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ORIGINAL ARTICLE

Impact of pre-diabetes, well-controlled diabetes, and poorly controlled diabetes on anastomotic leakage after esophagectomy for esophageal cancer: a two-center retrospective cohort study of 1901 patients

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Abstract

Background Diabetes is known to be associated with anastomotic leakage (AL) after esophagectomy. However, it is unknown whether well-controlled diabetes is also associated with AL.

Methods We conducted a two-center retrospective cohort database study of patients who underwent oncological esophagectomy (2011–2019). Patients were divided into four groups: normoglycemia, pre-diabetes, well-controlled diabetes (hemoglobin A1c [HbA1c] < 7.0%), and poorly controlled diabetes (HbA1c ≥ 7.0%). The occurrence of AL and length of stay were compared between groups using multivariable analyses. The relationship between categorical HbA1c levels and AL was also investigated in patients stratified by diabetes medication before admission.

Results Among 1901 patients, 1114 (58.6%) had normoglycemia, 480 (25.2%) had pre-diabetes, 180 (9.5%) had well-controlled diabetes, and 127 (6.7%) had poorly controlled diabetes. AL occurred in 279 (14.7%) patients. Compared with normoglycemia, AL was significantly associated with both well-controlled diabetes (odds ratio 1.83, 95% confidence interval [CI] 1.22–2.74) and poorly controlled diabetes (odds ratio 1.95, 95% CI 1.23–3.09), but not with pre-diabetes. Preoperative HbA1c levels showed a J-shaped association with AL in patients without diabetes medication, but no association in patients with diabetes medication. Compared with normoglycemia, only poorly controlled diabetes was significantly associated with longer hospital stay after surgery, especially in patients with operative morbidity (unstandardized coefficient 14.9 days, 95% CI 5.6–24.1).

Conclusions Diabetes was associated with AL after esophagectomy even in well-controlled patients, but pre-diabetes was not associated with AL. Operative morbidity, including AL, in poorly controlled diabetes resulted in prolonged hospital stays compared with normoglycemia.

Keywords Diabetes mellitus · Esophageal cancer · Esophagectomy · Hemoglobin A1c · Anastomotic leakage

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Introduction

Esophagectomy is the mainstay of treatment for resectable esophageal cancer, but the associated morbidity rate is high (37.6–59.0%) [1–3]. Anastomotic leakage (AL) is the second most common postoperative complication after pneumonia, with a reported incidence of 11.4–16.2% [1–3]. AL worsens short-term outcomes and can also affect long-term survival [4, 5]. AL is also associated with the risk of stricture formation, which can negatively affect patients' quality of life [6, 7]. Thus, it is important to identify the exact risk factors for AL.

Diabetes mellitus adversely affects wound healing and is known to be associated with AL after esophagectomy [8]. In all patients with diabetes, HbA1c testing, which reflects average blood glucose levels over the previous 2–3 months, is recommended to assess glycemic control [9]. The importance of HbA1c as a preoperative screening test in patients without diabetes has also been reported [10]. Indeed, a recent study has reported that HbA1c ≥ 7.0% is a prognostic factor for AL after esophagectomy [11]. Diabetes with HbA1c < 7.0% has been defined as well-controlled diabetes because the American Diabetes Association, European Association for the Study of Diabetes, and the Japan Diabetes Society (JDS) all recommend a target of HbA1c < 7.0% for patients with diabetes [12, 13]. However, it remains unclear whether well-controlled diabetes is associated with AL because patients with well-controlled diabetes were not separated from those with normoglycemia or pre-diabetes in a prior study [11]. Moreover, the association between HbA1c levels and AL may differ between patients with and without pre-existing diabetes medication, but this was not considered in the prior analyses [11].

The aim of this large two-center study was to assess the impact of diabetes control status (normoglycemia, pre-diabetes, well-controlled diabetes, and poorly controlled diabetes) on AL after esophagectomy for esophageal cancer. Additionally, the relationship between preoperative HbA1c levels and AL was investigated in patients who were stratified on the basis of diabetes medication before admission.

Methods

Data source and study population

The Japanese National Clinical database (NCD) is a web-based data management system [1]. All consecutive patients who underwent surgery for esophageal cancer since January 2011 at a cancer center hospital and since January 2012 at the other cancer center hospital were registered in the NCD. We merged the backup data of NCD from both hospitals until December 2019 to create a two-center database, and conducted a retrospective cohort study of patients who underwent subtotal esophagectomy for esophageal cancer. Patients who underwent two-stage reconstruction or who were missing HbA1c values were excluded.

