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Association between stress hyperglycemia ratio and in-hospital outcomes: findings from the improving Care for Cardiovascular Disease in China-Acute Coronary Syndrome (CCC-ACS) Project

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ABSTRACT

BACKGROUND Stress hyperglycemia ratio (SHR) could provide accurate information on the acute status of hyperglycemia. The relationship between SHR and acute coronary syndrome (ACS) prognosis remains unclear. This study was conducted to identity the association between SHR and in-hospital outcomes in patients with ACS.

METHODS A total of 12,010 patients were eventually enrolled in the study. The relationship between SHR and in-hospital major adverse cardiovascular events (MACEs) was then modeled by restricted cubic spline (RCS) curves, and all patients were divided into three groups according to the results. The multivariate logistic regression analysis was used to determine the associations between the SHR and in-hospital outcomes, described as odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses were also performed on different diseases.

RESULTS The median age of this cohort was 63 (54, 71) years old, and 8942 (74.5%) were male. Group 1 was defined as SHR < 0.6 (n = 426), Group 2 was defined as SHR between 0.6 and 1 (n = 5821), and Group 3 was defined as SHR > 1 (n = 5763). Compared with Group 2, Group 1 (OR = 1.891, 95% CI: 1.028-3.479, P < 0.001) and Group 3 (OR = 1.868, 95% CI: 1.434-2.434, P < 0.001) had higher risks of suffering from in-hospital MACEs. SHR was associated with higher risks of in-hospital MACEs in the subgroups of DM [OR = 2.282, 95% CI: 1.477–3.524).

CONCLUSIONS Both low and high SHR levels were independently associated with in-hospital MACEs. Young males with DM, hypertension, and decreased renal function had much higher risks of suffering from SHR-correlated MACEs.

Acute coronary syndrome (ACS) is the leading cause of mortality worldwide.[1] Previous research has demonstrated that metabolic disorders, especially hyperglycemia, could contribute to a poor prognosis in patients with ACS during hospitalized and long-term follow-up periods, even with no history of diabetes mellitus (DM).[2] And it has been proved that the incidence of stress hyperglycemia (SH) at ACS is between 51% and 58%.[3] Stress hyperglycemia is an important physiological manifestation that occurs in people suffering from trauma or critical illness.[4] Previous studies illustrated that SH, characterized by the elevated blood glucose concentration at admission, was related to malignant outcomes in patients from the intensive care unit (ICU).[5,6] Emerging studies have demonstrated that SH may substantially contribute to adverse outcomes by inducing oxidative stress response, triggering inflammation, and accelerating endothelial dysfunction.[7,8] However, in patients with DM, both chronic poor glycemic control and reaction to acute illness could lead to an indistinguishable high admission blood glucose (ABG) level. Consequently, a novel definition of SH using stress hyperglycemia ratio (SHR) has been put forward and widely used. SHR is adjusted by glycosylated

hemoglobin (HbA1c), which reflects the average glucose status over the last 2-3 months and is independent of acute disease status.[9] Thus, SHR could provide more accurate information on the acute status of hyperglycemia.

Some studies have reported the association between stress hyperglycemia ratio and mortality in ACS patients.[10,11] However, most studies are single-center and may have comprehensive effects on a heterogeneous population. It is necessary to further evaluate the relationship between SHR and ACS prognosis in different populations. Therefore, this study was conducted to identity the association between SHR and in-hospital outcomes in patients with ACS from a large multicenter cohort.

METHOD

Study Design and Data Sources

The CCC-ACS (Improving Cardiovascular Care in China-ACS) program is a national registry study with a database of ongoing updates in order to improve the quality of ACS care. The project, initiated in 2014, is a collaboration between the American Heart Association and the Chinese Society of Cardiology. All design and methodology details of the CCC-ACS project have been published on the standard web-based data collection platform.[12] Suitable patients were selected from each participating hospital and reported to the CCC-ACS management group on a continuous monthly basis, and required data were collected by trained doctors by the middle of the following month. A third-party clinical study institution was engaged to conduct a quality audit to guarantee that case reporting was continuous and not selective. In addition, 5% of reported cases were randomly selected from each participating center. The original medical records were also used to ensure the accuracy and integrality of reported data. Under the guidance of quality audit reports, the data in this research were recorded appropriately with a permissible incidence of missing data or errors.

110,114 patients diagnosed with ACS were collected from November 2014 to December 2019 in 240 hospitals registered. Missing and abnormal data were excluded in 96,903 cases, tumors were excluded in 390 cases, severe hepatic insufficiency in 130 cases, and pulmonary infections in 263 cases. A total of 12,010 patients were eventually enrolled in the study (Figure 1).

