Comparison of Outcomes in Patients With Takotsubo Syndrome With-vs-Without Cardiogenic Shock

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There is limited data on the in-hospital outcomes of cardiogenic shock (CS) secondary to takotsubo syndrome (TS). We aimed to assess the incidence, predictors, and outcomes of CS in hospitalized patients with TS. All patients with TS were identified from the National Inpatient Sample database from September 2006 to December 2017. The cohort was divided into those with versus without CS and logistic regression analysis was used to identify predictors of CS and mortality in patients admitted with TS. A total of 260,144 patients with TS were included in our study, of whom 14,703 (6%) were diagnosed with CS. In-hospital mortality in patients with CS was approximately six-fold higher compared with those without CS (23% vs 4%, p <0.01). TS patients with CS had a higher incidence of malignant arrhythmias like ventricular tachycardia or ventricular fibrillation (15.0% vs 4%, p <0.01) and non-shockable cardiac arrests (12% vs 2%, p <0.01). Independent predictors of CS were male gender, Asian and Hispanic ethnicity, increased burden of co-morbidities including congestive heart failure, chronic pulmonary disease, and chronic diabetes. Independent predictors of mortality were male gender, advanced age, history of congestive heart failure, chronic renal failure, and chronic liver disease. In conclusion, CS occurs in approximately 6% of patients admitted with TS, in-hospital mortality in TS patients with CS was approximately six-fold higher compared with those without CS (23% vs 4%, p <0.01), male gender and increased burden of co-morbidities at baseline were independent predictors of CS and mortality.   © 2020 Elsevier Inc. All rights reserved. (Am J Cardiol 2020;136:24−31)

Takotsubo syndrome (TS) is a neurologically mediated acute heart failure syndrome characterized by transient reversible left ventricular dysfunction affecting more than 1 coronary artery territory in a circumferential distribution.[1,2] The syndrome is classically associated with a lack of culprit lesion on coronary angiography and is often triggered by physical or emotional stress.[2] TS is variably referred to as stress cardiomyopathy, apical ballooning syndrome, or broken heart syndrome and is increasingly recognized in approximately 2% of patients initially presenting with acute coronary syndromes.[2−4] It was initially thought to be a benign disease characterized by complete recovery and favorable overall prognosis, however, contemporary studies have shown that TS can be associated with several acute complications including heart failure, cardiogenic shock (CS), malignant arrhythmias, left ventricular thrombus with thromboembolism, and stroke.[5] Moreover, acute and long-term mortality associated with TS is comparable to acute coronary syndromes.[6−9] There is paucity of real-world data on the trends, predictors, and outcomes of CS in patients with TS. Our objective is to assess these parameters from a large nationally representative sample of hospitalized patients in the United States.

Methods

The National inpatient sample (NIS) is the largest publicly available all-payer administrative claims-based database and is a part of Healthcare Cost and Utilization Project databases. These data are stratified to represent 20% of US inpatient hospitalizations across different hospitals and geographic regions (random sample). National estimates of the entire US hospitalized population were calculated using discharge weights provided. NIS has data on demographics (age, gender, race, and ethnicity), hospital characteristics, income, and insurance status in addition to diagnostic and procedural fields.[10] Standard Elixhauser co-morbidities were used in basleine tables and for regression anaylsis.[11] Institutional review board approval and informed consent were not required for this study given the de-identified nature of the NIS database and public availability.

We analyzed NIS data from September 2006 to December 2017 using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes and International Classification of Diseases, 10th Revision, Clinical Modification ICD-10-CM codes (ICD-10-CM). All patients with TS who are 18 years and older were identified using ICD-9-CM code of 429.83 & ICD-10-CM code of I51.81. The study cohort was then divided into 2 groups (TS with CS vs without CS). CS was identified using ICD-9-CM of 785.51 and ICD-10-CM of R57.0 (Figure 1). Patients without CS but

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National Inpatient sample for all hospitalization from year October 2006 to December 17 was queried to identify Takotsubo cardiomyopathy who are 18 years and older using ICD-9-CM code of 429.83 and ICD-10-CM code of I51.81

Total of weighted 265,423 cases identified

Patients without cardiogenic shock but with concomitant codes suggesting possibility of shock (vasopressors [0017,3E033XZ, 3E043XZ], Intra-aortic balloon pump [P3761,5A02110,5A02210] and percutaneous ventricular assist devices [3768, 02HA3RZ,5A0221D]) were removed from analysis

Total of weighted 260,144 cases identified

Cardiogenic shock population was identified using ICD-9-CM of 785.51 and ICD-10-CM of R57.0.

