European Journal of Surgical Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Arterial calcification is a risk factor for anastomotic leakage after esophagectomy: A systematic review and meta-analysis

Vincent T. Hoek [a,*], Pim P. Edomskis [a], Anand G. Menon [b], Gert-Jan Kleinrensink [c], Sjoerd M. Lagarde [a], Johan F. Lange [a,b], Bas P.L. Wijnhoven [a]

[a] Department of Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Department of Surgery, IJsselland Ziekenhuis, Capelle aan den IJssel, the Netherlands
[c] Department of Neuroscience-Anatomy, Erasmus University Medical Center, Rotterdam, the Netherlands

A R T I C L E I N F O

Article history:
Received 13 April 2020
Received in revised form
8 June 2020
Accepted 12 June 2020
Available online xxx

Keywords:
Calcification
CT-Scan
Anastomotic leakage
Risk factor
Esophagectomy

A B S T R A C T

Background: Leakage of the esophago-gastrostomy after esophagectomy with gastric tube reconstruction is a serious complication. Anastomotic leakage occurs in up to 20% of patients and a compromised perfusion of the gastric tube is thought to play an important role. This meta-analysis aimed to investigate whether arterial calcification is a risk factor for anastomotic leakage in esophageal surgery.
Method: Embase, Medline, PubMed, Cochrane databases and Google scholar databases were systematically searched for studies that assessed arterial calcification of the thoracic aorta, celiac axis including its branches, or the superior mesenteric artery in patients that underwent esophagectomy with gastric tube reconstruction. The degree of calcification was classified as absent, minor or major. A “random-effects model” was used to calculate pooled Odds Ratios (OR) and 95% confidence intervals (CI). Heterogeneity was assessed using the Q-test and I^2-test.
Results: From the 456 articles retrieved, seven studies were selected including 1.860 patients. The median (range) of anastomotic leakage was 17.2% (12.7−24.8). Meta-analysis showed a statistically significant association between increased calcium score and anastomotic leakage for the thoracic aorta (OR 2.18(CI 1.42−3.34)), celiac axis (OR 1.62(CI 1.15−2.29)) and right post-celiac axis (common hepatic, gastroduodenal and right gastroepiploic arteries) (OR 2.69(CI 1.27−5.72)). Heterogeneity was observed for analysis on calcification of the thoracic aorta and celiac axis ($I^2 = 71\%$ and 59%, respectively) but not for the right branches of the celiac axis ($I^2 = 0\%$).
Conclusion: This meta-analysis, including good quality studies, showed a statistically significant association between arterial calcification and anastomotic leakage in patients who underwent esophagectomy with gastric tube reconstruction.

Introduction

Anastomotic leakage after esophagectomy with gastric tube reconstruction is a serious complication and occurs in up to 20% of patients [1]. Although some leaks can be managed in a conservative way, most patients need reinterventions ranging from percutaneous drainage to surgery. Anastomotic leaks may lead to a prolonged hospital stay, increased in-hospital mortality, increased costs and decreased quality of life [1,2]. Moreover, a recent study showed that the occurrence and severity of anastomotic leakage, after minimally invasive esophagectomy, negatively affects long-term survival of esophageal cancer patients [3]. Hence, reducing the risk of anastomotic leakage is important to improve the care for patients that undergo esophagectomy.

Several studies identified risk factors for anastomotic leakage including age of the patient, nutritional status, smoking behavior, body mass, use of neoadjuvant therapy, cardiac comorbidity, renal insufficiency and diabetes mellitus [4,5]. Smoking, neoadjuvant radiotherapy, hypertension and diabetes all share the potential to compromise the (micro)vascularization at the site of the anastomosis potentially leading to insufficient blood flow of the gastric

* Corresponding author. Department of Surgery, Erasmus University Medical Center, Wytemaweg 80, 3015 CN, Rotterdam, Room Ee-173, the Netherlands.
E-mail address: v.hoek@erasmusmc.nl (V.T. Hoek).

https://doi.org/10.1016/j.ejso.2020.06.019

Please cite this article as: Hoek VT et al., Arterial calcification is a risk factor for anastomotic leakage after esophagectomy: A systematic review and meta-analysis, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.06.019

tube, which may be the main contributing factor for anastomotic leakage [6,7]. Vascular calcification is one of those potential compromising factors, hypothetically causing impaired blood flow. Although, impaired perfusion and oxygenation is a multifactorial problem and the amount in which calcification plays a role has to be defined.

Partial devascularization of the stomach is needed to pull up the stomach and use it as a conduit after esophagectomy. This leads to a compromised perfusion of the gastric tube and may lead to poor oxygenation at the site of the esophagogastric anastomosis [8].

In colorectal surgery, several studies reported on an association between vascular calcification and anastomotic leakage [9–11]. This may have clinical consequences and in patients at high risk for anastomotic leakage a defunctioning protective stoma may be created to limit clinical consequence of anastomotic leakage.

Van Rossum et al. found that arterial calcification was associated with the presence of anastomotic leakage in patients after esophagectomy with gastric tube reconstruction [12]. Whilst some studies confirmed this observation [13–17], Jefferies et al. did not [18].

Therefore, the aim of this study was to investigate whether arterial calcification is a risk factor for anastomotic leakage in patients after esophagectomy with gastric tube reconstruction.

Methods

The study protocol was published in the International Prospective Register of Systematic Reviews database (www.crd.york.ac.uk/prospero/), registration number CRD42020157628. The Preferred Reporting Items for Systematic Review (PRISMA) guidelines were used [19]. A biomedical information specialist performed a literature search on the June 14, 2019. The search was updated on the November 19, 2019. Embase, MEDLINE, Pubmed, Cochrane and Google Scholar were searched. The following search terms were used: calcification OR cardiovascular calcification OR calcium score OR calcium scoring OR calcinosis OR calcium OR arteriosclerosis AND anastomosis leakage OR anastomotic leak or anastomotic rupture or anastomotic tear or anastomotic heal. References of relevant articles were also manually reviewed to identify possible relevant studies [20].

Study selection

Studies that met the following inclusion criteria were selected: studies that assessed the association between calcification of the aorta-iliac trajectory (as measured by CT-scanning) and anastomotic leakage after esophagectomy with gastric tube reconstruction. Inclusions were restricted to studies in the English or Dutch language and studies in humans only. Studies including patients under eighteen years of age, case reports, comments, reviews, letter to the editor or studies where no full-text was available were excluded. Two researchers (P.E. and V.H.) screened all retrieved studies independently. First, studies were screened based on title and abstract. Thereafter, the full articles were read and screened for eligibility. When disagreement in article selection occurred, consensus was sought after discussion between the two researchers.

Data extraction

Data extraction was performed by both researchers (V.H. and P.E.) independently. Standard forms were used covering study characteristics (year of publication, journal, study design), baseline characteristics (number of patients, sex, age, body mass index, comorbidities, use of drugs, smoking habits, neoadjuvant radiotherapy, follow-up), operative characteristics (type of surgery, type of anastomosis, emergency or elective procedure), outcome characteristics (anastomotic leakage), calcification characteristics (type of calcium measurement, arteries screened). The calcium score introduced by van Rossum et al. is presented in detail in Appendix Table 3 [12]. Due to missing data in some studies, absolute numbers did not always match up to total amounts of patients. Discrepancies were resolved by discussion and consensus was sought amongst the two researchers. Corresponding authors were contacted when incomplete or uncertain study results were found.

