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The impact of body mass index on complication and survival in resected oesophageal cancer: a clinical-based cohort and meta-analysis

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Background: Body mass index (BMI) has been associated with the risk of oesophageal cancer. But the influence of BMI on postoperative complication and prognosis has always been controversial.

Methods: In total, 2031 consecutive patients who underwent oesophagectomy between 1998 and 2008 were classified according to Asian-specific BMI (kg m^{-2}) cutoff values. The impact of BMI on overall survival (OS) was estimated using the Kaplan–Meier method and Cox proportional hazard models. We performed a meta-analysis to examine the association of BMI with OS and postoperative complication.

Results: Patients with higher BMI had more postoperative complication ($P=0.002$), such as anastomotic leakage ($P=0.016$) and cardiovascular diseases ($P<0.001$), but less incidence of chylous leakage ($P=0.010$). Logistic regression analysis showed that BMI ($P=0.005$) was a confounding factor associated with postoperative complication. Multivariate analysis showed that overweight and obese patients had a more favourable survival than normal weight patients (HR (hazard ratio) = 0.80, 95% CI (confidence interval): 0.70–0.92, $P=0.001$). Subgroup analysis showed that the association with higher BMI and increased OS was observed in patients with oesophageal squamous cell carcinoma (ESCC) ($P<0.001$), oesophageal adenocarcinoma (EA) ($P=0.034$), never-smoking ($P=0.035$), ever-smoking ($P=0.035$), never alcohol consumption ($P=0.005$), weight loss ($P=0.003$) and advanced pathological stage ($P<0.001$). The meta-analysis further corroborated that higher BMI was associated with increased complication of anastomotic leakage (RR (risk ratio) = 1.04, 95% CI: 1.02–1.06, $P=0.001$), wound infection (RR = 1.03, 95% CI: 1.00–1.05, $P=0.031$) and cardiovascular diseases (RR = 1.02, 95% CI: 1.00–1.05, $P=0.039$), but decreased incidence of chylous leakage (RR = 0.98, 95% CI: 0.96–0.99, $P<0.001$). In addition, high BMI could significantly improved OS (HR = 0.78, 95% CI: 0.71–0.85, $P<0.001$).

Conclusion: Preoperative BMI was an independent prognostic factor for survival, and strongly associated with postoperative complications in oesophageal cancer.

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Oesophageal cancer is one of the most common cancers in the world, with >480 000 new cases and 400 000 deaths annually, of which about half occurred in China (Jemal *et al*, 2011). Despite advances of surgical techniques and incorporation of new therapeutic approaches, oesophageal cancer is still a highly devastating disease with poor prognosis (van Hagen *et al*, 2012). There is a strong evidence that lifestyle factors such as physical activity, diet and obesity may have an effect on survival for some cancers (Davies *et al*, 2011).

The association between body mass index (BMI) and the risk of oesophageal cancer has been established (Oh *et al*, 2005; Tran *et al*, 2005; Kubo and Corley, 2006; Smith *et al*, 2008; Turati *et al*, 2012). However, there is no general consensus on the influence of BMI on survival in oesophageal cancer. Some studies suggested that patients with higher BMI had a significantly better prognosis than those with lower BMI (Smith *et al*, 2008; Hayashi *et al*, 2010; Melis *et al*, 2011; Kayani *et al*, 2012; Scarpa *et al*, 2012), whereas others yielded conflicting results (Healy *et al*, 2007; Morgan *et al*, 2007; Schumacher *et al*, 2009; Skipworth *et al*, 2009; Grotenhuis *et al*, 2010; Madani *et al*, 2010; Yoon *et al*, 2011; Blom *et al*, 2012). In addition, whether patients with higher BMI would have an increased incidence of postoperative complication is still debated. Several studies described no differences in postoperative complications after oesophagectomy (Morgan *et al*, 2007; Scipione *et al*, 2007; Melis *et al*, 2011; Blom *et al*, 2012), whereas some reported that a higher incidence of severe complications were noted in patients with higher BMI (Healy *et al*, 2007; Grotenhuis *et al*, 2010; Hayashi *et al*, 2010).

Therefore, we analysed a large cohort of Chinese patients with oesophageal cancer and carried out a comprehensive meta-analysis to elucidate these two controversial issues.

MATERIALS AND METHODS

Patients. We identified consecutive patients with oesophageal cancer who underwent surgical resection at Sun Yat-sen University Cancer Center between December 1998 and December 2008. Patients were excluded if they received neoadjuvant or adjuvant therapy, had an unknown BMI or history of other cancer. Patient characteristics and postoperative complications were collected from retrospective medical record review using a standardized data collection form. Surgical procedure was performed as previously described in our studies (Liu *et al*, 2012). The most common surgical approaches included the left transthoracic procedure, the Ivor-Lewis approach and the cervicothoracoabdominal procedures. Lymph node dissection including standard or extended dissection

of thoracic and abdominal lymph nodes was performed in patients with no evidence of metastatic disease that included cervical or coeliac lymph node metastases. Pathologic stage was determined according to the 7th edition AJCC staging system (Rice *et al*, 2010). The study was approved by the Ethics Committee of Sun Yat-sen University Cancer Center. All patients provided a written informed consent according to the ethical approval.

BMI value. Body mass index (kg m^{-2}) was calculated based on a direct measurement of height and weight at diagnosis. Patients were asked whether they had weight loss when compared with their usual weight when their weight was measured at diagnosis. Patients were classified according to Asian-specific BMI cutoff value (Choi *et al*, 2013) as follows: underweight ($<18.5 \text{ kg m}^{-2}$); normal weight ($18.5\text{--}22.9 \text{ kg m}^{-2}$) (reference group); overweight and obese ($\geq 23.0 \text{ kg m}^{-2}$). These values were chosen because there is evidence that excess risks of mortality from all-cause occur at lower BMI levels in Asians than in Caucasian (Wen *et al*, 2009). Besides, the mean BMI of Chinese population was relatively low (Smith *et al*, 2008).

