Original Article

Clinical characteristics and risk factors for death in patients with stress cardiomyopathy in the ICU

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Background: This study aimed to investigate the clinical manifestations and risk factors for 28-day mortality in patients with stress cardiomyopathy (SC) in the intensive care unit (ICU).

Methods: This retrospective study was carried out from April 2015 to March 2021. Fifty-five patients in the ICU were diagnosed with SC. Two patients were excluded due to a history of atrial fibrillation (AF), and 53 patients were enrolled in the study. Baseline demographics and clinical characteristics were collected, and the 28-day mortality rate was calculated. Multivariate and univariate logistic regression analyses were used to determine the significant predictors of 28-day mortality.

Results: Of the 53 patients, almost half (47.17%) were male. The most common stress trigger was sepsis (37.74%). Due to sedation and tracheal intubation, 49.06% of SC patients were unable to express their symptoms, and only 3.77% of patients presented with chest pain. The proportion of patients with complications of systolic heart failure and cardiogenic shock was 77.36% and 39.62%, respectively. The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score when patients were admitted into the ICU was 21.17±8.41, and the Sequential Organ Failure Assessment (SOFA) score at diagnosis of SC was 9.30±4.56. Eighteen (33.96%) SC patients had new-onset AF while in the ICU. The 28-day mortality rate in patients with SC in the ICU was 64.15%. Univariate analysis found that 5 variables [SOFA score at diagnosis of SC, estimated glomerular filtration rate (eGFR) <60 mL/min at diagnosis of SC, maximum norepinephrine dose, new-onset AF, and systolic heart failure] were correlated with 28-day mortality in patients with SC in the ICU. Multivariate logistic regression analysis suggested SOFA score at diagnosis of SC (P=0.042), eGFR <60 mL/min at diagnosis of SC (P=0.027), and new-onset AF (P=0.043) as independent predictors of 28-day mortality.

Conclusions: Male patients with SC were relatively more common in the ICU than in the cardiology unit. Sepsis was a common stress trigger. The 28-day mortality rate was very high. The SOFA score and eGFR <60 mL/min at diagnosis of SC and new-onset AF may have influenced patients' short-term prognosis.

Keywords: Stress-induced cardiomyopathy; takotsubo cardiomyopathy; apical ballooning syndrome; intensive care unit; retrospective study

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Introduction

Stress cardiomyopathy (SC), also referred to as 'takotsubo syndrome' or 'apical ballooning syndrome', was first described in 1990. As reflected in its Japanese name 'takotsubo', the left ventricle (LV) has an octopus trap-like appearance at end systole in acute attacks (1). This condition is characterized by transient diastolic and systolic LV dysfunction, with various wall-motion abnormalities. SC usually occurs after physical or psychological stress and predominantly affects postmenopausal women, although in several registries and case series, up to 10% of SC patients are male (2,3).

The pathophysiology of SC is complex and not fully understood. Through enhanced adrenergic stimulation and excess catecholamine concentration, inflammatory, genetic, neuroendocrine, and metabolic factors may participate in the pathogenesis of the reversible myocardial stunning related to SC (3-5). Patients in the intensive care unit (ICU) have multiple critical illnesses causing severe stress, including respiratory hypoxia, hypercapnic respiratory failure, sepsis, coma, and shock, and thus they have a high risk of SC. Several mechanisms or aetiologies may explain the occurrence of SC in ICU and are may be combined: catecholamine toxicity, psychological stress, neurological impairment, ischemia and left ventricular outflow track obstruction (6). Previous studies have reported that SC incidence in the ICU ranged from 1.5% to 5.6% (6-8). One study showed that >20% of patients admitted to the ICU displayed SC-like LV apical ballooning (9). The initial diagnosis of SC is challenging, especially for ICU patients as they are given sedation or intubation and thus are unable to complain of their symptoms. Identifying specific clinical features might contribute to the screening of SC in the ICU. Hence, we conducted a retrospective investigation of the clinical features and outcomes of SC patients in need of intensive care therapy at a university-affiliated hospital in China. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3223).

Methods

Ethical approval and consent

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Fourth Hospital of Hebei Medical University (No. 2021KS045). Individual consent for this retrospective analysis was waived.