Bias and quality assessment

The methodological quality assessment was carried out using the Methodological Index of Non-Randomized Studies (MINORS) score [21]. Methodological quality was considered as follows: MINORS score under 12 as poor, 12–17 as moderate and over 17 as good. Assessment of duration of follow-up for each study within the MINORS score system was as follows: 0 points is not reported, 1 point is less than 14 days, 2 points is more or equal to 14 days. Quality assessment was performed by two authors (P.E. and V.H.) and discrepancies resolved by consensus.

Statistical analysis

A meta-analysis was performed for the following vascular trajectories: thoracic aorta, celiac axis, right post-celiac axis (common hepatic, gastroduodenal and right gastroepiploic arteries) and left post-celiac axis (splenic and left gastroepiploic arteries). Presence of calcification was compared with absence of calcification in every single trajectory named above. Patients with minor- and major calcification, defined by the calcium score of van Rossum et al., were incorporated into the group 'calcification present' (Table Appendix 3) [12]. Also, 'calcification absent' was compared with 'major calcification' if applicable [12]. In addition, subgroup analysis according to site of the anastomosis (cervical- and intrathoracic anastomosis) was performed. Calculation of pooled odds ratios (ORs), were performed using the random-effects model, which takes between-study and within-study variance into account. A 95% Confidence Interval (CI) was calculated to evaluate the statistical difference between the calcium score and the association with AL. The heterogeneity was assessed by calculating Q statistics and the I^2 statistic. I^2 results were considered as follows: under 30% as low, 30–60% as moderate and over 60% as substantial heterogeneity. Continuous variables were presented as mean (SD) or median (IQR) depending on distribution. Analyses were performed using R (version 3.4.1.). A P value < 0.05 (two-tailed) was considered statistically significant.

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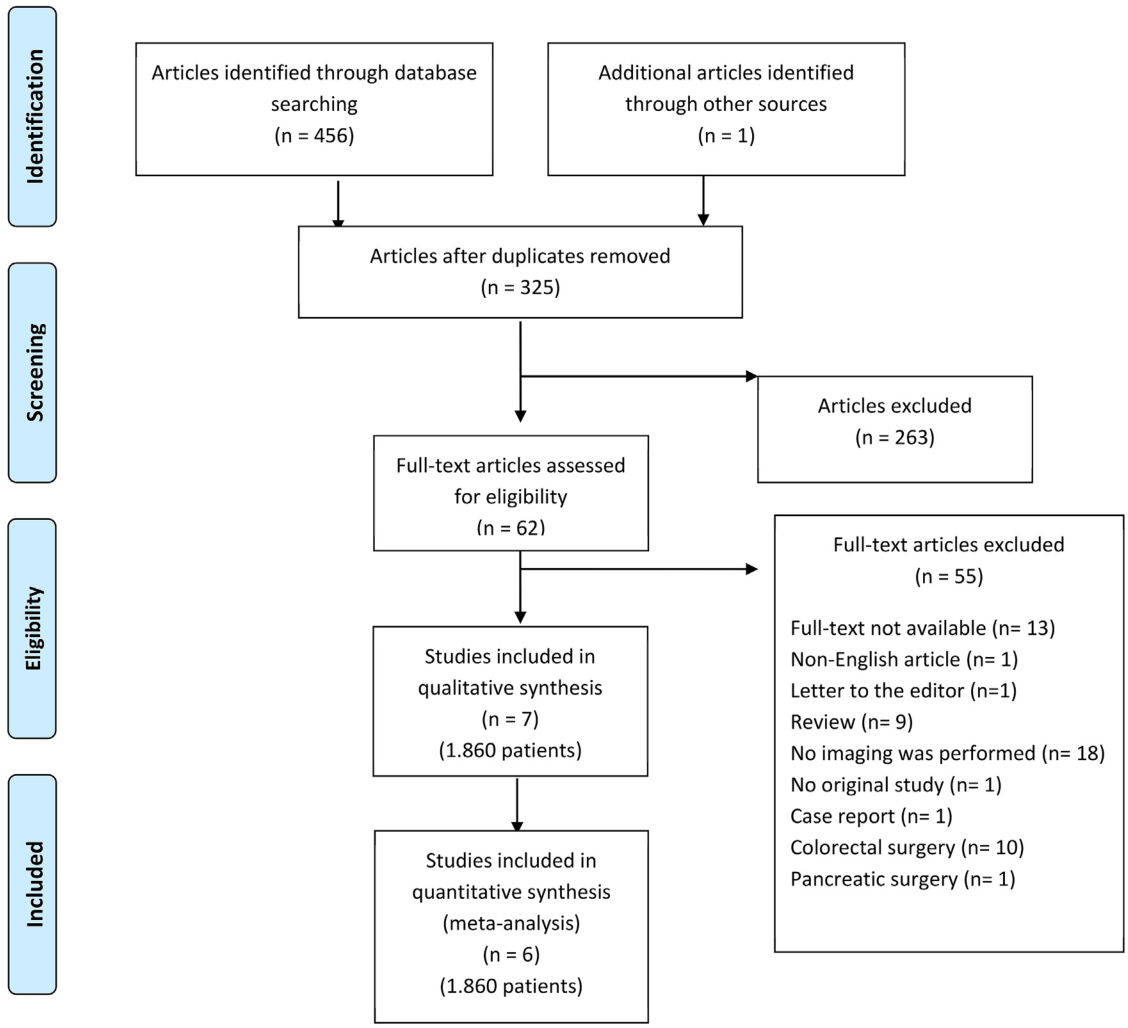

Fig. 1. Flow diagram.

Results

Study selection

Detailed search results are shown in the PRISMA flow diagram in Fig. 1. In total, seven studies involving 1.860 patients were included.Articles were checked for the possibility of duplicate publication (identical or very similar data are published in multiple papers) [22]. The study by Borggreve et al. (2018) and van Rossum et al. (2014) used the same institutional database [12,15]. Borggreve et al. was the most recent study and was therefore included in the total patient count. The study by van Rossum et al. was not excluded because additional trajectories were measured compared to Borggreve et al. For the meta-analysis only one of these two studies was included and when both studies were eligible Borggreve et al. was chosen. In addition, Chang et al. and Brinkmann et al. included patients treated in the same hospital during the same time period and may have used the same cohort [16,17]. Therefore, only the study by Chang et al. was included in the meta-analysis since the reported calcium scores were more relevant for our analysis.

Study characteristics

There were six retrospective cohort studies [12–16,18] and one prospective cohort study [17]. All patients underwent elective esophagectomy with gastric tube reconstruction for malignancy. Some 331 patients had an intrathoracic anastomosis (Ivor-Lewis procedure), 1.115 patients had a cervical anastomosis and in 414 patients the site of the anastomosis was not defined. Study characteristics, patient's and treatment characteristics and operative details are shown in Table 1 and Table Appendix 4 and Appendix 5.

Assessment of bias of the studies

The median (IQR) MINORS score for bias was of 18 [18–20]. Overall, the quality of the included studies was defined as good (MINORS score >17). CT-scans were analyzed in a blinded fashion for patient outcomes in all studies. Only two studies reported the duration of follow-up. No studies reported possible loss to follow-up [12,14]. Brinkmann et al. was the only prospective study [17]. None of the studies reported on a sample size calculation. Chang et al. did not perform a multivariable analysis and was therefore

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Table 1
Study characteristics.

