

Frailty as a predictor of adverse in-hospital outcomes in older patients with Takotsubo cardiomyopathy

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ABSTRACT

Background Takotsubo cardiomyopathy (TCM), defined by transient left ventricular dysfunction, is commonly triggered by acute emotional/physical stress. It is recognized as a cause of acute coronary syndrome, particularly in the elderly population, as they are vulnerable due to multiple comorbidities, including frailty, a condition marked by reduced functional reserve and increased susceptibility to stressors.

Methods A retrospective analysis of the National Inpatient Sample (2016–2021) was performed to identify patients aged 65 and older hospitalized with TCM using ICD-10-CM codes. Patients were classified based on frailty, defined by Johns Hopkins ACG frailty-defining diagnoses. Multivariable mixed-effects logistic regression was used to identify independent predictors of in-hospital outcomes and compare the groups. Propensity score matching was applied to 736 pairs to control for confounders and assess outcomes.

Results Frail patients had significantly high in-patient mortality (5.71 vs. 1.09%, $P < 0.001$), cardiogenic shock (8.47 vs. 4.70%, $P = 0.003$), sudden cardiac arrest (3.12 vs. 1.49%, $P = 0.037$), sepsis (2.85 vs. 0.95%, $P = 0.008$), and major adverse cardiac events (22.55 vs. 18.21%, $P = 0.038$). There was no significant difference in acute stroke, pulmonary embolism, mechanical circulatory support utilization, cardiac arrhythmias, acute kidney injury, pacemaker insertion, and length of stay between the two groups.

Conclusion Frailty is associated with an increased in-hospital mortality among elderly patients with TCM. Understanding the importance of frailty in elderly population with TCM helps us in optimizing management strategies and improving patient outcomes.

Takotsubo cardiomyopathy (TCM), often referred to as “broken heart syndrome,” was first described in Japan in 1990.^[1] It is a temporary and reversible form of left ventricular dysfunction that closely mimics myocardial infarction, presenting similar electrocardiographic abnormalities, elevated cardiac biomarkers, and echocardiographic findings. TCM is typically triggered by acute emotional or physical stress. The term “Takotsubo” is derived from a Japanese octopus trap, characterized by a narrow neck and rounded bottom, which reflects the heart’s altered shape during this

condition. This unique morphology results from apical wall dysfunction, causing ballooning of the left ventricle’s apex during systole. Despite its dramatic onset, most TCM cases resolve within days to weeks, with patients returning to their baseline systolic function.

While initially considered rare, TCM is now recognized as a cause of acute coronary syndrome, accounting for approximately 2% of patients presenting with acute coronary symptoms.^[2] It is particularly prevalent among older adults, especially women, who are more susceptible due to multiple comorbidities, in-

cluding frailty. Data from the International Takotsubo Registry—a multicenter consortium of 26 institutions across Europe and the United States—revealed that among 1,750 patients with TCM, 89.9% were women, with a mean age of 66.4 years.^[3]

Frailty is conceptually defined as a clinically recognizable state in older adults characterized by increased vulnerability, resulting from age-associated declines in physiologic reserve and function across multiple organ systems. This decline compromises their ability to cope with every day or acute stressors.^[4] Multiple indices exist to assess frailty, which has been associated with increased hospital mortality, prolonged hospital stays, and a higher likelihood of institutionalization.^[5,6] Among patients with cardiac disease, previous meta-analyses have shown that frailty significantly predicts adverse clinical outcomes following invasive procedures, such as transcatheter aortic valve implantation and percutaneous coronary intervention.^[7,8]

However, the impact of frailty on in-hospital outcomes for elderly patients with Takotsubo cardiomyopathy has not been thoroughly explored. This study aims to provide valuable insights by identifying the role of frailty in TCM, potentially guiding clinical management and improving outcomes for this vulnerable population.

METHODS

Data Source

Data were drawn from the National Inpatient Sample (NIS) database, which is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ), the largest publicly available all-payer inpatient healthcare database in the United States, providing nationally representative estimates of inpatient utilization, access, outcomes, cost, and quality.^[9] A 20% random sample of patients within each stratum is selected, and their demographic information, diagnoses, and resource utilization are entered into the database. Each discharge is then weighted (weight = total number of discharges from all U.S. acute care hospitals/number of discharges in the 20% sample) to ensure the NIS is nationally representative. The NIS is the most comprehensive hospital database in the country, allowing researchers to investigate healthcare delivery and outcomes. Data were queried

from the years of 2016 to 2021. Our study follows the methodological design checklist proposed by Khera, *et al.*^[10] to address common study design errors in NIS-based research. Since the NIS is a publicly available, anonymized national database with prior ethical approval from the AHRQ, our study was exempt from Institutional Review Board (IRB) approval.

Study Population

Elderly patients (≥ 65 years of age) who were admitted to the hospital with a principal diagnosis of TCM between January 1st, 2016, and December 31st, 2021, were included in the study. TCM was defined using the ICD-10-CM code “I5181”. Patients were divided into two groups based on the presence of frailty. Frailty was defined using the Johns Hopkins Adjusted Clinical Groups (ACG) frailty-defining diagnoses indicator, which is an instrument based on 10 clusters of frailty-defining diagnoses, including malnutrition, impaired vision, dementia, urinary incontinence, weight loss, decubitus ulcer, barriers to healthcare access, poverty, walking difficulty, and falls. This binary indicator identifies frailty by the presence of ≥ 1 diagnostic cluster that has been designed and validated for research on frailty-related outcomes and resource use using administrative data.^[11] Johns Hopkins ACG’s definition of frailty has been employed in previous NIS studies.^[12–14] The list of ICD-10 codes for frailty-defining diagnosis is demonstrated in Supplementary Tables 1, 2, and 3. The ICD-10-CM codes were validated through an independent review by two authors with minimal interobserver variability ($< 5\%$), and discrepancies were resolved through consultation with a third author and further code iteration as needed.

