

# Calcification of arteries supplying the gastric tube increases the risk of anastomotic leakage after esophagectomy with cervical anastomosis

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**Background:** Anastomotic leak is an important cause of morbidity and mortality after esophagectomy for esophageal cancer patients. Calcification of the arteries supplying the gastric tube has been found to be associated with leakage after esophagectomy with cervical anastomosis in Europeans. The purpose of this study is to evaluate the association between calcifications of the supplying arteries of the gastric tube and the occurrence of anastomotic leakage after esophagectomy with cervical anastomosis in Chinese patients with esophageal cancer.

**Methods:** The demographic, clinical, and pathological features as well as the vascular calcification of arteries of 709 esophageal cancer patients who had undergone esophagectomies with cervical anastomosis were analyzed. Univariable and multivariable logistic regression were used to identify the association between the postoperative anastomotic leakage and calcifications of the arteries supplying the gastric tube.

**Results:** Among the 709 patients, 122 (17.2%) had developed anastomotic leakage. Thirty-day mortality and length of hospital stay were higher for patients with anastomotic leakage. Upper digestive tract ulcer, peripheral vascular disease, renal insufficiency, American society of Anesthesiologists (ASA) risk class, and calcifications of aorta and celiac axis were found to be independent risk factors for the anastomotic leakage.

**Conclusions:** Calcification of the aorta and celiac axis that supply the gastric tube is an independent risk factor for cervical anastomotic leakage after esophagectomy in Chinese esophageal cancer patients.

**Keywords:** Esophagectomy; cervical anastomotic leakage; calcification; risk factor; esophageal cancer

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## Introduction

Improvements in surgical techniques and perioperative care have led to a steady decrease in postoperative mortality of esophagectomy over the years (1). Anastomotic leakage, a radiologically or clinically apparent esophagogastronomy

anastomotic dehiscence and one of the major complications of esophagectomy, is an important cause of perioperative morbidity and mortality. Thoracic and cervical anastomosis is the two main methods used for upper gastrointestinal tract reconstruction. In Chinese population, the

intrathoracic anastomotic leakage rate is reported to be 2.8% to 6.6% while the rate of cervical anastomotic leakage is 7.9% to 20.7% (2,3). A relatively higher incidence may result in an increased risk of stricture and perioperative death (4,5).

According to the results of related studies, risk factors of anastomotic leakage after esophagectomy include older age, ischemia of the gastric tube, malnutrition, hypotension, hypoxemia, renal insufficiency, neoadjuvant therapy, steroid use, smoking, diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular disease, high body mass index, surgical approach, and the small number of esophagectomy procedures performed in a hospital (4,6-8). In all these factors, poor tissue perfusion is considered a major cause of anastomotic leakage.

Atherosclerosis, a known cause of ischemia, has been reported to compromise the blood supply of the gastric tube and cervical anastomosis (9). It has also been reported that calcification of the aortic wall and supra-aortic arteries can be used to predict cardiovascular events (10). Another study in European patients showed that calcification of the arteries supplying the gastric tube was independently associated with leakage after esophagectomy with cervical anastomosis (11). However, according to our knowledge, whether calcification of the gastric tube supplying arteries leads to a higher risk of leakage after esophagectomy with cervical anastomosis in Chinese esophageal cancer patients has not been investigated. In China, esophageal squamous cell carcinoma (ESCC) is the dominant subtype of esophageal cancer, which is different from western countries, where esophageal adenocarcinoma (EAC) is most commonly observed (12). Additionally, Asians have different adipose contents, partitioning, adipocyte morphology, and greater predisposition to cardiometabolic disease than Caucasians (13). Thus, the association between artery calcification and anastomotic leak for Chinese esophageal cancer patients requires further research.

In the current study, we retrospectively summarized the clinical characteristics of esophageal cancer patients who had received esophagectomy with cervical anastomosis and investigated leakage related factors. Especially, we aimed to identify the association between calcification of the supplying arteries of the gastric tube and anastomotic leakage in Chinese patients.

