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Impact of high body mass index on surgical outcomes and long-term survival among patients undergoing esophagectomy

A meta-analysis

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Abstract

Background: The impact of high body mass index (BMI, >23/25 kg/m^2) on surgical outcomes and prognosis in patients with esophageal carcinoma (EC) after undergoing esophagectomy remains controversial. We herein conducted a systematic review and meta-analysis to determine the relationship between high BMI and surgical outcomes and prognosis in patients undergoing esophagectomy for EC.

Methods: The study search was conducted by retrieving publications from the PubMed, Embase, Web of Science, and CNKI (up to September 8, 2017). Nineteen studies with 13,756 patients were included in this meta-analysis.

Results: We found that high BMI was closely associated with a higher incidence of wound infection (odds ratio [OR]: 1.41, 95% confidence interval [CI]: 1.02–1.97, $P=.04$), cardiovascular complications (OR: 2.51, 95% CI, 1.65–3.81, $P<.0001$), and anastomotic leakage (OR: 1.50, 95% CI, 1.21–1.84, $P=.0002$), but a lower incidence of chylous leakage (OR: 0.59, 95% CI, 0.40–0.88, $P=.01$) when compared with normal BMI. The high BMI group was not associated with better or worse overall survival (OS) (hazard ratio [HR]: 0.95, 95% CI, 0.85–1.07, $P=.4$) and disease-free survival (HR: 0.95, 95% CI, 0.72–1.25, $P=.72$) than the normal BMI group. However, in the subgroup analysis, the pooled result of HRs generated from multivariate analyses suggested that high BMI could improve OS in EC patients (HR: 0.84, 95% CI, 0.76–0.93, $P<.01$).

Conclusions: Overweight patients with EC should not be denied surgical treatment, but intraoperative prevention and careful postoperative monitoring for several surgical complications must be stressed for this population. Besides, high BMI might be a prognostic predictor in EC patients; further studies are warranted.

Abbreviations: BMI = body mass index, DFS = disease-free survival, EC = esophageal carcinoma, OS = overall survival.

Keywords: body mass index (BMI), esophagectomy, meta-analysis, prognosis

1. Introduction

Esophageal carcinoma (EC) is a malignancy of the digestive system, and a great threat to human health. At present, EC is the sixth leading cause of mortality worldwide, and the fourth leading cause of mortality in China.[1] The primary curative treatment for resectable EC is transthoracic esophagectomy with radical lymphadenectomy. This procedure is rather intricate, invasive, and lengthy due to the large incision made through the abdominal and thoracic walls, which might result in a significantly higher rate of postoperative complications and surgery-related mortality, especially among elderly EC patients.[2–4] Despite advancements in surgical techniques, preoperative preparation, and perioperative management, EC patients treated with curative esophagectomy are still confronted with a high risk of postoperative complications.[5] In addition, the TNM staging system is usually used to predict the prognosis of patients with EC, but its accuracy is unsatisfactory.[6] Therefore, studies focusing on decreasing the risk of postoperative morbidity in patients with EC and identifying additional prognostic predictors with TNM staging to guide individualized therapy remain one of the hot spots in the field of EC surgery.

Body mass index (BMI) is a free and easily calculable indicator for evaluating the baseline of nutritional status. According to the criteria of the World Health Organization (WHO), normal and high BMI for Asian populations are considered to be 18.5 to 23 kg/m^2 and >23 kg/m^2, respectively, whereas normal and high BMI are defined as 18.5 to 24.9 kg/m^2 and >25 kg/m^2, respectively, in non-Asian populations.[7] It has been reported that overweight and obesity (BMI >25/30 kg/m^2) usually burden people with decreased expiratory reserve volume and cardiac remodeling,[8,9] and also suggest higher incidence of medical

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comorbidities, such as cardiovascular disease, diabetes mellitus, and hypertension, in comparison with patients with normal BMI.[10] Furthermore, in comparison with patients with normal BMI, patients with high BMI have more visceral adipose tissue, which might prolong the operative time and cause more blood loss during various types of surgery.[11–15] Therefore, numerous studies have been performed to evaluate the impacts of BMI on surgical outcomes in patients undergoing esophagectomy. Several studies have reported that EC patients with high BMI tend to suffer from worse surgical outcomes after esophagectomy, including the increased incidence of severe complications, pulmonary complications, anastomotic leakage, and so on.[16,17] However, other studies showed that there was no substantial relationship between high BMI and surgical outcomes in EC patients after esophagectomy.[18–20] Similarly, a consensus regarding the impact of high BMI on long-term survival has not been reached in this regard either. For instance, some studies indicated that high BMI did not impact the survival of EC patients,[17,20,21] whereas other studies found inconsistent results.[16,22,23]

Considering several limitations of the published studies on this topic, including single-institutional experience, conflicting data, and small sample sizes, a systematic review and meta-analysis with a large sample size are needed to determine the correlation of high BMI with surgical outcomes and prognosis in postesophagectomy EC patients. Therefore, we herein performed a meta-analysis of the eligible literature to systematically evaluate the impact of high BMI on surgical outcomes, including severe complications, pulmonary complications, wound infection, cardiovascular complications, anastomotic leakage, chylous leakage, and in-hospital mortality, as well as prognosis in EC patients undergoing curative esophagectomy.

2. Methods

This study is a systematic review, and does not involve individual data. Thus, it does not need approval of ethics committee.

2.1. Literature search

We searched for eligible studies published in PubMed, Embase, Web of Science, and the China National Knowledge Infrastructure from inception till September 8, 2017. The following terms were used to conduct the search: "Body Mass Index or BMI," and "esophagectomy or esophageal cancer or esophagus cancer or esophageal carcinoma or esophagus carcinoma," and "prognosis or prognostic or survival or outcomes or mortality or complication or morbidity." There were no language and area limitations in our meta-analysis.

2.2. Literature selection

Two investigators screened the articles with the following inclusion criteria: the patients enrolled in eligible studies with esophageal cancer were histopathologically confirmed; prospective or retrospective studies; and studies assessed the prognostic value of high BMI on survival and postoperative outcomes. In addition, we excluded studies which met the following criteria: studies that did not differentiate low BMI patients from those with normal BMI, but rather combined low BMI patients and those with normal BMI into a control group when investigating the association of high BMI with surgical outcomes and prognosis; studies that were published as letters, case reports, reviews, meeting abstracts, comments, and noncomparative studies; studies that investigated the relationship between high BMI and nonesophageal cancer; and studies that were submitted by the same authors or institution which may have duplicated patients.

