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Association of hospital volume and long-term survival after esophagectomy: A systematic review and meta-analysis

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Background: It remains controversial whether esophageal cancer patients may benefit from esophagectomy in specialized high-volume hospitals. Here, the effect of hospital volume on overall survival (OS) of esophageal cancer patients post esophagectomy was assessed.
Methods: PubMed, Embase, and Cochrane Library were systematically searched for relevant published articles between January 1990 and May 2022. The primary outcome was OS after esophagectomy in high- vs. low-volume hospitals. Random effect models were applied for all meta-analyses. Subgroup analysis were performed based on volume grouping, sample size, study country, year of publication, follow-up or study quality. Sensitivity analyses were conducted using the leave-one-out method. The Newcastle-Ottawa Scale was used to assess the study quality. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidance, and was registered (identifier: INPLASY202270023).
Results: A total of twenty-four studies with 113,014 patients were finally included in the meta-analysis. A significant improvement in OS after esophagectomy was observed in high-volume hospitals as compared to that in their low-volume counterparts (HR: 0.77; 95% CI: 0.71–0.84, $P < 0.01$). Next, we conducted subgroup analysis based on volume grouping category, consistent results were found that high-volume hospitals significantly improved OS after esophagectomy than their low-volume counterparts. Subgroup analysis and sensitivity analyses further confirmed that all the results were robust.
Conclusions: Esophageal cancer should be centralized in high-volume hospitals.

KEYWORDS
esophageal carcinoma, esophagectomy, hospital volume, overall survival, centralization

1. Introduction

Centralization of demanding cancer surgeries to improve the safety and effectiveness of cancer treatment is a topic of ongoing concern in many countries around the world (1–4). Esophagectomy is one of the most complex surgery with high morbidity and mortality, and whether it should be centralized in high-volume hospitals remains controversial (5–9).

Abbreviations
CI, confidence interval; HR, hazard ratio; HV, hospital volume; HVH, high-volume hospital; LVH, low-volume hospital; No., number; NR, not reported; ref, reference; USA, United States of America.

Clinical long-term outcomes of esophageal cancer after surgery are usually affected by standardization of surgical procedures, chemotherapy, radiation therapy, molecular targeted therapy and immunotherapy (10–12); moreover, hospital volume also influences mortality after esophagectomy (13). Some previous studies have been reported that esophagectomy for cancer centralized in high-volume hospitals benefited long-term prognosis outcomes (6, 7, 14, 15), whereas, there are also some reports showing inconsistent results (5, 8, 9, 16). Therefore, whether a better long-term overall survival after esophagectomy showing high-volume hospitals remains to be established.

In the present study, we evaluated the influence of high- vs. low-volume hospitals on the long-term OS of patients with esophageal cancer after esophagectomy.

2. Materials and methods

2.1. Literature search strategy

This systematic review was registered in https://doi.org/10.37766/inplasy2022.7.0023 (identifier: INPLASY202270023) (17). We conducted a systematic search for all relevant articles on the relationship between hospital volume of esophagectomies and long-term OS (17). The search was performed in PubMed, Embase, and Cochrane Library. For example, we combined Medical Subject Headings (MeSH) terms and text terms for the search in PubMed. The following search terms were used: ("esophagectomy" OR "esophageal surgery " OR "esophageal cancer surgery" OR "esophageal resection" OR "esophageal cancer resection") AND ("hospital volume" OR "high volume" OR "low volume" OR "healthcare institution size" OR "surgical volume"). We also searched the references of the included studies to search for potentially eligible articles. The last search was completed on May 30, 2022. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidance (PRISMA) (17, 18).

2.2. Study selection and eligibility criteria

As we previously described, after the retrieval of the relevant articles, they were screened to remove the duplicates (17). All studies were published in English. Search results were screened by two authors (Q.W. and C.D.Z.) independently according to the titles and abstracts. To better reflect modern surgical practices and perioperative management, this study focuses only on articles published after 2002. Next, the retained studies were searched for their full text and further were screened according to the following eligibility criteria: publication in English language; surgery for esophageal carcinoma as the theme; primary outcomes included hospital volume and long-term OS; comparison of OS between high- and low-volume hospitals; original articles with informative data; articles reporting adjusted hazard ratios (HRs) in multivariate analysis; publication before 2002; and articles in which procedural volume was an exact cutoff. Any disagreements were resolved through consultation with the third author (17).

