Original Article

# The correlation between high body mass index and survival in patients with esophageal cancer after curative esophagectomy: evidence from retrospective studies

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**Objective:** To investigate the predictive value of high body mass index (H-BMI) on the survival of patients with esophageal cancer (EC) after curative esophagectomy. **Methods:** Studies were systematically identified to investigate the relationship between overweight and obese (H-BMI) and clinical outcomes in EC patients treated with curative esophagectomy. Measured clinical outcomes were disease-free survival (DFS) and overall survival (OS). The pooled hazard ratio (HR) with 95% confidence interval (CI) was estimated. Subgroup analyses were performed according to tumour type and body mass index (BMI). **Results:** Fourteen studies with 4823 cases were included in the final pooled quantitative analysis. In EC patients overall, H-BMI was associated with improved DFS (HR, 0.83; 95% CI: 0.75-0.90) and OS (HR, 0.79; 95 % CI: 0.73-0.85), as compared with normal BMI. The results were consistent with those who were overweight. Among patients with esophageal adenocarcinoma (EAC), a better prognosis, as reflected by OS, was observed with H-BMI (HR, 0.81; 95% CI: 0.73-0.89). The same results were also observed in EAC patients who were obese and overweight. In contrast, among patients with esophageal squamous cell carcinoma (ESCC), H-BMI was associated with a worse prognosis, as reflected by DFS (HR, 2.26; 95% CI: 1.29-3.24). **Conclusions:** H-BMI has distinctly different impacts on the postoperative survival of EAC and ESCC patients. H-BMI is a potential predictor for better prognosis in EC patients overall, and particularly in EAC patients, treated with curative esophagectomy. However, in ESCC patients, H-BMI is a potential predictor for a worse prognosis of postoperative survival.

**Key Words: high body mass index, survival, esophageal cancer, esophagectomy, pooled quantitative analysis**

## INTRODUCTION

Esophageal cancer (EC) is one of the most aggressive human malignancies. The disease has two predominant histological subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Although ESCC is the most common subtype worldwide, EAC is more prevalent in Western countries at present.[1] Despite the use of aggressive therapy, the long-term survival of EC patients remains poor.[2] Increasingly, it is importance to understand the prognostic variables of this often fatal disease.

High body mass index (H-BMI), including overweight and obese, has become a significant global problem. The World Health Organization (WHO) defines H-BMI as BMI ≥25 kg/m$^2$; normal BMI and normal weight as BMI 18.5-24.9 kg/m$^2$; overweight as BMI 25-29.9 kg/m$^2$; and, obese as BMI ≥30 kg/m$^2$.[3] In China, H-BMI is defined as BMI ≥24 kg/m$^2$ and normal BMI as BMI <24 kg/m$^2$.[4]

Recently, it has been determined that H-BMI influences the prognosis of several kinds of cancer: obesity correlates with poor prognosis in breast and colon cancers, but with favourable prognoses in gastric and renal cancers.[5-8] The influence of H-BMI on long-term survival of EC patients who undergo curative esophagectomy also has been investigated, again with contradictory results.[9-13]

In this study, we conducted a pooled quantitative analysis to evaluate the association of H-BMI and prognosis of survival in patients with EC after treatment with curative esophagectomy.

## MATERIALS AND METHODS

### *Publication search*

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Systematic computerized searches of Pubmed, Embase and the Chinese Biomedical Database (up to December 31, 2013) were performed using the following search terms: (1) esophageal or oesophageal or esophagus or oesophagus and cancer or carcinoma; and (2) Body Mass Index or BMI; and (3) overweight or obese or excessive body weight. The local ethics committee of Shanghai Chest Hospital approved this study (KS(Y)1507).

All eligible studies were retrieved, and the references cited in the original studies were screened for further relevant publications. When multiple studies of the same patient population were identified, only the larger or latest was selected in the analysis. Overlapping study populations were excluded.

### *Inclusion criteria*

The following measures were used to determine inclusion in this pooled quantitative analysis.

