



Predictive Value of Body Mass Index for Short-Term Outcomes of Patients with Esophageal Cancer After Esophagectomy: A Meta-analysis

Peiyu Wang, MD¹, Yin Li, MD, PhD^{1,2}, Haibo Sun, MD, PhD¹, Shilei Liu, MD¹, Ruixiang Zhang, MD, PhD¹, Xianben Liu, MD¹, and Zhengshuai Zhu, MD¹

¹Department of Thoracic Surgery, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan, China; ²Department of Thoracic Surgical Oncology, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ABSTRACT

Background. The association between body mass index (BMI) and short-term outcomes after esophagectomy remains controversial.

Methods. A meticulous search for articles describing the association between BMI and perioperative outcomes after esophagectomy was conducted using PubMed, EMBASE, and the Cochrane Library. The study classified BMI according to the World Health Organization definitions and Asian-specific BMI cutoff values. Normal weight was selected as the comparator, and the odds ratio (OR) was calculated as the primary effect.

Results. This meta-analysis included 13 studies with 5480 patients. Obese patients exhibited higher risks of overall complication (OR 1.37; $P = 0.013$), anastomotic leakage (OR 1.74; $P = 0.001$), and thromboembolic complications (OR 2.05; $P = 0.039$). Subgroup analysis indicated that obese patients from Western countries had a higher risk of wound infection (OR 2.22; $P = 0.022$), whereas obese Asians were more likely to experience pulmonary complications (OR 1.64; $P = 0.002$). Overweight patients displayed no significant differences in major complications relative to normal-weight patients, except for the increased risk of overall complications (OR 1.32; $P = 0.030$). Additionally, underweight patients showed increased incidence of pulmonary complications (OR 1.92; $P = 0.020$) and anastomotic leakage (OR 1.64; $P = 0.034$). Morbid obesity

also was analyzed separately with limited data, and this group displayed a higher risk of wound infection (OR 1.62; $P = 0.027$) and thromboembolic complications (OR 2.65; $P = 0.003$). No significant differences in mortality were observed among patients in different BMI categories.

Conclusions. Obesity and underweight statuses were confirmed risk factors for several complications after esophagectomy, whereas overweight patients tended to experience greater benefit from surgery.

Esophageal cancer is the 11th most common cancer and the 6th most common cause of perioperative mortality worldwide¹. Esophagectomy or neoadjuvant chemoradiotherapy followed by surgery is the standard curative treatment for esophageal cancer.^{2,3} Although surgery techniques and perioperative management have significantly improved during the past few decades, esophagectomy for malignant disease still is associated with a high incidence of morbidity, with pneumonia, atrial dysrhythmia, and anastomotic leakage as the most common individual complications.⁴

Studies have confirmed that major perioperative complications are associated with early recurrence and unfavorable long-term survival after esophagectomy.^{5,6} Therefore, patients with esophageal cancer may benefit from the early prevention and detection of perioperative complications.

Body mass index (BMI), calculated as weight in kilograms divided by height in square meters (kg/m^2), is a confirmed risk factor for esophageal and gastroesophageal junction adenocarcinomas (ACs).^{7,8} However, the association between BMI and short-term perioperative outcomes remains controversial. Differences in demographic data

and various BMI categories make it difficult to obtain a consensus definition among studies.^{9–21} A meta-analysis by Kayani et al.²² did not report significant differences in perioperative mortality or complications between obese patients and non-obese patients. A recent meta-analysis including only Western studies confirmed a higher incidence of anastomotic leakage in obese patients than in non-obese patients.²³ From our perspective, normal weight is a better comparator for investigating the risks associated with individual BMI categories.

Disease characteristics differ significantly between Western and Eastern populations. Whereas obesity in Western countries is congruously defined as a BMI of 30 kg/m² or higher, a BMI of 25 kg/m² or higher is more commonly used to diagnose obesity in Asians, according to the Asian-specific BMI cut-off, and this classification suits the nutritional status and comorbidities of Asians.^{24–27} In this meta-analysis, we attempted to combine the obese patients in Western studies (BMI \geq 30 kg/m²) and Asian studies (BMI \geq 25 kg/m²) to investigate the risks of mortality and postoperative complications.

This study aimed to investigate the predictive value of BMI in determining short-term outcomes for patients with esophageal cancer after esophagectomy.

MATERIALS AND METHODS

The protocol of this meta-analysis was registered with the international prospective register of systematic reviews, PROSPERO, with the identification code CRD42018085853. The meta-analysis was performed under the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁸

Search Strategy

Two reviewers (Z.Z. and P.W.) independently performed a systematic literature search using the databases PubMed, EMBASE, and the Cochrane Library for papers published until May 2018. The following medical subject headings were combined: “esophageal cancer or esophageal neoplasms”, “esophagectomy or esophageal surgery”, “body mass index or obese or overweight”, and “complications or outcomes.” References of retrieved articles were manually checked for additional relevant studies. Any disagreement was resolved by an advisory group consisting of three senior authors (Y.L., H.S. and S.L.). When overlapping data from the same patient population were included in more than one publication, only the most recent and informative publication was included in the meta-analysis.

Study Selection

Studies were included if they fulfilled the following criteria: patients with esophageal cancer who underwent surgery, a clear definition of individual BMI categories according to the World Health Organization (WHO) classification or Asian-specific BMI cutoff value, homogeneous cohorts of patients with BMI as an independent variable between groups, an analysis of at least one of the outcomes of interests, and publication in English. The exclusion criteria ruled out reviews or case reports, studies sharing the same population, studies in which esophageal cancer could not be independently analyzed, and studies in which data from normal-weight patients were unavailable.

Outcomes of Interest

The following outcome measures were used to compare the different BMI groups: mortality (30-day or in-hospital), overall complications, pulmonary complications (or pneumonia), cardiac complications (or arrhythmia), anastomotic leakage, wound infection (or surgical-site infection), thromboembolic complications (or pulmonary embolus), and anastomotic stenosis. The former measure in each group was the preferred target for different complication types, and the latter measure was adopted if the former was not available.

Data Extraction

The extracted data included the first author, year of publication, country in which the study was conducted, study type, inclusion period, population size, demographic characteristics (age, smoking history, diabetes, weight loss, American Society of Anesthesiologists [ASA] score and BMI cutoff), disease characteristics (tumor location, histology, clinical and pathologic stage), multimodal treatment (neoadjuvant therapies and type of surgical procedure), and surgical outcomes (operation time, mortality and complications).

Quality Assessment

The Newcastle-Ottawa Scale (NOS), consisting of eight clauses and nine scoring points, was used to determine methodologic quality.²⁹ Studies with a total score higher than 7 points were considered to have been adequately conducted. Two authors (Z.Z. and P.W.) independently extracted the evaluation program and assessed the full texts. Any disagreement was resolved by discussion with the advisory group. Additional information and data

needed for the meta-analysis were obtained by e-mailing the authors.

BMI Categories

In this meta-analysis, BMI was classified according to the WHO definitions and Asian-specific BMI cutoff as follows: underweight (BMI < 18.5 kg/m²), normal weight (BMI 18.5–24.9 kg/m²), overweight (BMI 25.0–29.9 kg/m² for Western studies), obesity (BMI ≥ 30.0 kg/m² for Western population and BMI ≥ 25.0 kg/m² for Asian population), and morbid obesity (BMI ≥ 35.0 kg/m²).^{24,26} It was difficult to group obese patients due to the lack of corresponding BMI categories in original articles. We attempted to investigate the characteristics of morbidly obese patients, although some overlap in data existed between obesity group and morbid obesity group in our BMI categories. Normal-weight group was selected as the comparator.

Statistical Analysis

We assessed and quantified statistical heterogeneity for each pooled estimate using Cochran's Chi square (χ^2 -based Q statistical test and the I-squared (I^2) statistic. Significant heterogeneity was confirmed if P was 0.1 or less or I^2 was 50% or more. Once high heterogeneity was confirmed, a random effects model was adopted or a subgroup analysis was performed. Otherwise, a fixed effects model was used. Pooled analysis was performed using the Mantel–Haenszel (MH) model, and the data are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A two-tailed P value lower than 0.05 was considered statistically significant. A funnel plot was used to assess publication bias. Sensitivity analyses were conducted to evaluate the overall results after specific studies were omitted. All analyses were conducted with STATA version 12 software (Stata Corporation, College Station, TX, USA).

RESULTS

Search Results and Included Trials

During the initial screen, 250 articles were identified. A review of titles and abstracts led to the exclusion of 170 articles, and 13 articles were ultimately eligible after the evaluation of full articles.^{9–21} The meticulous literature search and filtering process are shown in the PRISMA flowchart (Fig. 1).

This meta-analysis involved 5480 patients, with 3528 patients from nine Western studies and 1952 patients from four Asian studies. The NOS quality scores ranged from 6

to 7 points, suggesting that the quality of the eligible articles was moderate to high. The characteristics of the patients examined in the selected articles are shown in Table 1.