2.3. Data extraction

Two authors (QW and CDZ) independently extracted data from the included studies and collated the following information: author, published year, country, study period, population, the unit of exposure (hospital volume), volume classification for hospitals, volume grouping (dichotomies, tertiles, quartiles, quintiles or others) and the longest follow-up and clinical outcomes (OS) (17). Any disagreements were resolved by discussion with the third author. We further assessed the extent of risk adjustment (17).

2.4. Study quality evaluation

All included studies were rigorously assessed for methodological quality and risk of bias by two authors (QW and CDZ) by using the Newcastle-Ottawa Scale (17, 19). This scale assesses the quality of studies from three aspects: selection of study population (0–4 points), comparability between groups (0–2 points), and outcome measurement (0–3 points) (17). The total score is 9 points.

2.5. Data integration

High-volume hospitals or low-volume hospitals were defined by the authors of the included studies. We used hazard ratios (HRs) in low-volume groups as the reference. If an included study reported more than two surgical volume groups, only the lowest and highest volume groups were compared in the analysis. The primary outcome was OS at the last follow-up, excluding 30-day mortality, 90-day mortality, in-hospital mortality, and postoperative mortality (17).

2.6. Statistical analyses

The results were calculated by HRs with 95% confidence intervals (CIs) for long-term outcomes. Heterogeneity among the studies was quantified by the I^2 test, and studies with a statistic of 25%–50% of I^2 were regarded as low heterogeneous, 51%–75% as moderate, and more than 75% as highly heterogeneous (20). Regarding the clinical heterogeneity (inconsistency in pathological staging, therapeutic regimens, and other confounding factors among the studies), we applied random-effect models for all the analyses. To obtain adequate statistical power, subgroup analysis was conducted based on volume grouping category. Then meta-analyses of at least five included studies were performed for different cutoff values (high-volume hospital vs. low-volume hospital). In addition, subgroup analyses in relation to volume group, sample size, study country, year of publication, follow-up or study quality and sensitivity analyses of a leave-one-out method were conducted to verify the results. Funnel plots were used to evaluate potential publication bias. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed by Review Manager 5.4.1 and Stata 13.1.

3. Results

3.1. Study selection and characteristics

This systematic review was registered in https://doi.org/10.37766/inplasy2022.7.0023 (identifier: INPLASY202270023). Figure 1 shows the process of literature selection. We retrieved 115 articles from PubMed and 66 from Embase; of these, 136 studies were retained for primary selection after 59 duplicate studies were excluded. After screening of titles and abstracts, 30 studies were excluded. Among the remaining 106 articles, which were related to the volume-outcome relationship in esophageal cancer surgery, we further excluded 24 reviews without primary data, three articles not related to esophagectomy, 23 articles without data of long-term survival, 10 articles without data of hospital volume, three articles without data of low-volume hospitals, four articles published before 2002. Finally, 24 studies published from 2002 to May 2022 with 113,014 participants were included in the meta-analysis.

Among the 24 included studies, six were from the United States (6–8, 21–23), four from Sweden (9, 15, 24, 25), three each from Australia (26–28) and Netherlands (29–31), two each from Japan (32, 33) and England (14, 34), and one each from China (35), Korea (36), Brazil (37), and Canada (38) (Table 1). The longest follow-up period was 24 years.

