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*Review Article*

# Effect of higher pre-operation body mass index on overall survival of esophageal, gastric and pancreatic cancer: a systematic review and meta-analysis

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**Abstract:** Although high body mass index (BMI) has been identified as a risk factor for several common cancers, the important question of whether pre-operation BMI influences the overall survival (OS) of digestive system cancers (DSCs) has not been explicated thoroughly. Therefore, we performed a meta-analysis to investigate whether pre-operation BMI was associated with esophageal cancer (EC), gastric cancer (GC), and pancreatic cancer (PC) prognosis. Fifteen relevant studies involving a total of 8,984 cancer cases (4,502 EC, 3,004 GC, and 1,478 PC cases) were finally included in this study. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) for OS in different BMI categories from individual studies were extracted, and pooled by random-effect model. The overall HR of EC, GC, and PC for OS of higher pre-operation BMI was 0.83 (95% CI = 0.68-0.98), 0.68 (95% CI = 0.25-1.11), and 0.85 (95% CI = 0.65-1.05), respectively. Combined cases of EC, GC, and PC with higher pre-operation BMI were at decreased risk for OS (HR = 0.81, 95% CI = 0.69-0.93). Increased pre-operation BMI was also related to lower risk of death from EC with 1.03% percent for every 5-unit BMI increment. Our meta-analysis indicated increased OS among EC survivors with higher pre-operation BMI, but not in GC and PC. Higher BMI before operation may be an important prognostic factor that indicate an increased survival from EC.

**Keywords:** Body mass index, pre-operation, esophageal cancer, overall survival

## Introduction

In 2016, 304,930 new digestive system cancer (DSC) cases, including esophageal cancer (EC), gastric cancer (GC) and pancreatic cancer (PC), are expected with 153,030 estimated deaths in the United States every year [1]. Colorectal cancer, hepatic cancer, gastric cancer, pancreatic cancer and esophageal cancer are most dangerous and account for high morbidity and mortality rate [2]. Overweight is defined by the World Health Organization as body mass index (BMI) of 25.0 to 29.9 kg/m$^2$, and obesity is defined as BMI ≥ 30.0 kg/m$^2$. It has been estimated by various authorities that one-third of cancers in Western high-income societies are attributable to factors relating to weight gain and obesity. Keeping normal BMI was recommended by the World Cancer Research Fund for cancer patients [3, 4]. Nevertheless, inconsistent results have been reported by studies on the relationship between pre-operation BMI and mortality among EC, GC, and PC survivors [5, 6]. For one thing, some studies suggested that significant association was found between pre-operation BMI and overall mortality of EC, GC, and PC [7-9]. For another, some research revealed that higher pre-operation BMI was not associated with overall survival (OS) from above cancers [10-12]. Additionally, most results were not statistically significant. In 2013, Zhang et al also revealed that high BMI could significantly improve OS of EC, and associated with postoperative complications [13]. Recently, Shi et al have made a meta-analysis and showed that obesity in adulthood shortened OS of pancreatic cancer patients [9]. Furthermore, cancer survivors need recommendations on lifestyle factors, and pre-operation BMI is an important research question to enhance the survival and life quality of particular patients. We performed a meta-analysis of published articles to explicate the relationship between higher pre-operation BMI and survival among EC, GC, and PC patients. Moreover, we summarized the evidence on pre-operation BMI, and analyzed

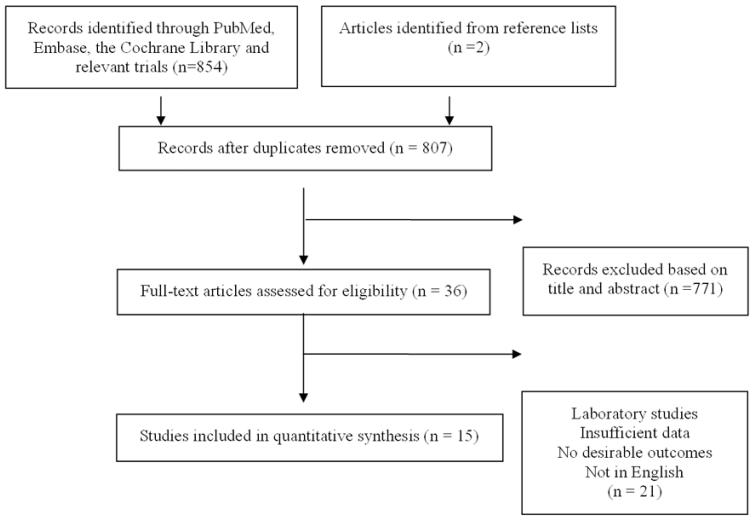


**Figure 1.** Selecting the flowchart for the inclusion of studies in the meta-analysis.

the highest versus the lowest category of higher pre-operation BMI and OS of all above cancers.

## Materials and methods

### *Literature retrieval*

PubMed, Embase, and the Cochrane Library were searched by two authors from the earliest available date to March 20, 2017. The key-words were as follows: esophageal, esophagus, gastric, stomach, pancreatic, pancreas, tumor, cancer, neoplasm, mortality, survival, overall survival, BMI, body mass index, pre-operation BMI, and BMI before operation. Boolean logic words were jointly used to combine the key words. Two reviewers investigated potentially relevant articles seriously. The references of retrieved articles were also checked for further relevant studies. Disagreements were solved by group discussion.