Design and setting

This retrospective observational study involved 55 patients with SC in a general ICU at The Fourth Hospital of Hebei Medical University from April 2015 to March 2021. We defined SC in accordance with the International Takotsubo (InterTAK) Diagnostic Criteria (10) (*Table 1*). The criteria for exclusion were: (I) age <18 years, (II) previous medical history of atrial fibrillation (AF), and (III) lack of fulfilment of the InterTAK Diagnostic Criteria. After excluding 2 patients on the basis of the above criteria, 53 patients were included in the study (*Figure 1*). The patients were divided into 2 groups: the survival group and nonsurvival group. Clinical characteristics of the patients were collected. A comparison of the clinical features, electrocardiogram (ECG), transthoracic echocardiography (TTE), and laboratory data in the survival group (n=19) and nonsurvival group (n=34) was carried out. The research was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Data collection

We collected demographic parameters such as age, sex, body mass index, stress triggers, medical history, symptoms, and drugs on admission. The Acute Physiology and Chronic Health Evaluation (APACHE) II score at admission to the ICU and Sequential Organ Failure Assessment (SOFA) score at diagnosis of SC were documented. Diastolic blood pressure (DBP), heart rate (HR), systolic blood pressure (SBP), ECG, TTE, hemoglobin, lactic acid, and serum creatinine were detected and documented at diagnosis of SC. In addition, the estimated glomerular filtration rate (eGFR) was determined using the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease equation (IDMS-MDRD) (11). Peak creatine kinase-MB, peak troponin-I, peak brain natriuretic peptide, acute heart failure complications, ICU interventions, and clinical outcomes were also collected. The TTEs and ECGs were independently reviewed by an experienced intensivist and an experienced cardiologist to reaffirm the diagnosis of SC.

Statistical analyses

SPSS version 23 (IBM Corp., Armonk, NY, USA) was

Table 1 InterTAK diagnostic criteria cited from International Expert Consensus Document on Takotsubo Syndrome (Part I): Clinical Characteristics, Diagnostic Criteria, and Pathophysiology

1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. In addition to these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS)
2. An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory
3. Neurologic disorders (e.g., subarachnoid haemorrhage, stroke/transient ischaemic attack, or seizures) as well as pheochromocytoma may serve as triggers for takotsubo syndrome
4. New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes
5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common
6. Significant coronary artery disease is not a contradiction in takotsubo syndrome
7. Patients have no evidence of infectious myocarditis
8. Postmenopausal women are predominantly affected

Website link: https://academic.oup.com/eurheartj/article/39/22/2032/5025412. InterTAK, International Takotsubo; ECG, electrocardiogram.

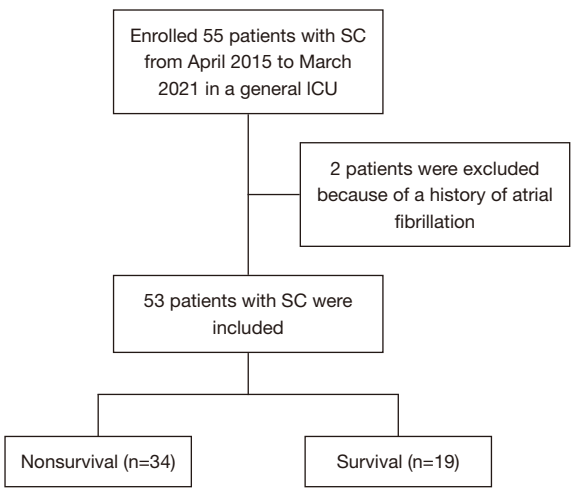

Figure 1 Study flow chart. SC, stress cardiomyopathy.

used for statistical analyses. Data are expressed as average value ± standard deviation or median (interquartile range) for continuous data with normal distribution or non-normal distribution, respectively. Frequency (%) was used for categorical data. The Kolmogorov-Smirnov test was applied to evaluate the normality of the distribution. The Mann-Whitney U-test and Student's *t*-test were utilized to compare continuous data with non-normal and normal distributions, respectively. The χ^2 or Fisher exact test was applied to compare categorical data between different groups. Mean imputation was performed for mean values of missing variables. Logistic regression models were used to identify multivariate and univariate risk factors for 28-day mortality in SC patients. The variables with significant difference in univariate analysis were included in the multivariate model. All statistical tests were 2-sided. $P<0.05$ was regarded as statistically significant.