## Methods

### *Patients and clinical data*

The clinical data of 709 patients who had received elective

esophagectomy with cervical anastomosis between January 2010 and May 2015 in Cancer Institute and Hospital, Chinese Academy of Medical Sciences (CAMS) were collected for the study. The demographic, clinical, and pathological features were obtained through reviewing their medical records. All patients were confirmed to have primary esophageal cancer by two independent pathologists (XL-F and SS-S). All the patients had received an abdominal-thoracic computed tomography (CT) scan and upper gastrointestinal endoscopic examination before surgery. TNM stages of the patients were determined according to the seventh edition of the Union for International Cancer Control (UICC) staging system. This study had been approved by the ethics committee of Cancer Institute and Hospital, CAMS and written informed consent was obtained from all patients before surgery.

### *Surgical procedures*

Esophagectomy was performed via the left chest, or McKeown approach via the right chest with a cervical anastomosis in all patients. Slender conduit (3–5 cm Width) was used in 477 patients, and whatever kind of conduit was used for the other 232 patients. All the patients obtained cervical anastomosis. For better exposition of the operative field, the patient was took a supine position and placed with an extended neck and head turned to the right side. Through an oblique incision of the skin and the muscles on the left side of the neck, the cervical esophagus was mobilized, after which the specimen was removed through the cervical incision, with which the gastric tube was pulling up to the neck. An end-to-side esophagogastric anastomosis was performed in the neck using either the single-layer hand-sewn or circular stapled anastomotic technique by using an end-to-end anastomosis (EEA) stapler (DST Series™ EEA™ 25 mm Stapler, 4.8 mm staple size; Covidien).

### *Postoperative care*

After surgery, enteral nutrition was given on the postoperative day (POD) 1 to 3 through a jejunal feeding tube. The amount of enteral nutrition was gradually increased if the patient did not complain nausea, vomiting, abdominal distension, abdominal pain or diarrhea. The drainage in the neck was usually removed on POD 3 to POD 5. Without postoperative complications, oral feeding started around POD 7 to POD 9. Intravenous proton pump

inhibitors (PPIs) or H<sub>2</sub>-blockers were usually prescribed on POD 1 and were given orally after oral feeding. The majority of patients were discharged between POD 11 and POD 13. All the patients were followed up 2 weeks after discharge, and every 3 months afterwards.

### *Diagnosis of anastomotic leakage*

A cervical anastomotic leakage was first suspected if any clinical signs of leakage (e.g., fever or presence of purulent or salivary discharge from cervical wound or chest tube), radiologic signs of leakage (e.g., contrast leakage or fluid and air levels surrounding the anastomosis), or signs of anastomotic dehiscence during endoscopy or reoperation appeared during the follow-up period. In case anastomotic leakage was clinically suspected, a CT scan, water-soluble contrast swallow study or endoscopy was performed. No routine diagnostic tests were performed (14).

### *Imaging acquisition and assessment*

A visual calcification grading system was modified from a previously reported score for grading aortic wall abnormalities in the prediction of cardiovascular events in our study. Considering whether such a system can be applied to the Chinese population is still uncertain. Only the presence or absence of calcification in vessels was considered in our study. Due to the lack of the imaging data of 36 of the 709 patients enrolled, CT imaging of 673 patients who underwent preoperative chest and abdominal CT examinations were eventually included to be analyzed. All preoperative CT studies were independently reviewed by two experienced thoracic surgeons (B-Q and JG-L, with 10 and 9 years of experience performing thoracic surgery, respectively) who were blinded to patient and operation related characteristics and clinical outcome in terms of anastomotic leakage. To ensure the reliability of this study, another radiologist (J-J), who was also blinded to the data of patients, was also invited to evaluate CT imaging. The selection of investigated vessels was based on anatomic studies, which showed that the right gastroepiploic artery exclusively supplies the gastric tube and originates from the aorta via the celiac axis, common hepatic artery, and gastroduodenal artery (9,15). Furthermore, calcifications in the splenic and left gastroepiploic arteries were assessed because it has been reported that about 20% of the gastric tube is supplied by the left gastroepiploic arteries before divided (15). To facilitate the evaluation the calcification

and ensure the accuracy of the results, we divided the vessels mentioned into four parts: aorta (i.e., descending part of thoracic aorta and abdominal part of aorta above celiac level), celiac axis, right postceliac arteries (i.e., common hepatic artery, gastroduodenal artery, and right gastroepiploic artery) and left postceliac arteries (i.e., splenic artery and left gastroepiploic artery). Calcifications in the vessels were judged in the transverse plane (reconstruction thicknesses and intervals were 5 mm and 5 mm, respectively) and were reviewed with the standard mediastinal window (window width, 300–400 HU; window level, 40–50 HU). Discrepancies in interpretation between observers were resolved by consensus.

