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Impact of obesity on the outcomes after gastrectomy for gastric cancer: A meta-analysis

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SUMMARY

The impact of body mass index (BMI) on surgical outcomes has previously been studied in relation to several oncological procedures. Regarding gastric cancer surgery, published results have been contradicting in terms of degree of technical difficulty, risk of postoperative complications and survival. In an attempt to clarify these issues, we performed a meta-analysis to evaluate the impact of obesity (defined as BMI $\geq$ 30 kg/m^2) on outcomes after gastrectomy for gastric cancer. The meta-analysis was performed according to the PRISMA guidelines. Eligible studies were identified through search of PubMed, EMBASE, Web of Science and Cochrane Library databases. Quality assessment was performed using the Newcastle-Ottawa scale. The meta-analysis was conducted using random-effects modeling. A total of 11 studies with 13 538 patients were eligible for analysis. Obesity was associated with a significantly longer operation time (WMD = 19.38 min, 95% CI 12.72−26.04; $p < 0.001$), increased risk of overall complications (RR = 1.23, 95% CI 1.06−1.42; $p = 0.005$) and pulmonary complications (RR = 3.81, 95% CI 2.24−6.46; $p < 0.001$). These findings remained irrespective type of surgery (laparoscopic vs. open) and type of gastrectomy. No differences were found regarding blood loss, number of resected lymph nodes, anastomotic leakage, hospital stay, 30-day mortality and 5-year overall survival. The conclusion of the current meta-analysis is that high BMI in gastric cancer patients is associated with longer operative time and more frequent overall postoperative complications. However, it has no negative impact on survival, indicating that gastrectomy is a safe procedure for this group of patients.

1. Introduction

Gastric cancer (GC) has been the leading cause of cancer related mortality until the 1980s, when it was overtaken by lung cancer.[1] During the last decades its global incidence has continued to decline, probably due to the recognition of dietary and environmental risk factors and the decreasing prevalence of *H. pylori* infection. Nevertheless, GC still represents one of the most common malignancies, being the third leading cause of cancer-related death worldwide.[2] Surgical resection including D2 lymphadenectomy is the gold standard and the only potentially curative treatment for advanced GC.[3–5] Still, this is a technically demanding procedure associated with complications and a considerable mortality rate, especially in Western countries. Although prognosis heavily depends on disease stage, several patient-related factors also influence outcomes.

Obesity is recognized as one of the most important global public health problems, with an increase in its prevalence in almost all

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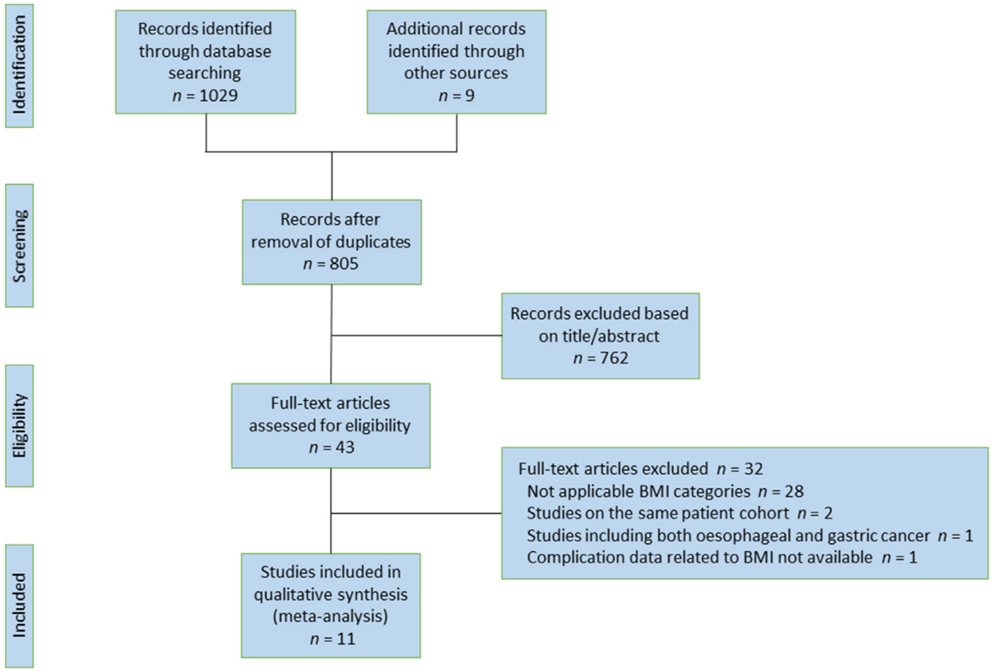

Fig. 1. PRISMA flow chart of the literature search and study selection.

countries, rising as high as two-fold in 70 countries since 1980.[6] As a result, surgeons encounter an increasing number of obese patients during their routine clinical practice. Furthermore, obesity seems to be associated with a higher risk for gastroesophageal cancer.[7,8] The impact of body mass index (BMI) on surgical outcomes has previously been studied in relation to several oncological procedures, e.g. colorectal surgery,[9] pancreaticoduodenectomy,[10] liver surgery[11] and esophagectomy.[12] Regarding gastric cancer surgery, the published results have been somewhat contradicting; most studies have reported that obesity is associated with a technically more difficult operation (as reflected by the prolonged operation time, increased intraoperative blood loss, lower number of retrieved lymph nodes) and a higher risk for postoperative complications,[13–16] while other studies have demonstrated that the adequacy of lymph node dissection and the complication rate are not influenced by high BMI.[17–20] The interpretation of these results becomes more complicated as the majority of studies originating from Asian centers use a BMI value of 25 kg/m^2 as a cut-off to classify patients as obese, which is not in accordance with the current World Health Organization (WHO) definition of obesity.[21]

In an attempt to clarify these issues, we performed a meta-analysis to investigate the impact of obesity (defined as BMI $\geq$ 30 kg/m^2) on the outcomes after gastrectomy for gastric cancer.

2. Methods

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[22]

2.1. Search strategy

A systematic literature search was carried out using the PubMed, EMBASE, Web of Science and Cochrane Library databases. The following search algorithm and Medical Subject Headings (MeSH) terms were used: [(gastric cancer OR gastric neoplasm) AND (gastrectomy OR gastric surgery) AND (body mass index OR obesity OR obese)]. The search was restricted to studies conducted in human subjects and published in English and in full text up to the 31st January 2020. The reference lists of the selected articles were also screened in order to identify additional papers of relevance.

