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Low preoperative hemoglobin A1c level is a predictor of perioperative infectious complications after esophagectomy: A retrospective, single-center study

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Abstract: This retrospective, single-center study aimed to evaluate the impact of blood glucose (BG) markers on perioperative complications after esophagectomy in a cohort of 176 patients. Study analyses included the correlation of daily maximum BG level and hemoglobin A1c (HbA1c) with clinicopathological factors. Maximum BG levels were significantly higher on postoperative day (POD) 0 than on PODs 2, 3, 5, and 7 ($p < 0.05$). Additionally, maximum BG levels on PODs 1, 2, and 7 were significantly higher in patients with preoperative HbA1c levels of ≥ 5.6% than in those with preoperative HbA1c levels of < 5.6% ($p < 0.05$ for all). The rates of any complications and infectious complications were higher in patients with preoperative HbA1c levels of < 5.6% than in those with preoperative HbA1c levels of ≥ 5.6% ($p < 0.05$ for both). A preoperative HbA1c level of < 5.6% was a significant predictor of infectious complications after esophagectomy by logistic regression analysis ($p < 0.05$). Maximum BG level after esophagectomy remained high in patients with high preoperative HbA1c levels, whereas a normal HbA1c level was an independent risk factor for infectious complications.

Keywords: blood glucose, esophageal surgery, postoperative hyperglycemia, HbA1c

Introduction

Despite considerable advances in surgical techniques, esophageal surgery remains associated with high morbidity and mortality (*1-3*). Many patients undergoing esophagectomy experience postoperative hyperglycemia due to increased stress and intraoperative administration of steroids to prevent postoperative acute respiratory distress syndrome. Studies investigating the relationship between blood glucose (BG) and infectious complications after esophageal surgery revealed the association of high BG levels on postoperative days (PODs) 3–5 with infectious complications, including pneumonia. Studies also reported that a high BG level was a predictor of morbidity and mortality (*4-7*).

Hemoglobin A1c (HbA1c) is a useful marker to evaluate long-term BG control over the previous 8–12 weeks in patients with diabetes, with its significant impact on perioperative mortality and prognosis demonstrated in many surgical procedures (*8,9*). Intriguingly, lower HbA1c levels were reported to be associated with worse prognosis after esophagectomy (*10*). In management of patients admitted to the intensive care unit (ICU), lower or higher HbA1c levels can significantly impact morbidity and mortality (*11*).

In the present study, we investigated changes in maximum BG (mBG) levels after esophagectomy and the impact of daily mBG and preoperative HbA1c levels on perioperative complications. Our analyses revealed that mBG levels remained high in patients with high preoperative HbA1c levels and that a high mBG level was not associated with perioperative complications. However, a normal preoperative HbA1c level was an independent risk factor for infectious complications in patients undergoing esophagectomy.

Patients and Methods

Patients

This was a retrospective study including 233 consecutive patients who underwent esophagectomy for esophageal cancer from January 2013 to October 2021 in the Department of Surgery, National Center for Global Health and Medicine. Among these, 55 patients, including 24, 5, 9, 14, and 3 patients who underwent two-stage surgery, esophageal bypass surgery, proximal gastrectomy of junctional cancer, salvage surgery after definitive chemoradiation, and exploratory thoracotomy, respectively, were excluded. Additionally, one patient with missing data on preoperative HbA1c was excluded. Therefore, the final analysis included 176 patients (Figure 1). The study was conducted after approval by the National Center for Global Health and Medicine Review Board (NCGM-G-004166-00).

Perioperative glucose control

All patients received methylprednisolone at 250 mg/body weight before esophagectomy to prevent postoperative acute respiratory distress syndrome. After surgery, all patients were admitted to the ICU, and postoperative BG levels were monitored every 6 h, starting at the time of ICU admission, and continuous insulin therapy using an insulin pump was performed in patients with BG levels of >150 mg/dL. The continuous insulin dose was adjusted to maintain BG levels below 150 mg/dL. In patients with BG levels of ≤ 100 mg/dL, the dose of continuous insulin was reduced. In patients with hypoglycemia (BG level < 70 mg/dL), insulin was discontinued and 20 mL of 20% glucose was administered until the BG level reached ≥ 80 mg/dL.

