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Research letter

Spontaneous coronary artery dissection (SCAD) and takotsubo cardiomyopathy (TCM) - A potential association



ARTICLE INFO

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ABSTRACT

Background: Spontaneous coronary artery dissection and takotsubo cardiomyopathy are increasingly recognized in the last two decades. Case reports have shown both entities can present concomitantly - however, little is known about their association.

Methods: In this retrospective study we aimed to explore a potential association between SCAD and TCM using the Nationwide Inpatient Sample. The odds of having TCM among patients with SCAD compared with those who did not have SCAD were calculated as an odds ratio. Conversely, the odds of having SCAD among patients with TCM compared with those who did not have TCM were also calculated. The primary outcome was the odds of TCM among patients with a primary diagnosis of SCAD and vice versa. The secondary endpoint was the odds of in-hospital mortality among patients with SCAD, and/or TCM.

Results: Hospitalized patients who had SCAD were 7.12 (95 % CI: 6.28–8.08) times more likely to also have TCM than those who did not have SCAD ($p < 0.0001$), while patients with TCM were 6.91 (95 % CI: 6.07–7.85) times more likely to have SCAD compared to those who didn't have TCM adjusted for age, gender, race, hypertension, hyperlipidemia, and diabetes mellitus ($p < 0.0001$).

Conclusion: This data indicate that patients with either SCAD or TCM are seven times more likely to be diagnosed concomitantly with both, compared to the patients without either diagnosis [after adjusting for age, gender, race, hypertension, hyperlipidemia, and diabetes mellitus]. Our data are consistent with the growing body of evidence supporting an association between SCAD and TCM and raise the question of a common pathophysiologic mechanism.

1. Introduction

Spontaneous coronary artery dissection (SCAD) and takotsubo cardiomyopathy (TCM) are two separate conditions that have gained more recognition over the past two decades. Patients with SCAD present with spontaneous and non-iatrogenic tear of the coronary arterial wall, while TCM present with the characteristic apical ballooning and acute systolic dysfunction in the absence of significant obstructive coronary artery disease. Both conditions usually present as acute myocardial infarction, or sudden cardiac death, and occur predominantly in women [1–4]. Given the clinical similarities and the fact that both conditions can result in acute myocardial infarction or acute coronary syndrome, there are published reports about the coexistence of these clinical entities, which raises the possibility of a potential association between the two, and underscores the need for further research [5,6]. Understanding whether there is a genuine association between SCAD and TCM is crucial for improving our understanding of these entities and optimizing patient care. Thus, we aimed to investigate the potential association of SCAD with TCM in a national-level patient population.

2. Methods

This is a retrospective cohort study that explores a potential association between SCAD and TCM using the Nationwide Inpatient Sample (NIS). The NIS is the largest, publicly available, nationally

representative registry of hospitalized adults in the United States. The NIS represents roughly 8 million hospitalizations annually and approximates a stratified sample of 20 % of community hospitals in the United States. The discharge data were extracted from the Nationwide Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality from years 2015 to 2017 using 9th and 10th revisions of International Classification Disease (ICD-9-CM code 414.12, ICD-10-CM Code I25. 42) for SCAD and TCM (ICD-9-CM code 429.83, ICD-10-CM code 151.81) [7,8]. This database (NIS) allows for weighting variables in order to extrapolate and calculate national estimates. SCAD, TCM, and comorbidity flags were generated based on the primary or secondary diagnosis. Demographic characteristics (age, gender, race, and comorbidities) were collected. Odds of having TCM among patients with SCAD compared with those who did not have SCAD were calculated as odds ratio (OR). Conversely, odds of having SCAD among patients with TCM compared with those who did not have TCM were also calculated. Odds ratios were adjusted for age, gender, race, and a history of hypertension, hyperlipidemia, or diabetes mellitus. Age, gender, race, and risk-adjusted OR's were also calculated for in-hospital mortality. The primary outcome was the odds of TCM among patients with a primary diagnosis of SCAD and vice-versa. The secondary endpoint was the odds of in-hospital mortality among patients with SCAD, and/or TCM.

