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REVIEW

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Systematic review of prognostic roles of body mass index for patients undergoing lung cancer surgery: does the 'obesity paradox' really exist?

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Summary

The paradoxical benefit of obesity, the 'obesity paradox', has been recently identified in surgical populations. Our goal was to evaluate by a systematic review with meta-analysis the prognostic role of body mass index (BMI) and to identify whether the 'obesity paradox' exists in lung cancer surgery. Comprehensive literature retrieval was conducted in PubMed to identify the eligible articles. The odds ratios (OR) and hazard ratios (HR) with the corresponding 95% confidence intervals (CI) were used to synthesize in-hospital and long-term survival outcomes, respectively. The heterogeneity level and publication bias between studies were also estimated. Finally, 25 observational studies with 78 143 patients were included in this review. The pooled analyses showed a significantly better long-term survival rate in patients with higher BMI, but no significant benefit of increased BMI was found for in-hospital morbidity. The pooled analyses also showed that overall morbidity (OR: 0.84; 95% CI: 0.73–0.98; $P = 0.025$) and in-hospital mortality (OR: 0.78; 95% CI: 0.63–0.98; $P = 0.031$) were significantly decreased in obese patients. Obesity could be a strong predictor of the favourable long-term prognosis of lung cancer patients (HR: 0.69; 95% CI: 0.56–0.86; $P = 0.001$). The robustness of these pooled estimates was strong. No publication bias was detected. In summary, obesity has favourable effects on in-hospital outcomes and long-term survival of surgical patients with lung cancer. The 'obesity paradox' does have the potential to exist in lung cancer surgery.

Keywords: Body mass index • Obesity • Lung cancer surgery • Prognosis • Systematic review

INTRODUCTION

Lung cancer is the leading cause of malignancy-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and its 5-year survival rate is generally less than 15% [1, 2]. Surgical therapy remains the cornerstone of multidisciplinary treatment for lung cancer and is widely accepted as the optimal treatment for early-stage NSCLC. Advanced surgical techniques, anaesthetic techniques and perioperative management have significantly improved the feasibility and safety of standard treatments but have had only a slight benefit on the prognosis of lung cancer [3]. A number of coexisting invasive clinicopathological predictors have led to the poor prognosis of NSCLC. Surgical patients frequently have a variety of comorbidities, such as diabetes mellitus (DM), chronic obstructive pulmonary disease, and coronary artery diseases, that have also been proven to have adverse effects on survival outcomes [4, 5].

During the last few decades, the prevalence of obesity has dramatically increased in many nations and become a worldwide challenge to human health. In the United States, the proportion of obese patients identified by body mass index (BMI) $\geq$30 kg/m^2 was higher than 35% in 2010 and higher than 65% in current overweight or obese individuals [6]. The latest large-scale studies suggest a strong correlation between obesity and many medical comorbidities such as hypertension, DM and hyperlipidaemia [7]. In addition, a recent systematic review also demonstrated that obese patients may have a higher risk of many cancers [8]. Given such concerns, surgeons have begun to note the impact of obesity during the in-hospital period since performing operations on obese patients has become a routine part of clinical practices.

It was commonly believed that obesity could increase the morbidity and mortality of surgical patients, especially those undergoing cardiac operations [9, 10]. In recent years, this traditional view has been strongly challenged by a new discovery termed the 'obesity paradox', which refers to a better prognosis in obese patients compared to normal/underweight patients [11]. The paradoxical benefit of obesity has been found in a wide range of cardiovascular and pulmonary diseases as well as in the surgical population. However, the effects of increased BMI and obesity on the surgical outcomes of lung cancer patients remain controversial because some inconsistent results reported in previous studies have not yet been well interpreted. No consensus has been reached on the prognostic value of BMI in lung cancer surgery.

Meta-analysis is a well-designed statistical method that integrates the appropriate data from homogeneous studies quantitatively to determine global conclusions [12]. By applying evidence-based methods to a large sample size, the pooled estimates may help to clarify the effects of BMI and obesity on surgical outcomes. Therefore, the objective of our study is to evaluate the prognostic roles of BMI and identify by performing a systematic review with a meta-analysis whether the obesity paradox exists in patients having lung cancer surgery.

MATERIALS AND METHODS

Protocol

No protocol had been previously published for this review. We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. An additional PRISMA checklist is available as Supplementary material 1.

Eligibility criteria

Articles that met the following criteria were included in this meta-analysis.

(i) Study design
Articles that included a quantitative comparative analysis of consecutive patients were included. Case reports, reviews, preclinical experiments, conference abstracts and letters were excluded because they do not contain quantitative comparative analyses.

(ii) Participants
The target disease was lung cancer, including primary and secondary lesions. Studies of cohorts of patients diagnosed with mixed lung malignances were included in this meta-analysis. No limitation was imposed for age or gender.

(iii) Interventions
Studies of elective pulmonary resections performed on lung cancer patients through both classical thoracotomy and video-assisted thoracoscopic surgery (VATS) were eligible.
Studies in which the impact of BMI/obesity was analysed independently instead of with other comorbidities were included. Per the definitions of World Health Organization, BMI (kg/m^2) was categorized as underweight (<18.5), normal (18.5 to <25), overweight (25 to <30) and obese ($\geq$30). Patients with BMI $\geq$ 30 kg/m^2 were regarded as obese for this meta-analysis.

(iv) Outcome measures
Studies reporting any of the following outcome data were included: short-term outcomes including in-hospital mortality and overall morbidity and pulmonary and cardiovascular and other surgical complications. The overall survival (OS) with at least a 3-year follow-up served as the long-term prognostic outcome. Studies containing sufficient statistics or demographics to estimate the odds ratio (OR), relative risk (RR) and hazard ratio (HR) were included.
In addition, the most recent studies were included if they were performed on overlapping patients. Only full-text articles published in English peer-reviewed journals were included.

Search strategy

A comprehensive literature retrieval was conducted between 19 May and 25 May 2016. No publication date restriction was imposed.

We searched the PubMed database to identify the eligible articles. We combined the following seven key words, including four 'BMI/obesity' words and three 'lung cancer' words, with Boolean operators to formulate three search strings (Supplementary material 2): BMI/obesity terms: 'body mass index', 'BMI', 'obesity' and 'overweight'; lung cancer terms: 'lung cancer', 'lung carcinoma' and 'lung neoplasm'.