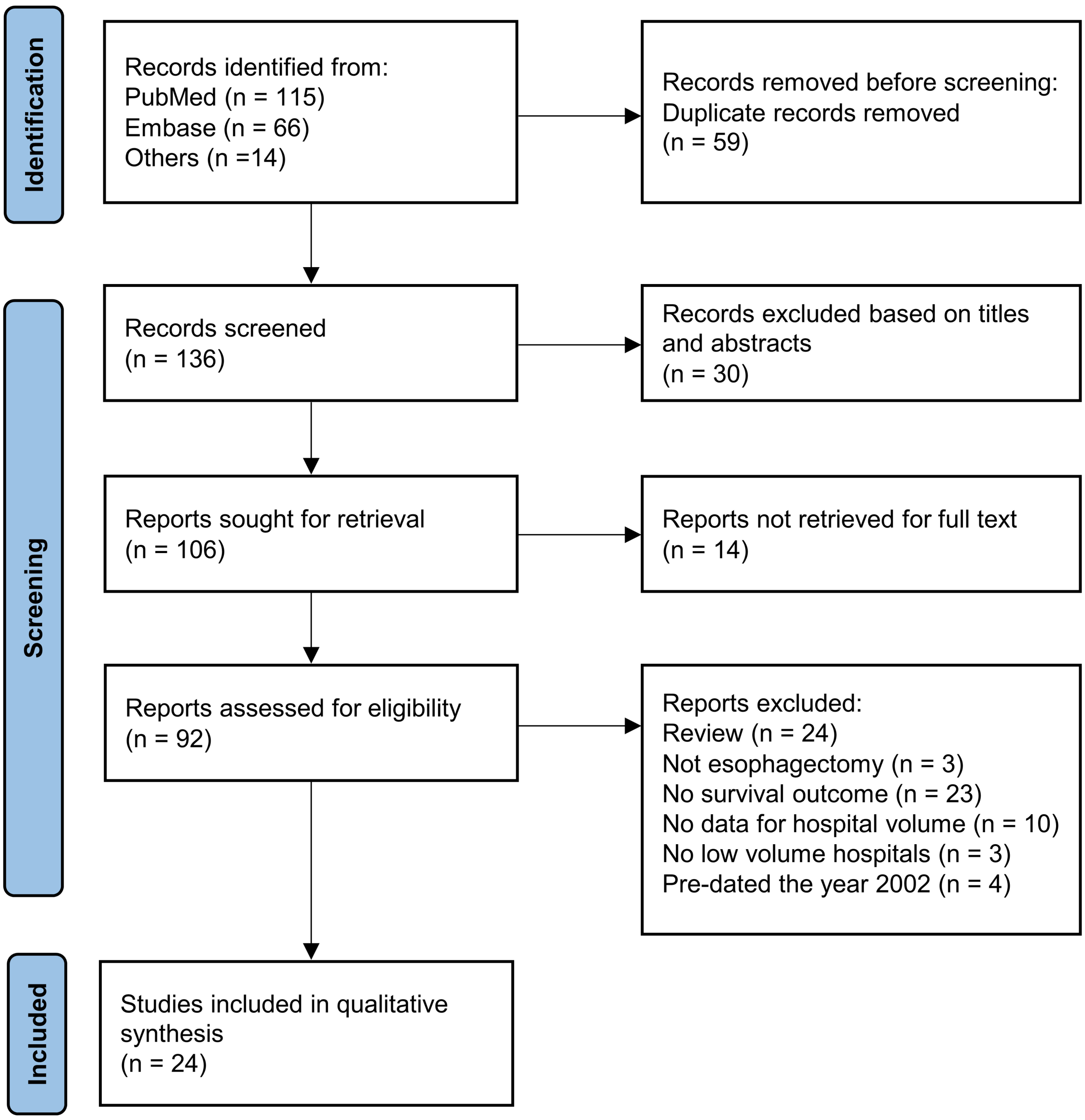

FIGURE 1
The PRIMSA flow diagram for included studies.

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TABLE 1 Basic characteristics of all included studies for meta-analysis on the relation between hospital volume and outcome of esophagectomies for cancer.

