Surgery Today (2023) 53:907–916
https://doi.org/10.1007/s00595-023-02641-9

ORIGINAL ARTICLE

The impact of postoperative blood glucose levels on complications and prognosis after esophagectomy in patients with esophageal cancer

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Received: 2 September 2022 / Accepted: 29 November 2022 / Published online: 20 January 2023

Abstract

Purpose This study aimed to characterize postoperative blood glucose fluctuation in patients who underwent esophagectomy for esophageal cancer, and to define its impact on complications and prognosis.

Methods The subjects of this retrospective study were 284 patients who underwent esophagectomy at Osaka University Hospital between 2015 and 2017. Data analyzed included clinicopathological background, the immediate postoperative blood glucose level (IPBG), postoperative blood glucose variability (PBGV), insulin dosage, postoperative complications, and prognosis.

Results The median IPBG and PBGV were 170 (64–260) mg/dl and 64.5 (11–217) mg/dl, respectively. Postoperative pneumonia was more common in patients with PBGV > 100 mg/dl ($P = 0.015$). Patients with IPBG < 170 mg/dl had significantly worse 5-year overall survival (OS) and 5-year recurrence-free survival (RFS) than those with IPBG > 170 mg/dl (54.5% vs. 80.4%, respectively, [$P < 0.001$] and 44.3% vs. 69.3%, respectively, [$P = 0.001$]). The 5-year OS rates were 43.5%, 68.3%, 80.6%, and 79.0% for patients with IPBG < 154, 154–170, 170–190, and ≥ 190 mg/dl, respectively. The corresponding 5-year RFS rates were 38.1%, 52.4%, 77.0%, and 61.3%, respectively. Multivariate analysis revealed that IPBG < 154 mg/dl and pathological stage were independent poor prognostic factors for OS.

Conclusion PBGV was associated with postoperative pneumonia, and low IPBG was an independent poor prognostic factor for patients with esophageal cancer.

Keywords Esophageal cancer · Esophagectomy · Postoperative blood glucose · Postoperative complications · Overall survival

Introduction

Previous studies have shown that high preoperative blood glucose and hemoglobin A1c (HbA1c) levels are not only associated with postoperative complications [1–3], but they are also risk factors for an unfavorable prognosis for patients with gastrointestinal cancer, including esophageal cancer [4, 5]. However, there are few reports on the impact of postoperative blood glucose levels on short- and long-term postoperative outcomes.

Esophagectomy is a very invasive procedure associated with a high incidence of postoperative complications [6] and it is estimated that intraoperative and postoperative blood glucose levels fluctuate widely. Furthermore, as patients with cancer age, the number of those with comorbidities such as impaired glucose tolerance is expected to increase [7]. However, the status of changes in blood glucose levels after esophagectomy has not been determined. In this study, we hypothesized that high glycemic variability in response to radical esophagectomy for esophageal cancer can predict poor short- and long-term outcomes. This is an important research topic because the findings may improve the management of this patient population.

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Materials and methods

Patients

We collected the data of patients who underwent esophagectomy at Osaka University Hospital between January, 2015 and December, 2017, to clarify the fluctuation of blood glucose levels after esophagectomy. The eligibility criteria for this retrospective study were subtotal esophagectomy and histologically confirmed primary esophageal cancer. The exclusion criteria were trans-hiatal esophagectomy and residual esophageal cancer. A total of 284 patients were eligible for the study. The study protocol was approved by the institutional review board of Osaka University (approval number: 08226-10).

Surgical procedures

All patients underwent subtotal esophagectomy followed by esophageal reconstruction. Subtotal esophagectomy with mediastinal lymphadenectomy was performed via right thoracotomy or thoracoscopy. The abdominal procedure included upper abdominal lymphadenectomy and preparation of a gastric conduit or reconstruction of other organs. Reconstructed organs were pulled up through the retrosternal, posterior mediastinal, or subcutaneous route, and cervical or pro-sternal subcutaneous anastomosis was performed. Supraclavicular lymph node dissection was performed in patients with upper thoracic esophageal cancer and those with lower or middle thoracic esophageal cancer with metastasis in the upper mediastinal lymph nodes [8, 9]. Methylprednisolone (250 mg/body) was administered intraoperatively to all patients immediately before the thoracotomy incision.

