THE RELATIONSHIP BETWEEN AORTIC CALCIFICATION AND ANASTOMOTIC LEAK FOLLOWING GASTROINTESTINAL RESECTION

Aortic calcification and anastomotic leak: A systematic review

KA Knight, PG Horgan, DC McMillan, CSD Roxburgh, JH Park.

Academic Unit of Surgery, Glasgow Royal Infirmary, School of Medicine, University of Glasgow, UK.

Corresponding author:

Katrina Knight

Academic Unit of Surgery

University of Glasgow

Level 2, New Lister Building, Glasgow Royal Infirmary, UK.

G31 2ER

Katrina.Knight@glasgow.ac.uk

Declaration of Interest: none.

Abstract

Background

Anastomotic leak (AL) is a significant complication of gastrointestinal (GI) surgery. Impaired perfusion of the anastomosis is thought to play an important role. The degree of aortic calcification (AC) visible on preoperative CT imaging may be associated with an increased risk of AL following GI resection. This review assessed the relationship between AC and AL in patients undergoing GI resection.

Materials and Methods

MEDLINE, EMBASE and the Cochrane library were systematically searched between 1946 and 2019. Relevant keywords were grouped to form a sensitive search strategy: surgical procedure (e.g. digestive system surgical procedure), calcification (e.g. vascular calcification, calcium score) and outcome (e.g. anastomotic leak). Studies assessing the degree of AC on preoperative imaging in relation to AL in adult patients requiring resection and anastomosis were included. The quality of each study was assessed using the Newcastle-Ottawa scale. Bias was assessed using the RevMan risk of bias tool.

Results

Nine observational studies were included: four in patients undergoing oesophageal resection (n=1446) and five in patients undergoing colorectal resection (n=556). AL occurred in 20% of patients following oesophagectomy and 14% of patients following colorectal resection.

Adjustment for relevant confounders was limited in most studies. Two studies reported a relationship between the degree of AC and AL in patients undergoing oesophagectomy, independent of age and comorbidity.

One study reported an association between AC and AL following colorectal resection, while three studies reported higher calcium scores in the iliac arteries of patients who developed colorectal AL. Overall study quality was moderate to good using the Newcastle-Ottawa scale. Detection and reporting bias was evident in the studies examining AL following colorectal resection.

Conclusion

The current evidence suggests that the degree of AC may be associated with the development of AL, in particular in patients undergoing oesophagectomy. Further prospective data with adequate adjustment for confounders is required.

PROSPERO Registration Number: CRD42018081128.

1 Introduction

The development of anastomotic leak (AL) following gastrointestinal (GI) surgery remains a major arbiter of long-term outcome, with impact on healthcare resource use as well as quality of life and return to function [1-3]. Reported rates vary by site from approximately 15% for oesophageal [4-6] and 10% for colorectal resection [7-8]. Comorbidity is recognised risk factor [7,9]. Regardless of anastomotic site, peripheral vascular (PVD) and cardiovascular disease (CVD) are regarded as predictors of major morbidity and mortality following GI resection [10-14]. However, a proportion of patients undergoing GI resection have subclinical disease that is not detectable on clinical assessment. Identifying such patients requires a more tailored risk assessment.

Vascular calcification occurs early in the development of atherosclerosis [15], a process common to PVD, CVD and related disorders including diabetes and obesity. The degree of coronary arterial calcification on computed tomography (CT) is prognostic of future cardiovascular events in asymptomatic patients, independent of traditional risk factors including smoking and hypertension [16-18]. The burden of aortic calcification (AC) on the preoperative CT has also been associated with postoperative complications after major abdominal surgery [19] and AL following oesophagectomy [20-22].

Several risk factors predispose to AL, although it is well-established that inadequate perfusion resulting in anastomotic ischaemia is a critical component of the pathogenesis. Systemic factors such as global hypoperfusion can predispose to poor perfusion of the opposed bowel ends, while local factors including tension across the anastomosis can restrict adequate flow and result in ischaemia. Limitation of blood flow to the vessels supplying the anastomotic region can compound both systemic and local factors. In patients with a high burden of aortic calcification, flow limitation could be a critical aetiological element in the development of AL. The present systematic review aims to investigate the relationship between AC and AL in patients undergoing GI surgery.

2 Methods

An a priori protocol was developed and published on PROSPERO (CRD42018081128). This review is reported in concordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [23,24].

MEDLINE, Embase and the Cochrane Library was systematically searched from inception to June 2019 with input from an academic librarian. Keywords were grouped under three categories to form a sensitive search strategy: surgical procedure (e.g. digestive system surgical procedure), calcification (e.g. vascular calcification, calcium score) and outcome (e.g. postoperative complications). An example search strategy is displayed in the appendix. The PICO characteristics of the research question used to develop the search strategy are detailed as follows:

- Patients: adults with gastrointestinal disease requiring resection and anastomosis formation
- Intervention: assessment of preoperative CT for the presence of aortic calcification
- Comparator interventions: not applicable
- Outcomes: anastomotic leak
- Study design: observational studies

No restriction was placed on publication status. Articles without an English language translation were excluded. Reference lists of included studies were hand-searched to identify further relevant articles. Authors were contacted to secure relevant information not presented in the studies. The last search was performed on 25.06.2019.

2.1 Data collection and analysis

Two authors (KK and JP) independently screened the titles and abstracts against pre-defined eligibility criteria. The full texts of eligible abstracts were then obtained. One assessor (KK) extracted data including study characteristics, mode of calcification assessment, surgery type and outcome variable(s) reported. Risk of bias was assessed using the Cochrane Collaboration tool (RevMan 5.3, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Methodological quality was evaluated by two authors (KK and JP) using The Newcastle-Ottawa Scale [25]. Discrepancies were resolved by discussion. Qualitative summary of all included studies was undertaken. Meta-analysis was planned if clinically similar studies were available.