Data Collection and Definition

The standard data collection platform (Oracle Clinical Remote Data Capture, Oracle) was used. Electronic data included patient clinical characteristics, medical history, diagnosis and risk assessment, inpatient management, discharge medication, and inpatient outcomes. Regular quality audits are conducted by a third-party clinical research associate to guarantee that case reporting is continuous and not selective. Records of hypertension and hy-

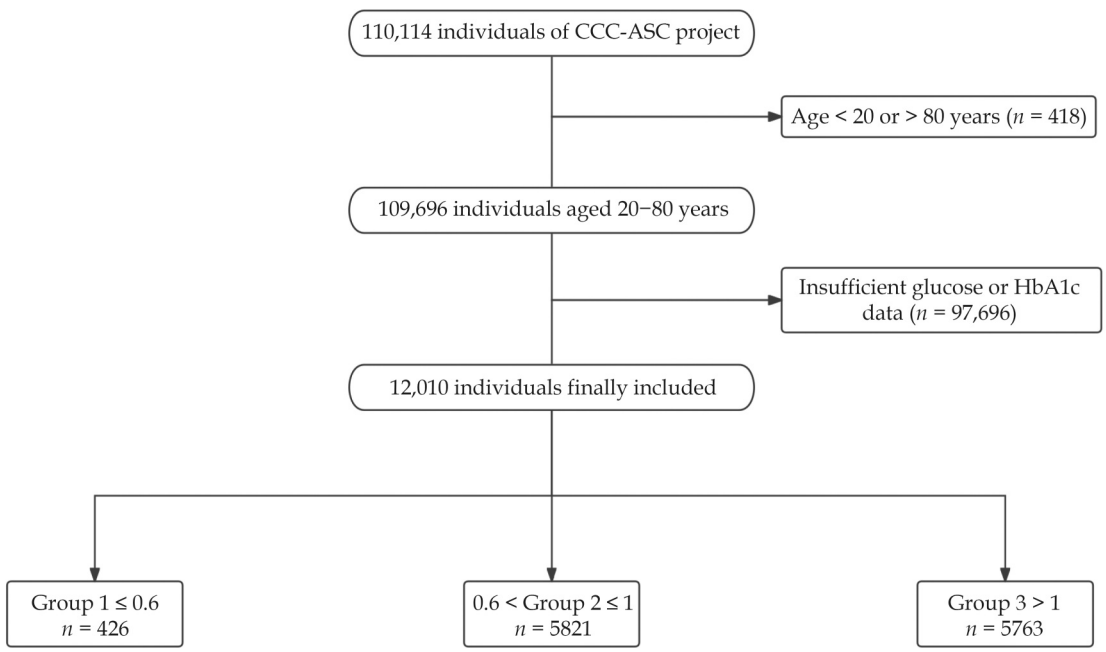

Figure 1 The flow chart.

perlipidemia could be obtained according to the patient's previous medical history. ABG was defined as the first measured random plasma glucose within the first 24 h of admission. SHR was calculated according to the following equation: SHR = ABG (mmol/L)/[1.59 × HbA1c(%) − 2.59].[11] Creatinine was collected on the day of admission. The baseline estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Diseases (MDRD) equation for Chinese patients: eGFR (mL/min per 1.73 m^2) = 175 × serum creatinine (SCr) (mg/dL) − 1.234 × Age − 0.179 (× 0.79 for women).[13] The primary endpoint was in-hospital major adverse cardiovascular events (MACEs), which included all-cause death, cardiac arrest, cardiogenic shock, myocardial infarction, and ischemic stroke.

Statistical Analysis

Because of the non-normally distributed, continuous variables are represented as median and interquartile range (Q25, Q75). Categorical variables are shown as numbers (percentages). Kruskal-Wallis continuous variables were tested using the test, and differences between categorical variables were examined using the χ^2 test or Fisher's exact probability method. The association between SHR and in-hospital MACEs was then modeled by the restricted cubic spline (RCS) curves, and all patients were finally categorized according to the results.

The multivariate logistic regression analysis was used to clarify the associations between the SHR and in-hospital MACEs by controlling the potential confounders, described as odds ratios (ORs) and 95% CIs. The adjusted factors included age, sex, history of hypertension, diabetes status, smoking, creatinine, peripheral vascular disease, statins, subcutaneous insulin or not, cerebrovascular disease, previous myocardial infarction, triglycerides, and low-density lipoprotein cholesterol (LDL-C). Considering potential modifiers, we also performed stratified analyses based on diagnosis and important covariates to verify the stability of the results. In addition, we divided all patients into 5 groups according to eGFR to explore the association between SHR and in-hospital MACEs in ACS patients with different renal functions. Finally, the population was also analyzed into subgroups by the logistic regression analysis, which were categorized according to age, sex, smoking status, DM, hyperlipidemia, renal function, hypertension, and previous percutaneous coronary intervention (PCI) history.