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2.1. Statistical analysis

A weighted multivariable logistic regression model was generated using age, gender, race, a history of hypertension, diabetes mellitus, hyperlipidemia, and the presence of TCM. OR's with a 95 % confidence interval (CI) were calculated to determine whether an association exists between SCAD with TCM or vice versa. P-value was calculated by using the Cochran-Armitage test. Data management and analyses were completed in SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R studio (R version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria). A p-value of <0.05 was considered statistically significant, and all p-values were two-sided.

3. Results

The total NIS sample size from 2015 to 2017 was 18,155,507 discharges. These discharges were weighted to represent a national total of 90,777,496 hospitalizations. Of these, 1340 (weighted) discharges had a primary diagnosis of SCAD, 23,850 had a primary or secondary diagnosis of SCAD, and 114,185 discharges with a primary or secondary diagnosis of TCM. In hospitalized patients during this period, those who had SCAD were 7.12 (95 % CI: 6.275–8.083) times more likely to also have concomitant TCM compared to the cohort without SCAD, adjusted for age, gender, race, hypertension, hyperlipidemia, diabetes mellitus and the interaction of SCAD and TCM (Table 1) ($p < 0.0001$). Comparable results were found among hospitalized patients with TCM (Table 2). Between 2015 and 2017, patients with TCM were 6.91 (95 % CI: 6.07–7.85) times more likely to have concomitant SCAD diagnosis compared to those who didn't have TCM, adjusted for age, gender, race, hypertension, hyperlipidemia, and diabetes mellitus ($p < 0.0001$). Patients who had TCM were 2.29 (OR 2.29, 95 % CI: 2.23–2.35) times more likely to die during hospitalization compared to those who did not have TCM adjusted for age, gender, race, hypertension, hyperlipidemia, and diabetes mellitus ($p < 0.0001$). Similarly, patients with SCAD were 2.98 (OR 2.98, 95 % CI: 2.82–3.16 times) more likely to die during

Table 1
Outcome: presence of takotsubocardiomyopathy (weighted analysis).

Parameter	Level	OR (95% CI)	p-Value
Gender	Male	Reference	
	Female	4.963 (4.882, 5.046)	<.0001
Age	76+	Ref	
	18–25	0.172 (0.162, 0.182)	<.0001
	26–35	0.236 (0.227, 0.245)	<.0001
	36–45	0.798 (0.776, 0.821)	<.0001
	46–55	1.904 (1.867, 1.942)	<.0001
	56–65	2.652 (2.608, 2.697)	<.0001
	66–75	2.814 (2.768, 2.861)	<.0001
	Race	White	Ref
Black	0.507 (0.495, 0.518)	<.0001	
Hispanic	0.617 (0.601, 0.632)	<.0001	
Asian or Pacific Islander	0.785 (0.753, 0.818)	<.0001	
Native American	1.106 (1.027, 1.192)	.0076	
Other	0.744 (0.714, 0.776)	<.0001	
SCAD	No	Ref	
Yes	7.12 (6.275, 8.083)	<.0001*	
Hypertension	No	Ref	
Yes	0.961 (0.948, 0.973)	<.0001	
Hyperlipidemia	No	Ref	
Yes	1.345 (1.328, 1.362)	<.0001	
Diabetes mellitus	No	Ref	
Yes	0.736 (0.724, 0.749)	<.0001	

SCAD - spontaneous coronary artery dissection.

Inclusion: All the adults.

Year 2015–2017.

TC, SCAD and comorbidity flags are generated based on primary or secondary diagnosis.

* Bolded p value is statistically significant after adjustments for multiple testing.

Table 2
Outcome: presence of SCAD (weighted).