2.2. Study selection criteria

Studies were considered eligible if they fulfilled the following criteria: (i) original articles reporting on outcomes after gastric cancer surgery (either open or laparoscopic), (ii) clear definition of BMI categories according to the WHO classification (obesity defined

Table 1
General characteristics and quality assessment of the included studies.

Reference	Country	Type of study	Inclusion period	Sample size	Type of surgery (lap/open)	Type of gastrectomy (total/partial)	NOS
Chen et al.[27]	China	Retrospective	2007–2015	122	122/0	0/122	8
Ejaz et al.[28]	USA	Retrospective	2000–2012	775	70/705	313/462	8
Jung et al.[29]	S. Korea	Retrospective	2006–2012	1512	1512/0	0/1512	7
Kim et al.[30]	S. Korea	Retrospective	2004–2010	1480	1480/0	0/1480	7
Lee et al.[32]	S. Korea	Retrospective	2000–2016	7765	–	1865/5900	8
Lin et al.[31]	Taiwan	Retrospective	1987–2006	947	0/947	260/687	8
Pata et al.[33]	Italy	Retrospective	2005–2011	161	0/161	161/0	7
Struecker et al.[34]	Germany	Retrospective	2005–2012	249	0/249	194/55	8
Tan et al.[35]	China	Retrospective	2008–2016	210	210/0	90/115	8
Wang et al.[36]	China	Retrospective	2010–2013	131	131/0	0/131	7
Wong et al.[37]	USA	Retrospective	1997–2012	186	–	–	8

NOS, Newcastle-Ottawa Scale; lap, laparoscopic.

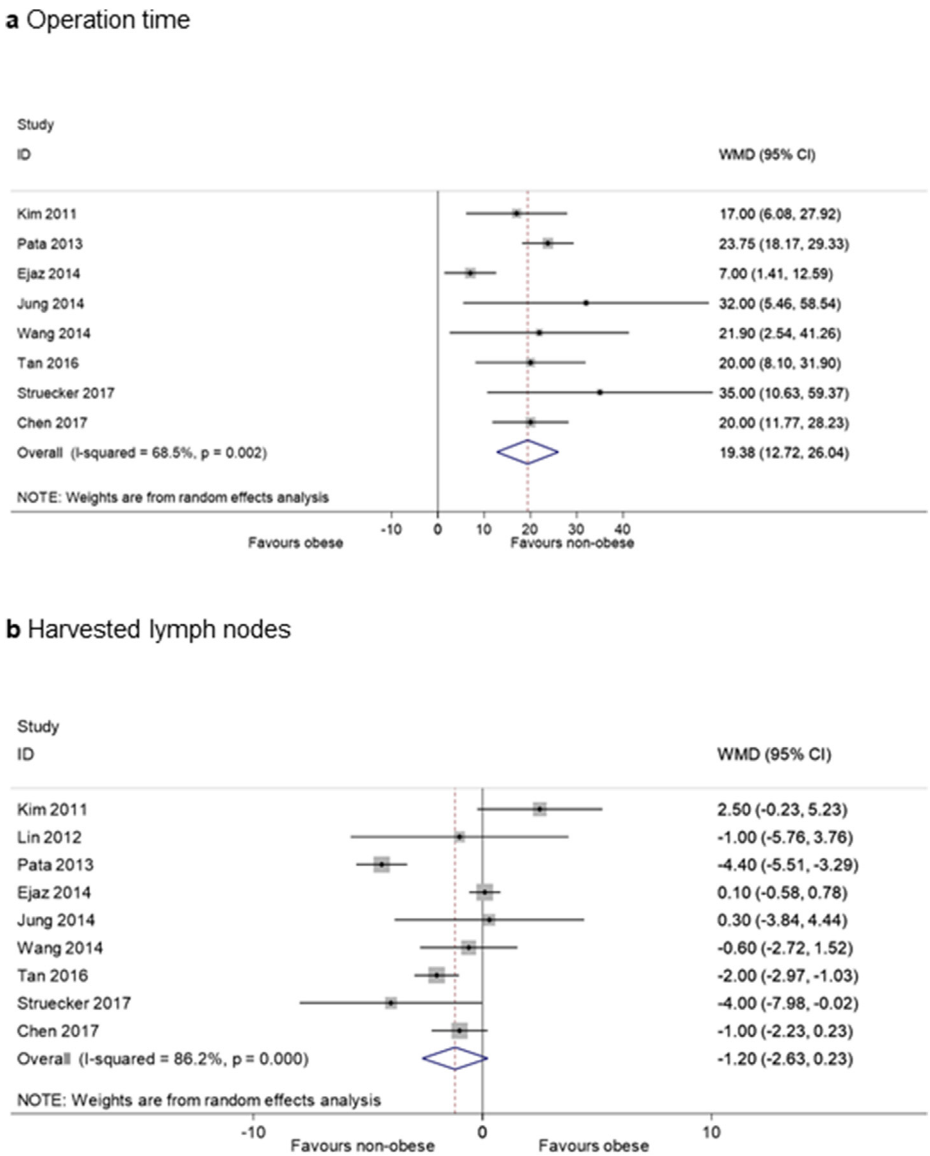

Fig. 2. Forest plots evaluating the impact of obesity on operation time and number of harvested lymph nodes.

as BMI $\geq$ 30 kg/m^2), (iii) homogeneous cohorts of patients with BMI as an independent variable between groups and (iv) analysis of at least one of the outcomes of interest. When overlapping data from the same patient cohort were presented in more than one publication, only the most recent one was included in the meta-analysis. The exclusion criteria were as follows: (i) reviews or case reports, (ii) duplicates or studies reporting on the same patient cohort, (iii) studies that included patients with previous esophageal or gastric surgery, (iv) studies that did not define obesity according to the WHO classification, (v) studies in which data from normal-weight patients were not available. Eligible papers were selected by two reviewers independently (AL and DC) and any disagreements were resolved by discussion between the authors until consensus was reached.

2.3. Outcomes of interest

The following outcome measures were compared between the different BMI groups: (i) operation time, (ii) number of harvested lymph nodes, (iii) intraoperative blood loss, (iv) transfusion, (v) overall complications, (vi) severe complications (defined as Clavien-Dindo III − V), (vii) pulmonary complications, (viii) cardiac complications, (ix) wound infection, (x) anastomotic leakage, (xi) reoperation, (xii) 30-day-mortality, (xiii) time to soft diet, (xiv) length of hospital stay and (xv) 5-year overall survival.

