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ORIGINAL RESEARCH

Prognostic Utility of Society for Cardiovascular Angiography and Interventions Shock Stage Approach for Classifying Cardiogenic Shock Severity in Takotsubo Syndrome

Andrea Camblor-Blasco, MD*; Ivan J. Nuñez-Gil, MD, PhD*; Albert Duran Cambra, MD; Manuel Almendro-Delia, MD, PhD; Eduard Ródenas-Alesina, MD; Clara Fernández-Cordon, MD; Oscar Vedia, MD; Miguel Corbí-Pascual, MD, PhD; Emilia Blanco-Ponce, MD, PhD; Sergio Raposeiras-Roubin, MD, PhD; Marta Guillén Marzo, MD; Alejandro Sanchez Grande Flecha, MD; Jose Maria Garcia Acuña, MD, PhD; Jorge Salamanca, MD; Juan M. Escudier-Villa, MD; Agustin C. Martin-Garcia, MD, PhD; Marco Tomasino, MD; Ravi Vazirani, MD; Alberto Perez-Castellanos, MD; Aitor Uribarri, MD, PhD*

BACKGROUND: Cardiogenic shock (CS) is a significant complication of Takotsubo syndrome (TTS), contributing to heightened mortality and morbidity. Despite this, the Society for Cardiovascular Angiography and Interventions (SCAI) staging system for CS severity lacks validation in patients with TTS and CS. This study aimed to characterize a patient cohort with TTS using the SCAI staging system and assess its utility in cases of TTS complicated by CS.

METHODS AND RESULTS: From a TTS national registry, 1591 consecutive patients were initially enrolled and stratified into 5 SCAI stages (A through E). Primary outcome was all-cause in-hospital mortality; secondary end points were TTS-related in-hospital complications and 1-year all-cause mortality. After exclusions, the final cohort comprised 1163 patients, mean age 71.0±11.8 years, and 87% were female. Patients were categorized across SCAI shock stages as follows: A 72.1%, B 12.2%, C 11.2%, D 2.7%, and E 1.8%. Significant variations in baseline demographics, comorbidities, clinical presentations, and in-hospital courses were observed across SCAI shock stages. After multivariable adjustment, each higher SCAI shock stage showed a significant association with increased in-hospital mortality (adjusted odds ratio: 1.77–29.31) compared with SCAI shock stage A. Higher SCAI shock stages were also associated with increased 1-year mortality.

CONCLUSIONS: In a large multicenter patient cohort with TTS, the functional SCAI shock stage classification effectively stratified mortality risk, revealing a continuum of escalating shock severity with higher stages correlating with increased in-hospital mortality. This study highlights the applicability and prognostic value of the SCAI staging system in TTS-related CS.

Key Words: cardiogenic shock ■ extracorporeal membrane oxygenation ■ heart failure ■ SCAI ■ Takotsubo syndrome

Correspondence to: Aitor Uribarri, MD, PhD, Cardiology Department, Hospital Universitari Vall d'Hebron, Pg. de la Vall d'Hebron, 119, 08035 Barcelona, Spain. Email: auribarrig@gmail.com

*A. Camblor-Blasco and I. J. Nuñez-Gil contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- This is the first investigation that validates the use of the Society for Cardiovascular Angiography and Interventions shock stage classification in patients with Takotsubo syndrome.
- This classification system was able to predict in-hospital mortality and the incidence of complications in a large multicenter registry.
- In addition, we establish a recommendation on how to stratify patients with Society for Cardiovascular Angiography and Interventions shock stage A, a patient profile that had not been clearly described in previous research.

What Are the Clinical Implications?

- The results of this study suggest that the use of the Society for Cardiovascular Angiography and Interventions classification in patients admitted for Takotsubo syndrome can identify patients at higher risk of death and complications and, therefore, could help in earlier recognition and facilitate decision-making and the treatment strategy.

Nonstandard Abbreviations and Acronyms

CS	cardiogenic shock
LVOTO	left ventricular outflow tract obstruction
SCAI	Society for Cardiovascular Angiography and Intervention
TTS	Takotsubo syndrome

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy or *broken heart syndrome*, was first described in Japan in 1990.[1] Its presentation mimics an acute myocardial infarction, with similar clinical presentation, electrocardiographic changes, and transient systolic dysfunction. However, the main difference with a myocardial infarction is the absence of complicated coronary artery disease in TTS.[2] The pathophysiology of TTS remains largely unknown. Although there are several different theories proposed to explain the condition, one prominent theory involves the role of catecholamines in causing cardiac stunning.[2] This condition is usually triggered by an emotional or physical stress, which is why TTS is also known as *broken heart syndrome*.[3]

Despite often being reversible and benign, TTS can be serious and has the potential to lead to life-threatening and acute complications, including fatal ventricular arrythmias, acute heart failure, and cardiogenic shock (CS). The reported incidence of CS in patients with TTS varies in different series, ranging from 5% to 20%, with clear increases in mortality and morbidity rates in this subgroup of patients with TTS.[2,4,5]

In addition, the use of catecholamines (especially inotropes) can be potentially harmful in this subgroup of patients, potentially making the management of CS in these patients more challenging.[6,7] In this regard, early identification of risk factors associated with CS in patients with TTS and creating a scheme to uniformly characterize CS severity across research protocols and individual centers may be helpful to facilitate patient care and research.

In 2019, the Society for Cardiovascular Angiography and Intervention (SCAI) proposed a new approach to define CS severity, which categorizes patients into 5 stages (A–E) ranging from *at-risk* to *extreme* cardiogenic shock.[8] Many studies have reported the association of SCAI stages with mortality in cardiogenic shock and its validation to predict mortality in this setting.[9,10] However, the association of SCAI shock stages with outcomes in the subgroup of patients with TTS has not been well established. Therefore, the aim of this study was to describe a cohort of patients with TTS using this SCAI staging approach and its association with in-hospital mortality and complications using the large multicenter registry.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

All data were collected from the Spanish multicenter (Registry of Takotsubo Syndrome). It is a voluntary observational study that enrolled patients with TTS from 23 centers in Spain. Its rationale and design have been previously described.[11]

Baseline patient characteristics, triggering factors, in-hospital course, procedures and therapies performed at the discretion of the attending physician, and short-and long-term outcomes were captured through a dedicated electronic case report form. The admission value of all vital signs, clinical measurements, and laboratory values was defined as either the first value recorded after hospital admission or the value recorded closest to hospital admission. The study complied with the Declaration of Helsinki, and was approved by the Institutional Ethics Committee. All patients provided written informed consent.

Study Population

We analyzed a database of consecutive unique adult patients >18 years of age admitted to the hospital with diagnosis of TTS between January 1, 2003 and December 31, 2022.