### *Statistical analysis*

Continuous variables were presented with mean and standard deviation. Frequencies and percentages were presented by categorical variables. Continuous variables were compared between groups with Wilcoxon two-sample test while categorical variables by Chi-square test. Variables were entered in a multivariable logistic regression model to evaluate whether these factors were independently associated with the occurrence of anastomotic leakage if they were associated to the cervical anastomotic leak in the univariate analysis. Probability values of less than 0.05 were considered to be statistically significant, and there was no adjustment made for multiplicity of comparisons.

## **Results**

A total of 709 patients in our study underwent esophagectomy with cervical anastomosis, among which 17.2% (122 of 709) had postoperative anastomotic leakage. The average length of hospital stay after surgery was 13.05 days for patients without anastomotic leakage and 34.85 days for those with anastomotic leakage ( $P < 0.0001$ ). Postoperative 30-day mortality rate was 4.92% (6 of 122) and 0.34% (2 of 587) for patients with and without anastomotic leakage, respectively ( $P = 0.0010$ ) (Table 1).

Comparison of demographic and clinical characteristics of patients with or without leakage (Table 2) showed that American society of Anesthesiologists (ASA) risk class, prior thoracic surgery, upper digestive tract ulcer, COPD, hypertension, peripheral vascular disease, renal insufficiency, forced expiratory volume in one second (FEV<sub>1</sub>) predicted and diffusion capacity for carbon monoxide of the lung (DLCO) predicted were significantly associated with an

**Table 1** Mortality and length of stay for patients with and without anastomotic leakage

Characteristics	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
Days after operation (mean ± SD)	13.05±6.97	34.85±22.51	16.80±13.95	<0.0001
In-hospital or 30-day mortality				0.0010
Yes	2 (0.34)	6 (4.92)	8 (1.12)	
No	585 (99.66)	116 (95.08)	701 (98.90)	

SD, standard deviation.

**Table 2** Demographic and clinical features of patients and their association with anastomotic leakage

Characteristics	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
Age at time of surgery (y) (mean ± SD)	59.25±7.98	58.81±8.21	59.17±8.01	0.582
Age at time of surgery (y)				0.9391
<60	291 (49.57)	62 (50.82)	353 (49.79)	
≥60 and <70	238 (40.55)	47 (38.52)	285 (40.20)	
≥70	58 (9.88)	13 (10.66)	71 (10.01)	
Sex				0.2703
Male	465 (79.22)	102 (83.61)	567 (79.97)	
Female	122 (20.78)	20 (16.39)	142 (20.03)	
ASA risk class				0.0005
I	128 (21.81)	17 (13.93)	145 (20.45)	
II	416 (70.87)	83 (68.03)	499 (70.38)	
III	43 (7.33)	22 (18.03)	65 (9.17)	
Body mass index (kg/m <sup>2</sup> )				0.403
Mean ± SD	23.44±3.23	23.71±3.61	23.39±3.30	
Body mass index (kg/m <sup>2</sup> )				0.6917
<18.5	30 (5.11)	11 (9.02)	41 (5.78)	
≥18.5 and <24.99	381 (64.91)	67 (54.92)	448 (63.19)	
≥25	176 (29.98)	44 (36.07)	220 (31.03)	
Prior neck surgery				0.6126
Yes	23 (3.92)	6 (4.92)	29 (4.09)	
No	564 (96.08)	116 (95.02)	680 (95.91)	
Prior thoracic surgery				0.0048
Yes	13 (2.21)	9 (7.38)	22 (3.10)	
No	574 (97.79)	113 (92.62)	687 (96.90)	
Prior abdominal surgery				0.4338
Yes	67 (11.41)	17 (13.93)	84 (11.85)	
No	520 (88.59)	105 (86.07)	625 (88.15)	