2.4. Data extraction

Relevant data were extracted by two reviewers (AL and DC). The collected data included: (i) Study characteristics (first author, year of publication, country of origin, study design, inclusion period, population size), (ii) Patients' demographic characteristics (age, sex, BMI in kg/m^2), (iii) Disease characteristics (clinical stage, tumor location), (iv) Multimodal treatment details (neoadjuvant treatment, type of surgical procedure, type of lymph node dissection, adjuvant treatment), and (v) Surgical outcomes of interest as described above.

In the current meta-analysis, BMI was classified according to the WHO guidelines[21]: underweight (BMI $<$ 18.5 kg/m^2), normal weight (BMI 18.5−24.9 kg/m^2), overweight (BMI 25.0−29.9 kg/m^2), obesity

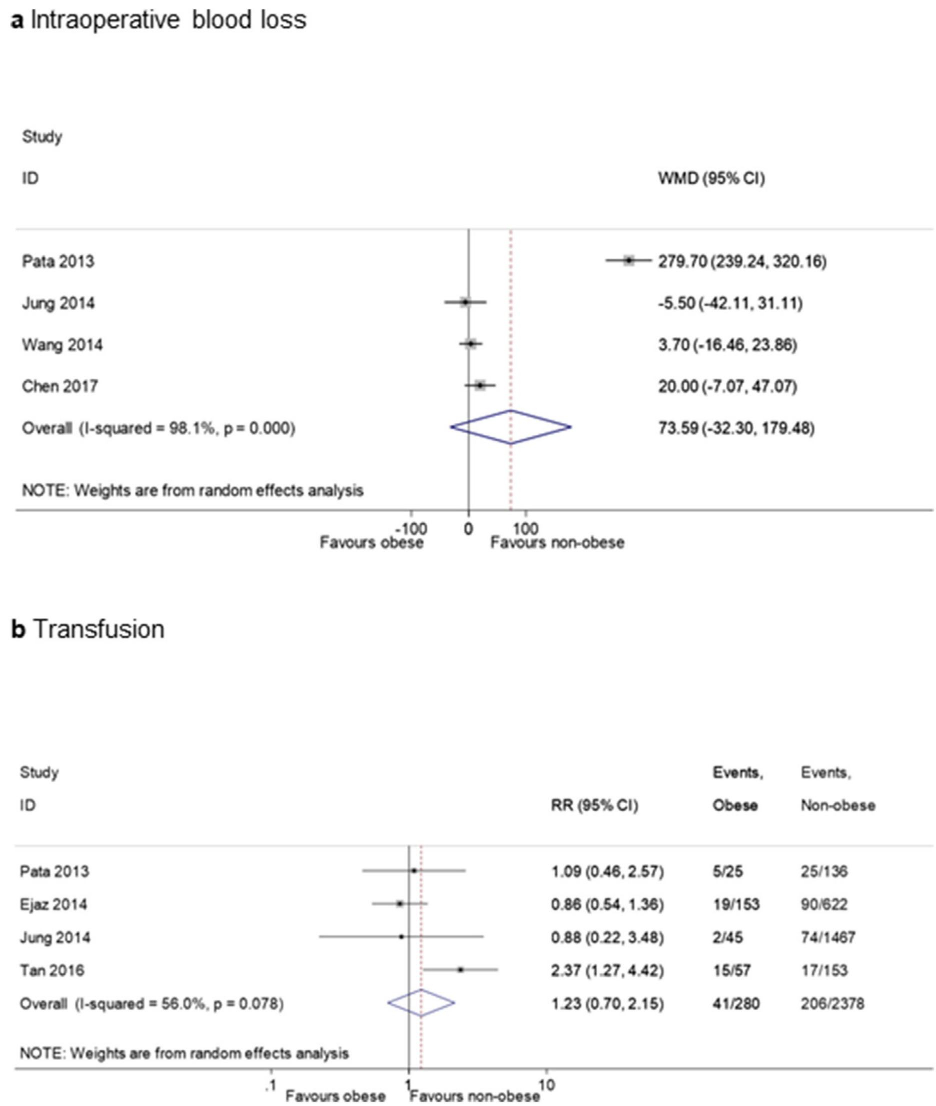

Fig. 3. Forest plots evaluating the impact of obesity on intraoperative blood loss and need of transfusion.

(BMI 30.0–35.0 kg/m^2), and morbid obesity (BMI $>$ 35.0 kg/m^2). To conduct the meta-analysis, the patients were divided into non-obese (BMI < 30.0 kg/m^2) and obese (BMI ≥ 30.0 kg/m^2) and comparisons were performed between these two groups.

2.5. Quality of evidence assessment

The quality of the selected studies was assessed using the Newcastle-Ottawa Scale (NOS).[23] The scale takes into account the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. This assessment was carried out by two investigators (AL and DC). A total score of at least 6 points indicated high quality of the study.

2.6. Statistical analysis

A meta-analysis was performed to assess the impact of obesity on outcomes after gastrectomy for gastric cancer. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. RR > 1 indicated outcome more frequently present in obese patients. For continuous data such as operation time, blood loss, number of resected lymph nodes, time to soft diet and hospital stay, the weighted mean difference (WMD) with 95% CIs was calculated. Using the inverse-variance method, random-effects models were fitted to estimate pooled RRs or WMDs and their 95% CIs. To meta-analyze proportions from 5-year overall survival, proportions were obtained from Kaplan-Meier risk tables which accounts for censoring, and the comparisons between obese and non-obese groups were performed using RR as the measure of effect calculated by a mixed-effects meta-regression model. Additionally, stratified meta-analyses by type of surgery (laparoscopic vs. open) as well as type of gastrectomy (partial vs. total) were performed to further assess potential differences of the impact of BMI on outcomes among these groups of patients. Forest plots were used to display the pooled estimates graphically. Sensitivity analyses were carried out by excluding the studies in which eligibility for the meta-analysis was doubtful for any reason. Higgins' I^2 value was used to assess heterogeneity.[24] An I^2 value of more than 75% was considered significant. The presence of publication bias such as small-study effects was examined by Harbord test for binary data[25] and Egger test for continuous data[26] and illustrated graphically by Funnel plots. All statistical analyses were performed in Stata® version 16.1 (StataCorp LP, College Station, Texas, USA) except for 5-