Definition of postoperative complications. All complications from surgery to discharge from hospital were prospectively documented. Respiratory diseases complications consisted of pneumonia, respiratory failure. Pneumonia required positive sputum cultures or clear clinical and radiographic evidence of consolidation. Respiratory failure was defined as the requirement for mechanical ventilation for >24 h after surgery. Anastomotic leakage was defined as extravasation of water-soluble contrast medium documented by radiography. Chylous leakage was defined as the milky and elevated triglyceride level drained fluid. Wound infection was defined as purulent discharge from a closed surgical wound, with signs and symptoms of inflammation of the surrounding tissue together with abnormal smell. Vocal cord paresis was defined as hoarseness, pain in the throat when speaking and aspiration (due to poor swallowing reflex) with frequent resultant coughing. Cardiovascular diseases were defined as the myocardial infarction and arrhythmia detected by electrocardiogram.

The standardized manner of postoperative complications was reported according to the classification system composed by Dindo *et al* (2003). This system was based on the therapeutic consequences of complications and consists of five grades. Grading of complications was performed according to the most severe complication in each patient.

Statistical analysis. Statistical analysis was performed using the SPSS 16.0 for windows software system (SPSS Inc., Chicago, IL, USA). Differences between three groups were tested by the

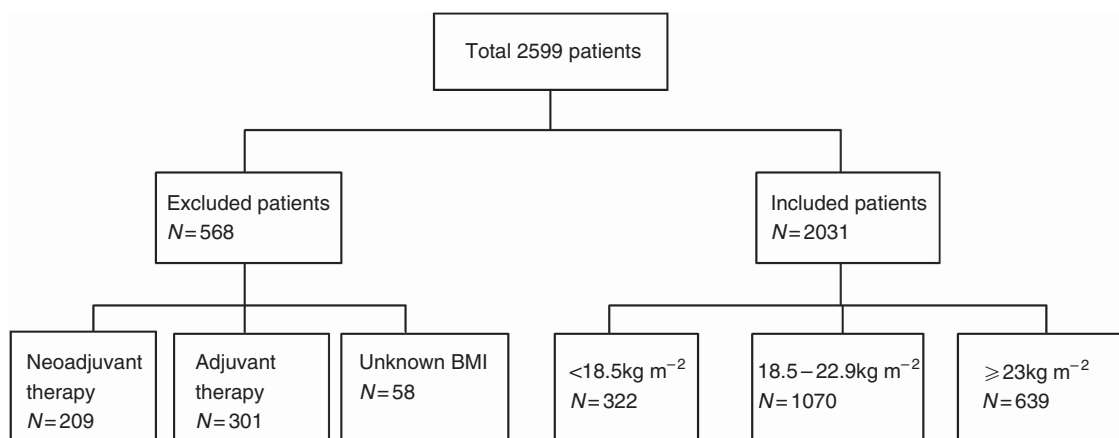


Figure 1. Flowchart of included esophageal cancer patients who underwent surgical resection between December 1998 and December 2008.

Table 1. The clinical and pathologic characteristics at baseline, stratified by BMI categories

Characteristic	No. of patients (%)				P-value
	Overall (n = 2031)	< 18.5 kg m ⁻² (underweight) (n = 322)	18.5–22.9 kg m ⁻² (normal weight) (n = 1070)	≥ 23.0 kg m ⁻² (overweight and obese) (n = 639)	
Hp					0.003
ESCC	1776 (87.4)	291 (90.4)	952 (89.0)	533 (83.4)	
EA	201 (9.9)	22 (6.8)	96 (9.0)	83 (13.0)	
Others	54 (2.7)	9 (2.8)	22 (2.0)	23 (3.6)	
Age					0.353
≤ 58 years	1048 (51.6)	156 (48.4)	551 (51.5)	341 (53.4)	
> 58 years	983 (48.4)	166 (51.5)	519 (48.5)	298 (46.6)	
Gender					0.367
Female patients	481 (23.7)	82 (25.5)	240 (22.4)	159 (24.9)	
Male patients	1550 (76.3)	240 (74.5)	830 (77.6)	480 (75.1)	
Smoking					<0.001
Never	734 (36.2)	96 (29.8)	364 (34.0)	274 (42.9)	
Ever (former + current)	1296 (63.8)	226 (70.2)	706 (66.0)	364 (57.1)	
Alcohol					0.044
Never	1419 (69.9)	226 (70.2)	724 (67.7)	469 (73.4)	
Ever (former + current)	612 (30.1)	96 (29.8)	346 (32.3)	170 (26.6)	
Weight loss					<0.001
No	1086 (53.5)	141 (43.8)	554 (51.8)	391 (61.2)	
Yes	945 (46.5)	181 (56.2)	516 (48.2)	248 (38.8)	
Surgical procedures					
Cervicothoracoabdominal	384 (18.9)	61 (18.9)	215 (20.1)	108 (16.9)	0.283
Ivor-Lewis	224 (11.0)	29 (9.0)	115 (10.7)	80 (12.5)	
Left transthoracic	1423 (70.1)	232 (72.1)	740 (69.2)	451 (70.6)	
Radicality of surgery					0.063
R0	1885 (92.8)	290 (90.1)	993 (92.8)	602 (99.8)	
R1	146 (7.2)	32 (9.9)	77 (7.2)	37 (0.2)	
Differentiation					0.401
G1	1377 (67.8)	230 (71.4)	721 (67.4)	426 (66.7)	
G2–3	654 (32.2)	92 (28.6)	349 (32.6)	213 (33.3)	
Tumour location					0.012
Upper	334 (16.4)	48 (14.9)	176 (16.4)	110 (17.2)	
Middle	1074 (52.9)	171 (53.1)	583 (54.5)	320 (50.1)	
Lower	434 (21.4)	82 (25.5)	223 (20.8)	129 (20.2)	
EGJ	189 (9.3)	21 (6.5)	88 (8.2)	80 (12.5)	
Pathological stage					0.168
Stage I–II	1127 (55.5)	168 (52.2)	614 (57.4)	345 (54.0)	
Stage III–IV	904 (44.5)	154 (47.8)	456 (42.6)	294 (46.0)	
In-hospital mortality	30 (1.5)	8 (2.5)	18 (1.7)	4 (0.62)	0.101
Postoperative complication	277 (13.6)	35 (10.9)	130 (12.1)	112 (17.5)	0.002
Respiratory diseases	50 (2.5)	6 (1.9)	29 (2.7)	15 (2.3)	0.674
Anastomotic leakage	110 (5.4)	9 (2.8)	55 (5.1)	46 (7.2)	0.016
Chylous leakage	17 (0.84)	7 (2.2)	8 (0.74)	2 (0.31)	0.010
Wound infection	42 (2.1)	6 (1.9)	20 (1.9)	16 (2.5)	0.669
Vocal cord paresis	18 (0.89)	1 (0.31)	10 (0.93)	7 (1.1)	0.458
Cardiovascular diseases	40 (2.0)	6 (1.9)	8 (0.75)	26 (4.1)	<0.001
Complications according to Dindo					0.012
Grade 0	1552 (76.4)	263 (81.7)	827 (77.3)	462 (72.3)	
Grade I–IIIb	404 (19.9)	54 (16.8)	204 (19.1)	146 (22.8)	
Grade IVa–V	75 (3.7)	5 (1.5)	39 (3.6)	31 (4.9)	
Duration of surgery (median, IQR) (min)	200 (120–405)	192 (120–350)	195 (120–410)	210 (120–420)	<0.001