The statistical analyses were all performed using R software version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 26.0 (IBM Corporation, Chicago, IL). Two-sided *P* values ≤ 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

A total of 12,010 patients were included in the final analysis. We stratified all patients into three groups according to the result of the RCS curve (Figure 2). The RCS curve elucidated the U-shaped trend between SHR and in-hospital MACEs in both unadjusted and adjusted models. After being adjusted, the nadir point of the SHR level in this MACEs curve was pinpointed at 0.83, coinciding with the 0.60-1.00 interval. Thus, Group 1 was defined as SHR ≤ 0.6 (*n* = 426), Group 2 was defined as SHR between 0.6 and 1 (*n* = 5821), and Group 3 was defined as SHR > 1 (*n* = 5763).

The baseline characteristics of all ACS patients and different groups were presented in Table 1. As the result showed, the median age of this cohort was 63 (54, 71) years old, and 8942 (74.5%) were male. Among all participants, 3410 (28.4%) had DM, and 793 (6.6%) individuals underwent insulin therapy while 2002 (16.7%) had oral hypoglycemic drugs at admission. Patients with higher SHR tended to have higher TC, LDL-C, TG, FBG, and HbA1c levels. In addition, for the type of ACS status, 6873 (57.2%) patients were STEMI, and the others were UA (18.3%) and NSTEMI (24.5%). Furthermore, Figure 3 showed the composition of in-hospital MACEs in all ACS patients. The percentage of all-cause death, cardiac arrest, cardiogenic shock, myocardial infarction, and ischemic stroke was 34.1%, 15.2%, 32.2%, 10.1% and 8.3%, respectively.

SHR and In-hospital Outcomes

As preliminary analysis results of the RCS curve showed above, patients in both the lowest and highest SHR groups were associated with a higher incidence of MACEs during the hospitalization. Therefore, we used the middle group (Group 2) as the reference in the multivariate logistic regression analysis. It was discerned that compared with Group 2, Group 1 (OR = 1.891, 95% CI: 1.028-3.479, *P* < 0.001) and Group 3 (OR = 1.868, 95% CI: 1.434-2.434, *P* < 0.001) had higher risks of suffering from in-hospital MACEs (Table 2).

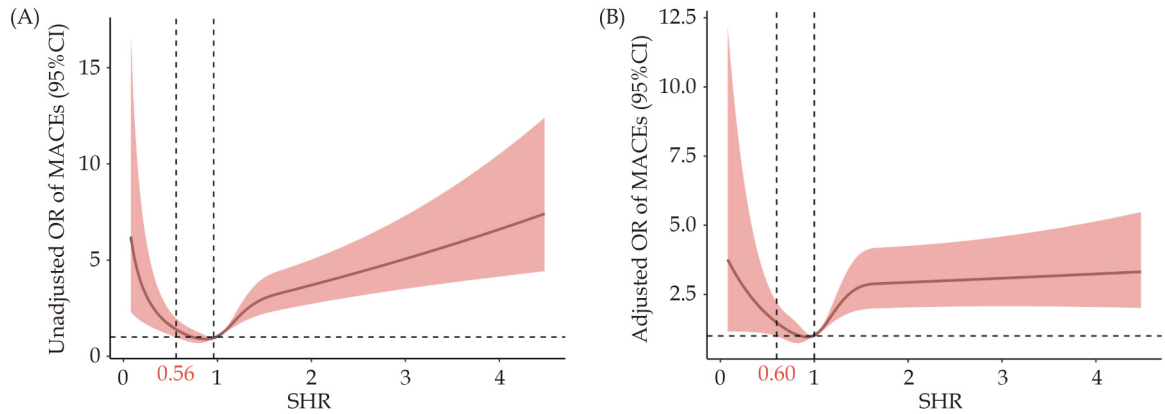

Figure 2 Restricted cubic spline analysis. The U-shaped association between SHR and in-hospital MACEs was observed in both (A) unadjusted model and (B) adjusted model. Adjusted model included age, sex, history of hypertension, diabetes, smoking status, creatinine, peripheral vascular disease, statins, subcutaneous insulin or not, cerebrovascular disease, previous myocardial infarction, triglycerides, and low-density lipoprotein cholesterol. MACEs: major adverse cardiovascular events; SHR: stress hyperglycemia ratio.