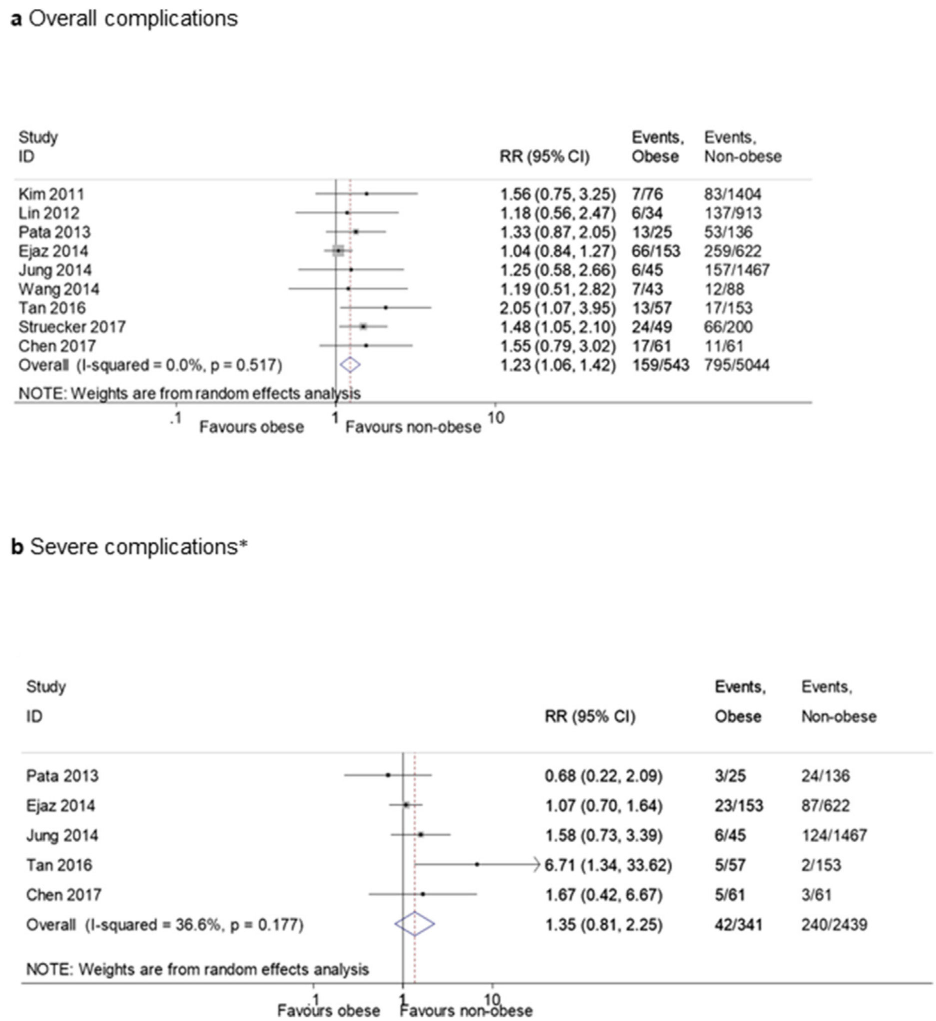

Fig. 4. Forest plots evaluating the impact of obesity on overall and severe complications*. *defined as Clavien-Dindo III − V.

year survival, which was calculated in R version 3.5.3 using the packages Metafor 2.1 and Meta 4.1.2.

3. Results

A total of 1038 potentially relevant articles were identified through electronic search of bibliographic databases and manual search of reference lists, of which 233 were directly excluded as duplicates. After preliminary screening of titles and abstracts, another 762 articles were excluded because they were irrelevant, didn't meet the inclusion criteria, or their full text was not accessible. Of the remaining 43 articles that underwent full-text evaluation, 32 were excluded for the following reasons: different categories of BMI used (BMI cut-off value other than 30 kg/m^2), studies reporting on the same patient cohort, both esophageal and gastric cancers included in the study or lack of complication data related to BMI. Finally, 11 studies with a total of 13 538 patients (8869 males and 4669 females; 12 726 patients with BMI < 30 kg/m^2 and 812 patients with BMI $\geq$ 30 kg/m^2) fulfilled the inclusion criteria and were included in the quantitative data synthesis.[27–37] The PRISMA flow diagram of the literature search and study selection is shown in Fig. 1. All 11 articles were retrospective, observational cohort studies, published between 2011 and 2018 and were assessed to be of high quality. The majority of them (7/11) were from East Asian institutions. The general characteristics and quality assessment of the included studies are summarized in Table 1. Moreover, details on patient and tumor characteristics as well as oncological and surgical details are provided in Supplementary Table 1.

3.1. Surgical outcomes

Operation time was reported in 8 studies.[27-30,33-36] There was a statistically significant difference between the groups, with longer operation time in obese compared to non-obese patients (WMD = 19.38 min, 95% CI 12.72–26.04; $p < 0.001$, $I^2 = 68.5\%$) (Fig. 2a). The number of resected lymph nodes was reported in 9 studies and, although it was higher in non-obese patients, no significant difference was found (WMD = -1.20, 95% CI -2.63 − 0.23; $p = 0.101$, $I^2 = 86.2\%$)[27-31,33-36] (Fig. 2b). Intraoperative blood loss was reported in 4 studies and was lower in the non-obese group, even if the difference was not statistically significant (WMD = 73.59 ml, 95% CI -32.30–179.48; $p = 0.173$, $I^2 = 98.1\%$)[27 29 33 36] (Fig. 3a). Similarly, there was no difference between the groups regarding the need of perioperative blood transfusion (RR 1.23, 95% CI 0.70–2.15; $p = 0.472$, $I^2 = 56.0\%$)[28 29 33 35] (Fig. 3b).

3.2. Postoperative outcomes

The overall complication rate was reported in 9 studies.[27-31,33-36] The analysis showed that obesity correlates with a higher risk of

