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EDITED BY
Marija Vavlukis,
University Clinic for Cardiology,
Ss. Cyril and Methodius University in Skopje,
North Macedonia

REVIEWED BY
Biljana Kuzmanovska,
Saints Cyril and Methodius University of Skopje,
North Macedonia
Mirjana Shosholcheva,
Saints Cyril and Methodius University of Skopje,
North Macedonia
Gereon Schälte,
University Hospital RWTH Aachen, Germany

*CORRESPONDENCE
Hua Jin
✉ jhdqq2011@qq.com
Qi Liu
✉ lq243727710@163.com
Zhe-yun Wang
✉ wangzheyungl@163.com
Min Ge
✉ gemin2000@outlook.com

[†]These authors have contributed equally to this work

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Unveiling the nexus of postoperative fever and delirium in cardiac surgery: identifying predictors for enhanced patient care

Ya-peng Wang[1†], Bei-bei Shen[2†], Cui-cui Zhu[2†], Li Li[2†], Shan Lu[2], Dong-jin Wang[1,2], Hua Jin[2*], Qi Liu[3*], Zhe-yun Wang[2*] and Min Ge[2*]

[1]Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Nanjing, China, [2]Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, The Afliated Hospital of Nanjing University Medical School, Nanjing, China, [3]Department of Critical Care Medicine, Xiangya Hospital of Central South University, Changsha, China

Background: Postoperative delirium (POD) is a significant complication observed in cardiac surgery patients, characterized by acute cognitive decline, fluctuating mental status, consciousness impairment, and confusion. Despite its impact, POD often goes undiagnosed. Postoperative fever, a common occurrence after cardiac surgery, has not been comprehensively studied in relation to delirium. This study aims to identify perioperative period factors associated with POD in patients undergoing cardiopulmonary bypass, with the potential for implementing preventive interventions.
Methods: In a prospective observational study conducted between February 2023 and April 2023 at the Department of Cardio-Thoracic Surgery, Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University Medical School, a total of 232 patients who underwent cardiac surgery were enrolled. POD assessment utilized the Confusion Assessment Method for the ICU (CAM-ICU), while high fever was defined as a bladder temperature exceeding 39°C. Statistical analysis included univariate and multivariate analyses, logistic regression, nomogram development, and internal validation.
Result: The overall incidence of postoperative delirium was found to be 12.1%. Multivariate analysis revealed that postoperative lactate levels [odds ratio (OR) = 1.787], maximum temperature (OR = 11.290), and cardiopulmonary bypass time (OR = 1.015) were independent predictors of POD. A predictive nomogram for POD was developed based on these three factors, demonstrating good discrimination and calibration. The prediction model exhibited a C-statistic value of 0.852 (95% CI, 0.763–0.941), demonstrating excellent discriminatory power. Sensitivity and specificity, based on the area under the receiver operating characteristic (AUROC) curve, were 91.2% and 67.9%, respectively.
Conclusion: This study underscores the high prevalence of POD in cardiac surgery patients and identifies postoperative lactate levels, cardiopulmonary bypass duration, and postoperative fever as independent predictors of delirium. The association between postoperative fever and POD warrants further investigation. These findings have implications for implementing preventive strategies in high-risk patients, aiming to mitigate postoperative complications and improve patient outcomes.

KEYWORDS
cardiac surgery, fever, CPB, postoperative delirium, prediction model

1. Introduction

Delirium is a disease characterized by acute cognitive decline, fluctuating mental status, consciousness impairment, lack of attention, or confusion (1). It is a recognized adverse prognostic marker in intensive care unit (ICU) patients, associated with increased incidence, mortality, and the development of long-term neurocognitive deficits (2). The incidence of postoperative delirium in cardiac surgery patients ranges from 16% to 73% (3–7), and is associated with early postoperative mortality, prolonged hospitalization, discharge to long-term care facilities, functional and cognitive decline, and increased healthcare costs (8, 9). While delirium is typically considered a short-term cognitive impairment, long-term consequences, such as functional and cognitive decline, are possible.

Given the high incidence of postoperative delirium in cardiac surgery patients, and its impact on functional outcomes and quality of life, it is essential to study the association between delirium and functional outcomes in this population. However, cardiac surgeons, anesthesiologists, intensivists, and nurses may fail to recognize delirium in up to 84% of patients (10, 11). Although the EuroSCORE, a cardiac surgical risk assessment system, is associated with postoperative mortality and delirium, no studies have reported on the association between postoperative fever and delirium (7, 12, 13). Postoperative fever is more common in cardiac surgery and is associated with increased cerebral embolic load after cardiopulmonary bypass and increased release of chemotactic factors (14).