1. Studies exploring the relationship between the H-BMI and postoperative survival outcomes in esophageal cancer patients.
2. Studies of EC patients treated with potentially curative esophagectomy.
3. Studies in which the exposure of interest was H-BMI, including obesity and overweight, defined by BMI according to the WHO criteria or China criteria; BMI status had to be recorded at cancer diagnosis.
4. Studies using the following as outcome measurement to assess prognosis: DFS and/or OS.
5. Studies published in English or Chinese with English abstract.

### *Excluded criteria*

The following measures were used to determine exclusion in this pooled quantitative analysis.

1. Studies including patients who were not treated with esophagectomy.
2. Studies only investigating the postoperative complications, not including DFS or OS.
3. Studies lacking of key information, including hazard ratio (HR) and 95% confidence interval (CI).

### *Data extraction*

Data were extracted for the first author's name, year of publication, origin of country, study design, total number of patients in the study, tumour type, and the definition of BMI status. At the same time, time-to-event data, DFS and OS for each trial were summarized by the log HR and its variance of the overweight, obese, and H-BMI group compared with the normal BMI group, respectively. If a study stratified to two groups and provided separate HR estimates accordingly, we treated it as two different studies. When a study provided separate HR estimates for EC patients and EAC patient groups, we used them, respectively. If the studies reported log HR and variance directly, the reported values were used. For those studies that did not provide this information, data were extracted from published survival curves where available, to estimate the values of log HR and variance according to previously described methods.[14]

Three reviewers (Wenbiao Pan, Zhiyong Sun, and Yangwei Xiang) independently scrutinized the papers for eligibility and quality. Disagreements were resolved by a fourth reviewer (Wentao Fang).

### *Statistical analysis*

To evaluate the association between H-BMI and survival outcomes of EC treated with esophagectomy, the HR with 95% CI were calculated using pooled data from the studies. We pooled the HR for H-BMI vs normal BMI from each study. To estimate a summary HR for EC in all H-BMI status combined, combined estimates were used if provided. Otherwise, all estimates were included, such as overweight and obese, in the analysis if obtained from different studies. A HR <1 indicated an improvement in DFS and/or OS for H-BMI status compared with normal BMI. A HR >1 indicated a worse DFS and/or OS for H-BMI status compared with normal BMI.

The Stata version 11.0 software (Stata Corporation, College Station, TX, USA) was used for all data analyses. Heterogeneity of effect sizes across the studies was examined using the Q statistic.[15] Statistical significance was set at 0.10 for heterogeneity.[16] The DFS and OS were analyzed based on a fixed-effects model, using the Mantel-Haenszel method. The random-effects model was used for further analysis when significant heterogeneity was less than 0.10. In order to detect a possible publication bias, a $p$ value the Begg's test <0.10 was considered representative of a statistically significant bias.[17,18]

Subgroup analysis was performed according to tumour type and BMI status. Sensitivity analyses were carried out to check whether modification of the inclusion criteria of the pooled quantitative analysis affected the final results.

## RESULTS

### *Characteristics of the included studies*

The search strategy generated 585 citations, of which 26 were considered of potential value and the full text was retrieved for detailed evaluation. Thirteen of these 26 articles were subsequently excluded from the pooled quantitative analysis for various reasons. One additional article was included from the reference review. Finally, fourteen studies involving 4823 patients that reported at least one of the outcomes of interest were identified.[9-13,19-27] One of these fourteen studies provided the HR and 95% CI for ever-smokers and never-smokers respectively,[20] and another study provided the HR and 95% CI for preoperative weight loss and no-weight loss respectively.[21] Each of these studies was treated as two independent studies when analyzed. Tables 1-2 show the main characteristics and effects; all studies were retrospective. The sample sizes in the eligible studies ranged from 93 to 925. Eleven of the studies were conducted in European or North American populations (4222 patients),[9-13,19-23,27] whereas three were conducted in East Asian populations (601 patients).[24-26] Five studies provided data for EC patients covering all histological subtypes (1803);[9-11,23,24] one study provided data for esophageal cancer patients overall (925) and EAC patients alone (665), respectively;[12] six studies provided data only for EAC patients (1758);[13,19-22,27] and two studies provided data only for ESCC patients (337).[25,26]