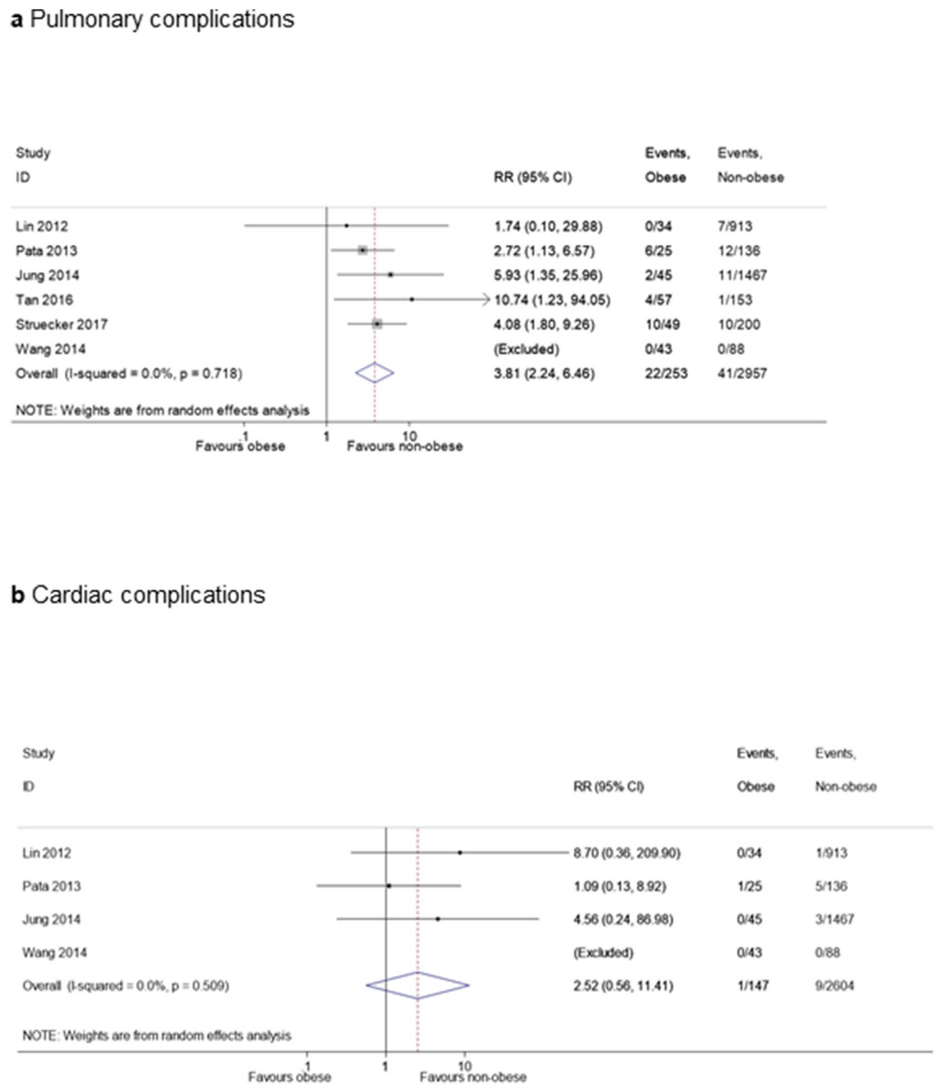

Fig. 5. Forest plots evaluating the impact of obesity on pulmonary and cardiac complications.

overall complications (RR = 1.23, 95% CI 1.06–1.42; $p = 0.005$, $I^2 = 0.0\%$) (Fig. 4a). The severe complication rate on the other hand, defined as Clavien-Dindo grade III – V, was not different between obese and non-obese patients (RR = 1.35, 95% CI 0.81–2.25; $p = 0.245$, $I^2 = 36.6\%$)[27-29 33 35] (Fig. 4b). With regards to specific complications, pulmonary complications were reported in 6 studies and were significantly higher in obese patients (RR = 3.81, 95% CI 2.24–6.46; $p < 0.001$, $I^2 = 0.0\%$)[29,31,33-36] (Fig. 5a), while there was no difference in cardiac complications (RR = 2.52, 95% CI 0.56–11.41; $p = 0.229$, $I^2 = 0.0\%$)[29,31,33,36] (Fig. 5b). A trend towards fewer wound infections in non-obese patients could be observed but this did not reach the level of statistical significance (RR = 1.57, 95% CI 1.00–2.47; $p = 0.052$, $I^2 = 12.0\%$)[28-31,33-36] (Fig. 6a). Likewise, there was no difference in anastomotic leakage (Fig. 6b), reoperation rate (Fig. 7a), and 30-day mortality (Fig. 7b) between the two groups. Time to soft diet and length of hospital stay were not affected by high BMI (Fig. 8a and b). Finally, no difference was found in terms of 5-year overall survival between obese and non-obese patients (RR = 0.89, 95% CI 0.76–1.04; $p = 0.270$, $I^2 = 30.3\%$) (Fig. 9).

Funnel plots assessing for publication bias are presented in Supplementary Fig. 1–8.

3.3. Outcomes of subgroup analyses by type of surgery and type of gastrectomy

Five studies[27,29,30,35,36] included purely laparoscopic procedures with a total of 3450 patients. Three studies[31,33,34] included only open procedures with a total of 1357 patients while the remaining 3 studies[28,32,37] included both procedures. The analysis showed a statistically significant longer operation time in obese compared to non-obese patients regardless type of surgery. Furthermore, lower BMI was associated with higher number of resected lymph nodes in open gastrectomy (WMD = -4.21, 95% CI -5.25 – - 3.16; $p < 0.001$, $I^2 = 0.0\%$) (Supplementary Fig. 9). The correlation of obesity and high risk of overall complications and specifically pulmonary complications remained significant in both procedures even after stratification (Supplementary Fig. 10). Finally, a higher 30-day mortality was observed in the obese group who had undergone open gastrectomy compared to the non-obese (RR = 3.34, 95% CI 1.21–9.20; $p = 0.020$, $I^2 = 0.0\%$) (Supplementary Fig. 11). No other differences across the groups were noted (data not shown).

Four studies[27,29,30,36] reported on exclusively partial gastrectomy with a total of 3245 patients. On the other hand only one study[33] included data purely on total gastrectomy therefore further