A manual search of the reference lists of retrieved studies was also performed to identify any possible study with no duplication.

Data collection

We designed a Microsoft Office Excel spreadsheet to record the following data items from each included study:

(i) Publication data including the authors, publication year and country of origin;
(ii) Experimental data including the study design, study period, cut-off values of BMI, operative mode, surgical approach, follow-up and outcome measures;
(iii) Demographic data including the total sample size, gender, age and clinical stage;
(iv) Statistical data including the types of incorporative variables, outcome statistics with their extractions, and the corresponding statistical analysis methods.

Quality assessment

The Newcastle–Ottawa Scale (NOS) was used to quantify the quality levels of original non-randomized studies [14]. Three perspectives including selection, comparability and exposure were considered for a semi-quantitative estimation. The 'star system' with a maximum of nine stars was used to grade all the included studies. We regarded 8–9 stars as good quality, 6–7 stars as fair quality, and lower than 6 stars as poor quality.

Statistical analysis

The following statistical analyses were all performed using STATA 12.0.

(i) Summary measures
For assessments of in-hospital morbidity and mortality, an OR with a 95% CI served as the appropriate summarized statistics. In general, OR could be extrapolated from the demographic data reported in the original articles. Our priority was to integrate the OR statistics derived from multivariate analysis because of the adequate elimination of confounding factors. Moreover, if multivariate RR or HR was reported, we could also incorporate it into the meta-analysis [15].
For assessments of long-term OS, the HR with 95% CI was considered to be combined because HR was the only appropriate statistic compatible for both censoring and time-to-events values [15]. Similarly, incorporating the multivariate

HR statistics was also our priority. If no multivariate statistic was reported, we extrapolated the HR from the survival data with the log-rank *P* value according to a practical method described by Tierney *et al.* [16].

(ii) Synthesis of results

Both the Cochrane's Q test and I^2-statistic were adopted to estimate the heterogeneity within this meta-analysis. Fine heterogeneity was defined by $I^2 < 50\%$ and $P > 0.1$, and a standard fixed-effect model test (Mantel–Haenszel method) was required for synthesis. Otherwise, a random-effect model test (DerSimonian and Laird method) would be used when a prominent heterogeneity was revealed by $I^2 \geq 50\%$ or $P \leq 0.1$ [17].

A significant improvement in postoperative outcomes in obese patients was suggested by the pooled OR and HR with 95% CI less than 1.

(iii) Additional analyses

We conducted a sensitivity analysis to examine the stability of all summarized outcomes, in which the impact of each study on overall estimates could be detected by omitting the individual study sequentially. The robustness of our meta-analysis would be verified if there was no substantial variation between the adjusted estimates and primary estimates [17].

(iv) Publication bias

Both Begg's test and Egger's test were used to evaluate the potential publication bias between studies. The presence of bias was suggested by visual symmetry of Begg's funnel plot, in which log ORs and log HRs were plotted against their corresponding standard errors [18]. Meanwhile, significant bias was also suggested by Egger's *P* value <0.05.

RESULTS

Study selection

The literature retrieval scheme for this review is shown in Fig. 1. A total of 2813 publications were identified from the PubMed database. A manual search of reference lists also yielded four potential studies. After excluding the duplicates, 1576 items were filtered by screening their titles and abstracts; 491 of these were excluded because of article type. We read through the remaining 1085 citations and excluded 1058 articles that focused on irrelevant issues; the remaining 27 studies were considered eligible. However, we found that the three largest studies each used the Society of Thoracic Surgeons (STS) database and that two earlier related analyses contained a large percentage of overlapping patients captured in the other US institutional studies [19, 20]. We excluded these two studies from the meta-analysis and kept the most recent one because its study period had no overlap with the other two US studies [21]. Finally, 25 studies met all of the eligibility criteria and were included in the meta-analysis [21–45].

Study characteristics

Baseline characteristics for all included studies are summarized in Table 1. Their statistical characteristics are presented in Supplementary Table S1.

(i) Study designs

All 25 studies were observational studies, including 23 retrospective studies [21–41, 43, 45] and two prospective studies [42, 44], published between 2001 and 2016. In addition, there were two propensity-score analyses among the 23 retrospective studies. One of these yielded 332 well-matched pairs of patients and another one yielded 7417 patients for propensity-score analysis [23, 29].

(ii) Participants and interventions

Our meta-analysis actually comprised a total of 78143 patients undergoing pulmonary resections for cancers, including 43 890 patients from North and South America (ratio = 56.2%) [21, 24, 25, 29, 32, 35, 38, 45]; 29 195 patients from Europe (ratio = 37.4%) [22, 23, 26, 27, 34, 39–44]; and 5058 patients from East Asia (ratio = 6.5%) [28, 30, 31, 33, 36, 37]. These patients were consecutively enrolled from 1990 to 2014. The sample size ranged from 36 to 27 844 across the included studies. The majority of included studies targeted only those cases with primary NSCLC (*n* = 67757, ratio = 86.7%) [21–28, 30, 32–35, 37–45]. A total of 7381 patients were considered obese, although 10 included studies did not sufficiently report the relevant demographics [21, 22, 24, 28, 30, 34, 36, 37, 44, 45]. The clinical data of 45 555 patients (ratio = 58.3) enrolled in 17 studies were initially analysed as a sample including a variety of resections ranging from wedge resection to pneumonectomy [21, 23, 25–27, 30–34, 36–38, 42–45]. The remaining eight studies reported the outcomes of a single mode, including 27 702 patients undergoing lobectomy [24, 28, 29, 35, 40], 4827 patients undergoing pneumonectomy [39, 41] and 59 patients undergoing wedge resection [22]. The demographics for gender, age and clinical stage are also summarized in Table 1.

(iii) Outcome measures

The multivariate results for continuous variables of BMI were directly reported in 13 studies, including 10 HR statistics for long-term OS [22, 24, 27, 30, 33, 34, 36, 43–45] and 3 OR statistics for in-hospital morbidity [25, 28, 37] (Supplementary Table S1). In-hospital outcomes were followed for 30 days. Long-term OS follow-up ranged from 3 to 5 years (Table 1).