3 Results

3.1 Study selection

The study selection process is outlined in Figure 1. The search yielded 667 articles, which after removal of duplicates resulted in 557 articles suitable for screening. Following screening of the title and abstract against the pre-defined inclusion criteria, 539 articles were excluded. The majority were excluded as they involved non-GI surgery in the form of vascular procedures (n=511), did not assess calcification (n=20) or were animal studies (n=4). Studies of patients undergoing liver transplantation or hepaticopancreaticobiliary surgery were also excluded (n=4). Full texts of 18 studies were then reviewed, with a further 9 exclusions at this stage. One study [20] was excluded on the basis that the cohort was included in a more recent study [26]. A total of 9 publications including 2002 patients were included in the qualitative review [21, 22, 26-32].

3.1.1 Characteristics of included studies

Study characteristics are displayed in Table 1. Four studies [21, 22, 26, 31] examined the relationship between aortic calcification and anastomotic leak in patients undergoing oesphagectomy for cancer (n=1446) and five studies [27-30, 32] were undertaken in patients undergoing colorectal resection for benign disease or cancer (n=556). No studies of AC in patients undergoing gastric resection were identified. Seven studies were conducted in

Europe (five in the Netherlands), one in Iran and one in China (Table 1). One study [32] was carried out prospectively and the remainder were retrospective cohort studies, of which one was a case-control study [28]. The studies were published between 2011 and 2018.

3.1.2 Method of assessment and prevalence of aortic calcification

An overview of the method of assessment of aortic calcification by type (visual/software) is presented in Tables 2a and b. Visual grading of aortic calcification was performed in all studies of patients undergoing oesophagectomy. Three studies used a score devised by van Rossum and colleagues [20][20] which categorised AC as absent (score 0), minor (score 1, less than 9 visible foci or less than 3 foci extending over 3 segments) or major (score 2, more than 9 visible foci or more than 3 foci extending over 3 segments) [21, 26, 31]. Visual assessment of AC was used in the study by Zhao et al [22] and categorised AC as absent or present.

The prevalence of AC in patients undergoing oesophagectomy ranged from 56% to 65% in the studies from Europe [21, 26, 31]. Calcification was less prevalent among participants in the study from China (26%) [22]. The aortic trajectory assessed extended from the thoracic aorta to the post-celiac arteries in three of four studies of patients undergoing oesophagectomy [21, 22, 31]. One study also included the coronary and supra-aortic arteries proximally and extended to the iliac arteries distally [26].

Software was used to determine the calcium score of the aorta in four of five studies of patients undergoing colorectal resection [27, 28, 30, 32]. Calcium scores were reported as mean in three studies [27, 28, 30] and by the median by Pochhammer and co-workers [32].

The study by Eveno and colleagues [29] used visual assessment of the degree of circumferential AC to grade it as absent, minor (<50%) or major (>50%).

The prevalence of AC in patients undergoing colorectal resection was reported in one study at 82% [29]. It was not possible to estimate the prevalence in the studies using software as only the mean or median calcium score was reported; absence of calcification was not reported. The trajectory assessed included the descending aorta and iliac arteries in four studies [27, 28, 30, 32], with the degree of AC reported separately to calcification of other arteries. The abdominal aorta alone was assessed in the remaining study [29].

Due to the heterogeneity in methods used to assess and report the degree of calcification, it was not possible to perform a meta-analysis to examine the pooled effect of calcification on AL.

3.1.3 Anastomotic leak

Anastomotic leak was reported in all studies, with a total of 290 events in the 1446 patients (20%) undergoing oesophageal resection and 59 events in the 421 patients (14%) undergoing colorectal resection. One study (n=135) was excluded as the leak rate could not be considered representative due to the case-control design [28].

The criteria used to define AL was reported in all studies. AL was diagnosed on imaging and/or at re-operation in the majority of studies. However, the study by Chang and co-workers [31] included only AL diagnosed at endoscopy or re-operation, excluding those diagnosed radiologically and managed conservatively. The study by Boersema and colleagues [28] included only radiologically-diagnosed AL.

3.1.4 Risk factors for anastomotic leak

The reporting of relevant risk factors for AL and subsequent adjustment for such confounders in the analysis of the relationship between AC and AL was examined in each study. Risk factors have been grouped in relation to the pre- and intra-operative stages of treatment and are discussed in relation to the type of surgery (oesophageal or colorectal).

3.1.5 Preoperative risk factors for AL: oesophageal resection

One study [22] reported all recognised preoperative risk factors for AL and subsequently adjusted for factors which were significant on univariate analysis in the multivariate analysis assessing the relationship between AC and AL. It was found that ASA, PVD, renal insufficiency and calcification of the aorta and celiac arteries were independently associated with AL in this study. The remaining studies reported variably on recognised risk factors and reported no association between preoperative risk factors and AL. The reporting of recognised risk factors for AL by study is displayed in Table 3.

The use of neoadjuvant chemotherapy and/or radiotherapy was considered in three studies and found not to be significant when comparing those with and without AL [21, 22, 26]. The use of steroids was examined and was not found to relate to AL in two studies [22, 26]. Finally, the preoperative albumin level was reported in a single study as a marker of potential increased risk of AL due to malnutrition [22]. It was not associated with AL in this study.

3.1.6 Preoperative risk factors for AL: colorectal resection

None of the included colorectal studies reported all the recognised preoperative risk factors. Assessment of the relationship between risk factors and AL was limited to univariate analysis in all studies. It was therefore not possible to fully assess the role of aortic calcification in colorectal AL given that adjustment for relevant confounders such as cardiovascular disease was not performed. The reporting of recognised risk factors for AL by study is displayed in Table 3.

3.1.7 Intra-operative risk factors for AL: oesophageal resection

Technical factors including the configuration of the anastomosis and technique used (stapled versus handsewn) alongside operative duration were considered in three of four studies [21, 22, 26]. No association between intra-operative technical factors and AL was reported in these studies. Intra-operative technical failure and revision of anastomoses were not reported. Three studies reported pathological tumour type [22, 26, 31], two of which were performed in patients undergoing cervical anastomosis [22, 26]. There was no association between either tumour type or anastomotic site and AL.