Parameter	Level	OR (95 % CI)	p-Value
Gender	Male	Ref	
	Female	1.015 (0.988, 1.043)	0.2841
Age	76+	Ref	
	18–25	0.147 (0.124, 0.174)	<.0001
	26–35	0.628 (0.587, 0.671)	<.0001
	36–45	2.042 (1.947, 2.142)	<.0001
	46–55	2.135 (2.049, 2.226)	<.0001
	56–65	1.927 (1.853, 2.004)	<.0001
	66–75	1.531 (1.471, 1.593)	<.0001
Race	White	Ref	
	Black	0.619 (0.592, 0.647)	<.0001
	Hispanic	0.728 (0.692, 0.767)	<.0001
	Asian or Pacific Islander	0.813 (0.742, 0.891)	<.0001
	Native American	0.949 (0.796, 1.132)	.5618
	Other	0.934 (0.861, 1.014)	.1045
	TC	No	Ref
Yes	6.91 (6.078, 7.851)	<.0001*	
Hypertension	No	Ref	
Yes	1.249 (1.215, 1.284)	<.0001	
Hyperlipidemia	No	Ref	
Yes	2.851 (2.770, 2.934)	<.0001	
Diabetes mellitus	No	Ref	
Yes	0.843 (0.813, 0.873)	<.0001	

SCAD - spontaneous coronary artery dissection; TC - takotsubo cardiomyopathy.

Inclusion: All the adults.

Year 2015–2017.

TC, SCAD and comorbidity flags are generated based on primary or secondary diagnosis.

* Bolded p value is statistically significant after adjustments for multiple testing.

hospitalization compared to those who did not have SCAD adjusted for age, gender, race, hypertension, hyperlipidemia, and diabetes mellitus ($p < 0.0001$). Forest plot with adjusted odds ratio is shown in Fig. 1 year to year trend of in-hospital mortality (%) of SCAD and TCM, are shown in Fig. 2. The effect of TCM on in-hospital mortality is the same for SCAD and non-SCAD samples, the interaction of SCAD and TCM on odds of inpatient mortality was not statistically significant ($p = 0.081$). In other words, the effect of TCM won't statistically change the odds of inpatient mortality among people with SCAD Table 3.

4. Discussion

Our study reveals that in this sample of patients from the NIS there is an association between SCAD and TCM. Patients with a diagnosis of SCAD were seven times more likely to be concomitantly diagnosed with TCM than those without SCAD. Similarly, patients with a diagnosis of TCM were also approximately seven times more likely to be concomitantly diagnosed with SCAD than those without TCM. Our findings add to the body of evidence suggesting a common pathophysiologic pathway for both conditions [9]. TCM and SCAD can present as acute myocardial infarction without angiographic evidence of atherosclerotic obstructive coronary artery disease. There is radiological evidence of apical ballooning and transient systolic dysfunction in patients with TCM. Women of younger to middle age (51.8 ± 10.2) mostly, with no classic cardiovascular risk factors are more likely to have SCAD; while TCM affects postmenopausal women disproportionately. It is imperative to recognize and treat these entities in a timely fashion. Case reports have shown that SCAD and TCM may present together. Both entities share a similar demographic profile and clinical presentation and are thought to be multifactorial [10,11]. The widespread availability of advanced intracoronary imaging modalities and a heightened awareness among cardiologists have led to the increasing prevalence of SCAD nationwide [12]. It is widely accepted that SCAD contributes significantly to ACS among middle-aged women who do not have well-established atherosclerotic risk factors. Although it has been hypothesized that

