measurement was 158.33 cm^3 ($\pm$ 68.24 cm^3), 167.56 cm^3 ($\pm$ 90.24 cm^3), 164.36 cm^3 ($\pm$ 59.72 cm^3) and 157.20 cm^3 ($\pm$ 78.0 cm^3) prior to the procedure, following and at 12-month and 24-month follow-up (14). These long-term outcomes seem to be congruent a previous 2018 study, where chronic dissection patients showed significant TL expansion (15 $\pm$ 17 mm to 28 $\pm$ 2 mm) ($p = 0.001$) and FL diameter drop (40 $\pm$ 11 mm to 32 $\pm$ 17 mm) ($p = 0.026$) 2 years following the procedure (15). Additionally, Usai et al. (14) confirmed that in their study almost all Thoraflex Hybrid™ patients had significant TL expansion and reported only 1 patient required reintervention, due to a FL aneurysm. Furthermore, the authors also noted that the most significant growth in the surface TL measurement was at the level of the diaphragm ($p = 0.00193$) (14).

There appears to be some controversy in the literature regarding the impact of presentation on the aortic remodeling following FET procedures. It was initially expected that there is no difference between acute and chronic dissections, however, in a study involving 100 patients who had Thoraflex Hybrid™ implanted, FL thrombosis was achieved at a much more accelerated pace in acute, rather than chronic dissection patients. Despite this, full FL thrombosis was achieved in 100% of patients within 24 months at the proximal segment of the aorta. Additionally, as expected, distal segments of the aorta had less successful rates (16). An international multicentre registry which used E-Vita in 137 patients (65 acute and 72 chronic) also confirmed that acute dissections are associated with greater aortic remodeling rates (10). When comparing the FL thrombosis rates in both studies together, Thoraflex™ Hybrid came out on top with improved results.

As reported by Shrestha et al. (17), the 100% rate of FL thrombosis achieved using Thoraflex™ shows its superiority to other devices as seen by the 82.1% and 89.4% rates reported by Kobayashi et al. (16) and Chen et al. (18), respectively. Yet it is important to take into consideration the differences amongst these 3 independent studies. Kobayashi et al. (16) carried out a simplified FET technique in 34 patients with complicated acute type A aortic dissections. The "simplified" approach involves using gelatine-resorcinol adhesive to attach the dissected aortic arch wall layers, followed by an antegrade open arch approach to deploy the aortic stent-graft into the arch or proximal descending aorta. Post-operatively, only 82.1% of patients had FL thrombosis seen in the aortic arch using the TAG, Talent and E-Vita stent-grafts (16). On the other hand, Chen et al. (18) reported complete FL thrombosis in 89.4% of patients around the triple-branched stent-graft, created by Yuhengjia Science and Technology. In this study, 122 patients underwent total arch replacement for acute type A aortic dissection, with open placement of this triple-branched stent graft (18). Similarly, in a study involving 41 acute type A dissection patients who underwent TAR with FET using E-Vita, a FL thrombosis rate of 93.9% at the pulmonary trunk level was achieved (19). The above evidence shows beyond doubt that Thoraflex Hybrid™ offers the highest rate of FL thrombosis.

The Thoraflex™ Hybrid Plexus has also demonstrated TL expansion not only at the level of pulmonary bifurcation (covered by the stent), but also at the distal descending aorta, with complete FL thrombosis in 73.1% of cases at the former site (20). Similar to other findings in the literature, there was a small, albeit significant, expansion of aortic diameter at the level of the abdominal aorta. Further benefit yielded Terumo Aortic's Thoraflex™ Hybrid was highlighted in a study by Fiorentino et al. (20), where pre-planned second-stage procedures were prevented in 18.2% of patients due to the promising aortic remodeling rates. Additionally, when comparing Thoraflex™ Hybrid to other devices, the need for endoprosthetic extensions due to incomplete FL thrombosis was less by 6% with the Thoraflex™ Hybrid in comparison with the E-Vita HP (21).

In a more detailed study on aortic remodeling after FET with Thoraflex Hybrid™ for acute ($n = 31$) and chronic dissections ($n = 34$) at the stent, thoracoabdominal transition and coeliac trunk levels, significant TL and FL changes were noted (15). A summary of the findings showing the favorable aortic remodeling associated with Thoraflex Hybrid™ is illustrated in **Tables 1**, **2**.

The same aforementioned international multicentre registry which used E-Vita in 137 patients (65 acute and 72 chronic) also measured TL diameter preoperatively and at follow-up, which had a median of 32 months (21–53 months) (10). A summary of the results can be found in **Table 3**. Additionally, in a different study using the Cronus device, authors reported no change in TL diameter at the level of the aortic arch (22). Comparing the results from the three devices, Thoraflex Hybrid™ clearly yields the optimum aortic remodeling.

Variations of reported aortic remodeling data in the literature could be attributed to multiple factors. For instance, differences in results could be a result of the varying pathologies that the FET procedure is used to treat, in addition to the heterogenous population included in these studies. Such variance in demographics and comorbidities, such as advanced age, can have a negative prognostic effect on the procedure outcomes (14). It is also important to note that there was an evident lack of large cohort, multicentre trials and comparative studies involving the Thoraflex Hybrid™ device and further studies must take place to evidence the promising results of this novice tool. **Table 4** Summarizes all the findings in Distal Stent Induced New Entry.

DISTAL STENT INDUCED NEW ENTRY

As mentioned earlier, dSINE is a serious complication associated with FET where a new intimal entry tear develops distally due to the stent graft portion of the FET HP. Untreated dSINE has showed a mortality rate of up to 25% following endovascular aortic intervention (9, 25). The distal landing zone of the

TABLE 1 | Summary of TL diameter results from Berger et al. (Thoraflex Hybrid) (15).

Aortic Level	Dissection	FL Diameter (mm)				
		Preoperatively	6 months	12 months	24 months	36 months
L1	Acute	23 ± 11	16 ± 10 ($p = 0.14$)	14 ± 8 ($p = 0.16$)	8 ± 3 ($p = 0.019$)	4 ± 2 ($p = 0.53$)
	Chronic	40 ± 11	29 ± 13 ($p < 0.001$)	32 ± 17 ($p = 0.004$)	32 ± 16 ($p = 0.026$)	24 ± 13 ($p = 0.003$)
L2	Acute	20 ± 11	20 ± 11 ($p = 0.61$)	18 ± 12 ($p = 0.97$)	13 ± 7 ($p = 0.22$)	12 ± 12 ($p = 0.50$)
	Chronic	29 ± 11	26 ± 12 ($p = 0.03$)	28 ± 13 ($p = 0.062$)	24 ± 7 ($p = 0.001$)	14 ± 11 ($p = 0.059$)
L3	Acute	15 ± 12	11 ± 11 ($p = 0.35$)	11 ± 9 ($p = 0.69$)	12 ± 10 ($p = 0.11$)	11 ± 11 ($p = 0.50$)
	Chronic	21 ± 9	22 ± 9 ($p = 0.89$)	22 ± 9 ($p = 0.53$)	27 ± 3 ($p = 0.79$)	15 ± 11 ($p = 0.24$)

L1, segment at the stent level; L2, segment at the thoracoabdominal transition; L3, segment at the coeliac trunk.

TABLE 2 | Summary of FL diameter results from Berger et al. (Thoraflex Hybrid) (15).

Aortic Level	Dissection	TL Diameter (mm)				
		Preoperatively	6 months	12 months	24 months	36 months
L1	Acute	23 ± 12	28 ± 6 ($p = 0.88$)	28 ± 4 ($p = 0.83$)	27 ± 2 ($p = 0.058$)	27 ± 0 ($p = 0.56$)
	Chronic	15 ± 7	24 ± 6 ($p < 0.001$)	25 ± 5 ($p = 0.002$)	28 ± 2 ($p = 0.001$)	29 ± 2 ($p = 0.063$)
L2	Acute	17 ± 13	26 ± 11 ($p = 0.22$)	25 ± 7 ($p = 0.60$)	24 ± 10 ($p = 0.097$)	22 ± 8 ($p = 0.21$)
	Chronic	15 ± 8	18 ± 9 ($p = 0.003$)	22 ± 8 ($p = 0.001$)	27 ± 3 ($p = 0.001$)	28 ± 2 ($p = 0.008$)
L3	Acute	17 ± 11	21 ± 10 ($p = 0.023$)	20 ± 8 ($p = 0.75$)	18 ± 9 ($p = 0.049$)	17 ± 12 ($p = 0.80$)
	Chronic	14 ± 8	15 ± 5 ($p = 0.035$)	17 ± 7 ($p = 0.069$)	15 ± 6 ($p = 0.27$)	18 ± 8 ($p = 0.47$)

L1, segment at the stent level; L2, segment at the thoracoabdominal transition; L3, segment at the coeliac trunk.

TABLE 3 | Summary of TL diameter results from Iafrancesco et al. (E-Vita) (10).

Aortic Level	Dissection	TL Diameter (mm)		
		Preoperatively	Follow-up	*p*-value
L1	Acute	26 (20–30)	28 (25–30)	0.009
	Chronic	29 (25–33)	30 (26–32)	0.448
L2	Acute	25 (20–30)	27 (24–30)	<0.001
	Chronic	25 (21–30)	27 (25–30)	0.082
L3	Acute	24 (19–28)	26 (22–29)	0.002
	Chronic	25 (21–28)	26 (24–29)	<0.001
L4	Acute	22 (17–26)	24 (19–27)	0.014
	Chronic	26 (22–29)	25 (22–29)	0.261

L1, stent graft level; L2, just below the end of the stent graft; L3, 10th thoracic vertebra level; L4, coeliac artery level.

stent is often located in the diseased zone of the aorta, as a result, the stent graft portion of the FET device can induce injury to the intima of the aorta due to the fragile and mobile dissection membranes mismatching with a stiff stent graft (26, 27). dSINE necessitates secondary intervention which negates the benefit of FET being a 1-stage process. Nevertheless, secondary endovascular reintervention has shown to have excellent clinical outcome (25). Therefore, oversizing the FET graft is strongly suggested to increase the risk of dSINE forming, however, this has been challenged (25, 27, 28). This relationship between dSINE occurrence and the size of the graft will be discussed further on in this review. As will also be discussed later in this review, formation of dSINE perfuses the FL and can lead to a new patent FL, which significantly impede positive aortic remodeling (26, 29, 30).

The incidence of dSINE for any device is varied between different studies using the same device, this is likely to be associated with the difference in the study design, population (baseline morbidity), and surgical technique or device size and length used. For example, the incidence of dSINE reported in the studies identified ranged from 0 to 14.5% with Thoraflex Hybrid™, 1–18.2% with E-Vita, and 0–27.3% with Frozenix™. The size and length of device used are interconnected with the incidence of dSINE (9, 20, 24, 25, 31–37). A summary of all the dSINE findings to-be discussed in this section can be found in **Table 5**.

Terumo Aortic's Thoraflex™ Hybrid is an excellent FET device with very favorable survival outcomes that are to some extent superior to those offered by other commercially available devices. The incidence of dSINE with Thoraflex Hybrid™ can be considered the lowest within the aortic arch prostheses market as demonstrated above (9, 20, 24, 25, 31–37).

One of the many studies that reported a relatively low incidence of dSINE is Kreibich et al. (26), with 12.7% of patients developing dSINEs 27 months following FET with Thoraflex Hybrid™. Other than the aforementioned fact that the dSINE group of patients had smaller true lumen diameters at the level of the stent graft (L1; $p = 0.251$) and the level of thoracoabdominal transition (L2; $p = 0.44$), there was no difference in type of dissection or clinical characteristics between patients that did and did not develop dSINE. Another study by the same authors

TABLE 4 | Summary of studies included in Distal Stent Induced New Entry and their aortic remodeling data reported.

References	Year	Cohort	Acute/Chronic	HP(s) Used	Stent Size	Outcomes			
						TL Diameter	**FL Diameter**	**FL thrombosis**	**Other findings**
Mehanna et al. (13)	2021	22	8 acute 14 chronic	Thoraflex	Median Stent outer diameter was 28 mm (24–40 mm) and length was 125 mm (100–150 mm).	Significant increase in the TL: total aortic diameter ratio ($P = 0.031$), with a median increase from 0.31 to 0.4 mm.	Significant decrease in the FL: total aortic diameter ratio ($P = 0.024$), with a median drop from 0.66 to 0.54 mm.	N/A	No significant changes in aortic remodeling between acute and chronic ($p = 0.26$).
Usai et al. (14)	2021	20	Not specified	Thoraflex	Not specified	Mean TL (in cm^3): **Pre-operatively**: 77.03, SD 47.96 **At discharge**: 87.99, SD 33.98 **12-months**: 113.83, SD 37.33 **24-months**: 133.84, SD 28.10 ($p = 0.04$)	Mean FL (in cm^3): **Pre-operatively:** 158.33, SD 68.24 **At discharge:** 167.56, SD 90.24 **12-months:** 164.36, SD 59.72 **24-months:** 157.20, SD 78.0	N/A	The most significant growth in the surface TL measurement was at the level of the diaphragm ($p = 0.00193$).
Berger et al. (15)	2018	65	Acute (A): 31 Chronic (C): 34	Thoraflex	**Length:** 100 mm	**At the stent level:** C: from 15 ± 7 mm to 28 ± 2 mm after 24 months ($p = 0.001$). A: from 23 ± 11 mm to 8 ± 3 mm ($p = 0.019$) **At thoracoabdominal transition**: C: from 15 ± 8 mm to 28 ± 2 mm after 36 months ($p = 0.008$) A: from 17 ± 13 mm to 23 ± 8 mm ($p = 0.01$) postoperatively **At the coeliac trunk** (after 6 months): C: from 14 ± 8 mm to 15 ± 5 mm ($p = 0.035$) A: 17 ± 11 mm to 21 ± 10 mm ($p = 0.023$)	**At the stent level:** C: from 40 ± 11 mm to 24 ± 13 mm after 36 months ($p = 0.003$) **At thoracoabdominal transition**: C: 29 ± 11 mm to 24 ± 7 mm after 24 months ($p = 0.001$) **At the coeliac trunk**: A: 15 ± 12 mm to 11 ± 9 mm ($p = 0.001$) postoperatively.	N/A	N/A
Fiorentino et al. (20)	2021	28	Chronic: 28	Thoraflex	The **proximal graft diameter**: between 26 and 30 mm. The **distal stent graft diameter** between 28 and 40 mm. **Length**: 150 mm in 19 cases (67.9%), and 100 mm in 9 patients (32.1%).	Mean **proximal descending aorta**: increased from 13.0 (±6.4) to 23.4 (±7.8) ($p < 0.001$) **Distal descending aorta**: from 12.1 (±4.7) to 19.1 (±9.8) ($p = 0.009$) **Abdominal aorta**: from 10.8 (±2.9) to 11.5 (±3.1).	Mean **proximal descending aorta**: decreased from 37.2 (±12.2) to 27.1 (±16.7) ($p = 0.012$) **Distal descending aorta**: from 32.7 (±13.9) to 25.5 (±13.0) ($p = 0.042$) **Abdominal aorta**: from 17.2 (±5.9) to 17.8 (±5.6).	**Proximal descending aorta**: partial in 3 patients (11.5%) and complete thrombosis in 19 (73.1%). **Distal descending aorta:** 3 partial (12.5%) and complete thrombosis in 10 (41.7%). **Abdominal aorta**: partial in 1 (4.2%).	N/A

(Continued)

TABLE 4 | Continued

References	Year	Cohort	Acute/Chronic	HP(s) Used	Stent Size	Outcomes			
						TL Diameter	FL Diameter	FL thrombosis	Other findings
Di Marco et al. (21)	2020	318	Acute: 119 Chronic: 25 Other indications: 174	E-Vita (173) Thoraflex (145)	**Not specified**		N/A		Endoprosthetic extensions were performed (often for incomplete FL thrombosis) in: E-Vita: 45 patients Thoraflex: 40 patients
Shrestha et al. (17)	2016	100	Acute: 37 Chronic: 31 Aneurysms: 32	Thoraflex	**Diameter** of stented portion: 26- 40 mm. The **length** of the stented part was either 100 or 150 mm.		N/A	100% achieved within 24 months.	FL thrombosis occurred much more quickly in acute, in contrast to chronic dissections.
Kobayashi et al. (16)	2016	34	Acute: 34	TAG: 6 Talent: 5 E-Vita: 23	**Mean diameters**: TAG: 34.5 ± 3.5 mm Talent: 34.2 ± 1.6 mm E-Vita: 32.4 ± 2.9 mm	Overall diameter of the aortic arch significantly reduced ($p < 0.05$).	Distal to the aortic stent, 30% (7/34) patients showed significant FL diameter decrease.	82.1% (23/34) at the aortic arch.	N/A
Chen et al. (18)	2013	122	Acute: 122	Triple-branched stent graft (Yuhengjia Science and Technology, Corp, Ltd, Beijing, China)	**Length**: 145 mm **Proximal diameter**: 30 or 32 mm **Distal diameter**: 26 or 28 mm		N/A	89.4% (101/113) at the stent level, 3-months follow-up.	N/A
Akbulut et al. (19)	2019	41	Acute: 41	E-Vita	**Not specified**	Aortic diameters increased from pre-operatively (37.4 ± 8.9) to postoperative (31.8 ± 4.9, $p < 0.001$) aortic diameters. The mean difference between the two groups was 5.60 mm (95% confidence interval [8.10–3.09])	N/A	93.9% at the pulmonary trunk level.	N/A
Iafrancesco et al. (10)	2017	137	Acute: 65 Chronic: 72	E-Vita	**Median [interquartile range] diameter:** 28 mm [24–30 mm].	Please refer to **Table 3**			
Song et al. (22)	2020	16	Acute: 16	Cronus	**Length:** 100–150 mm	Please refer to Figures in original article			
Panfilov et al. (23)	2021	44	Not specified	E-Vita	**Diameter:** 24–30 mm **Length:** 150 mm		N/A	Zone 2: 60% Zone 3: 77% ($p = 0.046$).	Reintervention rate: Zone 2:25.9% Zone 3: 8.3%
Berger et al. (24)	2019	88	Acute: 88	Thoraflex E-Vita	FET length: Thoraflex: 100 mm E-Vita: 130 mm		N/A	Thoraflex: 74% at 1-year follow-up	N/A

TABLE 5 | Summary of results in Is Aortic Remodeling Correlated With dSINE?

Study	Year	FET Cohort	FET Device	dSINE
Kreibich et al. (9)	2020	126	Thoraflex™	13%
Charchyan et al. (32)	2021	20	Thoraflex™ ($n = 3$)	13%
			E-Vita™ ($n = 13$)	4.5%
			Valiant™ ($n = 4$)	23.5%
Tsagakis et al. (33)	2018	286	E-Vita™	1%
Berger et al. (24)	2019	88	Thoraflex™ ($n = 55$)	14.5%
			E-Vita™ ($n = 33$)	18.2%
Fiorentino et al. (20)	2020	28	Thoraflex™	7.10%
Hirano et al. (34)	2019	76	Frozenix™	4.00%
Yoshitake et al. (35)	2020	139	Custom-made Frozenix™	0.72%
Iino et al. (36)	2020	50	Frozenix™ and Gelweave™ combination	0%
Yamane et al. (37)	2020	15	Frozenix™	27.30%
Nomura et al. (25)	2021	70	Frozenix™	12.90%
Furutachi et al. (31)	2019	19	Frozenix™	15.80%

(26) showed the safety, efficacy and consistency of THP™ by reporting a dSINE rate of 11.4%.

Charchyan et al. (32) compared the rate of dSINE in different operative stent devices. Group one was treated with distal Z shaped nitinol stent grafts (E-Vita), group two was treated with ring shaped nitinol stent graft (Thoraflex™ Hybrid) and group three used distal dissection-specific stent grafts (Valiant™ retrograde stent graft, Medtronic Vascular, Santa Rosa, CA, USA). Upon univariate and multivariate risk factor analysis, the study determined two statistically significant predictors of developing dSINE, which included connective tissue disorder and stent graft diameter. Univariate risk factor analysis of connective tissue disorder being associated with developing dSINE was derived to have a hazard ratio of 4.02 (95% CI, 0.89–18.27; $p = 0.072$). Moreover, multivariate analysis showed connective tissue disorder to have a hazard ratio of 5.62 (95% CI, 0.68–46.59; $p = 0.110$). Univariate risk factor analysis of the association of stent graft diameter with developing dSINE showed to have a hazard ratio of 1.36 (95%CI,1.08–1.71; $p = 0.009$). Furthermore, multivariate analysis derived a hazard ratio of 1.37 (95% CI, 1.02–1.83; $p = 0.034$). This study is helpful as it provides significant evidence supporting the numerical trends suggested by Kreibich et al. (9). Charchyan et al. (32) also suggested using a dissection specific stent graft with a tapered structure thus preventing oversizing at the distal edge or using a longer stent graft to minise the occurrence of dSINE.

This study proved that with the E-Vita Z-shaped nitinol stent grafts, dSINE occurrence was significantly higher than the Thoraflex Hybrid™ ring shaped nitinol stent graft. In the E-Vita group, 13% of patients developed dSINE whereas in the Thoraflex Hybrid™ group this was only 4.5%, which was significantly less ($p = 0.043$, Cramer's V = 0.24). The mean follow up time was 16 months and 14.5 months respectively for group one and two. This study contradicts Kreibich et al. (9) study, as it provides a direct comparison between devices and confirms Thoraflex Hybrid™ superiority over E-Vita (32). Only one study looking at E-Vita Open device reported a relatively low dSINE occurrence of 1% of a patient population of 286. However other complications such as endoleak occurred in 5% of patients which is more than any study investigating Thoraflex™ Hybrid (33).

Berger et al. (24) also directly compared Thoraflex™ and E-Vita Open and further proved Thoraflex Hybrid's more favorable results as 14.5% of patients in the Thoraflex Hybrid™ developed dSINE post-FET relative to 18.2% with E-Vita Open ($P = 0.19$). To extend this claim, a dSINE rate of 7.1% was reported by Fiorentino et al. (20) in their study which used Thoraflex Hybrid™ in 28 patients with chronic dissections/post-dissection aneurysms.

Custom-made graft and J Graft Open Stent Graft (Frozenix™) studies have reported relatively positive dSINE results, however, these are widely varied between studies. Hirano et al. (34) reported that dSINE occurred in 4% of J Graft Open Stent Graft patients. Again, a replicated study found that dSINE occurred in only 1 patient (0.72%) with the J Graft Open Stent graft which required TEVAR reintervention (35). Interestingly, none of the patients 50 in Iino et al. (36) suffered from dSINE post-FET. However, the authors here used the Frozenix graft in combination with the Gelweave™ graft (Terumo Aortic, Scotland, UK). This shows the extent of the positive affect induced by the Terumo Aortic line of aortic arch prostheses (36). On the other hand, Yamane et al. (37) also used Frozenix™ HP alone in 11 patients out of whom 3 developed dSINE (27.3%). Another study reported 9 cases of dSINE amongst 70 patients receiving Frozenix™ HP (12.9%). All 9 patients underwent successful reintervention with TEVAR (25). Finally, Furutachi et al. (31) reported a dSINE rate of 15.8% amongst their Frozenix™ FET group. Spring back force from the stent graft has been established to be one of the underlying mechanisms for dSINE, causing injury to aortic intimal when the spring force straightens its configuration (27). Furutachi et al. (31) also stated that the Frozenix™ graft is said to exert a strong spring back force on the aortic wall which increases the risk of dSINE developing. On the contrary, the Thoraflex Hybrid™ design has been shown to actually reduce the stress on the aortic wall (38).

Very surprisingly, despite a comprehensive and thorough literature search using multiple databases, no evidence on dSINE directly associated with Cronus™ could be identified. Tan et al. (39) is the only FET study identified which used Cronus™ and reported on untreated entry tears (63.6%), however, these were distal to the stent graft itself therefore not directly induced by it. It is worth noting that Cronus™ is geographically confined mainly to China, hence why there is little to no data on it making it difficult to draw a definitive conclusion on its effectiveness regarding dSINE (38).

If dSINE is diagnosed, the initial management involves optimizing blood pressure. If the false lumen continues to grow larger in diameter, pseudoaneurysm formation, malperfusion or development of symptoms occur then secondary endovascular reintervention with TEVAR is necessary. The artery of Adamkiewicz is identified in the preoperative CT and preserved to the best ability to prevent the risk of paraplegia. Secondary

reintervention with TEVAR for dSINE has been reported to achieve excellent results (25, 40).

Several preventive procedures can be undertaken to prevent the development of dSINE, firstly endografts with tapered configuration can potentially be used to prevent excessive oversizing. This tapering effect in diameter and area comprises of using a small stent graft distally and a larger stent graft proximally (38). In TEVAR, Hsu et al. (41) demonstrated dSINE occurrence decreased from 34.7 to 8.3% using this endografting technique. This was also supported by Janosi et al. (42), who also demonstrated the effectiveness of this TEVAR technique in reducing the incidence of dSINE. Janosi et al. (42) found that patients who developed dSINE showed a significantly higher taper ratio of the true lumen of the aorta (40.9 ± 14.13% vs. 25.36 ± 20.2%, $p < 0.05$). The same principle applies in FET as proven by Ma et al. (38), who described tapered stent grafts as the "ideal" ones. In fact, this same fascinating review indicated that Thoraflex™ Hybrid is the only FET HP available commercially with a different proximal and distal diameter of its stent graft portion. Unlike other FET devices, Thoraflex™ Hybrid is unique in that is has a wide and versatile portfolio with varying combinations of stent-graft diameters as well as stent graft lengths. In addition, as aforementioned its interrupted pattern projects minimal radial forces on the diseased aortic wall relative to the other aortic arch hybrid prostheses, confirming Thoraflex Hybrid™ to be the optimal FET device choice for TAR (13, 38). It is essential to correctly choose the FET graft size after careful TL measurement, to avoid aortic remodeling mismatch in the distal transition zone between the stent-covered aorta and non-stent-covered aorta, thereby minimizing the risk of dSINE developing and maximizing the rate of aortic remodeling.

IS AORTIC REMODELING CORRELATED WITH dSINE?

The culmination of the process of aortic remodeling is marked by the complete thrombosis and elimination of the FL with the normalization of the TL diameter. This achieved by the action of the stent graft portion of the hybrid prosthesis (HP) sealing off any entry tears and cutting the perfusion to the FL (29, 30). Developing dSINE means the FL remains perfused and patent, thereby negatively influencing aortic remodeling, this concept has been discussed in several studies (29, 30). Nomura et al. (25) stated that all patients who developed dSINE also developed enlargement of the thoracic aortic diameter, including the FL, whereas thoracic aortic remodeling did not occur. This is significantly incomparable with the 57.3% thoracic aortic remodeling rate in the non-dSINE group ($p = 0.0013$). Furthermore, a Russian single-center study (32) reported that 11% of their FET patient population who experienced dSINE also showed negative aortic remodeling which necessitated reintervention with thoracic endovascular aortic repair (TEVAR). In addition, Wada et al. (27) stated that the non-stent-covered aorta is unlikely to undergo sufficient remodeling due to the expansion of the FL and the pulsatile wall stress in the FL, both caused by dSINE. Another study which showed an identical trend is Kreibich et al. (9), which found that patients who developed dSINE showed to have smaller true lumen diameters at the level of the stent graft (L1; $p = 0.251$) and the level of thoracoabdominal transition (L2; $p = 0.44$). To further prove the relationship between dSINE and aortic remodeling, both Huang et al. and Chen et al. (43, 44) conducted studies on TEVAR in type B aortic dissection (TBAD). Results demonstrated that patients who suffered from dSINE post-TEVAR also showed significantly worse aortic remodeling.

FET INSERTION LENGTH, GRAFT SIZE, AORTIC REMODELING, AND dSINE: REALITY OR MYTH?

Aortic remodeling and dSINE are connected together, but might also be associated with a FET graft length and size, as some studies study revealed that these two variables strongly influence both of the rate of aortic remodeling and the incidence of dSINE, both concomitantly and independently.

When it comes to aortic remodeling and dSINE associated with FET, in addition to the difference between anatomical sites and the presentation of the dissection, another significant factor to consider is the distal landing site for the prosthetic anastomosis. The landing zone in the FET technique has historically been zone 3, at the proximal descending aorta, after the left subclavian artery. However, novel evidence has suggested that zone 2, between the left common carotid and subclavian artery, yields more benefit (23). The Society of Vascular Surgery/Society of Thoracic Surgeons (SVS/STS) Aortic Dissection Classification System of dissection subtype according to zone location of primary entry tear is well-illustrated in Lombradi et al. (45). Firstly, a 2019 study of 282 patients reported that proximilisation of the anastomosis led to a reduced visceral ischaemia time ($p = 0.001$) and other complications such as recurrent laryngeal nerve injury (46). Another 2018 study supported this by evidencing significantly lower rates of post-FET renal ($p = 0.004$) and pulmonary failure ($p < 0.001$). Additionally, these benefits were observed long-term, where the 5-year survival rates were also superior with zone 2 implantation ($p = 0.022$) (33). Therefore, we thought it would be of excellent academic merit to evaluate whether aortic remodeling rates would also be influenced by the distal landing zones of the anastomosis, to improve future practice and establish its connection to both aortic remodeling rate and dSINE incidence.

Despite the overarching principal that proximilisation of the distal anastomosis offers superior results in general, a study by Panfilov et al. (23) describes zone 2 anastomosis as a "double-edged sword." This 2021 study concluded that proximilisation decreases the extent of the FET procedure, in addition to the ischaemic time, and overall post-operative morbidity and mortality (23). However, complete FL thrombosis was significantly higher with zone 3 anastomosis. At 24 months post-FET, FL thrombosis in zone 2 was 60 and 77% in zone 3 ($p = 0.046$). Additionally, this increased remodeling was thought to explain the lower reintervention rates in zone 3 (8.3 vs. 25.9%).

Panfilov et al. (23) hypothesized that failure of FL thrombosis may be due to the reduced length of coverage in the aorta, causing the higher rates of reintervention. This is congruent to Berger et al. (24) findings that aortic remodeling could be improved with longer coverage of the descending aorta and hence further stabilization.

This notion to use longer FET stent grafts was also fully supported by Yamane et al. (37), who discovered a strong association between the FET insertion length and dSINE incidence as a short insertion length was much more common in the dSINE group, thereby further confirming our earlier statement on this relationship. However, for future practice using the Thoraflex™ Hybrid, Leone et al. (46) made a different recommendation of using the shorter graft length of 100 mm for better aortic remodeling outcomes. The authors suggested that the 100 mm endograft can sufficiently stabilize the dissection flap and that a large intimal tear is often located proximally near the left subclavian artery. Moreover, a recent study has shown that elongated grafts were associated with a 13% increase in freedom from negative remodeling (47). Nevertheless, the majority of evidence favors greater FET insertion lengths for improved remodeling. Regarding graft size, a 2015 review noted that oversized stents in acute dissection could attribute to new intimal tears and subsequently impair aortic wall healing and remodeling (12, 21). As shown in **Table 4**, varying lengths and diameters of the Thoraflex™ Hybrid were used in different studies.

Kreibich et al. (9) used the 100 mm Thoraflex Hybrid™ graft used in 123 patients, 14 (11.4%) developed dSINE, and out of 3 patients treated with the 150 mm graft, 2 (66.7%) developed dSINE. The authors also found that larger stent graft diameters and oversizing were more common in dSINE patients. This is another study that supported using longer FET stent grafts to increase the insertion length and extend the stent graft coverage of the aorta more distally, to reduce the risk of dSINE in this case, in addition to Berger et al. (24), Yamane et al. (37), and Panfilov et al. (23) mentioned above. On the other hand, Nishi et al. presented a counter argument that some surgeons recommend using a short FET stent to decrease the direct coverage to the segmental arteries and ensure the blood supply to the spinal cord. However, this was countered by Tan et al. (39), who stated that this alone is insufficient to avoid paraplegia and that the stent should be extended distally to treat any distal entry tears. Thoraflex™ Hybrid is licencesed to be implanted across the entire arch (zone 0–4), thus the distal anastomosis zone will determine the length of graft needed (48).

The compelling evidence in this review strongly establishes the connection between dSINE, aortic remodeling, and the insertion length of the FET stent graft. Kreibich et al. (9), Yamane et al. (24), Berger et al. (37), Tan et al. (39), and Panfilov et al. (23) alls agreed that using longer FET stent grafts is very likely to reduce the incidence of dSINE or boost aortic remodeling. With the proven negative relationship between the latter two, the nature of the relationship between these three variables is a three-way one.

Excessive oversising of the FET graft distally has also been strongly associated with dSINE occurrence. Several studies have established that oversizing is a risk factor for dSINE development, however, a few other studies have argued against this. Di Marco et al. (1), Wada et al. (27), Berger et al. (24), Tsagakis et al. (28) and Canaud et al. (49) all recommended against unnecessary graft oversizing as they argued that excessive oversizing is a significant risk factor for development of dSINE. Janosi et al. (42), Jang et al. (50) and Huang et al. (51) studied the relationship between distal oversizing and dSINE and presented solid evidence showing a significant difference in oversizing ratios between patients who did and did not develop dSINE, further extending the validity of the above argument. On the other hand, although Kreibich et al. (9) also recommended avoidance of oversizing, there was a numeric but not statistically significant trend toward oversizing in their dSINE patient group ($P = 0.613$). In addition, in contrast to the majority of reports both Nomura et al. (25) and Yamane et al. (37) did not find a significant different in oversizing between patients with and without dSINE post-FET. Finally, Tochii et al. (3) presented both sides of the argument by stating that although graft oversizing may induce intimal damage, undersizing the FET stent graft may also increase the risk of type 1b endoleak which can negatively influence aortic remodeling through impeding FL thrombosis. Damberg et al. (52) also supported the use of 10–20% oversized grafts to reduce the risk of type Ib endoleak by allowing a tighter distal stent-graft anastomosis. It is worth noting the studies highlighted used different definitions and calculations for oversizing. Yet, all evidence considered, it is clearcut that excessively oversizing the stent-graft, particularly distally, significantly increases the risk of forming dSINE. Given the already established relationship between dSINE and aortic remodeling, it is safe to say that FET graft size is in turn associated with aortic remodeling.

CONCLUSION

In conclusion, aortic remodeling has been a significant indicator for patient prognosis following the FET procedure. The Thoraflex™ Hybrid device has evidenced significantly increased TL diameter, decreased FL diameter, and favorable FL thrombosis in both CT angiography and volumetric measurement studies. Moreover, these effects were superior to the other HP available commercially and were also maintained long-term. Not only does the Thoraflex™ Hybrid show excellent aortic remodeling, but it has also shown reduced dSINE rates in comparison with other HPs, encouraging further studies into the effectiveness of this device and its increased implementation in future practice given its favorable outcomes and high versatility. With dSINE negatively influencing aortic remodeling distally and with FET insertion length interconnecting with both outcomes, the choice of both FET graft size and length must be made with great care to achieve optimal results.

AUTHOR CONTRIBUTIONS

MJ, FK, PS, and DA were involved in literature review design, literature search, and manuscript writing. YR was involved in literature search. ST, MM, SH, IM, and MB involved in manuscript revision. All authors contributed to the article and approved the submitted version.

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Aortic Balloon Occlusion Technique Does Not Improve Peri-Operative Outcomes for Acute Type A Acute Aortic Dissection Patients With Lower Body Malperfusion

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Background: The management of malperfusion is vital to improve the outcomes of surgery for acute type A acute aortic dissection (ATAAD). Open arch repair under hypothermic circulatory arrest with selective antegrade cerebral perfusion (HCA/sACP) is safe and efficient but associated with inevitable hypothermia and ischemia-reperfusion injury. The aortic balloon occlusion (ABO) technique is shown to be organ protective by allowing higher temperature and shorter circulatory arrest time. In this study, we aimed to evaluate the safety and efficacy of this new technique for ATAAD patients with lower body malperfusion.

Methods: Between January 2013 and November 2020, 355 ATAAD patients with lower body malperfusion who underwent arch repair in our institute were enrolled. The patients were divided into 2 groups: ABO group ($n = 85$) and HCA/sACP group ($n = 271$). Propensity score matching was performed to correct baseline differences.

Results: Using the propensity score matching, 85 pairs were generated. Circulatory arrest time was significantly lower in the ABO group compared with the HCA/sACP group (median, 8 vs. 22 min; $p < 0.001$). The incidence of in-hospital mortality (10.6 vs. 12.9%; $p = 0.812$), stroke (7.1 vs. 7.1%; $p = 1.000$), dialysis (25.9 vs. 32.9%; $p = 0.183$), hepatic dysfunction (52.9 vs. 57.6%; $p = 0.537$), tracheostomy (4.7 vs. 2.4%; $p = 0.682$), paraplegia (1.2 vs. 4.7%; $p = 0.368$) were comparable between ABO and HCA/sACP groups. Other outcomes and major adverse events were comparable. The multivariable logistic analysis did not recognize ABO technique protective against any major adverse outcomes.

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Conclusions: For ATAAD patients with lower body malperfusion, the ABO technique allows the performance of arch repair with frozen elephant trunk (FET) under higher temperature and shorter circulatory arrest time. However, ABO technique did not improve perioperative outcomes. Future studies are warranted to evaluate the efficacy of this technique.

Keywords: acute type A aortic dissection, malperfusion, frozen elephant trunk, aortic arch repair, aortic balloon occlusion

INTRODUCTION

Malperfusion is a life-threatening complication of acute type A acute aortic dissection (ATAAD). With a reported incidence of 30–40% (1, 2), it is associated with adverse post-operative outcomes (3). Malperfusion to the lower body (visceral organs, lower limbs, and spinal cord) accounts for over 70% of cases. Open-end anastomosis under hypothermic circulatory arrest in combination with selective antegrade cerebral perfusion (HCA/sACP) is the currently recommended technique for arch repair for ATAAD (4–6). The lower body is inevitably exposed to ischemia and subsequent reperfusion injury. Lower body organ injuries associated with hypothermia and ischemia-reperfusion injury remain a major concern, especially for those who already suffer from malperfusion.

By blocking the back flow with an inflated balloon inserted in the descending aorta, the aortic balloon occlusion (ABO) technique allows perfusion of the lower body *via* femoral arterial cannulation during the bulk time for open-end anastomosis, thereby shortening the lower body circulatory arrest time and permitting higher temperature. The ABO technique is shown to alleviate renal and hepatic injury in ATAAD surgery compared with the conventional HCA/sACP technique (7). The effect of the ABO technique in lower body reperfusion has never been examined. The present study discusses patients treated with the ABO technique and evaluates its efficacy in the treatment of ATAAD complicated by lower body malperfusion.

MATERIALS AND METHODS

Patients

Between January 2013 and November 2020, a total of 1,226 patients underwent arch repair for ATAAD in our institute, and a total of 355 patients were diagnosed with lower body malperfusion at admission. Furthermore, 271 patients underwent arch repair with conventional HCA/sACP while the rest 85 patients underwent surgical repair with the ABO technique. Our study complied with the Declaration of Helsinki. The hospital's ethics committee approved the study (approval no. KY-Q-2021-073-01), and the patient consent was waived due to the study's retrospective nature.

Definition of Lower Body Malperfusion

Lower body malperfusion was defined as compromised blood flow to a lower limb, visceral organ, spinal cord, or kidney by using a combination of clinical history, physical examination, radiographic studies, and laboratory values. Cerebral malperfusion, upper limb malperfusion, and coronary malperfusion were not considered as lower body malperfusion. For the diagnosis of lower limb malperfusion, pulse deficit, or loss of sensory or motor function of lower extremities in combination with radiographic evidence was used. Visceral malperfusion was defined as mesenteric or liver ischemia and was determined *via* a combination of clinical, laboratory, and radiographic factors, such as abdominal pain or distention, elevation of hepatic enzymes, lactic acid, and radiographic evidence of flow obstruction. Radiographic evidence of occlusion of the renal arteries or delayed enhancement with a rise in creatinine was considered evidence of renal malperfusion. Patients with transient or permanent paraplegia were considered to have spinal malperfusion. The isolated presence of a dissection flap into a branch vessel without demonstrable flow impedance by enhanced CT alone was not considered malperfusion.

Surgical Procedure

For the ABO group, cardiopulmonary bypass (CPB) is instituted through both the right axillary and one of the femoral arteries.

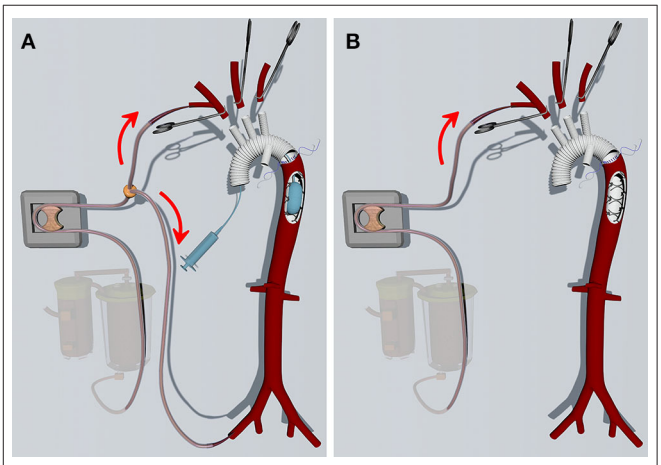

FIGURE 1 | (A) The ABO technique. The FET is inserted into the descending aorta with selective cerebral perfusion. Then a foley tip is placed into the stented graft and inflated. Subsequently, the femoral artery cannulation is opened, and the lower body is perfused through a bifurcated arterial line when distal arch anastomosis is performed. **(B)** The conventional HCA/sACP technique. The femoral artery is not cannulated. The lower body is not perfused when the distal arch anastomosis is performed.

TABLE 1 | Pre-operative characteristics.

Variables	Unmatched					Matched				
	Total *n* = 356	ABO *n* = 85	HCA/sACP *n* = 271	*P*-value	SMD	Total *n* = 170	ABO *n* = 85	HCA/sACP *n* = 85	*P*-value	SMD
Demographic										
Age [median (IQR)]	50.0 [43.0, 56.0]	50.0 [42.0, 58.0]	50.0 [43.0, 56.0]	0.874	0.042	50.0 [43.75, 57.0]	50.0 [42.0, 58.0]	51.0 [45.5, 57.0]	0.878	0.061
Male (%)	312 (87.6)	72 (84.7)	240 (88.6)	0.346	0.113	148 (87.1)	72(84.7)	76 (89.4)	0.361	0.140
Medical history										
Circulatory collapse (%)	16 (4.5)	1 (1.2)	15 (5.5)	0.132	0.243	3 (1.8)	1 (1.2)	2 (2.4)	1.000	0.089
Hypertension (%)	226 (63.5)	59 (69.4)	167 (61.6)	0.193	0.164	113 (66.5)	59 (69.4)	54 (63.5)	0.417	0.124
Connective tissue disorder	17 (4.8)	0 (0.0)	17 (6.3)	0.016	0.365	2 (1.2)	0 (0.0%)	2 (2.4)	0.497	0.218
Diabetes mellitus (%)	10 (2.8)	1 (1.2)	9 (3.3)	0.462	0.145	3 (1.8)	1 (1.2)	2 (2.4)	1.000	0.089
Smoking (%)	55 (15.4)	12 (14.1)	43 (15.9)	0.697	0.049	36 (21.2)	12 (14.1)	24 (28.2)	0.024	0.349
History of stroke (%)	16 (4.5)	2 (2.4)	14 (5.2)	0.376	0.148	6 (3.5)	2 (2.4)	4 (4.7)	0.682	0.127
Coronary heart disease (%)	19 (5.3)	3 (3.5)	16 (5.9)	0.581	0.112	10 (5.9)	3 (3.5)	7 (8.2)	0.329	0.200
Chronic renal dysfunction (%)	14 (3.9)	2 (2.4)	12 (4.4)	0.532	0.468	3 (1.8)	2 (2.4)	1 (1.2)	1.000	0.089
History of heart/aortic surgery (%)	8 (2.2)	0 (0.0)	8 (3.2)	0.206	0.246	0 (0.0)	0 (0.0)	0 (0.0)	–	<0.001
Atrial fibrillation (%)	1 (0.3)	0 (0.0)	1 (0.4)	1.000	0.086	0 (0.0)	0 (0.0)	0 (0.0)	–	<0.001
COPD (%)	5 (1.4)	1 (1.2)	4 (1.5)	0.026	0.026	2 (1.2)	1 (1.2)	1 (1.2)	1.000	<0.001
Malperfuison										
Cerebral (%)	19 (5.3)	6 (7.1)	13 (4.8)	0.418	0.095	9 (5.3)	6 (7.1)	3 (3.5)	0.496	0.157
Coronary (%)	84 (23.6)	1 (24.7)	3 (23.2)	0.782	0.034	42 (24.7)	21(24.7)	21(24.7)	1.000	<0.001
Renal (%)	260 (73.0)	62 (72.9)	198 (73.1)	0.982	0.003	121 (71.2)	62 (72.9)	59 (69.4)	0.611	0.078
Gastrointestinal (%)	113 (31.7)	20 (23.5)	93 (34.3)	0.062	0.239	47 (27.6)	20 (23.5)	27 (31.8)	0.230	0.184
Iliofemoral (%)	55 (15.4)	14 (16.5)	41 (15.1)	0.765	0.037	28 (16.5)	14 (16.5)	14 (16.5)	1.000	<0.001
Spinal (%)	16 (4.5)	5 (5.9)	11 (4.1)	0.479	0.084	8 (4.7)	5 (5.9)	3 (3.5)	0.7	0.111

ABO, aortic balloon occlusion; HCA/sACP, hypothermic circulatory arrest/selective antegrade cerebral perfusion; COPD, chronic obstructive pulmonary disease.

During the cooling phase, aortic root procedures are performed as indicated. When the nasopharyngeal temperature reaches 24–26°C, the femoral artery cannulation was clamped and the arch is longitudinally opened. The right axillary artery (RAX) was used for unilateral ACP. For bilateral ACP, both RAX and left common carotid artery (LCCA) were used. A stented graft (frozen elephant trunk, FET) (Cronus; MicroPort Scientific, Shanghai, China) was inserted into the true lumen of the descending aorta. A Foley catheter was threaded into the graft, inserted into the metal portion of the stent, and inflated with saline. Once the dilated tip of the Foley catheter is fixed against the inner wall of FET, perfusion of the lower body is resumed through the femoral artery with 2/3 of the full rate. Any back flow that does occur can be removed with suction. After the distal anastomosis was finished, the femoral arterial line was temporarily clamped. The Foley was deflated and removed, and the proximal end of the graft was clamped after de-airing. The CPB flow was gradually returned to normal and rewarming was initiated. The circulatory arrest time of the lower body was about 8 min. The ascending aorta was reconstructed during the rewarming phase.

The HCA/sACP technique was largely based on Sun's procedure as previously described (8). The procedure differs from the ABO technique in the following ways. For most patients, the right axillary artery was cannulated for CPB and selective cerebral perfusion while the femoral artery was not cannulated. For patients unsuited for RAX cannulation, femoral artery cannulation, or central aortic cannulation under TEE guidance was used. For these patients, direct LCCA cannulation was used for unilateral ACP. ACP is instituted when the nasopharyngeal temperature reaches 22–24°C. Distal anastomosis was performed with circulatory arrest of the lower body. The circulatory arrest time was about 23 min. Proximal repair and arch branches replacement were performed as indicated (**Figure 1**).

Statistical Analysis

Continuous data were evaluated for normality using the Kolmogorov–Smirnov test. The skewed data were expressed as median with interquartile range (IQR). Mann–Whitney *U*-test was used for non-normally distributed variables. Categorical variables are presented as percentages. Pearson's χ^2 or Fisher's exact test was used for categorical variables.

To minimize the pre-operative differences between the ABO and HCA/sACP groups, a propensity score match analysis was done. A logistic regression analysis was used to calculate the propensity score for the selection of patients for the ABO and HCA/sACP groups, using pre-operative variables described in **Table 1**. ABO vs. HCA/sACP was the dependent variable in the logistic regression model used to compute the propensity scores. Each patient was matched to a single patient (no replacement) using the nearest neighbor matching technique and a caliper

of 0.2. After matching, 85 patients for each group (ABO vs. HCA/sACP) were obtained for comparison. After matching, we assessed balance within the matched pairs using the standardized differences in covariate means. For the matched groups, means were compared using the paired Student's *t*-test and frequencies were compared using the McNemar test. Continuous variables not normally distributed were compared with Wilcoxon signed-rank test.

The multivariable logistic regression analysis was applied to determine the independent risk factors of adverse events, such as in-hospital mortality, post-operative stroke, hepatic dysfunction, dialysis, paraplegia, tracheostomy, prolonged intensive care unit (ICU) stay (>7 days), and prolonged post-operative hospital stay (>21 days). Pre-operative and intraoperative variables with a $p < 0.1$ in univariate analysis were included in the multivariable logistic regression analysis.

Statistical analyses were performed in R version 3.6.0 (R Foundation) and SPSS software v22.0 (SPSS, Inc., Chicago, IL, USA). The values of $p < 0.05$ were considered statistically significant.

RESULTS

Baseline Characteristics

The baseline characteristics are summarized in **Table 1**. The HCA/sACP groups had more diagnosed connective tissue disorder (0.0 vs. 6.3%, $p = 0.016$). The incidences of malperfusion syndrome of the brain, heart, kidneys, lower limbs, and spinal cord were comparable in the 2 groups. The HCA/sACP group had a trend of more gastrointestinal malperfusion but the difference was not statistically significant (34.3 vs. 23.5%, $p = 0.062$). After propensity score matching, most of the pre-operative characteristics of the 2 groups ($n = 85$ in each) were comparable.

Operative Details of Propensity Score Matching Groups

Operative details of both the full original cohort and the propensity score matched cohort are presented in **Table 2**. After matching, for root procedure, the Bentall operation was less used in the ABO group (24.7 vs. 43.5%, $p = 0.010$) while more commissure suspension technique was used in the ABO group (41.2 vs. 24.7%, $p = 0.022$). For distal repair, the rate of the branched graft was significantly lower in the ABO group (11.8 vs. 95.3%, $p = 0.001$) while the en-bloc technique was used for the majority of patients with ABO (88.2 vs. 4.7%, $p = 0.001$). These differences in surgical strategies were largely due to the surgeon's preference. The CPB time was comparable between the two groups (median, 241 vs. 242 min, $p = 1.000$). The ABO group demonstrated longer aortic cross-clamp time (median, 146.0 vs. 125 min, $p = 0.001$) (**Supplementary Table 2**) but the difference was no longer significant after matching (median, 146.0 vs. 130 min, $p = 0.167$). Circulatory arrest time was significantly shorter in the ABO group (median, 8 vs. 22 min; $p < 0.001$). The lowest temperature was significantly higher in the ABO group before (24.6 vs. 21.6°C; $p < 0.001$). Operative details of both the full original cohort are summarized in **Supplementary Table 2**.

TABLE 2 | Operative characteristics (propensity score matching cohort).

Variables	Total ($n = 170$)	ABO ($n = 85$)	HCA/sACP ($n = 85$)	*P*-value
Proximal repair				
Sino-tubular junction collection (%)	37 (97.6)	21 (24.7)	16 (18.8)	0.353
Commissure suspension (%)	56 (32.9)	35 (41.2)	21 (24.7)	0.022
Wheats (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Bentall (%)	58 (34.1	21 (24.7)	37 (43.5)	0.010
VSRR (%)	20 (11.8)	9 (10.6)	11 (12.9)	0.634
Concomitant procedures				
CABG (%)	11 (6.5)	5 (5.9)	6 (7.1)	1.000
MVP/MVR/TVP (%)	3 (1.8)	2 (2.4)	1 (1.2)	1.000
Distal				
branched graft (%)	91 (53.9)	10 (11.8)	81 (95.3)	0.001
En-bloc (%)	79 (46.5)	75 (88.2)	4 (4.7)	0.001
FET (%)	170 (100.0)	170 (100.0)	170 (100.0)	–
SCP				
Unilateral ACP (%)	75 (44.1)	3 (3.5)	72 (84.7)	<0.001
Bilateral ACP (%)	92 (54.1)	82 (96.5)	10 (11.8)	<0.001
RCP (%)	3 (1.8)	0 (0.0)	3 (3.5)	0.246
Time/temperature				
CPB time [median (IQR)]	241.5 [215.75, 282.0]	241 [215.5, 287.0]	242 [216.5, 278.0]	1.000
ACC time [median (IQR)]	136.0 [112.0, 164.25]	146.0 [116.0, 171.0]	130.0 [99.50, 157.5]	0.167
HCA time [median (IQR)]	15.0 [8.0, 22.0]	8.0 [7.0, 10.0]	22 [19.0, 25.0]	<0.001.
Lowest temperature [IQR]	23.4 [21.175, 24.725]	24.6 [23.2, 27.0]	21.6 [20.4, 23.6]	<0.001.

ABO, aortic balloon occlusion; HCA, HCA/sACP, hypothermic circulatory arrest/selective antegrade cerebral perfusion; VSSR, valve-sparing root replacement; CABG, coronary artery bypass grafting; MVP/MVR/TVP, mitral valvuloplasty/mitral vitral replacement/tricuspid valvuloplasty; ACP, antegrade cerebral perfusion; RCP, retrograde cerebral perfusion; CPB, cardiopulmonary bypass; ACC, aortic cross clamp; HCA, hypothermic circulatory arrest.

Perioperative Outcomes of Propensity Score Matching Groups

As shown in **Table 3**, there were no significant differences between the ABO and HCA/sACP groups in revisiting for bleeding (11.8 vs. 4.7%; $p = 0.161$), extracorporeal membrane oxygenation (ECMO) (5.9 vs. 2.4%; $p = 0.443$), mediastinitis (1.2 vs. 4.7%; $p = 0.368$), transient neurological deficit (TND) (31.8 vs. 32.9%; $p = 0.870$), paraplegia (1.2 vs. 5.9%; $p = 0.210$), dialysis (25.9 vs. 35.3%; $p = 0.183$), hepatic dysfunction (52.9 vs. 57.6%; $p = 0.537$), tracheostomy (4.7 vs. 2.4%; $p = 0.682$), post-operative stroke (7.1 vs. 7.1%; $p = 0.834$), and in-hospital mortality (10.6 vs. 12.9%; $p = 0.812$).

The post-operative mechanical ventilation time was longer in the ABO group before match [6 (3.5, 9.5) vs. 4 (2.0, 7.0); $p = 0.0001$] (**Supplementary Table 2**) but the difference was not statistically significant [6 (3.5, 9.5) vs. 6 (2.0, 8.0); $p = 0.0084$].

TABLE 3 | In-hospital outcomes (propensity score matching cohort).

Variables	Total ($n = 170$)	ABO ($n = 85$)	HCA/sACP ($n = 85$)	*P*-value
Revisiting for bleeding (%)	40 (11.2)	10 (11.8)	30 (11.1)	0.860
ECMO (%)	10 (2.8)	5 (5.9)	5 (1.8)	0.063
Mediastinitis (%)	12 (3.4)	1 (1.2)	11 (4.1)	0.307
TND (%)	104 (29.2)	27 (31.8)	77 (28.4)	0.553
Paraplagia (%)	12 (3.4)	1 (1.2)	11 (4.1)	0.307
dialysis (%)	111 (31.2)	22 (25.9)	89 (32.8)	0.227
Hepatic dysfunction (%)	164 (46.1)	45 (52.9)	119 (43.9)	0.145
Tracheostomy (%)	17 (4.8)	4 (4.7)	13 (4.8)	1.000
Stroke (%)	27 (7.6)	6 (7.1)	21 (7.7)	0.834
In-hospital mortality (%)	48 (13.5)	9 (10.6)	39 (14.4)	0.370
Ventilation time, d [median (IQR)]	5.0 [2.0, 7.0]	6.0 [3.5, 9.5]	4.0 [2.0, 7.0]	0.001
ICU stay, d [median (IQR)]	9.0 [6.0, 15.0]	10.0 [7.0, 19.0]	8.0 [6.0, 13.0]	0.003
Hospital stay, d [median (IQR)]	22.5 [16.0, 33.0]	25.0 [20.0, 38.5]	21.0 [15.0, 32.0]	0.008

ABO, aortic balloon occlusion; HCA, hypothermic circulatory arrest; ECMO, Extracorporeal membrane oxygenation; TND, transient neurological deficit; ICU, intensive care unit.

ICU stay [10.0 (7.0, 19.0) vs. 9.0 (5.0, 15.0); $p = 0.0017$], hospital stay [25.0 (20.0, 38.5) vs. 21.0 (16.0, 31.0); $p = 0.0034$] were both longer in the ABO group compared with the HCA group.

Risk Factors for Adverse Outcomes (Full Original Cohort)

The ABO technique was not an independent predictor for any adverse outcome in the multivariable regression analysis. The multivariable risk analysis for in-hospital mortality revealed no risk factors. History of stroke [$p = 0.022$; hazard ratio (*HR*), 4.216; 95% *CI*, 1.229, 14.460] was recognized as risk factor for post-operative stroke. CPB time ($p = 0.036$; *HR*, 1.006; 95% *CI*, 1.000, 1.011) was risk factor for dialysis post-operatively. In addition, the multivariable risk analysis revealed that the spinal malperfusion ($p < 0.001$; *HR*, 11.803; 95% *CI*, 2.970, 46.913) was a risk factor for paraplegia. The age ($p = 0.020$; *HR*, 1.075; 95% *CI*, 1.011, 1.142) and spinal malperfusion ($p < 0.001$; *HR*, 13.482; 95% *CI*, 3.404, 53.393) were risk factors for tracheostomy. The multivariable risk analysis revealed hypertension ($p = 0.012$; *HR*, 1.832; 95% *CI*, 1.142, 2.940) as a risk factor for prolonged ICU stay (>7 days). No risk factor for prolonged hospital stay (>21 days) was identified (**Table 4**).

TABLE 4 | Multivariable logistic analysis for risk factors associated with post-operative stroke, CRRT, paraplegia, prolonged ventilation requiring tracheostomy, and prolonged ICU stay (full original cohort, $n = 356$).

Variables	OR (95% CI)	*P*-value
Stroke		
History of stroke	4.216 (1.229–14.460)	0.022
Cerebral malperfusion	3.310 (0.985–11.117)	0.053
Dialysis		
Chronic renal disease	2.860 (0.937–8.725)	0.065
CPB time	1.006 (1.000–1.011)	0.036
Paraplegia		
Spinal malperfusion	11.803 (2.970–46.913)	0.001
Traecheostomy		
Age	1.075 (1.011–1.142)	0.020
Spinal malperfusion	13.482 (3.404–53.393)	0.001
Prolonged ICU stay		
HT	1.832 (1.142–2.940)	0.012

CPB, cardiopulmonary bypass.

DISCUSSION

The main findings of this study are as follows: the ABO technique allows arch repair to be performed under higher temperature and with shorter circulatory arrest time compared with conventional HCA/sACP technique. However, for patients with lower body malperfusion, the ABO technique did not reduce the incidence of adverse outcomes, such as in-hospital mortality, post-operative stroke, dialysis, liver dysfunction, paraplegia, and prolonged ventilation requiring tracheostomy.

The open-end anastomosis with systemic circulatory arrest under hypothermia has been a mainstream technique for arch repair among patients with ATAAD. The open-end anastomosis allows optimal exposure of the anastomotic site and complete visualization of the arch to rule out additional entry tears (4) and has been shown to improve both perioperative and long-term outcomes (9, 10). However, organ injuries associated with hypothermia and prolonged circulatory arrest time have been shown to be associated with adverse outcomes (11). For patients with lower body malperfusion, minimizing intraoperative ischemic injury is vital for survival.