2.3. Data extraction and quality assessment

Two investigators independently extracted necessary data from the included studies, and disagreements appearing during data extraction were resolved by discussions among all coauthors. The main characteristic data were as follows: the first author's name, year of publication, country, study design, study duration, the number of patients, tumor stage, tumor histological type, mean follow-up time, and cutoff value for high BMI. In addition, the endpoints of interest included overall survival (OS), disease-free survival (DFS), and postoperative complications including severe complications defined as Clavien–Dindo grade IVa–V, wound infection, cardiovascular complications, anastomotic leakage, chylous leakage, pulmonary diseases, and postoperative in-hospital mortality. Furthermore, we chose anastomotic leakage and OS as primary endpoints, considering their clinical significance and the high number of eligible studies involving anastomotic leakage and OS. The results of the multivariate analysis were superior to univariate analysis if they were both conducted in the studies. The Engauge Digitizer version 4.1 (http://digitizer.sourceforge.net/) and the Tierney method were used to extract hazard ratios (HRs) for survival outcomes if they were presented as Kaplan–Meier curves.[24] Besides, the quality of included studies was assessed based on the Newcastle–Ottawa Scale (NOS).[25]

2.4. Statistical analysis

Statistical analyses were performed using Stata version 14.0 (Stata Corporation, College Station, TX). Synthesized HRs and their 95% confidence intervals (CIs) were used to evaluate the association between high BMI and OS and DFS of EC patients, whereas odds ratios (ORs) with 95% CIs were used to assess the relationship between high BMI and surgical outcomes. Cochran Q and Higgins I^2 statistics were used to assess heterogeneity among studies, with $P<.01$ and $I^2>50\%$ considered as significant heterogeneity, and the random-effects model was applied to synthesize data. Otherwise, a fixed-effects model was used. If the 95% CI did not span unity, HRs or ORs >1 indicated that EC patients with high BMI had poor survival and higher incidence of postoperative complications or mortality. Sensitivity analyses were carried out by sequentially excluding single studies step by step and subgroup analysis based on tumor histopathological type, study region, cutoff value, and analysis type to explore the possible source of the heterogeneity and to determine the robustness of our results regarding the association between high BMI and the 2 primary endpoints. Publication bias was described by using Begg funnel plot and the Egger tests.[26]

3. Results

3.1. Search results

The initial search yielded 652 potentially relevant studies (152 articles from PubMed, 219 from Web of Science, 247 from Embase, 34 from the China National Knowledge Infrastructure). Overall, 86 duplicate studies were excluded. In the 566 articles retained for title and abstract screening, 492 publications were

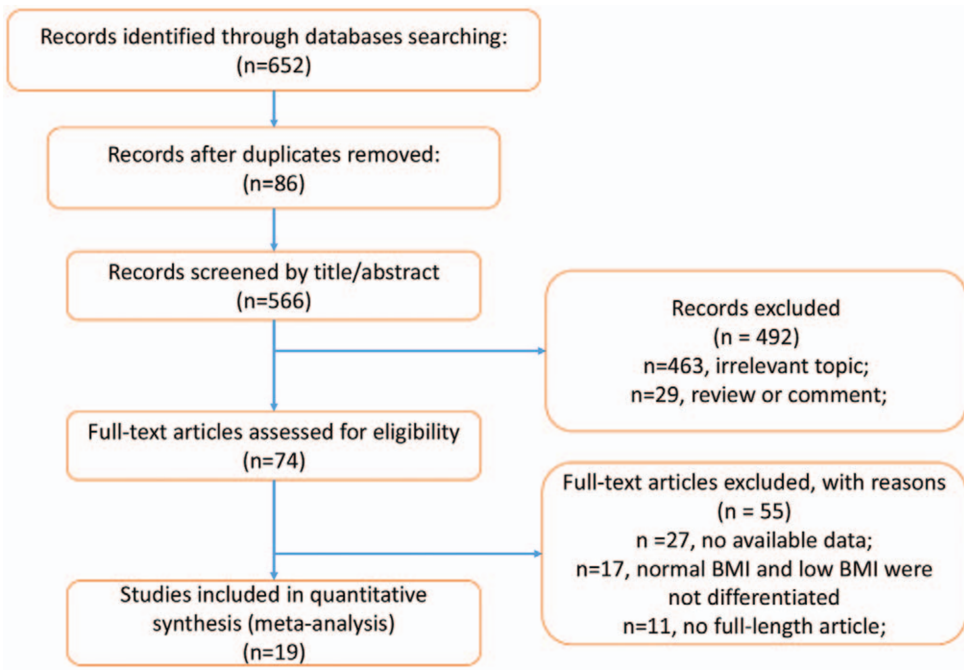

Figure 1. The flow chart of the literature selection.

excluded, including reviews and comments (n=29) and irrelevant articles (n=463). In the full-text review, 55 articles were further excluded. Among these studies, 11 were not full-length texts, 17 did not differentiate between normal and low BMI groups, and 27 studies had no available data. Finally, 19 studies containing a total of 13,756 patients were included in our meta-analysis.[16–20,22,27–39] The selection process is shown in Figure 1.

3.2. Characteristics of included studies and quality assessment

As outlined in Table 1, all the eligible articles had retrospective designs, and were published between 2011 and 2017. Among the included studies, 11 were conducted in China,[22,27,29–32,34–37,39] and the remaining 8 studies were conducted in the United States[19,33,38] Japan,[16,17] the Netherlands,[20,28] and

Table 1

The main characteristics of the included studies.

Author/year/country	Study design	Study duration	Sample size	Tumor stage	Tumor histological type	Type of surgery	Median follow-up	Body mass index: Normal weight	Body mass index: Over weight	Body mass index: Obesity	Outcomes
Blom/2012/the Netherlands	R	1993–2010	736	Mix	EC	TTE, THE	NA	<25	25–30	>30	AL, CL, SC, PD, M
Duan/2017/China	R	2005–2008	153	I, II, III, IV	ESCC	TTE	30	18.5–23	23–27.5	>27.5	OS
Grotenhuis/2010/ the Netherlands	R	1991–2007	516	NA	EC	THE	NA	18.50–24.99	25.00–29.99	≥30	OS
Hasegawa/2014/Japan	R	2002–2012	245	I, II, III, IV	ESCC	THE	NA	18.5–24.99	>25.0	NA	OS, DFS, CL, AL, SC, M, CC, WI
Ji/2016/China	R	2000–2009	944	0, I, II, III	ESCC	THE, ILE, McKeown	90	18.5–23	≥23	NA	OS, M
Kan/2016/China	R	2014–2015	419	NA	EC	NA	NA	18.5–24.9	≥25	NA	CL, AL, PD, M, WI
Kruhlikava/2017/Denmark	R	2003–2010	263	I, II, III, IV	EC	NA	NA	18.5–24.9	25–29.9	≥30	OS, AL, PD, SC, WI
Melis/2011/USA	R	1994–2008	490	NA	EC	NA	25	20–24	25–29	≥30	OS, DFS, AL, PD, M
Miao/2014/China	R	2006–2012	1342	Mix	EC	ILE	30	18.5–24.99	>25.0	NA	OS, AL, CL, M, WI
Qi/2016/China	R	2010–2012	405	Mix	ESCC	ILE	NA	18.5–24.9	≥25	NA	PD, CL, AL, M, CC, WI
Raymond/2015/USA	R	2012–2014	4194	NA	EC	ILE, THE, MIE, MIE-Mck, MIE-THE, McKeown	NA	18.5–25	25–30	>30	M
Sun/2013/China	R	2007–2008	427	I, II, III, IV	ESCC	NA	30	18.5–24.9	≥25	NA	OS
Wang/2015/China	R	2000–2007	371	I, II, III	ESCC	NA	39	18.5–22.9	≥23.0	NA	OS, DFS
Watanabe/2013/Japan	R	2005–2010	208	Mix	ESCC	TTE, THE, ILE	25.7	18.5–24.9	≥25	NA	OS, DFS, PD, AL, CC
Wu1/2016/China	R	2003–2008	225	0, I, II, III	EC	NA	37	20–25	>25	NA	OS, CL, PD, M
Wu2/2016/China	R	2014–2015	151	NA	EC	NA	NA	18.5–23.9	≥24	NA	AL, CL, PD, CC, WI
Yoon/2011/USA	R	1980–1997	778	I, II, III	EAC	ILE, THE	12.9	18.5–24.9	≥25	NA	OS, DFS
Zhang/2013/China	R	1998–2008	1709	Mix	EC	ILE, THE	64	18.5–22.9	≥ 23	NA	OS, PD, AL, CL, SC, M, CC, WI
Zhu/2011/China	R	2000–2007	180	NA	EC	NA	NA	18.5–24.9	≥25	NA	OS, AL, CL, PD, M, CC, WI

