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ORIGINAL ARTICLE

Blood flow ratio in the gastric conduit measured by laser Doppler flowmetry: A predictor of anastomotic leakage after esophagectomy

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Abstract

Background: Anastomotic leakage after esophagectomy is a common complication. Laser Doppler flowmetry (LDF) can quantitatively evaluate the blood flow in the gastric conduit.

Methods: A total of 326 patients who underwent thoracoscopic/robot-assisted esophagectomy followed by gastric conduit reconstruction and end-to-side anastomosis were enrolled. We divided the gastric conduit into zones I (dominated by the right gastroepiploic vessels), II (dominated by the left gastroepiploic vessels), and III (perfused with short gastric vessels). Before pulling up the gastric conduit to the neck, LDF values were measured at the pylorus, the border between zones I and II (zone I/II), the border between zones II and III (zone II/III), and the gastric conduit tip (tip). The blood flow ratio was calculated as the LDF value divided by the LDF value at the pylorus.

Results: Anastomotic leakage developed in 32 of 326 patients. Leakage was significantly associated with the blood flow ratio at the tip ($p<0.001$), but not at zone I/II, zone II/III, and the anastomotic site. The receiver-operating characteristic curve analysis identified an anastomotic leakage cutoff ratio of 0.41 (at the tip). A multivariate Cox analysis showed that a blood flow ratio <0.41 at the tip was an independent risk factor for anastomotic leakage ($p<0.001$).

Conclusion: Anastomotic leakage after esophagectomy was significantly associated with the blood flow ratio at the tip of the gastric conduit. Preservation of the blood supply to the tip via the gastric wall might contribute to a decreased incidence of anastomotic leakage.

KEYWORDS
anastomotic leakage, end-to-side anastomosis, gastric conduit, laser Doppler flowmetry

1 | INTRODUCTION

Anastomotic leakage is a common complication after esophagectomy. The reported incidence of leakage, which can cause postoperative mortality and longer hospital stay lengths, is as high as 31%.[1–4] Therefore, methods to reduce the incidence of this complication are urgently needed to improve the quality of life of patients and reduce postoperative mortality. One of the major causes of anastomotic leakage is thought to be reduced blood flow in the gastric conduit. Laser Doppler flowmetry (LDF) can quantitatively measure the tissue blood supply and evaluate the blood flow in the gastric conduit during esophagectomy.[5–7] Only a few studies have investigated the correlation between LDF values and anastomotic leakage after esophagectomy and the possibility that the tissue blood flow at the anastomotic site of the gastric conduit might be a predictor of anastomotic leakage[8,9]; however, those studies included fewer than 50 cases, and a method of reducing leakage based on LDF values has not been established.

End-to-side (ES) anastomosis is traditionally used as the esophagogastric anastomosis. A caliber mismatch between the esophagus and gastric conduit does not need to be considered for the ES anastomosis; however, it is unclear whether anastomotic leakage is associated with the blood flow in the area proximal to the anastomotic site.

During this study, we aimed to clarify the correlation between the tissue blood flow of the gastric conduit and anastomotic leakage after esophagectomy in the ES group.

2 | MATERIALS AND METHODS

2.1 | Patients and clinicopathological data

We studied 326 patients with esophageal cancer who underwent thoracoscopic or robot-assisted esophagectomy followed by the gastric conduit reconstruction and cervical ES esophagogastric anastomosis at Tohoku University Hospital between April 2015 and March 2023 (Table 1). The exclusion criteria were as follows: reconstruction of other organs; salvage surgery (underwent definitive chemoradiotherapy before esophagectomy); staged surgery (anastomosis performed another day); and lack of clinicopathological data, including LDF values.

The clinical information of all patients examined was carefully reviewed. The location and TNM staging were determined according to the eighth edition of the American Joint Committee on Cancer/Union for International Cancer Control TNM staging system.[10] The nutritional status of patients was evaluated using the Controlling Nutritional Status score and Prognostic Nutritional Index as previously described.[11,12] The study protocol was approved by the Ethics Committee of Tohoku University School of Medicine (accession no. 2019-1-429), and informed consent was obtained from all patients for participation and publication.

