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Fibromyalgia as an independent risk factor for takotsubo cardiomyopathy: a national inpatient sample case-control study

Ishani Desai[1]*, Poojita Chinmay[1], Gyanendra K. Sharma[2], Neal L. Weintraub[2]

[1]Medical College of Georgia at Augusta University, Augusta, GA 30912, USA
[2]Department of Medicine, Cardiology Division, Augusta, GA 30912, USA

***Correspondence:** Ishani Desai, Medical College of Georgia at Augusta University, 1120 15th Street, Augusta, GA 30912, USA. idesai@augusta.edu

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Abstract

Aim: Takotsubo cardiomyopathy (TTC) is an acute form of systolic dysfunction triggered by physical or emotional stress, most commonly seen in postmenopausal women. Its pathophysiology involves catecholamine surge, autonomic imbalance, and microvascular dysfunction. Fibromyalgia is a chronic pain disorder observed primarily in premenopausal women characterized by autonomic dysregulation, central sensitization, and high psychiatric comorbidity—mechanisms that overlap substantially with TTC. Nevertheless, fibromyalgia has not been established as an independent risk factor for TTC. This study evaluated the association between fibromyalgia and TTC using a nationally representative sample.

Methods: A retrospective case-control study was conducted using the 2022 National Inpatient Sample. Adult hospitalizations with TTC (ICD-10-CM I51.81) were identified, and a 1% random sample of non-TTC admissions served as controls. Fibromyalgia was defined by ICD-10 code M79.7. Survey-weighted multivariable logistic regression assessed the association between fibromyalgia and TTC, adjusting for demographics, comorbidities, and severity of illness.

Results: Among 9,376 TTC and 65,690 control hospitalizations, fibromyalgia was present in 282 (3.0%) TTC cases and 827 (1.3%) controls. After multivariable adjustment, fibromyalgia was independently associated with TTC (OR 1.19; 95% CI 1.00–1.42, $P = 0.044$). This association persisted after accounting for psychiatric comorbidities.

Conclusions: Fibromyalgia was associated with increased odds of TTC. These findings highlight the need for vigilance in evaluating fibromyalgia patients with chest pain and warrant further research into mechanisms underlying stress-induced cardiomyopathy.

Keywords

Takotsubo cardiomyopathy, fibromyalgia, autonomic dysfunction, stress cardiomyopathy, National Inpatient Sample

Introduction

Takotsubo cardiomyopathy (TTC)—also termed stress-induced cardiomyopathy or "broken-heart syndrome"—is an acute, left-ventricular systolic dysfunction that clinically and electrocardiographically mimics acute coronary syndrome (ACS) but typically lacks obstructive epicardial coronary disease on angiography. First characterized in Japan in 1990, the name reflects the characteristic shape of a Japanese octopus trap ("takotsubo"), which resembles the typical apical "ballooning" silhouette on ventriculography or echocardiography [1–3]. TTC occurs predominantly in postmenopausal women and is commonly precipitated by intense emotional or physical stress [1–4]. It is associated with risk of heart failure, dynamic left-ventricular outflow tract (LVOT) obstruction, life-threatening ventricular arrhythmias, and cardiogenic shock. Recurrences also occur in a subset of patients and may present with different variants across episodes, underscoring the heterogeneous and unpredictable nature of the disease [1, 3, 5]. Current models of TTC pathophysiology center on catecholamine excess leading to myocardial stunning, microvascular dysfunction, oxidative stress, and autonomic imbalance; estrogen deficiency appears to lower the threshold for these events, which may help to explain postmenopausal female predominance [1–3]. Adjunct mechanisms such as coronary spasm and heterogeneous β-adrenergic receptor density/distribution have also been previously established [1–3, 6, 7].

