Calcification of the Aorta-Iliac Trajectory as a Risk Factor for Anastomotic Leakage in Colorectal Surgery: Individual Patient Data Meta-Analysis and Systematic Review

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ABSTRACT

Objective: The purpose of this review is to evaluate the relevance of vascular calcification as a potential risk factor for anastomotic leakage in colorectal surgery.

Method: The Embase, Medline, PubMed, and Cochrane databases and Google Scholar were systematically searched. Studies that assessed calcification of the aorta-iliac trajectory in patients who underwent colorectal surgery were included. An independent patient data meta-analysis was performed as follows: based on the heterogeneity of the study population, a “random-effects model” or “fixed-effects model” was used to perform a multivariable logistic regression and calculate pooled Odds Ratios (OR) and 95% confidence intervals (CI). Heterogeneity was assessed using the Q-test and I^2-test.

Results: From a total of 457 articles retrieved, eight fell within the scope of the review, with a total of 2010 patients. Anastomotic leakage was found at a mean rate of 11.1% (SD 4.9%). In these eight studies, four different calcification scoring methods were used, which made a single structured meta-analysis not feasible. Therefore,

an independent patient data meta-analysis on the most frequently used calcification scoring method was performed, including three studies with a total of 396 patients. After multivariable analyses, no significant association was found between anastomotic leakage and the amount of calcification in the aorta-iliac trajectory. The remaining three scoring methods were evaluated. In four of the five studies, vascular calcification was associated with anastomotic leakage after colorectal surgery.

Conclusion: In contrast to previous studies, an individual patient data meta-analysis found no association between calcification and anastomotic leakage in colorectal surgery after multivariable analysis that considered a single calcification measurement method. In addition, this study demonstrated several scoring methods for arterial calcification and the need for a standardized technique. Therefore, the authors would recommend prospective studies using a calcification scoring method that includes grade of stenosis due to its potential to preoperatively improve perfusion by endovascular treatment.

INTRODUCTION

Anastomotic leakage (AL) is not uncommon in colorectal surgery and can lead to severe morbidity and mortality.[1-5] The reported incidence of AL varies between 1% and 19% depending on the surgical procedure.[4,6,7] Over the past few decades, many patient and surgical characteristics have been analyzed and shown to be risk factors, including male gender, low level anastomosis, American Society of Anesthesiologists (ASA) Physical Status classification system >3, diabetes, obesity, smoking, malnutrition, corticosteroids, chemo- or radiotherapy and long operation duration.[4,7-11] Nevertheless, AL remains a major problem in gastrointestinal surgery with a noteworthy incidence.[12]

Measures to reduce the risk of clinical AL include the creation of a temporary diverting ileostomy in cases of rectal resection. Surgeons normally decide whether an ileostomy is necessary based on their expertise and experience with regard to risk factors.[6] However, about 19% of diverting ileostomies will become permanent, which can seriously impact the patient's quality of life.[2] Moreover, closure of a loop ileostomy carries a surprisingly high morbidity, with a 17% complication rate.[13]

Although AL may be a multifactorial problem, identification of the most relevant risk factors is valuable when preventive measures are considered. According to many publications, sufficient blood supply is one of the most important factors for anastomotic healing.[14,15] It is hypothesized that vascular calcification can compromise blood flow and thus increase the risk of insufficient healing of the anastomosis.

Komen et al. and Shen et al. both found a correlation between aorta-iliac calcification and AL.[16,17] Vascular calcification has been investigated using computed tomography (CT) imaging software.[16] Furthermore, the assessment of vascular calcium, including local stenosis with CT scans in multiple trajectories, has been a topic of research.[18] Despite promising results, an obvious association between vascular calcification and AL could not be confirmed.[18,19] Overall, the matter remains largely in the realm of speculation.[20] The aim of this review was to evaluate current literature to provide insights regarding vascular calcification as a potential risk factor for anastomotic leakage in colorectal surgery. In addition, an individual patient data meta-analysis (IPDM) was performed to validate reported results.

MATERIALS AND METHODS

Literature search

This systematic review and meta-analysis were carried out according to the Preferred Reporting Items for Systematic Review (PRISMA) guidelines.[21] The literature search was performed on November 19, 2019, by a biomedical information specialist. An update of the search was performed on March 8, 2021. 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 manually reviewed to identify additional relevant studies.[22]

Study selection

Studies that evaluated vascular calcifications in the aorta-iliac trajectory by CT scan in relation to AL after colorectal surgery were included in this review. Included papers were based on a human study-population and written in English. Exclusion criteria were pediatric patients (less than 18 years of age), case reports, comments, reviews, letters to the editor or studies for which the full-text was not available. Blinded eligibility screening was performed by two readers (PE and VH) in two phases. First, the articles were screened based on title and abstract. Secondly, a thorough screening of full-text articles was performed. In cases of disagreement, the paper was discussed by the two readers until a consensus was reached regarding in- or exclusion. Raw (anonymized) data of papers using the Agatston calcium score (computer software)[23] were requested, collected, checked, reanalyzed and pooled for an IPDM.

Data extraction

Extraction of data was performed by two researchers (PE and VH) independently. The following data were extracted: study characteristics (author, year, design), baseline characteristics (number of patients, gender, age, body mass index, comorbidities, use of medicine, smoking, neoadjuvant radiotherapy), operative characteristics (type of surgery, type of anastomosis, emergency or elective procedure, AL), and calcification characteristics (calcium measurement method, including Hounsfield threshold value, arteries screened). To guarantee consistency within the individual patient data meta-analysis, only patient and perioperative characteristics were included and presented.

