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Short communication

Clinical impact of advanced chronic kidney disease on outcomes and in-hospital complications of Takotsubo Syndrome (broken-heart-syndrome): Propensity-matched national study

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ABSTRACT

Multiple studies evaluated the outcomes and complications rate of Takotsubo Syndrome (TTS) in patients with and without advanced chronic kidney disease (CKD), revealed conflicting results. This study aims to assess the clinical outcomes and impact of advanced CKD on patients hospitalized with Takotsubo Syndrome. Patients who presented with Takotsubo cardiomyopathy between 2010 and 2014 were identified in the National Inpatient Sample (NIS) database using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), and subsequently were divided into two groups, with advanced CKD and without advanced CKD. NIS is the largest all-payer inpatient stays database in the United States. The primary outcome was the effect of advanced CKD on inpatient mortality in comparison to the non-advanced CKD group. Secondary outcomes were the impact of CKD on TTS in-hospital complications. We also evaluated the length of hospital stay and the cost of hospitalization. Propensity score-matched analysis was performed to address potential confounding. The advanced CKD group had no significant increase in the risk of In-hospital mortality (OR 0.99; 95% CI 0.75–1.31, P = 0.269). However, advanced CKD patients were more likely to develop acute kidney injury (AKI) requiring dialysis (OR: 5.12, 95% CI: 3.16–8.30, P = <0.0001), and were more likely to stay longer at the hospital (OR 1.12; 95% CI 1.03 to 1.22, P 0.010). In conclusion, advanced chronic kidney disease does not increase immediate in-hospital mortality, neither most of the TTS in-hospital complications, apart from AKI and hospital length of stay, in comparison to the patients with non-advanced CKD.

1. Introduction

Since it was first described in Japan by Satoh et al. in 1990, Takotsubo Syndrome (TTS) became increasingly-reported as a cause of transient focal myocardial dyskinesis following major stress [1]. TTS is characterized by transient-reversible regional wall-motion abnormalities usually extending beyond single coronary artery territory [1]. TTS can present as an acute coronary syndrome (ACS) or acute heart failure, usually but not always triggered by physically or emotionally stressors [2]. It is widely-accepted that sympathetic hyperstimulation has a pivotal role in the pathophysiology of TTS [1]. Simultaneously, in chronic kidney disease (CKD) patients there is overwhelming evidence for sympathetic hyper-activation [3]. CKD patients have considerably higher mortality risk than age-matched controls and renal dysfunction is an independent predictor of adverse-outcomes among heart failure patients [3,4]. However, comparative outcomes of TTS in patients with and without renal dysfunction are conflicting [5–8]. Our study aim to evaluate the impact of advanced CKD on in-hospital outcomes of TTS patients using real practice data derived from the national inpatient sample (NIS).

2. Methods

Our study utilized the NIS database, which is part of the Healthcare Cost/Utilization Project (HCUP), sponsored by Agency for Healthcare Research and Quality (AHRQ) [9]. NIS data were queried using the International Classification of Diseases, 9th-Revision, Clinical Modification (ICD-9-CM) to identify the study variables. All adult patients presented with TTS as a primary diagnosis from 2010 to 2014 were included. TTS patients who had concomitant diagnosis of advanced CKD (eGFR < 60 mL/min/1.73 m^2) were identified by ICD-9 codes (585.3585.4585.5585.6 representing CKD Stage III, IV, V and End-stage-renal-disease (ESRD), respectively). TTS patients who had a concomitant diagnosis of mild or no CKD (eGFR > 60 mL/min/1.73 m^2) were identified by ICD-9 codes (000.0,585.1585.2 representing No CKD, CKD Stage I and II, respectively). We

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compared baseline characteristics, mortality, hospital outcomes, length of stay and cost of hospitalization in both groups. The primary outcome was all-cause in-hospital mortality. Secondary outcomes were the in-hospital complications. To test the differences between categorical variables, we used the chi-square-test; wherever chi-square is considered an inappropriate test due to low expected frequencies, we substituted it with the Fisher's-exact-test. To test the differences between continuous variables, we will use the Student's-test, P-value < 0.05 will be considered statistically significant. Secondary outcomes were determined based on the Patient Safety Indicators established by the AHRQ to monitor adverse-events during hospitalization. These indicators are based-on ICD-9-CM codes, and each PSI has specific inclusion and exclusion criteria [10,11]. To calculate the estimated cost of hospitalization, the NIS data were merged with cost-to-charge ratios available from the HCUP. Adjusted cost for each year was calculated in terms of the 2017 cost, after adjusting for inflation according to the latest consumer-price-index data released by US-government on 2018 [12]. Counting for demographic factors, we included race, gender, health-insurance, and income-level based-on the zip code.