The FET has been widely used since 2006. It expands the true lumen, improves thrombosis of the residual false lumen, and also made distal anastomosis easier to perform (12, 13). The ABO technique takes advantage of this stent placed in the descending aorta by placing an aortic balloon in it to block the backflow from femoral cannulation. This allows perfusion of the lower body during the bulk time of distal anastomosis. In the present study, the circulatory arrest time was shortened to ∼8 min and allowed the lowest temperature to be raised to about 24°C.

Despite the significant reduction of circulatory arrest time and elevation of the lowest temperature, the ABO technique did not improve survival or reduce stroke. A recent analysis of 1,708 cases of aortic arch surgery found the circulatory arrest time >38 min as a risk factor for mortality and permanent neurologic dysfunction (14). The average circulatory arrest time of 22 [19.0, 25.0] min in the HCA/sACP group is safe enough and is not associated with an increased risk of mortality and stroke.

In a previous study, the ABO technique was shown to reduce liver damage and predispose to low-grade AKI by providing almost continuous blood flow to the liver and kidney compared with the HCA/sACP method (7). However, in the present study, the ABO technique did not reduce hepatic dysfunction or the

need for dialysis among patients with lower body malperfusion. Malperfusion to lower body organs can be secondary to either static or dynamic obstruction (4). In dynamic obstruction, the pressurized false lumen intermittently displaces the mobile dissection flap over the orifice of the branch vessel. The dynamic obstruction can be relieved by depressurizing the false lumen and the true lumen flow can be restored by the ABO technique. In static obstruction, true or false lumen thrombosis formed distal to the pressurized false lumen and static obstruction may not be released by opening of the proximal aorta, in this case, the ABO technique would be futile to relieve malperfusion.

This study has several inherited limitations. First, the study is a retrospective review, bias and confounding may persist despite our attempts to control for them with propensity score-matching. All procedures were treated at a single center, our results may not translate to other clinical settings, as disparities exist across institutes. The number of patients in the study was relatively small. Multi-centered, large sample studies are warranted in the future.

CONCLUSION

The ABO technique allows the performance of arch repair with FET under higher temperature and shorter circulatory arrest for ATAAD patients with lower body malperfusion. However, the ABO technique did not reduce the incidence of major adverse outcomes. Future large-sample, randomized, multicenter studies are warranted to thoroughly evaluate the efficacy of this technique.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Guangdong Provincial People's Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

RF, TS, and GT conceived the research question and conceived and designed the analysis. SZ, ZC, DZ, YL, YY, and ZL undertook data collection and conducted the study. GT, ZS, and JW drafted the manuscript. All authors reviewed the results, commented on the manuscript, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Surgical Repair of Two Kinds of Type A Aortic Dissection After Thoracic Endovascular Aortic Repair

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Background: Retrograde dissection is now recognized as an important complication following thoracic endovascular aortic repair (TEVAR). The purpose of this study is to describe two different situations of TAAD after TEVAR. We will introduce the surgical methods used to repair TAAD following TEVAR at our center, and evaluate its long-term prognosis.

Methods: Between January 2010 and October 2019, 50 patients who had previously received TEVAR treatment for TBAD were admitted to our center for repair of a type A aortic dissection. According to the patients' CT angiographies and intra-operative findings, we identified two distinct groups: a retrograde group (stent-induced new aortic injury, with retrograde extension involving the ascending aorta) and an antegrade group (entry tear located in the aortic root, ascending aorta or the aortic arch, away from the edges of the stent grafts). The options for treatment of the proximal aorta were Bentall procedure (12/50, 24.0%) and ascending aorta replacement (38/50, 76.0%). All patients underwent total arch replacement (TAR) and frozen elephant trunk (FET) implantation. Survival over the follow-up period was evaluated with the Kaplan–Meier survival curve and the log-rank test.

Results: The median interval time from prior TEVAR to reoperation was 187 days (IQR: 30.0, 1375.0 days). 18.0% of TAAD after TEVAR did not have any obvious symptoms at the time of diagnosis, most of which were found on routine follow-up imaging. The patients in the retrograde group were younger than those in the antegrade group (44.0 ± 9.4 vs. 51.4 ± 10.5 years, $P = 0.012$). No significant differences in the incidence of post-operative complications or mortality were noted between the two groups. The mean follow-up time was 3 years. No late death or complications occurred after one year following surgery upon follow-up. The asymptomatic survival rate one year after surgery was 90.0%.

Conclusion: The TAR and FET technique was feasible and effective for complicated TAAD after TEVAR. The surgical success rate and long-term prognosis of patients undergoing the timely operation are satisfactory.

Keywords: total arch replacement, frozen elephant trunk, type A aortic dissection, thoracic endovascular aortic repair, retrograde dissection

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INTRODUCTION

Thoracic endovascular aortic repair (TEVAR) was initially designed to treat disease of the descending thoracic aorta more than 20 years ago (1). With the development of hybridization techniques, complex aortic arch lesions no longer present as many challenges in the treatment of type B aortic dissection (TBAD) (2). Retrograde type A aortic dissection (rTAAD) is the most serious complication, which has a low incidence but high mortality rate (3, 4). The causes of rTAAD have been studied extensively, but for recurrent TAAD after TEVAR, clinical data are scarce and there is no consensus on treatment modalities. Here, we describe the clinical characteristics of two distinct forms of TAAD following TEVAR, introduce our center's choice of surgical methods for this situation and report the long-term prognosis of treatment.

PATIENTS AND METHODS

Patient Population

Between January 2010 and October 2019, 50 patients that had undergone previous primary TEVAR were referred to our hospital for TAAD. We retrospectively collected the clinical data of the patients through the electronic medical record management system. By reviewing the surgical records and the imaging data and reports, we divided the 50 patients into two groups (retrograde group, N = 28 and antegrade group, N = 22) based on individual anatomical features (**Figure 1**). Clinical information was retrospectively collected. Basic clinical characteristics and anatomical details of pathology are summarized in **Table 1**.

The location of the entry tear in the retrograde group was at the proximal ending of the previous stent and closely correlated with the previous proximal landing zone. All echocardiography data were obtained pre-operatively. Interestingly, about 18.0% of patients were diagnosed as TAAD by routine follow-up imaging examination and did not experience any associated symptoms.

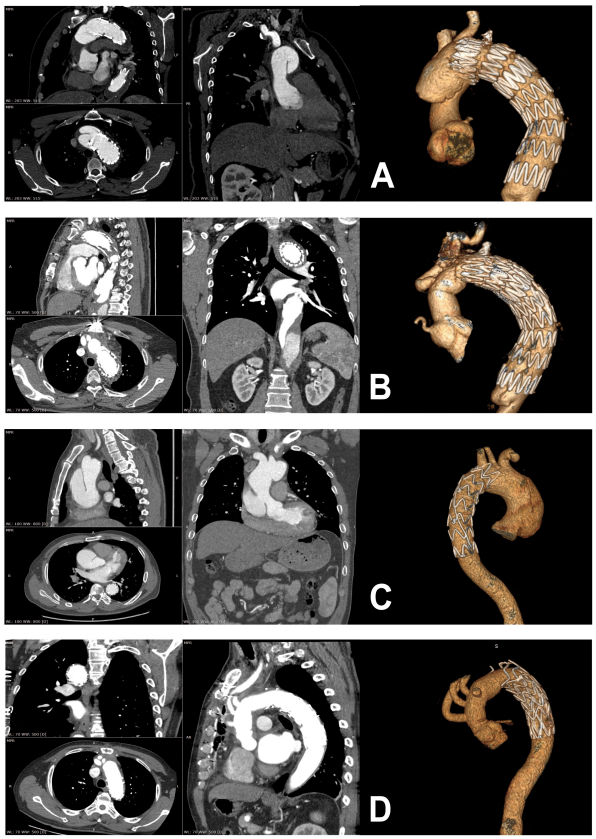

FIGURE 1 | Preoperative and postoperative computed tomographic scans of patients with retrograde type A dissection **(A,B)** and antegrade type A dissection **(C,D)**.

Initial Thoracic Endovascular Aortic Repair Details

The vast majority of patients' initial TEVARs were completed by other hospitals. The median interval between the primary TEVAR procedure and TAAD was 187 days (IQR: 30.0–1375 days). The details of the previous TEVAR procedure were summarized in **Table 2**.

Since the vast majority of patients were referred from other medical centers, we could not collect specific TEVAR details, but all stent positions were able to be clarified by CT aortography and intraoperative findings on operation records.

Operative Technique

The surgical technique, known as Sun's procedure (total arch replacement using a tetra-furcate graft and stented elephant trunk implantation) (5), has been described in detail previously (6, 7). Specifically, right axillary artery cannulation is used for cardiopulmonary bypass (CPB) and unilateral selective antegrade cerebral perfusion under moderate hypothermic circulatory arrest at 25°C. Patients who present with an innominate artery malperfusion may not have adequate perfusion for CPB. In this case, the femoral artery is cannulated in addition to the axillary artery. Cooling was started immediately after the initiation of CPB. The proximal manipulations were carried out during the cooling period, including reinforcement of the detached commissures with ascending aorta or aortic root replacement. Once the target temperature was reached, all supra-aortic vessels were clamped and transected. The unilateral selective antegrade cerebral perfusion was initiated *via* the right axillary artery. The flow was adjusted to maintain a left radial artery pressure $\geq$20 mmHg. The most critical aspect of this secondary procedure was to identify any damage to the aortic wall from the proximal bare springs of the previous stents. After cutting the steel wires of the bare spring, the stented elephant trunk (Cronus, MicroPort, China) was deployed in the true lumen of the descending aorta, and TAR was performed with a tetra-furcated graft (**Figure 2**). Once the distal anastomosis was completed, distal reperfusion was initiated. The left common carotid artery was reconstructed first, and rewarming was then started. The ascending aorta was anastomosed to resume myocardial perfusion, followed by the left subclavian artery (LSCA), and finally the innominate artery. In some cases, we bypass the LSCA to expand the spatial range

TABLE 1 | Baseline characteristics of participants.

Characteristic	Total (*n* = 50)	Retrograde (*n* = 28)	Antegrade (*n* = 22)	*P*-value
Age, Mean ± SD	47.2 ± 10.5	44.0 ± 9.4	51.4 ± 10.5	0.012
Male, *n* (%)	37 (74.0)	22 (78.6)	15 (68.2)	0.612
BMI, Median (IQR)	25.0 (23.7, 27.4)	25.0 (23.6, 27.9)	24.9 (23.7, 26.7)	0.799
Pre-operative comorbidity				
Hypertension, n (%)	39 (78.0)	23 (82.1)	16 (72.7)	0.503
Smoking, *n* (%)	25 (50.0)	16 (57.1)	9 (40.9)	0.393
Diabetes, *n* (%)	5 (10.0)	1 (3.6)	4 (18.2)	0.155
Marfan Syndrome, *n* (%)	2 (4.0)	1 (3.6)	1 (4.5)	1
Location of entry tear				<0.001
Root, *n* (%)	4 (8.0)	0 (0)	4 (18.2)	
Ascending, *n* (%)	15 (30.0)	1 (3.6)	14 (63.6)	
Arch, *n* (%)	31 (62.0)	27 (96.4)	4 (18.2)	
LVEF, Mean ± SD	61.6 ± 5.6	59.9 ± 5.6	63.9 ± 4.8	0.010
Ascending-aorta-diameter, Mean ± SD	44.7 ± 8.2	42.2 ± 6.7	47.9 ± 9.1	0.015
Aortic-sinus-diameter, Median (IQR)	40.0 (36.0, 46.0)	39.5 (35.8, 43.2)	44.0 (36.0, 47.0)	0.347
Aortic-regurgitation, *n* (%)				0.208
Mild, *n* (%)	28 (56.0)	19 (67.9)	9 (40.9)	
Moderate, *n* (%)	9 (18.0)	3 (10.7)	6 (27.3)	
Severe, *n* (%)	2 (4.0)	1 (3.6)	1 (4.5)	
Clinical symptoms				
None, *n* (%)	9 (18.0)	4 (14.3)	5 (22.7)	0.481
Sudden pain, *n* (%)	35 (70.0)	20 (71.4)	15 (68.2)	1

BMI, body mass index; LVEF, left ventricular ejection fraction.

TABLE 2 | Details of previous TEVAR procedure.

Variables	Total (*n* = 50)	Retrograde (*n* = 28)	Antegrade (*n* = 22)	*P*-value
Intervals, Median (IQR)	187.0 (30.0, 1375.0)	180.0 (30.0, 832.5)	540.0 (35.2, 1810.0)	0.278
Proximal landing zone, *n* (%)				<0.01
0	1 (2.0)	1 (3.6)	0 (0)	
1	4 (8.0)	4 (14.3)	0 (0)	
2	12 (24.0)	8 (28.6)	4 (18.2)	
3	19 (38.0)	15 (53.6)	4 (18.2)	
4	14 (28.0)	0 (0)	14 (63.6)	

of operation and better protect cerebral perfusion, depending on anatomical location.

FOLLOW-UP

The primary endpoint of this study was death after the surgical repair, and the secondary endpoint was reoperation after this surgery. Follow-up was performed on all patients after discharge until the end of the study period in September 2020, or death. Survival data were obtained through clinical follow-up and phone calls. Patients who did not return to review, those whom we could not contact, and patients for whom we could not otherwise ascertain reintervention status were considered lost to follow-up. An annual computed tomography (CT) scan was recommended to detect thrombosis and obliteration of the false lumen, evaluate the sizes of the true lumen, false lumen, stented and unstented distal aortic segments, and any complications. Early mortality was defined as death at 30 days after surgery, and late mortality was defined as a death event reported at a follow-up visit other than 30 days after surgery.

STATISTICAL ANALYSIS

All analyses were performed using R Statistical Software[1] (The R Foundation) and Free Statistics analysis platform. The Kolmogorov–Smirnov test was used to assess the normal or non-normal distribution of continuous data. Normally distributed continuous data were presented as means ± SD and assessed by Student's *t*-test. Data showing non-normal distribution were presented as median and interquartile range, and the Mann-Whitney *U*-tests were performed. Chi-squared or Fisher's exact tests were used in categorical variables. Statistical significance is presented by *P* values. P value < 0.05 was considered significant. Kaplan–Meier curves were generated to assess survival data.

RESULTS

Demographics and Comorbidities

In total, 78.6% of the patients who developed retrograde TAAD were men with a mean age of 44.0 ± 9.4 years. The gender composition was not significantly different from the antegrade group, but the age was significantly smaller (44.0 ± 9.4 vs. 51.4 ± 10.5 years; $P = 0.012$) than that of the antegrade group. The retrograde group had a smaller size of ascending aorta than the antegrade group (42.2 ± 6.7 vs. 47.9 ± 9.1 mm; $P = 0.015$), and the LVEF of the retrograde group was significantly lower than the antegrade group (59.9 ± 5.6 vs. 63.9 ± 4.8%; $P = 0.010$). We did not find any statistically significant differences between the two groups in terms of gender, BMI, pre-operative comorbidity, aortic regurgitation, and clinical symptoms.

Details of the Previous Thoracic Endovascular Aortic Repair Procedure

The interval times between TEVAR and subsequent TAAD between the retrograde and antegrade groups were [180.0 (30.0, 832.5) vs. 540.0 (35.2, 1810.0) days; $P = 0.278$]. The proximal landing zone was recorded in line with the reporting standards of endovascular repair (2, 8). **Table 2** outlines the clear and significant difference between the zone

[1]http://www.R-project.org

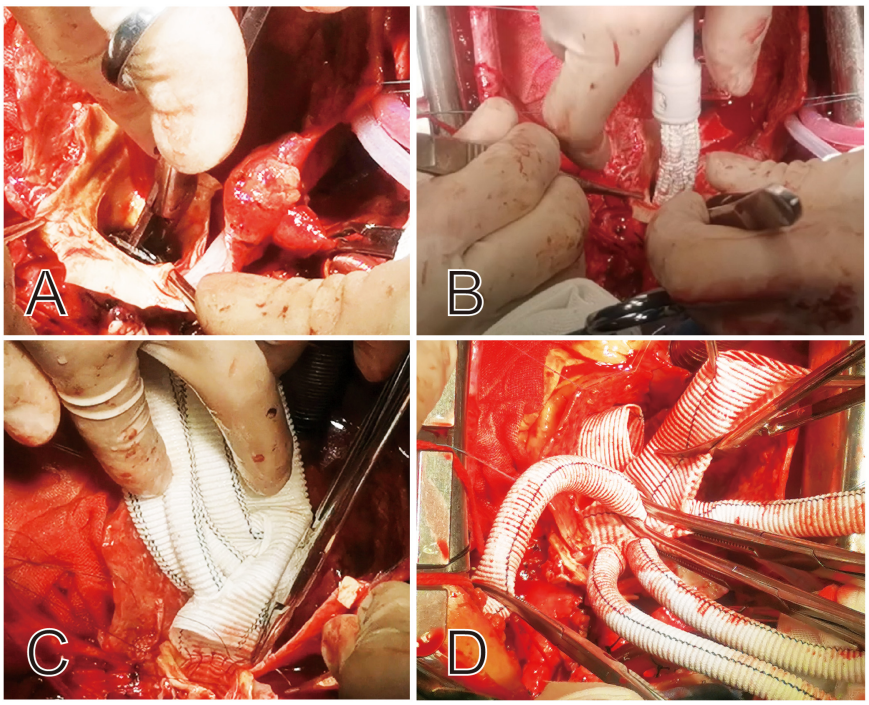

FIGURE 2 | Intraoperative view of the proximal portion of the deployed stent graft and the bare springs was cut off before completion of this anastomosis **(A,B)**. The proximal ends of the stent graft and aortic wall are sewn together to tetra-furcated graft **(C,D)**.

of proximal stent landing in the antegrade and retrograde dissection groups. 53.6% of the retrograde group had the initial proximal stent placed in landing zone 3 (<2 cm of the LSCA), and none had proximal landing in zone 4. In contrast, more than half of the antegrade group patients had proximal landing in zone 4. One patient of the retrograde group received debranching and TEVAR initially, leading to the location of the entry tear in the ascending aorta, corresponding to zone 0.

Interoperative Data and Surgical Details

As **Table 3** shows, in the choice of the surgical method, we mainly considered the anatomical location and severity of the new lesions. Chief aspects of lesion severity included the extent of the dissection tear and whether it was combined with a structural heart disorder. Sun's procedure was chosen in all patients to deal with complicated aortic arch lesions. Because all patients had recurrent type A dissection on the basis of TEVAR treatment for type B dissection, with aortic roots involvement, resulting in aortic valve regurgitation or coronary ischemia, our center selected Bentall procedure for repair. Patients without the above conditions underwent ascending aortic replacement for the proximal aorta. Concurrent use of Bentall procedure in the retrograde and antegrade groups were 25.0 and 22.7% (P = 1), respectively, whilst concurrent ascending aorta replacement procedure in the retrograde and antegrade groups were 75.0 and 77.3% (P = 1). Across both cohorts, coronary artery bypass grafting was performed in three patients (2%) and mitral valve repair in one patient (1%). The lengths of cardiopulmonary bypass time, cross-clamped time, and circulatory arrest time were 196.1 ± 41.1, 111.2 ± 30.6, and 28.0 (22.2, 34.8) minutes, respectively.

TABLE 3 | Intraoperative data.

Variables	Total (n = 50)	Retrograde (n = 28)	Antegrade (n = 22)	P-value
Operative time (h), Median (IQR)	7.5 (6.5, 8.9)	7.0 (6.0, 8.0)	8.0 (7.0, 9.9)	0.053
CPB-time (min), Mean ± SD	196.1 ± 41.1	186.9 ± 40.2	207.9 ± 40.1	0.073
ACCT (min), Mean ± SD	111.2 ± 30.6	104.0 ± 27.3	120.3 ± 32.7	0.060
DHCA-time (min), Median (IQR)	28.0 (22.2, 34.8)	28.0 (24.0, 33.0)	28.0 (21.2, 39.8)	0.696
Nasopharyngeal temperature (°C)	23.9 (23.0, 24.3)	23.9 (23.3, 24.3)	23.8 (22.9, 24.1)	0.487
Operative technique				
Bentall	12 (24.0)	7 (25)	5 (22.7)	1
Ascending aorta replacement	38 (76.0)	21 (75)	17 (77.3)	1
Concomitant procedures				
MVR	1 (2.0)	0 (0)	1 (4.5)	0.44
CABG	2 (4.0)	2 (7.1)	0 (0)	0.497

CPB, cardiopulmonary bypass; ACCT, aortic cross-clamp time; DHCA, deep hypothermia circulatory arrest; MVR, mitral valve replacement; CABG, coronary artery bypass grafting.

The cooling nasopharyngeal temperature was 23.9 (23.0, 24.3) °C.

The follow-up data were available for all survivors. Follow-up was performed on all patients after discharge until the end of the study period on September 5, 2020, or death. The mean follow-up period was 3 years. As **Table 4** shows, there was no statistical difference between the two groups in the major adverse events (neurological complications, respiratory failure, renal insufficiency requires dialysis, or secondary thoracotomy). All operations were successfully completed. The early mortality rate was 4.0% (2/50).

Five deaths occurred during the follow-up period, with the main causes of death after surgery listed in **Table 5**. Two patients with Marfan Syndrome had a thoracoabdominal aortic replacement one year after second surgery.

Kaplan–Meier survival curves (**Figure 3**) found no difference in post-operative survival between the two groups.

DISCUSSION

Thoracic endovascular aortic repair has been performed for more than 20 years since its first development for the treatment of aortic aneurysms (1) and dissections (9). In treating uncomplicated type B aortic dissection with appropriate anatomical conditions, current guidelines recommend an endovascular approach (10, 11). This strategy is technically effective and has the advantages of reduced trauma and quicker recovery. TEVAR promotes aortic remodeling in both acute and chronic dissections, increasing the true lumen diameter at the level of the stent graft (12). However, with the promotion of this technology and the increasing indications for hybrid surgery (2), retrograde TAAD (rTAAD) induced by previous endovascular stent-grafts is becoming increasingly recognized as the most catastrophic potential complication (3, 13). Whilst incidence of rTAAD is low, it has a high mortality (4). This can present as an early or late complication after TEVAR. It is a life-threatening complication that can be managed safely with early recognition and rapid delivery of open or hybrid repair (14). From January 2010 to October 2019, a total of 50 patients underwent surgery in our hospital for TAAD after a prior TEVAR, including antegrade dissection (n = 22) and retrograde dissection (n = 28). We selected open aortic repair in all patients, and the overall surgical outcomes were satisfactory, with repairs of both types of dissection having good long-term results upon post-operative follow-up. However, we should also note that there were two patients with rTAAD who died suddenly while waiting for surgery, and two patients that presented with rTAAD who were unconscious due to severe cerebral ischemia and their families refused surgery.

The inducement of retrograde dissection after TEVAR, and how to optimize the procedure to avoid this complication, has been widely studied.

Firstly, we believe that the TEVAR procedure is a technique that requires extensive surgical experience, which tends to be better performed in larger centers with better staffing and equipment as recommended by the guidelines (11). It's also important that this center have a team experienced in surgical repair to address any emergency surgical needs in the case of initial procedural failure. In this study, a large number of patients were referred from primary hospitals.

Secondly, it was previously supposed that retrograde dissection cases were associated with the use of proximal bare spring stent grafts (4), however, the results of further study found that the proximal endograft configuration was not associated with any difference in the incidence of retrograde dissection (15). In our study, it was found that all patients with retrograde dissection used proximal bare spring stent-grafts, and it could be found that the steel frame punctured the aortic intima. More studies have focused on the release strategy of stents, in particular,

TABLE 4 | Post-operative outcomes.

Variables	Total (n = 50)	Retrograde (n = 28)	Antegrade (n = 22)	P-value
Hospitalization-days (d), Median (IQR)	13.0 (10.0-20.0)	13.5 (9.8, 19.2)	13.0 (9.2, 24.5)	0.930
ICU-retention-times (d), Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0, 3.2)	2.0 (1.0, 6.2)	0.448
Ventilator-times (h), Median (IQR)	36.0 (17.2-91.6)	31.0 (16.6, 69.4)	39.5 (18.5, 168.1)	0.358
Post-operative complications				
Neurological complications, *n* (%)	3 (6.0)	3 (10.7)	0 (0)	0.246
Dialysis, *n* (%)	3 (6.0)	1 (3.6)	2 (9.1)	0.576
Respiratory failure, *n* (%)	2 (4.0)	1 (3.6)	1 (4.5)	1
Secondary thoracotomy, *n* (%)	5 (10.0)	2 (7.1)	3 (13.6)	0.643

ICU, intensive care unit.

TABLE 5 | Details of deaths during the follow-up period.

No	Gender	Age	PLZ	Interval times	Group	Operative procedures	Death times	Cause of death
1	Male	40	2	6 months	Retro.	Bentall + TAR + FET	37 days	Sepsis, lung infection, hepatic failure
2	Male	65	4	6 years	Ante.	Ascending aorta replacement + TAR + FET	4 days	Hemorrhagic shock, gastrointestinal bleeding
3	Female	51	2	4 years	Ante.	Ascending aorta replacement + TAR + FET	38 days	Cerebral infarction, post-operative infection
4	Male	35	1	2 months	Retro.	Ascending aorta replacement + TAR + FET	94 days	Multiple organ failure
5	Male	65	3	6 hours	Retro.	Ascending aorta replacement + TAR + FET	14 days	Liver and kidney failure

PLZ, proximal landing zone; TAR, total arch replacement; FET, frozen elephant trunk.

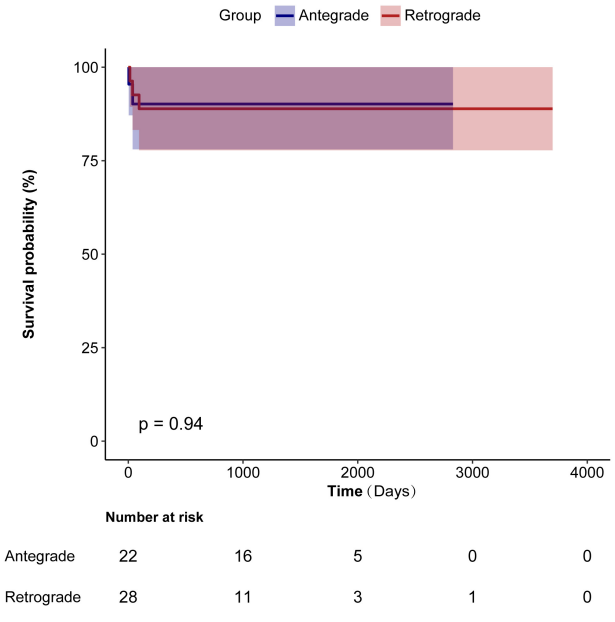

FIGURE 3 | Kaplan-Meier curves show overall survival comparing retrograde group and antegrade group.

during stent implantation across the arch, the adaptability of the stent to the aortic arch morphology must be considered. Lack of a secure landing zone, too close to the left subclavian artery, can lead to aortic mural damage due to inflexibility of the stent itself and the impact of prolonged blood flow (16). We noted that the previous proximal stent landing zones in the retrograde group were all in the unsafe zone, at-or-before zone 3, even if some were combined with surgical bypass surgery. Patients with evidence of a bird-beak configuration, after TEVAR with proximal landing zone 1 or 2, were more prone to stent-induced complications (17). A short proximal neck or steep angulation of landing zones were significantly correlated with greater incidence of TEVAR failure (18). Balloon expansion during stent release as well as the degree of oversizing of the stent itself is also an important factor responsible for retrograde dissection (15, 19). As Luehr et al. (20) pointed out, the use of stent grafts with protruding proximal bare springs and the implementation of oversizing and post-deployment ballooning should be avoided in patients undergoing hybrid arch procedures, particularly if the ascending aorta is dilated.

Thirdly, the fragility of the aortic wall and disease progression are potential contributing factors to rTAAD after TEVAR, especially in patients with Marfan syndrome, so we should avoid aortic arch stent grafting in Marfan patients (13). In our study, 2 Marfan patients developed antegrade TAAD after TEVAR treatment. After open repair, two patients underwent a later total thoracoabdominal aortic replacement after 1 year, with good outcomes at follow up. It seems that for such patients, aggressive expansion of open surgery rather than minimally invasive seems to be a better long-term option considering the likely need for further intervention.

From a hemodynamic point of view, retrograde dissection is typically more moderate in terms of blood flow velocity and false lumen perfusion than in antegrade dissection (21). Unsurprisingly, we found greater ascending aorta diameters and higher left ventricular ejection fractions in the antegrade dissection patient group. The location of primary tear in an aortic arch dissection can influence the degree of progression of the lesion. In cases involving the posterior pathway, there was generally a primary tear located in the arch or descending aorta, and cervical branch compromise was rare. However, lesions in the anterior aspect of the aortic arch were more likely to extend into the cervical branches. A false lumen pathway through the arch was strongly associated with cervical branch compromise in acute TAADs (22). Patients with primary intimal tears located in the convexity of the distal arch may be more likely to develop retrograde TAAD than patients with tears in the distal concavity (23). There was one retrograde dissection with an entry tear on the concave side, corresponding to the opening of the innominate artery, that underwent replacement of the ascending aorta alone.

Our protocol for managing the antegrade dissection groups was performed according to the standard surgical strategy for complicated TAAD, involving TAR and FET. Despite the high-risk nature of the complications, secondary open surgical or interventional procedures can be successfully performed with acceptable outcomes (24). For the treatment of retrograde dissection, many previous studies have explored this emergency situation. Zhang et al. (25) reported the use of coils and Onyx glue to create a thrombogenic environment in the retrograde false lumen, inducing thrombosis of the false lumen to enhance a proximal landing zone prior to stent graft deployment. An et al. (26) used elephant trunk implantation to treat eight retrograde TAADs. In patients who had received prior hybrid aortic repair, they successfully removed the proximal part of the stent while the distal part was left in place. Giles et al. (27) found increased propensity for secondary aortic intervention in cases with younger age, acute dissection with larger maximal aortic diameter at presentation, Marfan syndrome, when there was usage of arch vessel adjunctive procedures with the index TEVAR. Importantly, they also found that the occurrence of aorta-related reintervention does not affect survival. Dun et al. (28) described secondary open arch operations in the treatment of aortic arch disease after TEVAR, including 24 cases of retrograde type A aortic dissection, and eight cases of new antegrade aortic dissection, and found acceptable early and midterm outcomes.

However, in considering that the patient has undergone endovascular treatment, if there is then a subsequent TAAD, it may predict that the condition of the patient's aortic wall is unsuitable for the relevant procedural elements of stent release and proximal anchoring. There will also be significant limitations in the treatment of partial arch branch vessels. We hold a positive attitude toward the selection of the total arch replacement and the effectiveness of FET in the treatment of TAAD (after TEVAR) has been confirmed in previous studies (26, 29, 30). We believe that reconstructing the stability of the whole arch system is of chief importance. We should also consider the effect of the distal end of the existing stent on vascular compliance. The key to the procedure is to establish a stable relationship between the

elephant trunk stent and the previous stent. We prefer to trim the bare area at the proximal end of the previous stent and staple the frozen elephant trunk and the covered segment of the stent, as well as the vessel wall, in a "sandwich" fashion. Furthermore, in cases where the dissection does not involve the greater curvature of the aortic arch, we prefer the island anastomosis of the branching vessels to the graft, which can reduce the complexity of surgery to a certain extent and reduce the number of sutures. For cases that have undergone hybrid aortic repair in the past, our preference is to anastomose the supra-arch branches to the ascending aorta when performing ascending segment replacement.

Patients receiving open repair after prior TEVAR have good early outcomes and preservation of the stent-graft in the majority of cases (31). Canaud et al. (32) reported the results of open repair due to device failure or adverse events after TEVAR, a low mortality rate achieved despite the precarious pre-operative conditions and complex aortic pathologies of patients, including 4 retrograde type A dissections, eight stent-grafts were left *in situ*. Higashigawa et al. (33), reported some TEVAR-associated TAADs, the entry tear of 8 patients was located in the ascending aorta or the aortic arch away from the edges of stent grafts, similar to our description of the antegrade group, for the choice of their treatment modality, it is not completely consistent. However, all patients in our study were treated with TAR + FET, the 30-day mortality rate in our study was 4.0%. In comparison to the classic TAR with FET cohort in which the 30-day mortality rate was 7.8% (34), this result is satisfactory and reliable. We emphasized the purpose of our follow-up recommendation because we were concerned about the distal unstented aorta segments, especially in patients with Marfan syndrome. According to the imaging data during follow-up available to us, 32/50 patients underwent CTA in our hospital for the first time within one year after the operation, and most of them chose to undergo CTA scanning in 3 months after discharge. Through our comparison of CTA before and after discharge, we found that FET as the stable bridge between the tetra-furcate graft and the distal TEVAR stent had achieved good results. Since the proximal end of the FET is sutured on the aortic wall, when the blood flows through the FET to the inside of the distal TEVAR stent, it would not have a blow to the aorta. In 30 patients, good morphological compliances were observed. It is worth noting that during a follow-up period of about one year, we found aneurysm-like dilation of the distal aorta in two cases of Marfan patients, who received another surgical treatment in our hospital. Other patients came to our hospital outpatient consultation with imaging films, and the outpatient visit records were also an important basis for us to review the survival status.

The study is limited by its retrospective nature, small sample size, and the lack of a control group. Only eight patients in this study had their first TEVAR treatment in our hospital, so we could not know all the details about their initial TEVAR procedures. Hence, we were unable make any conclusion about the risk factors of recurrent dissection without further analysis. The mortality rate of dissection after TEVAR may be relatively low in patients who can receive timely and effective surgical treatment. Importantly, many patients with retrograde TAAD may die outside the hospital, so there is possibility of a selection bias. Most patients were located in areas that were far away from our hospital, and due to economic considering, many patients chose to review CTA in the local hospital for the first review after discharge, due to regulatory and privacy policy restrictions, we were unable to obtain their raw DICOM data. There were also some patients with poor compliance, during the follow-up process, they replied that they did not undergo the required CTA scan because they did not feel uncomfortable. Lack of some CT scan information at follow-up represent also an important limitation. Lastly, in evaluating the choice of surgical approach, we are a single central research site and would need to further expand the sample size, and expand our comparison to other novel surgical techniques.

CONCLUSION

In conclusion, this study showed that the total arch replacement with frozen elephant trunk technique was feasible and effective for patients with type A aortic dissection following previous thoracic endovascular repair. The antegrade TAAD group had longer cardiopulmonary bypass time and aortic-clamp time, but in terms of long-term follow-up, there was no difference in post-operative survival between the antegrade and retrograde groups. The surgical success rate and long-term prognosis of patients undergoing timely surgery are satisfactory.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Anzhen Hospital. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

HZ and WJ designed the whole conception. HL, JZ, YL, and LS provided the administrative support and completed the surgical operations. ZF and HL provided the data of patients. ZF collected and assembled the data. ZF, HL, and TW contributed in writing the manuscript. All authors contributed to the article and approved the submitted version.

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Preoperative Nomogram and Risk Calculator for Postoperative Hypoxemia and Related Clinical Outcomes Following Stanford Type A Acute Aortic Dissection Surgery

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Background: Hypoxemia is a common complication after Stanford type A acute aortic dissection surgery (AADS), however, few studies about hypoxemia after AADS exist. The aims of this study were to identify independent risk factors for hypoxemia after AADS and to clarify its association with clinical outcomes.

Methods: Patients undergoing AADS from 2016 to 2019 in our hospital were identified and used as a training set. Preoperative variables were first screened by univariate analysis and then entered into a multivariate logistic regression analysis to identify independent risk factors. A nomogram and an online risk calculator were constructed based on the logistic model to facilitate clinical practice and was externally validated in an independent dataset.

Results: Severe hypoxemia developed in 119 of the 492 included patients (24.2%) and poorer clinical outcomes were observed in these patients. Five independent risk factors for severe hypoxemia after AADS were identified by multivariate analysis, including older age, smoking history, renal insufficiency, higher body mass index, and white blood cell count. The model showed good calibration, discrimination, and clinical utility in the training set, and was well validated in the validation set. Risk stratification was performed and three risk groups were defined as low, medium, and high risk groups. Hypertension was identified as an independent risk factor for moderate hypoxemia besides the five predictors mentioned above, and renal insufficiency was not significant for mild hypoxemia by multivariate analysis. In addition, although frozen elephant

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trunk was associated with increased risk of postoperative hypoxemia in the univariate analysis, frozen elephant trunk was also not identified as an independent risk factor for postoperative hypoxemia in the multivariate analysis.

Conclusion: Hypoxemia was frequent following AADS, related to poorer clinical outcomes. Predictors were identified and a nomogram as well as an online risk calculator predicting severe hypoxemia after AADS was developed and validated, which may be helpful for risk estimation and perioperative management.

Keywords: hypoxemia, Stanford type A aortic dissection, risk factor, prediction model, nomogram

INTRODUCTION

Stanford type A acute aortic dissection is known as a lethal cardiovascular emergency, associated with high disability and mortality (1). Prompt surgical interventions remain the most important treatment despite of considerable improvements have been achieved in diagnostic techniques and medical options over the past few decades (2). Frustratingly, the circumstances of the overall survival after Stanford type A acute aortic dissection surgery (AADS) is hardly optimistic and a high percentage of patients may develop multiple postoperative complications (1).

Postoperative hypoxemia is one of the most common complications after cardiovascular surgery, related to increased risk of morbidity and mortality (3–5). The prevalence of hypoxemia varies widely in the literature due to different definitions and surgical populations sampled in different studies (3, 5–7). Several studies aimed to identify risk factors for the development of hypoxemia after cardiac surgery have been conducted and some predictors have been reported such as smoking history and obesity (3, 5–10). However, only very few studies were carried out in patients undergoing AADS and without exception those studies were performed on small sample sizes. Furthermore, most of those studies included preoperative, intraoperative, and postoperative variables, which may limit the clinical utility of early prediction. Moreover, none of those previous studies developed or externally validated a reasonable visual model such as risk score and risk calculator, which may facilitate clinical application. In addition, no previous studies have systematically investigated the predictors, respectively, for mild, moderate, and severe postoperative hypoxemia. Therefore, our understanding of the risk factors for hypoxemia after AADS is still limited, and the construction and validation of an authentic clinical risk prediction model is still urgently needed. Another noteworthy point is that previous studies only reported the relationship between hypoxemia and clinical outcomes with the results of univariate analysis, which may be largely influenced by confounding factors. Nonetheless, no previous studies have deeply explored the relationship between postoperative hypoxemia and clinical outcomes through multivariate analysis or propensity score matching analysis in patients undergoing AADS.

Abbreviations: AADS, Stanford type A acute aortic dissection surgery; AUC, area under the receiver operating characteristic curve; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PaO_2–FiO_2, arterial oxygen tension–inspired oxygen concentration; ROC, receiver operating characteristic curve.

The aims of this study were first to identify independent risk factors for the development of severe, moderate, and mild hypoxemia, respectively, in patients undergoing AADS and develop risk prediction models; and second to deeply explore the relationship between hypoxemia and clinical outcomes by univariate and propensity score matching analysis.

MATERIALS AND METHODS

Ethics Statement

This study was conducted in accordance with ethical statement of the Declaration of Helsinki. The Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No. IORG0003571) approved this study. Written informed consent was waived because of its observational, retrospective nature.

Study Population and Data Extraction

Consecutive adult patients (age ≥18 years) who underwent AADS in a single cardiovascular center from January 2016 to December 2019 were enrolled. Patients who died intraoperatively were excluded from this study. Clinical data were collected using the hospital's electronic medical records management system. Preoperative variables incorporated in this study were as follows: demographic variables included sex, age, height, weight, body mass index, smoking, and drinking history; underlying conditions included diabetes mellitus, hypertension, chronic bronchitis, pulmonary emphysema, peripheral vascular disease, cerebrovascular disease, renal insufficiency, gastrointestinal tract disease, atrial fibrillation, cardiac surgery history, general surgical history, New York Heart Association class, pulmonary artery hypertension, pericardial effusion, left ventricular ejection fraction, diameter of the left atrium, left ventricle, right atrium, and right ventricle; laboratory blood tests included white blood cell count, red blood cell count, hemoglobin, platelet count, serum creatinine, serum albumin, and serum globulin. Operative variables included combined surgical types, aortic root surgery, and frozen elephant trunk implantation.

In addition to the data obtained from our hospital, we extracted some clinical data from the MIMIC-IV database[1] to externally validate the risk prediction model for severe hypoxemia. MIMIC-IV database is a large, longitudinal database

[1]https://mimic.mit.edu/

that incorporates critical care data at the Beth Israel Deaconess Medical Center between 2008 and 2019. Patient identifiers were removed in this database to strictly protect patient confidentiality. The database is publicly available and allows for data sharing only after passing the Collaborative Institutional Training Initiative examination. One of the authors who had access to MIMIC-IV in our study group specialized in data extraction from this database. Following diagnostic codes of the International Classification of Diseases editions (ICD-9 and ICD-10), the patients diagnosed with "thoracic aortic dissection" and treated with surgical interventions were extracted from the MIMIC-IV database.

Endpoints and Definitions

The primary endpoint of this study was hypoxemia after AADS. The arterial oxygen tension–inspired oxygen concentration (PaO_2–FiO_2) ratios were calculated for the perioperative period. The Berlin definition has been widely accepted for acute respiratory distress syndrome which proposes three categories of hypoxemia on the basis of the degree of the condition. In the present study, according to the diagnostic criteria of the Berlin definition, we defined severe hypoxemia as $PaO_2/FiO_2 \leq 100$ mmHg, moderate hypoxemia as 100 mmHg $< PaO_2/FiO_2 \leq 200$ mmHg, and mild hypoxemia as 200 mmHg $< PaO_2/FiO_2 \leq 300$ mmHg. Afterward, all patients were divided into one of the categories based on the worst values of the recorded PaO_2/FiO_2 ratios within the first 24 h postoperatively.

The secondary endpoints were postoperative pneumonia, reintubation, tracheostomy, readmission to intensive care unit (ICU), in-hospital mortality, the lengths of mechanical ventilation, ICU stay, and hospital stay.

Statistical Analysis

Statistical analyses were performed using SPSS (IBM SPSS Statistics 26.0, SPSS Inc., Chicago, IL, United States) and R software (version 4.0.5[2]). *P*-values less than 0.05 (two-tailed) were considered statistically significant.

The Kolmogorov–Smirnov test was used to evaluate whether continuous variables were distributed normally. Continuous variables were expressed as means ± standard deviations when normally distributed and as medians (interquartile ranges) when skewed. Categorical variables were expressed as counts (percentages). A multiple imputation approach was used to handle with missing data. Univariate analysis was first conducted to screen potential risk factors. Normally distributed continuous variables with homogeneous variance were compared using Student's *t*-test and otherwise using Mann–Whitney *U*-test. Categorical variables were compared by Chi-square test or Fisher's exact test. Variables screened by univariate analysis were then entered into a forward stepwise multivariate logistic regression analysis procedure to identify significant risk factors. The odds ratio (OR) was calculated with 95% confidence interval (CI). A nomogram on the basis of the logistic rule was then constructed and an online risk calculator was generated.

[2]www.R-project.org/

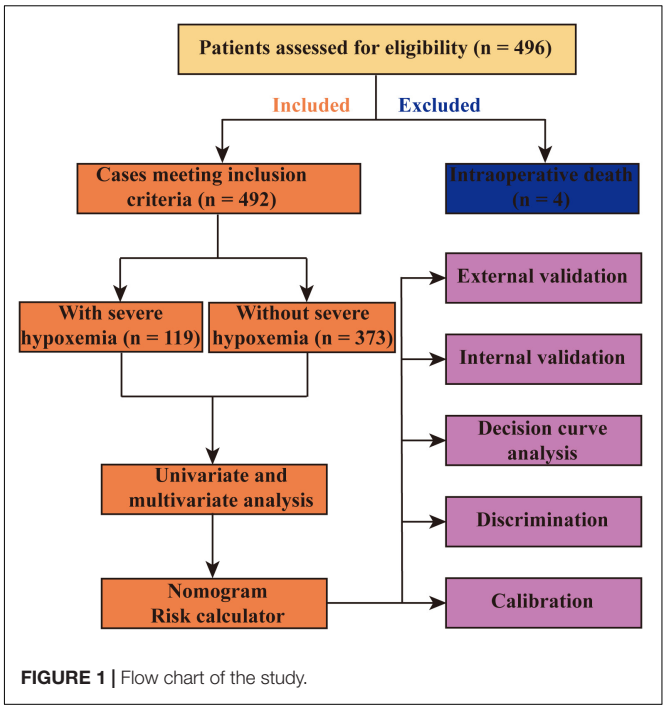

FIGURE 1 | Flow chart of the study.

The development and internal validation (bootstrap method using 1000 replications) of the model were performed in the training set and the external validation was performed using data from the MIMIC-IV database. Both visual inspection and Hosmer–Lemeshow goodness-of-fit test were used to evaluate the calibration. The area under the receiver operating characteristic (ROC) curve (AUC) or c-index were used to assess the discrimination. The difference between two AUCs was compared by Delong method (11). Decision curve analysis was performed to assess the clinical utility. To balance important patient characteristics between groups, the propensity score matching analysis was performed with a 1:1 nearest neighbor matching algorithm (a caliper of 0.02) without replacement, and the propensity scores were calculated by the logistic regression model. The flow chart of this study is presented in **Figure 1**.

RESULTS

Demographic Characteristics

Among the 496 eligible patients who underwent AADS, 4 died intraoperatively and were excluded. The remaining 492 patients met the inclusion criteria and were included in the present study (**Figure 1**). The mean age of the included patients was 49.6 ± 11.3 years and 75.6% of them were male patients. The overall morbidity rate of severe hypoxemia within the first 24 h after AADS was 24.2%, moderate hypoxemia was 46.1%, and 93.9% of the patients had a PaO_2/FiO_2 value of ≤300 mmHg.

Multiple underlying conditions and comorbidities existed in this study population. Hypertension was the most common comorbidity, existed in 68.1% of the patients, smoking history in 43.9%, drinking history in 35.8%, renal insufficiency in 35.2%,

chronic bronchitis in 21.5%, cerebrovascular disease in 17.9%, peripheral vascular disease in 13.6%, gastrointestinal tract disease in 8.5%, cardiac surgery history in 6.5%, diabetes mellitus in 4.3%, and pulmonary artery hypertension in 2.8% of the patients.

Development of the Risk Prediction Model

The development of the risk prediction model for severe hypoxemia after AADS was conducted using data from our hospital. Firstly, we conducted univariate analysis to screen possible risk factors, the results of which are presented in **Table 1**. Collinearity diagnostics were conducted prior to the construction of a multivariate model. Factors with $P < 0.1$ or considered to be clinically important were further analyzed by multivariate logistic regression analysis. After screening, the variables that entered into the multivariate regression included male, age, body mass index, smoking history, drinking history, chronic bronchitis, pulmonary emphysema, peripheral vascular disease, renal insufficiency, diameter of the left atrium, white blood cell count, red blood cell count, hemoglobin, serum creatinine, combined surgical types, aortic root surgery, and the implantation of frozen elephant trunk. Multivariate analysis identified five significant risk factors in the final model, including older age, smoking history, renal insufficiency, higher body mass index, and white blood cell count (**Table 2**). A nomogram on the basis of these predictors and the logistic rule was then constructed to predict the probability of severe hypoxemia after AADS (**Figure 2**). The relative importance of these risk factors can be reflected by scaling their scores to 0–100 points based on the corresponding regression coefficients.

By summing the points of all the predictors, the probability of severe hypoxemia in a postoperative patient can be easily predicted on the nomogram. Older patients who have smoking history, renal insufficiency, higher body mass index, and higher white blood cell count may have higher scores and resultant higher probabilities of severe hypoxemia. A concrete case is shown in **Figure 2**. To better accommodate the needs of modern clinical work, we also created and provided an interactive network risk calculator for severe hypoxemia after AADS which is available online.[3]

Validation and Assessment of the Risk Prediction Model

The external validation of the risk prediction model for severe hypoxemia after AADS was conducted using data from MIMIC-IV database. After a series of screening, 272 eligible cases with complete medical records were finally extracted and further analyzed as a validation set. The model calibrated well in two datasets by both visual inspection and goodness-of-fit test, with Hosmer–Lemeshow χ^2 values of 6.364 ($P = 0.607$, **Figure 3A**) in the training set and 3.271 ($P = 0.916$, **Figure 3B**) in the validation set. The model showed good discrimination in both the training set [AUC = 0.795, 95% CI, (0.754–0.837)] and the validation set [AUC = 0.776, 95% CI, (0.716–0.835)], without significant

[3]https://hypoxemia-prediction.shinyapps.io/dynnomapp/

TABLE 1 | Univariate analysis of possible risk factors for severe hypoxemia after AADS.

Characteristic	Without severe hypoxemia *n* = 373 (%)	With severe hypoxemia *n* = 119 (%)	χ^2/Z/*t*	*P*-value
Demographics				
Male	266 (71.3)	106 (89.1)	15.434	<0.001
Age (years)	49.42 ± 11.27	50.35 ± 11.44	0.785	0.433
Body mass index (kg/m^2)	24.71 ± 3.51	27.30 ± 3.60	6.968	<0.001
Smoking history	145 (38.9)	71 (59.7)	15.833	<0.001
Drinking history	124 (33.2)	52 (43.7)	4.291	0.038
Underlying conditions				
Hypertension	248 (66.5)	87 (73.1)	1.820	0.177
Diabetes mellitus	18 (4.8)	3 (2.5)	1.173	0.279
Chronic bronchitis	87 (23.3)	19 (16.0)	2.890	0.089
Pulmonary emphysema	20 (5.4)	4 (3.4)	0.778	0.378
Cerebrovascular disease	71 (19.0)	17 (14.3)	1.385	0.239
Peripheral vascular disease	58 (15.5)	9 (7.6)	4.892	0.027
Renal insufficiency	100 (26.8)	73 (61.3)	47.195	<0.001
Gastrointestinal tract disease	32 (8.6)	10 (8.4)	0.004	0.952
Atrial fibrillation	2 (0.5)	2 (1.7)	1.465	0.226
Cardiac surgery history	24 (6.4)	8 (6.7)	0.012	0.912
General surgery history	76 (20.4)	25 (21.0)	0.022	0.882
New York Heart Association III–IV	32 (8.6)	9 (7.6)	0.122	0.727
Pulmonary artery hypertension	13 (3.5)	1 (0.8)	2.283	0.131
Pericardial effusion	100 (26.8)	33 (27.7)	0.039	0.844
Diameter of the left atrium (cm)	3.5 (3.1, 3.8)	3.7 (3.4, 4.0)	3.861	<0.001
Diameter of the left ventricle (cm)	4.8 (4.4, 5.2)	4.9 (4.6, 5.3)	1.260	0.208
Diameter of the right atrium (cm)	3.7 (3.4, 4.0)	3.7 (3.5, 4.0)	0.906	0.365
Diameter of the right ventricle (cm)	3.6 (3.3, 3.8)	3.6 (3.4, 3.9)	1.378	0.168
Left ventricular ejection fraction (%)	62 (60, 65)	62 (60, 65)	0.398	0.691
Laboratory values				
White blood cell count ($\times 10^9$/L)	9.5 (7.0, 12.0)	12.0 (9.2, 14.2)	5.682	<0.001
Red blood cell count ($\times 10^{12}$/L)	4.2 (3.7, 4.5)	4.3 (3.9, 4.6)	2.556	0.011
Hemoglobin (g/L)	125 (113, 138)	133 (122, 141)	3.137	0.002
Platelet count ($\times 10^9$/L)	159 (128, 207)	156 (120, 196)	1.059	0.290
Serum creatinine (μmol/L)	76.7 (63.9, 101.4)	98.3 (74.0, 136.7)	5.144	<0.001
Serum albumin (g/L)	37.9 (34.9, 40.9)	37.8 (34.9, 40.6)	0.328	0.743
Serum globulin (g/L)	25.6 (22.9, 28.5)	25.3 (22.5, 27.5)	1.158	0.247
Operative variables				
Surgical types			7.833	0.098
Isolated AADS	241 (64.6)	81 (68.1)		
Combined valve surgery	88 (23.6)	22 (18.5)		
Combined coronary surgery	21 (5.6)	5 (4.2)		
Combined valve and coronary surgery	16 (4.3)	11 (9.2)		
Combined other surgical types	7 (1.9)	0 (0.0)		
Aortic root surgery			1.964	0.580
Ascending aorta replacement	246 (66.0)	76 (63.9)		
David procedure	17 (4.5)	4 (3.4)		
Bentall procedure	94 (25.2)	36 (30.2)		
Other procedures	16 (4.3)	3 (2.5)		
Frozen elephant trunk	210 (56.3)	80 (67.2)	4.451	0.035

AADS, Stanford type A acute aortic dissection surgery.

TABLE 2 | Multivariate analysis of independent risk factors for severe hypoxemia after AADS.

Characteristic	Coefficient	Standard error	OR (95% CI)	*P*-value
Renal insufficiency	1.010	0.243	2.746 (1.707–4.418)	<0.001
Smoking history	0.881	0.242	2.414 (1.503–3.879)	<0.001
Age (years)	0.039	0.012	1.040 (1.016–1.065)	0.001
Body mass index (kg/m^2)	0.193	0.038	1.213 (1.125–1.307)	<0.001
White blood cell count (×10^9/L)	0.130	0.033	1.139 (1.067–1.216)	<0.001

AADS, Stanford type A acute aortic dissection surgery; CI, confidence interval; OR, odds ratio.

difference between the two AUCs (P = 0.594, **Figure 3C**). To assess the clinical utility of the model, we conducted decision curve analysis and plotted decision and clinical impact curves. The decision curves indicated that patients could obtain more clinical net benefits across almost the whole range of threshold probabilities than either the treat-all scheme and the treat-none scheme in both the training and validation sets (**Figure 3D**). The clinical impact curves also indicated that the model had remarkable clinical usefulness (**Figures 3E,F**).

We further investigated to identify independent risk factors for moderate and mild hypoxemia. The screening process was similar to that described above, which was also conducted using a univariate analysis and a multivariate logistic regression analysis. For moderate hypoxemia, in addition to the five independent risk factors identified above, hypertension was identified as another independent risk factors (**Supplementary Table 1**). The model showed good discriminative ability [AUC = 0.815, 95% CI, (0.770–0.859)] and calibrated well (Hosmer–Lemeshow χ^2 = 4.668, P = 0.792). For mild hypoxemia, renal insufficiency was not significant by multivariate analysis and finally only four variables (age, smoking history, body mass index, and white blood cell count) remained in the logistic model (**Supplementary Table 2**). This model also showed excellent discrimination [AUC = 0.861, 95% CI, (0.795–0.927)] and calibration (Hosmer–Lemeshow χ^2 = 4.898, P = 0.768).

Risk Stratification

Based on the prediction model for severe hypoxemia and clinical practice, we further performed a risk stratification to facilitate clinical application (**Table 3**). We selected predicted probabilities of 0.1 and 0.3 as the cutoff values and stratified the study population into 3 risk intervals named low, medium, and high risk groups, corresponding to points of <215, 215–251, and >251 on the graphical nomogram. In this study, approximately one-third of the patients were, respectively, divided into low (31.1%), medium (36.4%), and high risk groups (32.5%).

Clinical Outcomes

The overall mortality of the included patients was 9.96% (49/492), with a rate of 6.7% in patients without severe hypoxemia versus 20.2% in those with severe hypoxemia (P < 0.001). Significant differences of other poor outcomes were also observed between patients with and without severe hypoxemia in the results of univariate analysis (**Table 4**). To further reveal the relationship between severe hypoxemia and

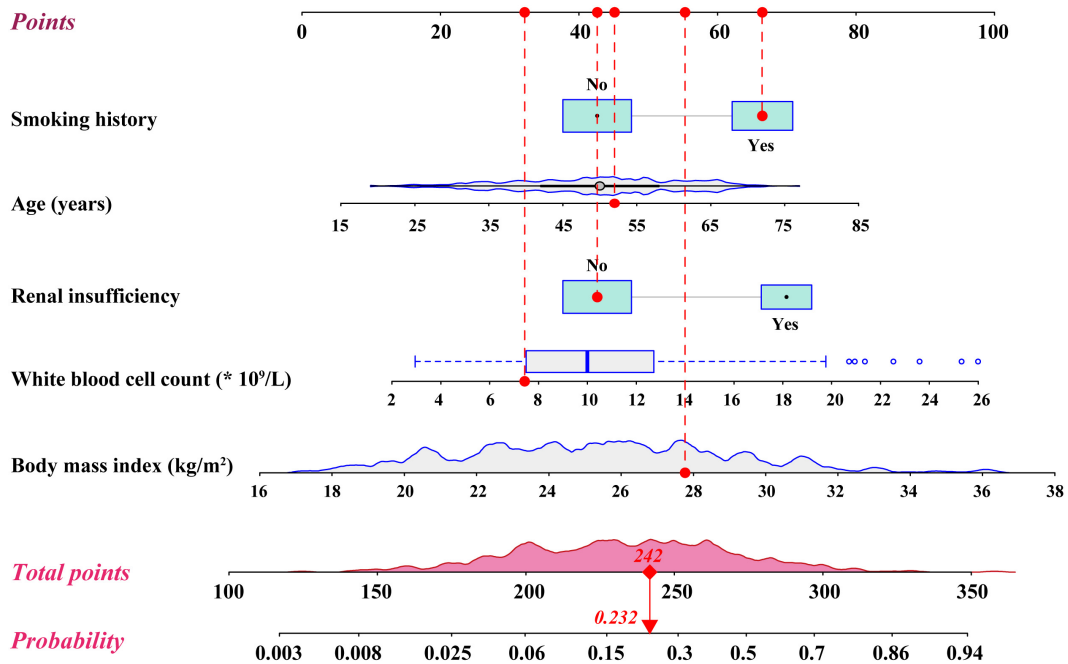

FIGURE 2 | Nomogram for the prediction of severe hypoxemia in patients undergoing Stanford type A acute aortic dissection surgery.