### *Literature inclusion and exclusion criteria*

Search eligible studies by two authors independently and finally negotiate to reach consensus. The criteria were as follows: (1) comparing OS of EC, GC, and PC patients with different pre-operation BMI ranges, containing comparison and referent BMI group. (2) presenting an association estimate with 95% CI or survival curve. (3) only full texts written in English were included. The full texts of all potentially eligible studies were retrieved, and their references were carefully browsed to find other studies that met the criteria. If different articles reported the same study, we only included the publication with the largest size.

### *Quality assessment*

Two authors independently drew up the evaluation program and assessed full texts included. The Newcastle Ottawa scale (NOS), which was recommended by the Cochrane Non-Randomized Studies Methods Working Group, was used in this meta-analysis for quality assessment [14]. This quality evaluation method assessed observational studies in three dimensions with a total score of 9 stars. Among the 9 stars, 4 stars represented for the appropriate selection of exposure and non-exposure cohort participants, 2 stars represented for the comparability of cohort, and the last 3 stars described the assessment of outcome and follow-up. Studies that scored ≥ 7 were considered as adequately conducted. A third person was involved to solve the disagreement in the scores by consensus.

### *Data extraction*

Extract data from eligible studies included: first author, year, region where the study conducted, study type, study period, cancer type, histology, sample size, maximum and minimum BMI categories, both univariate HR (95% CI) and multivariate HR (95% CI) from each BMI category, and confounding factors. Three authors extracted information independently, and disagreements resolved by consensus. If data above had not been referred in original articles, items were deemed as "NA". Engauge Digitizer version 2.11 software was used to extract relevant numerical value from survival curves and calculate the HR (95% CI) while only Kaplan-Meier survival curves were provided in the original texts [15].

### *Statistical analysis*

This meta-analysis was performed to evaluated the reported OS of EC, GC, and PC with pre-operation BMI categories. The highest and low-

est pre-operation BMI group were compared to assess the survival difference of EC, GC, and PC. We performed analysis of pooled HR with 95% CI using a random-effect model in case that there was significant heterogeneity. Multivariate HRs with 95% CI were commonly adopted to estimate included studies. Univariate HRs were used instead if multivariate HRs were not available. Study-specific study size and 95% CI was showed by forming forest plots [16]. For dose-response evaluation, midpoint of the maximum and minimum BMI group was used to quantitatively calculate the OS change. If the BMI category was open-ended, midpoints was estimated using the width of the adjacent close-ended category [17]. Subgroup analysis of highest versus lowest BMI category and OS of EC patients included study type (retrospective or prospective study), geographic area (North America or other regions), histology (adenocarcinoma (AC) or AC and squamous cell carcinoma(SCC)), number of cases (< 500 or ≥ 500), and adjustment for covariates (yes or no). We also performed sensitivity analysis to assess whether the summary estimates are robust to inclusion of studies. One study was removed every time, and the rest were analyzed to evaluate whether the results could have been affected significantly by a single study. A pooled HR > 1 revealed that the highest BMI group had worse prognosis than the lowest group for DSC patients. Oppositely, a pooled HR < 1 suggested the highest BMI group suggested a more favorable survival. When the 95% CI of HR did not overlap 1, the result was regarded as statistically significant. Heterogeneity was assessed by Q and $I^2$ statistics. An $I^2$ value < 25% indicates a low level of heterogeneity, while values of 25%-50% and ≥ 50% represent moderate and high levels of heterogeneity, respectively [18]. Publication bias was evaluated by Begg funnel plots and Egger regression asymmetry test. All *P* values were 2-sides. P<0.05 was considered as statistically significant. All analyses were performed using STATA version 12.0 software (Stata Corporation, College Station, TX). Given that our study was a review of previous published studies, ethical approval or patient consent was not required.

## Results

### *Identification of relevant studies*

854 studies were identified in accordance with the established search strategies. Excluding irrelevant articles, laboratory studies, duplicates and other unsuitable objects, remaining 16 full texts were assessed for eligibility. Additional two records were retrieved from reference lists. Although providing survival curve, some articles were excluded because we cannot extract or calculate HR and 95% CI. In total, 15 articles were included in this meta-analysis according to the criteria (**Figure 1**). For studies included, we combined and evaluated three kinds of cancers: esophageal [5-7, 10, 19-23], gastric [8, 11, 24], and pancreatic cancer [9, 12, 25].

### *Study characteristics and quality assessment*

All studies referred the OS of cancer patients and pre-operation BMI. All of the included articles were published between 2007-2016; Eligible studies contained 12 prospective studies and 3 retrospective studies. 7 studies were distributed in the North American, and the remaining 8 studies were from other regions. The case number of 7 included studies was more than 500 cases, and the remaining 8 had less than 500 patients. The referent group from half studies was normal BMI category. Most studies provided multivariate HR and 95% CI. Multivariate results were adjusted by age, gender, race, smoking, diabetes, tumor stage, lymph node metastasis, treatment and other covariates. According to the qualitative assessment criteria, all studies that scored ≥ 7 were considered as adequately conducted (**Table 1**).