EAC=esophageal adenocarcinoma, EC=esophageal cancer (enrolling all histological subtypes), ESCC=esophageal squamous cell carcinoma, ILE=Ivor–Lewis esophagectomy, MIE=minimally invasive esophagectomy, Mix=including all the tumor stage, NA=not available, R=retrospective design; RP, THE=transhiatal esophagectomy, TTE=transthoracic esophagectomy.
Outcomes: AL=anastomotic leakage, CC=cardiovascular complications, CL=Chylous leakage, DFS=disease-free survival, M=mortality, OS=overall survival, PD=pulmonary complications; SC=severe complications, WI=wound infection.

Table 2

The Newcastle–Ottawa Scale (NOS) quality assessment of the enrolled studies.

Study ID	Selection: Representativeness of the exposed cohort	Selection: Selection of the nonexposed cohort	Selection: Ascertainment of exposure	Selection: Demonstration that outcome of interest was not present at start of study	Comparability: Comparability of cohorts on the basis of the design or analysis	Outcome: Assessment of outcome	Outcome: Was follow-up long enough for outcomes to occur	Outcome: Adequacy of follow-up of cohorts	Total
Blom 2012	★	☆	★	★	★☆	☆	★	★	6
Duan 2017	★	★	☆	★	★☆	★	★	★	7
Grotenhuis 2010	☆	★	☆	★	★☆	★	★	☆	6
Hasegawa 2014	★	★	★	★	★☆	★	☆	★	7
Ji 2016	★	★	★	★	★☆	★	★	☆	7
Kan 2016	★	★	★	★	★☆	★	☆	★	7
Kruhlikava 2017	★	★	★	★	★☆	★	☆	★	7
Melis 2011	★	★	★	★	★☆	★	☆	★	7
Miao 2014	★	★	★	★	★☆	★	★	☆	7
Qi 2016	★	★	★	★	★☆	★	★	☆	7
Raymond 2015	★	☆	★	☆	★☆	★	★	☆	5
Sun 2013	★	★	☆	★	★☆	★	★	☆	6
Wang 2015	★	☆	★	★	★☆	★	★	★	7
Watanabe 2013	★	★	☆	★	★☆	★	★	☆	7
Wu1 2016	★	★	☆	★	★☆	★	★	★	7
Wu2 2016	★	★	★	★	★☆	★	☆	☆	6
Yoon 2011	★	★	★	★	★☆	★	★	☆	7
Zhang 2013	★	★	☆	★	★☆	★	★	☆	6
Zhu 2011	★	★	★	★	★☆	★	☆	☆	6

Denmark.[18] For patients enrolled in the included studies, 7222 were allocated to the normal BMI group and 6534 to the high BMI group (4631 were overweight and 1903 were obese). In addition, 14 articles studied the relationship between OS in EC patients and BMI,[16–19,22,27–29,31,34,35,37–39] 5 articles reported DFS,[16,17,19,35,38] and a total of 14 publications reported data of postoperative complications including severe complications,[17,18,20,22] postoperative in-hospital mortality,[17,19,20,22,29–33,37,39] anastomotic leakage,[16–20,22,30–32,36,39] chylous leakage,[17,20,22,30–32,36,37,39] pulmonary diseases,[16–20,22,30,32,36,37,39] cardiovascular diseases, [16,17,22,32,36,39] and wound infection.[17,18,22,30–32,36,39] The quality of the included studies was assessed according to the NOS, and the scores ranged from 5 to 7, suggesting that the quality of eligible articles was moderate to high (Table 2).

3.3. Impacts of BMI on surgical outcomes

A total of 14 articles provided adequate data on surgical outcomes for the meta-analysis.[16–20,22,29–33,36,37,39] Of these studies, 11 articles with 6790 patients investigated the relationship between high BMI and anastomotic leakage.[16–20,22,30–32,36,39] After merging the data, we observed that the patients with high BMI might have a higher incidence of anastomotic leakage after surgery (OR: 1.50, 95% CI, 1.21–1.84, $P=.0002$) (Fig. 2). Significant heterogeneity was not found among these studies ($I^2=24\%$, $P=.21$), and these data were analyzed using a fixed-effects model. There were 9 articles involving 6078 patients that reported the association of high BMI with chylous leakage,[17,20,22,30–32,36,37,39] and interestingly the results indicated that high BMI might be a protective factor for postoperative chylous leakage among EC patients (OR: 0.59, 95% CI, 0.40–

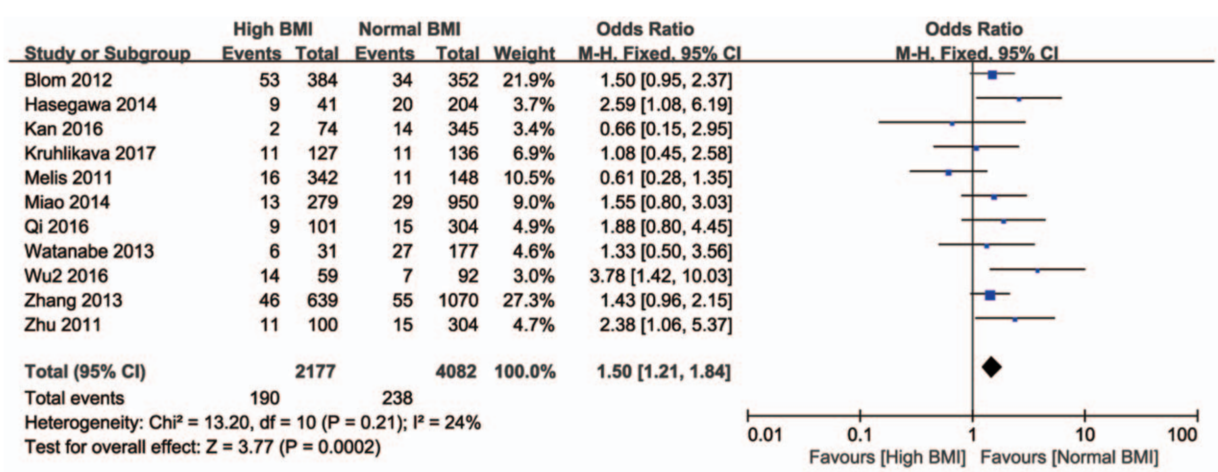

Figure 2. The forest plot of the correlation between BMI and anastomotic leakage (AL) in EC patients.

