

Does high body mass index influence the postoperative complications and long-term survival in patients with esophageal squamous cell carcinoma after minimally invasive esophagectomy?

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Abstract

Introduction: The prognostic value of high body mass index (BMI) in patients with esophageal squamous cell carcinoma (ESCC) is still controversial.

Aim: To evaluate the impact of high BMI on postoperative complications and survival after minimally invasion esophagectomy (MIE) for ESCC patients.

Material and methods: Three hundred and fourteen consecutive ESCC patients were used to analyze the potential association between high BMI and postoperative complications and survival.

Results: Patients were divided into two groups. There was no significant difference between high and low BMI groups in terms of postoperative complications, including respiratory disease ($p = 0.8362$), pneumothorax ($p = 0.6058$), anastomotic leakage ($p = 0.8678$), chylothorax ($p = 0.9062$), cardiovascular disease ($p = 0.5763$), vocal cord paresis ($p = 0.8349$), wound infection ($p = 0.5763$) and perioperative death ($p = 0.7179$). Patients in the high BMI group had a longer operative time ($p = 0.003$) and more blood loss ($p = 0.002$) than in the low BMI group. There was no difference in number of retrieved lymph nodes between the two groups ($p = 0.728$). Patients could not benefit from high BMI in overall survival (OS) ($p = 0.2459$). High BMI was not an independent prognostic factor for survival ($p = 0.1735$, HR = 0.776 and 95% CI: 0.5386–1.1180).

Conclusions: High BMI is associated with prolonged operative time and increased blood loss in MIE. However, high BMI is not associated with postoperative complications and not an independent prognostic factor for survival in ESCC patients who undergo MIE.

Key words: esophageal carcinoma, minimally invasive esophagectomy, body mass index, complications, survival.

Introduction

Esophageal squamous cell carcinoma (ESCC) is the major type of esophageal cancer (EC) in China, and poor nutritional status is one of most important risk factors. Interestingly, with the socioeconomic level elevation and lifestyle modification, the incidence of ESCC has decreased whereas the popu-

lation of high body mass index (BMI) patients has increased in the past decades [1]. As known, high BMI is associated with an increased incidence of cardiorespiratory disease. Therefore, the risk of postoperative morbidity and mortality may be increased in these patients [2]. Meanwhile, surgery in high BMI patients can be troublesome; it is difficult to distinguish the dissection plan because of more adipose

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tissue adhering to targeted organs and vessels in the surgical field. With the development of minimally invasive esophagectomy (MIE), which can provide an enlarged view making the surgical field more clearly visible, the incidence of postoperative complications and mortality rate are decreased without compromising the oncological outcome [3, 4]. However, whether MIE can provide more advantages in high BMI patients is still unknown.

Some previous studies indicated that high BMI predicted better survival in EC patients [5, 6]. To the contrary, others found no relationship between high BMI and survival [7]. These findings suggest that the prognostic value of high BMI in EC patients remains inconclusive and requires further elucidation. In addition, most previous studies have been performed in patients with both ESCC and esophageal adenocarcinoma (EAC) and including different surgical types, such as conventional open esophagectomy and different types of MIE (Ivor-Lewis and McKeown procedure). Because of the heterogeneity of histopathologic types and different surgical procedures, large variation makes comparison difficult and inaccurate.

Aim

In this study, homogeneous histopathologic type and unified surgical procedure are used to assess the feasibility and safety of MIE in high BMI patients

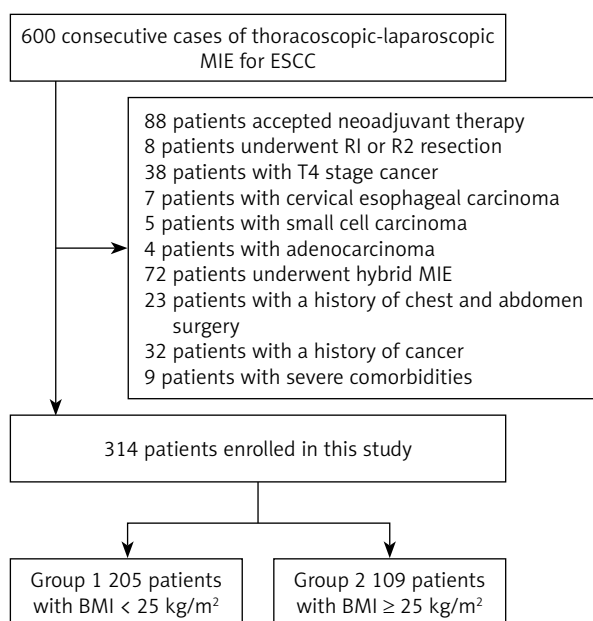


Figure 1. Number of patients excluded for each of the exclusion criteria

and investigate the influence of high BMI on long-term survival.