14,703 patients had cardiogenic shock
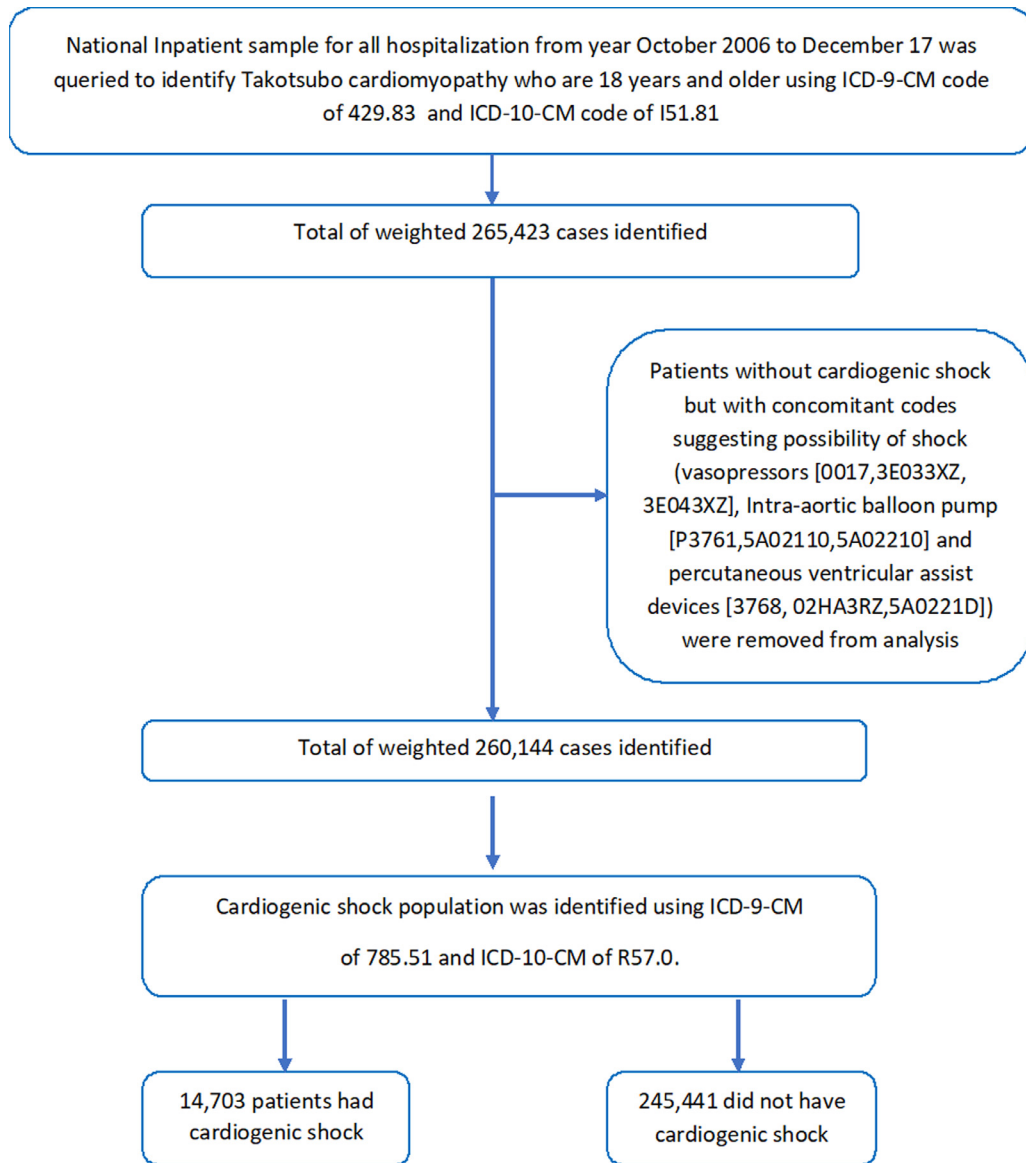
245,441 did not have cardiogenic shock

Figure 1. Flow chart of our paper.

with concomitant codes suggesting possibility of shock were removed from analysis (concomitant codes for vasopressors [0017, 3E033XZ, 3E043XZ], Intra-aortic balloon pump [P3761, 5A02110, 5A02210], and percutaneous ventricular assist devices [3768, 02HA3RZ, 5A0221D]).The primary end point of the study was the incidence of CS and mortality in patients admitted with TS and to study the temporal trends in these complications over time. Secondary end points were surrogates of severe disability, cost of hospitalization, and length of stay in TS with CS compared with those without CS. Descriptive statistics were presented as frequencies with percentages for categorical variables and as medians with interquartile range (IQR) for continuous variables. Baseline characteristics were compared using a Pearson chi-squared test and independent samples *t* test for continuous variables. Mann Whitney U test was used for comparing medians.

Initially, binomial logistic regression model was used to identify variables from demographic data (Table 1) that were significantly associated with patient mortality ($p < 0.05$). These variables were then subsequently utilized in a multiple forward entry stepwise logistic regression model (with removal for $p > 0.1$) to identify predictors of CS in TS cohort. Forward entry stepwise logistic regression model (with removal for $p > 0.1$) was also used to identify predictors of mortality in study cohort. For this study, a $p < 0.05$ was considered statistically significant. All statistical analyses were performed using statistical package for social science (SPSS) version 26 (IBM Corp) and R studio 3.5.