Main inclusion criteria required a definitive TTS diagnosis (at hospital discharge or within the first 6 months of follow-up) based on the modified Mayo Clinic criteria[1]: (1) transient left ventricular (LV) dysfunction with apical, midventricular, or basal segmental alterations extending beyond the territory supplied by a single coronary artery; (2) angiographic absence of significant obstructive coronary disease (luminal narrowing >50%) or a complicated (ruptured/thrombosed) atheroma; (3) new electrocardiographic changes (ST-segment elevation or negative T waves) and moderate elevation of cardiac troponins; and (4) absence of myocarditis or pheochromocytoma. Complete normalization of wall motion abnormalities and LV ejection fraction (LVEF) were required, except in patients who died before complete normalization of LVEF[2] The diagnosis of CS was physician adjudicated at each site and was defined as a sustained episode of systolic blood pressure <90 mm Hg for at least 30 minutes or vasopressors required to achieve a blood pressure≥90 mm Hg, pulmonary congestion or elevated LV filling pressures, and signs of impaired organ perfusion (altered mental status, cold, clammy skin, oliguria or increased serum lactate).

Definition of shock stages: the investigators of this study defined SCAI stages at admission retrospectively according to the shock classification system proposed and updated in 2022 by the SCAI.[12] Stage A patients (*at risk*) were defined as hemodynamically stable patients without CS but with acute cardiovascular disease putting them at risk of developing CS. In this context, we consider patients with LVEF <45%, patients with the development of new severe valve disease, patients with ventricular arrhythmias, or patients with obstructive intraventricular gradient. Figure 1 shows the criteria used to stratify the SCAI stages.

Statistical Analysis

The primary end point was all-cause in-hospital mortality. Summary statistics included mean and SD for continuous variables, with groups compared by the ANOVA test, and number and percentage for categorical variables, with groups compared by the Pearson chi-square test. Univariate logistic regressions were run to test the association of baseline covariates with in-hospital mortality. The SCAI shock stage was treated as an ordinal variable to determine the risk associated with each of its categories. A backwards stepwise logistic regression analysis (inclusion $P<0.05$, exclusion $P<0.1$) was then performed to identify potential confounding variables and predictive factors for in-hospital mortality. All covariates with $P<0.1$ from the univariate analysis were included in the stepwise regression. The trigger for TTS,

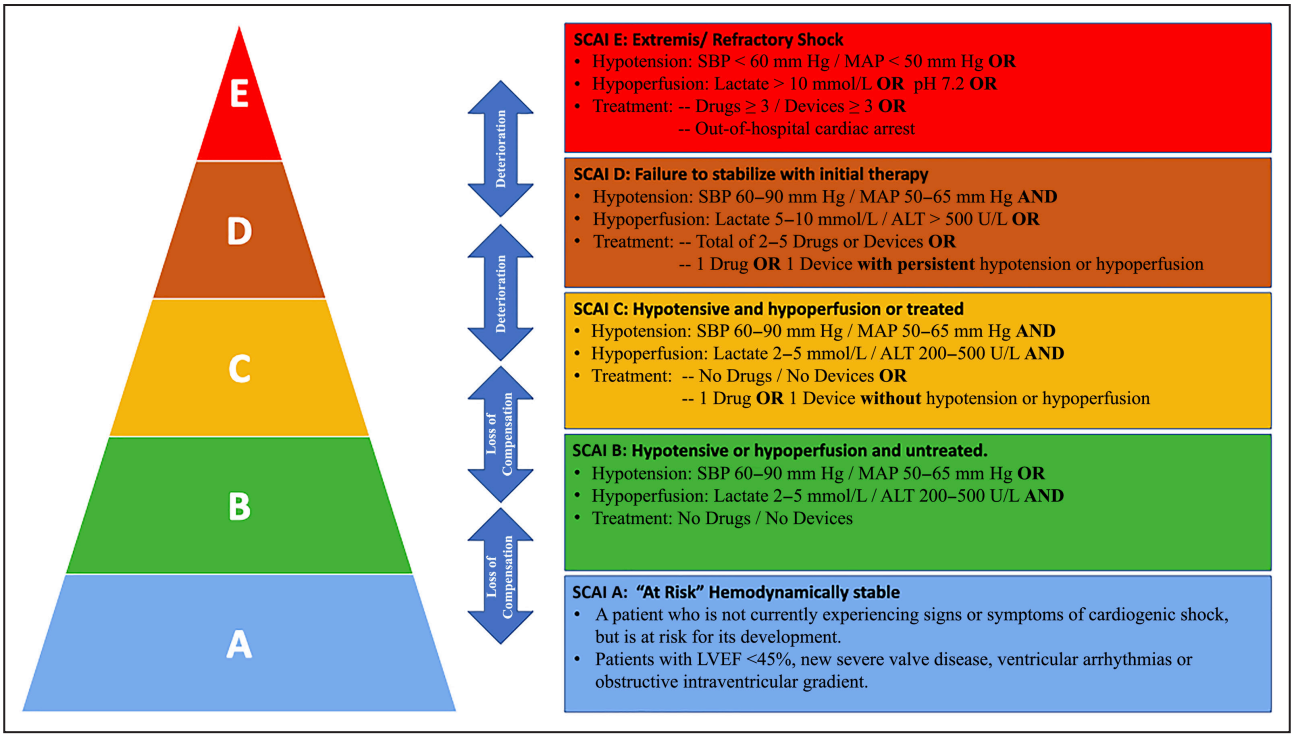

Figure 1. Criteria used to stratify the SCAI stages.
ALT indicates alanine aminotransferase; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; SBP, systolic blood pressure; and SCAI, Society for Cardiovascular Angiography and Interventions.

right ventricular involvement, and LV outflow tract obstruction (LVOTO), variables previously described to be associated with worse prognosis and not captured by other scores, were forced within the stepwise regression. Missing was <10% in most of the covariates (Table S1) and variables with significant collinearity (variance inflation factor >4) were excluded from the model. Discrimination of the final multivariable model was tested using the area under the curve of the receiver-operating characteristics curve, and calibration was assessed with the Hosmer–Lemeshow chi-square test. The change in the area under the curve using the SCAI stage at 24 hours instead of SCAI stage at admission was tested with the De Long test. Two-tailed *P* values <0.05 were considered statistically significant. Statistical analysis was performed with the IBM SPSS software package (version 20.0; IBM Corp., Armonk, NY).

RESULTS

Study Population

From January 1, 2003 until December 31, 2022, 1591 patients were included in the RETAKO registry. After excluding 428 patients who did not meet the inclusion criteria, the final study population included a total of 1163 patients diagnosed with TTS (Figure 2). The incidence of shock in our cohort was 20.2%. Overall, the mean age was 71.4±11.9 years, and 87% were female. A previous stressful trigger was described in more than two-thirds of the patients. Fifteen patients had suffered prehospital cardiac arrest, representing only 1.3% of the cohort. Most of the patients were cataloged as SCAI shock stage A. The proportion of patients with SCAI shock stages A through E was 72.1%, 12.2%, 11.2%, 2.7%, and 1.8%, respectively.