**Table 2** (continued)

Table 2 (continued)

Characteristics	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
Upper digestive tract ulcer				0.0020
Yes	19 (3.24)	12 (9.84)	31 (4.37)	
No	568 (96.76)	110 (90.16)	678 (95.63)	
Pulmonary tuberculosis				0.8606
Yes	11 (1.87)	2 (1.64)	13 (1.83)	
No	576 (98.13)	120 (98.36)	696 (98.17)	
COPD				0.0377
Yes	19 (3.24)	9 (7.38)	28 (3.95)	
No	568 (96.76)	113 (92.62)	681 (96.05)	
Cardiac arrhythmia (1 week before surgery)				0.3389
Yes	77 (13.12)	20 (16.39)	97 (13.68)	
No	510 (86.88)	102 (83.61)	612 (86.32)	
Coronary artery disease				0.3080
Yes	18 (3.07)	6 (4.92)	24 (3.39)	
No	569 (96.93)	116 (95.08)	685 (96.61)	
Hypertension				0.0043
Yes	134 (22.83)	43 (35.25)	177 (24.96)	
No	453 (77.17)	79 (64.75)	532 (75.04)	
Peripheral vascular disease				0.0001
Yes	13 (2.21)	12 (9.84)	25 (3.53)	
No	574 (97.79)	110 (90.16)	684 (96.47)	
Diabetes				0.0716
Yes	43 (7.33)	15 (12.30)	58 (8.18)	
No	544 (92.67)	107 (87.70)	651 (91.82)	
Hepatic dysfunction				0.7653
Yes	544 (92.67)	114 (93.44)	658 (92.81)	
No	43 (7.33)	8 (6.56)	51 (7.19)	
Renal insufficiency				0.0163
Yes	8 (1.36)	6 (4.92)	14 (1.97)	
No	579 (98.64)	116 (95.08)	695 (98.03)	
Hyperlipidemia				0.2071
Yes	94 (16.01)	14 (11.48)	108 (15.23)	
No	491 (83.65)	108 (88.52)	601 (84.77)	
Steroids				0.1442
Yes	5 (0.85)	3 (2.46)	8 (1.13)	
No	582 (99.15)	119 (97.54)	701 (98.87)	

Table 2 (continued)

Table 2 (continued)

Characteristics	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
NSAIDs				0.6892
Yes	13 (2.21)	2 (1.64)	15 (2.12)	
No	574 (97.79)	120 (98.36)	694 (97.88)	
Cigarette smoker				0.5870
Yes	355 (60.48)	77 (63.11)	432 (60.93)	
No	232 (39.52)	45 (36.89)	277 (39.07)	
Brinkman index				0.7530
Mean ± SD	398.65±471.80	384.10±433.44	396.15±465.16	
Long-term drinker				0.1113
Yes	349 (59.45)	82 (67.21)	431 (60.79)	
No	238 (40.55)	40 (32.79)	278 (39.21)	
Alcohol consumption (drink)				0.7401
Mean ± SD	11.84±14.01	11.41±12.87	11.77±13.82	
Preoperative ALB				0.4381
Normal	531 (90.46)	108 (88.52)	641 (90.41)	
Abnormal	54 (9.20)	14 (11.48)	68 (9.59)	
Preoperative PALB				0.6135
Normal	405 (68.99)	87 (71.31)	492 (69.39)	
Abnormal	182 (31.01)	35 (28.69)	217 (30.61)	
FEV1 predicted				0.0066
<60	27 (4.60)	7 (5.74)	34 (4.80)	
≥60 and <80	134 (22.83)	44 (36.07)	178 (25.11)	
≥80	426 (72.57)	71 (58.20)	497 (70.10)	
DLCO predicted	n=563	n=119	n=682	0.0228
<60	84 (14.92)	27 (22.69)	111 (16.28)	
≥60 and <80	195 (34.64)	43 (36.13)	238 (34.90)	
≥80	284 (50.44)	49 (41.18)	333 (48.83)	
Neoadjuvant treatment				0.5984
Radiotherapy	11 (1.87)	3 (2.46)	14 (1.97)	
Chemotherapy	12 (2.04)	0 (0.00)	12 (1.69)	
Chemoradiotherapy	45 (7.67)	9 (7.38)	54 (7.62)	
None of both	519 (88.42)	110 (90.16)	629 (88.72)	