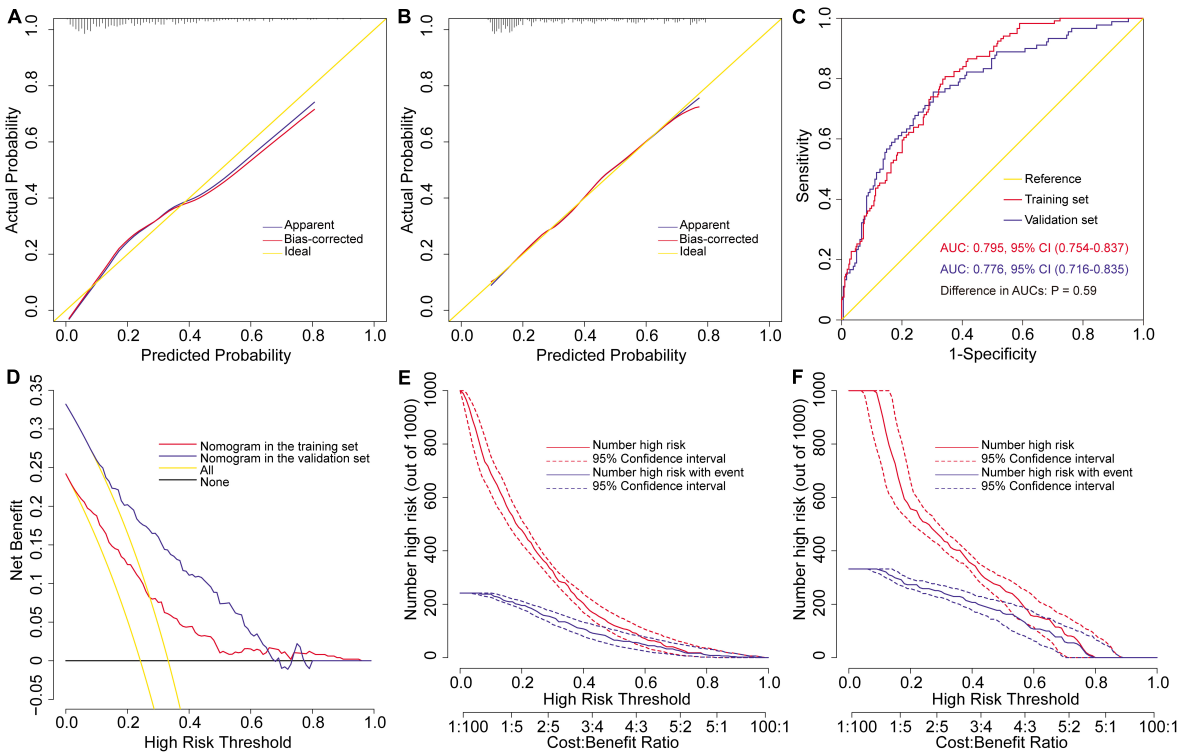

FIGURE 3 | Assessment and validation of the preoperative nomogram for severe hypoxemia in patients undergoing Stanford type A acute aortic dissection surgery. Calibration plots in the training set **(A)** and the validation set **(B)**, ROC curves in the two sets **(C)**, decision curves in the two sets **(D)**, and clinical impact curves in the training set **(E)** and the validation set **(F)**. AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic curve.

outcomes, we performed propensity score matching analysis and yielded 103 matched pairs of patients. In this new study population, the differences of mechanical ventilation, pneumonia, the length of ICU stay, the length of hospital stay and mortality remained significant between two groups. However, the statistical differences were eliminated concerning reintubation, tracheotomy and readmission to ICU, despite the absolute numbers and rates were higher in patients with severe hypoxemia (**Table 5**).

In the same way, we compared these outcomes between patients with and without moderate hypoxemia and mild hypoxemia. Compared to those without moderate hypoxemia, patients with moderate hypoxemia had significantly poorer outcomes in the results of univariate analysis (**Supplementary Table 3**). Nevertheless, the differences were eliminated concerning pneumonia, reintubation, readmission to ICU and the length of hospital stay after propensity score matching (**Supplementary Table 4**). The results of univariate analysis between patients with and without mild hypoxemia are displayed in **Supplementary Table 5**. After propensity score matching, no differences were observed with regard to those outcomes between patients with and without mild hypoxemia (**Supplementary Table 6**).

TABLE 3 | Risk intervals of severe hypoxemia based on the nomogram and clinical practice.

Risk intervals	Low risk (<215 points)	Medium risk (215–251 points)	High risk (>251 points)
Estimated probability (%)	<10	10–30	>30
Observed probability, % (95% CI)	5.2 (4.8–5.6)	18.8 (18.0–19.7)	48.3 (46.0–50.7)
No. of patients (%)	153 (31.1)	179 (36.4)	160 (32.5)

CI, confidence interval.

DISCUSSION

Hypoxemia has been recognized as an important indicator of increased risk of poor outcomes in patients undergoing cardiovascular surgery (11), which was again confirmed by the results of this study. The morbidity rate reported in the literature varied due to different definitions and surgical populations (3, 5–7). In this study, the observed incidence of severe hypoxemia after AADS was 24.2%, moderate hypoxemia was 46.1%, and 93.9% of the patients had a PaO_2/FiO_2 value of $\leq$300 mmHg. Adverse outcomes after AADS were more common than other cardiovascular surgeries due to the complicated procedures with greater trauma and longer surgical time. The

TABLE 4 | Clinical outcomes in patients with and without severe hypoxemia after AADS.

Variables	All patients *n* = 492 (%)	Without severe hypoxemia *n* = 373 (%)	With severe hypoxemia *n* = 119 (%)	χ^2/Z	*P*-value
Mechanical ventilation (h)	63.1 (40.3, 94.9)	57.1 (38.2, 86.8)	92.8 (63.1, 157.5)	7.389	<0.001
Pneumonia	170 (34.6)	102 (27.3)	68 (57.1)	35.421	<0.001
Reintubation	72 (14.6)	45 (12.1)	27 (22.7)	8.152	0.004
Tracheostomy	55 (11.2)	30 (8.0)	25 (21.0)	15.274	<0.001
Readmission to ICU	44 (8.9)	24 (6.4)	20 (16.8)	11.919	0.001
ICU stay (h)	154.3 (108.1, 254.5)	135.5 (91.0, 207.0)	230.2 (155.6, 368.6)	7.430	<0.001
Hospital stay (days)	21 (17, 27)	20 (16, 26)	23 (19, 33)	3.937	<0.001
Mortality	49 (10.0)	25 (6.7)	24 (20.2)	18.242	<0.001

AADS, Stanford type A acute aortic dissection surgery; ICU, intensive care unit.

TABLE 5 | Clinical outcomes in patients with and without severe hypoxemia following AADS after propensity score matching.

Variables	Included patients *n* = 206 (%)	Without severe hypoxemia *n* = 103 (%)	With severe hypoxemia *n* = 103 (%)	χ^2/Z	*P*-value
Mechanical ventilation (h)	70.0 (43.9, 120.0)	61.1 (40.5, 92.8)	91.2 (61.7, 141.3)	4.171	<0.001
Pneumonia	86 (41.7)	31 (30.1)	55 (53.4)	11.498	0.001
Reintubation	41 (19.9)	18 (17.5)	23 (22.3)	0.761	0.383
Tracheostomy	33 (16.0)	13 (12.6)	20 (19.4)	1.768	0.184
Readmission to ICU	25 (12.1)	9 (8.7)	16 (15.5)	2.231	0.135
ICU stay (h)	180.1 (114.3, 317.2)	144.0 (109.0, 275.1)	210.3 (154.5, 326.5)	4.049	<0.001
Hospital stay (days)	22 (18, 29)	21 (16, 27)	23 (19, 32)	2.134	0.033
Mortality	25 (12.1)	7 (6.8)	18 (17.5)	5.509	0.019

AADS, Stanford type A acute aortic dissection surgery; ICU, intensive care unit.

overall mortality of this study population was 9.96%, similar to previous reports (1). However, the risk of mortality and several other poor outcomes increased significantly in patients suffering from severe and moderate hypoxemia, which highlighted the necessity of identifying significant predictors and constructing risk prediction models.

In this study, we used data from 492 patients who underwent AADS at a single cardiovascular center to identify independent risk factors and develop risk prediction models for severe, moderate, and mild hypoxemia. By univariate and multivariate logistic regression analysis, a total of six independent predictors related to the development of postoperative hypoxemia were identified, including age, body mass index, smoking history, hypertension, renal insufficiency, and white blood cell count. A nomogram predicting the probability of severe hypoxemia after AADS was then constructed and externally validated using data from MIMIC-IV database. The nomogram model preformed well with regard to discrimination, calibration, and clinical utility in both the training and validation sets. To our knowledge, this is the first attempt to construct and validate a nomogram and the first online risk calculator available in this field worldwide. No significant difference was found regarding the discriminative ability between the two sets, which minimized the possibility of overfitting and improved the reliability of generalization. Finally, three risk intervals were defined as low, medium, and high risk groups on the basis of the nomogram and clinical practice.

Older age has been reported to be associated with the development of hypoxemia in various surgeries (7, 12–14), which was consistent with the results of this study. Shi et al. investigated the incidence and risk factors for early postoperative hypoxemia in patients undergoing on-pump coronary artery bypass grafting (7). They found that the incidence rate of postoperative hypoxemia ($PaO_2/FiO_2 \leq 200$ mmHg) within the first 24 h was 37.8% and older age was an independent predictor associated with early postoperative hypoxemia by multiple logistic regression analysis. Szeles et al. explored the risk factors for severe hypoxemia after myocardial revascularization, finding that age was an independent predictors of severe hypoxemia by multivariate analysis. In this study, the average age of the included patients was 49.6 years, which was younger than that of previous reports. Nevertheless, the incidence rate of postoperative hypoxemia increased significantly with age.

Another significant predictor identified by multivariate analysis for postoperative hypoxemia was body mass index, which contributed the widest range of weight among all these predictors. This was in agreement with the results of many previous studies, in which higher body mass index or obesity have been widely reported to be independently associated with the development of postoperative hypoxemia (5–8, 10, 13, 15, 16). Marco et al. conducted a single-center retrospective study in 5023 patients who underwent cardiac surgery to investigate the incidence and predictors of postoperative hypoxemia and its relationship with the length of ICU stay (5). They found that postoperative hypoxemia developed in 30.6% of the patients and obesity was an independent risk factor for postoperative hypoxemia, which was a determinant of the length of ICU stay.

Another recent single-center study conducted by Gong et al. reported that the incidence of severe hypoxemia was 36.6% and increased body mass index was an independent predictors for severe hypoxemia in patients undergoing surgery for acute type A aortic dissection (6). They believed that the obvious decrease in lung compliance and respiratory resistance in obese patients may be associated with the breathing difficulties and resultant hypoxemia. In addition, inflammatory response and oxidative stress may be involved in the process of lung injury of aortic dissection caused by obesity, which provided new ideas for the treatment (6).

Smoking history as an independent predictor for postoperative hypoxemia has also been reported in various surgeries, which was also identified in our analysis (10, 17, 18). Santos et al. conducted a retrospective cohort study in patients undergoing coronary artery bypass graft to detect factors associated with the occurrence of hypoxemia and found that the incidence of hypoxemia was 55% and higher body mass index and smoking were significant predictors (10). Wetterslev et al. conducted a prospective study to explore the predictors for postoperative hypoxemia after upper abdominal surgery in patients without preoperative cardiopulmonary dysfunction (18). They found that PaO_2 during anesthesia and an elaborated history of former smoking habits and pack-years were two independent risk factors which may provide new tools to select patients for further research in prevention of postoperative hypoxemia and complications. Another pilot cross-sectional study conducted by Mohamed et al. reported that smoking carried more risk of intraoperative deterioration of arterial oxygen tension compared to non-smokers during one lung ventilation for patients undergoing video-assisted thoracoscopic surgery and prediction of such intraoperative respiratory complication should be considered for such patients (17).

White blood cell count was also identified as independent risk factors for all the three categories of postoperative hypoxemia by multivariate analysis. As a biomarker reflecting systemic inflammatory response, the increase of white blood cell represents higher inflammatory responses which may contribute to respiratory dysfunction and thus relates to hypoxemia (19). Ge et al. conducted a single-center retrospective study to identify the independent risk factors for postoperative hypoxemia in patients with acute aortic dissection and developed and validated a nomogram model to facilitate the prediction (9). They found that white blood cell was independently associated with postoperative hypoxemia, with an OR value of 1.21 (95% CI: 1.06–1.40, $P = 0.008$). Another study designed to identify the risk factors for hypoxemia following surgical repair of acute type A aortic dissection by Liu et al. reported that hypoxemia occurred in 30% of the included patients and preoperative white blood cell count was independently related to the development of postoperative hypoxemia (20). Recently, the relationship between inflammatory response and hypoxemia has attracted increasing attention, which may provide new and enlightening insight (21).

Although not identified to be significant for the development of severe hypoxemia, hypertension was identified as an independent predictor for moderate hypoxemia in our analysis. This was very similar to the results of a previous study conducted by Zhou et al., in which they found that only hypertension was independent risk factors for postoperative hypoxemia ($PaO_2/FiO_2 \leq 200$ mmHg) using logistic regression (3). However, when they evaluated the risk factors for severe hypoxemia ($PaO_2/FiO_2 \leq 100$ mmHg), body mass index, preoperative white blood cell, and postoperative APACHE II score were significant by univariate analysis and body mass index and postoperative APACHE II score were independent risk factors by multivariate analysis. In addition, previous studies have identified that hypertension was associated with the development of postoperative headache, which may be also associated with postoperative hypoxemia due to the fact that hypoxemia may cause secondary headaches (22, 23). However, a retrospective study conducted to investigate the incidence, risk factors and outcomes of preoperative hypoxemia in patients with type A acute aortic dissection by Guo et al. reported that AAD patients treated with lower systolic blood pressure were more likely to have low oxygenation levels and systolic blood pressure was identified as an independent risk factor for preoperative hypoxemia (24). They believed that altered pulmonary circulation and insufficient tissue perfusion related to low blood pressure were responsible for the development of hypoxemia. In addition, they found that patients with preoperative hypoxemia had significantly higher mortality, longer intubation time, longer ICU stay, longer hospital stay, and lower daily living scale score.

Renal insufficiency was another independent predictors for both moderate and severe hypoxemia in our results. The relationship between renal insufficiency and respiratory system complications has been reported previously (25, 26). However, available studies focused on the association between hypoxemia and renal insufficiency are still limited. Zhou et al. reported that APACHE II score was independently associated with the development of severe postoperative hypoxemia, in which renal function may play an important role (3). Liu et al. reported that both postoperative relative hypoxemia and acute kidney injury were independent factors for endotracheal re-intubation following coronary artery bypass grafting, which may also reveal an inherent connection. The exact mechanism still needs further investigation, however, we speculate that inflammatory response and the regulation of erythropoietin production by the kidney and resultant oxygen delivery may play a role (27).

Several other preoperative predictors for postoperative hypoxemia have also been previously reported in the literature but were not identified to be significant by multivariate analysis in this study, such as female sex, low left ventricular ejection fraction, chronic obstructive pulmonary disease, and diabetes (6, 28–30). Some intraoperative variables have also been reported to be associated with the development of postoperative hypoxemia, such as surgical types and deep hypothermic circulatory arrest (9, 15, 20), however, these variables were also not significant in multivariate analysis in this study. Sheng et al. reported that the use of deep hypothermic circulatory arrest may increase the risk of postoperative hypoxemia to 11.6-fold (15), and Liu et al. reported that deep hypothermic circulatory arrest time >25 min may significantly also increase the risk of postoperative hypoxemia, with an OR value of 3.26 (95% CI, 1.18–8.99,

P = 0.023) (20). However, the implantation of frozen elephant trunk did not significantly increase the risk of postoperative hypoxemia in multivariate analysis in this study. In addition, some studies included postoperative variables, such as blood transfusion, into multivariate analysis, and identified these factors as independent predictors in the final model (20), however, we did not include postoperative variables in our analysis. We did this primarily with the consideration that postoperative variables were not available early and this may affect the purpose of early prediction. Even so, our model performed and validated well in various aspects.

Our prediction models may make sense in individualized risk prediction, high-risk populations identification, and early prevention. Recent guidelines on mechanical ventilation in acute respiratory distress syndrome have provided evidence-based recommendations related to six interventions which may be also appropriate when applied to the high-risk populations identified by our risk models, including prone positioning, low tidal volume and inspiratory pressure ventilation, higher versus lower positive end-expiratory pressure, high-frequency oscillatory ventilation, lung recruitment maneuvers, and extracorporeal membrane oxygenation (31). Appropriate preventive interventions and specific treatment targeting high-risk populations identified by our model may achieve considerable economic benefits and better clinical outcomes.

There existed several limitations in this study. First, the data of the training set was retrospectively collected from a single cardiovascular center, which may limit the generalizability of the model due to the small sample size. However, we adapted appropriate statistical methods and externally validated the model in another independent dataset, which may reduce this weakness to some extent. Second, some possible predictors that may relate to the development of postoperative hypoxemia were not available in this study, such as preoperative oxygenation index and involved tracts of aortic dissection. Nonetheless, the established model using current predictors also demonstrated good calibration, discrimination and clinical utility. Third, the time frame in this study was within the first 24 h postoperatively and the values used to define the severity of hypoxemia was the worst one. The changes of PaO_2/FiO_2 with time was not analyzed. However, we believe that this practice fulfilled the purpose of our work and would not largely influence the quality of this study. Fourth, we only analyzed the relationship between hypoxemia and in-hospital outcomes and long-term follow-up after discharge was not performed, which should be strengthened in future work.

CONCLUSION

Postoperative hypoxemia was prevalent in patients undergoing AADS, related to poor outcomes. This study first developed and externally validated a multivariate prediction model for severe hypoxemia after AADS using five independent predictors and conducted a nomogram and an online risk calculator. The model performed well with regard to calibration, discrimination and clinical usefulness. Three risk intervals were defined as low, medium, and high risk groups based on the nomogram and clinical practice. The model may have clinical utility in risk prevention and informed decision-making through individualized risk assessment and identification of high-risk patients. In addition, we identified six independent predictors for moderate hypoxemia and four independent predictors for mild hypoxemia in patients undergoing AADS, which also performed and fitted well.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No. IORG0003571). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

XD, XH, LW, JX, and PY: conception and design. XC, HW, and SW: administrative support. WS, SL, CT, and DW: provision of study materials or patients. DW, SL, WS, YS, and YD: collection and assembly of data. JW, JL, RL, and WS: data analysis and interpretation. All authors manuscript writing and final approval of manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.851447/full#supplementary-material

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REVIEW
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Kinking of Frozen Elephant Trunk Hybrid Prostheses: Incidence, Mechanism, and Management

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Introduction: Kinking of the Frozen Elephant Trunk (FET) stent graft is one of the most devastating complications of the FET procedure. It can present post-operatively with reduced arterial pressures in the lower limbs and intermittent claudication. However, it can also be visualized intra-operatively by the surgeons. Unresolved kinking of the stent graft can result in intraluminal thrombus formation and subsequent multi-organ septic emboli.

Aims: The main scope of this review is to collate, summarize and present all the evidence in the literature on kinking of FET stent grafts.

Methods: We carried out a comprehensive literature search on multiple electronic databases including PubMed, EMBASE, Ovid, and Scopus to collate all research evidence on the incidence, mechanism, and management of FET graft kinking.

Results: Incidence of kinking is variable, ranging from 0% to 8% in the literature, with varying rates associated with each stent graft type. The Thoraflex Hybrid™ prosthesis seemed to be the most commonly used and superior graft, and out of all the 15 cases of kinking reported in the literature, 5 (33.3%) were associated with just the Frozenix graft which had the highest incidence. There are multiple theories regarding the mechanism of kinking, including the direction of blood flow, the length of the stent grafts used, and the position of the prosthesis in relation to the flexure of the aorta. Multiple reparative management techniques have been suggested in the literature and include total endovascular repair, open repair, balloon dilatation, and deploying a second stent graft.

Conclusion: Graft kinking is one of the most critical complications of the FET technique. Its life-threatening sequelae warrant appropriate follow-up of these patients post-operatively, in addition to time management if kinking is suspected. Given the limited evidence in the literature, future studies should incorporate graft kinking into their outcomes reporting.

Keywords: Frozen Elephant Trunk, hybrid prosthesis, kinking, aortic dissection, aortic aneurysm

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INTRODUCTION

Pathologies involving the aortic arch and descending thoracic aorta, such as thoracic aortic aneurysms and dissections, pose a prominent challenge to cardiovascular surgeons, carrying a significant risk of morbidity and mortality. In 1983, Borst was the first to describe the Elephant Trunk technique (ET), a two-stage procedure to repair complex thoracic aorta pathologies that were limited by the fact that many patients did not make it to the second operation (1–3). Later on, in 2003, these two surgeries were combined into a single-step hybrid procedure that was named the 'Frozen Elephant Trunk' (FET). In FET, the proximal aspect of the aortic arch is reconstructed surgically and the distal is repaired endovascularly during the same hybrid operation (1). Multiple FET hybrid prostheses are currently available commercially and globally, including the Frozenix J Open Graft, Cronus, E-Vita, and Thoraflex Hybrid. Each type has its unique design, thus they each vary in terms of technical aspects, as well as their clinical outcomes, with Thoraflex Hybrid showing superior results, both regionally and globally (4).

Despite excellent results yielded by the FET technique, multiple complications associated with its use have been reported. One of the major drawbacks to FET is its array of potential neurological complications, such as spinal cord injury (SCI), paraplegia, and stroke (5, 6). Other complications reported include coagulopathy, postoperative bleeding, recurrent nerve palsy, vocal cord paralysis, renal failure necessitating dialysis, prolonged mechanical ventilation, and multi-organ failure (5, 7–11). In-hospital and 30-day mortality rates associated with FET range from 0 to 17.2% and 0 to 18.2%, respectively (11). In a retrospective study by Kreibich et al. (12), 35 patients (33% of the sample) had FET-related complications necessitating reintervention, out of which 2 patients (6%) had significant kinking of the stent graft.

The presentation of FET stent graft kinking is variable, and while it may be simply detected on follow-up imaging after FET with CT angiography (CTA), in many cases it may be distinguished by low arterial pressure in the lower limbs relative to upper limbs (13). Other case reports have stated that kinking may also manifest as intermittent claudication (14). Additionally, studies have mentioned that the diagnosis of endostent graft kinking can occur both intra- and post-operatively (13–15).

Due to the underlying mechanism of this pathology, which will be discussed in detail in this review, kinking is associated with an array of life-threatening consequences for the FET patient. Turbulence and stasis of blood flow are thought to encourage intraluminal thrombus formation secondary to the stenosis; this can have devastating outcomes, such as septic embolism and multi-organ ischemic damage (16). Subsequently, appropriate preventative measures and thorough follow-ups are essential.

This review aims to collate, summarize and present the evidence in the literature on the incidence, mechanism, and management of FET stent graft kinking.

INCIDENCE

Incidence of kinking following the FET procedure is seldom reported in the literature. As seen in **Table 1**, in the limited studies found, the variable incidence of kinking was reported, ranging from 0% in Thoraflex Hybrid and E-Vita and up to 8% in a branched one-piece graft by Yuhengjia Sci-Tech Co. Ltd, Beijing, China (17, 18).

Thoraflex Hybrid was one of the most commonly used devices with the best outcomes when it comes to stent graft kinking, as demonstrated in **Table 1**. The aforementioned study by Kreibich et al. (12) reported 2 cases of postoperative graft kinking in 107 patients (2%) who underwent total arch replacement (TAR) with FET using Thoraflex Hybrid, both of whom required reintervention. However, the association between stent graft kinking and aortic reintervention was not statistically significant ($p = 1.00$) (12). Additionally, Öz et al. (25) reported one case of kinking of this prosthesis post-FET. Here, the patient's 2- and 2.5-year follow-up CTA revealed graft kinking with proximal migration of the endograft portion of the FET, resulting in new thrombus formation, thus necessitating endovascular reintervention which was performed successfully. Lastly, 2 relatively large studies using Thoraflex Hybrid did not observe any cases of graft kinking amongst their study population of 92 and 167 patients, respectively (17, 24).

In a similar trend to Thoraflex Hybrid, no cases of kinking were reported in association with the E-Vita device. Ho et al. (23) assessed the use of the branched version of E-vita Open NEO in 3 patients that underwent TAR using FET for type B aortic dissection with an arch aneurysm. In this case series, a post-operative CT aortogram was done that showed no kinking in all 3 patients (23). Additionally, in a study by Detter et al. (17), none of the 92 patients who also underwent TAR with FET using the E-Vita Open Plus hybrid prosthesis (HP) developed kinking.

Interestingly, it is worth noting that, unlike Thoraflex Hybrid, studies on E-Vita seldom featured graft kinking in their design and outcomes reporting. On the other hand, more FET studies using Thoraflex Hybrid included kinking in their data collection methodology for larger patient populations, thereby increasing the reliability of the evidence supporting its superiority.

Incidence of graft kinking with the Frozenix HP was more variable, and overall, the highest, which represents a great concern over the safety and effectiveness of this FET graft. Uchida et al. (13) reported 2 cases of TAR with FET using the Frozenix J Open Graft, both of whom developed stent graft kinking which was related to the stent graft's structural property (13). Here, during the first case, specifically, after the Frozenix HP was inserted into the downstream aorta and its distal anastomosis completed, high cardiopulmonary bypass (CPB) flow-line pressure (300 mm Hg) and low femoral arterial pressure were noted, suggesting FET graft obstruction. Transoesophageal echocardiography (TOE) showed kinking of the Frozenix HP. Similarly, during the second case, Frozenix graft kinking was luckily also discovered intraoperatively. Additionally, 2 cases of Frozenix kinking post-FET for acute Type A aortic dissection were reported by Morisaki et al. (14). In the first case, after emergency TAR with FET, the patient developed intermittent

TABLE 1 | Overall summary of the studies reporting on FET graft kinking, the type of graft used, and the incidence of kinking.

References	Year	Type of FET Graft	Incidence of kinking n (%)
Kreibich et al. (12)	2020	Thoraflex Hybrid	2/35 (5%)
Uchida et al. (13)	2019	Frozenix	2 cases
Morisaki et al. (14)	2018	Frozenix	2 cases
Nakagawa et al. (15)	2022	120-mm-long woven Dacron graft with a Gianturco Cook-Z stent (Cook Medical, Inc., Bloomington, Ind) attached only to the distal end	1 case
Imamura et al. (16)	2021	Hand-made FET (UBE graft, UBE Industries, Ltd., and Z-shaped stent, William Cook)	1 case
Detter et al. (17)	2019	E-Vita Open Plus (Jotec, Hechingen, Germany) and Thoraflex Hybrid	0/92 (0%)
Shen et al. (18)	2012	A branched 1-piece graft (Yuhengjia Sci-Tech Co. Ltd, Beijing, China).	3/38 (8%)
Shrestha et al. (19)	2014	Vascutek Siena	0/179 (0%)
Toda et al. (20)	2009	4-branched arch graft (Hemashield Platinum, MAQUET Cardiovascular LLC, Wayne, NJ)	0/111 (0%)
Spielvogel et al. (21)	2005	Handmade and graft by Boston Scientific, Natick, MA	0/109 (0%)
Uchida et al. (22)	2016	Frozenix	1/60 (2%)
Ho et al. (23)	2021	E-Vita Open NEO	0/3 (0%)
Ouzounian et al. (24)	2020	Homemade, Thoraflex Hybrid (Vascutek, Glasgow, Scotland), Evita Open Plus (Jotec, Hechingen, Germany/CryoLife, Kennesaw, GA, USA), and Cook Hybrid (Cook Medical, Bloomington, IN, USA) graft.	0/167 (0%)
Öz et al. (25)	2021	Thoraflex Hybrid	1 case
Baraki et al. (26)	2007	Hybrid prosthesis (Chavan-Haverich endograft, Curative GmbH, Dresden, Germany).	1/39 (3%)
Karck et al. (27)	2005	Hybrid prosthesis ["Chavan–Haverich" (CH) endograft, Curative GmbH, Dresden, Germany]	1/22 (5%)

claudication post-operatively, which on CTA showed to be kinking between the non-stent and stent parts of the Frozenix HP that required endovascular reintervention. Patient 2 experienced decreased blood pressure in the lower body and intermittent claudication following a reimplantation root procedure and translocated TAR with the FET. On CTA, this was also discovered to be kinking between the non-stent and stent parts of the Frozenix HP that also required endovascular reintervention (14).

Furthermore, a 2016 multicentre study in Japan set out to evaluate the incidence of major adverse outcomes in patients using the Frozenix stent graft. Here, 2% of patients developed kinking of this prosthesis intraoperatively (22). As aforementioned and illustrated in **Table 1**, a total of 15 cases of kinking were reported out of which 5 (33%) were associated with Frozenix. The high incidence of Frozenix graft kinking must be taken into consideration very carefully in current and future practice.

Other FET devices which are less commonly used have also been described in the literature to be associated with kinking, a summary of these along with their kinking incidence can be found in **Table 1** (15, 16, 18–21, 26, 27).

MECHANISM

Multiple factors have been suggested in the literature to cause kinking of the FET grafts. Firstly, the most significant consideration of surgical technique in total arch repair is in the direction of blood flow. In an evaluation of 30 years of experience involving 179 patients who underwent TAR with FET, Shrestha et al. (19) emphasized the significance of establishing antegrade blood flow through the FET graft. Retrograde flow is thought to cause kinking and unfolding of the distal graft at the descending thoracic aorta. This includes cannulation for cardiopulmonary bypass, where a retrograde direction of flow is encouraged (19).

Secondly, a longer prosthesis has been linked to an increased risk of developing kinking and a length of 7–8 cm is thought to be ideal (28). This was supported by Morisaki et al. (14). On the other hand, in a 10-year experience analysis, Toda et al. (20) reported no incidences of kinking in 111 patients, despite using a mean graft length of 15.9 $\pm$ 3.1 cm (10–22 cm), a significantly longer trunk than initially suggested. These findings are concomitant with a 5-year prospective study of 109 patients, where no kinking postoperatively was reported using the same longer graft length (21). The ideal length of the graft remains a topic of dispute, with longer grafts being unfavorable to some surgeons due to the increased risk of spinal cord ischemia (29). The fluttering of the non-stented distal end of the elephant trunk with the longer grafts also increases the risk of dislodging peripheral emboli, although this is more associated with conventional ET, and less with FET (3, 30, 31). However, it is important to note that the length of the prosthesis may be dictated by the patient presentation and characteristics as well as complications during the procedure, including aortic calcification, multifocal aneurysmal extensions, and concomitant aortic kinking (32). Graft measurements should ideally be done before surgery as during circulatory arrest the aorta collapses and shortens, impairing the accuracy of the measurements (33).

Unlike the other aortic arch prostheses on the global commercial market, Thoraflex Hybrid represents a diverse HP option offering a variety of graft lengths and diameter combinations, allowing for a more personalized patient approach (4).

Thirdly, kinking can also occur if the stent graft is positioned at the flexure of the aorta (16). Uchida et al. (22), for instance, described one case of stent graft kinking at the border between the stented and non-stented part of the Frozenix HP. Unlike Frozenix, the Thoraflex Hybrid design does not feature a non-stent portion of the graft which does help prevent such cases of kinking between the distal anastomosis site and the stent (8, 14). Additionally, in a 2021 study involving the E-Vita HP, increased anastomotic space to the left subclavian artery was thought to reduce the risk of kinking. This wider gap was achieved by increasing the distance (20 mm) between the third-side branch of the prosthesis and the sewing collar (23). Moreover, manipulation of the graft architecture to prevent kinking was also discussed by Ma et al. (4). In some FET devices including Thoraflex Hybrid, it is possible to accustom the length of the side branches before forming an anastomosis or ordering a custom-made Thoraflex Hybrid prosthesis to accommodate specific patient anatomy with a 4-week delivery timeframe.

Concerning the graft-stent type and its association with kinking, only suggestions regarding the limitations of the prosthesis architecture were highlighted. For example, in comparison to other hybrid devices, Thoraflex Hybrid exerts a lower radial force onto the aortic walls. Although this is associated with positive outcomes in acute pathology, in chronic dissection this amplitude and force may cause compression and kinking of the stent, potentially introducing the need for ballooning and further intervention (24). Frozenix, on the other hand, was reported to cause functional obstruction of the graft due to impingement of the distal end of the prosthesis with the intimal flap. This is evident in the aforementioned case report by Morisaki et al. (14) which described 2 cases of FET obstruction secondary to kinking of Frozenix, these were thought to have occurred due to the sharp angulation of the aorta in both patients.

Interestingly, oversizing the graft has also been described as a prophylactic measure against kinking. For example, Chu et al. (34) recommend oversizing by 10–20%. It is thought that the curvature of the prosthesis, in combination with the low radial force within the aorta may cause proximal migration and subsequent kinking of the stent. Hence, in an attempt to counteract the vector forces causing the kinking, longitudinal support, in the form of interrupted interconnecting wires, has also been suggested in the literature (25, 35).

Finally, in addition to intraoperative technique changes and stent graft adjustments, the use of intravascular ultrasound during surgery has been recommended. This would ensure the correct placement of the wire that guides the prosthesis into the true lumen and would reduce the risk of kinking or depression of the stent (36). Further benefit yielded by the intraoperative ultrasound scan is highlighted in a different study by Baraki et al. (26), where failure to advance the guidewire and the introducer system resulted in perforation of the aorta. The Canadian Thoracic Aortic Collaborative also suggested using transoesophageal echocardiography to ensure correct stent placement with no kinking (24).

Multiple explanations of the mechanism of kinking following FET exist in the literature, often only based on an individual surgeon or single-center experiences, and further analysis of this topic on a wider scale is essential to implement further guidance.

MANAGEMENT

Different approaches to the management of FET stent graft kinking have been described throughout the limited literature. One common way is to relieve kinking is by intervening endovascularly with thoracic endovascular aortic repair (TEVAR). Öz et al. (25) described "unfreezing" the kinked Thoraflex stent with TEVAR. Here, the authors inserted an extra-stiff guidewire into the securely cannulated kinked region, and with the use of an appropriately sized compliant balloon, balloon dilation was done twice (25). When inserting a guidewire into a kinked segment, caution should be taken as to not perforate the aortic wall and thus necessitating an extra open surgical repair (27).

By straightening out the kinked graft and realigning the FET, the surgeons were able to lengthen the graft, in addition to the proximal landing zone to achieve an Ishimaru landing zone 3 (25). In addition, Öz et al. (25) described placing the TEVAR where less curvature occurs, as in FET as well, to avoid malalignment and bird-beaking. As described earlier, because Thoraflex Hybrid enforces lower radial forces, during TEVAR, the FET was relined with Relay TEVAR endovascular graft to support its vertical arch. The Thoraflex Hybrid and Relay TEVAR, manufactured by Terumo Aortic, ensured that stent in-stent assessment was performed to provide reliable yet optimal clinical efficacy.

In addition to balloon dilatation, inserting a second stent graft can correct and reorient the FET, especially when significant stenosis is present (37). For instance, Nakagawa et al. (15) described the dilemma of correcting a structurally poor surgeon-modified prosthesis. Due to its weak architecture, with no graft-lining stent in the core of the graft, their surgeon-modified FET prosthesis became significantly kinked. Similar to Öz et al. (25), an extra-stiff guidewire was used to straighten the FET graft, however, balloon pre-dilatation was not necessary. A fenestrated stent graft was then delivered and placed at proximal aortic zone 0 (15).

Other reported cases of kinking identified intraoperatively were treated by pulling out of the non-stent part of the graft proximally and then re-anastomosing the distal part into a distal site. Uchida et al. (13) described performing this technique on a patient in Japan where the Frozenix stent graft was initially used. Similarly, for another patient, the same authors described taking out the Frozenix graft, trimming it, and re-anastomosing the graft more distally (13).

In addition to the previously mentioned management strategies, Kreibich et al. (12) investigated the use of open repair of the stent graft. This was often performed if there was evidence for extensive kinking or if other complications and comorbidities

were present, such as connective tissue disorders, atherosclerotic plaques, or in the case of an inadequate distal landing zone (12).

It is important to take into consideration that, often, post-FET complications do not present in isolation, and the corrective management may vary from patient to patient. This can depend on the extent of the dissection or aneurysm, any concomitant aortic pathology, and the presence of other complications (12, 13).

In addition to corrective procedures or surgery to repair the kinked stent, adjunctive treatment to manage the complications of the kinking may also be necessary. For instance, this can occur where post-FET kinking is seen with evidence of thrombosis on CTA. As the kinking gets progressively worse, so can the stent occlusion. As a result, treatment with direct oral anticoagulation can be initiated before further surgical intervention, to decrease the likelihood of thromboembolic events perioperatively (25).

Despite the limited literature, sufficient evidence is available to support the continued and increasing application of Thoraflex Hybrid as well as the necessary re-evaluation of Frozenix's safety and effectiveness as a FET HP. As mentioned previously, although the single-step FET procedure does yield excellent results, particularly positive aortic remodeling, there remain several complications associated with it, only one of which is graft kinking. These were addressed in 2 recent studies by Tan et al. (38) and Jubouri et al. (39) who proved the efficacy of FET and the well-established Thoraflex Hybrid as the superior FET HP available commercially.

CONCLUSION

FET graft kinking is a serious complication of this hybrid procedure that must be approached swiftly but attentively, as although it is rare in incidence, it can lead to devastating results. Surgeons must carefully consider their choice of FET graft as well as their surgical technique while bearing in mind their management strategy in case of kinking occurrence intra- or post-operatively. Finally, future FET studies must incorporate graft kinking into their outcomes reporting.

AUTHOR CONTRIBUTIONS

FK, SQ, MJ, and RC were involved in literature review design, literature search, and manuscript writing. ST and MB were involved in manuscript revision. All authors contributed to the article and approved the submitted version.

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Single-Center Experience With the Thoraflex™ Hybrid Prosthesis: Indications, Implantation Technique and Results

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Objective: The aim of this study was to evaluate the early and mid-term results after the frozen elephant trunk (FET) procedure for the treatment of complex arch and proximal descending aortic disease in a single-center institution.

Methods: From April 2015 to July 2021, 72 patients (25 women, 60.4 ± 10.3 years) underwent Thoraflex™ Hybrid implantation at our institution. The indications were thoracic aortic aneurysm (TAA) (n = 16, 22.2%), post-dissection aneurysm (n = 21, 29.2%), and acute aortic dissection (AAD) (n = 35, 48.6%). Antegrade cerebral perfusion under moderate hypothermia (28°C) was employed in all cases. Eighteen patients (25%) have already been operated due to heart or aortic disease.

Results: Overall in-hospital mortality was 12.5% (9 patients). Rates of permanent neurological dysfunction and spinal cord injury were 9.7 and 5.5%, respectively. The in-hospital mortality rate among patients operated on AAD, TAA, and post-dissection aneurysm were 8.6, 6.2, and 23.8%, respectively. At a mean follow-up of 26 ± 20 months, mortality was 9.7%. Furthermore, 23 patients (31.9%) required a subsequent procedure in distal aorta: endovascular stentgraft extension in 19 patients (26.4%) and open aortic surgery in 4 patients (5.5%). The mid-term survival of patients with type A aortic dissection was 97%.

Conclusions: Our experience with the Thoraflex Hybrid prosthesis demonstrates its surgical applicability for different types of aortic pathologies with promising outcomes during early and midterm follow-up. Our technique and perioperative management lead to comparable or even superior neurological outcomes and mortality in urgent cases considering other high-volume centers.

Keywords: frozen elephant trunk (FET), Thoraflex Hybrid prosthesis, acute aortic dissection (AAD), thoracic aortic aneurysm (TAA), post-dissection aneurysm

INTRODUCTION

The Thoraflex™ Hybrid prosthesis was first introduced in 2010 (1) for the treatment of combined diseases of the aortic arch and the proximal descending aorta (2).

Since then, the application of Thoraflex™ Hybrid prosthesis with two modifications (Thoraflex™ Plexus 4® and Ante Flo®, Vascutek, Terumo, Inchinnan, Scotland, UK) has become a widely established approach for the treatment of acute and post-dissection aneurysms as well as aneurysms of the thoracic aorta (thoracic aortic aneurysm, TAA) (3–5).

With the addition of the latest model, the frozen elephant trunk (FET), the surgeons' armamentarium has grown significantly in recent years and hybrid prostheses have become applicable to a wider field of indications. The 4-branched Thoraflex™ hybrid graft and its counterparts, such as the Jotec E-vita NEO (Jotec GmbH, Hechingen, Germany), not only enable a distinctive surgical approach (in case of dissection) of the supra-aortic vessels but also the endoluminal treatment of the proximal descending aorta. Thus, the FET technique not only affects the stent-grafted segment but also the downstream aorta with positive effects on aortic remodeling. It also enables subsequent procedures, either one or second stage (i.e., endovascular stent extension or open aortic repair).

Various groups (6–8) demonstrated the benefits of the hybrid stentgraft technique on true lumen collapse avoidance and aortic remodeling, besides other benefits (i.e., lower body malperfusion, mortality and secondary aortic intervention, and neurological complications) (4, 9–12).

At our institution, the first Thoraflex™ Hybrid prosthesis was implanted in April 2015. This study aimed to present our single-center experience regarding the indications, implantation technique, as well as the perioperative and mid-term results.

MATERIALS AND METHODS

Patients

From April 2015 to July 2021, 72 patients (25 women, 60.4 ± 10.3 years) with pathologies of the ascending aorta and aortic arch underwent surgical treatment with the Thoraflex™ Hybrid prosthesis (*Terumo Aortic, Vascutek Ltd., Inchinnan, UK)* at our department. The ethical committee of our institution approved this retrospective study (2020-126-f-S). Data from the perioperative patients were reviewed retrospectively. The follow-up data regarding survival were retrieved from the residents' registration offices. The follow-up was completed in October 2021. The data were analyzed according to the underlying aortic disorder (aneurysm, acute dissection, and post-dissection aneurysm). Patients' demographics are presented in **Table 1**. Coronary angiography, echocardiography, and computed tomography angiography (CTA) were routinely performed for all elective cases. In patients with acute aortic dissection (AAD), the diagnosis was confirmed by (ECG-triggered) CTA. The same surgical team performed all cases.

Abbreviations: AADA, Acute Aortic Dissection Type A; AADB, Acute Aortic Dissection Type B; AAR, Ascending aortic replacement; CABG, Coronary artery bypass graft; CPB, Cardiopulmonary bypass; CPR, Cardiopulmonary resuscitation; CSF, Cerebrospinal fluid; CTA, Computed tomography angiography; ECLS, Extracorporeal life support; FET, Frozen elephant trunk; HCA, Hypothermic circulatory arrest; ICU, Intensive care unit; NIRS, Near-infrared spectroscopy; PDAA, Post-dissection aortic aneurysm; SACP, Selective antegrade cerebral perfusion; TAA, Thoracic aortic aneurysm.

Surgical Technique and Perioperative Management

Standard access for complex aortic lesions at our institution is median sternotomy. Arterial cannulation was performed directly through the right axillary artery and venous cannulation through the right atrium in most cases. The left side of the heart was vented through the right superior pulmonary vein. In selected cases, permanent antegrade perfusion of the heart made it possible to perform an aortic prosthetic repair on a beating heart. The carbon dioxide insufflation was administered in the operative field to minimize the risk of air embolism. Cold blood cardioplegia was our first choice for myocardial protection and was administered mostly retrograde through the coronary sinus or directly into the coronary ostia.

Replacement of the aortic arch was performed under moderate hypothermic (28°C on average) circulatory arrest and selective antegrade cerebral perfusion (SACP) with the application of near-infrared spectroscopy (NIRS). Initially, unilateral SACP with permanent monitoring of cerebral tissue oxygenation was performed. If needed, the conversion from unilateral perfusion to bilateral was performed through direct cannulation of the left common carotid artery. After reaching the desired temperature and circulatory arrest, the aortic arch in Zone 2 or 3 was transected distally and the endoprosthesis was deployed into the descending aorta. A sewing collar simplifies and reinforces the distal anastomosis. Additional sealing is achieved with (Teflon) felt strips and the application of the two-component BioGlue® Surgical Adhesive (CryoLife, Inc.) on the suture line. After completion of the distal anastomosis, lower body reperfusion is obtained *via* the extracorporeal circulation branch of the graft.

To keep cardiac arrest to a bare minimum, cardiac perfusion is reestablished after repair of the subclavian artery and/or proximal anastomosis of the ascending aorta in the case of supracoronary replacement. The remaining vessels are then anastomosed after clamp removal. In the case of the Bentall procedure, we perform aortic root replacement after anastomosing all supracoronary vessels. After de-airing the heart, the coronary circulation was reinitialized (**Figure 1**). Concomitant procedures, e.g., mitral valve replacement and coronary artery bypass grafting, were typically performed after the repair of the left subclavian artery and after the reestablishment of lower body perfusion. Under normothermia, the cardiopulmonary bypass (CPB) was terminated, and the fourth graft branch, used for antegrade perfusion, was ligated and resected.

The perioperative management is standardized for procedures in our center. Prophylactic cerebrospinal fluid (CSF) drainage was not perioperatively performed. All patients with diagnosed

TABLE 1 | Demographic and pre-operative clinical data.

	All—*n*/mean (IQR/%/SD)	Acute dissection, *N* = 35	Post-dissection aneurysm, *N* = 21	Aortic aneurysm, *N* = 16	*P*-value
Age (years)	60.4 (61)	57.3 (56)	59.2 (60)	68.7 (70)	**<0.0001**
Sex (female)	25 (34.7%)	7 (20%)	8 (38.1%)	10 (62.5%)	0.013
Body Mass Index	26.7 (26)	27.0 (27)	27.5 (26)	25.1 (23.5)	0.21
History of smoking	22 (30.5%)	6 (17.1%)	6 (28.6%)	10 (62.5%)	**0.006**
Diabetes mellitus	4 (5.6%)	0 (0%)	3 (14.3%)	1 (6.2%)	0.058
Dyslipidemia	18 (25.0%)	3 (8.6%)	7 (33.3%)	8 (50.0%)	**0.003**
Arterial hypertension	53 (73.6%)	22 (62.8%)	19 (90.5%)	12 (75.0%)	0.078
Peripheral vascular disease	3 (4.2%)	0 (0%)	1 (4.8%)	2 (12.5%)	0.074
Cerebrovascular disease	5 (6.9%)	2 (5.7%)	2 (9.5%)	1 (6.25%)	0.84
Abdominal aortic aneurysm	15 (21.0%)	1 (2.8%)	6 (28.6%)	8 (50.0%)	**0.0001**
Pulmonary disease (COPD)	9 (12.5%)	1 (2.8%)	2 (9.5%)	6 (37.5%)	**0.003**
Connective tissue disorder	5 (6.9%)	1 (2.8%)	4 (19.0%)	0 (0%)	0.05
Pre-operative history of stroke	9 (12.5%)	2 (6.7%)	4 (19.0%)	3 (18.75%)	0.19
New-onset cerebral ischemia	4 (5.6%)	3 (8.6%)	0 (0%)	1 (6.25%)	0.44
Pre-operative paraplegia	4 (5.6%)	4 (11.4%)	0 (0%)	0 (0%)	0.18
Pre-operative atrial fibrillation	6 (8.3%)	2 (5.7%)	1 (4.8%)	3 (18.75%)	0.34
Previous surgery	18 (25.0%)	1 (2.8%)	16 (79.2%)	1 (6.2%)	**<0.0001**

Statistically significant values are in bold.

spinal ischemia received post-operative CSF drainage and MRI. To reduce the duration of hypothermic circulatory arrest (HCA), rewarming and perfusion of the lower body were restarted after completion of the distal aortic arch anastomosis. Patients received CT angiograms (CTA) from the neck vessels to the iliac or femoral arteries routinely before discharge. In the case of suspected ischemia, CTA is performed immediately after the procedure.

An important component of anesthesiologic support was the prevention of excessive blood loss in the early post-operative stage. Before intervention, the patient was given a fibrinolysis inhibitor—tranexamic acid as a short infusion, then continuously during the intervention. For optimal assessment of the blood coagulation, during the weaning of the patient of the CPB, the thromboelastography was performed simultaneously with activated clotting time control after administration of protamine sulfate.

Statistical Analysis

The statistical analysis was accomplished with Statistica 13.3 (StatSoft, TIBCO Software, Palo Alto, CA, USA) for Windows. Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR). Categorical variables were given as total numbers and percentages. Fisher's exact test and its Freeman–Halton extension were used to analyze differences in dichotomous variables. The non-parametric Mann–Whitney *U*-test was used for group comparisons of continuous variables. The Kruskal–Wallis test was used for multiple group comparisons of continuous variables. The Kaplan–Meier survival estimate was used for survival analysis. Statistical differences in Kaplan-Meier survival were determined with the log-rank test.

RESULTS

The detailed intraoperative and the post-operative data are presented in **Tables 2**, **3**, respectively. Overall, this study population showed a high operative risk, and 35 cases (48.6%) had an AAD: 29 patients had type A dissection (acute aortic dissection type A, AADA) and 6 with type B dissection (acute aortic dissection type B, AADB). There were 16 cases (22.2%) with TAA and 21 patients (29.2%) were diagnosed with post-dissection aortic aneurysms (PDAAs). Arterial cannulation through the right axillary artery was performed in 98.6% of our cases. In two cases, femoral artery cannulation was needed, in one case due to local dissection of the axillary artery and another case due to reoperation and adhesions. The Thoraflex Hybrid prosthesis was applied successfully in all cases. In our investigated cohort, patients with aortic aneurysms were significantly older ($p < 0.0001$) than patients with acute and post-dissection aneurysm. In all groups, patients were predominantly men. Patients with aneurysm had shorter operation times and were more often accompanied by concomitant procedures (3 cases with coronary artery bypass graft [CABG]). Contrastingly, post-dissection aneurysm treatment was significantly longer ($p < 0.0001$). The mean hospital stay of the whole cohort lasted 16 days. Patients with AAD patients had a prolonged intensive care unit (ICU) stay and overall longer hospital stay, 9.7 and 19.5 days, respectively ($p < 0.12$). The mean ventilation time in the entire cohort was 24 h and was significantly shorter (<1 day) in elective cases. Only patients with AAD required ventilation of ∼33 h. Furthermore, 17 patients (23.6%) required temporary hemofiltration due to acute kidney injury (9 were patients with AAD). Only one patient required permanent dialysis after discharge.

Four patients (5.5%) suffered from paraparesis, three of them were patients with AAD where the stentgraft was

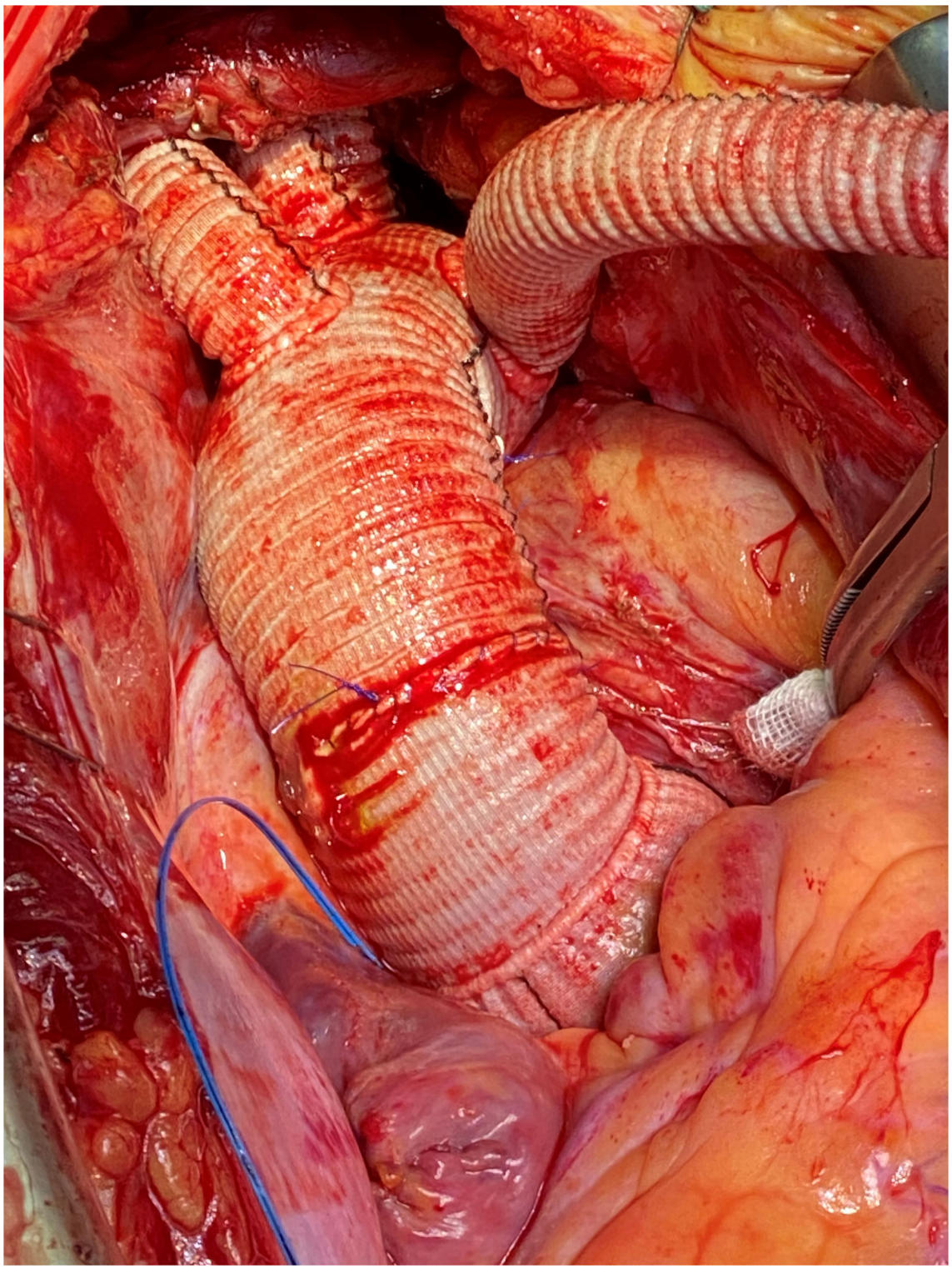

FIGURE 1 | Intraoperative photography, complete implantation of the Thoraflex Hybrid prosthesis with mechanical conduit.

TABLE 2 | Intraoperative data.

	All—*n*/mean (IQR/%/SD)	Acute dissection, *N* = 35	Post-dissection aneurysm, *N* = 21	Aortic aneurysm, *N* = 16	*P*-value
Duration of surgery (min.)	345.7 (±78)	338.9 (±65)	390.0 (±95)	302.2 (±51)	**0.007**
CPB time (min.)	221.3 (±62)	215.9 (±41)	252.0 (±85)	192.7 (±47)	**0.007**
Cross clamp time (min.)	133.4 (±55)	139.4 (±54)	133.6 (±70)	120.2 (±34)	0.46
Distal HCA time (min.)	46.2 (±11)	48.3 (±9)	46.2 (±13)	41.5 (±11)	0.18
HCA temperature (°C)	28.0 (±1.2)	27.9 (±1.5)	28.2 (±1.2)	27.9 (±0.3)	0.74
Supracoronary AAR	60 (83.3%)	27 (77.1%)	17 (80.9%)	16 (100%)	0.096
Bentall with biological conduit	9 (12.5%)	5 (14.3%)	4 (19.0%)	0 (0%)	0.17
Bentall with mechanical conduit	3 (4.2%)	3 (8.5%)	0 (0%)	0 (0%)	0.31
Additional mitral valve replacement	1 (1.39%)	0 (0%)	1 (4.8%)	0 (0%)	0.51
Additional CABG	7 (9.7%)	2 (5.7%)	2 (9.5%)	3 (18.7%)	0.39
Prosthesis diameter (mm)	26 (24–30)	26 (24–26)	26 (26–30)	30 (30–30.5)	**<0.0001**
Stent diameter (mm)	28 (26–32)	28 (26–28)	28 (26–32)	34 (32–36.5)	**<0.0001**
Stent length-−150 mm	23 (31.9%)	14 (40.0%)	4 (19.0%)	5 (31.2%)	0.29
Distal anastomosis in Zone 0	1 (1.4%)	1 (2.8%)	0 (0%)	0 (0%)	1.0
Distal anastomosis in Zone 1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.0
Distal anastomosis in Zone 2	21 (29.2%)	9 (25.7%)	8 (38.1%)	4 (25.0%)	0.59
Distal anastomosis in Zone 3	50 (69.4%)	25 (71.4%)	13 (61.9%)	12 (75.0%)	0.71

CPB, Cardiopulmonary bypass; HCA, Hypothermic circulatory arrest; AAR, Ascending aortic replacement; CABG, Coronary artery bypass graft. Statistically significant values are in bold.

TABLE 3 | Post-operative data.

	All—*n*/mean (IQR/%/SD)	Acute dissection, *N* = 35	Post-dissection aneurysm, *N* = 21	Aortic aneurysm, *N* = 16	*P*-value
Inhospital mortality	9 (12.5%)	3 (8.6%)	5 (23.8%)	1 (6.2%)	**0.04**
Length of ICU stay (d)	7.9 (3–9)	9.7 (3–11)	4.8 (3–5)	8.2 (3–11.5)	0.12
Length of stay (d)	15.7 (10–19)	19.5 (13–26)	11.5 (8–15)	13.5 (10.7–15.2)	**<0.0001**
Tracheostomy	6 (8.3%)	5 (14.3%)	0 (0%)	1 (6.2%)	0.17
Reintubation	9 (12.5%)	5 (14.3%)	2 (9.5%)	2 (12.5%)	0.9
Ventilation time (h)	24.2 (±45)	33.3 (±62)	15.7 (±16)	15.6 (±17)	0.31
Myocardial infarction	1 (1.4%)	1 (2.8%)	0 (0%)	0 (0%)	1.0
Re-exploration for bleeding	8 (11.1%)	4 (11.4%)	3 (14.3%)	1 (6.2%)	0.89
ECLS	5 (6.9%)	0 (0%)	3 (14.3%)	2 (12.5%)	0.036
post-operative CPR	7 (9.7%)	3 (8.6%)	3 (14.3%)	1 (6.2%)	0.77
Permanent neurological deficit	7 (9.7%)	4 (11.4%)	3 (14.3%)	0 (0%)	0.35
Paraparesis	4 (5.5%)	3 (8.6%)	1 (4.8%)	0 (0%)	0.81
Recurrent nerve palsy	5 (6.9%)	2 (5.7%)	1 (4.8%)	2 (12.5%)	0.70
Mesenteric ischemia	5 (6.9%)	2 (5.7%)	2 (9.5%)	1 (6.2%)	0.83
Atrial fibrillation	8 (11.1%)	5 (14.3%)	0 (0%)	3 (18.7%)	0.10
Temporary Hemofiltration	19 (26.4%)	9 (25.7%)	7 (33.3%)	3 (18.7%)	0.61
Presternal wound infection	2 (2.7%)	1 (2.8%)	1 (4.8%)	0 (0%)	1.0

ICU, Intensive care unit; ECLS, Extracorporeal Life Support; CPR, Cardiopulmonary resuscitation. Statistically significant values are in bold.

anastomosed in Zone 3 but only one of them received a 150 mm stentgraft. Paresis of the recurrent laryngeal nerve occurred in 5 cases (6.9%), mainly in patients with aortic aneurysm procedures. Permanent neurological deficit occurred in 7 cases (9.7%). We experienced only two cases of wound infection. One case of myocardial infarction after acute dissection was observed. Overall 5 patients (6.9%) suffered from mesenteric ischemia. In 8 cases (11%), atrial fibrillation occurred post-operatively. Cardiopulmonary reanimation was necessary in 7 cases (9.7%), three of them (14.3%) were post-dissection aneurysm patients. Extracorporeal life support (ECLS) was necessary in none of the acute dissection cases, while patients with post-dissection aneurysms and degenerative aneurysms were supported in 3 (14.3%) and 2 (12.5%) cases, respectively. Surgical re-exploration because of bleeding was needed in 8 cases (11%).