Baseline demographics, comorbidities, and clinical presentations varied significantly across each of the SCAI shock stages as represented in Table 1 and Figure 3. The proportion of patients with a physical trigger was significantly higher in SCAI shock stages C, D, and E compared with stages A and B. LVEF on admission significantly decreased across SCAI stages, from 38.9% in stage A to 29.9% in stage E (Figure 4). The presence of other common echocardiographic findings in TTS, such as mitral regurgitation, right ventricular involvement, or LVOTO, was more prevalent as the SCAI stages increased. No significant association was found regarding TTS pattern or multiple comorbidities (with the exception of the classical cardiovascular risk factors) (Table 1).

Severity of Illness Scores, Vital Signs, Laboratory Data, and Therapies During Hospitalization

Hypotension, tachycardia, and hypoperfusion were significantly associated with higher SCAI stages. Mean lactate levels increased from 1.2 mmol/L in stage A to 8.3 mmol/L in stage E. Similar significant increases were also found with creatinine levels, peak troponin T, and NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels across SCAI stages (Table 2). Higher Shock Index scores and lower Glasgow Coma Scale scores were also associated with higher SCAI stages.

The number of vasoactive drugs, vasoactive inotropic score, and norepinephrine equivalent in the first 24 hours upon admission were strongly associated with higher stages of SCAI. Higher vasoactive inotropic score and norepinephrine equivalent were observed in the SCAI D group compared with the SCAI E group, probably related to the fact that a significant percentage of the patients in the SCAI E group were classified within it because they had presented an out-of-hospital cardiac arrest. The use of mechanical circulatory support (MCS) was low in the overall cohort. An intra-aortic balloon pump was placed in 24 patients, and Impella or extracorporeal membrane oxygenation support was used in 3 and 8 patients, respectively. Nonetheless, the use of all supportive therapies significantly increased across the SCAI shock stages.

In-Hospital Course

Death from any cause during hospitalization was significantly higher across SCAI shock stages. There was a progressive increase in unadjusted in-hospital mortality with each higher SCAI shock stage, rising from 2.3% in SCAI stage A to 71.4% in SCAI stage E (*P* for linear trend <0.001; Table 3). Although in the less severe stages of SCAI (A, B and C) the main cause of in-hospital mortality was noncardiovascular, in those patients who developed more profound CS (SCAI D and E), cardiovascular mortality was predominant (Table 3). Our data show that the main cause of intrahospital noncardiovascular death in patients with TTS were infections (45.0%), followed by malignancies (15.0%) and lung diseases (12.5%). The incidence of other complications, such as noncardiovascular death, atrial or ventricular arrythmias, major bleeding, infections, acute kidney injury, and length of hospital stay, was also directly associated with higher SCAI stages. No trend or significant association with higher SCAI stages was found for the incidence of stroke in this cohort (Table 3).

Figure 5 shows the evolution of patients in their SCAI stage from admission to 24 hours. Five patients died within 24 hours of admission. Figure 6 shows in-hospital mortality and 1-year mortality when the SCAI stage at admission versus SCAI stage at 24 hours were compared. The rates of 1-year mortality were slightly higher than those reported for in-hospital mortality across the subgroup of patients categorized in less severe shock stages (SCAI A, B, and C). However, the

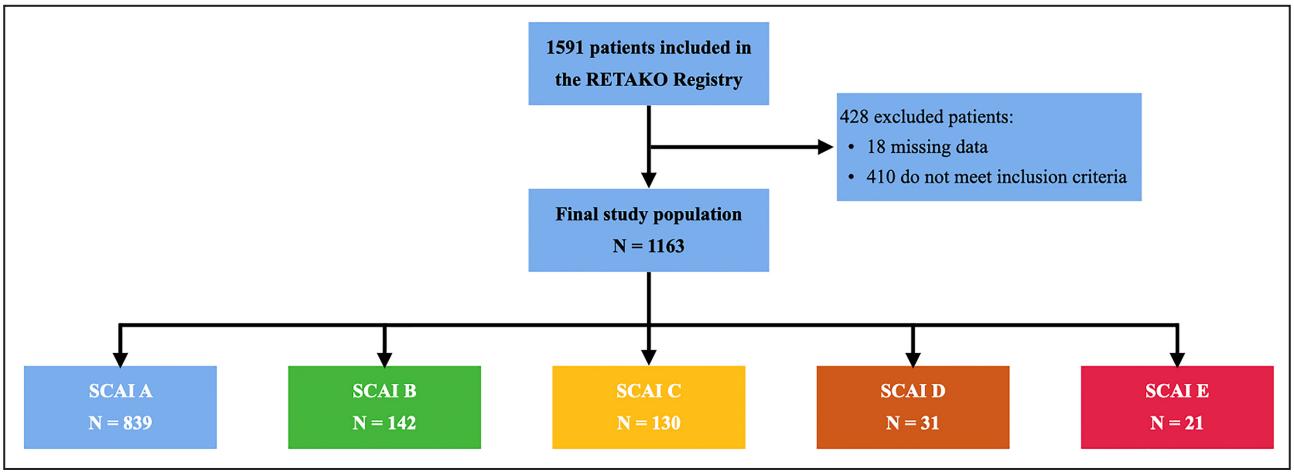

Figure 2. Algorithm of the study population.
RETAKO indicates Registry of Takotsubo Syndrome; and SCAI, Society for Cardiovascular Angiography and Interventions.

rates of in-hospital and 1-year mortality were similar for the patients cataloged as SCAI stage D and SCAI stage E. Among the 848 (75.7%) patients that remained within the same SCAI stage at 24 hours, 3.2% died during admission, compared with 1.3% of patients who died among the 157 (13.6%) patients who improved their SCAI stage at 24 hours. Instead, among the 125 (10.8%) patients whose SCAI stage worsened at 24 hours, mortality rates were 26.4% (odds ratio [OR], 10.9 compared with unchanged SCAI stage at 24 hours [95% CI, 6.28–18.8]).

Adjusted Analysis for In-Hospital Mortality

After adjusting for potential confounders in the multivariable analysis, the SCAI shock stage remained a significant predictor for in-hospital mortality (Table 4). Using SCAI shock A as a reference, the OR for in-hospital mortality increased in a stepwise fashion, with OR 1.77 (95% CI, 0.66–4.73), 2.20 (95% CI, 0.87–5.58), 5.86 (95% CI, 1.54–22.24), and 29.31 (95% CI, 6.99–122.97) for SCAI stages B, C, D, and E, respectively. The area under the curve for the final multivariable model to predict in-hospital mortality was 0.886 (95% CI, 0.837–0.934) in the overall population, with appropriate calibration (Hosmer–Lemeshow chi-square *P* value 0.86). When SCAI stage at admission was replaced within the model by SCAI stage at 24 hours, the model discrimination significantly improved to an area under the curve of 0.931 (95% CI, 0.888–0.974; De Long test *P* value of 0.010 when compared with the model using baseline SCAI stage).