Meanwhile, the association between SHR and in-hospital MACEs in ACS patients with different renal functions was depicted in Table 3. Notably, the investigation demonstrated that in the 90 > eGFR ≥ 60 (mL/min per 1.73 m^2) and 45 > eGFR ≥ 30 (mL/min per 1.73 m^2) population, Group 1 had increased risks of in-hospital MACEs, featuring adjusted ORs of 3.290 (95% CI: 1.072–10.103) and 7.088 (95% CI: 1.292–38.891). No significant associations were described in other renal functions in Group 1. For Group 3, significant interactions between SHR and in-hospital MACEs were presented in eGFR ≥ 90 (mL/min per 1.73 m^2), 90 > eGFR ≥ 60 (mL/min per 1.73 m^2), and 60 > eGFR ≥ 45 (mL/min per 1.73 m^2) groups, in which the ORs (95% CI) were 1.588 (1.104–2.284), 2.067 (1.216–3.514) and 3.986 (1.458–10.896), respectively (all $P < 0.001$). However, the same difference was not observed in eGFR < 45 (mL/min per 1.73 m^2) groups.

Subgroup Analyses

Subgroup analyses were conducted for in-hospital MACEs by satisfying the following variables: age, sex, smoking status, DM, hyperlipidemia, renal function, hypertension, and previous PCI history (Figure 4). SHR had an interactive relationship between age, sex, DM, and renal function in developing in-hospital MACEs (with all P for interaction < 0.05). Furthermore, SHR was associated with higher risks of in-hospital MACEs in the subgroups of age < 60 years (OR = 1.367; 95% CI: 1.076–1.736), male (OR = 1.492; 95% CI: 1.202–1.853), DM (OR = 2.282; 95% CI: 1.477–3.524), non-hyperlipidemia (OR = 2.737; 95% CI: 1.793–4.177), and hypertension (OR = 1.356; 95% CI: 1.020–1.801). However, no significant results were observed in non-DM patients (OR = 1.131; 95% CI: 1.000–1.278, $P = 0.05$).

DISCUSSION

As a multicenter cohort study, our research aimed to find specific evidence illustrating the association between SHR and in-hospital MACEs in patients with ACS. Notably, SHR was independently associated with in-hospital MACEs, and the U-shaped correlation demonstrated that both low and high SHR levels were linked to elevated mortality rates. In addition, the results were also found in patients with different renal functions, except for eGFR < 30 (mL/min per 1.73 m^2). Furthermore, SHR had a stronger correlation with in-hospital MACEs in the following groups: age < 60 years, male, DM, non-hyperlipidemia, and hypertension subjects.

SHR and In-hospital MACEs in ACS

Stress hyperglycemia, a temporary increase in blood glucose levels associated with critical illness stress, occurs in 20% to 50% of patients admitted to hospital with acute myocardial infarction (AMI).[14] Previous studies have demonstrated that elevated ABG levels were associated with an increased risk of in-hospital death in ACS patients.[15,16] For example, Qin, *et al*.[17] suggested that ABG could be regarded as an independent prognostic factor for patients with AMI during 1-year follow-up. However, Xiong, *et al*.[18] believed that the ABG level was greatly affected by diabetes status and was not suitable for predicting long-term MACEs risks. In that condition,

Table 1 Baseline characteristics according to groups of the SHR.