Author	Year	Centers (n)	Design	Study period	Included patients (n)	Type of surgery	Measurement of calcification	Trajectories reviewed	Follow-up duration	Losses to follow-up (n)
Borggreve(15)	2018	1	retro	Oct 2003–Oct 2015	406	Esophagectomy with cervical anastomosis	Calcium score[a]	Supra-aortic arteries, coronary arteries, aortic valve, thoracic aorta, abdominal aorta, celiac axis, common iliac arteries (left and right), external iliac arteries (left and right)	n.r.	n.r.
Brinkmann(17)	2019	1	pro	Jan 2014–Dec 2014	154	Esophagectomy with intrathoracic anastomosis	Nascet formula	Celiac axis, superior mesenteric artery	n.r.	n.r.
Chang(16)	2018	1	retro	Jan 2014–Dec 2014	164	Esophagectomy with intrathoracic anastomosis	Nascet Formula and Calcium score[a]	Thoracic aorta, celiac axis, right post-celiac arteries, left post-celiac arteries	n.r.	n.r.
Goense(13)	2016	2	retro	April 2012–March 2015	167	Esophagectomy with intrathoracic anastomosis	Calcium score[a]	Thoracic aorta, celiac axis, right post-celiac arteries, left post-celiac arteries	n.r.	n.r.
Jefferies(18)	2019	1	retro	2006–2018	414	Esophagectomy with esophagogastric anastomosis	Calcium score[a]	Proximal aorta, celiac axis, right post-celiac arteries, left post-celiac arteries, distal aorta, aortic bifurcation	n.r.	n.r.
van Rossum(12)	2014	1	retro	2003–2012	246	Esophagectomy with cervical anastomosis	Calcium score[a]	Thoracic aorta, celiac axis, right post-celiac arteries, left post-celiac arteries	30 days	n.r.
Zhao(14)	2016	1	retro	Jan 2010–may 2015	709	esophagectomy with cervical anastomosis	Calcium present yes/no.	Thoracic aorta, celiac axis, right post-celiac arteries, left post-celiac arteries	>3 months	n.r.

[a] Calcium score introduced by van Rossum et al.; n.r = not reported; pro = prospective cohort study; retro = retrospective cohort study.

given one point for statistical analysis [16]. The MINORS score for each study is shown in Table 2.

Anastomotic leak

The median (range) anastomotic leakage rate was 17.2% (12.7–24.8). For cervical anastomoses the leakage rate was 21.4% (17.2–25.6) and for intrathoracic anastomoses this was 16.3% (8.5–24).

Arterial calcification and anastomotic leak

Van Rossum et al. and Zhao et al. reported a statistically significant association between anastomotic leakage and calcification of the thoracic aorta and right post-celiac branches [12,14]. Goense et al. found a significant correlation between thoracic aortic calcification and anastomotic leakage [13]. Borggreve et al. reported an association between anastomotic leakage and calcification of the coronary arteries, supra-aortic arteries (i.e. the brachiocephalic trunk, left common carotid artery and left subclavian artery) and

Table 2
Methodological Item for Non-Randomized Studies (MINORS) score.

Methodological item for non-randomized studies	Borggreve(15)	Brinkmann(17)	Chang(16)	Goense(13)	Jefferies(18)	van Rossum(12)	Zhao(14)
1. A clearly stated aim	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	2	2	2	2	2	2	2
6. Follow-up period appropriate to the aim of the study	0	0	0	0	0	2	2
7. Loss to follow up less than 5%	0	0	0	0	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0	0
Additional criteria in the case of comparative studies							
9. An adequate control group	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	1	2	2	2	2
Total score	18	18	17	18	18	20	20

24 point is the maximum score, 0 = not reported, 1 = reported but not adequate, 2 = adequate reported; Methodological quality was considered as follows: MINORS score under 12 as poor, 12–17 as moderate and over 17 as good.

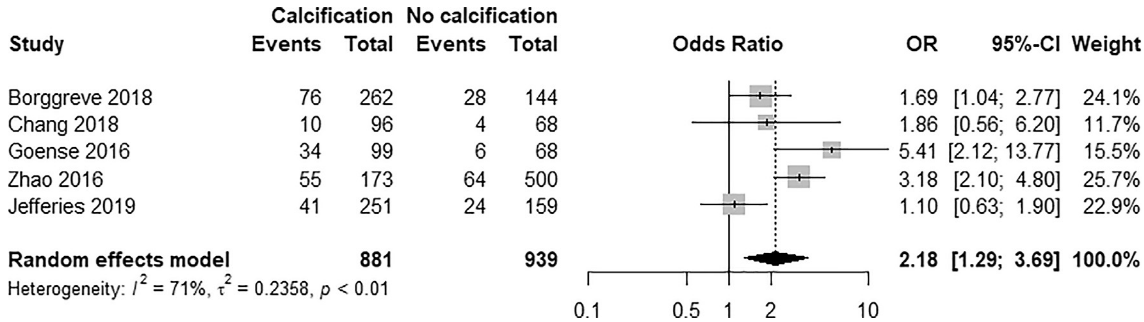

Fig. 2. Thoracic aorta, calcification present vs not present.

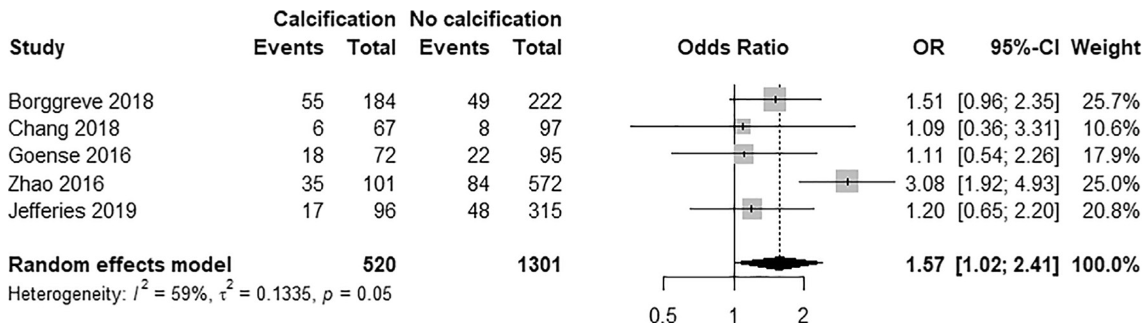

Fig. 3. Celiac axis, calcification present vs not present.

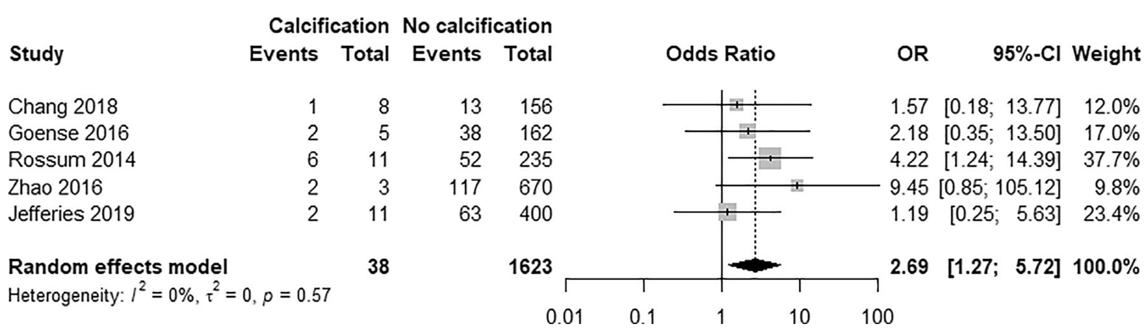

Fig. 4. Right post-celiac axis, calcification present vs not present.

