Original article

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Stress hyperglycemia ratio and its association with outcomes among patients admitted with ST-segment elevation myocardial infarction (STEMI) in Coronary Care Unit: An observational prospective study

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Abstract

***Background*: Patients with acute myocardial infarction (MI) frequently have elevated blood glucose levels at the time of admission to the hospital. Admission hyperglycemia and relative hyperglycemia adversely impact cardiovascular outcomes among patients with MI.**

***Objective*: This study aimed to assess the stress hyperglycemia ratio (SHR) and its association with in-hospital complications and mortality among patients with ST-segment elevation myocardial infarction (STEMI).**

***Design and setting*: A prospective study was conducted in the Coronary Care Unit (CCU) between May 2019 and April 2020.**

***Patients and participants*: This study was conducted among 152 patients hospitalized with STEMI in the CCU between May 2019 and April 2020. Based on the SHR, patients were categorized into three groups: Group 1 included SHR≤1.0, Group 2 included SHR 1.01 to 1.25, and Group 3 included SHR≥1.26. Patients enrolled were followed until discharge from the hospital or death. Outcome and in-hospital complications were compared across the three groups. Stress hyperglycemia ratio and admission blood glucose (in mg/dl) cut-off predicting the major adverse events (MAE) studied with the highest sensitivity and specificity was calculated using the receiver operating characteristic (ROC) curve.**

***Results*: Among 152 studied patients, the majority were males (n=109, 71%). Seventy-four patients with SHR≥1.26 (Group 3) had significantly higher thrombolysis in myocardial infarction (TIMI) scores (p value<0.0001). One hundred thirty-nine patients survived; non-survivors were 13, with an observed mortality rate of 8.5%. SHR among STEMI patients was significantly associated with death, acute kidney injury requiring dialysis, and atrioventricular block (p value=0.043, p value=0.04, p value=0.037, respectively). SHR cut-off of 1.36 had a sensitivity 73.3% and specificity 73.8% in predicting MAE (AUC-0.8, p value=0.0005). Admission blood glucose of 260 mg/dl had a sensitivity 66.4% and specificity 66.7% in predicting MAE (AUC-0.7, p value=0.0005).**

***Conclusion*: SHR is a good prognostic marker in predicting death and adverse cardiovascular outcomes among patients with acute MI. SHR had better predictive superiority than admission blood glucose in prognostication of major adverse events among patients with STEMI.**

Key words: Diabetes, hyperglycemia, STEMI, outcome, myocardial infarction.

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Introduction

Ischemic heart disease (IHD), also called coronary artery disease (CAD), is the leading cause of premature death worldwide, despite significant advances in managing CAD. (1) According to the World Health Organization (WHO), IHD was responsible for 8.1 million world deaths in 2013, and there has been a 42% increase in the number of IHD deaths since 1990. (2) Patients with diabetes mellitus have an early onset and increased risk of CAD compared to non-diabetic individuals. (3) CAD accounts for

more than 80% of deaths among patients with diabetes. (4) Hyperglycemia in hospitalized patients with acute coronary syndrome (ACS) is a common occurrence, and it is associated with increased mortality, yet it remains under-recognized as a risk factor. Stress hyperglycemia is a temporary rise in blood glucose levels in the absence of diabetes during acute physiological stress. (5) In critically ill patients, this phenomenon may be observed, and the glucose levels are 140-300 mg/dl. (6) Hyperglycemia and decreased glucose tolerance are common during acute myocardial infarction (MI). (5) Hyperglycemia seen at the onset of acute MI is closely related to ongoing stress mechanisms, which include the release of steroid hormones, adrenaline, and glucagon, high levels of free fatty acids, and insulin resistance. (7) As a result of mitochondrial and endothelial damage, oxidative stress, and cardiac potassium channel dysfunction, hyperglycemia negatively affects the course of critically ill patients. (8,9)