### *Relation of H-BMI and DFS*

Eight studies contributed data on DFS.[9,11,12,19,20,23,25,26] Two studies reported HR and variance directly.[19,20] HR and variance were estimated from original data provided by five studies.[9,12,23,25,26] One study reported original data without a survival curve, which could not be converted to HR and variance.[11] Therefore, HR and variance from seven studies on DFS were pooled in the pooled quantitative analysis.[9,12,19,20,23,25,26] Three studies of the seven provided combined estimates of H-BMI directly;[12,25,26] others provided estimates of overweight and/or obese, which were all pooled.

The HR of DFS in EC patients overall with H-BMI over those with normal BMI was 0.90 (95% CI: 0.77-1.02; Table 2), based on a random-effects model (*p* for heterogeneity=0.04; Table 2) with significant publication bias (*p* for Begg's test=0.01; Table 2). A sensitivity analysis was performed by excluding the two studies only of ESCC patients.[25,26] After this exclusion, the pooled HR of DFS in EC patients overall with H-BMI over those with normal BMI was 0.83 (95% CI: 0.75-0.90; Figure 1a; Table 2). The heterogeneity (*p*=0.19; Figure 1a; Table 2) and publication bias (*p*=0.12; Table 2) disappeared.

Stratified results by BMI status and tumour type are shown in Table 2.

Based on BMI status, those who were overweight had a better prognosis and a longer DFS than those who were normal weight (HR: 0.87; 95% CI: 0.74-0.92; Table 2), while those who were obese did not have this advantage (HR: 0.96; 95% CI: 0.68-1.23; Table 2).

By tumour type, three studies only of EAC patients[12,19,20] and two studies only of ESCC[25,26] patients provided data on DFS. In EAC patients, DFS for H-BMI (HR: 0.93; 95% CI: 0.83-1.03; Table 2) and overweight (HR: 0.91; 95% CI: 0.75-1.08; Table 2) was marginally better than for normal BMI. However, obesity did not confer a significantly different DFS (HR: 1.09; 95% CI: 0.65-1.52; Table 2). The studies of ESCC patients merely provided combined estimates of H-BMI. A worse prognosis and a shorter DFS were found in ESCC patients with H-BMI (HR: 2.26; 95% CI: 1.29-3.24; Figure 2; Table 2).

### *Relation of H-BMI and OS*

All fourteen studies provided data on OS. Five studies reported HR and variance directly.[12,19,20,22,23] HR and variance were estimated from original data provided by the other nine studies. Therefore, HR and variance from all fourteen studies on OS were pooled in the pooled quantitative analysis. Five of these studies provided combined estimates of H-BMI directly;[10,12,21,25,26] others provided estimates of overweight and/or obese. We pooled them all.

The HR of OS in EC patients overall with H-BMI over those with normal BMI was 0.79 (95% CI: 0.73-0.85), based on a fixed-effects model (*p* for heterogeneity=0.14; Table 2), with significant publication bias (*p* for Begg's test=0.07; Table 2). A sensitivity analysis was performed by excluding the two studies only of ESCC patients.[25,26] After this exclusion, the pooled HR of OS in EC patients overall with H-BMI over those with normal BMI was 0.79 (95% CI: 0.73-0.85; Figure 1b; Table 2), based on a fixed-effects model (*p* for heterogeneity=0.32; Figure 1b; Table 2) without publication bias (*p* for Begg's test=0.34; Table 2).

By BMI status, EC patients who were overweight (HR: 0.78; 95% CI: 0.70-0.86; Table 2) and obese (HR: 0.79; 95% CI: 0.69-0.89; Table 2) had a better prognosis and a longer OS.