Postoperative control

Postoperative blood glucose was monitored every 4 h and insulin was administered using a sliding scale, with a target blood glucose level of 80 ~ 180 mg/dl. Enteral nutrition was started the day after surgery, and the postoperative infusion of maintenance fluid was administered at approximately 80 ~ 200 ml/hr while monitoring urine volume and vital signs.

Outcomes

Blood glucose levels were measured immediately after surgery and during the postoperative intensive care unit (ICU) stay. The immediate postoperative blood glucose level (IPBG) was defined as the blood glucose level measured within 1 h after surgery, and postoperative blood glucose variability (PBGV) was defined as the difference between the maximum and minimum blood glucose levels during the ICU stay within 3 days after surgery. We evaluated whether the IPBG and PBGV correlated with clinicopathological factors; specifically, postoperative complications and prognosis. Complications from the day of surgery until hospital discharge were reviewed by the attending physicians at the time of discharge, and were categorized according to the Clavien–Dindo classification system [10]. Diabetes was defined as preoperative fasting blood glucose ≥ 126 mg/dL or HbA1c ≥ 6.5%, and pneumonia was defined as an infiltrative shadow on chest X-ray and an increased inflammatory response.

Statistical analysis

Associations between IPBG or PBGV and clinical parameters; specifically, age, gender, serum C-reactive protein (CRP), serum albumin, serum HbA1c, clinical stage, Charlson comorbidity index (CCI), preoperative treatment, surgical procedure, number of lymphadenectomy fields, operation time, intraoperative blood loss, pathological stage, and postoperative complications, were analyzed using the Chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. Recurrence-free survival (RFS) and overall survival (OS) were evaluated for groups stratified by IPBG or PBGV. These survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios were estimated in both univariate and multivariate analyses using Cox proportional hazards regression models. $P < 0.05$ was considered significant. Evaluation factors were blood glucose-related factors in addition to general prognostic factors, and factors with $P < 0.05$ in the univariate hazard analysis were entered in the multivariate analysis. Statistical analyses were performed using JMP version 16 software (SAS Institute, Cary, NC).

Results

Patients

Table 1 summarizes the patients' characteristics. The median age was 69 (41–90) years, 40 patients (14.1%) had diabetes and 42 patients (14.8%) had a preoperative HbA1c of 6.5 or higher. The clinical stage of esophageal cancer (Union for International Cancer Control TNM classification) was Stage I, II, III, and IV in 60, 53, 126, and 45 patients, respectively. Eighty patients had a CCI of 2 or higher. Intraoperative insulin was administered to 17 patients, for hyperglycemia in 11 patients, for hyperkalemia in 5, and for both in 1.

Table 1 Patients' characteristics

		$N=284$
Age (years)	Median, range	69, 41–90
Sex	Male/female	248/36
Tumor location	Ut/Mt/Lt	63/142/79
cT	1/2/3/4	49/52/128/55
cN	0/1/2/3	99/144/36/5
cStage (UICC 7th)	I/II/III/IV	60/53/126/45
CCI	0, 1/2 or higher	204/80
Preoperative treatment	None/chemotherapy/CRT(RT)	49/187/48
Operation time (min)	Median, range	488.5, 227–1101
Blood loss (ml)	Median, range	300, 0–2160
Surgical procedure	Open/MIE/trans-hiatal	146/134/4
Postoperative complications(Clavien–Dindo classification)	Grade 0/1/2/3/4/5	83/8/69/100/24/0
Length of postoperative stay in hospital (days)	Median, range	26, 16–143
Diabetes	±	40/244
Preoperative HbA1c (%)	≥ 6.5/ < 6.5	42/242
IPBG (mg/dl)	Median, range	170, 64–260
PBGV (mg/dl)	Median, range	64.5, 11–217
Intraoperative insulin administration	±	17/267
Volume of intraoperative infusion	Median, range	3195, 320–7300
Postoperative insulin administration	±	108/176

Ut upper third of thoracic esophagus, *Mt* middle third of thoracic esophagus, *Lt* lower third of thoracic esophagus, *UICC* Union for International Cancer Control, *CCI* Charlson comorbidity index, *CRT* Chemoradiotherapy, *RT* radiotherapy, *MIE* minimally invasive esophagectomy, *HbA1c* hemoglobin A1c, *IPBG* immediate postoperative blood glucose level, *PBGV* postoperative blood glucose variability