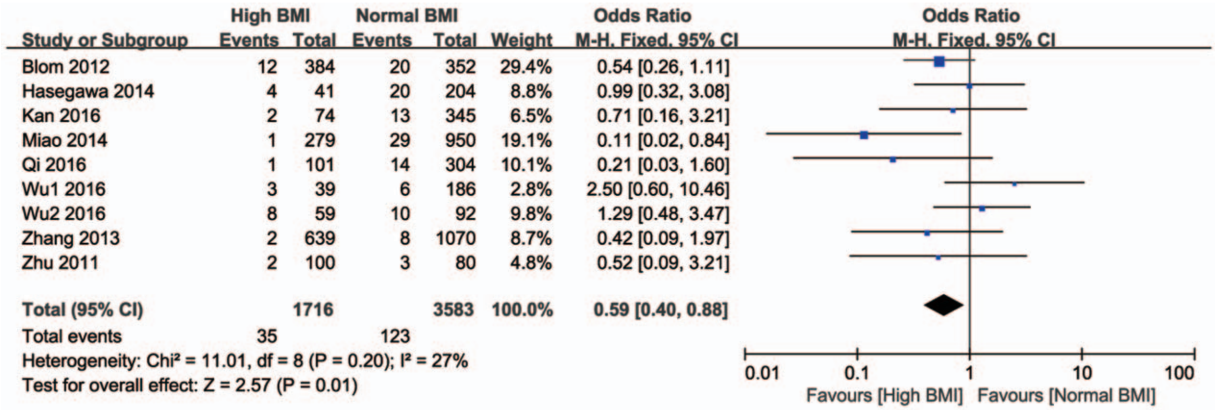

Figure 3. The forest plot of the correlation between BMI and chylous leakage (CL) in EC patients.

0.88, $P=.01$) (Fig. 3). A fixed-effects model was used to synthesize these data because of the absence of significant heterogeneity among the included studies ($I^2=27\%$, $P=.20$). In addition, cardiovascular complications were reported in 6 studies.[16,17,22,32,36,39] Among 3443 patients in these studies, patients with high BMI might have higher risk of experiencing cardiovascular complications after surgery (OR: 2.51, 95% CI, 1.65–3.81, $P<.0001$; heterogeneity: $I^2=27\%$, $P=.26$) (Fig. 4). In addition, 8 articles with 5321 patients reported data regarding wound infection,[17,18,22,30–32,36,39] and the synthesized OR suggested that high BMI was a risk factor for wound infection among EC patients (OR: 1.41, 95% CI, 1.02–1.97, $P=.04$; heterogeneity: $I^2=0\%$, $P=.49$) (Fig. 5).

With respect to severe complications and pulmonary complications, although the results showed that there was no statistically significant association of high BMI with severe complications according to the Clavien–Dindo (grade IVa–V) classification and pulmonary complications, extreme marginal trends of high BMI to higher incidence of severe complications (OR: 1.26, 95% CI, 0.96–1.65, $P=.09$) (Fig. 6) and pulmonary

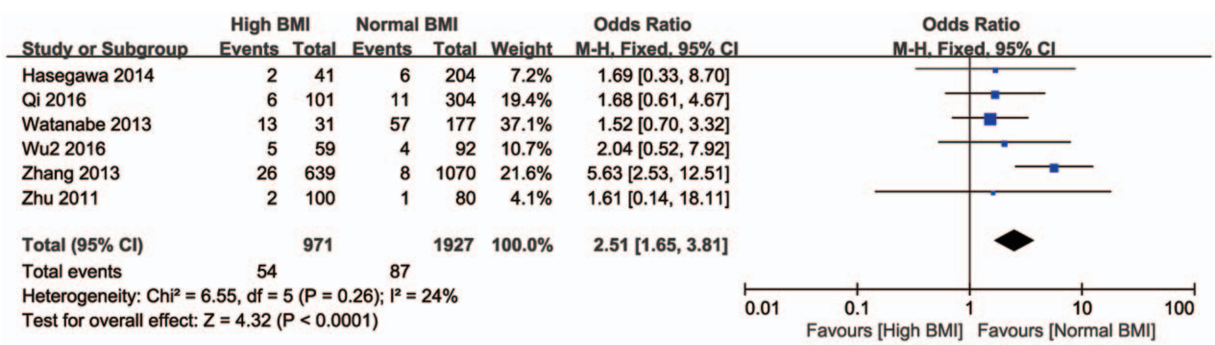

Figure 4. The forest plot of the correlation between BMI and cardiovascular complications (CC) in EC patients.

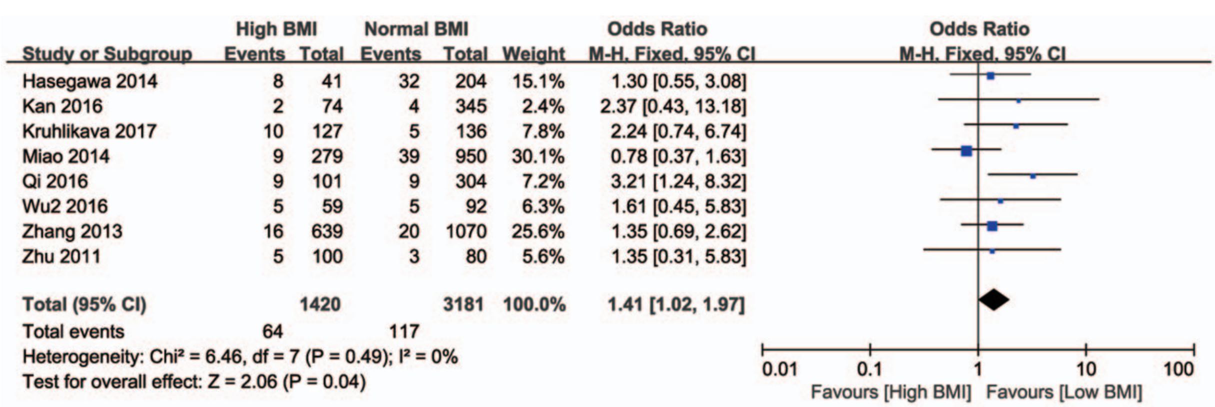

Figure 5. The forest plot of the correlation between BMI and wound infection (WI) in EC patients.