Discrepancies in data registration were discussed by the two researchers until they reached a consensus regarding final conclusive registration. In cases of uncertainty regarding the reported study results, the corresponding authors were contacted for clarification

Bias and quality assessment

The Methodological Index of Non-Randomized Studies (MINORS) score was used to assess the methodological quality.[24] A MINORS score of less than 12 was considered to be poor, 12-17 was moderate and more than 17 was good methodological quality. Regarding the follow-up duration (MINORS score system), the following score system was used: 0 points = not reported, 1 point = less than 14 days, 2 points = more than 14 days. Discrepancies in quality assessment outcomes were resolved by discussion and agreement.

Statistical analyses

The meta-analysis was performed using Statistical Product and Service Solutions software (SPSS Inc., Chicago, IL, USA, version 25.0 for Windows) and R (version 3.4.1; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are reported as counts (proportion) and continuous variables are presented as mean (standard deviation) or median (interquartile range) depending on the distribution. Differences between groups were assessed by using the X^2 test or Fisher's exact test for expected counts <5 for categorical variables and the Mann-Whitney U-test for continuous variables. A P value <0.05 (two-tailed) was considered statistically significant.

A '2-stage' approach was used for the IPDM.[25] First, a univariate analysis within studies was performed and heterogeneity within studies was assessed using Cochran's Q-test. Values of I^2 were used to represent heterogeneity and interpreted as follow: 0%–40%: likely minimal; 30%–60%: likely moderate; 50%–90%: likely substantial; and 75%–100%: likely considerable.

Secondly, fixed-effects models were used to perform a multivariable logistic regression and to calculate odds ratios (OR) and 95% confidence intervals (CI) in trajectories with minimal heterogeneity. For moderate, substantial or considerable heterogeneity, multivariable logistic regression analyses were performed within each individual study, including calculation of pooled OR's using a random-effects model.

For the individual patient data meta-analysis, raw data from papers by Boersema et al., Pochhammer et al. and Komen et al. were obtained by request. Boersema et al. used a calcium score based on thresholds of both 300 and 500 Hounsfield Units (HU). Data from Pochhammer et al. were pooled with those from Boersema et al. with a 300 HU threshold. In addition, data from Komen et al. were pooled with those from Boersema et al. with a 500 HU threshold. The following trajectories were screened: all trajectories combined (total trajectory), abdominal aorta (starting from level T12-L1 to bifurcation), left common iliac artery, right common iliac artery, left internal iliac artery, right internal iliac artery, right and left common iliac arteries combined, and right and left internal iliac arteries combined. The number of confounders included in the multivariable analysis was limited to one variable per 10 instances of anastomotic leakage.[25]

RESULTS

Study selection

From a total of 457 articles retrieved, eight were included within the scope of this review, with a total of 2010 patients. The details of the study selection are provided in a PRISMA flow diagram (Fig. 1). Among these eight studies, four different calcification scoring methods were used, which made a single structured meta-analysis not feasible. Therefore, a meta-analysis was performed for the most frequently used calcification scoring method, including the full databases of these studies for an individual patient data meta-analysis (subcategory A). Furthermore, the remaining three calcification scoring methods in patients who underwent colorectal surgery were reviewed for a complete view of the current literature (subcategory B).

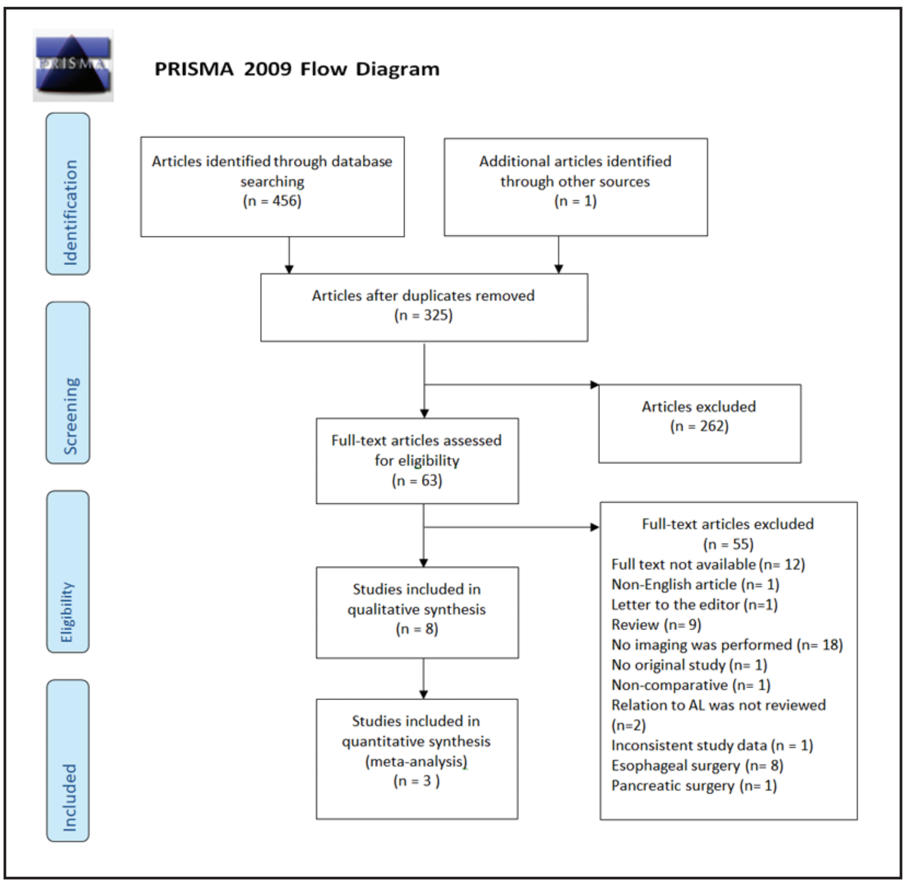

Figure 1. Flow diagram.