By tumour type, seven studies only of EAC patients and two studies only of ESCC patients provided data on OS. In EAC patients, a better prognosis and a longer OS was found with H-BMI (HR: 0.81; 95% CI: 0.73-0.89; *p* for heterogeneity=0.58; Figure 3; Table 2); overweight (HR: 0.76; 95% CI: 0.64-0.88; Table 2), and obese (HR: 0.81; 95% CI: 0.67-0.94; Table 2). In ESCC patients, H-BMI was associated with worse OS (HR: 2.01; 95% CI: 0.92-3.01; Table 2), as compared with normal BMI, though this association did not reach statistical significance.

## DISCUSSION

Increased BMI has been shown to correlate with increased risk for EAC, but with decreased risk for ESCC.[28] Elevated BMI has been associated also with variable outcomes in many cancers.[5-8] The findings from studies of H-BMI on survival of EC patients after esophagectomy were controversial.

A previous pooled quantitative analysis, which included six studies and a total of 1988 cases of EAC, suggested that excess body weight did not affect the survival for patients with EAC.[29] However, that pooled quantitative analysis did not include studies on ESCC, which is the most common subtype worldwide, especially in Eastern Asia.[30] ESCC is epidemiologically and clinically distinct from EAC. Therefore, we conducted a comprehensive pooled quantitative analysis to derive a more precise estimate of the predictive and prognostic values of H-BMI on survival of EC patients after operation. One of six studies included in that pooled quantitative analysis was excluded from our pooled quantitative analysis because of overall treatment modalities rather than esophagectomy was focused on in the study.[31]

In contrast to the previous pooled quantitative analysis, this pooled quantitative analysis found that the pooled HR of OS and DFS for H-BMI over normal BMI in EC patients overall, after esophagectomy, was significantly associated with a better prognosis. The results were consistent with the pooled HR of OS in EAC patients with H-BMI, including overweight and obese. Subjects of these studies were mainly adenocarcinoma, and even in the studies which targeted all histological subtypes, the percentage of patients with EAC was 53-90%. Hayashi et al. demonstrated that better survival of EC patients with H-BMI was mainly because of low baseline clinical stage.[12] EAC patients with H-BMI are more likely to have endoscopic surveillance for history of gastroesophageal reflux disease (GERD), which could result in earlier diagnosis of EAC. This may partly explain why EAC patients with H-BMI had a better prognosis and favourable survival.

Our pooled quantitative analysis found that, in EAC patients, H-BMI predicted a favourable OS, but not DFS. The possible reason is that not all the studies provided data on OS and DFS. Only three studies provided data on DFS for EAC patients. Insufficient data resulted in the statistical power reduction, so pooled HR of DFS for

**Table 1.** Main characteristics of studies included in the pooled quantitative analysis

| First author, year, region | Study design | Patients assessed | Tumour histological type | Median follow-up (month) | Type of surgery | Normal BMI (kg/m$^2$) | High BMI (kg/m$^2$) | | Adjustments |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | BMI reference | Overweight | Obese | |
| Watanabe, 2013, Japan | Retrospective | 243 | ESCC | 25.7 | ILE, THE, TTE | 18.5-24.9 | ≥25 | | Age, sex, stage, comorbities |
| Cheng, 2013, China | Retrospective | 94 | ESCC | NR | ILE, McKeown | <24 | ≥24 | | NR |
| Scarpa, 2013, Italy | Retrospective | 278 | EC | NR | ILE, McKeown | 20-24.9 | 25-29.9 | ≥30 | NR |
| Shridhar, 2012, USA | Retrospective | 303 | EAC | NR | THE, TTE | ≤25 | 25-30 | >30-35 | Age, sex, stage, comorbities |
| Hayashi, 2012, USA | Retrospective | 925 | EC | 33 | ILE, THE, MIE | <25 | ≥25 | | NR |
| | | 665 | EAC | 33 | ILE, THE, MIE | <25 | ≥25 | | NR |
| Yoon, 2011, USA | Retrospective | 236 (NS) | EAC | 12.9 | ILE, THE | 18.5-24.9 | 25-29.9 | ≥30 | Age, stage, grade, sex, weight loss |
| | | 542 (ES) | EAC | 12.9 | ILE, THE | 18.5-24.9 | 25-29.9 | ≥30 | Age, sex, stage, grade, weight loss |
| Melis, 2011, USA | Retrospective | 490 | EC | 25 | TTE, THE, MIE | 20-24 | 25-29 | ≥30 | Age, sex, alcohol, smoking |
| Zhu, 2011, China | Retrospective | 264 | EC | NR | ILE | 18.5-24.99 | 25-29.99 | ≥30 | NR |
| Grotenhuis, 2010, Netherlands | Retrospective | 556 | EC | NR | THE, TTE, McKeown | 18.5-24.99 | 25-29.99 | ≥30 | Age, sex |
| Madani, 2010, Canada | Retrospective | 142 | EAC | 62 | ILE, THE | <25 | 25-30 | ≥30 | NR |
| Skipworth, 2009, UK | Retrospective | 48 (NWtL) | EAC | NR | ILE | <25 | >25 | NR | |
| | | 45 (WtL) | EAC | NR | ILE | <25 | >25 | NR | |
| Healy, 2007, Ireland | Retrospective | 150 | EAC | 39 | ILE, THE, McKeown | <25 | 25-30 | ≥30 | Age, sex, alcohol, smoking |
| Morgan, 2007, UK | Retrospective | 215 | EC | 26 | TTE,THE | <25 | ≥25 | NR | |
| Trivers, 2005, USA | Retrospective | 292 | EAC | 90 | NR | <25 | 25-29.9 | ≥30 | Age, area, education, sex, alcohol, smoking, NSAID use |