Meta-analysis of Patient Characteristics

Compared with patients of normal weight, prominent differences were detected in the clinical characteristics of obese and underweight patients. Considering the influence of these confounding factors, we performed meta-analyses to investigate the differences in these factors among different BMI categories, and the outcomes are shown in Table 2.

Obese patients were more likely to experience diabetes than normal-weight patients,^{10–12,15–19} with fewer having a history of smoking^{9–12,17–19} before surgery (OR 2.52; $P < 0.001$ and OR 0.77; $P = 0.006$, respectively). Additionally, this group displayed a greater percentage of AC^{9–11,13} (OR 4.92; $P < 0.001$) and an earlier clinical tumor stage^{10–16} (OR 1.67; $P < 0.001$). Similar characteristics were observed among morbidly obese patients, but an increased rate of cardiac disease^{10,20} (OR 1.52; $P = 0.030$) was identified than for normal-weight patients. Compared with normal-weight patients, overweight patients also displayed a greater prevalence of diabetes^{10–12,15} (OR 1.62; $P = 0.011$) and a greater percentage of AC^{9–11,13} (OR 2.67; $P < 0.001$) but a smaller scale of ASA scores (3–4)^{9,11–13} (OR 0.70; $P = 0.003$). A meta-analysis of underweight patients showed a greater percentage of patients with a history of smoking,^{9–11,17–19} (OR 1.63; $P = 0.001$) a greater percentage of squamous cell carcinoma (SCC),^{9–11} (OR 0.23; $P < 0.001$), and more advanced pathologic tumor stages^{10,11,16–19} (OR 0.63; $P < 0.001$) than normal-weight patients.

Meta-analyses of the Incidence Rates (IRs) for Mortality and Postoperative Complications

Meta-analyses of the IRs for mortality and postoperative complications were performed, and the outcomes are shown in Table 3. Normal-weight patients displayed the lowest IRs for most postoperative complications, whereas the lowest IR for pulmonary complications was observed in the overweight group. Obese patients showed the highest IRs for thromboembolic complications (IR, 7.1%; 95% CI 1.3–12.8%) and anastomotic stenosis (IR, 12.6%; 95% CI, 8.7–16.5%) but the lowest IR for mortality (IR, 2.0%; 95% CI 1.1–3.0%). Underweight patients displayed higher IRs for overall complications (IR, 62.3%; 95% CI 35.2–89.4%) and pulmonary complications (IR, 25.6%; 95% CI 15.8–35.5%) than the other groups. Morbidly obese patients were more likely to experience anastomotic

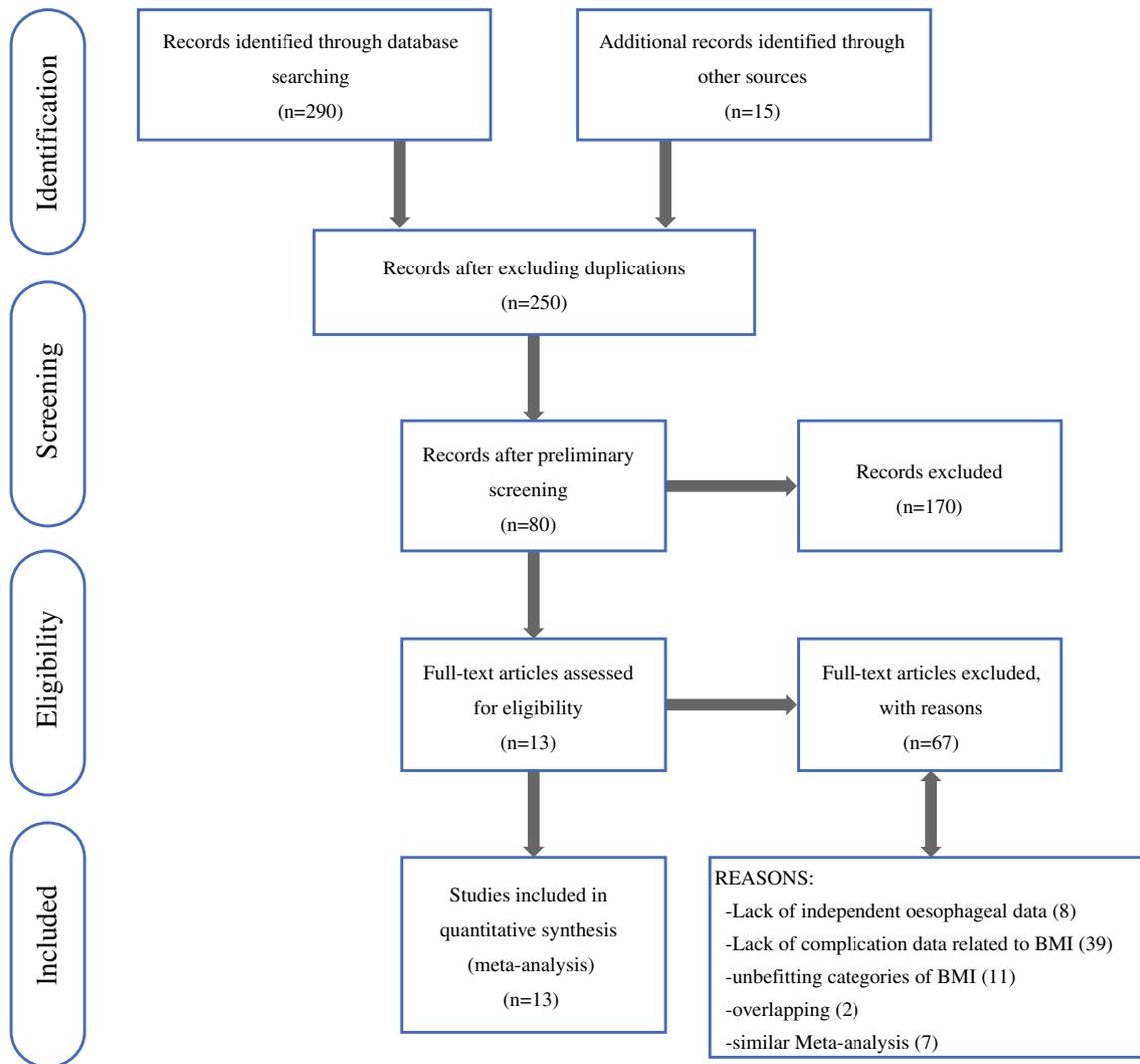


FIG. 1 Literature search/PRISMA flow-chart displaying the meticulous literature search and filtering process used in the meta-analysis without special instructions. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

leakage (IR, 12.7%; 95% CI 0.8–24.7%) and wound infection (IR, 9.9%; 95% CI 1.7–18.1%) after esophagectomy.

Meta-analyses of Mortality and Postoperative Complications for Different BMIs Compared with the Normal-Weight Group

Pooled outcomes for obese patients compared with outcomes for normal-weight patients are shown in Fig. 2. For obese patients, studies show significantly increased risks of overall complications,^{10–14,16} (OR 1.37; $P = 0.013$) anastomotic leakage,^{9,12–19} (OR 1.74; $P = 0.001$), and thromboembolic complications^{10,12–14} (OR 2.05; $P = 0.039$). Additionally, this group has displayed trends toward higher risks of pulmonary complications,^{9–19} (OR 1.18; $P = 0.050$) cardiac complications,^{10–14,17–19} (OR

1.32; $P = 0.071$), and wound infection,^{9,12–14,17,18} (OR 1.35; $P = 0.155$) but the differences have not been statistically significant.

Considering the substantial heterogeneity in the comparison of pulmonary complications ($I^2 = 37.0\%$; $P = 0.270$), a subgroup analysis examined the country of each study. Asian studies^{16–19} showed a significant increase in pulmonary complications (OR 1.64; $P = 0.002$) for obese patients compared to the normal-weight patients, whereas Western studies^{9–15} did not report significant differences between the two groups (OR 0.91; $P = 0.528$). A subgroup analysis of wound infection also was performed, but only Western studies^{9,12–14} showed an increased risk (OR 2.22; $P = 0.022$) for obese patients. No significant publication bias was observed for any comparisons, nor was the positive outcome affected by the sensitivity analysis.