Table I
Study characteristics

Lead Author	Year	Centers (n)	Design	MINORS	Study period	Included patients (n)	Subcategory	Type of surgery	Measurement of calcification	Trajectories reviewed	Significantly associated trajectories
Boersema[19]	2016	3	case-control	18	2009 - 2011	35	A	Primary left sided colorectal anastomosis.	Calcium score *	Aorta abdominalis, common iliac arteries, internal iliac arteries, external iliac arteries	None
Eveno[27]	2016	1	pro/retro	19	Jul 2007 – Sep 2010	60	B	Left colonic and rectum surgery	NASCET formula	Aorta abdominalis	Aorta abdominalis
Komen[16]	2011	2	retro	16	2002-2006 and 2005 -2007	122	A	Primary colorectal anastomosis	Calcium score *	Aorta abdominalis, common iliac arteries, internal iliac arteries, external iliac arteries	Left internal iliac artery, left common iliac artery and right common iliac artery
Kornmann[18]	2014	1	retro	18	Jan 2010 – Dec 2010	242	B	Primary colorectal anastomosis	NASCET formula	Celiac trunk, superior mesenteric artery, inferior mesenteric artery, aorta abdominalis, common iliac arteries, internal iliac arteries	None
Lee[29]	2020	1	retro	16	Jan 2013 – Dec 2015	583	B	Rectal cancer surgery	Aortoiliac calcification score	Aorta abdominalis, common iliac arteries	Calcification score ≥3 for the aorta and common iliac arteries combined
Pochhammer[26]	2018	1	pro	22	Oct 2014 – Feb 2016	139	A	Colorectal resection with rectal anastomosis	Calcium score *	Aorta abdominalis, common iliac arteries, internal iliac arteries	Total trajectory, abdominal aorta, left common iliac artery, left internal iliac artery, right and left common iliac arteries, right and left internal iliac arteries
Postaire[28]	2018	1	retro	18	Jan 2011 – Dec 2016	253	B	Right-sided colon surgery	NASCET formula	Celiac trunk, superior mesenteric artery, first segment of the superior mesenteric artery, distal segment of the superior mesenteric artery	A combined calcium score of ≥3 and >50% stenosis of the celiac trunk
Shen[17]	2019	1	pro/retro	18	Feb 2009 – Feb 2017	423	B	Colorectal resection with rectal anastomosis	ACI	Aorta abdominalis	Aorta abdominalis

* Software based; ACI = Aorta calcification index; NASCET = The North American Symptomatic Carotid Endarterectomy Trail; pro = prospective cohort study; retro = retrospective cohort study; pro/retro = study based on a prospectively recorded database; n.r. = not recorded; MINORS = Methodological index for non-randomized studies.

Study characteristics

Subcategory A included three studies with a total of 396 patients. Pochhammer et al., Komen et al. and Boersema et al. provided full databases for the IPMD.[16,19,26] Subcategory B included five studies with a total of 1614 patients. Study, patient and peri-/postoperative characteristics are shown in Tables I and II and Appendices I and II. The mean MINORS score (both subcategories A&B) was 18.1 (SD 1.8). Data were blindly reviewed in three studies.[17,18,26] Pochhammer et al. was the only study with a prospective design and sample size calculation.[26] The quality assessment with details of the MINORS score is presented in Table II.

Anastomotic leakage

The mean AL rate was 11.1% (SD 4.9%) overall and 8.1% (SD 1.8%) in studies on rectal anastomoses. Subcategory A had a mean AL rate of 10% (SD 1%); Boersema et al. was not included in the mean calculation because of the study design (case-control). The mean AL rate in subcategory B was 11.6% (SD 5.8%).

Subcategory A: Independent patient data meta-analysis

Studies in subcategory A applied a software-based calcium scoring referred to as the Agatston score.[16,19,23,26] This method measures the calcified area with a threshold of either 300 HU or 500 HU. The individual patient data meta-analysis was performed separately using threshold values of 300 HU and 500 HU.[16,19,26] Univariate analyses of the pooled studies including patient and perioperative characteristics and calcium scores are shown in Tables III and IV. For the 300 HU analysis, significantly more patients with a BMI ≥ 30 and ASA > 3 were found in the AL group than in the group that did not develop AL. The median calcium score was significantly higher in the AL group compared to the no-AL group for the total trajectory (No-AL 3.07 (IQ 0.24 – 18.04) vs AL 8.90 (IQ 2.76 – 27.00), p=0.025), abdominal aorta (No-AL 1.87 (IQ 0.06 – 9.67) vs AL 4.23 (IQ 1.46 – 23.74), p=0.022), left common iliac artery (No-AL 0.15 (IQ 0.0 – 2.32) vs AL 1.04 (0.19 – 2.22), p=0.023), right common iliac artery (No-AL 0.29 (0.0 – 2.46) vs AL 1.13 (0.31 – 4.25), p=0.007) and right & left common iliac arteries (No-AL 0.52 (IQ 0.0 – 5.05) vs AL 2.42 (IQ 0.56 – 6.70), p=0.010).

Table II
Methodological item for non-randomized studies (MINORS) score

Methodological item for non-randomized studies	Boersema[19]	Eveno[27]	Komen[16]	Kornmann[18]	Lee[29]	Pochhammer[26]	Postaire[28]	Shen[17]
1. A clearly stated aim	2	2	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2	2	2
4. Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	2	0	2	0	2
6. Follow-up period appropriate to the aim of the study	2	2	0	0	0	2	2	0
7. Loss to follow up less than 5%	0	2	0	0	0	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	2	0	0
Additional criteria in the case of comparative studies								
9. An adequate control group	2	2	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2	2	2
12. Adequate statistical analyses	2	1	2	2	2	2	2	2
Total score	18	19	16	18	16	22	18	18

The maximum score is 24 points. 0 = not reported, 1 = reported but not adequate, 2 = adequate reported; A MINORS score of 12< was considered to be poor-, 12-17 was moderate- and >17 was good methodological quality