Results

Fifty-five patients with SC participated in this retrospective observational study. Two patients were excluded due to a history of AF, and the remaining 53 patients were included in the study (*Figure 1*). The mean age of the participants was 70.70±12.13 years (range, 33–89 years). Almost half (47.17%) of the participants were male, and the mean body mass index (BMI) was 23.01±3.43 (kg/m^2). The majority of patients had clear stress triggers, including physical (88.68%) and emotional (7.55%) triggers. The most common physical stress trigger was sepsis (37.74%), followed by operative procedure (28.30%), comatose state (11.32%), and cancer pain (3.77%). The other physical triggers (7.55%) included ventricular tachycardia, cardiac arrest, hemoptysis, and hematemesis. The patients' previous medical histories included malignancy (69.81%), hypertension (41.50%), diabetes (26.42%), coronary heart disease (16.98%), prior stroke (15.09%), chronic obstructive pulmonary disease

Table 2 Clinical features of the study population

Variables	Mean (n=53)
Demographic data	
Age (year)	70.70±12.13
Male (%)	28 (47.17)
Body mass index (kg/m^2)	23.01±3.43
Stress triggers (%)	
None	2 (3.77)
Emotional	4 (7.55)
Physical	47 (88.68)
Sepsis	20 (37.74)
Operative procedure	15 (28.30)
Comatose state	6 (11.32)
Cancer pain	2 (3.77)
Other	4 (7.55)
Medical history (%)	
Malignancy	37 (69.81)
Hypertension	22 (41.50)
Diabetes	14 (26.42)
Coronary heart disease	9 (16.98)
Prior stroke	8 (15.09)
Chronic obstructive pulmonary disease	2 (3.77)
Hyperlipidemia	1 (1.89)
Epilepsy	1 (1.89)
Symptoms (%)	
Inability to express symptoms	26 (49.06)
Dyspnea	18 (33.96)
Chest pain	2 (3.77)
Drugs on admission (%)	
CCB	11 (20.75)
Antiplatelet drugs	8 (15.09)
Diuretics	6 (11.32)
ACEI/ARB	5 (9.43)
Beta-blocker	2 (3.77)
Acute heart failure complications (%)	
Acute respiratory failure	42 (79.25)
Systolic heart failure	41 (77.36)
Cardiogenic shock	21 (39.62)
ICU interventions (%)	
Use of norepinephrine	47 (88.70)
Use of brain natriuretic peptide	41 (77.36)
Use of levosimendan	27 (50.94)
Invasive mechanical ventilation	42 (79.25)
CRRT	18 (33.96)
IABP insertion	2 (3.77)
During ICU stay	
APACHE II score (admission to ICU)	21.17±8.41
SOFA score (at diagnosis of SC)	9.30±4.56
Clinical outcomes	
28-day mortality (%)	34 (64.15)

CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CRRT, renal replacement therapy; IABP, intra-aortic balloon counterpulsation; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

(3.77%), hyperlipidemia (1.89%), and epilepsy (1.89%). Due to sedation and tracheal intubation, 49.06% of SC patients in the ICU were unable to express their symptoms, 33.96% of patients had dyspnea, and only 3.77% of patients presented with chest pain. The most common acute heart failure complication was acute respiratory failure (79.25%), followed by systolic heart failure (77.36%), and cardiogenic shock (39.62%). Eighteen (33.96%) patients had new-onset AF. During intensive care treatment, 86.79% of patients used norepinephrine, 77.36% brain natriuretic peptide, and 50.94% levosimendan. In some cases, support techniques were also used: 79.25% of patients required mechanical ventilation, 33.96% were on continuous renal replacement therapy (CRRT), and 3.77% were implanted with an intra-aortic balloon pump (IABP). The mean APACHE II score upon admission to the ICU was 21.17±8.41, and the mean SOFA score at diagnosis of SC was 9.30±4.56. The 28-day mortality rate in SC patients in the ICU was 64.15% (*Table 2*).

