Comparison of Complications and In-Hospital Mortality in Takotsubo (Apical Ballooning/Stress) Cardiomyopathy Versus Acute Myocardial Infarction

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There are limited data on the incidence of complications and in-hospital outcomes, in patients with Takotsubo cardiomyopathy (TC), as compared with acute myocardial infarction (AMI). From 2007 to 2014, a retrospective cohort of TC was compared with AMI using the National Inpatient Sample database. Complications were classified as acute heart failure, ventricular arrhythmic, cardiac arrest, high-grade atrioventricular block, mechanical, vascular/access, pericardial, stroke, and acute kidney injury. Temporal trends, clinical characteristics, and in-hospital outcomes were compared. During the 8-year period, 3,329,876 admissions for AMI or TC were identified. TC diagnosis was present in 88,849 (2.7%). Compared with AMI admissions, those with TC were older, female, and of white race. Use of pulmonary artery catheter and mechanical ventilation was higher, but hemodialysis lower in TC. The overall frequency of complications was higher in TC (38.2% vs 32.6%). Complication rates increased in both groups over time, but the delta was greater for TC (23% [2007] vs 43% [2014]) compared with AMI (27% vs 36%). The TC cohort had a higher rate of heart failure (29% vs 16.6%) and strokes (0.5% vs 0.2%), but lower rates of other complications (all p <0.001). In-hospital mortality was lower for TC (2.6% vs 3.1%; p <0.001). TC was an independent predictor of lower in-hospital mortality in admissions with complications. In conclusion, compared with AMI, TC is associated with greater likelihood of heart failure, but lower rates of other complications and mortality. There has been a temporal increase in the rates of in-hospital complications and mortality due to TC. **(Am J Cardiol 2020;132:29−35)**

Takotsubo cardiomyopathy (TC; stress cardiomyopathy or apical ballooning syndrome) is an acute reversible cardiac syndrome that frequently mimics acute myocardial infarction (AMI) and is characterized by reversible wall motion abnormalities in the absence of obstructive coronary disease.[1] Early cohorts of TC were found to be low risk with similar prognosis to healthy age- and gender-matched controls with respect to long-term outcomes.[2] Recent data suggest that TC patients have mortality that is comparable to AMI.[3,4] It is conceivable that greater recognition of the entity has resulted sicker patients being diagnosed with TC to account for the higher mortality.[5] The presence of hemodynamic and electrical instability in TC may predispose the patients to adverse in-hospital outcomes.[6,7] However, there is a paucity of data regarding complications from TC, with most publications to date limited to case reports and single-center series.[8−10] Thus, analysis of systematically collected large datasets is needed to better characterize the clinical course, complications and outcomes of TC.[3,6,11] The aim of this study was to determine rates and trends of complications and in-hospital mortality in TC; and compare to AMI using a nationwide United States registry.

Methods

The Healthcare Cost and Utilization Project-National (Nationwide) Inpatient Sample (HCUP-NIS) is the largest all-payer database of hospital inpatient admissions in the United States that contains a 20% stratified sample of community hospitals.[12] The database contains information on each patient discharge including patient demographics, primary payer, hospital characteristics, principal diagnosis, up to 24 secondary diagnoses, and procedural diagnoses.

Using the HCUP-NIS data from 2007 to 2014, a retrospective cohort of patients hospitalized with TC and AMI were identified. Consistent with prior literature, patients admitted with TC were identified using International Classification of Diseases-9 Clinical Modification (ICD-9CM) code of 429.83.[5] We excluded admissions with a diagnosis of TC that did not receive diagnostic coronary angiography (ICD-9CM 36.06, 37.22, 37.23, 88.53 to 88.56), those who received percutaneous coronary intervention (PCI) or surgical revascularization (ICD-9CM 00.66, 36.01, 36.02, 36.05, 36.07, 88.57, 36.10 to 36.19, and 36.2). The control group