Material and methods

Patients

A retrospective study was performed by reviewing the records of 600 consecutive patients who underwent MIE (McKeown procedure) performed by a single surgeon between 2012 and 2020. According to the World Health Organization criteria [8], patients were divided into two groups based on BMI status: low BMI group (< 25 kg/m²) and high BMI group (≥ 25 kg/m²). Based on clinical assessments, the inclusion criteria of this study were as follows: (1) patients with clinical stage T1-3N0-3M0 cancer; (2) patients without a previous history of cancer; (3) patients without a history of neck, chest and abdomen surgery; (4) patients without neoadjuvant chemotherapy or chemoradiotherapy; (5) the application of a mechanical circular stapler for anastomosis by the same manufacturer. The exclusion criteria of this study were as follows: (1) non-R0 resection; (2) patients with pre-existing chronic obstructive pulmonary disease (COPD)/asthma/interstitial/lung disease; (3) patients with heart/liver/renal/diabetes dysfunction; (4) patients underwent hybrid MIE; (5) patients with small cell carcinoma and adenocarcinoma of esophagus; (6) patients with cervical segmental EC. The number of patients excluded for each of the exclusion criteria is shown in Figure 1. All included patients were diagnosed with ESCC of the thoracic esophagus before surgery and closely monitored for any clinical symptoms or alterations that might indicate complications. Data were collected retrospectively by reviewing the charts and were analyzed. Post-operative death was defined as death within 30 days after surgery or before discharge from hospital. All patients were assessed by endoscopy and computed tomography (CT) scan preoperatively. The anastomosis was consistently checked for leak using radiography with water-soluble contrast medium 7 days after surgery. Written consent was obtained from patients included in this study, and the study was approved by the Ethics Committee of our hospital.

Surgical procedure

All operations were performed under single-lumen intubation, and the details of the operation pro-

cedure were as described in our previous studies [9]. Thoracoscopic esophagectomy was performed with the patient in the semi-prone position and four trocars were inserted: a 30°12-mm thoracoscope was inserted through a 12-mm port in the eighth intercostal space (ICS) at the posterior axillary line (PAL); a 5-mm port was placed in the sixth ICS immediately cephalic and posterior to the tip of the scapula; a 12-mm port and 5-mm port were placed halfway between the spine and the original fourth and sixth intercostal port separately. The surgeon and camera operator stood at the patient's right side, and the video monitor was positioned on the patient's left side. Esophageal mobilization and dissection were performed essentially in the same manner as in open surgery; the surgery began by cauterizing the mediastinal pleura overlying the anterior aspect of the esophagus and mobilizing the esophagus from the hilum and the pericardium. Mobilization extended to the level of the azygous vein, which was skeletonized and ligated with 10-mm Liga clips. With electrocautery, the parietal pleura posterior to the esophagus was opened from the level of the azygous vein to the crus. After dissecting the esophagus and mediastinal lymph nodes, the thoracic duct was routinely mass ligated immediately above the diaphragmatic hiatus. After completing the thoracic procedure, the patient was rotated to a supine position, with the neck extended and turned toward the right. During the laparoscopic procedure, the entire greater curvature of the stomach was first mobilized, followed by division of the omentum. Then, the lymph nodes were dissected from the common hepatic artery to the left gastric artery, including the proximal splenic artery and the celiac artery. All these nodes, including the common hepatic nodes (station 18th lymph node), the splenic nodes (station 19th lymph node), the left gastric nodes (station 17th lymph node), and the celiac nodes (station 20th lymph node) were en bloc dissected. The left gastric vessels were divided after ligation with hem-o-lok clips. Lastly, the right and left crura of the diaphragm were dissected, and the abdominal cavity was linked to the mediastinum. In the last step, a 5-cm oblique incision along the anterior border of the left sternocleidomastoid muscle was made. The cervical esophagus was mobilized and transected. After placing the anastomatic component in the proximal end, the distal end was connected with a belt. Subsequently, the subxiphoid incision was enlarged to 3 cm, the esophagus and

stomach were pulled out, and the gastric tube was formatted with a stapler, with a width of 3 cm and a length of 35 cm. The gastric tube was pulled up to the left neck through the posterior mediastinum. After completing the esophagogastric anastomosis with a circular stapler, we closed the gastric stump with a stapler and placed an 18 Fr drainage tube in the cervical incision.