SC patients in the ICU were assigned to 2 groups: the survival group and nonsurvival group. A comparison of the clinical features, ECG, TTE, and laboratory data of the survival (n=19) and nonsurvival groups (n=34) is shown in *Tables 3,4*. No significant difference was observed between the groups in sex ratio, age, medical history, symptoms, or

Table 3 Comparison of clinical characteristics between survival and nonsurvival groups

Variables	Survival (n=19)	Nonsurvival (n=34)	P
Demographic data			
Age (year)	70.00 (62.00, 78.00)	72.50 (64.75, 72.50)	0.282
Male (%)	6 (31.58)	19 (55.88)	0.089
Body mass index (kg/m^2)	23.27±4.38	22.86±2.83	0.684
Stress triggers (%)			
Emotional	1 (5.26)	3 (8.82)	1.000
Physical	18 (94.74)	29 (85.29)	0.556
Sepsis	6 (31.58)	14 (41.18)	0.489
Operative procedure	6 (31.58)	9 (26.47)	0.692
Comatose state	3 (15.79)	4 (11.76)	1.000
Cancer pain	1 (5.26)	1 (2.94)	1.000
Others	2 (10.53)	2 (5.88)	0.539
Medical history (%)			
Malignancy	12 (63.16)	25 (73.53)	0.634
Hypertension	9 (47.37)	13 (38.24)	0.518
Diabetes	6 (31.58)	8 (23.53)	0.524
Coronary heart disease	7 (36.84)	7 (20.59)	0.579
Prior stroke	1 (5.23)	7 (20.59)	0.274
COPD	0 (0.00)	2 (5.89)	0.177
Hyperlipidemia	0 (0.00)	1 (2.94)	0.343
Epilepsy	0 (0.00)	1 (2.94)	0.343
Symptoms (%)			
Inability to express symptoms	9 (47.37)	17 (50.00)	1.000
Dyspnea	7 (36.84)	11 (32.35)	0.741
Chest pain	0 (0.00)	2 (5.88)	0.177
Drugs on admission (%)			
CCB	2 (10.53)	9 (26.47)	0.177
Antiplatelet drugs	3 (15.79)	5 (14.71)	0.100
Diuretics	2 (10.53)	4 (11.76)	1.000
ACEI/ARB	2 (10.53)	3 (8.82)	1.000
Beta-blocker	1 (5.26)	1 (2.94)	0.677
Acute heart failure complications (%)			
Acute respiratory failure	12 (63.16)	30 (88.24)	0.071
Systolic heart failure	11 (57.89)	30 (88.24)	0.029
Cardiogenic shock	9 (47.37)	12 (35.29)	0.389

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Survival (n=19)	Nonsurvival (n=34)	P
ICU interventions			
Use of norepinephrine (%)	16 (84.21)	31 (91.18)	0.752
Norepinephrine dose (μg/kg/min)	0.35 (0.13, 0.64)	0.8 (0.43, 2.00)	0.008
Use of brain natriuretic peptide (%)	12 (63.16)	29 (85.29)	0.132
Use of levosimendan (%)	9 (47.37)	18 (52.94)	0.697
Invasive mechanical ventilation (%)	14 (73.68)	28 (63.64)	0.694
CRRT (%)	5 (26.32)	13 (38.24)	0.380
IABP insertion (%)	0 (0.00)	2 (5.88)	0.697
During ICU stays			
APACHE II score	16.00 (13.00, 24.00)	23.00 (15.00, 29.25)	0.058
SOFA score	6.68±3.64	10.76±4.40	0.001

COPD, chronic obstructive pulmonary disease; CCB, calcium channel blockers; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; ICU, intensive care unit; CRRT, renal replacement therapy; IABP, intra-aortic balloon counterpulsation; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, sequential organ failure assessment.

drugs on admission. Participants in the nonsurvival group showed a higher prevalence of systolic heart failure (88.24% *vs.* 57.89%, P=0.029) than those in the survival group. The maximum norepinephrine dose [0.8 (0.43, 2.00) *vs.* 0.35 (0.13, 0.64), P=0.008] and the SOFA score (10.76±4.40 *vs.* 6.68±3.64, P=0.001) at diagnosis of SC were higher in the nonsurvival group. Although there was no significant difference in APACHE II score between the groups [23.00 (15.00, 29.25) *vs.* 16.00 (13.00, 24.00), P=0.058], the nonsurvival group had an increasing trend (*Table 3*). No significant difference was observed between the groups in SBP, DBP, or HR at diagnosis of SC. New-onset AF (47.06% *vs.* 10.53%, P=0.007) was more frequent in the patients who died, but there was no significant difference between the 2 groups in other ECG changes, such as ST elevation, ST depression, inverted T-waves, and left bundle branch block (P>0.05). As shown by the TTE results, compensatory hyperkinesia in the basal segments and a typical pattern of apical ballooning with akinesia in the apical LV segments were observed in most patients (n=50). The results also revealed obviously reduced LV ejection fraction in the survival and nonsurvival groups (37.7%±10.97% and 33.68%±7.24%, respectively), and the nonsurvival group had a decreasing trend. Although there was no significant difference between the groups in peak values of troponin-I, creatine kinase-MB, and brain natriuretic peptide (P=0.111), the nonsurvival group showed an increasing trend. Patients in the nonsurvival group showed a higher prevalence of eGFR <60 mL/min (70.56% *vs.* 36.84%, P=0.017) than those in the survival group.

