Heart & Lung 48 (2019) 79–84

Contents lists available at ScienceDirect

Heart & Lung

journal homepage: www.heartandlung.com

Care of Patients With Heart Failure

Regional disparity in outcomes among patients hospitalized for Takotsubo cardiomyopathy in the United States[☆]

Oluwole Adegbala [a,*], Olakanmi Olagoke [b], Adeyinka Adejumo [c], Adegbola Oluwole [d], Emmanuel Akintoye [e], Tomo Ando [f], Matthew Tavares [a], Karlene Williams [a], Luis Afonso [f]

[a] Department of Internal Medicine, Englewood Hospital and Medical Center, Seton Hall University-Hackensack Meridian School of Medicine, 360 Engle Street, Englewood, NJ, United States
[b] Department of Medicine, John H Stroger Jr. Hospital of Cook County, Chicago, IL 60612, United States
[c] Department of Internal Medicine, North Shore Medical Center, Salem, MA, United States
[d] Department of Internal Medicine, Einstein Medical Center Philadelphia, Philadelphia, PA, United States
[e] Division of Cardiovascular Medicine, University of Iowa Hospitals and Clinics, Iowa City, IA, United States
[f] Division of Cardiology, Wayne State University/Detroit Medical Center, Detroit, MI, United States

ARTICLE INFO

Article history:
Received 12 August 2018
Received in revised form 6 October 2018
Accepted 18 October 2018
Available online 14 November 2018

ABSTRACT

Introduction: Takotsubo cardiomyopathy (TTCM), an entity first described in Japan over two decades ago following myocardial stunning cases without evidence of coronary stenosis, has emerged as a unique entity with global recognition. We sought to investigate the extent and magnitude of regional variations in its outcomes.
Method: We used the National Inpatient Sample (NIS) of the Agency for Healthcare Research and Quality (2010–2014). Risk-adjusted rates of outcomes across the US geographical regions were calculated by fitting a Poisson regression model with a robust error variance under generalized estimating equations. Discrete numeric variables with over-dispersed count distributions -length of stay and continuous variables with a right skewed spread- cost of hospitalization were modeled using a generalized linear regression with a negative binomial function and gamma function respectively.
Result: We found significant regional variations in-patient mortality. While there was significantly higher risk of in-hospital death in the West (5.28 [4.34–6.44]) vs 4.40 [3.57–5.43] vs 4.10 [3.38–498] vs 4.78 [3.96–5.77]), there was a different pattern of variation in the length of days with longer hospital stay in the Northeast. Likewise, the risk-adjusted rate of non-routine home discharges was highest for Northeast. The West had the highest cost of hospitalization (West: $40,217 vs. South: $28,465)
Conclusion: Significant geographic variation exists in the cost of hospitalization and in-hospital mortality of TTCM across the US. Understanding this variation requires a detailed understanding of the processes of care and identification of effective strategies to eliminate these disparities.

Background

Takotsubo cardiomyopathy (TTCM), an entity first described in Japan over two decades ago following the reporting of five cases of myocardial stunning without coronary stenosis on angiography,[1] has emerged as a unique entity with global recognition. Based on recent reported multinational studies, it represents about 2% of suspected cases of myocardial infarction cases[2] and concurrently, studies have demonstrated increasing trend in the hospitalization for TTCM in the United States.[3,4]

Regional variations in health care spending and outcomes has long been used as a population-based metrics of healthcare utilization and quality and as a strategic window to understanding and improving the quality and value of healthcare systems across the US. regions. Despite extensive efforts to address these variations however, expenditures and quality remain inconsistent across regions.[5–8] While the clinical and cost implications of TTCM hospitalization are well documented,[9–12] the existence of regional variation in its outcomes is unknown. Therefore, using a nationally representative database, we sought to investigate the extent and magnitude of regional difference in TTCM outcomes with regards to cost, invasive diagnostic procedures and mortality. This will engender opportunities to focus resources at addressing and narrowing outcome disparity in TTCM patients across the US.

[☆]Disclosures: Authors have no disclosures.