TABLE 1 Patient characteristics of 13 studies included in the meta-analysis

| Author (publication year) | NOS score | Study design | Country | Inclusion period | Sample size | Histology (%) | Neoadjuvant therapy (%) | Type of surgery TTE/THE/MIE | Original categories of BMI: kg/m ² (no. of patients) | Groups in the study | | | | | |
|---------------------------------------|-----------|--------------|-------------|------------------|-------------|---------------------|-------------------------|-----------------------------|---|---------------------|-----|-----|-----|-----|--|
| | | | | | | | | | | UW | NW | OW | OB | MO | |
| Kruhlikava et al. ⁹ (2017) | 7 | Retro | Denmark | 2003–2010 | 285 | AC (66) SCC (29) | 0 | NR | <18.5, 18.5–24.9, 25–29.9, ≥ 30 (22/136/104/23) | 22 | 136 | 104 | 23 | – | |
| Wightman et al. ¹⁰ (2017) | 7 | Retro | USA | 2000–2013 | 388 | AC (75) SCC (17) | nAT (55) | 78/143/ 134 | <18.5, 18.5–24.9, 25–29.9, 30–34.5, ≥ 35 (21/107/117/85/43) | 21 | 107 | 117 | 128 | 43 | |
| Salem et al. ¹³ (2016) | 7 | Retro | USA | 2010–2013 | 129 | AC (88) SCC (8) | nAT (76) | 0/0/129 | 18.5–25, 25–29.9, ≥ 30 (28/56/45) | – | 28 | 56 | 45 | – | |
| et al. ¹⁹ (2016) | 6 | Retro | China | 2003–2008 | 306 | AC (32) SCC (68) | 0 | 239/0/0 | <20, 20–24.9, ≥ 25 (81/186/39) | 81 | 186 | – | 39 | – | |
| Hasegawa et al. ¹⁸ (2015) | 6 | Retro | Japan | 2002–2012 | 304 | SCC (100) | nAT (36) | 304/0/0 | <18.5, 18.5–24.9, ≥ 25 (59/204/41) | 59 | 204 | – | 41 | – | |
| Miao et al. ¹⁷ (2014) | 7 | Retro | China | 2006–2012 | 1342 | AC (2) SCC (95) | 0 | 1342/0/0 | <18.5, 18.5–24.9, ≥ 25 (113/950/279) | 113 | 950 | – | 279 | – | |
| Bhayani et al. ²⁰ (2013) | 6 | Retro | USA | 2005–2010 | 794 | NR | nCT (8) nRT (29) | 490/–/– | 18.5–25, ≥ 35 (578/216) | – | 578 | – | – | 216 | |
| Melis et al. ¹² (2013) | 7 | Retro | USA | 1994–2011 | 540 | AC (100) | nAT (60) | 373/49/ 117 | 18.5–24.9, 25–29.9, ≥ 30 (155/198/187) | – | 155 | 198 | 187 | – | |
| Scarpa et al. ¹¹ (2013) | 6 | Pro | Italy | 2000–2008 | 278 | AC (50) SCC (47) | nAT (47) | 278/0/0 | <20, 20–24.9, 25–29.9, ≥ 30 (15/81/121/61) | 15 | 81 | 121 | 61 | – | |
| Watanabe et al. ¹⁶ (2013) | 7 | Retro | Japan | 2005–2010 | 243 | SCC (100) | nCT (21) nCRT (19) | 240/7/0 | <18.5, 18.5–24.9, ≥ 25 (35/177/31) | 35 | 177 | – | 31 | – | |
| Blom et al. ¹⁵ (2012) | 6 | Pro | Netherlands | 1993–2010 | 736 | AC (74) SCC (22) | 0 | 271/465/0 | <25, 25–29.9, ≥ 30 (352/308/72) | – | 352 | 308 | 72 | – | |
| Shridhar et al. ¹⁴ (2012) | 6 | Retro | USA | 2000–2011 | 303 | AC (100) | nCRT (100) | 246/57/0 | <25, 25–29.9, 30–35, ≥ 35 (103/109/59/32) | – | 103 | 109 | 59 | 32 | |
| Scipione et al. ²¹ (2007) | 6 | Retro | USA | 1997–2006 | 204 | AC (91) SCC (9) | nCT (50) nRT (50) | 0/204/0 | 18.5–30.0, ≥ 35 (102/102) | – | 102 | – | – | 102 | |

NOS Newcastle-Ottawa Scale, TTE transthoracic esophagectomy, THE transhiatal esophagectomy, MIE minimally invasive esophagectomy, BMI body mass index, UW underweight (BMI < 18.5 kg/m²), NW normal-weight (BMI 18.5–24.9 kg/m²), OW overweight (BMI 25.0–29.9 kg/m²), OB obesity (BMI ≥ 30.0 kg/m² for western studies and BMI ≥ 25.0 kg/m² for Asian studies), MO morbid obesity (BMI ≥ 35.0 kg/m²), Retro, retrospective cohort study, AC adenocarcinoma, SCC squamous cell carcinoma, NR not reported, USA United States of America, nAT neoadjuvant therapy, Pro prospective cohort study, nCT neoadjuvant chemotherapy, nRT neoadjuvant radiotherapy, nCRT neoadjuvant chemoradiotherapy

TABLE 2 Meta-analysis of characteristics of patients with different categories of BMI

| Comparisons (vs NW) | No. of studies | No. of cases | <i>P</i> value | OR (95% CI) | Heterogeneity | |
|---|----------------|--------------|--------------------|-------------------------------|--|-----------------------------|
| | | | | | <i>I</i> ² (%) ^a | <i>P</i> value ^b |
| Smoking history | | | | | | |
| OB | 7 | 2577 | 0.006 | 0.77 (0.63–0.93) | 42.3 | 0.109 |
| OW | 3 | 1019 | 0.307 | 0.87 (0.67–1.14) | 0 | 0.667 |
| UW | 6 | 1975 | 0.001 | 1.63 (1.23–1.25) | 16.5 | 0.307 |
| MO | 2 | 944 | < 0.001 | 0.46 (0.32–0.66) | 0 | 0.435 |
| Diabetes | | | | | | |
| OB | 8 | 3047 | < 0.001 | 2.52 (1.91–3.31) | 0 | 0.858 |
| OW | 4 | 1439 | 0.011 | 1.62 (1.12–2.36) | 0 | 0.825 |
| UW | 6 | 2031 | 0.088 | 0.65 (0.40–1.07) | 0 | 0.887 |
| MO | 2 | 944 | < 0.001 | 2.15 (1.45–3.19) | 0 | 0.475 |
| Cardiac disease | | | | | | |
| OB | 6 | 1397 | 0.175 | 1.24 (0.91–1.70) | 0 | 0.720 |
| OW | 3 | 779 | 0.683 ^c | 1.15 (0.59–2.22) ^c | 68.4 | 0.042 |
| UW | 5 | 966 | 0.319 ^c | 0.61 (0.23–1.62) ^c | 57.6 | 0.051 |
| MO | 2 | 944 | 0.030 | 1.52 (1.04–2.22) | 0 | 0.629 |
| ASA score (3–4) | | | | | | |
| OB | 5 | 1080 | 0.937 | 1.01 (0.75–1.36) | 0 | 0.514 |
| OW | 5 | 1469 | 0.003 | 0.70 (0.55–0.88) | 0 | 0.941 |
| UW | 2 | 251 | 0.765 | 1.12 (0.53–2.39) | 0 | 0.905 |
| Histopathology (AC) ^d | | | | | | |
| OB | 4 | 962 | < 0.001 | 4.92 (2.93–8.25) | 0 | 0.478 |
| OW | 5 | 1349 | < 0.001 | 2.67 (2.06–3.47) | 14.7 | 0.320 |
| UW | 3 | 354 | < 0.001 | 0.23 (0.12–0.45) | 15.2 | 0.307 |
| Clinical stage (early stage) ^e | | | | | | |
| OB | 6 | 1263 | < 0.001 | 1.67 (1.25–2.23) | 44.5 | 0.109 |
| OW | 6 | 1546 | 0.116 | 1.24 (0.95–1.61) | 0 | 0.664 |
| UW | 3 | 422 | 0.068 | 0.46 (0.20–1.06) | 33 | 0.225 |
| MO | 2 | 252 | 0.006 | 2.38 (1.29–4.41) | 0 | 0.860 |
| Pathologic stage (early stage) ^f | | | | | | |
| OB | 7 | 2666 | 0.143 | 1.16 (0.95–1.41) | 29.4 | 0.204 |
| OW | 3 | 1072 | 0.191 | 1.23 (0.91–1.64) | 33.4 | 0.223 |
| UW | 6 | 2001 | < 0.001 | 0.63 (0.49–0.80) | 0 | 0.642 |

BMI body mass index, *OR* odds ratio, *CI* confidence interval, *NW* normal weight (BMI 18.5–24.9 kg/m²), *OB* obesity (BMI ≥ 30.0 kg/m² for western studies and BMI ≥ 25.0 kg/m² for Asian studies), *OW* overweight (BMI 25.0–29.9 kg/m²), *UW* underweight (BMI < 18.5 kg/m²), *MO* morbid obesity (BMI ≥ 35.0 kg/m²), *ASA* American Society of Anesthesiologists, *AC* adenocarcinoma

^aCalculated with *I*-square (*I*²) statistic

^bCalculated with Cochran's Chi square (χ^2)-based *Q* statistic test

^cCalculated with random-effects Mantel–Haenszel model

^dOnly Western studies were included, and the histopathology types were restricted to adenocarcinoma and squamous cell carcinoma