Perioperative nutrition therapy

In all patients, we inserted central venous catheter or peripherally inserted central venous catheter before surgery and we underwent catheter jejunostomy or gastrostomy from stomach roll during esophagectomy. Postoperative nutritional therapy was performed through continuous intravenous or enteral feeding. For daily caloric intake, the central venous catheter was used and enteral caloric intake from jejunostomy was gradually increased to provide 80–100% of the required calories until POD 7. Jejunal tube feeding was initiated with a protein-enriched digestive nutrients at 200 kcal/day on POD 1, and the amount was increased to 400 and 800 kcal/day on PODs 3 and 5, respectively. Starting on POD 7, the diet was changed to semidigested nutrients at 1,200 kcal/day. Subsequent nutritional therapy was adjusted as appropriate depending on the oral intake status of each patient.

Study design

The present study was designed to investigate changes in mBG levels until POD 7 and to explore the relationship of mBG and preoperative HbA1c levels with perioperative complications. In addition, risk factors for infections complications and the relationship of HbA1c level with nutritional markers and prognosis were analyzed. mBG level was defined as the highest daily BG level on PODs 0, 1, 2, 3, 5, and 7. Hypoglycemia was defined as a BG level below 70 mg/dL. HbA1c was measured before surgery in an outpatient setting. The cutoff value for the HbA1c level with the best predictive accuracy was determined using receiver operating characteristic curve analysis. Postoperative complications were defined using the Common Terminology Criteria for Adverse Events version 5.0, and complications related to surgical procedures were evaluated according to the Clavien–Dindo classification (*12*).

Statistical analysis

All statistical analyses were performed using JMP version 17 software (SAS Institute, Cary, NC). We investigated the relationship of preoperative HbA1c and postoperative mBG levels with various clinical factors. The clinical factors included age, sex, body mass index, Eastern Cooperative Oncology Group performance scale score, history of smoking, comorbidities, American Society of Anesthesiologists (ASA)-physical status (PS) score, Charlson comorbidity index (*13*), albumin, prealbumin, hemoglobin, prognostic nutritional index, controlling nutrition status score, tumor location, TNM stage, histology, operation time, blood loss, approach (thoracic *vs.* abdominal), lymphadenectomy, and postoperative complications. Data were presented as medians with interquartile ranges. The Mann–Whitey *U*

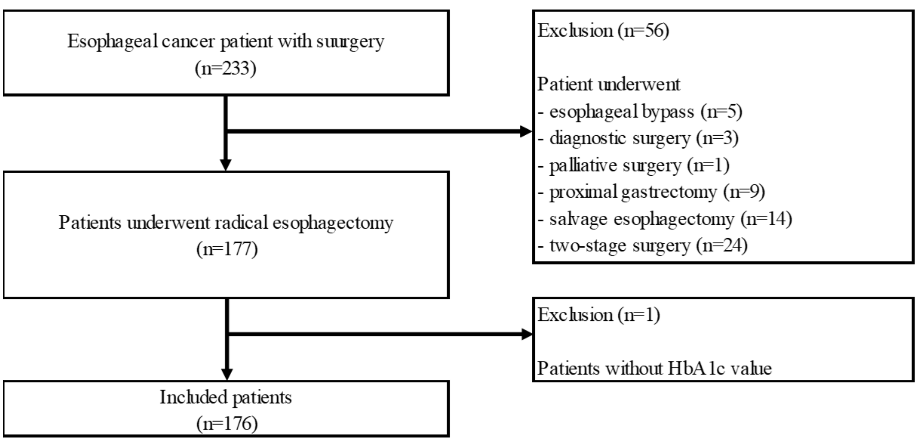

Figure 1. Inclusion criteria.

test was used for comparisons between two groups; the chi-square or Fisher's exact test was used to compare qualitative variables; and the Kruskal–Wallis test was used to compare quantitative variables. Univariate analysis was performed to identify risk factors for infectious complications, and variables were selected using backward elimination for multivariate logistic regression analysis. In all statistical analyses, a p value of < 0.05 indicated statistical significance.