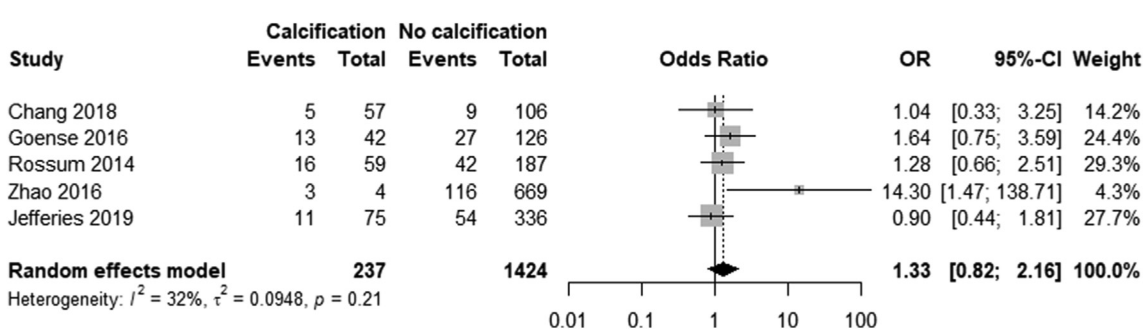

Fig. 5. Left post-celiac axis, calcification present vs not present.

thoracic aorta [15]. Brinkmann et al. and Chang et al. found an association between celiac axis stenosis and anastomotic leakage [16,17]. In contrast with other publications, Jefferies et al. found no association between calcification and anastomotic leak rate [18].

Five of seven studies used the calcium score described by van Rossum et al. [12,13,15,16,18]. The calcium score (0–2) contains the following descriptions: 0 (calcification absent), 1 (minor calcification), 2 (major calcification) [12]. Zhao et al. only reported presence (yes or no) of calcification [14].

A meta-analysis was performed on six studies comprising a total of 1.860 patients. Pooled odds ratios of 2.18 (CI 1.29–3.69, $I^2 = 71\%$) in the thoracic aorta, 1.57 (CI 1.02–2.41, $I^2 = 59\%$) in the celiac axis, 2.69 (CI 1.27–5.72, $I^2 = 0\%$) in the right-post celiac axis and 1.33 (CI 0.82–2.16, $I^2 = 32\%$) left-post celiac axis were found (Figs. 2-5). A calcium score of 2 was compared with a calcium score of 0 in the thoracic aorta and celiac axis. The calcium score of both post-celiac arteries was limited to 0 or 1 due to the small diameter and could not be included in this analysis. Zhao et al. was excluded due to the more simplified scoring system, only presence of calcification was scored [14]. A pooled OR of 2.26 (CI 1.25–4.08, $I^2 = 45\%$) in the thoracic aorta and 1.53 (CI 0.96–2.42, $I^2 = 0\%$) in the celiac axis was found (Supplementary Figs. 6–7).

Calcium score and leak rate according to site of anastomosis

The study by Jefferies et al. which did not discriminate between intrathoracic and cervical anastomosis was excluded for the subgroup analysis [18]. Three studies, containing 1.115 patients, analyzed only cervical anastomoses, a pooled OR of 2.35 (CI 1.27–4.36, $I^2 = 73\%$) in the thoracic aorta and 2.15 (CI 1.06–4.34, $I^2 = 79\%$) in the celiac axis was found (Appendix Figs. 8–9). Only van Rossum et al. and Zhao et al. analyzed the right and left post-celiac axis, containing 919 patients, an OR of 4.98 (CI 1.67–14.87, $I^2 = 0\%$) in the right-post celiac axis and 3.32 (CI 0.33–33.45, $I^2 = 75\%$) in the left post-celiac axis was found (Appendix Figs. 10–11). Two studies analyzed only intrathoracic anastomoses, including 331 patients, finding a pooled OR of 3.40 (CI 1.20–9.60, $I^2 = 47\%$) in the thoracic aorta, 1.10 (CI 0.60–2.01, $I^2 = 0\%$) in the celiac axis, 1.90 (CI 0.47–7.69, $I^2 = 0\%$) in the right-post celiac axis and 3.18 (CI 0.25–40.53, $I^2 = 0\%$) left post-celiac axis (Appendix Figs. 12–15).

Discussion

This study showed an association between anastomotic leakage after esophagectomy with gastric tube reconstruction and calcification of the thoracic aorta, celiac axis and right post-celiac axis. A logical explanation for this finding is that vascularization of the gastric tube is (in)directly supplied via the celiac axis and more specifically via the right post-celiac axis branches. Only the left post-celiac axis (splenic-and left gastroepiploic arteries) was not associated with anastomotic leakage and could be explained by the fact that these arteries are not contributing to the blood supply of the gastric conduit.

Cervical anastomoses have a higher incidence of anastomotic leakage compared to the intrathoracic anastomoses. In the neck, the anastomosis is created more towards the tip of the gastric tube. The vascularization of this part of the gastric tube is thought to be worse due to the lack of direct blood flow from the right gastroepiploic artery [4]. In the subgroup analysis, only an association between anastomotic leakage and calcification of the celiac axis and right post-celiac axis was found for intrathoracic anastomoses. This may be explained by the small number of patients in this group but also by a better perfusion of the gastric tube at the site of the anastomosis in patients with an intrathoracic anastomosis. In patients with a cervical anastomosis, calcification of the arteries may be more crucial given the indirect submucosal blood flow at the distal end of the gastric tube where the anastomosis is created. Hence, the present study showed a significant association between all sites of calcification and anastomotic leakage.

Van Rossum et al. calculated the calcium score to assess the association between arterial calcification and anastomotic leak after esophagectomy. This score was introduced in cardiology to assess calcification of aortic wall abnormalities to predict cardiovascular events [23]. The score is easy to assess without special software and with high intra- and interobserver reliability [12,15,23]. It has to be noted that this score does not take into account the absolute percentage of stenosis. Secondly, long small calcifications are not differentiated from stenoses with a relatively large diameter. In addition, an increased calcium score gives a general vascular impression but does not necessarily mean the actual perfusion of the anastomosis is impaired.

Vascular calcification is associated with impaired blood flow and could thereby restrict perfusion and oxygenation. However, blood pressure, collateral vascularization and percentage of stenosis may also influence blood flow and should be considered. No prospective studies looking at anastomotic perfusion pressure in relation to a preoperative calcium score have been conducted. It is important to know whether the calcium score is indeed related to impaired perfusion at the site of the anastomosis. Patients may benefit from interventions to optimize the perfusion pressure of the gastric tube. Indeed, some interventions and techniques have been described previously. For example, leaving the collaterals of the left gastroepiploic artery in situ to maintain the blood flow by taking a wide omental flap, improvement of microcirculation by transient bloodletting of the short gastric vein, construction of microvascular anastomoses by recipient vessels at the level of the gastric tube or preoperative embolization/division of the left post-celiac axis (or left gastric artery) to stimulate grow of collateral vascularization [24–28]. However, most of these approaches are not used in clinical practice due to the absence of good clinical studies supporting the efficacy of the intervention. If a calcium score represents the individual risk for anastomotic leakage, it remains difficult which preventive clinical measures can be taken. Changing the surgical approach (i.e. creation of a intrathoracic anastomosis instead of at the cervical site) and closely monitoring patients with high calcium scores postoperatively for anastomotic leaks may be recommended.