ASA, American Society of Anesthesiology; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal antiinflammatory drugs; ALB, albumin; PALB, prealbumin; FEV1, forced expiratory volume in one second; DLCO, diffusion capacity for carbon monoxide of the lung.

**Table 3** Surgical features and their association with anastomotic leakage

Characteristics	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
Operative time (min)				0.1469
<300	147 (25.04)	23 (18.85)	170 (23.98)	
≥300	440 (74.96)	99 (81.15)	539 (76.02)	
Intraoperative blood transfusion				0.6333
Yes	114 (19.42)	26 (21.31)	140 (19.75)	
No	473 (80.58)	96 (78.69)	569 (80.25)	
Transthoracic approach				0.0968
Right side	549 (93.53)	119 (97.54)	668 (94.22)	
Left side	38 (6.47)	3 (2.46)	41 (5.78)	
Surgical approach				0.0770
Thoracoscopic-laparotomic	81 (13.80)	12 (9.84)	93 (13.12)	
Thoracotomic-laparoscopic	4 (0.68)	0 (0.00)	4 (0.56)	
Thoracolaparoscopic	278 (47.36)	70 (57.38)	348 (49.08)	
Thoracolaparotomic	224 (38.16)	40 (32.79)	264 (37.24)	
Esophageal substitute				0.0599
Subtotal stomach	201 (34.24)	31 (25.41)	232 (32.72)	
Slender gastric tube	386 (65.76)	91 (74.59)	477 (67.28)	
Anastomosis method				0.9282
Hand-sewn	190 (32.37)	40 (32.79)	230 (32.44)	
Stapled	397 (67.63)	82 (67.21)	479 (67.56)	
Lymph node dissection				0.6126
Three-field	23 (3.92)	6 (4.92)	29 (4.09)	
Two-field	564 (96.08)	116 (95.08)	680 (95.91)	

increased risk of anastomotic leakage ( $P<0.05$ ).

We next evaluated the effect of surgical and pathological factors on anastomotic leakages. The results of the comparison showed that none of the surgical (*Table 3*) or pathological features (*Table 4*) had significant association with cervical anastomotic leakage.

Further, we investigated whether calcification of gastric tube supplying arteries would affect an anastomotic leakage in the 673 patients with preoperative CT scan. The proportion of patients with calcification in the aorta, celiac axis, right postceliac arteries and left postceliac arteries were 25.71% (173 of 673), 15.01% (101 of 673), 0.45% (3 of 673) and 0.59% (4 of 673), respectively. Chi-square test revealed that patients with calcification of aorta ( $P<0.0001$ ), celiac

axis ( $P<0.0001$ ) and left postceliac arteries ( $P=0.0218$ ) had significantly higher rate of anastomotic leakage in univariate analysis. No significant increased risk of anastomotic leak was discovered for calcification of the right postceliac arteries (*Table 5*). Examples of the image characteristics are presented in *Figure 1*.

To define independent risk factors of postoperative cervical anastomotic leak for patients who underwent esophagectomy, the calcification of the aorta, celiac axis, and left postceliac arteries were entered into the multivariate logistic regression model, along with ASA risk class, prior thoracic surgery, upper digestive tract ulcer, pulmonary tuberculosis, hypertension, peripheral vascular disease, renal insufficiency, FEV1 predicted and DLCO predicted.