Table III
Subcategory A; Pochhammer et al.[26] & Boersema et al.[19]; Univariate analysis with a threshold of 300 Hounsfield Units

	n= 230 No anastomotic leakage (%)	n= 44 Anastomotic leakage (%)	P-value
Patient characteristics			
Age (y)	66 (56 - 74)	65.5 (55.25 - 78)	0.638
BMI ≥30	33 (14.8)	13 (30.2)	**0.014**
Gender			0.906
Male	118 (51.3)	23 (52.3)	
Female	112 (48.7)	21 (47.7)	
ASA ≥3	35 (15.8)	12 (30.0)	**0.032**
Cardiac comorbidity	76 (33.0)	18 (40.9)	0.314
Diabetes Mellitus	26 (11.3)	6 (13.6)	0.659
Neoadjuvant radiotherapy	9 (3.9)	2 (4.5)	0.692
Approach*			0.085
Laparotomy	128 (55.7)	30 (69.8)	
Laparoscopy	102 (44.3)	13 (30.2)	
Emergency	10 (4.3)	2 (4.5)	1.000
Diverting stoma*	39 (17.2)	7 (16.3)	0.885
Type of anastomosis*			0.274
Colon-colon	26 (11.4)	2 (4.7)	
Colorectal+	203 (88.6)	41 (95.3)	
Calcium Score	**Median (interquartile range 25-75)**	**Median (interquartile range 25-75)**	
Total trajectory	3.07 (0.24 – 18.04)	8.90 (2.76 – 27.00)	**0.025**
Abdominal aorta	1.87 (0.06 – 9.67)	4.23 (1.46 – 23.74)	**0.022**
Left common iliac artery	0.15 (0.0 – 2.32)	1.04 (0.19 – 2.22)	**0.023**
Right common iliac artery	0.29 (0.0 – 2.46)	1.13 (0.31 – 4.25)	**0.007**
Left internal iliac artery	0.03 (0.0 – 0.65)	0.27 (0.0 – 1.14)	0.053
Right internal iliac artery	0.03 (0.0 – 0.66)	0.08 (0.0 – 1.01)	0.479
Right and left common iliac arteries	0.52 (0.0 – 5.05)	2.42 (0.56 – 6.70)	**0.010**
Right and left internal iliac arteries	0.15 (0.0 -1.31)	0.36 (0.0 – 2.00)	0.204

Data are mean (SD), n (%), or median (IQR); *does not sum to 274 due to occasional missing data; +Colorectal anastomosis includes sigmoid-rectum and colon-rectum; The American Society of Anesthesiologists (ASA); Original calcium scores are divided by 100.

Table IV
Subcategory A; Komen et al.[16] & Boersema et al.[19] Univariate analysis with a threshold of 500 Hounsfield Units

	n= 217 No anastomotic leakage (%)	n= 40 Anastomotic leakage (%)	P-value
Patient characteristics			
Age (y)	66 (55 - 74)	62.5 (53 - 74)	0.651
BMI ≥ 30	35 (18.3)	11 (29.7)	0.114
Gender			0.549
Male	125 (57.6)	21 (52.5)	
Female	92 (42.4)	19 (47.5)	
ASA ≥ 3*	33 (16.1)	6 (16.7)	0.932
Cardiac comorbidity*	35 (16.4)	11 (28.2)	0.080
Diabetes Mellitus	22 (10.3)	3 (7.7)	0.776
Neoadjuvant radiotherapy	25 (11.3)	3 (7.5)	0.588
Approach*			0.598
Laparotomy	164 (75.6)	31 (79.5)	
Laparoscopy	53 (24.4)	8 (20.5)	
Type of anastomosis*			0.085
Colorectal	142 (65.7)	30 (76.9)	
Colon-colon	45 (20.8)	4 (10.3)	
Ileorectal	24 (11.1)	2 (5.1)	
Ileum - colon	5 (2.3)	3 (7.7)	
Emergency surgery*	15 (6.9)	2 (5.1)	1.000
Diverting stoma	39 (18.2)	6 (15.4)	0.670
Calcium Score	**Median (interquartile)**	**Median (interquartile)**	
Total trajectory	2.71 (0.0 – 15.38)	5.57 (0.0 – 28.04)	0.088
Abdominal aorta	1.51 (0.0 – 9.94)	3.92 (.18 – 14.36)	0.152
Left common iliac artery	0.0 (0.0 – 2.14)	0.26 (0.0 – 3.51)	0.172
Right common iliac artery	0.11 (0.0 – 1.80)	0.61 (0.0 – 4.24)	0.081
left internal iliac artery	0.0 (0.0 – 0.27)	0.0 (0.0 – 0.59)	0.314
Right internal iliac artery	0.0 (0.0 – 0.26)	0.0 (0.0 – 0.43)	0.867
Right and left common iliac arteries	0.41 (0.0 – 3.87)	1.35 (0.0 – 8.95)	0.116
Right and left internal iliac arteries	0.0 (0.0 – 0.52)	0.02 (0.0 – 0.69)	0.665

Data are mean (SD), n (%), or median (IQR); *does not sum to 274 due to occasional missing data; +Colorectal anastomosis includes sigmoid-rectum and colon-rectum; The American Society of Anesthesiologists (ASA); Original calcium scores are divided by 100.

For the 500 HU analysis, univariate analysis did not show significant differences in patient characteristics or vascular trajectories.

For the evaluation of heterogeneity, I^2 for each trajectory is shown in Table V. I^2 ranged from 0% to 83.6%. In the 300 HU analysis, the left internal iliac artery (IIA), right internal iliac artery, and right and left common iliac arteries were likely heterogeneous (I^2 values of 83.6%, 75.2% and 82.0% respectively). The total trajectory (abdominal aorta, left common iliac artery, right common iliac artery and right & left internal iliac arteries combined) was minimally heterogeneous with an I^2 value of 0%.

For the 500 HU analysis, the total trajectory (I^2=73.0%), abdominal aorta (I^2=56.7%), left common iliac artery (I^2=81.9%) and right common iliac artery (I^2= 73.9%) were defined as substantially heterogeneous. The left internal iliac artery (I^2= 11.8%), right internal iliac artery (I^2= 0%), right & left internal iliac arteries (I^2= 0%) and right & left common iliac arteries (I^2= 0%) were minimally heterogeneous.