TABLE 1 Clinicopathological characteristics of the study population.

	All ($n = 326$)
Age, median (range)	68 (40–86)
Sex	
Male/Female	247/79
Location	
Upper/middle/lower	40/132/154
Histological type	
SqCC/adenocarcinoma/other	241/54/31
Stage	
I and II/III and IV	144/182
Preoperative treatment[a]	
Performed/none	199/127
Smoking	
Yes/No	244/82
Hypertension	
Yes/No	137/189
Diabetes mellitus	
Yes/No	39/287
CONUT score, median (range)	1 (0–8)
PNI, median (range)	47.7 (29.8–64.3)
Approach	
Thoracoscopic/robot	232/94
Open/HALS/laparoscopic/robot	56/254/4/12
Routes	
Retrosternal/posterior mediastinal	31/295
Operation time (min), median (range)	616 (406–1032)
Blood loss (mL), median (range)	116 (7–2509)
Anastomotic method	
Hand-sewn/stapler	250/76
Arcade[b] ($n = 228$)	
Present/absent	114/114

Abbreviations: CONUT, controlling nutritional status; HALS, hand-assisted laparoscopic surgery; PNI, prognostic nutritional index; SqCC, squamous cell carcinoma.

[a]Preoperative treatment includes neo-adjuvant chemotherapy and neo-adjuvant chemoradiotherapy.

[b]Arcade between the right and left gastroepiploic arteries.

2.2 | Surgical procedures

We performed thoracoscopic or robot-assisted subtotal esophagectomy with radical lymphadenectomy while the patient was in the left semi-prone position (McKeown procedure).[13,14] The lymph node dissection field and cervical, intrathoracic, and abdominal lymph nodes were determined based on the tumor location, preoperative clinical stage, and status of the patient. During the abdominal procedure, we performed upper abdominal lymphadenectomy and prepared the gastric conduit via hand-assisted laparoscopic surgery, conventional open laparotomy, laparoscopic, or robot-assisted procedures. A 4-cm-wide gastric conduit was created by dividing the lesser curvature of the stomach 4 cm from the pylorus and cutting to the fundus along the greater curvature. The right gastroepiploic artery was preserved to provide the vascular supply. The presence or absence of arcade between the right and left gastroepiploic arteries was confirmed. The gastrosplenic ligament was removed from the greater curvature of the stomach, especially in the short gastric vessels area. Then, the gastric conduit was pulled up through the posterior mediastinal or retrosternal routes, and esophagogastric anastomosis was performed in the neck. The hand-sewn method using Gambee sutures or a mechanical anastomosis using linear staplers was performed on the greater curvature of the gastric conduit for the ES anastomosis. Wrapping the surplus omentum around the anastomotic site is not one of our routine procedures. When the end of the gastric conduit is long, the end is removed at 4 cm proximal to the anastomosis.

Esophagography was performed to evaluate the anastomotic site on postoperative day 7. If anastomotic leakage was suspected, then computed tomography and/or endoscopy were performed. During this study, anastomotic leakage was defined as Clavien–Dindo classification of grade II or higher.[15]

2.3 | Laser Doppler flowmetry

LDF can quantitatively evaluate the local blood flow as continuous real-time data. The results of LDF are displayed after the units are converted to mL/min/100 g of tissue.