Univariate analysis found that 5 variables (SOFA score at diagnosis of SC, eGFR <60 mL/min at diagnosis of SC, maximum norepinephrine dose, new-onset AF, and systolic heart failure) were correlated with 28-day mortality in SC patients in the ICU. Multivariate analysis showed that the risk factors for 28-day mortality in SC patients in the ICU were SOFA score at diagnosis of SC [odds ratio (OR), 1.262; 95% confidence interval (CI): 1.008–1.580; P=0.042], eGFR <60 mL/min at diagnosis of SC (OR, 6.049; 95% CI: 1.224–29.897; P=0.027), and new-onset AF (OR, 7.789; 95% CI: 1.063–57.088, P=0.043) (*Table 5*).

Discussion

In this retrospective study, the clinical manifestations of patients with SC in the ICU were investigated, and the risk factors that influenced 28-day mortality were evaluated. In our study, nearly half of the participants were men. At 88.68%, patients with physical triggers were far more common than those with emotional triggers. Only 3.77% of patients presented with chest pain. The proportion of patients in our study with complications of systolic heart failure and cardiogenic shock, was 77.36% and 39.62%, respectively. A total of 86.79% of patients were given

Table 4 Comparison of clinical parameters, ECG, echocardiography and laboratory data between survival and nonsurvival

Variables	Survival (n=19)	Nonsurvival (n=34)	P
Clinical parameter			
Systolic blood pressure (mmHg)	126.16±23.940	119.38±26.66	0.362
Diastolic blood pressure (mmHg)	73.11±16.77	72.76±20.32	0.951
Heart rate (bpm)	108.79±19.69	114.38±25.44	0.411
ECG changes			
ST elevation (%)	3 (15.79)	10 (29.41)	0.440
ST depression (%)	10 (52.63)	17 (50.00)	0.854
Inverted T-waves (%)	8 (42.11)	5 (14.70)	0.059
Ventricular fibrillation (%)	1 (5.26)	3 (8.82)	1.000
New-onset atrial fibrillation (%)	2 (10.53)	16 (47.06)	0.007
Corrected QT interval (ms)	492.26±43.66	496.97±56.18	0.754
TTE data			
LVEF	37.74±10.97	33.68±7.24	0.111
Apical ballooning (%)	18 (94.74)	32 (94.12)	1.000
Non-apical ballooning (%)	1 (5.26)	2 (5.88)	1.000
Laboratory data			
Peak troponin-I (mg/dL)	4.11 (0.79, 6.18)	1.52 (0.27, 5.74)	0.425
Peak creatine kinase-MB (U/L)	39.29 (14.00, 66.86)	45.88 (23.19, 103.95)	0.085
Peak brain natriuretic peptide (ng/mL)	2,012.18 (977.56, 4,264)	3,405.13 (2,063.34, 4,767.55)	0.056
Hemoglobin (g/dL)	112.98±6.24	105.29±4.02	0.284
Serum potassium (mmol/L)	3.94±0.61	4.26±0.56	0.054
Lactic acid (mmol/L)	1.4 (1.20, 2.80)	2.22 (1.45, 5.25)	0.111
eGFR <60 mL/min (%)	7 (36.84)	24 (70.59)	0.017

ECG, electrocardiogram; TTE, transthoracic echocardiography; SC, stress cardiomyopathy; LVEF, left ventricle ejection fraction; eGFR, estimated glomerular filtration rate.