Stress hyperglycemia in hospitalized patients with acute MI increases the risk of major cardiovascular adverse events, regardless of revascularization strategy like percutaneous coronary intervention (PCI). (10) Among patients with ST-segment elevation myocardial infarction (STEMI), regardless of diabetes status, an elevated blood glucose level on admission is an indicator of in-hospital and long-term adverse outcomes. Compared with patients with normoglycemia, hyperglycemia was associated with a greater area of infarct size. (11-14) Among acute MI patients with diabetes, those with blood glucose on admission more than or equal to 180 mg/dl have a 70% relative increase in the risk of in-hospital death compared to patients with diabetes and euglycemia. Previous research considered blood glucose at admission (ABG) as the predictor of stress hyperglycemia. (15-18) However, both acute and chronic glycemic levels may influence admission blood glucose levels, and hence blood glucose on admission alone may not be accurate in identifying actual hyperglycemia. A novel index of stress hyperglycemia ratio (SHR), also known as acute-to-chronic glycemia ratio or relative hyperglycemia, has been suggested. (19) Studies indicate that among acutely ill patients, stress hyperglycemia ratio (ratio of admission blood glucose to estimated chronic glycemia derived from glycated hemoglobin, HbA1c) is found to be a better marker of prognosis than the absolute rise in glucose during MI. This ratio has been shown to be an effective tool for predicting prognosis, particularly among diabetic patients with MI. (10) Studies on the prognostic significance of stress hyperglycemia ratio in predicting outcomes among patients with STEMI are limited, particularly in Asian countries.

Objectives

1. This study aimed to assess the SHR and its association with in-hospital complications and mortality among patients with STEMI.
2. The prognostic superiority of SHR compared to admission hyperglycemia in predicting major adverse events (MAE) was studied.

Material and methods

This prospective observational study was conducted in a tertiary care teaching hospital in South India between May 2019 and April 2020. Study participants were enrolled in the Coronary Care Unit (CCU). Patients aged more than 18 years who were admitted to CCU with a diagnosis of STEMI were included in this study.

Exclusion criteria included (i) patients developing STEMI as a complication of elective percutaneous coronary intervention (PCI), (ii) patients with non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina, (iii) those who have hemoglobinopathy, polycythemia, and anemia, (iv) chronic kidney disease (CKD), (v) systemic infections, and (vi) history of cerebrovascular accident (CVA) in the past.

The study was approved by Institutional Ethics Committee (1629/IEC/2019). Informed consent was obtained before enrollment from all the study patients. Consecutive patients admitted to the CCU with the diagnosis of STEMI were enrolled in the study. A total of 152 patients satisfying inclusion and exclusion criteria were included in the study. A structured proforma was used to collect all relevant data.

Laboratory, anthropometric, and clinical data collection

Age, sex, height in centimeters, weight in kilograms, body mass index (BMI, kg/m^2), duration of diabetes, blood glucose values at admission (mg/dl), glycosylated hemoglobin (HbA1c, %), and serum creatinine were noted. Blood samples were taken at admission in a standard vacuum potassium ethylene diamine tetraacetate tube for measuring admission blood glucose levels (mg/dl) and HbA1c.

Average chronic glucose levels were estimated according to the formula: Estimated chronic glucose levels (mg/dl) = 28.7× HbA1c (%) - 46.7.

Admission hyperglycemia was defined as a blood glucose level greater than or equal to 198 mg/dl. (20) The SHR was calculated by dividing admission blood glucose (mg/dl) with estimated average blood

glucose levels (mg/dl) derived from glycosylated hemoglobin. SHR was calculated for all patients included in the study. Patients were categorized into three groups based on SHR. Group 1 included patients with SHR ≤1.0, Group 2 included patients with SHR from 1.01 to 1.25, and Group 3 included patients with SHR≥1.26. We arrived at the ratio based on earlier work done by Marenzi G et al. in patients with acute myocardial infarction. (20) Thrombolysis in myocardial infarction (TIMI) score on admission and an echocardiogram to assess left ventricular ejection fraction (LVEF) were done for all patients.

Outcomes studied were death and in-hospital complications, which include acute pulmonary edema, cardiogenic shock, atrioventricular (AV) block, ventricular tachycardia (VT)/ventricular fibrillation (VF), atrial fibrillation (AF), mechanical ventilation, and acute kidney injury (AKI) requiring dialysis. Death and in-hospital complications were compared across patients in three groups of stress hyperglycemia ratio. MAE was defined as acute pulmonary edema, cardiogenic shock, need for mechanical ventilation, and arrhythmias, including VT, VF, and AF. SHR and admission blood glucose cut-off predicting the MAE studied with the highest sensitivity and specificity was calculated using the receiver operating characteristic (ROC) curve.