The database includes the following information: patients' age, sex, and body mass index at admission; history of smoking; weight loss (> 10% in 6 months); comorbidities at admission; clinical cancer stage based on the seventh edition of the Union for International Cancer Control (available only for patients from 2012); histological type (available from 2017); preoperative chemotherapy and radiotherapy (available from 2012); preoperative laboratory findings (HbA1c, albumin, and creatinine); surgical procedures; operative morbidity; operative mortality; and length of hospital stay after surgery. Comorbidities include: diabetes (medication and insulin use before admission were also recorded); hypertension; cardiovascular disease (congestive heart failure, angina, history of old myocardial infarction, history of percutaneous coronary intervention, or history of cardiac surgery); and cerebrovascular disease. Surgical procedures include: thoracic approach, abdominal approach (available from 2014), organ reconstruction (available from 2016), route of reconstruction (available from 2016), and anastomosis site (available from 2016). Operative morbidity includes: AL; surgical site infection (Clavien–Dindo grade ≥ I) without AL; respiratory complications (pneumonia grade ≥ II, unplanned intubation, or prolonged ventilation > 48 h); cardiovascular complications (pulmonary embolism, acute cerebrovascular disease, acute myocardial infarction, or cardiac arrest); operative morbidity grade ≥ II; and operative morbidity grade ≥ III. In our institutions, AL was defined as a clinical sign of salivary fistula, confirmed by swallowing examination using water-soluble radiographic contrast, or endoscopic confirmation of anastomotic dehiscence or fistula [7].

Patients were divided into four groups on the basis of preoperative HbA1c and diabetes medication before admission, as follows: normoglycemia (HbA1c < 5.7% without diabetes medication); pre-diabetes (HbA1c 5.7–6.4% without diabetes medication); well-controlled diabetes (HbA1c < 7.0% with diabetes medication or HbA1c 6.5–6.9% without diabetes medication); and poorly controlled diabetes (HbA1c ≥ 7.0% with or without diabetes medication). Preoperative HbA1c measurements closest to the day of surgery, but within 90 days, were recorded in the database. HbA1c was typically measured at the initial visit and the day (or two days) before surgery. HbA1c values were recorded using the JDS values in 2011 and the National Glycohemoglobin

Standardization Program (NGSP) values after 2011. The JDS value of HbA1c was converted into the NGSP value using the following formula in accordance with the JDS guidelines: NGSP value (%) = JDS value (%) + 0.4 [14]. Patients who underwent esophagectomy after 2011 were recorded as having HbA1c < 5.7% if they had HbA1c values below 5.7% and the specific values were unknown. When the HbA1c values were compared between the groups, the HbA1c level for patients with HbA1c < 5.7% after 2011 was approximated as 5.3%, which was the mean HbA1c level of these patients in 2011.

Surgical procedures and preoperative treatment in our institutions

Our standard procedure for esophageal cancer is transthoracic extended esophagectomy with three-field lymph node dissection. Gastric tube reconstruction by retrosternal route and cervical anastomosis is the first choice in our institutions, as described previously [7]. In one hospital, we mainly used a circular stapled anastomosis after esophagectomy until November 2014, but this was changed to a totally mechanical Collard anastomosis in December 2014 [7]. In the other hospital, a hand-sewn anastomosis was mainly used until March 2017, and we changed to a totally mechanical Collard anastomosis in April 2017. All procedures were performed by or under the supervision of specialists certified by the Japan Esophageal Society [15]. For preoperative treatment, chemotherapy (two cycles of 5-fluorouracil/cisplatin or three cycles of docetaxel/5-fluorouracil/cisplatin) or chemoradiotherapy (two cycles of 5-fluorouracil/cisplatin) were considered for patients with advanced cancer (clinical T2–4 any N or T1 N +) according to national guidelines [16].

Postoperative management

After surgery, all patients were admitted to the intensive care unit for 1–3 days. During the intensive care unit stay, postoperative glucose levels were routinely checked at least four times a day, regardless of diabetes control status, and controlled to a target of < 180 mg/dL using intravenous insulin infusion and/or subcutaneous insulin injection on a conventional sliding scale, as needed. Tube feeding via jejunostomy or indwelling nasojejunal tubes was started the day after surgery. Oral intake was started on postoperative day 6 or 7 after a contrast swallow confirmed that there was no sign of AL.

Endpoints

The primary outcome of this study was the occurrence of AL. The secondary outcomes were surgical site infection, respiratory complications, cardiovascular complications, operative morbidity (grade ≥ II and ≥ III), operative mortality, and length of hospital stay after surgery.