Histopathologic examination

The resection specimens were fixed with formaldehyde (4%) for 24 h. The complete tumor was cut in slices of 0.5 cm. All lymph nodes were dissected and analyzed. The tissue was paraffin embedded and stained with hematoxylin, eosin and van Gieson stain. All specimens were classified by two experienced pathologists according to the American Joint Committee on Cancer (AJCC) Staging System, 8th edition [10].

Follow up

Patients were followed up every 3 months in the first 2 years, then every 6 months in the following 3 years, and then annually after 5 years. The duration of follow-up was calculated from the completion of treatment to the last contact or death. The final follow-up was on May 1, 2021.

Statistical analysis

All statistical analyses were performed using MedCalc 12 (MedCalc Software, Ostend, Belgium). Values are expressed as the mean \pm standard deviation. The categorical data of the two groups were compared by χ^2 test or *t* test, and *p*-values of < 0.05 were considered statistically significant. OS was estimated and plotted using the Kaplan-Meier method and log-rank test. Cox proportional hazards regression modeling was applied to calculate the crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI).

Results

After exclusion of 286 patients according to our exclusion criteria, the remaining 314 patients were divided into two groups according to the Asia-specific BMI cutoff value (kg/m^2). The pertinent demographic data and clinical characteristics are summarized in Table I. The median duration of follow-up

Table I. Demographic and clinicopathologic characteristics of ESCC patients in different BMI groups

Characteristics	BMI < 25 kg/m ²	BMI ≥ 25 kg/m ²	P-value [†]
Age:			0.0522
≤ 60	54	41	
> 60	151	68	
Gender:			0.8988
Male	170	89	
Female	35	20	
Smoking:			0.2109
Never	58	23	
Ever	147	86	
Tumor location:			0.8828
Upper	48	23	
Middle	104	56	
Lower	53	30	
pT stage:			0.7034
Tis	14	11	
T1	42	24	
T2	44	20	
T3	105	54	
pN stage:			0.3827
N0	117	73	
N1	52	21	
N2	27	12	
N3	9	3	
Differentiation:			0.4417
G1	40	28	
G2	116	56	
G3	49	25	
pStage:			0.2397
I	52	34	
II	82	47	
III	71	28	
Total	205	109	

Data are presented as number of patients. Tumors were staged according to the TNM classification system (8th edition). [†]Comparison between low-BMI group and high-BMI group. BMI – body mass index, ESCC – esophageal squamous cell carcinoma, pT stage – pathological depth of tumor invasion, pN – pathological lymph node metastasis, pStage – pathological TNM stage.

for all patients was 25.6 months (range: 9.8–67.4 months). In the enrolled patients, 219 were older than 60, and patients' age ranged between 40 and 85 years (63.7 ± 7.6 years). 259 were male, and the sex ratio (male/female) was 4.71/1. Two hundred thirty-three (74.2%) patients had smoking history; and the rest were non-smokers (25.8%). The tumor was situated in the middle third of the esophagus in 160 (50.9%) patients, in 83 (26.4%) it was located in the lower third of the esophagus, and in the remaining 71 (22.7%) cases in the upper third of the EC. There was no difference in age ($p = 0.0522$), gender ($p = 0.8988$), smoking status ($p = 0.2109$), tumor location ($p = 0.8828$), T stage ($p = 0.7034$), N stage ($p = 0.3827$), differentiation ($p = 0.4417$) or pathological stage ($p = 0.2397$) among the subgroups stratified by the BMI.

Surgical outcomes

All the patients in these two groups underwent MIE (McKeown procedure), including two-field lymphadenectomy. The total operative time for patients in the high-BMI group was 212.6 ± 46.4 min, which was significantly longer than that in the low-BMI group (197.7 ± 36.3 min) ($p = 0.003$). Similarly, in both the thoracic and abdominal part, the time of the operation was significantly longer in the high-BMI group (85.8 ± 27.4 min) (36.7 ± 12.3 min) than in the low-BMI group (80.1 ± 27.4 min) ($p = 0.013$) (33.1 ± 10.2 min) ($p = 0.023$). Intraoperative blood loss was also significantly higher in the high-BMI group (145.6 ± 145.5 ml) than in the low-BMI group (133.6 ± 113.2 ml) ($p = 0.002$). There was no difference in the number of retrieved lymph nodes between the two groups ($p = 0.728$). The rate of conversion to open surgery in the high BMI patients was 1.4%, which was equal to that in low BMI group (0.9%) ($p = 0.906$) (Table II).

