Original Article

The stress hyperglycemia ratio, a novel index of relative hyperglycemia, predicts short-term mortality in critically ill patients after esophagectomy

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Background: Postoperative mortality and severe complications are associated with both long-term blood glucose management and the severity of stress hyperglycemia. The purpose of this study was to assess the predictive value of a novel index, the stress hyperglycemia ratio (SHR), for short-term mortality in critically ill patients following esophagectomy.

Methods: A total of 356 patients who underwent esophagectomy for esophageal squamous cell carcinoma (ESCC) and were admitted to the intensive care unit (ICU) were included in this retrospective study. Based on the SHR values, patients were divided into low (SHR <1.14) or high (SHR ≥1.14) groups in the overall and diabetic populations. The major outcomes of this study were the 30- and 90-day all-cause mortalities. We used Cox proportional hazard regression, Kaplan-Meier survival analysis, and competing risk regression models to analyze the relationships between risk factors and outcomes.

Results: The 30- and 90-day mortality in the high-SHR group were significantly higher compared to the low-SHR group in the total population (30-day: 1.3% *vs.* 10.5%, P<0.001; 90-day: 5.8% *vs.* 20.0%, P<0.001) and the diabetic population (30-day: 2.6% *vs.* 17.3%, P=0.026; 90-day: 5.1% *vs.* 36.5%, P<0.001). After adjusting for covariables, the risk of the 30-day mortality [1.770 (1.442, 3.170)] and 90-day mortality [1.869 (1.289, 3.409)] remained significant (P=0.035, P=0.045) in the total population. A similar result was observed in patients with diabetes [30-day: 1.642 (1.131, 2.710), P=0.015; 90-day: 2.136 (1.254, 3.946), P=0.005]. The Kaplan-Meier survival estimates for the 30-/90-day mortality also showed comparable results. The multivariable logistic regression analysis, including all glucose-related indices and the Acute Physiology and Chronic Health Evaluation (APACHE) II score, showed that SHR was independently correlated with the 30- and 90-day mortality; each 0.1-increase was related to a 3–4% elevation in the 30-/90-day mortality [odds ratio (OR), 1.044; 95% confidence interval (CI), 1.036–1.069; OR, 1.036; 95% CI, 1.021–1.051].

Conclusions: In this study, we found that a relative increase in blood glucose, as quantified by the SHR ≥1.14, was independently related to the higher 30-/90-day mortality in patients admitted to the ICU with severe complications following esophagectomy, while absolute hyperglycemia was not.

Keywords: Stress hyperglycemia; critical care; mortality; esophagectomy; cancer

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Introduction

Esophageal cancer (EC) is the eighth most common type of cancer worldwide, with more than 480,000 newly diagnosed patients every year. Despite successful perioperative management, the administration of improved surgical techniques, undergoing primary surgery, and having positive microscopic resection edges (R1), EC patients have a much lower survival rate than expected, with a 5-year survival rate of less than 40% (1-5). Therefore, it is essential to explore valuable factors to predict the prognosis of EC patients and provide early treatments.

In diabetic patients, poor glucose management has adverse clinical outcomes, including postoperative site infections, poor wound healing, and prolonged hospitalization (6-12). Meanwhile, acute hyperglycemia can occur in people suffering from a severe disease as a result of physiological stress, even in the absence of previous diabetes. Stress-induced hyperglycemia has also been associated with a significantly greater risk observed in patients without a history of diabetes compared to those with a known diagnosis of diabetes (8,13-16). Previously, the majority of research has used admission blood glucose (ABG) levels or random glucose concentrations to determine the degree of stress hyperglycemia (10,11,17,18). In 2004, Vriesendorp's team reported that postoperative hyperglycaemia was associated with increased length of in-hospital stay in patients undergoing highly invasive surgery for EC (19). However, the stress-related blood glucose elevation may be caused by poor chronic blood glucose control, physiological reaction of acute illness or both, and it is incomplete to evaluate the prognosis only by absolute hyperglycemia, which ignores the background blood glucose. Roberts *et al.* (20) recently introduced the stress hyperglycemia ratio (SHR), a novel index that is calculated by dividing the absolute blood glucose by the estimated average glucose obtained from glycosylated hemoglobin (HbA_{1c}): [glucose (mg/dL)/18]/[(1.59*HbA_{1c}) – 2.59]. Additionally, Roberts' team found that the SHR was a more precise critical disease (in-hospital mortality or critical care) predictive marker than absolute glucose because it controls background glucose levels.