Statistical analysis

Multivariable logistic regression for AL, respiratory complications, and operative morbidity (grade ≥ II and ≥ III) was performed to analyze the association between diabetes control status and these outcomes. The candidate explanatory variables were: age ≥ 70 years; male sex; obesity (body mass index ≥ 27.5 kg/m^2; the cut-off point for Asia–Pacific populations recommended by the World Health Organization [17]); history of smoking; hypertension; cardiovascular disease; cerebrovascular disease; weight loss > 10%; histological type (squamous cell carcinoma/adenocarcinoma/others/unspecified [2011–2017]), clinical stage (0–II/III–IV/X/missing data/unspecified [2011]); preoperative chemotherapy (no/yes/unspecified [2011]); preoperative radiotherapy (no/yes/unspecified [2011]); serum albumin < 4.0 mg/dL; serum creatinine ≥ 1.2 mg/dL; thoracic approach (minimally invasive/open thoracic); abdominal approach (minimally invasive/open abdominal/unspecified [2011–2013]); organ reconstruction (stomach/colon/others/missing data/unspecified [2011–2015]); route of reconstruction (retrosternal/posterior mediastinal/ante-thoracic/missing data/unspecified [2011–2015]); anastomosis site (cervical/intra-thoracic/missing data/unspecified [2011–2015]); and two hospitals in Japan. Multicollinearity among these candidate variables was checked using variance inflation factors. Variables with variance inflation factors > 10 were omitted from multivariable regression analysis. Additionally, we conducted multivariable logistic regression (adjusted for age and body mass index) to analyze the association between the categorical HbA1c levels and AL in patients stratified by diabetes medication before admission.

The association of diabetes control status and length of stay after surgery was evaluated using multivariable linear regression with adjustment similar to that for analysis for AL. As a subgroup analysis, multivariable linear regression was also performed in patients with AL, patients with operative morbidity grade ≥ II, and patients without operative morbidity grade ≥ II.

In summary statistics, one-way analysis of variance was used for comparing continuous variables and the chi-square test was used for comparing categorical variables between the groups. All statistical analyses were conducted using SPSS for Windows version 26 (IBM, Armonk, NY, USA), and differences were considered significant at $p < 0.05$. This study was reported in line with the STROCSS criteria [18].

Results

Patient demographics

Overall, 2154 patients with esophageal cancer who underwent subtotal or total esophagectomy from January 2011 to December 2019 were identified. Among them, we excluded patients with two-stage reconstruction ($n = 136$) and missing HbA1c values ($n = 117$). Of the 1901 eligible patients, 1114 (58.6%) had normoglycemia, 480 (25.2%) had pre-diabetes, 180 (9.5%) had well-controlled diabetes, and 127 (6.7%) had poorly controlled diabetes (Table 1). Among patients with well-controlled diabetes and those with poorly controlled diabetes, 88 (28.6%) were not treated with diabetes medication before admission.

The mean age was 66 years, and 1564 patients (82.3%) were men. Squamous cell carcinoma, adenocarcinoma, others, and unspecified (2011–2015) accounted for 487 (25.6%), 54 (2.8%), 9 (0.5%), and 1351 (71.1%) cancers, respectively. In 1348 (70.9%) patients, minimally invasive esophagectomy was performed, and 553 (29.1%) underwent open thoracic esophagectomy.

Patient characteristics were compared between the groups on the basis of diabetes control status (Table 1). Patients with pre-diabetes, well-controlled diabetes, and poorly controlled diabetes were older than those with normoglycemia. Patients with well-controlled diabetes or poorly controlled diabetes were more likely to be male and to have hypertension, cardiovascular disease, and a history of smoking. The percentage of patients with obesity was highest among patients with well-controlled diabetes.

Comparison of postoperative outcomes by diabetes control status

Postoperative outcomes are shown in Table 2. Overall, 279 (14.7%) patients had AL, and AL was increased in patients with well-controlled diabetes or poorly controlled diabetes. The proportions of patients with operative morbidity grade ≥ II, operative morbidity grade ≥ III, and operative morality were 42.9% (815/1901), 25.7% (489/1901), and 1.2% (23/1901), respectively, and were similar between the groups. The length of hospital stay after surgery was increased in patients with poorly controlled diabetes.