3.1.8 Intra-operative risk factors for AL: colorectal resection

Drain use [27-29] and formation of diverting stomas [28, 29, 32] were both reported in three studies respectively. There was no evidence of an association with either drain use or stoma formation and the development of AL. Urgency of surgery (emergency versus elective) was reported in four of five studies [27, 29, 30, 32] but no association was found with AL. Anastomotic site and urgency of surgery were associated with AL on univariate analysis in one study [29]. There was no association with other intraoperative risk factors and AL in the remaining colorectal studies.

3.1.9 Relationship between AC and AL: oesophageal resection

Two studies reported a relationship between the degree of aortic calcification and anastomotic leak [21, 22]. Borggreve et al [26] reported a correlation between calcification of the coronary and supra-aortic (subclavian, innominate, common carotid, external carotid and vertebral) arteries and AL but found no association with aortic calcification and AL. The study by Chang and co-workers [31] reported no relationship between the degree of AC or stenosis of the mesenteric arteries and AL.

3.2 Relationship between AC and AL: colorectal resection

A higher burden of aortic calcification was associated with the development of AL in one study of patients undergoing colorectal resection [29]. The case-control study by Boersema et al [28] found no association between the calcium score of the aortoiliac tract and AL. Two studies reported associations between higher calcium scores in the iliac arteries and AL [27, 32]. One study reported a higher burden of aortic and iliac arterial calcification in patients who developed AL [30].

3.3 Quality assessment

The results of the quality assessment using the Newcastle-Ottawa scale are presented in Table 4. Scores ranged from three to eight of a possible nine points. Studies with total scores less than or equal to 4 were considered poor quality [27, 28, 31], studies scoring 5-7 moderate [21, 22, 26, 29, 30] and studies scoring 8-9 high quality [32]. Two studies scored poorly for quality assessment due to lack of clarity on selection of controls and comparability of groups (leak vs. no leak) [28, 31]. A further study [27] scored poorly due to inadequate comparability between groups and insufficient follow-up data (outcome reporting).

3.4 Validity assessment

The RevMan Risk of Bias Summary tool was used to depict the risk of study bias (Figure 2). Since all the included studies were observational in nature, no risk of bias assessment could be performed for random sequence generation, allocation concealment or blinding of participants and personnel.

3.4.1 Detection bias

The blinding status of personnel assessing CTs for calcification was well described in 5 studies [21, 22, 26, 31, 32]. In the remainder, it was not clear whether assessors were blinded to patient and perioperative details [28-30]. Two studies reported intra- and inter-observer agreement for calcification scores with both confirming high levels of agreement [26, 31].

3.4.2 Reporting bias

Reporting bias was evident in several papers. Komen and colleagues [27] reported incomplete data on calcification across some trajectories due to the inclusion of CT scans which did not cover the complete anatomic region under analysis. Norooz and colleagues [30] reported an association between higher mean calcium score in the aorta and iliac arteries in patients who experienced a colorectal AL but did not account for other factors noted to be associated including emergency surgery and low rectal anastomoses. A discrepancy in the number of cases included in outcome reporting (n=709) and number with preoperative CT available (n=673) was noted in the study by Zhao and colleagues [23]. The study by Chang and co-workers selectively reported risk factors in those who experienced leak and matched controls (14:28) [31]. It was not clear how the controls were selected and whether they formed part of the overall study cohort.

3.4.3 Other bias

Studies at risk of other bias included those that did not control for the effect of confounding factors [28] in multivariate analysis or restricted analysis to univariate only [29, 30].

4 Discussion

Currently, the literature examining the relationship between aortic calcification and anastomotic leak in patients undergoing GI resection is limited to a small number of published studies of modest cohort size. This, coupled with the differing methodology used to assess the burden of aortic calcification, precluded meaningful meta-analysis of the results. Furthermore, the included studies varied in their consideration of recognised risk factors for AL, rendering an incomplete picture of the potential role AC may play in determining the risk of leak following oesophageal or colorectal resection and anastomosis. However, it appears that AC may be associated with AL, in particular in patients undergoing oesophagectomy. The relationship between postoperative complications, particularly infective complications, and inferior long-term outcomes suggests that further examination of the value of AC in preoperative identification of high-risk patients is warranted.

The prevalence of calcification was notably higher in the studies carried out in Europe and in Iran when compared with the single study from China. However, five studies originated in the Netherlands [21, 26-28, 31] and only two were undertaken outside Europe [22, 30]. All studies were single centre, providing little data to assess the role of ethnicity. However, mortality rates for cardiovascular disease continue to rise in South and East Asia, where early-onset CAD and PVD is a growing problem [33, 34]. It is likely that the relatively low prevalence of calcification in this cohort is not representative of the true prevalence in the Asian population undergoing GI surgery.

Geographical differences in tumour factors also influence the reported rates of AL. Asia has the highest incidence of oesophageal and colorectal cancer and associated mortality [35]. A greater proportion of oesophageal tumours are of squamous subtype in Asia [36], while use of induction therapy prior to resection is more common in Europe and North America [37]. Both factors are associated with higher incidence of AL [4, 38]. It is clear that such variation necessitates large international, multi-centre studies to assess the contribution of AC to AL following GI resection.

The method used to determine calcification burden on CT also varied in the included studies. Software designed specifically for quantification of AC is not yet commercially available. Validated visual methods adapted from coronary calcification scoring systems have been described [39-41]. Currently, there is no data available comparing both software and visual scoring methods, highlighting the need for such studies to enable standardisation of technique. It is also unclear as to what extent macrovascular calcification relates to microvascular disease of the mesenteric circulation and by extension, end-organ perfusion. Development of non-invasive, imaging-based techniques to assess mesenteric flow may enable greater clarity in this area.