Table 1. (Continued)

Characteristic	No. of patients (%)				P-value
	Overall (n = 2031)	< 18.5 kg m ⁻² (underweight) (n = 322)	18.5–22.9 kg m ⁻² (normal weight) (n = 1070)	≥ 23.0 kg m ⁻² (overweight and obese) (n = 639)	
Perioperative blood loss (median, IQR) (ml)	200 (100–400)	200 (100–400)	200 (100–400)	200 (100–500)	0.195
In-hospital stay, median (IQR) (day)	21 (18–26)	21 (13–24)	21 (14–27)	21 (14–26)	0.131
ICU stay, median (IQR) (day)	2 (1–6)	2 (1–4)	(1–5)	(1–6)	0.233
No. of collected lymph Nodes (median, IQR)	13 (3–35)	12 (3–32)	13 (3–36)	13 (3–34)	0.530
No. of metastatic lymph node (median, IQR)	0 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	0.163
Lymph node ratio, median (IQR)	0.00 (0.00–0.64)	0.045 (0.00–0.63)	0.00 (0.00–0.67)	0.035 (0.00–0.62)	0.092

Abbreviations : BMI = body mass index; Hp = histopathology; EA = oesophageal adenocarcinoma; EGJ = oesophagogastric junction; ESCC = oesophageal squamous cell carcinoma; G = grade; IQR = interquartile range.

Kruskal–Wallis test. The association between BMI categories and clinicopathologic parameters or postoperative complication was analysed by χ^2 -square test or Fisher's exact test. Follow-up time was calculated from the date of surgery to the event or date of the last contact. Follow-up continued until June 2012. The primary endpoint was overall survival (OS), which was calculated from the time of surgery to the time of death from any causes. The second endpoints were postoperative complication and disease-free survival (DFS). Disease-free survival was calculated from the time from surgery to the first recurrence of index cancer or to all-cause death. Multivariate logistic regression models were used to account for potential confounding factors associated with postoperative complication. Survival curves were calculated by the Kaplan–Meier method and analysed by log-rank test. Multivariate analysis was performed using Cox's proportional hazards regression model with a forward stepwise procedure (the entry and removal probabilities were 0.05 and 0.10, respectively). A significant difference was declared if the *P*-value from a two-tailed test was <0.05.

Meta-analysis. Two reviewers independently performed systematic literature search of the following databases: PubMed, Embase, Web of Science and CNKI database (last search up to December 2012). The following search terms were used: 'oesophageal cancer or oesophageal neoplasms', 'body mass index or overweight or obesity' and 'survival or prognosis'. All potentially eligible studies were retrieved. Studies were included if they met all of the following criteria: (1) patients with oesophageal cancer who underwent surgery, (2) BMI as an exposure interest, (3) information provided for estimating parameters and (4) published in English, German and Chinese with English abstract. Disagreements between reviewers were resolved by a third reviewer or by discussion and consensus. We assessed and quantified statistical heterogeneity for each pooled estimate using the *I*² statistic. If heterogeneity existed, a random effects model was adopted; otherwise, a fixed effects model was used. Pooled analysis was performed using the Mantel–Haenszel model and reported as hazard ratio (HR) with 95% confidence intervals (CIs) for the assessment of the influence of BMI on OS and risk ratio (RR) with 95% CIs for the association between BMI and postoperative complication. Where possible, the HR and associated variance were obtained directly from each study. When the association between BMI and HRs of survival was not reported, HRs were calculated by the methods of Parmer *et al* (1998) and Tierney *et al* (2007). The Begg's funnel plot and Egger's test were employed to estimate the potential publication bias. Sensitivity analysis was conducted to re-evaluate the overall results by omitting specific studies. The significance of the pooled HR or RR was determined by the *Z*-test

and *P*<0.05 was considered as statistical significance. All analyses were performed with the software STATA version 12 (StataCorp, College Station, TX, USA).