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of AMI was identified using ICD-9CM codes for ST-segment elevation AMI (ICD-9CM 410.1x-410.6x, 410.8x, 410.9x) and non-ST-segment elevation AMI (ICD-9CM 410.70 to 410.79) in the primary diagnosis field. Admissions with a primary diagnosis of AMI without diagnostic coronary angiography, those with a secondary diagnosis of AMI, or admissions with a primary diagnosis of ischemic or hemorrhagic stroke (ICD-9CM 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 436.0, 437.1, 430, 431, 432.0, 432.1, and 432.9) were excluded from this study. The Deyo's modification of Charlson co-morbidity index was used to identify the burden of co-morbid diseases.[13] Diagnostic/therapeutic cardiovascular procedures were identified using previously validated algorithms used by our group and others (Supplementary Table 1).[14−21] Previously validated codes were used to identify complications, which were grouped as (1) in-hospital mortality; (2) acute heart failure − systolic heart failure, cardiogenic shock, and acute respiratory failure[14,22,23]; (3) arrhythmic − ventricular fibrillation and ventricular tachycardia[24]; (4) cardiac arrest; (5) mechanical − ventricular septal defect, papillary muscle rupture[25]; (6) vascular/access − arterial injury, postoperative hemorrhage or hematoma, need for blood transfusion[26]; (7) pericardial − hemopericardium and cardiac tamponade[27]; (8) high-grade AVB (second degree, type II and complete)[24]; (9) ischemic and hemorrhagic stroke[26]; and (10) AKI.[23,28,29]

The primary outcome was the rates of complications in TC compared with AMI during this 8-year period. The secondary outcomes included temporal trends, in-hospital mortality, hospital lengths of stay, hospitalization costs and discharge disposition in admissions with complications in TC and AMI.

As recommended by HCUP-NIS, survey procedures using weighted discharges provided with HCUP-NIS database were used to generate national estimates. Using the weighted trends provided by the HCUP-NIS, samples from 2000 to 2011 were re-weighted to adjust for the 2012 HCUP-NIS re-design.[30] The inherent restrictions of the HCUP-NIS database related to research design, data interpretation, and data analysis were reviewed and addressed. Pertinent considerations included not assessing individual hospital-level volumes (due to changes to sampling design detailed above), treating each entry as an 'admission' as opposed to individual patients, restricting the study details to inpatient factors since the HCUP-NIS does not include outpatient data, and limiting administrative codes to those previously validated and used for similar studies. Chi-square and *t* tests were used to compare categorical and continuous variables respectively and odds ratio with 95% confidence interval (CI) were used to represent the results of the univariable and multivariable analyses. For the multivariable modeling, regression analysis with purposeful selection of statistically ($p < 0.20$) and clinically relevant variables was conducted. Multivariable logistic regression analysis for in-hospital mortality in admissions with complications using age, sex, race, primary payer, year of admission, hospital characteristics, co-morbidity, socioeconomic stratum, acute organ dysfunction, use of PCI, invasive hemodynamic monitoring, use of mechanical circulatory support, mechanical ventilation, and hemodialysis. A priori adjusted analyses were performed in each complication subgroup for in-hospital mortality in TC versus AMI. Two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS version 25.0 (IBM Corp, Armonk, NY).

Results

During the 8-year period from January 1, 2007 to December 31, 2014, there were a total of 3,329,876 admissions for AMI or TC meeting study criteria, of which 88,849 (2.7%) were diagnosed with TC. There was a steady increase in the frequency of TC during the study period, though the relative rates remained low − 1.1% to 3.6% (Supplementary Figure 1). In the AMI cohort, 37.3% were ST-elevation AMI. Clinical characteristics of the cohorts with TC and AMI are detailed in Table 1. Diagnostic coronary angiography was performed in all admissions; PCI and coronary artery bypass grafting were performed in 65.6% and 10.5%, respectively, in the AMI admissions.