DISCUSSION

The main conclusions of the present study can be summarized as follows: in a large multicenter registry on TTS (1) we validated the association between SCAI shock classification and hospital mortality and complications; (2) CS was a relatively common clinical complication; (3) overall, cardiovascular mortality was the leading cause of death in patients with TTS and CS; (4) the use of mechanical support in our cohort was very low; and (5) patients who remain in shock 24 hours after admission have higher mortality.

CS represents one of the leading causes of mortality in the acute phase and occurs in a considerable number of patients with TTS, with an incidence of ≈10%[13] The high rate of in-hospital mortality and the controversies regarding medical therapy emphasize the need for early identification of patients with TTS with initial signs of CS or at high risk of developing hemodynamic instability during hospitalization. Likewise, there are no established recommendations on medical management in these patients and some authors advocate avoiding positive inotropic drugs. We identified a continuum of significant increase in all-cause mortality across all the SCAI shock stages. Thus, this new approach for shock classification correlated well with mortality and adverse clinical outcomes in patients with TTS, and its use may help in the classification of these patients. We also observed that higher SCAI shock stages are significantly associated with features of clinical presentation of TTS that may be associated with a more severe presentation such as being older, male, physical triggers for TTS, lower LVEF, LVOTO, presence of mitral regurgitation, and right ventricular involvement. Severity illness scores, such as Shock Index and laboratory parameters of hypoperfusion, as well as the use of supportive therapies, were also directly associated with higher stages of SCAI.

In 2019, the SCAI proposed this new shock classification system in a consensus statement[8] and, to date, many studies have validated its use to effectively

Table 1. Baseline Characteristics and Clinical Presentation Across Each SCAI Shock Stage Group

	Stage A, N=839	Stage B, N=142	Stage C, N=130	Stage D, N=31	Stage E, N=21	*P* value
Age, y	72.3±11.2	70.2±12.6	69.8±13.6	66.4±14.2	64.9±12.0	0.001
Male sex	97 (11.6)	18 (12.7)	29 (22.3)	5 (16.1)	4 (19.0)	0.015
Hypertension	576 (68.7)	96 (67.6)	69 (53.1)	21 (67.7)	14 (66.7)	0.015
Diabetes	160 (19.1)	22 (15.5)	24 (18.2)	10 (32.3)	6 (28.6)	0.205
Smoking	191 (22.8)	32 (22.5)	43 (33.1)	6 (19.4)	10 (47.6)	0.009
Chronic kidney disease	30 (3.6)	9 (6.3)	4 (3.1)	2 (6.5)	2 (9.5)	0.192
Stroke/transient ischemic attack	65 (7.7)	12 (8.5)	9 (6.9)	4 (12.9)	2 (9.5)	0.947
Chronic obstructive pulmonary disease	180 (21.5)	37 (26.1)	36 (27.7)	8 (25.8)	5 (23.8)	0.456
Vascular disease	183 (21.8)	31 (21.8)	34 (26.2)	6 (19.4)	4 (19.0)	0.822
Ischemic heart disease	52 (6.2)	5 (3.5)	4 (3.1)	0 (0.0)	0 (0.0)	0.165
Stress trigger						
None	279 (33.2)	43 (30.3)	28 (21.5)	8 (25.8)	4 (19.0)	<0.001
Emotional	290 (34.6)	47 (33.1)	24 (18.5)	4 (12.9)	2 (9.5)	
Physical	270 (32.2)	52 (36.6)	78 (60.0)	19 (61.3)	15 (71.4)	
Clinical presentation						
Takotsubo syndrome pattern						0.206
Apical	759 (90.5)	121 (85.2)	114 (87.7)	24 (77.4)	17 (81.0)	
Midventricular	43 (5.1)	14 (9.9)	10 (7.7)	4 (12.9)	3 (14.3)	
Basal	8 (1.0)	5 (3.5)	2 (1.5)	1 (3.2)	0 (0.0)	
Focal	28 (3.3)	2 (1.4)	4 (3.1)	2 (6.5)	1 (4.7)	
LV ejection fraction at admission, %	38.9±9.7	36.9±11.6	33.2±10.8	31.3±10.1	29.9±12.7	<0.001
Severe mitral regurgitation	80 (9.7)	18 (12.7)	20 (15.6)	8 (26.7)	7 (33.3)	0.004
ST-segment elevation	450 (53.6)	69 (48.5)	68 (52.3)	15 (48.4)	11 (52.4)	0.854
LV outflow tract obstruction	106 (12.6)	16 (11.3)	28 (21.5)	7 (22.6)	7 (33.3)	0.002
Right ventricular involvement	12 (1.4)	6 (4.2)	7 (5.4)	5 (12.9)	4 (19.0)	<0.001
Prehospital cardiac arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (71.4)	<0.001
Charlson Comorbidity Index	4.1±1.9	4.0±2.1	4.0±2.1	4.1±2.5	4.1±2.4	0.904

Data are presented as mean±SD or n (%). LV indicates left ventricular; and SCAI, Society for Cardiovascular Angiography and Intervention.

stratify mortality risk.[9,10,14,15] However, this scale does not clarify which patients should be classified as stage A. There are also no data on how to do this in a patient profile as particular as TTS. Our proposal is to include in this category those patients who present an LVEF <45%, patients with the development of new severe valve disease, patients with ventricular arrhythmias, or patients with obstructive intraventricular gradient. In our cohort, of the 428 patients excluded from the analysis, as they did not meet the criteria to be included in any of the stages of the SCAI classification, only 1 patient died (0.2%).

The vast majority of patients with TTS were classified as hemodynamically stable (72% of the patients were categorized as SCAI A stage), with only 15.7% of the patients considered as being in established CS (SCAI C, D, or E). Regarding the baseline characteristics of our cohort, patients who presented with a presumed physical trigger as the cause for their TTS were more prevalent in higher SCAI shock stages, as the presumed physical trigger may possibly be correlated with higher rates of morbidity in these patients.[16,17] Also, cardiogenic shock in patients with TTS is frequently associated with dynamic LVOTO and severe mitral regurgitation, as well as LV systolic dysfunction.[4,18] These echocardiographic findings were also associated with more severe SCAI shock stages.

The rate of cardiac arrest in patients with TTS varies from different registries ranging from 5% to 10%.[19,20] In our cohort, the rate of prehospital cardiac arrest was low (≈1% in the overall cohort of patient with TTS) but is common in patients with CS. In addition, vital and laboratory data evidencing hemodynamic instability and hypoperfusion, as well as cardiac biomarkers, were also significantly associated with higher SCAI shock stages, reflecting more severe CS presentations.