A relative increase in blood glucose refers to a sharp increase in blood glucose concentration compared with the background levels due to the inflammatory and neurohormonal derangements of the stress response. Surgical trauma induces stress hormone secretion, which is mainly mediated by glucagon, in turn promotes insulin resistance and oxidative stress, and finally leads to the blood glucose shoot up. According to recent studies, relative hyperglycemia is more correlated with adverse outcomes than an increase in absolute blood glucose concentration (20-23). However, on the basis of clinical observation, patients with critical postoperative complications after esophagectomy have varying degrees of postoperative hyperglycemia, regardless of whether they had diabetes or not. The intractable inpatient hyperglycemia will lead to a protracted disease course, and greatly increase the length of hospitalization and medical expenses. Designing personalized blood glucose management strategies that are based on the different background glucose concentrations, may, at least in part, benefit these patients. However, previous studies have rarely focused on the relationship between an increase in blood glucose and the prognosis of postoperative critically ill patients with EC based on background blood glucose concentration. The purpose of this study was to determine whether SHR could be used to predict adverse outcomes of severe complications in individuals with variable baseline blood glucose levels following esophagectomy.

We present the following article in accordance with the STARD reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-11/rc).

Methods

Study population

This retrospective study was carried out at the Fudan University Shanghai Cancer Center from January 2018 to December 2020. The study analyzed data from 428 consecutive patients who underwent potential curative esophagectomy for esophageal squamous cell carcinoma (ESCC) and were admitted to the intensive care unit (ICU) due to acute postoperative complications. Preoperative HbA1c levels were determined in all patients. The ICU team documented the reasons for admission to the ICU. The following criteria were used to exclude patients: hypoglycemia, diabetes ketoacidosis, or hyperosmolar hyperglycemia syndrome as the glycemic-related primary reasons for ICU admission (n=4), incomplete laboratory data on preoperative HbA1c (n=31), glucose levels within 24 hours of operation (n=2), and no Acute Physiology and Chronic Health Evaluation II (APACHE II) score (n=1) assessment. Additionally, patients who had conditions that affect HbA1c levels were excluded from the study, including

anemia [defined as hemoglobin less than 10 g/dL (n=17)], serum creatinine levels >2.0 mg/dL [indicating overt renal failure (n=11)], and patients receiving hemodialysis or peritoneal dialysis (n=6). Finally, 356 patients were included.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of the Fudan University Shanghai Cancer Center, Shanghai, China. Because this study used retrospective data routinely collected during health screening process, the ethics committee exempted the requirement of obtaining informed consent.

Data collection

The baseline information and perioperative variables of all included patients were obtained. The baseline data included the following: age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status score, and preoperative laboratory data. The Charlson Comorbidity Index (24) was calculated on the basis of diabetes mellitus (DM), cerebrovascular disease, congestive heart failure, myocardial infarction, chronic pulmonary disease, peripheral vascular disease, rheumatic disease, dementia, leucocythemia, lymphoma, metastatic solid tumour, mild and severe liver disease, renal disease, peptic ulcer disease, paraplegia, and acquired immune deficiency syndrome (AIDS). Preoperative laboratory findings included HbA1c, ABG levels, serum creatinine (Cr) and hemoglobin (Hb), the blood glucose-related indexes determined within 24 hours after operation, APACHE II score, and the need for vasopressors or mechanical ventilation in the ICU. Each patient's APACHE II score was calculated to determine the disease-specific risk of death [as defined by Knaus *et al.* (25)].

The postoperative complications included the following: *pulmonary complications* [defined as the presence of one or more of the following: acute respiratory distress syndrome (ARDS), pneumothorax and respiratory failure requiring more than 48 hours of ventilatory support], pneumonia *cardiovascular complications* (including severe arrhythmia, heart failure, myocardial infarction, cardiogenic pulmonary edema and pulmonary embolism), *anastomotic leakage* (defined as any clinical signs of leakage and confirmation of fistula by imaging or endoscopy, with or without mediastinitis, pleural empyema/abscess, tracheobronchial lesion, and anastomotic bleeding), *recurrent laryngeal nerve palsy* (confirmed by bedside visualization of the glottis), *chylothorax* (diagnosed using the chylous test for thoracic fluid drainage), and *sepsis* (determined by visually identified infection or positive microbial culture, and clinical signs of systemic inflammatory response syndrome (SIRS) occurring during hospitalization within 30 days of surgery), were recorded.