Logistic regression for AL, respiratory complications, and operative morbidity

The results of the univariable and multivariable regression models for AL are presented in Table 3. Among the explanatory variables, variance inflation factors were > 10 for organ reconstruction, route of reconstruction, and anastomosis site. Therefore, the route of reconstruction and anastomosis site were excluded from the multivariable analysis to avoid multicollinearity. In the multivariable analysis, AL was significantly associated with well-controlled diabetes (odds ratio [OR], 1.83; 95% confidence interval [CI] 1.22–2.74; $p = 0.003$) and poorly controlled diabetes (OR, 1.95; 95% CI 1.23–3.09; $p = 0.005$) compared with normoglycemia, but not with pre-diabetes (OR, 0.81; 95% CI 0.58–1.13; $p = 0.21$). In multivariable logistic analysis, diabetes control status was not associated with respiratory complications, operative morbidity grade ≥ II, or operative morbidity grade ≥ III (Supplementary Table 1).

Analysis stratified by diabetes medication

The relationship between HbA1c levels and AL was investigated in patients stratified by diabetes medication before admission (Fig. 1). HbA1c showed a J-shaped association with AL in patients without diabetes medication. The proportion of patients with AL was lowest at HbA1c levels around 6.0%–6.4%. Both HbA1c 6.5–6.9% and HbA1c ≥ 7.0% were significantly associated with AL (OR, 1.97; 95% CI 1.05–3.71; $p = 0.035$, and OR, 2.78; 95% CI 1.23–6.31; $p = 0.014$, respectively, compared with HbA1c < 5.7%). However, HbA1c levels were not associated with AL in patients who were taking diabetes medication. Among patients with diabetes medication, the association with AL was similar even between HbA1c < 6.0% and HbA1c ≥ 8.0% ($p = 0.99$).

Linear regression for length of stay after surgery

Table 4 shows the results of multivariable linear regression for the length of stay after surgery. Compared with normoglycemia, only poorly controlled diabetes was significantly associated with a longer hospital stay for all patients (unstandardized coefficient, 9.1 days; 95% CI 4.3–13.8; $p < 0.001$). In a subgroup analysis of patients with AL, poorly controlled diabetes patients tended to have a longer hospital stay compared with normoglycemia patients, but the difference was not significant (unstandardized coefficient, 16.9 days; 95% CI − 0.2 to 34.1; $p = 0.053$). In a subgroup analyses of patients with operative morbidity grade ≥ II, poorly controlled diabetes patients had a longer hospital stay than normoglycemia patients had (unstandardized coefficient, 14.9 days; 95% CI 5.6–24.1; $p = 0.002$), but the length of hospital stay was comparable among groups in a subgroup analysis of patients without operative morbidity grade ≥ II.