RESULTS

Patient characteristics by BMI. After excluding patients who receiving neoadjuvant or adjuvant therapy or with unknown BMI, 2031 consecutive patients with oesophageal cancer were included in the study and were divided into three groups according to BMI (Figure 1). Patient characteristics were shown in Table 1. Patients with higher BMI were more likely to be diagnosed with oesophageal adenocarcinoma (EA) and less likely to be oesophageal squamous cell carcinoma (ESCC) (*P*=0.003). Besides, overweight and obese patients were less likely to be smoker (*P*<0.001) and alcohol consumers (*P*=0.044), had lower likelihood of weight loss (*P*<0.001) when compared with normal weight.

Postoperative complication. With respect to perioperative complication, overweight and obese patients had more postoperative complication (*P*=0.002), such as anastomotic leakage (*P*=0.016) and cardiovascular disease (*P*<0.001). In addition, they had a longer operative time (*P*<0.001) than those with normal weight. Interestingly, overweight and obesity was associated with less incidence of chylous leakage in comparison to normal weight (*P*=0.010). There was significant difference in the rate of postoperative complication for different surgical procedures, 29.2% for cervicothoracoabdominal procedure, 12% for the Ivor-Lewis and 8% for the left transthoracic procedure (*P*<0.001) (data not shown). Logistic regression analysis showed that BMI (*P*=0.005), surgical procedures (*P*<0.001) and age (*P*=0.046) were confounding factors associated with postoperative complication (Supplementary Table 1). When all postoperative complications were categorised according to the Dindo classification, there were also significant differences between patients with underweight, normal weight, overweight and obesity (*P*=0.012, Table 1).

Univariate and multivariate analysis. The median of follow-up was 64 months. Univariate survival analysis showed a strongly significant difference in OS among three groups of patients. The 5-year OS and 10-year OS of patients with higher BMI were significantly longer than those of patients with lower BMI (*P*<0.001, Table 2, Figure 2). In addition, there was also significant difference in 5-year DFS among three groups of patients, 34.7% for underweight group, 37.3% for normal weight and 40.7% for

Table 2. Univariate and multivariate survival analysis for OS in patients with oesophageal cancer

Prognostic factor	Overall survival (OS)				Univariate survival analysis		Multivariate survival analysis	
	Mean	Median	5-year OS (%)	10-year OS (%)	HR (95% CI)	P-value	HR (95% CI)	P-value
Age					1.20 (1.07–1.35)	0.002	1.23 (1.10–1.38)	0.001
≤ 58 years	84.5	41.0	44.0	36.3				
> 58 years	69.9	34.0	38.3	27.1				
Gender					0.72 (0.62–0.83)	<0.001	0.86 (0.74–0.98)	0.04
Male patients	72.3	34.0	38.6	28.2				
Female patients	93.5	56.0	49.6	43.1				
pT category					1.78 (1.56–2.01)	<0.001	1.46 (1.28–1.68)	<0.001
T1–2	100.4	82.0	55.8	45.1				
T3–4	66.6	29.0	34.6	25.5				
pN category					2.50 (2.22–2.82)	<0.001	2.22 (1.96–2.51)	<0.001
N0	103.3	95.0	57.5	47.3				
N1–3	49.5	22.0	23.6	15.4				
Differentiation					1.51 (1.34–1.70)	<0.001	1.37 (1.21–1.54)	<0.001
G1	85.1	47.0	46.6	36.2				
G2–3	61.2	26.0	29.7	23.0				
Tumour location					1.09 (1.01–1.16)	0.019	0.94 (0.88–1.01)	0.094
Upper	66.4	40.0	41.0	30.0				
Middle	82.0	41.0	43.7	34.4				
Lower	72.6	32.0	39.4	29.6				
EGJ	41.4	31.0	30.3	0.0				
BMI					0.89 (0.83–0.95)	0.001	0.83 (0.77–0.91)	<0.001
< 18.5 kg m ⁻² (underweight)	63.7	28.0	36.5	22.8	1.19 (1.02–1.39)	0.024	1.13 (0.97–1.32)	0.111
18.5–22.9 kg m ⁻² (normal weight)	77.4	34.0	40.3	32.9	1 (reference)		1 (reference)	
≥ 23.0 kg m ⁻² (overweight and obese)	86.7	44.0	45.8	35.8	0.85 (0.75–0.97)	0.019	0.80 (0.70–0.92)	0.001
Weight loss					1.31 (1.17–1.47)	<0.001	1.18 (1.05–1.32)	0.006
No	85.5	43.0	45.5	36.2				
Yes	68.5	32.0	36.3	26.9				
Smoking					1.35 (1.19–1.52)	<0.001	1.15 (1.01–1.31)	0.038
Never	90.3	52.0	47.4	40.6				
Ever (former + current)	70.0	33.0	37.7	26.6				
Alcohol					1.39 (1.23–1.57)	<0.001	1.23 (1.08–1.40)	0.002
Never	84.0	42.0	44.6	35.8				
Ever (former + current)	61.2	27.0	33.1	22.1				

Abbreviations : BMI = body mass index; EGJ = oesophagogastric junction; G = grade; HR = hazard ratio; 95% CI = 95% confidence interval.

overweight and obese ($P=0.009$, Supplementary Table 2). As given in Table 2, patients with old age, male, advanced pT category, lymph node metastasis, oesophagogastric junction tumour location, weight loss, a history of smoking and alcohol consumption and poor histologic differentiation were found to have a significantly shorter OS. In the final multivariate survival analysis with adjustment for covariates, we found that overweight and obese patients had a 20% lower risk of dying from any cause including oesophageal cancer when compared with normal weight patients (HR = 0.80, 95% CI: 0.70–0.92, $P=0.001$).

In order to reduce possible effects of reverse causality due to prior diagnosed diseases or undiagnosed diseases, the sensitivity analyses were performed by excluding patients with prior diagnosed diseases (HR = 0.86, 95% CI: 0.78–0.95, $P=0.003$) or died during the first 1 year of follow-up (HR = 0.85, 95% CI: 0.78–0.92, $P<0.001$). The results did not substantially differ from the main results. We re-run the univariate survival analysis using a traditional BMI value 25 for overweight and obese instead of 23,

and the increased OS for overweight and obese patients was also found (HR = 0.83, 95% CI: 0.71–0.98, $P=0.031$) when compared with normal weight (BMI < 25 kg m⁻²).