**Table 4** Pathological factors and association with anastomotic leakage

Characteristic	No leak (n=587), n (%)	Leak (n=122), n (%)	Total (n=709), n (%)	P value
TNM staging				0.2208
I	139 (23.68)	22 (18.03)	161 (22.71)	
II	173 (29.47)	36 (29.51)	209 (29.48)	
III	193 (32.88)	46 (37.70)	239 (33.71)	
Uncertain	82 (13.97)	18 (14.75)	100 (14.10)	
Pathologic subtype				0.6610
Squamous cell carcinoma	572 (97.44)	118 (96.72)	690 (97.32)	
Adenocarcinoma	15 (2.56)	4 (3.28)	19 (2.68)	
Tumor location				0.7562
Upper	175 (29.81)	31 (25.41)	206 (29.06)	
Middle	246 (41.91)	60 (49.18)	306 (43.16)	
Lower	138 (23.51)	25 (20.49)	163 (22.99)	
Multiple	28 (4.77)	6 (4.92)	34 (4.79)	
Tumor length (cm)				0.301
<3	128 (21.81)	19 (15.57)	147 (20.73)	
≥3 and <5	248 (42.25)	55 (45.08)	303 (42.74)	
≥5	211 (35.95)	48 (39.34)	259 (36.53)	
Neoadjuvant therapy response	n=68	n=12	n=80	0.0931
Mild	23 (33.82)	1 (8.33)	24 (30.00)	
Moderate	19 (27.94)	4 (33.33)	23 (28.75)	
Severe	26 (38.24)	7 (58.33)	33 (41.25)	

The results of the analysis showed that the upper digestive tract ulcer (OR =2.666; 95% CI: 1.128–6.300; P=0.0255), peripheral vascular disease (OR =2.963; 95% CI: 1.166–7.530; P=0.0225), renal insufficiency (OR =3.686; 95% CI: 1.117–12.169; P=0.323), ASA risk class (OR =1.725; 95% CI: 1.098–2.710; P=0.0180), calcifications of aorta (OR =2.300; 95% CI: 1.429–3.704; P=0.0006) and celiac axis (OR =1.823; 95% CI: 1.051–3.162; P=0.326) were independently associated with increased risk of anastomotic leak (Table 6).

## Discussion

The assessment of calcification in our study was based on a previously described and validated visual grading system used to score aortic abnormalities (e.g., calcifications, irregularity, plaques, and elongation of the aortic wall)

observed on routine diagnostic CT images that was shown to be useful in the prediction of cardiovascular events (10,16). However, besides calcifications, the addition of these parameters did not lead to substantial improvement of the prediction model (10). Furthermore, scores for calcifications of the thoracic aorta can be used to predict the incidence rate of cardiovascular events (10). According to these studies, another recent study focused on the calcification of the arteries supplying the gastric tube and showed that a higher score of calcification in the aorta and right postceliac arteries conferred a higher chance of cervical anastomotic leakage (11). Because Chinese patients are different from those of the western countries in terms of pathological subtype and other biochemical factors (12,13), it was uncertain whether a quantitative system could be used in the study of Chinese people. We decided to use a

**Table 5** Calcification of the supplying arteries of gastric tube based on preoperative CT scan and their association with anastomotic leakage

Characteristics	No leak (n=554), n (%)	Leak (n=119), n (%)	Total (n=673), n (%)	P value
Aorta				<0.0001
Yes	118 (21.30)	55 (46.22)	173 (25.71)	
No	436 (78.70)	64 (53.78)	500 (74.29)	
Celiac axis				<0.0001
Yes	66 (11.91)	35 (29.41)	101 (15.01)	
No	488 (88.09)	84 (70.59)	572 (84.99)	
Right postceliac arteries				0.0676
Yes	1 (0.18)	2 (1.68)	3 (0.45)	
No	553 (99.82)	117 (98.32)	670 (99.55)	
Left postceliac arteries				0.0218
Yes	1 (0.18)	3 (2.52)	4 (0.59)	
No	553 (99.82)	116 (97.48)	669 (99.41)	