Fibromyalgia (FM) is a prevalent, female-predominant chronic pain syndrome, particularly affecting premenopausal women. It is characterized by widespread pain accompanied by profound fatigue, nonrestorative sleep, cognitive dysfunction ("fibro-fog"), and high rates of anxiety and depression, all of which contribute to significant functional impairment and healthcare utilization [8, 9]. Contemporary models of FM emphasize central pain amplification, autonomic dysregulation, and stress-axis abnormalities. Autonomic testing shows sympathetic predominance, reduced heart-rate variability, impaired baroreflex function, and abnormal cortisol dynamics, reflecting a hyperreactive yet dysregulated stress system [8, 9]. Genetic susceptibility, prior trauma or infection, and psychosocial stress likely contribute to symptom development and fluctuation [8–10].

Given the biologically compelling overlap of TTC and FM, FM has not been established as an independent TTC risk factor after accounting for psychiatric and other confounders.

Clarifying this relationship between TTC and FM has direct clinical relevance, as FM patients frequently present with chest pain and dyspnea, symptoms that overlap with acute cardiac syndromes and may be prematurely attributed to noncardiac causes. In some cases, these presentations may represent underlying TTC requiring further evaluation. Using a nationally representative inpatient dataset, this study evaluates whether FM is independently associated with TTC.

Materials and methods

Data source and study population

We performed a retrospective case-control study using the 2022 National Inpatient Sample (NIS), a component of the Healthcare Cost and Utilization Project (HCUP). The NIS is the largest publicly available, all-payer inpatient database in the United States, capturing approximately 20% of hospital discharges and enabling generation of nationally representative estimates. All adult hospitalizations (≥ 18 years) were eligible for inclusion.

Hospitalizations with TTC were identified using the ICD-10-CM diagnosis code I51.81. Control hospitalizations were selected from the same database as a 1% simple random sample of non-TTC discharges, generated with PROC SURVEYSELECT in SAS using a fixed random seed to ensure reproducibility. A 1% random sample was used to maintain computational feasibility while preserving representativeness of the underlying population through application of survey weights.

Exposure and covariates

The primary exposure was FM, identified using the ICD-10-CM code M79.7, as recorded in any of up to 40 diagnosis fields. ICD-10-CM codes used to define TTC, FM, and all covariates are provided in Table S1.

Multivariable models adjusted for demographics (age, sex, and race/ethnicity) as well as covariates chosen a priori to capture both established TTC risk factors and potential diagnostic confounders. Established risk factors included hypertension, neurologic disease (e.g., stroke, seizures, migraines), and psychiatric disorders (e.g., depression, anxiety, mood disorders). Potential confounders included conditions with overlapping clinical presentations (e.g., chest pain, dyspnea, fatigue) or those contributing to reduced ejection fraction, such as coronary artery disease, atrial fibrillation, chronic kidney disease, obesity, diabetes, cancer, and chronic obstructive pulmonary disease.

To further account for baseline illness severity, we incorporated severity measures from the NIS severity file. Specifically, we used the All Patient Refined Diagnosis Related Group (APR-DRG) severity of illness classification, which categorizes hospitalizations into four levels (minor, moderate, major, and extreme) based on secondary diagnoses and resource utilization. This adjustment helped ensure that the observed association between FM and TTC was not confounded by overall acuity of illness.

Statistical analysis

Baseline characteristics were compared using chi-square tests for categorical variables and *t*-tests for continuous variables. Multivariable survey-weighted logistic regression was used to estimate the association between FM and TTC, reporting odds ratios (ORs) with 95% confidence intervals (CIs). Analyses incorporated NIS discharge weights (DISCWT), hospital-level clustering (HOSP_NIS), and stratification variables (NIS_STRATUM) to account for the complex sampling design and produce nationally representative estimates. Because the control group consisted of a 1% random sample of non-TTC hospitalizations, discharge weights for controls were rescaled accordingly to preserve representation of the underlying population**.** Statistical significance was defined as a two-sided $P < 0.05$. All analyses were conducted using standard statistical software (SAS).

Results

Study population

A total of 9,376 hospitalizations with TTC and 65,690 non-TTC control hospitalizations were included. Patients with TTC were older (mean age 66 vs. 58 years, $P < 0.001$), more frequently female (86% vs. 61%, $P < 0.001$), and had a higher prevalence of cardiovascular and psychiatric comorbidities compared with controls (Table 1). FM was present in 282 TTC cases (3.0%) compared with 827 control hospitalizations (1.3%) ($P < 0.001$).