It is possible that AC is simply a surrogate marker of cardiovascular disease. Exploring the association between AC, cardiovascular disease and related pathophysiological processes such as systemic inflammation is required to contextualise its prognostic value. Additional insight may also be gained from investigation of the relationship between AC and dynamic tests of cardiovascular function such as cardiopulmonary exercise testing in patients prior to GI surgery.

Clearly, there are a number of methodological and mechanistic aspects that require to be addressed to clarify the potential contribution of AC to failure of anastomotic healing. This review was limited by the restriction of the literature search to studies published in the English language which may have excluded relevant studies. It is however a systematic description of the current published evidence in this area. Further well-designed, prospective studies utilising a standardised method of assessing AC are required to develop a clearer picture of the importance of AC in patients undergoing GI resection.

5 Conclusion

The current literature addressing the relationship between aortic calcification and anastomotic leak following GI surgery is modest in quantity and quality but points towards a potential role as a risk predictor of AL. The evidence base requires further prospective studies with adequate control in the analysis for common confounders, particularly in patients undergoing colorectal resection. This may enable clinical translation of AC assessment to a useful screening tool in the identification of high-risk patients who may benefit from optimisation of comorbidity prior to surgery.

6 Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

7 Conflict of interest statement

The authors have no conflict of interests to declare.

8 Acknowledgements

The authors wish to thank Paul Cannon, College Librarian for Medical, Veterinary and Life Sciences at the University of Glasgow, for his assistance in developing the search strategy.

References

1. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 2005;242(3): 326-341; discussion 341-3. https://www.doi.org/10.1097/01.sla.0000179621.33268.83

2. Bouras G, Burns EM, Howell AM, Bagnall NM, Lee H, Athanasiou T, Darzi A. Systematic review of the impact of surgical harm on quality of life after general and gastrointestinal surgery. Ann Surg 2014;260(6): 975-983. https://www.doi.org/10.1097/SLA.0000000000000676

3. Straatman J, Cuesta MA, de Lange-de Klerk ES, van der Peet DL. Long-Term Survival After Complications Following Major Abdominal Surgery. J Gastrointest Surg 2016;20(5): 1034-1041. https://www.doi.org/10.1007/s11605-016-3084-4.

4. Kassis ES, Kosinski AS, Ross P Jr, Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. Ann Thorac Surg. 2013 Dec;96(6):1919-26. https://www.doi.org/10.1016/j.athoracsur.2013.07.119

5. Low DE, Alderson D, Cecconello I, Chang AC, Darling GE, D'Journo XB, Griffin SM, Hölscher AH, Hofstetter WL, Jobe BA, Kitagawa Y, Kucharczuk JC, Law SY, Lerut TE, Maynard N, Pera M, Peters JH, Pramesh CS, Reynolds JV, Smithers BM, van Lanschot JJ. International Consensus on Standardization of Data Collection for Complications Associated With

Esophagectomy: Esophagectomy Complications Consensus Group (ECCG). Ann Surg. 2015 Aug;262(2):286-94. https://www.doi.org/10.1097/SLA.0000000000001098

6. Ryan C E, Paniccia A, Meguid R A, McCarter M D. Transthoracic anastomotic leak after esophagectomy: Current trends. Ann Surg Oncol 2017; 24: 281–90. https://www.doi.org/10.1245/s10434-016-5417-7

7. McDermott FD, Heeney A, Kelly ME, Steele RJ, Carlson GL, Winter DC. Systematic review of preoperative, intraoperative and postoperative risk factors for colorectal anastomotic leaks. Br J Surg. 2015 Apr;102(5):462-79. https://www.doi.org/10.1002/bjs.9697

8. Gooszen JAH, Goense L, Gisbertz SS, Ruurda JP, van Hillegersberg R, van Berge Henegouwen M. Intrathoracic versus cervical anastomosis and predictors of anastomotic leakage after oesophagectomy for cancer. Br J Surg. 2018 Apr;105(5):552-560. https://www.doi.org/ 10.1002/bjs.10728

9. Wright CD, Kucharczuk JC, O'Brien SM, Grab JD, Allen MS. Predictors of major morbidity and mortality after esophagectomy for esophageal cancer: a Society of Thoracic Surgeons General Thoracic Surgery Database risk adjustment model. J Thorac Cardiovasc Surg. 2009 Mar;137(3):587-96. https://www.doi.org/10.1016/j.jtcvs.2008.11.042.

10. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004 May 26;291(20):2441-7. https://www.doi.org/10.1001/jama.291.20.2441

11. Read WL, Tierney RM, Page NC, Costas I, Govindan R, Spitznagel EL, Piccirillo JF. Differential prognostic impact of comorbidity. J Clin Oncol. 2004 Aug 1;22(15):3099-103. https://www.doi.org/10.1200/JCO.2004.08.040

12. Dhungel B, Diggs BS, Hunter JG, Sheppard BC, Vetto JT, Dolan JP. Patient and peri-operative predictors of morbidity and mortality after esophagectomy: American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), 2005-2008. J Gastrointest Surg. 2010 Oct;14(10):1492-501. https://www.doi.org/10.1007/s11605-010-1328-2

13. Warschkow R, Steffen T, Thierbach J, Bruckner T, Lange J, Tarantino I. Risk factors for anastomotic leakage after rectal cancer resection and reconstruction with colorectostomy. A retrospective study with bootstrap analysis. Ann Surg Oncol. 2011 Oct;18(10):2772-82. https://www.doi.org/10.1245/s10434-011-1696-1

14. van Gestel YR, Lemmens VE, de Hingh IH, Steevens J, Rutten HJ, Nieuwenhuijzen GA, van Dam RM, Siersema PD. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. Ann Surg Oncol. 2013 Feb;20(2):371-80. https://www.doi.org/10.1245/s10434-012-2663-1.