EC: esophageal cancer (covering all histological subtypes); ESCC: esophageal squamous cell carcinoma; EAC; esophageal adenocarcinoma; NS: never smokers; ES: ever smokers; NWtL: no weight loss; WtL, weight loss; NR: not reported; TTE: transthoracic esophagectomy; ILE; Ivor-Lewis esophagectomy; THE: transhiatal esophagectomy; MIE: minimally invasive esophagectomy.

**Table 2.** Pooled HR of EC with DFS and OS by BMI

| Characteristic | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | No. of studies | *p* for heterogeneity | HR (95% CI) | *p* for Begg's test | No. of studies | *p* for heterogeneity | HR (95% CI) | *p* for Begg's test |
| H-BMI (EC) | 13 | 0.04 | 0.90 (0.77-1.02) | 0.01 | 24 | 0.14 | 0.79 (0.73-0.85) | 0.07 |
| H-BMI (EC) (excluded ESCC) | 11 | 0.19 | 0.83 (0.75-0.90) | 0.12 | 22 | 0.32 | 0.79 (0.73-0.85) | 0.34 |
| Overweight (EC) | 5 | 0.62 | 0.87 (0.74-0.92) | 0.46 | 8 | 0.34 | 0.78 (0.70-0.86) | 0.39 |
| Obese (EC) | 5 | 0.05 | 0.96 (0.68-1.23) | 0.46 | 9 | 0.19 | 0.79 (0.69-0.89) | 1.00 |
| H-BMI (EAC) | 7 | 0.28 | 0.93 (0.83-1.03) | 0.23 | 13 | 0.18 | 0.81 (0.73-0.89) | 0.58 |
| Overweight (EAC) | 3 | 0.47 | 0.91 (0.75-1.08) | 1.00 | 4 | 0.22 | 0.76 (0.64-0.88) | 1.00 |
| Obese (EAC) | 3 | 0.06 | 1.09 (0.65-1.52) | 1.00 | 6 | 0.10 | 0.81 (0.67-0.94) | 1.00 |
| H-BMI (ESCC) | 2 | 0.81 | 2.26 (1.29-3.24) | 1.00 | 2 | 0.10 | 2.01 (0.92-3.10) | 1.00 |

EC: esophageal cancer (covering all histological subtypes); ESCC: esophageal squamous cell carcinoma; EAC: esophageal adenocarcinoma; H-BMI: high body mass index; DFS: disease-free survival; OS: overall survival; HR, hazard ratio; CI: confidence interval.