The independent patient data meta-analysis is presented in Table V, including odds ratios, according to 95% CIs and P-values. The multivariable analysis with a threshold of 300 HU was corrected for ASA classification ≥3, BMI ≥ 30 and study (Pochhammer or Boersema). The analysis with a threshold of 500 HU was corrected for type of anastomosis, cardiac comorbidity and study (Boersema or Komen).

None of the included trajectories with a 300 HU threshold or 500 HU threshold were significantly associated with anastomotic leakage after a multivariable meta-analysis.

Subcategory B

Subcategory B included five papers. In most (n=4) of these papers, vascular calcification was associated with anastomotic leakage after colorectal surgery (Table I).[17,27-29] In addition, three of the five studies considered calcified-associated stenosis of evaluated trajectories by CT scan. The grade of stenosis was classified as either no stenosis, <50% stenosis or ≥50% stenosis. Eveno et al. found that an aortic stenosis of at least 50% was associated with AL after colorectal surgery.[27] Postaire et al. found an association between AL and stenosis (minimal 50%) of the celiac trunk after right colectomy. However, no association was found with mesenteric artery (SMA) stenosis.[28] Kornmann et al. could not confirm these findings using a similar scoring method in patients who underwent colorectal surgery.[18] Secondly, two of the five studies in subcategory B considered the total amount of calcification. This method is consistent with subcategory A, but measurements were performed manually without software. No percentage of stenosis was taken into account. Both studies found that aortic and aortoiliac calcification was associated with AL in patients receiving low anterior resection for rectal cancer.[17,29]

DISCUSSION

This systematic review questioned the role of vascular calcification in relation to anastomotic leakage. This individual patient data meta-analysis showed no significant association between an increased calcium score of the aorta-iliac trajectory and anastomotic leakage after colorectal surgery.

The software designed for the calcium score included in the IPDM was originally validated in cardiology to measure coronary calcification using a threshold of 130 HU.[30] Calcification is associated with a ≥120 HU score on CT scan, which explains the original threshold of 130 HU.[30,31] Due to regular use of contrast agent in CT scans prior to colorectal surgery, studies included in the meta-analysis used a threshold of 300 HU or 500 HU. Contrast agent itself has a density of 100-300 HU and thus could affect outcomes in the case of a threshold lower than 300 HU.[32] Nonetheless, outcomes may be compromised when the 120-300 HU window for calcification assessment is left out. An additional low-dose CT scan without contrast would offer the opportunity to perform a 120-130 HU

Table V
Independent patient data meta-analysis subcategory A

Trajectory	Heterogeneity I^2 (%)	Odds ratio	Confidence interval 95% (lower-upper)	P-value
Pochhammer[26] and Boersema[19] (300 HU threshold) †				
Total trajectory	0.0	1.001	(0.991 - 1.011)	0.869
Abdominal aorta	0.0	1.001	(0.986 - 1.016)	0.926
Left common iliac artery	0.0	0.991	(0.925 - 1.061)	0.786
Right common iliac artery	0.0	1.007	(0.949 - 1.069)	0.819
Left internal iliac artery*	83.6	1.227	(0.742 – 2.030)	0.425
Right internal iliac artery*	75.2	1.115	(0.936 – 1.328)	0.222
Right and left internal iliac arteries*	0.0	1.084	(0.900 – 1.305)	0.395
Right and left common iliac arteries	82.0	1.000	(0.966 - 1.034)	0.978
Komen[16] and Boersema[19] (500 HU threshold) ‡				
Total trajectory*	73.0	1.016	(0.996 – 1.037)	0.127
Abdominal aorta*	56.7	1.019	(0.995 – 1.043)	0.122
Left common iliac artery*	81.9	1.102	(0.910 – 1.333)	0.320
Right common iliac artery*	73.9	1.098	(0.967 – 1.245)	0.144
Left internal iliac artery	11.8	1.161	(0.873 – 1.545)	0.305
Right internal iliac artery	0.0	1.130	(0.850 – 1.500)	0.400
Right and left internal iliac arteries	0.0	1.093	(0.985 – 1.212)	0.094
Right and left common iliac arteries	0.0	1.045	(0.996 – 1.097)	0.071

I^2 represents the severity of heterogeneity: 0%–40%: likely minimal; 30%–60%: likely moderate; 50%–90%: likely substantial; and 75%–100%: likely considerable. The analysis was corrected for study and characteristics with p-value <0.1. †Corrected for study, ASA classification ≥3 and BMI ≥30;

‡ Corrected for study, type of anastomosis and cardiac comorbidity. A fixed-effects model was used to perform multivariable logistic regression analyses;
*due to moderate, substantial or considerable heterogeneity a multivariable analysis was performed within individual studies; odds ratios were then pooled using a random-effect model.

threshold assessment and improve the quality of the software-determined calcium score. In addition, the software-based score of subcategory A has some limitations. First, patient characteristics (height and weight) were not taken into account. Secondly, no stenosis was included in addition to vascular calcification. Therefore, this score gives a general impression of the vascular state and can only be used to assess the risk of AL. Any additional value compared to risk factors such as BMI, ASA and smoking has yet to be demonstrated.

In general, it is assumed that arterial calcification is associated with impaired blood flow and may restrict perfusion and oxygenation. However, blood pressure, collateral vascularization and grade of stenosis, including atheromatous disease, also influences blood flow and should be taken into consideration. Until now, no prospective measurements of anastomotic blood flow in relation to any calcium score have been performed. If impaired perfusion is related to an increased calcium score, improving blood supply can be a fruitful activity. In the case of significant stenosis, improved blood supply might be achieved by angioplasty.