Variable	All patients (*n* = 12,010)	Group 1 (*n* = 426)	Group 2 (*n* = 5821)	Group 3 (*n* = 5763)	*P*-value
Clinical characteristics					
Age, yrs	63 (54, 71)	65 (57, 72)	63 (54, 71)	63 (54, 71)	0.001
Male	8942 (74.5%)	299 (70.2%)	4389 (75.0%)	4254 (73.8%)	0.018
Smoking	2167 (18.0%)	65 (15.3%)	1088 (18.6%)	1014 (17.6%)	0.097
Diabetes	3410 (28.4%)	223 (52.3%)	1366 (23.3%)	1821 (31.6%)	< 0.001
Hypertension	6475 (53.9%)	249 (58.5%)	3119 (53.3%)	3107 (53.9%)	0.151
Hyperlipidemia	7460 (62.1%)	260 (61.0%)	3615 (62.1%)	3585 (62.2%)	0.890
Previous MI	1013 (8.4%)	47 (11.0%)	504 (8.6%)	471 (8.2%)	0.601
Previous stroke	902 (7.5%)	38 (8.9%)	406 (6.9%)	458 (7.9%)	0.074
Previous PCI	1079 (9.0%)	47 (11.0%)	579 (10.2%)	453 (1.9%)	< 0.001
Renal insufficiency	1057 (8.8%)	61 (14.3%)	439 (7.5%)	205 (3.6%)	< 0.001
Laboratory examinations					
SBP, mmHg	130 (116, 147)	130 (116, 147)	131 (118, 148)	130 (116, 147)	< 0.001
DBP, mmHg	79 (70, 89)	77 (68, 86)	79 (70, 89)	77 (68, 86)	0.011
TC, mmol/L	4.43 (3.67, 5.23)	4.21 (3.41, 5.04)	4.4 (3.65, 5.2)	4.52 (3.75, 5.33)	< 0.001
LDL-C, mmol/L	2.71 (2.09, 3.37)	2.56 (1.99, 3.25)	2.69 (2.09, 3.35)	2.80 (2.16, 3.43)	< 0.001
HDL-C, mmol/l	1.05 (0.88, 1.26)	1.02 (0.85, 1.26)	1.04 (0.88, 1.25)	1.06 (0.88, 1.27)	0.083
Triglycerides, mmol/L	1.44 (1.00, 2.15)	1.38 (0.99, 2.02)	1.44 (1.01, 2.10)	1.46 (0.99, 2.21)	0.206
FPG, mmol/L	7.0 (5.7, 9.6)	4.9 (3.9, 6.3)	5.85 (5.2, 6.87)	8.9 (7.2, 12.2)	< 0.001
HbA1c, %	6.0% (5.6%, 7.1%)	7.7% (6.4%, 9.8%)	6.0% (5.6%, 6.7%)	7.73% (6.4%, 9.82%)	< 0.001
eGFR, mL/min per 1.73 m^2	98.62 (76.65, 121.34)	92.24 (67.62, 117.96)	99.08 (78.95, 121.24)	98.57 (74.82, 121.83)	< 0.001
Creatinine, mmol/L	75 (62, 91)	75 (61, 96)	75 (63, 89)	75 (62, 92)	0.011
LVEF, %	63% (54%, 71%)	58% (50%, 64%)	58% (51%, 64%)	56% (49%, 62%)	< 0.001
ACS status					
UA	2202 (18.3%)	100 (23.5%)	1425 (24.5%)	677 (11.7%)	< 0.001
NSTEMI	2935 (24.5%)	113 (26.5%)	1548 (26.6%)	1274 (22.2%)	< 0.001
STEMI	6873 (57.2%)	213 (50.0%)	2848 (48.9%)	3812 (66.1%)	< 0.001
In-hospital treatment					
Aspirin	11481 (95.6%)	397 (93.2%)	5547 (95.3%)	5537 (96.1%)	0.006
Clopidogrel/Ticagrelor	7885 (65.7%)	290 (68.1%)	3910 (67.2%)	3685 (63.9%)	< 0.001
Statins	11475 (95.4%)	398 (93.4%)	5558 (94.6%)	5519 (95.8%)	0.074
ACEI	3117 (26.0%)	118 (27.7%)	1519 (26%)	1480 (25.7%)	0.619
ARBs	2004 (16.7%)	117 (27.5%)	1553 (26.5%)	1432 (24.8%)	0.058
β-Blocker	7358 (61.3%)	260 (61.0%)	3615 (62.1%)	3585 (62.2%)	0.022
Insulin	793 (6.6%)	67 (15.7%)	289 (4.9%)	437 (7.6%)	< 0.001
Oral hypoglycemic drugs	2002 (16.7%)	129 (30.3%)	802 (13.7%)	1071 (18.6%)	< 0.001
Target vessel territory					
LM	194 (16.2%)	7 (1.6%)	83 (1.4%)	104 (1.8%)	0.27
LAD	3473 (28.9%)	106 (24.9%)	1436 (24.7%)	1929 (33.5%)	< 0.001
LCX	1236 (10.3%)	39 (9.2%)	528 (9.1%)	669 (11.6%)	< 0.001
RCA	2360 (19.7%)	76 (17.8%)	968 (16.6%)	1316 (22.8%)	< 0.001

Continued

Variable	All patients (n = 12,010)	Group 1 (n = 426)	Group 2 (n = 5821)	Group 3 (n = 5763)	P-value
Angiographic data					
LM lesion	327 (2.7%)	14 (3.3%)	160 (2.7%)	153 (2.7%)	0.731
Multi-vessel lesion	1579 (13.1%)	67 (15.7%)	894 (15.4%)	618 (10.7%)	< 0.001

Continuous data are presented as median (25^{th}, 75^{th} percentiles). Categorical data are presented as n (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high sensitivity C-reactive protein; LAD: left anterior descending artery; LCX: left circumflex artery; LDL-C: low-density lipoprotein cholesterol; LM: left main coronary artery; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; SBP: systolic blood pressure; SHR: stress hyperglycemia ratio; STEMI: ST-segment elevation myocardial infarction; UA: unstable angina. Group of SHR: Group 1 < 0.6, Group 2 = 0.6-1, Group 3 > 1.

