Impact of family history of coronary artery disease on clinical outcomes in Takotsubo cardiomyopathy

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ABSTRACT

Family history of coronary artery disease (FHxCAD) is a critical risk factor for CAD, underscoring the contribution of genetic factors to disease pathogenesis and susceptibility. Takotsubo cardiomyopathy (TCM) simulates the clinical features of and frequently coexists with CAD. However, the association between FHxCAD and TCM is unclear. Here, we retrospectively examined the impact of FHxCAD on in-hospital outcomes of patients with TCM. Using the National Inpatient Sample database (2016–2018), we identified 4733 patients admitted to hospital with a primary diagnosis of TCM. We compared in-hospital outcomes and complications between TCM patients with (n=646, 13.7%) and without FHxCAD (n=646) in the unmatched and in a propensity-score matched cohort (1:1 ratio). TCM with FHxCAD patients had a reduced incidence of cardiogenic shock, acute kidney injury (AKI), and acute respiratory failure (ARF); lower mortality rates; shorter length of stay (LOS); and decreased total charge compared with TCM without FHxCAD patients (p<0.05). In the matched cohort, TCM with FHxCAD patients (vs TCM without FHxCAD patients) had a lower incidence of cardiogenic shock (2.2% vs 6.3%, p<0.001; OR 0.33, 95% CI 0.18 to 0.61), AKI (5.1% vs 8.7%, p=0.016; OR 0.57, 95% CI 0.36 to 0.88), and ARF (5.7% vs 12.7%, p<0.001; OR 0.42, 95% CI 0.28 to 0.63); decreased in-hospital mortality (<11% vs 3.1%, p=0.002; OR 0.2, 95% CI 0.07 to 0.57); shorter LOS (2.66±1.96 days vs 3.40±3.05 days, p<0.001); and a reduced total charge (p=0.001), respectively. FHxCAD was associated with favorable outcomes in both unmatched and propensity-matched cohorts.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Family history of coronary artery disease (CAD) is a critical risk factor for CAD.
⇒ Takotsubo cardiomyopathy simulates the clinical features of and frequently coexists with CAD.
⇒ CAD is associated with worse clinical outcomes in Takotsubo cardiomyopathy.

WHAT THIS STUDY ADDS

⇒ Of patients admitted to hospital with a primary diagnosis of Takotsubo cardiomyopathy, 13.7% had a family history of CAD.
⇒ Patients with Takotsubo cardiomyopathy and a family history of CAD had a reduced incidence of cardiogenic shock, acute kidney injury, and acute respiratory failure and lower mortality rates.
⇒ Patients with Takotsubo cardiomyopathy and a family history of CAD had a shorter length of stay and decreased total charges than those without a family history of CAD.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Evaluating genetic predisposing factors, in-hospital medical care, and pharmaceutical treatment may improve outcomes in patients with Takotsubo cardiomyopathy and a family history of CAD.

INTRODUCTION

Takotsubo cardiomyopathy (TCM), also known as apical ballooning syndrome or stress cardiomyopathy, was first described in the 1990s by Japanese authors. Characterized by transient regional systolic dysfunction of the left ventricle, TCM resembles the clinical presentation, electrocardiographic features, and biomarker profiles of acute myocardial infarction[1] but lacks the angiographic evidence of coronary artery obstruction.[2 3] The term "Takotsubo" refers to the Japanese name for an octopus trap that has a similar shape to the apical ballooning of the dysfunctional systolic left ventricle seen on echocardiogram in patients with TCM.[4 5] Although the related etiology of myocardial infarction and TCM is incompletely understood, the morbidity and mortality rates of TCM are substantial and similar to those of acute coronary syndrome.[4] The pathogenetic mechanisms of TCM are unclear, but coronary vasculature impairment and catecholamine cardiotoxicity have been postulated.[6 7] Furthermore, genetics has been suggested as a predisposing factor.[8 9]

Coronary artery disease (CAD) is the leading cause of death in the USA and worldwide,[10 11] accounting for approximately