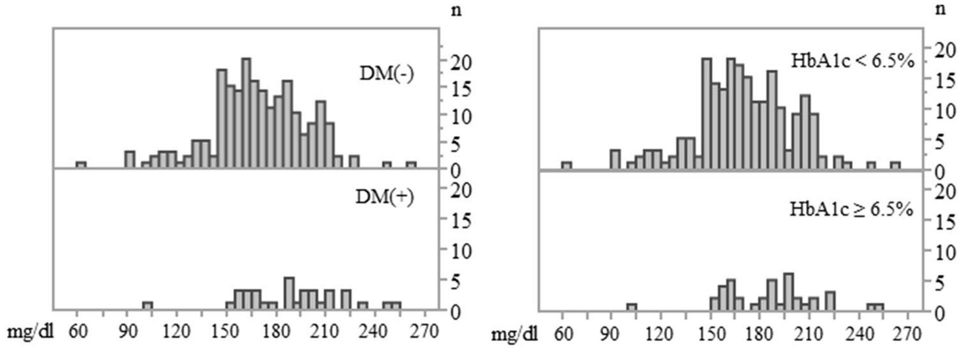
One hundred and eight patients required insulin administration for postoperative hyperglycemia. The IPBG was significantly higher in patients with diabetic comorbidities ($P<0.001$, Fig. 1) and a preoperative HbA1c of 6.5 or higher ($P=0.003$). The PBGV was significantly higher in patients with diabetes ($P<0.001$) and a preoperative HbA1c of 6.5% or higher ($P=0.003$).

Postoperative complications

Postoperative pneumonia and anastomotic leakage developed in 118 (41.5%) and 31 (10.9%) patients, respectively. Table 2 shows the relationship between postoperative complications and clinical factors. The development of pneumonia was significantly related to high PBGV (100 mg/dl or higher, $P=0.021$). Although the incidence of anastomotic leakage was significantly correlated with a longer operation time ($P=0.002$) and high CCI ($P<0.001$), it was not correlated with preoperative HbA1c, diabetic comorbidity, IPBG, or PBGV.

Prognosis

Figure 2 shows postoperative survival stratified by indicators related to blood glucose. Preoperative factors, including a history of diabetes and HbA1c level, were not related to the prognosis of patients with esophageal cancer. On the other hand, patients with a low IPBG (≤ 170 mg/dl) had significantly worse 5-year OS and RFS rates than those with a higher IPBG (54.5% vs. 80.4%, respectively [$P<0.001$] and 44.3 vs. 69.3%, respectively [$P=0.001$]). Furthermore, in a comparison of four groups classified by IPBG quartiles, the 5-year OS rates in the lowest group (IPBG < 154 mg/dl, Q1), second group (154–169 mg/dl, Q2), third group (170–189 mg/dl, Q3), and the highest group (≥ 190 mg/dl, Q4) were 43.5%, 68.3%, 80.6%, and 79.0%, respectively. The 5-year RFS rates in the Q1, Q2, Q3, and Q4 groups were 38.1%, 52.4%, 77.0%, and 61.3%, respectively. PBGV was not a prognostic factor for patients with esophageal cancer. Univariate analysis of OS identified low IPBG (≤ 154 mg/dl), postoperative complications, high CCI, pT stage, and pN stage as being significantly associated with unfavorable prognosis, but PBGV was not a significant factor (Table 3). Multivariate analysis revealed that the independent poor prognostic factors for OS were IPBG (hazard ratio [HR], 2.05; 95% confidence interval [CI], 1.28–3.28; $P=0.003$), pT stage (HR, 2.28; 95% CI, 1.44–3.63; $P<0.001$), and pN stage (HR, 1.81; 95% CI, 1.05–3.10; $P=0.032$). The analysis of RFS identified the same factors. Multivariate analysis revealed that pT stage (HR, 2.00; 95% CI, 1.33–2.95;



	N	Average (mg/dl)	*P* value
DM (-)	215	169.3	< 0.001
DM (+)	35	189.2	

	N	Average (mg/dl)	*P* value
HbA1c < 6.5%	211	169.6	0.003
HbA1c ≥ 6.5%	39	185.2	

	N	Average (mg/dl)	*P* value
DM (-)	244	70.0	< 0.001
DM (+)	40	110.6	

	N	Average (mg/dl)	*P* value
HbA1c < 6.5%	242	71.8	0.003
HbA1c ≥ 6.5%	42	98.4	

Fig. 1 Upper row: distribution of postoperative blood glucose levels measured within 1 h after surgery. Lower row: range of postoperative glycemic excursion. *DM* diabetes mellitus, *HbA1c* hemoglobin A1c

$P<0.001$) and pN stage (HR, 2.33; 95% CI, 1.44–3.75; $P<0.001$) were independent poor prognostic factors.