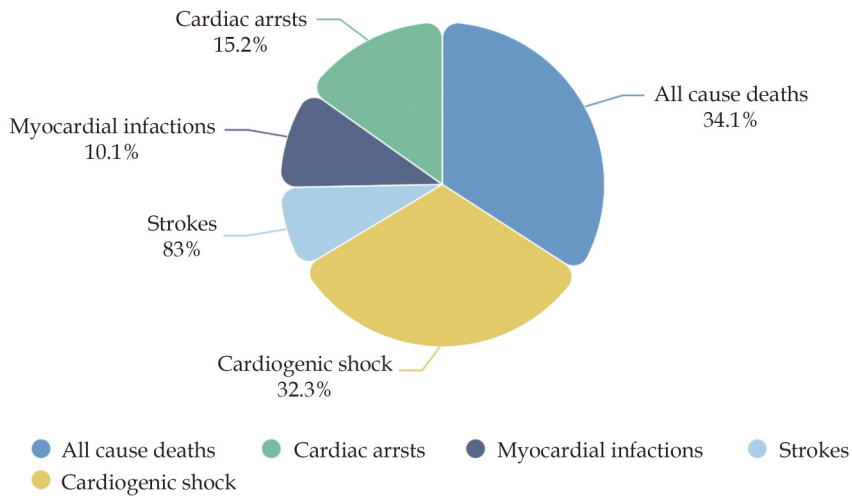

Figure 3 The pie chart of the composition of the major adverse cardiovascular events in all ACS patients. ACS: acute coronary syndrome.

Table 2 The multivariate logistic regression analysis of associations between SHR and MACEs.

SHR	OR (95% CI)					
	Model 1	P-value	Model 2	P-value	Model 3	P-value
Group 2	Reference		Reference		Reference	
Group 1	2.488 (1.531–4.046)	< 0.001	2.346 (1.441–3.822)	< 0.001	1.891 (1.028–3.479)	< 0.001
Group 3	2.329 (1.86–2.916)	< 0.001	2.336 (1.865–2.927)	< 0.001	1.868 (1.434–2.434)	< 0.001
P-value for trend	< 0.001		< 0.001		< 0.001	

Model 1: original data. Model 2: Minimally adjusted models were adjusted for age and sex. Model 3: Multivariable adjusted models were additionally adjusted for history of hypertension, diabetes, smoking status, creatinine, peripheral vascular disease, statins, subcutaneous insulin or not, cerebrovascular disease, previous myocardial infarction, triglycerides, low density lipoprotein. Group of stress hyperglycemia ratio: Group 1 < 0.6, Group 2 = 0.6-1, Group 3 > 1. SHR: stress hyperglycemia ratio; MACEs: major adverse cardiovascular events.

as SHR controlled the baseline blood glucose level over the past 8 to 12 months and combined both acute and chronic glycemic states, growing evidence illustrated that SHR was a better substitute factor for stress hyperglycemia than ABG in critical conditions, including ACS, which could also predict outcomes irrespective of the diabetes status.[19,20] A study proved that in patients with ACS undergoing PCI, both low and high SHR were related to the higher risks of all-cause and cardiovascular mortality during four years of follow-up, which HR was 1.43 (95% CI: 1.01–2.03) and 1.51 (95% CI: 1.03–2.21), respectively.[21] In addition, Chen, *et al*.[22] found a dose-response association between SHR and adverse in-hospital outcomes in patients more than 75 years old with AMI, with or without DM. Moreover, a cohort study including 613 AMI patients illustrated that after being adjusted by SHR, the

Table 3 Associations between SHR and MACEs in different renal function groups.

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	*P*-value for trend	*P*-value
eGFR ≥ 90 mL/min per 1.73 m^2			< 0.001	
Group 2	Reference	Reference		-
Group 1	0.484 (0.117–1.992)	0.591 (0.141–2.478)		0.314
Group 3	1.855 (1.352–2.546)	1.588 (1.104–2.284)		< 0.001
60 ≤ eGFR < 90 mL/min per 1.73 m^2			< 0.001	
Group 2	Reference	Reference		-
Group 1	3.161 (1.361–7.343)	3.290 (1.072–10.103)		0.007
Group 3	2.337 (1.534–3.559)	2.067 (1.216–3.514)		< 0.001
45 ≤ eGFR < 60 mL/min per 1.73 m^2			0.003	
Group 2	Reference	Reference		-
Group 1	3.534 (0.676–18.484)	6.716 (1.094–41.218)		0.135
Group 3	4.584 (1.892–11.108)	3.986 (1.458–10.896)		0.001
30 ≤ eGFR < 45 mL/min per 1.73 m^2			0.005	
Group 2	Reference	Reference		-
Group 1	6.478 (1.878–22.348)	7.088 (1.292–38.891)		0.003
Group 3	3.167 (1.384–7.249)	3.004 (0.975–9.25)		0.006
eGFR < 30 mL/min per 1.73 m^2			0.067	
Group 2	Reference	Reference		-
Group 1	4.761 (1.094–20.728)	1.371 (0.168–11.17)		0.038
Group 3	3.358 (1.078–10.464)	0.668 (0.150–2.972)		0.037

SHR: stress hyperglycemia ratio; MACEs: major adverse cardiovascular events; eGFR: estimated glomerular filtration rate.