Statistical analysis

The results were analyzed statistically by SPSS software version 23.0. In the descriptive statistics frequency analysis, categorical variables were described as percentages, and continuous variables were expressed as mean ± standard deviation. Analysis of variance (ANOVA) and Tukey's posthoc multiple comparison tests were used to find the significant difference between the groups. The chi-square test was used to find the significance of categorical data. The level of probability <0.05 was considered to be statistically significant.

Results

In this prospective observational study, a total of 152 patients were enrolled. The majority were between 51 to 70 years of age (n=60, 59%), with males being predominant (n=109, 71%). The most commonly observed comorbid illness was diabetes (n=116, 76%), followed by hyperlipidemia (n=79, 52%). Diabetes was newly diagnosed in 56.8% (n=66) of study patients. Based on the SHR, the patients in the study were categorized into three groups. The first group included patients with SHR ratio ≤1.0 (n=30), the second group included patients with SHR from 1.01 to 1.25 (n=48), and the third group represented patients with SHR ≥1.26 (n=74). **Table 1** shows the baseline characteristics of the study patients. The risk of having a high SHR ratio among patients with STEMI was significantly associated with admission blood glucose, and the presence of hyperlipidemia (p value<0.0001, p value=0.05, respectively). Patients with SHR≥1.26 had significantly higher TIMI scores (p value<0.0001). The presence of diabetes had a significant association with admission blood glucose and TIMI score (p value<0.0005, p value=0.05, respectively). Among patients with diabetes, the mean TIMI score was higher (7.4±2.4) than in those without diabetes (6.6±2.1). **Table 2** compares admission blood glucose, SHR, and TIMI scores among diabetics and non-diabetics among study participants. Most of the diabetic patients had high SHR (>1.26) (51.7%, n= 60). Non-diabetic patients were equally distributed across the three groups, 39% (n=14) each in the second and the third groups and 22% (n=8) in the first group.

In our study, 139 patients survived (91.4%) and 13 died, with a mortality rate of 8.5%. Most patients who died were in the third group with higher SHR (n=10). The stress hyperglycemia ratio was significantly associated with death among patients with STEMI (p value=0.043). The cumulative number of events observed for in-hospital complications among study patients was 63 (acute pulmonary edema, cardiogenic shock, VT/VF, AF, AV block, need for mechanical ventilation, and AKI requiring dialysis). The most frequently observed complications were AKI requiring dialysis (n=27), followed by cardiogenic shock (n=13). Patients with SHR of 1.26 to 2.50 had a maximum number of events reported as in-hospital complications (49 out of 63 observed in-hospital complications). Among the in-hospital complications studied, AKI requiring dialysis and AV block were significantly associated with SHR (p value=0.04, p value=0.037, respectively). **Table 3** compares death and in-hospital complications among study patients in three groups of SHR. The mean length of stay in the CCU had a significant association with SHR (p value<0.0001).

Using ROC curve analysis, sensitivity and specificity in predicting MAE (composite of pre-specified major adverse events which include cardiogenic shock, acute pulmonary edema, need for MV, arrhythmias) were calculated for SHR and admission blood glucose (mg/dl) (**Figure 1**). SHR cut-off of 1.36 had a sensitivity of 73.3% and specificity of 73.8% in predicting MAE (area under curve [AUC]=0.8, p value=0.0005). Admission blood glucose cut-off of 260 mg/dl had sensitivity of 66.4% and specificity of 66.7% in predicting MAE (AUC=

0.71, p value=0.0005). In our study, 96 patients (63%) had SHR≤1.36, and 56 patients (37%) had SHR>1.36. Since SHR of more than 1.36 was a better predictor of outcome in our study, outcomes, which included death, cardiogenic shock, and acute pulmonary edema, were compared between the two groups (patients with SHR≤1.36 and patients with SHR>1.36) as shown in **Table 4**. Most non-survivors had SHR>1.36 (9 out of 12). SHR of more than 1.36 had a significant association with death among patients with STEMI (p value=0.009).

In our study, five patients (5.2%) with SHR<1.36 and eight patients (14.3%) with SHR>1.36 had cardiogenic shock. Similarly, only one patient with SHR<1.36 developed acute pulmonary edema, whereas four patients (7%) with SHR>1.36 had acute pulmonary edema. Among 91 patients with admission hyperglycemia, cardiogenic shock was observed in 9 (10%) and acute pulmonary edema in 5 (5.5%). Cardiogenic shock and acute pulmonary edema were not significantly associated with admission hyperglycemia in our study (**Table 5**).