Definitions and Outcomes

The primary outcome was in-hospital all-cause mortality. Secondary outcomes were: morbidity as measured by the development of acute stroke, cardiogenic shock, sudden cardiac arrest (SCA), need for percutaneous coronary intervention (PCI), mechanical circulatory support (MCS) utilization, need for pacemaker insertion and defibrillation, sepsis, myocardial infarction, major adverse cardiac and cerebrovascular events (MACCE), and acute kidney injury (AKI); resource utilization as measured by LOS and total hospitalization charges and costs (Supplementary Table 4). All the abovementioned outcomes were identified using ICD-10-



CM diagnoses and procedure codes (Supplementary Table 1). Patients' demographics, LOS, and total hospitalization charges were directly obtained from the NIS database. Total hospital charges reflect the amount a patient was billed for the entire hospital stay, but they do not reflect the actual cost of care. The HCUP provides data with hospital-specific cost-to-charge ratios based on inpatient costs across all payers.^[15] Using this information, total hospital costs were calculated by multiplying the hospital charges by the corresponding cost-to-charge ratio. All hospitalization costs and charges were adjusted for inflation over time using the hospital services part of the consumer price index and are represented in 2021 US dollars.^[16] Patient demographics included age (in years), sex, race (categorized as Caucasian, Black, Hispanic, Asian or Pacific Islander, Native American, and other), primary expected payer (Medicare, Medicaid, private insurance, and uninsured), hospital bedside (small, medium, and large), teaching status, hospital region (Northeast, Midwest, South, and West), and urban location.^[15] The comorbidity burden was assessed using Claims-based Disease-specific refinements, Matching translation to the ICD-10, and Flexibility (CDMF-CCI) model.^[17]

Statistical Analysis

Continuous variables were compared using the Student's *t*-test in the unadjusted analyses and are presented as mean $\pm$ SD. Continuous variables were tested for normality of distribution using the Shapiro-Wilk test and reported as means with SD or medians with interquartile ranges (IQR), depending on their distribution. Categorical variables were compared with the chi-square test for unadjusted analyses and are presented as frequencies and percentages.

The NIS is built on a complex sampling design that incorporates stratification, clustering, and weighting. STATA software enables analysis to generate nationally representative, unbiased results, along with variance estimates and *P* values. All analyses utilized weighted NIS data in compliance with the HCUP guidelines.^[18] Each hospital admission was assigned a discharge weight to estimate national in-hospital outcomes to account for clustering, weighting, and stratification to represent the broader United States population accurately. The following variables had missing data: race, insurance status, month of admission day and month of admission, and elective versus non-elective admission. These missing

data were addressed and treated using multiple imputations by predictive mean matching, preserving the distribution and variability of the observed data while incorporating the relationships among variables.^[19,20]

Trends in TCM hospitalizations, mortality, and study outcomes over time were analyzed using Jonckheere-Terpstra and Cuzick's trend tests. A two-staged multivariable mixed-effects logistic regression analysis was employed to identify independent predictors of study outcomes and in-hospital complications. The analysis incorporated patient-level variables such as age, sex, race, medical comorbidities, and socioeconomic status, as well as hospital-level variables such as size, type, location, nature, and day of admission.

Propensity score matching was performed to further adjust for confounders. Propensity scores were generated from a multivariable logistic regression model that included covariates such as age, race, primary payer, type of admission (elective versus nonelective), hospital bed size, region, teaching status, and existing comorbidities, allowing a more accurate and unbiased estimation of the impact of frailty on outcomes in patients with TCM. A 1 : 1 matching algorithm was used with a caliper width of 0.2 times the SD of the logit of the propensity score.^[21]

We conducted two secondary analyses. First, we compared the prognostic impact of frailty on TCM vs. other cardiac conditions, including ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), acute heart failure, valvular heart disease, dilated cardiomyopathy, acute pericarditis, endocarditis, atrial fibrillation, and ventricular tachycardia (VT) using multivariable logistic regression models. Second, we performed a sex-based subgroup analysis to assess frailty's impact on TCM outcomes separately in males and females. Statistical significance was set at $P < 0.05$, and interaction terms were examined. All statistical analyses were performed using STATA statistical software version 18 (Stata Corp LLC, College Station, TX), with a two-sided *P* value < 0.05 considered statistically significant.

RESULTS

Patient and Hospital Characteristics

A total of 29,595 patients with TCM were included in the study, of which 3,915 (13.2%) were classified as frail,



and 25,680 (86.8%) were not frail (Figure 1). The mean age of frail patients was significantly higher than that of non-frail patients (78.12 ± 7.46 vs. 75.19 ± 7.08 years) (Supplementary Figure 1). Female patients predominated in both the frail and non-frail groups (90.3% and 91.2%, respectively). Most patients were White, with no significant differences in racial distribution between the groups.

Frail patients exhibited a higher prevalence of pulmonary disease (30.1% vs. 18.9%, $P < 0.001$), protein-energy malnutrition (PEM) (34.7% vs. 1.6%, $P < 0.001$), complicated diabetes (14.9% vs. 10.2%, $P < 0.001$), anemia (6.1% vs. 3.3%, $P < 0.001$), renal failure (18.6% vs. 13.1%, $P < 0.001$), depression (22.4% vs. 17.2%, $P = 0.001$), complicated hypertension (36.7% vs. 29.1%, $P < 0.001$), and fluid and electrolyte disorders (45% vs. 27.3%, $P < 0.001$). Conversely, obesity (10.5% vs. 6.64%, $P = 0.001$) and dyslipidemia (56.1% vs. 51.1%, $P = 0.01$) were more common in non-frail patients. The frequency of smoking was similar between the two groups.