### *Higher pre-operation BMI improves OS of EC*

Association of pre-operation BMI with OS of EC was presented in 9 studies (eight prospective and one retrospective) (**Figure 2**). The pooled HR for higher pre-operation BMI of EC patients was 0.83 (95% CI = 0.68-0.98). This analysis was with a low level of heterogeneity, $I^2$ = 38.6% and $P_{heterogeneity}$ = 0.111. The study of Yoon et al and Healy et al just contributed to 3.31% and 4.22% of overall HR, respectively, while total weight of eight prospective study was 95.78%. Compared with the lowest BMI, increased pre-operation BMI was related to lower risk of death with 1.03% for every 5-unit increment.

### *Higher pre-operation BMI does not improve OS of GC and PC*

Respectively, three GC and three PC studies were included in the analysis of pre-operation

**Table 1.** Characteristic of relevant studies on pre-operation BMI and OS of DSC patients included in the meta-analysis

| Study | Country | Study Type | Duration | Cancer Type | Histology | Age* (range) | Gender (M/F) | Size | Maximum BMI | Minimum BMI | UV-HR (95% CI) | MV-HR (95% CI) | Covariates | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Morgan et al, 2007 | Wales | Prospective study | 1995-2005 | Esophagus | AC | 61 (31-81) | 162/53 | 215 | ≥ 25 | ≤ 25 | NA | 1.1 (0.73, 1.66) | Age, stage and ASA grade | 7 |
| Healy et al, 2007 | Ireland | Retrospective study | 1998-2005 | Esophagus | AC | 62 (29-79) | 129/21 | 150 | ≥ 30 | < 30 | 1.16 (0.66, 2.02) | NA | NA | 7 |
| Skipworth et al, 2009 | UK | Prospective study | 2001-2004 | Esophagus | NA | 67.3 | 57/36 | 93 | > 25 | < 25 | 0.78 (0.38, 1.6) | NA | NA | 7 |
| Madani et al, 2010 | Canada | Prospective study | 1991-2006 | Esophagus | AC | 62 | 118/24 | 142 | ≥ 30 | < 30 | 0.57 (0.38, 0.88) | 0.57 (0.35, 0.93) | Age, sex, resection, grade, stage, and lymph node metastasis | 8 |
| Grotenhuis et al, 2010 | Netherland | Prospective study | 1991-2007 | Esophagus | AC and SCC | NA | 450/106 | 556 | ≥ 30 | < 18.5 | 0.58 (0.32, 1.04) | NA | NA | 7 |
| Melis et al, 2011 | USA | Prospective study | 1994-2010 | Esophagus | AC and SCC | 64 (28-86) | 420/70 | 490 | ≥ 30 | 20-24 | 0.69 (0.51, 0.92) | NA | NA | 7 |
| Yoon et al, 2011 | USA | Prospective study | 1980-1997 | Esophagus | AC | 65 (22-89) | 692/86 | 778 | ≥ 30 | 18.5-24.9 | NA | 1.01 (0.67, 2.23) | Age, sex, stage, grade and weight loss | 8 |
| Blom et al, 2012 | Netherland | Prospective study | 1993-2010 | Esophagus | AC and SCC | 64 (56-73) | 569/167 | 736 | ≥ 30 | < 25 | 0.92 (0.8, 1.15) | NA | NA | 7 |
| Miao et al, 2014 | China | Prospective study | 2006-2012 | Esophagus | AC and SCC | 59 (66.9-51.1) | 1099/243 | 1342 | ≥ 25 | < 18.5 | 1.48 (1.07, 2.04) | 1.16 (0.84, 1.6) | Age, sex, drinking, smoking, hypertension, diabetes, tumor length, differentiation, grade, stage, weight loss, and adjuvant chemoradiation | 8 |
| Ejaz et al, 2014 | USA | Prospective study | 2000-2012 | Stomach | AC | 66.1 (56.8-71.4) | 446/329 | 775 | ≥ 30 | 18.5-24.9 | NA | 1.13 (0.79, 1.61) | Age, race, preoperative albumin, chemotherapy, comorbidities, tumor size, type, morphology, T stage, AJCC stage, grade, lymph-vascular invasion, perineural invasion, and signet ring cell | 8 |
| Lee et al, 2015 | Korea | Retrospective study | 2000-2008 | Stomach | AC | 58.3 (46.5-70.1) | 1294/615 | 1909 | ≥ 25 | 18.5-24.9 | NA | 0.64 (0.41, 1.02) | Age, sex, surgery, tumor stage, histology, and curative resection | 8 |
| Liu et al, 2016 | China | Prospective study | 2004-2013 | Stomach | AC | 64 (27-86) | 237/83 | 320 | 24-32.2 | 15.1–24 | 0.57 (0.37, 0.9) | 0.31 (0.12, 0.8) | Age, sex, albumin, total cholesterol, triglyceride, high- and low-density lipoprotein cholesterol, cell differentiation, invasion depth, lymph node metastasis, distant metastasis, and stage | 8 |
| Tsai et al, 2010 | USA | Prospective study | 1995-2005 | Pancreas | AC | 66.1 | 429/366 | 795 | ≥ 30 | 18.5-24.9 | 0.75 (0.58, 0.98) | 0.73 (0.56, 0.95) | Age, sex, race, tumor differentiation and size, surgical details, perineural invasion, margin and node status, and weight loss | 8 |
| Dandona et al, 2011 | USA | Retrospective study | 1995-2009 | Pancreas | AC | 65.5 (55.3-75.7) | 192/163 | 355 | ≥ 30 | 18.5-24.9 | 0.85 (0.61, 1.2) | NA | NA | 7 |
| Gaujoux et al, 2012 | USA | Prospective study | 2000-2005 | Pancreas | AC | 71 (63-77) | 154/174 | 328 | ≥ 30 | 18.5-24.9 | 1.1 (0.8, 1.52) | NA | NA | 7 |