In addition, the length of hospital and ICU stay was also recorded. The main outcome in this study was the 30- and 90-day all-cause mortality. All variables were acquired retrospectively by reviewing the electronic medical records. Postoperatively, all patients were followed-up for 3 months via telephone or outpatient follow-up system. After 3 months of follow-up, the patients were considered survivors (26,27).

Calculation of relative hyperglycemia

The Nathan equation was utilized to determine the average blood glucose concentration during the prior 3 months using HbA1c; the estimated average glucose concentration (mmol/L) was calculated as (1.59*HbA1c) – 2.59 (28). The SHR was used to define relative hyperglycemia; it was determined by dividing the first obtained plasma glucose concentration detected within 24 hours after surgery by the estimated average blood glucose (20). In the Roberts's original study, 1.14 and 1.38 corresponding to the average SHR values of fourth and fifth SHR quintile with higher mortalities and an SHR >1.14 is considered a more reliable predictor of adverse outcomes than absolute blood glucose levels in the presence or absence of previously known diabetes. The threshold of 1.14 was used in a study of patients undergoing orthopedic surgery, and SHR greater than 1.14 was confirmed to be associated with poor prognosis (29). In this study, patients who were being treated for a prior positive diabetic history or a preoperative HbA1c level ≥6.5% were considered to have DM.

Study cohort

On the basis of the SHR values, we categorized all patients into the low (SHR <1.14) or high (SHR ≥1.14) SHR groups. The diabetic population were divided into subgroups based on a SHR value <1.14 and ≥1.14.

Statistical analysis

The median (interquartile range) was used to express continuous variables. Comparisons were performed using the Kruskal-Wallis test. The chi-square test was applied to assess categorical variables that were provided as counts

Table 1 Basic characteristics and postoperative outcomes in the total and diabetic populations based on the stress hyperglycemia ratios

Variable	Total population			Diabetic population		
	SHR <1.14 (n=155)	SHR ≥1.14 (n=210)	P value	SHR <1.14 (n=39)	SHR ≥1.14 (n=52)	P value
Age (years)	65 [56–72]	67 [57–74]	0.786	64 [57–72]	67 [63–73]	0.018
BMI (kg/m^2)	23.18 (20.90, 25.21)	23.36 (20.64, 25.39)	0.986	22.8 (20.9, 24.5)	23.38 (21.36, 25.45)	0.073
ASA classification, n (%)			0.842			0.064
I	13 (8.4)	19 (9.0)		3 (7.6)	4 (7.7)	
II	124 (80.0)	164 (78.1)		30 (76.9)	35 (67.3)	
III	18 (11.6)	27 (12.9)		6 (15.4)	13 (25.0)	
APACHE II	8 [6–12]	10 [7–14]	0.006	7 [5–9]	8 [6–12]	0.013
PBG (mmol/L)	6.84 (6.21–7.47)	12.72 (9.43–15.82)	0.022	11.62 (7.91–16.43)	14.49 (10.59–21.13)	0.483
HbA1c (%)	5.3 (5.0–5.8)	5.6 (5.2–6.3)	0.278	6.8 (6.5–7.3)	7.0 (6.7–7.9)	0.324
Charlson Comorbidity Index	2.0 (1.0–3.0)	3.0 (1.0–4.0)	0.568	3.0 (1.0–4.0)	4 (1.0–6.0)	0.098
Vasopressor, n (%)	23 (14.8)	34 (16.2)	0.629	8 (20.5)	15 (28.8)	0.114
Ventilator, n (%)	21 (13.5)	55 (26.2)	<0.001	10 (25.6)	17 (32.7)	0.048
Laryngeal nerve palsy (%)	24 (15.5)	27 (12.8)	0.782	4 (10.2)	8 (15.4)	0.391
Chylothorax (%)	3 (1.9)	6 (2.9)	0.471	1 (2.6)	2 (3.8)	0.424
Sepsis (%)	7 (4.5)	15 (7.1)	0.611	3 (7.7)	5 (9.6)	0.384
Pulmonary complications (%)	60 (38.7)	81 (38.6)	0.761	16 (41.0)	14 (26.9)	0.057
Anastomotic leakage (%)	36 (23.2)	69 (32.9)	0.170	7 (17.9)	25 (48.1)	<0.001
Cardiovascular diseases (%)	7 (4.5)	15 (7.1)	0.482	2 (5.1)	7 (13.5)	0.046
Length of ICU stay	3 [1–6]	4 [1–11]	0.001	4 [2–11]	5 [2–14]	0.231
Length of hospital stay	17 [10–32]	18 [11–42]	0.066	28 [13–65]	22 [12–49]	0.914
30-day mortality	2 (1.3)	22 (10.5)	<0.001	1 (2.6)	9 (17.3)	0.026
90-day mortality	9 (5.8)	42 (20.0)	<0.001	2 (5.1)	19 (36.5)	<0.001

Patients were grouped based on SHR values (<1.14 or ≥1.14). ASA, American Society of Anesthesiologists; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation; PBG, Postoperative blood glucose; SHR, Stress hyperglycemia ratio.