Table 5 Multivariate analysis of 28-day mortality of patients with stress cardiomyopathy in the ICU

Variables	OR	95% CI	P
SOFA score at diagnosis of SC	1.262	1.008–1.580	0.042
eGFR <60 mL/min at diagnosis of SC	6.049	1.224–29.897	0.027
Norepinephrine dose at diagnosis of SC	1.504	0.494–4.578	0.473
New-onset atrial fibrillation	7.789	1.063–57.088	0.043
Systolic heart failure	5.188	0.857–31.420	0.073

SOFA, sequential organ failure assessment; SC, stress cardiomyopathy; eGFR: estimated glomerular filtration rate.

norepinephrine, and 79.25% of patients needed invasive mechanical ventilation. The 28-day mortality rate of patients with SC in the ICU was 64.15%. The independent risk factors of 28-day mortality in patients who had SC in the ICU were SOFA score at SC diagnosis, eGFR <60 mL/min at diagnosis of SC, and new-onset AF.

In 2005, Park *et al.* (9) reported a SC incidence of 28% in a medical ICU, although this report comes from a study without coronarography. More recently, Rowell *et al.* and Oras *et al.* reported SC incidences of 3.5% and 5.6% respectively (7,8). The APACHE II score has been validated as an accurate predictor of clinical outcomes and mortality in critically ill patients (12). Jo *et al.* (13) identified APACHE II score as significant predictors for in-hospital mortality in critically ill patients with SC, which developed in the medical or surgical ICU. In our study, although there was no significant difference in APACHE II score between the groups, the nonsurvival group had an increasing trend. Previous studies have reported that SC patients were predominantly women, especially postmenopausal women, and an associated stressor was identified in most patients. Emotional triggers were more common than physical triggers (4,14-18). However, the InterTAK Registry has reported that physical stimuli (including fracture, infection, disorders in central nervous system, acute respiratory failure, and stress after operation) were more commonly seen compared to emotional stimuli (including interpersonal conflict, anger anxiety, panic, fear, and grief), at 36.0% *vs.* 27.7%, respectively. Our study showed that nearly half of the patients were men and that at 88.67%, physical triggers were far more common. Indeed, SC related to physical stress has been found to occur more frequently in male patients than female (4), which provides an explanation for the higher number of male patients in our study. Physical stress-triggered SC was accompanied by more complications, which might be the reason for its higher rate (19). Patients with multiple organ failure were admitted into the ICU. Therefore, compared with emotional factor-triggered SC, patients with physical stress-triggered SC were more likely to be admitted into the ICU. Belcour *et al.* (20) reported that the prevalence of SC in patients admitted to the ICU for convulsive status epilepticus ranged from 34% to 62%, age and Simplified Acute Physiology Score II were the risk factors. Sepsis is a frequent cause of admission to ICUs and one of the leading causes of death among hospitalized patients. The most common ICU acquired infections were catheter-related bloodstream infections, pneumonia and abdominal infections. The presence of organ dysfunction and shock, severity of underlying diseases, comorbidities, and a few characteristics of infection were the related risk factors for death in ICU patients with sepsis (21). Doyen *et al.* (22) reported that sepsis and pulmonary diseases were the most common reasons (38.50% and 46.20%, respectively) for SC in the ICU. In our study, sepsis was the most frequent trigger (37.74%), which was similar to the findings of Doyen's study. We found that respiratory and hemodynamic instability in SC patients in the ICU was increased in comparison with SC patients in a cardiology setting. Based on InterTAK Registry data, Templin *et al.* (19) demonstrated that the usage of ventilation (17.3%) and catecholamines (12.2%) was lower and the occurrence of cardiogenic shock (9.9%) was decreased among patients with SC admitted to cardiology units. Brinjikji *et al.* (23) found that 31% of SC cases were complicated with heart failure. According to their results, respiratory status was affected by the complication of heart failure in only 6.7% of SC patients. Muratsu *et al.* (24) reported that 26% of patients in their study had the complication of heart failure. In our study, 77.36% and 39.62% of patients had complications of systolic heart failure and cardiogenic shock, respectively. Norepinephrine was given to 86.79% of patients, and 79.25% of patients needed invasive mechanical ventilation. These differences might have resulted from the different target patient groups; the patients transferred to the ICU had relatively severe illnesses.