Table 1 Patient characteristics based on diabetes control status

	Normoglycemia ($n=1114$)	Pre-diabetes ($n=480$)	Well-controlled diabetes ($n=180$)	Poorly controlled diabetes ($n=127$)	p value[a]
Age, years	65 ± 9	68 ± 8	68 ± 7	69 ± 7	< 0.001
Male, sex	897 (80.5)	391 (81.5)	162 (90.0)	114 (89.8)	0.002
BMI, kg/m^2	21.3 ± 3.1	21.6 ± 3.1	22.6 ± 3.8	22.2 ± 2.9	< 0.001
Obesity (BMI ≥ 27.5 kg/m^2)	32 (2.9)	15 (3.1)	18 (10.0)	5 (3.9)	< 0.001
History of smoking	914 (82.0)	397 (82.7)	165 (91.7)	112 (88.2)	0.005
Diabetes medication before admission	0 (0.0)	0 (0.0)	121 (67.2)	98 (77.2)	< 0.001
Insulin use before admission	0 (0.0)	0 (0.0)	18 (10.0)	21 (16.5)	< 0.001
Hypertension	354 (31.8)	192 (40.0)	93 (51.7)	64 (50.4)	< 0.001
Cardiovascular disease	28 (2.5)	9 (1.9)	10 (5.6)	10 (7.9)	0.001
Cerebrovascular disease	24 (2.2)	17 (3.5)	5 (2.8)	7 (5.5)	0.11
Weight loss > 10%	50 (4.5)	26 (5.4)	9 (5.0)	10 (7.9)	0.39
Histological type					0.018 (0.95)
Squamous cell carcinoma	276 (24.8)	146 (30.4)	46 (25.6)	19 (15.0)	
Adenocarcinoma	27 (2.4)	18 (3.8)	7 (3.9)	2 (1.6)	
Others	5 (0.4)	3 (0.6)	1 (0.6)	0 (0.0)	
Unspecified (2011–2017)	806 (72.4)	313 (65.2)	126 (70.0)	106 (83.5)	
Clinical stage					0.015 (0.30)
0–II	462 (41.5)	191 (39.8)	77 (42.8)	53 (41.7)	
III–IV	508 (45.6)	203 (42.3)	80 (44.4)	61 (48.0)	
X	107 (9.6)	60 (12.5)	21 (11.7)	7 (5.5)	
Missing data	7 (0.6)	0 (0.0)	0 (0.0)	2 (1.6)	
Unspecified (2011)	30 (2.7)	26 (5.4)	2 (1.1)	4 (3.1)	
Preoperative chemotherapy					0.004 (0.040)
No	440 (39.5)	173 (36.0)	88 (48.9)	57 (44.9)	
Yes	644 (57.8)	281 (58.5)	90 (50.0)	66 (52.0)	
Unspecified (2011)	30 (2.7)	26 (5.4)	2 (1.1)	4 (3.1)	
Preoperative radiotherapy					0.045 (0.56)
No	1033 (92.7)	429 (89.4)	169 (93.9)	120 (94.5)	
Yes	51 (4.6)	25 (5.2)	9 (5.0)	3 (2.4)	
Unspecified (2011)	30 (2.7)	26 (5.4)	2 (1.1)	4 (3.1)	
Laboratory findings					
HbA1c (%)	5.3 ± 0.3	6.0 ± 0.2	6.4 ± 0.5	7.7 ± 0.8	< 0.001
Albumin < 4.0 mg/dl	301 (27.0)	148 (30.8)	50 (27.8)	43 (33.9)	0.23
Creatinine ≥ 1.2 mg/dL	52 (4.7)	34 (7.1)	16 (8.9)	11 (8.7)	0.032
Thoracic approach					0.005
Minimally invasive	772 (69.3)	366 (76.3)	131 (72.8)	79 (62.2)	
Open thoracic	342 (30.7)	114 (23.8)	49 (27.2)	48 (37.8)	
Abdominal approach					< 0.001 (0.006)
Minimally invasive	587 (52.7)	300 (62.5)	111 (61.7)	59 (46.5)	
Open abdominal	275 (24.7)	89 (18.5)	44 (24.4)	33 (26.0)	
Unspecified (2011–2013)	252 (22.6)	91 (19.0)	25 (13.9)	35 (27.6)	
Organ reconstruction					0.003 (0.86)
Stomach	517 (46.4)	265 (55.2)	101 (56.1)	54 (42.5)	
Colon	28 (2.5)	14 (2.9)	8 (4.4)	2 (1.6)	
Others	8 (0.7)	5 (1.0)	1 (0.6)	0 (0.0)	
Missing data	9 (0.8)	4 (0.8)	4 (2.2)	0 (0.0)	
Unspecified (2011–2015)	552 (49.6)	192 (40.0)	66 (36.7)	71 (55.9)	

Table 1 (continued)

	Normoglycemia (n = 1114)	Pre-diabetes (n = 480)	Well-controlled diabetes (n = 180)	Poorly controlled diabetes (n = 127)	p value[a]
Route of reconstruction					< 0.001 (0.18)
Retrosternal	508 (45.6)	268 (55.8)	100 (55.6)	53 (41.7)	
Posterior mediastinal	42 (3.8)	14 (2.9)	10 (5.6)	2 (1.6)	
Ante-thoracic	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	
Missing data	9 (0.8)	4 (0.8)	4 (2.2)	0 (0.0)	
Unspecified (2011–2015)	555 (49.8)	192 (40.0)	66 (36.7)	72 (56.7)	
Anastomosis site					< 0.001 (0.69)
Cervical	540 (48.5)	281 (58.5)	107 (59.4)	54 (42.5)	
Intra-thoracic	10 (0.9)	3 (0.6)	3 (1.7)	1 (0.8)	
Missing data	9 (0.8)	4 (0.8)	4 (2.2)	0 (0.0)	
Unspecified (2011–2015)	555 (49.8)	192 (40.0)	66 (36.7)	72 (56.7)	

Data are presented as mean ± standard deviation or *n* (%)

BMI body mass index, *HbA1c* hemoglobin A1c

[a]*p* values in parentheses were calculated using the data excluding unspecified or missing