Results

Our total cohort included 260,144 patients with TS of whom 14,703 (6%) were diagnosed with CS . The baseline characteristics are shown in (Table 1). In our total study cohort of 260,144 patients with TS, mortality was approximately 5% (12,367). In-hospital mortality in patients with

Table 1
Baseline characteristics of study cohort

Variable	Cardiogenic Shock		p Value
	No (n = 245,441)	Yes (n = 14,703)	
Median age, (years)	68 (58−78)	67 (57−75)	p<0.01
Women	212,191 (87%)	11,621 (79%)	p<0.01
White	184,284 (82%)	10,469 (78%)	p<0.01
Black	16,627 (7%)	1,025 (7%)	
Hispanic	12,935 (5%)	857 (6%)	
Asians	4,266 (2%)	431 (3%)	
Others	13,16 (0.6%)	531 (4.0%)	
Atrial fibrillation	45,075 (18%)	3,695 (25%)	p<0.01
Non-shockable Arrests	5,140 (2%)	1,790 (12%)	p<0.01
Ventricular flutter, ventricular fibrillation, and Ventricular Tachycardia	10,786 (4%)	2,209 (15%)	p<0.01
Acquired immune deficiency syndrome	233 (0.1%)	20 (0.1%)	0.16
Alcohol abuse	10,656 (5%)	827 (6%)	p<0.01
Anemias	43,981 (19%)	3,410 (24%)	p<0.01
collagen vascular diseases	12,441 (5%)	544 (4%)	p<0.01
Congestive heart failure	99,765 (41%)	9,658 (66%)	p<0.01
Chronic pulmonary disease	69,237 (29%)	4,403 (31%)	p<0.01
Coagulopathy	13,611 (6%)	2,896 (20%)	p<0.01
Depression	41,528 (18%)	1,837 (13.0%)	p<0.01
Diabetes, uncomplicated	39,843 (17%)	2,144 (15%)	p<0.01
Diabetes with chronic complications	13,092 (5%)	1,055 (7%)	p<0.01
Drug abuse	9,839 (4%)	843 (6%)	p<0.01
Hypertension	149,642 (63%)	7,023 (50%)	p<0.01
Hypothyroidism	43,197 (18%)	2,032 (14%)	p<0.01
Liver disease	7,107 (3.0%)	749 (5%)	p<0.01
Lymphoma	2,205 (1%)	168 (1.5%)	p<0.01
Metastatic cancer	5,456 (2%)	456 (3%)	p<0.01
Cerebrovascular disease	17,680 (7%)	1,634 (11%)	p<0.01
Coronary artery disease	98,297 (40.0%)	5,082 (35%)	p<0.01
Smokers	40,231 (16%)	2,471 (17%)	0.19
Obesity	23,917 (10%)	1,394 (10%)	0.32
Paralysis	6,984 (3%)	591 (4%)	p<0.01
Peripheral vascular disorders	19,379 (8%)	1,402 (10%)	p<0.01
Psychoses	11,515 (5%)	589 (4%)	p<0.01
Pulmonary circulation disorders	6,817 (3%)	655 (5%)	p<0.01
Renal failure	26,328 (11%)	1,874 (13%)	p<0.01
Solid tumor without metastasis	5,325 (2%)	439 (3%)	p<0.01
Weight loss	20,535 (9%)	2,689 (19.0%)	p<0.01
Insurance/payer			
Medicare	154,569 (63%)	8,549 (58%)	p<0.01
Medicaid	20,731 (9%)	1,600 (11%)	
Private insurance	56,476 (23%)	3,716 (25%)	
Self-pay	7,703 (3%)	449 (3%)	
No charge/Others	5,696 (2%)	366 (3%)	
Household income (percentile)			
0−25th	59,981 (25%)	3,499 (24%)	0.04
26−50th	62,511 (26%)	3,762 (26%)	
51−75th	61,519 (26%)	3,619 (25%)	
76−100th	57,246 (24%)	3,571 (2%)	
Urban versus rural hospital			
Rural	16,861 (7%)	515 (4%)	p<0.01
Urban non-teaching	71,229 (29%)	3,411 (23%)	
Urban teaching	157,352 (64%)	10,776 (73%)	
Hospital size			
Small	30,832 (13%)	1,260 (9%)	p<0.01
Home	64,156 (26%)	3,261 (22%)	
Large	150,453 (61%)	10,182 (69%)	