Recently, intraoperatively measurement of perfusion by indocyanine green fluorescence angiography has been introduced to estimate the perfusion of the gastric tube in vivo and to select the optimal site of anastomosis on the gastric tube [29]. Randomized-controlled trials are warranted to verify its usefulness and benefit for the patient.

The risk for anastomotic leakage is likely to be multifactorial and cannot be predicted by a calcification score only. Besides patient-related factors (e.g. age, nutrition, body mass,

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neoadjuvant therapy, smoking, cardiac comorbidities, renal insufficiency and diabetes mellitus) [4], also the width of the gastric tube, anastomotic technique (end-to-side, end-to-end, stapling versus hand sown) and congestion due to insufficient venous drainage may all be important factors for anastomotic leakage [30–32].

Our study differs from the recent systematic review by Knight et al. on aortic calcification and anastomotic leakage in esophageal and colorectal surgical procedures [33]. Vascularization of the remnant large bowel after (partial) colectomy is via collateral blood supply of the mesenteric arteries and arcade. Especially in patients with atherosclerosis, the number of collaterals seem to increase [34–36]. The gastric tube is not perfused by collateral branches. Furthermore, our study included an additional three studies compared to Knight et al.

This study has several limitations. Only a limited number of original studies could be identified and all studies, except Brinkmann et al. were retrospective which could have introduced selection and information bias

Also, only a small number of patients were included. Furthermore, in only 38 of 1661 patients (2.3%) calcification in the right-post celiac axis was detected. A funnel plot, to assess publication bias, and meta-regression analysis were not performed due to the relatively small number of studies in the meta-analysis. Hence, no adjustment for risk factors (i.e. age, cardiovascular disease, age, diabetes, smoking) could be performed within the present study. Although, most of the individual studies did incorporate some of the confounders in a multivariable logistic regression. Moderate to substantial heterogeneity was observed in the meta-analysis of calcification of the thoracic aorta and celiac axis, but a low heterogeneity was found in the analysis of the right post-celiac axis. Surgical approach and variances in prevalence of confounders (i.e. cardiovascular disease, diabetes, age, race, smoking) between included studies could explain for the heterogeneity. Therefore, a random-effects model was chosen.

Despite these limitations, this meta-analysis showed a statistically significant association between anastomotic leakage and calcification of the thoracic aorta, celiac axis and right post-celiac axis in patients who underwent esophagectomy with gastric tube reconstruction. This score can be used for better risk assessment preoperatively. Whether an increased calcium score is related to impaired anastomotic perfusion has to be validated during a prospective cohort study. Furthermore, whether subsequently the risk could be mitigated through interventions also warrants further investigation.

Funding/Support

Nothing to disclose.

Declaration of competing interest

None.

Acknowledgments

The authors thank Wichor Bramer, biomedical information specialist at the Erasmus Medical Center, for his assistance with the search strategy and syntax.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2020.06.019.

Appendix Table 3
Calcium score by van Rossum et al. [12], definitions Used to Grade Calcification of the Supplying Arteries of the Gastric Tube Seen on Preoperative CT Images

Artery	Score 0	Score 1	Score 2
Aorta*	Absent	Minor calcifications: nine or fewer foci and three or fewer foci extending over three or more sections	Major calcifications: more than nine foci or more than three foci extending over three or more sections
Celiac axis	Absent	Minor calcifications: extending over fewer than three sections or MCSD of single focus 10 mm or smaller	Major calcifications: extending over three or more sections and MCSD of single focus larger than 10 mm or involving both the proximal (aortoceliac) and distal (hepatosplenic bifurcation) parts
Right post-celiac axis†	Absent	One or more calcifications	Not applicable
Left post-celiac axis‡	Absent	One or more calcifications	Not applicable

MCSD = maximum cross-sectional diameter.
*Aorta defined as descending part of thoracic aorta and abdominal part of aorta above celiac level.
†Right postceliac arteries defined as common hepatic artery, gastroduodenal artery, and right gastroepiploic artery.
‡Left postceliac arteries defined as splenic artery and left gastroepiploic artery.

Appendix Table 4
patient and treatment characteristics

Author	Year	n	Sex(M/F, n,%)	Age(years)	BMI(kg/m2)	ASA(n, %)	Neoadjuvante Chemoradiotherapy (n,%)	Neoadjuvante chemotherapy (n,%)
Overall								
Borggreve (15)	2018	406	300/ 106(73.9/ 26.1)	64	n.r.	I 89(21.9) II 248(61.1) III 68(16.7) IV 1(0.3)	153(37.7)	122(30.0)
Brinkmann (17)	2019	154	117/ 37(76.0/ 24.0)	62(52−72)	26.2(21.4 −31.0)	I and II 100(64.9) III and IV 54(35.1)	124(80.5)	n.r.
Chang(16)	2018	42	122/ 42(74.4/ 25.6)	61(30−86)	26(21.2 −30.8)	n.r.	n.r.	n.r.
Goense (13)	2016	167	139/ 28(83.2/ 16.8)	n.r.	n.r.	I 13(7.8) II 115(68.9) III 39(23.3) IV 0(0)	8(4.8)	145(86.9)
Jefferies (18)	2019	413	326/ 87(78.9/ 21.1))	64.8(55.3 −74.3)	26.8(21.9 −31.7)	I 78(19.6) II 222(55.9) III 89(22.4) IV 8(2.0)	n.r.	344(83.3)
van Rossum (12)	2014	246	180/ 66(73.2/ 26.8).	n.r.	n.r.	I 58(23.6) II 149(60.6) III 38(15.4) IV 1(0.4)	22(8.9)	112(45.5)
Zhao(14)	2016	709	567/ 142(80.0/ 20.0)	59.2(51.2 −67.2)	23.4(20.1 −26.7)	I 145(20.4) II 499(70.4) III 65(9.2) IV 0(0)	54(7.6)	12(1.7)
Anastomotic leakage group								
Borggreve (15)	2018	104	82/22(78.8/ 21.2)	65.5(56.7 −74.3)	25.8(21.5 −30.1)	I 23(22.1) II 55(52.9) III 26(25.0, IV 0(0.0)	40(38.5)	26(25.0)
Brinkmann (17)	2019	15	9/6(60.0/ 40.0)	62(58.5 −65.5)	26.7(21.6 −31.8)	I and II 8(53.3) III and IV 7(46.7)	13(86.7)	n.r.
Chang(16) .	2018	14	n.r.	n.r.	26(21.2 −30.8)	n.r.	n.r.	n.r.
Goense(13)	2016	40	34/6(85.0/ 15.0)	66.5(57.3 −75.7)	26.8(20.9 −32.7)	I 4(10.0) II 29(72.5) III 7(17.5) IV 0(0)	1(2.5)	35(87.5)
Jefferies(18)	2019	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
van Rossum (12)	2014	58	46/12(79.3/ 20.7)	64.9(55.7 −74.1)	25.7(21.4 −30.0)	I 16(27.6) II 30(51.7) III 12(20.7) IV 0(0)	4(6.9)	25(43.1)
Zhao(14)	2016	122	102/ 20(83.6/ 16.4)	58.8(50.6 −67.0)	23.7(20.1 −27.3)	I 17(13.9) II 83(68.0) III 22(18.1), IV 0(0)	9(7.4)	0(0)
No anastomotic leakage group								
Borggreve(15)	2018	302	218/ 84(72.2/ 27.8)	63.7(54.6 −72.8)	25.5(21.2 −29.8)	I 66(21.9) II 193(63.9) III 42(13.9) IV 1(0.3)	113(37.4)	96(31.8)
Brinkmann (17).	2019	139	108/ 31(77.7/ 22.3)	62(51.9 −72.1)	26.2(21.4 −31.0)	I and II 92(66.2), III and IV 47(33.8)	111(79.9)	n.r.
Chang(16)	2018	28	n.r.	n.r.	26(21.2 −30.8)	n.r.	n.r.	n.r.
Goense(13)	2016	127	105/ 22(82.7/ 17.3)	63.5(54.7 −72.3)	26.3(21.9 −30.7)	I 9(7.1) II 86(67.7) III 32(25.2) IV 0(0)	7(5.5)	110(86.6)
Jefferies(18)	2019	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
van Rossum (12)	2014	188	134/ 54(71.3/ 28.7)	63.8(54.6 −73.0)	25.7(21.7 −29.7)	I 42(22.4) II 119(63.3) III 26(13.8) IV 1(0.5)	18(9.6)	87(46.3)
Zhao(14)	2016	587	465/ 122(79.2/ 20.8))	59.3(51.3 −67.3)	23.4(20.2 −26.6)	I 128(21.8) II 416(70.9) III 43(7.3) IV 0(0)	45(7.7)	12(2.0)