Table 2 Postoperative outcomes based on diabetes control status

	Normoglycemia (n = 1114)	Pre-diabetes (n = 480)	Well-controlled diabetes (n = 180)	Poorly controlled diabetes (n = 127)	p value
Anastomotic leakage	149 (13.4)	57 (11.9)	43 (23.9)	30 (23.6)	< 0.001
Surgical site infection	70 (6.3)	25 (5.2)	9 (5.0)	9 (7.1)	0.73
Respiratory complications	139 (12.5)	68 (14.2)	26 (14.4)	22 (17.3)	0.41
Cardiovascular complications	13 (1.2)	4 (0.8)	2 (1.1)	4 (3.1)	0.20
Operative morbidity grade ≥ II	462 (41.5)	209 (43.5)	81 (45.0)	63 (49.6)	0.30
Operative morbidity grade ≥ III	272 (24.4)	126 (26.3)	53 (29.4)	38 (29.9)	0.32
Operative mortality	13 (1.2)	6 (1.3)	1 (0.6)	3 (2.4)	0.56
Length of stay after surgery, days	23 ± 20	23 ± 25	26 ± 24	33 ± 56	< 0.001

Data are presented as mean ± standard deviation or *n* (%)

Table 3 Univariable and multivariable logistic regression analysis for anastomotic leakage

Diabetes control status	Univariable		Multivariable	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Normoglycemia	Reference		Reference	
Pre-diabetes	0.87 (0.63, 1.21)	0.41	0.81 (0.58, 1.13)	0.21
Well-controlled diabetes	2.03 (1.39, 2.98)	< 0.001	1.83 (1.22, 2.74)	0.003
Poorly controlled diabetes	2.00 (1.28, 3.12)	0.002	1.95 (1.23, 3.09)	0.005

The explanatory variables were age, sex, body mass index, history of smoking, hypertension, cardiovascular disease, cerebrovascular disease, weight loss > 10%, clinical stage, preoperative chemotherapy, preoperative radiotherapy, albumin, creatinine, thoracic approach, abdominal approach, organ reconstruction, and two hospitals in Japan

CI confidence interval

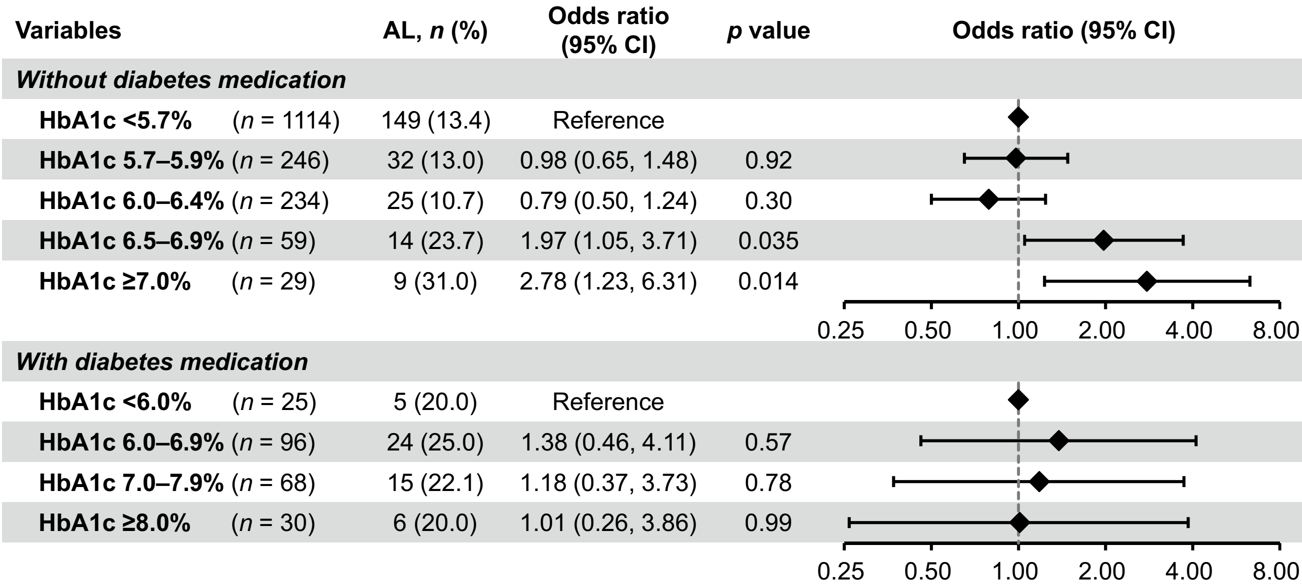

Fig. 1 Forest plot of multivariable logistic regression analysis for anastomotic leakage based on categorical HbA1c levels stratified by diabetes medication before admission. The explanatory variables were age and body mass index. *HbA1c* hemoglobin A1c, *AL* anastomotic leakage, *CI* confidence interval