Table 2
Outcomes of study cohort

Variable	Cardiogenic Shock		p Value
	No (n = 245,441)	Yes (n = 14,703)	
Died	9,004 (4%)	3,363 (23%)	p<0.01
Home	144,456 (59%)	4,186 (29%)	
Short term Rehab	6,300 (3%)	743 (5%)	
Skilled nursing facility	47,543(19%)	4,195 (29%)	
Home with home health	36,538 (15%)	2,137 (14%)	
Against medical advice	1,448 (0.6%)	69 (0.5%)	
Resource utilization and procedures			
Median (IQR) cost $	39,560 (23,371−72,442)	116,860 (63,732−219,886)	p<0.01
Median (IQR) length of stay, days	4 (2−7)	9(5−15)	p<0.01
Ventilator use	33,048 (14%)	9,577 (65%)	p<0.01
PEG	3,891 (2%)	707 (5%)	p<0.01
Tracheostomy	1,966 (1%)	604 (4%)	p<0.01
IABP	-	3,167 (22%)	p<0.01
pVADS	-	411 (3%)	p<0.01
Vasopressors	-	1,842 (13%)	p<0.01

Abbreviations: IABP = Intra-aortic balloon pump; PEG = Percutaneous gastrostomy tube; pVADS = Percutaneous ventricular assist devices.

TS-CS was almost six-fold higher compared with those without CS (23% vs 4%, p <0.01). CS patients also had a much higher burden of resource utilization, including use of mechanical ventilation (65.1% vs 13.5%, p <0.01), tracheostomy (4.1% vs 0.8%, p <0.01). Patients with CS also had a longer median length of stay (9 [IQR, 5 to 15] days vs 4 [IQR, 2 to 7] days, p <0.01) and a higher median cost of stay ($116,860 [IQR, 63,732 to 219,886], vs ($39,560 [IQR, 23,371 to 72,442], p <0.01). Patients with CS were less likely to be discharged home (28.5% vs 58.9%, p <0.01) and more likely to be discharged to short term rehabilitation facility (5.1% vs 2.6%, p <0.01) or skilled nursing facility (28.6% vs 19.4%, p <0.01) (Table 2).

Our analysis showed a significant uptrend in CS in patients with TS (Figure 2). There has been uptrend in mortality in patients admitted with TS and CS during our study period from 16% in 2007 to 25 % in 2017 (p <0.01) (Figure 3). Mean length of stay and mean cost of stay have also continued to increase in TS patients with CS during study period (2007 to 2017; from 8 days to 11 days and 103,034$ to 207,270$ respectively) (Figure 4). Also, the use of Intra-Aortic Balloon Pump (IABP) in CS patients has shown a significant decrease from 2007 to 2017 (38.3% to 13.3%, p <0.01) with a simultaneous increase in the use of percutaneous ventricular assist devices (pVAD) (0.7% to 4.9%, p <0.01) (Figure 4).