The scoring method in subcategory B based on the percentage of stenosis showed that stenosis of at least 50% is associated with AL. Atherosclerotic disease of the mesenteric arteries could impair mesenteric perfusion and result in bowel damage due to chronic mesenteric ischemia.[33] In most cases of chronic mesenteric ischemia, all major mesenteric arteries show stenosis or occlusions without clinically apparent symptoms except in advanced stages.[33] If mesenteric flow is compromised by such significant stenoses, localized vascular treatment could significantly improve perfusion and anastomotic healing.

However, high-quality prospective studies should first be performed to further explore the association between AL and stenosis of the main supplying arteries. Afterwards, assessment of mesenteric flow in relation to the calcification score might further clarify whether end-organ-perfusion is actually compromised.

Surgeons often evaluate the anastomosis during an operation macroscopically. However, the quality of this evaluation may not be sufficient.[34,35] Near-infrared imaging was introduced to evaluate vascularization perioperatively, but is not widely applied in daily clinical practice and randomized controlled trials are still warranted to prove its clinical value.[36] A combination of both preoperative vascular risk assessment and perioperative control of perfusion is expected to result in well-considered precautionary measures regarding the prevention of AL.[37,38]

In esophageal surgery, a recent meta-analysis demonstrated that vascular calcification was associated with esophageal anastomotic leakage.[39] The gastric tube, which is part of the esophageal anastomosis, is exclusively supplied by the right gastric and gastroepiploic arteries and therefore is prone to impaired perfusion.[40,41] In colorectal surgery, however, similar outcomes could not be con-

Appendix Table I
Preoperative patient characteristics

Author	Year	n	Sex (M/F)	Age (y)*	BMI (kg/m²)	ASA (n, %)	
Overall							
Boersema[19]	2016	135	74/61(54.8/45.2)	n.r.	n.r.	I 25(20.3, II 78(63.4)	III 20(16.3), IV 0(0)
Eveno[27]	2016	60	30/30(50/50)	70.7(57.8 -78.2)	23.3(22-27.9)	I 12(20), II 40(66.7)	III 8(13.3), IV 0(0)
Komen[16]	2011	122	71/51(58.2/41.8)	n.r.	n.r.	I 50(42.0, II 49(41.2)	III 17(14.3), IV 3(2.5)
Kornmann[18]	2014	242	131/111(54.1/45.9)	65(55–74)	25.5(23.0–28.4)	I 44(18.2), II 167(70.0)	III 31(12.8), IV 0(0)
Lee[29]	2020	576	n.r.	n.r.	n.r.	n.r.	
Pochhamme[26]	2018	139	n.r.	n.r.	n.r.	n.r.	
Postaire[28]	2018	306	n.r.	72(19-94)	25.9(14-45)	I 60(19.6), II 157(51.3)	III 78(25.5) IV 11(3.6)
Shen[17]	2019	423	264/159(62.4/37.6)	64.9(53.7-76.1)	23.9(20.4-27.4)	I 50(11.8), II 306(72.4)	III 67(15.8) IV 0(0)
Anastomotic leakage group							
Boersema[19]	2016	30	16/14(53.3/46.7)	64.5(52.9-76.1)	28.3(21.7-35.0)	I 5(19.2), II16(61.6)	III 5(19.2), IV 0(0)
Eveno[27]	2016	13	8/5(61.5/38.5)	73(59-80)	23.8(21.8-25.1)	I 2(15.4), II 9(69.2)	III 2(15.4), IV 0(0)
Komen[16]	2011	11	5/6(7/12)	60.3(47.9-72.7)	24.6(21.9-27.3)	I 5(45.4), II 4(36.4)	III 1(9.1), IV 1(9.1)
Kornmann[18]	2014	34	20/14(58.8/41.2)	64(57–76)	25.1(23.1–28.7)	I 5(14.7), II 24(70.6)	III 5(14.7), IV 0(0)
Lee[29]	2020	30	25/5(83.3/16.7)	n.r.	n.r.	I / II 25(86.2)	III/IV 4(15.8)
Pochhamme[26]	2018	15	7/8(46.7/53.3)	73(50–86)	≥30 2(13.3)	n.r.	>III 8(53.3)
Postaire[28]	2018	23	n.r.	n.r.	n.r.	n.r.	
Shen[17]	2019	33	n.r.	n.r.	n.r.		
No anastomotic leakage group							
Boersema[19]	2016	105	58/47(55.2/44.8)	66.5(55.1-77.9)	26.9(22-31.8)	I 20(20.6), II 62(63.9)	III 15(15.5), IV 0(0)
Eveno[27]	2016	47	22/25(46.8/53.2)	69(56-77.5)	23.3(22-28.4)	I 10(21.2), II 31(66)	III 6(12.8), IV 0(0)
Komen[16]	2011	111	66/45(59.5/40.5)	59.9(43.4-76.4)	25.5(21.3-29.7)	I 45(41.7), II 45(41.7)	III 16(14.8) IV 2(1.8)
Kornmann[18]	2014	208	111/97(53.4/46.6)	65(55–74)	25.5(22.9–28.4)	I 39(18.8), II 143(68.7)	III 26(12.5), IV 0(0)
Lee[29]	2020	546	372/174(68.1/31.9)	n.r.	n.r.	I / II 506 (92.7)	III/IV 34(6.2)
Pochhammer[26]	2018	124	59/65(47.6/52.4)	66(32–88)	≥30 8(6.5)	n.r.	>III 20(16.1)
Postaire[28]	2018	23	n.r.	n.r.	n.r.	n.r.	
Shen[17]	2019	390	n.r.	n.r.	n.r.		

*Age and Body mass index (BMI) are reported as the mean (SD). American Society of Anesthesiologists (ASA) score, n.r. = not reported firmed. This might be explained by the collateral vascularization of the colon and rectum, i.e., the mesenteric arteries, iliac arteries and marginal artery of the colon. It has also been observed that the number of collaterals seems to increase when atherosclerosis is present.[42-45] Furthermore, in this IPDM, the main supplying arteries (superior or inferior mesenteric artery) were not included. In addition, the esophageal analysis considered the percentage of stenosis, while the present study did not.