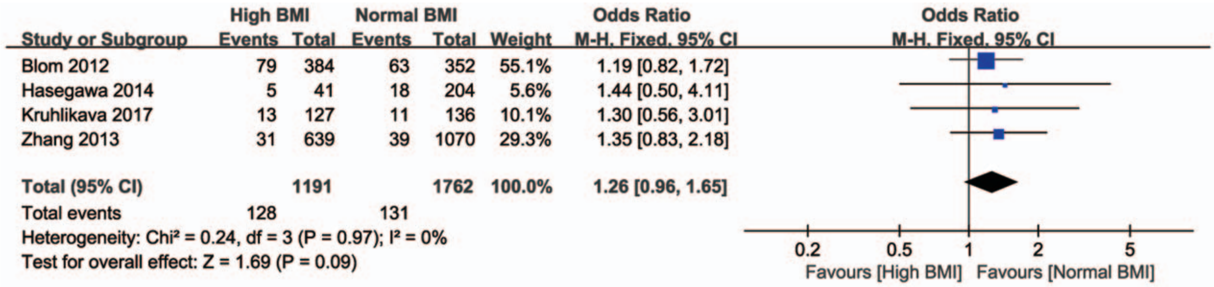

Figure 6. The forest plot of the correlation between BMI and severe complication (SC) in EC patients.

complications (OR: 1.26, 95% CI, 0 .95–1.68, $P=.11$) (Fig. 7) existed. However, from the results of this meta-analysis, we found that neither a statistically significant relationship between increased BMI and postoperative mortality, nor a marginal trend of higher incidence of mortality (HR=0.85; 95% CI, 0.65–1.11, $P=.23$) (Fig. 8) existed in high BMI patients treated with esophagectomy when compared with normal BMI patients.

3.4. Prognostic effect of high BMI on survival outcomes in EC patients

A total of 14 studies with 8396 patients came up with available data for the pooled analysis of the correlation between OS and BMI.[16–19,22,27–29,31,34,35,37–39] Considering the significant heterogeneity among the included studies ($P=.002$, $I^2=60\%$), a random-effects model was used to analyze the data. As shown in

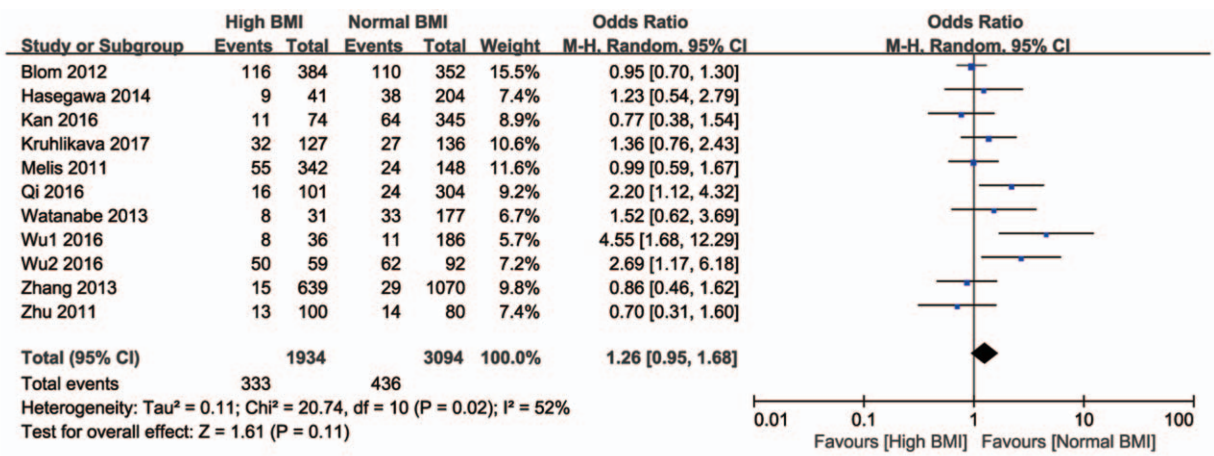

Figure 7. The forest plot of the correlation between BMI and pulmonary complication (PC) in EC patients.

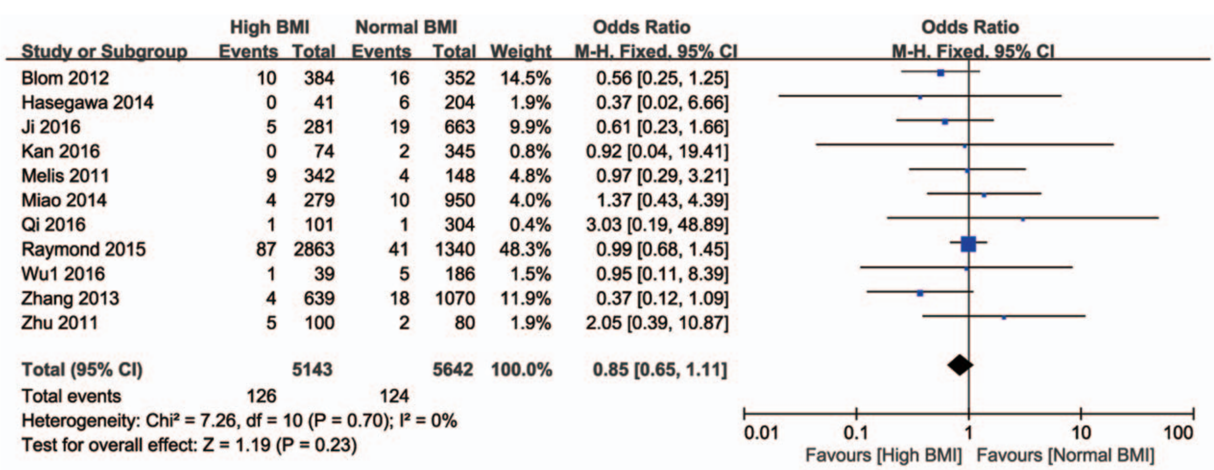

Figure 8. The forest plot of the correlation between BMI and postoperative in-hospital mortality (IHM) in EC patients.