Therefore, this study aims to determine the preoperative, operative, and postoperative fever-related factors associated with postoperative delirium in patients undergoing cardiopulmonary bypass. Successful identification of these factors could lead to preventative interventions in high-risk patients, with the hope of preventing subsequent complications.

2. Materials and methods

2.1. Study design

Participants between February 2023 and April 2023, we conducted a prospective observational study at the Department of Cardio-Thoracic Surgery. The study was ethically approved by the institutional review board was registered on the Chinese Clinical Trial Registry (ChiCTR2000038762).

2.2. Participants

Between February 1, 2023, and April 14, 2023, this study recruited patients who underwent cardiac surgery under general anesthesia for cardiopulmonary bypass with the inclusion criteria of being admitted to the Cardio-Thoracic Surgery ICU for more than 24 h and providing written informed consent after receiving information sheets and potential risk disclosures. Exclusion criteria included patients under the age of 18, those diagnosed with delirium and stroke during admission, those with a Glasgow Coma Scale score of ≤8 points who required intubation and mechanical ventilation, those who were deeply sedated (as determined by Richmond Agitation Sedation Scale scores of −4 and −5), and those with alcohol withdrawal reactions (15), patients with infective endocarditis and preoperative fever. A total of 232 eligible patients were enrolled (**Figure 1**), and measures were taken to ensure the validity and robustness of the research findings.

Delirium is a challenging condition to diagnose in the intensive care unit (ICU), and many patients may go unrecognized. Despite the use of many delirium assessment instruments in published studies, the most widely used instrument is the Confusion Assessment Method (CAM) (16). CAM has a sensitivity of 94% and specificity of 89% compared to the gold standard diagnosis by psychiatrists (17). CAM-ICU was developed to accurately diagnose delirium in ICU patients who are often unable to speak due to mechanical ventilation. CAM-ICU has a sensitivity of 95% and specificity of 89% (16, 18).

2.3. Definition of end-points

In surgical patients who do not have permanent neurological impairment, postoperative delirium (POD) is identified using the Confusion Assessment Method for the ICU (CAM-ICU) (18) and evaluated twice daily for seven consecutive days. This method allows for consistent monitoring and diagnosis of POD, which is a common complication after surgery and can have significant negative effects on patient outcomes (19).

We define high fever as bladder temperature greater than 39°C and continuously monitor body temperature for 24 h postoperatively. This definition of high fever allows for consistent and accurate measurement of postoperative fever, which can indicate a pathological state and may require further evaluation and treatment.

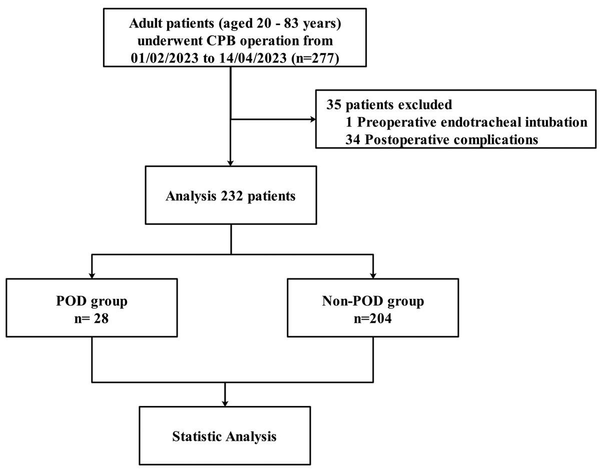

FIGURE 1
Study flowchart.

2.4. Statistical analysis

In this study, we conducted a comprehensive analysis of the data using a range of statistical methods. Continuous variables were assessed for normality using the Kolmogorov–Smirnov test and reported either as mean ± standard deviation or median with interquartile ranges (Q1–Q3), depending on their distribution. Student's *t*-test and Mann–Whitney *U*-test were used to analyze normally and non-normally distributed continuous variables, respectively. Categorical variables were presented as frequencies and percentages and analyzed using either chi-squared test or Fisher's exact test. All statistical analyses were two-tailed, and a *P*-value less than 0.05 was considered statistically significant. Additionally, we employed single-variable binary logistic regression analysis to assess the relationship between various variables and the outcome, calculating odds ratios and 95% confidence intervals.