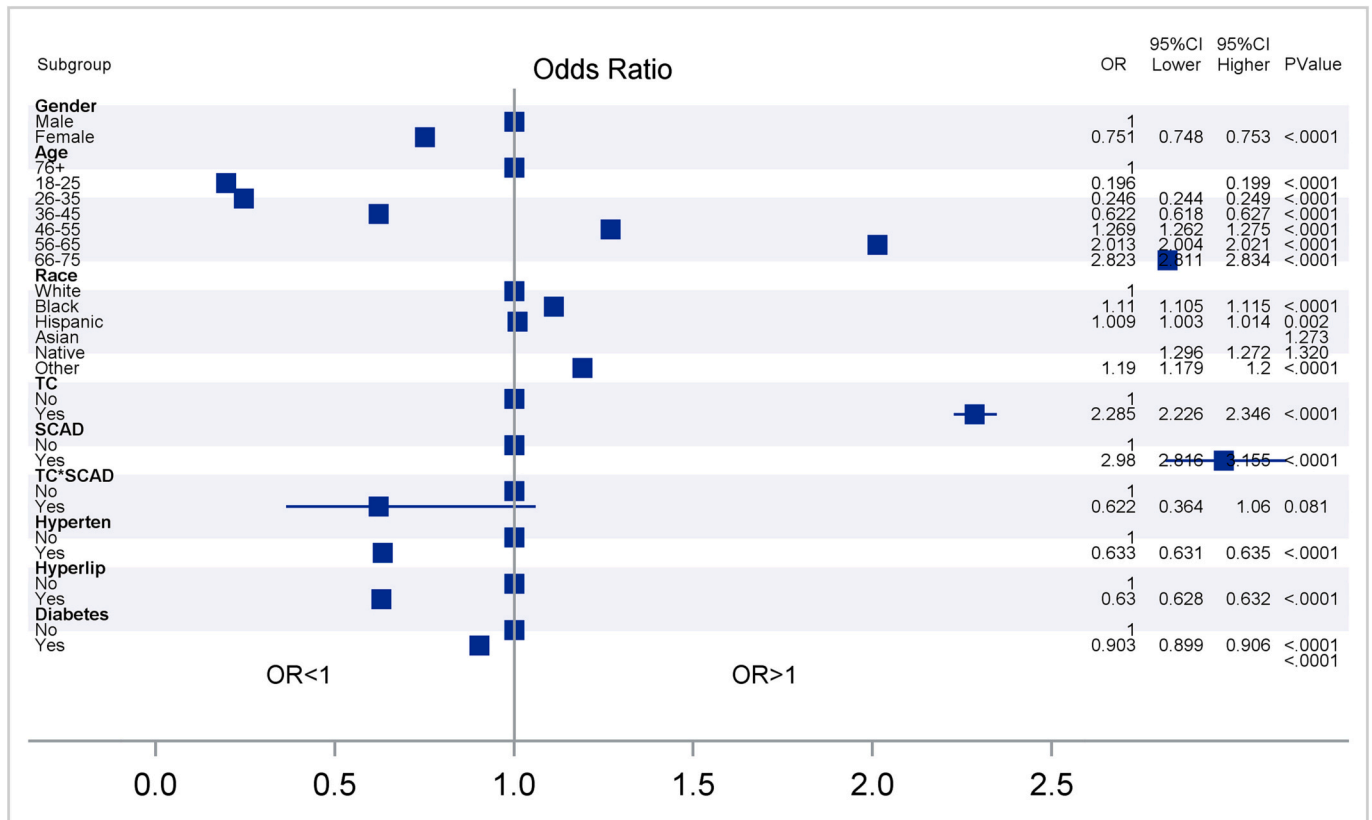


Fig. 1. Forest plot with adjusted odds ratio.