5,00,000–7,00,000 deaths each year in the USA alone. In patients who initially presented with CAD symptoms, approximately 1%–2% had TCM,[12] due to the resemblance of clinical features and examination profiles of TCM and CAD. Emerging evidence indicates that both conditions frequently coexist, and the presence of CAD is associated with worse clinical outcomes in patients with TCM.[13–15] In a recent study of 1016 patients with TCM who underwent coronary angiography, 23% had obstructive CAD and 41.2% had non-obstructive CAD.[13] The presence of CAD was associated with the increased incidence of shock, ventilation and death from any cause in TCM.[13]

Family history of CAD (FHxCAD) is a strong predictor for the incidence of the disease[16 17] and is correlated with clinical outcomes,[18] which indicates the genetic predisposition of CAD.[19] Nonetheless, evidence for the impact of CAD family history on TCM clinical outcomes is limited. Because CAD is highly prevalent in TCM and associated with worse clinical outcomes, FHxCAD would be considered an important factor for early risk stratification in patients with TCM. Here, we used the Nationwide Inpatient Sample (NIS) database (2016–2018) to create a retrospective cohort and study the correlation between FHxCAD and in-hospital outcomes of TCM.

MATERIALS AND METHODS

NIS is one of the largest publicly available, all-payer inpatient healthcare database maintained by the Agency for Healthcare Research and Quality (Rockville, Maryland, USA) in the USA and represents about a 20% stratified sample of discharges from community (non-federal) hospitals and about 97% of the US population.[20] The 2016–2018 NIS entails discharge data from 4500 hospitals in 48 states and totals 35 million records each year. Diagnoses are documented by using International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM) codes. As NIS data are deidentified and publicly available, this study was exempt from institutional review board evaluation.[21]

Using ICD-10-CM code I5181, we identified patients with a primary diagnosis of TCM from January 1, 2016 to December 31, 2018. Patients without discharge status were excluded. The patient selection process is shown in figure 1.

We collected patient demographic data from the NIS database (2016–2018), including age, sex, race, patient location, mean household income, primary payer for hospitalization, hospital type, region, and bed size. Common cardiovascular comorbidities, such as smoking, hypertension, hyperlipidemia, obesity, diabetes mellitus, chronic kidney disease (CKD), obstructive sleep apnea, and peripheral artery disease, were identified by using ICD-10-CM codes (online supplemental table 1) and included to further reduce selection bias.

The primary outcome of the current study is in-hospital mortality. The secondary outcomes comprise the incidence of cardiogenic shock, acute kidney injury (AKI), and acute respiratory failure (ARF); the length of stay (LOS); and total hospital charge.

Descriptive data are presented as percentages or mean±SD. Categorical data were analyzed using χ^2 test, and continuous variables were tested using the Student's t-test.

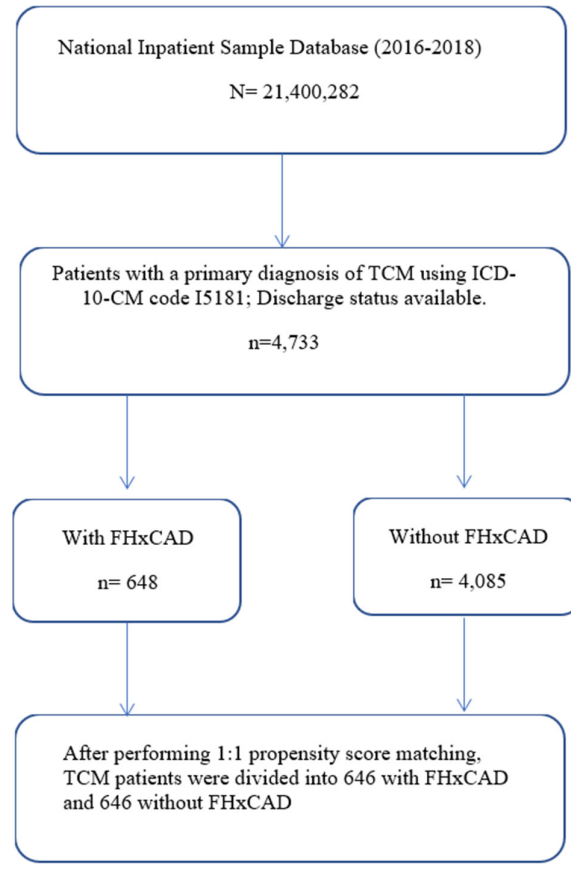

Figure 1 Flow chart of the selection process for the final patient sample used in this study. Patients who met the inclusion criteria were selected from the National Inpatient Sample 2016–2018 database. All eligible patients were matched at 1:1 ratio based on propensity score to generate the FHxCAD versus non-FHxCAD comparison cohorts. ICD-10-CM codes, International Classification of Disease, 10th edition, Clinical Modification codes; TCM, Takotsubo cardiomyopathy; FHxCAD, family history of coronary artery disease.