Results

Patients

Table 1 summarized the characteristics of patients included in the study. The median age was 70 (62–76) years, and 143 (81%) patients were male. Preoperative diabetes was present in 28 (16%) patients, with a median preoperative HbA1c level of 5.9% (5.6–6.2%), and 151 (86%) patients had a preoperative Charlson comorbidity index score of >3. The cohort included 63 (41%), 24 (14%), 49 (28%), and 40 (22%) patients with clinical stage I, II, III, and IV esophageal cancer, respectively. Neoadjuvant chemotherapy or chemoradiotherapy was administered in 98 (56%) patients. Thoracoscopic and laparoscopic surgical approaches were employed in 135 (77%) and 100 (57%) patients, respectively. Three-field lymph node dissection was performed in 121 (69%) patients. The operation time and blood loss were 610 (545–667) min and 180 (86–351) mL, respectively. Clavien–Dindo grade II or higher complications within 30 days after surgery were noted in 114 (65%) patients, and infectious complications occurred in 79 (45%) patients. Pneumonia and anastomotic leakage occurred in

Table 1. Patient characteristics

Variables	n = 176
Age (years)	
Median (IQR)	70 (62-76)
Sex	
Male/Female (%)	143/33 (81%/19%)
BMI	
Median (IQR)	21.6 (19.9-23.5)
PS (ECOG)	
0/1/2/3 (%)	102/44/27/3 (58%/25%/15%/2%)
History of smoking	
yes / no (%)	145/31 (18%/82%)
Comobidities	
Diabetes mellitus	
yes / no (%)	28/148 (16%/84%)
Hypertension	
yes / no (%)	71/105 (40%/60%)
Pulmonary disease	
yes / no (%)	23/153 (13%/87%)
PS (ASA)	
1/2/3/4 (%)	6/119/51/0 (3%/68%/29%/0%)
CCI	
0-2/3-5/6 or above	25/101/50 (14%/57%/29%)
Laboratory findings	
HbA1c (%)	
Median (IQR)	5.9 (5.6-6.2)
Albumin (mg/dL)	
Median (IQR)	3.9 (3.5-4.2)
Prealbumin (mg/dL)	
Median (IQR)	24.6 (21-30)
Hemoglobin (g/dL)	
Median (IQR)	12.2 (10.7-13.5)
PNI	
Median (IQR)	45.5 (41.6-49.6)
CONUT	
0-1/2-4/5-8/9 or above	74/67/18/1 (46%/42%/11%/1%)
Tumor Locations	
Ce/Ut/Mt/Lt/Jz	8/37/60/54/14 (4%/21%/34%/31%/10%)

Table 1. Patient characteristics (continued)

Variables	n = 176
TNM (UICC 8th)	
cT	
1/2/3/4 (%)	62/14/68/32 (35%/8%/38%/19%)
cN	
0/1/2/3 (%)	72/67/32/5 (41%/38%/18%/3%)
cM	
0/1 (%)	163/13 (93%/7%)
cStage	
I/II/III/IV (%)	63/24/49/40 (36%/14%/28%/22%)
Histology	
SCC/Adenocarcinoma/other	153/18/5 (87%/10%/3%)
Preoperative treatment	
None/chemotherapy/CRT (%)	78/79/19 (44%/45%/11%)
Operation time (min)	
Median (IQR)	610 (545-667)
Blood loss (mL)	
Median (IQR)	180 (86-351)
Thoracic approach	
Open/VATS (%)	41/135 (77%/23%)
Abdominal approach	
Open/HALS/Laparoscopy (%)	76/12/88 (43%/50%/7%)
Lymphadectomy	
2 field/3 field (%)	55/121 (31%/69%)
Postoperative complications	
Clavien-Dindo classification	
Grade 0, 1/2 or higher (%)	62/114 (35%/65%)
Infectious complication	
yes / no (%)	79/97 (45%/55%)
Pneumonia	
yes / no (%)	47/129 (27%/73%)
Anastomotic Leakage	
yes / no (%)	25/151 (14%/86%)
Others	
yes / no (%)	26/150 (85%/15%)