Likewise, severity illness scores, number of vasoactive drugs, vasoactive inotropic score, and the use of supportive measures, such as MCS, mechanical ventilation, or renal replacement therapy, were also strongly

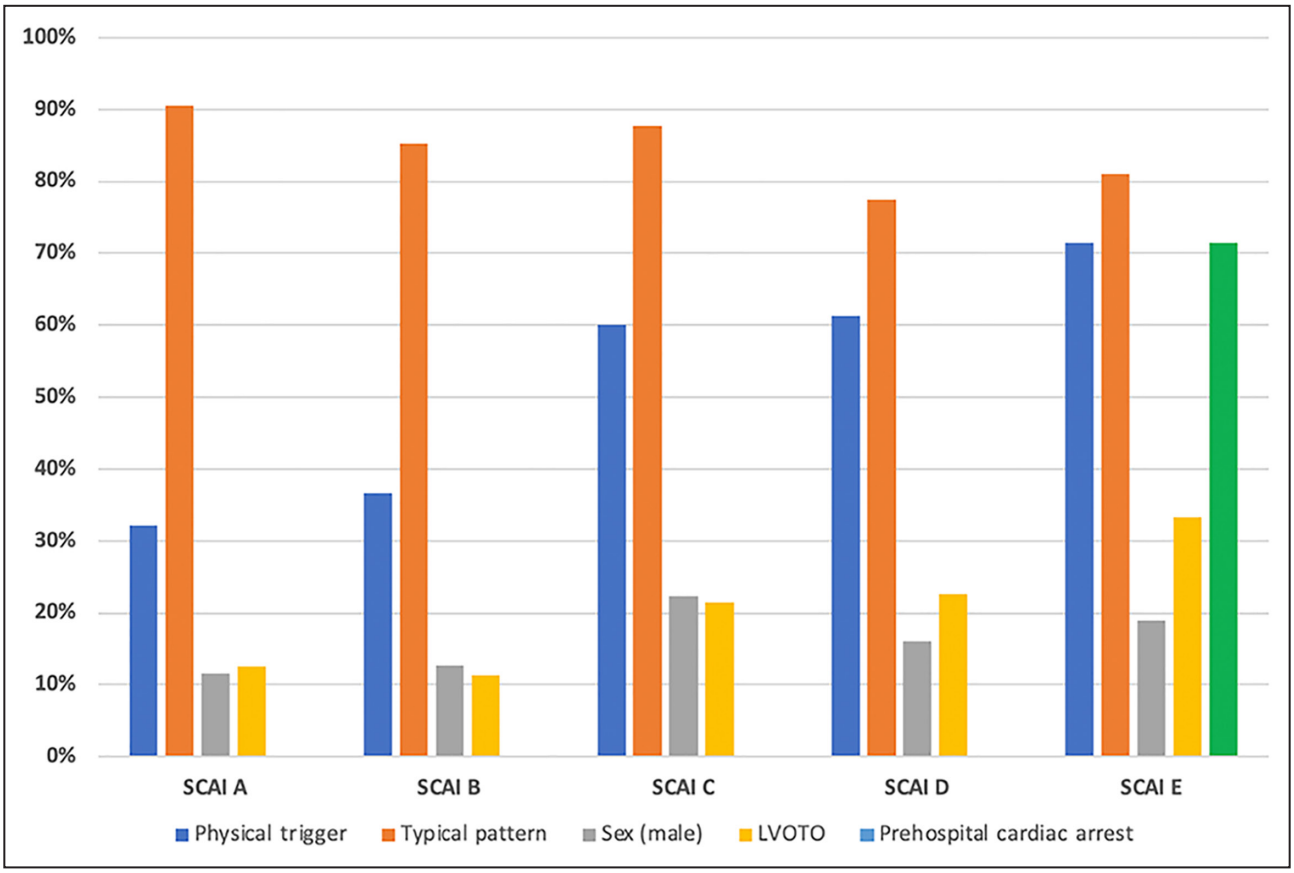

Figure 3. Main characteristics of patients with SCAI shock stages A through E at admission.
LVOTO indicates left ventricular outflow tract obstruction; and SCAI, Society for Cardiovascular Angiography and Interventions.

associated with higher stages of CS severity according to the SCAI classification. Of note, the use of MCS was low in the overall cohort, with less than half of patients with noncompensated CS (SCAI shock stages D and E) carrying any kind of mechanical support device. Previous metanalyses have proposed that MCS should be considered early in patients with TTS and CS to overcome limitations and risk of catecholamine use.[4,21] These findings can be justified for several reasons. On the one hand, it is not clear what type of device may

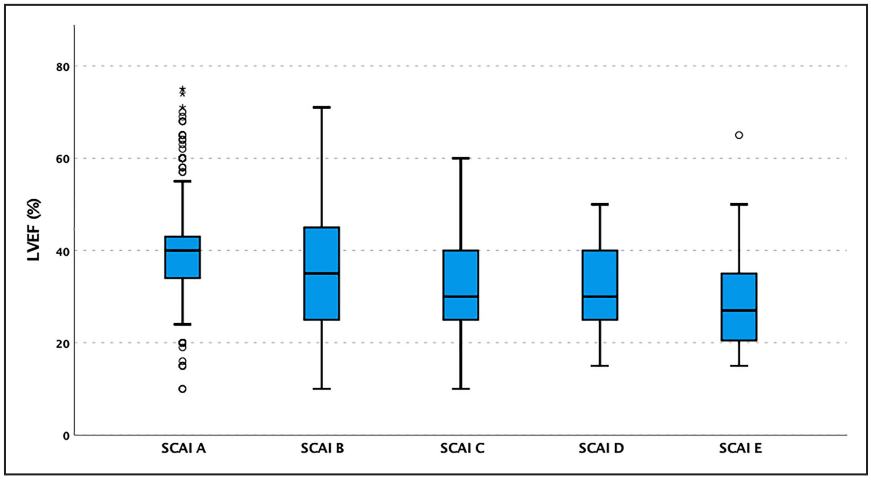

Figure 4. Variation of the left ventricular ejection fraction throughout the different SCAI stages.
LVEF indicates left ventricular ejection fraction; and SCAI, Society for Cardiovascular Angiography and Interventions.