Table 1. Baseline characteristics of TTC cases and controls.

Characteristic	TTC (*n* = 9,376)	Controls (*n* = 65,690)	*P* value
Age (mean ± SD)	66 ± 13	58 ± 15	< 0.001
Female (%)	86	61	< 0.001
Fibromyalgia (%)	3.0	1.3	< 0.001
Hypertension (%)	70	62	< 0.001
Coronary artery disease (%)	22	16	< 0.001
Atrial fibrillation (%)	15	8	< 0.001
Chronic kidney disease (%)	12	8	< 0.001
Type 2 diabetes mellitus (%)	18	15	< 0.001
Mood disorders (%)	27	18	< 0.001
Neurologic disease (%)	10	8	< 0.01
Cancer (%)	8	7	0.04
COPD (%)	12	10	0.03

TTC: Takotsubo cardiomyopathy; COPD: chronic obstructive pulmonary disease. *P* values from chi-square test (categorical) or *t*-test (continuous). *P* values are two-sided; $P < 0.05$ is considered statistically significant.

Primary analysis—association between FM and TTC

In multivariable logistic regression, FM was independently associated with increased odds of TTC. After adjusting for demographic characteristics, comorbidities, and APR-DRG severity of illness, FM conferred a 19% increase in odds of TTC (OR 1.19; 95% CI 1.00–1.42, $P = 0.044$).

Discussion

Our study is the first to identify FM as an independent factor associated with TTC in a nationally representative U.S. cohort. Using the 2022 NIS, we found that FM conferred a 19% increase in odds of TTC even after adjustment for demographics, comorbidities, and severity of illness. This finding extends beyond prior case reports and small institutional analyses and highlights an underrecognized intersection between chronic pain syndromes and stress-induced cardiomyopathy.

While this association was statistically significant, the magnitude of effect was modest and should be interpreted in the context of clinical relevance, likely representing one of multiple contributing factors rather than a primary driver of risk.

Prior studies have described TTC in rheumatic and autoimmune disease cohorts but have not isolated FM as an independent risk factor after accounting for psychiatric and cardiometabolic comorbidities. Our findings build on that gap while aligning with qualitative literature documenting the pervasive diagnostic bias faced by FM patients. Multiple studies have shown that FM symptoms are often minimized or attributed to psychological causes, leading to fragmented, delayed, or inappropriate care [11–15]. A 2025 qualitative study in Arab countries found that many patients felt dismissed by physicians who regarded FM as psychosomatic [12]. Complementary reports from French academic centers similarly revealed profound functional impairment and fear of not being believed [15]. These examples highlight potential underrecognition that is particularly concerning given the non-benign nature of the disease. Once considered transient, TTC is now known to carry long-term risk, with a 10-year recurrence rate near 20%, a major adverse cardiac and cerebrovascular event (MACCE) rate exceeding 50%, and an all-cause mortality above 20%, comparable to age-matched ACS populations [16]. Failure to consider TTC in FM patients presenting with acute cardiopulmonary complaints therefore may represent a missed opportunity to improve morbidity and mortality.

At the same time, the clinical relevance of this association may be informed by the demographic and physiologic characteristics of FM. As a female-predominant chronic pain syndrome that often affects younger and premenopausal individuals, FM may overlap with subgroups of TTC patients in whom stress-related and autonomic mechanisms are particularly prominent. Registry data provide important context in this regard. In the InterTAK Registry, which categorizes 2,098 TTC patients by age, younger patients represented a minority of cases but were more likely to exhibit identifiable emotional triggers, greater psychiatric comorbidity, and more severe hemodynamic compromise [17]. Similarly, findings from the multicenter GEIST Registry demonstrate age-related differences in presentation, with younger individuals more frequently exhibiting non-apical variants and higher rates of in-hospital complications [18]. While our study was not designed to evaluate effect modification by age, these findings highlight an important direction for future research to determine whether the association between FM and TTC differs across demographic subgroups.