* Corresponding author at: Department of Internal Medicine, Englewood Hospital and Medical Center, Seton Hall University-Hackensack Meridian School of Medicine, 360 Engle Street, Englewood, NJ, United States.
E-mail address: oluwoleadegbala@yahoo.com (O. Adegbala).

https://doi.org/10.1016/j.hrtlng.2018.10.024
0147-9563/$ - see front matter

Methods

This study was conducted using the National Inpatient Sample (NIS) of the Health Care Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality (AHRQ). Details of the design and description of the NIS is available online.[13] Briefly, this nationally-representative database is the largest all-payer inpatient care database in the United States and contains encounter-level information of hospital stays compiled in a uniform format with privacy protection of individual patients. Each year, over 7 million hospital stays are sampled nationwide which, when weighted, estimates more than 35 million hospitalizations annually. NIS therefore approximates a 20% stratified sample of discharges from U.S. nonfederal hospitals, excluding rehabilitation and long-term acute care hospitals. The database protects patient confidentiality while providing useful information on each hospitalization, including patient demographic characteristics, hospital characteristics, discharge status, length of stay, expected payment source, severity and comorbidity measures. Therefore, the use of the NIS data is exempted from an Institutional Review Board approval.

Patient population

Patient population evaluated in this study includes all adult patients (age $\geq$ 18 years) with a diagnosis of TTCM in the NIS database between 2010 and 2014. These were identified via the following International Classification of Diseases-Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 429.83. Given that diagnosing TTCM requires the absence of obstructive CAD or angiographic evidence of acute plaque rupture, we excluded those patients who underwent coronary angiography and did receive revascularization therapy percutaneous coronary intervention or coronary artery bypass grafting using ICD-9-CM codes in Supplementary Table 1.

Covariates

Data on patient- and hospital-level characteristics were provided for each patient in the NIS. However, identity variables were not included to preserve both patient and hospital privacies. Patient-level factors including demographics, diagnoses, co-morbidities, in-hospital procedures, cost of hospitalization, length of stay, discharge disposition etc., as well as hospital level factors including bed-size, location (i.e. rural vs urban), geographical region etc. were available via the NIS database. Cost information was obtained from the hospital accounting reports collected by the Centers for Medicare and Medicaid Services (CMS).

Regions

For this study, geographical region was classified based on Census region as defined by the U.S. Census Bureau, namely, Northeast, Midwest, West and South.

Endpoint

The main endpoint in this study was risk-adjusted rates of in-hospital mortality in patients with diagnosis of TTCM. In addition, we evaluated variation in length of stay, hospital cost and disposition of patients who survived to hospital discharge as secondary outcomes. Disposition was classified into non-routine home discharge (including home with home health care, transfer to short-term hospital, and transfer to extended care facility (i.e. skilled nursing facility, intermediate care facility, etc.) vs routine home discharge. In-hospital mortality was the primary outcome of interest. Other outcomes included stroke, mechanical ventilation, percutaneous circulatory support devices, vasopressor use, acute kidney injury with hemodialysis, cardiac arrest, cardiogenic shock and coronary angiography (ICD- 9 procedural codes in supplementary Table 1). To calculate estimated cost of hospitalization, the NIS data were merged with cost-to-charge ratios available from the Healthcare Cost and Utilization Project. We estimated the cost of each inpatient stay by multiplying the total hospital charge with cost-to-charge ratios. We adjusted hospitalization costs for inflation using the US Bureau of Labor Statistics Consumer Price Index, with the year 2017 as the index base.[14–15]

Statistical analysis

This study was conducted using the NIS of the Agency for Healthcare Research and Quality (2010–2014). We reported the effect sizes, 95% confidence intervals (CI), and the Bonferroni corrected p-values given multiple comparisons among regions. All the statistical models were performed in SAS 9.4.

National estimates including rate, average, proportion and their standard deviation were calculated using the hospital-level trend/discharge weights provided for the NIS by AHRQ. Risk-adjusted rates of outcomes variables were calculated by fitting a Poisson regression model with a robust error variance under generalized estimating equations approach. The robust error variance was estimated by using unique hospital identification number. We adjusted for patient-level covariates, including age, race, gender, median household income, type of insurance, Elixhauser co-morbidity index, as well as hospital-level covariates, including hospital bed size, hospital location or teaching status, and year of data collection. Contrast on linear regression was used to calculate the overall *p* value.[16]

We quantified comorbidity burden per hospitalization using Elixhauser comorbidity index.[17] Patient- and hospital-level characteristics were compared between region using chi-square test for categorical variables, analysis of variance (ANOVA) for normally distributed continuous variables, and Kruskal–Wallis test for continuous variables with skewed distribution.