15. Detrano R, Molloi S. Radiographically detectable calcium and atherosclerosis: the connection and its exploitation. Int J Card Imaging. 1992;8(3):209-15. https://www.doi.org/10.1007/BF01146839

16. Kondos GT, Hoff JA, Sevrukov A, Daviglus ML, Garside DB, Devries SS, Chomka EV, Liu K. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation. 2003 May 27;107(20):2571-6. https://www.doi.org/10.1161/01.CIR.0000068341.61180.55

17. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA. 2004 Jan 14;291(2):210-5. https://www.doi.org/10.1001/jama.291.2.210

18. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, Liu K, Shea S, Szklo M, Bluemke DA, O'Leary DH, Tracy R, Watson K, Wong ND, Kronmal RA. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008 Mar 27;358(13):1336-45. https://www.doi.org/10.1056/NEJMoa072100

19. Harbaugh CM, Terjimanian MN, Lee JS, Alawieh AZ, Kowalsky DB, Tishberg LM, Krell WR, Holcombe SA, Wang SC, Campbell DA, Englesbe DB. Abdominal aortic calcification and surgical outcomes in patients with no known cardiovascular risk factors. Ann Surg 2013;257(4):774-781. https://www.doi.org/10.1097/SLA.0b013e31826ddd5f

20. van Rossum PS, Haverkamp L, Verkooijen HM, van Leeuwen MS, van Hillegersberg R, Ruurda JP. Calcification of arteries supplying the gastric tube: a new risk factor for anastomotic leakage after esophageal surgery. Radiology 2015; 274(1): 124-132. https://www.doi.org/10.1148/radiol.14140410

21. Goense L, van Rossum PS, Weijs TJ, van Det MJ, Nieuwenhuijzen GA, Luyer MD, van Leeuwen MS, van Hillegersberg R, Ruurda JP, Kouwenhoven EA. Aortic Calcification Increases the Risk of Anastomotic Leakage After Ivor-Lewis Esophagectomy. Ann Thorac Surg. 2016 Jul;102(1):247-52. https://www.doi.org/10.1016/j.athoracsur.2016.01.093

22. Zhao L, Zhao G, Li J, Qu B, Shi S, Feng X, Feng H, Jiang J, Xue Q and He J. Calcification of arteries supplying the gastric tube increases the risk of anastomotic leakage after

esophagectomy with cervical anastomosis. J Thorac Dis 2016; 8(12): 3551-3562. https://www.doi.org/10.21037/jtd.2016.12.62.

23. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. BMJ. 2009; 339:b2535.Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. https://www.doi.org/10.1136/bmj.b2535

24. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008.

25. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 10 June 2019.

26. Borggreve AS, Goense L, van Rossum PSN, van Hillegersberg R, de Jong PA, Ruurda JP. Generalized cardiovascular disease on a preoperative CT scan is predictive for anastomotic leakage after esophagectomy. Eur J Surg Oncol 2018; 44(5):587-593. https://www.doi.org/10.1016/j.ejso.2018.01.225

27. Komen N, Klitsie P, Dijk JW, Slieker, J, Hermans J, Havenga K, Oudkerk M, Weyler J, Kleinrensink GJ, Lange JF. Calcium score: a new risk factor for colorectal anastomotic leakage. Am J Surg 2011; 201(6): 759-765. https://www.doi.org/10.1016/j.amjsurg.2010.01.033

28. Boersema GS, Vakalopoulos KA, Kock MC, van Ooijen PM, Havenga K, Kleinrensink GJ, Jeekel J, Lange JF. Is aortoiliac calcification linked to colorectal anastomotic leakage? A case-control study. Int J Surg 2016; 25: 123-127. https://www.doi.org/10.1016/j.ijsu.2015.12.008

29. Eveno C, Latrasse V, Gayat V, Lo Dico R, Dohan A, Pocard M. Colorectal anastomotic leakage can be predicted by abdominal aortic calcification on preoperative CT scans: A pilot study. J Visc Surg 2016; 153(4): 253-257. https://www.doi.org/10.1016/j.jviscsurg.2016.03.007

30. Norooz MT, Moradi H, Safdarian M, Jahangiri F, Amoli HA. Does calcium score in great pelvic vessels predict colorectal anastomotic leakage? A prospective study of one hundred anastomoses. Acta Gastroenterol Belg 2016; 79(4): 415-420.

31. Chang DH, Brinkmann S, Smith L, Becker I, Schroeder W, Hoelscher AH, Haneder S, Maintz D, Spiro JE. Calcification score versus arterial stenosis grading: comparison of two CT-based methods for risk assessment of anastomotic leakage after esophagectomy and gastric pull-up. Ther Clin Risk Manag 2018; 14: 721-727. https://www.doi.org/10.2147/TCRM.S157352

32. Pochhammer J, Troster F, Blumenstock G, Closset J, Lang S, Weller MP, Schaffer M. Calcification of the iliac arteries: a marker for leakage risk in rectal anastomosis-a blinded clinical trial. Int J Colorectal Dis 2018; 33(2): 163-170. https://www.doi.org/10.1007/s00384-017-2949-7

33. Joseph P, Leong D, McKee M, Anand SS, Schwalm JD, Teo K, Mente A, Yusuf S. Reducing the Global Burden of Cardiovascular Disease, Part 1: The Epidemiology and Risk Factors. Circ Res. 2017 Sep 1;121(6):677-694. https://www.doi.org/10.1161/CIRCRESAHA.117.308903.

34. Song P, Rudan D, Wang M, Chang X, Rudan I. National and subnational estimation of the prevalence of peripheral artery disease (PAD) in China: a systematic review and meta-analysis. J Glob Health. 2019 Jun;9(1):010601. https://www.doi.org/10.7189/jogh.09.010601.

35. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424. https://www.doi.org/10.3322/caac.21492

36. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol. 2013 Sep 14;19(34):5598-606. https://www.doi.org/10.3748/wjg.v19.i34.5598

37. Moaven O, Wang TN. Combined Modality Therapy for Management of Esophageal Cancer: Current Approach Based on Experiences from East and West. Surg Clin North Am. 2019 Jun;99(3):479-499. https://www.doi.org/10.1016/j.suc.2019.02.004

38. Juloori A, Tucker SL, Komaki R, Liao Z, Correa AM, Swisher SG, Hofstetter WL, Lin SH. Influence of preoperative radiation field on postoperative leak rates in esophageal cancer patients after trimodality therapy. J Thorac Oncol. 2014 Apr;9(4):534-40. https://www.doi.org/10.1097/JTO.0000000000000100

39. Gondrie MJ, Mali WP, Jacobs PC, Oen AL, van der Graaf Y; PROVIDI Study Group. Cardiovascular disease: prediction with ancillary aortic findings on chest CT scans in routine practice. Radiology. 2010 Nov;257(2):549-59. https://www.doi.org/10.1148/radiol.10100054

40. Huang YL, Wu FZ, Wang YC, Ju YJ, Mar GY, Chuo CC, Lin HS, Wu MT. Reliable categorisation of visual scoring of coronary artery calcification on low-dose CT for lung cancer

screening: validation with the standard Agatston score. Eur Radiol 2013; 23(5): 1226-1233. https://www.doi.org/10.1007/s00330-012-2726-5

41. Chiles C, Duan F, Gladish GW, Ravenel JG, Baginski SG, Snyder BS, DeMello S, Desjardins SS, Munden RF. Association of coronary artery calcification and mortality in the national lung screening trial: a comparison of three scoring methods. Radiology, 276 (1) (2015), pp. 82-90. https://www.doi.org/10.1148/radiol.15142062

Table 1: Study Characteristics

Study	Country	Study design	Cohort size	Pathology
Oesophageal resections				
Borggreve 2018	The Netherlands	Cohort	406	Cancer
Chang 2018	The Netherlands	Case-control	164	Cancer
Goense 2016	The Netherlands	Cohort	167	Cancer
Zhao 2015	China	Cohort	709	Cancer
Colorectal resections				
Boersema 2016	The Netherlands	Case-control	30: 105	Benign & cancer
Eveno 2016	France	Cohort	60	Benign & cancer
Komen 2011	The Netherlands	Cohort	122	Benign & cancer
Norooz 2016	Iran	Cohort	100	Cancer
Pochhammer 2018	Germany	Cohort	139	Benign & cancer

Table 2a: Overview of studies using visual grading for assessment of calcification.

Study	Outcome parameter	Event rate (AL)	Method of calcification assessment	Vessel(s) assessed	Prevalence of AC by grade in patients with AL	Prevalence of AC by grade in patients with no AL	Relationship between AC and AL?
Oesophageal resection							
Borggreve 2018	Anastomotic leakage	104 (26%)	Visual grading system (0/1/2)	Coronary, supra-aortic, CIAs & EIAs Coeliac axis Thoracic and abdominal aorta	0 – 28 (27%) 1 – 36 (37%) 2 – 40 (38%)	0 – 116 (38%) 1 – 106 (35%) 2 – 80 (26%)	No
Chang 2018	Anastomotic leakage	14 (8.5%)	Visual grading system (0/1/2)	Aorta Celiac axis Right and left post-celiac axis SMA	0 – 4 (29%) 1 – 4 (29%) 2 – 6 (42%)	0 – 64 (43%) 1 – 38 (25%) 2 – 48 (32%)	No
Goense 2016	Anastomotic leakage	40 (24%)	Visual grading system (0/1/2)	Thoracic aorta Celiac axis Post-celiac arteries	0 – 6 (15%) 1 – 18 (45%) 2 – 16 (40%)	0 – 62 (49%) 1 – 38 (30%) 2 – 27 (21%)	Yes
Zhao 2015	Anastomotic leakage	122 (17%)	Visual grading system (0/1)	Aorta Celiac axis Post-celiac arteries	0 – 64 (54%) 1 – 55 (46%)	0 – 436 (79%) 1 – 118 (21%)	Yes

Study	Outcome parameter	Event rate (AL)	Method of calcification assessment	Vessel(s) assessed	Prevalence of AC by grade in patients with AL	Prevalence of AC by grade in patients with no AL (%)	Relationship between AC and AL?
Colorectal resection (continued)							
Eveno 2016	Mortality Major morbidity (including AL)	13 (21.7%)	Visual grading system (0/1/2)	Abdominal aorta	0 – 0 (-) 1 – 6 (46%) 2 – 7 (54%)	0 – 11 (23%) 1 – 27 (57%) 2 – 9 (19%)	Yes

Abbreviations: AC aortic calcification, AL anastomotic leak, CIA common iliac artery, EIA external iliac artery, SMA superior mesenteric artery, IMA inferior mesenteric artery, LIIA left internal iliac artery, RIIA right internal iliac artery.

Table 2b: Overview of studies using software-derived calcium score for assessment of calcification.

Study	Outcome parameter	Event rate (AL)	Method of calcification assessment	Vessel(s) assessed	Prevalence of AC by mean calcium score in patients with AL	Prevalence of AC by mean calcium score in patients with no AL	Relationship between AC and AL?
Colorectal resection							
Boersema 2016	Anastomotic leakage (AL)	30 cases:105 controls	Software-derived calcium score (Mean + SD)	Aorta Iliac arteries	4.93 (2.93)	4.7 (3.1)	No

Study	Outcome parameter	Event rate (AL)	Method of calcification assessment	Vessel(s) assessed	Prevalence of AC by calcium score in patients with AL	Prevalence of AC by mean calcium score (SD) in patients with no AL	Relationship between AC and AL?
Colorectal resection (continued)							
Komen 2011	Anastomotic leakage	11 (9%)	Software-derived calcium score (Mean + SD)	Aorta Iliac arteries	1489 (SD 2054)	618 (SD 1248)	No
Norooz 2016	Anastomotic leakage	20 (20%)	Software-derived calcium score (Mean + SD)	Descending aorta Iliac arteries	792 (SD 39)	405 (SD 45)	Yes
Pochhammer 2018	Anastomotic leakage	15 (11%)	Software-derived calcium score (Median + range)	Infrarenal aorta Iliac arteries	250 (Range 0 – 659)	45 (Range 0 – 2572)	Yes

Abbreviations: AC aortic calcification, AL anastomotic leak, SD standard deviation.