A comparative analysis of obese patients and normal/underweight patients was conducted in 13 studies [21, 23, 26, 29, 31–33, 35, 38–42]. Eleven of them directly reported the outcome data derived from multivariate analysis, including 7 OR statistics for in-hospital mortality [21, 29, 32, 39–41], 10 OR statistics for in-hospital morbidity [21, 32, 33, 38, 40, 41] and 4 HR statistics for long-term OS [23, 26, 33]. The other ORs were extrapolated from dichotomous demographics based on univariate analysis (Supplementary Table S1) [23, 31, 35, 38]. In-hospital outcome follow-up ranged from 30 days to 90 days, and the long-term follow-up continued for 5 years (Table 1).

Quality assessment

We tabulated the complete details of quality assessments in Supplementary Table S2. The quality level of each study was

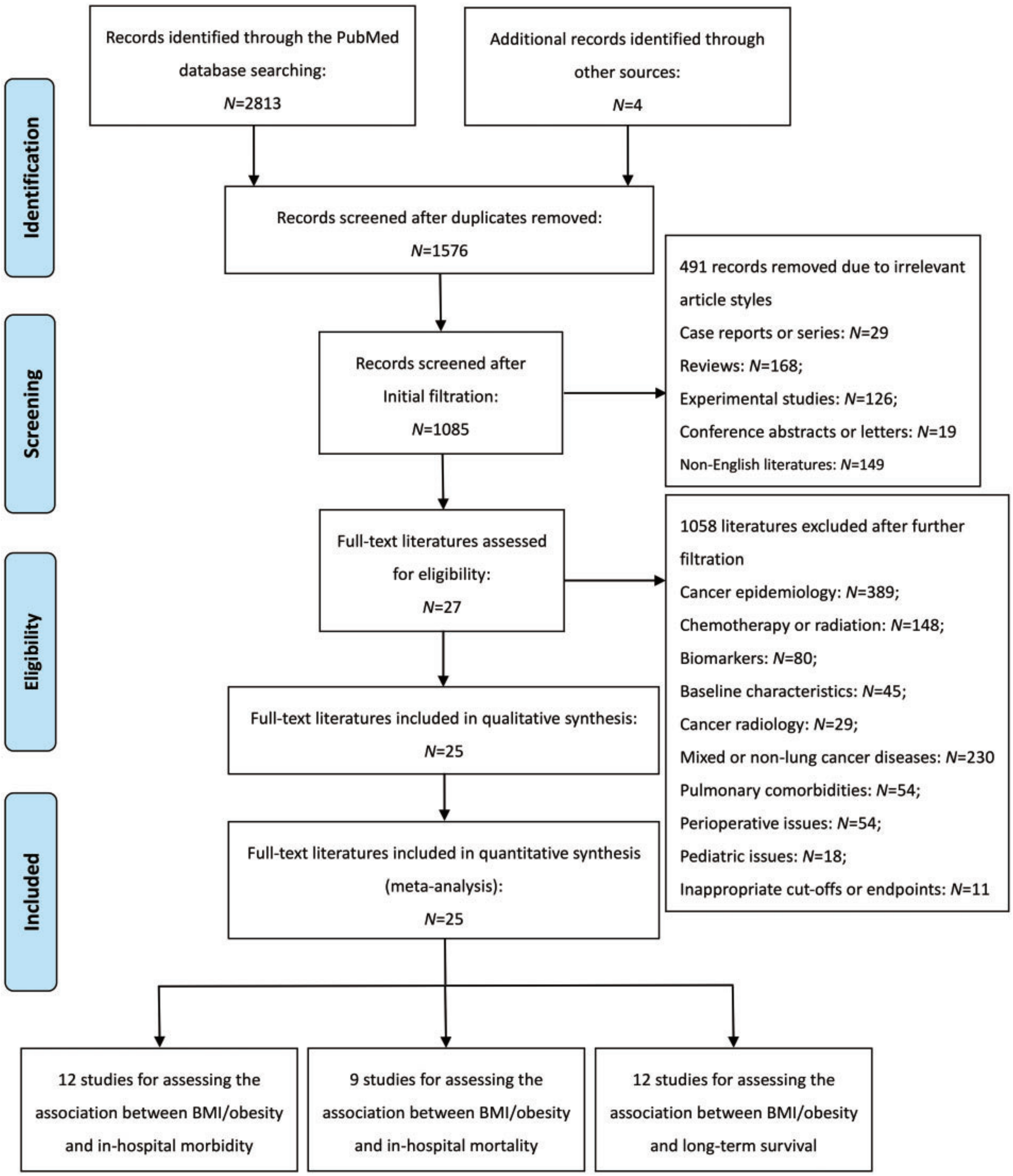

Figure 1: PRISMA flow diagram of literature retrieval.

given a Newcastle–Ottawa Scale score. Finally, these studies had a mean score of 7.8 (range 7–9), suggesting that they were of fairly good quality (Table 1).

Synthesis of results

(i) Overall morbidity

The pooled OR of continuous variables from three studies [25, 28, 37] was 0.97 (95% CI: 0.94–1.00; $P = 0.088$; $I^2 = 54.3\%$, $P = 0.112$), indicating that postoperative complications occurred less frequently in patients with higher BMI; this relationship was almost statistically reliable (Table 2; Fig. 2A).

When we compared obese patients and normal/underweight patients, the pooled analysis of nine studies [21, 31–33, 35, 38, 40–42] indicated that obesity was significantly associated with a lower morbidity rate (OR: 0.84; 95% CI: 0.73-0.98; $P = 0.025$; Table 2; Fig. 3A), with significant heterogeneity ($I^2 = 80.0\%$, $P < 0.001$).