We divided the gastric conduit into the following three zones as previously reported by Kumagai et al.: zone I, the area dominated by the right gastroepiploic vessels; zone II, the area dominated by the left gastroepiploic vessels; and zone III, the area initially perfused with short gastric vessels.[16] Before pulling up the gastric conduit to the neck, we measured the blood flow with LDF (CyberMed CDF-2000; Libmech, Tokyo, Japan) at the pylorus, the greater curvature side of the border between zones I and II (zone I/II), the greater curvature side of the border between zones II and III (zone II/III), and the gastric conduit tip (tip) (Figure 1). Additionally, blood flow at the anastomotic site after pulling up the gastric conduit was measured in 111 cases. Each measurement was repeated three times, and the mean LDF value was used.[7] We analyzed the blood flow ratio as previously reported, which was defined as each LDF value at the measured site divided by the LDF value at the pylorus.[8] During this study, the pylorus was defined as the distal side, whereas the gastric conduit tip was defined as the proximal side (Figure 1).

2.4 | Statistical analysis

JMP Pro version 16.1.0 software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. Continuous data were analyzed using Student's *t* test or the Mann–Whitney *U* test. Correlations between two variables were identified using Pearson's chi-squared test and Fisher's exact test. A multivariate logistic regression analysis was performed to evaluate the independent predictors for all significant variables in the univariate analysis. Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Blood flow ratio of the gastric conduit/arcade between the right and left gastroepiploic arteries

The median blood flow ratios at zone I/II, zone II/III, and the tip were 0.96, 0.75, and 0.50, respectively (range, 0.34–2.50, 0.12–1.51, and 0.11–1.51, respectively). The ratio at the proximal part of the gastric conduit significantly decreased compared to that at the distal part ($p < 0.001$) (Figure 2). Data regarding the arcade between the right and left gastroepiploic arteries of 228 cases were obtained, and it

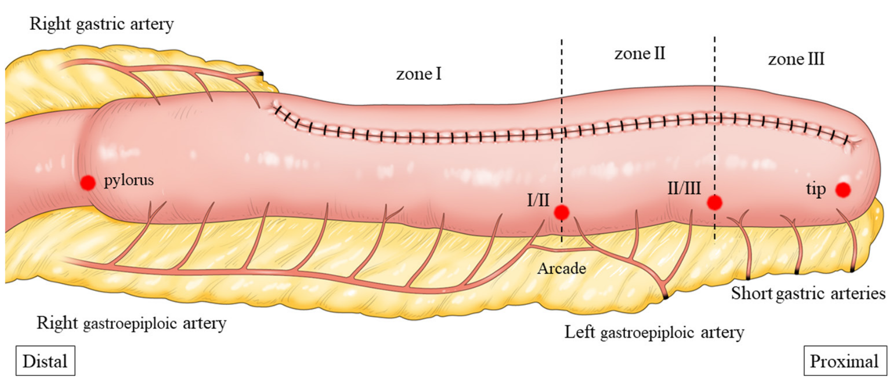

FIGURE 1 Diagram showing the gastric conduit divided as follows according to the vascular supply: zone I, the area dominated by the right gastroepiploic vessels; zone II, the area dominated by the left gastroepiploic vessels; and zone III, the area initially perfused with short gastric vessels. Blood flow was measured with laser Doppler flowmetry at the pylorus, the greater curvature side of the border between zones I and II (zone I/II), the greater curvature side of the border between zones II and III (zone II/III), and the tip of the gastric conduit (tip) (red circle). The pylorus was defined as the distal side, whereas the gastric conduit tip was defined as the proximal side.

was observed that the arcade significantly increased the blood flow ratio at zone I/II and zone II/III, but not at the tip (zone I/II, $p < 0.001$; zone II/III, $p = 0.003$; tip, $p = 0.53$) (Figure 3).