n.r = not reported, cardiac comorbidities including hypertension, cardiac comorbidities and vascular disease, Smokers both former and current, *Brinkmann et al. named specific heart diseases and could not be categorized in overall cardiac comorbidities. ^only current smoker, Chang et al. scored mean body mass index (BMI)I and comorbidities based on a total of 42 patients instead of the 164 included except for sex, the American Society of Anesthesiologists (ASA) score, Zhao et al. baseline characteristics were taken of 709 patients, only 673 patients were included in analysis of calcification.

Please cite this article as: Hoek VT et al., Arterial calcification is a risk factor for anastomotic leakage after esophagectomy: A systematic review and meta-analysis, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.06.019

Neoadjuvante radiotherapy (n,%)	Use of steroids (n,%)	COPD(n,%)	Cardiac comorbidity combined (n,%)	History of vascular disease (n,%)	Cardiac comorbidity (n,%)	Hypertension (n,%)	Diabetes mellitus (n,%)	Renal insufficiency (n,%)	Smoker (n,%)	Alcohol (n,%)
Overall										
n.r.	n.r.	61(15.0)	156(38.4)	n.r.	n.r.	n.r.	57(14.0)	n.r.	252(62.1)	n.r. 10(6.5)
n.r.	n.r.	38(24.7)	n.r.	8(5.2)	n.a.*	84(54.5)	23(14.9)	n.r.	82(53.2)	
n.r.	n.r.	n.r.	n.r.	2(4.8)	8(19.0)	n.r.	6(14.3)	n.r.	24(57.1)	n.r.
n.r.	n.r.	27(16.1)	n.r.	11(6.6)	38(22.8)	53(31.7)	28(16.8)	9(5.4)	32(19.2)	n.r.
n.r.	n.r.	31(7.5)	n.r.	n.r.	52(12.6)	n.r.	48(11.7)	4(1.0)	58(14.1)	8(1.9)
n.r.	4(1.6)	34(13.8)	53(21.5)	n.r.	n.r.	n.r.	34(13.8).	n.r.	141(57.3)	n.r.
14(2.0)	8(1.13)	28(4.0)	n.r.	25(3.5)	121(18.0)	177(25.0)	58(8.2)	14(2.0)	432(60.9)	431(60.8)
Anastomotic leakage group										
n.r.	n.r.	24(23.1)	46(44.2)	n.r.	n.r.	n.r.	20(19.2)	n.r.	66(63.5)	n.r.
n.r.	n.r.	6(40.0)	n.r.	1(6.7)	n.a.*	11(73.3)	4(26.7)	n.r.	10(66.7)	1(6.7)
n.r.	n.r.	n.r.	n.r.	1(7.1)	3(21.4)	n.r.	4(28.6)	n.r.	7(50.0)	n.r.
n.r.	n.r.	7(17.5)	n.r.	2(2.0)	12(30.0)	13(32.5)	6(15.0)	2(5.0)	8(20.0)^	n.r.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
n.r.	4(6.9)	11(19.0)	14(24.1)	n.r.	n.r.	n.r.	9(15.5)	n.r.	30(51.7)	n.r.
3(2.5)	3(2.5)	9(7.4)	n.r.	12(9.8)	26(21.3)	43(35.3)	15(12.3)	6(4.9)	77(63.1)	82(67.2)
No anastomotic leakage group										
n.r.	n.r.	37(12.3)	110(36.4)	n.r.	n.r.	n.r.	37(12.3)	n.r.	186(61.6)	n.r.
n.r.	n.r.	32(23.0)	n.r.	7(5.0)	n.a.*	73(52.5)	19(13.7)	n.r.	72(51.8)	9(6.5)
n.r.	n.r.	n.r.	n.r.	1(3.6)	5(17.9)	n.r.	2(7.1)	n.r.	17(60.7)	n.r.
n.r.	n.r.	20(15.7)	n.r.	9(7.1)	26(20.5)	40(31.5)	22(17.3)	7(5.5)	24(18.9)^	n.r.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
n.r.	0(0)	23(12.2)	39(20.7)	n.r.	n.r.	n.r.	25(13.3)	n.r.	111(59.0)	n.r.
11(1.9)	5(0.9)	19(3.2)	n.r.	13(2.2)	95(16.2)	134(22.8)	43(7.3)	8(1.4)	355(60.5)	349(59.5)

Appendix Table 5
per/post-operative characteristics

Author	Year	N	Operation Time(min)	Laprascopic transhiatal(n,%)	Open transhiatal(n,%)	Thoracolaparoscopic(n,%)	Thoracolaparotomic(n,%)	Thorascopic-laparotomic(n,%)	Thorascopic-laparascopic(n,%)
Overall									
Borggreve(15).	2018	406	n.r.	66(16.3)	32(7.9)	245(60.3)	48(11.8)	15(3.7)	n.r.
Brinkmann(17)	2019	154	n.r.	n.r.	n.r.	137(89.0)	17(11.0)	n.r.	n.r.
Chang(16)	2018	42	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Goense(13)	2016	167	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Jefferies(18)	2019	414	n.r.	n.r.	n.r.	224(54.2)	86 (20.8)	n.r.	103 (24.9)
van Rossum(12)	2014	246	n.r.	48(19.6)	30(12.2)	142(57.7)	12(4.9)	14(5.7)	n.r.
Zhao(14)	2016	709	539(76.0)	n.r.	n.r.	348(49.1)	264(37.2)	93(13.1)	4(0.6)
Anastomotic leakage group									
Borggreve(15)	2018	104	343(228−458)	24(23.1)	12(11.5)	59(56.7)	6(5.8)	3(2.9)	n.r.
Brinkmann(17)	2019	15	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Chang(16)	2018	14	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Goense(13)	2016	40	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Jefferies(18)	2019	65	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
van Rossum(12)	2014	58	341(248−434)	13(22.4)	10(17.2)	31(53.4)	1(1.7)	3(5.2)	n.r.
Zhao(14)	2016	122	99(81.2)	n.r.	n.r.	70(57.4)	40(32.8)	12(9.8)	0(0.0)
No anastomotic leakage group									
Borggreve(15)	2018	302	361(261−461)	42(13.9)	20(6.6)	186(61.6)	42(13.9)	12(4.0)	n.r.
Brinkmann(17)	2019	139	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Chang(16)	2018	28	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Goense(13)	2016	127	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Jefferies(18)	2019	346	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
van Rossum(12)	2014	188	367(265−469)	35(18.6)	20(10.6)	111(59.0)	11(5.9)	11(5.9)	n.r.
Zhao(14)	2016	587	440(75.0)	n.r.	n.r.	278(47.4)	224(38.2)	81(13.8)	4(0.7)