2.5. Model development

After conducting univariate analysis, variables that demonstrated statistical significance with a *P*-value less than 0.05 were included in a stepwise (backward: conditional) multivariate logistic regression analysis model to establish a predictive model. Furthermore, we constructed a nomogram using the variables with a *P*-value less than 0.05 in the multivariate analysis to facilitate clinical decision-making. This approach allowed us to identify the most significant predictors of the outcome of interest and develop a useful tool to aid in clinical management.

2.6. Model performance and internal validation

To assess the performance of the developed nomogram for predicting the probability of postoperative neurological complications in aortic surgery, we conducted internal validation using the bootstrap method with 1,000 resamples, evaluating both discrimination and calibration. The discrimination ability was assessed using the C-statistic, equivalent to the area under the receiver operating characteristic (ROC) curve (20). Calibration was assessed by plotting calibration curves and calculating the Brier score, which is the squared difference between observed and predicted probabilities (21). Furthermore, we conducted a decision curve analysis (DCA) to assess the clinical usefulness of the nomogram across various threshold probabilities. The statistical analysis was performed using IBM SPSS Statistics 26 and R.4.2.2, and significance was determined at $P < 0.05$. This rigorous approach enabled us to gain valuable insights into the data and identify potential predictors of the outcome of interest.

3. Results

3.1. Patients baseline characteristics

During the research period from February 1, 2023, to April 14, 2023, our analysis included a total of 232 patients, as shown in **Figure 1**.

TABLE 1 Basic characteristics in POD and Non-POD groups.

Characteristic	POD (*N* = 28)	Non-POD (*N* = 204)	*P*-value
Sex male (*N*, %)	15 (53.6)	114 (55.9)	0.817
Age (years)[a]	60.50 (50.0–64.0)	61.00 (52.0–69.0)	0.294
BMI (kg/m^2)[a]	25.0 (22.6–26.5)	23.43 (21.46–26.89)	0.421
Hypertension (*N*, %)	16 (57.1)	114 (55.9)	0.900
CAD (*N*, %)	6 (21.4)	63 (30.9)	0.305
Hepatitis (*N*, %)	2 (7.1)	8 (3.9)	0.771
Renal insufficiency (*N*, %)	1 (3.6)	7 (3.4)	1.000
Atrial fibrillation (*N*, %)	11 (39.3)	59 (28.9)	0.263
NYHK			0.301
Ⅰ (*N*, %)	3 (11.1)	22 (10.8)	
Ⅱ (*N*, %)	9 (33.3)	48 (23.6)	
Ⅲ (*N*, %)	15 (55.6)	122 (60.1)	
Ⅳ (*N*, %)	0 (0.0)	11 (5.4)	
Smoking (*N*, %)	4 (14.3)	38 (18.6)	0.576
Alcohol (*N*, %)	2 (7.1)	28 (13.7)	0.501
Surgery procedure			0.473
Valve surgery (*N*, %)	9 (32.1)	87 (42.6)	
CABG (*N*, %)	0 (0.0)	9 (4.4)	
Valve + CABG	2 (7.1)	17 (8.3)	
Valve + Maze operation	8 (28.6)	38 (18.6)	
Aortic surgery	7 (25.0)	43 (21.1)	
Congenital heart disease	2 (7.1)	10 (4.9)	
CBP time (min)[a]	168.00 (135.5–193.5)	122.00 (96.0–158.0)	0.0001
Lactate[a]	2.35 (1.53–3.60)	1.5 (1.20–2.10)	0.0001
Tmax (*N*, %)	20 (71.4)	34 (16.7)	0.0001
CCU day[a]	6.00 (4.00–8.00)	3.00 (2.00–4.00)	<0.0001
Length of stay[a]	19.50 (16.25–26.00)	18.00 (15.25–22.00)	0.151

BMI: body mass index; CAD: coronary artery disease; CABG: coronary artery bypass grafting; CPB: cardiopulmonary bypass.
[a]Values are expressed as interquartile spacing [median (¼–¾ digits)].