Table 1: Baseline characteristics of included studies

Authors (Year)	Country	Study design	Study period	Sample size	Age (Years)	Gender (Male/Female)	Stages	Operative modes	Approaches (Open/VATS)	Outcome measures[a]			Follow-up	NOS
										Morbidity	Mortality	OS		
Fernandez *et al.* [21]	USA	ROS	2012–14	27844	67.2	12647/15197	I–IV	PN,LB,WR,BL, ST,SL	10691/17153	✓	✓	✗	30 days	8
Ambrogi *et al.* [22]	Italy	ROS	2006–12	59	70.0	46/13	I	WR	29/30	✗	✗	✓	5 years	8
Attaran *et al.* [23]	UK	RCMA	2000–10	664	67.5	344/320	I–III	PN,LB,WR	All open	✗	✓	✓	5 years	9
De Leon *et al.* [24]	Brazil	ROS	1998–2004	36	64.0	22/14	I–II	LB	All open	✗	✗	✓	5 years	8
Dhakal *et al.* [25]	USA	ROS	2006–10	320	67.0	135/185	NI	PN,LB,WR	NI	✓	✗	✗	30 days	7
Fontaine *et al.* [26]	UK	ROS	2002–10	146	66.0	69/77	IIIa	PN,LB,WR,ST	All open	✗	✗	✓	5 years	9
Friedel *et al.* [27]	Germany	ROS	1993–2007	595	62.1	444/147	I–III	PN,LB,ST	NI	✗	✗	✓	5 years	8
Kawakami *et al.* [28]	Japan	ROS	2006–09	309	67.0	222/87	I–III	LB	All open	✓	✗	✗	30 days	7
Launer *et al.* [29]	USA	RCMA	2002–07	7417	66.6	NI	NI	LB	NI	✗	✓	✗	30 days	8
Lee *et al.* [30]	Korea	ROS	2003–07	237	63.0	189/48	I–II	PN,LB,WR,BL,SL	All open	✗	✗	✓	5 years	8
Matsunaga *et al.* [31]	Japan	ROS	2008–13	1508	67.0	867/641	I–IV	PN,LB,WR,ST	NI	✓	✓	✗	90 days	7
Mungo *et al.* [32]	USA	ROS	2005–12	6567	68.2	3195/3372	NI	PN,LB,ST	NI	✓	✓	✗	30 days	8
Nakagawa *et al.* [33]	Japan	ROS	2001–11	1311	68.1	862/449	I–III	PN,LB, less than LB	NI	✓	✗	✓	5 years	9
Poullis *et al.* [34]	UK	ROS	2001–11	1795	67.2	979/816	I–III	PN,LB	All open	✗	✗	✓	5 years	8
Sánchez *et al.* [35]	Brazil	ROS	1998–2004	305	63.7	209/96	I–IV	LB	All open	✓	✗	✗	30 days	7
Sekine *et al.* [36]	Japan	ROS	1990–2005	1461	63.9	991/470	I–IV	PN,LB,ST	All open	✗	✗	✓	5 years	8
Seok *et al.* [37]	Korea	ROS	2005–09	232	64.0	217/15	I–IV	PN,LB,WR,BL, ST,SL	193/39	✓	✗	✗	30 days	7
Smith *et al.* [38]	USA	ROS	2002–06	499	65.0	273/226	I–IV	PN,LB,BL,ST	456/43	✓	✓	✗	NI	8
Stolz *et al.* [39]	Czech	ROS	1998–2012	329	55.8	253/76	NI	PN	All open	✗	✓	✗	30 days	7
Thomas *et al.* [40]	France	ROS	2005–11	19635	63.2	14172/5463	I–IV	LB	18966/669	✓	✓	✗	30 days	8
Thomas *et al.* [41]	France	ROS	2003–13	4498	61.6	3653/845	I–IV	PN	All open	✓	✓	✗	30 days	8
Varela *et al.* [42]	Spain	POS	1998–99	81	63.6	71/10	NI	PN,LB,ST	All open	✓	✗	✗	NI	7
Warwick *et al.* [43]	UK	ROS	2001–11	1283	69.5	635/648	I–IV	LB,WR	NI	✗	✗	✓	5 years	8
Win *et al.* [44]	UK	POS	NI	110	69.0	66/44	I–IIIa	PN,LB,BL,WR	All open	✗	✗	✓	3 years	8
Zhai *et al.* [45]	USA	ROS	1992–2010	902	66.8	425/477	I–II	LB,WR, others	NI	✗	✗	✓	5 years	8

[a]The outcome measures involved in-hospital morbidity, mortality and long-term overall survival.
BL: bi-lobectomy; LB: lobectomy; NI: no information; NOS: Newcastle–Ottawa Scale; OS: overall survival; PN: pneumonectomy; POS: prospective observational study; RCMA: retrospective case-matched analysis; ROS: retrospective observational study; SL: sleeve lobectomy; ST: segmentectomy; VATS: video-assisted thoracoscopic surgery; WR: wedge resection.

Table 2: Meta-analysis of the association between body mass index/obesity and postoperative outcomes in patients undergoing lung cancer surgery

Pooled analyses	Data types	*N*	Sample size	Heterogeneity (I^2, *p*)	Model	Estimates with 95% CI[a]	*P*-value	Publication bias		Conclusion
								Begg (*p*)	Egger (*p*)	
Short-term outcomes										
In-hospital morbidity	Continuous	3	861	I^2=54.3%, *P*=0.112	Random	0.97 (0.94–1.00)	0.088	0.30	0.44	Not significant
	Dichotomous	9	62248	I^2=80.0%, *P*<0.001	Random	0.84 (0.73–0.98)	0.025	0.50	0.099	Significant
In-hospital mortality	Continuous	Abandoned because of the scarcity of available evidence								
	Dichotomous	9	68961	I^2=41.4%, *P*=0.082	Random	0.78 (0.63–0.98)	0.031	0.28	0.24	Significant
Long-term outcomes										
Overall survival	Continuous	10	7789	I^2=63.6%, *P*=0.003	Random	0.97 (0.95–0.98)	<0.001	0.72	0.13	Significant
	Dichotomous	3	2121	I^2=0.0%, *P*=0.708	Fixed	0.69 (0.56–0.86)	0.001	0.73	0.29	Significant

[a]Estimates for short-term outcomes and long-term survival were OR and HR, respectively.
CI: confidence interval; *N*: reference count.