Discrete numeric variables with over-dispersed count distributions -length of stay and continuous variables with a right skewed spread- cost of hospitalization were modeled using a generalized linear regression (GENMOD) with a negative binomial function and gamma function respectively. The GENMOD procedures were performed using the CLASS, WEIGHT and REPEATED statements to account for the clustered sampling and in- hospital correlations.[18]

Results

Baseline characteristics

An estimated 120, 838 TTCM-related hospitalizations occurred over the study period in the United States between 2010 and 2014 among patients $\geq$ 18years. Of these, 86.58% were females with the mean age of 66.98 (13.83) (Table 1). Racial distribution included 81.92% White, 7.33% Black, 5.87% Hispanic, 1.99% Asians, and 2.87% other races and one-quarter of the admissions (24.67%) occurred among patients within the first quartile of household income and 6.86% were in rural location and most admissions were from the South. Patient- and hospital-level characteristics vary between the four regions (Table 1). Asians hospitalization was highest in the West and lowest in the South. Also, there existed regional variations in comorbidities at admission. Notably, comorbidities including hypertension, diabetes, obesity, chronic lung disease, congestive heart failure, valvular heart disease, stroke and chronic kidney disease were more predominant in the South while peripheral artery disease and chronic liver disease were more common in the West. The Midwest

Table 1
Descriptive analysis Takotsubo by regions 2010–2014.

	Total N (%)/ Mean (SD)	Northeast N (%)/ Mean (SD)	Midwest N (%)/ Mean(SD)	South N (%)/ Mean (SD)	West N (%)/ Mean (SD)	P value
No. of observation, unweighted	24,595	4645 (18.87%)	6350 (25.69%)	8177(33.39%)	5423(22.05%)	
No. of observation, weighted	120,0838	22,802	31,036	40,354	26,647	
Age	66.98 (13.83)	68.03 (13.66)	67.09 (13.92)	66.54 (13.76)	66.63 (13.91)	<0.0001
Female	86.58	86.00	86.43	87.40	86.02	0.118
Race/Ethnicity						<0.0001
Whites	81.92	83.14	85.55	82.67	76.26	
Blacks	7.33	7.19	8.61	8.78	3.97	
Hispanics	5.87	5.18	2.21	5.36	10.81	
Asians	1.99	1.27	0.96	0.71	5.61	
Others[d]	2.87	3.22	2.67	2.48	3.37	
Chronic Medical Conditions						
Hypertension	64.01	60.34	67.61	65.15	61.24	<0.0001
Diabetes	22.31	20.66	23.40	22.43	22.25	0.019
Obesity	9.66	7.75	11.35	9.46	9.64	<0.0001
Chronic lung Disease	28.56	27.01	31.01	28.97	26.40	<0.0001
Congestive Heart Failure[c]	19.85	18.94	21.43	18.11	20.21	0.005
Deficiency Anemia	19.69	15.61	22.04	19.21	21.17	<0.0001
Valvular heart disease	5.19	4.88	5.44	5.37	4.87	0.410
Thyrotoxicosis	0.86	0.88	0.74	0.78	1.12	0.132
Prior TIA/Stroke	10.13	8.59	11.04	10.99	9.11	<0.0001
Tumor	2.06	2.16	2.34	1.97	1.77	0.196
Chronic Kidney Disease[a]	10.66	8.61	12.12	10.21	11.40	<0.0001
Peripheral Vascular Disease[b]	8.13	6.36	8.54	8.02	9.34	<0.0001
Alcohol abuse	4.76	4.50	5.17	4.01	5.64	0.0002
Chronic liver disease	2.87	2.23	2.18	2.80	4.30	<0.0001
Comorbidities,[c] Elixhauser score						<0.0001
0	5.42	6.26	4.25	5.46	5.99	
1–3	54.39	60.70	50.92	54.76	52.47	
>3	40.20	33.04	44.84	39.78	41.54	
Expected primary payer						<0.0001
Medicare	62.11	64.87	62.69	62.24	58.92	
Medicaid	7.95	8.70	8.45	6.48	8.94	
Private	23.67	22.81	23.62	23.16	25.26	
Others[e]	6.26	3.62	5.26	8.21	6.88	
Median Household income in quartile						<0.0001
1st	24.67	16.46	23.74	35.58	16.29	
2nd	25.72	18.48	30.94	27.49	23.09	
3nd	25.53	25.94	27.28	20.73	30.39	
4th	24.08	39.11	18.04	16.20	30.24	
Hospital bed side						<0.0001
Small	10.85	15.22	11.36	9.60	8.43	
Medium	24.79	26.06	23.59	25.50	24.00	
Large	64.36	58.72	65.05	64.90	67.57	
Hospital teaching status						<0.0001
Rural	6.86	4.94	8.07	8.82	4.12	
Urban, Non-teaching	32.36	21.32	24.01	34.21	48.66	
Urban, teaching	60.78	73.75	67.92	57.00	47.21	