Recurrence patterns

An analysis of recurrence patterns showed that patients in the Q1 group had a significantly higher recurrence rate than those in the Q2–4 groups (49.2% vs. 28.9%, respectively, $P=0.005$, Table 4). Recurrence rates were not associated with patterns of recurrence, such as lymph nodes, distant organs, disseminated recurrence, and local recurrence, but patients in the Q1 group had a significantly higher recurrence rate than the Q2–4 groups, involving multiple patterns (14.3% vs. 4.3%, respectively; $P=0.016$).

Factors correlated with IPBG

Table 5 shows the results of an analysis of factors correlated with low IPBG (≤ 154 mg/dl). Patients with a history of diabetes and high preoperative HbA1c were significantly more likely to have a high IPBG (≥ 154 mg/dl) ($P=0.003$ and 0.005, respectively). On the other hand, patients in the low IPBG group had higher CCI than those in the high IPBG group ($P=0.033$) and were significantly less likely to have received preoperative treatment ($P=0.022$). The preoperative serum CRP level, serum albumin level, and intraoperative insulin administration were similar between the groups. In the pathological findings, pN stage was significantly more advanced in the low IPBG group ($P=0.040$).

Discussion

The present study showed that esophageal cancer patients with postoperative hypoglycemia immediately after radical esophagectomy were at high risk of postoperative recurrence and had a very poor prognosis. However, low IPBG was not associated with the incidence of postoperative pneumonia or anastomotic leakage. Conversely, PBGV greater than 100 mg/dl was significantly correlated with a higher incidence of pneumonia.

The risk factors for perioperative pneumonia have been reported to include advanced age [11, 12], smoking history [13], low pulmonary function [14], poor nutrition [15], impaired glucose tolerance [16], and postoperative hyperglycemia [17, 18]. In this study, the incidence of postoperative

Table 2 Factors associated with pneumonia and anastomotic leakage

		Pneumonia (−) N = 166 (%)	Pneumonia (+) N = 118 (%)	P value	Anastomotic leakage (−) N = 253 (%)	Anastomotic leakage (+) N = 31 (%)	P value
Age (years)	Median, range	68, 45–88	71, 41–90	0.15	68, 41–90	72, 53–82	0.26
Sex	Male/female	140 (84)/26 (16)	108 (92)/10 (8)	0.10	219 (87)/34 (13)	29 (94)/2 (6)	0.23
cStage (UICC 7th)	I, II/III, IV	63 (38)/103 (62)	50 (42)/68 (58)	0.46	101 (40)/152 (60)	12 (39)/19 (61)	1.00
CCI	0, 1/2 or higher	121 (73)/45 (27)	83 (70)/35 (30)	0.61	191 (75)/62 (25)	13 (42)/18 (58)	< 0.001
Neoadjuvant chemotherapy	±	117 (71)/49 (30)	70 (59)/48 (41)	0.057	165 (65)/88 (35)	22 (29)/9 (71)	0.69
Operation time (min)	Median, range	480.5, 319–1101	499.5, 227–904	0.12	485, 227–1101	535, 363–895	0.002
Blood loss (ml)	Median, range	290, 0–2160	330, 10–1980	0.12	300, 0–2160	350, 30–1980	0.44
Surgical procedure	Open/MIE/transhiatal	83 (50)/81 (49)/2 (1)	63 (53)/53 (45)/2 (2)	0.76	132 (52)/118 (47)/3 (1)	14 (45)/16 (52)/1 (3)	0.60
Diabetes	±	18 (11)/148 (89)	22 (19)/96 (81)	0.083	37 (15)/216 (85)	3 (10)/28 (90)	0.59
Preoperative serum HbA1c (%)	≥ 6.5/ < 6.5	19 (11)/147 (89)	23 (19)/95 (81)	0.064	39 (15)/214 (85)	3 (10)/28 (90)	0.59
Diabetes and preoperative HbA1c ≥ 6.5%	±	17 (10)/149 (90)	22 (19)/96 (81)	0.054	26 (10)/227 (90)	2 (6)/29 (94)	0.75
IPBG (mg/dl)	≥ 170/ < 170	72 (49)/74 (51)	52 (50)/52 (50)	1.00	112 (51)/110 (49)	12 (43)/16 (57)	0.55
PBGV (mg/dl)	≥ 100/ < 100	137 (83)/29 (17)	83 (70)/35 (30)	0.021	197 (78)/56 (22)	23 (74)/8 (26)	0.65
Postoperative insulin administration	±	58 (35)/108 (65)	50 (42)/68 (58)	0.22	97 (38)/156 (62)	11 (35)/20 (65)	0.87