Complications were in noted 38.2% (33,960) admissions in the TC cohort compared with 32.6% (1,054,977) admissions in the AMI cohort, $p < 0.001$. Acute heart failure was the most common complication and noted in 29% of TC admissions as compared with 16.6% of AMI admissions. Compared with the AMI cohort, the TC cohort had lower rates of other complications (Table 2). In TC admissions, those with complications were marginally older (67.9 ± 12.8 vs 65.8 ± 12.7 years, $p < 0.001$), more likely to be male (13.9% vs 9.4%, $p < 0.001$), and more likely to have a Charlson co-morbidity index of >3 (76.6% vs 54.4%, $p < 0.001$), compared with those without complications (Supplementary Table 2). The temporal trends of any complications and admissions with ≥2 complications with TC and AMI are presented in Figure 1. The temporal trends of the individual complications are in Figure 2.

The unadjusted all-cause in-hospital mortality was lower in the TC cohort (2.6% vs 3.1%; odds ratio 0.81 [95% CI 0.78 to 0.85]; $p < 0.001$). Similarly, in the subset of admissions with complications, in-hospital mortality was lower in the TC cohort (6.3%) compared with AMI (9.1%); $p < 0.001$. In-hospital mortality was higher for those with complications, compared with those without (TC: 6.3% vs 0.3%; $p < 0.001$) and (AMI: 9.1% vs 0.3%; $p < 0.001$) for both diagnoses. In a multivariable analysis in the cohort with complications, TC was an independent predictor of lower in-hospital mortality compared with AMI (0.54 [95% CI 0.51 to 0.56]; $p < 0.001$; Supplementary Table 3). In a multivariable analysis within each type of complication domain, the presence of TC was associated with lower in-hospital mortality compared with AMI except in admissions with vascular/access or mechanical complications (Figure 3). TC admissions with complications had longer length of stay, lower costs, and less frequent discharges to home compared with AMI admissions with complications (Table 3).

Discussion

The major findings from this first large-scale study systematically comparing complications in TC to those with

Table 1
Clinical characteristics of TC and AMI cohorts

Characteristic		TC (N = 88,849)	AMI (N = 3,241,027)	p
Age (years)		66.6 ± 12.8	63.9 ± 13.1	<0.001
Women		88.9%	34.8%	<0.001
White race		83.5%	76.3%	<0.001
Black race	5.9%	9.7%		
Other races*	10.6%	14%		
Charlson co-morbidity index	**0-3**	37.1%	44.5%	<0.001
	4-6	46.8%	40.9%	
	≥ 7	16.0%	14.7%	
Hypertension	65.3%	71.3%	<0.001	
Hyperlipidemia†	48.1%	64.2%	<0.001	
Diabetes mellitus	1.7%	4.1%	<0.001	
Smoking (active or prior)	33.5%	42.8%	<0.001	
Prior stroke	5.1%	4.8%	0.001	
Atrial fibrillation	14.1%	13.3%	<0.001	
Acute organ failure	Respiratory	14.9%	7.4%	<0.001
	Hepatic	1.4%	1.1%	<0.001
	Neurologic	4.6%	2.7%	<0.001
Left ventricular thrombus	0.1%	0.1%	0.02	
Invasive hemodynamic monitoring‡	9.4%	6.0%	<0.001	
Invasive mechanical ventilation	12.1%	5.5%	<0.001	
Mechanical circulatory support	3.5%	6.9%	<0.001	
Hemodialysis	0.5%	0.7%	<0.001	

Represented as number (percentage) or mean ± standard deviation.
* Hispanic, Asian or Pacific Islander, Native American, others.
† Hyperlipidemia was defined as pure hypocholesteremia, familial hypercholesterolemia, pure hypertriglyceridemia, mixed hyperlipidemia, hyperchylomicronemia, other hyperlipidemia, unspecified hyperlipidemia, lipoprotein deficiency, disorders of bile acid and cholesterol mechanism, and other disorders of lipoprotein metabolism.
‡ Right heart catheterization or pulmonary artery catheterization.
AMI = acute myocardial infarction; TC = Takotsubo cardiomyopathy.