Discussion

Our study aimed to observe the prognostic significance of SHR with adverse outcomes among hospitalized patients with STEMI. Despite major advances in treatment strategy, impaired glucose metabolism continues to significantly impact morbidity and mortality rates in cardiovascular diseases globally over the past few decades. (21) In our study, we observed that both SHR above 1.36 and admission hyperglycemia (>198 mg/dl) had a significant association with MAE. Regardless of diabetes status, an elevated plasma glucose level on admission is a prognostic indicator of in-hospital and long-term adverse outcomes in patients with STEMI. (22) Shahid M et al. observed a higher mortality rate among hyperglycaemic STEMI patients than euglycemic STEMI patients. (23) Studies have shown that hyperglycemia is associated with a prothrombotic state. (24) Acute hyperglycemia causes platelet aggregation, a decrease in the half-life of fibrinogen, and increased levels of fibrinopeptide A, prothrombin fragments, and factor VII levels. (25,26) Acute hyperglycemia is associated with increased markers of vascular inflammation like C-reactive protein and interleukin-6. (24,27,28) Following primary percutaneous intervention (PCI) in patients with STEMI, reinfarction and bleeding are attributed to hyperglycemia. (29) Foo et al. showed a near-linear relationship between higher admission blood glucose levels and higher rates of left ventricular failure and cardiac death among patients with ACS. (30) In hyperglycemic MI patients, irrespective of diabetic status, Meier et al. showed higher long-term mortality rates and greater infarct size (measured by creatine kinase-MB fraction levels). (31) Stranders et al. observed admission hyperglycemia as a significant risk factor for adverse outcomes among non-diabetic patients with MI. (32) Hyperglycaemia's impact on adverse outcomes among MI patients does not depend on revascularization strategy, and it's prudent to achieve good glycaemic control among patients with acute MI to have a lesser risk of poor cardiovascular outcomes.

We observed SHR as a relatively better prognostic marker than admission hyperglycemia in predicting major adverse events among STEMI patients. SHR>1.36 had greater sensitivity and specificity than admission hyperglycemia in predicting in-hospital complications among patients with STEMI. Marenzi G. et al. showed that acute-to-chronic glycemic ratio >1.3 had a best prognostic power than admission hyperglycemia alone in predicting mortality and in-hospital complications among patients with acute MI. (20) Patients with diabetes had an increased incidence of in-hospital complications in our study. Korzh O. et al. observed diabetes as an independent predictor of rehospitalization due to a major adverse cardiovascular event among patients who had a myocardial infarction. (33) Yang et al. showed that relative hyperglycemia reliably predicted MACCE (major adverse cardiac and cerebrovascular events) in patients who underwent PCI to treat CAD. (34) Timmer et al. demonstrated a positive correlation between the admission hyperglycemia in STEMI patients and infarct size. (35) Admission hyperglycemia has been shown to be a better predictor of poor prognosis, particularly among patients without diabetes. (36-38)

TIMI score had a significant association with SHR in our study, and the observed score was higher among patients with diabetes. Ayhan H. et al. observed a positive correlation between TIMI score and admission blood glucose. (39) Though SHR>1.36 was a good predictor of composite of pre-specified major adverse events in our study, secondary subgroup analyses (SHR<1.36 vs SHR>1.36) did not have a significant association with cardiogenic shock and acute pulmonary edema. In contrast, Marenzi G. et al. showed that an acute-to-chronic glycemia ratio >1.3 was a powerful predictor of primary endpoints, including death, cardiogenic shock, and acute pulmonary edema. This might be due to the exclusion of patients who had NSTEMI and the small sample size in our study. The limitations of our study were the small sample size, and we did not include all the patients with acute coronary syndrome. A multicentric prospec-

tive study with a larger sample size in the future remains a possible area of research.

Conclusion

SHR is a good prognostic marker in predicting mortality and major adverse cardiovascular outcomes among patients with acute MI. SHR had better predictive superiority in terms of sensitivity and specificity than admission blood glucose in prognosticating major adverse events among patients with STEMI.