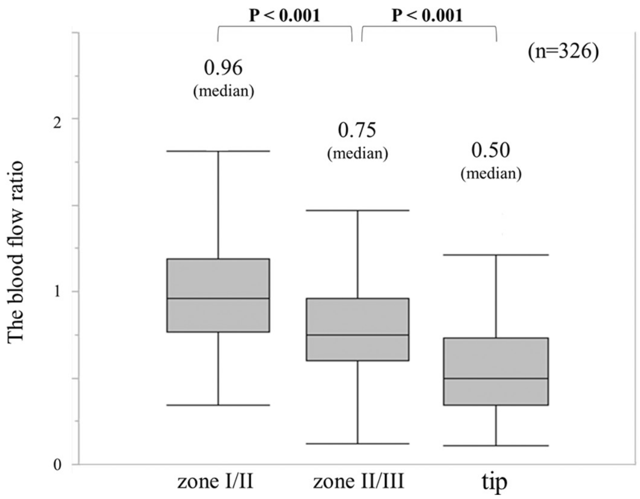

FIGURE 2 The blood flow ratio at the pylorus. The median blood flow ratio at zone I/II, zone II/III, and the tip of the gastric conduit (tip) were 0.96, 0,75, and 0.50, respectively. The ratio at the proximal part of the gastric conduit significantly decreased compared to that at the distal part ($p < 0.001$). The boxplots display medians, interquartile ranges, and total ranges (minimum and maximum).

3.2 | Details of the location of the anastomotic site and incidence of the anastomotic leakage

Data regarding the location of anastomotic site were obtained from 111 cases. In 35 out of the 111 cases (31.5%), the anastomotic sites were located at the border between zones II and III. In 20 cases (18.0%), the anastomotic sites were located 2 cm proximal from zone II/III. In 18 cases (16.2%), the anastomotic sites were located 3 cm proximal from zone II/III. The anastomotic sites were located in zone III in a total of 96 cases (86.5%) (Figure S1a). There was a significant correlation between the blood flow ratio of the tip of the gastric conduit and anastomotic site. A correlation coefficient of 0.43 with $p < 0.001$ indicated a positive correlation between these two variables (Figure S1b), and the blood flow ratio at the tip of the gastric conduit was lower than that at anastomotic site in 87 cases (78.4%).

Anastomotic leakage developed in 32 of the 326 patients (9.8%). All leakage occurred at the esophagogastric anastomosis, and we have never experienced the leakage at the tip of the gastric conduit. The occurrence of leakage was significantly associated with the blood flow ratio at the tip ($p < 0.001$, Figure 4). In contrast, the blood flow ratio at the anastomotic site after pulling up the gastric conduit was not correlated with anastomotic leakage in 111 cases (range, 0.31–1.28; $p = 0.78$) (Figure 4).