We explored the 28-day mortality rate of SC patients in the ICU. Our results showed a 28-day mortality rate of 67.50% in these patients. The mortality rate of SC patients in our study was much higher compared with those in the cardiology unit (67.50% in our study *vs.* 4.1%, respectively) (19). The status of the patients in the ICU was more unstable and patients more frequently presented with multiple organ failure in comparison with SC patients in a cardiology unit, who generally only had heart failure with a much lower mortality rate. There have been no large randomized controlled trials investigating the mortality rate of SC patients in ICUs. One prospective single-center study reported that 30.8% of SC patients in the ICU died within 30 days (22). Oras *et al.* (7) reported that the 30-day mortality rate of hemodynamically unstable patients with SC in the ICU was 42%. There are 2 reasons for the higher mortality rate in our ICU than in the literature. First, the tertiary nature of our hospital, with severely ill patients and those directly transferred from other hospitals admitted first, might have contributed to the high mortality rate. Another reason may be that the proportion of patients

with malignancies in our study was 69.80%, indicating that the basic condition of SC patients in our study was poor. The reason for the high proportion of malignant patients in our study was that our hospital also includes Hebei Cancer Hospital, which is a large comprehensive grade A tertiary hospital focusing on the diagnosis and treatment of cancer. Desai *et al.* (25) noted that patients suffering from malignancy had an increased risk of developing SC. Additionally, Joy *et al.* (26) reported that outcomes are significantly worse in patients with SC and malignancy. In this study, further analysis showed that the SOFA score, eGFR <60 mL/min at diagnosis of SC, maximum norepinephrine dose, new-onset AF, and systolic heart failure may have been risk factors of 28-day mortality in SC patients in the ICU. Subsequent analyses found that new-onset AF was an independent risk factor for mortality. As a major cardiac disorder affecting adults, AF is related to significant morbidity and mortality (27). Indeed, previous investigations have demonstrated that patients in critical condition with new-onset AF are at elevated risk of in-hospital death (28). AF may result in adverse events in SC patients via adverse hemodynamic effects, including atrial contraction loss, rapid ventricular rate, and atrioventricular synchronicity loss, contributing to a decline in cardiac output when the ejection fraction is depressed. Stiermaier *et al.* (29) showed that left atrium dysfunction was an additional characteristic of acute SC. Disturbances in the left atrium were potentially caused by systolic and diastolic dysfunction in LV, which resulted in overloaded pressure and volume in the left atrium and thus contributed to AF onset during SC. Additionally, SC exerted a direct effect on the left atrium. The autonomic nervous system might have also played an important role. Both parasympathetic and sympathetic tone have been found to participate in AF pathogenesis (30). Additionally, excess secretion of catecholamine and enhanced activity in sympathetic nerves are widely accepted mechanisms in SC (31). Sympathetically driven episodes of AF were also deemed conceivable in view of the presumed pathophysiologic connection with catecholamine excess and sympathetic overdrive. Another potential factor was inflammation. In this study, the most common frequent trigger was sepsis. Increased levels of circulating interleukin-6 and -10 have been reported in SC, and systemic inflammation is thought to result in initiating and perpetuating AF (32-35).

The SOFA score at diagnosis of SC was the next independent risk factor for 28-day mortality in this study, and is considered an excellent assessment for predicting short-term mortality in sepsis and other life-threatening conditions (36). In our study, SOFA score was considered an independent risk factor for 28-day mortality, and eGFR <60 mL/min at diagnosis of SC was another independent risk factor for 28-day mortality. After analysis of the results, we proposed the following reason: SC is an increasingly recognized form of acute heart failure. Notably, decreased cardiac output due to worsening LV function could result in injured renal function via underperfusion, the sympathetic nervous system, and the activated renin-angiotensin-aldosterone axis (37). One systematic review involving observational studies reported that decreased eGFR was related to an elevated risk of coronary heart disease (38). A meta-analysis found that low eGFR was related to cardiovascular and all-cause mortality in the general population (39). El-Battrawy *et al.* (40) reported eGFR <60 mL/min as an independent predictor of adverse outcomes in SC.

Limitations

Our study had some limitations. First, our work was a retrospective, single-center, observational study. The number of patients included was relatively low. Second, there were problems in acquiring certain data, including C-reactive protein, the duration time of AF, and the dynamic changes in cardiac function parameters. Thus, further prospective multicenter research is required on this topic.

Conclusions

Male SC patients with physical stress were relatively more common in the ICU than in the cardiology unit. The 28-day mortality rate was 67.50%. New-onset AF was common in SC patients in the ICU. New-onset AF, SOFA score at diagnosis of SC, and eGFR <60 mL/min at diagnosis of SC may have influenced patients' short-term prognosis. Positively addressing new-onset AF in SC patients in the ICU may contribute to the improvement of patient outcomes.

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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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of The Fourth Hospital of Hebei Medical University (No. 2021KS045). Individual consent for this retrospective analysis was waived.

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