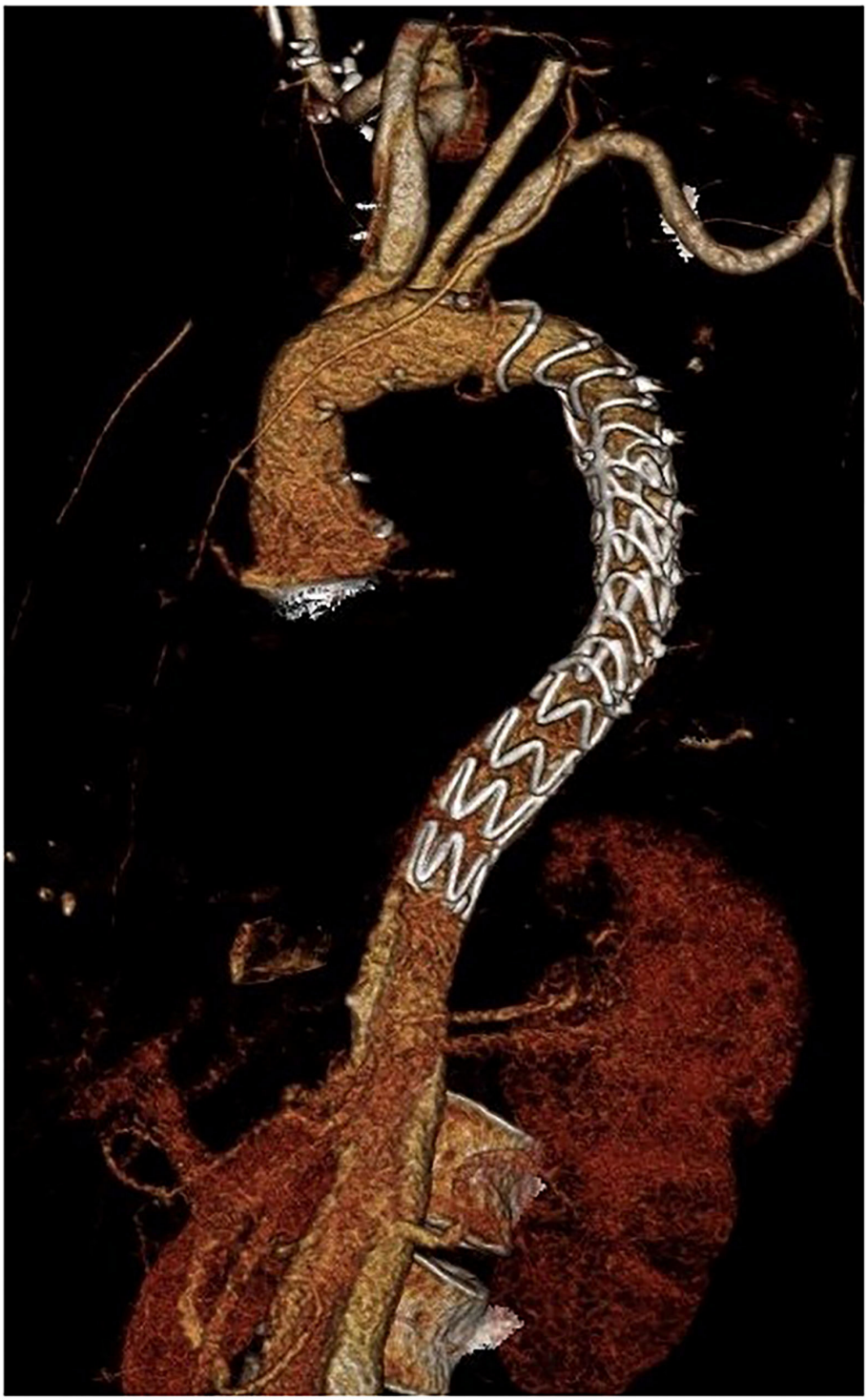

FIGURE 2 | Three-dimensional computer tomography angiography (CTA) after distal stentgraft extension succeeding after implantation of the Thoraflex Hybrid prosthesis.

Early mortality expressed as in-hospital mortality was 12.5% (9 perioperative deaths) in the whole population. In acute cases of aortic dissection, only 3 patients died (8.6%, due to multiple-organ failures and cardiac tamponade). After elective aneurysm operation, we observed only 1 lethal case (6.2%, due to mesenteric ischemia) and 5 in-hospital deaths after

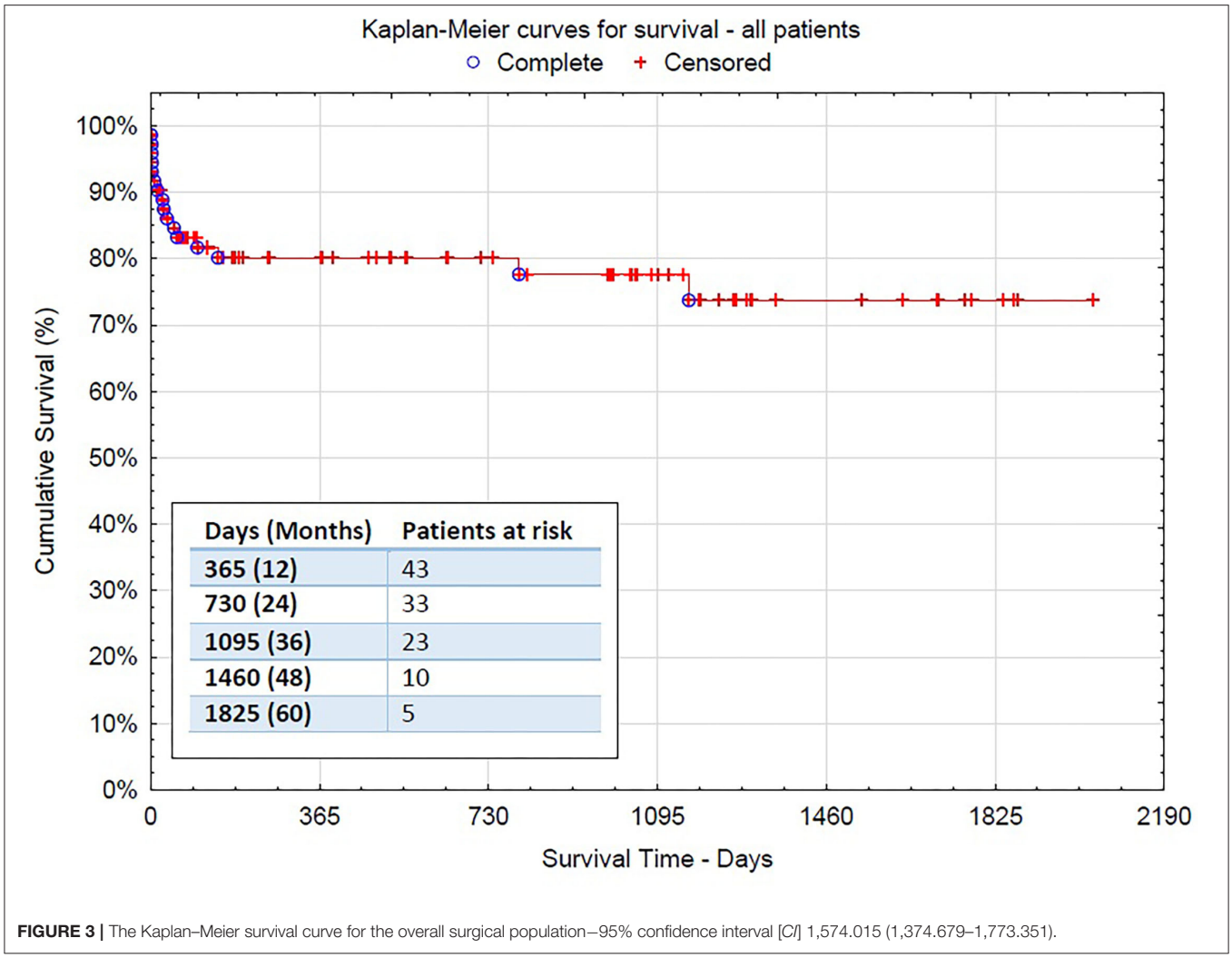

FIGURE 3 | The Kaplan–Meier survival curve for the overall surgical population−95% confidence interval [*CI*] 1,574.015 (1,374.679–1,773.351).

post-dissection aneurysm procedure, reaching relatively high mortality of 23.8% (due to excessive bleedings, mesenteric ischemia with multiple-organ failure, and heart failure with cerebral ischemia).

After a mean follow-up of 2 years, the mid-term mortality of patients was 9.7% (7 deaths-−3 due to aortic rupture, 3 due to infection or pneumonia, and 1 heart failure). All acute dissection patients but one survived after discharge and are doing well until the end of follow-up (2.8% mortality after discharge). In total, 19 patients (26.4%) received additional endovascular treatment with stentgraft implantation (thoracic endovascular aneurysm repair [TEVAR]) in the descending aorta (3 thoracoabdominal aortic aneurysm [TAAA], 9 PDAA, and 7 AAD) (**Figure 2**). Nine of them were performed during the same hospital stay after the FET procedure. Only in 4 cases, open surgical repair was needed due to the complexity of dissection in the thoracoabdominal aorta. Kaplan–Meier curves for survival are shown in **Figures 3**, **4**.

DISCUSSION

The Thoraflex Hybrid graft combines the advantages of the FET technique with the aortic arch treatment, such as supra-aortic vessel repair. Our institutional experience since 2015, including the treatment of 72 patients with the Thoraflex Hybrid prosthesis, demonstrates its surgical applicability for different types of aortic pathologies with excellent outcomes during early and midterm follow-up. Our study showed that particular properties of our surgical technique (i.e., right subclavian artery cannulation, SACP, and moderate hypothermia) and the standardized perioperative management lead to comparable or even superior outcomes about neurological complications and mortality in urgent cases considering other high volume centers (3, 4, 6, 9, 11, 12). Interestingly, in patients with type A aortic dissection, in-hospital mortality was seen in only 8.6% of all cases, whereas mid-term survival at 26 months of discharged survivors was 97%. This is especially surprising with regard to the urgent nature of the disease.

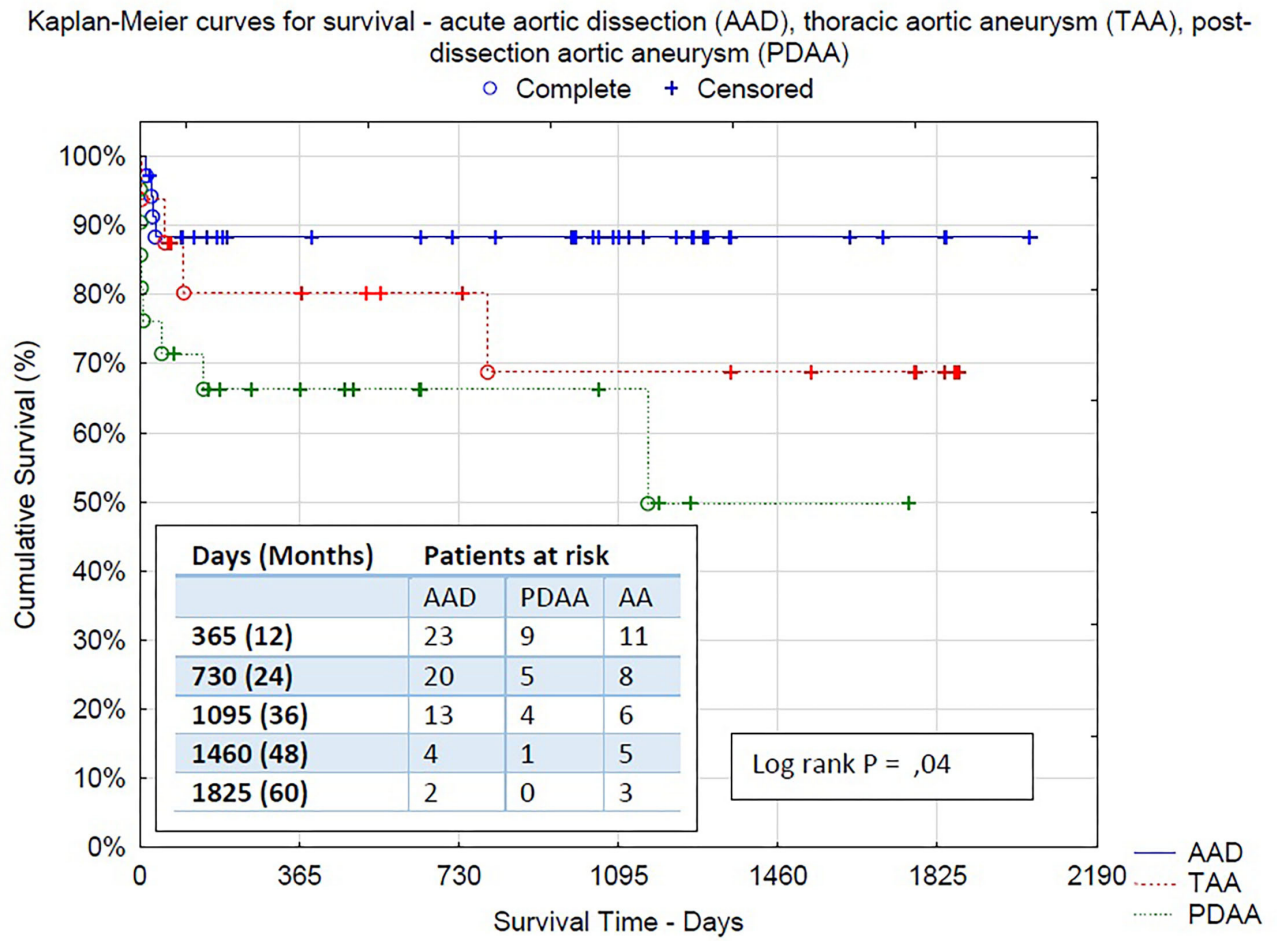

FIGURE 4 | Kaplan–Meier survival curves between all three groups: acute aortic dissection (AAD), thoracic aortic aneurysm (TAA), post-dissection aortic aneurysm (PDAA)—95% *CI* 1,801.015 (1,585.471–2,018.503), 95% *CI* 1,390.010 (986.730–1,793.290), 95% *CI* 1,574.015 (1,374.679–1,773.351), respectively.

Only in two cases, we use the Thoraflex Ante Flo with the "island technique" because of practical and technical issues. The use of a single branched graft facilitates suturing of the supraaortic vessels to the graft. Acute dissection membrane often extends to the left subclavian artery and requires proximal resection followed by a separate connection with a vascular interposition graft. The anastomosis of the brachiocephalic trunk and left common carotid artery in the form of a vascular island may be performed in an open fashion. This increases the duration of circulatory arrest, but this is technically more difficult due to the rigidity of the straightened stentgraft and antegrade perfusion branch, located in the same place. In our opinion, the Plexus version hybrid graft has a series of technical advantages, allowing better bleeding control of cranial vessels anastomosis, enabling partial clamping of the aorta, and complete removal of dissected tissue.

The Thoraflex stent size and length were determined pre-operatively according to the underlying disease and to total aortic diameter at the landing zone in patients with aneurysm or to the true lumen diameter in cases with acute dissection and post-dissection aneurysms. We avoided undersizing in dissected patients. In aneurysm, we performed a slight oversizing, ∼15% of the distal landing zone. The diameter of the FET is generally a compromise between the diameter of the true lumen and the total aortic diameter.

We prefer extra-thoracic antegrade arterial cannulation *via* the right subclavian or axillary artery. This ensures better perfusion of cerebral vessels and simplifies SACP, providing technical freedom in the prosthetic repair of the aortic arch. The arterial cannulation through the right subclavian artery has been proven to improve neurologic results (13). Compared with the direct aortic cannulation in patients with the aortic arch disease, cannulation of the right subclavian artery is an easily applicable and efficient method for perioperative cerebral protection, facilitating SACP (13, 14).

Although technical issues might be associated with extra-thoracic cannulation (i.e., injury of the right brachial plexus), our institutional experience does not show major disadvantages of this cannulation technique. Our comparatively good results might be partly explained by the experienced surgeons who

perform aortic surgery in our center. On the other hand, a major disadvantage of the direct aortic cannulation technique is the uncertainty regarding secure cerebral perfusion. In terms of the optimal arterial cannulation technique, it generally depends on the patient's hemodynamic condition, surgeon's experience, and anatomical variability. In urgent conditions, this is impossible to perform, as it is time consuming and a technically demanding method of cannulation.

In this technique of an SACP, mentioned in previous studies (13, 15), placement of a balloon catheter and manipulations of the carotid arteries are avoided, and reducing the chance for thromboembolic complications and/ or air embolism (13). Brain protection methods were well-assessed and proved as well as risk factors for permanent neurological injury, e.g., acute type A dissection and duration of circulatory arrest (15).

The advantages of unilateral and bilateral perfusion are still being discussed. Some teams are proving that results for both strategies are comparable, but the bilateral antegrade perfusion allows longer circulatory arrest (16, 17). Tsagakis et al. proposed four-sites perfusion achieving favorable results (18). Although very promising results were achieved with this sophisticated method, our institutional experience shows comparable results in a less complex approach.

In our cohort, permanent neurological deficits were found in 7 cases (9.7%). We believe there is still a place for improvement to minimize this detrimental complication. We do not perform pre-operative spinal cord protection as Shrestha and colleges do (6). In our experience, the percentage of paraplegic complication was lower than what they described (7 vs. 5.5% in our cohort). To the best of our knowledge, there is no sufficient evidence to recommend the usage of prophylactic CSF—monitoring/drainage, but more studies are necessary (5). Distal anastomosis occurred in 69.4% of cases (50 patients) in Zone 3 (distal to left subclavian artery), and only 29.2% (21 patients) in Zone 2. Majority of Zone 3 were cases of AAD (25 patients, 71.4% in this group).

Current options and recommendations for the treatment of thoracic aortic pathologies involving the aortic arch from the European Association for Cardio-Thoracic Surgery and the European Society for Vascular Surgery advise "proximalization" of the distal anastomosis from Zone 3 to 2 to shorten lower body circulatory arrest (5). In our experience, aortic dissection membrane often reaches into the left subclavian artery (secondary intimal ruptures localized in Zone 3) and descending part of the aorta. Unfortunately, this can be associated with a higher rate of laryngeal nerve palsy, which we observed in 3 cases (2 cases in Zone 2 deployment, overall 5 cases, 6.9%). Therefore, some authors recommend Zone 2 as the destination for the distal anastomosis (19).

In our latest experience, the avoidance of cardiac arrest may provide beneficial effect for patients' recovery as Martens et al. have shown in their protocol (20). In the case of retrograde AAD, where the dissection membrane does not spread extent proximally to the brachiocephalic trunk, it is also possible to perform aortic prosthetic repair as a beating heart procedure. Continuous perfusion of the heart is provided by a needle vent catheter used for antegrade perfusion and cooled to 32–34°C. The aorta is double-clamped in its proximal and distal parts and then transected to perform reconstruction on the aortic arch.

In patients with post-dissection aneurysm in our population, we observe relatively high mortality rates. The mean surgery time in this group was also the longest in our cohort due to the complexity of this pathology. Almost 80% of patients had undergone previous surgery before, and the majority of them suffered from multiple comorbidities. A relatively high rate of postprocedural exploration because of bleeding, neurological deficits, and mesenteric ischemia resulted in poorer results. In this group post-operatively cardiopulmonary reanimation or eventually ECLS was needed, resulting also in higher neurological deficits rates. However, these findings were not statistically significant due to relatively small numbers in post-dissection aneurysm subgroup. Further investigation is needed to better understand the peculiarity of this population.

In our cohort, all patients with AAD but one, who were discharged after FET operation were alive at last follow-up. In our view, Thoraflex Hybrid prosthesis facilitates successful surgical treatment for patients after such a high-risk event. The patients who survive early post-operative period are more likely to have uneventful midterm follow-up.

Our single-center experience shows the universal potential of this prosthesis for all kinds of aortic pathologies. Despite its initial purpose for distal aortic arch aneurysms, the international experience shows the versatile use of this prosthesis for all kinds of applications, such as penetrating aortic ulcers involving the aortic arch (21, 22). There are several reports where this prosthesis was even used upside down (reversed) for vascular surgery or post-dissection and thoracoabdominal aneurysm (23, 24).

Aortic arch prosthetic repair using an FET is also feasible in selected patients with AADB when the intimal tear is located directly beneath the left subclavian artery and there is no adequate landing length in Zone 2. It requires distal arch prosthetic repair with stentgrafting of the descending part of aorta, which is feasible on the beating heart.

A few limitations of this study should be outlined. It is retrospective by nature and limited to our single-center experience. Our results regrading low mortality and neurological deficits might be biased by the specialized team of surgeons.

Our experience demonstrates excellent perioperative results and, in our opinion, total aortic arch replacement with a Thoraflex Hybrid prosthesis is the most effective operative technique for type A aortic dissection. It causes rapid thrombosis of the false lumen and promotes a beneficial remodeling of the distal aorta, enabling first- and two-stage procedures. Next steps in our research will be further optimizing of perioperative management and extending follow-up for a more complete assessment and understanding of survival and freedom from reintervention.

DATA AVAILABILITY STATEMENT

The data analyzed in this study were not allowed to be made public according to the policy of our institute.

Requests to access these datasets should be directed to konrad.wisniewski@ukmuenster.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical Association of Westphalia-Lippe and the Faculty of Medicine, University of Münster (WWU Münster). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KW and AM were involved in the drafting of the manuscript. AD, AO, JS, AI, SM, and AR were involved in reviewing and providing feedback on the manuscript. All authors contributed to the article and approved the submitted version.

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Distal Aortic Failure Following the Frozen Elephant Trunk Procedure for Aortic Dissection

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Background: Aim of this study was to report and to identify risk factors for distal aortic failure following aortic arch replacement via the frozen elephant trunk (FET) procedure.

Methods: One hundred eighty-six consecutive patients underwent the FET procedure for acute and chronic aortic dissection. Our cohort was divided into patients with and without distal aortic failure. Distal aortic failure was defined as: (I) distal aortic reintervention, (II) aortic diameter dilatation to $\geq$ 6 cm or $>$ 5 mm growth within 6 months, (III) development of a distal stent-graft-induced new entry (dSINE) and/or (IV) aortic-related death. Preoperative, intraoperative, postoperative and aortic morphological data were analyzed.

Results: Distal aortic failure occurred in 88 (47.3%) patients. Forty-six (24.7%) required a distal reintervention, aortic diameter dilatation was observed in 9 (4.8%) patients, a dSINE occurred in 22 (11.8%) patients and 11 (6.4%) suffered an aortic-related death. We found no difference in the number of communications between true and false lumen ($p = 0.25$) but there were significantly more communications between Ishimaru zone 6–8 in the distal aortic failure group ($p = 0.01$). The volume of the thoracic descending aorta measured preoperatively and postoperatively within 36 months afterward was significantly larger in patients suffering distal aortic failure ($p < 0.001$; $p = 0.011$). Acute aortic dissection (SHR 2.111; $p = 0.007$), preoperative maximum descending aortic diameter (SHR 1.029; $p = 0.018$) and preoperative maximum aortic diameter at the level of the diaphragm (SHR 1.041; $p = 0.012$) were identified as risk factors for distal aortic failure.

Conclusion: The incidence and risk of distal aortic failure following the FET procedure is high. Especially those patients with more acute and more extensive aortic dissections or larger preoperative descending aortic diameters carry a substantially higher risk of developing distal aortic failure. The prospective of the FET technique as a single-step treatment for aortic dissection seems low and follow-up in dedicated aortic centers is therefore paramount.

Keywords: aortic dissection, frozen elephant trunk (FET), distal aortic failure, aortic reintervention, dSINE

Abbreviations: CTA, computed tomography angiography; FET, frozen elephant trunk; LSA, left subclavian artery; SACP, selective antegrade cerebral perfusion.

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INTRODUCTION

Total aortic arch replacement via the frozen elephant trunk (FET) technique has rapidly evolved over the last decade with broadened indications for several acute and chronic aortic pathologies (1–4). The FET procedure was initially almost exclusively carried out by experienced cardiovascular surgeons, but it has since become a highly standardized procedure safely performed by junior surgeons in the setting of an experienced team (5). The FET technique was originally intended as single stage procedure for pathologies involving the aortic arch. However, many surgeons have changed their perspective on this. There is ample research evidence of the high rate of subsequent aortic reinterventions regardless of the underlying aortic disease (6–8). Nevertheless, the reintervention rate remains an insufficient parameter for assessing the treatment success of proximal aortic procedures. A composite endpoint for these proximal index procedures is thus needed that also covers morphological and clinical aspects after the procedure such as distal stent graft-induced new entries (dSINE), aortic diameter or aortic-related death that determine distal aortic failure (9, 10).

Aim of this study was to report and to identify possible risk factors for distal aortic failure following the frozen elephant trunk procedure in patients with acute and chronic aortic dissection.

PATIENTS AND METHODS

Ethics Statement

IRB approval was obtained on 04/02/2021 (No. 20-1302) by the institutional review board of the University of Freiburg and the need for informed consent was waived.

Patients

One hundred eighty-six consecutive patients underwent total aortic arch replacement via the FET technique for acute and chronic aortic dissection at the University Hospital - Heart Centre Freiburg between March 2013 and September 2021. Our cohort was divided into patients with and without distal aortic failure.

Data Collection and Definition of Parameters

Data was extracted retrospectively from our aortic center's dedicated database. Acute aortic dissection was defined if symptom onset was fewer than 14 days before hospital admission and chronic thereafter. Stroke was classified according to the VARC-2 criteria using the modified Rankin scale (mRS) and subclassified as disabling stroke (mRS $\geq$ 3) and non-disabling stroke (mRS $\leq$ 2) (11). Distal aortic failure was defined as: (I) distal aortic reintervention, (II) aortic diameter dilatation to $\geq$ 6 cm or growth of $>$ 5 mm within 6 months, (III) occurrence of a dSINE and (IV) aortic-related death. Unknown deaths during follow-up were classified as aortic-related.

Surgical Technique

Our surgical technique has previously been described in detail (12–15). Briefly, the right axillary artery was routinely used for arterial cannulation. The intended core body temperature was 25 degrees. Bi- (additional selective perfusion cannula placed into the left common carotid artery) or trilateral (additional cannulation of the left axillary artery) antegrade cerebral perfusion was applied depending on the morphology of the Circle of Willis evaluated by preoperative computed tomography angiography (CTA) scans. Bifrontal near-infrared spectroscopy (NIRS) was applied to monitor cerebral oxygenation. Since we routinely implant the 100 mm version of the Thoraflex hybrid-graft (Terumo Aortic, Inchinnan, United Kingdom), cerebrospinal fluid drainage was generally not applied. The stent graft was sized according to the true lumen diameter without oversizing in patients with chronic aortic dissection. Zone 3 anastomoses were performed initially, and since 2017 distal anastomoses have been carried out normally in zone 2. The LSA was anastomosed end-to-end to an 8-mm dacron graft before implantation of the hybrid graft and anastomosed to the FET graft thereafter. This technique facilitates the anastomosis due to limited space at the distal arch. When the end-to-end anastomosis just described is not feasible either for reasons of exposure, because of the poor tissue quality of the native LSA or trilateral cerebral perfusion is done, we use an extra-anatomic approach. In this case, the LSA is closed by a running suture with additional 4.0 Prolene patch–counter–patch sutures or ligature. After that, the LSA prosthetic branch is guided to this location via the second intercostal space, and an end-to-side anastomosis is performed. We applied the beating-heart technique using 300 mL normothermic myocardial perfusion when feasible or cold-blood cardioplegia for myocardial protection (15, 16). We performed a staged approach in patients with chronic aortic dissection already fulfilling the criteria for aortic intervention or replacement in several downstream aortic segments: (I) FET, (II) subsequent thoracic endovascular aortic repair (TEVAR) to the level of the coeliac trunk and (III) open thoraco-abdominal replacement of the remaining involved aortic segments as previously reported (17).

Aortic Measurements and Follow-Up

CTA was carried out preoperatively, postoperatively, after six months and annually thereafter in at least 3 mm slices using our standard aortic scan protocol. All scans were transferred to imaging software (3mensio, Medical Imaging B.V., Maastricht, The Netherlands) for detailed morphological analysis and measurements of the entire aorta including volume and communication assessment. Follow-up was done at our dedicated aortic outpatient clinic based on our standard follow-up protocol (8).

Statistical Analysis

IBM SPSS Statistics 27 for Macintosh (Armonk; NY, United States) and R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analysis. All values are expressed as number (percentage), mean (standard deviation) or median [interquartile range] depending on normality of the respective values. Normality was assessed graphically using Q-Q plots. Group comparison for the univariable analysis was done via Student's t-test or Mann-Whitney-U test for continuous and Chi-squared or Fisher's Exact

test for categorial variables when appropriate. A competing risk analysis (competing risk: non-aortic related death) was performed to analyze the influence of clinically selected variables (age, distance from the left subclavian artery to end of dissection, connective tissue disorder, acute aortic dissection, preoperative maximum diameter of the descending aorta and preoperative maximum aorta diameter at the diaphragm level) on the risk for distal aortic failure. Missing values were imputed using predictive mean matching as implemented in the "mice" library (version 3.8.0) of the statistical programming language R. Imputation did not alter any p-values to a noteworthy degree. To compute yearly risk estimates and confidence intervals, we used a cubic smoothing spline. This addresses the scarcity of observations that causes purely non-parametric techniques to suffer from high variance. Smoothing ensures the estimates are more robust and stable.

RESULTS

Patients' Characteristics

Total aortic arch replacement using the FET technique was performed in 186 dissection patients (aged 59 [50-68], 66.1% male). A connective tissue disorder was observed in 12.9%. There were no differences between patients with and without distal aortic failure in terms of demographics and medical history. Eighty-eight patients (47.3%) had already undergone an previous aortic intervention or surgery. Patients' baseline characteristics are summarized in **Table 1**.

Aortic Characteristics

Ninety-one (48.9%) patients were treated for acute and 95 (51.1%) for chronic aortic dissection. The most frequent underlying pathology was a residual aortic dissection after previous type A repair ($n = 68$; 36.6%). Significantly more patients were treated for acute type A aortic dissection in the group without distal aortic failure (14.8 vs. 33.7%, $p = 0.004$). The dissection involved the descending thoracic, abdominal aorta and aortic bifurcation in 98.9, 81.4, and 53.1%, respectively. The abdominal aorta was involved more frequently in patients with distal aortic failure ($n = 77$, 91.7% vs. $n = 67$, 72%; $p < 0.001$). There was no difference in the total number of communications between true and false lumen (3.06 ± 2.73 vs. 2.5 ± 2.19, $p = 0.25$) but there were significantly more communications between Ishimaru zone 6-8 ($p = 0.01$) in the distal aortic failure group. The total volume of the thoracic descending aorta measured preoperatively and postoperatively within 36 months after the FET procedure was significantly larger in patients with distal aortic failure. All measured true lumen volumes were similar in both groups, whereas false lumen volume was significant larger

TABLE 1 | Demographic data and medical history.

	Total $n = 186$	**Distal aortic failure** $n = 88$	**No distal aortic failure** $n = 98$	***p*-value**
Age (years)	59 [50–68]	60 [48–68]	59 [51–69]	$p = 0.89$
Sex (male)	123 (66.1)	54 (61.4)	69 (70.4)	$p = 0.22$
BMI	26 [23–29]	25 [23–28]	27 [24–29]	$p = 0.052$
BSA (kg/m^2)	2 [1.8–2.1]	2 [1.8–2.2]	2 [1.9–2.2]	$p = 0.1$
Cardiovascular risk factors				
Diabetes (insulin)	5 (2.7)	1 (1.1)	4 (4.1)	$p = 0.37$
Dyslipidaemia	56 (30.1)	27 (30.7)	29 (29.6)	$p = 0.87$
Hypertension	149 (80.1)	72 (81.1)	77 (78.6)	$p = 0.59$
Previous stroke	20 (10.8)	12 (13.6)	8 (8.2)	$p = 0.25$
Previous acute kidney injury	18 (9.7)	7 (8.0)	11 (11.2)	$p = 0.47$
Dialysis	2 (1.1)	0 (0.0)	2 (2.0)	$p = 0.5$
Chronic obstructive pulmonary disease	15 (8.1)	9 (10.2)	6 (6.1)	$p = 0.42$
Coronary artery disease	42 (22.6)	21 (23.9)	21 (21.4)	$p = 0.73$
Connective tissue disorder	24 (12.9)	15 (17.0)	9 (9.2)	$p = 0.13$
Previous aortic or cardiac surgery				
Previous surgery	92 (49.5)	44 (50.0)	48 (49.0)	$p > 0.99$
Interval (years)	5 [1–11]	5 [1–10]	5 [1–12]	$p = 0.52$
Coronary artery bypass grafting	7 (3.8)	5 (5.7)	2 (2.0)	$p = 0.26$
Aortic valve replacement	28 (15.1)	18 (20.5)	10 (10.2)	$p = 0.06$
Mitral valve replacement	3 (1.6)	1 (1.1)	2 (2.0)	$p > 0.99$
Ascending replacement	79 (42.5)	39 (44.3)	40 (40.8)	$p = 0.66$
Hemiarch replacement	32 (17.2)	14 (15.9)	18 (18.4)	$p = 0.7$
Others	38 (20.4)	16 (18.2)	22 (22.4)	$p = 0.59$
Aortic Re-do	88 (47.3)	42 (47.7)	46 (46.9)	$p > 0.99$
Re-Sternotomy	76 (40.9)	35 (39.8)	41 (41.8)	$p = 0.88$

Data are presented as number (%), or median (interquartile range); BMI, body-mass-index; BSA, Body surface area.

TABLE 2 | Aortic characteristics and measurements (preoperative CTA).

	Total $n = 186$	Distalaortic failure $n = 88$	No distalaortic failure $n = 98$	*p*-value
Acute aortic dissection	91 (48.9)	42 (47.7)	49 (50.0)	$p = 0.77$
Type A	46 (24.7)	13 (14.8)	33 (33.7)	$p = 0.004$
Type B	20 (10.8)	12 (13.6)	8 (8.2)	$p = 0.25$
Non-A non-B	25 (13.4)	17 (19.3)	8 (8.2)	$p = 0.032$
Chronic aortic dissection	95 (51.1)	46 (52.3)	49 (50.0)	$p = 0.77$
Residual dissection after previous type A repair	68 (36.6)	31 (35.2)	37 (37.8)	$p = 0.76$
Type B	16 (8.6)	9 (10.2)	7 (7.1)	$p = 0.6$
Non-A non-B	11 (5.9)	6 (6.8)	5 (5.1)	$p = 0.76$
Diagnostic CTA				
Dissection extention	$n = 177$	$n = 84$	$n = 93$	
Aortic arch, small curvature	132 (74.6)	57 (67.9)	75 (80.6)	$p = 0.06$
Aotic arch, large curvature	131 (74.0)	57 (67.9)	74 (79.6)	$p = 0.09$
Thoracic descending aorta	175 (98.9)	84 (100.0)	91 (97.8)	$p = 0.5$
Abdominal aorta	144 (81.4)	77 (91.7)	67 (72.0)	$p < 0.001$
Coelic trunk involvement	14 (7.9)	6 (7.1)	8 (8.6)	$p = 0.78$
SMA involvement	28 (15.8)	14 (16.7)	14 (15.1)	$p > 0.99$
Left renal artery involvement	19 (10.7)	7 (8.3)	12 (12.9)	$p = 0.34$
Right renal artery involvement	9 (5.1)	4 (4.8)	5 (5.4)	$p > 0.99$
IMA involvement	1 (0.6)	1 (1.2)	19 (20.4)	$p = 0.5$
Aortic bifurcation	94 (53.1)	52 (61.9)	42 (45.2)	$p = 0.03$
Perfusion abdominal vessels	n = 168	n = 81	n = 87	
CT true lumen	133 (79.2)	61 (75.3)	72 (82.8)	$p = 0.26$
false lumen	11 (6.5)	8 (9.9)	3 (3.4)	$p = 0.12$
Both	24 (14.3)	12 (14.8)	12 (13.8)	$p > 0.99$
SMA true lumen	129 (76.8)	62 (76.5)	67 (77.0)	$p > 0.99$
false lumen	4 (2.4)	3 (3.7)	1 (1.1)	$p = 0.35$
Both	32 (19.0)	16 (19.8)	16 (18.4)	$p = 0.85$
LRA true lumen	92 (54.8)	41 (50.6)	51 (58.6)	$p = 0.35$
false lumen	34 (20.2)	20 (24.7)	14 (16.1)	$p = 0.18$
Both	35 (20.8)	16 (19.8)	19 (21.8)	$p = 0.85$
RRA true lumen	110 (65.5)	51 (63.0)	59 (67.8)	$p = 0.52$
false lumen	23 (13.7)	13 (16.0)	10 (11.5)	$p = 0.5$
Both	29 (17.3)	14 (17.3)	15 (17.2)	$p > 0.99$
Aortic length (mm)	$n = 177$	$n = 84$	$n = 93$	
Anulus to BCT	87 [74-95]	85 [74-96]	88 [74-95]	$p = 0.73$
BCT to LSA	36 [30-42]	35 [30-43]	36 [30-42]	$p = 0.593$
LSA to diaphragm	260 [236-281]	268 [244-290]	256 [228-275]	$p = 0.006$
LSA to CT	281 [258-300]	287 [263-314]	272 [250-294]	$p = 0.001$
LSA to SMA	299 [278-319]	304 [284-334]	289 [269-313]	$p = 0.002$
LSA to LRA	318 [293-339]	320 [307-349]	311 [287-332]	$p = 0.01$
LSA to RRA	314 [291-340]	318 [302-346]	311 [282-329]	$p = 0.008$
LSA to bifurcation	417 [392-446]	420 [395-460]	414 [391-440]	$p = 0.15$
Number of communications	2.76 ± 2.47	3.06 ± 2.73	2.5 ± 2.19	$p = 0.25$
Number of communications per Ishimaru zone				
Ishimaru 3	0.14 ± 0.35	0.13 ± 0.34	0.15 ± 0.04	$p = 0.83$
Ishimaru 4-5	1.32 ± 1.58	1.54 ± 1.75	1.12 ± 1.39	$p = 0.11$
Ishimaru 6-8	0.32 ± 0.66	0.44 ± 0.78	0.2 ± 0.5	$p = 0.01$
Ishimaru 9	0.51 ± 0.92	0.58 ± 0.92	0.45 ± 0.92	$p = 0.21$

Data are presented as number (%) or median (interquartile range); CTA, computed tomography angiography; CT, coeliac trunk; SMA, superior mesenteric artery; LRA, left renal artery; RRA, right renal artery; BCT, brachiocephalic trunk; LSA, left subclavian artery.

preoperatively and within 36 months postoperatively. Detailed aortic characteristics and measurements are provided in the **Supplementary Tables 1–2** and **Table 2**.

Intraoperative Data

Concomitant procedures were common. Aortic root replacements (conduits and valve-sparing techniques) were

TABLE 3 | Intraoperative data and clinical outcomes.

Concomitant procedures	Total $n = 186$	Distalaortic failure $n = 88$	No distalaortic failure $n = 98$	p-value
Aortic root conduit	20 (10.8)	10 (11.4)	10 (10.2)	$p = 0.82$
Valve-sparing root replacement	14 (7.5)	4 (4.5)	10 (10.2)	$p = 0.17$
Aortic valve replacement	24 (12.9)	7 (8.0)	17 (17.)	$p = 0.08$
Coronary artery bypass grafting	19 (10.2)	9 (10.2)	10 (10.2)	$p > 0.99$
Operation time (min)	398 [349-471]	398 [337-463]	394 [350-478]	$p = 0.89$
CPB time (min)	213 [175-258]	201 [170-255]	218 [183-262]	$p = 0.14$
Cross-clamp time (min)	122 [95-163]	113 [91-158]	129 [98-164]	$p = 0.14$
Lowest body temperature (°C)	24.8 [24-25.3]	24.7 [24-25.2]	24.8 [24.1-25.3]	$p = 0.5$
Beating-heart technique	43 (23.1)	25 (28.4)	18 (18.4)	$p = 0.12$
Unilateral cerebral perfusion	21 (11.3)	13 (14.8)	8 (8.2)	$p = 0.25$
Bilateral cerebral perfusion	133 (71.5)	65 (73.9)	68 (69.4)	$p = 0.73$
Trilateral cerebral perfusion	26 (14.0)	8 (9.1)	18 (18.4)	$p = 0.09$
Zone 2 distal anastomosis	137 (73.7)	65 (73.9)	72 (73.5)	$p > 0.99$
Postoperative outcomes				
In-hospital mortality	15 (8.1)	8 (9.1)	7 (7.1)	$p = 0.79$
Bleeding	20 (10.8)	9 (10.2)	11 (11.2)	$p > 0.99$
Stroke	26 (14.0)	6 (6.8)	20 (20.4)	$p = 0.011$
Disabling stroke	18 (9.7)	4 (4.5)	14 (14.3)	$p = 0.027$
Non-disabling stroke	8 (4.3)	2 (2.3)	6 (6.1)	$p = 0.28$
Dialysis	18 (9.7)	5 (5.7)	13 (13.3)	$p = 0.13$
Paraplegia	4 (2.2)	2 (2.3)	2 (2.0)	$p > 0.99$
Tracheotomy	11 (5.9)	4 (4.5)	7 (7.1)	$p = 0.55$

Data are presented as number (%) or median (interquartile range), distal aortic failure; CPB, cardiopulmonary bypass.

the most frequent ones. The beating-heart technique was applied in 43 (23.1%) patients and trilateral antegrade cerebral perfusion was used in 26 (14.0%) patients. There was no statistically significant intergroup difference between patients with and without distal aortic failure regarding intraoperative data (**Table 3**).

Clinical Outcome

In-hospital mortality was 8.1% while 14% ($n = 26$) suffered a perioperative stroke; 9.7% were classified as disabling strokes and were more frequently observed in patients without distal aortic failure ($p = 0.011$). In-hospital mortality in patients with acute aortic dissection was 12.1% ($n = 11$) and 4.2% ($n = 4$) in patients with chronic aortic dissection. Disabling stroke occurred in 15.4% ($n = 14$, acute aortic dissection) and 4.2% ($n = 4$, chronic aortic dissection), respectively, and Symptomatic spinal cord injury was observed in 4 (2.2%) patients. Postoperative clinical outcomes are summarized in **Table 3**.

Distal Aortic Failure and Follow-Up

One hundred seventy-one patients were discharged. Distal aortic failure occurred in 88 (47.3%) patients: 46 (24.7%) distal reinterventions (see **Supplementary Table 3** for indications), 9 (4.8%) aortic diameter dilatations to $\geq$ 6 cm/ $>$ 5 mm/growth within 6 months, 22 (11.8%) dSINE and 11 (6.4%) aortic-related deaths. Five of the 9 patients with aortic diameter progression and 15 of the 22 dSINE patients underwent an additional aortic reinterventions. Hence, the total number of performed reinterventions cumulates to 66 (35.5%). These reinterventions were done endovascularly in 46 (26.9%), conventionally with open surgery in 7 (4.1%) and via a staged hybrid approach in 13 (7.6%), respectively. The majority of dSINE occurred at the lesser curvature ($n = 13$, 76.5%). **Figure 1** shows a three dimensional CTA reconstruction of a patient with dSINE. Median follow-up was complete and 17 (5-4) months. The competitive risk regression model revealed, acute aortic dissection (SHR 2.111; $p = 0.007$), preoperative maximum aortic descending diameter (SHR 1.029; $p = 0.018$) and preoperative maximum aortic diameter at the level of the diaphragm (SHR 1.041; $p = 0.012$) as risk factors for distal aortic failure. The probability of distal aortic failure is as follows: 12 months 26% [95 CI 19-32%], 24 months 42% [95 CI 34-50%], 36 months 51% [95% CI 43-60%], 48 months 60% [95% CI 51-69%] and 60 months 71% [95% CI 60–81%]. The model is shown in **Table 4** and illustrated in **Figure 2**.

DISCUSSION

The most essential findings of our study can be summarized as: In patients with acute and chronic aortic dissection, (I) total aortic arch replacement via the FET technique is associated with favorable early postoperative outcome; (II) the incidence and risk for distal aortic failure following the FET technique is very high; (III) patients with more acute and more extensive aortic dissections or larger descending aortic diameters in preoperative CTA scans carry a significantly higher risk of developing distal aortic failure.

FIGURE 1 | Shows a three dimensional CTA reconstruction of a patient with dSINE (arrow) which causes recurrent false lumen perfusion.

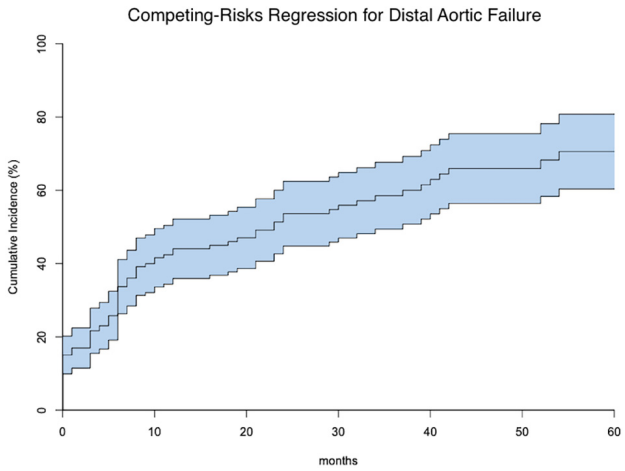

FIGURE 2 | Shows the competing risks for distal aortic failure (middle line) including the 95% confidence intervals within 60 months following the frozen elephant trunk procedure.

Our patients' demographics and medical history are in line with several other reports addressing the issue of total aortic arch replacement (1, 2, 18). In this study, we identified no statistically significant difference in baseline data between patients with and without distal aortic failure. In fact, even an underlying connective tissue disorder was not more common in patients with distal aortic failure and did not prove to be a significant variable in our competing risk regression model, nor was age. Note that this is an important finding, as it reveals that the FET procedure is a durable approach in patients with a connective tissue disorder or of younger age. Therefore, what seems likely is that it is not the disease or age at disease onset *per se* but rather its pathomorphological expression that has the most fundamental impact on treatment durability after total aortic arch replacement via the FET technique.

TABLE 4 | Competing risk regression: distal aortic failure.

Variable	*p*-value	SHR	95% CI
Distance left subclavian artery to end of dissection (mm)	0.054	1.002	1.000–1.003
Connective tissue disorder	0.370	1.358	0.628–2.645
Acute aortic dissection,	0.007	2.111	1.224–3.639
Preoperative maximum descending diameter (mm)	0.018	1.029	1.005–1.053
Preoperative maximum diameter diaphragm (mm)	0.012	1.041	1.009–1.075
Age (years)	0.750	0.997	0.979–1.016

In this study, significantly more patients without distal aortic failure were initially treated for an acute type A aortic dissection. However, there is a possible bias regarding a shorter follow-up in patients with more adverse events following repair of an acute type A aortic dissection. Correspondingly, postoperative strokes were more frequent in patients without distal aortic failure. As most strokes are of embolic origin, more manipulation might also trigger more embolic events (19). Therefore, both meticulous preoperative evaluation and patient selection are absolutely mandatory. Note that these patients are often already suffering from substantial disability and impairment in daily life, which is why they may tend to avoid making further visits to our outpatient clinic, in turn leading to less follow-up data on patients suffering from potential distal aortic failure. Hence, an even higher distal aortic failure incidence may be possible.

Our study also revealed that the main morphological aspect seems to be aortic enlargement in terms of total downstream aortic volume. More communications between both lumina lead to more false lumen perfusion, which inevitably results in aortic dilatation. Moreover, it seems conclusive that an initially enlarged aorta also carries a higher risk for distal failure (as our regression model shows). Note that although the true lumen appears to have no substantial impact, it is the preoperative and persisting higher false lumen volume postoperatively and during follow-up that plays the main role (12, 20).

Concomitant procedures and intraoperative data were similar between groups and therefore seem to play no major role in the development of distal aortic failure during follow-up. This is conclusive evidence, as no further distal, only proximal procedures, were carried out concomitantly. On the one hand, using the short (100 mm) version of the prosthesis may potentially reduce the risk for symptomatic spinal cord injuries, but it may also raise the risk for distal aortic failure due to less aortic coverage (3). This effect may be aggravated by a trend favoring a zone 2 anastomosis, which simplifies the procedure

from the surgical perspective, but proximalis further the distal FET stent-graft landing zone (8).

Distal aortic failure following total arch replacement via the FET technique occurred in about half of our cohort. The high incidence (33%) for aortic reinterventions has been reported before (6), but no risk factor for reinterventions was identified. In our opinion and in the opinion of others (9), reintervention rates *per se* do not sufficiently reflect proximal treatment failure. Distal aortic failure should not be limited to planned or unplanned distal reinterventions but expanded to other distal aortic adverse events during follow up. This necessarily requires a composite endpoint that also includes dSINE, downstream aortic enlargement, and aortic-related death. Taking these factors into account, the probability of distal aortic failure is consequently higher than previously reported reintervention rates. These factors require or might have required additional interventional or surgical treatment to prevent the underlying disease from progressing. Distal aortic failure due to dSINE is a relatively common problem following the FET procedure with higher reported incidences compared to conventional TEVAR (8, 21). One possible explanation may be a more rigid ring at the distal end of the FET stent-graft when using the Thoraflex device (22). Other potential factors are the zone 2 proximalisation of the distal anastomosis that may create a sharp angle of the stentgraft part to the descending's dissection membrane. Of note, this study also identified an acute aortic dissection as a significant risk factor for developing distal aortic failure following the FET procedure. The dissection membrane is more vulnerable in the acute phase of dissection, whereas it is substantially stiffer and fibrotic in the chronic state. Therefore developing a dSINE is more likely in acute aortic dissections (22).

As this study shows, distal aortic failure can and will occur following the FET procedure. Therefore, we postulate that the designation "single-step approach" is not contemporary anymore for aortic arch replacement via the FET technique. The key variable in determining the long-term success of the FET procedure seems to be the underlying aortic morphology that is crucial to any further decision-making process. This implies two major necessities: (I) a specific follow-up protocol including periodical outpatient visits as well as CTA scans and (II) dedicated aortic teams. Both are mandatory to both detect these events and provide ideal further treatment when needed.

Distal aortic failure often requires invasive treatment in terms of an endovascular extension via TEVAR or open thoracoabdominal replacement. While the Milan group observed no differences in in-hospital mortality comparing both approaches, the overall incidence of adverse events was higher in their open replacement group. They found that respiratory complications were especially likely to have substantial impact (23). We therefore take a three-step approach when treating extensive thoracoabdominal aortic dilatation following the FET procedure. First, we extend the stent-graft part of the FET prosthesis up to the coeliac trunk, usually using two stent-grafts. This approach has so far revealed excellent clinical results with 0% in-hospital mortality or permanent morbidity (8). Applying this strategy, in case of a third-step open surgical repair, we shift the proximal anastomosis more distally and ensure almost continuous ventilation of the left lung, and keep respiratory complications to a minimum during and after the open replacement of the remaining aortic segments (17).

LIMITATIONS

This is a retrospective single-center study with several limitations inherent to this study design. However, this study adds significant new, high quality data on the long-term success and remodeling in patients following the FET procedure.

CONCLUSION

In patients with acute and chronic aortic dissection, total aortic arch replacement using the FET technique is associated with very good early postoperative results. However, the incidence and risk for distal aortic failure following the FET procedure is high. In particular, patients with more acute and more extensive aortic dissections or larger descending aortic diameters in preoperative CTA scans carry a substantially higher risk of developing distal aortic failure. The key variable in determining the long-term success of the FET procedure seems to be the underlying aortic morphology that is crucial to any further decision-making process. Hence, the FET technique can no longer be regarded as a single-step therapy for acute and chronic aortic dissection but remains the treatment strategy of first choice for aortic arch and descending aortic pathologies. Moreover, follow-up in dedicated aortic centers is paramount.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of the requirements of our institutional review board. Individual reasonable requests will be evaluated by the corresponding author. Requests to access the datasets should be directed to TB, tim.berger@uniklinik-freiburg.de.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the University of Freiburg on 04/02/2021 (No. 20-1302). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TB: conceptualization, formal analysis, methodology, and writing—original draft. MG: data curation, formal analysis, and writing—original draft. BR and RG: supervision and writing—review and editing. TW and PD: writing—review and editing. MH: visualization and writing—review and editing.

SK: conceptualization, visualization, and writing—review and editing. MC: project administration, supervision, and writing—review and editing. MK: conceptualization, methodology, supervision, validation, and writing—original draft. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.911548/full#supplementary-material

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Conflict of Interest: MC and BR are consultants to Terumo Aortic and shareholders of Ascense Medical. MC is consultant to Medtronic, Endospan and NEOS, received speaking honoraria from Cryolife-Jotec and Bentley and is shareholder of TEVAR Ltd. MK has received speaking honoraria from Terumo Aortic.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prediction Nomogram for Postoperative 30-Day Mortality in Acute Type A Aortic Dissection Patients Receiving Total Aortic Arch Replacement With Frozen Elephant Trunk Technique

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Objective: To develop and validate a nomogram model to predict postoperative 30-day mortality in acute type A aortic dissection patients receiving total aortic arch replacement with frozen elephant trunk technique.

Method: Clinical data on 1,156 consecutive acute type A aortic dissection patients who got total aortic arch replacement using the frozen elephant trunk technique was collected from January 2010 to December 2020. These patients were divided into training and testing cohorts at random with a ratio of 7:3. To predict postoperative 30-day mortality, a nomogram was established in the training set using the logistic regression model. The novel nomogram was then validated in the testing set. The nomogram's calibration and discrimination were evaluated. In addition, we created four machine learning prediction models in the training set. In terms of calibration and discrimination, the nomogram was compared to these machine learning models in testing set.

Results: Left ventricular end-diastolic diameter <45 mm, estimated glomerular filtration rate <50 ml/min/1.73 m^2, persistent abdominal pain, radiological celiac trunk malperfusion, concomitant coronary artery bypass grafting and cardiopulmonary bypass time >4 h were independent predictors of the 30-day mortality. The nomogram based on these 6 predictors manifested satisfying calibration and discrimination. In testing set, the nomogram outperformed the other 4 machine learning models.

Conclusion: The novel nomogram is a simple and effective tool to predict 30-day mortality rate for acute type A aortic dissection patients undergoing total aortic arch replacement with frozen elephant trunk technique.

Keywords: nomogram, prediction model, aortic dissection (AD), surgery, FET, machine learning (ML)

INTRODUCTION

Acute type A aortic dissection (ATAAD) is a life-threatening disorder (1). The most effective treatment for the disease is emergent surgical repair (2). The surgical strategies for ATAAD lesions are varied due to the complicated and various nature of the lesions (3). Unlike western countries, in China, total aortic arch replacement (TAR) utilizing the frozen elephant trunk (FET) technique has become the most popular surgical procedure for ATAAD (4). As a complex procedure with higher risk, the outcome of TAR+FET is heavily influenced by the patient's preoperative status as well as the surgical components. Preoperative risk evaluation is of great importance in clinical practice and one of the most effective approaches is to use a prediction model. Although there are some prediction models for other heart procedures (5, 6), there are currently few models for TAR+FET surgery. Czerny et al. (7) established a model (GERAADA) for predicting the mortality of various ATAAD operations. GERAADA is, to our knowledge, the first multicenter data-based mortality risk prediction model for ATAAD surgery. It is a milestone in the risk evaluation of aortic dissection. However, a considerable percentage of GERAADA's training cohort had isolated ascending aortic (36.7%) or hemiarch (47.5%) replacement. Only 16% of the patients (n = 394) in their study had TAR surgery with or without FET. The aim of our research was to establish and evaluate a simple nomogram for predicting 30-day mortality in patients with ATAAD who underwent TAR+FET surgery.

METHODS

This study had been approved by institutional review board of Fuwai hospital, Peking union medical college and Chinese academy of medical sciences. Institutional Review Board (IRB) approval number: 2020-1402. Date: 2020-11-24.

Patients

All patients (n = 1,711) who were diagnosed with ATAAD and underwent surgical repair at Fuwai Hospital were enrolled from January 2010 to December 2020. Total 247 patients with isolated ascending aorta replacement and 308 patients with ascending aorta with hemi-arch replacement were excluded from the final study, remaining 1,156 individuals with TAR+FET (**Figure 1**). The acute phase of aortic dissection was defined as the time between onset and surgery, which was less than 2 weeks. In our institution, the indications for ATAAD patients to receive TAR+FET were as follow: (1) the dissection involved the distal aortic arch and/or descending aorta; (2) Aneurysm formation in the distal aortic

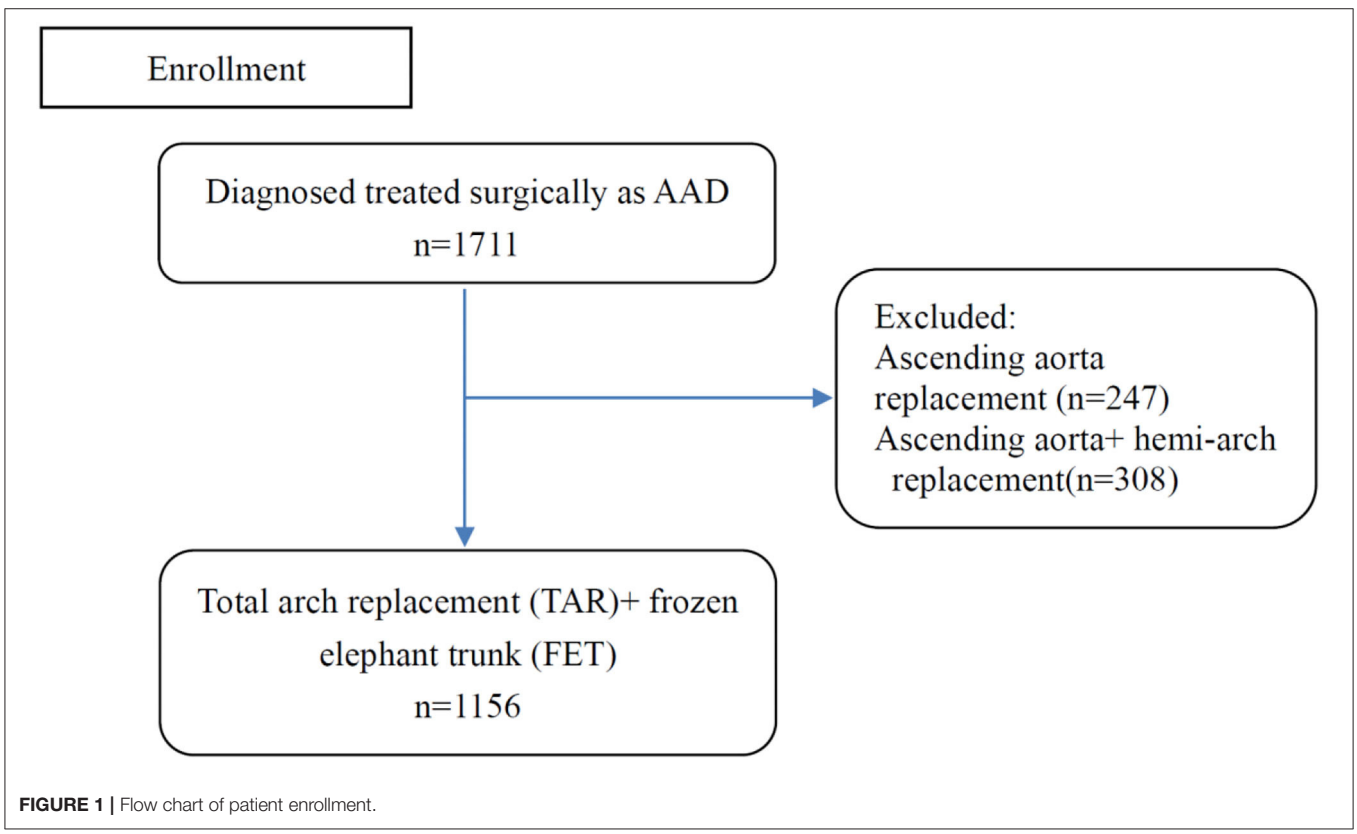

FIGURE 1 | Flow chart of patient enrollment.

arch and/or descending aorta (transverse diameter >40 mm). We collected demographic data, preoperative risk factors and important intraoperative information of all patients for analysis.