In regression analysis, independent predictors of CS were male gender (odds ratio [OR], 1.2, 95% confidence interval [CI] [1.15 to 1.23], p <0.01), Asian (OR, 1.37, 95% CI [1.23 to 1.53], p <0.01), Hispanic ethnicity (OR 1.08, 95% CI [1.00 to 1.169], p <0.01), history of congestive heart failure (OR, 1.52, 95% CI [1.45 to 1.58], p <0.01), chronic pulmonary disease (OR 1.10, 95% CI [1.07 to 1.16], p <0.01), cerebrovascular disease (OR, 1.25, 95% CI [1.17 to 1.33], p <0.01), chronic diabetes (OR, 1.13, 95% CI [1.06 to 1.22], p <0.01),obesity (OR, 1.07, 95% CI [1.01
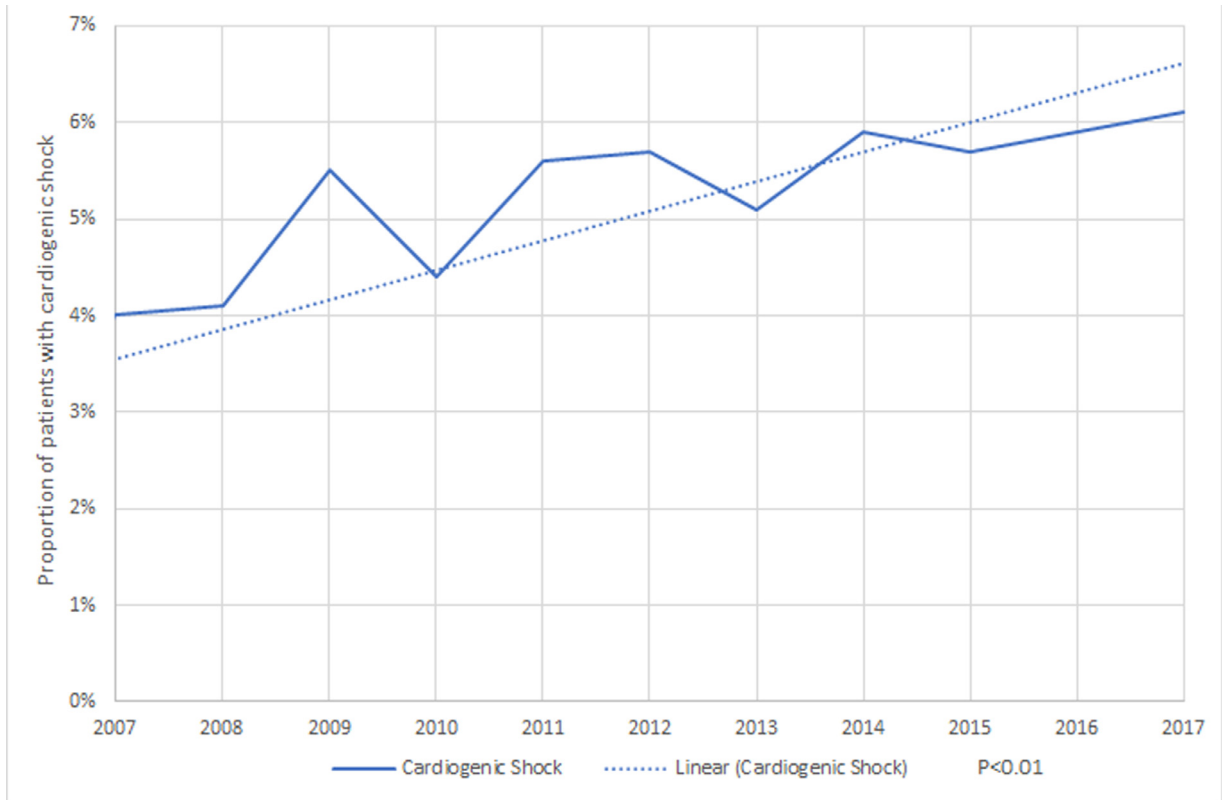
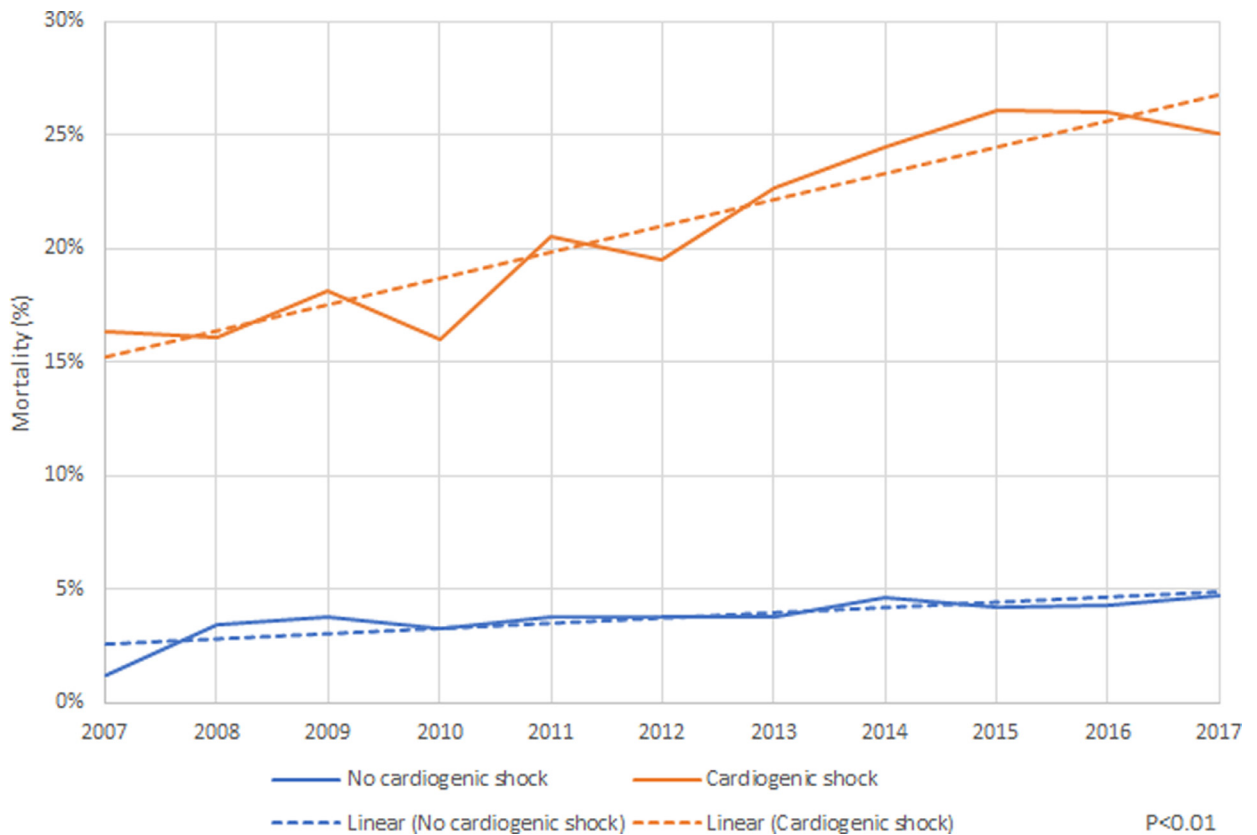Figure 2. Trends in Proportion of cardiogenic shock in Takotsubo Syndrome.