Table 2
Complications in TC and AMI cohorts

Complication	TC (N = 88,849)	AMI (N = 3,241,027)	p
Any complication	33,906 (38.2%)	1,054,977 (32.6%)	<0.001
≥2 complications	10,937 (12.3%)	383,233 (11.8%)	<0.001
Acute heart failure complications	**25,781 (29.0%)**	**539,586 (16.6%)**	**<0.001**
Systolic heart failure	15,370 (17.3%)	278,880 (8.6%)	<0.001
Cardiogenic shock	5,420 (6.1%)	181,498 (5.6%)	<0.001
Acute respiratory failure	13,206 (14.9%)	238,683 (7.4%)	<0.001
Acute kidney injury	8,967 (10.1%)	350,099 (10.8%)	<0.001
Arrhythmic complications	**4,922 (5.5%)**	**291,370 (9.0%)**	**<0.001**
Ventricular tachycardia	4,036 (4.5%)	214,107 (6.6%)	<0.001
Ventricular fibrillation	1,399 (1.6%)	106,890 (3.3%)	<0.001
Vascular/access complications	**4,890 (5.5%)**	**227,177 (7.0%)**	**<0.001**
Vascular injury	517 (0.6%)	31,948 (1%)	<0.001
Hemorrhage requiring blood transfusion	1,228 (1.4%)	62,369 (1.9%)	<0.001
Blood transfusion	4,471 (5.0%)	200,804 (6.2%)	<0.001
Cardiac arrest	2,763 (3.1%)	115,434 (3.6%)	<0.001
Mechanical complications	**41 (<0.01%)**	**4,672 (0.1%)**	**<0.001**
Ventricular septal defect	41 (<0.01%)	3,660 (0.1%)	<0.001
Papillary muscle rupture	—	1,026 (<0.01%)	<0.001
Pericardial complications	**157 (0.2%)**	**5,585 (0.2%)**	**0.75**
Hemopericardium	45 (0.1%)	1,410 (<0.01%)	0.18
Pericardial tamponade	142 (0.2%)	4,685 (0.1%)	0.13
High-grade atrioventricular block	776 (0.9%)	47,091 (1.5%)	<0.001
Stroke	**474 (0.5%)**	**6,793 (0.2%)**	**<0.001**
Ischemic stroke	93 (0.1%)	2,707 (0.1%)	0.02
Hemorrhagic stroke	386 (0.4%)	4,121 (0.1%)	<0.001

Represented as number (percentage).
AMI = acute myocardial infarction; TC = Takotsubo cardiomyopathy.