Preoperative Evaluation

All patients underwent preoperative radiological examinations such as aortic computed tomograph angiography (CTA, scanning from the level of the supra aortic vessels to bilateral

TABLE 1 | Patient demographics and clinical features.

Variables	Training (n = 806)	Testing (n = 350)	p-value
Patient-related			
Age, mean ± SD	46.95 ± 9.92	46.90 ± 10.27	0.939
Female, *n*(%)	160 (19.9)	73 (20.9)	0.755
BMI, mean ± SD	26.36 ± 4.21	26.12 ± 5.10	0.4
Marfan syndrome, *n*(%)	60 (7.4)	30 (8.6)	0.591
Diabetes mellitus, *n*(%)	23 (2.9)	4 (1.1)	0.119
Previous stroke, *n*(%)	33 (4.1)	13 (3.7)	0.889
Chronic kidney disease, *n*(%)	5 (0.6)	4 (1.1)	0.572
COPD, *n*(%)	2 (0.2)	2 (0.6)	0.753
ALT (unit/L), mean ± SD	30.87 ± 36.86	40.30 ± 12.78	0.224
EGFR (ml/min/1.73m^2), mean ± SD	101.35 ± 38.21	99.48 ± 34.64	0.432
EGFR < 50 ml/min/1.73m^2, *n*(%)	45 (5.6)	19 (5.4)	1
NYHA III or IV, n(%)	166 (20.6)	85 (24.3)	0.187
Hypertension, n(%)	520 (64.5)	224 (64.0)	0.919
Coronary artery disease, *n*(%)	58 (7.2)	23 (6.6)	0.797
Atrial fibrillation, *n*(%)	8 (1.0)	3 (0.9)	1
Previous cardiovascular surgery, *n*(%)	20 (2.5)	8 (2.3)	1
Previous TEVAR, *n*(%)	12 (1.5)	3 (0.9)	0.556
Instable hemodynamics, *n*(%)	35 (4.3)	23 (6.6)	0.147
TTE-related			
LVEDD < 45 mm, *n*(%)	90 (11.2)	47 (13.4)	0.32
Ejection fraction, *n*(%)	60.35 (4.31)	60.04 (4.63)	0.276
Severe aortic regurgitation, *n*(%)	81 (10.0)	50 (14.3)	0.051
Hydropericardium, *n*(%)	11 (1.4)	5 (1.4)	1
Dissection-related			
Severely compressed true lumenin descending aorta, *n*(%)	78 (9.7)	29 (8.3)	0.522
Persistent abdominal pain, *n*(%)	9 (1.1)	5 (1.4)	0.878
Lower limb ischemia, *n*(%)	54 (6.7)	18 (5.1)	0.382
Clinical coronary ostium involved, *n*(%)	116 (14.4)	50 (14.3)	1
Carotid ostium involved, *n*(%)	478 (59.3)	205 (58.6)	0.867
Radiological Celiac trunk malperfusion, *n*(%)	74 (9.2)	37 (10.6)	0.53
Radiological superior mesenteric artery malperfusion, *n*(%)	56 (6.9)	32 (9.1)	0.241
Renal malperfusion, *n*(%)	40 (5.0)	28 (8.0)	0.06
Radiological iliac-femoralmalperfusion, n(%)	82 (10.2)	37 (10.6)	0.921
Operation-related			
Concomitant with aortic root surgery, *n*(%)	216 (26.8)	108 (30.9)	0.18
CABG, *n*(%)	104 (12.9)	42 (12.0)	0.743
Salvage CABG, *n*(%)	14 (1.7)	8 (2.3)	0.694
Carotid bypass, *n*(%)	30 (3.7)	5 (1.4)	0.057
CPB time > 4 h, *n*(%)	146 (18.1)	58 (16.6)	0.584
DHCA temperature (degree centigrade), mean ± SD	22.04 ± 3.58	21.74 ± 3.39	0.179
DHCA time (minutes), mean ± SD	18.57 ± 6.90	19.37 ± 6.59	0.067
Outcome			
30-day postoperative deaths, *n*(%)	43 (5.3)	27 (7.7)	0.154

SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ALT, Alanine Aminotransferase; EGFR, estimated glomerular filtration rate; NYHA, New York heart association; TEVAR, thoracic endovascular aortic repair; TTE, transthoracic echocardiography; LVEDD, left ventricular end-diastolic diameter; CTA, computed tomographic angiography; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DHCA, deep hypothermia and circulatory arrest.

femoral arteries), transthoracic echocardiography (TTE) and coronary CTA.

Surgical Technique

After cardiopulmonary bypass (CPB) established, ascending aorta was clamped and cardioplegia was transmitted to coronary orifice directly. Aortic root repair was done during cooling phase. Circulatory arrest was instituted, if the nasopharyngeal temperature reached target temperature (usually 18–22°C). The supra-arch arteries were clamped and the aortic arch was open. Selective cerebral perfusion (SCP) was started through the right axillary artery. Aortic arch was resected between the origin of the left subclavian artery and the left carotid artery and supra-arch arteries were resected at their initial part. The FET was deployed into the true lumen of distal aorta. The distal aorta incorporating the stent graft was sewn to the distal end of a 4-branch prosthetic graft using distal first technique. After completion of distal anastomosis, the graft was cross-clamped, and antegrade systemic perfusion was achieved through a side branch.

The sequence of supra-arch arteries anastomosing to prosthetic graft branches was carried out from left common carotid artery, left subclavian artery, and innominate artery. Sometimes innominate artery was anastomosed after proximal aortic stump anastomosis was completed. Usually after the anastomosis of left common carotid artery was accomplished, SCP was discontinued, CPB gradually resumed to normal flow, and rewarming started.

Definition of Parameters

To identify the parameters that would influence the progress and outcome of ATAAD, we defined some institution-specific terms to describe them in **Table 2**.

Statistical Analysis

We followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement for reporting the development and validation of the prediction model (8). With a ratio of 7:3, all the patients were randomly divided into training set ($n = 806$) and testing set ($n = 350$). Categorical variables were presented as frequencies (percentages %) and were compared between groups with the chi-squared test. Continuous variables were presented as mean ± standard deviation (SD), and were compared with the two-sample t test or the Wilcoxon rank sum test as appropriate. According to restricted cubic spline analysis, we also converted some continuous variables into binary variables (**Supplementary Figures 1**–**3**). P value of > 0.05 was considered statistically significant.

In training set, all the possible risk factors were screened by univariate analyses and a multivariate logistic regression was performed using "enter" method to construct the initial model.

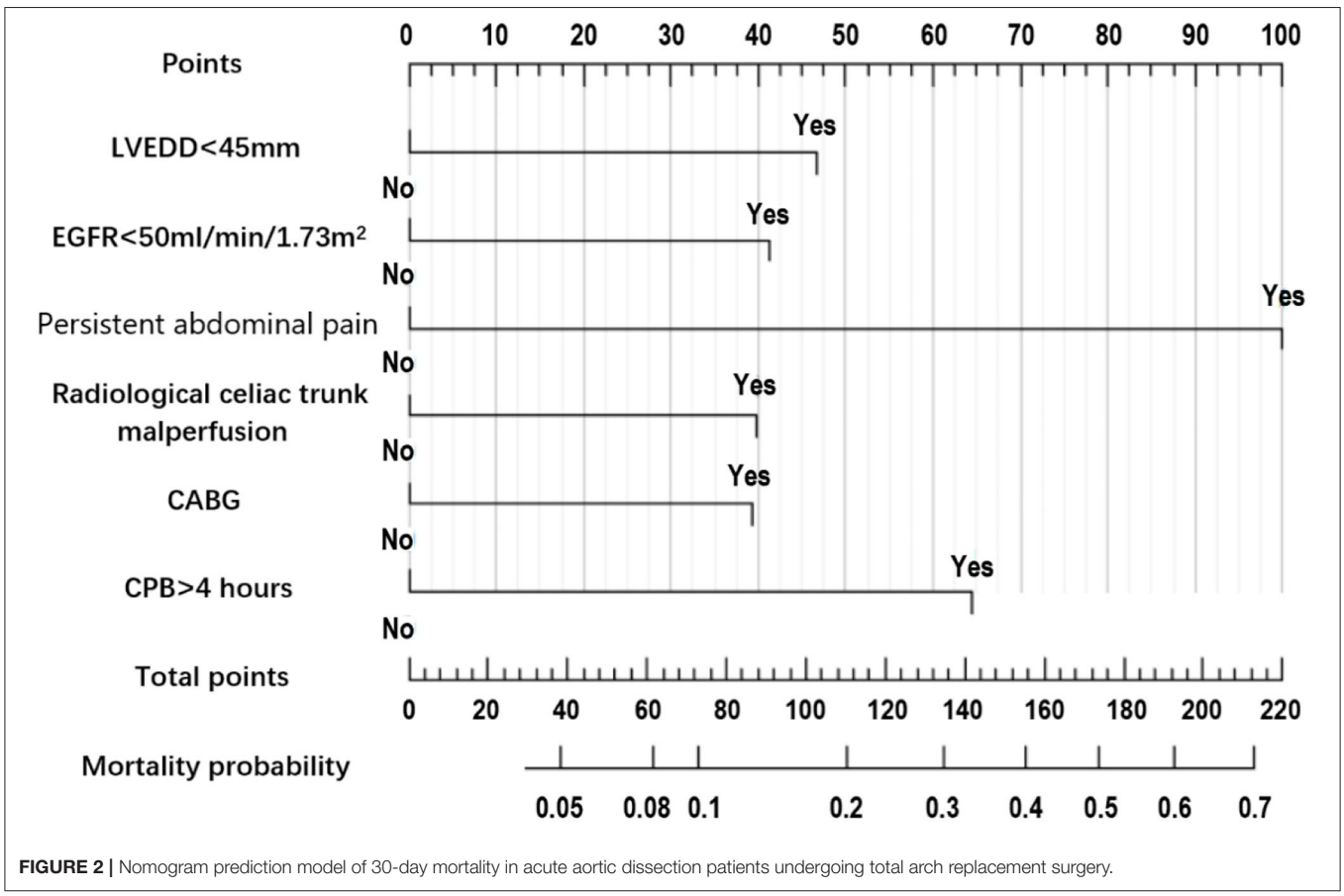

FIGURE 2 | Nomogram prediction model of 30-day mortality in acute aortic dissection patients undergoing total arch replacement surgery.

Next, to construct the final model, we performed the variable selection process by repeated multivariate logistic regression analyses using "stepwise both direction" method. The calculation of Akaike weights confirmed the importance of the final model parameters. Subsequently, we constructed a nomogram based on the last logistic regression model (**Figure 2**). Additionally,

TABLE 2 | Definitions of risk factors.

Variables	Definitions
Age	-
Female	-
BMI	Body mass index
Marfan syndrome	Documented past history or fulfilled the revised Ghent criteria
Diabetes mellitus	Documented past history or fulfilled the criteria of WHO 1999
Previous stroke	Documented past history
Chronic kidney disease	Documented past history or fulfilled the criteria of KDIGO 2012
COPD	Long-term use of bronchodilators or steroids for lung disease
ALT	-
EGFR	Estimated by the Modification of Diet in Renal Disease (MDRD) equation
NYHA III or IV	NYHA classification
Hypertension	Documented past history or SBP>140 mmHg and/or DBP > 90 mmHg
Coronary artery disease	Documented past history
Atrial fibrillation	Documented past history
Previous cardiovascular surgery	1 or more previous major cardiac operation involving opening the pericardium
Previous TEVAR	Documented past history
Instable hemodynamics	Need for catecholamines at referral
LVEDD	-
Ejection fraction	-
Severe aortic regurgitation	-
Hydropericardium	Massive pericardiac fluid
Severely compressed true lumenin descending aorta	Revealed by CTA
Persistent abdominal pain	Persistent severe abdominal pain associated with aortic dissection
Lower limb ischemia	Symptoms or signs of lower limb ischemia, such as pain, numbness, or weak pulse of dorsal foot artery etc.
Clinical coronary ostium involved	The coronary ostium lesion confirmed in operation
Carotid ostium involved	Carotid ostium lesion confirmed in operation
Radiological celiac trunk malperfusion	Celiac trunk malperfusion revealed by CTA
Radiological superior mesenteric artery malperfusion	Superior mesenteric artery malperfusion revealed by CTA
Renal malperfusion	Unilateral or bilateral renal malperfusion revealed by CTA, regardless of renal function
Radiological iliac-femoral malperfusion	Unilateral or bilateral iliac-femoral malperfusion revealed by CTA
Concomitant with aortic root surgery	Combined with bentall or valve sparing root replacement surgery
CABG	Combined with CABG surgery
Salvage CABG	The CABG was not planned preoperatively, and was performed because a post-operative hemodynamic instability (such as malignant arrhythmia or failing to wean from cardiopulmonary bypass) occurred with suspicion of myocardial ischemia
Carotid bypass	Combined with uni- or bilateral carotid bypass surgery.
CPB time > 4 h	-
DHCA temperature	Nasopharyngeal temperature
DHCA time	-
30-day postoperative deaths	All-cause mortality

BMI, body mass index; WHO, world health organization; KDIGO, kidney disease, improving global outcomes; COPD, chronic obstructive pulmonary disease; ALT, Alanine Aminotransferase; EGFR, estimated glomerular filtration rate; NYHA, New York heart association; SBP, systolic blood pressure; DBP, diastolic blood pressure; TEVAR, thoracic endovascular aortic repair; TTE, transthoracic echocardiography; LVEDD, left ventricular end-diastolic diameter; CTA, computed tomographic angiography; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DHCA, deep hypothermia and circulatory arrest.

TABLE 3 | Multivariable analysis of perioperative parameters.

Variables	Coefficients	SE	Wald	*p*-value
LVEDD < 45 mm	1.0128	0.314	3.225	0.001**
EGFR < 50 ml/min/1.73m^2	0.8983	0.4127	2.177	0.03*
Persistent abdominal pain	2.174	0.6318	3.441	<0.001***
Previous stroke	0.6512	0.5279	1.234	0.217
Clinical coronary ostium lesion	0.3637	0.5054	0.72	0.472
Radiological celiac trunk malperfusion	0.8631	0.3553	2.429	0.015*
CABG	0.8535	0.3122	2.734	0.006**
CPB time > 4 h	1.4003	0.2897	4.833	<0.001***
Age	0.014	0.0137	1.022	0.307
Intercept	−3.7806	0.2173	−17.4	

*SE, standard error; LVEDD, left ventricular end-diastolic diameter; EGFR, estimated glomerular filtration rate; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass. *0.01 ≤ p < 0.05; **0.001 ≤ p < 0.05; ***p < 0.001.*

in the training set, using algorithms of naive Bayesian (NB) classification, support vector machine (SVM), random forest (RF) and extreme gradient boosting (XGB), we also screened all variables shown in **Table 1** and constructed 4 machine learning (ML) models.

The calibration plot and Brier score were used to evaluate the calibration of the nomogram. The receiver operating characteristic (ROC) curve and the area under the receiver operating characteristic curve (AUC) were used to evaluate the discrimination of the model. In the testing set, the nomogram was compared to the other four ML models in terms of Brier scores for calibration and AUCs for discrimination. R software version 4.0.2 was used for statistical analysis. Graph pad Prism for Windows version 6.0 was used to create graphs.

RESULTS

Demographics and Predictor Candidates of Training and Testing Sets

Figure 1 depicted a flow chart of patient enrollment. **Table 1** presented a comparison of demographics and predictor candidates between the training and testing sets. With respect to these risk factors, there were no differences between the two groups. **Table 2** contained the definitions or explanations for all of the variables.

Postoperative outcomes 90 patients (6.1%) died within 30 days of surgery in the entire cohort (n = 1,156). Other major postoperative complications included 135 patients (11.7%) who received continuous renal replacement therapy (CRRT), 68 patients (5.9%) who had a stroke, 122 patients (10.6%) who had a prolonged ventilation time (>96 h), and 201 patients (17.4%) who were in the intensive care unit (ICU) for more than 7 days.

Univariate and Multivariate Analyses

The summary of univariate analyses was shown in **Supplementary Table 1**. The results of the multivariate analysis for the initial model before the variable selection were shown in **Supplementary Table 2**. The results of the multivariate analysis for the final model after the variable selection were shown in **Table 3**.The independent predictors selected to establish the final model were: Left ventricular end-diastolic diameter (LVEDD) <45 mm, estimated glomerular filtration rate (eGFR) <50 ml/min/1.73m^2, persistent abdominal pain, radiological celiac trunk malperfusion, concomitant coronary artery bypass grafting (CABG) and cardiopulmonary bypass (CPB) time > 4 h.

Model Development

The nomogram constructed according to the final logistic regression model was shown in **Figure 2**. In training set, the calibration plot was displayed in **Figure 3A**, the Brier score was 0.0523 and the ROC curve was showed in **Figure 4A**, with an AUC (c-index) of 0.7851.

Model Validation and Compared With Other Machine Learning Algorithms

In testing set, the calibration plot of the nomogram was showed in **Figure 3B**, the Brier score was 0.0613. The ROC curve was showed in **Figure 4B**, with a c-index of 0.7819. **Figure 5** demonstrated Brier scores of the nomogram and other ML models. We could find a lower Brier score of the nomogram than the other 4 ML models, which suggested superior calibration of the nomogram. **Figure 6** presented AUC values with 95% confidence intervals (95% *CIs*) of the nomogram and ML models. We could observe a larger AUC of the nomogram than the other 4 ML models, which suggested better discrimination of the nomogram.

DISCUSSION

The nomogram is a simple, pictorial, and effective tool for predicting the 30-day mortality rate in ATAAD patients who do have TAR+FET surgery. This nomogram only included 6 easily accessible predictors, less than the GERAADA score (7) (11 predictors) and Euroscore II (5) (more than 20 predictors). As the nomogram is convenient and user-friendly for clinical evaluation, we recommend that this bedside tool be used widely in clinical practice.

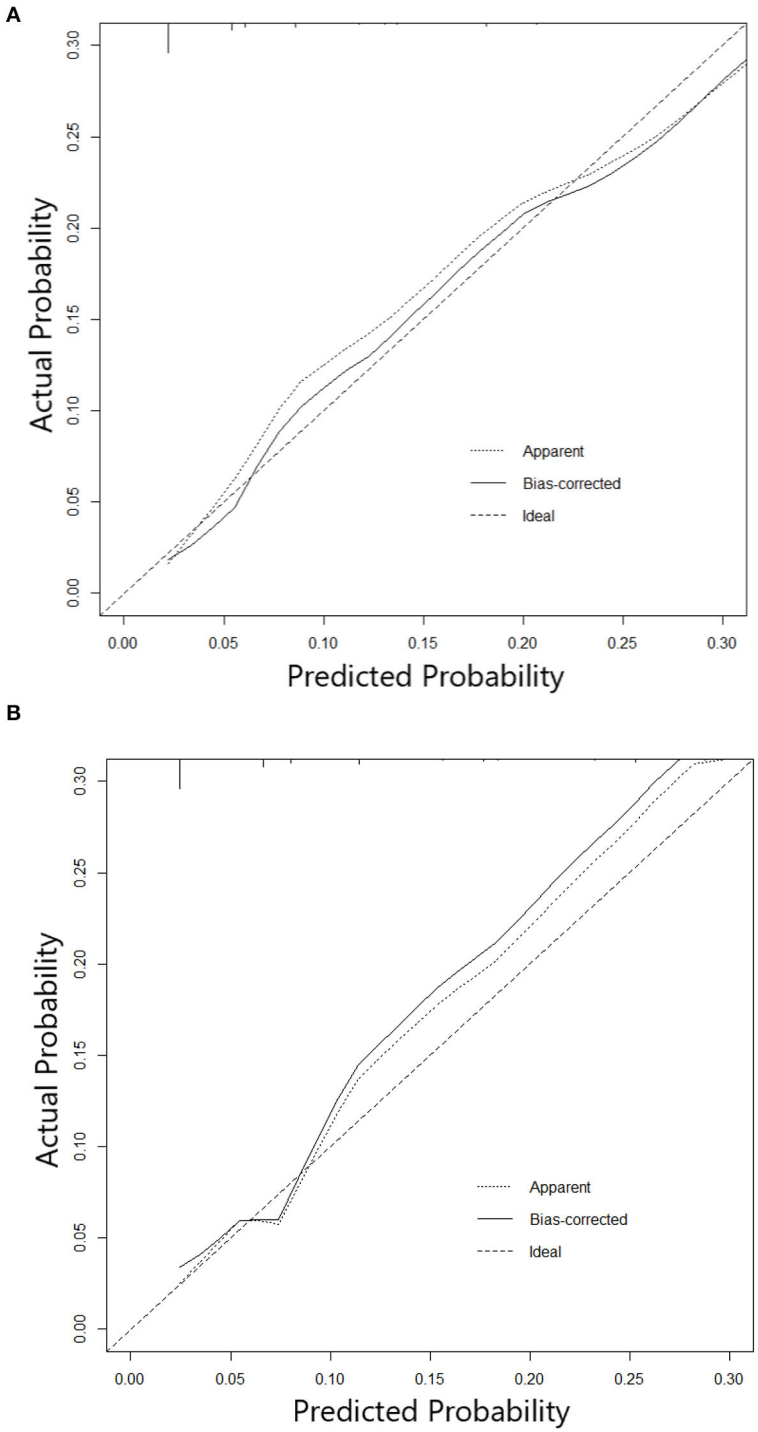

FIGURE 3 | (A) Calibration curve of Nomogram in training cohort. **(B)** Calibration curve of Nomogram in testing cohort.

The surgical management of extensive dissection affecting the aortic arch and descending aorta is difficult. TAR+FET combine the advantages of open surgical techniques and endovascular intervention, allowing simultaneous aortic arch repair and stabilization of the descending aorta. As a result of exactly sealed anastomosis of FET and proximal graft, TAR+FET can eliminate the risk of type I endoleak and retrograde aortic dissection. Meanwhile, FET could also benefit the thrombosis of

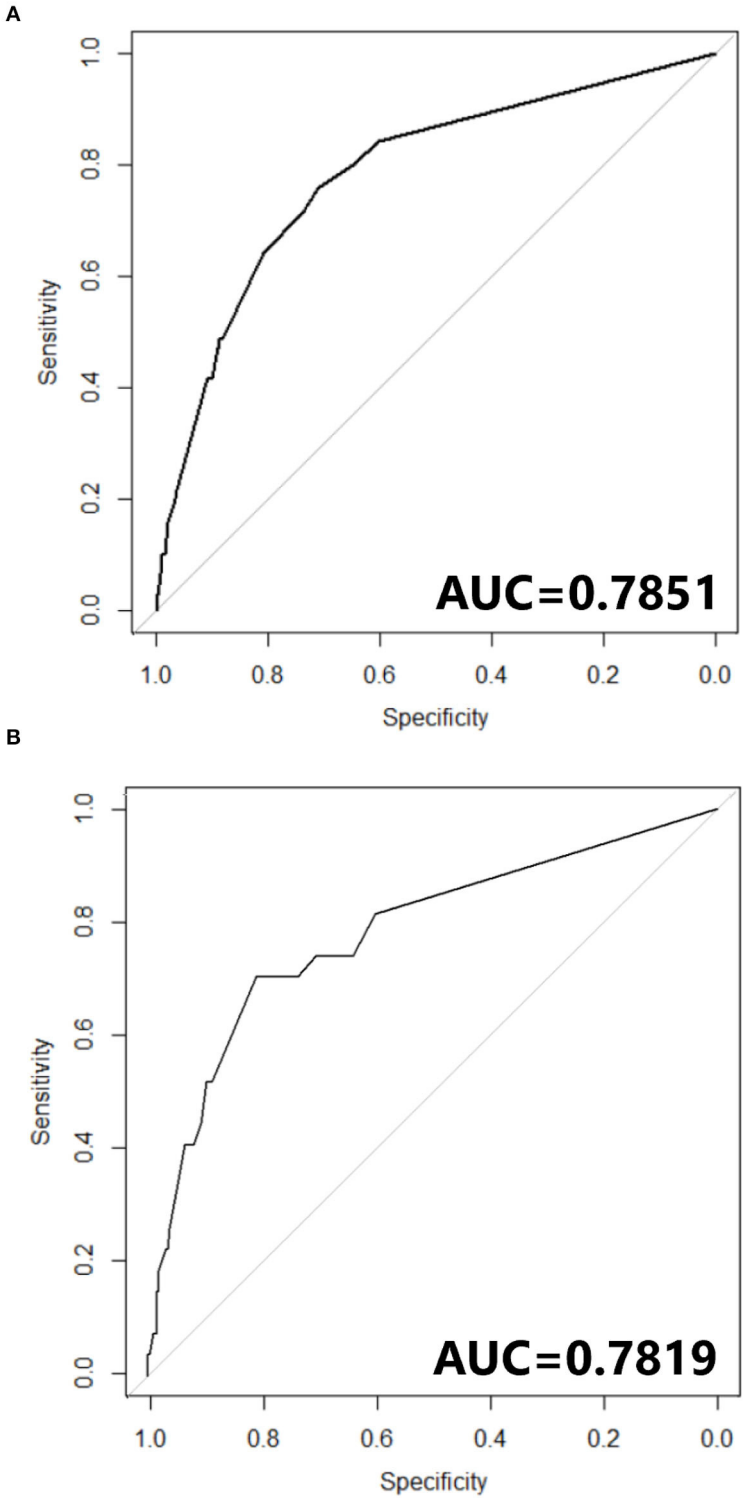

FIGURE 4 | (A) ROC curve of Nomogram in training cohort. **(B)** ROC curve of Nomogram in testing cohort.

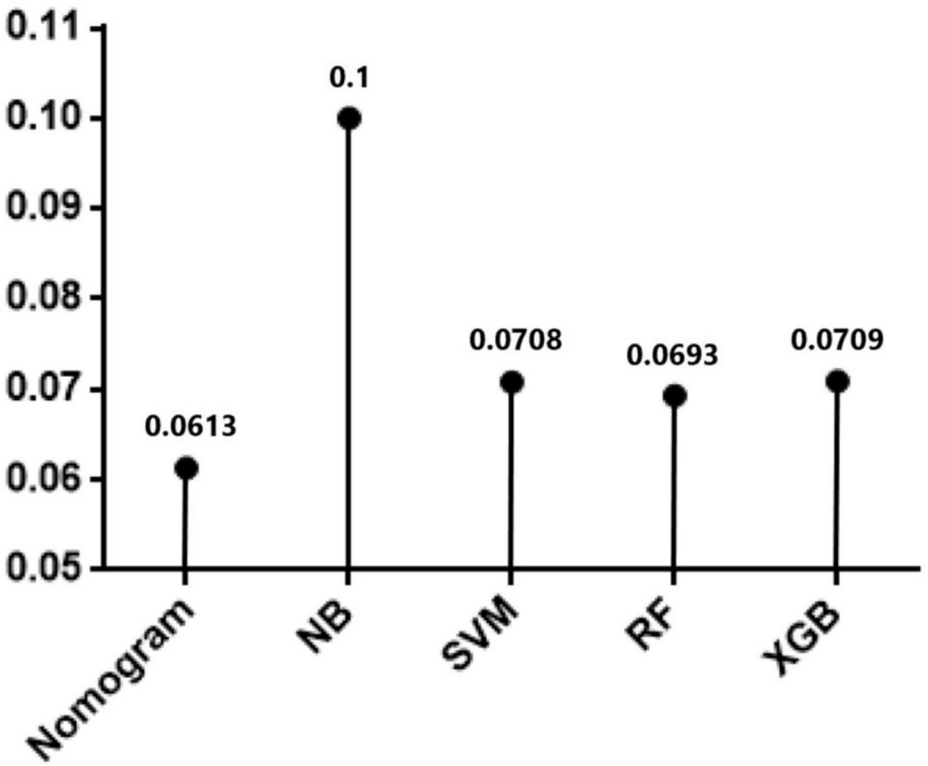

FIGURE 5 | Brier scores of Nomogram and the other 4 machine learning models in testing cohort.

false lumen, enable positive aortic remodeling (9). Additionally, TAR+FET could not only simplify the second-phase operation of the thoraco-abdominal aorta after arch repair in some extensive aortic dissection cases, (10) but also establish a stable and durable proximal landing zone for TEVAR if necessary. Kreibich, M et al. conducted a study (11) ($n = 66$) showing that downstream TEVAR following the FET procedure was associated with excellent clinical outcomes. Furthermore, in those with connective tissue disorder, like marfan syndrome, TAR+FET can be safely performed with favorable long-term survival and freedom from reoperation (12, 13). Berger, T and Kreibich, M et al. reported their studies (14, 15) suggesting that use of FET could provide acceptable morbidity and mortality for reintervention in patients requiring staged operations due to extensive aortic disease (concomitant thoraco-abdominal aortic pathologies).

Tamura et al. (16) conducted a retrospective study on ATAAD and discovered that TAR+FET were much more commonly chosen for patients under the age of 50. In fact, ATAAD patients in China are substantially younger than those in Western countries. In this study, the mean age was 46.9 ± 10.0 years, whereas the average age was 61.3 ± 13.5 years in GERAADA study cohort (7) and 61.5 ± 14.6 years in the International Registry of Acute Aortic Dissection (IRAD) cohort (17). As the life expectancy is longer in Chinese patients, surgeons prefer the TAR+FET strategy for its more favorable long-term outcomes. Consequently, in China, TAR+FET has become a widespread standard surgical method for ATAAD involving the entire aortic arch and descending aorta (4).

Prediction models should be region-specific: models designed for Western populations may be less appropriate to Asian or Chinese populations (18). Wessler et al. (19) conducted a research suggesting that clinical prediction models may have variable performance across various databases, especially in many areas of Eastern Europe, Asia, Central America, South America, and Africa where much remains unknown. This is especially important considering the many regional differences in etiology, access to technologies, care systems, and guidelines. Nežić et al. (20) reported their validation study ($n = 137$) on GERAADA score revealing that the discrimination of GERAADA score was poor, with an AUC of 0.55, much lower than the EuroSCORE II score (AUC = 0.799). Therefore, developing a prediction model for TAR+FET in the Chinese population is of major clinical importance.

In this study, we discovered that persistent abdominal pain and radiological celiac trunk malperfusion were independent risk factors for postoperative mortality, particularly persistent abdominal pain, which had a greater predictive power. The findings confirmed that visceral malperfusion was an immediate life-threatening concern in ATAAD patients, with 70 to 100% postoperative death (21). This fact motivated ATAAD patients

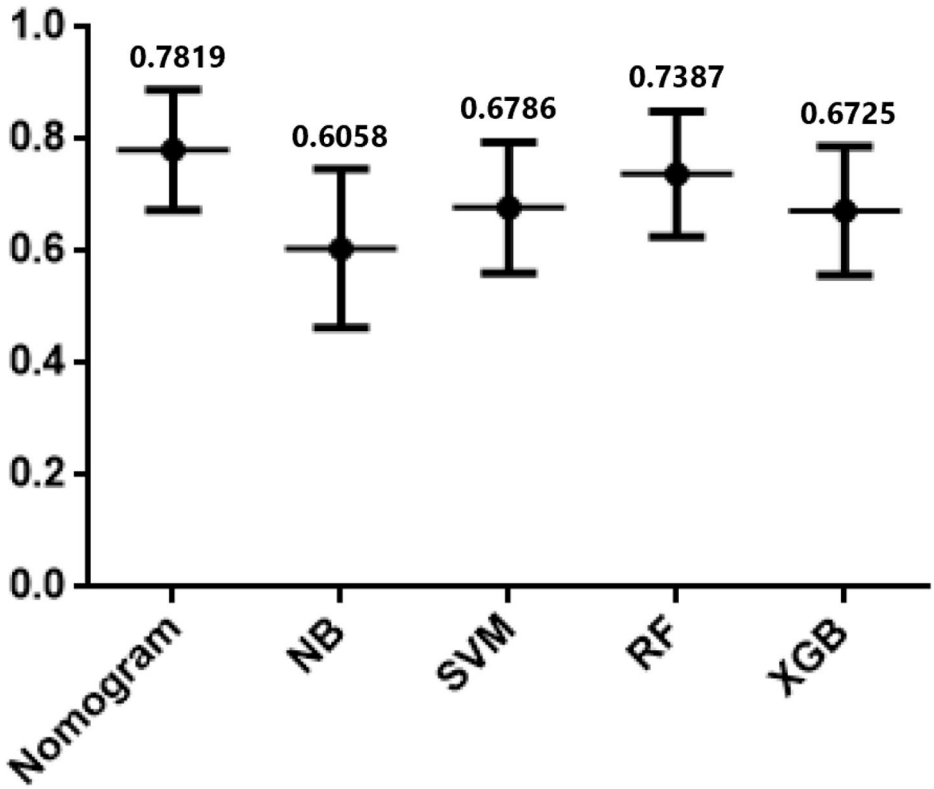

FIGURE 6 | AUCs of Nomogram and the other 4 machine learning models in testing cohort.

to undergo early visceral perfusion assessment and, for certain cases, endovascular reperfusion prior to surgical aortic repair.

Interestingly, we noted that preoperative LVEDD < 45 mm revealed by preoperative TTE was also an independent predictor for mortality. As an indicator of cardiac preload, low LVEDD might lead to inadequate cardiac output or end-organ perfusion which is in associated with mortality or neurological events (22, 23). The results indicated that insufficient cardiac preload or hypotension should be avoided in preoperative volume therapy. In addition, the enlarged false lumen in some of the ATAAD cases could store a large amount of blood, further reducing the circulating blood volume, manifested by low LVEDD or hypotension.

In current study, the nomogram demonstrated superior predictive performance than other ML models; with a lower Brier score (**Figure 5**) and higher AUC (**Figure 6**). As we all know, machine learning algorithms are frequently applied to larger datasets. Although the sample size in this study is sufficient for TAR+FET, it is at bit small for ML algorithms, which may result in poor ML model performance. Although the ML algorithms adopted in prediction model development is a popular subject nowadays, we still need to focus a lot more on thorough and accurate clinical data gathering, which is the foundation of clinical research.

This nomogram is not a reference to accept or reject a certain treatment. For ATAAD, open surgical repair is often a life-saving solution and remains the standard of care for patients. The nomogram is only a bedside tool to help clinical practitioners make a rapid initial prognosis assessment for patients receiving TAR+FET. We hope this novel nomogram could quickly identify potential risk factors and provide the opportunity for timely and prompt intervention during the emergency course of treatment.

Limitations

Due to the single center research, we only conducted internal validation. The nomogram's predictive ability needs to be evaluated by external validation using clinical data from other centers. Pending for further external validations; this model can only be applied to comparable cohorts since Chinese patient cohorts differ substantially from European or the US.

CONCLUSION

The novel nomogram is a simple and effective tool to predict 30-day mortality rate for acute type A aortic dissection patients

undergoing total aortic arch replacement with frozen elephant trunk technique.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

HL analyzed the data, collected the data, and was a major contributor in writing the manuscript. HG, XQ, XS, and CY were in charge of the surgery performing. YC was in charge of the study design, data collection, and manuscript modification. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.905908/full#supplementary-material

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RELAY^{TM} Branched–International Results of Vessel Patency and Reintervention

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Background: Surgical intervention remains the mainstay treatment for aortic arch aneurysm and dissection, but the high mortality and morbidity rates have led to a need for the development of minimally invasive alternatives to arch reconstruction. RELAY^{TM} Branched (Terumo Aortic, Inchinnan, UK) represents a viable option for complex endovascular aortic arch repair. We present multi-center data from Europe documenting the efficacy of the endograft in terms of its target vessel patency and reintervention rates.

Methods: Prospective data collected between January 2019 and January 2022 associated with patients treated with RELAY^{TM} single-, double-, and triple-branched endoprostheses from centers across Europe was retrospectively analyzed with descriptive and distributive analysis. Follow up data from 30 days and 6-, 12-, and 24 months postoperatively was included. Patient follow up was evaluated in terms of target vessel patency and reintervention rates.

Results: Technical success was achieved in 147 (99.3%) cases. Over 24 months period, target vessel patency was maintained in 80.2% (n = 118) of patients. Target vessel cannulation was achieved in 146 (99.3%) cases. Over the 24-month follow-up period, 30 reintervention procedures were required, of which 29 (97%) took place within the South Europe region which accounted for 19.6% (n = 29) of total cases. Zero reinterventions were required in patients that were treated with single- or triple-branched endoprostheses.

Discussion: The data presented herein demonstrates that RELAY^{TM} Branched is a technically efficacious device for endovascular aortic arch repair and is associated with favorable target vessel patency and reintervention rates. Key design features of the endoprosthesis and good perioperative management can contribute greatly to mitigating reintervention and loss of vessel patency following endovascular aortic arch repair.

Keywords: TEVAR, aortic arch, branched endograft, vessel patency, reintervention

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BACKGROUND

The pathologies of the thoracic aorta have been an area of great innovation in the last two decades focusing on reducing complications, interacting with complex anatomical situations and increasing ease of intervention. Since the introduction of the GORE TAG endograft for Thoracic Endovascular Aortic Repair (TEVAR) in 2005, endovascular intervention has become a promising avenue for treatment and has since become the preferred treatment for most thoracic aortic dissections and aneurysms (1). However, many centers and patients have continued to encounter relatively high complication rates and poor operative outcomes from the existing endografts due to issues with revascularization, stroke, graft patency and re-intervention rates (2). Although an open surgical approach remains the gold standard for total arch reconstruction (TAR), open surgery comes with its own set of risks and disadvantages. Patients must undergo cardiopulmonary bypass (CPB), and corresponding risks associated with general anesthesia and hypothermic circulatory arrest (HCA). Furthermore, the elderly and comorbid patients are at an even higher risk for surgical complications. In such cases endovascular repair is the safer and more promising option. The RELAY™ branched endoprosthesis allow for safer intervention and corresponding lower incidence of long-term complications (3).

Although there are many advantages for deployment of the RELAY™ branched device, there is need for clear clinical judgement when determining whether endovascular repair carries the best risk-benefit profile for patients. The criteria for RELAY™ branched graft placement in the aortic arch is chiefly based on the availability of a sufficient landing zone size and eligibility (or lack thereof) for open surgical repair.

Depending on the device used this varies slightly, but there should generally be at least 25 mm of viable aorta proximal to the dissection or aneurysm to safely plant the device (3). In cases where the vessel pathology is more proximal, patients could be considered for a Frozen Elephant Trunk (FET) operation, or custom made TEVAR endograft would suffice (3, 4).

The RELAY™ branched endoprosthesis offers significant advantages to patients of varying demographics. In addition to the benefits associated with minimally invasive intervention, patients with complicated anatomy which often result in compromised collateral circulation from single grafts can be safely revascularized with adequate entry tear coverage. With the options of single, double, and triple branched devices the RELAY™ device reduces invasiveness and risks by removing the need for aorto-cervical bypasses (4).

In the current study, we sought to assess the benefits of using the branched RELAY™ devices for aortic arch TEVAR while assessing the risk profile of the operation with a specific focus on vessel patency and re-intervention–two crucial metrics for assessing the appropriateness of endovascular repair. Vessel patency assesses the degree to which a vessel is not obstructed or leaking, which effectively summarizes the completeness of the vascular intervention. Re-intervention assesses the long-term efficacy of the intervention and whether patients need a secondary operation to treat the same issue again due to intervention failure (5).

DEVICE DESIGN

The RELAY™ branched system is indicated for on-label use in patients with thoracic aortic aneurysms (TAAs) and penetrating atherosclerotic ulcers (PAUs), though use in patients with dissections and trauma to the aorta remains off-label (6). The device is designed specifically for the aortic arch, from zone 0 to zone 4, as a modular system deployed retrograde via access through the femoral artery or the iliac axis. The system includes a self-alignment mechanism, where the pre-curved introduction tip aligns itself with the curve of the aortic arch upon insertion (6, 7). This helps to decrease operative time and increases insertion accuracy contributing to overall improved outcomes (7). Windows designed for the supra-aortic branches are mounted to streamline accurate alignment with the arch branches and prevent occlusion of the left subclavian artery (LSA). Furthermore, the radio-opaque markers situated around the cannulation window clearly label an origin and where it aligns with the vessel branches, allowing for better orientation to the arch of the aorta improving intra-operative functionality of the branched stents (6). The large window size also allows for the addition of multiple branches accelerating cannulation without compromising cerebral perfusion (7). Moreover, the main tube of the device contains two internal connecting tunnels (posterior and anterior) which connect supra-aortic branches of the brachiocephalic trunk and the left common carotid artery extensions correspondingly (6). The system also contains a dual-sheath system which consists of a tougher outer sheath which aids delivery in tortuous iliac vessels and a flexible inner sheath to improve trackability and maneuverability even in acute and complicated cases. With the introduction of support wires and proximal collapsing, the device enables reduction of aortic instrumentation and achieves precise proximal landing (3, 6, 7).

METHODOLOGY

Study Design

Between January 2019 and January 2022, a retrospective European international multi-center investigation of TEVAR was conducted utilizing RELAY™. The information was collected prospectively and maintained in a database. Ethical review and approval was not required for this study with human participants, in accordance with the local legislation and institutional requirements.

Patient Demographics

Between January 2019 and January 2022, a total of 148 TEVAR operations using RELAY™ were completed. This comprised 110 males and 38 females resulting in a M:F ratio of around 3:1. Patients with a mean age (IQR) of 70 (14.5) years were treated with RELAY™ for a variety of pathologies and differing levels of urgency (**Table 1**).

TABLE 1 | Demographics.

Gender (Male : female)		3:1
Mean age (IQR)		70 (14.5)
Pathology (%)		
Aneurysm	107 (72.3%)	
Dissection	41 (27.7%)	
Urgency (%)		
Acute	68 (46%)	
Elective	80 (54%)	
Total cases		148

TABLE 2 | Operative characteristics.

Mean procedural time (IQR)		258 (100)
Branching number (%)		
	Single	17 (11.5%)
	Double	108 (73%)
	Triple	23 (15.5%)
Technical success (%)		147 (99.3%)
Target vessel cannulation (%)		146 (99.3%)[a]

[a]*Following percentages are calculated out of 147, one case died during the procedure, unrelated to the device.*

TABLE 3 | Endovascular duration.

50–100	18
100–150	95
150–200	24
200–270	11

TABLE 4 | Follow-up periods results.

	30 Days	6 Months	12 Months	24 Months
Vessel patency	147 (100%)	134 (91.1%)	124 (84.3%)	118 (80.2%)
Reinterventions	8 (5.4%)	6 (4.4%)	5 (4.0%)	5 (4.0%)
Deaths	4 (2.7%)	0 (0%)	0 (0%)	0 (0%)

Follow-Up Periods

All patients were followed up at 30 days, 6 months, 12 months, and 24 months postoperatively. Patients were evaluated at follow-up appointments for post-operative complications and disease progression. These factors included target vessel patency at the time of the appointment, and reinterventions conducted between the previous and current appointments. At the end of each follow-up period, overall mortality was recorded.

Statistical Analysis

SPSS (IBM™ SPSS 28 for Windows) with the R plugin was used for all statistical analyses. A descriptive evaluation was carried out, and comparison investigations were performed where needed. In each analysis, propensity score matching was used to exclude any confounding variables. For normally distributed data confirmed by Shapiro Wilk W tests, the independent samples *t*-test was applied, and the the Mann-Whitney U served as the non-parametric equivalent. The Chi-Square method was used to determine differences in cumulative distribution frequency counts. Statistical significance for all two-tailed tests was set at $p < 0.05$.

RESULTS

Operative Characteristics

The RELAY™ endoprosthesis was used to treat all patients and the average procedure time (IQR) was 258 (100) min. In one patient, technical success was not achieved, and the target vessel was not cannulated as a result. Another patient died after achieving technical success, and the target vessel could not be cannulated, though this mortality was not device-related. **Table 2** summarizes operation parameters. Most patients' endovascular times were between 100 and 150 min. **Table 3** shows the endovascular time groups. **Tables 4–6** summarise the measured outcomes over the 24-month follow-up period.

Reintervention

All patients who eventually required reintervention during any of the follow-up periods were originally treated with a double branch stent. Significant differences in reintervention from the other types of branching was noted during the first 30 days, 6, 12, and 24 months after the procedure with $P = 0.005$, 0.029, 0.020, and 0.029, respectively.

During the first 30 days following the procedure, reintervention was required in 8 (5.4%) patients. Another 6 (4.4%) reinterventions were required during the following 6 months. During the subsequent 6 months (12-month follow-up), another 5 (4.0%) patients had undergone reintervention. All of them also required reintervention during the first 30 days and 8 of them during the second period. During the final follow-up period (24-months), another 5 (4.0%) reinterventions were recorded.

Vessel Patency

A 100% (147) target vessel patency was recorded by the end of the first 30 days post-operatively. All patients treated with a triple stent ($n = 23$) exhibited lasting vessel patency throughout all follow-up periods. At 24 months follow up, over 80% of the cohort maintained target vessel patency.

At the 6-months follow-up appointment, a 91.1% ($n = 134$) of patients displayed target vessel patency. 93.7% ($n = 16$) of patients treated with single-branched device maintained vessel patency at 6 months, while 88% ($n = 95$) of those treated with a double branch stent had vessel patency at 6 months. A statistically significant difference in vessel patency in different branching groups was not seen during the 6 months follow-up period ($P = 0.08$).

At the 12-months follow-up appointment, 84.3% ($n = 124$) of the cohort exhibited target vessel patency. One hundred percent of the patients treated with a single-branched endoprosthesis displayed continued vessel patency at 12 months. Of the patients

TABLE 5 | Relationship between branching number and vessel patency.

	Single	Double	Triple	Total	*p*-Value
30 Days	16 (10.9%)	108 (73.4%)	23 (15.6%)	147 (100%)	-
6 Months	15 (10.2%)	96 (65.3%)	23 (15.6%)	134 (91.1%)	0.080
12 Months	16 (10.9%)	85 (57.8%)	23 (15.6%)	124 (84.3%)	<0.001
24 Months	15 (10.2%)	80 (54.4%)	23 (15.6%)	118 (80.2%)	0.001

TABLE 6 | Relationship between branching number and reinterventions.

	Single	Double	Triple	Total	*p*-Value
30 Days	0	8 (5.4%)	0	8 (5.4%)	0.005
6 Months	0	6 (4.4%)	0	6 (4.4%)	0.029
12 Months	0	5 (4.0 %)	0	5 (4.0 %)	0.020
24 Months	0	5 (4.0%)	0	5 (4.0%)	0.029

treated with a double branching stent 78.7% maintained target vessel patency. Target vessel patency at 12 months was different between branching number groups ($P < 0.001$).

By the 24-months follow-up period, 80.2% ($n = 118$) patients exhibited target vessel patency. This included 93.7% ($n = 16$) of the single-branched group, and 74% ($n = 80$) of the double-branched group.

TABLE 7 | Cases per region[a].

West Europe	78 (52.7%)
East Europe	32 (21.6%)
South Europe	29 (19.6%)
North Europe	9 (6.1%)
Total	148

[a] *Based on UNSD Geoscheme.*

DISCUSSION

Our multi-center data on endovascular repair of aortic arch pathologies (dissections and aneurysms) with the RELAY™ Branched System clearly demonstrates that the device is associated with excellent vessel patency and low re-intervention rates. In our cohort of 148 patients undergoing TEVAR with RELAY™ branched system for aortic aneurysm ($n = 107$) and aortic dissection ($n = 41$), technical success was achieved in 147 (99.3%) cases and target vessel patency was maintained in 147 (99.3%).

The RELAY™ Branched endoprosthesis has demonstrated success in establishing vessel patency across all of the devices, with a 30-day follow up demonstrating 100% ($n = 147$) vessel patency. These findings stand clear testament to the adaptability and suitability of the RELAY™ Branched device in adapting to the various anatomies across all cases. Over the 24-month review period, vessel patency fell to 91.1% ($n = 134$), 84.3% ($n = 124$) and 80.1% ($n = 118$) at 6, 12, and 24 months, respectively. It is likely the progression of the underlying vessel pathology was a contributing factor to the decrease in target vessel patency (5). The double branched group also experienced the greatest failure in target vessel patency falling by 25.9% from 73.4% ($n = 108$) to 54.4% ($n = 80$) over the 24-month period. Whereas, single branched only fell by 6.25% from 10.9% ($n = 16$) to 10.2% ($n = 15$) and tripled branched maintained 100% target vessel patency across the 24-month follow-up period.

The geographical distribution (see **Tables 7**–**9**) of cases across the European multi-center trial had significant impacts on the data collected. While Southern Europe comprised only 19.6% of the population ($n = 29$) it explained a disproportionate 95.8% ($n = 23$) of re-interventions required and experienced the greatest fall in vessel patency across the 24-month period, falling by 50% from $n = 28$ to $n = 14$. This could be linked to the observations of lower patency and higher re-intervention rates seen in double branched RELAY™ system deployments, as the Southern Europe sample population was made up of 96.6% ($n = 28$) patients receiving the double branched RELAY™ branched system. In view of this, it is reasonable to suggest that the loss of target vessel patency was not associated with RELAY™ Branched design; rather it is more likely associated with other exogenous factors including patient demographic and variations in center-to-center practice.

Over the 24-month follow-up period a total of 24 re-interventions were required, however we must highlight that all these cases were of patients undergoing TEVAR with the double branched RELAY™ system. There were no re-interventions required for patients who received single and triple branched endoprosthesis. However, it is important to recognize that the patients receiving double branched RELAY™ systems constituted 73% ($n = 108$) of the population. Furthermore, the double branched group was also composed of the greatest percentage of acute patients 35.8% ($n = 53$). Collectively, these observations suggest that the RELAY™ branched system design and intra-operative aortic manipulation may not be the primary cause for reintervention; rather the complexity and progression

TABLE 8 | Geographical distribution of reinterventions.

	West	East	South	North	Total	*p*-value
30 Days	0	0	8	0	8 (5.4%)	<0.001
6 Months	1	0	5	0	6 (4.4%)	<0.001
12 Months	0	0	5	0	5 (4.0 %)	<0.001
24 Months	0	0	5	0	5 (4.0%)	<0.001

TABLE 9 | Geographical distribution and vessel patency.

	West	East	South	North	Total	*p*-value
30 Days	78	32	28	9	147 (100%)	-
6 Months	72	32	22	8	134 (91.1%)	0.017
12 Months	70	32	14	8	124 (84.3%)	<0.001
24 Months	65	31	14	8	118 (80.2%)	<0.001

of the vessel pathology are likely factors, either due to worsening vessel wall stability or increasing tortuosity and aortic pressure.

Re-interventions are a critical aspect of analysis when comparing TEVAR therapeutic options with the FET, the current gold standard for aortic arch reconstruction (8). As a new innovative treatment option for endovascular repair, aortic arch TEVAR provides many advantages over traditional open surgical intervention, not least the plethora of benefits associated with minimally invasive procedures (3). However, its advantages are being challenged with the current post operative reintervention rates observed (5). Zhang et al. observed an average reintervention rate of 14.6% post TEVAR in patients during their meta-analysis (5). They further identified the 3 main causes for post operative reintervention were type I endoleak, false lumen perfusion, and aortic dilation/new dissection. Type 1 endoleak is usually the result of insufficient proximal or distal landing seal zones in grafts, however, the RELAY™ branched endograft system offers the supra-aortic extensions via the internal connecting tunnels as an in-built mechanism to avoid the occurrence of endoleaks (3, 5). In cases where reintervention is required due to false lumen expansion, patients experience continuous perfusion of false lumen despite TEVAR; this could be due to graft failure or worsening vessel wall pathology regardless of stent placement (9).

Patients exhibiting postoperative disease progression are cause for greatest concern as they are at risk for late aortic related morbidity and mortality. Although distal re-entry tears can be sealed through an extension of the stent graft, there is a direct correlation between the length of aorta covered and the risk of spinal cord ischemia or even potential paralysis (10, 11). Decision making in these situations requires thorough planning and more evidence-based algorithm development to help ensure the correct therapeutic route is selected for patients. Risk factors for new dissection include patient age, prior interventions, and progression of vessel wall pathology (12). These factors can severely worsen a patient's condition and may result in the formation of a new tear and are very rarely associated with TEVAR or placement of a stent (5, 9).

Although branched systems like the RELAY™ branched endoprosthesis are designed to preserve and ensure target vessel patency after TEVAR, there are a range of complications that can occur to reduce post operative target patency in the mid-term. These include immediate occlusion of the target vessel due to coverage from the stent due to poor pre-operative planning, mal-alignment errors intra-operatively or incorrect graft sizing (13). Further late complications include migration of the graft, graft rotation and *in situ* thrombosis and stenosis arising due to intimal hyperplasia (2, 3).

In comparison to current market competitors the RELAY™ device demonstrates numerous advantages to both operator and patient. With the ability to withstand greater aortic contractile forces, without modification, endoprosthesis offers a single device solution. Competing devices like the Najuta™ endograft do not possess Z-stents between its first and second stent often required the use of a simple RELAY™ stent graft to provide adequate sealing from within, to ensure graft patency (14). Indeed, a recent systematic review found that a similar alternative–the Zenith Alpha endograft–carried a poorer technical success rate (96%) and a 13.3% ($n = 92$) reintervention rate, of which 26.1% ($n = 24$) patients required open surgical re-exploration (15). Additionally, the RELAY™ branched endoprosthesis provides a more effective delivery system. The dual sheath system and pre-curved introduction point allow for better alignment with the curvature of the aortic arch, thereby reducing manipulation difficulty and lowering surgical complications such as endoleaks (7). Toya et al. found that utilizing the RELAY™ branched endograft fits well and was adequate for landing in the compromised seal zone without introducing additional risks (16).

CONCLUSION

The RELAY™ branched endoprosthesis has shown great promise as a new therapeutic adjunct to aortic arch TEVARs, as an innovative solution and proven alternative for patients that may not be suitable for open surgical repair. As an innovative procedure it has an anticipated steep learning curve, with the need for more evidence based algorithms to support patient selection criteria. The findings reported herein highlight the clinical efficacy and surgical safety of the RELAY™ branched

endoprosthesis in treated aortic arch aneurysms and aortic dissection. This paper has emphasized the low re-intervention rates and great vessel patency obtainable through deployment of the device. It is an exceptional addition to the modern surgeon's armory in treating aortic arch vessel wall pathologies, complimenting existing gold standard treatments. The design and deployment technique of the device help promote faster and more precise arch repairs without compromising on desired surgical outcomes and reducing neurological complications. Further research and development of the device will help further reduce re-interventions and improve upon patency while flattening the learning curve through standardization of the device deployment technique.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

SS, AS, and ST were responsible for drafting the manuscript. MJ, DB, IW, and MB were responsible for reviewing and providing feedback on the draft. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Postoperative In-Stent Thrombus Formation Following Frozen Elephant Trunk Total Arch Repair

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Objectives: Our aim was to investigate the occurrence and clinical consequence of postoperative in-stent thrombus formation following the frozen elephant trunk (FET) procedure.

Methods: Postoperative computed tomography angiography (CTA) scans of all 304 patients following the FET procedure between 04/2014 and 11/2021 were analysed retrospectively. Thrombus size and location were assessed in multiplanar reconstruction using IMPAX EE (Agfa HealthCare N.V., Morstel, Belgium) software. Patients' characteristics and clinical outcomes were evaluated between patients with and without thrombus formation.

Results: During the study period, we detected a new postoperative in-stent thrombus in 19 patients (6%). These patients were significantly older ($p = 0.009$), predominantly female ($p = 0.002$) and were more commonly treated for aortic aneurysms ($p = 0.001$). In 15 patients (79%), the thrombi were located in the distal half of the FET stent-graft. Thrombus size was 18.9 mm (first quartile: 12.1; third quartile: 33.2). Distal embolisation occurred in 4 patients (21%) causing one in-hospital death caused by severe visceral ischaemia. Therapeutic anticoagulation was initiated in all patients. Overstenting with a conventional stent-graft placed within the FET stent-graft was the treatment in 2 patients (11%). Outcomes were comparable both groups. Female sex ($p = 0.005$; OR: 4.289) and an aortic aneurysm ($p = 0.023$; OR: 5.198) were identified as significant predictors for thrombus development.

Conclusion: Postoperative new thrombus formation within the FET stent-graft is a new, rare, but clinically highly relevant event. The embolisation of these thrombi can result in dismal postoperative outcomes. More research is therefore required to better identify patients at risk and improve perioperative treatment.

Keywords: frozen elephant trunk (FET), thromboembolism, thrombus, stent graft, postoperative

Abbreviations: CTA, Computed tomography angiography; FET, Frozen elephant trunk.

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INTRODUCTION

The frozen elephant trunk (FET) procedure has evolved as an effective treatment option in patients suffering from acute and chronic thoracic aortic pathologies including aortic dissection, aortic aneurysms, and penetrating aortic ulcers involving the aortic arch (1–4). However, we have clinically encountered early postoperative thrombus formation and thrombus embolisation within the FET stent-graft component (5). It is therefore our aim to evaluate the occurrence and clinical consequence of postoperative in-stent thrombus formation following the FET procedure.

PATIENTS AND METHODS

Ethics Statement

Our institutional review committee approved this retrospective study, and the need for informed consent was waived (number: 20–1302; approval date: February 4, 2021).

Patients and Follow-Up Protocol

Between 04/2014 and 11/2021, 304 patients underwent the FET procedure in one aortic centre currently performing over 60 total aortic arch procedures per annum (as of 2021). Computed tomography angiography (CTA) scans were done routinely preoperatively, before discharge, during every follow-up visit, and when clinically warranted. Follow-up was available in all patients after FET implantation.

Imaging Analysis

All immediate postoperative CTA scans were screened retrospectively. A slice thickness of 3 mm or less was present in all patients. Analysis was performed using IMPAX EE (Agfa HealthCare N.V., Morstel, Belgium). All measurements were taken in multiplanar reconstruction always in plane perpendicular to the manually corrected local aortic centreline.

Perioperative Approach

Our standardised, integrated surgical management of the FET technique has been reported (6–8). In short, we carry out a full sternotomy and generally cannulate the right axillary artery for arterial inflow for cardiopulmonary bypass. Any concomitant procedures (valve, aortic root, coronary artery) take place while the patients are cooled down a target core body temperature of 25°C. We routinely apply cold-blood cardioplegia or the beating-heart technique (using 300 mL of normothermic myocardial perfusion). Bilateral cerebral perfusion is normally used and we liberally perform trilateral antegrade cerebral perfusion (additional cannulation of the left subclavian artery) when needed. For this reason, our preoperative work-up includes a CTA of the supra-aortic vessels including the Circle of Willis. Zone 2 is our standard anastomosis site for FET implantation, and today, we use the short version (100 mm) of the Thoraflex (Terumo Aortic, Inchinnan, United Kingdom) hybrid-graft exclusively. In case of classical aneurysm formation, we oversize the stent-graft component by 10% at the distal landing zone and in case of aortic dissections we avoid oversizing and choose the FET stent-graft size according to institutional standards (1, 9, 10). The diameters of the implanted FET stent-grafts ranged from 22 to 40 mm in this study depending on the preoperative diameter of the aorta in the anticipated landing zone. We do not routinely implant cerebrospinal fluid drainage before surgery.

All patients are routinely transferred to our cardiovascular surgical intensive care unit postoperatively. Intraoperatively, we aim for an activated clotting time longer than 400 s. Intra- and postoperative coagulation is routinely managed *via* rotational thromboelastography (ROTEM) guided in our centre. We commence prophylactic intravenous heparin 6 h postoperatively (500 IU per hour). If therapeutic anticoagulation is required, we raise heparin dosages every 6 h to reach a target partial thromboplastin time of 60–80 s. Anti-platelet therapy (acetylsalicylic acid 100 mg) is routinely commenced on the first postoperative day at noon when no bleeding signs are visible and when only prophylactic heparin is administered.