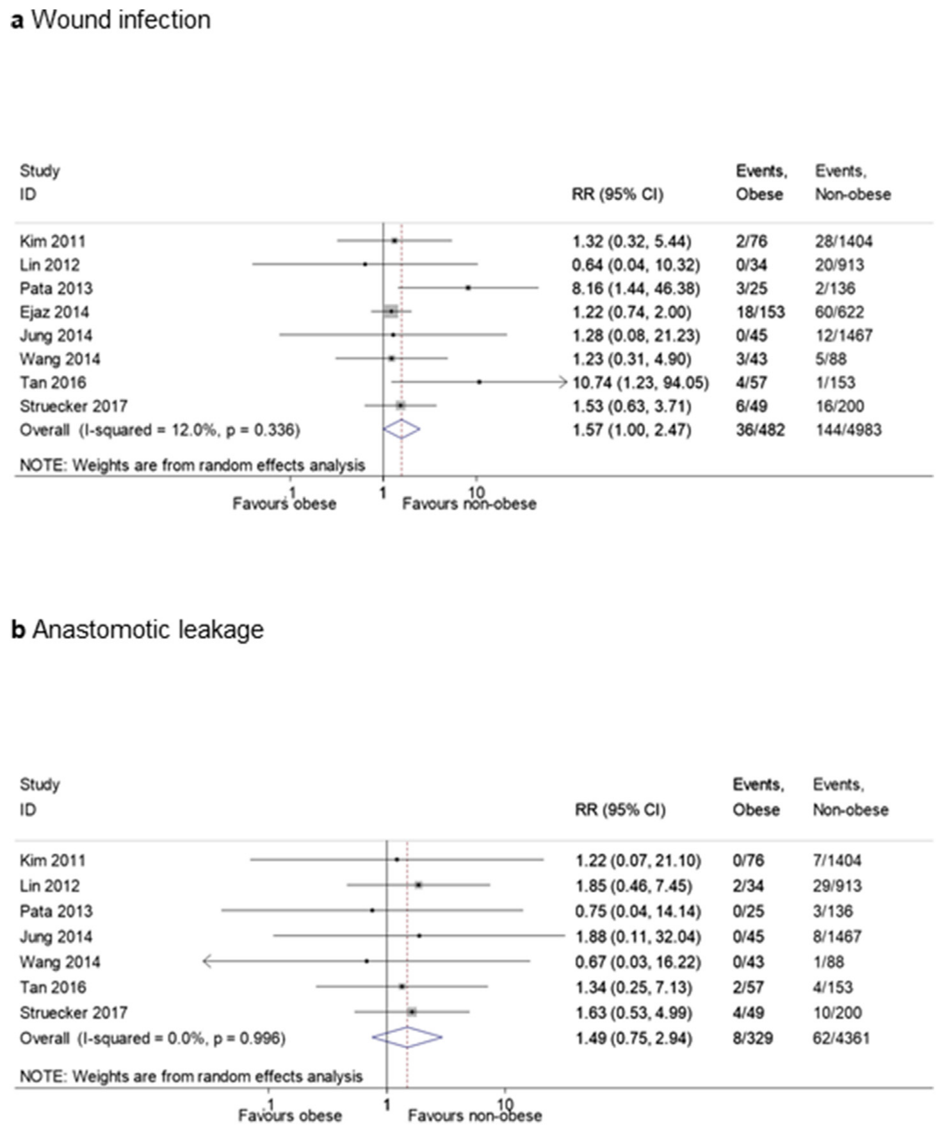

Fig. 6. Forest plots evaluating the impact of obesity on wound infection and anastomotic leakage.

stratified analysis for this group was not feasible with the available data. Among obese patients who underwent partial gastrectomy a longer operation time and higher risk for pulmonary complications was demonstrated (Supplementary Fig. 12) while no other differences were observed (data not shown).

4. Discussion

Obesity has evolved to a global epidemic, highlighted by a WHO report as a global health crisis already in 2000.[38] The impact of obesity and the associated comorbidities – e.g. type 2 diabetes, hypertension, cardiovascular disease, obstructive sleep apnea syndrome, non-alcoholic fatty liver disease – on the outcomes after major surgery cannot be ignored, as these conditions have an influence on the patients' physiological reserves and ability to cope with the surgical trauma and postoperative complications that may occur. Additionally, obesity has always been perceived as a condition that predisposes to technically more difficult procedures as a result of the excess adipose tissue.

In the context of gastric cancer surgery, these issues have been the subject of investigation by numerous studies with conflicting results, mainly from Asian countries where the prevalence of obesity is much lower compared to the West. Apart from that, the Asia-Pacific classification of obesity has usually been applied, which differs from the WHO classification as it defines obesity as BMI >25 kg/m.[2,39] Accordingly, the conclusions of most studies are not directly applicable to Western populations. In the current meta-analysis, we investigated the impact of obesity on surgical outcomes, postoperative complications and long-term survival following gastrectomy for gastric cancer, including studies where a BMI value of 30 kg/m^2 was used as a cut-off to define the groups of patients.

Our analysis of the operative results showed that higher BMI was associated with significantly longer operation times, a finding repeatedly demonstrated in most studies. A prolonged operation time is rather anticipated, as excessive visceral fat encasing the major vessels in the upper abdomen and fat accumulation in the pancreas may hinder the recognition of the optimal dissection plane. Furthermore, a voluminous omentum and small bowel mesentery lead to additional technical disadvantages during reconstruction, inevitably prolonging operation time. In contrast, we found no difference with regard to intraoperative blood loss and