Both frail and non-frail patients predominantly had Medicare as their primary insurance (94.1% and 90.8%, $P = 0.02$). Most admissions occurred in urban teaching hospitals for both groups, with no significant differences in hospital bed size, location, or teaching status. Week-

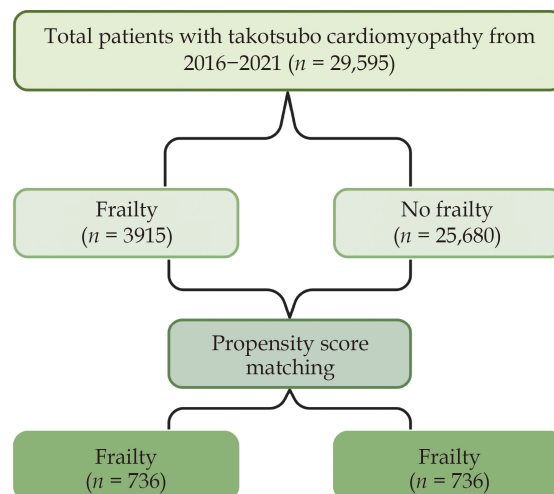


Figure 1 Flow diagram of included study population.

end admissions were slightly more common among frail patients (28.5% vs. 24.7%, $P = 0.022$). Table 1 shows the baseline characteristics of patients with TCM with and without frailty.

Crude and Adjusted Outcomes

Univariate analysis revealed that frailty was significantly associated with worse in-hospital outcomes. Frail patients had higher odds of in-hospital mortality (uOR:

Table 1 Baseline characteristics of patients with takotsubo syndrome with and without frailty.

	No-frailty (n = 25,680)	Frailty (n = 3,915)	P-value
Mean age, yrs	75.19 ± 7.08	78.12 ± 7.46	0.028
Male	2,265 (8.8%)	380 (9.7%)	0.430
Female	23,415 (91.2%)	3,535 (90.3%)	0.430
Race			0.053
White	21,385 (87.6%)	3,210 (86.2%)	
Black	1,270 (5.2%)	285 (7.7%)	
Hispanic	1,220 (5%)	160 (4.3%)	
Asian/PI	420 (1.7%)	65 (1.7%)	
Native American	120 (0.5%)	5 (0.1%)	
Payer type			0.020
Medicare	23,065 (90.8%)	3,650 (94.1%)	
Medicaid	235 (0.9%)	30 (0.8%)	
Private	1,970 (7.8%)	180 (4.6%)	
Self-pay	140 (0.6%)	20 (0.5%)	
Non-elective	24,595 (95.9%)	3,765 (96.3%)	0.624
Elective	1,045 (4.1%)	145 (3.7%)	0.624
Hospital Bed Size			0.156
Small	4,245 (16.5%)	635 (16.2%)	
Medium	6,875 (26.8%)	1,175 (30%)	
Large	14,560 (56.7%)	2,105 (53.8%)	

Continued

	No-frailty (n = 25,680)	Frailty (n = 3,915)	P-value
Hospital Location and teaching status			0.742
Rural	1,495 (5.8%)	255 (6.5%)	
Urban non-teaching	5,095 (19.8%)	765 (19.5%)	
Urban teaching	19,090 (74.3%)	2,895 (73.9%)	
Hospital region			0.638
Northeast	4,995 (19.5%)	840 (21.5%)	
Midwest	6,480 (25.2%)	970 (24.8%)	
South	8,065 (31.4%)	1,200 (30.7%)	
West	6,140 (23.9%)	905 (23.1%)	
Admission day			0.022
Mon-Fri	19,335 (75.3%)	2,800 (71.5%)	
Sat/Sun	6,345 (24.7%)	1,115 (28.5%)	
Obesity	2,705 (10.5%)	260 (6.64%)	0.001
Hypertension	18,840 (73.4%)	2,895 (73.9%)	0.731
Dyslipidemia	14,400 (56.1%)	2,000 (51.1%)	0.010
Smoking	8,080 (31.5%)	1,110 (28.4%)	0.076
Pulmonary disease	4,855 (18.9%)	1,180 (30.1%)	< 0.001
Prior MI	2,450 (9.5%)	455 (11.6%)	0.075
Prior PCI	1,355 (5.3%)	215 (5.5%)	0.803
Prior CABG	450 (1.7%)	55 (1.4%)	0.483
OSA	1,555 (6.1%)	175 (4.5%)	0.075
Immunocompromised	10 (0.04%)	5 (0.12%)	0.304
Hypothyroidism	5,685 (22.1%)	855 (21.8%)	0.852
Anemia	835 (3.3%)	240 (6.1%)	< 0.001
Liver disease	355 (1.4%)	90 (2.3%)	0.051
Valvular disease	3,826 (14.9%)	544 (13.9%)	0.490
Diabetes Mellitus	2,619 (10.2%)	583 (14.9%)	< 0.001
Renal failure	3,364 (13.1%)	728 (18.6%)	< 0.001
Peptic ulcer disease	128 (0.5%)	39 (1%)	0.061
Fluid and electrolyte disorder	7,011 (27.3%)	1,762 (45%)	< 0.001
Alcohol abuse	642 (2.5%)	121 (3.1%)	0.319
Drug abuse	616 (2.4%)	141 (3.6%)	0.060
Depression	4,417 (17.2%)	873 (22.3%)	0.001

Data are presented as mean $\pm$ SD or n (%).

3.58, 95% CI: 2.47–5.18, $P < 0.001$), cardiogenic shock (uOR: 1.79, 95% CI: 1.35–2.38, $P < 0.001$), sudden cardiac arrest (uOR: 1.81, 95% CI: 1.15–2.87, $P = 0.011$), and sepsis (uOR: 2.94, 95% CI: 1.77–4.88, $P < 0.001$). Additionally, frailty was associated with increased odds of acute stroke (uOR: 2.58, 95% CI: 1.19–5.62, $P = 0.016$) and acute kidney injury (AKI) (uOR: 2.07, 95% CI: 1.71–2.50, $P < 0.001$).