(frequencies). Kaplan-Meier (KM) survival analysis and the Cox proportional hazard regression model were utilized to assess the relationship between the groups and the 30- and 90-day mortality rates. Univariate and multivariate analyses were carried out using Cox regression analysis. Variables with a P value <0.05 in the univariate analysis were included in the multivariable Cox regression analysis. The odds ratio (OR) and its 95% confidence interval (CI) were estimated. The area under the receiver operating characteristic (AUROC) curve was used to assess the variables' potential to predict mortality. IBM SPSS Statistics for Windows, Version 20.0, was used to perform all statistical analyses (IBM Corp., Armonk, NY, USA). A two-tailed P value <0.05 was considered statistically significant.

Results

The 356 patients were allocated into groups as follows: in the general population, low (n=155) and high (n=210) SHR groups, and in the diabetes, low (n=39) and high (n=52) SHR groups. *Table 1* summarizes the patients' baseline characteristics. APACHE II score (P=0.006, P=0.013) and ventilator usage (P<0.001, P=0.048) were significantly different between the groups in both the general and diabetic populations. Also, there were no significant differences in age, BMI, ASA classification,

Table 2 HRs (95% CIs) for in-hospital complications between the general and diabetic populations

In-hospital complications	SHR <1.14	SHR ≥1.14	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Total population						
30-day mortality	2 (1.3)	22 (10.5)	1.893 (1.615–3.650)	0.004	1.770 (1.422–3.170)	0.035
90-day mortality	9 (5.8)	42 (20.0)	1.934 (1.563–3.689)	<0.001	1.869 (1.289–3.409)	0.045
Diabetic population						
30-day mortality	1 (2.6)	9 (17.3)	1.597 (1.237–1.811)	0.048	1.642 (1.131–2.710)	0.015
90-day mortality	2 (5.1)	19 (36.5)	1.745 (1.211–3.383)	0.002	2.136 (1.254–3.946)	0.005
Anastomotic leakage (%)	7 (17.9)	25 (48.1)	1.563 (1.103–3.269)	0.004	1.982 (1.246–3.541)	0.002
Cardiovascular diseases (%)	2 (5.1)	7 (13.5)	1.683 (1.372–3.024)	0.003	1.492 (1.879–2.142)	0.038

To calculate hazard ratios (HRs) with 95% confidence intervals (CIs), we used a Cox proportional hazards regression model (CIs). SHR, stress hyperglycemia ratio.

Charlson Comorbidity Index, HbA1c, vasopressor use, postoperative complications (chylothorax, sepsis, pulmonary complication), or median length of hospital stay between the high and low SHR groups in both the general and diabetic populations. In the total population, there was a marked difference in PBG between the low and high SHR groups (6.84 *vs.* 12.72 mmol/L, P=0.022); however, there was no significant variation among the diabetic population (11.62 *vs.* 14.49 mmol/L, P=0.483). In addition, there were significant differences in anastomotic leakage (17.9% *vs.* 48.1%, P<0.001) and cardiovascular diseases (5.1% *vs.* 13.5%, P=0.046) between the low and high SHR groups in the diabetic population; however, there was no significant difference among the total population (23.2% *vs.* 32.9%, P=0.170; 4.5% *vs.* 7.1%, P=0.482).

The median length of ICU stay in the total population was 3 (range, 1–6) and 5 (range, 1–11) days in the high and low SHR groups, respectively (P=0.001). In contrast, there was no notable difference in the median length of ICU stay between the low and high SHR groups in the diabetic population {4 [2, 11] *vs.* 5 [2, 14], P=0.231}. The 30-day mortality rate in the high SHR group was significantly higher than that in the low SHR group, both in the total population (1.3% *vs.* 10.5%, P<0.001) and the diabetic population (2.6% *vs.* 17.3%, P=0.026). Also, the 90-day mortality rate in the high SHR group was significantly higher than that in the low SHR group, both in the general population (5.8% *vs.* 20.0%, P<0.001) and the diabetic population (5.1% *vs.* 36.5%, P<0.001) (as shown in *Table 1*).