n.r = not reported, n.a. = not applicable due to missing- or inconsisting data, Tumor histologie others are adenosquamous carcinoma, mixed adenoneuroendocrine carcinoma and carcinosarcoma, ^Chang et al. presented tumor histology over a total of 42 patients instead of the 164 included in the study except for AL rate, Zhao et al. catagorised operation time in <300 min and >300, * Zhao baseline characteristics were taken of 709 patients but only 673 patients were included in analysis of calcification, Thoracolaparotomic included the open technique from Jefferies et al., Thoracolaproscopic included the hybrid procedure of Jefferies et al., Thorascopic-laparascopic included the minimal invasive esophagecotmie from Jefferies et al.

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End-to-end anastomosis(n,%)	End-to-side anastomosis(n,%)	Side-to-side anastomosis(n,%)	Sutured/ stapled(n, %)	Squamous cell carcinoma(n,%)	Adenocarcinoma (n,%)	Tumor histology, other(n,%)	Mortality (n, %)	Anastomotic leakage(n,%)
Overall								
4(1.0)	400(98.5)	2(0.5)	n.r.	92(22.7).	309(76.1)	5(1.2)	n.r.	104(25.6)
n.r.	n.r.	n.r.	0/154(0/100)	36(23.4)	118(76.6)	0(0)	4(2.6)	15(9.7)
n.r.	n.r.	n.r.	n.r.	13(31.0)	29(69.0)	0(0)	n.a.	14(8.5)^
n.r.	41(24.6)	126(75.4)	41/126(24.6/ 74.4)	n.r.	n.r.	n.r.	n.r.	40(24)
n.r.	n.r.	n.r.	n.r.	65(15.9)	322(78.7)	22(5.4)	n.r.	65(15.8)
9(3.7)	237(96.3)	0(0.0)	n.r.	n.r.	n.r.	n.r.	n.r.	55(30)
n.r.	n.r.	n.r.	230/479(32.4/ 67.6)	690(97.3)	19(2.7)	n.r.	n.r.	122(17.2)
Anastomotic leakage group								
2(1.9)	102(98.1)	0/0(0/0)	n.r.	21(20.2)	82(78.8)	1(1.0)	n.r.	n.a.
n.r.	n.r.	n.r.	0/15(0/100)	n.a.	8(53.3)	n.a.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	6(42.9)	8(57.1)	0(0)	2(14.3)	n.a.
n.r.	10(25.0)	30(75.0)	10/30(25.0/ 75.0)	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	4(6.0)	n.a.
3(5.2)	55(94.8)	0(0)	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	40/82(32.8/ 67.2)	118(96.7)	4(3.3)	n.r.	n.r.	n.a.
No anastomotic leakage group								
2(1.3)	298(98.7)	0/0(0/0)	n.r.	71(23.5)	227(75.2)	4(1.3)	n.r.	n.a.
n.r.	n.r.	n.r.	0/139(0/100)	n.a.	110(79.1)	n.a.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	7(53.8)	21(72.4)	0(0)	1(0.7)	n.a.
n.r.	31(24.4)	96(75.6)	31/96(24.4/ 75.6))	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
6(3.2)	182(96.8)	0(0)	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	190/397(32.4/ 67.6)	572(97.4)	15(2.6)	n.r.	n.r.	n.a.

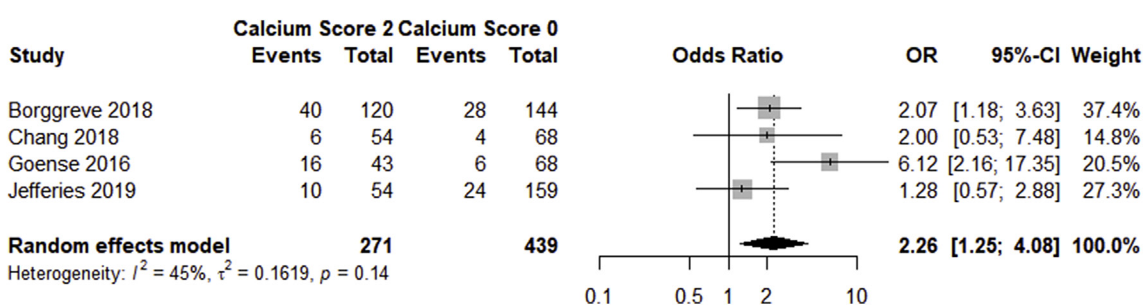

Fig. A6. Thoracic aorta, calcium score 2 vs 0.

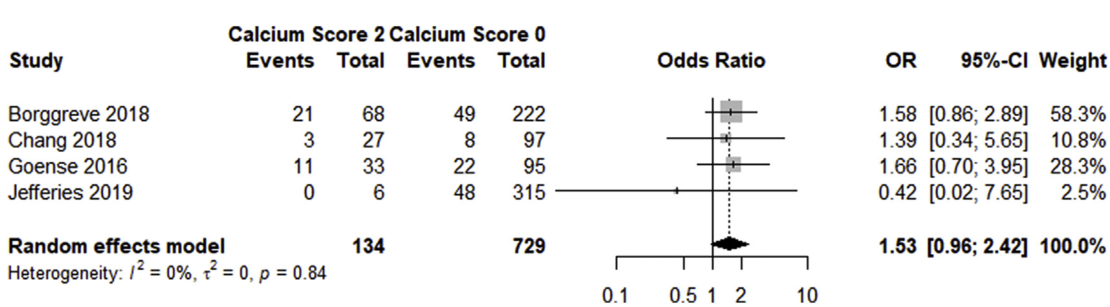

Fig. A7. Celiac axis, calcium score 2 vs 0.

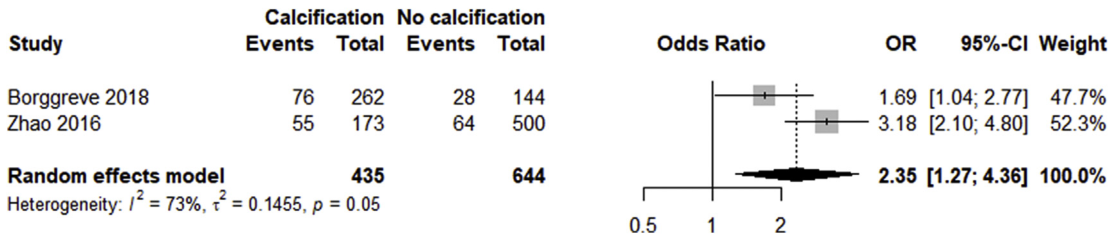

Fig. A8. Thoracic aorta, cervical anastomosis, calcification present vs not present.