After adjusting for confounders in the multivariate analysis, frailty remained an independent predictor of in-hospital mortality (aOR: 2.44, 95% CI: 1.45–4.12, $P < 0.001$). However, the association between frailty and oth-

er outcomes, such as cardiogenic shock (aOR: 1.10, 95% CI: 0.74–1.64, $P = 0.627$), sudden cardiac arrest (aOR: 1.58, 95% CI: 0.91–2.74, $P = 0.105$), sepsis (aOR: 1.00, 95% CI: 0.48–2.07, $P = 0.997$), and acute stroke (aOR: 1.58, 95% CI: 0.367–3.74, $P = 0.997$), was attenuated and no longer statistically significant (Supplementary Table 5). Table 2 compares univariate and multivariate regression analyses of outcomes in patients with TCM based on frailty status.

There was no statistically significant association in outcomes such as pulmonary embolism (aOR: 1.23, 95%



Table 2 Univariate and multivariate regression analyses of outcomes in patients with takotsubo cardiomyopathy based on frailty status.

Outcomes	Unadjusted OR			Adjusted OR		
	OR	95% CI	P-value	OR	95% CI	P-value
Mortality	3.58	2.47–5.18	< 0.001	2.44	1.45–4.12	< 0.001
MACCE	1.85	1.12–3.58	0.04	2.12	1.25–4.56	0.01
PCI	1.80	0.86–3.76	0.119	2.04	0.70–5.96	0.19
Acute stroke	2.58	1.19–5.62	0.016	1.58	0.67–3.74	0.3
Cardiogenic shock	1.79	1.35–2.38	< 0.001	1.10	0.74–1.64	0.627
SCA	1.81	1.15–2.87	0.011	1.58	0.91–2.74	0.105
Pulmonary embolism	1.65	0.79–3.44	0.183	1.23	0.46–3.33	0.678
MCS	1.32	0.73–2.38	0.363	0.57	0.23–1.43	0.231
Cardiac arrhythmias	1.36	1.17–1.59	< 0.001	1.03	0.85–1.25	0.73
Sepsis	2.94	1.77–4.88	< 0.001	1.00	0.48–2.07	0.997
AKI	2.07	1.71–2.50	< 0.001	1.25	0.96–1.62	0.099
PMI	1.83	0.68–4.94	0.235	2.38	0.75–7.62	0.143
Defibrillator	1.41	0.41–4.88	0.590	3.14	0.93–10.66	0.066

AKI: acute kidney injury; MCS: mechanical circulatory support; PCI: percutaneous coronary artery intervention; SCA: sudden cardiac arrest; PMI: pacemaker insertion.

CI: 0.46–3.33, $P = 0.678$) and mechanical circulatory support utilization (aOR: 0.57, 95% CI: 0.23–1.43, $P = 0.231$) between the two groups.

Propensity-Matched Outcomes

After propensity-score matching, 736 pairs of frail and non-frail patients were selected for analysis. Frailty was associated with significantly worse outcomes. In-hospital mortality was higher in frail patients (5.71% vs. 1.09%, $P < 0.001$). Similarly, frail patients had increased rates of cardiogenic shock (8.47% vs. 4.70%, $P = 0.003$), sudden cardiac arrest (3.12% vs. 1.49%, $P = 0.037$), and sepsis (2.85% vs. 0.95%, $P = 0.008$). The incidence of major adverse cardiac and cardiovascular events (MACCE) was also greater in frail patients (22.55% vs. 18.21%, $P = 0.038$).

There were no significant differences in the incidence of pulmonary embolism ($P = 1.000$), acute stroke ($P = 0.403$), or mechanical circulatory support utilization ($P = 0.692$). Table 3 summarizes propensity-matched outcomes in patients with TCM with and without frailty (Supplementary Table 6, Supplementary Figure 2).

Comparing Prognostic Impact of Frailty Across Cardiac Conditions

A comparative analysis of frailty's effect across different cardiac conditions revealed that frailty had the highest prognostic impact on mortality in STEMI pa-

tients (aOR: 3.52, 95% CI: 2.90–4.20, $P < 0.001$), followed by ventricular tachycardia (aOR: 3.15, 95% CI: 2.75–5.32, $P < 0.001$), and TTS (aOR: 2.44, 95% CI: 1.45–4.12, $P < 0.001$). Frailty was also significantly associated with higher mortality in endocarditis (aOR: 2.86, 95% CI: 2.40–3.50, $P < 0.001$), dilated cardiomyopathy (aOR: 2.20, 95% CI: 1.80–2.70, $P < 0.001$), and valvular heart disease (aOR: 1.95, 95% CI: 1.50–2.30, $P < 0.001$). In contrast, the effect of frailty on mortality was comparatively weaker in NSTEMI (aOR: 1.74, 95% CI: 1.10–3.56, $P = 0.012$) and atrial fibrillation (aOR: 1.65, 95% CI: 1.12–3.45, $P = 0.025$). The lowest impact was observed in acute pericarditis (aOR: 1.32, 95% CI: 0.97–4.15, $P = 0.079$). These findings highlight the variability in frailty's impact across different cardiovascular conditions (Figure 2).

Sex-based Subgroup Analysis of Frailty in TTS

Among female patients with TTS, frailty was significantly associated with increased in-hospital mortality (aOR: 3.07, 95% CI: 1.81–5.18, $P = 0.001$), cardiogenic shock (aOR: 2.11, 95% CI: 1.09–4.68, $P = 0.044$), sudden cardiac arrest (SCA) (aOR: 1.98, 95% CI: 1.12–3.26, $P = 0.025$), and MACCE (aOR: 2.23, 95% CI: 1.19–3.65, $P = 0.012$). In contrast, among male patients, frailty was significantly associated with in-hospital mortality (aOR: 1.20, 95% CI: 1.09–3.59, $P = 0.041$), percutaneous coronary intervention (PCI) utilization (aOR: 2.34, 95% CI: 1.08–5.24, $P = 0.032$), and sepsis (aOR: 2.10, 95% CI:

Table 3 Propensity-matched outcomes in patients with TCM with and without frailty.