Table 4 Multivariable linear regression analysis for length of stay after surgery

Diabetes control status	Length of stay after surgery, days							
	Overall patients		Patients with anastomotic leakage		Patients with operative morbidity grade ≥ II		Patients without operative morbidity grade ≥ II	
	(n = 1901)		(n = 279)		(n = 815)		(n = 1086)	
	Coef (95% CI)	p value	Coef (95% CI)	p value	Coef (95% CI)	p value	Coef (95% CI)	p value
Normoglycemia	Reference		Reference		Reference		Reference	
Pre-diabetes	0.3 (− 2.5, 3.0)	0.86	4.6 (− 8.7, 17.9)	0.50	0.9 (− 4.8, 6.6)	0.75	− 0.2 (− 1.5, 1.0)	0.70
Well-controlled diabetes	2.9 (− 1.2, 7.0)	0.16	6.5 (− 8.5, 21.5)	0.39	6.8 (− 1.5, 15.0)	0.11	− 0.2 (− 2.1, 1.7)	0.84
Poorly controlled diabetes	9.1 (4.3, 13.8)	< 0.001	16.9 (− 0.2, 34.1)	0.053	14.9 (5.6, 24.1)	0.002	1.2 (− 1.1, 3.5)	0.30

The explanatory variables were age, sex, body mass index, history of smoking, hypertension, cardiovascular disease, cerebrovascular disease, weight loss > 10%, clinical stage, preoperative chemotherapy, preoperative radiotherapy, albumin, creatinine, thoracic approach, abdominal approach, organ reconstruction, and two hospitals in Japan

CI confidence interval, *Coef* coefficient

Discussion

In this two-center cohort study, we assessed the impact of diabetes control status on AL after esophagectomy for esophageal cancer. Diabetes and pre-diabetes were observed in 16.1% and 25.2% of patients, respectively. Among patients with diabetes, 58.6% had well-controlled diabetes (HbA1c < 7.0%) and 41.4% had poorly controlled diabetes (HbA1c ≥ 7.0%). Compared with normoglycemia, both well-controlled diabetes and poorly controlled diabetes were significantly associated with a > 1.8-fold increased risk of AL, whereas pre-diabetes was not associated with AL. To the best of our knowledge, this study is the first to evaluate short-term outcomes after esophagectomy in well-controlled diabetes, poorly controlled diabetes, and pre-diabetes as separate subgroups.

Diabetes has been reported to reduce peripheral blood flow and local angiogenesis [19], and inhibit granulation tissue formation and maturation [20], which may contribute to impaired/delayed wound healing. Thus, the association between diabetes and AL after esophagectomy for esophageal cancer has been an area of interest over recent decades [8, 21]. A recently published meta-analysis showed that diabetes was associated with the risk of AL after esophagectomy [8]. Moreover, a recent nationwide database study, using a restricted cubic spline analysis, showed that HbA1c level ≥ 7.0% was associated with AL after esophagectomy [11]. However, the risk of AL in patients with well-controlled diabetes (HbA1c < 7.0%) remains unclear because previous studies have only evaluated the association between AL and pre-existing diabetes or preoperative HbA1c levels.

We highlighted the hidden risk of well-controlled diabetes. The risk of AL in well-controlled and poorly controlled diabetes was similar, and both types of patients had a higher risk of AL than normoglycemia patients had. Similarly, HbA1c was not associated with AL in a subgroup analysis of patients with diabetes medication. These findings are consistent with a systematic review that showed that elevated preoperative HbA1c in patients with diabetes was not definitively associated with increased operative morbidity in non-gastrointestinal (mainly cardiovascular and orthopedic) surgery [22]. The present study suggests that the diabetes impairs anastomotic healing even in well-controlled diabetes. Therefore, even if the diabetes is well controlled preoperatively, surgeons should not underestimate the risk of AL.

In a subgroup analysis of patients not taking diabetes medication before admission, HbA1c showed a J-shaped association with AL, revealing the risk for untreated/undiagnosed diabetes patients (HbA1c ≥ 6.5% without diabetes medication). Untreated/undiagnosed diabetes, even in patients with HbA1c 6.5–6.9%, was associated with AL compared with patients with HbA1c < 5.7%. To detect untreated/undiagnosed diabetes, we recommend preoperative HbA1c testing for all patients who are scheduled for esophagectomy, regardless of whether they have a history of diabetes.