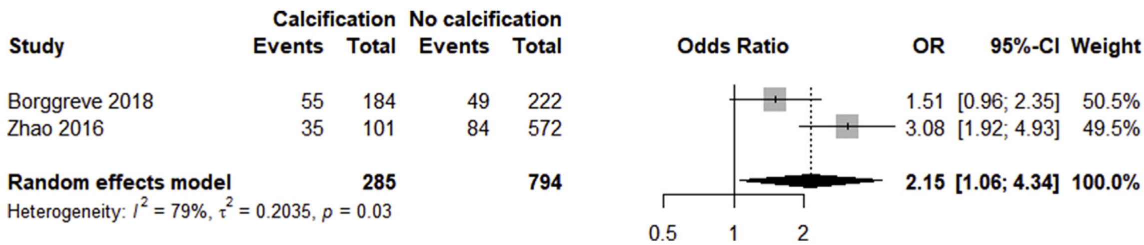

Fig. A9. Celiac axis, cervical anastomosis, calcification present vs not present.

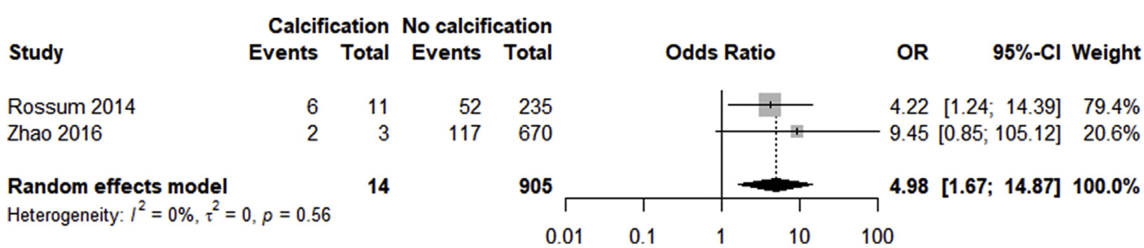

Fig. A10. Right post-celiac axis, cervical anastomosis, calcification present vs not present.

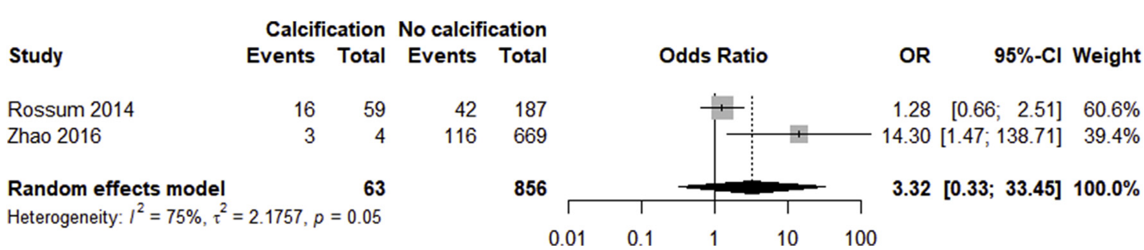

Fig. A11. Left post-celiac axis, cervical anastomosis, calcification present vs not present.

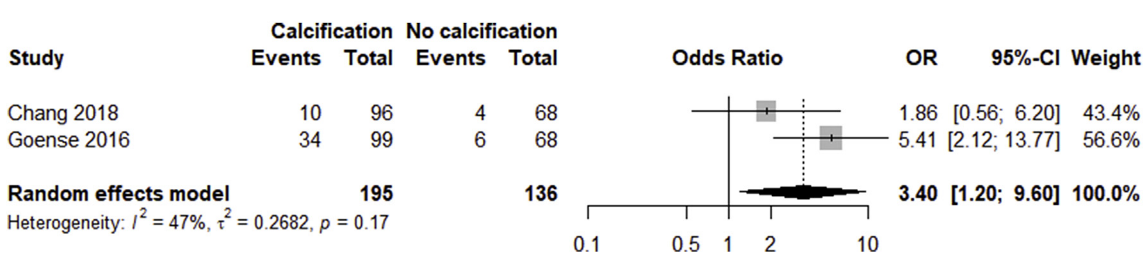

Fig. A12. Thoracic aorta, thoracic anastmosis, calcification present vs not present.

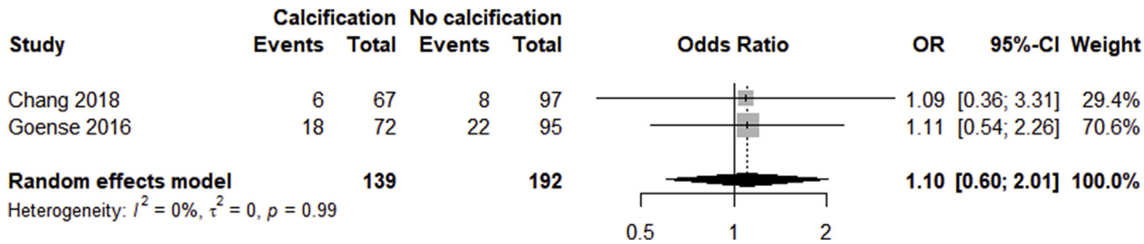

Fig. A13. Celiac axis, thoracic anastomosis, calcifcation present vs not present.

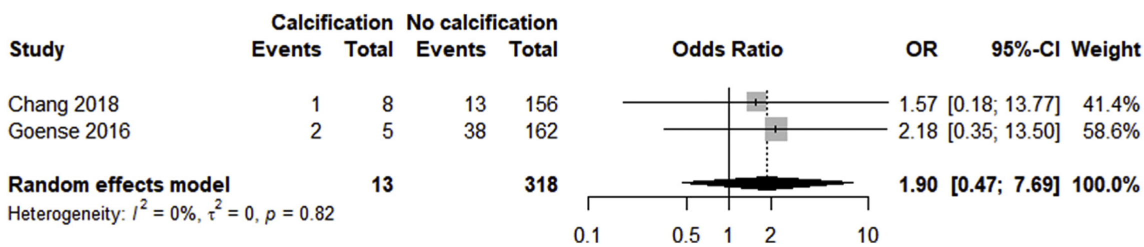

Fig. A14. Right post-celiac axis, thoracic anastomosis, calcification present vs not present.

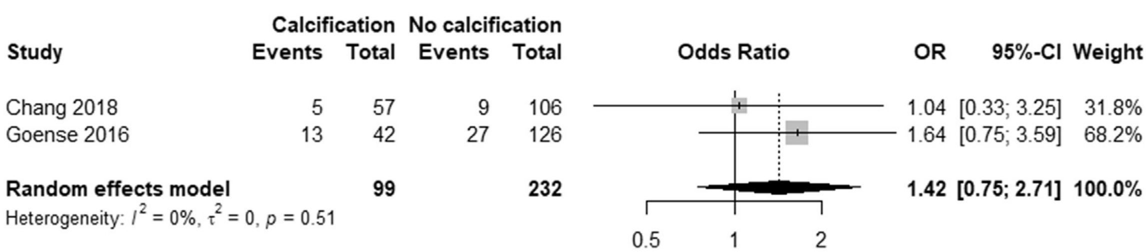

Fig. A15. Right post-celiac axis, thoracic anastomosis, calcification present vs not present.

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Please cite this article as: Hoek VT et al., Arterial calcification is a risk factor for anastomotic leakage after esophagectomy: A systematic review and meta-analysis, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.06.019

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Please cite this article as: Hoek VT et al., Arterial calcification is a risk factor for anastomotic leakage after esophagectomy: A systematic review and meta-analysis, European Journal of Surgical Oncology, https://doi.org/10.1016/j.ejso.2020.06.019