IQR interquartile range, *BMI* body mass index, *PS* performance status, *ECOG* Eastern Coopelative Oncology Group, *ASA* American Society of Anesthesiologists physical status, *CCI* Charlson comobidity index, *HbA1c* hemoglobin A1c, *PNI* prognostic nutritional index, *CONUT* controlling nutritional status, *Ce* cervical esophagaus, *Ut* upper third of thoracic esophagus, *Mt* middle third of thoracic esophagus, *Lt* lower third of thoracic esophagus, *Jz* abdominal esophagus, *UICC* Union for International Cancer Control, *SCC* squamous cell carcinoma, *VATS* video assisted thoracic surgery, *HALS* hand assisted laparoscopic surgery

47 (27%) and 25 (14%) patients, respectively.

Changes in mBG and HbA1c levels

Table 2 and Figure 2 show the changes in mBG levels between PODs 0 and 7 after esophagectomy. The median mBG level was highest on POD 0 (205 [182–234] mg/dL), with gradual decreases observed on POD 1 and 2 (185 [162–216] and 151 [137–169] mg/dL, respectively). The mBG levels correlated with other variables (Figure 2). On the other hand, hypoglycemia (< 70 mg/dL) occurred in 19 (11%) patients. Additionally, the median mBG levels on POD 1, 2, and 7 were significantly higher in patients with a preoperative HbA1c level of ≥ 5.6% (n = 133) than in those with a preoperative HbA1c level of < 5.6% (n = 43) (Table 3).

Postoperative complications associated with mBG and HbA1c levels

Table 4 shows the mBG levels on POD 0–7 in patients with perioperative complications. On POD3, the mBG levels were higher in patients with any complication (p = 0.014), in those with infectious complications (p = 0.009), and in those with pneumonia (p < 0.001) compared to those without these complications. Similar differences were not observed in other PODs. On the other hand, the rates of infectious complications and pneumonia were higher in those with high mBG levels (≥180 mg/dL) than in those with low mBG levels (<180 mg/dL) (37% *vs.* 20% and 45% *vs.* 21%, respectively; p = 0.011 and p = 0.002, respectively) (Table 5).

The rates of complications also significantly differed based on the preoperative HbA1c level. Specifically, the rates of any complications and infectious complications were higher in patients with normal preoperative HbA1c

Table 2. Changes in maximum blood glucose levels on postoperative days 0-7

POD	mBGL (mg/dL)
POD 0	205 (182-234)
POD 1	185 (162-216)
POD 2	151 (137-169)
POD 3	162 (146-183)
POD 5	149 (133-171)
POD 7	147 (135-171)

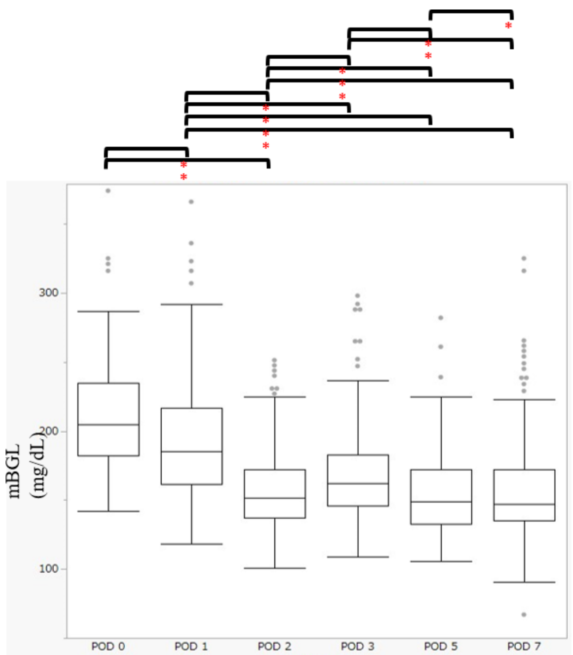

Figure 2. Changes in maximum blood glucose levels after esophagectomy from postoperative day 0 to 7 mBGL, maximum blood glucose level; POD, postoperative day. *p < 0.05 by Mann–Whitney U test.