Outcome Measures

Data were collected retrospectively relying on our prospectively maintained aortic database. The modified Rankin Scale (mRS) was used to classify the postoperative-stroke severity (11). Consulting neurologists evaluated all the strokes. Postoperative strokes causing no clinical symptoms (mRS 0), no significant disability (mRS 1), or slight disability (mRS 2) were classified as non-disabling postoperative strokes.

Statistical Analysis

Data are presented as absolute and relative frequency or as median [first quartile, third quartile]. The Student's *t*-test or the Mann-Whitney-*U*-test was used to compare continuous variables as appropriate. Categorical variables were compared using the Chi-squared test. In case of small group sizes ($n < 5$), Fisher's Exact test was used. Multivariable logistic regression analyses were performed to investigate the influence of clinically selected variables on postoperative in-stent thrombus formation (selected variables: female sex, age, acute pathology, penetrating aortic ulcer, aneurysm) Statistical analysis was performed using IBM SPSS 21.0 (SPSS Software, IBM Corp., Armonk, NY, United States).

RESULTS

Patient and Aortic Characteristics

Within the study period, we identified a new postoperative thrombus in 19 patients (6%). Patient characteristics are summarised in **Table 1**. Patients developing a thrombus were significantly older ($p = 0.009$), predominantly female ($p = 0.002$) and tended to have a lower incidence of cardiovascular risk factors. Most patients were being treated for a chronic underlying aortic pathologies, but the incidence was comparable between the two groups. Aortic aneurysms were significantly more common ($p = 0.001$), while aortic dissections were

TABLE 1 | Patient characteristics.

	In-stent thrombi (*n* = 19)	No thrombi (*n* = 285)	*P*-value
Age (years)	74 (66; 77)	67 (58; 73)	0.009
Male	6 (32)	193 (68)	0.002
Current smoker	4 (21)	69 (24)	1.000
Hyperlipidaemia	6 (32)	94 (33)	1.000
Arterial hypertension	14 (74)	242 (85)	0.234
Diabetes mellitus type 2	1 (5)	7 (2)	0.408
History of stroke	3 (16)	36 (13)	0.721
Chronic renal failure	2 (11)	39 (14)	1.000
Chronic obstructive pulmonary disease	5 (26)	25 (9)	0.029
Coronary artery disease	2 (11)	88 (31)	0.070
Connective tissue disease	0 (0)	27 (9)	0.236
Bicuspid aortic valve	0 (0)	14 (5)	1.000
Acute pathology	3 (16)	98 (34)	0.131
Chronic pathology	16 (86)	187 (66)	
Aortic dissection	6 (32)	192 (67)	0.035
Aortic aneurysm	11 (58)	71 (25)	0.001
Penetrating aortic ulcer	2 (11)	22 (8)	0.654

Values are n (%) or median (first quartile, third quartile).

TABLE 2 | Surgical details.

	In-stent thrombi (*n* = 19)	No thrombi (*n* = 285)	*P*-value
Cannulation			
Ascending aorta	0 (0)	7 (2)	1.000
Right subclavian artery	19 (100)	269 (94)	0.610
Femoral	1 (5)	7 (2)	0.408
Aortic root replacement	4 (21)	50 (18)	0.698
Aortic valve replacement	5 (26)	37 (13)	0.159
Coronary artery bypass grafting	1 (5)	45 (16)	0.327
Beating heart aortic arch replacement	6 (32)	58 (20)	0.384
Delayed sternum closure	0 (0)	27 (9)	0.236

Values are n (%) or median (first quartile, third quartile). CABG, coronary artery bypass graft.

significantly less common (p = 0.035) in patients with an in-stent thrombus. Of the patients with an in-stent thrombus, one suffered from the coagulation disorder factor-V-Leiden-mutation.

Surgical Details

As **Table 2** shows, our primary arterial cannulation was the right subclavian artery in most patients. Most concomitant procedures concerned the aortic root or valve. Beating heart technique was applied in almost one third of the patients. There were no statistically significant differences between the two groups. Of the patients with a new in-stent thrombus, one underwent the FET technique after previous thoracic endovascular aortic repair (TEVAR) with no thrombus visible in preoperative CTA scans but a large thrombus visible in the postoperative CTA scan (**Figure 1**).

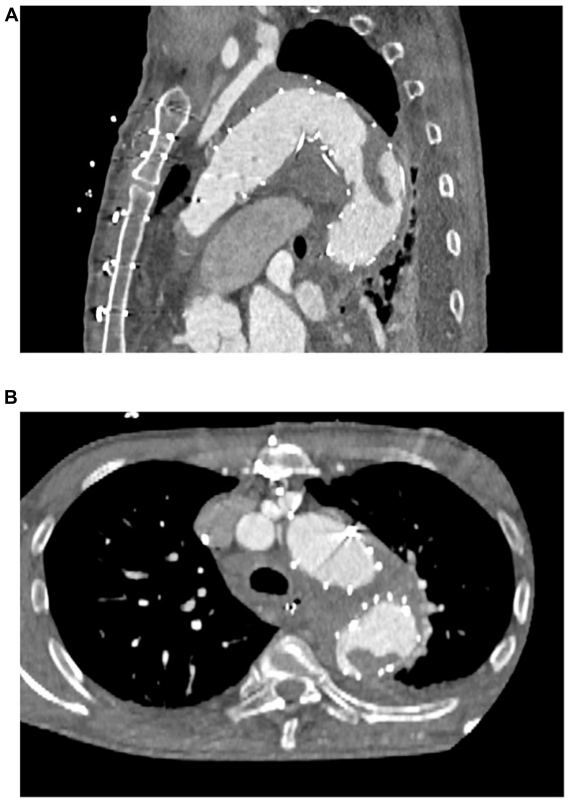

FIGURE 1 | Representative computed tomography angiographic images of a newly detected postoperative thrombus formation within the frozen elephant trunk stent-graft. **(A)** Sagittal plane **(B)** axial plane.

Thrombus Characteristics

Thrombus characteristics are summarised in **Table 3**. Median time to postoperative CTA was 7 [5; 11] days and median size of the thrombus was 18.9 [12.1; 33.2] mm. Most thrombi were located in the FET stent-graft's distal half (n = 15, 79%). A new thrombus was detected retrospectively in 9 patients (47%), in this analysis, but they had no clinical relevance during the hospital stay and these thrombi were not visible during follow-up visits (**Supplementary Figure 1**). Four patients suffered a thrombus embolisation (21%).

Thrombus Management

Of the 10 patients diagnosed with a new, relevant postoperative thrombus within the stent-graft, all received therapeutic anticoagulation. TEVAR was performed to over-stent the thrombus in two patients. In their following CTA scans, no thrombus was visible any longer. Oral anticoagulation was the sole treatment of choice in four patients, and their thrombi resolved without any clinical consequence and were no longer visible in follow-up CTA scans.

Embolisation Management and Outcome

Thrombus embolisation occurred in four patients (21%). In the first, embolisation led to a subtotal occlusion of the coeliac trunk

TABLE 3 | Thrombus characteristics.

	***N* = 19**
Location in stent-graft*	
Proximal	4 (21)
Distal	15 (79)
Size of thrombus (mm)	18.9 (12.1; 33.2)
Retrospectively detected, no clinical relevance	9 (47)
Embolisation	4 (21)
Coeliac trunk occlusion	3 (16)
Superior mesenteric artery occlusion	2 (11)
Renal artery occlusion	2 (11)
Iliac/femoral artery occlusion	0 (0)

*Values are n (%) or median (first quartile, third quartile). *proximal half of the stent-graft or distal half of the stent-graft.*

TABLE 4 | Postoperative and follow-up outcome.

	In-stent thrombi (*n* = 19)	**No thrombi (*n* = 285)**	***P*-value**
In-hospital mortality	1 (5)	24 (8)	1.000
Stroke	3 (16)	44 (16)	1.000
Non-disabling stroke	1 (5)	13 (5)	1.000
Disabling stroke	2 (11)	31 (12)	
Temporary renal replacement therapy	4 (21)	28 (9)	0.129

Values are n (%) or median.

TABLE 5 | Logistic regression analysis—in-stent thrombus formation.

Variable	***P*-value**	**OR**	**95% CI**
Age (years)	0.153	1.043	0.985–1.105
Female sex	0.005	4.289	1.534–11.989
Acute pathology	0.870	1.147	0.222–5.928
Penetrating aortic ulcer	0.203	3.362	0.519–21.759
Aortic aneurysm	0.023	5.198	1.255–21.540

CI, confidence interval; OR, odds ratio.

(**Figure 2**), the superior mesenteric artery and both renal arteries. Because of this patient frail state, we opted for an endovascular approach and were able to re-vascularise the superior mesenteric artery and both renal arteries *via* stent-graft [Advanta stent-grafts (Getinge Deutschland GmbH, Rastatt, Germany)] implantation. It was unfeasible to revascularise the coeliac trunk. Despite all our attempts, this patient developed severe visceral ischaemia and expired in multi-organ failure with circulatory depression. Embolisation in the second patient caused a total occlusion of the left renal artery entailing complete ischaemia of the left kidney. This patient's medical history included complex interventions and operations of the renal arteries including an iliaco-renal bypass; therapeutic anticoagulation was the treatment of choice. This patient required permanent postoperative dialysis. The third patient's embolisation caused infarctions in the liver and spleen and a subtotal occlusion of the ileocolic artery. A remaining thrombus was visible in the FET stent-graft that had not resolved in a control CTA scan despite therapeutic anticoagulation. Therefore, a conventional stent-graft (Relay NBS Terumo Aortic, Vascutek Ltd., Inchinnan, United Kingdom) was put in place to over-stent the thrombus. During another control CTA scan, the thrombus had disappeared. In the fourth and last patient, the thrombi embolised inside the coeliac trunk, the splenic, gastroduodenal, and left gastric arteries causing no clinically relevant malperfusion or organ infarction. After initiating therapeutic anticoagulation, the thrombi were no longer visible during the follow-up CTA scan.

All outcome characteristics are summarised in **Table 4**. There were no statistically significant differences between the two groups.

Logistic Regression Analysis

Female sex (p = 0.005; OR: 4.289) and an aortic aneurysm (p = 0.023; OR: 5.198) were identified as significant variables in our logistic regression analysis (**Table 5**).

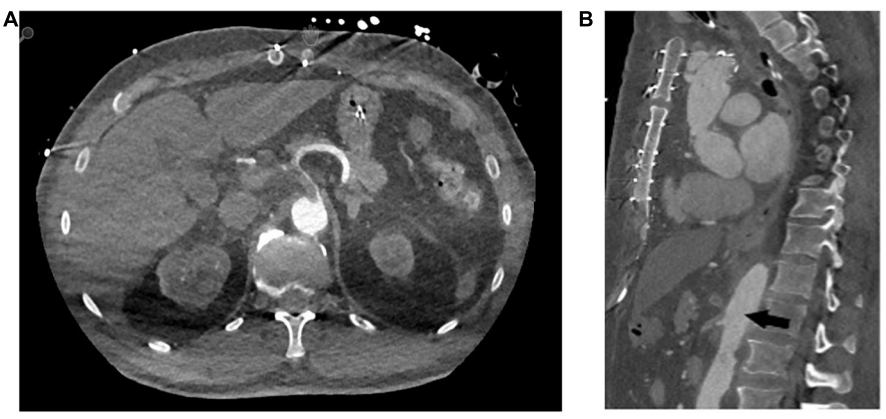

FIGURE 2 | Representative computed tomography angiography images of distal embolisation of the in-stent thrombi to the coeliac trunk **(A)** axial plane **(B)** sagittal plane.

DISCUSSION

Our study's most important findings can be summarised as: (i) new postoperative thrombus formation within the FET stent-graft is a clinically significant problem with a relevant incidence; (ii) although embolisations of these thrombi are rare, they potentially cause dismal postoperative outcomes; (iii) additional research evidence is needed to better identify patients at risk and improve perioperative treatment.

This cohort's chronic health conditions and risk factors were comparable to other patient cohorts undergoing total arch replacement using the FET technique (4, 12, 13). Nevertheless, note that thrombi were diagnosed predominantly in female patients who were significantly older. In fact, female sex was identified as a significant predictor for a new in-stent thrombus development in our logistic regression model. Following conventional TEVAR, female sex is a known risk factor for peripheral stent-thrombosis and stent-graft luminal narrowing (14, 15). Why female patients suffer this higher incidence is unknown, but it may be associated with different aortic flow/compliance in female and/or differences in their coagulation pathways (15). Note that one patient suffered from the factor-V-Leiden-mutation coagulation disorder. Much more research is needed to discover additional risk factors for the occurrence of stent-graft thrombi with a specific focus on gender-related aspects.

In addition, aneurysms were the predominant underlying pathology in this study and an aortic aneurysm was identified as a highly significant variable in our logistic regression model. These patients may have had chronic thrombi formation within the aneurysm sack, but we do not know how these thrombi became dislocated within the FET stent-graft. After all, a crimped stent-graft is introduced into the aorta and intraoperative perfusion in this cohort was always antegrade (axillary cannulation in all patients). The additional cannulation of the femoral artery in one patient who developed a new in-stent thrombus may have caused retrograde introduction of a thrombus to within the stent-graft, as retrograde embolisation has been reported in patients with femoral artery cannulation for cardiopulmonary bypass (16, 17). However, the statistically comparable cannulation approach between the two groups suggests that thrombi developed after FET deployment independent of the cannulation method even though the cause remains unclear.

One major limitation of this study is the lack of perioperative coagulation management data and transfusion requirements. Nevertheless, there is an urgent need for a general awareness of this serious problem to develop within the aortic community, since other large volume aortic centres have also preliminarily reported on this issue (18). Of note, we want to highlight the fact that we identified postoperative in-stent thrombi in 9 patients during our retrospective analysis of the postoperative CTA scans that had been previously undetected and were fortunately clinically irrelevant. Hence, there is an obvious need for in-depth analyses of perioperative coagulation management in larger case series, ideally in a multi-centre analysis of this complication including patients having received both commercially available stent-grafts in Europe. We also want to emphasise that there was no case of delayed sternum closure in patients with a new in-stent thrombus—an indirect marker for no significant bleeding necessitating massive transfusion that may have increased the likelihood of intravascular thrombus formation.

In four patients, the thrombi embolised, causing significant postoperative morbidity and mortality. Our treatment approach comprised therapeutic anticoagulation in all patients. When larger, restiform thrombi are diagnosed in CTA we liberally opt for endovascular over-stenting, thereby paying utmost attention to not dislocate the thrombus through our wire manipulation. By this approach, we implant a conventional stent-graft within the FET stent-graft that provides an excellent proximal landing zone (19) or we implanted smaller stent-grafts into visceral arteries. When thrombus embolisation occurs, we plan our treatment interdisciplinarily with our interventional specialists and our visceral surgeons. In this difficult clinical scenario, any attempt seems plausible to restore visceral perfusion, but outcomes in patients with visceral malperfusion remain dismal (20, 21).

This study shows that postoperative thrombi formation within the FET stent-graft is a new and clinically severe postoperative complication warranting further research and careful postoperative CTA analysis of all patients following the FET procedure. Postoperative surveillance following the FET procedure focussing on individual patient-specific factors is warranted.

Limitations and Strengths

While we describe a novel complication following the FET procedure, our study is obviously limited by its retrospective nature and the lack of data on the perioperative management of anticoagulation or potential postoperative coagulation disorders such as disseminated intravascular coagulation. In addition, we cannot rule out the development of any thrombus during later stages or in-between two CTA scans. Furthermore, we identified several thrombi in postoperative CTA scans during this retrospective analysis that had no clinical relevance. The possibility remains that buckling or flow effects may also be present in these patients. Nevertheless, our findings of particularly large thrombi clearly highlight this complication's urgent clinical importance and the need for further research.

CONCLUSION

Postoperative new thrombus formation within the FET stent-graft is a new but also clinically a highly relevant event. Female patients and patients with the aortic aneurysms seem to be at higher risk for a new in-stent thrombus formation. Embolisation of these thrombi can cause dismal postoperative outcomes, making additional investigations necessary to better identify patients at risk and improve their perioperative treatment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TW: conceptualisation, formal analysis, methodology, data curation, and writing—original draft. TB: data curation, formal analysis, and writing—review and editing. SK: visualisation and writing—review and editing. RG: data curation, methodology, and writing—review and editing. BR: supervision and writing—review and editing. MC: methodology, project administration, supervision, and writing—review and editing. MK: conceptualisation, methodology, supervision, validation, and writing—review and editing. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.921479/full#supplementary-material

Supplementary Figure 1 | Computed tomography angiographic images of a previously undetected thrombus in the distal end of the stent-graft **(A,C)** axial plane, **(B,D)** sagittal plane.

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Does endovascular duration impact clinical outcomes in aortic arch repair? The RELAY™ branched international stance

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Background: The high mortality and morbidity rates in surgical aortic arch repair are a barrier to therapy for a considerable proportion of patients with aortic arch aneurysm or dissection. There is hence a demand for the development and adoption of a minimally invasive alternative to aortic arch repair, such as thoracic endovascular aortic repair (TEVAR). Procedural duration is a key factor in the pathogenesis of complications in surgical aortic arch repair. Herein, we evaluate whether endovascular duration impacts neurological outcomes, target vessel patency, and reintervention rates in aortic arch TEVAR with RELAY™ Branched (Terumo Aortic, Inchinnan, UK), which is specifically developed for on-label use within the aortic arch.

Methods: Prospective data was collected between January 2019 and January 2022 on the clinical outcomes of TEVAR for aortic arch dissection and aneurysm with RELAY™ single-, double-, and triple branched endoprostheses from centers across Europe. They were then retrospectively analyzed with descriptive and distributive analysis. Follow-up data on the incidence of disabling stroke (DS), target vessel patency, and reintervention from 30 days and 6-, 12-, and 24 months postoperative was included in the analysis.

Results: 147 (99.3%) of all 148 cases were successful. Over the 24 month follow-up period, in total 6 (4.1%) patients suffered DS, 24 (16.3%) required reintervention, and target vessel patency was exhibited in 118 (80.2%) patients. The modal endovascular duration was 100–150 min (in 64.6%, $n = 95$ cases). Analysis revealed that endovascular duration was associated with a lower likelihood of reintervention at 30 days, 6-, and 12 months ($P = 0.011$, $P = 0.019$, $P = 0.037$), a greater likelihood of target vessel patency at 6- and 24 months ($P = 0.032$, $P = 0.035$). No relationship between endovascular duration and DS was revealed.

Discussion: The data demonstrates that RELAY™ Branched is associated with promising clinical outcomes for on-label aortic arch TEVAR. The underlying mechanism linking endovascular duration and reintervention rates, or target vessel patency is likely multifactorial and complex. Given that TEVAR is carried

out under general anesthetic only, it is unlikely that prolonged procedural duration has any major effect over neurological outcomes for arch TEVAR.

KEYWORDS

thoracic aortic aneurysm, aneurysm, RELAY^{TM}, TEVAR, branched RELAY, custom-made device technology

Background

Surgical innovations such as endovascular aneurysm repair (EVAR) and thoracic endovascular aortic repair (TEVAR) have revolutionized the management of life-threatening aortic pathologies by providing a minimally-invasive alternative to open surgical repair (OSR). However, OSR remains the mainstay treatment for aortic arch aneurysm and dissection. Despite its widespread application and impressive success rates, OSR continues to be associated with an exceptionally high rates of mortality and morbidity; mortality rates as high as 32.0% have been reported for the surgical repair of complicated type B aortic dissection, while ∼15.9% of patients undergoing open proximal aortic repair suffer permanent neurological complications (1). These statistics are especially striking when compared to those associated with TEVAR for type B aortic dissection. Furthermore, given the invasiveness of OSR for the aortic arch, which also requires cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA), the turn-down rate for open surgical arch reconstruction remains at an all-time high of up to 40% (2).

Clearly, given the risks associated with open surgical arch reconstruction, and the consequent limitations for patient eligibility, a similarly minimally invasive approach to aortic arch repair would be valuable. TEVAR, having been adopted as the mainstay approach to repair of the thoracic aorta, has been shown to be a promising alternative to OSR that negates the use of CPB, HCA, and aortic cross-clamping while facilitating deployment of custom-made endoprostheses to preserve native aortic stability while inducing false lumen (FL) obliteration or aneurysmal shrinkage (3).

As aortic arch TEVAR has increased in popularity, the challenges of endovascular navigation around the curvature of the aortic arch, avoiding iatrogenic coverage of the supra-aortic branches, preserving target vessel patency, and reducing reintervention rates have come to the fore (2). These have been met with the development of specialized custom-made branched and fenestrated endoprostheses. RELAY^{TM} Branched (Terumo Aortic, Scotland), for example, is designed specifically for on-label deployment throughout the aortic arch, and is available in single-, double-, or triple-branched configurations.

Of particular concern during proximal aortic repair is the effect that procedural duration may exert on the pathogenesis of neurological and structural complications, namely perioperative disabling stroke (DS), loss of target vessel patency, and the need for reintervention. This effect has been investigated at length in the context of proximal aortic OSR, though evidence remains mixed (4). Yet, since the advent of aortic arch TEVAR, there has hitherto been no published investigation into the role played by procedural duration on the pathogenesis of these key complications.

In light of these findings, the present study was designed to explore the potential relationships between procedural duration and the pathogenesis of DS, reintervention rates, and target vessel patency in aortic arch TEVAR with RELAY^{TM} Branched. We present a unique, multi-center analysis of prospective data from European centers, and provide unique insight into clinical outcomes.

TEVAR for aortic arch pathology: Challenges and strategies

Unlike EVAR for thoracoabdominal aortic pathology, or TEVAR for thoracic aneurysm or dissection, endovascular torque control may be severely limited by the anteroposterior and mediolateral curvature of the proximal thoracic aorta (5). This makes accurate placement and deployment of the endoprosthesis challenging and may necessitate the use of buddy wires or through-and-through catheterization to improve operator control (5). Introduction of a guidewire through the femoral vein, advancing it through the inferior vena cava, crossing into the left heart *via* the atrial septum, and subsequently into the proximal aorta and out *via* the femoral artery (i.e., the transeptal approach) has been suggested to confer greater torque control than simple direct retrograde catheterization of the proximal aorta *via* through-and-through manipulation (5). The transeptal approach has also been suggested to provide improved access to zone 0 compared to the transbrachiofemoral approach as it avoids the sharp turn at the innominate artery (IA) ostium (5). Notably, the RELAY^{TM} Branched delivery system features a pre-curved inner catheter and dual sheath to improve alignment with the aortic arch. The cannulation window situated on the dorsal aspect

(from which the supra-aortic branches are cannulated) has radiopaque markers to aid device positioning relative to the arch branch ostia.

Care must also be taken when selecting the proximal landing zone for endoprosthesis deployment. Preoperative transoesophageal echocardiography (TOE) is typically employed to measure the distance from the coronary ostia and sinotubular junction to the proximal entry tear (in the case of proximal aortic dissection) (2). Endovascular repair may be contraindicated in patients with a primary entry tear within 20 mm of the sinotubular junction to avoid compromising coronary supply, and in patients with a zone 0 aortic diameter >38 mm (2, 6).

It should be also highlighted that planting the endoprosthesis deep within zone 0 exposes it to maximal hemodynamic pressure, increasing the risk of malorientation as a result of the windsock effect (7). In view of these spatial constraints, shorter and wider endoprosthetic dimensions are favored, and 15% oversizing of the endoprosthesis relative to the native aortic diameter is considered to improve sealing (8). This clearly justifies the need for custom-made aortic arch endoprostheses licensed for on-label use throughout zones 0–4, to which RELAY™ Branched is eminently suited. Notably, most TEVAR endoprosthesis are limited to on-label use in the descending thoracic aorta.

Though TEVAR of the aortic arch does not require HCA or CPB, the risk of cerebrovascular accident remains omnipresent. In the absence of such invasive anesthetic techniques, DS typically arises from inadvertent embolization of luminal plaques by endovascular instrumentation or inadvertent iatrogenic occlusion of the supra-aortic branches (9, 10). The risk of occlusive ischemic stroke is thought to be greater in patients undergoing TEVAR with planned occlusion of the left subclavian artery (LSA) and in those with a proximal landing zone in close proximity to the sinotubular junction (11). Maintenance of LSA patency circumvents the risk of inadequate collateralization leading to left arm ischemia, avoids subclavian steal syndrome (and resultant vertebrobasilar insufficiency), and has also been shown to carry a lower risk of stroke (12). Bradshaw and colleagues reported a 1.9% stroke rate in patients who underwent endovascular or extraanatomical LSA revascularization, in comparison to a 14.3% stroke rate in those that underwent TEVAR with total LSA occlusion (12). The triple-branched RELAY™ endoprosthesis allows cannulation of all three supra-aortic branches, and in patients where LSA cannulation is not feasible, extra-anatomical bypass (such as carotid-subclavian) can be performed prior to TEVAR with a double- or single-branched RELAY™ (13). The effect that increased procedural duration in cases involving triple-branched RELAY™ endoprosthesis may have on the risk of causing perioperative DS remains unclear.

Target vessel patency is a key clinical evaluative metric, and maintenance thereof is pivotal to disease regression, patient quality of life, and event-free survival. Loss of aortic or arch branch patency may potentiate reintervention, which further exposes the patient to perioperative risks and impacts quality of life. Inadequate proximal sealing and intimal injury increase the likelihood of postoperative endoleak, which remains Achilles heel of endovascular repair (14, 15). This emphasizes the importance of custom-made, appropriately sized endoprostheses for long-term durability. Furthermore, retrograde dissection of extension of dissection involving the supra-aortic branches compromises vessel patency, though it is reasonable to suggest that endovascular cannulation of the arch vessels may attenuate this effect (15). As a custom-made endoprosthesis designed for on-label use throughout zones 0–4 of the aortic arch, RELAY™ Branched can be designed in a bespoke manner to fit well with each patient's unique anatomy. Its availability in single-, double-, or triple-branched configurations allows further flexibility in maintaining patency of both the supra-aortic branches and the aortic arch. The built-in cannulation branches avoids the need for the chimney technique, which has been associated with an increased risk of endoleak and subsequent loss of aortic patency (the risk of which presumably increases the more proximally the endoprosthesis is positioned, owing to the windsock effect) (16).

Methods

Study design

A 24-month international multi-center retrospective analysis of key outcomes (DS, reintervention, and target vessel patency) in patients treated for aortic arch pathology using the RELAY™ Branched endoprosthesis was carried out between January 2019 and January 2022. Data were collected in a prospective fashion from European centers and stored in a registered database. IRB ethical review and approval was not required for the present study with human participants, in accordance with local legislation and institutional requirements.

Patient characteristics

In total, 148 patients underwent endovascular repair of the aortic arch with the RELAY™ Branched endoprosthesis. Of these, 38 patients were female, resulting in a 3:1 male-female ratio. The mean age was 70 (IQR = 14.5) years. 72.3% ($n = 107$) of patients were treated for a proximal aortic aneurysm while 27.7% ($n = 41$) were treated for aortic dissection involving the aortic arch. 46% ($n = 68$) of patients were acute cases while 54% ($n = 80$) underwent elective endovascular repair. Patient characteristics are summarized in Table 1.

TABLE 1 Demographics.

Gender (male : female)		3:1
Mean age (IQR)		70 (14.5)
Pathology (%)		
Aneurysm	107 (72.3%)	
Dissection	41 (27.7%)	
Urgency (%)		
Acute	68 (46%)	
Elective	80 (54%)	
Regional distribution*		
West Europe	78 (52.7%)	
East Europe	32 (21.6%)	
North Europe	9 (6.1%)	
South Europe	29 (19.6%)	
Total cases		148

*Based on UNSD Geoscheme.

Follow-up

Patients were followed-up at 30-days and 6-, 12-, and 24-months postoperatively. During follow-up, patients were evaluated for DS and target vessel patency, and all cases requiring reintervention during these intervals were recorded. DS was defined in accordance with the VARC-2 criteria which categorizes DS as a modified Ranking score (mRS) > 3, reflecting that the patient has moderate disability; requiring some external help but able to walk without the assistance of another individual. Cumulative mortality was also recorded at each follow-up interval.

Statistical analysis

All statistical analyses were performed using SPSS (IBM™ SPSS 28 for Windows) using the R plugin. Propensity score matching was carried out to exclude confounding variables. Data were analyzed using the Shapiro Wilk W normality test, subsequently T-test analyses were performed for normally distributed data and the Mann-Whitney U-Test for non-parametric equivalents. Statistical significance for all two-tailed tests was set at $P < 0.05$.

Results

Operative characteristics

All 148 patients underwent endovascular intervention for aortic arch aneurysm or aortic arch dissection with the RELAY™ Branched endoprosthesis. Technical success was achieved in 147 (99.3%) patients. 17 (11.5%) patients were treated with the single-branched configuration, while 108 (73%) and 23 (15.5%) patients were treated with the double- and triple-branched configurations, respectively. The single (0.67%) mortality in our cohort was subsequent to a technically successful procedure, and the death was not device-related. Operative characteristics are summarized in Table 2. Mean procedural duration was 258 (IQR = 100) min. The modal endovascular duration was 100–150 min (n = 95). Endovascular durations are summarized in Table 3.

TABLE 2 Operative characteristics.

Mean procedural time (IQR) (minutes)		258 (100)
Branching number (%)		
	Single	17 (11.5%)
	Double	108 (73%)
	Triple	23 (15.5%)
Technical success (%)		147 (99.3%)
Target vessel cannulation (%)		146 (99.3%)[a]

[a]Following percentages are calculated out of 147, one case died during the procedure, unrelated to the device.

TABLE 3 Endovascular duration.

Duration (min)	*N* (%)
50–100	18 (12.2%)
100–150	95 (64.6%)
150–200	24 (16.3%)
200–270	11 (7.5%)

DS

Over the 24-month follow-up period, in total 6 patients (4.0%) were found to have DS after undergoing TEVAR with the double-branched RELAY™ endoprosthesis. 2 (1.3%) cases of DS were identified within the first 30 days postoperative. A further 2 (1.3%) cases of DS were identified at 6 months postoperative. At 12 months postoperative, 1 (0.7%) patient developed DS. A further single case (0.7%) of DS was identified at 24 months postoperative. The incidence of DS across the 24-month follow-up period is summarized in Table 4.

Reintervention

Over the 24-month follow-up period, a total of 24 cases of reintervention were recorded. All 24 cases involved patients who had been treated with the double-branched configuration of the RELAY™ Branched endoprosthesis. 8 (5.4%) reinterventions were carried out within the first 30 days postoperative. A

TABLE 4 Follow-up periods results.

	30 days	6 months	12 months	24 months	Total
Vessel patency	147 (100%)	134 (91.1%)	124 (84.3%)	118 (80.2%)	–
Reinterventions	8 (5.4%)	6 (4.4%)	5 (4.0%)	5 (4.0%)	24 (16.3%)
Disabling stroke	2 (1.3%)	2 (1.4%)	1 (0.7%)	1 (0.7%)	6 (4.1%)

further 6 (4.4%) reinterventions were required by 6 months postoperative. An additional 5 (4.0%) reinterventions were recorded by both 12- and 24 months postoperatively. A summary of recorded reinterventions across the 24-month follow-up period is provided in Table 4.

Target vessel patency

Target vessel patency was maintained in all (147) patients across all three branching configurations at 30 days postoperatively. The 23 (15.6%) patients that were treated with the triple-branched endoprosthesis maintained vessel patency throughout 24 months of follow-up. At 6 months postoperatively, target vessel patency was maintained in 15 (10.2%) and 96 (65.3%) patients that were treated with the single- and double- branched endoprosthesis, respectively. All 16 (10.9%) patients treated with the single-branched endoprosthesis exhibited target vessel patency at 12 months postoperatively, compared to 85 (57.8.%) of those treated with the double-branched configuration. At 24 months postoperatively, 15 (10.2%) and 80 (54.4%) patients treated with the single- or double- branched configurations were noted to have maintained target vessel patency. These findings are summarized in Tables 4, 5.

There was no relationships observed between the mean rank of endovascular duration and incidence of DS across all four follow-up intervals (30 days: $U = 263$, $P = 0.782$; 6 months: $U = 351$, $P = 0.476$; 12 months: $U = 222$, $P = 0.152$; 24 months: $U = 204$, $P = 0.326$). The Mann-Whitney U test also revealed a statistically significant relationship between endovascular duration and reintervention rates from 30 days to 12 months postoperative (30 days: $U = 642$, $P = 0.011$; 6 months: $U = 433$, $P = 0.019$; 12 months: $U = 518$, $P = 0.037$) however this relationship was shown to not be statistically significant at the 24-month interval ($U = 490$, $P = 0.055$). Finally, our analysis revealed a relationship between endovascular duration and target vessel patency at the 6- and 24-month intervals (6 months: $U = 560$, $P = 0.032$; 24 months: $U = 1{,}283$, $P = 0.035$), however this relationship was found to not be significant at the 12-month interval ($U = 1{,}072$, $P = 0.056$). We note that because target vessel patency remained at 100% across the entire cohort at the 30-day follow-up interval, the Mann-Whitney U test was not applied to this sub-group. These findings are summarized in Tables 6–8.

Discussion

The endovascular treatment of aortic arch pathologies using the RELAY™ Branched endoprosthesis yields desirable clinical outcomes, both in the short- and intermediate-term. The index procedures included in this series showed a 99.3% ($n = 147$) technical success rate and out of the cohort of 148 patients only one mortality was recorded over the 24-month follow-up period. The incidence of DS was 4.1% ($n = 6$) over 24 months with none treated with a single- or triple-branched RELAY™ endoprostheses. Similarly, none of the patients in these two subgroups required reintervention at any point during the follow-up period. Overall, endovascular arch repair with RELAY™ Branched was associated with a 16.3% ($n = 24$) reintervention rate, and by the 24-month interval, 80.2% ($n = 118$) of patients maintained target vessel patency. All patients ($n = 23$, 15.6%) treated with the triple-branched configuration maintained full target vessel patency throughout follow-up. Furthermore, the data show that the Relay™ Branched system enables rapid deployment of the endoprosthesis at the target site, with the modal endovascular duration in our series being 100–150 min.

The outcomes reported in the present series emphasize that despite the numerous advantages conferred by its minimally-invasive nature, endovascular repair of the aortic arch still carries significant risk of DS, loss of vessel patency, and the need for reintervention. These are complications that adversely impact a patient's quality of life, albeit at a lower rate than that of open surgical repair (17). Indeed, our data suggest that RELAY™ Branched is associated with a more favorable neurological risk profile than that reported by colleagues, whilst also ensuring that clinicians treat these complexities with on-label device use at all times (8, 15, 18).

Tazaki et al., in their analysis of outcomes associated with the Inoue™ triple-branched endoprosthesis, report a combined stroke rate of 40%, while Sato et al. reported a 16.7% ($n = 6$) stroke rate with the Najuta™ fenestrated endograft (16, 18). Czerny et al. observed a combined stroke rate of 20% in their series (8). Additionally, Sato et al. reported that aneurysmal shrinkage post-intervention was observed in only 11 (30.6%) patients, while no change in aneurysmal size was observed in 15 (41.7%) (16). However, increased aortic arch diameter was reported in 27.8% ($n = 10$) of patients in their series (16). In contrast, stable patency of the aortic arch, distal aorta, and the supra-aortic branches was observed in 80.2% ($n = 11.8$) of

TABLE 5 Relationship between branching number and vessel patency.

	Single	Double	Triple	Total	*P*
30 days	16 (10.9%)	108 (73.4%)	23 (15.6%)	147 (100%)	–
6 months	15 (10.2%)	96 (65.3%)	23 (15.6%)	134 (91.1%)	0.080
12 months	16 (10.9%)	85 (57.8%)	23 (15.6%)	124 (84.3%)	<0.001
24 months	15 (10.2%)	80 (54.4%)	23 (15.6%)	118 (80.2%)	0.001

TABLE 6 Endovascular time mean ranks vs. reintervention in each period.

	Mean ranks (reintervention = yes)	Mean ranks (reintervention = no)	Mann-Whitney *U*	*P*
30 days	48.63	77.1	642	0.011
6 months	45.36	76.32	433	0.019
12 months	49.67	76.16	518	0.037
24 months	50.59	75.89	490	0.055

TABLE 7 Endovascular time mean ranks vs. disabling strokes in each period.

	Mean ranks (disabling stroke= yes)	Mean ranks (disabling stroke= no)	Mann-Whitney *U*	*P*
Post-operative	50.25	76.9	668	0.017
30 days	79.75	73.84	263	0.782
6 months	86.0	73.49	351	0.476
12 months	100.5	73.07	222	0.152
24 months	94.38	73.43	204	0.326

TABLE 8 Endovascular time mean ranks vs. target vessel patency in each period.

	Mean ranks (vessel patency= yes)	Mean ranks (vessel patency= no)	Mann-Whitney *U*	*P*
30 days	74	0	-	-
6 months	76.32	50.08	560	0.032
12 months	76.85	58.61	1,072	0.056
24 months	77.63	59.24	1,283	0.035

patients in our study. Iwakoshi and colleagues reported an 83.5% freedom from reintervention rate in their series evaluating the Najuta™ fenestrated endograft (19). This paper shows similar outcomes, with an 83.7% freedom from reintervention rate at 24 months 24 reinterventions occurred during the follow-up period, of which 23 (95.8%) cases were recorded as having taken place in the South Europe region, accounting for 19.6% ($n = 29$) of the total procedures included in the series (Table 9).

TABLE 9 Geographical distribution of reinterventions.

	West	East	South	North	Total	*P*
30 days	0	0	8	0	8 (5.4%)	<0.001
6 months	1	0	5	0	6 (4.4%)	<0.001
12 months	0	0	5	0	5 (4.0%)	<0.001
24 months	0	0	5	0	5 (4.0%)	<0.001

A significant inverse relationship was seen between the duration of the endovascular procedure and reintervention rates at 30 days, 6 and 12 months. This is suggestive of lower reintervention rates within 1 year post-stenting in those undergoing prolonged endovascular intervention. Though the mechanism behind this relationship remains unclear, it is reasonable to suggest those with complex arch disease require more extensive and prolonged endovascular repair to achieve optimum results.

Following open surgical repair for acute type A aortic dissection, reduced reintervention rates are a well-documented benefit of extensive repair (in comparison to a more conservative approach) (20). Therefore, the statistically observed relationship highlighted may well be an indirect one; the reduced reintervention rate observed up to 12 months may not due to a prolonged procedural duration but a consequence of more extensive aortic repair.

A statistically significant relationship between endovascular duration and target vessel patency at 6- and 24 months postoperative was observed. This finding shows target vessel patency at 6 months is associated with a prolonged endovascular duration and a reduced likelihood for reintervention at 6 months' follow-up. Similarly, prolonged endovascular duration may be the product of more extensive aortic arch repair contributing to improved patency rates of the supra-aortic branches at 6 months.

A treatment option for patients undergoing endovascular aortic arch repair with single- or double-branched endoprostheses is occlusion of the LSA origin, either with extraanatomical revascularization or allowing collateralization to maintain perfusion to the territory supplied by the LSA (21). The data also demonstrate that there does not exist a statistically significant relationship between endovascular duration and the occurrence of perioperative DS at all follow-up intervals. This may perhaps be because perioperative stroke in the

context of endovascular aortic arch repair is usually ischemic (as a result of supra-aortic branch occlusion by endoluminal instrumentation or the deployed endoprosthesis) or embolic (due to embolization of particulate matter from the diseased aortic intima during endovascular manipulation of the aorta) (22). Since aortic arch TEVAR is carried out under general anesthetic, without the need for cardiopulmonary bypass, systemic cooling, and circulatory arrest, it is unlikely that procedural duration exerts any direct or independent effect over the pathogenesis of perioperative neurological injury (14). As a result, it could be argued that anesthetics of aortic arch TEVAR may involve no greater risk of perioperative stroke than would be expected for other elective procedures carried out under general anesthetic. In contrast, prolonged procedural duration has traditionally been regarded as a driving factor behind perioperative stroke in the context of open surgical aortic repair, given the need for circulatory arrest and cardiopulmonary bypass.

Conclusion

RELAY^{TM} Branched TEVAR for the aortic arch represents a promising step forward in on-label endovascular therapy for aortic arch pathology. Though significant advances have been made in this field, the risk of perioperative stroke, loss of vessel patency, and reintervention remain in the fore. Our investigation into the relationship between endovascular duration and the pathogenesis of these complications suggests that prolonged endovascular duration may indirectly correlate with improved target vessel patency and reintervention rates up to 12- and 6 months, respectively. Our analyses revealed that there it is unlikely that endovascular duration affects the incidence of perioperative DS. Further prospective research across different endoprosthetic devices is recommended.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

ST, AS, and MJ contributed to the drafting of the manuscript. AS was responsible for data analysis. MJ, DB, IW, and MB were responsible for critical review and feedback. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Efficacy of pump-controlled selective antegrade cerebral perfusion in total arch replacement: A propensity-matched analysis

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Background: Pump-controlled selective antegrade cerebral perfusion (PC-SACP) in total arch replacement (TAR) can regulate cerebral flow accurately, which might be beneficial for cerebral protection. However, the safety of PC-SACP for TAR combined with frozen elephant trunk implantation (FET) in patients with acute Type A dissections (ATAAD) is ambiguous.
Methods: A total of 192 patients with ATAAD underwent TAR at our institution from October 2019 to July 2021. The patients were divided into two groups based on PC-SACP used: PC group (SACP carried out by using a separate pump, $n = 35$) and Control group (SACP carried out as a traditional method, $n = 157$). Patients under PC-SACP were propensity-score matched to patients without PC-SACP, resulting in 35 pairs of patients.
Results: Preoperative characteristics, including age, gender, weight, and preoperative creatinine level, were similar between the two groups. Cardiopulmonary bypass time, cross-clamp time, circulatory arrest time, and minimum nasopharyngeal temperature did not differ between the two groups. However, SACP time (54 versus 40, $P = 0.001$) in the PC group was significantly longer than that in the Control group. The incidence of temporary neurologic dysfunction (5.7% versus 8.6, $P = 0.643$) showed a no significantly lower trend in the PC group compared with the Control group. Other clinical outcomes showed no significant intergroup differences.
Conclusions: PC-SACP in TAR is safe and feasible and might be beneficial for avoiding brain injury caused by "luxury" perfusion.

KEYWORDS

aortic dissection, selective antegrade cerebral perfusion, pump-controlled perfusion, upper hemisternotomy approach, total arch replacement

Introduction

Neurologic protection during aortic arch surgery is a challenging strategy for improving clinical outcomes in patients with acute Type A aortic dissection (ATAAD) (1). Deep hypothermic circulatory arrest (DHCA)–induced electrocerebral inactivity has been thought to ensure optimal neuroprotection, which reached the minimum

cerebral metabolic demand threshold (2). Moreover, the application of selective antegrade cerebral perfusion (SACP) has shifted the strategy from DHCA to moderate hypothermic circulatory arrest (MoHCA) or mild hypothermic circulatory arrest (MiHCA) (3, 4).

An earlier study demonstrated that bilateral SACP (BSACP) could maintain adequate cerebral blood supply at moderate hypothermia without an ischemic brain injury (5). The coupling of cerebral flow and metabolism is important for cerebral protection, and greater flow might increase the risk of cerebral edema and embolic phenomena (6). Although the suggested cerebral flow of selective cerebral perfusion is 6–10 ml/kg/min at 20–28 °C with a wide range of cerebral flow and temperature (7), our earlier study showed that 5 ml/kg/min of cerebral flow was sufficient for cerebral protection (8, 9), implying that excessive perfusion pressure and flow are unnecessary and should be avoided (6).

The application of SACP in the total arch replacement (TAR) surgery has been routinely carried out by using one main arterial line bifurcated for an SACP line and a systemic perfusion line via a Y connector (10). The flow of SACP and systemic perfusion depends on the resistance in cerebral arteries and systemic arteries, respectively. When the flow of the main arterial line is determined, occlusion of the systemic perfusion line can dramatically increase the flow of SACP, which may cause excessive SACP flow and pressure. This "luxury" perfusion might lead to brain injury. To solve this problem, a pump-controlled SACP (PC-SACP) has been implemented to avoid the excessive SACP that can occur during TAR surgery.

Materials and methods

Patients

Data were collected retrospectively from patients undergoing TAR for ATAAD. Patients with preoperative neurologic complications (cerebral infarction or cerebral hemorrhage), malperfusion syndrome, and concomitant operations (e.g., coronary heart disease, mitral valve disease, and congenital heart disease) were excluded. A total of 192 patients underwent TAR by the same surgery group, including surgeons, anesthetist, perfusionist, cardiologist, and nurses, at our institution between October 2019 and July 2021. The patients were divided into two groups: PC group ($n = 35$, PC-SACP was carried out) and Control group ($n = 157$, SACP carried out by a routine method) (**Table 1**). The study was approved by the Ethics Committee of General Hospital of Northern Theater Command, Shenyang, China. All patients provided their informed consent. The diagnosis of ATAAD was based on the patients' clinical history and computed tomography angiography.

Surgical procedure

All surgeries were carried out via a single upper hemisternotomy approach, and near-infrared spectroscopy monitoring was used for cerebral protection during surgery, as in our earlier studies (8, 9). The cannulation strategy in the two groups was to select the innominate artery as the first artery perfusion cannula and the right atrial cannulation as the venous drainage cannula. The right-angle artery cannulation was selected for artery perfusion with the direction of blood flow to the heart. The right subclavian artery and the right or left common carotid artery were used as alternative cannulation sites. The cardioplegia strategy was aortic root or coronary orifices after aortotomy antegrade delivery. The right superior pulmonary vein was cannulated for left ventricular vent. Cardiopulmonary bypass (CPB) was carried out after cannulation, and MoHCA was induced at the time of aortic root procedures. The cerebral perfusion strategy was based on BSACP, which was carried out by using arterial cannulation, and a 15Fr femoral arterial cannula was placed into the left/right common carotid artery after the brachiocephalic arteries were cross-clamped. The blood flow control of SACP depended on the group. In one group, routine SACP was perfused through the main arterial pump as in previous studies (10, 11) with a systemic line clamped (**Figure 1A**). In the other group, PC-SACP was perfused by the cardioplegia pump (8, 12) with the systemic line clamped and A–V shunt opened (**Figure 1B**). The flow of SACP was approximately maintained at 5 ml/kg·min, which was modulated on the basis of near infrared spectroscopy (NIRS) monitoring. Then, the frozen elephant trunk (FET) with and without lower body perfusion (LBP) was carried out as in earlier reports (8, 13). Briefly, a stent graft (MicroPort Medical Co., Ltd., Shanghai, China) was mainly placed into the distal aorta after the origin of the left subclavian artery and the left carotid artery transected. Then, through a four-branch prosthetic graft (VASCUTEK Ltd., a Terumo Co., Inchinnan, Scotland), an endotracheal cannula (Teleflex Medical Ltd., Wayne, PA, USA) with an inside diameter of 5.5 mm was placed into the distal artery for delivering oxygenated blood to the lower body and preventing the backflow as LBP with 25 ml/kg·min of flow (8). Moreover, LBP was switched to the four-branch prosthetic graft after the stent graft was attached to the four-branch prosthetic graft. The sequence of anastomosis to the prosthetic graft was carried out from the left common carotid artery, proximal aortic stump, innominate artery, and the left subclavian artery in succession. Special attention was paid to carrying out cerebral perfusion by using the cardioplegia pump until the innominate artery was anastomosed in the PC group (**Figure 2B**). The cerebral perfusion and LBP were carried out by using the main pump together in the Control group

TABLE 1 Perioperative characteristics of patients.

Variable	Raw data			Matched data			
	PC group ($n = 35$)	Control group ($n = 157$)	*P* value	PC group ($n = 35$)	Control group ($n = 35$)	*P* value	*SMD*
Preoperative characteristics							
Age (years)	52.0 (44.0, 59.0)	54.0 (46.0, 60.0)	0.730	52.0 (44.0, 59.0)	52.0 (44, 59)	0.431	0.02
Male (%)	27 (77.1)	117 (74.5)	0.746	27 (77.1)	27 (77.1)	1.000	<0.001
Weight (kg)	74.0 (66.5, 88.0)	78.0 (65.0, 88	0.274	74.0 (65.0, 88.0)	75.0 (70.0, 85.0)	0.549	0.125
LVEF (%)	58.0 (58.0, 60)	58.0 (57.0, 59.5)	0.087	58.0 (58.0, 60.0)	58.0 (57.0, 59.0)	0.497	0.125
Smoking (%)	22 (62.9)	81 (51.6)	0.227	22 (62.9)	20 (57.1)	0.626	0.117
Diabetes (%)	2 (5.7)	11 (7.0)	0.783	2 (5.7)	3 (8.6)	0.643	0.111
Hypertension (%)	25 (71.4)	105 (66.9)	0.063	25 (71.4)	26 (74.3)	0.788	0.064
Pre-Cr (μmol/L)	71.0 (61, 81.0)	59 (46.7, 72.0)	0.001	71.0 (61.0, 81.0)	75.0 (70.0, 85.0)	0.137	0.008
Intraoperative characteristics							
CPB time (min)	160 (144, 191)	158 (140, 187.5)	0.307	160 (144, 191)	185 (156, 202)	0.987	0.08
Cross-clamp time (min)	101 (85, 128)	93 (78.5, 107)	0.043	101 (85, 128)	107 (95, 137)	0.787	0.003
Circulatory arrest (min)	10 (8, 13)	11 (5, 15)	0.838	10 (8, 13)	11 (8, 16)	0.354	0.458
BSACP (min)	53 (41, 58)	28 (23, 34)	0.000	53 (41, 58)	40 (31, 42)	0.001	1.057
Min nasopharyngeal T (°C)	30 (27, 32)	29 (28, 30)	0.003	30 (27, 32)	30 (29, 32)	0.644	0.109
Operative outcomes of patients							
Ventilation time (h)	19 (16, 39)	22 (18, 65.5)	0.029	19 (16, 39)	20 (17, 40)	0.701	
ICU stay (h)	43 (32, 87)	44 (24.5, 90)	0.775	43 (32, 87)	44 (35, 62)	0.614	
First 24-h chest tube drainage (ml)	260 (170, 650)	200 (150, 310)	0.441	260 (170, 650)	350 (200, 560)	0.993	
Perioperative blood transfusion	25 (71.4)	101 (64.3)	0.424	25 (71.4)	24 (68.6)	0.794	
Reoperation for bleeding (%)	1 (2.9)	4 (2.5)	0.917	1 (2.9)	1(2.9)	1.000	
Reventilation (%)	1 (2.9)	1 (0.6)	0.242	1 (2.9)	1 (2.9)	1.000	
TND (%)	2 (5.7)	22 (14)	0.179	2 (5.7)	3 (8.6)	0.643	
PND (%)	1 (2.9)	6 (3.8)	0.783	1 (2.9)	2 (5.7)	0.555	
Acute renal failure (%)	2 (5.7)	17 (10.8)	0.360	1 ()	3 (5.7)	1.000	
Paraplegia (%)	1 (2.9)	2 (1.3)	0.495	1 (2.9)	1(2.9)	0.314	
Postoperative length of stay (d)	14.0 (10.0, 19.0)	15.0 (11.0–19.0)	0.491	14 (10, 19)	16 (11, 21)	0.333	
In-hospital death (%)	3 (8.6)	12 (7.6)	0.853	3 (8.6)	2 (5.4)	0.643	

(Figure 2A). After anastomosis to the left common carotid artery, CPB gradually returned, and rewarming started. Temporary pacing wire and a drainage tube were installed before sternal closure.

Definitions for complications

For the purposes of this study, temporary neurologic dysfunction (TND) was defined as the presence of reversible postoperative motor deficit, confusion, or transient delirium with complete resolution of symptoms before discharge from the hospital. Permanent neurologic deficit (PND) was defined as the presence of either new stroke or coma with permanent neurological dysfunction confirmed by means of computed tomography of the brain. Postoperative renal dysfunction was defined as a creatinine level >230 μmol/L (twice the normal value). Perioperative blood transfusion was defined as intraoperative and postoperative transfusion of red blood cells, fresh frozen plasma, and platelets.

Statistical analysis

Perioperative data were collected prospectively. Analyses were performed with SPSS version 22.0 software (SPSS, Inc., Chicago, IL). Normally distributed data were presented as group means ± SEM or SD, and non-normally distributed data were presented as the median and interquartile ranges. Student's *t*-test and Mann–Whitney *U* test were used to compare continuous variables.

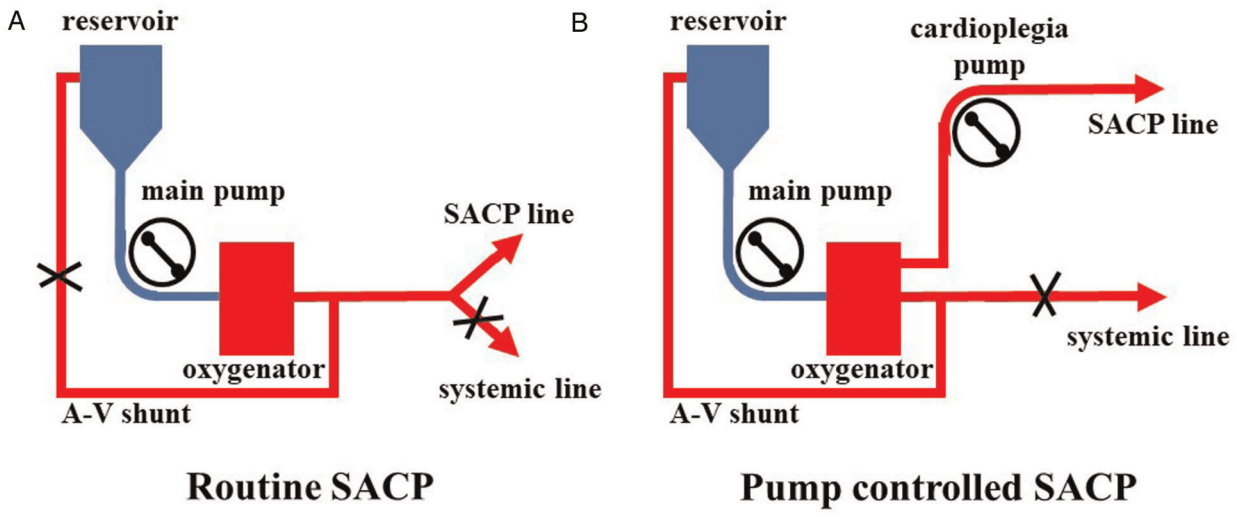

FIGURE 1
Application of pump-controlled SACP. (A) Routine SACP was carried out by clamping a systemic line and reducing flow of the main pump to 5 ml/kg·min. (B) Pump-controlled SACP was carried out by clamping the systemic line, opening A–V shunt, maintaining flow of the main pump at 2–3 L/min, and modulating cardioplegia pump to 5 ml/kg·min. SACP: selective antegrade cerebral perfusion.

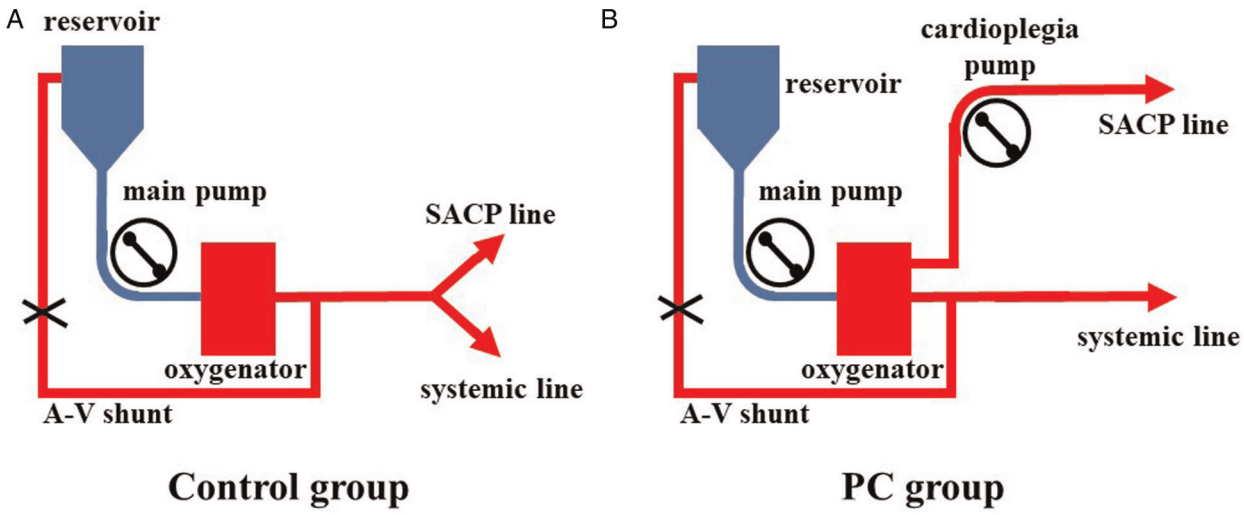

FIGURE 2
The application of LBP combined with SACP. (A) LBP and SACP were carried out by using the main pump together in the Control group. The cerebral flow was unclear. (B) LBP and SACP were carried out by using the main pump and the cardioplegia pump, respectively. LBP, lower body perfusion; SACP, selective antegrade cerebral perfuison; LBP, lower body perfusion; SACP, selective antegrade cerebral perfusion.

Categorical variables were analyzed by using the χ^2 test or Fisher's exact probability test (if necessary). Differences with $P < 0.05$ were considered statistically significant.

Propensity score (PS) matching was conducted between the two groups to simulate randomization in this observational study. PS was estimated by using the logistic model and matched between the two groups within a caliper of 0.2 PS standard deviations. The covariates were based on eleven clinical variables, namely, gender, age, height, left ventricular ejection fraction (LVEF), preoperative creatinine level, and the history of hypertension, diabetes, stroke, CPB time, cross-clamp time, and minimum nasopharyngeal temperature. Then, standardized mean difference (SMD) was carried out for assessing the balance between the groups, and SMD < 0.25 was considered as "balance satisfied". The Wilcoxon signed rank test was used to compare PS-matched pair variables.

Results

Baseline characteristics and propensity score matching

After PS matching, 70 patients (35 pairs) remained. The raw and matched data of preoperative and intraoperative characteristics are listed in Table 1. We did not observe any significant differences in preoperative and intraoperative characteristics between the two matched groups. Moreover, all time characteristics were found balanced by SMD.

Intra- and postoperative characteristics

We did not find any differences in CPB time, cross-clamp time, CA time, and minimum nasopharyngeal temperature between the two groups. However, BSACP time (54 min versus 40 min, $P = 0.001$) in the PC group was significantly longer than that in the Control group (Table 1).

Three patients (8.6%) died in the PC group, and two patients (5.4%) died in the Control group. In the PC group, one patient died of multiple organ failure, and two patients died of sudden hemodynamic changes that were thought to be due to aortic rupture. One patient died of postoperative massive cerebral infarction and one patient died of multiple organ failure in the Control group. We did not observe any differences in ventilation time, ICU stay, postoperative in-hospital stay, and the incidence of acute renal failure and paraplegia between the two groups. The incidence of TND showed a lower trend in the PC group compared with the Control group (5.7% versus 8.6%), but without reaching statistical significance ($P = 0.643$), as well as the incidence of PND. Other postoperative characteristics, including chest tube drainage, the incidence of perioperative blood transfusion, reoperation for bleeding, and reventilation, did not show any differences between the two groups (Table 1).