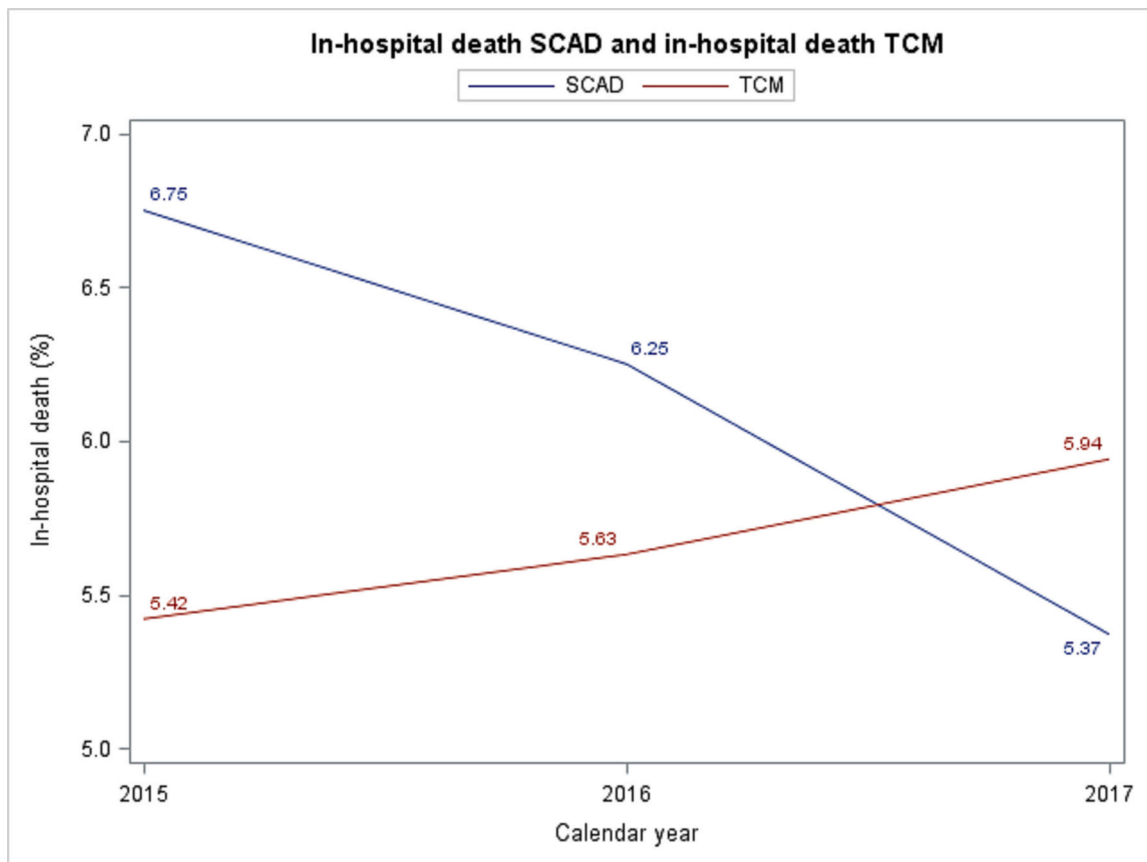


Fig. 2. Year to year trend of in-hospital mortality (%).

Table 3
Outcome: in-hospital mortality (weighted).

Parameter	Level	OR (95 % CI)	p-Value*
Gender	Male	Ref	
	Female	0.751 (0.748, 0.753)	<.0001
Age	76+	Ref	
	18–25	0.196 (0.194, 0.199)	<.0001
	26–35	0.246 (0.244, 0.249)	<.0001
	36–45	0.622 (0.618, 0.627)	<.0001
	46–55	1.269 (1.262, 1.275)	<.0001
	56–65	2.013 (2.004, 2.021)	<.0001
Race	66–75	2.823 (2.811, 2.834)	<.0001
	White	Ref	
	Black	1.110 (1.105, 1.115)	<.0001
	Hispanic	1.009 (1.003, 1.014)	.002
	Asian or Pacific Islander	1.273 (1.262, 1.284)	<.0001
	Native American	1.296 (1.272, 1.320)	<.0001
TC	Other	1.190 (1.179, 1.200)	<.0001
	No	Ref	
SCAD	Yes	2.285 (2.226, 2.346)	<.0001
	No	Ref	
TC * SCAD	Yes	2.980 (2.816, 3.155)	<.0001
	No	Ref	
Hypertension	Yes	0.622 (0.364, 1.060)	.081
	No	Ref	
Hyperlipidemia	Yes	0.633 (0.631, 0.635)	<.0001
	No	Ref	
Diabetes mellitus	Yes	0.630 (0.628, 0.632)	<.0001
	No	Ref	
	Yes	0.903 (0.899, 0.906)	<.0001

SCAD - spontaneous coronary artery dissection; TC - takotsubo cardiomyopathy.

Inclusion: All the adults.

Year 2015–2017.

TC, SCAD and comorbidity flags are generated based on primary or secondary diagnosis.