Table 3. Maximum blood glucose levels on postoperative days 0-7 in patients categorized according to preoperative HbA1c levels

POD	HbA1c < 5.6 n = 43	HbA1c ≥ 5.6 n = 133	p value
POD 0	198 (198-217.5)	210 (186-237)	0.052
POD 1	179 (176-201.5)	191 (164-223)	0.022*
POD 2	147 (146.5-161.25)	154 (138-174)	0.057
POD 3	161.5 (161-181)	163 (146-182)	0.656
POD 5	145 (143-168)	150 (137-172)	0.164
POD 7	141 (140-159)	149 (137-172)	0.029*

*p < 0.05 by Mann–Whitney U test

Table 4. Maximum blood glucose levels on postoperative days 0-7 in patients with postoperative complications

Variables	Any complications (+) n = 114	Any complications (-) n = 62	p value
POD 0	213 (182-241)	202 (186-218)	0.206
POD 1	191 (162-221)	181 (161-208)	0.299
POD 2	154 (141-167)	144 (133-177)	0.42
POD 3	166 (149-186)	155 (143-175)	0.014*
POD 5	150 (136-176)	148 (131-165)	0.194
POD 7	149 (136-173)	142 (133-171)	0.122
	Infectious complications (+) n = 79	Infectious complications (-) n = 97	p value
POD0	215 (182-244)	202 (182-222)	0.236
POD1	195 (165-235)	181 (161-207)	0.067
POD2	154 (142-173)	148 (135-170)	0.245
POD3	170 (149-193)	156 (145-176)	0.009*
POD5	151 (137-178)	148 (131-167)	0.08
POD7	150 (136-175)	145 (134-170)	0.172
	Pneumonia (+) n = 47	Pneumonia (-) n = 129	p value
POD0	217 (191-241)	203 (181-232)	0.152
POD1	196 (167-238)	181 (161-213)	0.067
POD2	158 (143-181)	148 (136-167)	0.117
POD3	175 (157-198)	157 (144-176)	< 0.001*
POD5	152 (140-185)	149 (131-168)	0.063
POD7	150 (135-176)	147 (135-171)	0.241

*p < 0.05 by Mann-Whitney U test

Table 5. Rates of postoperative complications in patients categorized according to maximum blood glucose levels on postoperative days 0-7

POD	mBGL (mg/dL)	Any complications (+) *n* = 114 (%)	Any complications (-) *n* = 62 (%)	*p* value
POD 0	<180	31	15	
	≥180	83	47	0.665
POD 1	<180	48	31	
	≥180	66	31	0.314
POD 2	<180	94	48	
	≥180	20	14	0.419
POD 3	<180	79	49	
	≥180	35	13	0.166
POD 5	<180	92	52	
	≥180	22	10	0.603
POD 7	<180	95	53	
	≥180	19	9	0.709
POD	PBG (mg/dL)	Infectious complications (+) *n* = 79 (%)	Infectious complications (-) *n* = 97 (%)	*p* value
POD0	<180	22	24	
	≥180	57	73	0.641
POD1	<180	31	48	
	≥180	48	49	0.174
POD2	<180	63	79	
	≥180	16	18	0.777
POD3	<180	50	78	
	≥180	29	19	0.011*
POD5	<180	63	81	
	≥180	16	16	0.520
POD7	<180	64	84	
	≥180	15	13	0.314
POD	PBG (mg/dL)	Pneumonia (+) *n* = 47 (%)	Pneumonia (-) *n* = 129 (%)	*p* value
POD0	<180	11	35	
	≥180	36	94	0.619
POD1	<180	16	63	
	≥180	31	66	0.081
POD2	<180	36	106	
	≥180	11	23	0.407
POD3	<180	26	102	
	≥180	21	27	0.002*
POD5	<180	35	109	
	≥180	12	20	0.127
POD7	<180	37	111	
	≥180	10	18	0.127

*$p < 0.05$ by chi-square or Fisher's exact test

levels (< 5.6%) than in those with high HbA1c levels (≥ 5.6%) (79% *vs*. 60% and 65% *vs*. 38%, respectively; $p = 0.024$ and $p = 0.002$, respectively) (Table 6). Additionally, the rate of pneumonia was higher in patients with normal HbA1c levels (< 5.6%) than in those with high HbA1c levels (≥ 5.6%), although the difference was not statistically significant (34% *vs*. 21%, $p = 0.073$).