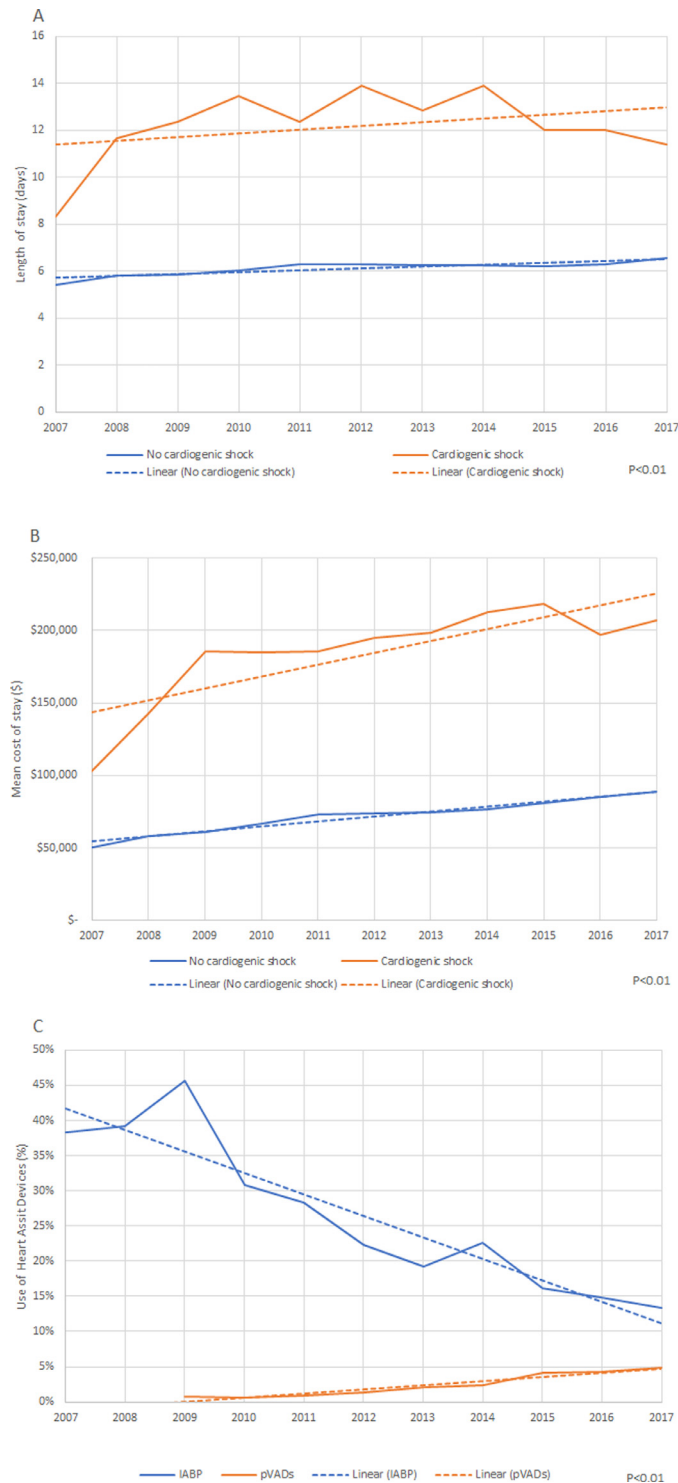Figure 3. Trends in mortality in Takotsubo Syndrome.

Figure 4. (A) Trends in mean length of stay in Takotsubo syndrome. (B) Trends in mean cost of stay in Takotsubo syndrome. (C) Trends in use of heart assist devices in Takotsubo syndrome.

to 1.15], p <0.01) and peripheral vascular disease (OR, 1.30, 95%CI [1.31 to 1.28], p <0.01) (Figure 5). Independent predictors of mortality in our analysis were male gender (OR, 1.78, 95% CI [1.70 to 1.85], p <0.01), advanced age (OR, 1.02, 95% CI [1.01 to 1.02], p <0.01), congestive heart failure (OR, 1.36, 95% CI [1.30 to 1.42], p <0.01), coagulopathy (OR, 2.35, 95%CI [2.23 to 2.48], p <0.01),