UICC Union for International Cancer Control, *CCI* Charlson comorbidity index, *HbA1c* hemoglobin A1c, *IPBG* immediate postoperative blood glucose level, *PBGV* postoperative blood glucose variability

pneumonia was higher in patients with large postoperative blood glucose fluctuations. A previous study of patients in the intensive care unit after cardiac surgery found that tight glycemic control with a target blood glucose level of 81–108 mg/dl increased the risk of death within 90 days compared with glycemic control with a target blood glucose level of 180 mg/dl or less [19]. Therefore, we maintained the postoperative blood glucose level at below 180 mg/dl, and patients with high IPBG often had postoperative hyperglycemia and received insulin. It was reported that high postoperative blood glucose levels caused leukocyte dysfunction and increased the risk of infectious complications [20], and that glycemic control with a target blood glucose level of less than 200 mg/dl reduced postoperative infectious complications and perioperative mortality [19]. Although it was unclear whether high PBGV caused pneumonia or vice versa based on the present results, postoperative complications might be reduced by management that does not increase postoperative PBGV. To explore this possibility, further detailed research should evaluate postoperative blood glucose fluctuations using prospective continuous blood glucose monitoring.

With regard to esophageal cancer and glucose tolerance-related factors, high preoperative HbA1c [21] and poor nutritional status [22] have been reported as prognostic factors, and complications of diabetes mellitus have been reported to be associated with recurrence [23]. However, to our knowledge, there are no reports on the relationship between IPBG and prognosis. The present study found that low IPBG was associated with poor prognosis. Factors that may influence postoperative blood glucose levels include age [24], glucose tolerance [22, 25], liver function [26], intraoperative glucose control, and surgical invasiveness. In this study, low postoperative blood glucose was correlated with the absence of a history of diabetes and with a preoperative HbA1c less than 6.5%, indicating that low postoperative blood glucose levels were more frequent in patients who did not have impaired glucose tolerance preoperatively. This suggests that IPBG fluctuations in patients with esophageal cancer may be due to intraoperative factors rather than to preoperative glucose intolerance, or that patients who undergo esophageal cancer surgery may have a poor glycemic response to the procedure, a characteristic that cannot be identified preoperatively with current evaluation methods.

There are three potential mechanisms for hypoglycemia occurring immediately after esophagectomy: insulin hypersecretion, increased insulin sensitivity of the peripheral tissues, and decreased secretion or function of