Outcomes	No-frailty (n = 736)	Frailty (n = 736)	P-value
In-hospital mortality	8 (1.09%)	42 (5.71%)	< 0.001
MACCE	134 (18.21%)	166 (22.55%)	0.038
PCI	4 (0.54%)	9 (1.22%)	0.164
Acute stroke	5 (0.68%)	8 (1.09%)	0.403
Cardiogenic shock	35 (4.70%)	63 (8.47%)	0.003
SCA	11 (1.49%)	23 (3.12%)	0.037
Pulmonary embolism	7 (0.95%)	7 (0.95%)	1.000
MCS	14 (1.90%)	12 (1.63%)	0.692
Cardiac arrhythmias	274 (37.23%)	299 (40.62%)	0.181
Sepsis	7 (0.95%)	21 (2.85%)	0.008
AKI	135 (18.34%)	158 (21.47%)	0.133
PMI	1 (0.14%)	5 (0.68%)	0.102
Defibrillator	1 (0.14%)	3 (0.41%)	0.317
LOS	3.43 ± 3.23	5.61 ± 5.69	
TOTCHG	53201.43 ± 51517.84	70001.02 ± 78173.43	

Data are presented as mean ± SD or *n* (%). AKI: acute kidney injury; HF: heart failure; LOS: length of stay; MCS: mechanical circulatory support; PCI: percutaneous coronary artery intervention; PMI: pacemaker insertion; SCA: sudden cardiac arrest; TCM: takotsubo cardiomyopathy; TOTCHG: adjusted total hospital charges.

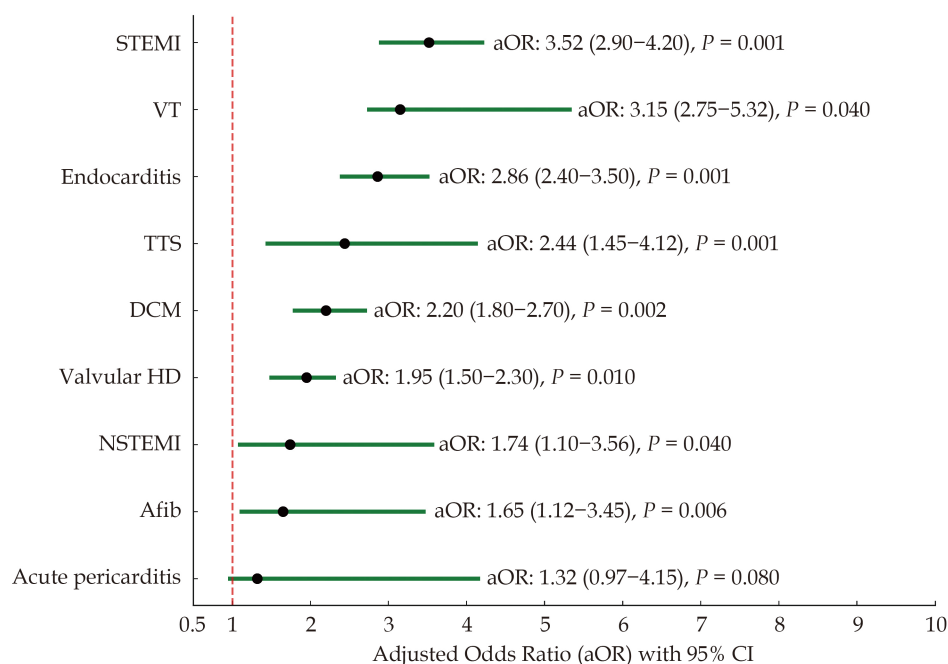


Figure 2 Impact of frailty on in-hospital mortality across cardiovascular conditions. Forest plot showing the aOR and 95% CIs for the impact of frailty on in-hospital mortality across cardiovascular conditions. Black dots represent aORs, and green lines indicate 95% CIs. The red dashed vertical line at OR = 1 denotes no effect. STEMI and VT had the highest frailty-associated risk, followed by TTS and endocarditis, while Afib and acute pericarditis had weaker associations. Statistical significance was set at $P < 0.05$. Afib: atrial fibrillation; aOR: adjusted odds ratios; STEMI: ST-elevation myocardial infarction; TTS: Takotsubo cardiomyopathy; VT: ventricular tachycardia.



1.21–3.22, $P = 0.020$). Notably, mechanical circulatory support (MCS) utilization was significantly lower among frail males (aOR: 0.12, 95% CI: 0.01–0.92, $P = 0.046$), while it showed no significant difference in frail females ($P = 0.481$). Other outcomes, including acute stroke, arrhythmias, and acute kidney injury (AKI), were not significantly associated with frailty in either gender subgroup (Table 4).

Resource Utilization

The length of stay (LOS) was significantly longer for frail patients with an average LOS of 5.61 days as compared to non-frail patients with an LOS of 3.43 days. Similarly, total adjusted hospital charges were higher in frail patients, with a mean of \$70,001, as compared to non-frail patients, which was \$53,201.

Trends in Outcomes Over Time

As shown in Supplementary Table 7, trends from 2016 to 2021 showed no significant changes in mortality for either group (P -value > 0.05). However, the incidence of MACCE, as seen in Supplementary Table 8, increased significantly among frail patients over time ($P = 0.011$) but not among non-frail patients ($P = 0.537$).

DISCUSSION

Takotsubo cardiomyopathy, also referred to as “Broken Heart Syndrome”, is characterized by transient left ventricular dysfunction typically precipitated by

acute emotional or physical stress. The condition is thought to result from a surge in catecholamines, leading to myocardial stunning and impaired contractility. TCM accounts for approximately 1%–2% of all patients presenting with symptoms suggestive of acute coronary syndrome.^[22,23] However, recent studies suggest that this condition may be more common than previously thought, as increased awareness and advanced diagnostic capabilities improve its identification. While earlier research suggested that TCM is more prevalent in postmenopausal women, recent studies have been investigating the potential association between TCM and frailty.^[24] Despite these developments, studies exploring the relationship between frailty, TCM, and various clinical outcomes remain limited. Previous studies have established the association between frailty and adverse outcomes in patients with TCM.^[25] However, our study extends these findings by focusing specifically on elderly patients (≥ 65 years) and providing a comprehensive assessment of a wide range of clinical outcomes. Moreover, we employed rigorous propensity score matching to minimize confounding and provide a more accurate estimate of the independent impact of frailty on outcomes. To the best of our knowledge and review of prior studies, our study is the first one to compare a multitude of clinical outcomes in frail elderly patients with TCM. Furthermore, to our knowledge, this is the first study to compare frailty's impact across multiple cardiovascular conditions, highlighting its disease-specific prognostic variability.