chronic liver disease (OR, 1.53, 95% CI [1.41 to 1.67], p <0.01), chronic renal failure (OR, 1.2, 95% CI [1.16 to 1.30], p <0.01), cerebrovascular disease (OR, 2.6, 95% CI [2.48 to 2.75], p <0.01), and peripheral vascular disease (OR, 1.34, 95% CI [1.26 to 1.43], p <0.01). On the contrary, factors associated with lower risk of in-hospital mortality in TS include female gender (OR, 0.56, 95% CI [0.54
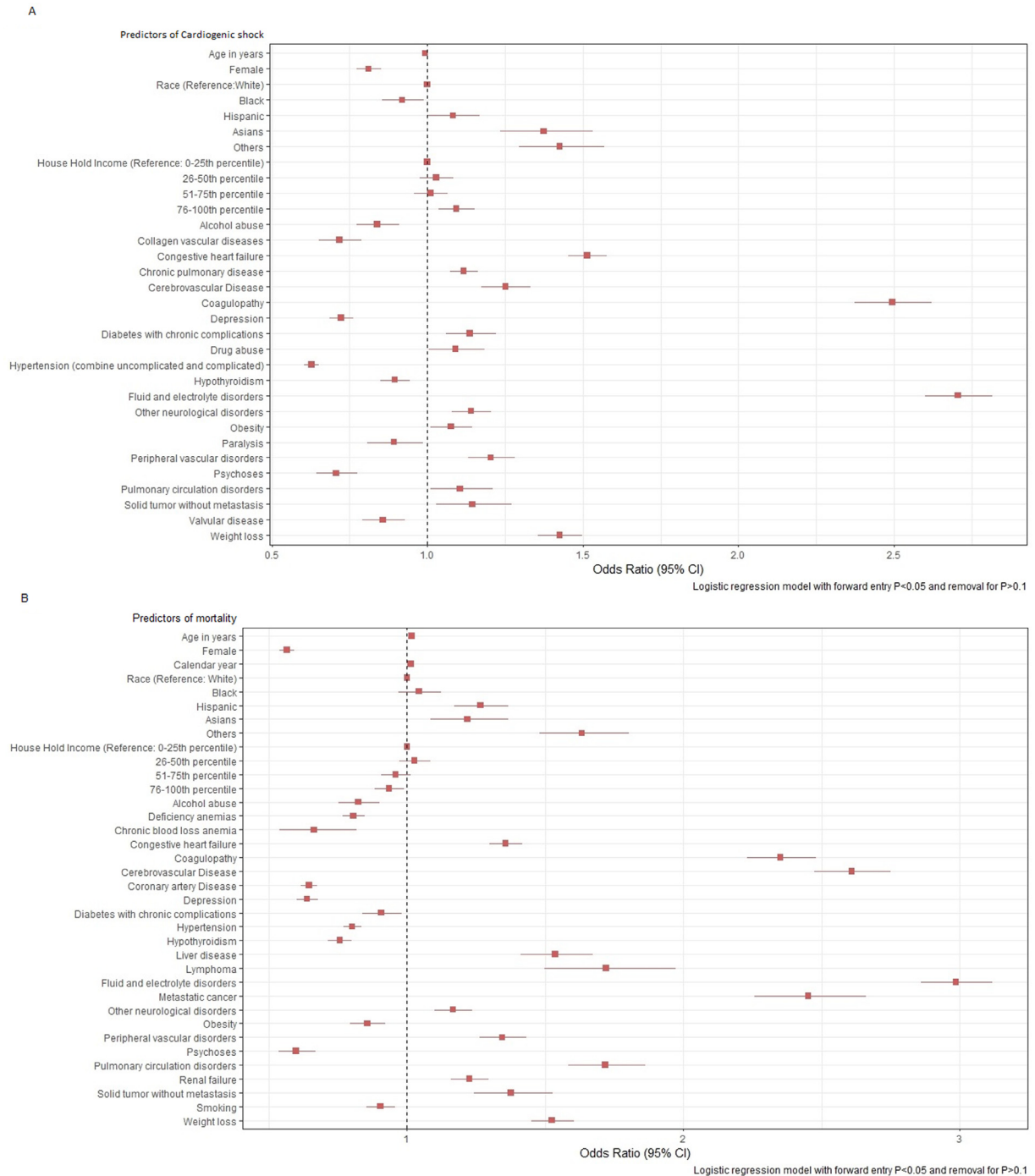
Figure 5. (A) Predictors of cardiogenic shock in Takotsubo syndrome. (B) Predictors of mortality in Takotsubo syndrome.

to 0.59], p <0.01),and psychiatric co-morbidities like depression (OR, 0.63, 95% CI [0.60 to 0.69], p <0.01) and psychoses (OR, 0.60, 95% CI [0.53 to 0.67], p <0.01) (Figure 5).

Discussion

The major findings of our study are: (1) TS is not a benign syndrome and is associated with significant risk of in-hospital mortality even in patients without CS. (2) CS occurs in approximately 6% of patients admitted with TS

and is associated with a six-fold increase in mortality (23% vs 4.0%) compared with TS patients without CS. (3) TS patients with CS are more likely to be males and have underlying medical co-morbidities such as congestive heart failure and diabetes. (4) There has been a significant uptrend in the incidence of CS and in hospital mortality in patients admitted with TS during our study period.