We performed a comparative analysis of the outcomes of TTS in patients advanced CKD and TC in patients without advanced CKD. Propensity score (PS) matching model was developed to account for potential confounding factors, reduce the selection bias and to derive two matched groups for comparative outcomes analysis [13]. PS was calculated using multivariable logistic models derived from hospitals level, clinical, and demographic covariates, including the Elixhauser-comorbidities. For the calculation of the PS, dependent variable was TTS with advanced CKD at baseline. We performed matching on the PS implementing a greedy algorithm to construct a balanced match of TTS with advanced CKD cases to non-advanced CKD TTS cases in a 1:1 ratio using a caliper of 0.1. Finally, 1478 TTS patients with advanced CKD cases were selected for the propensity-matched population. We assessed the success of the match by performing Mc-Nemar's-test for categorical variables and paired-*t*-test for normally distributed continuous variables. All variables were 100% present besides race (8.51%), health insurance type (0.10%), average household income by zip code (1.73%), hospital teaching status (0.31%) and hospital bed status (0.31%). Because these variables were all missing at random, all missing observations for the five variables were excluded, and a complete case analysis was performed.

All the data extraction/analyses were done with Statistical Analysis System (SAS-V.9.4, SAS-Institute Inc.). We chose a P-value of <0.05, reported the effect sizes, 95% confidence-intervals, and P-values. For the matched patient's clinical characteristics, we reported the mean and standard deviation for continuous variables and percentages for categorical variables. Binary outcomes were modeled with binomial logistic regressions. Discrete-numeric variables with an over-dispersed count distribution and continuous variables with a right-skewed spread were modeled with generalized linear regressions, accounting for the matching, and with a negative binomial function and gamma function respectively. We reported odds-ratio for our binary outcome, and mean-ratios for the numeric outcomes.

3. Results

The study population included 24,595 patients from NIS registry; all were hospitalized for TTS from 2010 to 2014, among them 86.58% were women and mean-age was 66.98 ± 13.83 years old. The prevalence of advanced CKD was 6.70%. The mean-age was (72.32 ± 12.86 years) for the TTS group with advanced CKD versus (66.6 ± 13.82 years) for

Table 1
Baseline characteristics of patients presented with Takotsubo Syndrome in the U.S., according to presence or absence of advanced CKD; before and after matched cohort 1: 1 Matching.