Several biologically plausible mechanisms may underlie the observed association between FM and TTC. FM has been associated with autonomic dysregulation, altered hypothalamic-pituitary-adrenal (HPA) axis function, reduced vagal tone, and psychiatric comorbidity, all of which may contribute to exaggerated physiologic responses to stress [8–10, 19–21]. Given that TTC is similarly linked to acute stress and catecholamine excess, the association observed here may reflect shared vulnerability to stress-mediated disease processes rather than a direct causal relationship [1–4, 7, 22].

Importantly, the modest effect size and observational design preclude causal inference. As such, the clinical implications of this finding are best viewed in terms of increased awareness in appropriate clinical contexts rather than as a basis for risk stratification or direct changes in management. Further studies

incorporating detailed clinical, physiologic, and imaging data are needed to better elucidate the mechanisms underlying this relationship (Figure 1).

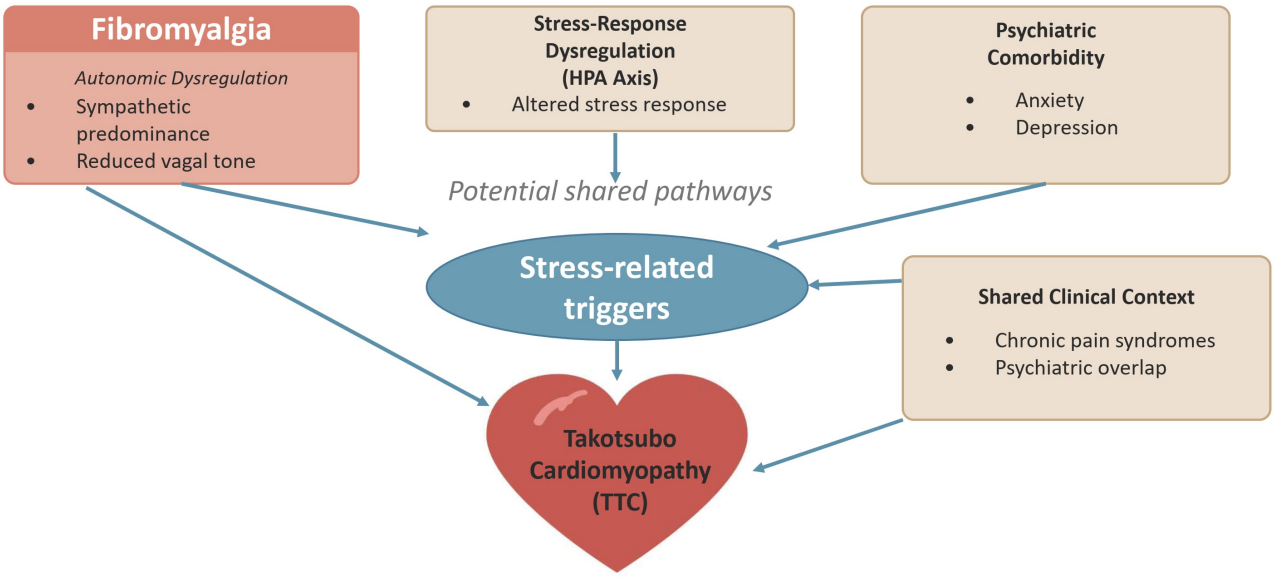

Figure 1. Conceptual model illustrating potential shared pathways linking fibromyalgia (FM) and Takotsubo cardiomyopathy (TTC). FM is associated with autonomic dysregulation, altered stress-response (HPA axis) function, and psychiatric comorbidity, which may contribute to heightened vulnerability to stress-related triggers. These overlapping features provide a biologically plausible framework for the observed association between FM and TTC. This conceptual model is hypothesis-generating and intended to illustrate biologically plausible shared pathways rather than establish a causal relationship between FM and TTC.

Limitations

This study has limitations that merit consideration.