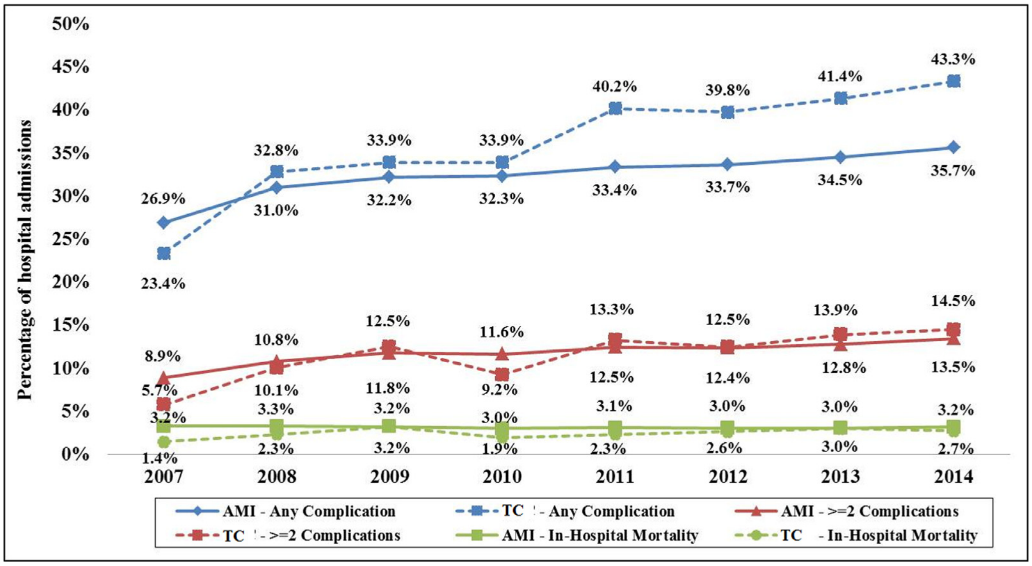

Figure 1. Temporal trends in any complication, ≥2 complications and in-hospital mortality in TC and AMI. All p <0.001 for trend for all complications. AMI = acute myocardial infarction; TC = Takotsubo cardiomyopathy.

AMI are that: (1) 1 or more complications occurs in just over one-third of TC admissions, and the frequency is higher than in AMI; (2) acute heart failure and stroke are more common in TC whereas other complications occur less often; (3) there was a temporal increase in most complications during this study period; (4) presence of a complication is associated with higher mortality in both groups, and (5) in-hospital mortality is lower in TC compared with AMI.

In this largest cohort of TC studied to date, 38.2% of admissions developed 1 or more complications. Murakami et al reported an identical (38%) complication rates using similar endpoints in 107 TC cases from the multicenter registry from Japan, however, detailed analysis was not provided due to the small sample size.[31] Using a more limited definition of complications that included cardiogenic shock, need for catecholamines, invasive or noninvasive ventilation support or cardiopulmonary resuscitation, and inclusive of in-hospital mortality, the international, multicenter InterTAK registry reported a rate of 21.8%; which unlike our study, was similar to their ACS control population.[7] Our much larger national cohort shows that in fact the incidence of complications in an all comers AMI population is lower; consistent with a younger age and lower co-morbidity burden.

Acute heart failure is by far the most common complication in TC. Indeed, the rates of each component of the endpoint, acute systolic failure, acute respiratory failure, and cardiogenic shock were all higher than that seen in the AMI cohort. We speculate that this may be due to a larger magnitude of acute myocardial dysfunction, higher rates of left ventricular outflow tract obstruction, and mitral regurgitation in TC.[5,9] Prior data have identified advanced age, presence of a physical stressor, first troponin-T >10 times the upper limit of normal, and left ventricular ejection fraction <40% as risk factors.[7,32] Overall, these data confirm that

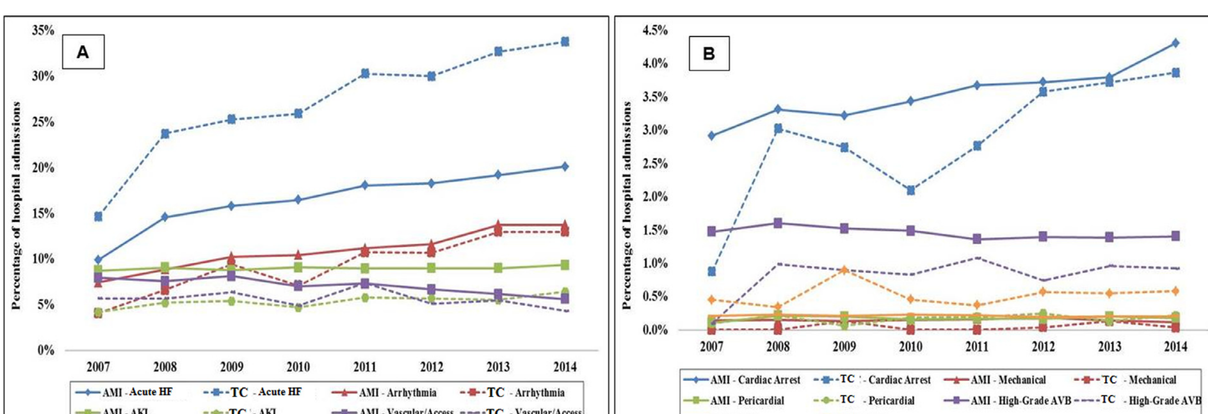

Figure 2. Temporal trends in individual complications in TC and AMI. Eight-year temporal trends of acute heart failure (systolic heart failure, cardiogenic shock, respiratory failure), arrhythmia (ventricular fibrillation, ventricular tachycardia), AKI, vascular/access complications, cardiac arrest, mechanical complications, pericardial complications (hemopericardium, cardiac tamponade), high-grade AVB and ischemic/hemorrhagic CVA; all p <0.001 for trend. AKI = acute kidney injury; AMI = acute myocardial infarction; AVB = atrioventricular block; CVA = cerebrovascular accident; HF = heart failure; TC = Takotsubo cardiomyopathy.