SCC = squamous cell carcinoma, AC = adenocarcinoma, M = male, F = female, UV = univariate, MV = multivariate, HR = hazard ratio, ASA = American Society of Anesthesiology, NA = not available. *Median or mean age.

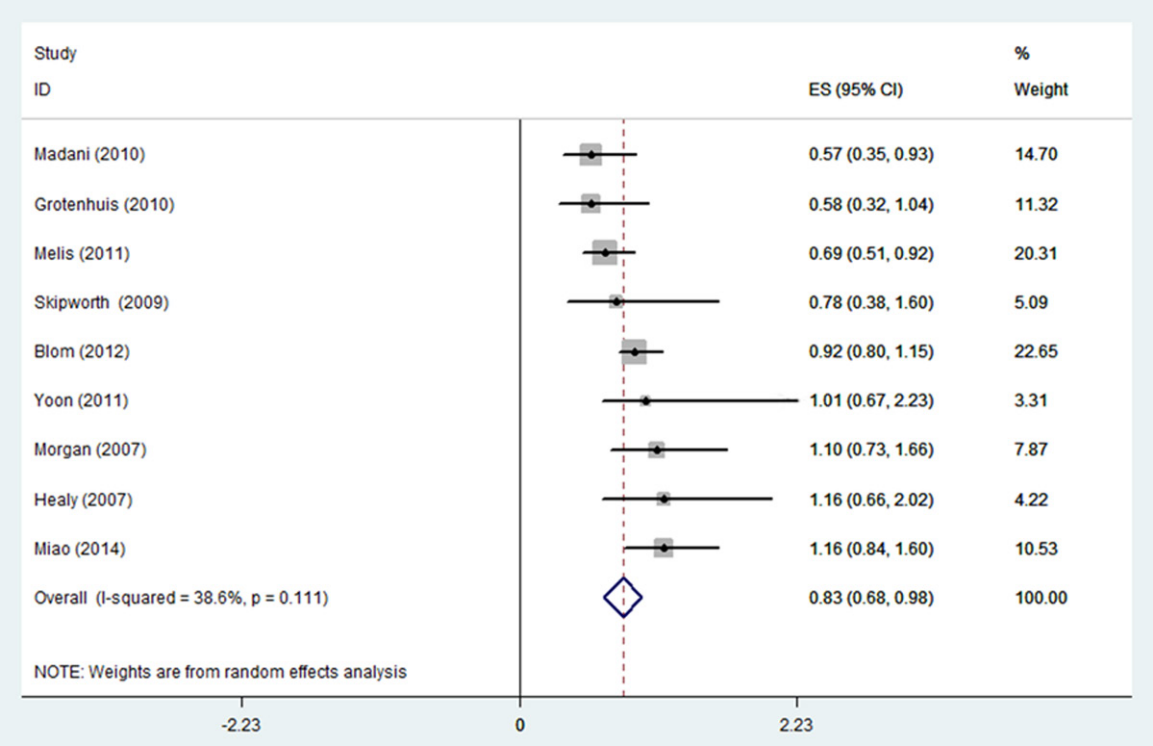


**Figure 2.** Forest plot showed hazard ratios (HRs) and 95% CIs for the highest versus lowest BMI category and overall survival of esophageal cancer. HRs are for pre-operation BMI.