Table 4 Sex-based subgroup analysis of frailty in patients with TCM.

Outcomes	Female		Male	
	aOR (95% CI)	P-value	aOR (95% CI)	P-value
Mortality	3.07 (1.81–5.18)	0.001	1.20 (1.09–3.59)	0.041
PCI	1.88 (0.95–3.86)	0.088	2.34 (1.08–5.24)	0.032
Acute Stroke	1.21 (0.43–3.40)	0.716	1.65 (0.92–2.78)	0.615
Cardiogenic Shock	2.11 (1.09–4.68)	0.044	1.12 (0.32–3.87)	0.853
SCA	1.98 (1.12–3.26)	0.025	1.23 (0.81–2.75)	0.54
MACCE	2.23 (1.19–3.65)	0.012	1.98 (1.1–3.56)	0.025
Pulmonary embolism	1.33 (0.48–3.66)	0.579	1.2 (0.86–2.13)	0.08
MCS Utilization	0.71 (0.28–1.82)	0.481	0.12 (0.01–0.92)	0.046
Arrhythmias	1.02 (0.83–1.25)	0.817	1.09 (0.58–2.07)	0.76
Sepsis	1.12 (0.51–2.45)	0.774	2.1 (1.21–3.22)	0.02
AKI	1.02 (0.45–3.12)	0.26	3.34 (0.8–6.15)	0.42
PMI	0.92 (0.36–2.32)	0.65	1.54 (0.86–4.42)	0.36

AKI: acute kidney injury; MACCE: major adverse cardiac and cardiovascular events; MCS: mechanical circulatory support; PCI: percutaneous coronary intervention; SCA: sudden cardiac arrest; TCM: takotsubo cardiomyopathy; PMI: pacemaker insertion.



The main findings of our analysis, which included patients aged 65 and older hospitalized with TCM, were as follows: (1) Frail individuals with TCM experienced significantly worse outcomes, including higher in-hospital mortality, cardiogenic shock, sudden cardiac arrest, sepsis, and major adverse cardiac and cerebrovascular events. (2) Frail patients also had longer hospital stays and higher total adjusted hospital charges. (3) Our study highlights the heterogeneous impact of frailty across cardiac conditions, with the strongest association in STEMI and VT, followed by TCM.

Our study demonstrates that frail individuals with TCM experienced significantly higher in-hospital mortality, consistent with prior research. A comparative study by Biccire, *et al.*^[26] highlighted frailty as an important precipitating trigger for TCM. Similarly, a study by Brinjikji, *et al.*^[27] reported an in-hospital mortality rate of 4.2% for TCM patients, with higher mortality in frail or critically ill patients. Complications such as renal failure, sepsis, and respiratory issues were more common among frail patients, significantly increasing their mortality risk (12.1% vs. 1.1% in non-frail patients).

A study conducted by Agarwal *et al.* demonstrated that frailty is an independent predictor of adverse in-hospital outcomes among patients with Takotsubo cardiomyopathy. The findings revealed that frail patients were more likely to develop cardiogenic shock and had longer hospital stays compared to non-frail individuals.^[28] These findings corroborate our observations. Frail older adults have a 1.6 times higher likelihood of experiencing orthostatic hypotension, indicating a link between autonomic dysfunction and frailty. Specific autonomic function alterations, such as reduced orthostatic heart rate increase and heart rate variability, are more common in frail older adults, highlighting the association between autonomic dysfunction and frailty. Furthermore, Takotsubo cardiomyopathy has been linked to excessive catecholamine release during acute stress, leading to myocardial stunning and transient left ventricular dysfunction. The pathophysiological role of excess catecholamine in TCM is well-documented, highlighting the impact of heightened sympathetic activity on cardiac function.^[3,29] Considering these findings, the impaired autonomic regulation observed in frail individuals may result in heightened sympathetic activity, increasing their vulnerability to stress-induced myocardial dysfunction such as TCM. A large Japanese registry study by Arao, *et al.*^[30] found that in-hospital mortality in TCM patients

was notably influenced by factors associated with frailty, including low body mass index and elevated C-reactive protein levels. Despite TCM being considered transient, these findings highlight that frailty-related characteristics can significantly worsen short-term outcomes, reinforcing the importance of early risk stratification in vulnerable elderly populations. Importantly, low BMI was associated with increased short- and long-term mortality, supporting the role of frailty in adverse outcomes. The authors also noted a lower prevalence of obesity and diabetes in patients with TCM, raising the possibility of a protective effect from these conditions.^[31] Complementing these findings, hypoalbuminemia, a surrogate of frailty, has been shown to be independently associated with increased in-hospital mortality in patients with TCM.^[32]

Our study also revealed that acute heart failure, acute stroke, cardiac arrhythmias, and acute kidney injury were more prevalent in frail individuals. Although studies exploring acute heart failure in frail individuals with TCM are limited, prior research has shown a strong association between frailty and heart failure. For instance, a prospective study by Pascual *et al.* in Spain found that frailty was associated with increased risks of 1-year mortality, hospital readmissions, and functional decline among older ambulatory patients with heart failure.^[33]

The development of acute kidney injury (AKI) in frail TCM patients may be attributed to significant catecholamine surges and prolonged hemodynamic instability, leading to renal hypoperfusion. This mechanism makes frail individuals particularly vulnerable to AKI. A study conducted by Boyd *et al.* provides further support for this explanation.^[33] While our study focused on in-hospital outcomes, it is important to acknowledge that frailty is a chronic and progressive condition with significant implications beyond the index hospitalization. Although Takotsubo cardiomyopathy is characterized by transient myocardial dysfunction, recurrence and long-term mortality remain important clinical concerns, particularly in elderly and vulnerable populations. Recent evidence by Hiruma, *et al.*^[34] demonstrated that qualitatively assessed frailty, even using simple patient photographs, was independently associated with increased long-term all-cause mortality following transcatheter aortic valve replacement (TAVR), highlighting the persistent and cumulative impact of frailty on cardiovascular prognosis. These findings underscore the need for future prospective studies to evaluate whether frailty



similarly contributes to adverse long-term outcomes in TCM, and to guide post-discharge risk stratification and care planning in this growing patient population.