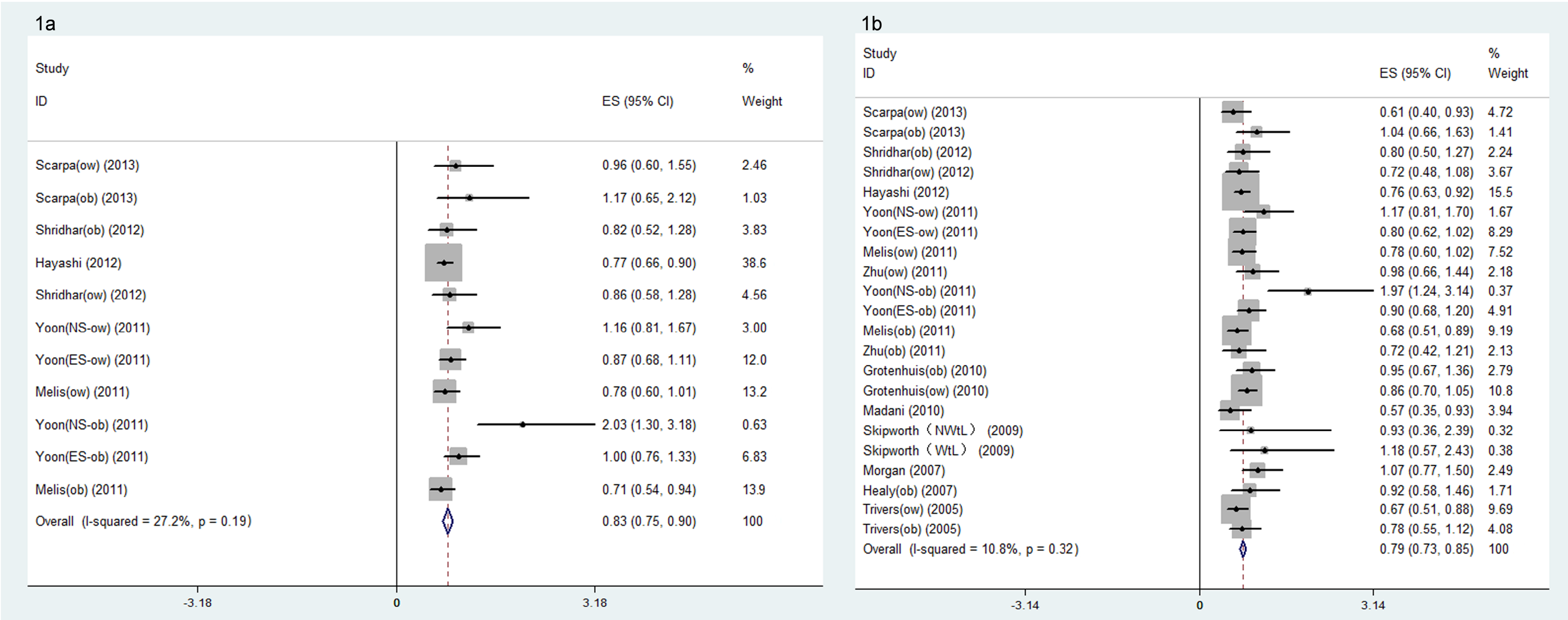


**Figure 1.** Forest plot of studies of DFS (1a) and OS (1b) in EC patients overall with H-BMI over those with normal BMI. ow: overweight; ob: obese; NS: never smokers; ES: ever smokers; NWtL: no weight loss; WtL: weight loss.