Postoperative complications

The postoperative complications are summarized in Table III. A total of 14 patients had postoperative respiratory disease ($p = 0.8362$), and 25 had pneumothorax ($p = 0.6058$). The incidence of anastomotic leakage was 9.6% (30/314), and most of them (22/314) developed a leakage at the cervical anastomosis ($p = 0.5475$). Because of routine ligation of the thoracic duct at the time of mobilization of the esophagus, the incidence of chylothorax was

Table II. Intraoperative characteristics in ESCC patients in different BMI groups

Characteristics	BMI < 25 kg/m ²	BMI ≥ 25 kg/m ²	P-value [†]
Operation time [min]	197.7 ±36.3	212.6 ±46.4	0.003
Thoracic procedure [min]	80.1 ±27.4	85.8 ±27.4	0.013
Abdominal procedure [min]	33.1 ±10.2	36.7 ±12.3	0.023
Blood loss [ml]	133.6 ±113.2	145.6 ±145.5	0.002
No. of retrieved lymph node	28.4 ±8.9	28.2 ±9.1	0.728
Rate of conversion to open surgery (%)	1.4 (3/205)	0.9 (1/109)	0.906
Total	205	109	

Data are expressed as mean ± standard deviation. [†]Comparison between low-BMI group and high-BMI group. BMI – body mass index, ESCC – esophageal squamous cell carcinoma.

Table III. Postoperative complications in ESCC patients in different BMI groups

Characteristics	No. of patients (%)	BMI < 25 kg/m ²	BMI ≥ 25 kg/m ²	P-value [†]
Respiratory disease:	14 (4.5%)			0.8362
Yes		10	4	
No		195	105	
Pneumothorax:	25 (8.0%)			0.6058
Yes		18	7	
No		187	102	
Anastomotic leakage:	30 (9.6%)			0.8678
Yes		20	10	
No		185	99	
Chylothorax:	4 (1.3%)			0.9062
Yes		3	1	
No		202	108	
Cardiovascular disease:	3 (1.0%)			0.5763
Yes		2	1	
No		203	108	
Vocal cord paresis:	8 (2.5%)			0.8349
Yes		5	3	
No		200	106	
Wound infection:	3 (1.0%)			0.5763
Yes		2	1	
No		203	108	
Perioperative death:	6 (1.9%)			0.7179
Yes		4	2	
No		201	107	
Total		205	109	

Data were presented as number (%) of patients, unless otherwise indicated. [†]Comparison between low-BMI group and high-BMI group. BMI – body mass index, ESCC – esophageal squamous cell carcinoma, No. – number.

1.3% (4/314), and all patients recovered spontaneously ($p = 0.9062$). There was no significant difference between the high-BMI group and low-BMI group in terms of other postoperative complications, including cardiovascular disease ($p = 0.5763$), vocal cord paresis ($p = 0.8349$), and wound infection ($p = 0.5763$). Totally, six postoperative deaths (6/314, 1.9%) occurred in 314 patients. One patient died from gastro-tracheal fistula, one died from ARDS, and 4 patients died from infection in the thoracic cavity resulting from anastomotic leakage. There was no difference in the incidence of postoperative death in the two groups ($p = 0.7179$). It was not found that patients in the high-BMI group had higher postoperative morbidity or mortality.