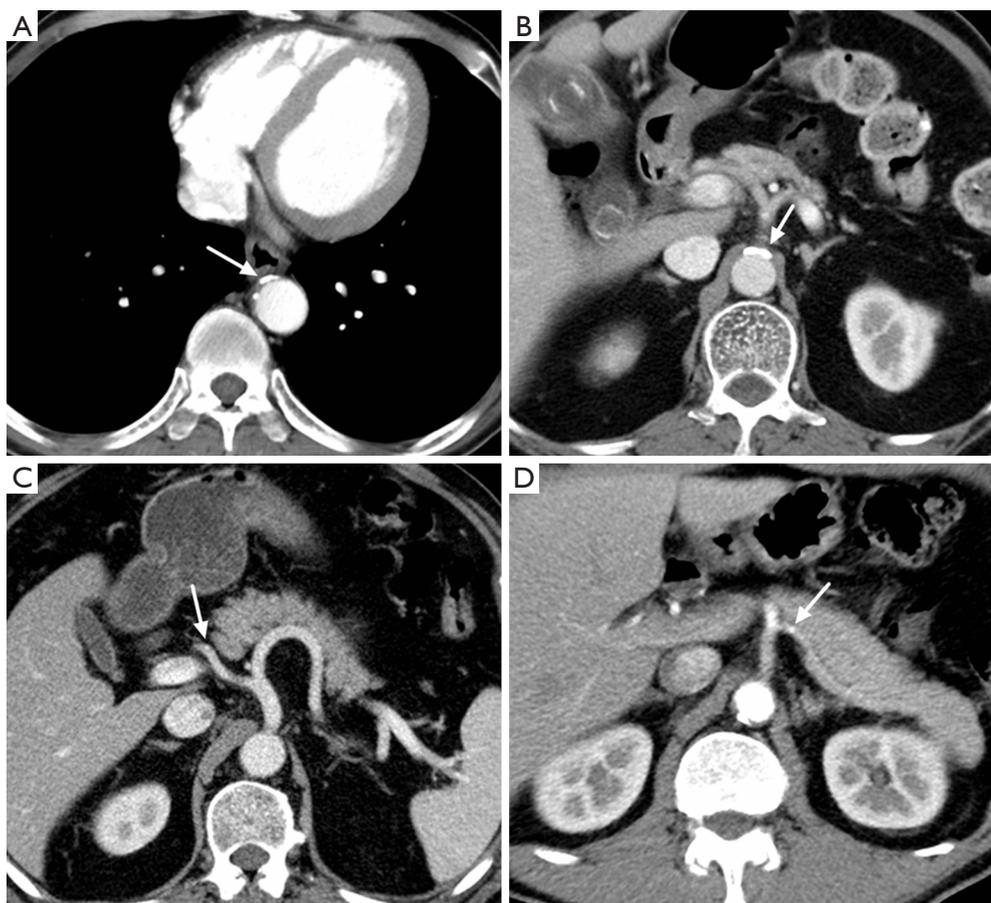
Aorta, defined as descending part of thoracic aorta and abdominal part of aorta above celiac level; right postceliac arteries, defined as common hepatic artery, gastroduodenal artery, and right gastroepiploic artery; left postceliac arteries, defined as splenic artery and left gastroepiploic artery.

qualitative research method to assess the presence or absence of calcifications in feeding arteries of the gastric tube. Fortunately, through the qualitative analysis of the image data of 673 patients, a similar result to European researchers was obtained, and we confirmed that calcification of the arterial supply of the gastric tube detected on routine preoperative CT images is esophagectomy in Chinese patients.

Pathophysiologically, the relationship between artery calcification and leakage is rational because the right gastroepiploic artery originating from this trajectory mainly supplies the gastric tube and anastomosis. Although the calcification in the right postceliac arteries, especially in the right gastroepiploic artery, may compromise the local perfusion of the gastric tube, different from the research based on European population (11), calcification in the right postceliac arteries was not significantly related to the leakage in the our final results. Compared with the previous study (11), we noticed that the proportion of calcification in the right postceliac arteries so small in our study (3 of 673 *vs.* 11 of 246) that it was difficult to make a conclusion with such a small number of patients. Calcification of the celiac axis, whose blood flow in the right gastroduodenal artery comes from, may also compromise the perfusion of gastric tube indirectly. The relation between the leakage and the calcification of the celiac axis was confirmed

in our research. However, studies focused on Europeans did not show a similar result (11,17). We speculated that the difference in the distribution and extent of the calcification between Western and Chinese population may finally result in different results. Thus, a larger sample size and further research may be necessary to clarify the difference.