Subgroup analysis. Univariate survival analyses stratified by histology, smoking status, alcohol consumption, weight loss and pathological stage were performed. We found that the association with higher BMI and increased OS were observed in patients with ESCC ($P<0.001$), EA ($P=0.034$), never-smoking ($P=0.035$), ever-smoking ($P=0.035$), never alcohol consumption ($P=0.005$), weight loss ($P=0.003$) and advanced pathological stage ($P<0.001$) (Supplementary Table 3).

Meta-analysis of BMI and postoperative complication. As the search flow diagram showed (Figure 3), 14 studies including the current study, were included in our meta-analysis (Table 3) (Trivers *et al*, 2005; Healy *et al*, 2007; Morgan *et al*, 2007; Schumacher *et al*, 2009; Skipworth *et al*, 2009; Grotenhuis *et al*, 2010; Hayashi *et al*, 2010; Madani *et al*, 2010; Melis *et al*, 2011;

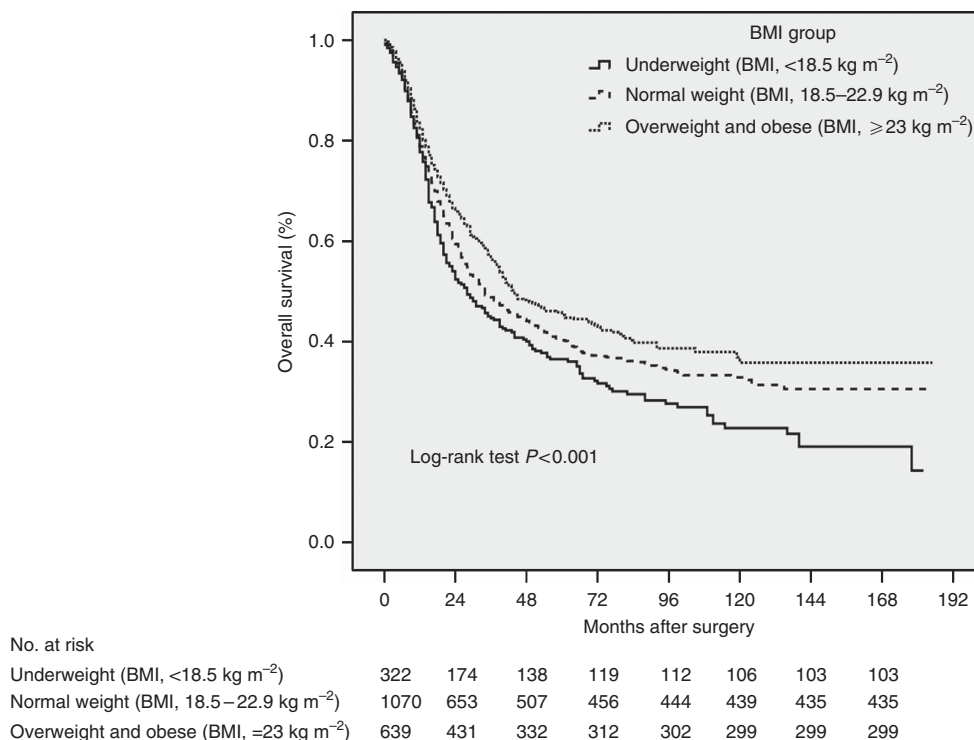


Figure 2. Kaplan–Meier curves of OS according to BMI categories. Abbreviation: BMI = body mass index.

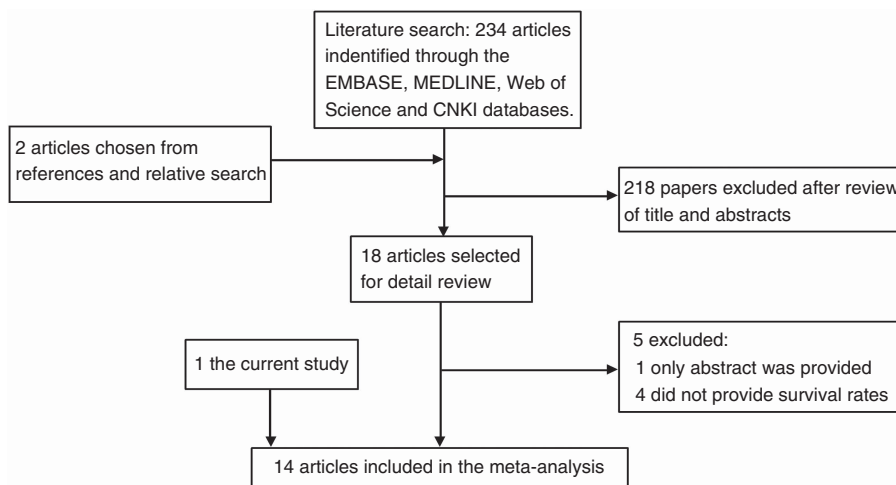


Figure 3. Flowchart of study selection for inclusion in the meta-analysis.

Yoon *et al*, 2011; Zhu *et al*, 2011; Blom *et al*, 2012; Scarpa *et al*, 2012). Of the 14 studies, 7 studies were conducted in Europe, 4 in the United States, 2 in China and 1 in Canada, 1 study published in German, 1 in Chinese with English abstract and others were all in English. Only patients with oesophageal cancer in one study which enrolled both of oesophageal and gastric cancer were included in our meta-analysis (Trivers *et al*, 2005). Owing to the varied cutoff of BMI in each study, we pooled estimate of comparison of the highest BMI group with the lowest group for consistency (Table 3).