We used propensity score matching to reduce bias in the unmatched data. We built a multivariate logistic regression model with adjustment of individual characteristics including age; sex; race; mean household income; hospital characteristics including hospital type, region, and size; and comorbidities. Nearest neighbor matching and a caliper match tolerance of 0.05 were implemented. Patients with FHxCAD were matched to patients without FHxCAD at a ratio of 1:1, with 646 patients in each group. The standardized mean difference was used to examine the balance of the covariate distribution between groups. A standardized mean difference of less than 0.1 was considered balanced.

We compared the incidence of primary and secondary outcomes between patients with FHxCAD and without FHx CAD in both the unmatched and propensity score-matched cohorts.

Statistical analysis was performed using R statistics software (V.3.6.1, R Development Core Team). The matching process was conducted using the MatchIt package in R software. All tests were two sided. The results were considered significant at $p < 0.05$.[22]

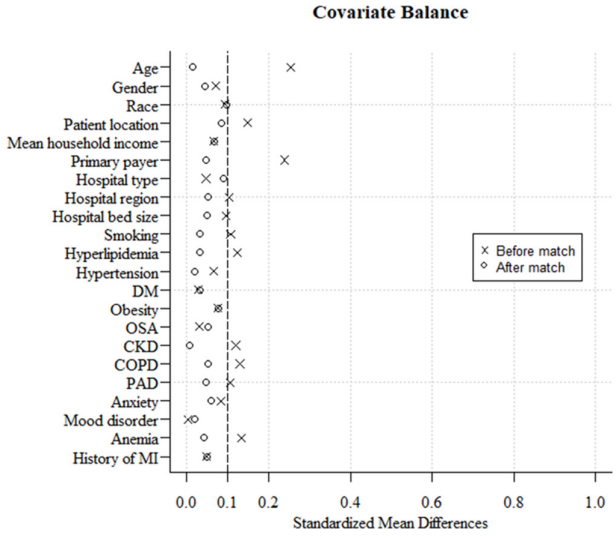

Figure 2 Standardized mean differences of covariates before and after propensity score matching between patients with Takotsubo cardiomyopathy with and without FHxCAD. The standardized mean difference is used to examine the balance of the covariate distribution between matched cohorts. All standardized mean differences of covariate distribution after propensity score matching were less than 0.1, which is considered balanced. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; FHxCAD, family history of coronary artery disease; HLD, hyperlipidemia; MI, myocardial infarction; PAD, peripheral artery disease; OSA, obstructive sleep apnea.

RESULTS

A total of 4733 patients admitted with a primary diagnosis of TCM (ICD-10 coding system) were identified using the NIS database (2016–2018); 648 (13.7%) patients had a FHxCAD, whereas 4085 patients did not (online supplemental table 2). Using propensity score matching in a 1:1 target ratio, we created two groups: TCM patients with and without FHxCAD (n=646 patients per group).

In the unmatched cohort, TCM patients with FHxCAD were younger than TCM patients without FHxCAD (63.89±12.18 years vs 67.06±12.82 years, respectively; p<0.001) and presented with a higher incidence of certain comorbidities, such as hyperlipidemia (54.3% vs 48.2%, p=0.004) and smoking (48.5% vs 43.1%, p=0.013) (online supplemental table 2). Furthermore, TCM patients with a FHxCAD had a lower incidence of CKD (6.6% vs 9.9%, p=0.009), chronic obstructive pulmonary disease (17.3% vs 22.5%, p=0.003), peripheral artery disease (4.6% vs 7.1%, p=0.025), and anemia (9.1% vs 13.3%, p=0.003) than those without FHxCAD. After propensity score matching, all baseline characteristics were comparable (p>0.05) (online supplemental table 2). All standardized mean differences between the two matched groups were less than 0.1 after propensity score matching (figure 2).