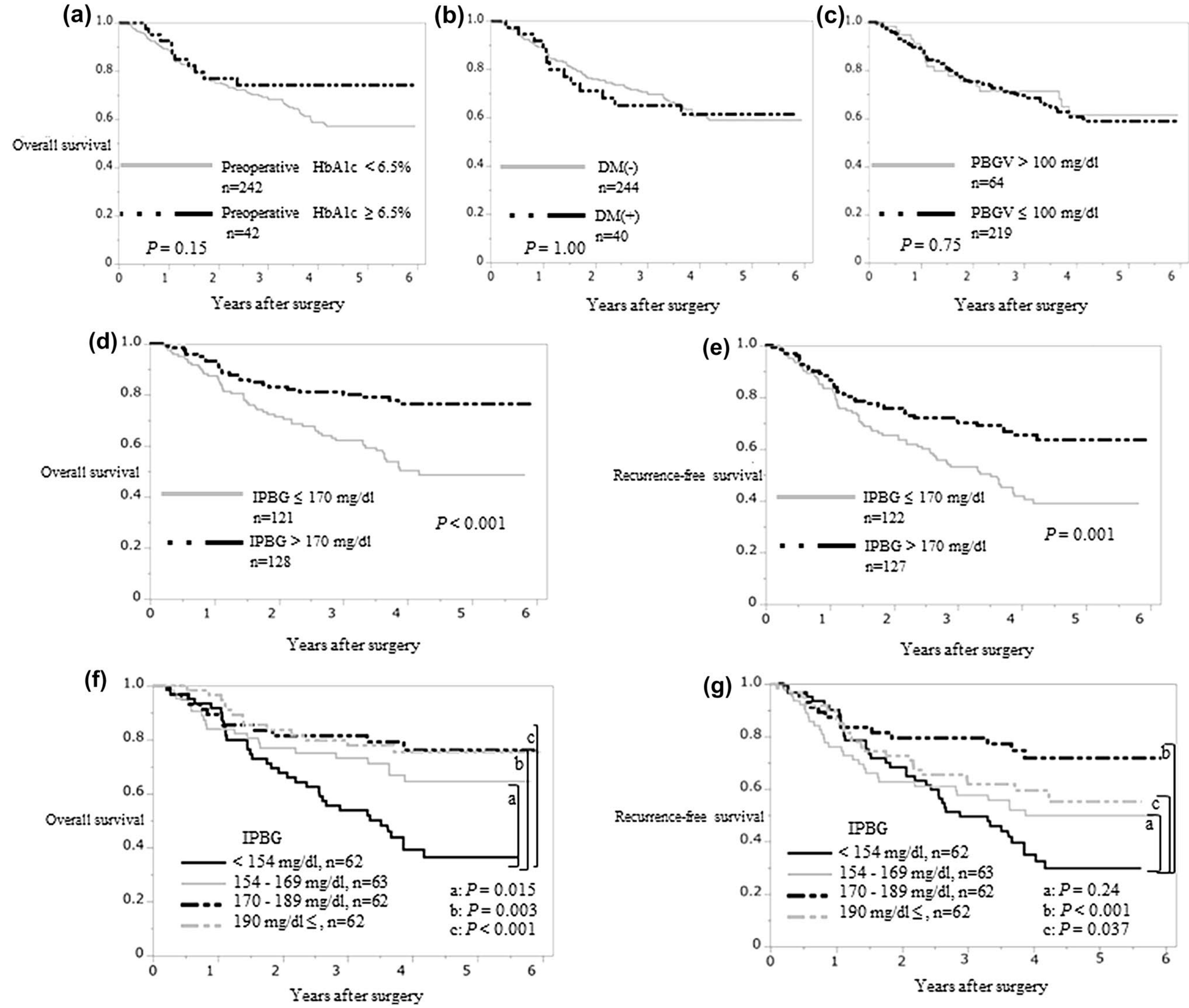


Fig. 2 Kaplan–Meier curves showing the correlation of blood glucose-related factors with overall survival, and the correlation of the immediate postoperative blood glucose level (IPBG) with overall survival and recurrence-free survival (**a**–**e**). Kaplan–Meier curves for overall and recurrence-free survival compared in groups defined by IPBG quartiles (**f**–**g**). *HbA1c* hemoglobin A1c, *DM* diabetes mellitus, *PBGV* postoperative blood glucose variability, *IPBG* immediate postoperative blood glucose level

insulin-counter-regulatory hormones, including growth hormone, glucagon, catecholamine, cortisol, and aldosterone. Although insulin hypersecretion is caused by the intravascular influx of glucose or glucagon-like peptide-1 (GLP-1) secretion, the latter usually being from the small intestine, these events are unlikely to occur during esophageal cancer surgery. Moreover, increased peripheral tissue sensitivity to insulin occurs in patients with a high preoperative glucose level or glucose intolerance. In the present study, preoperative blood glucose levels and impaired glucose tolerance were not found to be poor prognostic factors after esophagectomy. Furthermore, IPBG was unrelated to the preoperative blood glucose-related or nutritional factors. Therefore, the most likely cause of low IPBG seems to be decreased secretion or dysfunction of insulin-counter-regulatory hormones; however, data on these hormones were not collected in this study.