Risk factors for infectious complications

Logistic regression analysis was performed to examine

Table 6. Rates of postoperative infectious complications in patients categorized according to preoperative Hb A1c values

Variables	HbA1c < 5.6 *n* = 43	HbA1c ≥ 5.6 *n* = 133	*p* value
Any complications			
(+)	34	80	
(-)	9	53	0.024*
Infectious complication			
(+)	28	51	
(-)	15	82	0.002*
Pneumonia			
(+)	16	31	
(-)	27	102	0.073

*$p < 0.05$ by chi-square or Fisher's exact test

risk factors for infectious complications. Univariate analysis (Table 7) revealed that male sex, ASA-PS score > 3, HbA1c level < 5.6%, tumor in upper thoracic esophagus, surgical time > 590 min, blood loss > 220 mL, and nonthoracoscopic surgical approach were significantly predictors of infectious complications (p = 0.008, $p = 0.004$, $p < 0.001$, $p = 0.044$, $p < 0.001$, $p = 0.022$, and $p = 0.018$, respectively). Multivariate analysis including these factors revealed that age > 69 years (odds ratio [OR] 2.13, 95% confidence interval [CI] 1.01–4.49), ASA-PS score > 3 (OR 2.40, 95% CI 1.07–5.36), HbA1c level < 5.6% (OR 3.03, 95% CI 1.35–6.79), and operative time > 590 min (OR 3.05, 95% CI 1.47–6.33) were independent risk factors for infectious complications after esophagectomy (Table 8).

Prognosis

There was no significant difference in overall survival and relapse-free survival between the patients with high and low HbA1c values (Supplemental Figures S1, S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=79*).

Discussion

In this retrospective study elucidating the association of BG markers with perioperative complications after esophagectomy, the rate of infectious complications was higher in patients with preoperative HbA1c levels of < 5.6% than in those with preoperative HbA1c levels of ≥ 5.6%, although the mBG levels were lower in the former group than in the latter group. This is the first study reporting that a lower preoperative HbA1c is a risk factor for infectious complications after esophagectomy.

Many studies have demonstrated the association of perioperative hyperglycemia with morbidity and mortality (*4-7*). HbA1c is a useful marker to evaluate the status of diabetes treatment. Most studies reported that higher HbA1c levels were associated with higher rates of postoperative infectious complications and prognosis (*8,9*). However, various studies reported higher rates of

Table 7. Univariate analysis of factors predicting infectious complications

Variables	Odds ratio (95% CI)	*p* value
Age (years)		
≥69	1.33 (0.73-2.44)	0.341
Male	3.08 (1.30-7.29)	0.008*
Body mass index (kg/m^2)		
≥20.6	0.69 (0.37-1.29)	0.249
PS (ECOG)		
≥2	0.66 (0.30-1.49)	0.320
History of smoking	1.61 (0.72-3.59)	0.246
Comobidities		
Diabetes mellitus	1.08 (0.49-2.42)	0.858
Hypertension	1.35 (0.74-2.47)	0.334
Pulmonary disease	2.11 (0.86-5.16)	0.098
PS (ASA)		
≥3	1.98 (1.02-3.82)	0.004*
CCI		
≥5	1.70 (0.93-3.10)	0.081
Preoperative laboratory findings		
HbA1c (%)		
≥5.6	0.37 (0.18-0.77)	< 0.001*
Albumin (mg/dL)		
≥3.7	1.32 (0.68-2.57)	0.412
Prealbumin (mg/dL)		
≥26	1.55 (0.85-2.82)	0.150
Hemoglobin (g/dL)		
≥10.5	1.48 (0.72-3.05)	0.285
PNI		
≥48	1.48 (0.81-2.72)	0.202
CONUT		
≥4	0.77 (0.35-1.69)	0.518
Tumor location		
Ut	2.01 (1.01-4.00)	0.044*
TNM (UICC 8th)		
cT		
≥3	0.89 (0.48-1.65)	0.710
cN		
≥2	1.06 (0.51-2.19)	0.884
cM		
+	1.06 (0.34-3.28)	0.924
cStage		
≥III	1.00 (0.55-1.82)	0.988
SCC	1.31 (0.54-3.21)	0.552
Preoperative treatment		
+	0.76 (0.42-1.38)	0.362
Operation time (mins)		
≥590	3.01 (1.58-5.74)	< 0.001*
Blood loss (mL)		
≥220	2.02 (1.11-3.70)	0.022*
VATS approach	0.43 (0.21-0.87)	0.018*
Laparoscopic approach	0.76 (0.42-1.39)	0.377
Three-field lymphadectomy	0.78 (0.41-1.48)	0.450