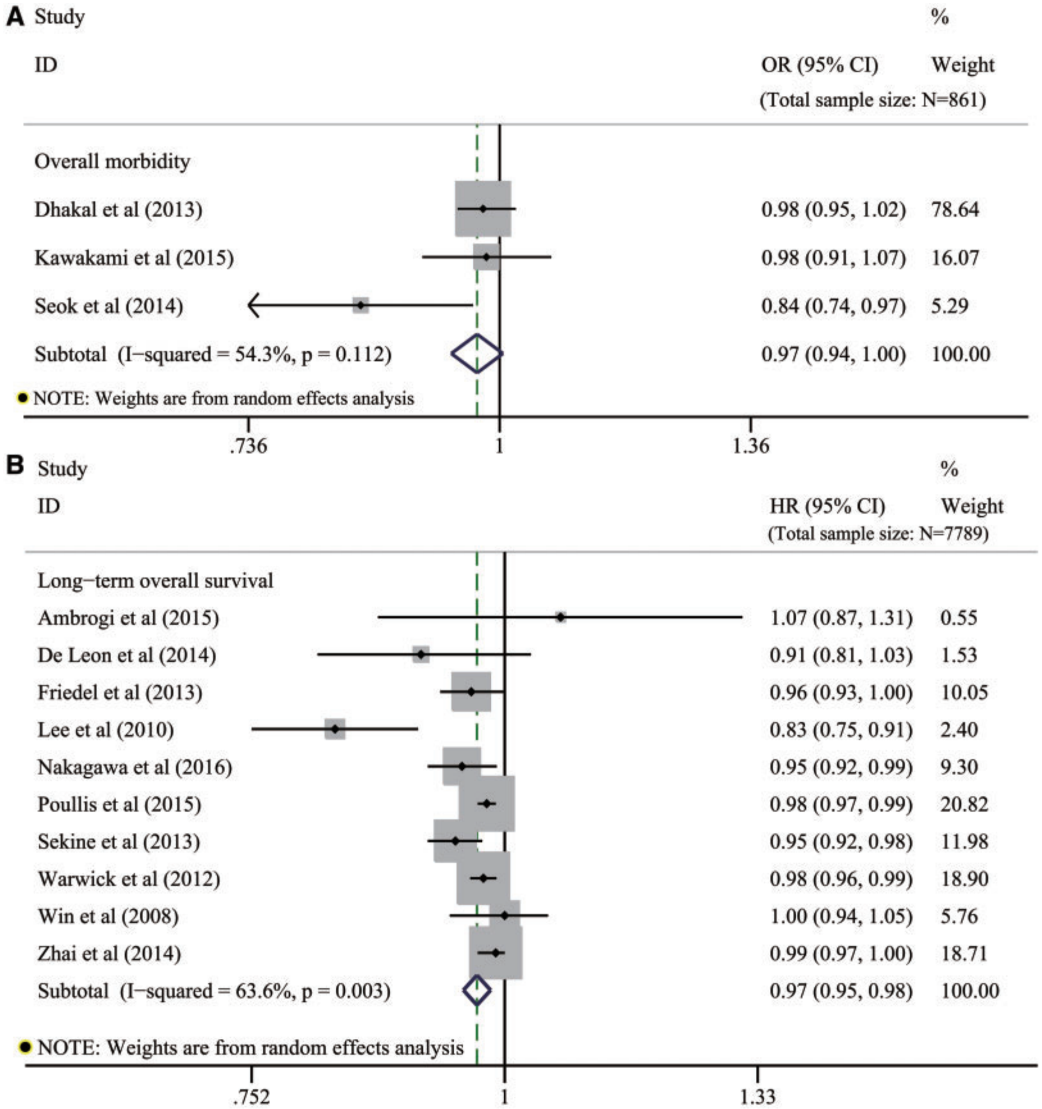

Figure 2: Meta-analysis of the impact of increased body mass index on (**A**) overall morbidity and (**B**) long-term overall survival of patients undergoing lung cancer surgery.

(ii) In-hospital mortality

None of the included studies reported outcome data about the association between continuous values of BMI and postoperative mortality. Thus, we discontinued further analysis of this point.

Nine studies compared in-hospital mortality rates of obese and non-obese patients [21, 23, 29, 31, 32, 38, 39–41]. The pooled analysis of these studies used a random-effect model ($I^2 = 41.4\%$, $P = 0.082$) and showed a significantly lower mortality rate in the obese patients (OR: 0.78; 95% CI: 0.63–0.98; $P = 0.031$; Table 2; Fig. 3B), indicating that obese patients had a significantly lower risk of in-hospital death compared with normal/underweight patients.

(iii) Long-term OS

The integrated HR of 10 studies [22, 24, 27, 30, 33, 34, 36, 43–45] reporting continuous BMI variables was 0.97 (95% CI: 0.95–0.98; $P < 0.001$; Table 2; Fig. 2B), suggesting that increased BMI could independently predict higher OS for patients undergoing lung cancer surgery. The heterogeneity between studies was sufficiently high that a random-effect model was adopted ($I^2 = 63.6\%$, $P = 0.003$).

Three studies compared the OS between obese patients and normal/underweight patients [23, 26, 33]. Their integrated estimates with a fixed-effect model ($I^2 = 0.0\%$, $P = 0.708$) indicated that obesity was significantly associated with better prognosis of operable lung cancer (HR: 0.69; 95% CI: 0.56–0.86; $P = 0.001$; Table 2; Fig. 3C).

Sensitivity analysis

By omitting the individual study sequentially, none of the outcome data from the included studies was found to be out of the estimated range in each quantitative synthesis (Fig. 4A–C). Substantial variations in the primary pooled outcomes were not identified. The robustness of our meta-analysis was thus confirmed.