To evaluate the association of higher BMI with increased incidence of postoperative complication, several studies reporting postoperative complication were included. As shown in Supplementary Table 4, higher BMI was significantly associated with increased complication of anastomotic leakage (RR = 1.04, 95% CI: 1.02–1.06, $P = 0.001$, Figure 4a), wound infection (RR = 1.03, 95% CI: 1.00–1.05, $P = 0.031$, Figure 4b) and

cardiovascular diseases (RR = 1.02, 95% CI: 1.00–1.05, $P = 0.039$, Figure 4c). More interestingly, patients with higher BMI inversely had a significantly decreased incidence of chylous leakage (RR = 0.98, 95% CI: 0.96–0.99, $P < 0.001$, Figure 4d). But with respect to the incidence of respiratory diseases and in-hospital mortality, there was no significant difference between the highest BMI group and lowest group. In all above pooled estimates, no significance of heterogeneity and publication bias was detected (Supplementary Table 4).

Meta-analysis of BMI and survival. All 14 studies were included to estimate the association of BMI and survival in oesophageal cancer. We found that patients with higher BMI had a significantly favourable OS (HR = 0.78, 95% CI: 0.71–0.85, $P < 0.001$, Figure 5a), there was no evidence of heterogeneity between the studies ($P = 0.188$, $I^2 = 24.7%$). The Begg’s funnel plots

Table 3. Characteristics of studies included in the meta-analysis

Author	Year	Country	Sample size (n)	Hp	Stage	BMI comparison (lowest/highest group) (n)	Covariates adjustment	Mortality ^a (lowest/highest group) (n)	Postoperative complication (lowest/highest group) (n)				
									RD	AL	CL	WI	CD
Schumacher <i>et al</i>	2009	Germany	108	A	All	<25 vs >25 (55/52)	None	U	U	3/4	0/1	U	2/6
Trivers <i>et al</i>	2005	USA	1142	A + S	All	<25 vs ≥30 (239/63)	Stage, sex and income	U	U	U	U	U	U
Healy <i>et al</i>	2007	Ireland	150	A	All	<30 vs >30 (114/36)	None	7/2	43/21	2/5	7/2	U	13/7
Morgan <i>et al</i>	2007	Wales	215	A + S	All	<25 vs >25 (97/118)	Age, stage and ASA grade	U	29/31	8/6	U	7/18	2/5
Skipworth <i>et al</i>	2009	UK	93	A	All	<25 vs >25 (39/54)	None	U	1/3	1/2	U	0/1	0/2
Grotenhuis <i>et al</i>	2010	Netherlands	556	A + S	All	<18.5 vs ≥30 (40/58)	None	1/5	11/12	5/16	1/5	1/7	0/2
Hayashi <i>et al</i>	2010	USA	301	A + S	All	<25 vs >25 (76/225)	Age, weight loss, PVD and stage	2/4	31/81	10/32	U	18/62	13/52
Madani <i>et al</i>	2010	Canada	142	A	All	<30 vs >30 (86/56)	Age, sex, extent of resection, grade, stage and ratio of positive lymph node	U	11/17	9/9	U	U	U
Melis <i>et al</i>	2011	USA	490	A + S	All	20–24 vs ≥30 (148/166)	None	4/6	24/29	11/9	U	8/12	0/0
Yoon <i>et al</i>	2011	USA	778	A	All	18.5–24.9 vs ≥30 (259/171)	Age, sex, stage, grade and weight loss	U	U	U	U	U	U
Blom <i>et al</i>	2012	Netherlands	736	A + S	All	<25 vs ≥30 (352/72)	None	16/1	110/20	34/15	20/0	U	U
Scarpa <i>et al</i>	2012	Italy	278	A + S + O	All	<20 vs >30 (15/61)	Age, sex, stage and weight loss	U	5/3	0/0	U	U	6/2
Zhu <i>et al</i>	2011	China	264	A + S	All	<18.5 vs ≥30 (84/29)	None	2/2	13/3	2/5	3/0	3/2	0/1

Abbreviations: A = adenocarcinoma; AL = anastomotic leakage; ASA = American Society of Anesthesiology; BMI = body mass index; CL = chylous leakage; Hp = histopathology; n = number of patients; O = others; PVD = peripheral vascular disease; RD = Respiratory diseases; S = squamous cell carcinoma; U = unavailable; UK = United Kingdom; USA = United States; WI = wound infection. ^aIn-hospital mortality.

showed no evidence of obvious asymmetry (Supplementary Figure 1), and Egger’s test indicated no significance of publication bias ($P > 0.05$). Sensitivity analysis was carried out to assess the influence of individual studies on the summary effect. Removal of one study published in German, one in Chinese with English and our current study, did not alter the overall result (HR = 0.80, 95% CI: 0.72–0.89, $P < 0.001$). To examine whether the association of higher BMI and increased OS was observed when using a traditional BMI cutoff value 25, five studies with the same BMI cutoff value 25 were included. We also found the similar result (HR = 0.82, 95% CI: 0.72–0.94, $P = 0.004$, Figure 5b).

DISCUSSION

Body mass index has been associated with the risk of oesophageal cancer. Nevertheless, the effect of BMI on postoperative complication and prognosis of oesophageal cancer remains controversial. The main reasons can be summarised as follows: lack of large-scale clinical studies; different BMI cutoff values in different studies; some patients receiving neoadjuvant or adjuvant therapy were enrolled in some studies. Therefore, in our large-scale cohort study,

patients were classified according to Asian-specific BMI cutoff values. In addition, patients who received neoadjuvant or adjuvant therapy were excluded. To our knowledge, our study consisting of 2031 Chinese patients cohort and meta-analysis was the first time to systematically elucidate the association of BMI with postoperative complication and prognosis in oesophageal cancer.