*$p < 0.05$ by logistic analysis

Table 8. Multivariate analysis of factors predicting infectious complications

Variables	Odds ratio (95% CI)	*p* value
Age (years)		
≧69	2.13 (1.01-4.49)	0.046
Male	2.46 (0.93-6.52)	0.070
PS (ASA)		
≧3	2.40 (1.07-5.36)	0.034
HbA1c (%)		
<5.6	3.03 (1.35-6.79)	0.007
PNI		
≧48	1.66 (0.80-3.44)	0.202
Operation time (min)		
≧590	3.05 (1.47-6.33)	0.003
VATS approach	0.49 (0.22-1.07)	0.076

*$p < 0.05$ by logistic analysis

perioperative complications and worse prognosis even in patients with lower HbA1c levels and no diabetes (*14-16*). In the present study, we found higher mBG levels after esophagectomy even in the absence of diabetes and higher rates of infectious complications, reflecting perioperative stress hyperglycemia. Patients without a history of diabetes or those with high HbA1c levels had worse morbidity and mortality compared to those with known diabetes (*10*).

Studies show that the etiology of perioperative stress hyperglycemia is multifactorial (*17*). More invasive surgery, general anesthesia, anesthetic agents, glucocorticoids, higher body mass index, and higher HbA1c levels are known predictors of stress hyperglycemia (*18*). In most patients undergoing emergency surgery, the diabetes status of the patient cannot be determined due to time limitations. In these patients, managing perioperative stress hyperglycemia to prevent infectious complications can be challenging. However, in the present cohort, almost all patients had undergone screening for diabetes through BG and HbA1c measurements at the time of diagnosis and neoadjuvant therapy for esophageal cancer prior to esophagectomy.

Kotgal found that insulin was underused in patients without diabetes and hypothesized that hyperglycemia indicated higher stress levels in these patients compared to those with diabetes (*19*). In our institution, an identical protocol for hyperglycemia was used to manage both those with and without diabetes. Specifically, continuous insulin therapy was performed using an insulin pump in patients with BG levels of > 150 mg/dL to achieve BG levels of < 150 mg/dL. Future studies should investigate the timing of insulin infusion therapy initiation in patients with higher BG levels depending on the presence of diabetes.

Transient insulin resistance and impaired insulin signaling, which appear to contribute to perioperative hyperglycemia in patients with and without diabetes, are considered to be due to circulating proinflammatory cytokines and counter-regulatory hormones. Thorell reported that insulin sensitivity decreased an average of 50% for up to five days in the immediate postoperative period, with a normalization period of 9–21 days following surgery (*20,21*).

Esophagectomy is considered one of the more invasive surgical procedures employed in patients with gastrointestinal cancer. Infectious complications such as postoperative pneumonia and anastomotic leakage are considered critical factors for poor prognosis (*3,22*). In particular, postoperative pneumonia is a significant prognostic factor after esophagectomy. During the intraoperative and perioperative periods, we often experienced hyperglycemia due to the high degree of stress and intraoperative injection of methylprednisolone to prevent acute respiratory distress syndrome. Perioperative control of high BG levels is important to prevent infectious complications. The American Diabetes Association recommends the control of postoperative BG levels with a target between 140 and 180 mg/dL (*23*). Furthermore, control measures should be implemented for both hyperglycemia and hypoglycemia. Not only hyperglycemia but also perioperative hypoglycemia is associated with ICU mortality (*11,24-26*). The importance of BG control during the first week after gastrointestinal and vascular surgery has been extensively investigated. While the higher perioperative risk associated with hyperglycemia is well recognized, studies also show that hyperglycemia in patients without a history of diabetes increases perioperative mortality.