Table 3: Reported risk factors for AL and relationship with AL in patients undergoing gastrointestinal resection.

Study	Patient factors	Comorbidity	Tumour factors	Anastomotic site	Technical factors	Statistical analysis	Relationship with AL
Oesophageal resection							
Borggreve	Age Gender BMI Smoking status	COPD CAD DM ASA	Pathological tumour type	Cervical	Anastomotic configuration (end-to-side vs. end-to-end) Operative time	Multivariate (adjusted for age, BMI, smoking, CAD, COPD, DM)	No association
Chang	BMI Smoking status	Heart failure DM PVD	Pathological tumour type	Intra-thoracic	-	Univariate	No association
Goense	Age Gender BMI Smoking status	COPD CAD PVD DM ASA Renal insufficiency	-	Intra-thoracic	Anastomotic configuration and technique (side-to-side stapled vs. end-to-side hand-sewn only)	Multivariate (adjusted for age and CAD)	No association

Study	Patient factors	Comorbidity	Tumour factors	Anastomotic site	Technical factors	Statistical analysis	Relationship with AL
Oesophageal resection (continued)							
Zhao	Age Gender BMI Smoking status Alcohol use	COPD CAD PVD DM Recent arrhythmia Hypertension Renal insufficiency Steroids NSAIDs	Pathological tumour type TNM stage Tumour location Tumour length NT response	Cervical	Previous neck/thoracic/abdominal surgery Operative time Surgical approach Oesophageal conduit type Stapled vs. handsewn anastomosis Extent of nodal dissection	Multivariate (adjusted for ASA, Hypertension, PVD, renal insufficiency)	ASA, PVD, renal insufficiency associated with AL
Colorectal resection							
Boersema	Age Gender BMI Smoking status Alcohol use	ASA CVD PVD DM Medication (anti-hypertensives, steroids, statins)	-	Left colonic and rectal	Operation type Operative approach Anastomotic configuration Anastomotic method (stapled vs. hand-sewn) Operating surgeon Drain use Stoma formation	Univariate	Cardiac comorbidity associated with AL on univariate analysis (results of multivariate analysis presented for calcium score only)

Study	Patient factors	Comorbidity	Tumour factors	Anastomotic site	Technical factors	Statistical analysis	Relationship with AL
Colorectal resection (continued)							
Eveno	Age Gender BMI	ASA	-	Left colonic and rectal	Emergency/elective surgery Operation type Anastomosis type (colocolic, colorectal, coloanal, ileorectal, ileoanal) Drain use Stoma formation Preservation of left colic artery	Univariate	Surgery type and anastomosis type associated with AL No association with patient factors or comorbidity
Komen	Age Gender BMI Smoking status	ASA CAD PVD DM Drugs	NT use	Colonic or rectal	Emergency/elective surgery Operation type Operative approach Anastomotic configuration (side-to-side vs. end-to-side) Anastomotic technique (stapled vs. hand-sewn) Drain use	Univariate	No association

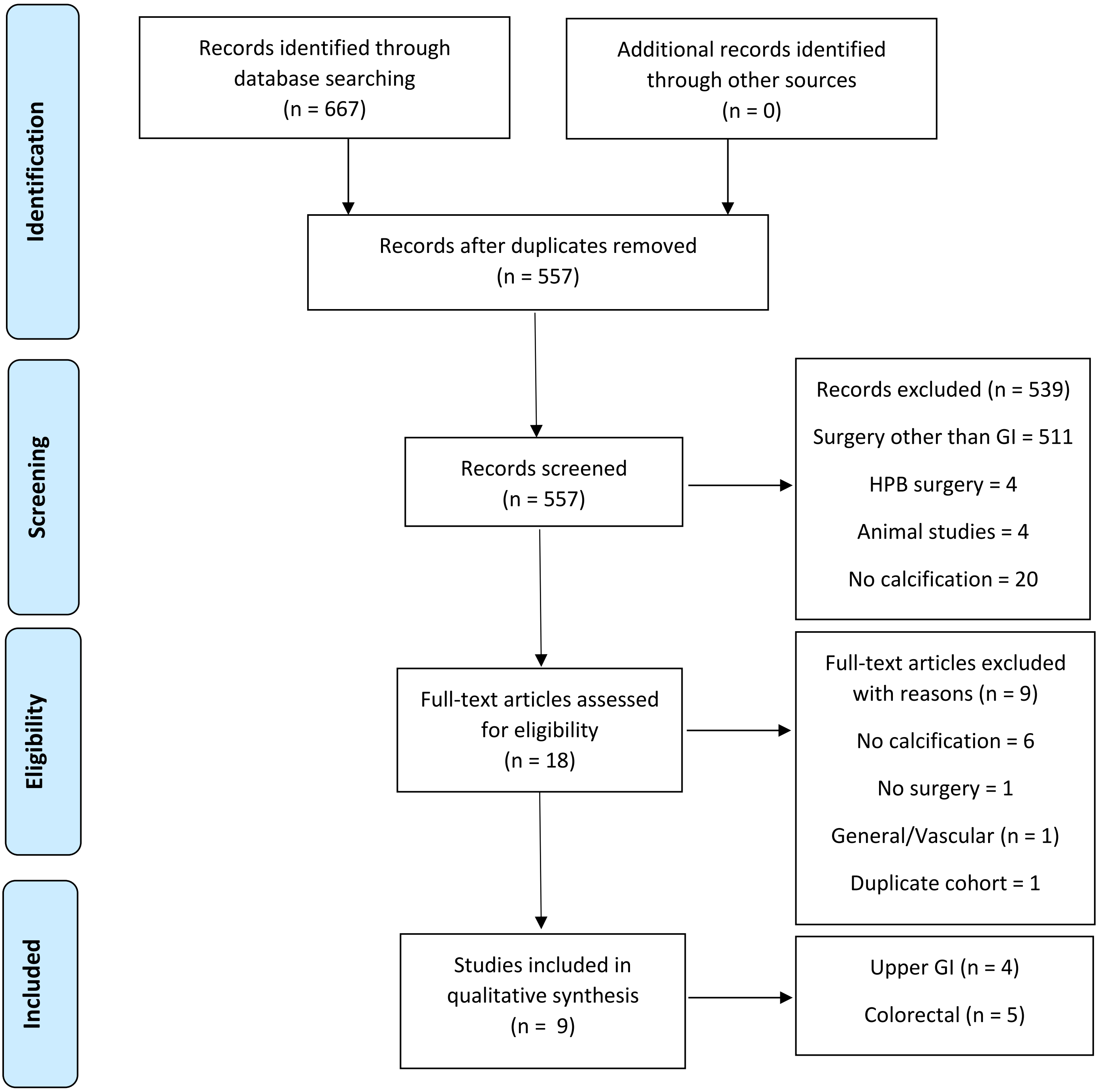
Study	Patient factors	Comorbidity	Tumour factors	Anastomotic site	Technical factors	Statistical analysis	Relationship with AL
Colorectal resection (continued)							
Norooz	Age Gender BMI Smoking status	Hypertension PVD Medication (steroids, NSAIDs)	NT use	Colonic or rectal	Emergency/elective surgery Stapled vs. handsewn anastomosis Operative time	Univariate	Male gender, DM, smoking associated with AL
Pochhammer	Age Gender BMI	ASA ≥ 3 Cardiac Renal Vascular Pulmonary	-	Rectal anastomosis	Emergency surgery Stoma formation Operative approach	Univariate	Age, renal disease, vascular disease, DM and ASA ≥ 3 associated with AL