As illustrated in *Table 2*, compared with the low SHR group, the high SHR group had a hazard ratio (HR) (95% CI) of 1.893 (1.615, 3.650) and 1.934 (1.563, 3.689) for the 30-day mortality and 90-day mortality, respectively, in the total population. After adjusting for APACHE II score, PBG, ventilator use, anastomotic leakage, cardiovascular diseases and length of ICU stay, the risk of the 30-day mortality [1.770 (1.442, 3.170)] and 90-day mortality [1.869 (1.289, 3.409)] was still significant (P=0.035, P=0.045). Similarly, in the diabetic population cohort, the 30-day mortality risk was greater in the high SHR group (64%) than in the low SHR group (P=0.015) after adjusting for covariables (APACHE II score, PBG, and ventilator use). The 90-day mortality was nearly double in the diabetic population with a high SHR than the low SHR group [2.136 (1.254, 3.946)] after adjusting for covariables (P=0.005). Moreover, the rates of anastomotic leakage [1.982 (1.246, 3.541)] and cardiovascular diseases [1.492 (1.879, 2.142)] were significantly higher in high SHR group. The Kaplan-Meier estimates of the 30-/90-day mortality also showed comparable results (*Figure 1*).

In univariate analyses, ABG (OR =1.083, P=0.022), PBG (OR =1.036; P<0.001), SHR (OR =1.096; P=0.001), and APACHE II score (OR =1.437; P<0.001) were significant predictors of 30-day mortality (*Table 3*). After adjustment for APACHE II score and the above glucose-related indices, SHR was found to be significantly associated with 30-day mortality (OR =1.044; P<0.001), whereas PBG was not (OR =1.012; P=0.130). The same result is shown in *Table 4*; after adjustment for APACHE II score and glucose-related indices, SHR was markedly associated with 90-day mortality (OR =1.036; P=0.013), whereas PBG was not (OR =1.009; P=0.210).

The 90-day mortality AUROC curve of SHR was 0.733 (0.654–0.812). As illustrated in *Figure 2*, the AUROC curve

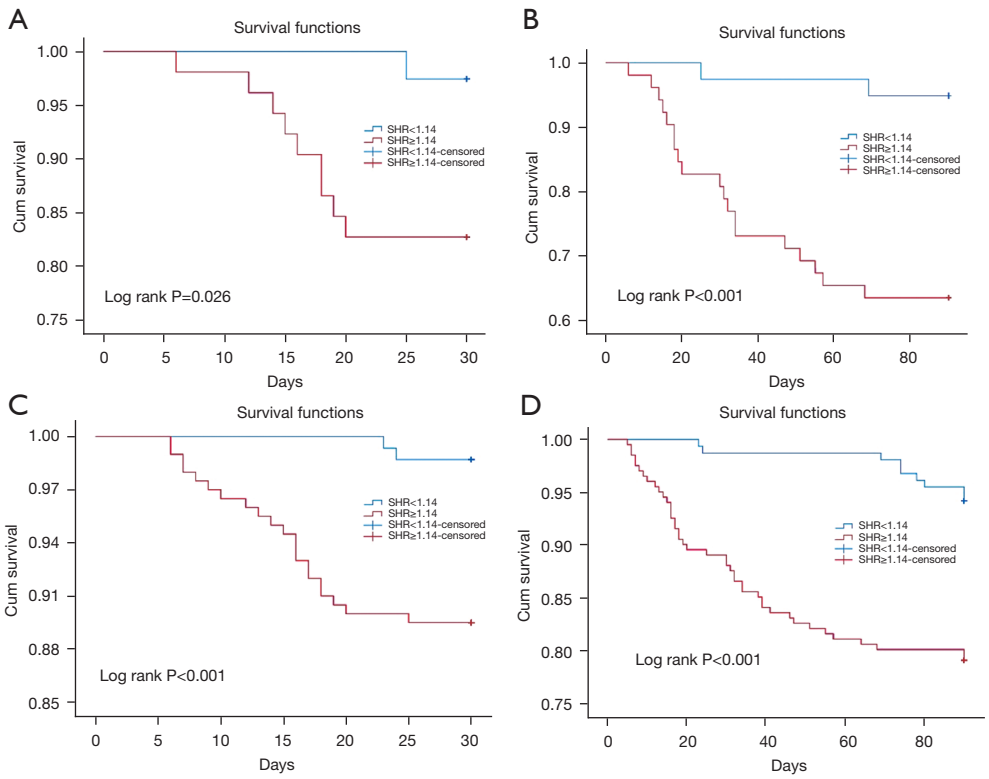

Figure 1 Kaplan-Meier survival curves demonstrating the probability of survival in the various groups. A P value for the Log-rank test <0.05 showed that patients in the high SHR group had a lower survival probability. (A) 30-day survival probability in the diabetic population; (B) 90-day survival probability in the diabetic population; (C) probability of survival for the total population after 30 days; (D) probability of surviving for 90 days in the overall population. SHR, stress hyperglycemia ratio.