On the other hand, morbidity and mortality associated with diabetes cannot be fully explained by higher preoperative HbA1c levels. Studies focusing on other risk factors reported that BG variability was associated with complications. Koga described that BG variability was associated with pneumonia and that BG level was an independent poor prognostic factor in patients with esophageal cancer (*4*).

Continuous glucose monitoring is useful for hyperglycemia in the perioperative period (*26,27*). In recent years, artificial pancreas therapy has been used to control both hyperglycemia and hypoglycemia and its utility has been demonstrated in some surgical procedures. We also used artificial pancreas for poorly controlled cases (*28*).

The technologies to utilize insulin therapy for hyperglycemia are still evolving, with various guidelines recommended by academic societies across the globe. Furthermore, perioperative BG control is performed not only by surgeons and nurses but also by medical care teams (*20*).

Studies evaluating the relationship between BG levels and infectious complications after esophageal surgery reported that BG levels up to POD 3 were associated with pneumonia and that the average BG level on PODs 3 and 5 was a predictive factor for infectious complications (*4-7*). BG levels might initially increase due to the invasion prior to pneumonia or other infectious complications. The knowledge that changes in BG precede systemic complications is a clinically important finding that may be utilized for effective preventive interventions.

Although the causal relationship between high PGL and pneumonia is unclear based on the current study findings, effective postoperative BG control may reduce the rate of infectious complications, especially pneumonia, and may be considered a good predictor of pneumonia. In cardiovascular surgery, the reported rate of hypoglycemia is 7.5–21.4% in patients with controlled BG levels of <150 mg/dL (*24-26*). In the current cohort, the rate of hypoglycemia was approximately 11%, comparable to that reported in previous studies. Some studies reported that hypoglycemia was associated with mortality and composite outcomes in patients in the ICU. In the present study, the rate of all postoperative complications was not higher in hypoglycemic patients compared to hypoglycemic patients, which might be due to the effective initiation of insulin infusion therapy in the early phase of the ICU stay.

Two factors might explain the relatively low HbA1c. HbA1c is an indicator for long-term BG control in the previous 8–12 weeks, and a low HbA1c level suggests malnutrition and anemia. In fact, our analyses revealed that a low HbA1c level of < 5.6% was significantly associated with anemia, low albumin level, and low prognostic nutritional index score ($p < 0.05$ for all) (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=79*). In the present study, we found that low preoperative HbA1c levels were associated with not only nutritional markers but also anemia due to bone marrow suppression resulting from preoperative treatment. Although these factors were not direct independent risk factors for infectious complications, they may be combined indicators of nutrition and anemia.

The present study has several limitations that should be acknowledged. First, this was a retrospective observational study including a small cohort and was conducted in a single institution; therefore, the possibility of selection bias remains and future studies with larger cohorts are necessary to confirm our findings. Second, the BG levels were determined using samples obtained from arteries or veins. Previous studies reported that BG levels determined using samples from arteries and veins differed and that the accuracy decreased slightly in patients with hyperglycemia (*29-31*). The methods used to measure BG varied depending on the patient's length of stay in the ICU, which might have had some impact on the study findings. Finally, many hormones and cytokines can be involved in perioperative hyperglycemia. Future studies should investigate the relationship of such factors with BG markers in the context of perioperative complications after esophagectomy.

In summary, in the present study investigating the relationship of BG markers with perioperative complications after esophagectomy, we found that the rate of infectious complications was higher in patients with HbA1c levels of < 5.6% than in those with HbA1c levels of ≥ 5.6%. This is the first study to report a lower preoperative HbA1c level as a risk factor for infectious complications after esophagectomy.

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