We identified that IPBG was a poor prognostic factor, but the mechanism remains unclear. As mentioned, we speculate that the cause of low IPBG is the inability to raise blood glucose levels in response to surgery. There have been several reports on the mechanism whereby disruption of various insulin-counter-regulatory hormones is related to the prognosis of cancer patients. High levels of thyroid hormones and cortisol were found to worsen the prognosis of patients with cancer [27, 28], and the

Table 3 Multivariate analysis of overall survival and recurrence-free survival

		Overall survival					
		Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Diabetes	–	1.00					
	+	1.01	0.56–1.80	0.99			
Preoperative HbA1c	< 6.5%	1.00					
	≥ 6.5%	0.62	0.32–1.20	0.13			
PBGV	> 100 mg/dL	1.00					
	≤ 100 mg/dL	1.09	0.65–1.81	0.75			
IPBG	≥ 154 mg/dl	1.00					
	< 154 mg/dl	2.53	1.62–3.94	< 0.001	2.05	1.28–3.28	0.003
Postoperative complications	–	1.00					
	+	1.76	1.08–2.86	0.020	1.45	0.86–2.47	0.17
CCI	0–1	1.00					
	2 or high	1.56	1.03–2.37	0.035	1.28	0.78–2.09	0.33
pT	0–2	1.00					
	3	2.90	1.94–4.40	< 0.001	2.28	1.44–3.63	< 0.001
pN	0	1.00					
	1–3	2.45	1.53–3.92	< 0.001	1.81	1.05–3.10	0.032
		Recurrence-free survival					
		Univariate			Multivariate		
		HR	95% CI	*P* value	HR	95% CI	*P* value
Diabetes	–	1.00					
	+	1.23	0.68–2.22	0.49			
Preoperative HbA1c	< 6.5%	1.00					
	≥ 6.5%	0.74	0.38–1.44	0.38			
PBGV	> 100 mg/dL	1.00					
	≤ 100 mg/dL	0.77	0.51–1.16	0.21			
IPBG	≥ 154 mg/dl	1.00					
	< 154 mg/dl	1.89	1.28–2.81	0.002	1.40	0.92–2.12	0.12
Postoperative complications	–	1.00					
	+	1.49	0.99–2.23	0.048	1.40	0.89–2.18	0.14
CCI	0–1	1.00					
	2 or high	1.53	1.06–2.21	0.025	1.42	0.92–2.18	0.11
pT	0–2	1.00					
	3	2.61	1.84–3.72	< 0.001	2.00	1.33–2.95	< 0.001
pN	0	1.00					
	1–3	2.81	1.84–4.29	< 0.001	2.33	1.44–3.75	< 0.001

HR hazard ratio, *CI* confidential interval, *HbA1c* hemoglobin A1c, *IPBG* immediate postoperative blood glucose level, *CCI* Charlson comorbidity index

stimulation of tumor glucagon receptors was reported to increase tumor growth [29]. However, the relevant mechanisms have not been identified. On the other hand, it is possible that low IPBG does not have a direct negative impact on the prognosis of patients with cancer; rather, the present results suggest that a population of patients with a poor prognosis from various other factors was selected based on the criterion of low IPBG. We found that patients in a low IPBG group were significantly less likely to have received preoperative treatment than those in a high IPBG group, despite the comparable clinical stage. This may be because a higher rate of comorbidities was observed in the low IPBG group, resulting in a significantly more advanced pN stage in this group. Lymph node metastasis

Table 4 Recurrence patterns classified by the immediate postoperative glucose level

	IPBG < 154 mg/dl N = 63 (%)	IPBG ≥ 154 mg/dl N = 187 (%)	P value
Lymph nodes	10 (15.9)	21 (11.2)	0.38
Distant organs	9 (14.3)	19 (10.2)	0.35
Local	0	1 (0.5)	1.00
Disseminated	1 (1.6)	3 (1.6)	1.00
Multiple recurrence patterns	9 (14.3)	8 (4.3)	0.016
All	31 (49.2)	54 (28.9)	0.005

IPBG immediate postoperative blood glucose level

in esophageal cancer patients is an indicator of systemic disease, which could explain the high incidence of multiple recurrences in the low IPBG group. On the other hand, since low IPBG was an independent prognostic factor, along with pT and pN stage, it is necessary to consider the possibility that high tumor proliferative potential, low antitumor immunity, and insufficient intensity of postoperative therapy could have affected the prognosis of the low IPBG group. Ultimately, this study shows that there is a group of patients with a poor prognosis that cannot be predicted preoperatively; namely, the low IPBG group, whose blood glucose levels cannot be raised in response to surgical invasion.