Preoperative risk factors, such as age, gender, BMI, hypertension, NYHA class, as well as important intraoperative risk factors, including surgical category and cardiopulmonary bypass time (CPB), were identified, as presented in **Table 1**. The overall incidence of POD was found to be 12.1%, as shown in **Table 1**, and was significantly associated with CPB and postoperative lactate levels. Moreover, there were significant variations in Tmax between the POD and Non-POD groups. POD was also found to be related to ICU length of stay.

3.2. Identifying predictors

The results of multivariate analysis for POD are listed in **Table 2**, For this phase of the analysis, three variables were determined to be statistically significant. Multivariate analysis identified that lactate [Odds ratio (OR) = 1.787, 95% CI, 1.192–2.785], Tmax (OR =

TABLE 2 Multivariable logistic regression analysis of independent risk factors for POD after cardiac surgery.

Variables	β	OR	95% CI
Lactate	0.581	1.787	1.192–2.785
Tmax	2.423	11.290	4.369–32.129
CPB (min)	0.014	1.015	1.004–1.026

β: regression coefficient; OR: odds ratio; 95% CI: 95% confidence interval; CPB: cardiopulmonary bypass.

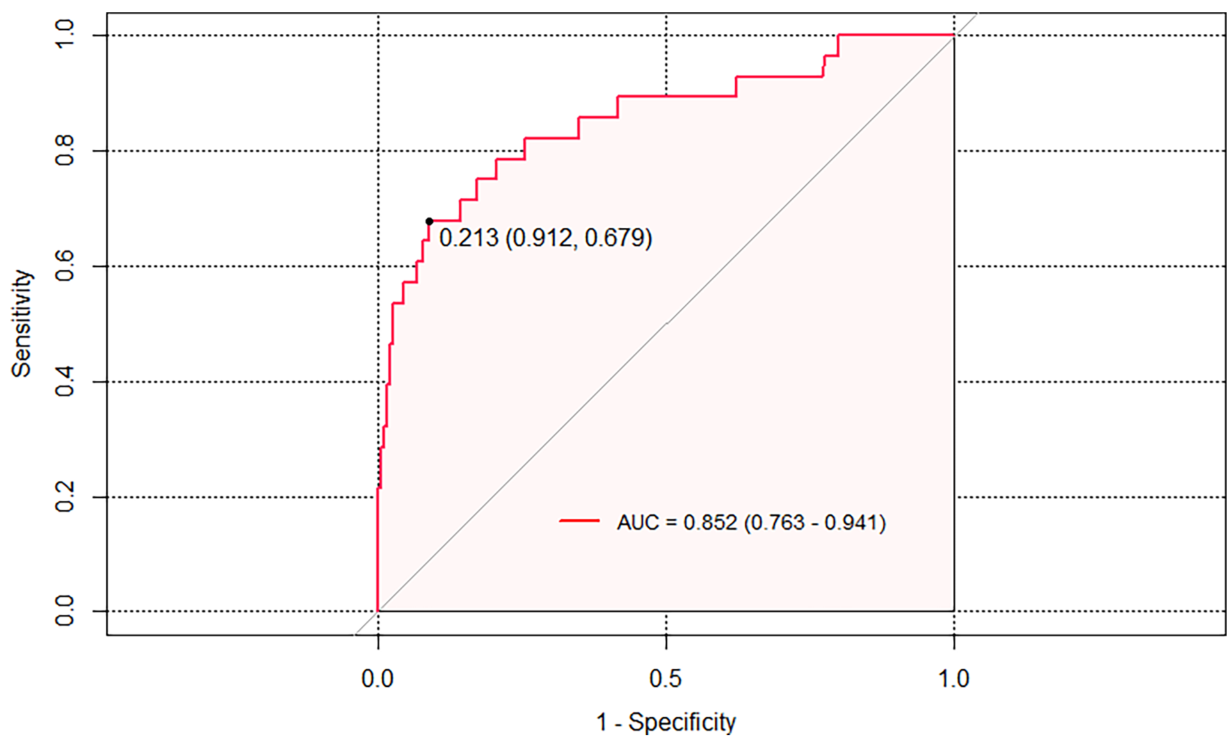

FIGURE 2
AUROC curve analysis of the model for POD; AUROC = 0.852 which is equal to a c-statistic.

11.290, 95% CI, 4.369–32.129), and CPB time (OR = 1.015, 95% CI, 1.004–1.026) were independent predictors for POD (Table 2).