A recent meta-analysis by Tong et al. concluded that an increased calcium score is associated with anastomotic leakage. The main difference between Tong et al. and this meta-analysis is the methodology, as analyses on individual patient data could be performed and corrected for confounders. Furthermore, in the study by Tong et al., the measurements with threshold values of 300 HU and 500 HU were pooled, probably impairing accuracy as the amount of calcification measured is obviously different. Therefore, in the present study, separate analyzes between the 300 and 500 HU methods were chosen. In addition, other calcification scores were stated to clarify the diversification.

The outcome of the IPDM should be interpreted with caution due to some limitations. For example, a limited number of studies were included. All of the studies, except for that by Pochhammer et al., were retrospectively designed, which includes the possibility of selection and information bias. A funnel plot, to assess publication bias, was not feasible because of the limited number of studies included in the meta-analysis.

Despite these limitations, a meta-analysis could be performed on subcategory A by using individual patient data. This offers the opportunity to correct for several confounders which could not be achieved in a 'conventional' meta-analysis. The authors recognize that not all confounders could be included in the multivariable analysis, due to a limitation of power.[46]

CONCLUSION

The individual patient data meta-analysis on the software-based calcium score did not detect any association between calcification and anastomotic leakage in colorectal surgery after multivariable analysis. In addition, this study demonstrated several methods for scoring arterial calcification and the need for a standardized technique. Although most of the literature found an association between vascular calcification and AL, this study could not confirm these findings for any calcification-measuring method that gave the software-based calcium score. New prospective studies are recommended using only calcification scoring methods that include grade of stenosis due to its potential to preoperatively improve perfusion by endovascular treatment. Furthermore, inclusion of the superior and inferior mesenteric arteries is also advisable. STI

Appendix Table I (continued)
Preoperative patient characteristics

Neoadjuvant radiotherapy (n,%)	Use of steroids (n,%)	Anti-hypertensive medication (n,%)	Use of statins (n,%)	History of vascular disease (n,%)	Cardiac comorbidity (n,%)	Hypertension (n,%)	Diabetes mellitus (n,%)	Smoker (n,%)	Alcohol (n,%)	Abdominal surgery in history (n,%)
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.	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.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
n.r.	n.r.	116(47.9)	43(17.8)	145(59.9)	159(65.7)	164(67.8)	143(59.1)	44(18.2)	98(40.5)	128(52.9)
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
3(2.2)	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.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
31(7.3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	223(52.7)	67(15.8)	87(20.6)
2(6.9)	1(3.3)	10(33.3)	5(17.9)	1(3.3)	9(30.0)	n.r.	3(10)	9(33.3)	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.
1(9.1)	3(27.3)	3(27.3)	2(18.2)	3(27.3)	3(27.3)	n.r.	1(9.1)	3(27.3)	n.r.	n.r.
n.r.	n.r.	16(47.1)	8(23.5)	21(61.8)	20(58.8)	22(64.7)	20(58.8)	8(23.5)	15(44.1)	20(58.8)
8(26.6)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
0(0)	n.r.	n.r.	n.r.	3(20)	10(66.7)	n.r.	4(26.7)	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.	n.r.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
6(5.7)	6(5.7)	39(37.5)	13(12.5)	8(7.6)	14(13.3)	n.r.	12(11.4)	29(30.9)	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.
19(17.1)	8(7.2)	25(22.5)	12(10.8)	19(17.1)	21(18.9)	n.r.	9(8.1)	18(16.2)	n.r.	n.r.
n.r.	n.r.	100(48.1)	35(16.8)	124(59.6)	139(66.8)	142(68.3)	123(59.1)	36(17.9)	83(41.5)	108(51.9)
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
3(2.4)	n.r.	n.r.	n.r.	7(5.6)	62(50)	n.r.	13(10.5)	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.	n.r.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

*Age and Body mass index (BMI) are reported as the mean (SD). American Society of Anesthesiologists (ASA) score, n.r. = not reported

Appendix Table II
Peri- and postoperative patient characteristics

Author	Year	n	Emergency vs Elective (n, %)	(Sub)total colectomy (n, %)	Right sided colon surgery± (n, %)	left sided colon surgery* (n, %)	Other+ (n, %)	end to end anastomosis (n, %)	end to side (n, %)
Overall									
Boersema[19]	2016	135	n.r.	0	0	131(97.0)	4(3.0)	58(43.3)	7(5.2)
Eveno[27]	2016	60	6/54(10/90)	3(5)	0	57(95.0)	0	n.r.	n.r.
Komen[16]	2011	122	16/105(13.2/86.8)	0	32(26.2)	90(73.8)	0	15(12.4)	9(7.4)
Kornmann[18]	2014	242	36/205(14.9/85.1)	7(2.9)	104(43.0)	96(39.7)	35(14.4)	n.r.	n.r.
Lee[29]	2020	576	n.r.	0	0	576(100)	0	n.r.	n.r.
Pochhammer[26]	2018	139	11/128(7.9/92.1)	11(7.9)	n.r.	125(89.9)	3(10.1)	n.r.	n.r.
Postaire[28]	2018	306	0/306(0/100)	0	306(100)	0	0	n.r.	n.r.
Shen[17]	2019	423	0/423(0/100)	0	0	423(100)	0	n.r.	n.r.
Anastomotic leakage group									
Boersema[19]	2016	30	n.r.	0	0	28(93.3)	2(6.7)	17(58.6)	2(6.9)
Eveno[27]	2016	13	0/13(0/100)	1(7.7)	n.r.	12(92.3)	0	n.r.	n.r.
Komen[16]	2011	11	1/9(10/90)	0	3(27.3)	8(72.7)	0	3(30)	0(0)
Kornmann[18]	2014	34	3/31(8.8/91.2)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Lee[29]	2020	30	n.r.	0	0	30(100)	0	n.r.	n.r.
Pochhammer[26]	2018	15	1/14(6.7/93.3)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Postaire[28]	2018	23	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Shen[17]	2019	33	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
No anastomotic leakage group									
Boersema[19]	2016	105	n.r.	0	0	103(98.1)	2(1.9)	41(47.1)	5(5.7)
Eveno[27]	2016	47	6/41(12.8/87.2)	2(4.3)	0	45(95.7)	0	n.r.	n.r.
Komen[16]	2011	111	15/96(13.5/86.5)	0	29(26.1)	82(73.9)	0	12(10.8)	9(8.1)
Kornmann[18]	2014	208	33/174(15.9/84.1)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Lee[29]	2020	546	n.r.	0	0	546(100)	0	n.r.	n.r.
Pochhammer[26]	2018	124	10/114(8.1/91.9)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Postaire[28]	2018	23	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Shen[17]	2019	390	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