Author, year	Year	Country	Study	Population	Age, years	Male	Exposure	Hospital volume		Volume grouping	The longest	Survival	Hospital
[Ref]			Period			(%)		High	Low	Category	Follow-up, year	After	Number
Dikken (4)	2012	Netherlands	1989–2009	10,025	NR	76.0%	HV	≥21	≤5	Quartiles	3 years	Surgery	44
Van de Poll-Fanse (5)	2011	Netherlands	1995–2006	638	66.0	76.5%	HV	15–20	<4	Tertiles	3 years	Surgery	NR
Yang (10)	2018	USA	2004–2013	2445	62.0	90.6%	HV	3.1–15.8	0.1–1.0	Tertiles	11 years	Surgery	450
Coupland (11)	2013	England	2004–2008	5403	NR	71.9%	HV	≥80	<20	Quintiles	6 years	Surgery	NR
Derogar (13)	2013	Sweden	1987–2005	1335	66.0	74.0%	HV	≥17	≤8	Tertiles	24 years	Surgery	NR
Patel (26)	2021	USA	2006–2013	11,739	62.0–63.0	85.1%	HV	>6	≤6	Dichotomies	5 years	Surgery	1018
Han (27)	2020	USA	2004–2016	37,695	NR	NR	HV	≥25	<5	Quintiles	5 years	Surgery	NR
Gasper (28)	2009	USA	1995–2004	2404	NR	75.9%	HV	>6	<2	Quintiles	5 years	Surgery	NR
Bilimoria (29)	2008	USA	1994–1999	12,246	64.0–65.0	NR	HV	>15	<3	Quintiles	6 years	Surgery	1154
Birkmeyer (30)	2007	USA	1992–2002	822	NR	79.6%	HV	>14	<4	Tertiles	5 years	Surgery	206
Sundelof (31)	2008	Sweden	1994–1997	232	67.0	83.2%	HV	≥10	6–9	Dichotomies	10 years	Surgery	33
Rouvelas (32)	2007	Sweden	1987–2000	1199	65.0–66.0	71.9%	HV	≥10	<10	Dichotomies	17 years	Surgery	53
Wenner (33)	2005	Sweden	1987–1996	1429	66.0–67.0	72.8%	HV	>15	<5	Tertiles	13 years	Surgery	74
Narendra (34)	2021	Australia	2001–2015	1167	NR	NR	HV	≥6	NR	Dichotomies	5 years	Surgery	24
Smith (35)	2014	Australia	2001–2008	908	NR	80.5%	HV	>6	≤6	Dichotomies	9 years	Surgery	42
Stavrou (36)	2010	Australia	2000–2005	321	NR	74.0%	HV	>20	≤10	Tertiles	3 years	Surgery	NR
Verhoef (37)	2007	Netherlands	1994–2002	213	NR	69.1%	HV	≥20	<20	Dichotomies	10 years	Surgery	18
Taniyama (38)	2021	Japan	2006–2013	3578	NR	83.5%	HV	54–70	≤10	Tertiles	10 years	Surgery	96
Ioka (39)	2007	Japan	1994–1998	2961	NR	NR	HV	>43	<8	Quartiles	5 years	Surgery	143
Bachmann (40)	2002	England	1996–1997	781	NR	NR	HV	60–83	7–32	Tertiles	3 years	Surgery	23
Hsu (41)	2014	China	2008–2011	2151	55.2	94.1%	HV	>22	≤22	Dichotomies	3 years	Surgery	58
Kim (42)	2021	Korea	2004–2017	11,346	64.2	92.6%	HV	≥48	<12	Tertiles	5 years	Surgery	122
Duarte (43)	2020	Brazil	2000–2013	1347	NR	84.9%	HV	>8	<5	Dichotomies	5 years	Surgery	NR
Simunovic (44)	2006	Canada	1990–2000	629	63.0–65.0	NR	HV	≥44	≤7	Quartiles	10 years	Surgery	68

Ref, reference.

3.2. Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale. The median Newcastle-Ottawa Scale score of the included studies was 7, with a range of 6–9 (**Table 2**).

3.3. Long-term os in relation to hospital volume

A total of 24 studies was included to assess the impact of high-volume vs. low-volume hospitals on long-term overall survival after esophagectomy. Regarding to the longest period of follow-ups, high-volume hospitals showed significantly better overall survival than low-volume hospitals (HR: 0.77; 95% CI: 0.71–0.84, $P < 0.01$) (**Figure 2**).

Next, we analyzed the pooled HRs of OS (high-volume hospital vs. low-volume hospital) for multiple cutoff values (**Table 3**). Consistent results were found that high-volume hospitals showed a significant improvement in OS after esophagectomy than their low-volume counterparts (all $P \le 0.05$).

3.4. Subgroup analysis

Subgroup analysis was conducted based on volume grouping category in **Figure 2**. A significant improvement in OS after esophagectomy was observed in high-volume hospitals as compared to that in their low-volume counterparts in each volume grouping category. The pooled HRs were 0.76 (95% CI: 0.71–0.81) for quintiles, 0.72 (95% CI: 0.61–0.85) for quartiles, 0.77 (95% CI:0.62–0.96) for tertiles, and 0.82 (95% CI:0.78–0.87) for dichotomies, respectively (**Figure 2**, **Table 4**).

In addition, we carried out subgroup analyses in relation to sample size, study country, year of publication, follow-up or study quality. Overall, the results were robust and that patients with esophagectomy significantly benefited from high-volume hospitals than from low-volume hospitals (**Table 3**).