Abbreviations: AL anastomotic leak, ASA American Society of Anaesthesiologists grade, BMI body mass index, CAD coronary arterial disease, COPD chronic obstructive pulmonary disease, DM diabetes mellitus, NT neoadjuvant therapy, NSAIDs non-steroidal anti-inflammatory drugs, PVD peripheral vascular disease, TNM tumour node metastases.

Table 4: Quality assessment using Newcastle-Ottawa scale

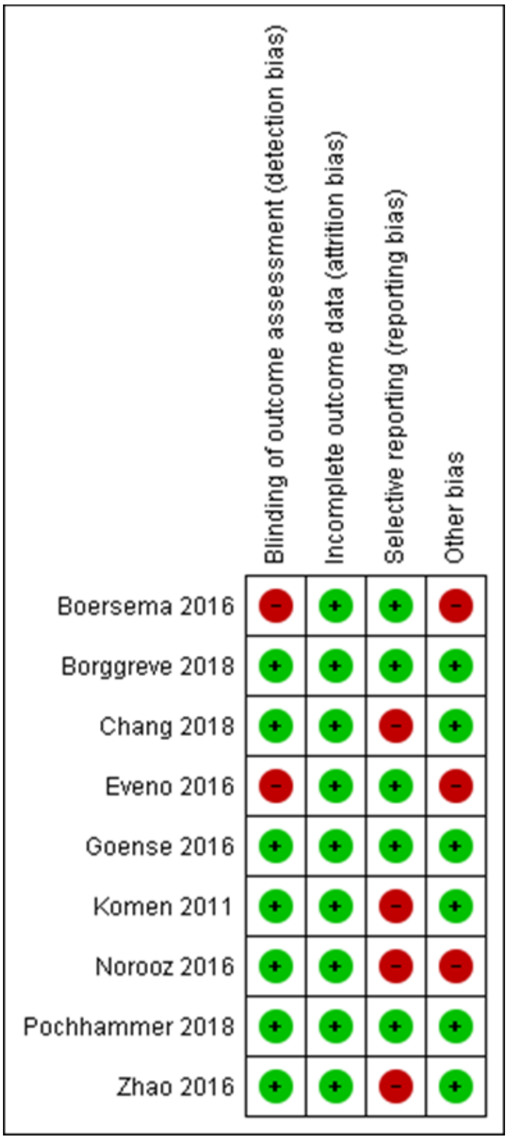
Study	Selection				Comparability		Outcome			
	1	2	3	4	5A	5B	6	7	8	Total
Boersema 2016	-	*	-	-	-	-	*	*	-	3
Borggreve 2018	*	*	*	*	*	-	*	-	*	7
Chang 2018	-	-	-	*	*	-	*	*	*	4
Eveno 2016	*	*	*	*	-	-	-	-	*	5
Goense 2016	*	*	*	*	-	*	*	-	*	7
Komen 2011	*	*	*	-	-	-	*	-	-	4
Norooz 2016	*	*	*	*	-	-	*	-	*	6
Pochhammer 2018	*	*	*	*	*	*	*	-	*	8
Zhao 2016	*	*	*	*	*	-	*	-	*	7

Figure 1: PRISMA flow diagram of study selection



Abbreviations: HPB hepatopancreaticobiliary.

Figure 2: Risk of bias summary (colour figure)



Appendix: Example search strategy (MEDLINE)

1. anastomosis, surgical/ or elective surgical procedures/ or colorectal neoplasms/ or esophageal neoplasms/ or gastric neoplasms/ or colectomy/ or esophagectomy/ or gastrectomy/ or digestive system surgical procedures/
2. (colorectal surgery* or colectomy* or colon cancer* or rectal cancer* or esophagectomy* or esophageal cancer* or gastrectomy* or gastric cancer*).mp
3. or/1-2
4. vascular calcification/ or calcinosis/ or arterial occlusive disease/ or atherosclerosis/ or iliac artery/ or aorta, abdominal/ or aorta, thoracic/
5. (aortic calcification* or calcium score* or calcium volume*).mp
6. or/4-5
7. postoperative complications/ or treatment outcome/ or risk factors/ or anastomotic leak/
8. (anastomotic leakage* or prognostic factor* or risk factor*).mp
9. or/7-8
10. 3 and 6 and 9