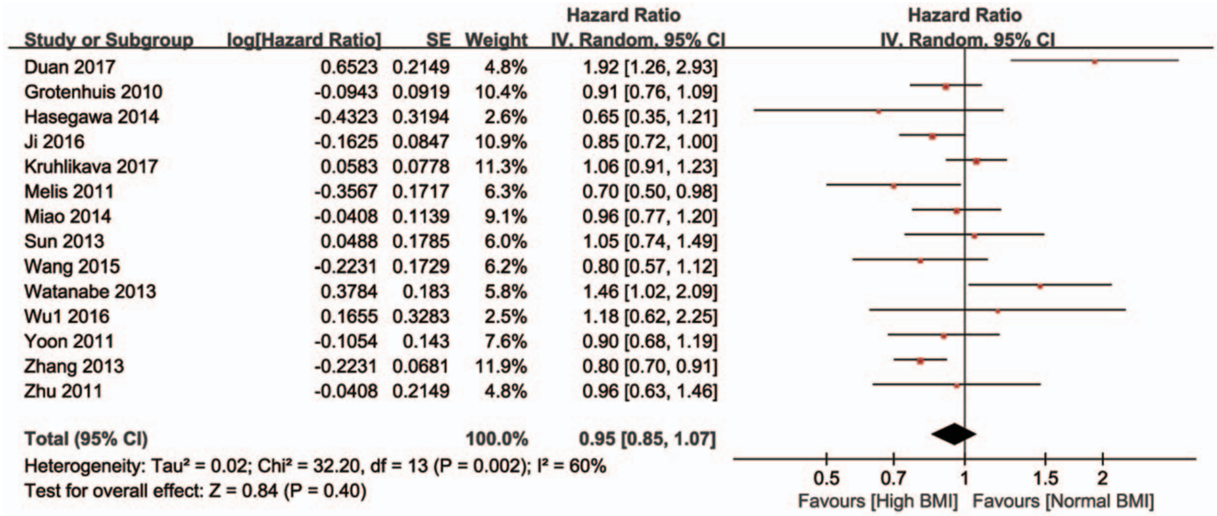

Figure 9. The forest plot of the correlation between BMI and overall survival (OS) in EC patients.

Figure 9, high BMI had no impact on OS among EC patients (HR: 0.95, 95% CI, 0.85–1.07, $P=.4$). Furthermore, to figure out if there was a difference in the impact of overweight and obesity on OS among EC patients, 5 studies were considered in calculating the HR,[18,19,27,28,39] and the result showed that overweight and obesity had similar effects on OS among EC patients (Fig. 10). In addition, 5 articles with 2239 patients were included for the meta-analysis of the association between BMI and DFS among EC patients.[16,17,19,35,38] Due to the existence of significant heterogeneity among the included studies ($P=.01$, $I^2=69\%$), a random-effects model was used to pool the HRs. As presented in Figure 11, high BMI did not impact DFS among EC patients after surgery (HR: 0.95, 95% CI, 0.72–1.25, $P=.72$).

3.5. Sensitivity and subgroup analysis

To explore the source of the heterogeneity and to verify the robustness of the pooled HR/OR for anastomotic leakage and OS, sensitivity analysis and subgroup analysis were performed. Our sensitivity analysis showed that the synthesized HR and OR

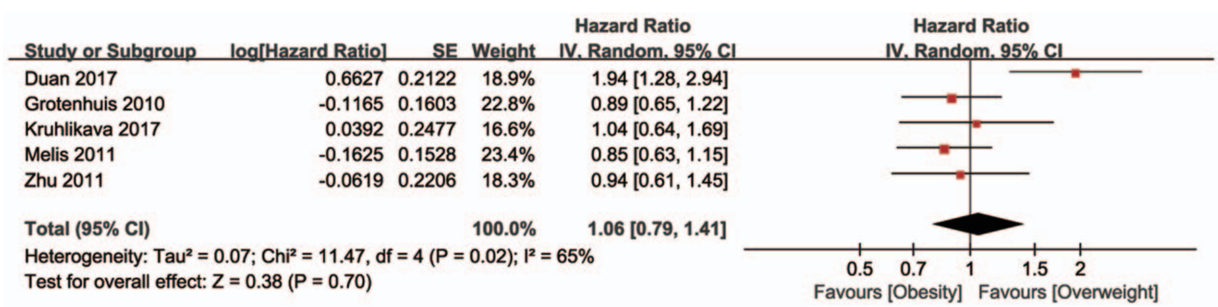

Figure 10. The forest plot of the effects of overweight and obesity on overall survival (OS) in EC patients.

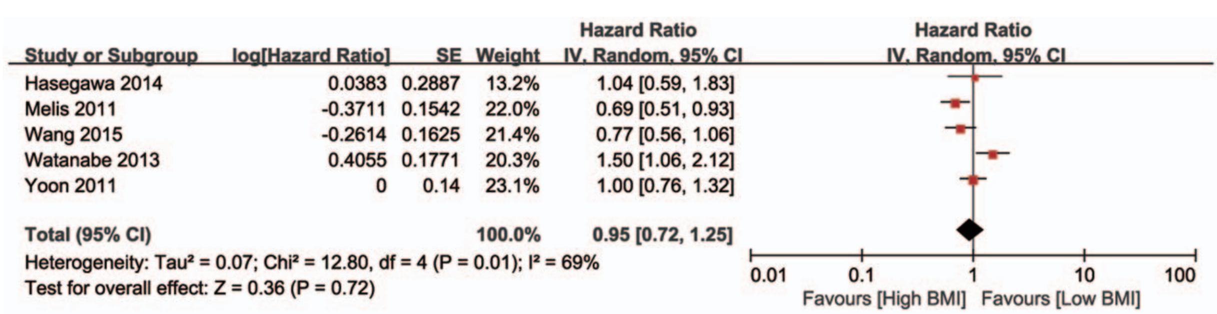

Figure 11. The forest plot of the correlation between BMI and disease-free survival (DFS) in EC patients.