In both the matched and unmatched cohorts, the TCM with FHxCAD group had a lower mortality rate than did the TCM without FHxCAD group (unmatched <11% vs 1.7%, p=0.064; matched <11% vs 3.1%, OR 0.2; 95% CI 0.07 to 0.57; p=0.001) and a shorter LOS (unmatched 2.66±1.95 days vs 3.61±3.87 days, p<0.001; matched 2.66±1.96 days vs 3.40±3.05 days, p<0.001) and lower total hospital charges (unmatched US$42,106.16±35,601.77 vs US$52,912.31±57,746.62, p<0.001; matched US$42,182.34±35,631.06 vs US$50,279.20±49,131.52, p=0.001) (table 1).

In both the matched and unmatched cohorts, the TCM with FHxCAD group had a lower incidence of complications compared with the TCM without FHxCAD group, such as cardiogenic shock (unmatched 2.2% vs 5.1%, p=0.001; matched 2.2% vs 6.3%, p<0.001), AKI (unmatched 5.1% vs 10.3%, p<0.001; matched 5.1% vs 8.7%, p=0.016), and ARF (unmatched 5.7% vs 13.0%, p<0.001; matched 5.7% vs 12.7%, p<0.001) (table 1). We found no significant differences in cardiac arrest and ventricular arrhythmia between TCM patients with and without FHxCAD in either cohort comparison. The adjusted ORs for in-hospital outcomes after propensity score matching are shown in figure 3.

Table 1 In-hospital outcomes and complications

	Unmatched cohort			Propensity-matched cohort		
Variables	TCM without FHxCAD	TCM with FHxCAD	P value	TCM without FHxCAD	TCM with FHxCAD	P value
n	4085	648		646	646	
Outcomes						
Death, n (%)	68 (1.7)	<11	0.064	20 (3.1)	<11	0.002
LOS (mean days (SD))	3.61 (3.87)	2.66 (1.95)	<0.001	3.40 (3.05)	2.66 (1.96)	<0.001
Total charge (mean dollars (SD))	52,912.31 (57746.62)	42,106.16 (35601.77)	<0.001	50,279.20 (49131.52)	42,182.34 (35631.06)	0.001
Complications						
Cardiac arrest, n (%)	68 (1.7)	<11	0.349	<11	<11	0.801
Cardiogenic shock, n (%)	210 (5.1)	14 (2.2)	0.001	41 (6.3)	14 (2.2)	<0.001
Ventricular arrhythmia	175 (4.3)	25 (3.9)	0.692	24 (3.7)	25 (3.9)	1
AKI, n (%)	419 (10.3)	33 (5.1)	<0.001	56 (8.7)	33 (5.1)	0.016
ARF, n (%)	533 (13.0)	37 (5.7)	<0.001	82 (12.7)	37 (5.7)	<0.001

Count less than 11 were not reported as per HCUP guidelines.
AKI, acute kidney injury; ARF, acute respiratory failure; FHxCAD, family history of coronary artery disease; HCUP, Healthcare Cost and Utilization Project; LOS, length of stay; TCM, Takotsubo cardiomyopathy.

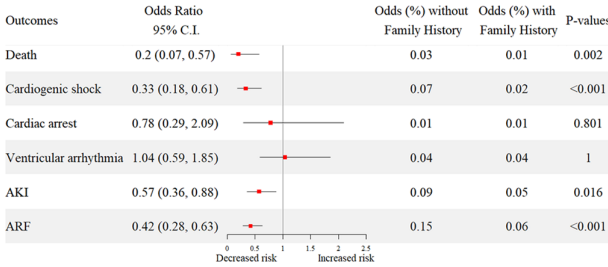

Figure 3 Forest plot graph showing adjusted ORs for in-hospital outcomes after propensity score matching. AKI, acute kidney injury; ARF, acute respiratory failure.

DISCUSSION

This is the first study to examine the association between CAD family history and TCM on in-hospital outcomes. TCM patients with a CAD family history had lower mortality and reduced hospital charges, LOS, and incidence of complications, such as cardiogenic shock, AKI, and ARF. Both before and after propensity score matching, TCM patients with FHxCAD had favorable clinical outcomes when compared with those without a family history of CAD.