Our findings align with prior research indicating that frailty worsens outcomes in cardiovascular disease, but its severity varies by disease-specific pathophysiology and compensatory mechanisms.^[35,36] This suggests that frailty's prognostic influence is modulated by the underlying cardiovascular pathology. The greater impact of STEMI may stem from acute hemodynamic stress and rapid circulatory collapse, which demand strong physiological reserves. STEMI, caused by complete coronary occlusion, leads to sudden ischemia, requiring robust cardiac compensation that frail patients often lack due to sarcopenia and autonomic dysfunction.^[37] Similarly, VT, characterized by life-threatening arrhythmias, can cause sudden circulatory failure, further exacerbating frailty's detrimental effects.^[38] This underscores the need for condition-specific frailty assessments to improve risk stratification and personalized management in elderly patients.

Our sex-based analysis revealed that frailty had a stronger association with mortality, cardiogenic shock, and MACCE in women with TTS, whereas in men, frailty was linked to higher PCI utilization and sepsis but not cardiogenic shock or sudden cardiac arrest. This aligns with prior studies suggesting that frail women with cardiovascular disease experience greater adverse outcomes due to lower muscle mass, autonomic dysregulation, and differences in inflammatory response, whereas men may receive more aggressive interventions despite similar risk profiles.^[39]

Limitations

Our study has several limitations inherent to its retrospective design, including the potential for selection bias. The data were obtained from the NIS, an administrative database that may be subject to coding inaccuracies and missing clinical details such as symptom severity, frailty scores, or echocardiographic findings.^[9] Additionally, the NIS lacks longitudinal follow-up, limiting our analysis to short-term, in-hospital outcomes and precluding assessment of long-term prognosis, recurrence, or post-discharge mortality. Lastly, unmeasured confounders, such as the severity of frailty or functional status, could not be accounted for, which may influence the observed associations. Given the chronic and progressive nature of frailty, future studies incorporating longitudinal data are

needed to fully understand its impact on long-term prognosis in patients with Takotsubo cardiomyopathy.

Conclusion

Our study highlights frailty as a significant and often underrecognized risk factor in patients with TCM. Given the heightened vulnerability of this population, early identification of frailty, particularly following acute physical or emotional stress, may facilitate timely recognition and management of TCM. Raising clinical awareness of this association may help reduce adverse outcomes through targeted interventions. Incorporating stress-reduction strategies, such as psychological counseling and relaxation therapies, could mitigate excessive catecholamine release and potentially lower the risk of TCM episodes in frail individuals. Future prospective and multicenter studies are warranted to better define the prognostic significance of frailty in TCM and to determine whether its impact differs compared to other cardiovascular conditions. Such efforts may inform more personalized approaches to risk stratification and care in this growing patient population.

Conflict of Interests

None.

REFERENCES

- [1] Sato H, Tateishi H, Uchida T. Takotsubo-Type Cardiomyopathy due to Multivessel Spasm. In *Clinical Aspects of Myocardial Injury: From Ischemia to Heart Failure*; Kodama K, Haze K, Hon M, Eds.; Kagakuhyouronsya Publishing Corporation: 1990; pp. 56–64.
- [2] Gianni M, Dentali F, Grandi AM, et al. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006; 27: 1523–1529.
- [3] Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med* 2015; 373: 929–938.
- [4] Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014; 9: 433–41.
- [5] Kwok CS, Zieroth S, Van Spall HGC, et al. The Hospital Frailty Risk Score and its association with in-hospital mortality, cost, length of stay and discharge location in patients with heart failure. *Int J Cardiol* 2020; 300: 184–190.
- [6] Kojima G. Frailty as a Predictor of Nursing Home Placement Among Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. *J Geriatr Phys Ther* 2018; 41: 42–48.
- [7] Anand A, Harley C, Visvanathan A, et al. The relationship between preoperative frailty and outcomes follow-