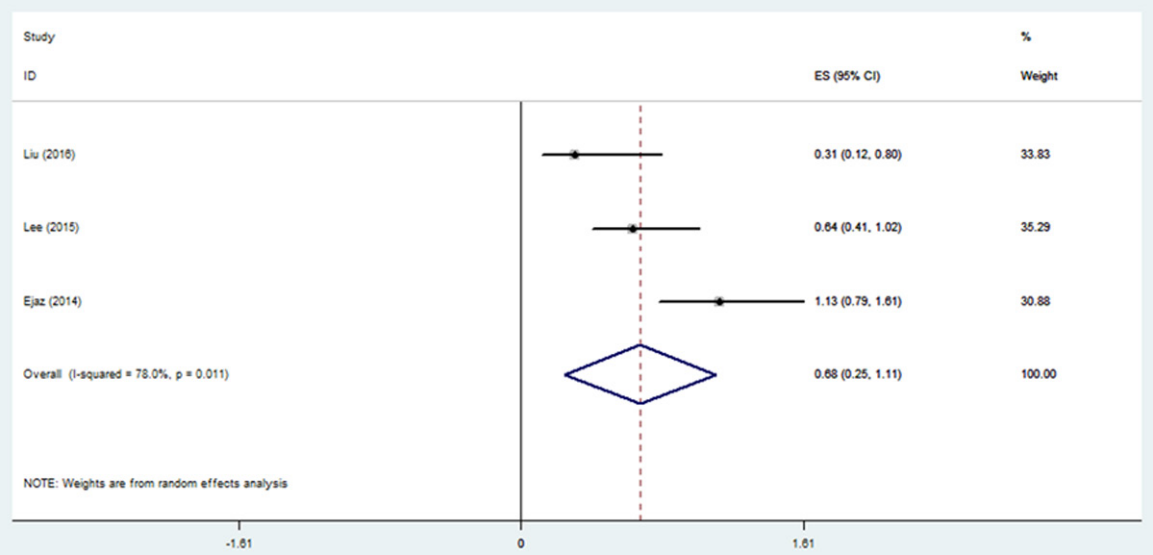


**Figure 3.** Forest plot showed hazard ratios (HRs) and 95% CIs for the highest versus lowest BMI category and overall survival of gastric cancer. HRs are for pre-operation BMI.

BMI and survival of cancer (**Figures 3** and **4**). Pooled HR of three GC studies for higher pre-operation BMI was 0.68 (95% CI = 0.25-1.11). However, a high level of heterogeneity was found ($I^2$ = 78.0%, $P_{heterogeneity}$ = 0.011). Meta-analysis of three PC studies on the association of higher pre-operation BMI and OS of PC participants revealed that pooled HR was 0.85 (95% CI = 0.65-1.05), without obvious heterogeneity ($I^2$ = 37.1%, $P_{heterogeneity}$ = 0.204).

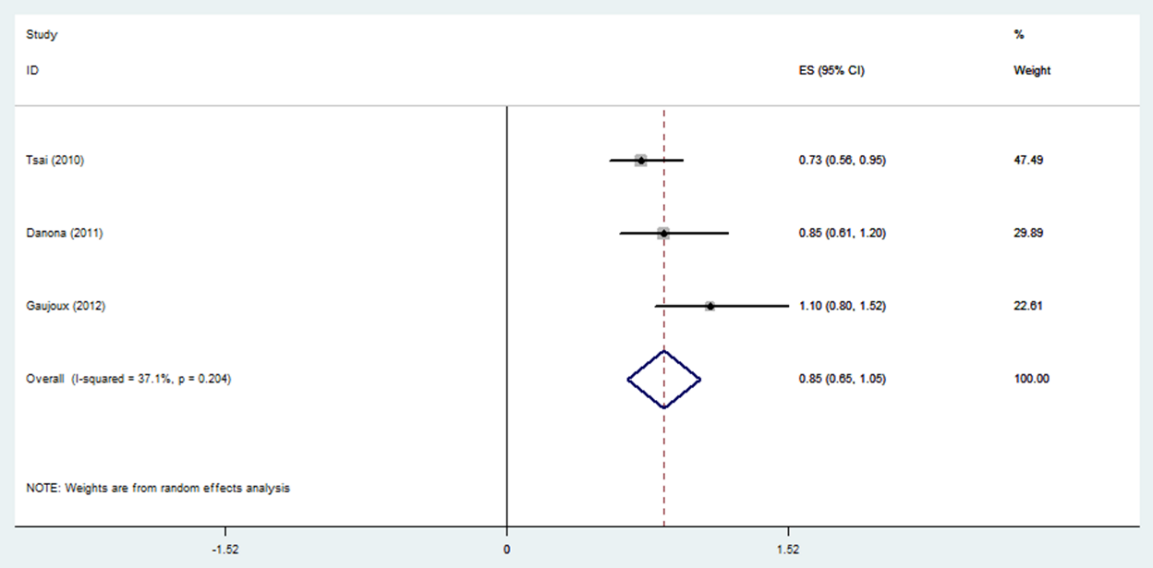


**Figure 4.** Forest plot showed hazard ratios (HRs) and 95% CIs for the highest versus lowest BMI category and overall survival of pancreatic cancer. HRs are for pre-operation BMI