3.5. Sensitivity analyses

Sensitivity analyses with the leave-one-out method further revealed the consistent results, which were observed a significant improvement in OS after esophagectomy in high-volume hospitals as compared to that in their low-volume counterparts, with HRs ranging from 0.75 (95% CI: 0.68–0.83) to 0.79 (95% CI: 0.73–0.85) (**Table 5**).

3.6. Publication bias

We further assessed the publication bias (**Figure 3**). Because of the relatively small number of included studies in some volume

TABLE 2 Quality assessment of all included studies by Newcastle-Ottawa scale.

Study	Selection				Comparability	Outcome			Total score
	I	II	III	IV	V	VI	VII	VIII	
Dikken 2012 (29)		★	★	★	★★	★	★	★	8
Van de Poll-Fanse 2011 (30)	★	★	★		★★	★	★	★	8
Yang 2019 (21)	★	★	★		★	★	★	★	7
Coupland 2013 (14)	★	★	★	★	★★	★	★	★	9
Derogar 2013 (15)	★	★	★	★	★★	★	★	★	9
Patel 2022 (6)	★	★	★		★★	★	★	★	8
Han 2021 (7)	★	★	★	★	★★	★	★	★	9
Gasper 2009 (8)	★	★	★	★	★★	★	★	★	9
Bilimoria 2008 (22)	★	★	★	★	★★	★	★	★	9
Birkmeyer 2007 (23)	★	★	★	★	★★	★	★	★	9
Sundelof 2008 (24)			★	★	★★	★	★	★	7
Rouvelas 2007 (9)			★	★	★★	★	★		6
Wenner 2005 (25)		★	★	★	★★		★		6
Narendra 2021 (26)		★	★	★	★	★	★		6
Smith 2014 (27)		★	★	★	★★	★	★	★	8
Stavrou 2010 (28)			★	★	★★	★	★	★	7
Verhoef 2007 (31)	★	★	★	★	★★	★	★		8
Taniyama 2021 (32)	★	★		★	★★	★	★		7
Ioka 2007 (33)			★	★	★★		★	★	6
Bachmann 2002 (34)	★	★	★	★	★	★	★	★	8
Hsu 2014 (35)			★	★	★★	★	★	★	7
Kim 2021 (36)	★	★	★	★	★	★	★		7
Duarte 2020 (37)		★	★	★	★	★	★		6
Simunovic 2006 (38)		★	★	★	★	★	★		6

*One score. I, representativeness of the exposed cohorts; II, selection of the non-exposed cohorts; III, ascertainment of exposure; IV, demonstration that outcome of interest was not present at start of study of interest; V, comparability of cohorts on the basis of the design or analysis; VI, assessment of outcomes; VII, was follow-up long enough for outcomes to occur; VIII, adequacy of follow-up of cohorts.