[a] Chronic Kidney Disease.
[b] Peripheral vascular disease.
[c] Comorbidities using Elixhauser Comorbidity index.
[d] Others include American Indians and Asians.
[e] Other health insurance types.

has the lower proportion of hospitalization with Elixhauser comorbid index greater than 3.

Multivariate analysis of outcomes

Table 2 shows in-hospital outcomes and procedures performed during hospitalization. Overall, we found significant regional variations in-patient mortality. While there was significant increased risk of in-hospital death in the West (5.28 [4.34–6.44]) vs 4.40 [3.57–5.43] vs 4.10 [3.38–498] vs 4.78 [3.96–5.77]) (figure 1), there was a different pattern of variation in the length of days on admission with significantly reduced length of hospitalization in the Midwest, South and West compared to Northeast. Also, the cost of hospitalization ranged from the lowest average of $28,465 in the South to highest average of $40,217 in the West. The rates of diagnostic coronary angiography performed was highest in the South and lowest in Northeast but did not reach statistical significance. Conversely, the risk-adjusted rate of non-routine home discharges was highest for Northeast.

In the West with the highest risk-adjusted mortality, the subgroup analysis showed higher mortality among patients aged < 45 years, males and urban, teaching hospital. However, the subgroup analysis of the Western region which has the highest risk-adjusted cost of hospitalization showed increased cost among patients aged ≥ = 45, males and in urban, teaching hospitals (Table 3).

Risk adjusted non-routine home discharges were highest in the Northeast, and subgroup analysis showed highest non-routine home discharge in urban, teaching hospitals.

Lastly, urban-teaching hospitals admissions demonstrated increased risk-adjusted rates of mechanical ventilation, cardiogenic shock and increased need for mechanical circulatory support devices compared to urban, non-teaching and rural hospitals.

Table 2
Multivariate regression model for the outcomes of Takotsubo Cardiomyopathy between regions in the US between 2010 and 2014.

	Northeast	Midwest	South	West	P value
Mortality	4.40 (3.57–5.43)	4.10 (3.38–498)	4.78 (3.96–5.77)	**5.28 (4.34–6.44)**	0.018
Length of hospital stay, Avg.(days)	10.50 (9.73–11.34)	**8.63 (8.07–9.24)**	**9.78 (9.11–10.50)**	**9.18 (8.51–9.90)**	<0.0001
Hospital cost, Avg. ($)	32,522 (29,584–35,751)	**28,761 (26,645–31,045)**	**28,465 (26,263–30,851)**	**40,217 (36,861–43, 879)**	<0.0001
Vasopressor use	1.39 (0.92–2.11)	1.30 (0.86–1.96)	**0.92 (0.61–1.38)**	1.19 (0.79–1.79)	0.052
Mechanical circulation support	1.16 (0.80–1.69)	1.14 (1.00–2.02)	1.30 (0.91–1.84)	1.00 (0.68–1.46)	0.108
Coronary angiography	47.08 (44.64–49.65)	**53.18 (50.86–55.61)**	**55.04 (52.92–57.24)**	**49.72 (47.45–52.10)**	<0.0001
Respiratory distress requiring Mechanical Ventilation	10.00 (8.79–11.39)	9.75 (8.58–11.09)	9.79 (8.71–11.00)	10.68 (9.46–12.05)	0.186
AKI requiring Hemodialysis	0.24 (0.10–0.55)	0.35 (0.16–0.75)	**0.45 (0.22–0.93)**	0.43 (0.21–0.91)	0.004
Cardiac Arrest	6.01 (5.03–7.20)	5.79 (4.93–6.79)	6.26 (5.37–7.30)	6.02 (5.15–7.04)	0.684
Cardiogenic shock	3.29 (2.65–4.09)	3.67 (3.02–4.47)	3.50 (2.89–4.23)	4.09 (3.34–5.01)	0.118
Non-Routine home discharge	35.78 (33.49–38.21)	**28.73 (26.94–30.65)**	**27.56 (25.88–29.35)**	**26.32(24.63–28.14)**	<0.0001

Each representing Adjusted rate %, (95% CI) Rates and Odds were adjusted for sex, age, insurance type, median household income national quartile for patient ZIP Code and Comorbidities using Elixhauser Comorbidity index. **Bold indicates significance *p* value ≤ 0.05 when compared to the reference region (Northeast). For mortality the reference region was Midwest**.