Table 3 Univariable and multivariable regression model results showing the relationship between the selected variables and 30-day mortality

Risk factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
ABG, mmol/L	1.083 (1.036–1.293)	0.022	0.927 (0.758–1.281)	0.864
PBG, mmol/L	1.036 (1.012–1.243)	<0.001	1.012 (0.807–1.039)	0.130
HbA1c, per 1%	1.772 (1.224–2.565)	0.080	–	–
SHR per 0.1 increment	1.096 (1.042–1.272)	0.001	1.044 (1.036–1.069)	<0.001
APACHE II score	1.437 (1.243–1.636)	<0.001	–	–

ABG and PBG were reported as per the change in mmol/L. HbA1c was reported as per change in 1%. SHR, stress hyperglycemia ratio was reported as per change in 0.1. APACHE II score is reported as per 1 change. OR, odds ratio; ABG, admission blood glucose; PBG, postoperative blood glucose.

of the APACHE II score + SHR was significantly greater than that for the APACHE II score alone [0.847 (95% CI, 0.784–0.911) *vs.* 0.824 (95% CI, 0.756–0.891); P=0.017]. However, there was no significant difference between the AUROC curve of 30-day mortality for the APACHE II score + SHR and that for the APACHE II score alone [0.864 (95% CI, 0.793–0.934) *vs.* 0.861 (95% CI, 0.788–0.933); P=0.175].

Table 4 Univariable and multivariable regression analysis results showing the relationship between the selected variables and 90-day mortality

Risk factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
ABG, mmol/L	0.893 (0.567–1.399)	0.108	–	–
PBG, mmol/L	1.061 (1.052–1.480)	<0.001	1.009 (0.928–1.059)	0.210
HbA1c, per 1%	1.653 (1.243–2.200)	0.091	–	–
SHR per 0.1 increment	1.078 (1.024–1.383)	<0.001	1.036 (1.021–1.051)	0.013
APACHE II score	1.567 (1.028–1.786)	0.001	–	–

ABG (admission blood glucose) and PBG (postoperative blood glucose), postoperative blood glucose were reported as per the change in mmol/L. HbA1c was reported as per change in 1%. SHR (stress hyperglycemia ratio) ratio was reported as per change in 0.1. APACHE II score is reported as per 1 change. OR, odds ratio.

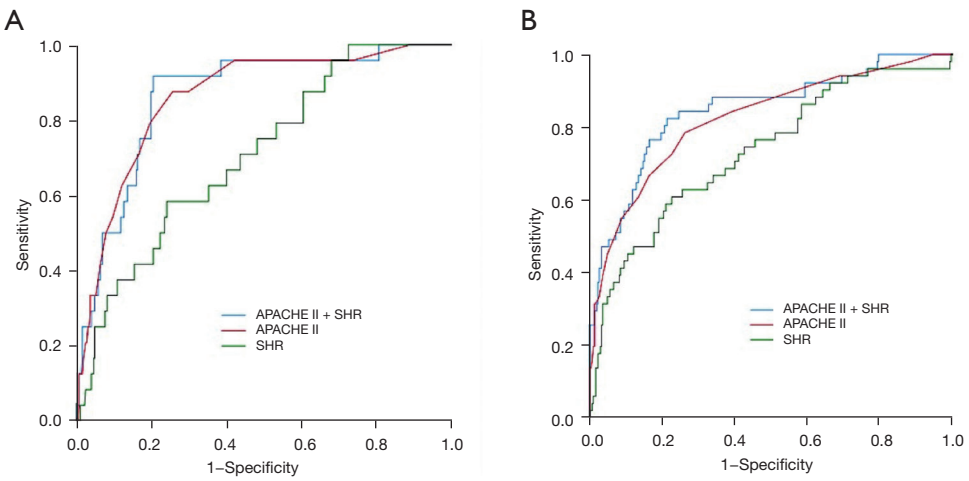

Figure 2 The effect of including the SHR into the 30- and 90-day mortality predictors in ICU. The ROC curves for 30-day mortality (A) and 90-day mortality (B) for SHR, Acute Physiology and Chronic Health Evaluation II (APACHE II), and combined SHR + APACHE II. SHR, stress hyperglycemia ratio; ICU, intensive care unit; ROC, receiver operating characteristic.