Acknowledgment

The study had no funding. All authors declare that there is no conflict of interest. Informed consent was obtained from all the participants enrolled in the research and the study was approved by Institutional Ethics Committee, SRM Medical College Hospital and Research Centre (IEC approval number: 1629/IEC/2019).

Table 1. Baseline characteristics of the study population

Variable	Group 1 (n=30)	Group 2 (n=48)	Group 3 (n=74)	p value
Age (years)	54±12	58±14	58±13	-
Male sex, n	19	37	53	-
Female sex, n	11	11	21	-
BMI (kg/m^2)	24±2	24±2	24±2	0.924
Body weight (kg)	67.1±6.0	67.2±5.2	68.1±5.3	0.575
Height (cm)	166.8±5.5	166.8±4.8	167.5±5.2	0.726
Diabetes, n (%)	22 (73)	34 (71)	60 (81)	0.392
Hypertension, n (%)	9 (30)	20 (42)	37 (50)	0.360
Smokers, n (%)	3 (10)	8 (16.7)	13 (17.6)	0.619
Hyperlipidemia, n (%)	10 (33)	25 (52)	44 (59)	0.05
Left ventricular EF (%)	45±10	44±11	39±15	0.066
TIMI risk score	6.3±1.8	5.9±1.5	8.4±2.4	<0.0001
Blood glucose (mg/dl)	159.2±73.8	206.1±78.0	306.2±117.4	<0.0001
HbA1c (%)	8.37±3.28	8.11±2.38	8.2±2.34	0.909
Serum creatinine (mg/dl)	0.9±0.4	0.9±0.5	1.1±0.7	0.096
eGFR (ml/min/1.73 m^2)	89±27	90±24	80±28	0.083
Hemoglobin (g/dl)	14.3±1.5	14.5±1.4	14.1±1.3	0.371

Legend: BMI=body mass index; EF=ejection fraction; TIMI=thrombolysis in myocardial infarction; eGFR=estimated glomerular filtration rate. All data are in mean±SD unless otherwise noted.

Table 2. Comparison of admission blood glucose, SHR, and TIMI among patients with diabetes and without diabetes

Parameter	With diabetes (n=116)	Without diabetes (n=36)	p value
Admission hyperglycemia, n (%) - Absent (<198 mg/dl) - Present (≥198 mg/dl)	 28 (24.1%) 88 (75.9%)	 33 (91.7%) 3 (8.3%)	 0.0005
Stress hyperglycemia ratio, n (%) - ≤1.00 - 1.01 to 1.25 - ≥1.26	 22 (19%) 34 (29.3%) 60 (51.7%)	 8 (22.2%) 14 (38.9%) 14 (38.9%)	 0.392
TIMI score, mean±SD	7.4±2.4	6.6±2.1	0.05

Legend: SHR=stress hyperglycemia ratio; TIMI=thrombolysis in myocardial infarction; SD=standard deviation.

Table 3. Association of stress hyperglycemia ratio with in-hospital complications observed in three groups of patients

Outcome	Group 1 (n=30)	Group 2 (n=48)	Group 3 (n=74)	p value
Death, n (%)	1 (3)	2 (2)	10 (14)	0.043
Acute pulmonary edema, n (%)	0	1 (2)	4 (5)	0.320
Cardiogenic shock, n (%)	2 (7)	1 (2)	10 (14)	0.081
Mechanical ventilation, n (%)	0	0	2 (3)	0.344
Atrial fibrillation, n (%)	1 (3)	0	4 (5)	0.379
VT/VF, n (%)	1 (3)	0	4 (5)	0.263
AV block, n (%)	0	0	6 (8)	0.037
AKI requiring dialysis, n (%)	3 (10)	5 (10)	19 (26)	0.045
CCU length of stay (days), mean±SD	1±0	2±1	4±2	<0.0001

Legend: VT/VF=ventricular tachycardia/ventricular fibrillation; AV=atrioventricular; AKI=acute kidney injury; CCU=Coronary Care Unit; SD=standard deviation.