^eDefined as American Joint Committee on Cancer (AJCC) stage 0–2 or T stage 0–2

^fDefined as AJCC stage 0–2

Figure 3 shows the forest plots for mortality and complications in overweight patients and normal-weight patients after esophagectomy. No significant difference in complications was observed for overweight patients

compared with normal-weight patients, except for an increased risk of overall complications^{10–14} (OR 1.32; *P* = 0.030). Moreover, overweight patients showed trends toward lower risks of mortality^{10–15} (OR 0.66; *P* = 0.137)

TABLE 3 Meta-analysis of the incidence rates (IRs)^a for motility and postoperative complications of patients in different BMI categories

| Outcomes | All patients | | UW | | NW | | OW | | OB | | MO | |
|------------------------------|--------------|-----------|------------------|------------|------|-----------|------------------|-----------|-------------------|-----------|-------------------|------------|
| | IRs | 95% CI | IRs | 95% CI | IRs | 95% CI | IRs | 95% CI | IRs | 95% CI | IRs | 95% CI |
| Mortality | 2.5 | 1.8–3.2 | 2.2 ^b | 0.0–4.3 | 2.7 | 1.6–3.7 | 2.3 ^b | 1.3–3.3 | 2.0 | 1.1–3.0 | 2.4 ^b | 0.8–4.0 |
| Overall complications | 42.6 | 33.5–51.7 | 62.3 | 35.2–89.4 | 37.8 | 28.3–47.3 | 44.4 | 30.3–58.6 | 44.7 | 33.3–56.1 | 54.4 ^b | 48.7–60.1 |
| Pulmonary complications | 16.2 | 12.3–20.1 | 25.6 | 15.8–35.5 | 16.7 | 12.4–21.1 | 15.2 | 7.6–22.7 | 17.2 | 13.0–21.5 | 17.3 | 11.2–23.3 |
| Cardiac complications | 11.1 | 7.5–14.6 | 12.6 | 4.4–20.8 | 8.9 | 6.0–11.8 | 15.5 | 9.5–21.5 | 12.0 | 6.5–17.5 | 12.2 | 2.4–22.0 |
| Anastomotic leakage | 6.2 | 5.5–6.9 | 7.8 ^b | 4.8–10.7 | 4.8 | 3.9–5.6 | 5.1 | 1.6–8.6 | 10.3 | 6.6–13.9 | 12.7 | 0.8–24.7 |
| Wound infection | 6.4 | 3.8–9.0 | 7.1 | – 0.8–15.1 | 6.1 | 3.5–8.7 | 6.8 ^b | 4.4–9.3 | 6.3 | 2.9–9.2 | 9.9 | 1.7–18.1 |
| Thromboembolic complications | 3.6 | 1.7–5.5 | – | – | 2.1 | 0.5–3.6 | 2.9 ^b | 1.4–4.4 | 7.1 | 1.3–12.8 | 5.8 ^b | 3.1–8.5 |
| Anastomotic stenosis | 6.0 | 1.2–10.8 | – | – | 4.5 | 0.6–8.3 | 7.3 | 1.0–15.6 | 12.6 ^b | 8.7–16.5 | 7.6 | – 0.6–21.2 |

UW underweight (BMI < 18.5 kg/m²), NW normal-weight (BMI 18.5–24.9 kg/m²), OW overweight (BMI 25.0–29.9 kg/m²), OB obesity (BMI ≥ 30.0 kg/m² for western studies and BMI ≥ 25.0 kg/m² for Asian studies), MO morbid obesity (BMI ≥ 35.0 kg/m²), IRs incidence rates, CI confidence interval

^aAll IRs were expressed as percentages

^bCalculated with fixed-effect Mantel–Haenszel model; other values calculated with random-effects Mantel–Haenszel model

and pulmonary complications^{9–15} (OR 0.86; $P = 0.187$) but higher risks of cardiac complications^{10–14} (OR 1.40; $P = 0.066$) and wound infection^{9,12,14} (OR 1.81; $P = 0.071$), but the differences were not statistically significant. Notably, significant publication bias was observed in the comparison of wound infection, thromboembolic complications, and anastomotic stenosis, according to the funnel plots.

Compared with the normal-weight group, the underweight group exhibited increased risks of pulmonary complications^{9–11,16–19} (OR 1.92; $P = 0.020$) and anastomotic leakage^{9,16–19} (OR 1.64; $P = 0.034$) (Fig. 4). No significant differences in mortality,^{10,11,17–19} (OR 1.04; $P = 0.921$) cardiac complication,^{10,11,17–19} (OR 1.63; $P = 0.163$) or wound infection^{9,17,18} (OR 0.93; $P = 0.824$) were observed between the two groups. Additionally, the underweight group displayed a trend toward a higher incidence of overall complication^{10,11,16} (OR 2.31; $P = 0.051$) but the difference was not significant according to the random effect model. Significant publication bias and positive outcomes for the sensitivity analysis were not observed for any comparisons. We did not perform a meta-analysis of thromboembolic complications and anastomotic stenosis due to the lack of corresponding data in the included studies.

We also investigated the risks of mortality and postoperative complications for morbidly obese patients, and the outcomes are shown in Fig. 5. This group displayed higher risk of wound infection^{14,20,21} (OR 1.62; $P = 0.027$) and thromboembolic complications^{10,14,20} (OR 2.65; $P = 0.003$) than the normal-weight group. No significant

differences in mortality (OR 0.69; $P = 0.303$), pulmonary complications (OR 1.06; $P = 0.723$), or cardiac (OR 0.90; $P = 0.647$) complications were identified between the two groups.^{10,14,20,21} In addition, the morbidly obese group showed a trend toward an increased incidence of overall complication^{10,14,20} (OR 1.30; $P = 0.055$), but the difference was not statistically significant.

DISCUSSION

The incidence of obesity is rapidly increasing in Western countries and is widely reported to be associated with a high risk of major complications after surgery.^{30,31} A meta-analysis by Kayani did not report significant differences in perioperative mortality or complications between obese patients and non-obese patients,²² whereas a recent meta-analysis including only Western studies confirmed a higher incidence of anastomotic leakage in obese patients than in non-obese patients.²³

Our meta-analyses demonstrated higher incidence of overall complications, anastomotic leakage, and thromboembolic complications for obese patients than for normal-weight patients. Moreover, obese patients in Western countries had a higher risk of wound infection, whereas obese Asians were more likely to experience pulmonary complications. An increased incidence of diabetes among obese patients was observed, and diabetes was confirmed to be a risk factor for wound infection and anastomotic leakage in previous studies.^{32,33} The similar percentage of subjects with cardiac disease and ASA scores of 3 to 4 among obese and normal-weight patients may