Discussion

This study analyzed data from 365 consecutive critically ill patients who underwent esophagectomy for ESCC. The results showed that SHR ≥1.14 was independently associated with 30-/90-day mortality. By including the APACHE II score, postoperative glucose, and SHR into the multivariable analysis, the relationship between mortality and relative hyperglycemia was still significant, whereas absolute glucose was not. Given that SHR controls background blood glucose, it is a more significant marker of severe postoperative illness than absolute hyperglycemia in the blood glucose spectrum. We also found that SHR performs similarly in predicting short-term mortality in patients with or without diabetes history. In addition, the predictive power of SHR ≥1.14 for anastomotic leakage and cardiovascular diseases was significant in the diabetic population.

According to previous studies, severe stress hyperglycemia may have adverse outcomes in critically ill patients due to direct cellular toxicity (30,31). During acute diseases, stress response including the hypothalamic-pituitary-adrenal axis and the sympathicoadrenal system aim to restore homeostasis. As a result of the consequential interaction of cytokines, catecholamines, and cortisol, an excessive hepatic glucose production, insulin resistance, and glucose tolerance might develop, leading to acute stress hyperglycemia.

In the central and peripheral neurons, epithelial, hepatocytes, endothelial, and immunological cells, non-insulin-dependent glucose uptake was proportional to blood glucose concentration occurs. It has been supposed that these cells are susceptible to cellular glucose excess, oxidative stress, and consequent damage in the presence of insulin resistance and hyperglycemia (32,33). Furthermore, severe hyperglycemia increases mitochondrial generation of reactive oxygen species while simultaneously compromising the scavenging systems, resulting in ultrastructural and functional anomalies. Previous study has revealed that postoperative hyperglycemia on day three is a predictor of infections following esophagectomy (6). However, another study reported that postoperative hyperglycemia is a risk marker, rather than a risk factor, of increased incidence of infections and prolonged hospital stay in patients undergoing esophagectomy (19). Their study focused on absolute blood glucose values rather than relative blood glucose elevations corrected by SHR. Our study demonstrated a correlation between postoperative glucose levels and 30-/90-day mortality in univariate analysis, but not in multivariate analysis. Therefore, we concluded that in this circumstance, absolute blood glucose cannot be utilized to independently predict mortality.

Prior studies have shown that background blood glucose levels and postoperative hyperglycemia are prognostic risk factors in multiple procedures (7,12,34,35) Okamura *et al.* [2017] evaluated the relationship between preoperative HbA1c levels and anastomotic leakage after esophagectomy (35). They identified a significant association between preoperative HbA1c levels and the development of anastomotic leakage following cervical esophagogastric anastomosis. This was the first study to indicate the usefulness of determining the HbA1c levels prior to esophageal surgery. In the second year, Okamura's team evaluated the survival of patients with ESCC following esophagectomy according to their diabetes and glycemic status, as evaluated by using HbA1c levels (36). They found that in individuals with advanced-stage ESCC, poor glycemic control was an independent risk factor for overall and disease-specific mortality following esophagectomy. The discovery of HbA1c is a milestone advance in the history of diabetes research, considering that it can be used as a diagnostic test and can also guide glucose-lowering therapy (37). In this study, we utilized HbA1c to determine background blood glucose, which enabled us to calculate the relative hyperglycemia and quantify it using SHR.

The role of stress hyperglycemia has not been clarified previously, especially in the presence of diabetes. Elevated blood glucose levels during stressful conditions may indicate the presence of stress hyperglycemia in individuals without a history of diabetes. However, the probability of newly diagnosed or unknown diabetes cannot be ruled out. As a result, Roberts *et al.* (20) introduced the SHR for controlling background blood glucose and recognizing individuals at risk of critical illness with relative hyperglycemia. This is analogous to BMI superiority over body weight as a predictor of health outcomes. The PBG of all patients was easily obtained; therefore, it is convenient to use PBG to calculate the SHR, which facilitates more precise detection and quantification of stress hyperglycemia, and is conducive to risk stratification soon after admission.