Table 2. Severity of Illness Scores, Vital Signs, Laboratory Data, and Therapies of Patients According to SCAI Shock Stage

	Stage A, N=839	Stage B, N=142	Stage C, N=130	Stage D, N=31	Stage E, N=21	*P* value
Admission vital sign data						
Systolic BP, mm Hg	135±29	88±9	85±14	85±11	85±13	<0.001
Diastolic BP, mm Hg	77±16	54±7	50±8	51±8	51±10	<0.001
Mean arterial pressure, mm Hg	96±19	65±7	61±9	63±8	63±11	<0.001
Heart rate, beats/min	86±21	90±22	102±24	107±24	103±25	<0.001
Shock Index score	0.67±0.21	1.08±0.89	1.24±0.36	1.27±0.37	1.22±0.34	<0.001
Glasgow Coma Scale score	14.6±2.0	13.7±2.5	13.4±3.1	10.1±4.9	8.1±5.1	<0.001
Admission laboratory data						
Creatinine, mg/dL	0.92±0.77	1.06±1.31	1.11±0.74	1.83±1.51	2.06±0.40	<0.001
Serum urea nitrogen, mg/dL	37±26	39±25	45±49	74±52	105±35	<0.001
Peak troponin T, mg/dL	941±2300	1110±2007	1505±2320	1498±2351	2346±2326	0.001
Peak N-terminal pro-B-type natriuretic peptide, pg/mL	5720±8400	7660±10 700	12 247±15 810	15 249±20 140	22 348±10 687	<0.001
Hemoglobin, g/L	13.1±1.7	13.2±1.8	12.9±2.0	11.8±2.1	11.9±2.2	0.001
Platelets, 109x10 g/L	244±87	253±101	251±126	248±118	246±81	0.776
Lactate, mmol/L	1.2±0.5	1.7±1.1	3.1±0.94	5.9±1.6	8.3±3.7	<0.001
Lactate peak 24 h, mmol/L	1.3±1.1	1.9±1.4	3.9±1.7	9.2±5.7	10.0±3.6	<0.001
pH	7.34±0.18	7.39±0.12	7.33±0.12	7.20±0.11	7.18±0.14	<0.001
Therapies and procedures						
Number of vasoactives first 24 h	0.0±0.2	0.2±0.5	1.5±0.6	2.3±0.5	2.2±0.7	<0.001
Vasoactive inotropic score first 24 h	0.5±6.7	6.5±29.3	37.2±39.2	105.3±53.7	81.8±60.2	<0.001
Norepinephrine equivalent first 24 h	0.01±0.06	0.06±0.29	0.33±0.38	1.01±0.75	0.77±0.57	<0.001
Noninvasive mechanical ventilation	65 (7.7)	25 (17.6)	31 (23.8)	8 (25.8)	6 (28.6)	<0.001
Invasive mechanical ventilation	31 (3.7)	14 (9.9)	52 (40.0)	25 (80.6)	17 (81.0)	<0.001
Mechanical ventilation, d	5.8±5.1	3.3±3.6	5.4±8.8	10.4±13.5	12.7±15.1	<0.001
Dialysis	12 (1.4)	2 (1.4)	7 (5.4)	6 (19.4)	5 (23.8)	<0.001
Intra-aortic balloon pump	0 (0.0)	0 (0.0)	14 (10.8)	4 (12.9)	4 (19.0)	<0.001
Impella	0 (0.0)	0 (0.0)	3 (2.3)	0 (0.0)	0 (0.0)	<0.001
Extracorporeal membrane oxygenation	0 (0.0)	0 (0.0)	1 (0.8)	5 (16.1)	2 (22.2)	<0.001
Mechanical support, days	0±0	0±0	3.3±1.2	5.3±4.4	5.6±5.3	0.006

Data are presented as mean±SD or n (%). BP indicates blood pressure; and SCAI, Society for Cardiovascular Angiography and Interventions.

be most useful in this context. In patients with LVOTO, intra-aortic balloon pump is contraindicated, and depending on the echocardiographic pattern, it may be difficult to achieve correct placement of the Impella to avoid suction events. On the other hand, patients with TTS tend to be older and have a greater number of comorbidities, which often restricts the use of these devices. It should also be noted that in Spain the use of mechanical support devices in CS is less frequent than in the United States.

In-hospital mortality in patients classified as being at risk of CS due to an acute condition such as TTS while maintaining hemodynamic stability (SCAI shock stage A) was low, ≈2.3%, meaning that more than two thirds of the cohort had a favorable prognosis. This mortality risk increased in patients cataloged as the next SCAI shock stage (B *beginning*) with signs of hemodynamic instability but without hypoperfusion and increased again (2 times higher than SCAI stage A) in patients showing signs of hypoperfusion with established *classic* CS (SCAI shock stage C). Patients with CS and deterioration (SCAI shock stage D), and patients with refractory or extremis CS (SCAI shock stage E), had a higher crude hospital mortality. This exponential mortality increase, especially seen in the CS stages with progressive deterioration (SCAI shock stages D and E) and unresponsiveness to initial stabilization measures, reflects the need for early identification and consideration of advanced hemodynamic support or early transfer to a higher level of care. This

Table 3. In-Hospital Course Across Each SCAI Shock Stage Group

	Stage A, N=839	Stage B, N=142	Stage C, N=130	Stage D, N=31	Stage E, N=21	*P* value
Death	19 (2.3)	7 (4.9)	14 (10.8)	13 (41.9)	15 (71.4)	<0.001
Cardiovascular	1 (5.3)	3 (42.9)	6 (42.8)	7 (53.8)	11 (73.3)	<0.001
Noncardiovascular	18 (94.7)	4 (57.1)	8 (57.1)	6 (46.2)	4 (26.7)	<0.001
Infection	7 (38.9)	2 (50.0)	6 (75.0)	1 (16.7)	2 (50.0)	
Malignancies	4 (22.2)	0 (0.0)	1 (12.5)	1 (16.7)	0 (0.0)	
Respiratory diseases	2 (11.1)	0 (0.0)	0 (0.0)	1 (16.7)	2 (50.0)	
Digestive diseases	2 (22.2)	1 (25.0)	0 (0.0)	1 (16.7)	0 (0.0)	
Others	3 (16.6)	1 (25.0)	1 (2.5)	2 (33.3)	0 (0.0)	
Ventricular arrhythmias	30 (3.6)	8 (5.6)	15 (11.5)	5 (16.1)	5 (23.8)	<0.001
Asystole/atrioventricular block	21 (2.5)	4 (2.8)	6 (4.6)	1 (3.2)	3 (14.3)	0.026
Atrial fibrillation	100 (11.9)	14 (9.9)	28 (21.5)	9 (29.0)	3 (14.3)	0.002
Major bleeding	22 (2.6)	5 (3.5)	10 (7.7)	3 (9.7)	8 (38.1)	<0.001
Infection	140 (16.7)	30 (21.1)	52 (40.0)	12 (38.7)	8 (38.1)	<0.001
Acute kidney failure	32 (3.8)	10 (7.0)	46 (35.4)	31 (100)	16 (76.2)	<0.001
Stroke	25 (3.0)	1 (0.7)	6 (4.5)	3 (8.3)	0 (0.0)	0.117
In-hospital, d	9.8±13.3	10.9±12.7	15.7±15.6	23.7±26.3	17.9±17.9	<0.001

Data are presented as mean±SD or n (%). SCAI indicates Society for Cardiovascular Angiography and Interventions.