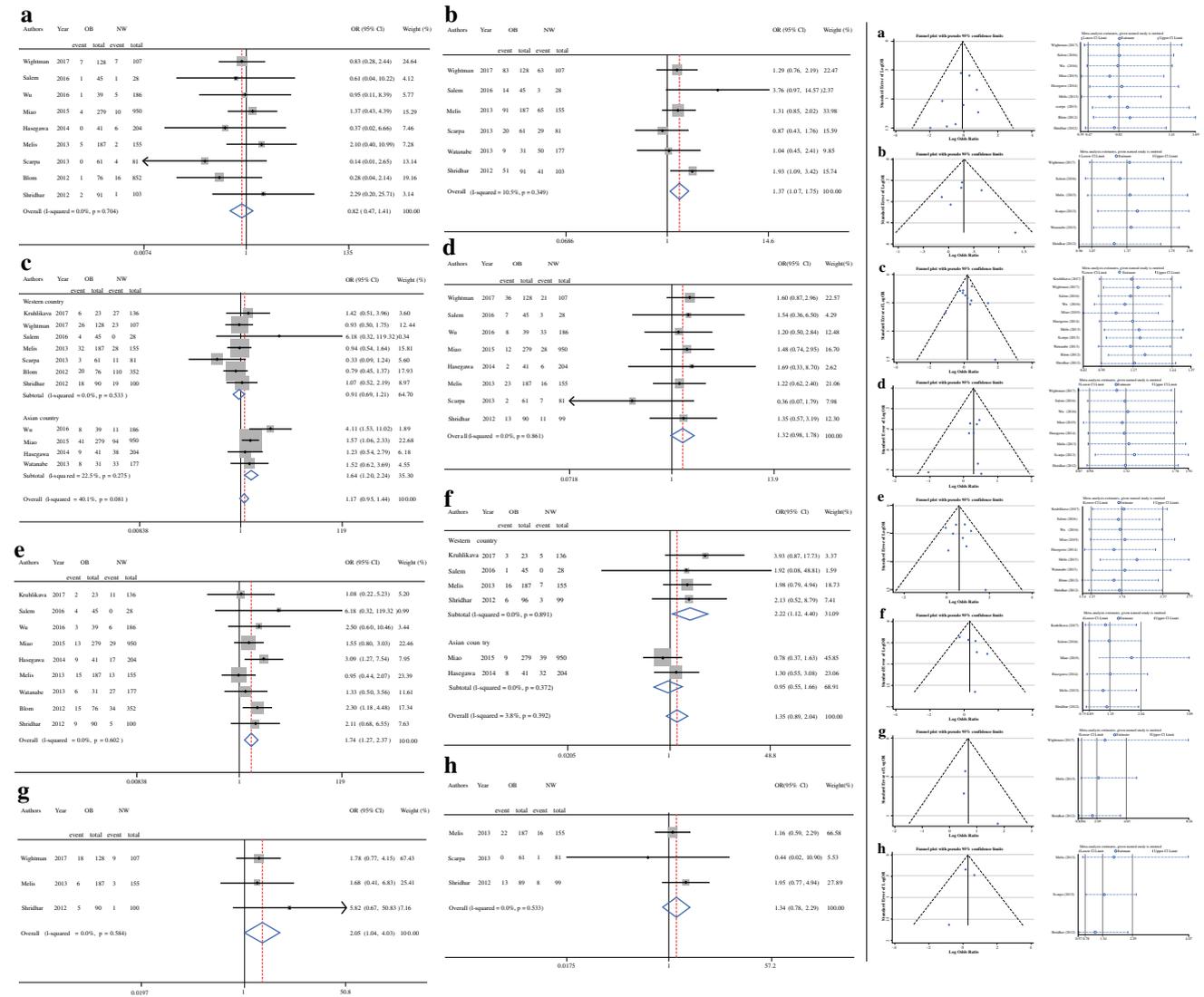


FIG. 2 Forest plots of mortality and complications among obese patients (OB) and normal-weight (NW) patients treated with esophagectomy. **a** Meta-analyses of mortality, **b** overall complications, **c** pulmonary complications, **d** cardiac complications, **e** anastomotic leakage, **f** wound infection, **g** thromboembolic complications, and **h** anastomotic stenosis are shown. The right

panel presents the outcomes of funnel plots and the sensitivity analysis corresponding to the forest plots shown in the left panel. A subgroup analysis according to the region involved in the study was performed for **c** pulmonary complications and **f** wound infection. *OR* odds ratios, *CI* confidence interval

confirm the “obese paradox”³⁴ in which obese patients have a lower adjusted risk of mortality and complications than normal-weight patients.

Studies have confirmed Barrett’s esophagus in the setting of gastroesophageal disorders, found primarily among obese individuals, to be the most important etiologic factor contributing to AC, accounting for the higher percentage of AC among obese patients.^{35–37} Additionally, symptoms from gastroesophageal reflux may motivate patients to seek further evaluation, resulting in a diagnosis at earlier stages.

Immune cells are believed to play an important role in protecting and maintaining the integrity of epithelial barriers, and a reduction in the function of immune cells has

been confirmed in obese patients, likely contributing to the increased incidence of wound infection after surgery.^{31,38}

According to previous studies, obesity is an important risk factor for venous thromboembolism in hospitalized patients, consistent with the results from our meta-analysis.^{39,40}

Overweight status was confirmed to confer the largest benefit on perioperative outcomes after esophagectomy. No significant difference was observed in short-term outcomes between overweight and normal-weight individuals, except for a higher incidence of overall complications, with trends toward lower incidences of mortality and pulmonary complications. Moreover, this group showed the lowest

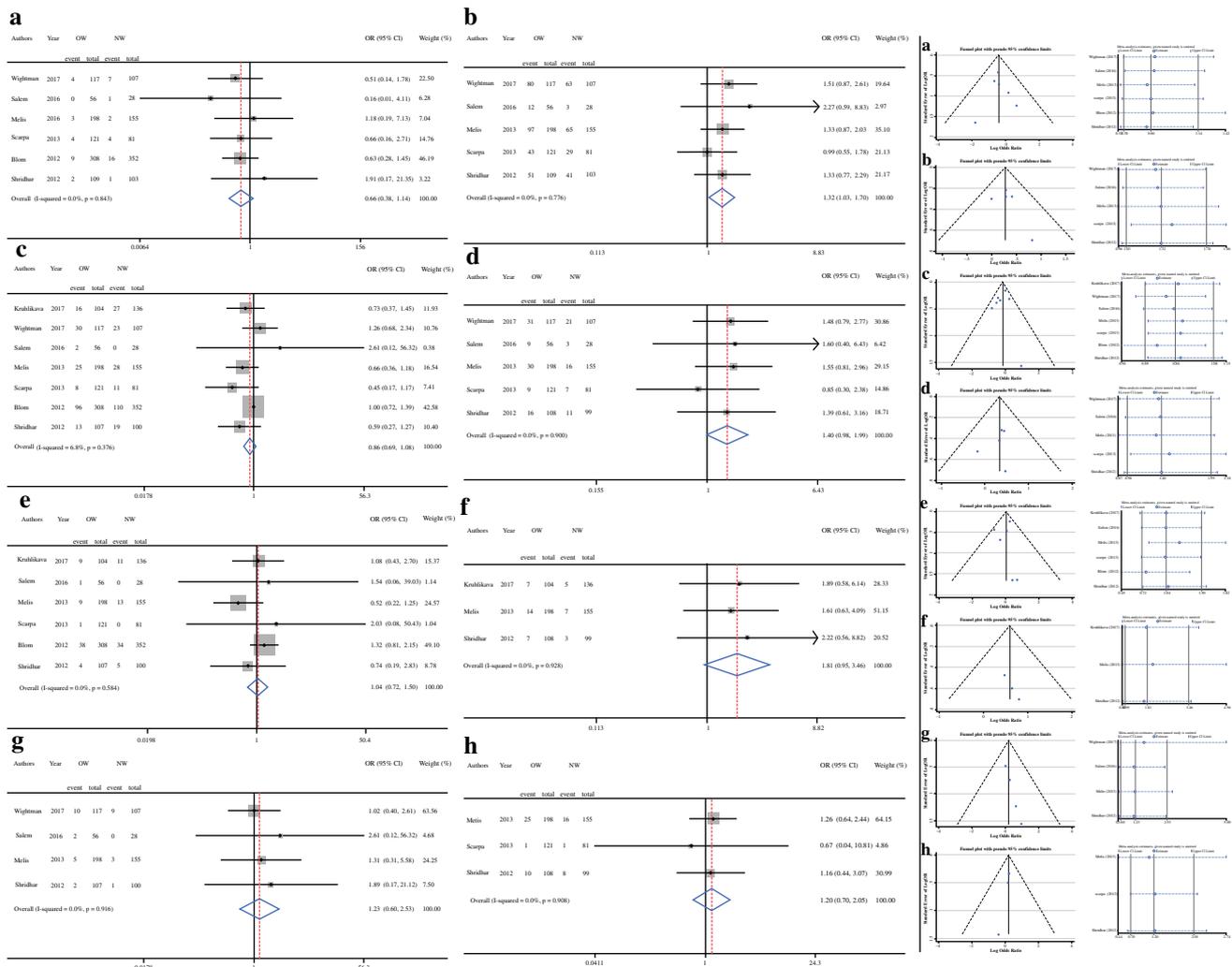


FIG. 3 Forest plots of mortality and complications among overweight (OW) and normal-weight (NW) patients treated with esophagectomy. Meta-analyses of **a** mortality, **b** overall complications, **c** pulmonary complications, **d** cardiac complications, **e** anastomotic leakage, **f** wound infection, **g** thromboembolic

complications, and **h** anastomotic stenosis are shown. The right panel presents the outcomes of funnel plots and the sensitivity analysis corresponding to the forest plots shown in the left panel. *OR* odds ratios, *CI* confidence interval

risk of pulmonary complications among different BMIs regarding the meta-analyses of the IRs. Our meta-analyses of comorbidities showed a higher prevalence of diabetes, but significant differences in smoking history and cardiac diseases between overweight and normal-weight patients were not observed. Interestingly, the incidence of an ASA score 3 or 4 was lower for overweight individuals than for normal-weight individuals, which may account for the better short-term outcomes recorded after surgery.³⁴ One study involving 529,955 samples obtained from the major resection of cancer from ACS-NSQIP (2005–2012) showed lower incidences of mortality, reoperation, and overall morbidity, but higher incidences of wound infection and

thromboembolic complications for overweight patients than for normal-weight patients.³¹ Further studies are needed to investigate the benefits of overweight status.