The SHR has been used in several studies. In 2017, Yang *et al.* determined the value of SHR in predicting mortality risk among patients with coronary artery disease (CAD) who had undergone percutaneous coronary intervention (PCI). They observed an elevated mortality risk in the upper SHR quartile of subjects (38). In 2020, a study involving 1,262 consecutive critically ill patients revealed that after correcting for covariables, independently, relative hyperglycemia was related to an increased risk of in-hospital mortality. However, mortality was not affected by background glycaemia (30).

In our study, after adjustment for APACHE II score and other glucose-related measures, each 0.1 rise in SHR was found to be associated with a 3–4% elevation in the OR for short-term mortality. On the face of it, this increment appears insignificant, and its clinical significance may be negligible. However, for a patient with a HbA1c of 5%, a 0.1-point rise in the SHR represents a 3–4% increase in the OR of mortality, and the absolute blood glucose of this patient would be 0.55 mmol/L (9.9 mg/dL) higher than the basic level calculated according to the SHR formula. From the perspective of absolute blood glucose, an increase of absolute blood glucose by 0.55 mmol/L is still easily ignored. However, from the perspective of relative blood glucose, the following assumptions can be made. In this study, the range of SHR was 0.80–4.24, the OR of mortality for the patient with the largest SHR value was 103–137% higher than that of the patient with the smallest SHR value. Considering that the APACHE II scoring system lacks blood glucose evaluation in critically ill patients, we also investigated whether the addition of SHR may increase the AUROC curve of the APACHE II score. The results indicated that adding the SHR to APACHE II increased the AUROC curve for 90-day mortality prediction by a small

but significant amount.

Presently, there are still some controversies in postoperative glucose management, such as the target blood glucose range of elective surgery. However, data on the use of an optimized postoperative glucose management target and outcomes in general surgery are still lacking. The American College of Physicians (ACP) suggested a 140–200 mg/dL (7.7–11.1 mmol/L) target blood glucose range in surgical and medical ICUs for patients with or without diabetes (39). However, in a retrospective investigation of critically ill patients, a higher glucose target of 5–7.8 mmol/L (90–140 mg/dL) had a lower rate of mortality in patients without diabetes, compared with a glucose target of 4.4–6.1 mmol/L (80–110 mg/dL) (40). In the non-diabetic population, a moderate blood glucose management strategy will increase surgical site infections, length of hospitalization, as well as the risk of poor wound healing. In contrast, the opposite was observed in diabetic patients; these patients could benefit from moderate blood glucose control and very tight glycemic control could result in a higher incidence of hypoglycemia. This means that postoperative blood glucose management needs to be personalized, and the SHR is an appropriate indicator. It is assumed that the Hba1c of a non-diabetic patient is 5%, excluding the possibility of pre-diabetes (HbA1c of 5.1–6.4%). According to the formula, the estimated average blood glucose level is 5.4 mmol/L over the preceding 3 months. In this study, we found that a SHR <1.14 could benefit patients, and thus, their blood sugar should be controlled at 4.4–6.2 mmol/L. We also found that for diabetic patients with a HbA1c level of 7% (with an estimated average blood glucose level of 8.6 mmol/L), the suitable blood glucose management goal was 7.7–9.8 mmol/L. Based on this, blood glucose management incorporating the SHR is more personalized and detailed.

This study had some limitations that should be considered. Firstly, our research was an observational study. In this study, we believed that the SHR is a suitable index (as opposed to absolute hyperglycemia) to evaluate the prognosis and individualize treatment in critically ill patients after esophagectomy, but we did not verify this view in a prospective randomized study. Secondly, this was a retrospective study conducted at a single center, and therefore, has a potential selection bias. Furthermore, the statistical power was limited by the small sample size. The study's strength was its precise patient selection, which ensured that the relative elevation in glucose was most likely caused by stress hyperglycemia. To our knowledge, this is the first study to determine that stress hyperglycemia based on the SHR is useful in controlling for background blood glucose in evaluating the prognosis of patients undergoing esophagectomy.

Conclusions

In summary, a relative increase in blood glucose, as quantified by the SHR, was found to be related to 30-/90-day all-cause mortality in patients who were admitted to the ICU with severe complications after esophagectomy, whereas absolute hyperglycemia was not. A SHR ≥1.14 could be used to identify people at an increased risk of adverse outcomes, particularly diabetic patients, and it may be conveniently calculated using the postoperative glucose and HbA1c levels, and applied to developing and individualizing a glycemic management strategy for all patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committees of the Fudan University Shanghai Cancer Center, Shanghai, China. Because this study used retrospective data routinely collected during health screening process, the ethics committee exempted the requirement of obtaining informed consent.

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