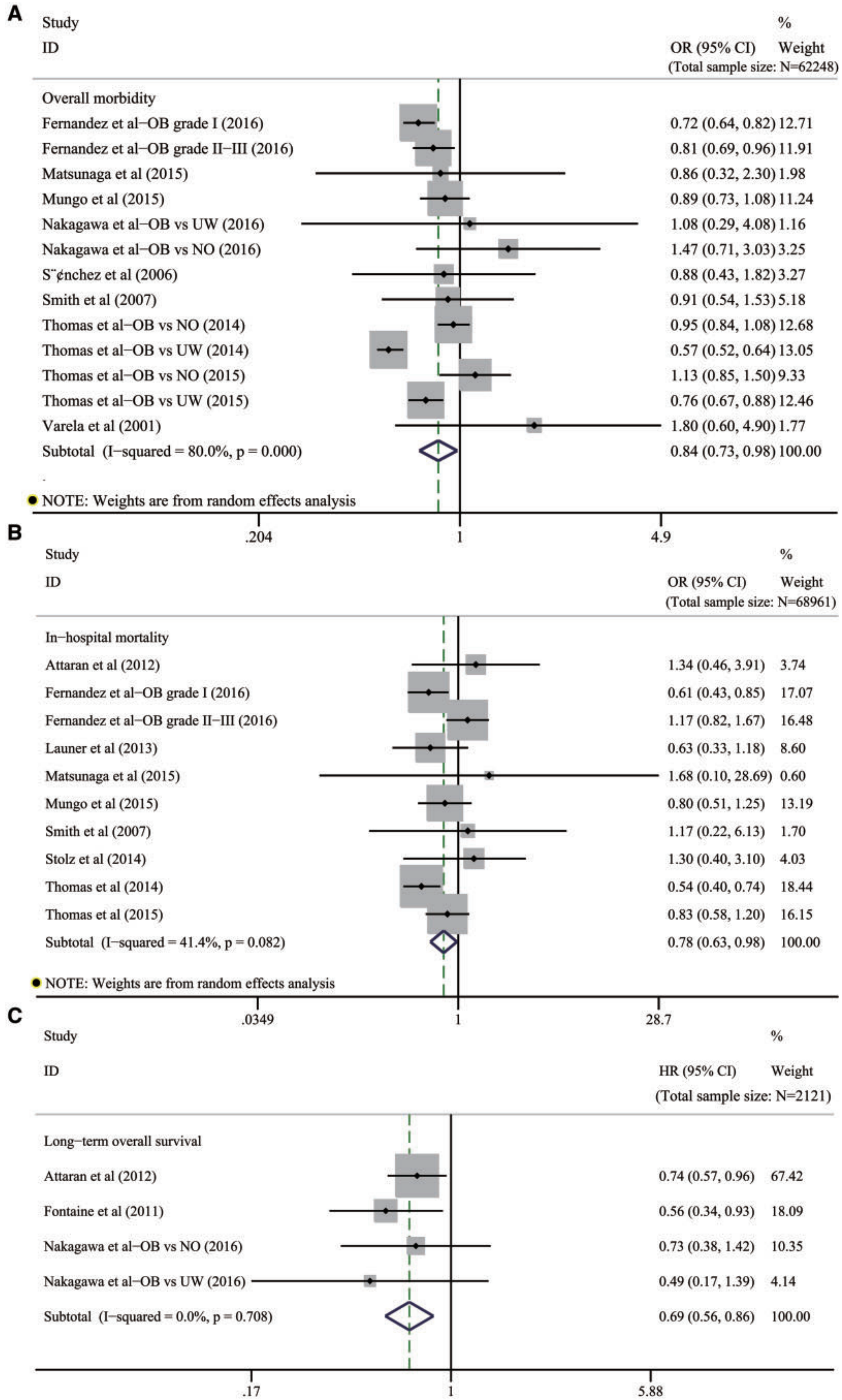

Figure 3: Meta-analysis of the impact of obesity on (**A**) overall morbidity, (**B**) in-hospital mortality and (**C**) long-term overall survival of patients undergoing lung cancer surgery. NO: normal; OB: obese; UW: underweight.

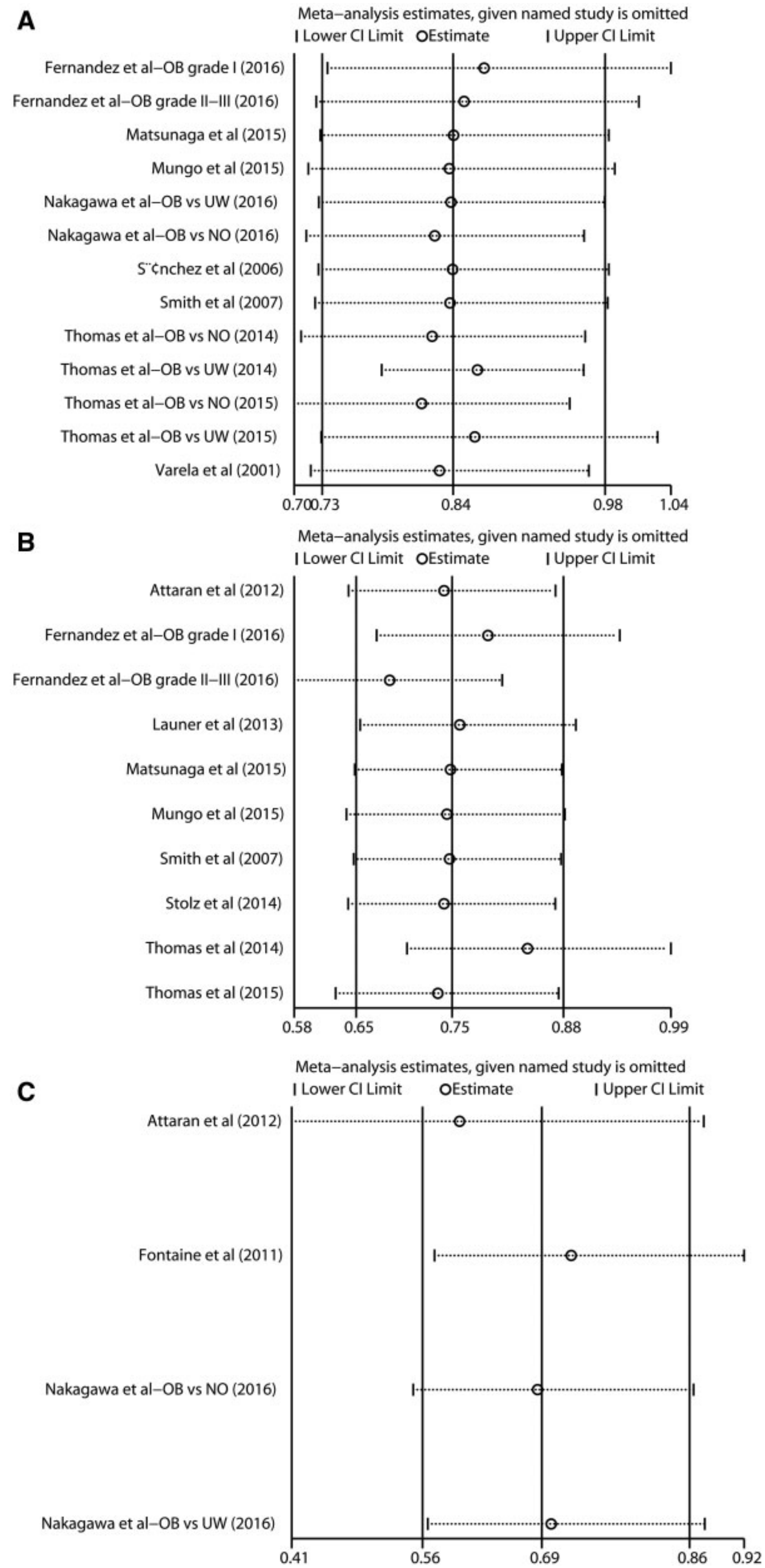

Figure 4: Sensitivity analysis of the impact of obesity on (**A**) overall morbidity, (**B**) in-hospital mortality and (**C**) long-term overall survival of patients undergoing lung cancer surgery. NO: normal; OB: obese; UW: underweight.