* Bolded p value is statistically significant after adjustments for multiple testing.

inflammation may trigger SCAD, there is mixed evidence to support this hypothesis [13]. Some studies have shown that SCAD can often be misdiagnosed as TCM [14]. Left ventricular ballooning, which is a hallmark of TCM, can be seen among SCAD patients and can be attributable to ischemia, particularly in the left anterior descending coronary territory [13,14]. Conversely, awareness about TCM has also increased since the initial reports in the 1990s, originally referred to as “takotsubo” cardiomyopathy because of the classical apical ballooning reminiscent of an octopus trap [15]. This condition was initially described as acute coronary syndrome with new left ventricular apical ballooning in the absence of significant epicardial coronary artery disease. It has now been encompassed under the term stress-induced cardiomyopathy, as there is usually an emotional or stress trigger (acute or repetitive) that can be identified in a majority of patients [16]. It has been hypothesized that the characteristic left ventricular pattern may be the result of a neurohumoral pathway with a hyperadrenergic state leading to prolonged coronary vasoconstriction, particularly in segments of subclinical atherosclerotic disease. Most recently, physical and psychological stress have been implicated as potential triggers for both SCAD and TCM [16,17]. This, along with reports of the concurrence of TCM with SCAD, raises the possibility of a common pathway through an *adrenergically mediated response with a catecholamine surge* from emotional or physical stress. A retrospective study looked into the proportion of SCAD cases in patients who were diagnosed with TCM provisionally and found that only 2.5 % of patients had a LAD territory SCAD. It is plausible that wrapped around LAD can give apical ballooning, however, there have been cases when patients with SCAD diagnosis had unique ‘characteristic’ left ventricular wall motion abnormalities consistent with TCM. However, this would require further query to understand variations of TCM type with SCAD territory [18,19]. Our study also revealed that the odds of in-hospital mortality for SCAD were slightly higher than TCM (2.98 vs 2.28) adjusted for covariates. This finding may not be surprising

to clinicians who have had experience with these patients, sometimes the SCAD presentation is indistinguishable from ST-segment elevation myocardial infarction. In some cases, there may be a persistent flow-limiting dissection that may be challenging to treat with primary PCI. This is in slight contrast with TCM where, despite initial signs of acute coronary syndrome, there is adequate perfusion in the epicardial circulation as assessed by coronary angiography. Several underlying mechanisms have been proposed in the literature to explain this potential association; both entities share several precipitating factors and similarities in clinical courses. First, SCAD can impede coronary blood flow and lead to post-ischemic stunning (left ventricle wall motion abnormality); superimposed by physical and emotional stressors of acute myocardial infarction in a subset of the population that has a predilection for TCM. Our study is limited by its retrospective design and the inherited weaknesses associated with utilizing the NIS database, such as the inability to explore SCAD artery distribution, miscoding of primary and secondary diagnoses. In addition, outcomes are only related to the hospitalization, and post-discharge outcomes are not recorded [20]. We want to mention the intrinsic weakness associated with utilizing ICD codes for SCAD and TCM; neither we can delineate coronary artery distribution in SCAD nor we can define variations of TCM using the NIS database. Future institutional-based prospective registries can further explore it. Despite these limitations, our findings in this relatively large sample size raise the possibility of a strong association between these two conditions and are hypothesis-generating. Our data further support the growing notion that SCAD and TCM may share a common pathophysiological pathway and deserve further study to identify optimal preventative and treatment strategies.

5. Conclusion

We found in this retrospective study of the NIS that patients with either SCAD or TCM are 7 times more likely to be diagnosed concomitantly with both as compared to the age, and gender matched patient cohorts without either diagnosis after adjusting for other risk factors. Our findings suggest that these two conditions may share common pathophysiology or triggers that contribute to their co-occurrence in some patients. Our data are consistent with the growing body of evidence supporting a potential association between SCAD and TCM and raise the question of a common pathophysiological mechanism.

Ethical statement

IRB was waived by the institution’s review committee.

CRedit authorship contribution statement

Mohsin Sheraz Mughal: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Hasan M. Mirza:** Writing – original draft. **Amit Bansal:** Conceptualization, Writing – original draft. **Xia Weiyi:** Data curation, Formal analysis, Methodology, Software. **Waqar Arshad Mughal:** Conceptualization, Writing – original draft. **Saba Ahmed:** Resources, Software, Writing – original draft. **Alon Yarkoni:** Supervision. **Fahad Waqar:** Conceptualization, Supervision, Writing – review & editing. **Najam Wasty:** Supervision. **Sergio Waxman:** Resources, Validation, Visualization. **Haris Usman:** Supervision, Visualization. **Mehboob Alam:** Supervision. **Afzal Rehman:** Project administration.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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