Survival analysis

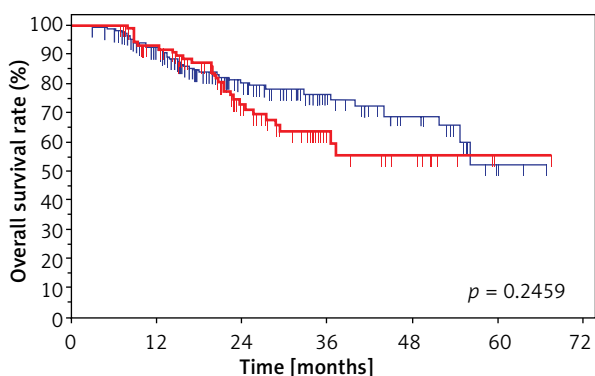
The median duration of follow-up for all patients was 25.6 months (range: 9.8–67.4 months). A total of 68 (68/314, 21.7%) patients died during the follow-up, and 55 (55/314, 17.5%) patients died from recurrence or metastasis of ESCC, while 13 patients died for other reasons, such as primary lung cancer, primary liver cancer, gastro-tracheal fistula, pneumonia and traffic accident. Among the alive patients, 17 of the 246 (17/246, 6.9%) survivors had locoregional or distant metastasis at the end of the follow-up period. Cervical lymph node (6/17, 35.3%) and lung (5/17, 29.4%) were the sites that most often tended to metastasis. The 5-year OS rate for all patients was

51.8%, and the mean OS time was 49.5 ± 1.8 months (95% CI: 45.9-53.1 months). When comparing the 5-year OS in different groups, Kaplan-Meier survival curve analysis did not reveal a significantly different OS rate between low-BMI and high-BMI groups (52.2% vs. 51.5%, log-rank test, $p = 0.2459$; Figure 2). In addition, to identify the independent prognostic factors of 5-year OS, factors were further investigated by univariate and multivariate hazard regression analysis. Univariate analysis indicated that T stage ($p < 0.0001$), N stage ($p < 0.0001$) and differentiation ($p = 0.0082$) were associated with the OS. However, BMI ($p = 0.2476$) and tumor location ($p = 0.2836$) did not influence the patients' survival significantly. In multivariate hazard regression analysis, the same results were obtained; BMI ($p = 0.1735$) and tumor location ($p = 0.7558$) were not independent prognostic factors for OS, whereas T stage ($p = 0.0301$), N stage ($p < 0.0001$) and differentiation ($p = 0.0438$) were significant influences on OS (Table IV).

Discussion

In the present study, we investigated the effects of high BMI on the postoperative complications and long-term survival in patients with ESCC. The results showed that patients with high BMI had significantly longer surgical time and more blood loss. However, besides that, the postoperative complications and long-term survival were not significantly different between different BMI groups. Additionally, Cox proportional hazard analysis showed that there was no difference in postoperative complications between different groups. Taken together, these results suggested that MIE (McKeown procedure) is a feasible and effective alternative for ESCC patients with high BMI.

Our study did not find a significant difference in postoperative complications between high and low BMI groups, which is consistent with the results of some previous studies about different kinds of tumors [11, 12]. Anastomotic leakage is one of the most common complications after upper-gastrointestinal surgery. In this study, the incidence of anastomotic leakage was 9.6%, which is in accordance with some previous studies [9, 13]. Some studies found that patients with gastric cancer had no significant difference in the surgical-related complication of anastomotic leakage between different BMI groups [14, 15]. However, other studies reported that



Number at risk

— Group: BMI > 25 kg/m ²	201	158	81	37	20	3	0
— Group: BMI ≥ 25 kg/m ²	107	87	44	16	8	1	0

Figure 2. Kaplan-Meier curves of survival rates for OS in patients who underwent MIE in this study. Data were compared using the log-rank test

Table IV. Overall survival after univariate analysis and multivariate Cox proportional hazard regression analysis in different groups of ESCC patients

Characteristics	No. of patients	Univariate long-rank <i>P</i> -value [†]	Multivariate regression <i>P</i> -value [†]	Hazard ratio	95% confidence interval
BMI:		0.2476	0.1735	0.776	0.5386–1.1180
< 25 kg/m ²	205				
≥ 25 kg/m ²	109				
Tumor location:		0.2836	0.7558	1.0628	0.7240–1.5602
Upper	71				
Middle	160				
Lower	83				
pT stage:		< 0.0001	0.0031	1.7624	1.2112–2.5643
Tis	25				
T1	66				
T2	64				
T3	159				
pN stage:		< 0.0001	< 0.0001	1.802	1.3915–2.3336
N0	190				
N1	73				
N2	39				
N3	12				
Differentiation:		0.0082	0.0438	1.6437	1.0138–2.6650
G1	68				
G2	172				
G3	74				

Data are presented as number of patients. Tumors were staged according to the TNM classification system (8th edition). [†]Comparison between low-BMI group and high-BMI group. BMI – body mass index, ESCC – esophageal squamous cell carcinoma, pT stage – pathological depth of tumor invasion, pN – pathological lymph node metastasis.

high BMI patients had a higher incidence of anastomotic leakage after esophagectomy [13, 16]. A possible explanation could be summarized as follows: high BMI patients in general had a higher rate of diabetes mellitus and cardiovascular disease which could adversely affect the healing of anastomosis [17]. It indicated that performing a cervical anastomosis in high BMI patients could be challenging. However, in our study, the incidence of anastomotic leakage is not higher in the high BMI group, a result contradicting a previous study; a potential reason could be that high BMI patients had a lower incidence of diabetes mellitus or cardiovascular disease in the present study. Nevertheless, the underlying mechanism was rarely elucidated and needs to be further investigated.