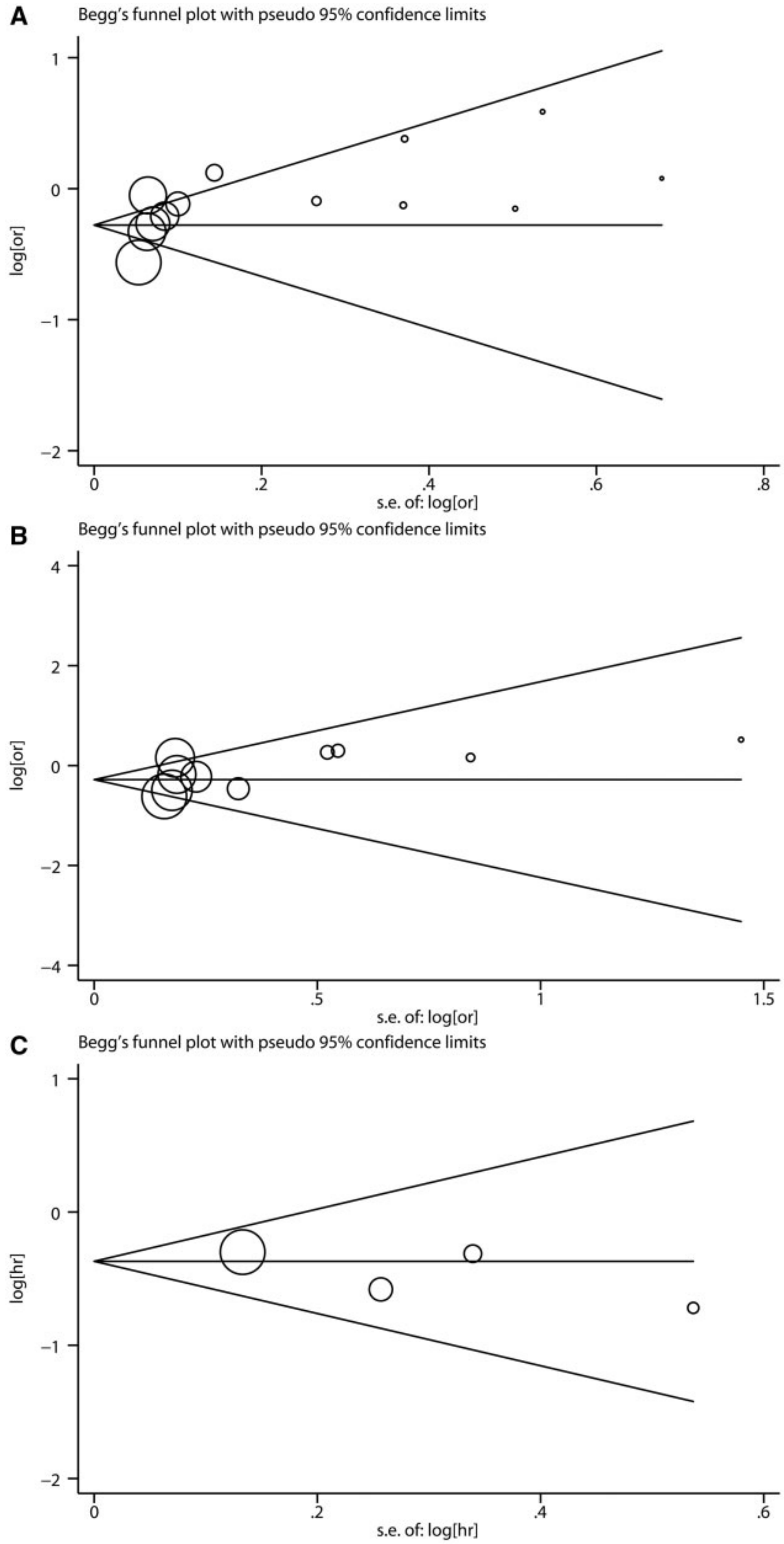

Figure 5: Begg's funnel plots for publication bias within the meta-analyses on the impact of obesity on (**A**) overall morbidity, (**B**) in-hospital mortality and (**C**) long-term overall survival of patients undergoing lung cancer surgery.

Publication bias

Complete results derived from publication bias tests are listed in Table 2 (Fig. 5A–C). No evidence for significant bias was detected within any one meta-analysis either by the Begg's test or the Egger's test.

DISCUSSION

Summary of evidence

When we pooling the current evidence, our initial impression was one of more favourable long-term survival in patients with higher BMI compared to those with lower BMI, as had been concluded in most studies [24, 27, 30, 33, 34, 36, 43–45]. According to multivariate analysis, increased BMI was an independent predictor for better OS in more than half of the included studies [27, 30, 33, 34, 36, 43, 45]. Similarly, a significantly higher survival rate was commonly reported among obese patients in three studies [23, 26]. Rare studies demonstrated a tendency towards unfavourable survival outcomes. Only one small retrospective analysis enrolling 59 patients undergoing wedge resection showed worse OS in patients with higher BMI [20]. Another large study reported by Win *et al.* [44] found that high BMI had no impact on lung cancer prognosis.

In terms of short-term morbidity and mortality, the largest study, which enrolled 27844 patients from the STS database, had applied a risk-adjustment model to analyse the role of obesity in predicting in-hospital outcomes [21]. Two other large-scale studies based on the STS database also evaluated the impact of increasing BMI on postoperative outcomes, although they were finally excluded because of their duplicate datasets [19, 20]. The outcome statistics from these three studies showed a significant benefit of higher BMI and obesity for in-hospital morbidity and mortality, which was consistent with results from another large study based on the French Society of Thoracic and Cardiovascular Surgery database [40]. Despite a trend towards decreased postoperative complications and deaths commonly observed in obese patients, no prominent paradoxical benefit of obesity was thus found in more than half of the remaining studies [29, 31–33, 35, 36, 38, 41, 42]. In addition, five studies reported a slightly higher morbidity or mortality rate in obese patients [23, 31, 33, 38, 42]. We speculated that the limited sample size in individual studies could cause a decline in the precision of effect size estimations.