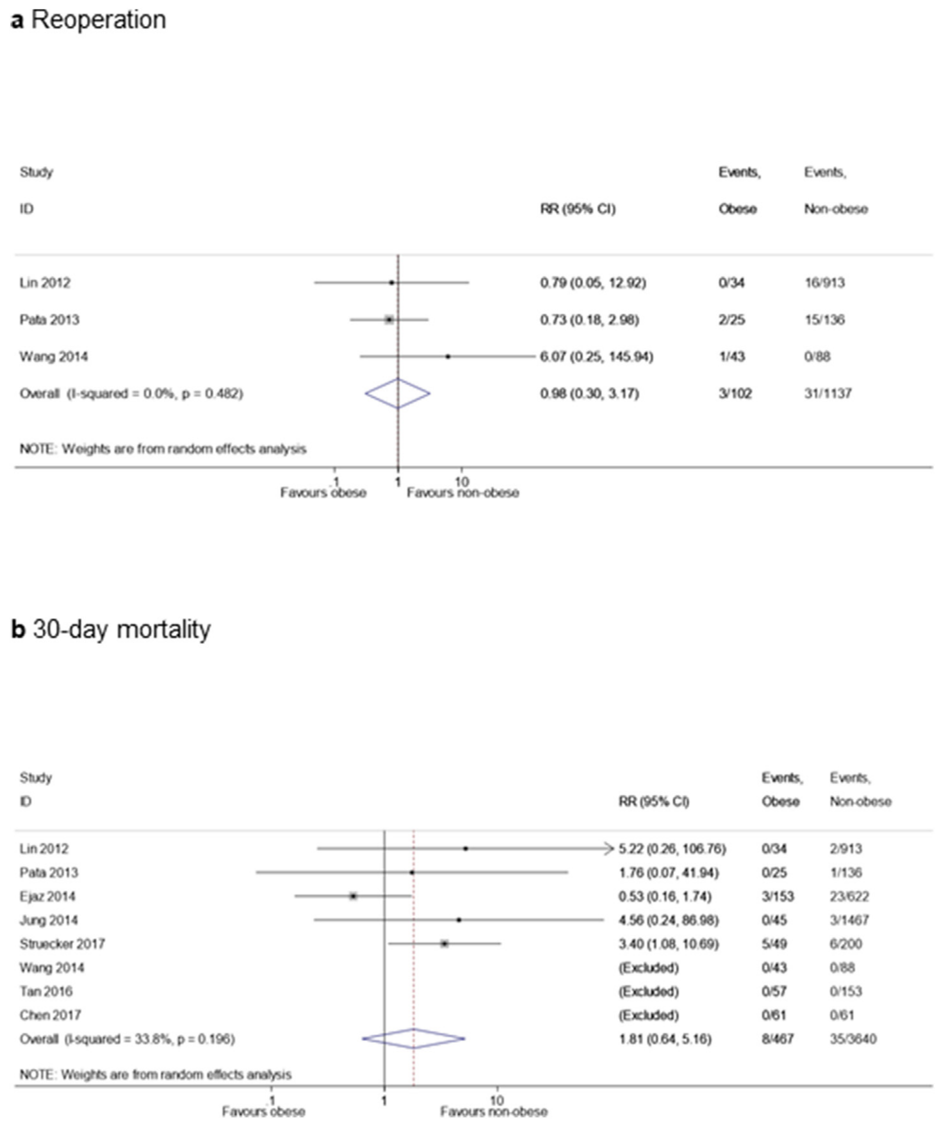

Fig. 7. Forest plots evaluating the impact of obesity on reoperation rate and 30-day mortality.

number of resected lymph nodes, variables that are also considered a proxy for technical difficulty. Although the number of resected lymph nodes was higher in non-obese patients, this difference was not statistically significant when comparing the whole cohort. A statistically significant difference though was observed in the open gastrectomy subgroup of patients; thus, we could not confirm the findings of previous meta-analyses[40,41], including two recent ones focusing on outcomes after laparoscopic gastrectomy.[42,43] Nevertheless, these meta-analyses used a different cut-off BMI value and are not directly comparable to ours. Furthermore, it has to be noted that the demonstrated difference in lymph node yield was very small in absolute numbers – with the highest weighted mean difference observed lying just above 2, which although statistically significant, is of questionable clinical importance; such small differences might as well reflect the difficulties that pathologists encounter in identifying lymph nodes in a specimen with abundant adipose tissue.

Regarding the relationship between BMI and surgical morbidity, we found that obesity correlates with a higher risk of overall complications, which is consistent with several previous reports.[44–46] More specifically, obese patients were at significantly increased risk of pulmonary complications. The most likely explanation is the prolonged anesthesia time, combined with high intra-abdominal pressure, which is known to impair pulmonary function. These factors, together with the metabolic implications of diabetes (insulin resistance, poor glycemic control and immune suppression), a common comorbidity in obese patients, predispose to the development of pulmonary complications. Similarly, a trend towards higher incidence of wound infections was observed in obese patients, but the difference was not significant. No difference was found in terms of severe complications (Clavien-Dindo grade III – V), which also reflects to the findings that the reoperation rate, length of hospital stay and 30-day mortality were comparable between the two groups.

Postoperative adverse events have been reported to be linked to unfavorable long-term outcomes, including survival[47,48], although this has been questioned in other studies.[46,49] This association was also examined in our meta-analysis, without any difference in 5-year overall survival demonstrated between obese and non-obese patients. This is an interesting finding, given that a worse overall survival could be expected in obese patients based solely on the related comorbidities and irrespective of their tumor

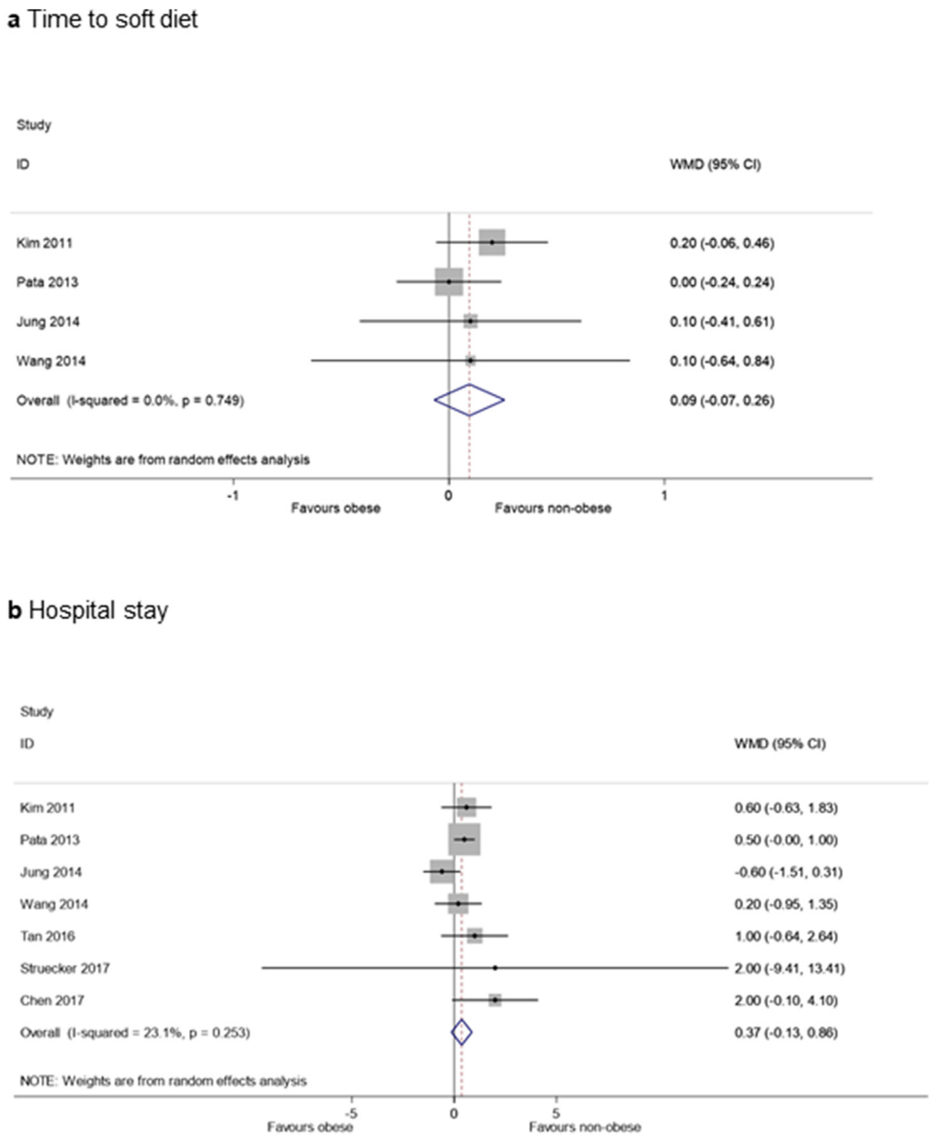

Fig. 8. Forest plots evaluating the impact of obesity on time to soft diet and length of hospital stay.

characteristics, disease stage or other oncological aspects.[50] In order to further investigate the impact of obesity on survival, it is necessary to conduct studies based not only on BMI, but on the metabolic profile of patients, i.e. comparing obese patients with associated comorbidities with obese patients otherwise "metabolically healthy", which is beyond the scope of the present meta-analysis.