First, reliance on administrative codes may lead to misclassification of both FM and TTC, as diagnostic accuracy can vary across institutions. The relatively low prevalence of FM observed in both groups likely reflects underdiagnosis or undercoding in administrative datasets, which may result in missed cases. This may lead to nondifferential misclassification of exposure status and underestimation of the true association. Additionally, the use of a 1% sampled control group may introduce selection bias; however, random sampling and application of survey weights were employed to minimize this and preserve representativeness.

Second, the NIS lacks granular clinical data including imaging confirmation, biomarker results, medication exposures, and other physiologic variables. Consequently, TTC diagnoses cannot be independently adjudicated, TTC variants cannot be distinguished, and important clinical contributors—such as precipitating stressors, hemodynamic parameters, or concurrent medication use—cannot be assessed. In addition, FM diagnoses cannot be characterized in terms of severity, chronicity, or symptom burden. These limitations restrict the ability to evaluate underlying mechanisms and introduce potential diagnostic uncertainty. As a result, interpretability is limited, and the observed associations must be understood within the constraints of administrative coding rather than detailed clinical phenotyping.

Third, FM is a heterogeneous condition with fluctuating symptom burden, yet reliance on a binary ICD-10 code cannot capture disease severity or chronicity.

Fourth, because the NIS is a cross-sectional database of hospitalizations, temporal sequencing cannot be established; we cannot determine whether FM preceded TTC or was identified incidentally during hospitalization.

Fifth, residual confounding is possible despite multivariable adjustment, particularly for psychosocial stressors and medications not well captured in administrative data. FM is closely associated with psychiatric comorbidities such as anxiety and depression, which are also established triggers for TTC. This

overlap raises the possibility that the observed association may, in part, reflect shared psychiatric and stress-related vulnerability rather than an independent effect of FM alone. Although adjustments were made for these conditions, psychiatric diagnoses may be incompletely captured or misclassified in administrative data, and detailed clinical information including severity, chronicity, treatment status, and active symptom burden is not available. In addition, key psychosocial factors such as acute emotional stressors or prior trauma, which are known contributors to TTC, are not directly measured in the NIS. As such, psychiatric overlap may partially explain the observed association, and the findings should be interpreted with appropriate caution.

Future work should leverage multicenter registries or prospective cohorts with detailed phenotyping to validate FM as a TTC risk factor, clarify autonomic mechanisms, and inform risk stratification in this population.

Conclusions

FM was associated with modestly increased odds of TTC. While the observed effect size was small and should not be interpreted as establishing causality or implying high absolute risk, this hypothesis-generating association highlights the importance of maintaining clinical vigilance in appropriate contexts and warrants further investigation into mechanisms underlying stress-induced cardiomyopathy.

Abbreviations

ACS: acute coronary syndrome

APR-DRG: All Patient Refined Diagnosis Related Group

CIs: confidence intervals

FM: fibromyalgia

NIS: National Inpatient Sample

ORs: odds ratios

TTC: Takotsubo cardiomyopathy

Supplementary materials

The supplementary table for this article is available at: https://www.explorationpub.com/uploads/Article/file/1012115_sup_1.pdf.

Declarations

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During the preparation of this work, the authors used ChatGPT (OpenAI) to assist with wording/clarity and figure concept rendering. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author contributions

ID: Conceptualization, Methodology, Formal analysis, Writing—original draft, Visualization. PC: Data curation, Formal analysis, Writing—original draft, Writing—review & editing. GKS: Supervision, Methodology, Validation, Writing—review & editing. NLW: Supervision, Methodology, Validation, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

This study utilized de-identified, publicly available data from the 2022 National Inpatient Sample (NIS), a component of the Healthcare Cost and Utilization Project (HCUP). As the dataset contains no individually identifiable information and was accessed in accordance with HCUP data use requirements, this study was exempt from institutional review board (IRB) review under 45 CFR 46.101(b).

Consent to participate

The requirement for informed consent was waived as this study utilized de-identified, publicly available data from the National Inpatient Sample (NIS) and met criteria for exemption under 45 CFR 46.101(b).

Consent to publication

Not applicable.

Availability of data and materials

The data analyzed in this study were obtained from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (https://www.hcup-us.ahrq.gov/). Requests for access should be directed to HCUP.

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