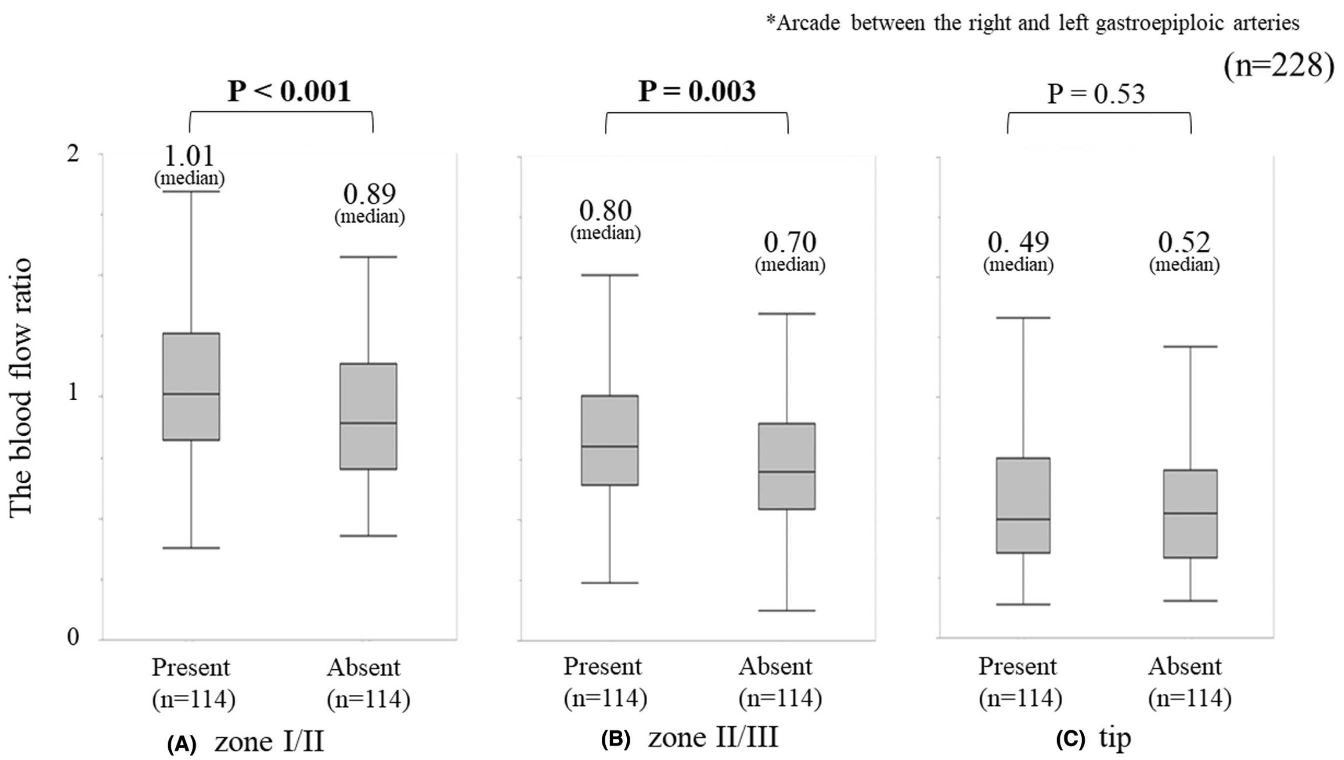

FIGURE 3 The blood flow ratio with and without an arcade between the right and left gastroepiploic arteries. The arcade significantly increased the blood flow ratio at (A) zone I/II and (B) zone II/III, but not at the (C) tip of the gastric conduit (tip) (Student's t test; zone I/II, $p < 0.001$; zone II/III, $p = 0.003$; tip, $p = 0.53$). The boxplots display medians, interquartile ranges, and total ranges (minimum and maximum).