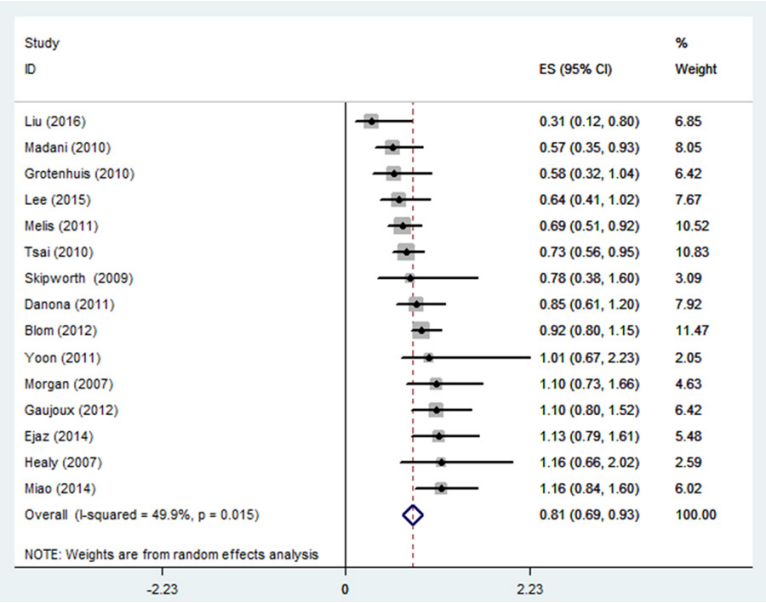


**Figure 5.** Forest plot showed hazard ratios (HRs) and 95% CIs for the highest versus lowest BMI category and overall survival of esophageal, gastric, and pancreatic cancer. HRs are for pre-operation BMI.

*Higher pre-operation BMI improves OS of all cancers*

Fifteen studies on highest versus lowest pre-operation BMI and mortality of EC, GC and PC were combined and analyzed (**Figure 5**). EC, GC and PC patients with highest BMI survived longer with a 19% lower risk of death (HR = 0.81, 95% CI = 0.69-0.93), with moderate heterogeneity ($I^2$ = 49.9%, $P_{heterogeneity}$ < 0.015), compared with lowest BMI category. The study of Yoon et al and Healy et al just contributed to 2.05% and 2.59% of overall HR, respectively. Total weight of studies on EC, GC and PC were 54.83%, 20.0%, and 25.17%, respectively.

*Subgroup analysis, sensitivity analysis and publication bias*

We conducted subgroup analysis based on information provided by these studies. We found that, comparing with the lowest BMI category, the highest category had a statistically significant positive effect on OS of EC patients in North America group (HR = 0.67; 95% CI = 0.50, 0.83), but not in non-North America group (**Table 2**). Moreover, the statistically significant effect was only found in the subgroup with sample size < 500. Regarding the highest versus lowest BMI category and OS of EC patients, there was significant association for prospective studies (HR = 0.81; 95% CI = 0.66, 0.97) and these adjusted for covariates

**Table 2.** Random-effect summary estimates of the hazard ratios (HRs) of the association of OS of esophageal cancer with highest versus lowest pre-operation BMI comparison

| | Study | HR (95% CI) | I-squared (%) | $P_{heterogeneity}$ |
|---|---|---|---|---|
| Region | | | | |
| North America | 3 | 0.67 (0.50, 0.83) | 0% | 0.543 |
| Other regions | 6 | 0.92 (0.76, 1.09) | 19.6% | 0.286 |
| Histology | | | | |
| AC | 4 | 0.88 (0.54, 1.22) | 44.0% | 0.147 |
| AC and SCC | 4 | 1.16 (0.84, 1.60) | 60.3% | 0.056 |
| Number of patients | | | | |
| < 500 | 5 | 0.76 (0.56, 0.95) | 24.7% | 0.012 |
| ≥ 500 | 4 | 0.90 (0.67, 1.12) | 39.5% | 0.021 |
| Study type | | | | |
| Retrospective | 1 | 1.16 (0.66, 2.02) | NA | NA |
| Prospective | 8 | 0.81 (0.66, 0.97) | 41.9% | 0.019 |
| Adjusted for covariates | | | | |
| Yes | 4 | 0.93 (0.59, 1.27) | 59.5% | 0.069 |
| No | 5 | 0.79 (0.64, 0.95) | 26.2% | 0.008 |

SCC = squamous cell carcinoma, AC = adenocarcinoma, HR = hazard ratio, NA = not available.

(HR = 0.79; 95% CI = 0.64, 0.95). Moreover, subgroup analysis of studies without adjustment for covariates, did not reveal significant association of OS of EC patients with highest versus lowest BMI comparison.

Every turn, we ignored one study and analyzed the rest articles in sensitivity analysis. When every single study was excluded, there was no significant change of pooled HR and 95% CI. Begg funnel plot and Egger regression test were used to assess publication bias. The funnel plot for OS and higher pre-operation BMI of EC (Begg test P = 0.801) or GC patients (Begg test P = 0.398) showed no asymmetry (**Figure 6**). Begg test for highest versus lowest BMI category and mortality of PC (P = 0.537) or all cancers (P = 0.508) failed to reveal any significant publication bias (**Figure 7**). Additionally, Egger regression test for all groups also suggested no obvious publication bias.

## Discussion

The prevalence of obesity worldwide and its link to cancer risk and worse outcomes after many cancer diagnoses make it a major and growing public health concern. Higher BMI (overweight or obesity) accounts for approximately 20% of all cancer patients, including esophageal cancer, colorectal cancer, and pancreatic cancer [26-28].