mortality increase across each of the SCAI stages is in line with previously reported results.[10] Furthermore, in-hospital mortality rates for patients with TTS among each SCAI shock stage in this study (2.3% for SCAI A, 4.9% for SCAI B, 10.8% for SCAI C, 41.9% for SCAI D, and 71.4% for SCAI E) are consistent with and similar to previously described mortality rates in patients with CS for any cause.[22,23] Furthermore, our data reveal that patients who persist in CS 24 hours after admission experience higher mortality, and this

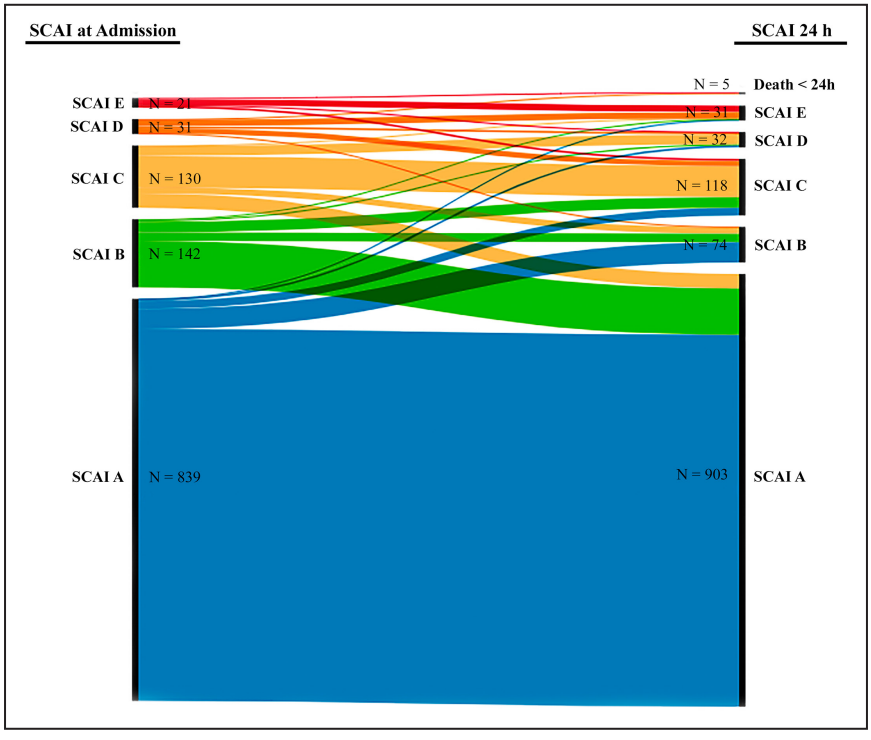

Figure 5. Alluvial diagram showing the change in patients' SCAI stage from admission to 24 hours.
SCAI indicates Society for Cardiovascular Angiography and Interventions.

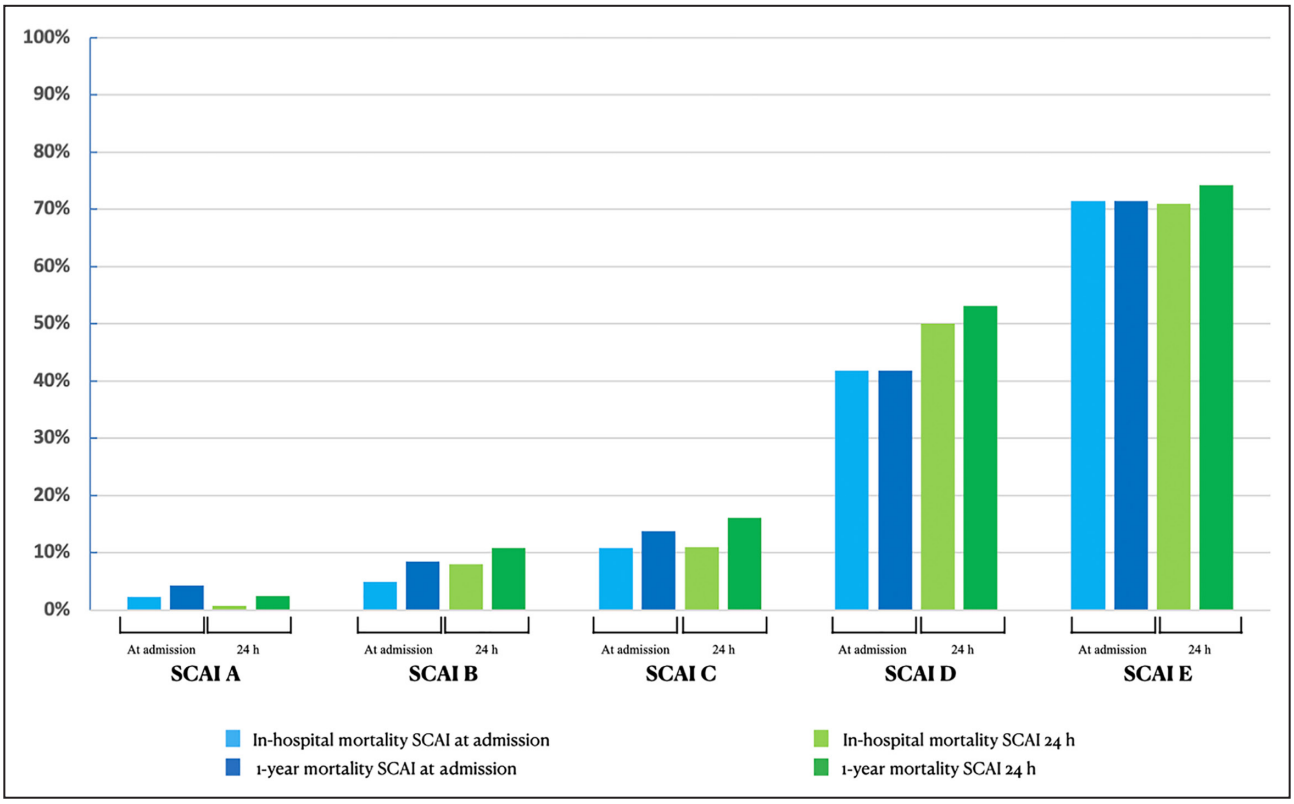

Figure 6. In-hospital and 1-year mortality as a function of SCAI shock stage at admission and 24 hours later.
SCAI indicates Society for Cardiovascular Angiography and Interventions.

mortality is also influenced by their SCAI stage at that time. Consequently, employing this classification in an evolving manner at the 24-hour mark enhances its ability to predict the life prognosis of these patients. Hence, it proves to be a highly valuable tool for identifying at-risk patients and assessing prognosis based on the initial clinical response to the medical treatment employed. It is important to emphasize that the increase of in-hospital mortality among SCAI shock stages remained significant after adjusting for known predictors of mortality such as age, the Charlson Comorbidity Index, norepinephrine equivalent, and mechanical ventilation. This underscores the applicability of this CS classification in patients with TTS.