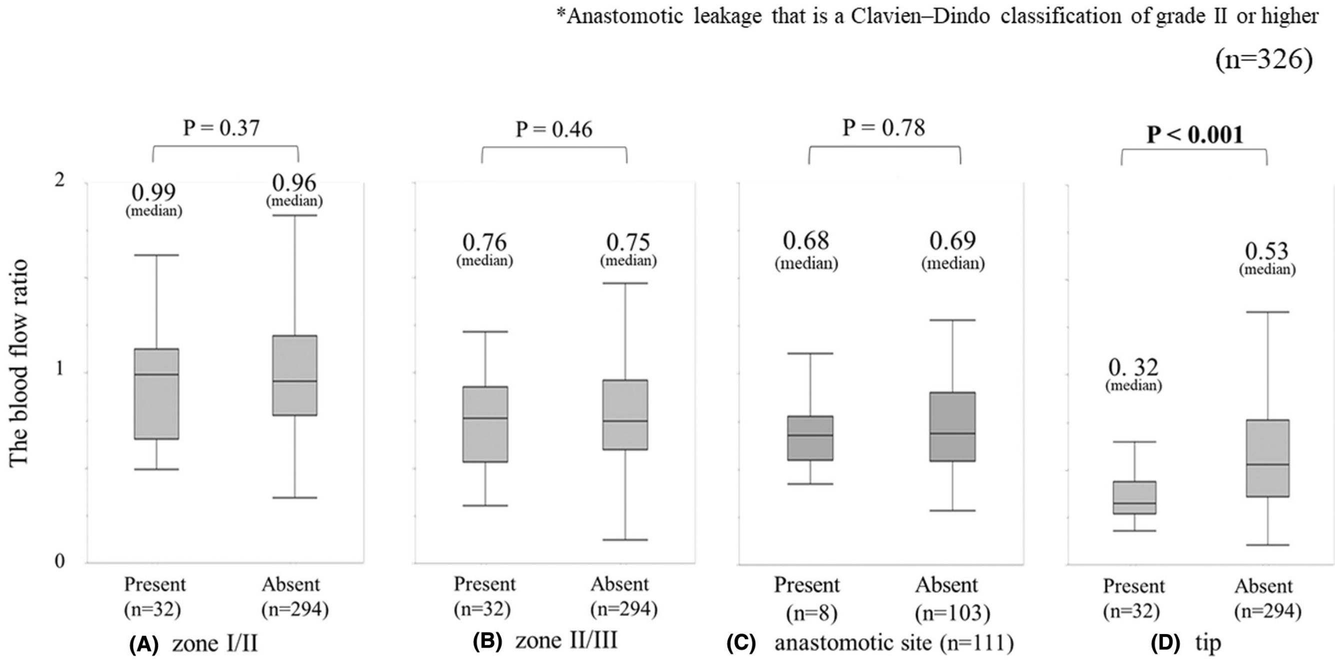

FIGURE 4 Correlations between anastomotic leakage and the blood flow ratio at zone I/II (A), zone II/III (B), anastomotic site (C), and the tip of the gastric conduit (tip) (D). The blood flow ratios at zone I/II (A), zone II/III (B), and anastomotic site (C) were not significantly associated with anastomotic leakage. The blood flow ratio at the tip (D) was significantly lower in cases with anastomotic leakage (Student's *t* test; $p < 0.001$). The boxplots display medians, interquartile ranges, and total ranges (minimum and maximum).

3.3 | Factors affecting the incidence of anastomotic leakage

The receiver-operating characteristic curve analysis identified an anastomotic leakage cutoff value of 0.41 (ratio at the tip; sensitivity, 0.70; specificity, 0.75; area under the curve, 0.75). All cases were classified into either the good gastric conduit blood flow group or the poor gastric conduit blood flow group using the cutoff value of 0.41 for the tip. A total of 216 patients with a gastric conduit with good blood flow demonstrated a significantly lower incidence of anastomotic leakage than those with poor blood flow (4.6% vs. 20.0%; $p < 0.001$) (Table 2). In addition, univariate analysis identified that the occurrence of leakage was significantly associated with sex (male), tumor location (upper esophagus), and smoking history. In contrast, anastomotic leakage was not associated with the presence of the arcade ($p = 0.13$) (Table 2). A multivariate Cox analysis showed that a blood flow ratio <0.41 at the tip was an independent risk factor for anastomotic leakage (odds ratio, 5.60; 95% confidence interval, 2.31–13.55; $p < 0.001$) (Table 2).

4 | DISCUSSION

The basic LDF theory was proposed by Bonner and Nossal in 1981.[17] Doppler shifts are generated by the laser light reflected from the moving red blood cells in the tissue, and the frequency of this scattered light is detected with an LDF probe.

We first identified a poor blood flow ratio at the tip of the gastric conduit as an independent risk factor for anastomotic leakage after esophagectomy in the ES group. Anastomotic leakage is associated with several factors; for example, diabetes mellitus, hypertension, kidney disease, steroid use, and nutritional status have been reported as systemic factors, and ischemia or congestion of the organs used for reconstruction and excessive anastomotic tension have been reported as local factors.[18–25] During this study, there were no significant correlations between the blood flow ratio of the gastric conduit and factors that could cause arteriosclerosis, such as smoking, diabetes mellitus, and hypertension (data not shown). The occurrence of leakage was significantly associated with the blood flow ratio at the tip of the gastric conduit; however, the blood flow ratio at the anastomotic site was not correlated with anastomotic leakage. Lai et al. also reported that the area proximal to the anastomosis might affect the blood supply, thus influencing anastomotic healing.[26] In fact, the ES anastomosis requires blood flow not only from the distal side but also from the proximal side because the suturing of the ES anastomosis includes both the distal and proximal sides of the gastric conduit (Figure S2). The blood flow ratio at the anastomotic site may mainly reflect the blood flow from the distal side, and that at the tip of the gastric conduit may indicate the blood flow in the proximal part of the ES anastomosis. Because the blood flow ratio at the tip of the gastric conduit was lower than that at anastomotic site in 87 cases (78.4%) (Figure S1b), the proximal side of the anastomosis may have more difficulty healing than the distal side;

TABLE 2 Univariate and multivariate analyses to identify significant risk factors for anastomotic leakage after esophagectomy.