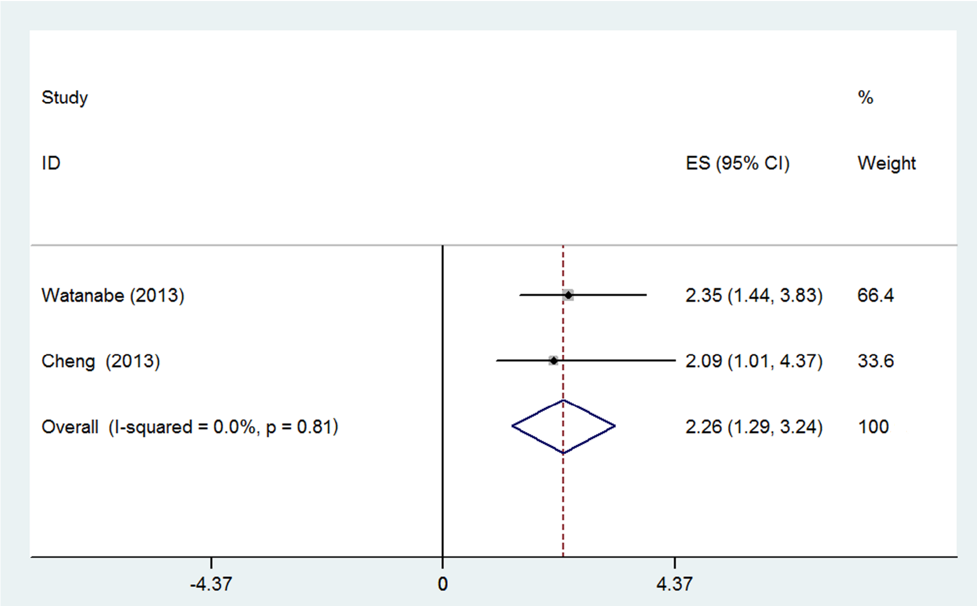


**Figure 2.** Forest plot of studies of DFS in ESCC patients with H-BMI over those with normal BMI.

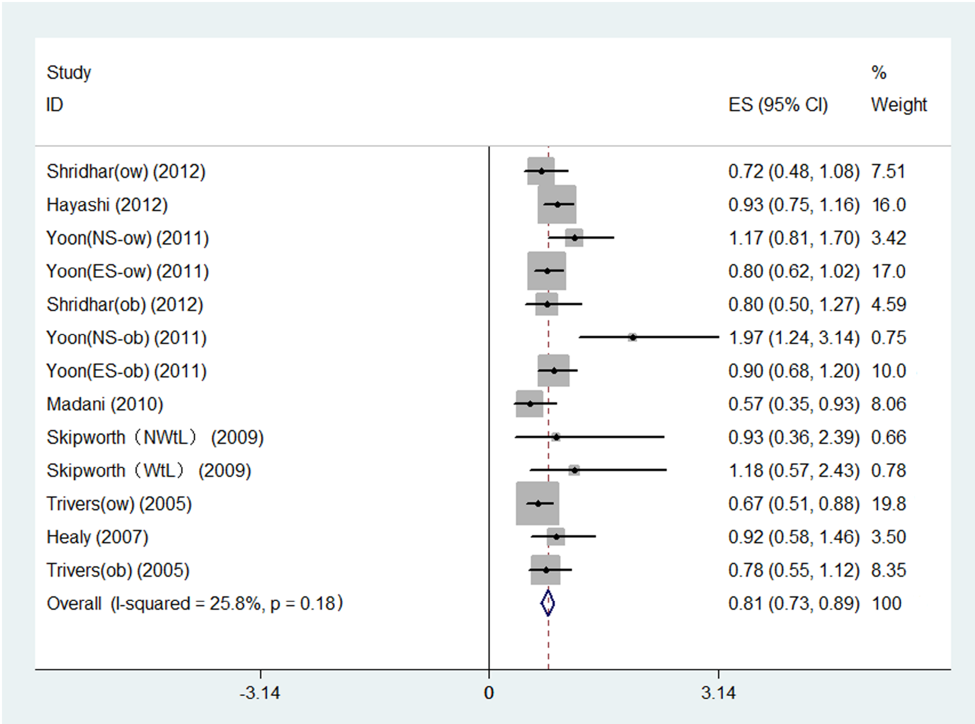


**Figure 3.** Forest plot of studies of OS in EAC patients with H-BMI over those with normal BMI. ow, overweight; ob: obese; NS: never smokers; ES: ever smokers; NWtL: no weight loss; WtL: weight loss.