Tissue ischaemia as a potential mechanism for anastomotic leakage is likely to be moderated by a combination of generalized vascular disease (marked by peripheral vascular disease) and compromised local perfusion (marked by calcification of celiac axis). In addition, anastomotic leakage has also been found to be related to congestion due to insufficient venous drainage, the method of anastomosis construction, the width of the gastric tube, mechanical tension, and poor nutrition (18-20). Regarding these factors, various attempts to optimize the conditions of the anastomosis have been reported. Related potential risk factors such as surgical procedures and pathological factors were also considered in our study, yet were not found to be associated in this cohort of patients. However, it is worth noting that some new cervical anastomosis methods, such as embedded three-layer anastomosis, hybrid-layered suture in hand sewn EEA, and cervical end-to-side triangulating anastomosis have significantly decreased the incidence of cervical anastomotic leakage (21-23).



**Figure 1** Findings of calcifications on preoperative transverse CT images obtained in four patients with esophageal cancer. (A) Calcifications of descending aorta (arrow): this patient experienced anastomotic leakage on POD 7; (B) calcifications of celiac axis (arrow): on the 5<sup>th</sup> day after esophagectomy, the patient experienced anastomotic leakage; (C) an isolated calcification spot of common hepatic artery [right postceliac arteries (arrow)]: anastomotic leakage occurred on POD 6; (D) a calcification of splenic artery [left postceliac arteries (arrow)]: this patient did not experience postoperative anastomotic leakage. POD, postoperative day.

**Table 6** Multivariate logistic regression analysis revealed independent factors associated with anastomotic leakage

Characteristics	OR (95% CI), multivariate	P value
Upper digestive tract ulcer	2.666 (1.128–6.300)	0.0255
Peripheral vascular disease	2.963 (1.166–7.530)	0.0225
Renal insufficiency	3.686 (1.117–12.169)	0.0323
ASA risk class	1.725 (1.098–2.710)	0.0180
Calcification of aorta	2.300 (1.429–3.704)	0.0006
Calcification of celiac axis	1.823 (1.051–3.162)	0.0326

ASA, American Society of Anaesthesiologists score; OR, odds ratio; CI, confidence interval.

It is worth mentioning that our qualitative assessment of artery calcification is simplified method. Although the extent of calcification was not assessed, the presence of calcification in arteries could still remind the surgeons which patient had a higher chance to have a cervical leakage so that more adequate preparation before surgery, more carefully in the operation, and better nutritional support in postoperative treatment could be provided. Thus, a quantitative visual grading system with good practicability and reproducibility, which is established to help surgeons to screen out patients with higher risk of anastomotic leakage will be helpful. Furthermore, a quantitative system may also help surgeons to decide whether a patient needs to take a radiological examination before serious clinical symptoms

appear so that a minor anastomotic leakage could be treated timely and correctly. With more studies validating the reliability of the association between calcification and cervical anastomotic leakage, this quantitative method could be potentially promoted in clinical practice.

There are a few limitations in our study. Firstly, this study was confined to a population that underwent elective esophagectomy with cervical anastomosis. Outcomes might be different in populations that undergo other surgical approaches. Secondly, artery calcification does not always lead to impaired perfusion, and there are more specific ways to determine the extent of vascular disease and local perfusion, such as use of laser Doppler flowmetry or CT angiography of the abdomen, which were not applied in the study. Furthermore, no prospective data are yet available to prove the clinical benefit of the calcification evaluation in reducing morbidity, and a well-designed quantitative study needs to be carried out.

## Conclusions

In this study, we found that vascular calcifications of the arteries that supply the gastric tube were significant risk factors of cervical anastomotic leakages. Further study with a larger sample size and a quantitative or semiquantitative model of calcification assessment should be carried out to confirm the findings and to optimize a risk prediction model for anastomotic leakage.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The study was approved by the ethics committee of Cancer Institute and Hospital, CAMS (NCC2014RE-001) and written informed consent was obtained from all patients.

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