Global Registry of Acute Coronary Events (GRACE) score had a stronger predictive ability for in-hospital mortality (the C-statistic value from 0.787 to 0.814), which showed it was possible to add SHR into the prognostic models.[23] Similarly, in patients with DM, the mortality risk prediction after AMI was significantly enhanced with the incorporation of SHR into the GRACE score.[24] In conclusion, all previous research proved that SHR was an independent prognostic predictor for MACEs in patients with ACS.

Some research illustrated that SHR was a transient dynamic disorder, which could only be used in predicting short-term outcomes, but not for long-term prognosis.[25] While another study showed that after 2.5 years of follow-up, patients with higher SHR had an increased possibility of developing MACEs (HR = 1.45; 95% CI: 1.02–2.06).[26] In the current study, we chose short-time outcomes, and in-hospital MACEs within 30 days of admission were collected to be the primary endpoints. Consistent with the studies mentioned above, our study has also proved that both low and high SHR were significantly correlated with in-hospital MACEs in patients with ACS, especially in patients with DM status. This may be due to the fact that patients with DM usually had higher FBG and HbA1c in the admission, so it was necessary to control blood glucose levels more strictly in DM patients under stress response. Meanwhile, previous studies have reported that stress hyperglycemia was one of the important risk factors for acute kidney injury (AKI) in ACS patients.[27] Our study also proved that with the further deterioration in renal function, patients with lower eGFR had higher risks of suffering from in-hospital MACEs associated with SHR. Thus, early interventions in SHR should be performed in patients with decreased renal function. However, this finding was not observed in the non-DM, hyperlipidemia, and eGFR < 30 mL/min per 1.73 m^2 group. The reason may be that this study only collected the outcome during hospitalization and without more follow-up data, so more prospective and long-term follow-up studies are needed in the future.

Previous studies located the "ideal" range for SHR within 0.75 to 1.68 depending on the outcome. However, in our study, stress hyperglycaemia ratios of 0.6 to 1.0 were associated with fewer in-hospital adverse events.