Discussion

Neurologic injury is a potentially devastating complication of ATAAD, and cerebral protection is vital during TAR surgery. SACP has been demonstrated as the best method of cerebral protection during TAR surgery (14–16). Different strategies of SACP affecting the outcomes include flow rates of SACP, unilateral or bilateral application, duration of DHCA, degree of hypothermia, and blood gas strategy (1, 6, 14, 17).

An intact circle of Willis is believed to be the base of unilateral SACP. However, incompleteness of the circle of Willis has been reported in up to 40% of patients (18). Earlier

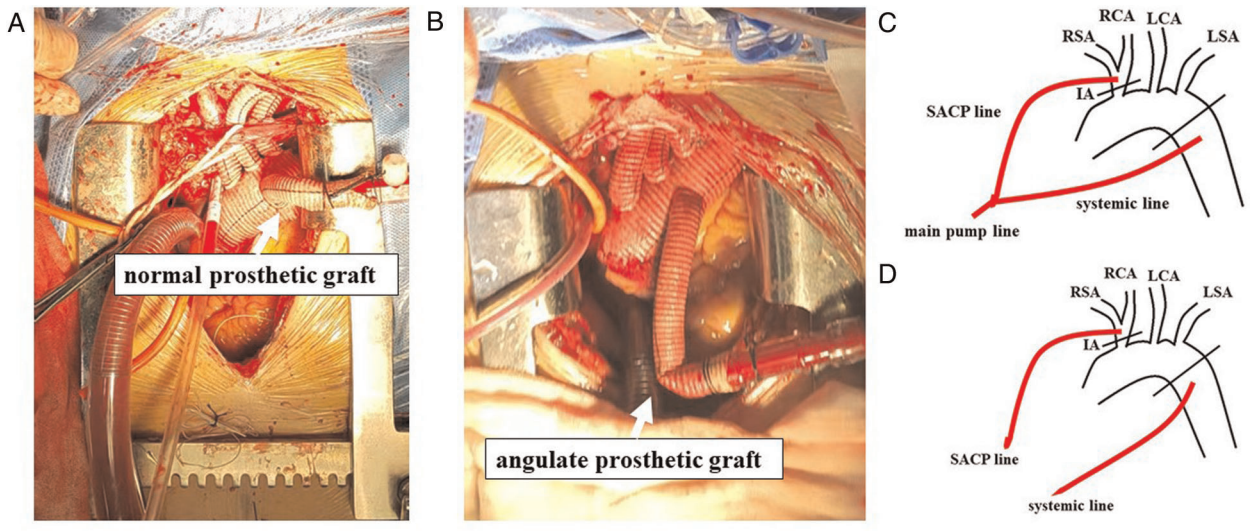

FIGURE 3
Angulated prosthetic graft and the advance of pump-controlled SACP. (**A**) A normal prosthetic graft for systemic (lower body) perfusion. (**B**) An angulated prosthetic graft for systemic (lower body) perfusion. (**C**) The main pump line split to the SACP line and the systemic line in the Control group. With the constant flow of the main pump, the decreased systemic flow caused by the angulated prosthetic graft increased SACP flow. (**D**) The main pump controlled the flow of the systemic line, while the cardioplegia pump controlled the flow of the SACP line. The angulated prosthetic graft influenced only the flow of the systemic line. The flow of the SACP line was always modulated accurately. SACP, selective antegrade cerebral perfusion; IA, innominate artery; RSA, right subclavian artery; RCA, right common carotid artery; LCA, left common carotid artery; LSA, left subclavian artery.

studies have demonstrated that BSACP offers better cerebral protection at a higher temperature (19–21). Therefore, BSACP was carried out in both groups to maintain the continuous cerebral perfusion through the innominate artery and the left common carotid artery, except when the left common carotid artery was anastomosed to the prosthetic graft. In the present study, we did not find any significant differences between the two groups, except for SACP time (53 min versus 40 min, $P = 0.001$). Because SACP time in the PC group was calculated from CA to the innominate artery anastomosed and the flow was controlled by using a cardioplegia pump throughout the process of SACP, the increased time was spent on the left common carotid and proximal aortic stump anastomosed. The routine SACP used a Y connector to separate the main arterial line to SACP and the systemic perfusion line. The flow between the SACP and the systemic perfusion line depended on the resistance of the two lines. In the Control group, SACP time was only during CA, and BSACP was initially controlled by using the main pump separately after the brachiocephalic arteries were cross-clamped. Then, the flow through the innominate artery was influenced by LBP when CA recovered, and the flow of LBP was controlled by using the main pump as well. So, the cerebral flow was unclear, leading to the possibility of "luxury" perfusion.

It is easy for a prosthetic graft to be out of shape. Thus, during surgery, some mistakes by surgeons caused the prosthetic graft to angulate, which increased the resistance of the systemic perfusion line and decreased the flow dramatically (**Figure 3**). Then, the pressure and flow of the SACP line to the innominate artery increased dramatically, which might have caused "luxury" perfusion to the brain and led to TND. This situation did not occur in the PC group because the cerebral flow was always controlled by using a separate pump. Although the prosthetic graft angulation might occur in the PC group, only the flow of LBP would decrease dramatically. The decreasing trend in the incidence of TND (5.7 versus 8.6, $P = 0.643$) might be caused by the effect of PC-SACP, which might be beneficial for cerebral protection, while also preventing "luxury" perfusion of the brain.

Limitations

This study had some limitations. First, this was a single-center retrospective study, although propensity score analysis was used to simulate randomization. Second, the small sample size, especially in the PC group, might have caused confounder bias. Third, the perioperative characteristics were insufficient, which might have influenced the evaluation of clinical outcomes. Thus, a prospective larger-sample study is necessary.

Conclusions

In this study, we found that PC-SACP in TAR was safe and feasible. This approach may be beneficial for avoiding neuroinjury caused by "luxury" perfusion.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by The Ethics Committee of General Hospital of Northern Theater Command. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL and HJ analyzed the data and drafted the manuscript. ZY and BW acquired and analyzed the data. YL and HW performed the statistical analysis and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Systematic total arch replacement with thoraflex hybrid graft in acute type A aortic dissection: A single centre experience

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Introduction: In the last two decades, a more aggressive approach has been encouraged to treat patients with acute type A aortic dissection (ATAAD), extending the repair to the aortic arch and proximal descending thoracic aorta with the frozen elephant trunk (FET) implantation. Here, we report our single-centre experience with the FET technique for the systematic treatment of emergency type A aortic dissection.

Materials and methods: Between December 2017 and January 2022, 69 consecutive patients were admitted with ATAAD; of those, 66 patients (62.9 ± 10.2 years of age, 81.8% men) underwent emergency hybrid aortic arch and FET repair with the multibranched Thoraflex hybrid graft and were enrolled in the study. Primary endpoints were 30 days- and in-hospital mortality. Secondary endpoints were postoperative morbidity and follow-up survival. To better clarify the impact of age on surgical outcomes, we have divided the study population into two groups: group A for patients <70 years of age (47 patients), and group B for patients ≥70 years (19 patients). Time-to-event analysis has been conducted using the Log-rank test and is displayed with Kaplan-Meier curves. A multiple Cox proportional Hazard model was developed to identify predictors of long-term survival with a stepwise backward/forward selection process.

Results: 30-days- and in-hospital mortality were 10.6 and 13.6%, respectively. Stroke occurred in three (4.5%) patients. Two (3.0%) patients experienced spinal cord ischemia. We did not find any statistically significant difference between the two groups in terms of main post-operative outcomes. The multivariable Cox proportional hazard model showed left ventricular ejection fraction (HR: 0.83, 95% CI: 0.79–0.92, p <0.01), peripheral vascular disease (HR: 15.8, 95% CI: 3.9–62.9, p < 0.01), coronary malperfusion (HR: 0.10, 95% CI: 0.01–0.77,

p =0.03), lower limbs malperfusion (HR: 5.1, 95% CI: 1.10–23.4, p = 0.04), and cardiopulmonary bypass time (HR: 1.02, 95% CI: 1–1.04, p = 0.01) as independent predictors of long term mortality.

Conclusions: Frozen elephant trunk repair to treat emergency type A aortic dissection appears to be associated with good early and mid-term clinical outcomes even in the elderly.

KEYWORDS

aortic arch surgery, FET, frozen elephant trunk, hybrid arch surgery, acute type A aortic dissection

Introduction

Acute type A aortic dissection (ATAAD) is one of the most dangerous and fatal cardiovascular emergencies. Aortic rupture and subsequent cardiac tamponade as well as systemic malperfusion are the most common cause of death as a result of this potentially deadly condition. In most of the cases, emergency surgery is the only therapeutic choice (1, 2). Although substantial improvements in surgical repair techniques and post-operative management have enhanced outcomes for this subset of patients, the largest registries still show high in-hospital mortality of 15–20% (3–6). Traditionally, a less aggressive approach limited to ascending aorta with or without hemiarch replacement has been adopted to reduce the surgical risk (7, 8). However, pathologic remodeling with dilation of the residual dissected aorta and subsequent risk of rupture requiring further intervention in the future may occur. Nowadays, the frozen elephant trunk (FET) technique has become a valuable alternative to treat aortic disease when the arch and the thoracic aorta are involved, both in elective and emergency settings (9–12). Particularly, in acute aortic dissection, the use of FET can lead to expansion and stabilization of the true lumen and can cover eventual additional tears in the stented part of the aortic arch or proximal descending thoracic aorta (DTA) (13, 14). Despite these potential advantages, only a restricted number of institutions have employed this procedure to treat aortic dissection (15–33).

Abbreviations: AKI, acute kidney injury; ATAAD, acute type A aortic dissection; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; CVA, cerebro-vascular event; CVVH, continuous veno-venous haemofiltration; DSINEs, distal stent graft induced new entries; DTA, descending thoracic aorta; eGFR, estimated glomerular filtration rate; FET, frozen elephant trunk; HCA, hypothermic circulatory arrest; LCA, left common carotid artery; LOS, length of stay; LSA, left subclavian artery; SD, standard deviation; TEVAR, thoracic endovascular aortic repair.

The aim of this study is to review our systematic experience with arch reconstruction and the FET technique for patients presenting with acute type A dissection. A secondary aim is to evaluate the impact of age on the postoperative outcome after this type of surgery.

Materials and methods

Study population and definitions

This is a single-center, retrospective, observational study based on prospectively collected data obtained from institutional cardiac surgery dataset at the University Hospital San Giovanni di Dio and Ruggi d'Aragona, Salerno, Italy. The study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional board approval was obtained for the study, and patient consent was waived. Between December 2017 and January 2022, 69 consecutive patients presented at our unit with the diagnosis of ATAAD. The Glasgow Coma Scale was used to assess the level of consciousness, and patients were classified into the following 3 subgroups based on their Glasgow Coma Scale scores: severe, 3–8; moderate, 9–12; and mild, 13–15 (34). We did not perform AAAD repair in patients whose severe coma persisted for more than 10 h. There was only 1 non-operative management patient in this study period. Two patients were treated with a more conservative approach (ascending aorta and hemiarch replacement) due to extremely poor general conditions at presentation. All the other 66 patients underwent repair with the FET technique using Thoraflex hybrid (Terumo Aortic, Scotland) prosthesis and were enrolled in the present study. Fifty-four (81.8%) were male and the mean age was 62.8 (±10.1) years. All the surviving patients were followed-up until May 2022. Patient demographics are summarized in Table 1. To better clarify the impact of age on surgical outcomes, we have divided the study population into two groups: group A for patients <70 years of age (47 patients) and group B for patients ≥70 years (19 patients, Table 1). Emergency surgery was defined as surgery conducted within 24 h of

TABLE 1 Preoperative characteristics.

Characteristics	Overall (66)	Group A (47)	Group B (19)	*p*-value
Age (years)	62.9 (10.2)	58 (7.9)	75 (3)	<0.001
Male gender	54 (81.8)	41 (87.2)	13 (68.4)	0.089
COPD	13 (19.7)	11 (23.4)	2 (10.5)	0.3
History of hypertension	57 (86.4)	41 (87.2)	16 (84.2)	0.7
CKD	6 (9.1)	6 (12.7)	0	na
History of cancer	3 (4.5)	2 (4.2)	1 (5.3)	>0.9
Diabetes mellitus	7 (10.6)	4 (8.5)	3 (15.7)	0.4
Peripheral vascular disease	8 (12.1)	4 (8.5)	4 (21.0)	0.2
Previous cardiac surgery	3 (4.5)	1 (2.1)	2 (10.5)	0.2
Previous cerebrovascular accident	1 (1.5)	1 (2.1)	0	na
Left ventricle ejection fraction (perc.)	57 (6.3)	57.4 (7.3)	59.1 (4.2)	0.28
Bicuspid aortic valve	1 (1.5)	1 (2.1)	0	na
Marfan syndrome	1 (1.5)	1 (2.1)	0	na
Coronary malperfusion at presentation	10 (15.2)	6 (12.8)	4 (21.0)	0.5
Preoperative hemoglobin level (g/dl)	12.7 (1.7)	13.1 (1.6)	11.9 (1.8)	0.017
eGFR	68.1 (27.5)	67.3 (27.7)	70.1 (27.8)	0.14
Cerebral malperfusion at presentation	8 (12.1)	4 (8.5)	4 (21.0)	0.2
Abdominal malperfusion at presentation	11 (16.7)	9 (19.1)	2 (10.5)	0.5
Lower limb ischaemia at presentation	7 (10.6)	6 (12.8)	1 (5.3)	0.7
Penn classification				0.8
Aa	32 (48.5)	23 (48.9)	9 (47.3)	
Ab	21 (31.8)	16 (34.0)	5 (26.3)	
Ac	6 (9.1)	4 (8.5)	2 (10.5)	
Abc	7 (10.6)	4 (8.5)	3 (15.8)	
Preoperative lactate level	1.68 (1.48)	1.62 (1.33)	1.84 (1.8)	0.7

Group A: age at surgery <70 years; group B: age at surgery ≥ 70 years; COPD, Chronic Obstructive Pulmonary Disease; CKD, Chronic Kidney Disease; eGFR: estimated glomerular filtration rate. Data are reported as mean (SD) for numerical variables and as count (%) for categorical variables.

unscheduled admission. Patients were considered to have a chronic obstructive pulmonary disease (COPD) if they had any of the following conditions: long-term use of bronchodilators or steroids for lung disease before admission; outpatient visits including a diagnosis of COPD; and preoperative lung function test with evidence of an obstructive pattern, Patients were considered to have diabetes if they had any of the following conditions: receipt of insulin or oral hypoglycemic medications before admission; outpatient visits including a diagnosis of diabetes mellitus on two occasions; or a previous inpatient stay with a discharge diagnosis of diabetes mellitus. Cardiogenic shock was defined as a preoperative systolic blood pressure <90 mmHg or a cardiac index <2.0 l/min/m2 at arrival. Malperfusion syndromes were defined as symptoms due to disrupted blood flow to the coronary arteries, central nervous system, or peripheral arteries. Any patient with neurological symptoms or syncope that was apparently caused by cardiogenic shock was excluded from the classification of cerebral malperfusion (35).

Thoraflex hybrid FET graft and size selection

The Thoraflex hybrid is a vascular graft designed for complex aortic arch surgery. It consists of a proximal not-stented tubular gelatin-coated Dacron graft and a distal polyester-made stent-graft with a self-expandable nitinol stent, which is deployed anterogradely into the aortic arch/DTA during circulatory arrest. The hybrid prosthesis has four integrated lateral branches: three on the dorsal side for the single reimplantation of supra-aortic vessels and one on the ventral side for systemic perfusion. Between the two portions, there is a sewing collar that makes the distal anastomosis of the prosthesis to the aortic arch wall easier. The Thoraflex hybrid comes in different sizes: the proximal part diameter varies from 22 to 32 mm, and the stented part from 24 to 40 mm. Two different distal lengths are available: 100 and 150 mm. The combination of the varied sizes and lengths allows us to tailorize the graft to the patient's anatomy and pathologic condition. In our series, the

decision on stented graft size was figured out by the total aortic diameter and relative diameters of the true and false lumen at the level of the landing zone, based on the exact evaluation of preoperative CT angiogram of the aorta for the entire cohort of patients. No oversizing was performed to reduce the risk of rupture or distal stent graft-induced new entries (DSINEs). To minimize the risk of spinal cord ischemia, we only implanted the 100 mm length stented graft.

Surgical technique

Our "debranching first" FET technique (Figure 1) has already been described in earlier reports (36, 37). The usual incision was normally extended in a small bilateral supra-clavicular cervicotomy to improve access to the epiaortic vessels. The right subclavian artery (isolated from anterior mediastinum) or the right axillary artery (isolated in the right sub clavicular region) were routinely employed as the arterial site for central cannulation. In all cases, an end-to-side Dacron vascular graft (8 or 10 mm, depending on the native vessel size) was interposed to avoid direct cannulation of the artery. The right atrium and right superior pulmonary vein were cannulated for venous return and left ventricle venting. A home-made 4-branched perfusion circuit was used for extracorporeal circulation. Cooling to 26, 28°C for hypothermic circulatory arrest was employed in all cases. During the first cooling phase, from a beating heart, the left common carotid artery (LCCA) and the left subclavian artery (LSA) were isolated and prepared for selective cannulation with the interposition of a vascular Dacron graft. The vessel perfusion was sequentially started to achieve complete antegrade "trilateral" cerebral perfusion before clamping the ascending aorta. After debranching completion, at 30°C core temperature, the ascending aorta was cross-clamped and opened and cardioplegia was administered. A single dose of Custodiol® cardioplegia was routinely administered selectively in the coronary ostia. The proximal aortic valve and root reconstruction were performed in different manners as required by the case as shown in Table 2. At a temperature of 26–28°C, the brachiocephalic artery was clamped and the selective antegrade perfusion began at 10–15 ml/kg/min, to stop the systemic circulation. The aortic arch was then opened and inspected. The landing zone (usually zone 2) was reinforced with internal and external teflon strips. At this stage, the distal stent graft of the Thoraflex hybrid was released into the DTA. The strengthened collar of the prosthesis was sutured to the aorta, and, after cannulation of the fourth lateral branch and accurate de-airing, systemic perfusion was resumed, starting to rewarm the body. In the last 19 cases, to reduce lower body ischemia time, a blood flow of around 1,200 ml for spinal and splanchnic perfusion was started through the lateral branch of the Thoraflex hybrid even before completing the collar's anastomosis. The anastomosis between the hybrid prosthesis and sino-tubular junction (either native or prosthetic, depending on the proximal repair) was then completed and the cross-clamp was released. The prosthesis-elongated supra-aortic vessels were then termino-terminally re-anastomosed to the corresponding branches of the Thoraflex hybrid, starting with the LSA to LCCA and finally at the brachiocephalic artery.

Endpoints

The primary endpoints of the study were 30-days and in-hospital mortality, defined as death due to any cause during the postoperative course at 30 days and until discharge, respectively.

Secondary endpoints included postoperative stroke (defined as clinical and radiological evidence of a new postoperative cerebrovascular event -CVA-), spinal cord injury, return to the operating room for cardiac causes, renal failure requiring replacement therapy, respiratory insufficiency requiring prolonged ventilation and/or tracheostomy, deep sternal wound infection involving sternal bone and/or mediastinal structures, recurrent laryngeal nerve palsy, and in-hospital length of stay.

Statistical analysis

Data are presented as mean and standard deviation (SD) for continuous numerical variables and as count and percentages for categorical variables. Numerical variables have been compared using the Student *t*-test or Mann-Whitney U test, while categorical variables have been compared with the chi-square test or Fisher exact test as appropriate. Time-to-event analysis has been conducted using the Log-rank test and displayed with Kaplan-Meier curves. A multiple Cox proportional Hazard model was developed to identify predictors of long-term survival with a stepwise backward/forward selection process. The alpha error was set at 0.05 for significance and all tests are two-sided. Missing values were screened before analysis: every variable with more than 5% of the missing value was eliminated from the final dataset. The remaining variables were imputed using simple imputation models. The statistical analysis was conducted with R version 3.6.0 (2019-04-26) (38).

Results

The mean follow-up was 19.7 ± 17.4 months. The distributions of baseline characteristics for the overall population are presented in Table 1. Three (4.5%) patients had already undergone cardiac surgery. Thirty-six patients (54.5%) were presented with peripheral malperfusion. Particularly, 10 (15.2%) patients were presented with coronary malperfusion, 8 (12.1%) patients with cerebral malperfusion, 11 (16.7%) with abdominal malperfusion, and 7 (10.6%) patients with peripheral

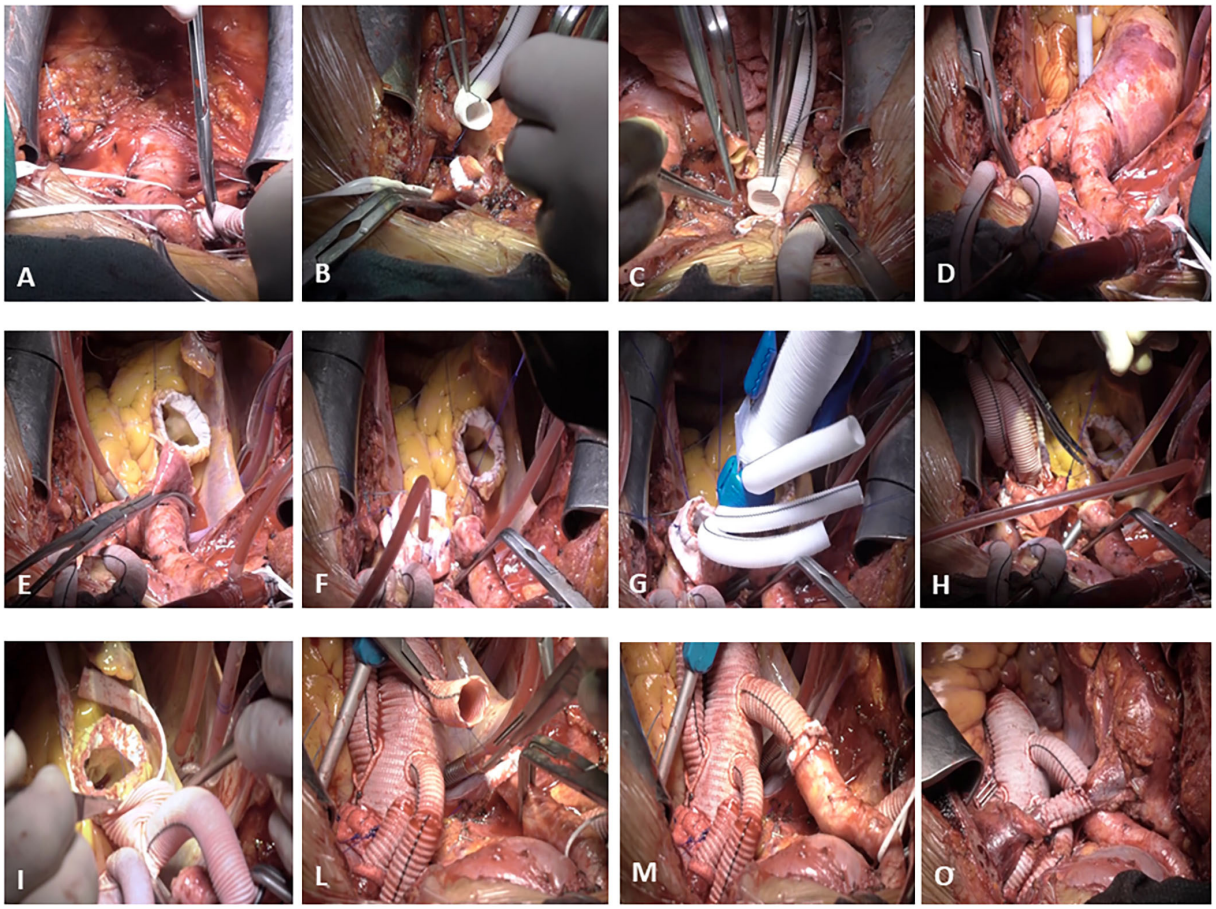

FIGURE 1
De-branching first surgical technique. The right subclavian artery is isolated from the anterior mediastinum and an end-to-side Dacron vascular graft (8 or 10 mm, depending on the native vessel size) is interposed to avoid direct cannulation of the artery **(A)**. During the first cooling phase, from a beating heart, the left common carotid artery (LCCA) **(B)** and the left subclavian artery (LSA) **(C)** are isolated and prepared for selective cannulation with the interposition of a vascular Dacron graft. After the completion of debranching **(D)**, the ascending aorta is cross-clamped and opened, cardioplegia is administered, and the proximal aortic valve and root reconstruction are performed in different manners as required by the case **(E)**. The brachiocephalic artery is clamped, the aortic arch is then opened and inspected, and the landing zone (usually zone 2) is reinforced with internal and external teflon strips **(F)**. At this stage, the distal stent graft of the Thoraflex hybrid is released into the DTA **(G)**. The strengthened collar of the prosthesis is sutured to the aorta **(H)**, and, after cannulation of the fourth lateral branch and accurate de-airing, a systemic perfusion is resumed. The anastomosis between the hybrid prosthesis and sino-tubular junction (either native or prosthetic, depending on the proximal repair) is then completed **(I)** and the cross-clamp is released. The prosthesis-elongated supra-aortic vessels are then termino-terminally re-anastomosed to the corresponding branches of the Thoraflex hybrid **(L)**, starting with the LSA to LCCA and finally to the brachiocephalic artery **(M)**. Finally, the anonymous vein is reconstructed with the interposition of an 8 mm Dacron vascular graft **(O)**.

limb ischemia. According to the Penn classification (39) for the overall study cohort, 32 (48.5 %) patients were in class Aa, 21 (31.8%) were in class Ab, 6 (9%) patients were in class Ac, and 7 (10.6%) patients were in class Abc. There were no significant differences in terms of significant preoperative comorbidities and clinical presentation between the groups, A (<70 yrs old) and B (≥ 0 yrs old). The Penn classification did not differ between the two groups with 49 vs. 47% patients in class Aa, 34 vs. 26% in class Ab, 8.5 vs. 11% in class Ac, and 8.5 vs. 16% in class Abc (group A vs. group B respectively, $p = 0.8$). However, patients in group A were more frequently male (87 vs. 68%, $p = 0.089$) and had higher preoperative hemoglobin levels (13.1 ± 1.6 vs. 11.9 ± 1.8, $p = 0.017$). No deaths were recorded during the procedure. Operative characteristics and their distributions among the two groups are shown in Table 2. Concomitant procedures were needed in 32 (48.5%) patients: 11 (16.7%) coronary artery bypass grafting, 4 (6.0%) aortic valve replacement, 17 (25.7%) aortic root surgery, such as 12 (18.2%) Florida sleeve procedures and 5 (7.6%) modified Bentall. There was no difference between the two groups in terms of cardiopulmonary bypass time (205.1 ± 43.5 min in group A vs. 203 ± 50.3 min in group B, $P = 0.7$) and aortic cross-clamp time (118 ± 35.8 min in group A vs. 108 ± 36.9 min in group B, P = 0.2) However, the mean moderate hypothermic

TABLE 2 Operative characteristics.

	Overall (66)	Group A (47)	Group B (19)	*p*-value
CPB time (min)	204.5 (45.2)	205.1 (43.5)	203 (50.3)	0.7
Aortic cross-clamp time (min)	115.1 (36.1)	118 (35.8)	108.1 (36.9)	0.2
HCA time (min)	28.7 (6.9)	30 (6.1)	25.5 (7.9)	0.046
Intraoperative lactate level (peak)	5.7 (2.8)	5.4 (2.2)	6.5 (3.8)	0.6
Concomitant procedures				
CABG	11 (16.6)	6 (12.8)	5 (26.3)	0.3
AV replacement	5 (7.6)	4 (8.5)	1(5.3)	0.4
Aortic root surgery				
Florida Sleeve	12 (18.2)	9 (19.1)	3 (15.8)	0.9
Modified Bentall	5 (7.6)	3 (6.4)	2 (10.5)	0.6

Group A: age at surgery <70 years; group B: age at surgery ≥ 70 years; CPB, Cardiopulmonary Bypass; HCA, Hypothermic Circulatory Arrest (including selective antegrade cerebral and visceral perfusion); CABG, Coronary Artery Bypass Graft; AV, Aortic Valve. Data are reported as mean (SD) for numerical variables and as count (%) for categorical variables.

TABLE 3 Post-operative outcomes.

	Overall (66)	Group A (47)	Group B (19)	*p*-value
30-days mortality	7 (10.6)	3 (6.4)	4 (21.0)	0.1
In-hospital mortality	9 (13.6)	4 (8.5)	5 (26.3)	0.11
ITU LOS (days)	15 (16.4)	15.3(16.9)	14.4 (15.4)	>0.9
In-hospital LOS (days)	27.7 (21.7)	27.5 (20.7)	28.3 (24.6)	0.78
Return to operating room	6 (9.1)	5 (10.6)	1 (5.3)	0.7
Prolonged ventilation	26 (39.3)	15 (31.9)	11 (57.9)	0.05
Respiratory failure	39 (59.1)	28 (59.6)	11 (57.9)	0.9
Tracheostomy	19 (28.8)	12 (25.5)	7 (36.8)	0.4
Pericardial effusion requiring drainage	15 (22.7)	11 (23.4)	4 (21.0)	>0.9
Pleural effusion requiring drainage	20 (30.3)	14 (29.8)	6 (31.6)	0.8
Deep sternal wound infection	7 (10.6)	4 (8.5)	3 (15.7)	0.4
Recurrent laryngeal nerve palsy	6 (9.1)	5 (10.6)	1 (5.3)	>0.9
AKI requiring CVVH	20 (30.3)	16 (34.0)	4 (21.0)	0.3
Spinal cord injury/paraplegia	2 (3.0)	1 (2.1)	1 (5.3)	0.069
Permanent CVA	3 (4.5)	1 (2.1)	2 (10.5)	0.2
Lower limb ischaemia	2 (3.0)	1 (2.1)	1 (5.3)	0.5

Group A: age at surgery <70 years; group B: age at surgery ≥ 70 years; ITU, Intensive Therapy Unit; LOS, Length of stay; CO, Cardiac Output; AKI, Acute Kidney Injury; CVVH, Continuous Veno-Venous Haemofiltration; CVA, Cerebrovascular Accident. Data are reported as mean (SD) for numerical variables and as count (%) for categorical variables.

circulatory arrest time with a selective antegrade trivascular cerebral perfusion was significantly higher in group A (30 ±6.1 min in group A vs. 25.5 ± 7.9 min in group B, P = 0.046). Postoperative outcomes are summarized in Table 3. 30 days mortality was 10.6% for the entire cohort of patients (6.4% in group A vs 21% in group B, $P = 0.1$). Cumulative in-hospital mortality was 13.6% (8.5% in group A vs. 26% in group B, $P = 0.11$). No differences were found in terms of postoperative CVA (2.1% in group A vs. 10.5% in group B, $P = 0.2$), spinal cord injury (2.1% in group A vs. 5.3% in group B, $P = 0.069$) and AKI requiring hemodialysis (34% in group A vs. 21% in group B, P = 0.3). Also, the incidence of reopening for bleeding (10.6 vs. 5.3%, P=0.7), deep sternal wound infection (8.5 vs. 15.8%), respiratory failure requiring tracheostomy (25.5 vs 36.8%, P=0.4), and laryngeal nerve palsy (10.6 vs. 5.3%) did not differ among the two groups.

Overall survival for the entire cohort at 3, 6, 12, and 24 months was 85, 80.3, 76.5, and 74.4% respectively (Figure 2). Survival rates by group were 91 vs. 73.7% at 3 months, 85.6 vs. 68% at 6 months, 79.9 vs. 68% at 12 months, and 77 vs. 68% at 24 months, all group A vs. group B, respectively (Figure 3).

The multivariable Cox proportional hazard model (Table 4) showed left ventricular ejection fraction (HR: 0.83, 95% CI: 0.79–0.92, $p < 0.01$), peripheral vascular disease (HR: 15.8, 95% CI: 3.9–62.9, $p < 0.01$), coronary malperfusion (HR: 0.10, 95% CI: 0.01-0.77, p =0.03), lower limbs malperfusion (HR: 5.1, 95% CI:

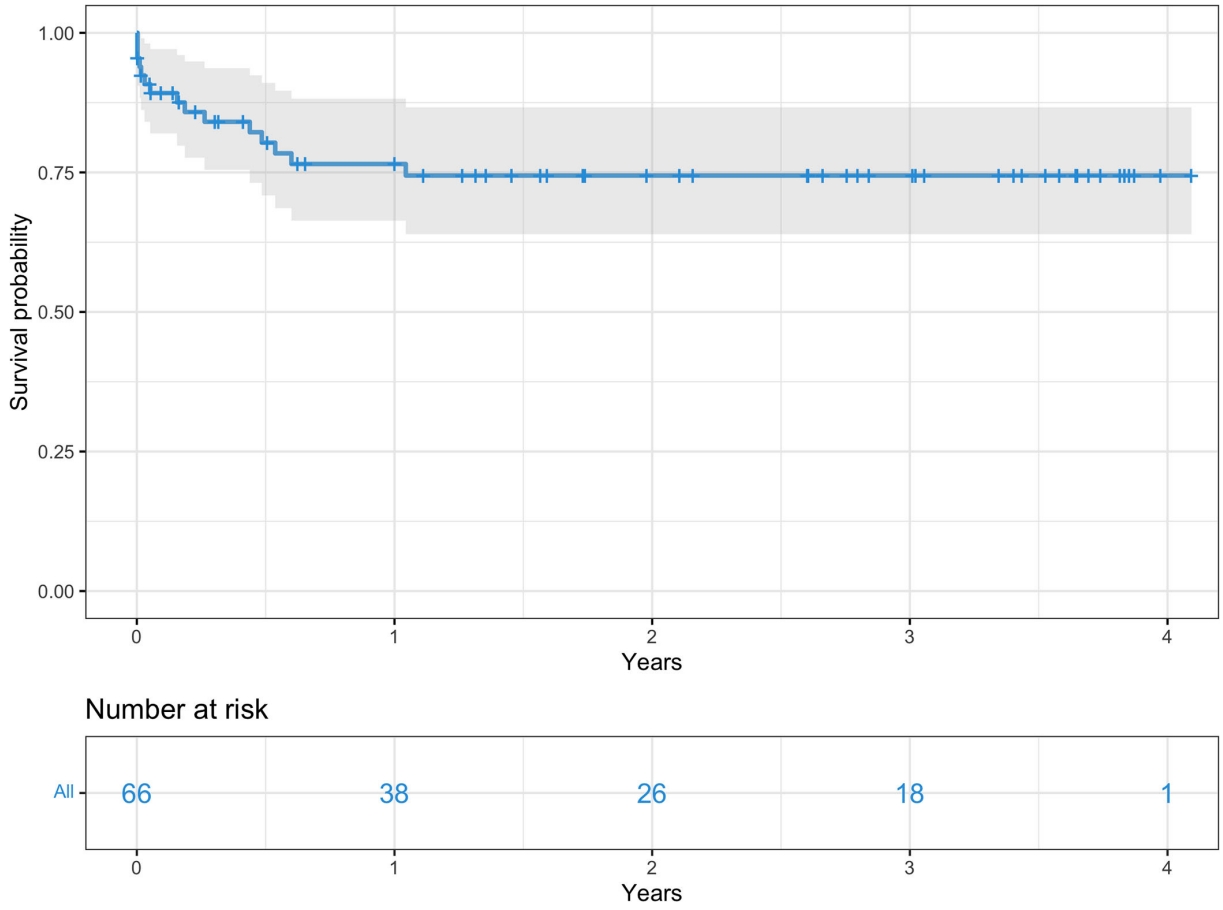

FIGURE 2
Kaplan-Meier survival curve for the overall surgical population.

1.10–23.4, $p = 0.04$), and cardiopulmonary bypass time (HR: 1.02, 95% CI: 1 – 1.04, $p = 0.01$) as independent predictors of long term mortality.

All survived patients underwent clinical and imaging follow-up until May 2022. According to our protocol, a postoperative CT angiogram was planned at 3, and 12 months after surgery and once yearly for the following 2 years. During this period, 11 patients required further aortic interventions: 10 patients (eight in group A and two in group B) underwent endovascular extension of the stent graft (TEVAR) using Relay Plus (Terumo Aortic, Scotland) covered endograft due to partial false lumen thrombosis/negative aortic remodeling as defined by Shesthra et al. (12). One patient developed a pseudoaneurysm at the level of proximal anastomosis which was successfully treated by positioning a vascular plug percutaneously under fluoroscopy *via* the right femoral artery. Freedom from aortic reinterventions for the entire cohort at 6, 12, and 24 months was 97, 92.2, and 80.6%, respectively (Figure 4); if considered by the group, freedom from aortic re-intervention rate was 97.9 vs. 100% at 6 months, 88.8 vs. 100% at 12 months and 78.1 vs. 88.2% at 24 months, all group A vs. group B, respectively (Figure 5).

Discussion

There is an ongoing discussion about the most appropriate management of the aortic arch in the context of ATAAD, and particularly whether the FET technique should be consistently and systematically employed to treat these patients regardless of the primary involvement of the arch itself in the pathologic process. Our series proves that systematic use of the FET technique in an emergency setting to treat patients with ATAAD is feasible with good short-term and mid-term outcomes. In our study, 30-days and in-hospital mortality, CVA, and spinal cord injury were overall satisfactory and in line with the range reported in a contemporary review of literature recently published by our group where the FET technique was used as a surgical procedure in such complex setting (15). These results are even superior if compared to the data reported by recent

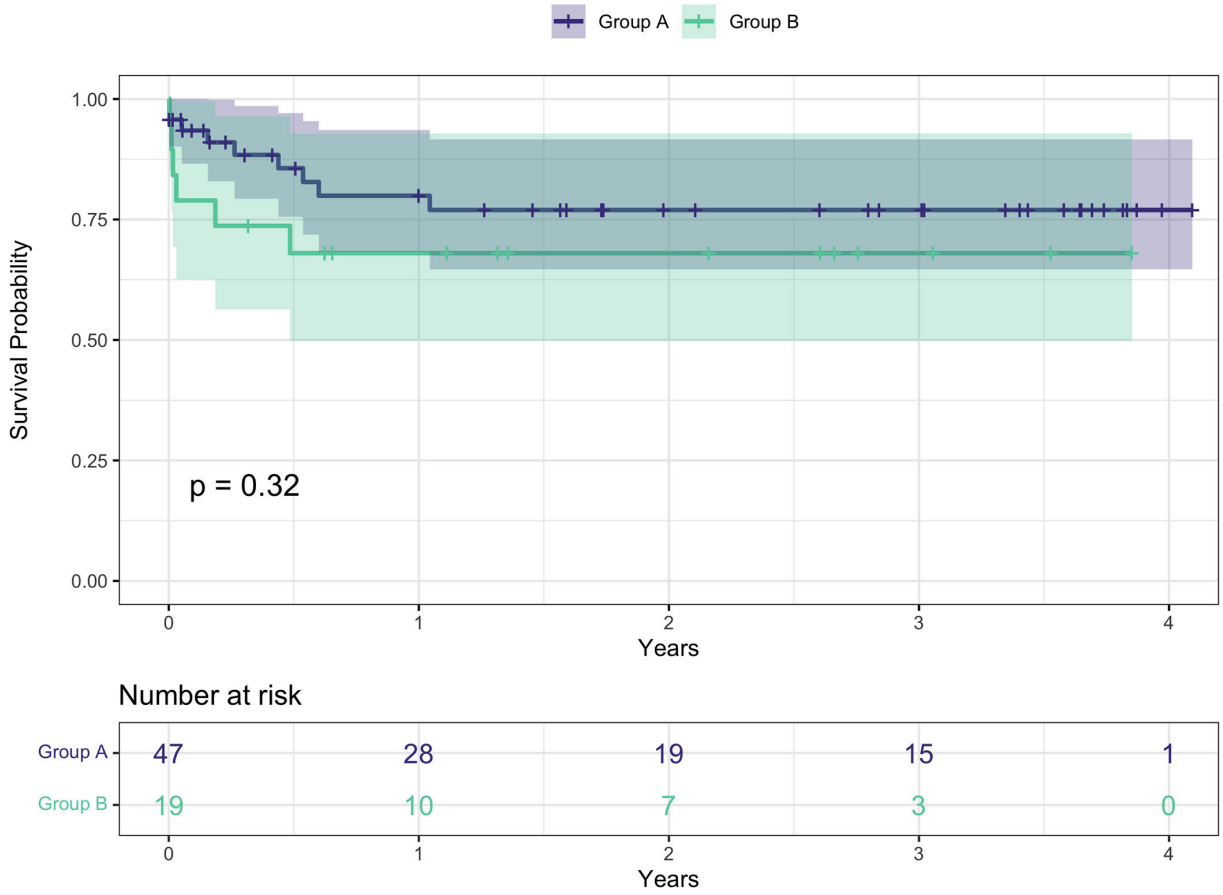

FIGURE 3
Kaplan-Meier survival curves between the two groups. Group A: age at surgery <70 years; group B: age at surgery ≥ 70.

reports of international registries where a more conservative approach with ascending aorta and hemiarch replacement was employed (3–5, 9).

Our experience with FET using Thoraflex hybrid in an emergency setting has been overall satisfactory; technical success was achieved in all patients. We did not pay attention to the physiological learning curve of this systematic approach in an acute setting with bad surgical results even in the first part of our experience. Correct cerebral perfusion during the hypothermic circulatory arrest is one of the main aspects determining neurological outcomes. As already reported, we believe that our peculiar "debranching first" strategy, as well as the trilateral selective antegrade cerebral perfusion during a moderate hypothermic circulatory arrest, is important to explain our particularly satisfactory results in terms of neurological complications, with a low overall incidence of permanent stroke (4.5%) compared to data from similar studies (36). This peculiar strategy allows uniform cerebral perfusion throughout the operation, except for the brief time needed for LCCA and LSA anastomosis, thus minimizing the cerebral ischemia time.

In our opinion, the claimed technical difficulties of this technique should not stop surgeons from adopting this surgical strategy in an acute setting, especially if a specialized centre with a high volume of aortic surgery is identified on a regional basis to receive and treat acute aortic syndrome (40–42). From a technical point of view, we believe that the FET hybrid prostheses, such as Thoraflex hybrid help to reduce the risk of aortic arch surgery in this context, by avoiding the need of performing a challenging distal anastomosis deeply at the level of the proximal DTA, where the risk of bleeding or rupture mainly due to the fragile dissected aortic wall is extremely high. Several authors, adopting systematically this strategy in an emergency setting, have stressed the importance of a hybrid prosthesis to face this challenging scenario (43).

Moreover, many patients affected by ATAAD present with distal aorta malperfusion due to the true lumen compression by the false lumen; in these cases, the FET technique can potentially

TABLE 4 Multiple Cox PH model for long-term survival.

Characteristics	HR	95% CI	*P*-value
Left ventricular ejection fraction	0.85	0.78–0.92	<0.01
Peripheral vascular disease	15.8	3.9–62.9	<0.01
Coronary malperfusion	0.10	0.01–0.77	0.03
Lower limb malperfusion	5.1	1.10–23.4	0.04
Cardiopulmonary bypass time	1.02	1.00–1.05	0.01

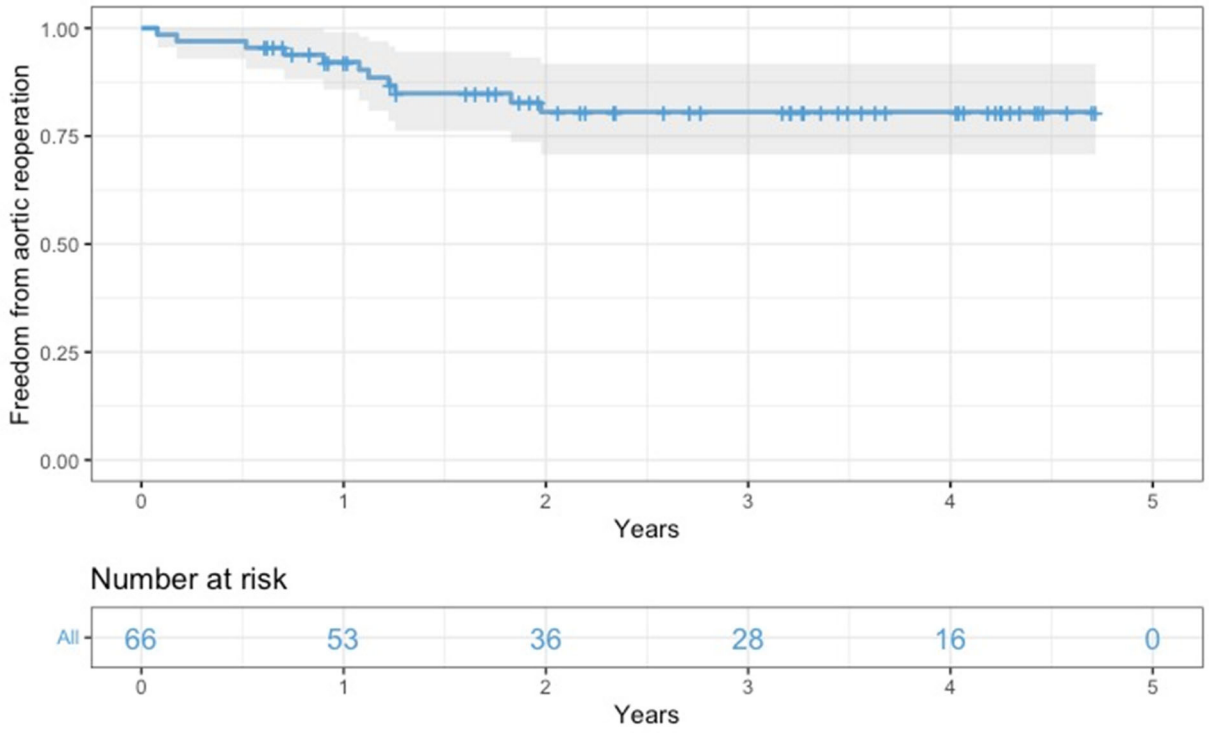

FIGURE 4
Kaplan-Meier freedom from aortic reoperations curve for the overall surgical population.

re-expand the compressed true lumen and cover supplementary entry tears at the level of the proximal DTA, which may well sustain pressurization of the false lumen, thus reverting the malperfusion and improving surgical outcomes (44).

It is well-known that aortic dissection is a progressive disease and the natural history of the distal false lumen of the aorta following a primary procedure of ascending aorta or hemiarch replacement may lead to degeneration, aneurysm, and/or rupture, thus requiring additional extensive interventions. Data from large registries and recent literature suggest that in 60 to 90% of cases, a negative remodeling of the distal aorta takes place, to the extent of requiring second-stage endovascular or open surgical completion. In acute dissection, the FET technique can reduce DTA dilatation by bringing both coverages of secondary entry tears located in the proximal DTA and obliteration of the false lumen at the proximal DTA, thus reducing aortic-related deaths and the requirement for challenging distal aortic reinterventions (45–49). In our series, only 11 patients have required further aortic interventions: 10 patients underwent endovascular extension of the stent graft (TEVAR) using Relay Plus (Terumo Aortic, Scotland) covered endograft due to partial false lumen thrombosis, and 1 patient developed a pseudoaneurysm at the level of proximal anastomosis which was successfully treated by positioning a vascular plug percutaneously under fluoroscopy *via* the right femoral artery. This aspect supports the idea that the rate of aortic reintervention is lower if compared to conventional conservative treatment. Also, the rate of success for those patients was 100%, mainly due to less complex endovascular procedures when a hybrid

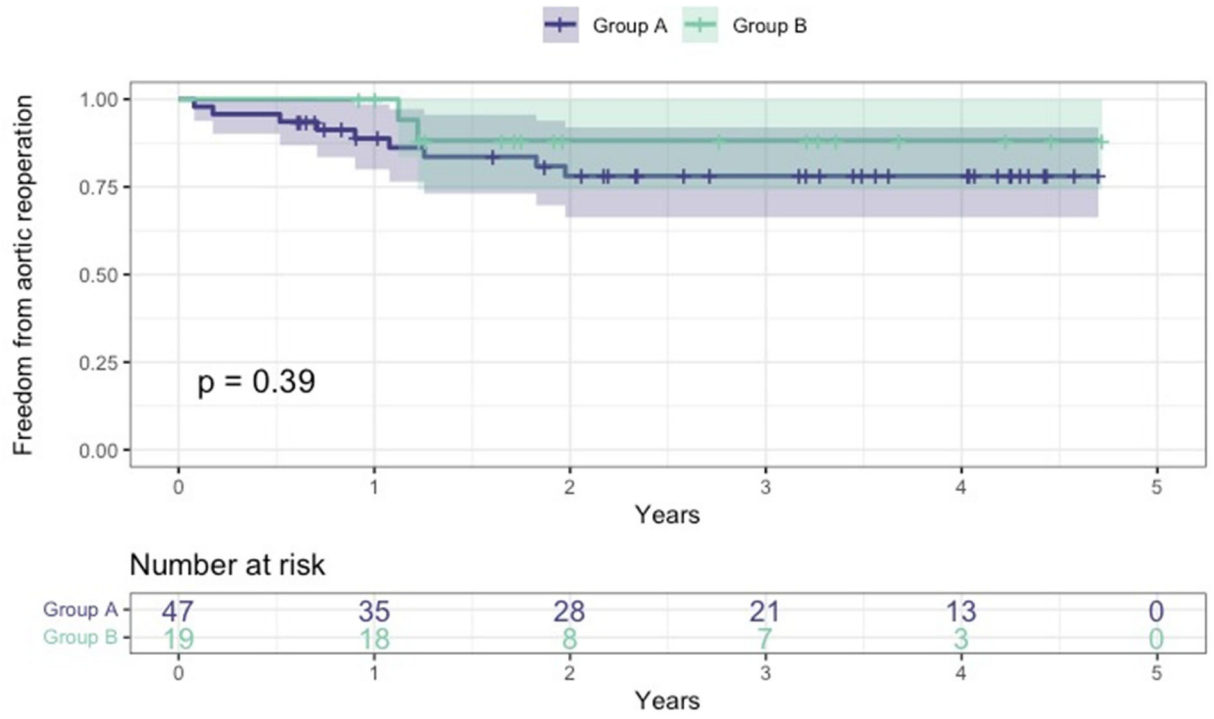

FIGURE 5
Kaplan-Meier freedom from aortic reoperation curves between the two groups. Group A: age at surgery <70 years; group B: age at surgery ≥70.

vascular prosthesis has been implanted during the first surgical treatment.

In a recent paper, Beckmann et al. (50) have reported the results of a series of patients treated for non-urgent total aortic arch replacement using the FET technique. In their study worse perioperative mortality and morbidity as well as long-term survival was proved in septuagenarians than in younger patients. For this reason, to better clarify the impact of age on our cohort of patients, we have divided our study population into two groups: group A <70 years old and group B ≥70 years old. Our results showed no significant differences both for primary and secondary outcomes, thus supporting the thesis that in an acute setting, the age above 70 years old on its own does not impact negatively on perioperative outcomes and demonstrating that the use of FET in this setting is safe and effective even in the elderly population.

Although deeper evidence on long-term benefits is still needed, we believe that patients presenting with ATAAD should be at least considered for surgical treatment using the FET technique. Surely, the condition of the patient must be taken into account in deciding which approach should be adopted to treat this condition. In fact, even if the anatomy of the dissection is suitable, total arch replacement may be not indicated, such as in significantly elderly patients or in particularly poor clinical conditions with signs and symptoms of systemic malperfusion (18). In this regard, our subanalysis based on Penn classification showed that patients in class Ac and Abc, presenting with poor haemodynamic conditions, had worse outcomes if compared to patients in class Aa and/or Ab; particularly, 30 days and in-hospital mortality were significantly higher in class Ac and Abc (see Supplementary Table E1).

Study limitations

The main limitation of this study is related to the retrospective and single-center nature of the study.

Moreover, the small number of patients included in this study represents a limitation in terms of statistical power and possible generalization of the results.

Conclusion

Hybrid aortic arch and FET repair with the Thoraflex Hybrid graft to systematically treat emergency type A aortic dissection appears to be associated with good early- and mid-term clinical outcomes even in the elderly. Our perfusional strategy with a single pump and head vessel reimplantation as the last step has proved to offer highly effective cerebral protection while

optimizing the heart and body ischemic time. Moreover, by inducing distal false lumen obliteration and thrombosis, the FET technique is likely to reduce the need for secondary procedures. Further studies to better clarify late complications are still needed.

Author's note

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Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by University Hospital San Giovanni di Dio e Ruggi d'Aragona. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design: PC, GM, VB, PM, and SI. Administrative support: EM, VB, RC, MM, EM, and MD. Provision of study materials or patients: PC, RL, MM, MC, and FC. Collection and assembly of data: PC, GM, MM, MC, MD, DT, FC, and RC. Data analysis and interpretation: PC, VB, GM, PM, RC, FC, and SI. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The evolution of arch surgery: Frozen elephant trunk or conventional elephant trunk?

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Treatment of aortic arch aneurysms and dissections require highly complex surgical procedures with devastating complications and mortality rates. Currently, repair of the complete arch until the proximal descending thoracic aorta consists of a two-stage procedure, called elephant trunk (ET) technique, or a single stage a single-stage technique referred to as frozen elephant trunk (FET). There is conflicting evidence about the perioperative results of ET in comparison with FET. We carried out a meta-analysis to investigate possible differences in perioperative and early (up to 30 days) outcomes of ET vs. FET, particularly for mortality, spinal cord injury (SCI), stroke, and renal failure. We also performed a meta-regression to explore the effects of age and sex as possible cofactors. Twenty-one studies containing data from interventions conducted between 1997 and 2019 and published between 2008 and 2021 with 3153 patients (68.5% male) were included. ET was applied to 1,693 patients (53.7%) and FET to 1460 (46.3%). Overall mortality after ET was 250/1693 (14.8%) and after FET 116/1460 (7.9%). Relative risk (RR) and 95% confidence interval (CI) were 1.37 [1.04 to 1.81], p = 0.027. There was no significant effect of age and sex. SCI occurrence after the second stage of ET was 45/1693 (2.7%) and after FET 70/1,460 patients (4.8%) RR 0.53 [0.35 to 0.81], p = 0.004. Age and sex were not associated with the risk of SCI. No significant differences were observed between ET and FET in the incidence of stroke and renal failure. Our results indicate that ET is associated with higher early mortality but lower incidence of SCI compared to FET. When studies published in the last 5 years were analyzed, no significant differences in mortality or SCI were found between ET and FET. This difference is attributed to a decrease in mortality after ET, as the mortality after FET did not change significantly over time.

KEYWORDS

elephant trunk, frozen elephant trunk, antegrade stent, aortic surgery, aortic aneurysm

Introduction

The incidence of aortic aneurysms and dissections is on the rise during the last two decades and can affect between 2 and 6 out of 100,000 people every year (1–4).

Aortic arch dissections arise from intimal tears within an aneurysm and are highly deadly with a mortality rate reaching up to 80% if there is a rupture. The risk of dying is around 21% for patients who reach the hospital alive (5, 6).

With increasing incidence and high mortality, there is a need for better management and treatment of both aortic aneurysms and dissections.

Aneurysms are permanent dilatations of the aorta with at least 50% increase of the expected normal diameter of the aorta. Dissections are highly fatal conditions in which disruptions (tears) of the aortic intimal layer cause rushing of blood within the vessel wall, forcing the layers to dissect (7). Aneurysms can occur without dissections and vice versa (7, 8). Current guidelines indicate that "total aortic arch replacement with or without an elephant trunk extension is indicated when a tear within the arch extends into the proximal descending aorta or extends throughout the arch on the greater curve's aspect, i.e., involves separation or disruption of the Ostia of the brachiocephalic vessels, precluding the ability to reconstruct a neomedia effectively" (9).

Treatment of both dissections and aneurysms in the aortic arch can be done with a two-stage surgical technique called "elephant trunk" (ET) (10). The first stage of ET involves a sternotomy and a reconstruction of the ascending aorta and the aortic arch. At the second stage, a floating extension (elephant trunk) in the descending aorta is used in order to extend the repair toward descending thoracic aorta. An important limitation of this technique is the fact that almost half of the patients that undergo the first step, never arrive at the second step, usually because they die or because they refuse a second operation (11).

The evolution of surgical and endovascular techniques has resulted in the development of a composite prosthesis, known as the "Frozen elephant trunk" (FET) (9, 11). In this technique a stent graft is implanted in the proximal descending thoracic aorta through the aortic arch prosthesis, during the primary procedure (9).

The use of FET instead of the conventional ET is increasing in the last years. However, there is contrasting evidence about which intervention has less complications and whether a real difference exists in their outcomes (12, 13).

Our aim in this meta-analysis was to assess the outcomes of the two techniques for Debakey type I or Stanford type A aortic dissections. We also analyzed separately the data from papers published during the last 5 years (2017–2021) in order to detect possible different outcomes, as newer devices are being developed and techniques evolved (14).

Materials and methods

Search strategy

The literature search was performed in accordance with the principles of the Cochrane Handbook (8) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15, 16).

An unrestricted literature search was performed in PubMed, Web of Science, Scopus, and the Cochrane library.

The search aimed at finding articles reporting outcomes in patients undergoing aortic arch surgery with ET or FET and contained separate relevant data for each type of intervention.

A systematic search was conducted in PubMed combining MeSH and free terms for the clinical situations, the treatments, and the outcomes. An additional search was conducted in the references of the examined articles.

The search strategy was designed by two authors (AM and JR), and their decisions were approved by a third author (SG). The literature search was performed by one author (AM). The eligibility of the selected articles eligibility and the risk of bias were assessed independently by two independent reviewers (EN, EB). The Risk of Bias in Non-randomized Studies-of Interventions (ROB-INS-I) tool (17) was used by two reviewers (GP and OP) for the assessment of bias of each study. A third reviewer (JGM) resolved any possible differences in the assessment.

The following domains were examined in each study for the risk of bias, according to the Cochrane Handbook: (1) in the confounding; (2) in the participant selection of each study; (3) in the classification of interventions; (4) in cases of deviations from intended interventions; (5) in cases of missing data; (6) in

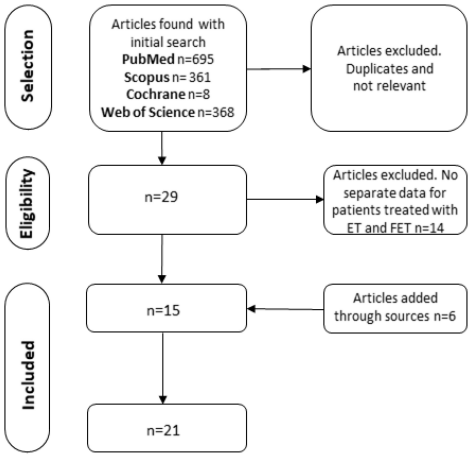

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the article selection process. ET, elephant trunk; FET, frozen elephant trunk.

the estimation of outcomes; (7) in the selection of the result to be reported; and (8) overall assessment of bias. The Risk-of-Bias VISualization (robvis) software was used for producing the plot for ROBINS-I (17).

Selection process

The following inclusion criteria were used for the selection of articles: (1) human studies; (2) full research articles containing data on the outcomes of both ET and FET and (3) studies including at least 10 patients.

The exclusion criteria for the article selection were: (1) non-human studies, (2) case reports, (3) previous reviews and/or meta-analyses, (4) editorials, and (5) studies without adequate demographic and/or outcome information on both ET and FET interventions, and (6) studies in languages other than English.