The dispute over the relationship between BMI and survival from gastrointestinal cancer has lasted for decades. Three published meta-analyses had evaluated the association of BMI with the mortality of digestive system cancer, including esophageal cancer, colorectal cancer, and pancreatic cancer [13, 29, 30]. Zhang et al found that highest BMI could significantly improve OS of esophageal cancer survivors, comparing with lowest BMI category (HR = 0.78, 95% CI = 0.71-0.85). However, the consideration of accurate BMI category and time point was missed in their study [13]. In addition, a study which enrolled 1324 esophageal cancer participants suggested that high BMI is not associated with increased overall morbidity after esophagectomy [23]. In April of 2016, a meta-analysis focusing on BMI and OS of pancreatic cancer cases was published. This analysis revealed that adult obesity of pancreatic cancer is related to shorter OS (HR = 1.29, 95% CI = 1.17-1.41), while obesity at diagnosis was not associated with the mortality [29]. Prognostic effect of higher pre-operation BMI on EC, GC, and PC has been searched. However, the role of pre-operation BMI on the mortality of cancers from digestive system is still unclear, though some meta-analysis on BMI and OS of DSC were reported. BMI is easily acquired, and clear effect of pre-operation BMI on OS may help the prognosis of cancers. Therefore, this meta-analysis was conducted to reveal the prognostic role of pre-operation BMI on OS from EC, GC, and PC.

Multivariate results were provided by eight included studies and four studies conducted both multivariate and univariate analysis. Because it was easier to find the relationship by analyzing the maximum and minimum BMI, we estimated the highest versus lowest pre-operation BMI category and cancer mortality. Most of the highest BMI category of included

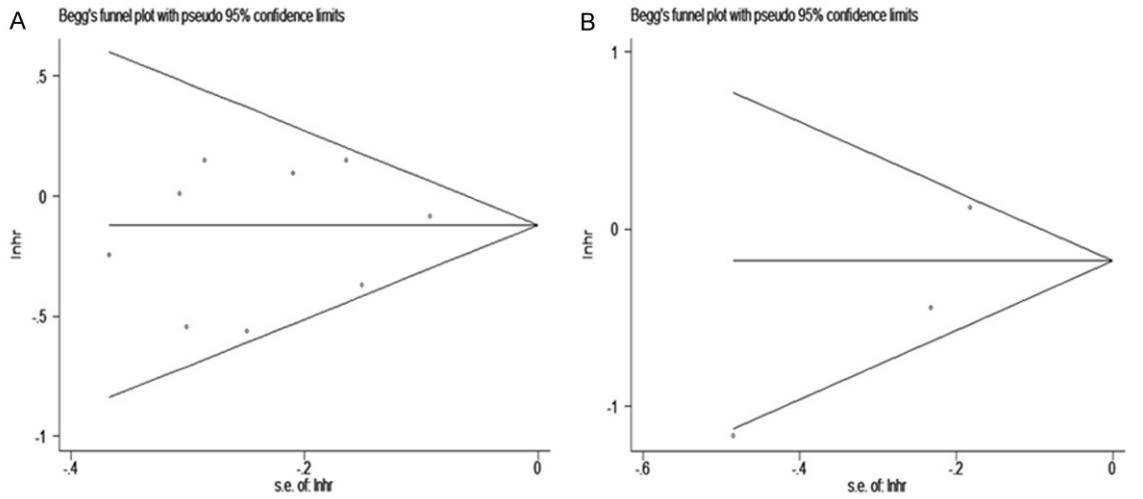


**Figure 6.** Begg funnel plot test for higher pre-operation BMI and overall survival of esophageal and gastric cancers. (A: Esophageal cancer, B: Gastric cancer).

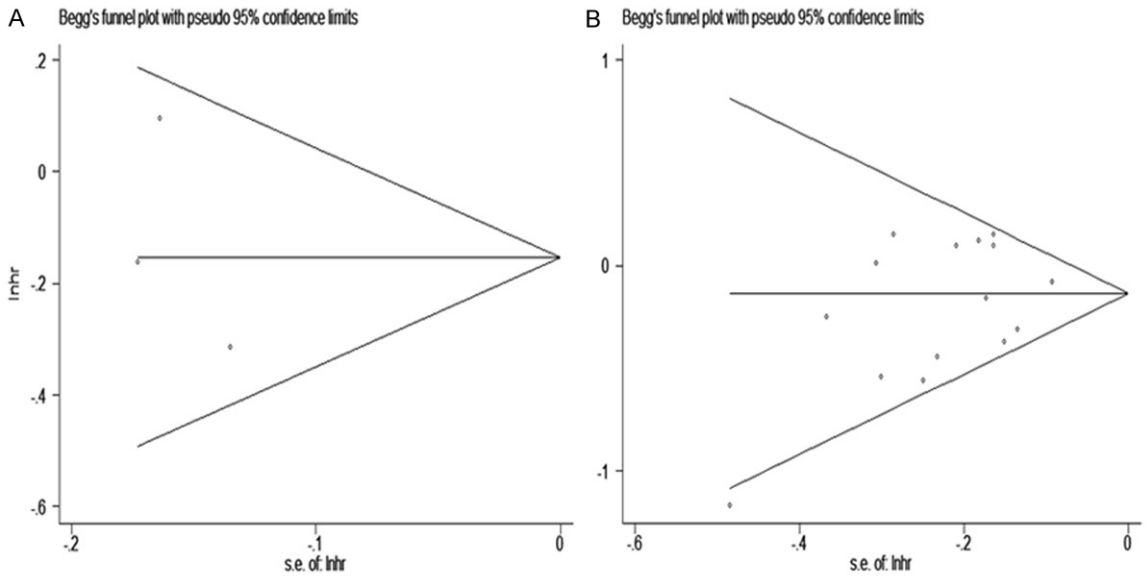


**Figure 7.** Begg funnel plot test for higher pre-operation BMI and overall survival of pancreatic and all cancers. (A: Pancreatic cancer, B: Esophageal, gastric, and pancreatic cancer).