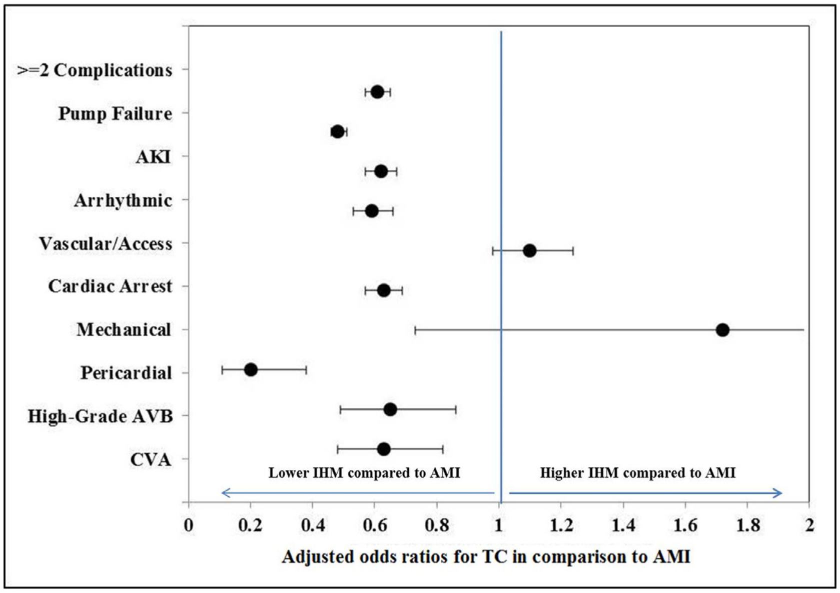

Figure 3. Multivariate predictors of in-hospital mortality in TC within the complication categories compared with AMI. Multivariable adjusted odds ratios (95% confidence intervals)* for in-hospital mortality in TC admissions with complications compared with AMI admissions with complications; all p <0.001 except vascular/access and mechanical complications. *Adjusted age, sex, race/ethnicity, year of admission, primary payer, socioeconomic status, hospital location/teaching status, hospital bedsize, hospital region, co-morbidity, acute organ failure, coronary angiography, invasive hemodynamic monitoring, mechanical circulatory support, mechanical ventilation, hemodialysis, all complication categories. AKI = acute kidney injury; AMI = acute myocardial infarction; AVB = atrioventricular block; CVA = cerebrovascular accident; TC = Takotsubo cardiomyopathy.

Table 3
Clinical outcomes of TC and AMI cohorts with complications

Clinical outcomes		TC with complications (N = 33,906)	AMI with complications (N = 1,054,977)	p
In-hospital mortality		6.3%	9.1%	<0.001
Length of stay (days)		8.2 ± 7.8	7.7 ± 7.6	<0.001
Hospitalization costs (United States Dollars)		95,391 ± 105,813	116,653 ± 117,329	<0.001
Discharge disposition	Home	54.7%	60.6%	<0.001
	Skilled nursing facility	2.8%	5.2%	
	Transferred to other hospitals	23.7%	17.4%	
	Home with home health care	18.4%	16.3%	
	Against medical advice	0.4%	0.5%	

Represented as number (percentage) or mean ± standard deviation.
AMI = acute myocardial infarction; TC = Takotsubo cardiomyopathy.

complications in TC occur in patients with greater myocardial dysfunction. Finally, sex is highly relevant to TC as over 90% of cases occur in females, and males have a worse prognosis. Of note, in a study restricted to 117 female TC patients and 117 AMI controls, Budnik et al found a lower rates of in-hospital complications and mortality.[9] In our study, TC patients with versus without complications were modestly older, more likely to be male, and had a significantly greater co-morbidity burden. Despite the increasingly common recognition in contemporary practice, TC constitutes <3% of all presentations in this cohort further amplifying the challenges with studying this disease entity.