3.3. Model performance and internal validation

The prediction model exhibited a C-statistic value of 0.852 (95% CI, 0.763–0.941), demonstrating excellent discriminatory power. Sensitivity and specificity, based on the area under the receiver operating characteristic (AUROC) curve, were 91.2% and 67.9%, respectively (Figure 2). The apparent calibration curve closely approximated the ideal 45° line, indicating consistent agreement between observed and predicted probabilities within the development cohort (Figure 3). To mitigate any potential overoptimism in the model, internal validation using the 1,000 bootstrap approach was performed, which confirmed its robust discrimination ability with a Brier score of 0.0686 (Figure 3). Utilizing these three candidate variables, we constructed a nomogram for predicting the probability of postoperative delirium (Figure 4). Furthermore, decision curve analysis demonstrated a favorable net clinical benefit (Figure 5).

4. Discussion

Postoperative fever after cardiac surgery is a well-known phenomenon (22, 23). It primarily arises from surgical tissue injury and the release of pro-inflammatory cytokines during CPB (22, 24, 25). Consequently, the etiology of fever in the majority of cases is non-infectious (26), particularly within the first 48 h post-surgery (27). While infections appear to be relatively rare (22, 23, 28), they represent a significant complication for patients with implanted cardiac prosthetic devices, being associated with high incidence and mortality rates (27, 29). Therefore, empirical antibiotic therapy is frequently initiated in patients experiencing postoperative fever after cardiac surgery, especially when prosthetic materials are used, potentially leading to overtreatment. Despite the recognized significance of CPB in the development of postoperative inflammation and fever following certain types of cardiac surgeries involving prosthetic materials, a comprehensive evaluation of the natural course of postoperative inflammation and fever related to CPB and implanted prosthetic materials is yet to be undertaken.

Although postoperative fever following cardiac surgery is a common occurrence (30), with an incidence as high as 38%, its etiology and significance remain incompletely understood (31). There are competing theories regarding its underlying pathophysiology. Fever may reflect an inflammatory response, which could be attributed to the surgical trauma itself or to the interaction between blood and foreign surfaces within the cardiopulmonary bypass (CPB) circuit (25, 32). Additionally, fever may serve as an indicator of altered hypothalamic thermoregulatory center function, signaling brain injury (33, 34).

Regardless of the underlying causes, fever has been demonstrated to be associated with adverse postoperative complications (25), including unfavorable cerebral outcomes (34, 35). In a recent study involving 300 patients, we described a significant relationship between postoperative hyperthermia at 6