Discussion

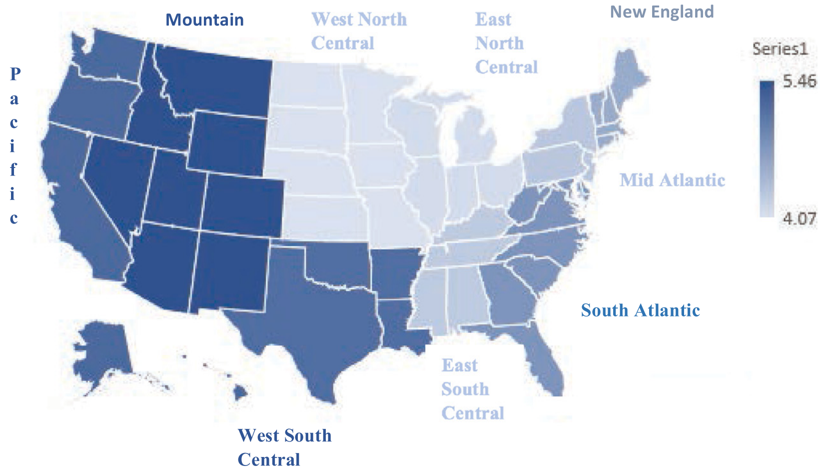
The salient findings of our analysis can be summarized as follows: i) There is significant geographic variation in the cost of hospitalization and in-hospital mortality across the US, ii) While the in-hospital mortality for TTCM was highest in the West, the West also had the highest cost of hospitalization without substantially prolonged hospital stay or increased rate of diagnostic coronary angiography, iii) Subgroup analysis showed the West had higher mortality among patients aged < 45 years, males and urban, teaching hospital. iv) There was also increased in-hospital mortality in urban-teaching hospitals across the different regions v) There were increased rates of admissions with mechanical ventilation and cardiogenic shock and increased need for mechanical circulatory support devices in urban teaching hospitals compared to urban, non-teaching hospitals and rural hospitals.

Several reports have shown that TTCM is predominantly seen in women and disproportionately worse outcomes in males have been reported in previous studies.[19] However, no previous studies have demonstrated comparative outcomes in patients diagnosed with TTCM across the U.S. regions. In this current study which to our knowledge is the first nationally representative data reporting

Table 3
Multivariate regression model for the outcomes of Takotsubo Cardiomyopathy between regions in the US between 2010 and 2014.