Since the first description of TS in 1990, the incidence of TS has been increasing, likely secondary to the increase in awareness and recognition of the disease.[12] The classical patient with TS is a post-menopausal woman who presents

with sudden onset of chest pain or dyspnea in setting of an emotional stress. The disease is characterized by transient reversible LV systolic dysfunction typically in the form of apical ballooning and return of normal LV contractile function within a few days to weeks.[4,9,13] Although initially thought to be a benign and reversible cardiac dysfunction associated with favorable long term prognosis, contemporary data from several studies have revealed the vicious nature of the disease with significant in-hospital complications including malignant arrhythmias, CS and mortality.[5,13−17]

In our study, TS was associated with a risk of in-hospital mortality of approximately 4.0% in patients without CS and much higher mortality rate of 23% in patients with CS. The mortality rate we report is similar to mortality rates reported in previous studies and a meta-analysis of TS studies with mortality ranging from 2.3% to 5%.[18] Ventricular arrhythmias and nonshockable cardiac arrests from underlying physical illness could be the events leading to a malignant outcome even in the absence of hemodynamic deterioration secondary to CS. The arrhythmias are likely attributable to high levels of circulating catecholamines.[19]

In our study, CS occurred in approximately 6% of patients with TS and was associated with a six-fold increase in-hospital mortality. The incidence of CS in our study is lower than reported in smaller registries where the reported incidence of CS was around 10%.[18] The mortality in the CS subgroup is similar to in-hospital mortality rate in the international takotsubo registry of 23.5%. The increased mortality in CS could be from multiple factors−−multi organ dysfunction that complicates CS and also fatal arrhythmias that are more common in CS patients. Moreover, acute respiratory failure secondary to pulmonary edema, frequently complicates CS in TS.[20]

Our analysis is consistent with previous literature that shows that CS is more likely to occur in males and younger patients[18,21−24] with medical co-morbidities including congestive heart failure, cerebrovascular disease, malignancy, chronic lung disease, and chronic liver disease as opposed to the prototypical TS patient who is an older postmenopausal woman with psychiatric co-morbidities like depression, higher mortality, and worse outcomes in men has also been shown in the data from national Registry on Takotsubo Syndrome registry and other single center studies.[25,26] A "secondary" phenotype of TS has been described that occurs in the setting of physical or surgical illness and predominantly in hospitalized patients. Secondary TS has much worse prognosis and higher mortality compared with "primary" TS.[27] Our analysis showing worse outcomes of TS in men is likely because they are more likely to develop a secondary "In hospital TS" which is known from to be associated with poorer outcomes and a higher mortality[27,28] compared with "primary" TS which is more likely to occur in setting of emotional stress in women.

Increasing trend in CS and mortality in TS patients is concerning. Possible explanations for the increasing trends in CS and mortality in TS is due to the aging population with multiple baseline co-morbidities predisposing to a secondary form of TS which is associated with higher incidence of CS and mortality, moreover the uptrend in the use of pVAD at the cost of IABP is also concerning especially in light of recent evidence from large retrospective studies showing higher mortality with use of pVADs compared with IABP.[29] Understanding the physiology of CS−−pump failure versus left ventricular outflow obstruction is key to guide the management of these patients to improve outcomes.[16] Decision pathways to treat CS due to above etiologies need further study to improve outcomes. The utility of mechanical circulatory support, the type of mechanical support (IABP vs pVAD) and extracorporeal life support in this patient population also needs evaluation.

Our study has a few limitations. First, the current study is retrospective in nature and hence it is vulnerable to potential selection bias and residual confounding, therefore, findings from the current analysis should be considered hypothesis generating, rather than hypothesis testing. Second, the NIS is an administrative claim-based database that uses ICD-9-CM and ICD-10-CM codes, which are prone to coding errors, however, the hard clinical end points used in this study such as CS, hospital mortality, and discharge disposition are less prone to diagnostic and coding errors. Third, patients are not followed longitudinally in NIS so long-term outcomes could not be assessed from present dataset. Finally, echocardiographic, laboratory, and medication data were not available due to inherent limitation of the dataset. Nonetheless our study is the largest to date to analyze the frequency of adverse outcomes including CS and in hospital morality in patients with TS and gives important insights into the predictors of CS and in hospital mortality in patients admitted with TS.

In conclusion, CS complicates approximately 6% of patients admitted with TS and is associated with almost six-fold increase in mortality (23% vs 4%, p <0.01). Independent predictors of CS and mortality are male gender and increased burden of co-morbidities at baseline like congestive heart failure, chronic lung disease, complicated diabetes mellitus, chronic kidney disease, and malignancy.

Authors contribution

Conceptualization and Methodology: Moinuddin Syed.

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Supervision: Sudarshan Balla.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

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