±Right-sided colon surgery includes ileocecal resection, right hemicolectomy, and transverse colon resection; *Left-sided colon surgery includes left hemicolectomy, sigmoidectomy, rectosigmoid resection, and (low) anterior resection; +Other includes not specified surgery or restoration procedures; n.r. = not reported; n.a. = not applicable

AUTHORS' DISCLOSURES

The authors state that there are no conflicts of interest.

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Appendix Table II (continued)
Peri- and postoperative patient characteristics

side to end (n, %)	side to side (n, %)	Laparotomy/ laparoscopy (n, %)	Conver-sion (n, %)	Stap led/sutured (n, %)	Protective Ileostomy (n, %)	Suction drain (n, %)	Pathology (benign/malign) (n,%)	Mortality (n, %)	Anasto-motic leak-age (n,%)
36(26.9)	15(11.2)	90/44 (67.2/32.8)	n.a.	81/53(60.4/39.6)	n.a.	n.a.	n.r.	3(2.2)	n.a.
n.r.	n.r.	n.r.	n.r.	40/20(66.7/33.3)	26(43.3)	37(61.7)	n.r.	3(5)	13(21.7)
33(27.3)	51(42.1)	105/17 (86.1/13.9)	n.r.	48/74(39.3/60.7)	n.r.	40(32.8)	n.r.	6(4.9)	11(9)
n.r.	n.r.	138/89 (60.8/39.2)	14(5.8)	n.r.	19(7.9)	n.r.	113/129 (46.7/53.3)	8(3)	34(14)
n.r.	n.r.	18/558(3.1/96.9)	n.r.	473/103(82.1/17.9)	188(32.6)	n.r.	0/576(0/100)	n.r.	30(5.5)
n.r.	n.r.	68/71 (48.9/51.1)	n.r.	n.r.	23(16.5)	n.r.	87/52 (62.6/37.4)	n.r.	15(11)
n.r.	306(100)	161/145 (52.6/47.4)	n.r.	0/306(0/100)	n.r.	n.r.	77/229 (25.2/74.8)	n.r.	23(9.1)
n.r.	n.r.	298/125 (70.4/29.6)	26(6.2)	n.r.	104(24.6)	n.r.	0/423 (0/100)	2(0.5)	33(7.8)
5(17.2)	5(17.2)	22/7 (75.9/24.1)	5(26.0)	14/15(48.3/51.7)	4(14.3)	20(69)	n.r.	1(3.3)	n.a.
n.r.	n.r.	n.r.	n.r.	7/6(53.8/46.2)	9(69.2)	12(92.3)	n.r.	n.r.	n.a.
2(20)	5(50)	10/1 (90.9/9.1)	n.r.	2/9(18.2/81.8)	n.r.	3(27.3)	n.r.	3(27.3)	n.a.
n.r.	n.r.	21/11 (65.6/34.4)	2(5.9)	n.r.	8(23.5)	n.r.	10/24 (29.4/70.6)	4(12)	n.a.
n.r.	n.r.	1/29(3.3/96.7)	n.r.	23/7(76.7/23.3)	7(23.3)	n.r.	0/30(0/100)	n.r.	n.a.
n.r.	n.r.	9/6 (60/40)	n.r.	n.r.	3(20)	n.r.	8/7 (53.4/46.6)	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	6(18.1)	n.r.	0/33 (0/100)	1(3.0)	n.a.
31(35.6)	10(11.5)	68/37 (64.8/35.2)	14(74.0)	67/38(63.8/36.2)	15(17.9)	51(49.5)	n.r.	2(1.9)	n.a.
n.r.	n.r.	n.r.	n.r.	33/14(70.2/29.8)	17(36.2)	25(53.2)	n.r.	n.r.	n.a.
31(27.9)	46(51.1)	95/16 (85.6/14.4)	n.r.	46/65(41.4/58.6)	n.r.	37(33.3)	n.r.	3(2.7)	n.a.
n.r.	n.r.	117/78 (60.0/40.0)	12(5.7)	n.r.	11(5.3)	n.r.	103/105 (49.5/50.5)	4(1.9)	n.a.
n.r.	n.r.	17/529(3.1/96.9)	n.r.	450/96(82.4/17.6)	181(33.2)	n.r.	0/546(0/100)	n.r.	n.a.
n.r.	n.r.	59/65 7.6/52.4)	n.r.	n.r.	20(16)	n.r.	86/38 (69.4/30.6)	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.
n.r.	n.r.	n.r.	n.r.	n.r.	98(25.1)	n.r.	0/390 (0/100)	1(0.3)	n.a.

±Right-sided colon surgery includes ileocecal resection, right hemicolectomy, and transverse colon resection; *Left-sided colon surgery includes left hemicolectomy, sigmoidectomy, rectosigmoid resection, and (low) anterior resection; +Other includes not specified surgery or restoration procedures; n.r. = not reported; n.a. = not applicable

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