The frequency ventricular tachycardia and fibrillation in TC has not been accurately captured to date. Early small studies reported an incidence of approximately 10% patients.[33,34] In the InterTAK registry, the rate of ventricular tachycardia were reported at 3.0%.[7] Our study provides an estimate from the largest cohort with a frequency of 5.5% in TC patients, as compared with 9.0% of AMI cohort. This is similar to prior work from a smaller HCUP-NIS database analysis (4.2%) and a French study (6.0%).[35,36] The incidence of cardiac arrest was 3.1% in our cohort, similar to that seen in AMI. The InterTAK registry recently reported cardiac arrest rates of 5.9%.[37]

We have previously reported in an early, and recently in a larger cohort from the Mayo Clinic registry that in-hospital mortality is 2% to 3%.[2,38] The in-hospital mortality in this nationwide cohort of 88,849 TC patients is identical at 2.6% confirming the prior estimates. Moreover, the mortality is marginally lower (3.1%) to that observed in the contemporaneous AMI cohort. Unlike AMI, where the in-hospital mortality is invariably due to cardiac causes, prior studies have shown that TC in-hospital mortality is due to a combination of cardiac and noncardiac causes, depending in large part to the initial trigger.[6] Data from SCAAR (Swedish Coronary Angiography and Angioplasty

Registry), found 30-day mortality of 4% which was similar to their non-ST-segment-elevation AMI patients, but lower than in ST-segment-elevation AMI patients. The InterTAK registry has also reported in-hospital mortality of 4.1%, comparable to their acute coronary syndrome controls.[4,7] We observed that mortality was largely limited to patients with complications, being rare (0.3%) in the absence of a complication.

A unique aspect of our study using this large nationally representative database was the analysis of temporal trends in complications of TC and AMI. As noted by other authors, the incidence of TC has increased over time, and in-hospital mortality has steadily increased during the study period.[3,7] This can be postulated to be due to the inclusion of patients with higher acuity in the TC cohort. Over time, there has been a steady increase in physical triggers such as sepsis and neurological injury. Severe sepsis or neurological catastrophes are associated with higher mortality which may be independent of the concomitant presence of TC.[39]

This study has several limitations, some of which are inherent to the retrospective analysis of a large administrative database. Coding errors, misrepresentation of procedural volumes and underreporting of co-morbidities and complications are potential limitations of using ICD-9CM codes. The HCUP-NIS attempts to mitigate potential errors by using internal and external quality control measures. Nevertheless, the HCUP-NIS sampling design has been widely used for research in the past and provides a large nationally representative sample for a detailed outcome analysis. The ICD-9CM codes for TC and AMI have been previously validated which likely reduces the inherent errors in the study. Although we adjusted for differences in cohort characteristics using multivariable analysis, it is possible that the observed outcomes could have been influenced, to some extent, by unidentified or unmeasured confounders. Since the data were derived from an administrative database, we did not have information regarding triggers, hemodynamic measures, ECG changes, and biomarker levels. Lastly, due to the absence of cardiac magnetic resonance imaging, it is possible that a portion of TC cases may have concomitant myocarditis, which might explain the higher rates of ventricular arrhythmias.[40]

In conclusion, this 8-year national study noted a steady increase in complications in both TC and AMI between 2007 and 2014. Acute heart failure and strokes were more common in TC, whereas AMI had higher rates of AKI, ventricular arrhythmias and cardiac arrest. Though the in-hospital mortality in TC increased during the study period, it consistently remained lower than AMI.

Disclosures

All authors have reported that they have no relations relevant to the contents of this study to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.015.

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