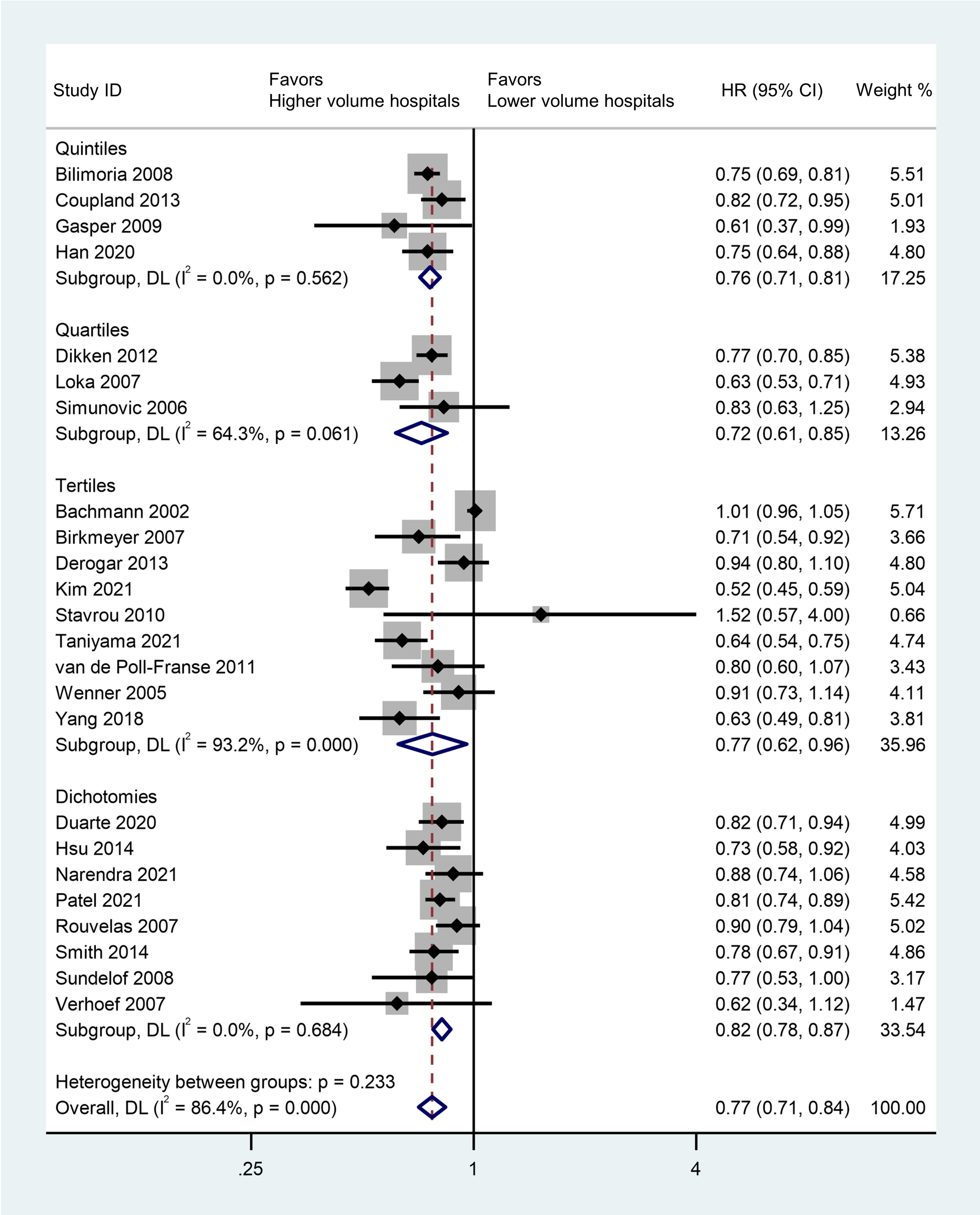

FIGURE 2
Forest plot of long-term survivals following esophagectomy comparing high- with low-volume hospitals (reference) according to volume grouping.

grouping category meta-analyses, we consider that publication bias should exist.

4. Discussion

This meta-analysis outlined the most up-to-date evidence on the relationship between hospital volume and long-term survival outcomes in esophagectomy. We found for the first time that centralization of esophagectomy in high-volume hospitals improved OS as compared to that in low-volume hospitals and patients with esophageal cancer will benefit from an esophagectomy conducted in a higher volume hospital than in a lower one, whether in total or in volume grouping category. However, we were still unable to decide the optimal cutoff value of dividing high- and low-volume hospitals in current study.

Centralization of esophageal cancer surgery has been common in the Netherlands, England, and Canada (18, 39, 40), Comparing a

TABLE 3 Comparisons of the overall survivals between high- and low-volume hospitals by different cutoff values of hospital volume.

Cutoff values of hospital volume (CV) HVH (≥CV) vs. LVH (<CV)	No. of studies	No. of patients	Effect estimate		
			HR	(95% CI)	*P* value
5	6	55,152	0.76	0.71–0.80	<0.001
6	11	80,408	0.79	0.75–0.84	<0.001
7	8	66,606	0.79	0.73–0.85	<0.001
8	9	67,261	0.79	0.74–0.84	<0.001
9	10	68,596	0.78	0.74–0.83	<0.001
10	12	74,347	0.77	0.72–0.83	<0.001
11	11	73,148	0.77	0.72–0.83	<0.001
12–14	12	84,494	0.75	0.68–0.83	<0.001
15	11	83,672	0.75	0.68–0.84	<0.001
16	9	80,741	0.72	0.65–0.80	<0.001
17	8	68,494	0.72	0.63–0.81	<0.001
18–19	7	67,159	0.71	0.61–0.82	<0.001
20	9	77,976	0.71	0.63–0.81	<0.001
21	8	71,427	0.72	0.63–0.82	<0.001
22	7	63,232	0.64	0.56–0.73	<0.001
23–25	6	61,081	0.70	0.60–0.82	<0.001
26–32	5	23,386	0.69	0.57–0.84	<0.001
33–43	6	24,167	0.75	0.59–0.95	0.02
44	5	21,737	0.74	0.55–1.00	0.05

CI, confidence interval; HR, hazard ratio; HVH, high-volume hospital; LVH, low-volume hospital; No., number.