articles in this analysis belonged to overweight and obese populations. Lowest or referent BMI category contained cases with normal and underweight BMI. Some studies, which only provided univariated outcomes, were also adapted to achieve more credible pooled results. As the same histology of adenocarcinoma and limitation of study numbers, all 15 studies were included and estimated the highest versus lowest pre-operation BMI and combined mortality of EC, GC, and PC survivals.

The outcome revealed that patients with higher pre-operation BMI had lower mortality from EC cases. Moreover, we included several studies of PC and GC on pre-operation BMI and OS to conduct analysis. The current HR of the highest versus lowest pre-operation BMI and OS of PC survivors was 0.85 (95% CI = 0.65-1.05), and the result was not coincidence with the former study of pancreatic cancer [29]. This difference may be caused by the pre-operation BMI status and limited sample size in this study.

To further demonstrate the predictive value of pre-operative BMI and OS of EC patients, subgroup analyses for covariates adjusting were performed as a supplement. The analysis results of North America, sample size < 500, and prospective study groups showed significant association between higher pre-operation BMI group and OS of EC patients, comparing with lowest BMI group. Combined analysis of studies from other regions and sample size ≥ 500 revealed contrary results, pooled HR of was 0.92 (95% CI = 0.76-1.09) and 0.90 (95% CI = 0.67-1.12), respectively. When we analyzed the studies unadjusted for covariates, the association between highest versus lowest pre-operation BMI category and OS of EC survivals was statistically significant (HR = 0.79, 95% CI = 0.64-0.95). However, we did not obtain meaningful result (HR = 0.93, 95% CI = 0.59-1.27) from studies adjusted for covariates. Only four studies included in this meta-analysis were adjusted for effect of tumor grade in EC cases. Survival of EC patients was strongly dictated by tumor stage after neoadjuvant chemotherapy [31]. Both univariate (P = 0.007) and multivariate (P = 0.011) analysis revealed that better tumor grade was associated with longer survival in esophageal cancer cases [32]. Loss of weight, especially loss of skeletal muscle, may indicate the bad outcome of several cancers [33]. Additionally, pancreatic cancer patients who suffer from higher weight loss at diagnosis or during first-line chemotherapy had shortened survival [34].

The potential mechanisms of the effect of higher pre-operation BMI on EC patients have not been clarified and elucidated thoroughly. For many kinds of chronic diseases including cancer, overweight and obese mean a better nutrition status and potential survival advantages comparing with normal or lower BMI [35]. After operation and during chemotherapy, EC survivals who has higher pre-operation BMI had more nutrient and energy stores. They had larger appetites and higher lipid concentration for preserving energy, fat and muscle mass. Enough energy storage is critical for tissue repair, physiological activities, immune effect and body elements balance. However, higher BMI is also accompanied by higher incidence of complication after treatment. In esophageal survivors, higher BMI may induce anastomotic leakage, wound infection, slow growth of anastomosis, and cardiovascular diseases (all P < 0.05) [6, 13, 19-21]. In addition, obese cases had higher rate of diabetes mellitus, which may influence the healing of cancer patients after treatment [20]. Further and thorough study is needed to explore the mechanisms behind the relationship between higher pre-operation BMI and OS of particular cancers.

As we know, this study is the first meta-analysis evaluating the effect of pre-operation BMI on OS from EC, GC, and PC. Analysis of three types of cancer, adjustment of covariates, the relatively large sample size and the summarized evidence of single study are strengths in our study. However, there are some limitations in this meta-analysis. Although only two included studies were from developed countries, techniques, devices, therapies, and other factors may restrict the research. Comprehensive and through analysis needs more research information from developing countries. Except EC, the number of included articles about GC and PC was limited, and the combined result of GC or PC maybe inaccurate.

The preoperative weight loss and abdominal obesity may influence the mortality of general population and decrease the overall survival of digestive system cancers. However, most of the included studies did not provide any information about both the risk factors [10, 36]. In addition, some usual covariates for survival of cancer cases, including tumor grade, differentiation, lymph node metastasis, diabetes status, and treatment, were not adjusted in some studies. To our knowledge, comparing with prospective studies, lower clinical evidence level and more uncontrollable biases in retrospective studies may affects our results. Therefore, we conducted this analysis using as many multivariate data as possible. Our analysis cannot avoid selection bias, because inclusion of participants depends on survival time. Additionally, the number of severe cases were less than actual proportion in cancer patients.

In conclusion, our research indicated that pre-operation BMI increased the overall survival of EC. Additionally, higher pre-operation BMI did not show any association with the survival of GC and PC patients. With the gradual deepening of the study, pre-operation BMI may become

an important predictor of mortality of EC, GC, and PC survivals.

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## Disclosure of conflict of interest

None.

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