		Before 1:1 propensity matching			After 1:1 propensity matching		
Variables	Total	With advanced CKD	Without advanced CKD	P value	With advanced CKD	Without advanced CKD	P value
No. of observation, un-weighted	24,595	1644 (6.70)	22,951 (93.30)		1478	1481	
No. of observation, weighted	120,838	8101	112,737		7291	7288	
Age, mean (SD)	66.98 (13.83)	72.32 (12.86)	66.60 (13.82)	<0.0001	72.20 (13.01)	72.46(11.79)	0.564
Female	86.58	82.26	86.89	<0.0001	82.95%	83.50%	0.675
Race/ethnicity				<0.0001			0.819
White	81.93%	74.78%	82.44%		75.12%	76.78%	
Black	7.33%	12.31%	6.97%		12.20%	10.86%	
Hispanic	5.87%	6.27%	5.85%		6.24%	5.92%	
Asia	1.99%	4.27%	1.83%		4.21%	4.33%	
Peripheral vascular disease	8.13%	15.23%	7.62%	<0.0001	15.57%	16.64%	0.431
Hypertension	64.01%	78.27%	62.99%	<0.0001	77.77%	77.24%	0.732
Dyslipidemia	43.92%	47.29%	43.68%	0.007	46.58%	47.23%	0.732
Diabetes mellitus	22.31%	41.39%	20.93%	<0.0001	41.83%	42.69%	0.637
Rheumatologic disorder	5.01%	7.37%	4.84%	<0.0001	7.32%	8.12%	0.445
Obese	9.66%	12.93%	9.43%	<0.0001	13.18%	13.47%	0.813
Congestive heart failure	19.85%	33.31%	18.88%	<0.0001	33.05%	33.87%	0.637
Chronic obstructive pulmonary disease	28.56%	29.37%	28.50%	0.457	28.90%	29.03%	0.936
Anemia	19.69%	44.98%	17.87%	<0.0001	45.61%	45.68%	0.972
Alcohol abuse	4.76%	2.18%	4.95%	<0.0001	1.94%	1.28%	0.138
Smoking	33.19%	26.20%	33.69%	<0.0001	26.35%	26.25%	0.954
Coagulopathy	6.74%	10.91%	6.44%	<0.0001	10.50%	10.83%	0.775
Cerebrovascular disease	7.93%	11.22%	7.69%	<0.0001	11.32%	11.51%	0.877
Coronary artery disease	41.58%	49.41%	41.02%	<0.0001	49.22%	48.27%	0.612
Chronic liver disease	2.87%	4.09%	2.78%	0.002	3.93%	3.67%	0.720
Elixhauser score				<0.0001			1.00
0	5.42	0.06	5.80		0.07	0.07	
1–3	54.39	17.68	57.02		18.06	18.03	
≥4	40.20	82.25	37.18		81.87	81.90	
Primary payer				<0.0001			0.422
Medicare	62.11%	82.54%	60.64%		83.00%	83.22%	
Medicaid	7.95%	4.28%	8.21%		4.23%	3.83%	
Private	23.67%	10.79%	24.60%		10.65%	9.97%	
Others	6.26%	2.39%	6.54%		2.12%	3.00%	
Median household income				0.412			0.851
1st quartile	24.67%	23.34%	24.77%		24.34%	23.04%	
2nd quartile	25.72%	27.34%	25.60%		26.85%	27.73%	
3rd quartile	25.53%	25.84%	25.51%		25.29%	25.11%	
4th quartile	24.08%	23.48%	24.12%		23.51%	24.12%	
Hospital bed size				0.038			
Small	10.85%	11.89%	10.78%		11.67%	11.8%	
Medium	24.79%	26.99%	24.63%		27.52%	26.52%	
Large	64.36%	61.12%	64.59%		60.80%	61.64%	
Hospital location				0.091			0.467
Rural	6.86	7.34	6.82		7.27	6.10	
Urban non-teaching	32.36	29.65	32.55		31.43	32.08	
Urban teaching	60.78	63.01	60.62		61.30	61.83	

Table 2
Clinical outcomes of Takotsubo Syndrome in advanced CKD group versus non-advanced CKD group.

Variables	With advanced CKD	Without advanced CKD	OR/MR (95% CI)	P value
In-patient mortality	7.10%	7.11%	0.99 (0.75, 1.31)	0.269
Cardiogenic shock	5.55%	6.74%	0.82 (0.60, 1.11)	0.106
Mechanical support	1.57%	2.50%	0.62 (0.39, 1.03)	0.064
Vasopressor use	2.83%	3.23%	0.87 (0.57, 1.33)	0.520
Cardiac arrest, ventricular tachycardia and ventricular fibrillation	7.72%	7.58%	1.03 (0.78, 1.35)	0.841
Ischemic stroke	0.22%	0.20%	1.00 (0.20, 4.97)	1.000
Acute respiratory failure	30.77%	31.68%	0.97 (0.83, 1.13)	0.692
Post-operative deep vein thrombosis/pulmonary embolism	4.64%	5.00%	0.93 (0.66, 1.30)	0.665
Post-operative sepsis	17.50%	16.90%	1.04 (0.86, 1.26)	0.232
Acute kidney injury	44.96%	22.73%	2.80 (2.38, 3.28)	<0.0001
Acute kidney injury requiring dialysis	6.34%	1.36%	5.12 (3.16, 8.30)	<0.0001
Non-routine home discharge‡	61.33%	58.78%	1.13 (0.97, 1.31)	0.265
Cost	27,632	26,519	1.04 (0.94, 1.16)	0.434
Length of stay	9.01	8.05	1.12 (1.03, 1.22)	0.010

the group without advanced CKD. Baseline clinical characteristics between the groups before and after propensity matching are depicted in Table 1.