Quality assessment

A rating scale based on the Downs and Black checklist for measuring was used for assessing the quality of included studies (18). The assessment was done using a version with 18 items. The items were ranked with the use of a binary score (0 or 1) except for two items that were rated on a scale from 0 to 2 and from 0 to 5, respectively.

The ratings were collected by two independent researchers (AIM and JLRR). A third reviewer (OP) resolved divergences and quantified the ratings with the use of Cohen's kappa (19).

Statistical analysis

The R software v. 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for conducting the meta-analysis. The relative risk (RR) was used as index statistics. The results of RR are presented with two decimal points followed by the 95% confidence interval (CI) in brackets in the form: RR (lower CI, upper CI). As heterogeneity among studies was expected, the random effects model was used. The statistical inconsistency Higgin's I^2 test was used for the evaluation of heterogeneity (20). I^2 values $>$ 75% were considered to have high heterogeneity and I^2 values $<$ 40% were considered to have low heterogeneity. The Egger's test of the intercept was used for assessing publication bias. A meta-regression analysis was conducted in order to assess the impact of the potential interaction factors, such as age and sex p-values $<$ 0.05 were considered statistically significant.

TABLE 1 Studies included in the meta-analysis.

Study #	References	Clinical situation (as reported)	Study type	Centers	Period	Total patients (n)
1	Jakob et al. (27)	Acute DeBakey type I dissection	Retrospective observational	1	2001–2007	45
2	Pochettino et al. (34)	Acute DeBakey I dissection	Retrospective observational	1	2005–2008	78
3	Uchida et al. (39)	Acute type A aortic dissection	Retrospective observational	1	1997–2008	120
4	Sun et al. (38) acute	Type A aortic dissection acute	Retrospective observational	1	2003–2008	214
5	Sun et al. (38) chronic	Type A aortic dissection chronic	Retrospective observational	1	2003–2008	197
6	Hofferberth et al. (25)	DeBakey type I dissection	Retrospective observational	1	2003–2011	37
7	Leontyev et al. (29)	Total aortic arch replacement	Retrospective observational	1	2003–2011	171
8	Di Eusanio et al. (22)	Extensive aortic aneurysm	Retrospective observational	2	2003–2011	57
9	Preventza eyt al. (35)	Acute type I aortic dissection	Retrospective observational	1	2005–2012	112
10	Vallabhajosyula et al. (40)	Acute DeBakey type I aortic dissection	Retrospective observational	1	2005–2012	242
11	Shrestha et al. (37)	Total aortic arch replacement	Retrospective observational	1	2001–2013	277
12	Matt et al. (30)	acute type A aortic dissection	Prospective observational	1	2010–2016	74
13	Preventza et al. (36)	Chronic dissecting and atherosclerotic aneurysms	Retrospective observational	1	2010–2015	129
14	Alhussaini et al. (21)	Aortic arch repair	Retrospective observational	1	2003–2016	118
15	Furutachi et al. (23)	Type A acute aortic dissection	Retrospective observational	1	2010–2018	50
16	Inoue et al. (26)	Type A acute aortic dissection	Retrospective observational	1	2012–2018	148
17	Mkalaluh (31)	Total arch replacement	Retrospective observational	1	2001–2017	50
18	Mutsuga et al. (32)	Total arch replacement	Retrospective observational	1	1997–2015	91
19	Hage et al. (24)	Aortic arch repair	Retrospective observational	9	2002–2018	390
20	Ogino et al. (33)	Aortic arch repair	Retrospective observational	41	2016–2019	388
21	Vendramin et al. (41)	Aortic arch replacement	Retrospective observational	1	2017–2021	39
22	Koizumi et al. (28)	Total aortic arch replacement	Retrospective observational	1	2011–2019	126

TABLE 2 Included studies and patients' characteristics.

		Conventional elephant trunk (ET)							Frozen elephant trunk (FET)						
Study #	References	Patients (*n*)	Male	Age	In-hospital/30 day mortality	SCI	Stroke	RF	Patients (*n*)	Male	Age	In-hospital/30 day mortality	SCI	Stroke	RF
1	Jakob et al. (27)	23	18	55 ± 15	5	0	2	11	22	17	57 ± 12	2	0	2	12
2	Pochettino et al. (34)	42		61 ± 13	6	1	4	7	36		59 ± 13	5	3	1	6
3	Uchida et al. (39)	55	25	72.3	2	0	0	1	65	28	64.4	3	0	0	3
4	Sun et al. (38) acute	66	36	46 ± 13	4	1	1	2	148	126	45 ± 11	7	3	4	1
5	Sun et al. (38) chronic	54	36	45 ± 14	2	0	0	0	143	112	45 ± 10	2	4	3	2
6	Hofferberth et al. (25)	18	13	59 ± 13	2	1	3	6	19	16	54 ± 12	1	0	2	5
7	Leontyev et al. (29)	125	80	61 ± 13	51	5	20	23	46	23	69 ± 10	8	10	6	11
8	Di Eusanio et al. (22)	36	19	64.3 ± 10.8	5	4	2	2	21	18	65.6 ± 7.3	1	3	2	2
9	Preventza et al. (35)	87	63	57 (48–66)	25	1	9	10	25	22	64 (48–73)	6	2	3	4
10	Vallabhajosyula et al. (40)	180	125	59.4 ± 13.9	25	4	15	42	62	40	58.2 ± 11.9	6	4	3	13
11	Shrestha et al. (37)	97	59	59.7 ± 12.7	24	5	12	12	180	126	59.8 ± 13.2	22	9	24	25
12	Matt et al. (30)	37	26	60 (± 12)	5	1	9		37	22	60 (± 15)	0	0	3	
13	Preventza et al. (36)	92	68	64.0 (53.5–69.5)	21	3	5	0	37	21	68.0 (64–73)	15	2	2	2
14	Alhussaini et al. (21)	70	42	65.67 ± 13.3	9	4	10		48	31	64 ± 11	8	2	3	
15	Furutachi et al. (23)	30	17	58.5 ± 12.5	3	2	2		20	15	58.8 ± 9.4	1	0	0	
16	Inoue et al. (26)	115	74	67 ± 11	16	0			33	19	0	4	0		
17	Mkalaluh (31)	25	15	66 [58–76]	8	4	2	6	25	14	69 [60–72]	5	1	6	6
18	Mutsuga et al. (32)	37	32	68.5 ± 9.6	0	2	3	1	54	41	68.5 ± 9.6	2	9	5	4
19	Hage et al. (24)	218	138	63 ± 13	28	4	27		172	120	65 ± 13	15	9	22	
20	Ogino et al. (33)	194	144	68.4 ± 12.5	0	1	15	9	194	137	68.9 ± 10.7	2	6	16	11
21	Vendramin et al. (41)	26	15	66 ± 2	1	2	5	18	13	8	55 ± 9	0	1	1	5
22	Koizumi et al (28)	66	53	74.1 ± 9.4	8	0	2	8	60	51	76.2 ± 5.9	1	2	4	3

SCI, spinal cord injury including paraplegia/quadriplegia; RF, renal failure.

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TABLE 3 Elephant trunk (ET) vs frozen elephant trunk (FET) odds ratios and 95% confidence intervals (CI) and probability (p) of effects of age and sex (% male patients).

Parameter	Articles published in years:	ET vs. FET relative risk [95% CI]	*p*	I^2 value and p	Egger's test: x-intercept [95% CI]	Funnel plot asymmetry test p	Effect of age	Effect of sex (% male)
Mortality	2008–2021	1.37 [1.04–1.81]	**$p = 0.027$**	27.71%, $p = 0.19$	0.15 [−0.50 to 0.80]	$p = 0.50$	$p = 0.435$	$p = 0.804$
	2017–2021	1.11 [0.71–1.74]	$p = 0.646$	32.38%, $p = 0.11$	−0.29 [−1.65 to 1.06]	0.34	$p = 0.785$	$p = 0.968$
SCI	2008–2021	0.53 [0.35–0.81]	**$p = 0.004$**	11.93%, $p = 0.53$	−1.23 [−2.55 to 0.09]	$p = 0.21$	$p = 0.612$	$p = 0.275$
	2017–2021	0.61 [0.34–1.12]	$p = 0.113$	3.85%, $p = 0.43$	−1.36 [−3.18 to 0.45]	$p = 0.33$	$p = 0.131$	**$p = 0.029$**
Stroke	2008–2021	1.06 [0.83–1.37]	$p = 0.639$	0.0%, $p = 0.89$	−0.03 [−0.38 to 0.32]	$p = 0.64$	$p = 0.508$	$p = 0.349$
	2017–2021	1.06 [0.76–1.47]	$p = 0.732$	0.0%, $p = 0.43$	−0.14 [−0.96 to 0.68]	$p = 0.56$	**$p = 0.044$**	$p = 0.326$
Renal failure	2008–2021	0.98 [0.79–1.23]	$p = 0.892$	0.0%, $p = 0.72$	0.17 [−0.69 to 1.02]	$p = 0.37$	$p = 0.947$	$p = 0.896$
	2017–2021	1.15 [0.71–1.88]	$p = 0.569$	12.93%, $p = 0.19$	1.11 [4.78 to −2.56]	$p = 0.15$	$p = 0.803$	$p = 0.813$

SCI, spinal cord injury. Results for all the examined articles published. Statistically significant probabilities ($p < 0.05$) are in bold.

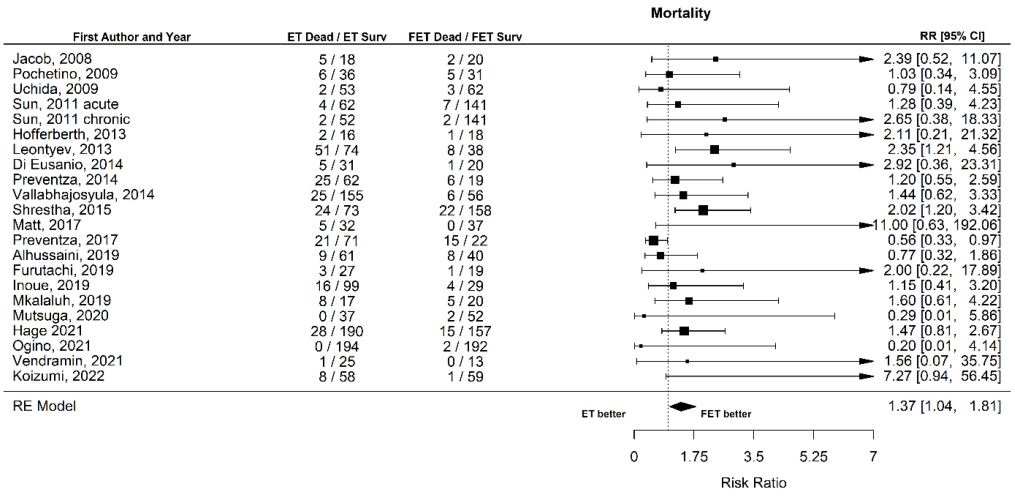

FIGURE 2
Relative risk of mortality in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Forest plot. ET vs. FET $p = 0.027$.

Endpoints

The primary endpoints of this study were: early mortality, defined as the occurrence of mortality during hospitalization or up to 30 days after the intervention, spinal cord injury/ischemia (SCI) and/or paraplegia and/or quadriplegia, stroke, and renal failure. The possible impact of age and sex on the above-mentioned parameters was also examined.

Results

Search results and characteristics of the studies

The initial search resulted in 695 results from PubMed, 368 from Web of Science, 361 from Scopus, and 8 from the Cochrane library. After the elimination of duplicates and the application of the inclusion and exclusion criteria, 29 articles containing data on ET and FET were found. The full text of these articles was then examined. Fourteen articles did not contain separate data for patients treated with ET and FET and were excluded. An additional search in the references of the selected articles resulted in 6 additional articles that were also included (Figure 1). Overall, twenty-one studies were included in the analysis.

The 21 selected studies (21–41) included a total of 3153 patients. The studies contained data from interventions conducted between 1997 and 2019 and were published between 2008 and 2021. The ET was applied in 1693 patients (53.7%) and FET in 1460 (46.3%). In 17 out of the 18 studies that contained detailed data about sex, 2,105 of 3,075 patients (68.5%) were male. One of the selected studies (38) contained two different cohorts, one with acute and one with chronic dissections.

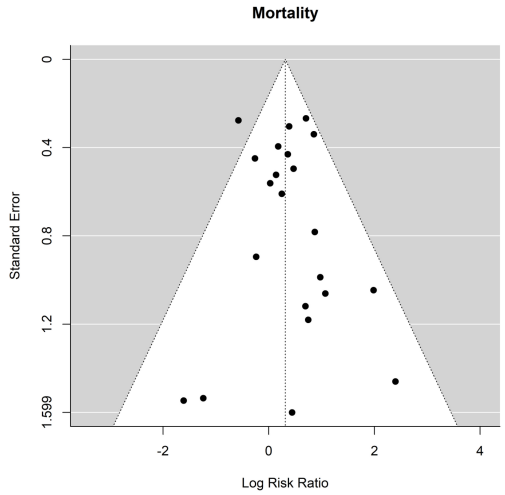

FIGURE 3
Relative risk of mortality in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Funnel plot.

These cohorts were included as separate. One article contained two overlapping cohorts, one cohort with all the patients examined and one with propensity-matched patients (33). Only the matched cohort was included in the statistical evaluation.

The studies that were included in this meta-analysis are shown in **Table 1**. The patients' characteristics are shown in **Table 2**.

Of the 21 selected studies, 10 were published until 2016 and 11 were published in the last 5 years between 2017 and 2021. The studies published until 2016 included data on interventions conducted from 1997 to 2013. The 11 most recent studies published in 2017 and after, included data on more recent interventions ranging until 2021. A total of 1,603 patients, of which 1103 (72.3%) were male were included in these studies. ET was applied in 910 patients (56.8%) and FET in 693 (43.2%).

Quality of the studies

The average quality rating of all the studies was 0.83 ± 0.08. The quality assessment is shown in **Supplementary Table 1** in the supplement. The studies were rated with a median rating of 0.83 [IQR 0.78 to 0.89], ranging from 0.67 to 1.00.

Elephant trunk vs. frozen elephant trunk

The RR of ET vs. FET, the I^2 values and respective p-values, the Egger's test results, the funnel plot asymmetry tests p-values, and the p-values of the meta-regression for the effects of age and sex are presented in **Table 3**. The results for all the examined papers published between 2008 and 2021 and for those published between 2017 and 2021 are presented in separate lines in the table.

The overall mortality after ET was 250 of 1,693 patients (14.8%) and after FET 116 of 1,460 patients (7.9%). The relative risk of mortality after ET vs. after FET was 1.37 [1.04 to 1.81], (p = 0.027, I^2 = 27.71%, p-value I^2 = 0.19; Egger's test 0.15 [−0.50 to 0.80], indicating a trend for higher mortality risk with conventional ET (**Figure 2**, Forest plot). The funnel plot is shown in **Figure 3** (asymmetry test: p = 0.50). There was no significant effect of age and sex (percentage of male patients) on mortality according to the meta-regression analysis (**Table 3**).

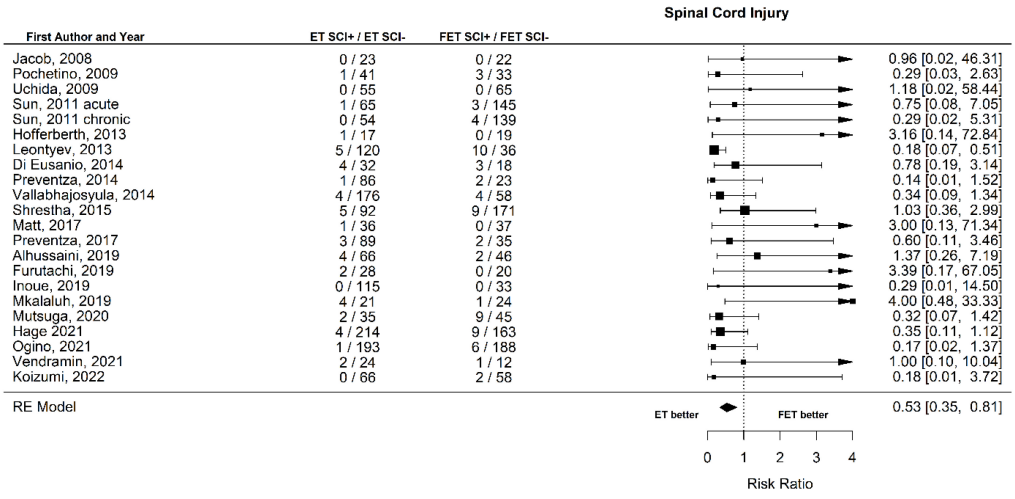

FIGURE 4
Relative risk of spinal cord injury (SCI) and hemiplegia/paraplegia in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Forest plot. ET vs. FET: p = 0.004.

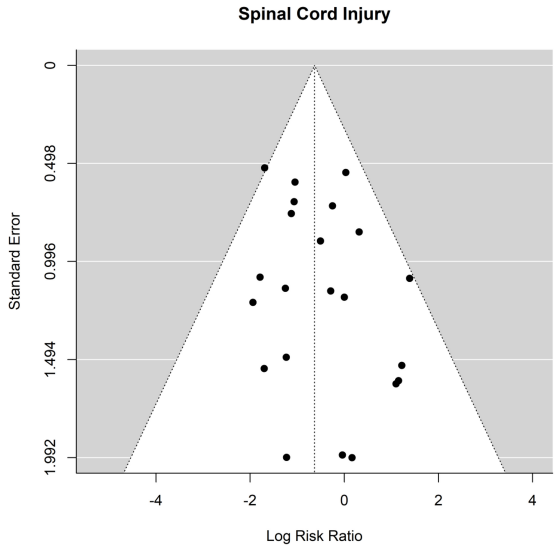

FIGURE 5
Relative risk of spinal cord injury (SCI) and hemiplegia/paraplegia in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Funnel plot.

The occurrence of SCI after ET was 45 out of 1693 patients (2.7%) and after FET was 70 out of 1,460 patients (4.8%). The RR for SCI of ET vs. FET was found to be 0.53 [0.35 to 0.81], (p = 0.004, I^2 = 11.93%, p-value I^2 = 0.53; Egger's test −1.23 [−2.55 to 0.09]. FET was associated with a significantly higher risk for SCI (**Figure 4**, Forest plot). The funnel plot is shown in **Figure 5** (asymmetry test: p = 0.21). Age and sex were not associated with the risk of SCI (**Table 3**).

Twenty out of the twenty-one studies contained sufficient data on the occurrence of stroke. No significant differences were found between ET and FET in the risk of stroke. The occurrence of stroke was 9.4% (148 of 1,578 patients) after ET and 7.8% (112 of 1,427 patients) (**Figure 6**, Forest plot). The RR was 1.06 [0.83 to 1.37] (p = 0.64, I^2 = 0.0%, p-value I^2 = 0.89; Egger's test −0.03 [−0.38 to 0.32]. The funnel plot is shown in **Figure 7** (asymmetry test: p = 0.64). There was no effect of age or sex on the outcome of stroke (**Table 3**).

Sixteen of the twenty-one studies contained data about renal failure. The occurrence of renal failure was 12.9% (158 of 1,223 patients) after ET and 10.0% (115 of 1,150 patients) (**Figure 8** Forest plot). The RR of ET vs. FET was 0.98 [0.79 to 1.23] (p = 0.89, I^2 = 0.0%, p-value I^2 = 0.72; Egger's test 0.17 [−0.69 to 1.02]. The funnel plot is shown in **Figure 9** (asymmetry test: p = 0.37). There was no significant effect of age or sex on the outcome of renal failure (**Table 3**).

We hypothesized that the evolution of techniques and the availability of newer devices, and the subsequent experience, particularly for FET, could have a positive impact on the outcomes and likely reduce mortality and perioperative complications. To test this hypothesis, the statistics were re-run including only the articles that were published between 2017 and 2021 and contained data from newer studies ranging up to 2021. The results of this second analysis are presented below and are shown in **Table 3** and **Figures 10**, **11** and **Supplementary Figures 1–8**.

In the papers published in the last 5 years, the overall mortality was 99 out of 910 (10.9%) in patients that underwent ET and 53 out of 693 (7.6%) in patients that underwent FET. There was no statistically significant difference in the risk between ET and FET. The RR for mortality of patients that

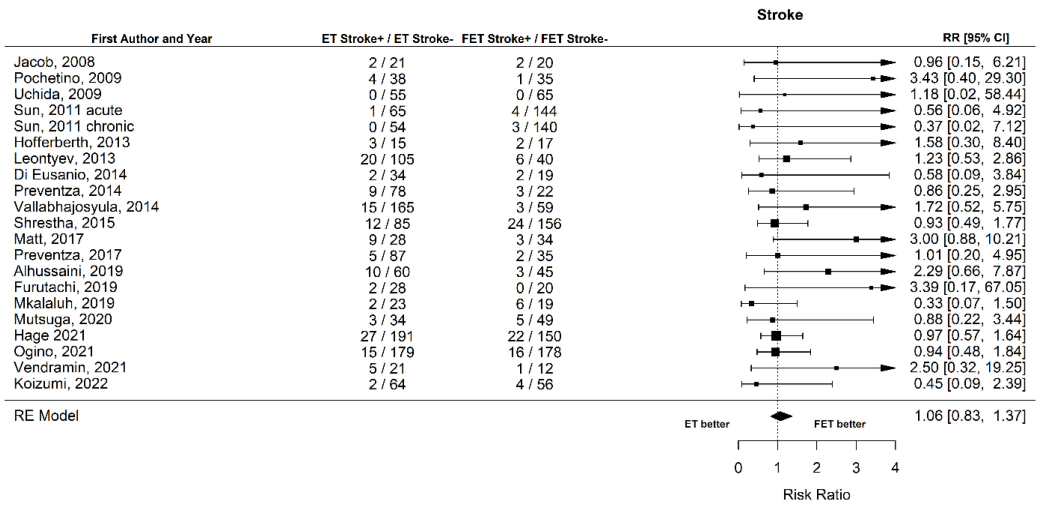

FIGURE 6
Relative risk of stroke in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Forest plot p = 0.89.

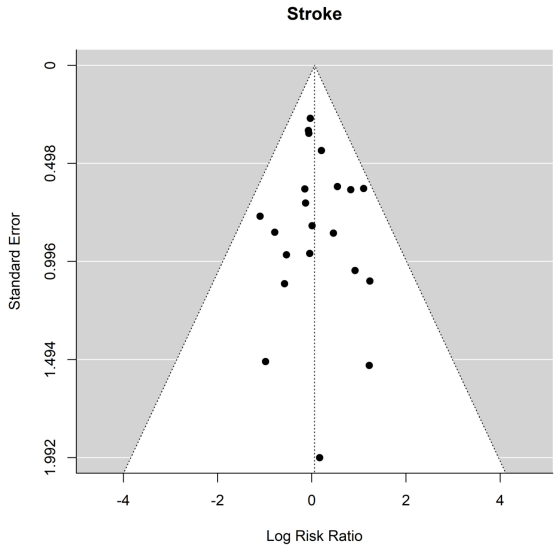

FIGURE 7
Relative risk of stroke in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Funnel plot.

underwent ET vs. patients that underwent FET was 1.11 [0.71 to 1.74] (p = 0.65), (Forest plot, **Figure 10**). There was no effect of age or sex on this outcome (**Table 3**).

When spinal cord injury and related neurological implications were examined in the papers published between 2017 and 2021, the RR of SCI of patients that underwent ET vs. patients that underwent FET was 0.61 [0.34 to 1.12]. In contrast with what was observed when all papers were examined, the trend for lower SCI did not reach statistical significance (p = 0.112) (Forest plot, **Figure 11**). A non-significant trend for SCI was observed with increasing age (p = 0.131). Male sex was associated with higher odds for SCI (p = 0.029).

The RR for stroke in the papers published between 2017 and 2021 was 1.06 [0.76 to 1.47] (**Table 3**). Increasing age was found to increase the risk for stroke (p = 0.044). There was no significant effect of sex on this outcome (**Table 3**).

When renal failure was examined in papers published in the last 5 years, the RR of ET vs. FET was 1.15 [0.71 to 1.88]. There was no significant effect of either age or sex on the outcome of renal failure (**Table 3**).

Discussion

The ET technique was introduced in the early 80 s for the correction of aortic arch aneurysms. The FET technique was introduced and developed between 1996 and 2003 in order to achieve similar results, to optimize the placement of the prosthesis in a single operative session and to combat the high interstage mortality that had been observed with the two-step ET technique (11, 13, 42). Since then, significant technical developments have occurred, including patient-tailored prostheses which are becoming increasingly popular (11).

The examined studies report conflicting results on the outcomes examined in this meta-analysis. Most of the examined studies reported no differences in mortality between ET and FET (21–23, 25–29, 31, 34–36, 38–41). Shrestha et al. (37) found significantly higher 30-day mortality in the ET group (24.7%) than in the FET group (12.2%), p = 0.011. Hage et al. (24) found a higher mortality rate after ET (13%) vs. FET (9%) (p = 0.022).

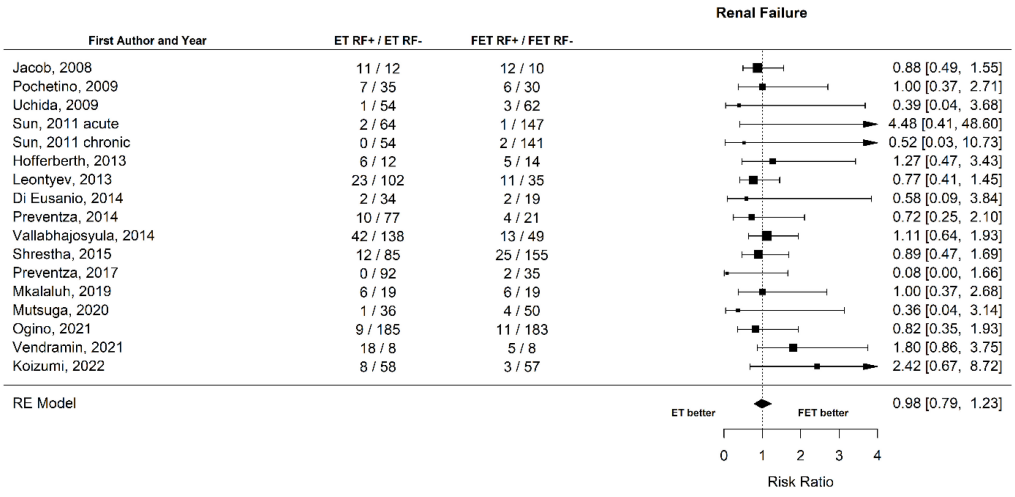

FIGURE 8
Relative risk of renal failure (RF) in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Forest plot p = 0.72.

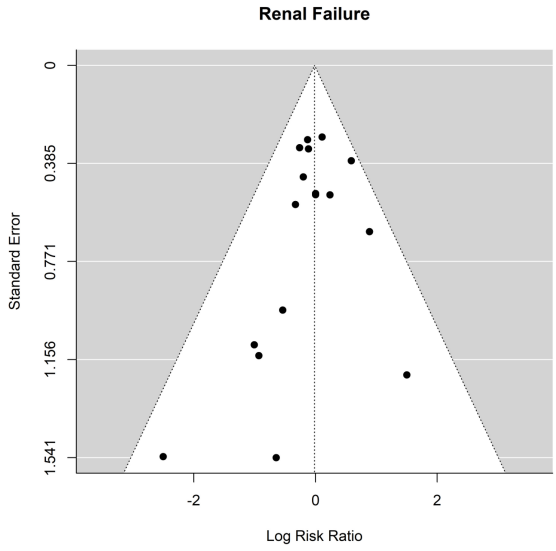

FIGURE 9
Relative risk of renal failure (RF) in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Funnel plot.

According to a previous meta-analysis (12), the FET technique appears to have a lower perioperative mortality rate.

Our results also indicate that FET is probably associated with lower early mortality. As the RR (1.37 [1.04 to 1.81], $p = 0.027$) is relatively close to 1, this observation needs to be interpreted with caution. When papers published in the last 5 years (2017–2021) were examined, there was no statistically significant difference in early mortality. We hypothesized that the availability of better devices and the evolution of techniques and training of the personnel would contribute to a reduction of the mortality rate of FET. However, the mortality rate was similar in papers published in all years (7.9%) and in the last 5 years (7.6%). Notably, mortality in aortic arch replacement, especially type A dissection is confounded by several operative and patient specific factors, encumbering this comparison in a retrospective fashion.

Interestingly, while the FET technique has over the years a constant relatively low mortality rate, the ET technique has evolved and achieved reduced mortality rates in the last years. This improvement in mortality rate was observed in ET group within the last 5 years (10.9%) as compared to earlier years (14.8%). The improvement in mortality rates with primary procedure in conventional ET could be at least partially attributed to the evolution of the used techniques in cerebral protection and cardiopulmonary bypass.

It must be noted here, that this meta-analysis only examined early mortality up to 30 days after intervention. It is not known if the long-term mortality follows similar trends. In fact, the ET techniques is followed by a second procedure, which potentially increases the complication and mortality rate significantly. Nevertheless, the reported late mortality rates were conflicted and most studies report no differences after prolonged follow up. Jacob et al. (27) reported similar late mortality at follow-up (average follow-up ET 48 months, FET 23 months). Uchida et al. (39) found a survival rate of 69.0% after conventional arch replacement and 95.3% after FET after 5 years follow-up.

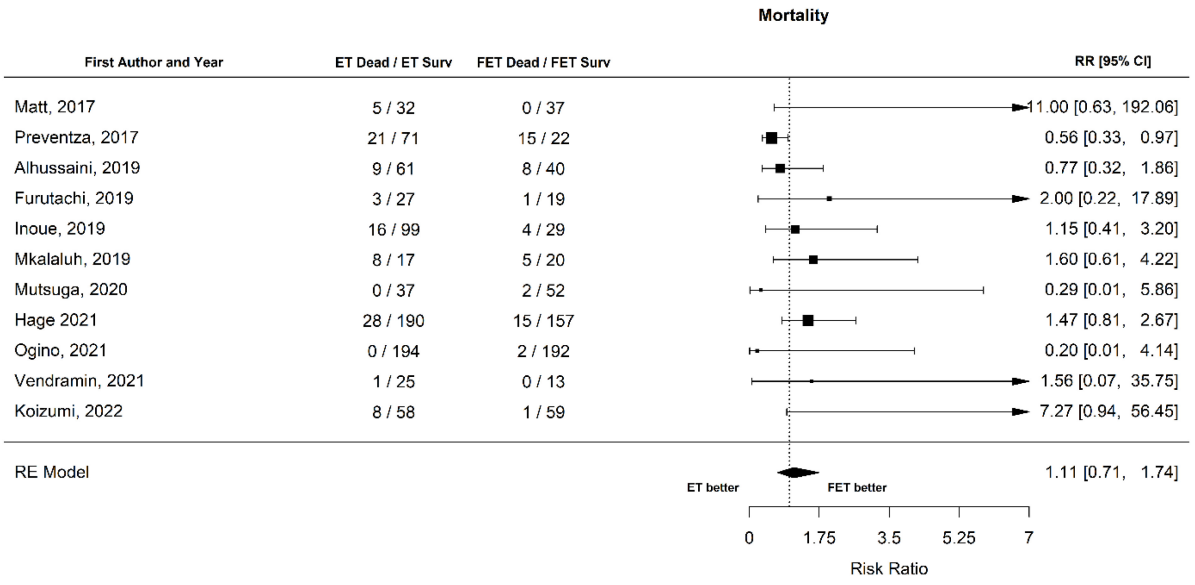

FIGURE 10
Relative risk of mortality in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Data only from studies published between 2017 and 2021. Forest plot $p = 0.646$.

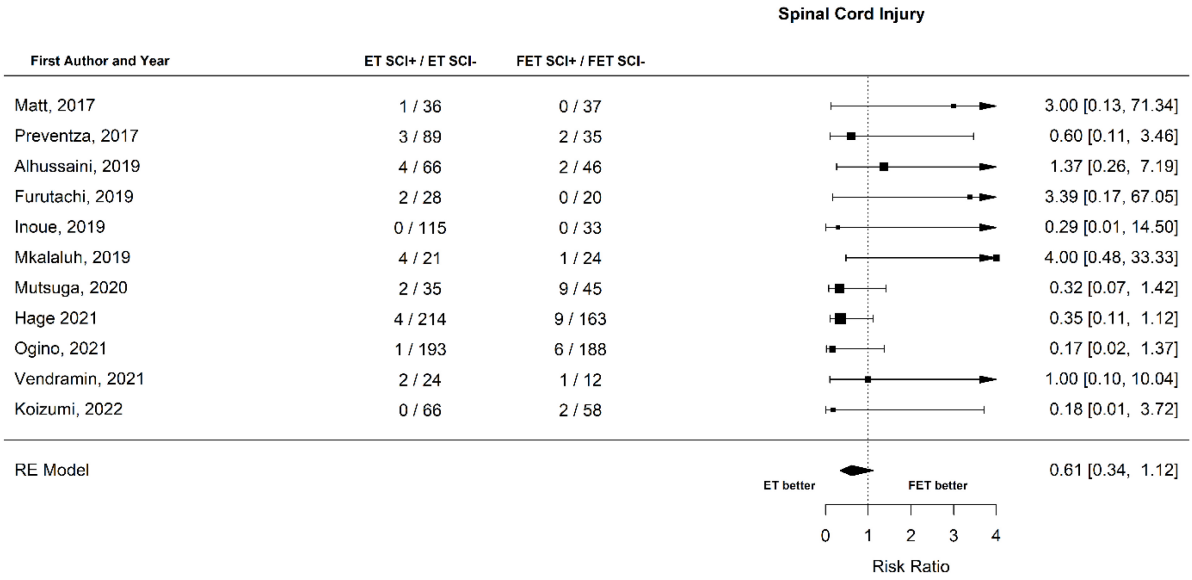

FIGURE 11
Relative risk of spinal cord injury (SCI) and hemiplegia/paraplegia in patients undergoing aortic interventions with conventional elephant trunk (ET) vs. frozen elephant trunk (FET). Data only from studies published between 2017 and 2021. Forest plot. ET vs. FET: $p = 0.113$.

Hofferberth et al. (25) reported survival rate 80% in ET vs. 87% in FET after a mean follow-up of 50 months. Mutsuga et al found an overall survival of 83% after ET and was 73% after FET at 5 years with no significant difference ($p = 0.73$). Koizumi et al. (28) reported no differences in mortality after 3 years follow-up.

According to previous studies there is a relatively high risk for a wide range of neurological complications in aortic arch surgery and these complications are well recorded (13, 43). However, there are studies showing that FET has more neurological complications when it comes to spinal cord injury, even suggesting that ET should be considered for patients who are expected to have more time under circulatory arrest in more moderate hypothermia. Leontyev et al. (29) reported lower occurrence of new-onset paraplegia after ET (4.0%) than after FET (21.7%), $p < 0.001$. Ogino et al reported lower rates of stroke (2.2 vs. 5.7% respectively, $p = 0.022$) and paraplegia (0 vs. 1.6%, $p = 0.023$) after ET as compared to FET respectively. These findings are partially confirmed by our analysis of all examined articles, where the RR for SCI of ET vs. FET was found to be 0.53 ($p = 0.004$). Nevertheless, when only the papers published within the last 5 years were examined, the RR was 0.61 and there was no statistical significance. It is possible that current evolution of the FET technique and improved devices have contributed to this outcome. Male sex was found to be associated with higher risk for SCI only in the analysis of the papers published in the last 5 years.

Renal failure resulting from hypoperfusion is another important complication related to aortic arch surgery. We found no significant difference in renal failure for both techniques, although comparing the most recent studies, a significant effect of increasing age in the occurrence of renal failure was observed.

Limitations

There are some limitations in this study.

There were no randomized controlled studies in this meta-analysis. Most of the studies were retrospective cohorts which results in selection bias.

Different types of devices were used in the examined studies and different operators with varying levels of experience performed the surgeries in centers with different settings and experiences. It is reasonable to assume that the outcomes of the interventions, particularly FET, are affected by the types of the devices used and the above mentioned parameters.

Not all the included studies contained data about all the examined outcomes (i.e., mortality, SCI, stroke, renal failure).

Further, it is also important to note that not all patients had the exact same type of lesion.

Conclusion

In conclusion, aortic arch surgery is a complex procedure where the outcome is related to a myriad of confounding factors including the surgical technique. In a retrospective fashion where the effect of inclusion bias is evident, we attempted to compare the evolution of outcomes of the commonly used ET and FET techniques. We found that the procedures

show comparable results in complication and mortality rates, while the outcomes have improved in the most recent studies. Although there is a trend in higher rates of spinal cord injury in FET, for a complete comparison, the results of the second procedure in the ET technique should also be considered. Future studies should focus on prospective analysis of arch replacement techniques and consider less invasive hybrid procedures where debranching of aortic vessels are followed by stenting of the aneurysmatic arch.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

AM: conceptualization and writing—original draft preparation. EB and EN: methodology. GP: software. SG: validation and writing—review and editing. OP: formal analysis and data curation. JR: investigation. JM: project administration. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.999314/full#supplementary-material

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Both J- and L-shaped upper hemisternotomy approaches are suitable for total arch replacement with frozen elephant trunk in patients with Type A dissection

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Background: Minimally invasive total arch replacement (TAR) with frozen elephant trunk (FET) implantation can be carried out through J-, L-, and inverted T-shaped upper ministernotomy. L- and inverted T-shaped upper ministernotomy are selected mostly for their better surgical view compared to J-shaped. However, few studies have paid attention to the difference in clinical effects between J- and L-shaped upper hemisternotomy in acute Type A aortic dissection (ATAAD).

Materials and methods: We retrospectively analyzed 74 consecutive patients with ATAAD who underwent TAR with FET implantation between December 2019 and October 2020. Patients were divided into the L group (n = 31, L-shaped upper hemisternotomy) and the J group (n = 43, J-shaped upper hemisternotomy). Perioperative characteristics were recorded.

Results: No significant difference was found in any of the pre-operative, post-operative, or follow-up variables between the two groups. However, the CPB establishment time in the J group was significantly shorter than that in the L group (65.0 ± 17.9 min vs. 77.9 ± 17.2 min, $P < 0.05$). Other intraoperative variables showed no significant difference.

Conclusion: Total arch replacement with frozen elephant trunk implantation is feasible and can be carried out safely through J-shaped or L-shaped incision. A J-shaped incision might be beneficial for single incision, while an L-shaped incision might be beneficial if an extra incision is required to achieve better artery perfusion.

KEYWORDS

aortic dissection, total arch replacement, minimal invasive incision, hemisternotomy, frozen elephant trunk

Introduction

Acute Type A aortic dissection (ATAAD) is a lethal disease that requires prompt diagnosis and surgical intervention (1). The frozen elephant trunk (FET) procedure facilitates distal aortic anastomosis during total arch replacement (TAR) (2), which is a widely used procedure in China with a low prevalence of morbidity and mortality (3, 4). However, all four studies mentioned employed full sternotomy.

Recently, minimally invasive approaches in cardiovascular surgery have led to faster recovery, enhanced thoracic stability, and less pain (5, 6). Consequently, the use of ministernotomy for aortic surgery is becoming more widespread, especially for surgery of the aortic valve, aortic root, and ascending aorta (7, 8). However, minimally invasive approaches are seldom performed in the treatment of ATAAD. Previously, we demonstrated the benefits of J-shaped upper hemisternotomy in ATAAD recovery (9, 10). However, previous studies on minimally invasive aortic procedures were mostly carried out through L-shaped or inverted T-shaped upper ministernotomy. Specifically, inverted T-shaped upper ministernotomy is considered to provide better surgical view compared to J-shaped (11, 12). Few studies have paid attention to the difference between J- and L-shaped upper hemisternotomy in ATAAD.

Here, we retrospectively analyze 74 patients with ATAAD who underwent surgery for TAR with FET through single (J- or L-shaped) hemisternotomy at our cardiovascular surgery center, aiming to advance the development of minimally invasive aortic surgery.

Materials and methods

Patient characteristics

We retrospectively collected data of 74 patients diagnosed with ATAAD based on CT angiography (CTA) who underwent TAR with FET between December 2019 and October 2020. Based on the type of hemisternotomy, these patients were divided into the L group (upper-left hemisternotomy approach, $n = 31$) and the J group (upper-right hemisternotomy, $n = 43$). Operation in the J group was carried out between December 2019 and May 2020, while operation in the L group was carried out between June 2020 and October 2020. The main inclusion criterion was diagnosis of ATAAD involving the aortic arch. Exclusion criteria included neurologic complications including cerebral infarction and cerebral hemorrhage, malperfusion syndrome, and concomitant operations that required full sternotomy (such as coronary heart disease, mitral valve disease, and congenital heart disease). The study was approved by the Ethics Committee of the General Hospital of Northern Theater Command, Shenyang City, China [K(2020)19]. All patients provided informed consent.

Surgical procedure

Surgery in both groups was performed as described in our previous study (10). Briefly, a single incision from the sternal notch to the level of the fourth intercostal space was made and then extended to the right fourth intercostal space (J group, **Figures 1A,C**) or the left fourth intercostal space (L group, **Figures 1B,D**). Other surgical procedures were the same in the two groups.

The strategy of cannulation in cardiopulmonary bypass (CPB) was based on surgical exploration. Direct innominate artery cannulation was mainly selected for artery perfusion, and right atrial cannulation was selected for venous drainage. When the innominate artery was dissected, the right subclavian artery and the right or left common carotid artery were used as alternative cannulation sites. Blood cardioplegia was used for myocardial protection. The right superior pulmonary vein was cannulated as left ventricular vent (**Figures 1E,F**).

Moderate hypothermia circulatory arrest was carried out after aortic root procedures were completed and the systemic temperature cooled to 28–30°C. Cerebral perfusion was achieved through bilateral selective antegrade cerebral perfusion (bSACP) as previously reported (9, 10). Near-infrared spectroscopy (NIRS) monitoring was used for cerebral protection. Circulatory arrest was conducted after occlusion of the innominate artery, and the FET was placed as previously reported (10, 13). Briefly, after arch arteries were transected and the proximal segment was sutured, a stent graft (MicroPort Medical Co. Ltd., Shanghai, China) was inserted into the true lumen of the distal aorta in a bound, compressed state after the distal aorta was transected between the origin of the left subclavian artery (LSCA) and the left carotid artery. Then, a four-branch prosthetic graft (Vascutek Ltd., Terumo Aortic, Inchinnan, Scotland, United Kingdom) was firmly attached to the distal aorta. After anastomosis was completed, lower body perfusion was recovered through the four-branch prosthetic graft. To decrease the duration of SACP and the cross-clamp time, the left common carotid artery, proximal aortic stump, LSCA, and innominate artery were successively anastomosed to the prosthetic graft. All patients in both groups received a temporary pacing wire to the right ventricle and one drainage tube for pericardial draining.

Definitions for complications

Permanent neurological deficit (PND) was defined as previously described. Post-operative renal dysfunction was defined as a creatinine level of >230 mM (twice the normal value). Perioperative blood transfusion was defined as intraoperative and/or post-operative transfusion of red blood cells, fresh frozen plasma, and/or platelets. CPB establishment time was calculated from skin incision to the start of CPB.

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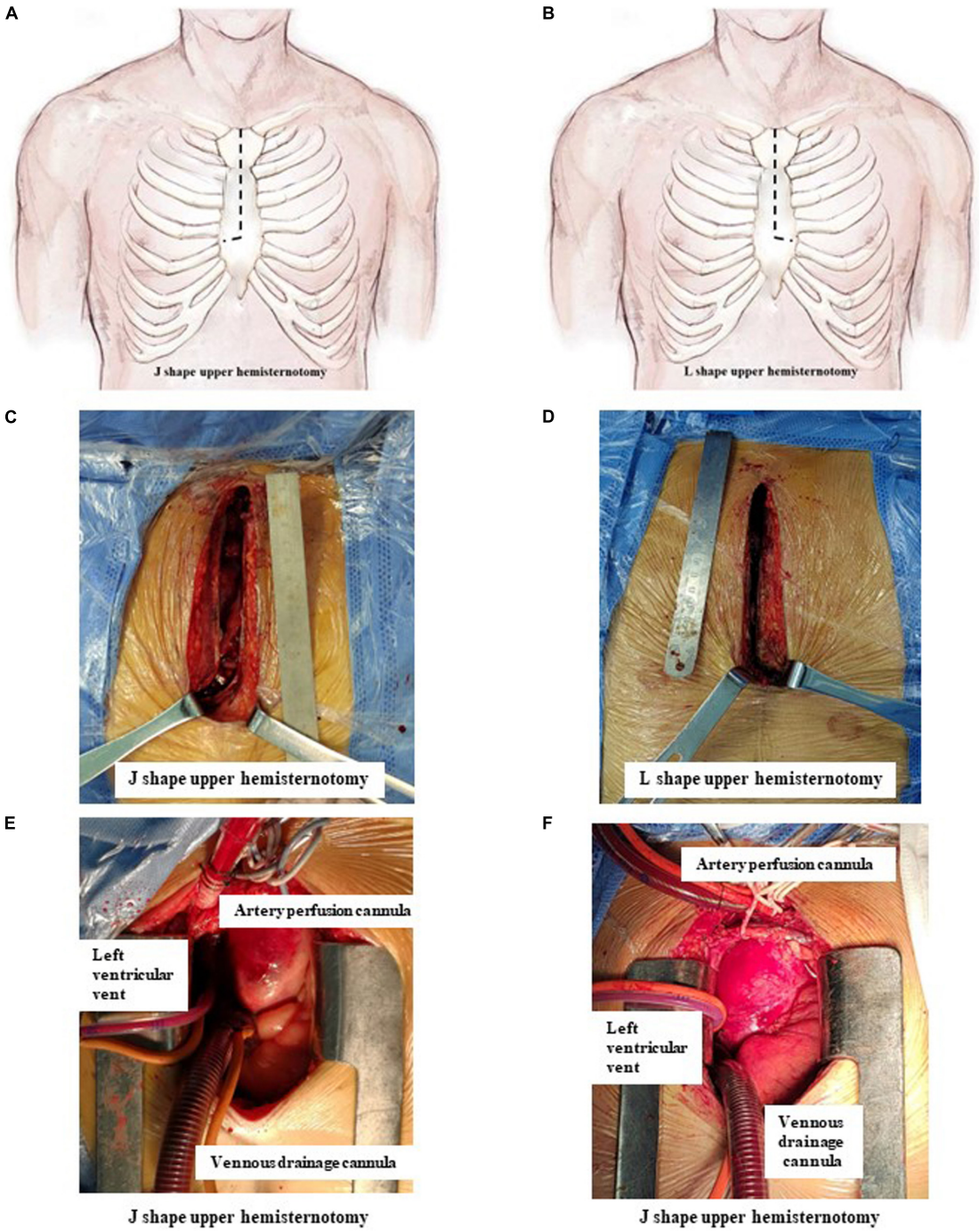

FIGURE 1
J- and L-shaped upper hemisternotomy. **(A,C)** J-shaped upper hemisternotomy is opened from the sternal notch to the fourth intercostal space and then extended to the right fourth intercostal space. **(B,D)** L-shaped upper hemisternotomy is opened from the sternal notch to the fourth intercostal space and then extended to the left fourth intercostal space. **(E)** Cannulation finished *via* J-shaped upper hemisternotomy. **(F)** Cannulation finished *via* L shape upper hemisternotomy.

Statistical analysis

Data were retrospectively collected. Continuous variables are described as mean ± standard deviation or as median (interquartile range), and categorical variables are described as frequency (%). Data were analyzed using SPSS Version 20.0 (SPSS Inc., Chicago, IL, USA). A Chi-squared test or Fisher's exact test was used to compare the distribution of categorical

variables between groups. Continuous variables were analyzed using Student's *t*-test or the Wilcoxon rank sum test. A two-sided *P*-value of less than 0.05 was considered to indicate a significant difference.

Results

The pre-operative data of the 74 patients are presented in Table 1. Patients were divided into the J group ($n = 43$) and the L group ($n = 31$) based on the different incisions. There was no significant difference in baseline characteristics between groups.

Intraoperative variables are listed in Table 2. No difference in surgical procedures, arterial perfusion position, CPB time (163.3 ± 34.4 min vs. 174.5 ± 35.3 min, $P = 0.177$), cross-clamp time (98.3 ± 23.8 min vs. 96.6 ± 27.0 min, $P = 0.776$), and circulatory arrest time (16.4 ± 16.6 min vs. 22.7 ± 19.0 min, $P = 0.142$) was observed between the J and L groups. The CPB establishment time in the J group was significantly shorter than that in the L group (65.0 ± 17.9 min vs. 77.9 ± 17.2 min, $P = 0.003$).

The post-operative variables are shown in Table 3. In total, six patients died (four in the J group and two in the L group) after the operation (9.3% vs. 6.5%, $P = 0.658$) due to post-operative massive cerebral infarction (3), multiple organ failure (1), sudden hemodynamic changes (1), and malignant arrhythmia (1). There was no difference between groups in ventilation time, intensive care unit (ICU) stay, first 24 h chest tube drainage, intraoperative or post-operative transfusion, reventilation, PND, acute renal failure, post-operative length of stay, and hospital costs.

After surgery, 39 patients in the J group and 29 patients in the L group were followed-up with. The median follow-up time was 30 (28, 31) months in the J group and 24 (22, 26) months in the L group ($P < 0.001$; this difference is caused by the different start time points for follow-up between the two groups). During follow-up, eight patients died (five patients in the J group and three patients in the L group); the mortality rate was not significantly different between the two groups (12.8 vs. 10.3, $P = 0.754$) (Table 3).

TABLE 1 Baseline demographics.

Clinical variables	J group ($n = 43$)	L group ($n = 31$)	*P*-value
Age (Years)	52.4 ± 10.2	48.4 ± 12.1	0.130
Male, *n* (%)	30 (69.8)	22 (71.0)	0.911
Body Weight (kg)	76.2 ± 15.4	79.4 ± 13.2	0.370
BMI (%)	26.0 (24.2, 28.7)	26.1 (24.1, 28.5)	0.891
LVEF (%)	59.1 ± 3.0	57.7 ± 3.2	0.253
Smoking, *n* (%)	20 (46.5)	18 (58.1)	0.327
Diabetes, *n* (%)	2 (4.7)	0	0.223
Hypertension, *n* (%)	32 (74.4)	22 (71.0)	0.742
Bicuspid aortic valve, *n* (%)	0	1 (3.2)	0.193
Marfan's syndrome, *n* (%)	3 (7.0)	3 (9.7)	0.675
Onset time (d)	3 (2, 4)	2 (1, 4)	0.113

BMI, body mass index; LVEF, left ventricular ejection fraction.

TABLE 2 Intraoperative data of patients.

Clinical variables	J group ($n = 43$)	L group ($n = 31$)	*P*-value
CPB time (min)	163.3 ± 34.4	174.5 ± 35.3	0.177
CPB establishment time (min)	65.0 ± 17.9	77.9 ± 17.2	0.003
Cross-clamp time (min)	98.3 ± 23.8	96.6 ± 27.0	0.776
Circulatory arrest time (min)	16.4 ± 16.6	22.7 ± 19.0	0.142
Minimum nasopharyngeal temperature (°C)	29.3 ± 1.4	29.0 ± 1.7	0.534
Arterial perfusion position			
Innominate artery, *n* (%)	30 (69.8)	20 (64.5)	0.823
Right subclavian artery, *n* (%)	1 (2.3)	1 (3.2)	0.814
Right common carotid artery, *n* (%)	1 (2.3)	0	0.393
Left common carotid artery, *n* (%)	2 (4.7)	2 (6.5)	0.710
Surgical procedures			
Aortic valvuloplasty, *n* (%)	10 (23.3)	6 (19.4)	0.688
Aortic valve replacement, *n* (%)	1 (2.3)	1 (3.2)	0.814
Bentall procedure, *n* (%)	7 (23.3)	7 (22.6)	0.495
Total arch replacement + FET [*n* (%)]	43 (100.0)	31 (100.0)	1.000
ECMO [*n* (%)]	0	1 (3.2)	0.193

CPB, cardiopulmonary bypass; FET, frozen elephant trunk; ECMO, extracorporeal membrane oxygenation.

TABLE 3 Post-operative data of patients.

Clinical variables	J group ($n = 43$)	L group ($n = 31$)	*P*-value
Ventilation time, (h)	35.2 ± 31.5	40.2 ± 50.0	0.610
ICU stay, (h)	51.3 ± 38.8	55.2 ± 53.7	0.718
First 24 h chest tube drainage, (ml)	235.2 ± 142.5	224.6 ± 115.2	0.772
Transfusion, *n* (%)	23 (76.7)	16 (51.6)	0.873
Reventilation, *n* (%)	2 (4.7)	1 (2.5)	0.223
PND, *n* (%)	4 (13.3)	0	0.081
Acute renal failure, *n* (%)	2 (4.7)	4 (12.9)	0.077
In-hospital death, *n* (%)	4 (9.3)	2 (6.5)	0.658
Post-operative length of stay	15 (13–20)	17 (11.5–21)	0.713
Hospital costs (10,000 CNY)	20.3 (18.7–22.2)	21.0 (17.9–24.6)	0.463
Follow-up time (months)	30 (28, 31)	24 (22, 26)	0.000
Follow-up rate (%)	43 (100)	31 (100)	
Late death, *n* (%)	5 (12.8)	3 (10.3)	0.754

PND, permanent neurological deficit; CNY, Chinese Yuan.
The number of follow-up patients were 39 in J group and 29 in L group.

Discussion

Upper hemisternotomy has been shown to be safe and effective in aortic valve surgery. It has the advantages of fast post-operative recovery, short ventilation time, short ICU stay, little blood transfusion, and little incision pain (14, 15). However, few studies on TAR surgery through a UHS have been reported. Ahmad et al. carried out TAR with FET through L-shaped hemisternotomy with artery perfusion in the right axillary artery (12). Inoue et al. reported T-shaped hemisternotomy instead of L-shaped hemisternotomy as a standard incision procedure (11). Staromłyński et al. reported hemi-arch replacement through V-shaped hemisternotomy with an incision of only 6 cm (16).

Our study included 74 patients who required TAR with FET, which was performed through a single UHS in which the sternum was incised in a J shape or an L shape from the sternal notch down to the fourth intercostal space. In both J-shaped and L-shaped hemisternotomy, TAR with FET can be successfully carried out through a single incision if the surgeon has enough experience in total arch surgery through full sternotomy, aortic valve replacement, and the Bentall approach through upper hemisternotomy. Based on our experience, there are some differences between J-shaped and L-shaped TAR with FET through a single upper hemisternotomy approach.

First, the J-shaped incision provides better exposure of the outline of the aortic valve field, the surrounding tissue, and the right ventricular outflow tract, which is beneficial for innominate artery cannulation, right atrial cannulation, and left ventricular vent cannulation; the L-shaped incision provides poor exposure of the brachiocephalic trunk artery and the right atrium, and hence, it is more difficult to make the incision for cannulating the right upper pulmonary vein and atrium. Specifically, in some patients with Marfan's syndrome or with severe dilatation of the ascending aorta, the right atrium is compressed by the aorta, which may impede exposure of the operating field, forcing the surgeon to perform vent cannulation through the pulmonary artery or to canulate the right upper pulmonary vein after CPB. When the trunk of the brachiocephalic artery is damaged by dissection, cannulation should be performed in the right common carotid artery or the right subclavian artery, which makes artery perfusion canulation more difficult. Therefore, previous studies selected the right axillary artery or one of the femoral arteries for artery perfusion (11, 12), avoiding the innominate artery cannulation, but adding the need for another incision. Second, the exposure of the left subclavian artery was poor after J-shaped incision, which makes LSCA anastomosis to the prosthetic graft difficult. In our experience, anastomosis could be facilitated using an elastic occlusion band instead of an occlusion clamp to occlude LSCA, combined with reasonable pulling by an assistant. L-shaped incision provides better exposure of the LSCA, facilitating anastomosis. However, care must be taken not to damage the left internal mammal artery, which might affect future coronary artery bypass surgery. Third, when the pericardium is lifted after thoracotomy, the L-shaped incision leads to a smaller deviation of the heart toward the right side of the chest compared with J-shaped incision, which may have less influence on the circulatory hemodynamics and lead to a smaller fluctuation of arterial blood pressure. After the L-shaped incision, it is easier to place a pacemaker on the epicardial surface than after a J-shaped incision.

In the present study, only CPB establishment time was significantly longer in the L group than in the J group (65.0 ± 17.9 min vs. 77.9 ± 17.2 min, $P = 0.003$). This might be because the surgeon was more experienced in making J-shaped incisions than L-shaped incisions (9, 10). However, other intraoperative characteristics and follow-up variables showed no difference between the two groups, which might indicate that with enough practice, J-shaped incision and L-shaped incision will result in the same clinical effects. All results demonstrated that J-shaped and L-shaped incisions are both safe and feasible for TAR with FET. Moreover, J-shaped incision might be more suitable for single incision with innominate artery cannulation, and L-shaped incision might be more suitable if a second incision with cannulation on the right axillary artery or one of the femoral arteries is required.

Limitations

There are some limitations in the present study. First, the study has a time bias. Second, this is a retrospective study, which may cause selection bias. Third, the study is a single-center study with small sample size, which might cause confounder bias. All these limitations should be avoided in future studies through improving sample size, using randomized controlled trials, and using long-term follow-up.

Conclusion

Total arch replacement with frozen elephant trunk implantation is feasible and can be carried out safely through J-shaped incision and L-shaped incision. A J-shaped incision might be more suitable for single incisions, while an L-shaped incision might be more suitable if an extra incision to improve artery perfusion is necessary.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of General Hospital of Northern Theater Command. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

ZY and YL drafted the manuscript and collected the data. HJ and YG carried out the surgeries. HW provided guidance for this study. ZY acquired and analyzed the data and carried out the surgeries. All authors contributed to the manuscript and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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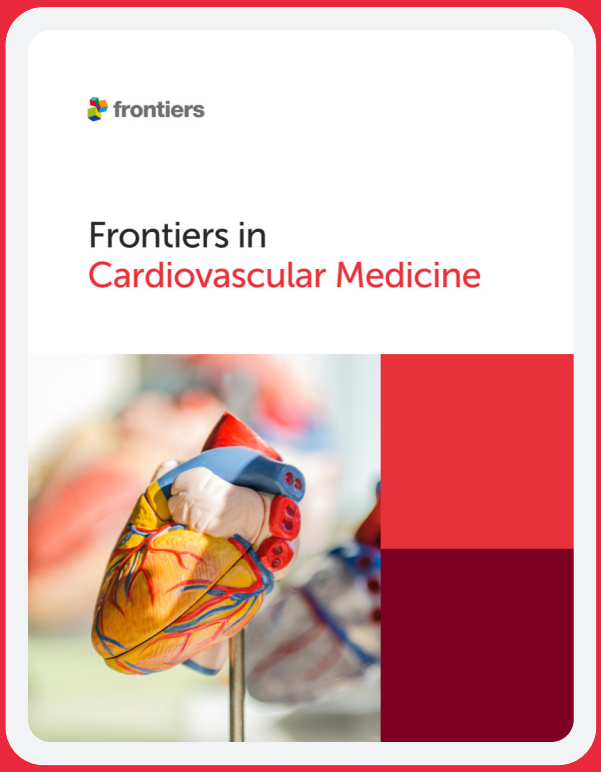

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