Due to the small percentage of patients, underweight status has been rarely investigated in Western studies.^{12,41} In our analysis, underweight patients had a higher incidence of smoking habits, which surely contribute to the increased incidence of pulmonary complications.^{42,43} Current smoking also is reported to be a dominant risk factor for anastomotic leakage in patients undergoing esophageal surgery and other types of gastrointestinal surgery.^{44,45} A BMI lower than 18.5 kg/m² and weight loss of 5% or more during the 3 months before surgery are strong indicators of malnutrition, which studies have confirmed to be a risk factor for postoperative complications,

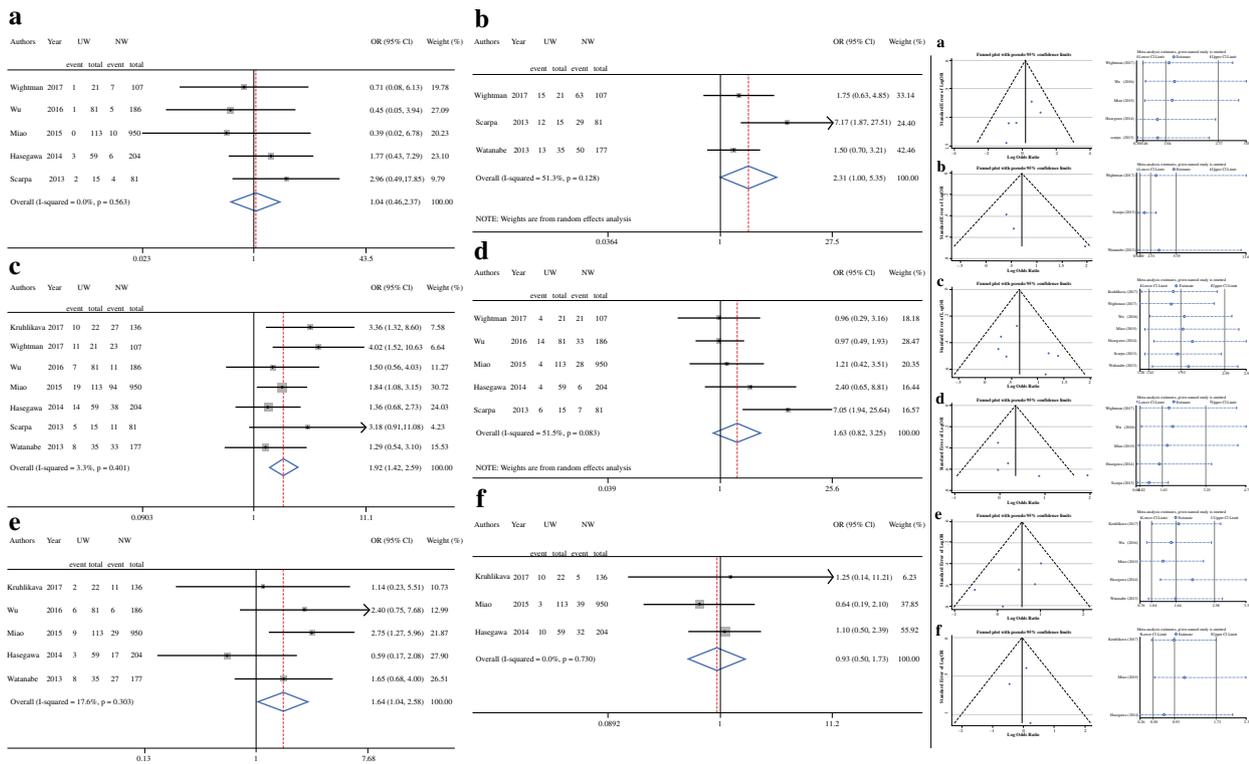


FIG. 4 Forest plots of mortality and complications among underweight (UW) and normal-weight (NW) patients treated with esophagectomy. Meta-analyses of **a** mortality, **b** overall complications, **c** pulmonary complications, **d** cardiac complications,

e anastomotic leakage, and **f** wound infection are shown. The right panel presents the outcomes of funnel plots and the sensitivity analysis corresponding to the forest plots shown in the left panel. *OR* odds ratios, *CI* confidence interval

particularly anastomotic leakage.^{46–48} Additionally, the underweight population experiencing esophageal cancer likely will face extreme nutritional risk for a high incidence of preoperative weight loss.^{25,31} Moreover, patients with severe preoperative weight loss and advanced tumor stage are more likely to face risks of cachexia and sarcopenia,^{49,50} which are reported to be associated with increased risks of pulmonary complications and anastomotic leakage after esophagectomy.^{51–53} Therefore, underweight status can be recognized as a preliminary screening condition for intensive perioperative management to reduce the risk of postoperative complications.

Morbid obesity was analyzed independently and shown to be associated with increased IR of wound infection and thromboembolic complications, with the highest IR of anastomotic leakage among different BMIs. According to our analysis, this group displayed a higher incidence of comorbidities, including diabetes and cardiac diseases, consistent with a previous study.³¹ Morbidly obese patients likely face problems with undertreatment, including operation and radiation therapy, because of the comorbidities associated with obesity.²⁰ Surgeons may decide against performing more challenging surgical procedures for these patients due to a higher risk of anesthetic and surgical

complications, longer operative times, and greater estimated intraoperative blood loss.^{54–56} However, our analysis did not demonstrate a significant difference in mortality and cardiopulmonary complications between morbidly obese individuals and normal-weight individuals. From our perspective, patients with esophageal pathologic conditions should not be prevented from undergoing resection based on morbid obesity alone, although more careful perioperative management is necessary to reduce the incidences of postoperative complications.

We were not able to conduct a subgroup analysis by ASA score, tumor stage, neoadjuvant therapy, surgical techniques, and other important confounding factors due to the lack of original data in the enrolled studies. However, the impacts of these factors on mortality and postoperative complications should be carefully considered. Patients with an ASA score of 3 or 4 always experience severe systemic diseases and dysfunction before surgery, which appear to affect postoperative complications and mortality after esophagectomy.^{57–59} The impact of advanced tumor stage on short-term outcomes remains controversial, and it is more likely to be associated with long-term survival.^{60–62} Neoadjuvant therapy is reported to cause skeletal muscle loss in esophageal cancer patients and reduce their

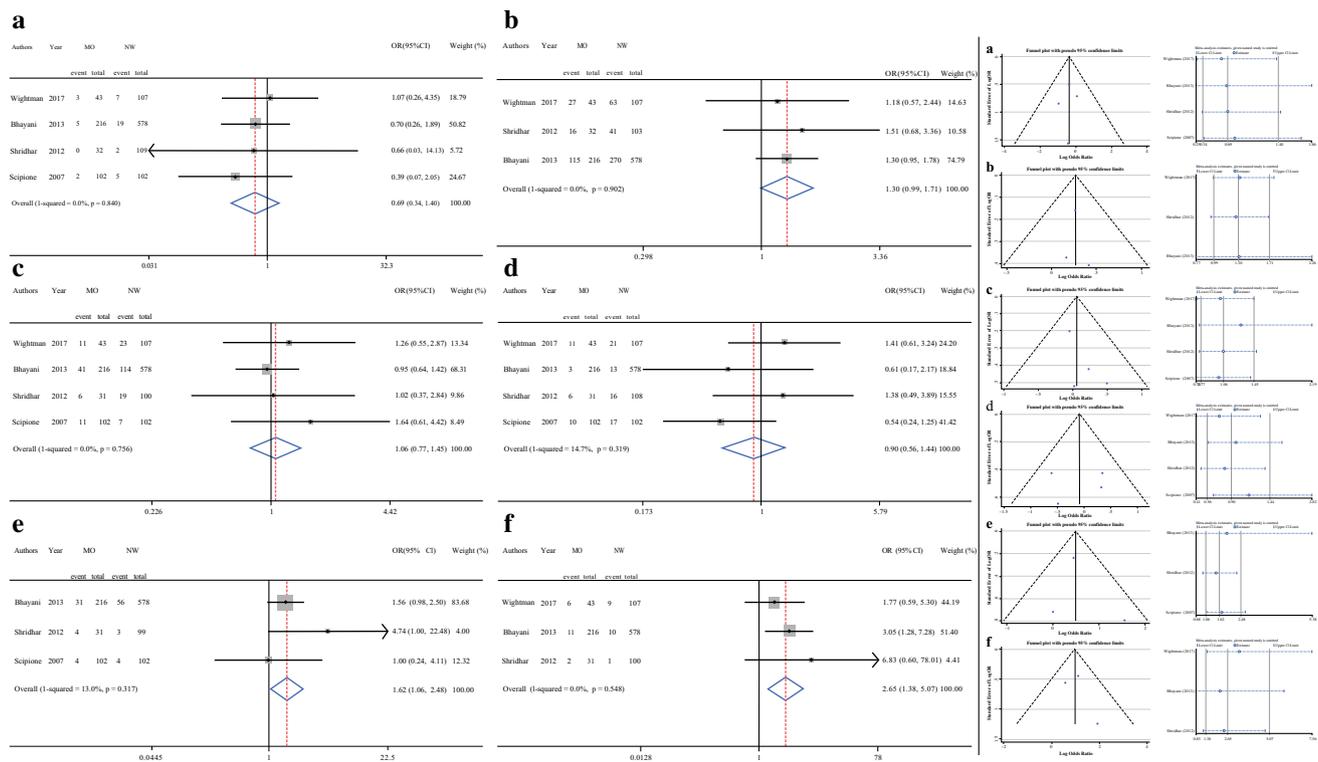


FIG. 5 Forest plots of mortality and complications among morbidly obese (MO) and normal-weight (NW) patients treated with oesophagectomy. Meta-analyses of **a** mortality, **b** overall complications, **c** pulmonary complications, **d** cardiac complications,

cardiopulmonary function.^{63,64} A meta-analysis including 1058 patients demonstrated that neoadjuvant chemoradiation for esophageal SCC patients significantly increased postoperative mortality and cardiopulmonary complications.⁶⁵ However, this was not reported in some other studies.^{66,67} The impacts of surgical approach on postoperative complications also have been widely studied. A risk adjustment model based on the Society of Thoracic Surgeons (STS) database (2011–2014) demonstrated that McKeown esophagectomy is an independent predictor of combined postoperative morbidity or mortality compared with the Ivor Lewis esophagectomy.⁶² A study by Schlottmann et al.⁵⁹ with 4053 patients reported that transthoracic esophagectomy was associated with higher incidences of postoperative pneumonia, whereas transhiatal esophagectomy had higher incidences of infection and sepsis. A nationwide study conducted in France demonstrated that intrathoracic anastomosis has a lower 30-day postoperative mortality rate than cervical anastomosis, and that performing a thoracotomy is not associated with the postoperative mortality rate.⁶⁸