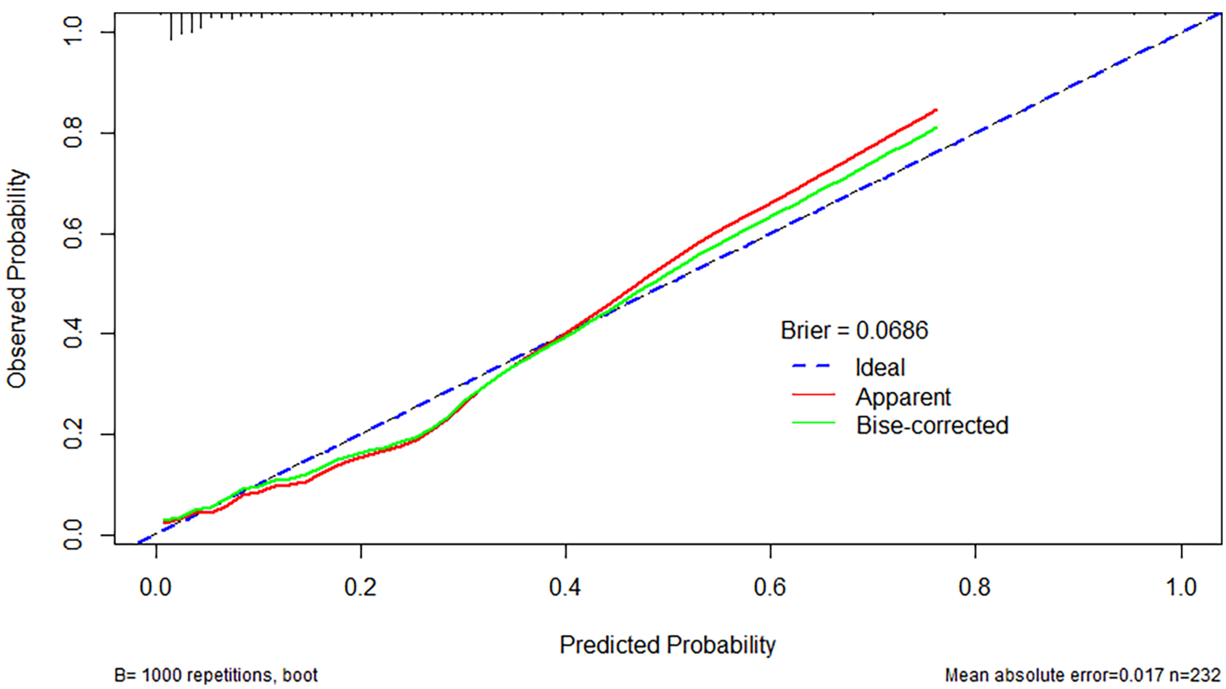

FIGURE 3
The brier score of the model was 0.0686, indicating good calibration.

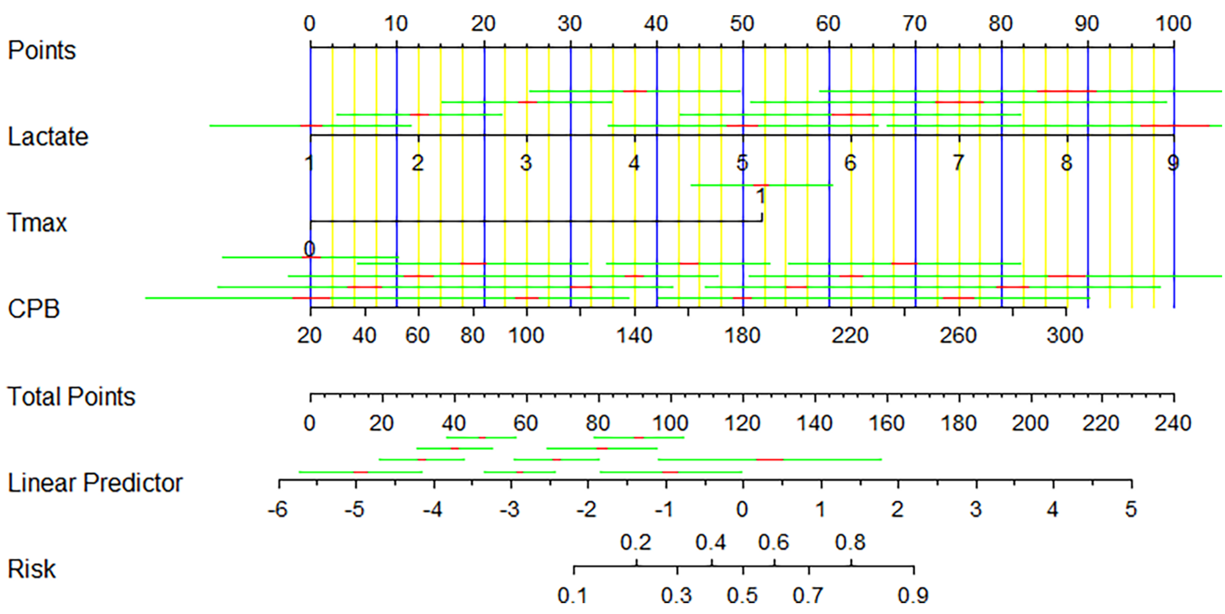

FIGURE 4
Diagnostic nomogram of model for predicting POD after cardiac surgery.

weeks following coronary artery bypass graft surgery and decline in neurocognitive function (25). The association between fever and stroke following bypass surgery remains unclear. However, even mild hyperthermia (1–2°C) in non-cardiac surgical cases has been shown to result in poorer outcomes, such as increased infarct size, deteriorating neurological function, and elevated mortality rates (25, 36).