In our study, higher BMI was proved to be a risk factor for postoperative complication, such as anastomotic leakage and cardiovascular diseases. Previous studies reported that patients with higher BMI had a higher incidence of anastomotic leakage (Healy *et al*, 2007; Grotenhuis *et al*, 2010; Blom *et al*, 2012). The potential mechanisms might be summarised as follows: overweight and obese patients were performed a more challenge of a cervical anastomosis procedure and had higher rate of diabetes mellitus which could adversely affect the growth of anastomosis (Blom *et al*, 2012). Interestingly, we found that patients with higher BMI had less incidence of chylous leakage when compared with lower BMI. This result was in accordance with some previous studies (Morgan *et al*, 2007; Blom *et al*, 2012). However, the underlying mechanisms were rarely elucidated and in need to be further studied. The number of event for postoperative complication in each study was small and our results still needed further confirmation.

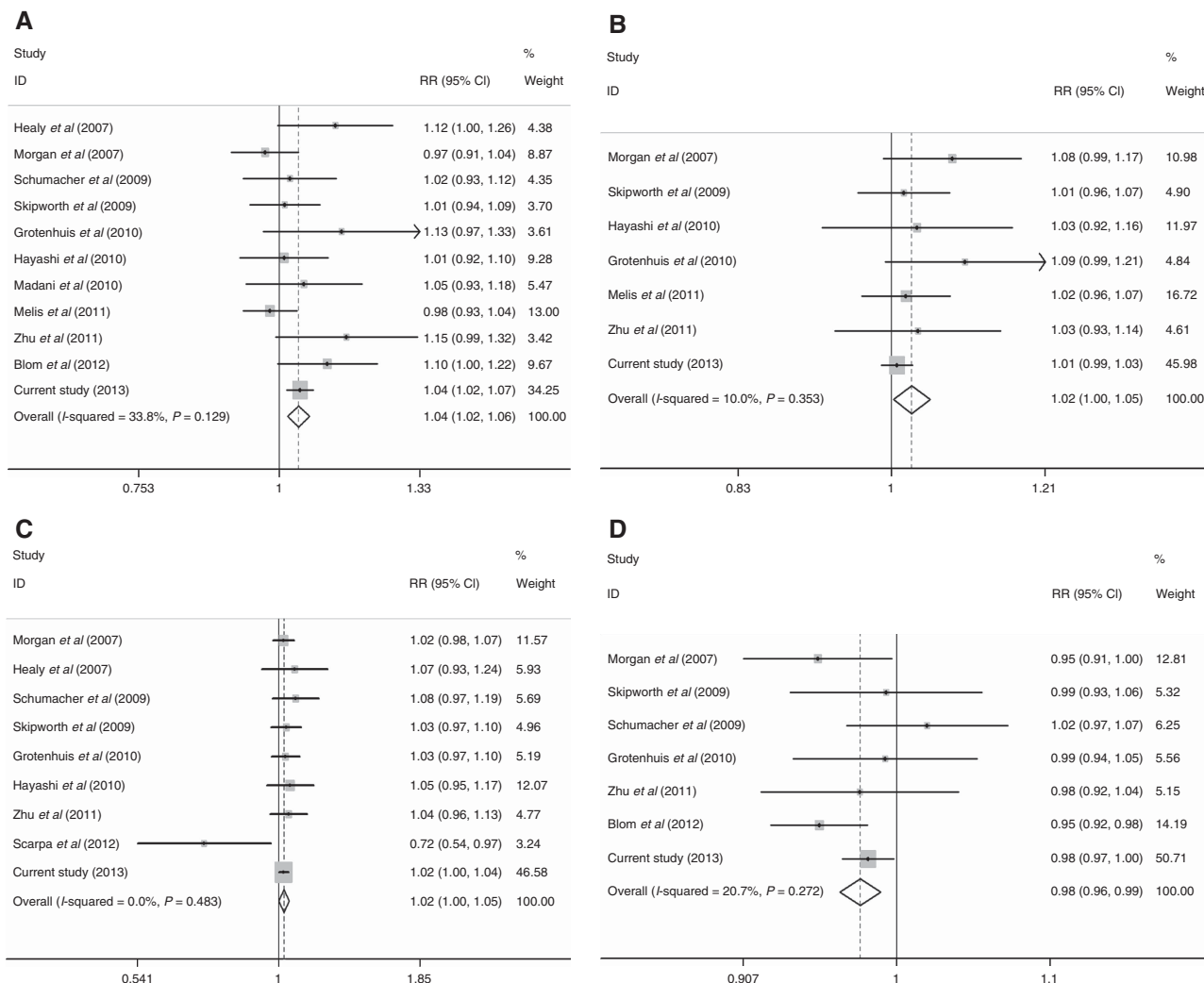


Figure 4. Forest plot of RR for postoperative complication of patients with highest vs lowest BMI category. (A) Anastomotic leakage. (B) Wound infection. (C) Cardiovascular diseases. (D) Chylous leakage. Abbreviation: RR = risk ratio.

The clinical cohort study and meta-analysis both suggested that patients with higher BMI had a favourable survival when compared with lower BMI. In our cohort study, overweight and obese patients had an apparently longer 5-year OS than normal weight. Multivariate survival analysis showed that BMI was an independent prognostic factor in oesophageal cancer. Sensitivity analysis by excluding patients with prior diagnosed diseases or who died within the first 1 year of follow-up showed the similar result. Given most studies used a traditional BMI value 25 for overweight and obese, we re-run the univariate survival analysis using 25 as BMI cutoff. And we found that higher OS for overweight and obese patients was still noted. What is more, meta-analysis by pooling five studies with the same BMI cutoff value 25 confirmed this result. Our finding was similar to some previous studies (Smith *et al*, 2008; Hayashi *et al*, 2010; Melis *et al*, 2011; Scarpa *et al*, 2012), including one meta-analysis based on small sample size (Kayani *et al*, 2012). In addition, a survival advantage in patients with higher BMI has been repeatedly described for renal cancer and sporadically reported for gastric cancer (Dindo *et al*, 2003; Mullen *et al*, 2008).