After adjusting for patient- and hospital-level characteristics, in-hospital mortality difference was statistically not significant between TTS group with advanced CKD versus TTS group without advanced CKD (OR:0.99; 95%CI 0.75–1.31, P = 0.269). Advanced CKD group was associated with higher rates of acute kidney injury (AKI) requiring dialysis and longer length of stay. There was no statistically significant difference between the two groups in term of cardiac complications, vasopressors requirements, ischemic stroke, non-routine discharges and cost of hospitalization. Table 2 shows clinical outcomes of TTS in patients with advanced CKD versus without advanced CKD.

4. Discussion

Our study attempted to assess the impact of renal dysfunction on TTS by comparing patients with advanced CKD (eGFR < 60 mL/min/1.73 m^2) to patients with mild or no CKD (eGFR > 60 mL/min/1.73 m^2). We have the largest sample size of all studies that evaluated the impact of renal dysfunction on TTS outcomes [5–8]. Furthermore, we conducted a propensity-matched analysis to account for confounders. Advanced CKD patients were more likely to develop AKI requiring dialysis and to have a longer hospital stay. Our result came in agreement with the Santoro et al. and Murakami et al. studies which suggested that lower eGFR values or advanced CKD during hospitalization are associated with longer length of stay [5,8]. Furthermore, from a pathophysiologic standpoint, it is conceivable that advanced CKD patients were more likely to develop AKI during acute TTS giving the higher risk of contrast nephropathy and the concomitant cardiac insult [14].

Advanced CKD patients in our study had no significant increase in the risk of in-hospital mortality or other complications, compared to the other group. Murakami et al. evaluated similar cohorts of patients hospitalized with TTS [8]. Advanced CKD group in Murakami et al. study needed more cardiopulmonary supportive therapies (including mechanical ventilation and intra-aortic balloon pumping) than non-advanced CKD group [8]. Nevertheless, there was no difference in cardiac death in both groups [8]. Bill et al. study showed no differences in-hospital adverse-events in both groups (eGFR < 60 mL/min/1.73 m^2 Vs eGFR > 60 mL/min/1.73 m^2) [7]. Although, the in-hospital mortality rate was higher in patients with eGFR < 60 mL/min/1.73 m^2 however, it did not reach significance [7]. Contradictorily, in the study by Ando et al. CKD patients had the highest risk of in-hospital mortality and complications [6]. Furthermore, the lowest glomerular filtration rate corresponded with highest adverse-event rate [6]. Explanations for this discrepancies with our study are unclear but may include a more extensive control for confounding factors through propensity-matched analysis in our study [13]. Another point to raise, is 34% of the Ando et al. study patients were diagnosed with TTS without cardiac catheterization, owing to general conditions and/or clinical course. Therefore, coronary artery disease could not be excluded, and this might explain the recorded higher mortality in that study [6]. Also, the recorded in-hospital mortality in all these studies, including our study, could be dominated by the primary diagnoses and this could in-validate any effect of CKD on mortality. Historically, patients with CKD have a strong risk of ACS. Furthermore, mulitple studies showed increased ACS adverse outcomes in patients with worse chronic kidney disease stages, mostly higher rate of AKI and mortality [15–18]. However, there is no studies compared the impact of advanced CKD on ACS versus TTS outcomes.

Our study has some limitations to be considered. Firstly, NIS database doesn't capture variables related to the severity of TTS (e.g. Ejection-fraction), rate of contrast-nephropathy, baseline functional status, cardiac-imaging data, inotropes, antithrombotic agents use and long-term outcomes. Another limitation of NIS database is that no validation studies for the TTS code (429.83) have been carried out, and there is a possibility that cases of TTS may have been coded incorrectly as ACS thus leading to underestimation or overcoding of the incidence of TTS. Again, the use of a registry database to calculate the prevalence of advanced CKD is also at risk of coding-errors [19].

In conclusion, after adjusting for confounding factors advanced CKD did not increase in-hospital mortality, however, this could be mainly related to the short follow-up data in our study. Advanced CKD was associated with increased rate of AKI, dialysis and hospital stay length in patients presenting with TTS, concluding that advanced CKD is a predictor of increased renal complications in such population. Giving the available conflicting evidence, prospective studies are needed to further evaluate the impact of renal impairment in short and long-term outcomes of TTS.

Conflict of interest

None of the authors have any conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.098.

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