		Anastomotic leakage	Univariate analysis			Multivariate analysis		
Variable	*n*	Present	OR	95% CI	*p* value	OR	95% CI	*p* value
Age								
<65	107	13 (12.1%)	1.46	0.69–3.07	0.33			
≥65	219	19 (8.7%)	1					
Sex								
Male	247	29 (11.7%)	3.37	1.00–11.4	**0.02**	1.29	0.31–5.29	0.72
Female	79	3 (3.8%)	1			1		
Location								
U	40	8 (20%)	2.73	1.13–6.58	**0.04**	2.58	0.94–7.12	0.07
ML	286	24 (8.4%)	1			1		
Stage								
I/II	144	13 (9.0%)	1		0.67			
III/VI	182	19 (10.4%)	1.17	0.56–2.47				
Preoperative treatment[a]								
Yes	199	23 (11.6%)	1.71	0.77–3.83	0.19			
No	127	9 (7.1%)	1					
Smoking								
Yes	244	30 (12.3%)	5.61	1.31–24.0	**0.02**	4.79	0.95–24.24	0.06
No	82	2 (2.4%)	1			1		
Hypertension								
Yes	137	14 (10.2%)	1.08	0.52–2.26	0.84			
No	189	18 (9.5%)	1					
Diabetes mellitus								
Yes	39	2 (5.1%)	1		0.31			
No	287	30 (10.5%)	2.16	0.50–9.41				
Routes								
Retrosternal	31	5 (16.1%)	1.91	0.61–5.03	0.25			
Posterior mediastinal	295	27 (9.2%)	1					
Anastomotic methods								
Hand-sewn	250	22 (8.8%)	1		0.27			
Stapler	76	10 (13.2%)	1.57	0.71–3.48				
Arcade[b] (*n* = 228)								
Present	114	8 (7.0%)	1		0.13			
Absent	114	15 (13.2%)	2.00	0.82–4.94				
Laser Doppler flowmetry (tip/pylorus)								
<0.41	110	22 (20.0%)	5.75	2.44–13.59	**<0.001**	5.60	2.31–13.55	**<0.001**
≥0.41	216	10 (4.6%)	1			1		

Note: Bold values are statistical significance ($p < 0.05$).
Abbreviations: CI, confidence interval; L, lower; M, middle; OR, odds ratio; U, upper.
[a]Preoperative treatment includes neo-adjuvant chemotherapy and neo-adjuvant chemoradiotherapy.
[b]Arcade between the right and left gastroepiploic arteries.

therefore, the occurrence of leakage was significantly associated with the blood flow ratio at the tip of the gastric conduit in this study. To reduce the incidence of leakage, it is important to preserve the blood supply in the proximal part of the gastric conduit for the ES anastomosis.

Our results demonstrated that the arcade between the right and left gastroepiploic arteries significantly increases the blood supply at least in zone II of the gastric conduit. Liebermann-Meffert et al., who performed research involving 30 cadavers, reported that the arcade did not affect blood flow in zones II and

III.[27] However, the left gastroepiploic artery of the gastric conduit was divided on the proximal side; therefore, the blood supply to the gastric conduit, especially that to zone II, could be preserved if the arcade exists, and our LDF results showed an increase in the blood supply to zone II through the arcade. In contrast, the arcade did not increase the blood supply in zone III, and the result indicated that the blood flow of the gastric conduit in zone III is considered dependent on the flow through the gastric wall. These results were also rational in terms of the anatomy of the vessel. Even the increased blood supply through the arcade did not significantly reduce the occurrence of anastomotic leakage, possibly because most anastomotic sites were located in zone III.