The mechanism by which overweight and obese patients might improve survival is not well understood. The prognostic advantage for overweight and obese patients might be attributed to the fact that overweight and obese was associated with never-smoking, never alcohol consumption and no weight loss in our present study. All of these factors were proved to affect survival not only in

our study but also in other studies (Thrift *et al*, 2012). Besides, patients with overweight and obese were more likely to be diagnosed with EA and less likely to be ESCC when compared with normal weight. Patients with EA were reported to have a better prognosis than those with ESCC (Holscher *et al*, 1995). However, when we performed univariate survival analyses stratified by smoking status, alcohol consumption, weight loss and histology, the association with higher BMI and increased OS were observed in patients with never-smoking, ever-smoking, never alcohol consumption, weight loss, ESCC and EA subgroup. The findings indicated that weight loss rather than smoking or alcohol consumption status or histology might be responsible for the survival difference. In essence, the decreased oesophageal cancer death led to the better prognosis for higher BMI patients because higher DFS for them was noted in our study.

In addition, a recent study indicated that preoperative nutritional deficiency was associated with poor survival in cancer patients (Morgan *et al*, 2011). Overweight and obese patients might have a better nutritional status and potential survival advantage because they had large appetites and high lipid concentration, and could adequately preserve their fat and muscle mass (Davos *et al*, 2003). We should acknowledge that the association between BMI and survival might be influenced by unmeasured confounding factors such as selection criteria and specially the socioeconomic status. Patients with overweight and obese were thought to be

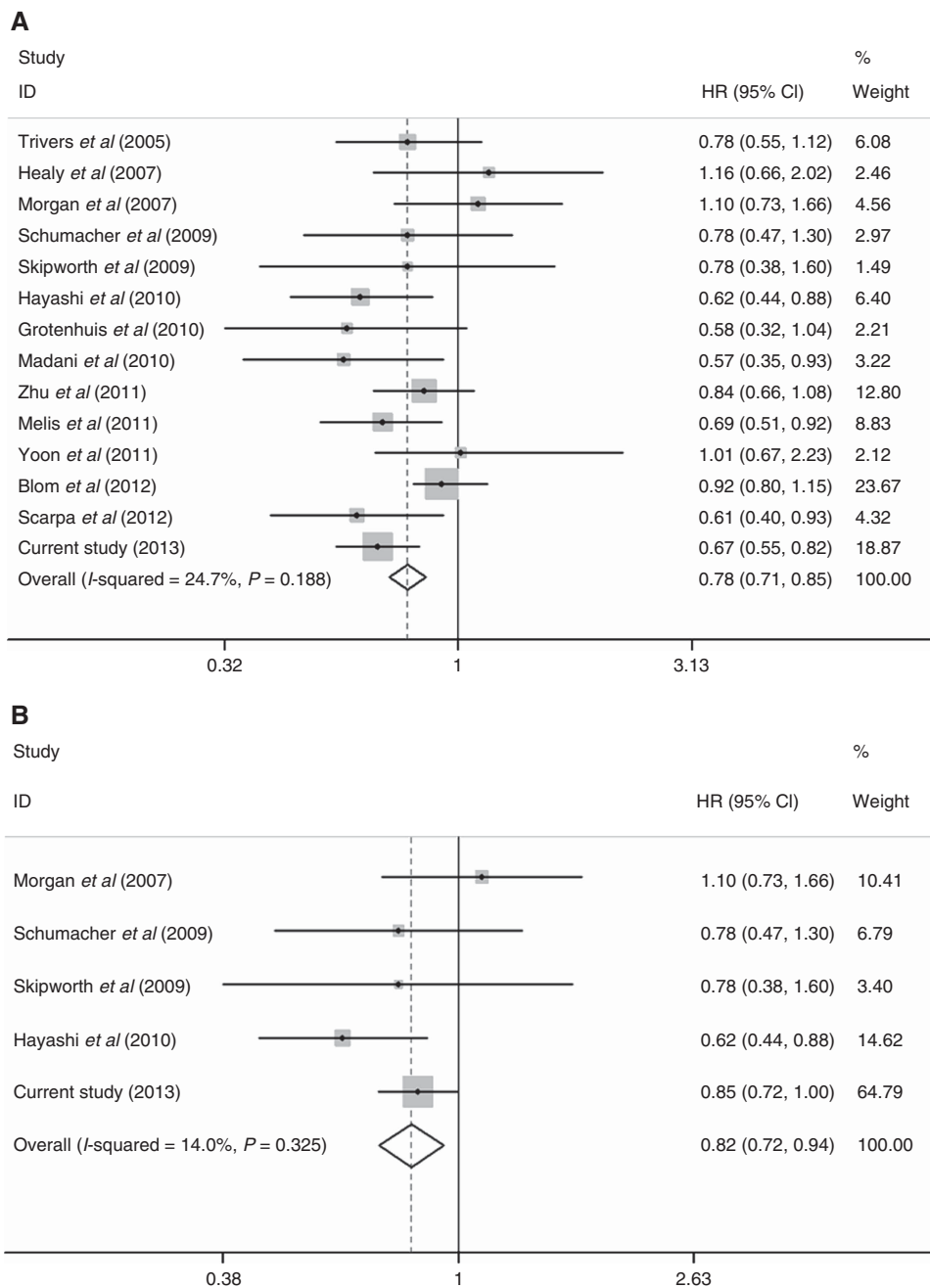


Figure 5. Forest plot of HR for OS of patients with highest vs lowest BMI category (A) and pooling estimate of using a traditional BMI cutoff value 25 (B). Abbreviation: HR = hazard ratio.

associated with higher income and higher education condition in China. They were more likely to receive chemotherapy and/or radiotherapy after recurrence than patients with lower BMI because of the financial support.

In conclusion, our larger scale Chinese cohort study and meta-analysis provided more definite and quantitative evidence that higher BMI was associated with favourable survival and some postoperative complications including anastomotic leakage, wound infection and cardiovascular diseases in oesophageal cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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