The present study clearly showed that pre-diabetes was not associated with AL. Patients with previously diagnosed diabetes with HbA1c 5.7%–6.4% with dietary/exercise therapy alone were classified as having pre-diabetes and not well-controlled diabetes, and the proportion of these patients with AL was low (1/22; 4.5%). In patients without diabetes medication, those with HbA1c levels of 6.0–6.4% had the lowest risk of AL, although the difference compared with patients with HbA1c < 5.7% was not significant. These findings suggest that the optimal HbA1c cutoff point for detecting patients at high risk for AL in those without diabetes medication is not 6.0% (the cutoff point for pre-diabetes diagnosis) but 6.5% (the cutoff point for diabetes diagnosis).

In our study, only poorly controlled diabetes was significantly associated with a prolonged hospital stay, compared with normoglycemia. We conducted a subgroup analysis of patients with and without operative morbidity. The analysis showed that patients with poorly controlled diabetes had a longer hospital stay than those with normoglycemia, but only among those with operative morbidity. These findings suggest that poor preoperative glycemic control causes delayed recovery after operative morbidity, including AL. This may be explained by dividing wound healing into primary and secondary healing. Primary healing is defined as uncomplicated healing of a noninfected, well-approximated wound, and an anastomosis after esophagectomy can be classified as primary healing. Our study showed that both well-controlled diabetes and poorly controlled diabetes patients were associated with AL, suggesting that primary healing is impaired in these patients because the diabetes condition may reduce peripheral blood flow and local angiogenesis in the surgical area [19]. Secondary healing is defined as a form of wound healing that could not be closed due to contamination, infection, or massive tissue loss: if AL occurs, the secondary healing stage begins with the formation of granulation tissue [23]. Thus, only in poorly controlled diabetes patients, secondary healing may be impaired due to inhibiting granulation tissue formation and maturation [20], causing delayed recovery after surgical complications. Furthermore, the recovery time from infectious complications in poorly controlled diabetes patients may also be longer because of a compromised immune system [24]. When a postoperative complication occurs in poorly controlled diabetes patients, early and focused management (e.g., nutritional intervention and rehabilitation) by a multidisciplinary team should be considered in anticipation of prolonged hospitalization to prevent deterioration of nutritional status and physical function.

We believe that routine HbA1c testing and confirmation of diabetes medication history at preoperative evaluation is useful for accurate identification of patients with diabetes, who are at a high risk of AL after esophagectomy. Early identification of diabetes patients allows provision of clear preoperative explanations to these patients and enables early management of diabetes. For diabetes patients, treatment of postoperative hyperglycemia with insulin has been reported to decrease surgical complications after non-cardiac and cardiac surgery [25]. A preoperative diabetes management program aimed at optimizing treatment for all patients with diabetes irrespective of their HbA1c levels has been reported to improve glycemic control on the day of surgery and decrease length of hospital stay [26].

There were some limitations to our study that should be addressed. First, the type and duration of diabetes may have had an impact on our findings that was not possible to assess; this information warrants inclusion in further investigations. Second, perioperative blood glucose levels were unavailable from the database although postoperative blood glucose levels were routinely checked in all patients. The blood glucose level and insulin use might have affected the occurrence of AL. Third, for patients with preoperative chemotherapy/radiotherapy, information on whether HbA1c values were measured before or after preoperative therapy was not available from the database. In most cases, however, HbA1c values measured after preoperative therapy were recorded in the database because we typically measured HbA1c within two days before surgery and were supposed to record the value closest to the day of surgery. Finally, our database did not include information on the anastomotic technique. However, we previously reported that there was no significant difference in the occurrence of AL between the totally mechanical Collard and circular stapled anastomoses [7]. The occurrence of AL has also been reported to be similar between the totally mechanical Collard and hand-sewn anastomoses [27].

Conclusions

Diabetes was associated with AL after esophagectomy for esophageal cancer even in patients with well-controlled, but pre-diabetes was not associated with AL. Preoperative HbA1c showed a J-shaped association with AL in patients without diabetes medication and no association in patients with diabetes medication. Operative morbidity, including AL, in poorly controlled diabetes may result in prolonged hospital stay compared with normoglycemia. Our analyses suggest that diabetes is a principal risk factor for AL after oncological esophagectomy, irrespective of preoperative HbA1c levels.

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Declarations

Ethical Statement This two-center retrospective study was approved by the Ethics Committee at NCCH (2020-303).

Conflict of interest The authors have no conflicts of interest to declare.

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