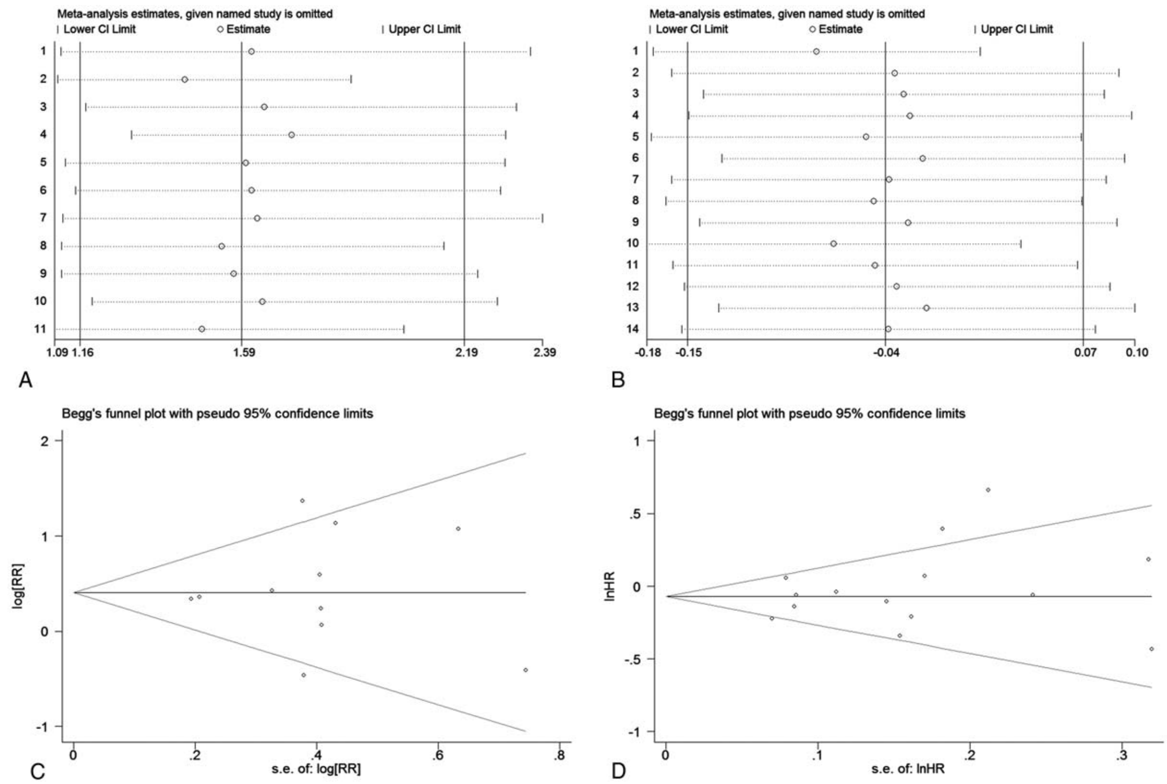

Figure 12. Sensitive analysis of meta-analysis results for anastomotic leakage (A) and overall survival (B); Begg funnel plot reflects the absence of significant publication bias in the meta-analysis of anastomotic leakage (C) and overall survival (D).

for the impact of high BMI on anastomotic leakage (Fig. 12A) and OS (Fig. 12B) was not significantly altered after excluding any single study, indicating the strength of the results of our meta-analysis. In addition, subgroup analyses were conducted based on tumor histopathological type, region, analysis types, and cutoff value. From the results of the subgroup analysis, we found that high BMI was still closely correlated with higher incidence of anastomotic leakage in the Asian population (OR = 1.69; 95% CI, 1.31–2.19; $P<.01$), cutoff value group (25 kg/m^2) (OR = 1.52; 95% CI, 1.19–1.94; $P<.01$), as well as in the EC or esophageal squamous cell carcinoma (ESCC) group (OR = 1.44; 95% CI, 1.14–1.80; $P<.01$; or OR = 1.89; 95% CI, 1.13–3.17; $P<.01$) (Table 3). It was observed that high BMI was closely correlated with a better OS in the multivariate analysis group (HR = 0.84; 95% CI, 0.76–0.93; $P<.01$), whereas there was still no significant correlation in the univariate analysis subgroup and other subgroups (Table 3). In general, the results of the subgroup analysis indicated that tumor histopathological type, region, analysis types, and cutoff value might not be responsible for the heterogeneity in OS, and that the pooled result of OS was stable, except that analysis type might influence the stability of our pooled results of OS.

3.6. Publication bias

The Begg test and Egger test, with Begg funnel plot, were performed to assess the publication bias among the included articles for anastomotic leakage and OS. The results suggested that there was no significant bias for the pooled HR/OR of anastomotic leakage (Begg test, $P=.938$; Egger test, $P=.754$) and OS (Begg tests, $P=.412$; Egger tests, $P=.298$), which were confirmed by the symmetry of the Begg funnel plots for anastomotic leakage (Fig. 12C) and OS (Fig. 12D). In general, the results of tests for publication bias suggested that our pooled results of anastomotic leakage and OS were reliable.

4. Discussion

Overall, in our meta-analysis, we found that increased BMI was closely associated with a higher incidence of wound infection, cardiovascular complications, and anastomotic leakage, but a lower incidence of chylous leakage as compared with normal BMI. In addition, although our meta-analysis showed that there was no statistically significant association between high BMI and severe complications and pulmonary complications, extreme marginal trends of higher incidence of severe complications and pulmonary complications in patients with high BMI were observed. However, our study indicated that there was neither a statistically significant relationship between increased BMI and postoperative mortality, nor marginal trends of higher incidence of mortality exist in high BMI patients undergoing esophagectomy when compared with patients with normal BMI. Furthermore, it was also observed that high BMI was not associated with better or worse OS and DFS, as compared with normal BMI, and obesity was not linked with better or worse OS in comparison with overweight either. Moreover, our subgroup analysis by tumor histopathological type also showed that BMI was not associated with postoperative OS in patients with ESCC. These results indicated that high BMI might not impact the prognosis of patients undergoing esophagectomy for EC.

Table 3

Subgroup analysis of predictive significance of high BMI in EC.

Variables	Studies	Patients	HR (95% CI)	*P*	Model	Heterogeneity I^2 (%)	Heterogeneity *P*
1. OS							
1.1 Tumor type							
ESCC	6	2348	1.05 [0.80–1.39]	.72	Randomized	76	<.01
EC	7	4689	0.91 [0.81–1.02]	.1	Fixed	44	.1
EAC	1	778	0.95 [0.85–1.07]	.46	–	—	—
1.2 Region							
Asian	10	5768	0.99 [0.84–1.16]	.89	Randomized	66	<.01
Non-Asian	4	2047	0.92 [0.79–1.07]	.29	Fixed	46	.14
1.3 Analysis type							
Univariate	10	3741	1.01 [0.87–1.17]	.93	Randomized	64	<.01
Multivariate	4	4074	0.84 [0.76–0.93]	<.01	Fixed	0	.43
1.4 Cutoff value							
23 kg/m^2	4	3177	0.95 [0.74–1.23]	.7	Randomized	80	<.01
25 kg/m^2	10	4638	0.97 [0.87–1.08]	.59	Fixed	30	.17
2. Anastomotic leakage							
2.1 Tumor type							
ESCC	3	858	1.89 [1.13–3.17]	.02	Fixed	0	.61
EC	8	5110	1.44 [1.14–1.80]	<.01	Fixed	38	.13
2.2 Region							
Asian	8	5257	1.69 [1.31–2.19]	<.01	Fixed	0	.46
Non-Asian	3	1489	1.19 [0.83–1.70]	.35	Fixed	46	.15
2.3 Cutoff value							
23 kg/m^2	1	1709	1.43 [0.96–2.15]	.08	—	—	—
25 kg/m^2	10	4259	1.52 [1.19–1.94]	<.01	Fixed	31	.16

BMI = body mass index, EAC = esophageal adenocarcinoma, EC = esophageal carcinoma, ESCC = esophageal squamous cell carcinoma, OS = overall survival.