TABLE 4 Subgroup analyses of comparisons of the overall survivals between high- and low-volume hospitals.

Subgroup HVH vs. LVH	No. of studies	No. of patients	Effect estimate	
			HR (95% CI)	*P* value
Total	24	113,014	0.77 (0.71–0.84)	<0.001
Volume group				
Dichotomies	8	18,956	0.82 (0.78–0.87)	<0.001
Tertiles	9	22,695	0.77 (0.62–0.96)	0.02
Quartiles	3	13,615	0.72 (0.61–0.85)	<0.001
Quintiles	4	57,748	0.76 (0.71–0.81)	<0.001
Sample size				
>5,000	6	88,454	0.73 (0.65–0.82)	<0.001
<5,000	18	24,560	0.79 (0.72–0.87)	<0.001
Study country				
Western countries	20	98,381	0.82 (0.76–0.88)	<0.001
Eastern countries	4	20,036	0.61 (0.53–0.70)	<0.001
Year of publication				
2002–2012	13	33,900	0.80 (0.70–0.90)	<0.001
2013–2022	11	79,114	0.75 (0.67–0.83)	<0.001
Follow-up				
Longest follow-up ≥10 years	8	11,060	0.79 (0.69–0.91)	<0.001
Longest follow-up <10 years	16	101,954	0.76 (0.69–0.85)	<0.001
Study quality				
High	19	107,243	0.74 (0.67–0.83)	<0.001
Moderate	5	5771	0.87 (0.80–0.94)	<0.001

CI, confidence interval; HR, hazard ratio; HVH, high-volume hospital; LVH, low-volume hospital; No., number.

TABLE 5 Sensitivity analysis using leave-one-out method for overall survival of high-volume hospitals vs. low-volume hospitals.

Given named study is omitted	Hazard ratio	95% CI	*P* value
Dikken (29)	0.77	0.70–0.84	<0.001
Van de Poll-Fanse (30)	0.77	0.71–0.84	<0.001
Yang (21)	0.78	0.71–0.85	<0.001
Coupland (14)	0.77	0.70–0.84	<0.001
Derogar (15)	0.76	0.70–0.83	<0.001
Patel (6)	0.77	0.70–0.84	<0.001
Han (7)	0.77	0.71–0.84	<0.001
Gasper (8)	0.75	0.68–0.83	<0.001
Bilimoria (22)	0.77	0.70–0.85	<0.001
Birkmeyer (23)	0.77	0.71–0.84	<0.001
Sundelof (24)	0.77	0.70–0.84	<0.001
Rouvelas (9)	0.76	0.70–0.84	<0.001
Wenner (25)	0.77	0.70–0.84	<0.001
Narendra (26)	0.77	0.70–0.84	<0.001
Smith (27)	0.77	0.70–0.84	<0.001
Stavrou (28)	0.77	0.70–0.84	<0.001
Verhoef (31)	0.77	0.71–0.84	<0.001
Taniyama (32)	0.78	0.71–0.85	0.02
Ioka (33)	0.78	0.72–0.85	0.05
Bachmann (34)	0.76	0.71–0.81	<0.001
Hsu (35)	0.77	0.71–0.84	<0.001
Kim (36)	0.79	0.73–0.85	<0.001
Duarte (37)	0.77	0.70–0.84	<0.001
Simunovic (38)	0.77	0.70–0.84	<0.001

CI, confidence interval.

centralized country (England) with a non-centralized country (U.S.), a previous study of 13,291 patients illustrated a lower in-hospital mortality in England hospitals than those in the U.S. (4.2% vs. 5.5%) (41). Regarding this, centralization is urgently required, in terms of high-volume hospitals with sufficient surgical volumes, skillful interdisciplinary teams, to provide the optimal treatment for patients with esophageal cancer.