	Northeast	Midwest	South	West	P value
Mortality rate, AR% (95%CI)					
Full model	4.40 (3.57–5.43)	4.10 (3.38–498)	4.78 (3.96–5.77)	5.28 (4.34–6.44)	0.018
Age < 45 years	2.39 (1.08–5.26)	3.54 (1.93–6.49)	4.49 (2.53–7.98)	6.69 (3.73–1.20)	0.022
Age ≥ 45 years	4.08 (3.28–5.07)	3.70 (3.02–4.55)	4.23 (3.48–5.13)	4.61 (3.74–5.66)	0.089
Female	3.27 (2.55–4.19)	2.72 (0.21–3.49)	3.37 (2.67–4.25)	3.73 (2.92–4.78)	0.011
Male	4.38 (2.75–6.98)	5.50 (3.64–8.29)	5.47 (3.58–8.36)	6.22 (4.07–9.53)	0.265
Rural	3.45 (1.17–10.19)	2.99 (1.16–7.72)	5.01 (2.15–11.65)	4.39 (1.50–1.28)	0.424
Urban, Non-teaching	2.73 (1.67–4.48)	1.89 (1.19–3.01)	2.61 (1.71–3.97)	3.74 (2.51–5.57)	0.0007
Urban, teaching	6.03 (4.48–7.52)	5.96 (4.83–7.36)	6.58 (5.33–8.13)	6.58 (5.18–8.36)	0.603
Hospital cost ($)					
Full model	32,522 (29,584–35,751)	28,761(26,645–31,045)	28,465 (26,263–30,851)	40,217 (36,861–43,879)	<0.0001
Age < 45 years	28,087 (21,567–36,578)	26,769(21,625–33,138)	27,969 (21,957–35,628)	37,798 (30,955–46,154)	0.018
Age ≥ 45 years	34,692 (31,549–38,148)	30,546(28,273–33,001)	30,310 (27,935–32,887)	42,896 (39,211–46,926)	<0.0001
Female	27,539 (24,828–30,547)	23,994(22,079–26,075)	23,592 (21,664–25,692)	33,514 (30,483–36,846)	<0.0001
Male	31,613 (26,773–37,328)	30,093 (26,332–34,391)	31,828 (27,739–36,519)	42,829 (36,997–49,579)	0.0003
Rural	25,505 (18,907–34,405)	20,545(17,433–24,212)	17,697 (15,018–20,853)	26,206 (21,698–31,650)	0.0005
Urban, Non-teaching	21,933 (19,233–25,011)	21,990(19,372–24,962)	29,554 (25,870–33,763)	21,042 (18,621–23,779)	<0.0001
Urban, teaching	41,636 (37,321–46,450)	35,193(32,248–38,406)	36,044 (32,579–39,878)	50,346 (45,009–56,315)	<0.0001
Length of stay (Mean days)					
Full model	10.50 (9.73–11.34)	8.63 (8.07–9.24)	9.78 (9.11–10.50)	9.18 (8.51–9.90)	<0.0001
Age < 45 years	7.18 (5.78–8.93)	6.11 (5.02–7.44)	7.74 (6.33–9.47)	6.85 (5.77–8.1248)	0.107
Age ≥ 45 years	10.80 (10.00–11.67)	8.86 (8.28–9.48)	9.97 (9.28–10.70)	9.41 (8.71–10.16)	<0.0001
Female	9.06 (8.37–9.81)	7.42 (6.90–7.97)	8.42 (7.80–9.08)	7.89 (7.26–8.5538)	<0.0001
Male	10.33 (8.95–11.91)	8.60 (7.65–9.66)	9.71 (8.69–10.85)	9.32 (8.17–10.64)	0.066
Rural	7.25 (6.08–8.63)	5.52 (4.77–6.37)	6.28 (5.48–7.20)	5.20 (4.37–6.19)	0.0015
Urban, Non-teaching	8.39 (7.51–9.37)	6.72 6.03–7.49)	7.50 (6.78–8.29)	6.97 (6.27–7.76)	<0.0001
Urban, teaching	12.73 (11.66–13.90)	10.55 (9.77–11.39)	12.05 (11.05–13.13)	11.50 (10.44–12.67)	<0.0001
Non-routine Home discharge, AR % (95%CI)					
Full model	35.78 (33.49 - 38.21)	28.73 (26.94–30.65)	27.56 (25.88–29.35)	26.32(24.63–28.14)	<0.0001
Age < 45 years	28.96 (23.21 - 36.12)	25.36 (20.59–31.24)	24.02 (1961–2944)	27.15 (22.12–33.31)	0.4263
Age ≥ 45 years	32.24(30.07 – 34.56)	25.74 (24.04–27.55)	24.49 (22.91–26.17)	23.36 (21.77–25.07)	<0.0001
Female	28.09 (25.87 30.49)	22.12 (20.37–24.03)	21.36 (19.71–23.16)	20.32 (18.65–22.13)	<0.0001
Male	34.16 (29.32 39.81)	29.66 (25.52–34.48)	26.43 (22.78–30.66)	26.95 (23.08–31.46)	<0.0001
Rural	26.33 (18.29 37.91)	18.87 (13.42–26.54)	19.60 1(4.00–27.44)	14.86 (10.12–21.82)	0.0007
Urban, Non-teaching	29.05 (25.27- 0.3339)	20.75 (18.02–23.88)	2131 (18.62–24.39)	20.67 (18.03–23.71)	<0.0001
Urban, teaching	34.08 (31.24 - 37.17)	28.46 (26.14–30.99)	26.23 (24.09–28.55)	25.32 (23.14–27.71)	<0.0001

AR; Adjusted rates. Rates were adjusted for sex, age, insurance type, median household income national quartile for patient ZIP Code and Comorbidities using Elixhauser Comorbidity index.