Our meta-analysis confirmed the prognostic value of preoperative BMI for several perioperative complications to some extent. Individualized management during the

perioperative period is thus recommended for patients with different BMIs. Obese and underweight patients should receive extra attention for the early detection and prompt treatment of anastomotic leakage. Timely wound care and strict sterilization procedures may be beneficial to prevent wound infection. Moreover, a weight-based regimen of low-molecular-weight heparin may be a good choice to prevent perioperative venous thromboembolism after esophagectomy in obese individuals.^{39,69} Systematic cooperation of surgical and intensive care teams is vital for the smooth discharge of underweight patients. Additionally, underweight patients may benefit from preoperative nutritional assessments and nutritional supplementation due to their higher risk of malnutrition and cachexia.^{70,71} Preoperative pulmonary promotion and perioperative pulmonary care may be helpful in reducing pulmonary complications for underweight patients, particularly current smokers.

Several limitations in this meta-analysis must be considered. Most of the studies included in this meta-analysis were retrospective and uncontrolled. A consensus on the standardization of perioperative complications among the involved articles was not achieved. Only four Eastern studies were included in this meta-analysis. Thus a

wound infection, and **f** thromboembolic complications are shown. The right panel presents the outcomes of funnel plots and the sensitivity analysis corresponding to the forest plots shown in the left panel. *OR* odds ratios, *CI* confidence interval

comprehensive comparison between Western and Eastern patients was difficult to conduct. The obesity paradox may reduce the real risk of extreme BMI, which must be noted. Adjustment of confounding factors for BMI must be performed to obtain more accurate outcomes.

CONCLUSIONS

Obesity was found to be a risk factor for overall complications, anastomotic leakage, and thromboembolic complications. Obese patients in Western countries had a higher risk of wound infection, whereas obese Asians were more likely to experience pulmonary complications. Overweight patients may experience the greatest benefit from surgery, without increased risks of mortality or major complications. Moreover, underweight status was a risk factor for pulmonary complications and anastomotic leakage, and this group had the highest IR of overall complications. The morbid-obesity group had a higher risk of wound infection and thromboembolic complications than the normal-weight group, with the highest IR of anastomotic leakage among different BMIs. Individualized management during the perioperative period is thus recommended for patients with different BMIs.

ACKNOWLEDGMENT We thank M. K. Ferguson (Department of Surgery, The University of Chicago Medicine, Chicago, Illinois, USA) for providing advice and sharing data, and we also thank all the authors of the studies included in our article. The study was funded by the Project of Science and Technology of Henan Province (Grant No. 152102310160) and Spatiotemporal Data Analysis of Cancer Burden in China (Grant No. 2018-I2M-3-003).

DISCLOSURE There are no conflicts of interest.

REFERENCES

- Global Burden of Disease Cancer Collaboration. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. *JAMA Oncol.* 2017;3:524–48.
- Jain S, Dhingra S. Pathology of esophageal cancer and Barrett's esophagus. *Ann Cardiothorac Surg.* 2017;6:99–109.
- Pasquali S, Yim G, Vohra RS, et al. Survival after neoadjuvant and adjuvant treatments compared to surgery alone for resectable esophageal carcinoma: a network meta-analysis. *Ann Surg.* 2017;265:481–91.
- Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking complications associated with esophagectomy. *Ann Surg.* 2019;269:291–8.
- Lerut T, Moons J, Coosemans W, et al. Postoperative complications after transthoracic esophagectomy for cancer of the esophagus and gastroesophageal junction are correlated with early cancer recurrence: role of systematic grading of complications using the modified Clavien classification. *Ann Surg.* 2009;250:798–807.
- Baba Y, Yoshida N, Shigaki H, et al. Prognostic impact of postoperative complications in 502 patients with surgically resected esophageal squamous cell carcinoma: a retrospective single-institution study. *Ann Surg.* 2016;264:305–11.
- Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med.* 2005; 143:199–201.
- Lagergren J, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med.* 1999;130:883–90.
- Kruhlikava I, Kirkegaard J, Mortensen FV, Kjaer DW. Impact of body mass index on complications and survival after surgery for esophageal and gastro-esophageal-junction cancer. *Scand J Surg.* 2017;106:305–10.
- Wightman SC, Posner MC, Patti MG, Ganai S, Watson S, Prachand V, Ferguson, MK. Extremes of body mass index and postoperative complications after esophagectomy. *Dis Esophagus.* 2017;30:1–6.
- Scarpa M, Cagol M, Bettini S, et al. Overweight patients operated on for cancer of the esophagus survive longer than normal-weight patients. *J Gastrointest Surg.* 2013;17:218–27.
- Melis M, Weber J, Shridhar R, Hoffe S, Almhanna K, Karl RC, Meredith KL. Body mass index and perioperative complications after oesophagectomy for adenocarcinoma: a systematic database review. *BMJ Open.* 2013;3:e001336.
- Salem AI, Thau MR, Strom TJ, et al. Effect of body mass index on operative outcome after robotic-assisted Ivor-Lewis esophagectomy: retrospective analysis of 129 cases at a single high-volume tertiary care center. *Dis Esophagus.* 2016;30:1–7.
- Shridhar R, Hayman T, Hoffe SE, et al. Body mass index and survival in esophageal adenocarcinoma treated with chemoradiotherapy followed by esophagectomy. *J Gastrointest Surg.* 2012;16:1296–302.
- Blom RL, Lagarde SM, Klinkenbijn JH, Busch OR, van Berge Henegouwen MI. A high body mass index in esophageal cancer patients does not influence postoperative outcome or long-term survival. *Ann Surg Oncol.* 2012;19:766–71.
- Watanabe M, Ishimoto T, Baba Y, Nagai Y, Yoshida N, Yamana T, Baba H. Prognostic impact of body mass index in patients with squamous cell carcinoma of the esophagus. *Ann Surg Oncol.* 2013;20:3984–91.
- Miao L, Chen H, Xiang J, Zhang Y. A high body mass index in esophageal cancer patients is not associated with adverse outcomes following esophagectomy. *J Cancer Res Clin Oncol.* 2014;141:941–50.
- Hasegawa T, Kubo N, Ohira M, et al. Impact of body mass index on surgical outcomes after esophagectomy for patients with esophageal squamous cell carcinoma. *J Gastrointest Surg.* 2015;19:226–33.
- Wu N, Zhu Y, Kadel D, Pang L, Chen G, Chen Z. The prognostic influence of body mass index, resting energy expenditure, and fasting blood glucose on postoperative patients with esophageal cancer. *BMC Gastroenterol.* 2016;16:142.
- Bhayani NH, Gupta A, Dunst CM, Kurian AA, Halpin VJ, Swanstrom LL. Does morbid obesity worsen outcomes after esophagectomy? *Ann Thorac Surg.* 2013;95:1756–61.
- Scipione CN, Chang AC, Pickens A, Lau CL, Orringer MB. Transhiatal esophagectomy in the profoundly obese: implications and experience. *Ann Thorac Surg.* 2007;84:376–82 (discussion 383).
- Kayani B, Okabayashi K, Ashrafian H, et al. Does obesity affect outcomes in patients undergoing esophagectomy for cancer? A meta-analysis. *World J Surg.* 2012;36:1785–95.
- Mengardo V, Pucetti F, Mc Cormack O, Chaudry A, Allum WH. The impact of obesity on esophagectomy: a meta-analysis. *Dis Esophagus.* 2018. <https://doi.org/10.1093/dote/dox149>.