In an attempt to interpret the inconsistency of reports in the literature, and the fact that our own findings did not conform with previous meta-analyses, one can speculate that BMI is not an appropriate means of estimating neither the grade of difficulty of a procedure, nor the role of obesity as a risk factor for postoperative complications and unfavorable outcomes. For example, a low BMI might be an expression of malnutrition and impaired physiology — often associated with more aggressive tumor biology — rather that an indicator of "normal" nutritional and immunological status. This might explain the unfavorable outcome of patients with very low BMI ($\leq$18.5 kg/m^2) demonstrated in a number of studies.[51,52] In a large cohort study including 7765 patients, Lee et al showed that patients who were overweight or obese at diagnosis had better overall and disease specific survival than those who were normal-weight or underweight.[32] As stated by Ejaz et al, overall nutritional status and weight loss, rather than baseline weight, may play a more important role.[28] Most studies do not address this issue and group malnourished high-risk patients together with the normal-weight population, causing a selection bias. Alternative indices are currently explored as potential prognostic factors of survival and postoperative complications, such as the prognostic nutritional index.[53] Additionally, visceral fat area (VFA) has been proposed as a better predictor of the difficulty of gastric resection than BMI,[54–56] but its widespread use is yet to come.

Several limitations of our study should be mentioned. First, all studies were retrospective, so their results could have been influenced by confounding factors. Nevertheless, all the studies included in this meta-analysis were rated as high quality. Second, the studies were heterogenic including different types of surgery (laparoscopic and open procedures) as well as different types of gastrectomies (open and total). We tried to tackle this issue by performing stratified analyses based on these factors. Third, a risk of publication bias exists, even though no significant such was detected by

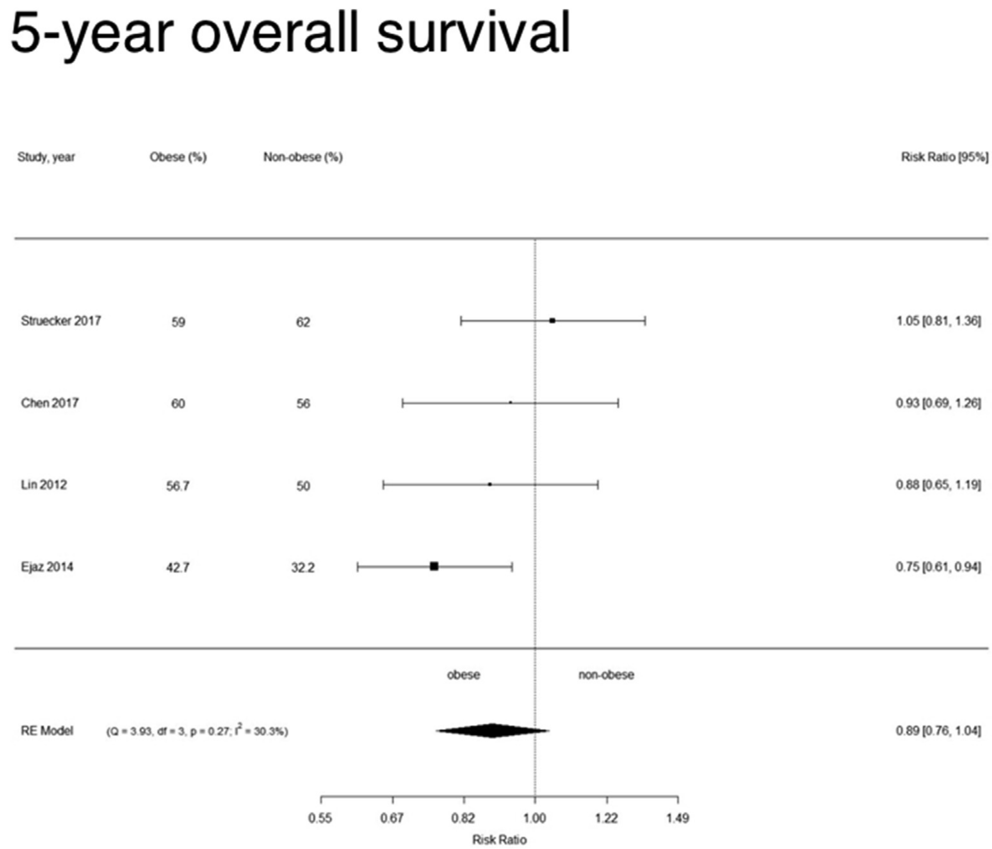

Fig. 9. Forest plots evaluating the impact of obesity on 5-year overall survival.

our confirmatory analysis. Fourth, the definition of complications' severity may differ between studies. Fifth, a stratified and thus more precise analysis of outcomes based on several BMI categories was not feasible with the available data. Finally, although BMI is a widely accepted index, it is a quite rough criterion to discriminate overweight and obesity, not taking into account the distribution of adipose tissue in the body, which is highly relevant for surgeons and may differ substantially between individuals.

In conclusion, our results indicate that obese patients have longer operation times, but otherwise similar operative outcomes compared to non-obese patients after surgery for gastric cancer. The overall risk of postoperative adverse events is significantly higher in obese patients, in particular pulmonary complications. Despite that, high BMI has no negative impact on short- and long-term survival, indicating that gastrectomy is a safe procedure for obese patients. Further research should focus on the development of novel indices that can more accurately calculate the operative risk related to obesity, ideally including the presence or absence of associated metabolic comorbidities as well as patients' nutritional status and weight loss prior to surgery, hopefully producing more uniform results.

Conflicts of Interest/Disclosures: The authors have no related conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2021.04.033.

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