The fluctuation in serum lactate levels serves as a reliable prognostic biomarker for mortality in critically injured patients (37). Another study demonstrates that lactate values reflect ischemia reperfusion more rapidly and reliably than novel biomarkers (38). Elevated lactate levels in cardiac surgery patients during the perioperative period are associated with adverse postoperative outcomes. Perioperative lactate levels can

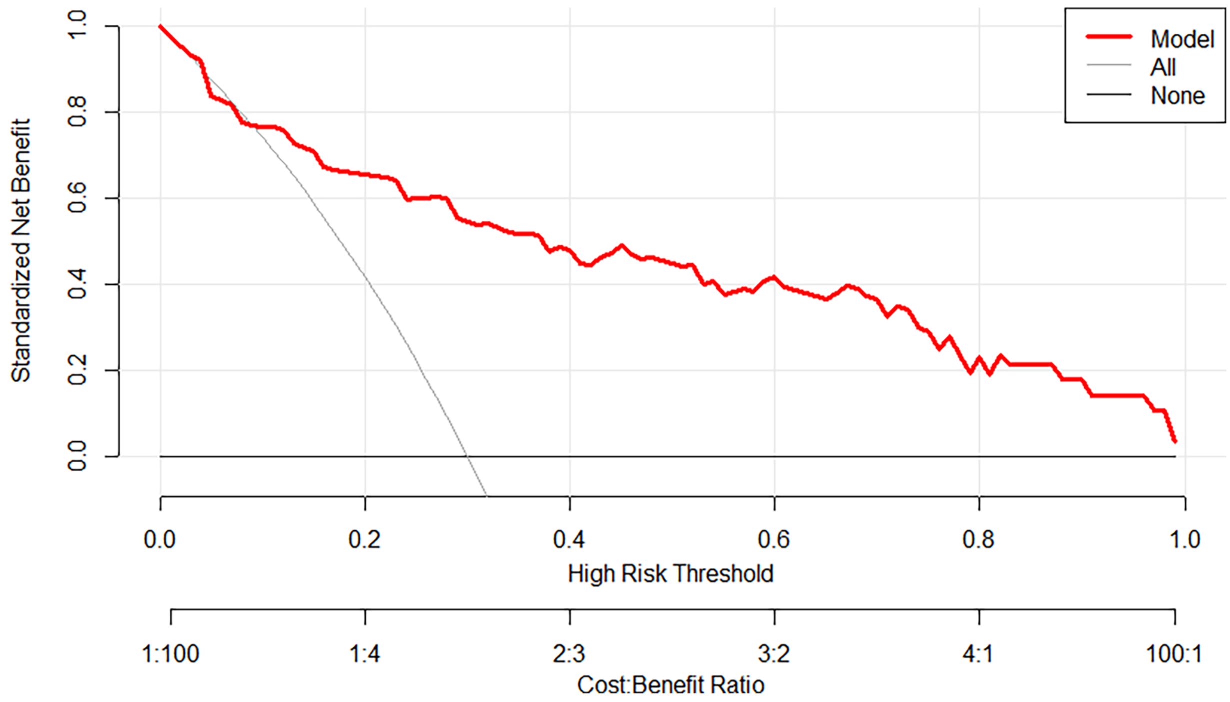

FIGURE 5
Decision curve analysis (DCA) for the study's nomogram.

serve as a predictor for the occurrence of POD in elderly trauma patients (39, 40). In our study, postoperative hyperlactatemia reflects the circulatory state during surgery and therefore correlates with the development of POD. Our research findings are consistent with these study results.

5. Conclusion

In conclusion, our study findings indicate that POD is highly prevalent among cardiac surgery patients. Postoperative lactate levels, cardiopulmonary bypass duration, and postoperative fever emerge as independent predictive factors for the development of postoperative delirium. Furthermore, the identification of postoperative fever, which is one of the intraoperative variables, may be related with the occurrence of POD.

6. Limitation

In summary, our study has some limitations that should be taken into consideration when interpreting the findings. Firstly, our study was performed at a single center, which could potentially restrict the generalizability of the findings. Secondly, the relatively small sample size could have an impact on the statistical power of the study. Additionally, the study's observational design prevents the establishment of causal relationships, and there may be additional factors not considered in the analysis. External validation of the predictive nomogram is necessary before its clinical implementation.

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 authors.

Ethics statement

The studies involving humans were approved by Institutional review board of The Nanjing Drum Tower Hospital of the Affiliated Hospital of Nanjing University Medical School. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

Y-pW and B-bS conducted a comprehensive literature review and performed the statistical analysis. D-jW, MG, and Z-yW were responsible for the study's conception and design. HJ, SL, and QL carried out data collection and managed the database. Y-pW and C-cZ drafted the manuscript. Y-pW and QL made substantial contributions to manuscript revisions and finalization. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1237055/full#supplementary-material

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