A narrow gastric conduit was often selected because it can allow maximal extension of the length, effectively promote gastric emptying, and significantly reduce postoperative gastroesophageal reflux.[26,28] However, Lai et al. reported a higher occurrence of anastomotic leakage for patients who underwent reconstruction using a narrow gastric conduit rather than a gastric conduit with a 5-cm-wide proximal end.[26] During this study, the blood supply to zone III seemed to occur through a microscopic network of capillaries and arterioles. Because some of the submucosal vessels in the gastric wall were resected in the narrow gastric conduit, a gastric conduit with a wide proximal end might preserve the blood flow via the gastric wall and decrease the incidence of anastomotic leakage after esophagectomy,[26] thus supporting our finding that preserving the blood supply through the gastric wall could be important to reducing leakage.

If the blood flow ratio at the tip of the gastric conduit is poor, then an end-to-end (EE) anastomosis may be one of the options to avoid anastomotic leakage. In our database, the EE group with poor blood flow at the tip of the gastric conduit had a lower incidence of anastomotic leakage than the ES group (8.7% vs. 20.0%) (Table S1). This could be because the tip of the gastric conduit was resected before the EE anastomosis; therefore, the reduced blood flow in the tip does not affect leakage.

Near-infrared fluorescence imaging with indocyanine green can visualize the blood flow in the gastric conduit; however, traditionally, its visualization has relied on subjective evaluations, and quantitative assessments have been challenging. However, recently, it has been reported that software and cameras can enable quantitative evaluation of the blood flow[29]; therefore, the combination of LDF and near-infrared fluorescence imaging might be able to more accurately assess the blood flow in the gastric conduit in the future.

This study had some limitations. First, during this study, we focused on only the LDF values; however, near-infrared fluorescence imaging with indocyanine green has been used to evaluate the blood flow of the gastric conduit.[30] Second, LDF can assess the ischemic status of tissues, but it cannot quantitatively evaluate congestion. Because congestion is one of the factors associated with anastomotic leakage,[31] near-infrared spectroscopy, which can assess the congestion status, may be a useful device for predicting anastomotic leakage.[31,32] Third, at this juncture, it is difficult to determine the position of the anastomotic site using LDF values because the anastomotic site strongly depends on the position of the gastric conduit after pulling it to the neck. Therefore, esophagogastric anastomosis was performed at a more distal site because it is a better site in terms of the blood supply. Further studies are necessary to assess the distance between the tip of the gastric conduit and anastomotic site.

5 | CONCLUSIONS

This study first revealed that anastomotic leakage after esophagectomy was significantly associated with the blood flow ratio at the tip of the gastric conduit in the ES group. Using quantified LDF values and the largest scale of samples, the importance of the preservation of the blood supply via the gastric wall was indicated to reduce the incidence of anastomotic leakage.

AUTHOR CONTRIBUTIONS

Hirotaka Ishida: conceptualization, methodology, formal analysis, investigation, data curation, resources, writing—original draft. Toshiaki Fukutomi: conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft. Yusuke Taniyama: conceptualization, methodology, investigation, resources, writing—review and editing. Chiaki Sato: investigation, writing—review and editing. Hiroshi Okamoto: investigation, writing—review and editing. Yohei Ozawa: investigation, writing—review and editing. Yu Onodera: conceptualization, methodology, formal analysis, investigation, data curation, writing—review and editing. Ken Koseki: investigation, writing—review and editing. Michiaki Unno: writing—review and editing, supervision. Takashi Kamei: conceptualization, methodology, investigation, resources, writing—review and editing, supervision. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENT

The study protocol was approved by the ethics committee of our institution (accession number of Tohoku University Hospital: 2019–1–429).

INFORMED CONSENT

Informed consent was obtained from all patients for participation and publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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