This study had several limitations. First and most importantly, it was a single-center, retrospective study with a limited number of patients. Second, it analyzed blood glucose levels measured only at time points when blood glucose monitoring was performed. Detailed studies with continuous blood glucose monitoring and other methods are required to rigorously compare perioperative blood glucose fluctuations and short- and long-term postoperative outcomes after esophageal cancer surgery. Third, the mechanism by which IPBG adversely affects prognosis

Table 5 Factors affecting the immediate postoperative blood glucose level

		IPBG < 154 mg/dl N = 63 (%)	IPBG ≥ 154 mg/dl N = 187 (%)	P value
Age (years)	Median, range	69, 41–88	69, 45–90	0.95
Sex	Male/female	55 (87)/8 (13)	166 (89)/21 (11)	0.82
cT	1, 2/3, 4	26 (41)/37 (59)	63 (34)/124 (66)	0.29
cN	0/1–3	24 (38)/39 (62)	67 (36)/120 (64)	0.76
cStage (UICC 7th)	I/II/III/IV	16 (25)/11 (18)/27 (43)/9 (14)	37 (20)/38 (20)/82 (44)/30 (16)	0.81
Diabetes	±	2 (3)/61 (97)	33 (18)/154 (82)	0.003
Preoperative HbA1c (%)	≥ 6.5/ < 6.5	3 (5)/60 (95)	36 (19)/151 (81)	0.005
CCI	0, 1/2 or higher	39 (62)/24 (38)	143 (76)/44 (24)	0.033
Preoperative treatment	±	45 (71)/18 (29)	159 (85)/28 (15)	0.022
Preoperative serum albumin (mg/dl)	Median, range	3.7, 2.7–4.5	3.7, 2.5–4.6	0.92
Preoperative serum CRP (mg/dl)	Median, range	0.13, 0.04–0.57	0.08, 0.04–3.46	0.41
BMI (kg/m^2)	Median, range	20.7, 15.0–26.9	21.7, 15.0–34.7	0.31
Operation time (min)	Median, range	479, 326–884	490, 227–1101	0.25
Blood loss (ml)	Median, range	270, 50–1250	300, 0–2160	0.080
Surgical procedure	Open/MIE/trans-hiatal	30 (48)/31 (49)/2 (3)	97 (52)/88 (47)/2 (1)	0.48
Postoperative complications (Clavien–Dindo classification)	±	46 (73)/17 (27)	130 (70)/57 (30)	0.64
Intraoperative insulin administration	±	4 (6)/59 (94)	12 (6)/175 (94)	1.00
The amount of intraoperative insulin administration	Median, range	0, 0–22.2	0, 0–10	0.34
Volume of intraoperative infusion	Median, range	3100, 570–5150	3250, 320–7300	0.24
pT	0–2/3	40 (64)/23 (36)	119 (64)/68 (36)	1.00
pN	0/1–3	20 (32)/43 (68)	88 (47)/99 (53)	0.040
pStage (UICC 7th)	0/I/II/III/IV	4 (6)/13 (21)/20 (32)/17 (27)/9 (14)	19 (10)/49 (26)/50 (27)/51 (27)/18 (10)	0.61

IPBG immediate postoperative blood glucose level, *UICC* Union for International Cancer Control, *HbA1c* hemoglobin A1c, *CCI* Charlson comorbidity index, *BMI* body mass index, *MIE* minimally invasive esophagectomy is unknown, and additional studies, including those examining intraoperative blood glucose variability and insulin-counter-regulatory hormones measurements, are needed.

In conclusion, the present study demonstrated that patients with esophageal cancer and postoperative hypoglycemia immediately after radical esophagectomy were at high risk of a poor prognosis. While low postoperative blood glucose levels were not associated with the incidence of postoperative pneumonia or anastomotic leakage, PBGV greater than 100 mg/dl was significantly associated with the incidence of pneumonia.

Funding This study did not receive any financial support.

Declarations

Conflict of interest We have no conflict of interest or financial ties to disclose.

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