Although the etiological basis and pathogenetic mechanisms of TCM are not clearly understood, coronary microvascular impairment and catecholamine cardiotoxicity are indicated as possible underlying contributors to TCM. TCM and CAD may not be mutually exclusive, and a high proportion of patients with TCM have coexisting CAD on coronary angiography.[13 15] Studies have shown that coexisting CAD impairs short-term outcomes in patients with TCM[13] and is associated with higher all-cause mortality, progression to congestive heart failure, and the development of cardiogenic shock after 2-year follow-up.[14]

Reports of familial cases of TCM have raised the possibility of genetic predisposition to the disease.[8 9 23] Concomitantly, substantial evidence supports and identifies genetic risk factors contributing to the susceptibility to CAD,[19 24] which are also associated with CAD family history. Given the high coexistence of CAD in patients with TCM, genetic factors predisposing to CAD susceptibility could also affect the clinical presentation, disease severity, and outcomes of patients with TCM. Many studies have shown that genetic polymorphisms may contribute to the pathogenesis of TCM, including the various subtypes of adrenoceptors.[25] Among those, several polymorphisms of the beta-2 adrenergic receptor gene were associated with either TCM[26] or CAD.[27] In a rat model of TCM, investigators elegantly showed that myocardial protection, which relies on the switch from Gs to Gi coupling of the beta-2 adrenergic receptor, can be induced with high-dose intravenous epinephrine.[28] This mimicked the physiological response to catecholamine toxicity observed in patients with TCM and demonstrated the importance of the functional role of adrenergic receptors in TCM pathogenesis.[7] More studies are necessary to analyze if the coexistence of polymorphisms in TCM and CAD is associated with better outcomes in TCM patients with CAD family history.

Also, family history is an important risk factor for guiding medical decision-making for patients with chest pain in the hospital and is a variable considered in the HEART[29] and TIMI scores.[30] Thus, patients with FHxCAD are more likely to be hospitalized and to subsequently receive more thorough, facilitated medical care. TCM mimics the clinical features of acute myocardial infarction,[4] and the incidence of TCM is about 1%–2% in patients presenting with coronary syndrome.[12] Thus, the early management and hospitalization of patients with chest pain might lead to early recognition, diagnosis, and initiation of prompt therapy for TCM, which could contribute to better in-hospital clinical outcomes, a lower incidence of complications, and improved prognosis.[31] This also supports findings from previous studies showing that FHxCAD is associated with better clinical outcomes in patients with CAD.[18 32]

Our study has several strengths. First, by using the NIS from 2016 to 2018, we identified 4733 patients, even though TCM is a rare disease. Furthermore, we generated an adjusted cohort with reduced bias in both baseline characteristics and CAD comorbidities by using propensity score matching, which minimized confounding factors. Additionally, our study is the first to describe the correlation between CAD family history and TCM outcomes. We believe our data are novel and may be valuable in improving clinical practice.

However, our study has limitations. First, because this is a retrospective observational study, our findings can indicate associations but cannot be used to interpret causality. Second, the NIS is a claim-based database, and data on specific medications, laboratory variables, clinical examinations, and radiology results are lacking. Thus, we could not further stratify the data to assess the degree of cardiac injury and total comorbidity burden. Third, we were unable to validate or determine the mode of diagnosis of TCM in our cohort due to the lack of clinical information, such as echocardiogram or coronary angiogram results in the NIS. However, the ICD-10-CM code of TCM has been previously shown to have a high accuracy and positive predictive value.[33 34] Coding errors may exist in the NIS database, and we are unable to verify the accuracy of coding, which may affect our analysis. Fourth, although we have included "history of MI" as a variable in the propensity score matching, we could not provide the incidence of non-obstructive CAD in our cohorts, which may adversely affect the strength of our study. Finally, with propensity score match, the total sample size was reduced and may affect the final result.

Compared with TCM patients without CAD family history, TCM patients with CAD family history had better in-hospital outcomes, lower mortality rates, and a decreased incidence of complications, such as cardiogenic shock, AKI, and ARF. Further investigations are necessary to evaluate the role of genetic predisposing factors, in-hospital medical care, and pharmaceutical treatment in contributing to better TCM outcomes in patients with FHxCAD.

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