The mortality increase across SCAI stages was mostly driven by an increase of in-hospital mortality. In-hospital and 1-year mortality rates were the same in the subgroups of patients with more severe CS (SCAI D and E) compared with patients with mild or no CS (SCAI A, B and C) who had slightly higher rates of 1-year mortality than in-hospital mortality (Figure 5). This may be due to the fact that patients in the SCAI stages D and E have a much higher chance of dying during hospitalization due to CS and other associated complications. It is relevant to highlight a higher percentage of noncardiovascular in-hospital mortality in those patients with less severe CS. Of the 30 patients who died of noncardiovascular causes in the group of patients with SCAI A-B-C, 20 (66.7%) presented a physical trigger and had higher Charlson Comorbidity Index (5.71 versus 5.02, P=0.387); therefore, it is likely that TTS may reflect greater severity of the underlying disease. However, in those patients with more profound CS, cardiovascular mortality was more frequent. Although in this group of patients (SCAI D and E), 71.4% had a physical trigger, the greater severity of CS, as well as a higher incidence of out-of-hospital cardiac arrest, influenced this higher percentage of cardiovascular mortality. Previous studies have already shown higher short- and long-term mortality of patients with TTS with physical triggers.[16]

Limitations

Our study has certain inherent limitations due to its retrospective nature that should be considered when interpreting the results, including possible missing data and selection bias limiting its generalizability. The lack of available invasive hemodynamic data may have limited the correct diagnosis of cardiogenic shock with misclassification of other types of non-CS as CS. Because of its observational nature, unmeasured confounding variables may have influenced the results. To try to

Table 4. Univariate and Multivariable Analysis of Variables Related to In-Hospital Mortality in Patients With CS and TTS

	Univariable		Multivariable	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (per 1-y increase)	1.02 (1.00–1.05)	0.087	1.04 (1.00–1.08)	0.040
Male sex	1.96 (1.08–3.58)	0.028	…	…
Type of trigger			…	…
No trigger	1.00 (reference)	…	…	…
Psychological trigger	0.48 (0.22–1.04)	0.062	…	…
Physical trigger	1.64 (0.94–2.87)	0.087	…	…
Charlson Comorbidity Index (per 1-point increase)	1.38 (1.23–1.54)	<0.001	1.39 (1.20–1.61)	<0.001
LV ejection fraction (per 1-point increase)	0.95 (0.93–0.98)	<0.001	…	…
Right ventricle involvement	2.30 (0.78–6.73)	0.130	…	…
Lactate (per 1 mmol/L)	1.66 (1.47–1.87)	<0.001	…	…
Shock Index (per 1-point increase)	2.02 (1.07–3.83)	0.031	…	…
Invasive mechanical ventilation	14.37 (8.50–24.30)	<0.001	4.47 (1.95–10.23)	<0.001
Norepinephrine equivalent (per 1-point increase)	14.51 (8.06–26.12)	<0.001	2.97 (1.30–6.81)	0.010
LV outflow tract obstruction	1.48 (0.79–2.77)	0.225	…	…
Acute renal failure	11.3 (6.74–19.0)	<0.001	…	…
Mechanical support	4.14 (1.64–10.47)	0.003	…	…
SCAI stage				
SCAI A	1.00 (ref)	…	1.00 (ref)	…
SCAI B	2.34 (0.92–5.42)	0.075	1.77 (0.66–4.73)	0.257
SCAI C	5.21 (2.54–10.67)	<0.001	2.20 (0.87–5.58)	0.095
SCAI D	31.1 (13.4–72.6)	<0.001	5.86 (1.54–22.24)	0.009
SCAI E	107.9 (37.7–308.4)	<0.001	29.31 (6.99–122.97)	<0.001

CS indicates cardiogenic shock; LV, left ventricular; OR, odds ratio; SCAI, Society for Cardiovascular Angiography and Interventions; and TTS, Takotsubo syndrome.

overcome this limitation, we performed a multivariable analysis adjusting for many variables considered as possible confounders. Also, despite a large number of patients included in the study cohort, there was a low proportion of patients included in SCAI shock stages D and E, and a low proportion of patients in these stages were treated with MCS, which may have influenced the study findings. Therefore, considering these limitations, the results of this study should be interpreted with caution as prospective validation is needed.

CONCLUSIONS

In a large and multicenter cohort of patients diagnosed with TTS, we proved the utility and prognostic association of the novel classification of the 5 shock stages proposed by the SCAI. In our study, this SCAI shock stage classification reflected a continuum of increasing shock severity and was associated with higher in-hospital mortality across each shock stage (A through E). Therefore, for patients with TTS, this functional SCAI shock stage classification system effectively stratified mortality risk and could easily be applied when treating patients with TTS for risk stratification to improve early recognition of CS and treatment decisions, as well as standardize transfer and research protocols.

ARTICLE INFORMATION

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Affiliations

Cardiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain (A.C.-B., E.R.-A., M.T., A.U.); Instituto Cardiovascular, Hospital Clínico San Carlos, Universidad Complutense, Madrid, Spain (I.J.N.-G., O.V., R.V.); Universidad Europea, Madrid, Spain (I.J.N.-G., O.V., R.V.); Cardiology Department, Hospital de Sant Pau, Barcelona, Spain (A.D.C.); Cardiology Department, Hospital Universitario Virgen Macarena, Sevilla, Spain (M.A.-D.); CIBERCV, Madrid, Spain (E.R.-A., A.U.); Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain (C.F.-C.); Cardiology Department, Complejo Hospitalario de Albacete, Albacete, Spain (M.C.-P.); Cardiology Department, Hospital Universitario Arnau de Vilanova, Lérida, Spain (E.B.-P.); Cardiology Department, Hospital Álvaro Cunqueiro, Vigo, Pontevedra, Spain (S.R.-R.); Cardiology Department, Hospital Joan XXIII, Tarragona, Spain (M.G.M.); Cardiology Department, Hospital Universitario de Canarias, La Laguna, Spain (A.S.G.F.); Cardiology Department, Hospital Clinico Universitario de Santiago de Compostela, Santiago de Compostela, Spain (J.M.G.A.); Cardiology Department, Hospital Universitario de La Princesa, Instituto de Investigación Sanitaria Princesa (IIS-IP), Madrid, Spain (J.S.); Cardiology Department, Hospital Puerta de Hierro, Majadahonda, Spain (J.M.E.-V.); Cardiology Department, Complejo Asistencial Universitario

de Salamanca, Salamanca, Spain (A.C.M.-G.); Servicio de Cardiología, Instituto de Investigación Sanitaria Islas Baleares (IdISBa), Hospital Universitario Son Espases, Palma, Spain (A.P.-C.); and Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain (A.U.).

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Disclosures

None.

Supplemental Material

Table S1

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