Table 4. Association of SHR with the outcome

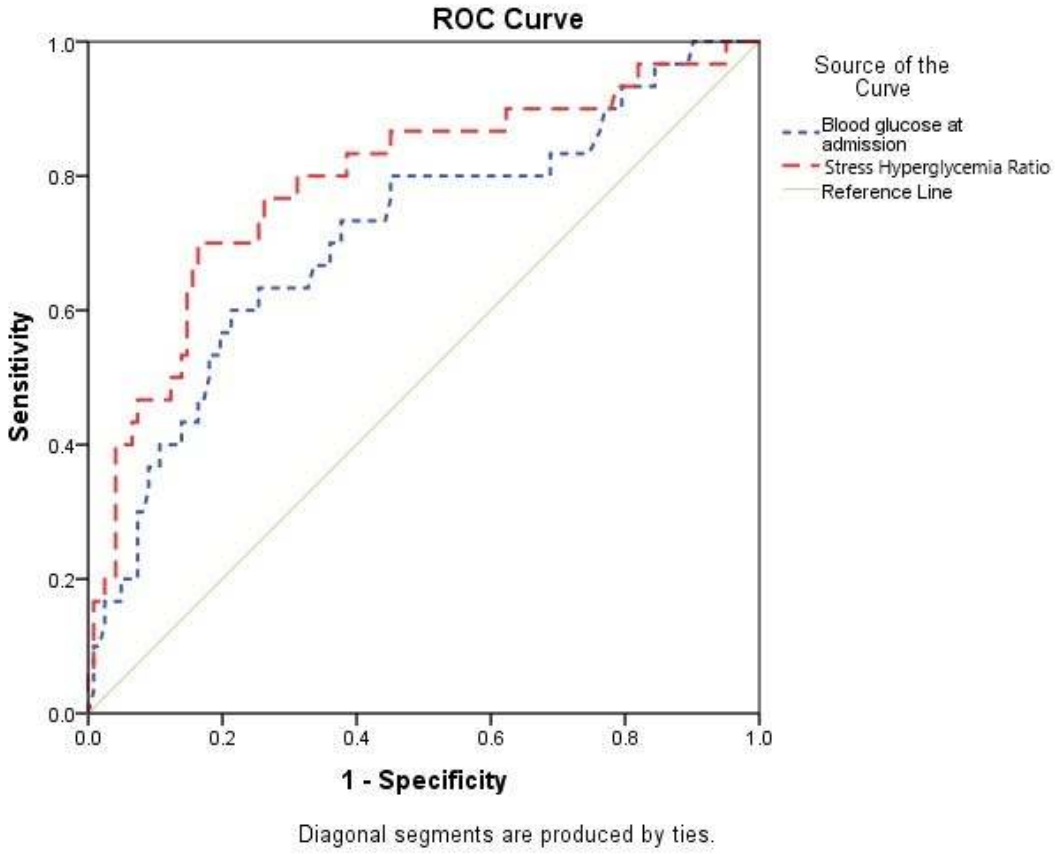
Outcome	SHR≤1.36 (n=96)	SHR>1.36 (n=56)	p value
- Survivors (n=140), n (%) - Non-survivors (n=12) , n (%)	93 (96.9) 3 (3.1)	47 (83.9) 9 (16.1)	0.009
Cardiogenic shock - Present (n=13), n (%) - Absent (n=139), n (%)	 5 (5.2) 91 (94.8)	 8 (14.3) 48 (85.7)	 0.054
Acute pulmonary edema - Present (n=5), n (%) - Absent (n=147), n (%)	 1 (1) 95 (99)	 4 (7) 52 (93)	 0.062

Legend: SHR=stress hyperglycemia ratio.

Table 5. Association of admission hyperglycemia with in-hospital complications, which includes cardiogenic shock and acute pulmonary edema

Outcome	Admission blood glucose <198 mg/dl (n=61)	Admission blood glucose ≥ 198 mg/dl (n=91)	p value
Cardiogenic shock, n (%) - Present (n=13) - Absent (n=139)	 4 (6.6) 57 (93.4)	 9 (10) 82 (90)	 0.564
Acute pulmonary edema, n (%) - Present (n=5) - Absent (n=147)	 0 (0) 61 (100)	 5 (5.5) 86 (94.5)	 0.083

Figure 1. ROC curve analysis for variables admission blood glucose (in mg/dl) and SHR in predicting the outcome



Legend: ROC=receiver operating characteristic; SHR=stress hyperglycemia ratio.
Admission blood glucose: Cut-off 260 mg/dl, AUC 0.71, sensitivity 66.4%, specificity 66.7%, p value 0.0005.
SHR: Cut-off 1.36, AUC 0.8, sensitivity 73.3%, specificity 73.8%, p value 0.0005.

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