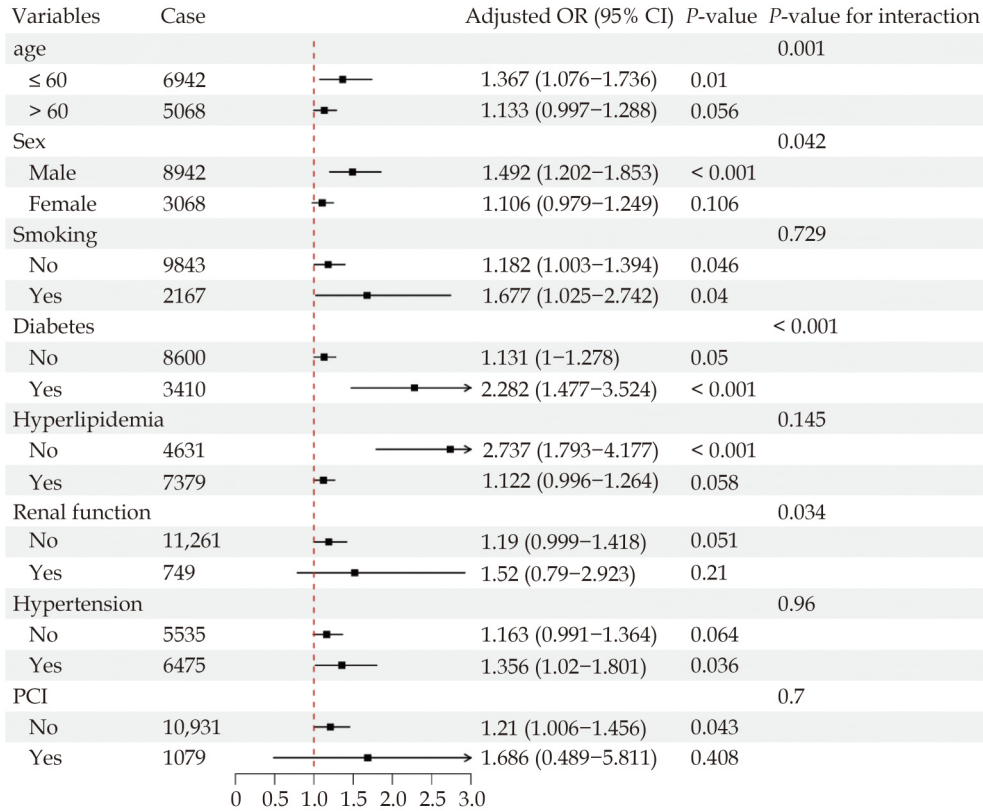

Figure 4 The subgroup analysis of associations between SHR and MACEs. MACEs: major adverse cardiovascular events; SHR: stress hyperglycemia ratio.

Therefore, we should reduce the SHR in patients with ACS, but we should not reduce the SHR indefinitely, because too low SHR increase the risk of MACEs in the hospital.

Mechanisms and Implications

The activation of the sympathetic nerve after ACS leads to the increased secretion of glucagon, growth hormone, glucocorticoids, and catecholamines.[28] In addition, attacking by critical illness stress could lead to the dysfunction of β cells and insulin resistance (IR) even in patients without DM, which are all associated with the elevation of blood glucose.[29] Meanwhile, stress hyperglycemia has also been recognized as one of the major determinants of atherosclerotic plaque instability and rupture, which affects the composition of coronary artery thrombosis and myocardial infarct size (MIS).[30] The potential mechanisms were illustrated as follows. First, SH was related to vascular endothelial dysfunction and the decrease of nitric oxide (NO) bioavailability, which could further lead to microcirculation disturbance and hypoxia of myocardial cells.[31] Second, SH induced reactive oxygen species and exacerbated the oxidative stress, further promoted the reperfusion injury, which was associated with the increase of MIS and cardiac remodeling after AMI.[32] In our research, we found that young males with DM and hypertension had much higher risks of suffering from SHR-correlated MACEs. It was obvious that young males had stronger oxidative stress responses to the critical illness, and endothelial cells of patients with DM and hypertension were much more susceptible to the damage.

From what we have discussed above, it is necessary to manage blood glucose levels in patients with ACS regardless of diabetes status. The guidelines recommended that it was reasonable to maintain blood glucose in ACS patients less than 11 mmol/L in the acute phase, but hypoglycemia should be avoided.[33] Studies have shown that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) can reduce oxidative stress response and ventricular remodeling in AMI patients, which was associated with decreased risks for MACEs (HR = 0.72; 95% CI: 0.56–0.92), especially in re-infarction and stroke.[34] Moreover, sodium-glucose cotransporter 2 inhibitors (SGLT2i) could improve left ventricular (LV) mass index and left atrial volume index in DM patients with ACS.[35] How-

ever, the use of insulin and other hypoglycemic agents during hospitalization may also carry an increased risk of improper hypoglycemia. Therefore, more large studies are needed to determine which kinds of hypoglycemic drugs are safer, more effective, and could offer greater benefits to ACS patients.

Strength and Limitations

Our study was a large multicenter cohort study, which firstly investigated the association between SHR and in-hospital MACEs using the RCS curves to divide all ACS patients into different groups. We also performed analyses in different renal function groups based on the eGFR levels. However, the research also had some limitations. First, the study was a retrospective cohort including short-term outcomes, which means the association between SHR and in-hospital mortality was not a causal relationship. Second, most of our patients were STEMI (57.2%), which could lead to a potential bias. Third, the population included only Asian patients, and the specific mechanisms of SHR and mortality remain unknown. More multicenter research should be conducted in the future. Fourth, this was a multicenter study, and the way in which blood glucose was managed differed at each center. Different glucose management protocols may affect SHR.

Conclusions

In conclusion, this study demonstrates a U-shaped relationship between SHR and in-hospital MACEs in patients with ACS, which means both low and high SHR levels are linked to elevated mortality rates. Furthermore, young males with DM, hypertension, and decreased renal function have much higher risks of suffering from SHR-correlated MACEs. More research should be conducted in the future to explore the potential mechanisms.

DECLARATION

Acknowledgments

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Author Contributions

WANG WJ carried out the experiments, acquired the data and wrote the first draft of the paper; WANG> KX carried out the experiments and wrote sections of the manuscript; NIU JL, and LIU YX recruited the subjects, performed the patients' assessments and critically reviewed the paper for intellectual content. WANG WJ and WANG KX performed the statistical analyses; GE HL and SHEN H conceived and designed the study and handled funding and supervision.

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Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Beijing Anzhen Hospital Ethics Committee of Capital Medical University, and all participants signed an informed consent form. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for Publication

Not applicable.

Conflict of Interest

None.

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