Actually, several meta-analyses have been previously conducted to explore the impact of BMI on the surgical outcomes and postoperative prognoses of patients undergoing esophagectomy for EC.[21,22,40,41] Nevertheless, the conclusions from those meta-analyses were conflicting. For instance, as opposed to our study, the meta-analyses conducted by Zhang et al and Pan et al reported that high BMI was a potential predictor of better OS among EC patients overall treated with esophagectomy.[22,41] However, the meta-analysis conducted by Hong et al indicated that high BMI did not improve the prognosis in esophageal adenocarcinoma patients,[21] which was in accordance with our study. Furthermore, as compared with our meta-analyses, those meta-analyses had several limitations. First of all, most of the studies included in these meta-analyses did not differentiate between patients with low BMI and those with normal BMI, but rather combined patients with low BMI and normal BMI into a control group when investigating the association of high BMI with surgical outcomes and prognosis.[22,40,41] Actually, as compared with normal BMI, low BMI usually means that patients have malnutrition and poor tolerance to operations, which might worsen the surgical outcomes and prognosis. Hence, those previous meta-analyses might not accurately mirror the impact of high BMI on the surgical outcomes and prognosis in EC patients undergoing esophagectomy with the interference of the impacts of low BMI on outcomes. On the contrary, our meta-analysis used stricter inclusion criteria in that only studies in which low and normal BMI were clearly classified into 2 separate groups were included. Second, our meta-analysis included several recently published studies and had a larger sample size, which might make our pooled results more reliable. Third, although the meta-analysis conducted by Hong et al also differentiated between patients with normal BMI and those with low BMI and compared the influence of normal BMI and overweight on the prognosis, they only assessed the relationship between BMI and postoperative survival in patients with esophageal adenocarcinoma, but not to survival in patients with ESCC and surgical outcomes.[21]

From our meta-analysis, we found that there was a marginal trend of high BMI patients to a higher incidence of severe complications. However, only 4 studies with a small sample size provided available data for this pooled analysis, which might impact the reliability of the results and further studies are warranted to validate this finding. Patients with high BMI usually have more subcutaneous fat. Thus, patients with high BMI more frequently experience liquefaction of the incision site and sweating, which contribute to bacterial infection. Consistent with this, our meta-analysis showed that high BMI significantly increased the risk of wound infection. In general, wound infection might directly prolong the hospital stay and increase the risk of postoperative pulmonary complications, which might partly explain our finding in this meta-analysis that there was an extreme marginal trend of high BMI to higher incidence of pulmonary complications. Anastomotic leakage is the most horrible morbidity after esophagectomy for EC and the major cause of postoperative mortality. It has been reported that about 24% of patients would suffer from anastomotic leakage after esophagectomy.[42] Several studies reported that there was no significant association between high BMI and anastomotic leakage,[18,19,31] but our present meta-analysis, consistent with other previous studies, indicated that increased BMI was closely correlated with higher incidence of anastomotic leakage.[17,20] This could be due to the fact that overweight patients often tend to have comorbidities of pathoglycemia and dyslipidemia that are closely associated with microvascular injury, consequently dampening the microcirculation and promoting the development of anastomotic leakage. In addition, we also observed that high BMI was correlated with a higher incidence of cardiovascular complications as compared with normal BMI. However, the potential mechanisms have not fully been elucidated and need to be studied further. With respect to the incidence of postoperative in-hospital mortality, there was no significant difference between the normal and high BMI groups, although our meta-analysis indicated that high BMI was associated with higher incidence of several surgical outcomes in EC patients treated with esophagectomy, including severe complications, pulmonary complications, anastomotic leakage, cardiovascular complications, and wound infection. This could be partly be due to the low absolute incidence of postoperative mortality. Besides, the heterogeneity in our meta-analysis might also impact the robustness of our findings. Therefore, higher quality clinical trials with large sample sizes are still warranted to probe into the relationship between high BMI and postoperative mortality of EC patients treated with esophagectomy. Interestingly, high BMI patients inversely had a substantially reduced incidence of chylous leakage when compared with those with normal BMI. One of possible explanations for high BMI as a protective factor for the postoperative chylous leakage might be that high BMI patients have thicker surrounding tissues of esophagus, which leads to a lower risk of misinjury of thoracic duct during esophagus dissection. Generally, high BMI is associated with a higher incidence of several surgical complications as compared with normal BMI, but not with a higher risk of postoperative mortality. Thus, patients with EC should not be denied surgical treatment on account of being overweight. However, intraoperative prevention and careful postoperative monitoring for anastomotic leakage, wound infection, pulmonary complications, and cardiovascular complications must be stressed for overweight patients undergoing esophagectomy for EC.

With respect to prognosis in patients after esophagectomy for EC, some studies have reported better or worse impacts of high BMI on prognosis in EC patients treated with esophagectomy, whereas others have indicated no significant impact of high BMI on prognosis. Grotenhius et al showed that obesity significantly improved prognosis and indicated that a higher percentage of tumor-free circumferential resection margins might be obtained during esophagectomy for cancer in high BMI patients because more fat tissue in high BMI patients surround the tumor as compared with patients with normal BMI.[28] Contradictorily, obesity has been considered to have the potential to promote tumor progression by enhancing insulin signaling and chronic inflammation, which was characterized by altered modulation of cytokines and adipokines, such as tumor necrosis factor alpha, interleukin-6, leptin, and adiponectin.[38,43] The results of our meta-analysis suggested that high BMI exerted no impact on OS and DFS in EC patients overall, but the pooled result of HRs generated from multivariate analyses suggested that high BMI could improve OS in EC patients. Hence, the influence of high BMI on postoperative prognosis in EC patients is still controversial, and further studies are warranted.

There are some limitations in our meta-analysis. First, all the included studies were retrospectively designed, which might cause heterogeneity and bias. Although we have tried to find the sources of heterogeneity by performing subgroup analysis based on tumor histopathological type, study region, cutoff value, and analysis type, the results indicated that these factors might not mainly account for the sources of significant heterogeneity. Actually, the determinants of the long-term prognosis of cancer patients are very complex. In addition to those factors mentioned in the subgroup analysis of our meta-analysis, there are many other factors influencing the long-term prognosis, which might also lead to the significant heterogeneity of the results about OS and DFS, such as tumor stage, tumor location, surgical type, chemotherapy regimens, surgeon experience, and surgery volume. Second, the baseline characteristics of patients were inconsistently matched among the included studies, which might also lead to heterogeneity in our meta-analysis and reduce the robustness of our findings. Third, the cutoff value of high BMI was not identical across all the included studies. Fourth, only few studies with small sample sizes were available for the pooled analysis of the impact of high BMI on severe complications and DFS as compared with normal BMI, and of obesity on OS when compared with high BMI. Finally, in our subgroup analysis by tumor histopathological type, only 6 studies were available to explore the impact of BMI on survival in ESCC patients, but there was a lack of data to evaluate the influence of high BMI on survival in esophageal adenocarcinoma patients undergoing curative esophagectomy, which limited the clinical practice of our findings.

In summary, despite the aforementioned limitations, our study might still indicate that patients with EC should not be denied surgical treatment due to being overweight, but intraoperative prevention and careful postoperative monitoring for anastomotic leakage, wound infection, pulmonary complications, and cardiovascular complications should be stressed for overweight patients undergoing esophagectomy for EC. Besides, the influence of high BMI on the postoperative prognosis of EC patients remains controversial, and further studies are warranted.

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