Therefore, we proposed that the key point to be addressed should be whether the prognostic value of BMI/obesity was statistically reliable. To our knowledge, this is the first systematic meta-analysis to summarize the effects of BMI and obesity on surgical outcomes after operations for lung cancer. According to the quantitative syntheses, increased BMI was significantly associated with better OS of lung cancer patients. In addition, the in-hospital morbidity rate was lower in patients with higher BMI, but no statistical significance was found. The pooled analyses based on dichotomous variables indicated that in-hospital morbidity and mortality were both significantly decreased in obese patients. Moreover, obesity could be predictive of more favourable long-term prognosis of surgical patients with lung cancer. Therefore, based on the above estimates, we concluded that the 'obesity paradox' might really exist in lung cancer surgery.

The obesity paradox mechanisms

The possible mechanisms underlying the obesity paradox remain under debate. The following perspectives are generally considered when trying to explain this unexpected phenomenon.

First, with the popularity of fatty fast food and the reduction of physical exercise, an increasing number of people are becoming obese at a young age [46]. The higher proportion of obese young people was supported by Bundhun *et al.* [47] in their meta-analysis. Stronger physiological functions and better recovery capabilities in young patients may provide improved tolerance to surgical attacks and help maintain the postoperative internal environment. These factors may be the primary reasons for lower in-hospital morbidity and mortality rates among obese patients.

Second, because obese patients are considered at higher risk of cardiovascular disorders, they are generally treated at an early age with medicines to control blood pressure and prevent hyperglycaemia. In addition, physicians advise these patients to do regular exercise and cardiac rehabilitation and to form healthy dietary habits. Few patients with normal BMIs receive such attentive care and health tips, so they tend to ignore their own health until they suffer from severe diseases [48]. This situation may be another important reason for the obesity paradox.

Third, obese patients can better store nutrients to resist surgical interventions compared to normal/underweight patients [47]. The protective effects of peripheral adipose tissues have been proved in previous investigations, and they also contribute to the better prognosis for surgical patients [49].

Finally, another plausible viewpoint suggests that obesity may not be protective but that being underweight is associated with worse postoperative outcomes. Nutritional depletion is generally accepted as a predictor of the poor prognosis of surgical patients, and significant weight loss is an important component [50, 51]. Underweight patients tend to be affected more by adverse events, such as cancers, smoking, chronic obstructive pulmonary disease and DM [47]. Almost all of the current evidence indicates that low BMI and being underweight are independent risk factors for poor surgical outcomes. These findings can easily create an illusion that obesity has a paradoxical benefit in surgical populations [31, 50, 51].

LIMITATIONS

This meta-analysis has some major limitations that should be acknowledged.

First, no high-quality RCT but 25 observational studies were included in this meta-analysis. A large decline in evidence level was unavoidable because of the retrospective nature of 23 of the studies [21–41, 43, 45].

Second, the majority of the data incorporated in this meta-analysis was derived from multivariate analyses, which had adequately eliminated the bias risks from other confounding factors [22–30, 32–34, 36–41, 43–45]. However, there were still eight univariate OR statistics without sufficient elimination of selection bias within the in-hospital outcome assessments, resulting in slightly negative effects on the validity of pooled ORs [23, 31, 33, 35, 38, 42].

For instance, DM is one of the most frequent comorbidities in obese patients because extensive fat storage can predispose one to insulin resistance, which correlates directly with the development of DM [12]. However, DM can cause serious pathological damage to the cardiovascular system and increase postoperative morbidity and mortality [4, 5, 12]. Therefore, DM can easily complicate the actual value of obesity in lung cancer patients, although thoracic surgeons usually make efforts to control DM-induced cardiovascular disorders during the perioperative period. Similarly, if multivariate analysis was not conducted, other comorbidities in obese patients could also add confounding biases to a meta-analysis. Therefore, the accuracy of our findings should be further evaluated in the future by more high-quality multivariate analyses.

Third, the definition of operable morbidity differed between studies and could cause significantly increased heterogeneity in reported complication rates. That was another major confounding factor.

Fourth, Asian patients accounted for only 6.5% of all enrolled patients. The prognostic significance of higher BMI was identified in both Western and Eastern populations. However, compared with Western populations, the impact of obesity on in-hospital outcomes and long-term OS remained controversial in Asian patients. According to current evidence, the obesity paradox did not appear in Asian populations, although an obvious tendency towards better postoperative outcomes was revealed [28, 31, 33]. As Goran *et al.* [52] proposed, significant ethnic differences have been found in obesity-related phenotypes and may affect the prevalence and prognosis of obesity-induced diseases. Another important reason for the ambiguous effects of obesity in Asian populations might be the limited number of Asian participants enrolled in only three retrospective studies, resulting in an insufficient evidence intensity. Anyway, potential ethnic differences in the obesity paradox need to be further clarified. The validity of our findings should be judiciously considered in the clinical settings of Eastern countries.

Fifth, publication bias is an issue that must be addressed in a meta-analysis because studies reporting beneficial intervention effects generally are published more frequently than studies showing negative results [18]. Therefore, we must mention the poor sensitivity of the current publication bias tests when fewer than 20 studies are included in a meta-analysis, although no evidence of significant publication bias was detected in this study.

Finally, restricting articles to those published in English could also increase the selection bias. More papers might enrich our meta-analysis if more electronic databases in English and other languages had been carefully searched. We plan to include a subgroup analysis based on a larger number of studies in an updated review.

CONCLUSIONS

Our study demonstrates the favourable effects of higher BMI and obesity on the in-hospital outcomes and long-term survival of patients undergoing operations for lung cancer. The prognostic roles of BMI and obesity are confirmed and suggest that the obesity paradox may really exist in patients having lung cancer surgery. Potential ethnic differences may weaken the validity of this conclusion in different clinical settings, and they are still not well interpreted. Therefore, our findings need to be further verified and modified by well-designed worldwide studies.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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