EAC patients with H-BMI over normal BMI had only borderline significance. The same result was also observed in obese EC patients overall.

H-BMI has different effects on risk for EAC and ESCC. This pooled quantitative analysis also found that, in ESCC patients, in contrast with EC overall and EAC patients alone, H-BMI predicts a worse prognosis and a shorter survival. Cheng et al and Dhar et al demonstrated that overweight patients often received relatively unsuccessful lymphadenectomy, which may result in more frequent metastases and recurrence, and thus shorter survival.[25,32] The reasons behind this finding are not clear. Perhaps ESCC in H-BMI patients is more aggressive than in patients of normal BMI, but there is no data supporting that hypothesis at present. Further analysis is required to clarify the influence of H-BMI on the biological features of ESCC.

One of the strengths of this pooled quantitative analysis is that this is the first study to investigate the relationship between the H-BMI and the survival of EC patients comprehensively. It is also the first to demonstrate that H-BMI has distinctly different impact on the survival of EAC compared with ESCC patients.

Our pooled quantitative analysis has several limitations.

First, all the included studies were retrospective. Not all the studies provided sufficient data. Inadequate reporting of survival curves precluded conversion to HR and variance from original data.[11,33] Second, not all the studies provided adjusted estimates or adjusted for the same factors; confounding factors could have been introduced. Third, the cut-off point for BMI was not the same. Fourth, the findings only included two studies of ESCC patients and the sample size was small.

Despite these limitations, our study confirmed that H-BMI has distinctly different impact on the postoperative survival of EAC and ESCC patients. H-BMI is a potential predictor for a better prognosis and a favourable survival in EAC and EC patients. In contrast, H-BMI negatively affects prognosis for patients with ESCC. Further large prospective cohort studies, stratified for ESCC and EAC, and with careful control of confounding factors, are needed to reach a more definitive conclusion.

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**AUTHOR DISCLOSURES**
The authors declare that they have no conflict of interest.

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Original Article

# The correlation between high body mass index and survival in patients with esophageal cancer after curative esophagectomy: evidence from retrospective studies

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# 高体重指数与食管癌根治性切除术后患者生存关系的回顾性研究

**目的：**探讨食管癌患者术前高体重指数（high body mass index，H-BMI）对食管癌根治性切除术后长期生存的影响及其预测价值。**方法：**通过系统、全面的文献检索，收集已公开发表的有关食管癌患者术前 H-BMI（包括超重和肥胖）对术后生存期影响的所有临床研究，按累计定量分析的要求对检索到的原始研究的质量进行评估，对符合条件的所有研究结果进行累计定量分析，计算数据合并后的 H-BMI 对正常 BMI 的危险比（hazard ratio，HR）及 95%置信区间（confidence interval，CI），并根据体重指数（body mass index，BMI）及食管癌亚型进行亚组分析，评价术前 H-BMI 对食管癌患者根治性切除术后生存期的影响。**结果：**共 14 篇文献符合纳入标准，总样本量 4823 例。累计定量分析结果表明，H-BMI 改善了总体食管癌患者术后无疾病生存率（disease-free survival，DFS）和总体生存率（Overall survival，OS），合并的 HR 分别为 0.83（95% CI：0.75-0.90）和 0.79（95% CI：0.73-0.85）；在亚组分析的超重患者中也得出了相似结果。根据肿瘤亚型进一步分层分析发现，H-BMI 显著改善了食管腺癌患者术后 OS，合并的 HR 为 0.81（95% CI：0.73-0.89），在超重和肥胖的亚组分析中也得出了相似的结果。然而在食管鳞癌中，术前 H-BMI 缩短了患者术后 DFS，合并的 HR 为 2.26（95% CI：1.29-3.24）。**结论：**H-BMI 对食管鳞癌和食管腺癌患者术后长期生存的影响完全不同。H-BMI 是食管癌总体、特别是食管腺癌术后生存预后较佳的一个潜在性预测指标，而对食管鳞癌来说，H-BMI 则预示着较差的术后生存。

**关键词：高体重指数、生存、食管癌、食管切除术、累计定量分析**