Similarly, in our study the incidence of chylothorax was 1.3%, which was not different between the groups ($p = 0.9062$). As mentioned in our previous study [13], routine ligation of the thoracic duct at the time of esophagectomy could reduce the incidence of chylothorax. To our knowledge, ligation of the thoracic duct is not associated with a poor quality of life and shorter time of survival.

With the development of the surgical technique, MIE is well accepted by more and more surgeons worldwide, which will reduce the postoperative complications and enhance the recovery [18–20]. However, some surgeons believe that there is increased incidence of intraoperative complications, such as more blood loss, less lymph node retrieval, prolonged surgical time and an increased conversion rate in

high BMI patients who undergo MIE. In view of the conflicting results, we performed this study to evaluate the impact of BMI on surgical safety and feasibility of MIE for ESCC. Indeed, in our study, both blood loss and surgical time are increased significantly in high BMI patients. One of the possible reasons may be that high BMI patients have more adipose tissue adhering to the alimentary tract; it is difficult to delineate the fascial space and vasculature, which can be troublesome, inevitably requiring longer surgical time and increased blood loss. In contrast to some previous studies, the rate of conversion to open surgery and number of harvested lymph nodes in high BMI patients were equal to those in the low BMI group in our study, which would guarantee the safety and oncological adequacy. Nevertheless, patients would benefit from MIE, which was demonstrated as a feasible and safe surgical procedure, with potentially faster postoperative recovery and fewer complications in comparison to conventional open surgery [3, 4].

In contrast to previous studies, we only included ESCC patients and MIE (McKeown procedure) in this study. As is known, ESCC and EAC are two different diseases with many different aspects, including incidence, risk factors, genetic susceptibility, pathogenesis, clinical features and prognosis. Similarly, different surgical types can result in different intraoperative surgical and postoperative complication and survival rates.

Because of heterogeneity of histopathologic types and different surgical procedures, the large variation makes comparison difficult and inaccurate. Therefore, a homogeneous histopathologic type and unified surgical procedure are used in our study to minimize the error. Furthermore, participants included in this article were selected from the 150th case after beginning, skipping the early phase of the surgical learning curve, guaranteeing the efficacy and safety of surgery [21]. In this study, the surgical procedures, pathologic examinations, and follow-up period were highly uniform throughout. Therefore, we believe that our results are robust and reasonable.

In the present study, there were no statistically significant differences in OS between different BMI groups. This is in accordance with some previous studies [22–24]. It demonstrated that MIE is an efficient method in high BMI patients. Interestingly, some studies reported an improved survival rate in high BMI patients [5, 6, 25]. One possible reason

may be that more early clinical tumor stage cases were included in those studies. In general, high BMI patients are usually at an early clinical tumor stage and have a better nutritional status with fewer symptoms induced by the tumor, such as dysphagia, vomiting and reduced intake. In the present study, there was no difference in the baseline clinical tumor stage between different BMI groups; it may be helpful to balance the bias. Consequently, high BMI should not be an exclusion criterion for BMI.

Certainly, there are some limitations in our study. Firstly, this is a retrospective study and the sample size is not large enough. Secondly, we used an Asia-specific BMI cutoff, which is not suitable for western patients. Thirdly, only squamous cell carcinoma was included in this study, so our results were not suitable for any other histopathological type. In the future, multicenter prospective randomized controlled trials should be performed.

Conclusions

In this study, high BMI was associated with prolonged operative time and increased blood loss for MIE. However, high BMI was not found to be an independent prognostic factor for survival and was not associated with postoperative complications in ESCC. MIE is safe and effective for high BMI ESCC patients.

Acknowledgments

Ying-Jian Wang and Xiao-Long Zhao contributed equally to this work, and both should be considered first author.

Conflict of interest

The authors declare no conflict of interest.

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