24. World Health Organization. BMI classification. Retrieved 1 May 2018 at http://apps.who.int/bmi/index.jsp?introPage=intro_3.html.
25. Zhang SS, Yang H, Luo KJ, et al. The impact of body mass index on complication and survival in resected oesophageal cancer: a clinical-based cohort and meta-analysis. *Br J Cancer*. 2013;109:2894–903.
26. Park SK, Ryoo JH, Oh CM, et al. Effect of overweight and obesity (defined by Asian-specific cutoff criteria) on left ventricular diastolic function and structure in a general Korean population. *Circ J*. 2016;80:2489–95.
27. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363:157–63.
28. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. *JAMA*. 2015;313:1657–65.
29. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved 1 May 2018 at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
30. STARSurg Collaborative. Multicentre prospective cohort study of body mass index and postoperative complications following gastrointestinal surgery. *Br J Surg*. 2016;103:1157–72.
31. Zogg CK, Mungo B, Lidor AO, Stem M, Rios Diaz AJ, Haider AH, Molena D. Influence of body mass index on outcomes after major resection for cancer. *Surgery*. 2015;158:472–85.
32. Ata A, Valerian BT, Lee EC, Bestle SL, Elmendorf SL, Stain SC. The effect of diabetes mellitus on surgical-site infections after colorectal and noncolorectal general surgical operations. *Am Surg*. 2010;76:697–702.
33. Okamura A, Watanabe M, Imamura Y, Kamiya S, Yamashita K, Kuroguchi T, Mine S. Preoperative glycosylated hemoglobin levels predict anastomotic leak after esophagectomy with cervical esophago-gastric anastomosis. *World J Surg*. 2017;41:200–7.
34. Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing non-bariatric general surgery. *Ann Surg Oncol*. 2009;250:166–72.
35. American Gastroenterological Association. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011;140:1084–91.
36. Nilsson M, Johnsen R, Ye W, Hveem K, Lagergren J. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA*. 2003;290:66–72.
37. Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol*. 2013;19:5598–606.
38. Cheung KP, Taylor KR, Jameson JM. Immunomodulation at epithelial sites by obesity and metabolic disease. *Immunol Res*. 2012;52:182–99.
39. Rondina MT, Wheeler M, Rodgers GM, Draper L, Pendleton RC. Weight-based dosing of enoxaparin for VTE prophylaxis in morbidly obese, medically-ill patients. *Thromb Res*. 2010;125:220–3.
40. Thomas DC, Arnold BN, Hoag JR, et al. Timing and risk factors associated with venous thromboembolism after lung cancer resection. *Ann Thorac Surg*. 2018;105:1469–75.
41. Kilic A, Schuchert MJ, Pennathur A, Yaeger K, Prasanna V, Luketich JD, Gilbert S. Impact of obesity on perioperative outcomes of minimally invasive esophagectomy. *Ann Thorac Surg*. 2009;87:412–5.
42. Yoshida N, Watanabe M, Baba Y, et al. Risk factors for pulmonary complications after esophagectomy for esophageal cancer. *Surg Today*. 2014;44:526–32.
43. Bluman LG, Mosca L, Newman N, Simon DG. Preoperative smoking habits and postoperative pulmonary complications. *Chest*. 1998;113:883–9.
44. Van Daele E, Van de Putte D, Ceelen W, Van Nieuwenhove Y, Pattyn P. Risk factors and consequences of anastomotic leakage after Ivor Lewis oesophagectomy. *Interact Cardiovasc Thorac Surg*. 2016;22:32–7.
45. Baucom RB, Poulouse BK, Herline AJ, Muldoon RL, Cone MM, Geiger TM. Smoking as dominant risk factor for anastomotic leak after left colon resection. *Am J Surg*. 2015;210:1–5.
46. Correia MI, Waitzberg DL. The impact of malnutrition on morbidity, mortality, length of hospital stay, and costs evaluated through a multivariate model analysis. *Clin Nutr*. 2003;22:235–9.
47. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition: an ESPEN consensus statement. *Clin Nutr*. 2015;34:335–40.
48. Thomas MN, Kufeldt J, Kisser U, et al. Effects of malnutrition on complication rates, length of hospital stay, and revenue in elective surgical patients in the G-DRG-system. *Nutrition*. 2016;32:249–54.
49. Sun L, Quan XQ, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its diagnostic and treatment status. *Nutr Cancer*. 2015;67:1056–62.
50. Muscaritoli M, Anker SD, Argiles J, et al. Consensus definition of sarcopenia, cachexia, and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) “cachexia-anorexia in chronic wasting diseases” and “nutrition in geriatrics”. *Clin Nutr*. 2010;29:154–9.
51. Mesquita AF, Silva ECD, Eickemberg M, Roriz AKC, Barreto-Medeiros JM, Ramos LB. Factors associated with sarcopenia in institutionalized elderly. *Nutr Hosp*. 2017;34:345–51.
52. Harada K, Ida S, Baba Y, et al. Prognostic and clinical impact of sarcopenia in esophageal squamous cell carcinoma. *Dis Esophagus*. 2016;29:627–33.
53. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Ann Surg Oncol*. 2015;22:4432–7.
54. An X, Zhao Y, Zhang Y, Yang Q, Wang Y, Cheng W, Yang Z. Risk assessment of morbidly obese parturient in cesarean section delivery: a prospective, cohort, single-center study. *Medicine Baltimore*. 2017;96:e8265.
55. De Jong A, Verzilli D, Geniez M, Chanques G, Nocca D, Jaber S. Why is the morbidly obese patient at high risk of anesthetic complications. *Presse Med*. 2018;47:453–63.
56. Carson JT, Shah SG, Ortega G, Thamyongkit S, Hasenboehler EA, Shafiq B. Complications of pelvic and acetabular fractures in 1331 morbidly obese patients (BMI \geq 40): a retrospective observational study from the National Trauma Data Bank. *Patient Saf Surg*. 2018;12:26.
57. Hopkins TJ, Raghunathan K, Barbeito A, et al. Associations between ASA physical status and postoperative mortality at 48 h: a contemporary dataset analysis compared to a historical cohort. *Perioper Med London*. 2016;5:29.
58. Ondeck NT, Bohl DD, Boveratwet P, et al. Predicting adverse outcomes after total hip arthroplasty: a comparison of demographics, the American Society of Anesthesiologists class, the Modified Charlson Comorbidity Index, and the Modified Frailty Index. *J Am Acad Orthop Surg*. 2018;26:735–43.
59. Schlottmann F, Strassle PD, Patti MG. Transhiatal vs transthoracic esophagectomy: a NSQIP analysis of postoperative outcomes and risk factors for morbidity. *J Gastrointest Surg*. 2017;21:1757–63.

60. Fuentes E, Ahmad R, Hong TS, et al. The impact of neoadjuvant therapy for gastroesophageal adenocarcinoma on postoperative morbidity and mortality. *J Surg Oncol.* 2016;113:560–4.
61. Sunpaweravong S, Ruangsri S, Laohawiriyakamol S, Mahattanobon S, Geater A. Prediction of major postoperative complications and survival for locally advanced esophageal carcinoma patients. *Asian J Surg.* 2012;35:104–9.
62. Raymond DP, Seder CW, Wright CD, et al. Predictors of major morbidity or mortality after resection for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery database risk adjustment model. *Ann Thorac Surg.* 2016;102:207–14.
63. Mayanagi S, Tsubosa Y, Omae K, et al. Negative impact of skeletal muscle wasting after neoadjuvant chemotherapy followed by surgery on survival for patients with thoracic esophageal cancer. *Ann Surg Oncol.* 2017;24:3741–7.
64. Thomson IG, Wallen MP, Hall A, et al. Neoadjuvant therapy reduces cardiopulmonary function in patients undergoing oesophagectomy. *Int J Surg.* 2018;53:86–92.
65. Sathornviriyapong S, Matsuda A, Miyashita M, et al. Impact of neoadjuvant chemoradiation on short-term outcomes for esophageal squamous cell carcinoma patients: a meta-analysis. *Ann Surg Oncol.* 2016;23:3632–40.
66. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366:2074–84.
67. Mungo B, Molena D, Stem M, et al. Does neoadjuvant therapy for esophageal cancer increase postoperative morbidity or mortality? *Dis Esophagus.* 2015;28:644–51.
68. Degisors S, Pasquer A, Renaud F, et al. Are thoracotomy and/or intrathoracic anastomosis still predictors of postoperative mortality after esophageal cancer surgery? A nationwide study. *Ann Surg.* 2017;266:854–62.
69. Hurewitz AN, Khan SU, Groth ML, Patrick PA, Brand DA. Dosing of unfractionated heparin in obese patients with venous thromboembolism. *J Gen Intern Med.* 2011;26:487–91.
70. Gockel I, Niebisch S, Ahlbrand CJ, et al. Risk and complication management in esophageal cancer surgery: a review of the literature. *Thorac Cardiovasc Surg.* 2016;64:596–605.
71. Pavia R, Barresi P, Piermanni V, Mondello B, Urgesi R. Role of artificial nutrition in patients undergoing surgery for esophageal cancer. *Rayss.* 2006;31:25–9.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.