Census Regions:	West	Midwest	South	Northeast
Census Division:	Pacific (5.22)	West North Central (4.07)	West South Central (5.18)	New England (4.58)
	Mountain (5.46)	East North Central (4.12)	East South Central (4.29)	Mid Atlantic (4.31)
			South Atlantic (4.80)	

Fig. 1. Observed in-hospital mortality rates among patients admitted for Takotsubo Cardiomyopathy in the United States in 2010 to 2014, stratified by Census division.

geographic variation in outcomes of TTCM, we demonstrated that regional variation exists in the hospitalization outcomes of TTCM with higher mortality and cost observed in the West. In addition, the West demonstrated significantly higher mortality among males, younger patients and those admitted to urban teaching hospital. After considering levels of comorbidities and patient demographic factors, we confirmed that remarkable regional differences in all-cause mortality rates are still apparent. Part of the variance in mortality rates between regions can be explained by differences in patients' characteristics and hospital settings. These findings are comparable to that of Krumholz et al. who reported poorer outcomes in patients admitted with acute myocardial infarction and heart failure among five western states.[20] While the exact reason for increase mortality rate in the West remains unknown. It is plausible that the observed difference reflects true variations in effectiveness of healthcare services. It is worth noting that Murugiah et al. found lower, 1.6%–3%, in-hospital morality rate in TTCM in a cohort of patients admitted between 2007 and 2012 using Medicare inpatient claims data and Medicare enrollment data from the Centers for Medicare & Medicaid Services.[3] However, a meta-analysis demonstrated in-hospital mortality rate of 4.5% in TTCM and another study using NIS data showed in-hospital mortality of 4.2%.[13,20]

Unexpectedly, despite increased mortality in the west, there is a significantly higher cost of hospitalization. It would be expected that higher healthcare spending should lead to better outcomes. However, this is not always the case as shown in the current study. Previous studies have recently emphasized that more spending does not translate to better health outcomes.[6,21,22] The increased spending in the west compared to other regions may reflect the differences in physician practices, local supply of physicians and hospital resources in the region.[23]

Increase in length of hospitalization seen in the Northeast is similar to previous studies that showed significantly longer hospitalization time for cardiovascular diseases in the Northeastern states.[2,6] In contrast to previous studies however, mortality rate for TTCM is not higher in Northeastern states. Previous studies focused on heart failure and acute myocardial infarction and may not be generalized to TTCM. Increased length of hospitalization in this region may be related to variation in practice. Non-routine home discharge is commoner in this region and may impact discharge planning, prolonging the length of stay.

Although, it may be argued that patients admitted to urban teaching hospitals had poorer outcomes across all regions, this may be related to the severity and complexity of patients referred to these tertiary centers as reflected by a higher proportion of these patients having conditions requiring mechanical ventilation, cardiogenic shock and use of circulatory support devices.

Further studies to understand regional variation in health economics of various cardiovascular diseases may help to further elucidate the variation and identify effective strategies to eliminate health outcomes disparities in TTCM.

Our study has some limitations that need to be considered. The use of the HCUP database being an administrative database may reflect multiple admissions and care must be taken in interpreting the findings from this study. Also, there may be some coding error with some cases erroneously missed or included. One of the important strengths of the present study is that it leverages on the significant size of this nationally-representative, largest all-payer inpatient care database in the United States which has been extensively validated against other surveys and confirmed to perform very well for many estimates.[24]

In conclusion, there is significant regional variation in outcomes, cost and length of hospitalization among patients with TTCM. Outcomes appear to be worse in the West compared to other regions of the country despite increased cost of hospitalization in this region. Observed differences in-hospital mortality rates across these regions may not solely result from differences in patient characteristics and hospital settings but may reflect differences in currently unknown aspects of patient care. Understanding this variation requires a detailed understanding of the processes of care.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hrtlng.2018.10.024.

References

1. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. *J Cardiol*. 1991;21 (2):203–214.

2. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med*. 2005;352(6):539–548.
3. Murugiah K, Wang Y, Desai NR, Spatz ES, Nuti SV, Dreyer RP, et al. Trends in short-and long-term outcomes for Takotsubo Cardiomyopathy among medicare fee-for-service beneficiaries, 2007 to 2012. *JACC*. 2016;4(3):197–205.
4. Khera R, Light-McGroary K, Zahr F, Horwitz PA, Girotra S. Trends in hospitalization for Takotsubo Cardiomyopathy in the United States. *Am Heart J*. 2016;172:53–63.
5. Zhang Y, Baicker K, Newhouse JP. Geographic Variation in Medicare Drug Spending. *N Engl J Med*. 2010;363(5):405–409.
6. Fisher ES, Wennberg DE, Stukel TA, Gottlieb DJ, Lucas FL, Pinder É L. The implications of regional variations in medicare spending. Part 1: the content, quality, and accessibility of care. *Ann Intern Med*. 2003;138(4):273–287.
7. Institute of Medicine. Variation in Health Care Spending: Target Decision Making, Not Geography. In: Newhouse JP, Garber AM, Graham RP, McCoy MA, Mancher M, Kibria A, eds. *Variation in Health Care Spending: Target Decision Making, Not Geography*. Washington, DC: The National Academies Press; 2013:206.
8. Prices don't drive regional medicare spending variations. *Health Aff*. 2010;29(3):537–543.
9. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, et al. Clinical features and outcomes of Takotsubo (Stress) cardiomyopathy. *N Engl J Med*. 2015;373(10):929–938.
10. Glaveckaitė S, Šerpytis P, Pečiūraitė D, Puronaitė R, Valevičienė N. Clinical features and three-year outcomes of Takotsubo (stress) cardiomyopathy: observational data from one center. *Hellenic J Cardiol*. 2016;57(6):428–434.
11. Sobue Y, Watanabe E, Ichikawa T, Koshikawa M, Yamamoto M, Harada M, et al. Physically triggered Takotsubo cardiomyopathy has a higher in-hospital mortality rate. *Int J Cardiol*. 2017;235:87–93.
12. Becher T, El-Battrawy I, Baumann S, Fastner C, Behnes M, Loßnitzer D, et al. Characteristics and long-term outcome of right ventricular involvement in Takotsubo Cardiomyopathy. *Int J Cardiol*. 2016;220:371–375.
13. Singh K, Carson K, Shah R, Sawhney G, Singh B, Parsaik A, et al. Meta-analysis of clinical correlates of acute mortality in Takotsubo Cardiomyopathy. *Am J Cardiol*. 2014;113(8):1420–1428.
14. U.S. Bureau of Labor Statistics. Consumer price index for all urban consumers: hospital and related services [CUSR0000SEMD]; 2018. retrieved from FRED, Federal Reserve Bank of St. Louis; [updated January 30; 2018. https://fred.stlouisfed.org/series/CUSR0000SEMD.
15. Consumer Price Index Data from 1913 to 2017 [Internet]. [cited January, 31st, 2018. http://www.usinflationcalculator.com/inflation/consumer-price-index-and-annual-percent-changes-from-1913-to-2008/.
16. Williams R. Using the margins command to estimate and interpret adjusted predictions and marginal effects. *Stata J*. 2012;12(2):308–331.
17. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8–27.
18. Khera R, Angraal S, Couch T, et al. Adherence to methodological standards in research using the national inpatient sample. *JAMA*. 2017;318(20):2011–2018.
19. Brinjikji W, El-Sayed AM, Salka S. In-hospital mortality among patients with Takotsubo Cardiomyopathy: a study of the national inpatient sample 2008–2009. *Am Heart J*. 2012;164(2):215–221.
20. Krumholz HM, Merrill AR, Schone EM, Schreiner GC, Chen J, Bradley EH, et al. Patterns of hospital performance in acute myocardial infarction and heart failure 30-day mortality and readmission. *Circul*. 2009;2(5):407–413.
21. Gutacker N, Bojke C, Daidone S, Devlin NJ, Parkin D, Street A. Truly inefficient or providing better quality of care? Analysing the relationship between risk-adjusted hospital costs and patients' health outcomes. *Health Econ*. 2013;22(8):931–947.
22. McKay NL, Deily ME. Cost inefficiency and hospital health outcomes. *Health Econ*. 2008;17(7):833–848.
23. Song Y, Skinner J, Bynum J, Sutherland J, Wennberg JE, Fisher ES. Regional variations in diagnostic practices. *N Engl J Med*. 2010;363(1):45–53.
24. DeShazo JP, Hoffman MA. A comparison of a multistate inpatient EHR database to the HCUP nationwide inpatient sample. *BMC Health Serv Res*. 2015;15(1):384.