- ing transcatheter aortic valve implantation: a systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes* 2017; 3: 123–132.
- [8] Tse G, Gong M, Nunez J, *et al.* Frailty and Mortality Outcomes After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. *J Am Med Dir Assoc* 2017; 18(12): 1097. e1–1097. e10.
- [9] Agency for Healthcare Research and Quality. National (Nationwide) Inpatient Sample (NIS) Database Documentation. 2024. Available online: <https://hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp> (accessed 2024 November 13).
- [10] Khera R, Angraal S, Couch T, *et al.* Adherence to Methodological Standards in Research Using the National Inpatient Sample. *JAMA* 2017; 318: 2011–2018.
- [11] Abrams LR, Weiner JP. Development and evaluation of the Johns Hopkins University risk adjustment models for Medicare Choice plan payment. 2003. Available online: <https://www.hopkinsag.org/document/development-and-evaluation-of-the-johns-hopkins-university-risk-adjustment-models-for-medicarechoice-plan-payment/> (accessed 2003 November 28).
- [12] Xu D, Fei M, Lai Y, *et al.* Impact of frailty on inpatient outcomes in thyroid cancer surgery: 10-year results from the U. S. national inpatient sample. *J Otolaryngol Head Neck Surg* 2020; 49: 51.
- [13] Asemota AO, Gallia GL. Impact of frailty on short-term outcomes in patients undergoing transsphenoidal pituitary surgery. *J Neurosurg* 2020; 132: 360–370.
- [14] Lee DU, Kwak J, Karagozian R. The clinical impact of frailty on the postoperative outcomes of patients undergoing gastrectomy for gastric cancer: a propensity-score matched database study. *Gastric Cancer* 2022; 25: 450–458.
- [15] Agency for Healthcare Research and Quality. NIS Description of Data Elements. 2024. Available online: <https://hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp> (accessed 2024 November 14).
- [16] U. S. Bureau of Labor Statistics. Consumer Price Index. 2024. Available online: <https://www.bls.gov/cpi/> (accessed 2024 November 14).
- [17] Glasheen WP, Cordier T, Gumpina R, *et al.* Charlson Comorbidity Index: ICD-9 Update and ICD-10 Translation. *Am Health Drug Benefits* 2019; 12: 188–197.
- [18] Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). 2024. Available online: <https://www.ahrq.gov/data/hcup/index.html> (accessed 2024 November).
- [19] Bailey BE, Andridge R, Shoben AB. Multiple imputation by predictive mean matching in cluster-randomized trials. *BMC Med Res Methodol* 2020; 20: 72.
- [20] Austin PC, van Buuren S. Logistic regression vs. predictive mean matching for imputing binary covariates. *Stat Methods Med Res* 2023; 32: 2172–2183.
- [21] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011; 10: 150–161.
- [22] Kurowski V, Kaiser A, von Hof K, *et al.* Apical and mid-ventricular transient left ventricular dysfunction syndrome (takotsubo cardiomyopathy): frequency, mechanisms, and prognosis. *Chest* 2007; 132: 809–816.
- [23] Prasad A, Lerman A, Rihal CS. Incidence and angiographic characteristics of patients with apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: an analysis from a multicenter, international study of ST-elevation myocardial infarction. *Catheter Cardiovasc Interv* 2014; 83: 343–348.
- [24] Gudmundsson T, Redfors B, Råmunddal T, *et al.* Importance of hospital and clinical factors for early mortality in Takotsubo syndrome: Insights from the Swedish Coronary Angiography and Angioplasty Registry. *BMC Cardiovasc Disord* 2024; 24: 359.
- [25] Diaz-Arocutipa C, Hernandez AV. Prognostic value of frailty in patients with takotsubo cardiomyopathy. *Clin Cardiol* 2025; 48: e70054.
- [26] Biccirè FG, Bucciarelli V, Madonna R, *et al.* Clinical frailty and triggers in Takotsubo syndrome: the notable role of a new classification. *J Cardiovasc Med (Hagerstown)* 2020; 21: 144–149.
- [27] Brinjkiji W, El-Sayed AM, Salka S. In-hospital mortality among patients with takotsubo cardiomyopathy: A study of the National Inpatient Sample 2008 to 2009. *Am Heart J* 2012; 164: 215–221.
- [28] Agrawal A, Garg L, Garg A, *et al.* Contemporary characteristics, outcomes and novel risk score for Takotsubo cardiomyopathy: a national inpatient sample analysis. *Open Heart* 2024; 11(2).
- [29] Debain A, Dachy A, Costenoble A, *et al.* Frail older adults are more likely to have autonomic dysfunction: A systematic review and meta-analysis. *Ageing Res Rev* 2023; 87: 101925.
- [30] Arai K, Yoneyama K, Kobayashi Y, *et al.* A study of takotsubo syndrome over 9 years at the Tokyo Cardiovascular Care Unit Network Registry. *J Cardiol* 2023; 82: 93–99.
- [31] Madias JE. Prevalence of obesity and diabetes in patients with takotsubo syndrome from the Tokyo Cardiovascular Care Unit Network Registry. *J Cardiol* 2023; 82: 84.
- [32] Watanabe Y, Arai K, Yoneyama K, *et al.* Impact of hypoalbuminemia on in-hospital mortality in patients with takotsubo syndrome: A multicenter registry of the Tokyo Cardiovascular Care Unit Network. *J Cardiol* 2023; 82: 356–362.
- [33] Yang X, Lupón J, Zamora E, *et al.* Impact of Frailty on Mortality and Hospitalization in Chronic Heart Failure: A Systematic Review and Meta-Analysis. *J Am Heart Assoc* 2018; 7: e008251.
- [34] Hiruma T, Nozato T, Kiyose K, *et al.* Frailty assessment using photographs in patients undergoing transcatheter aortic valve replacement. *J Cardiol* 2024; 83: 155–162.
- [35] James K, Alpert CM, Tang WHW, *et al.* Frailty and Cardiovascular Health. *J Am Heart Assoc* 2024; 13: e031736.
- [36] Richter D, Guasti L, Walker D, *et al.* Frailty in cardiology: definition, assessment and clinical implications for general cardiology. A consensus document of the Council for Cardiology Practice (CCP), Association for Acute Cardio



Vascular Care (ACVC), Association of Cardiovascular Nursing and Allied Professions (ACNAP), European Association of Preventive Cardiology (EAPC), European Heart Rhythm Association (EHRA), Council on Valvular Heart Diseases (VHD), Council on Hypertension (CHT), Council of Cardio-Oncology (CCO), Working Group (WG) Aorta and Peripheral Vascular Diseases, WG e-Cardiology, WG Thrombosis, of the European Society of Cardiology, European Primary Care Cardiology Society (EPCCS). *Eur J Prev Cardiol* 2021; 29: 216–227.

- [37] Hosseini F, Gale CP, Fox KAA, *et al.* Association of Frailty With In-hospital and Long-term Outcomes Among STEMI Patients Receiving Primary Percutaneous Coronary Intervention. *CJC Open* 2024; 6: 1004–1012.
- [38] Singh M, Stewart R, White H. Importance of frailty in patients with cardiovascular disease. *Eur Heart J* 2014; 35: 1726–1731.
- [39] Archer SH, Petersen J, MacGeorge CA, *et al.* Sex differences in the impact of physical frailty on outcomes in heart failure. *Heart Lung* 2023; 61: 66–71.

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