Although the reasons why high-volume hospitals are associated with better long-term survival are still not fully understood, high-volume hospitals may provide patients with better multidisciplinary teams, more comprehensive preoperative examinations, more accurate preoperative diagnosis, perioperative management, and high-quality surgical care, more specialized surgeons who have more consistent skills of performing curable operations for esophageal cancer patients (42–45). Compared with low-volume hospitals, high-volume hospitals not only have a lower complication rate after esophagectomies, but also the ability of managing complications (46). In addition, the applications of neoadjuvant chemoradiation, perioperative chemotherapy, and postoperatively follow-up can improve long-term outcomes after esophagectomies; therefore, high-volume hospitals are more likely to provide a better overall cancer therapy and care, and the size of hospital volume may serve as a significant indicator of the overall medical quality and health care (47).

Unfortunately, it is difficult for patients to know the overall quality of nearby hospitals. Based on the main findings of current study, patients can select relatively higher volume hospitals nearby. Considering the importance of such knowledges, policy makers should make efforts to educate people for selecting the optimal hospitals for the treatments of specific diseases (e.g., esophagectomy for esophageal cancer), through public reporting systems.

Our study still has limitations. First, this study has the potential for selection bias of individual studies because of

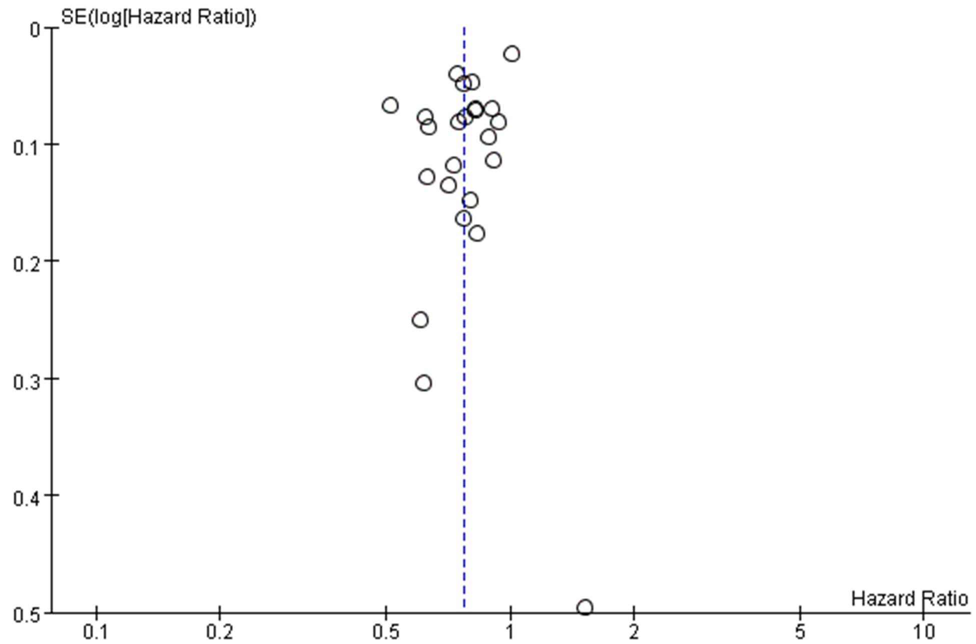

FIGURE 3
Funnel plot of survival benefit following esophagectomy comparing high- with low-volume hospital (reference).

the original data, even with case mix adjustment. Second, all the included studies were observational and retrospective. Third, some of the included studies used the same database (e.g., Sweden), and some participants might be overlapped, even though the study period were different; however, sensitivity analyses of a leave-one-out method confirmed that all the current results were robust. Fourth, as some of the data in the included studies were obtained from the National Cancer Registry, some details of the surgery, such as surgical approach and the extent of lymph nodes dissection, were unknown. Fifth, the volume grouping categories of the annual hospital volumes across the included studies varied greatly, and there was still no optimal threshold, and the main findings of current study thus need to be verified in further studies.

5. Conclusion

In summary, high-volume hospitals significantly improved long-term OS of patients with esophageal cancer after esophagectomy as compared to their low-volume counterparts. Esophagectomy should be centralized in high-volume hospitals.

Data availability statement

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

Author contributions

Conceptualization: QW, CDZ. Methodology: QW, SN. Software: QW. Validation: QW, MN, TF, SN, CDZ, SM. Formal analysis: QW, CDZ. Investigation: QW, MN, TF, SN, CDZ, SM. Resources: QW, CDZ. Data curation: QW, CDZ. Writing—original draft preparation: QW. Writing—review and editing: MN, SM. Visualization: QW. Supervision: SM. Reading and approving the final manuscript: QW, MN, TF, SN, CDZ, SM. 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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