The Octopus in the Room: a Retrospective Cross-Sectional Analysis of the Influence of Mental Disorders on Takotsubo Cardiomyopathy

Abstract

Background: Takotsubo Cardiomyopathy (TTC) is a stress-induced cardiomyopathy affecting 2% of suspected acute coronary syndrome cases, with annual diagnosis rates rising [1, 2]. Despite having a long-term mortality rate higher than that of ST-Elevation Myocardial Infarction (STEMI) patients [3], it remains under-researched and under-diagnosed [4]. Aims: To investigate the differential impact of distinct groups of mental disorders on the incidence of Takotsubo Cardiomyopathy, considering the modifying effects of sex and age demographics. Methods: a cross-sectional analysis using National Inpatient Sample data, logistic regression modelling, chi-squared tests, t-tests and stratified subgroup analyses. Results: anxiety, acute reaction to stress, adjustment disorders and substance disorders are significantly associated with increased rates of TTC, while dementia, schizophrenia and personality disorders have a protective effect on TTC incidence. There are statistically significant sex and age disparities in TTC incidence. Male patients over 80 with depression are at the highest risk of developing TTC. Conclusions: These findings suggest that stress management and mental health interventions may be an effective preventative treatment for TTC.

1. Introduction

Takotsubo Cardiomyopathy (TTC), also known as broken heart syndrome, apical ballooning cardiomyopathy, and stress-induced cardiomyopathy [5], is a form of reversible, non-ischaemic cardiomyopathy, characterised by transient systolic left ventricular dysfunction [6] and mimics acute myocardial infarction. It is often preceded by an intense emotional or physical stressor [7], and is most prevalent in postmenopausal women. It is named after the Japanese octopus trap *Takotsubo* [8] due to the characteristic ballooning of the left ventricular apex.

Despite the known association between stress triggers and TTC, there have been few studies investigating the relationship between mental health and Takotsubo cardiomyopathy, likely due to the rarity of TTC. Studies that *have* investigated this connection have only done so at a high level. One study found an association between mood spectrum disorders, anxiety disorders and schizophrenia and TTC [9], another study found that among patients with one mental health disorder, the odds of developing TTC were lower among those with personality disorders [10], and another study found an association between TTC and depressive disorders and antidepressant use [11].

The novel research question that this paper will investigate is: **to investigate the differential impact of distinct groups of mental disorders on the incidence of Takotsubo Cardiomyopathy, considering the modifying effects of sex and age demographics**. Despite TTC's benign reputation, it can be life threatening [12], with one study finding a 3.5% mortality rate [13]. Given the known link between TTC and stress, it is critical to understand how mental disorders influence TTC, to accurately identify at-risk patients, implement preventative measures, and tailor interventions to address both mental and cardiovascular health. Despite the incidence of TTC increasing annually [2], there is currently no preventative therapy available [1], and no consensus on treatment [14, 15], thus this research question aims to fill a crucial knowledge gap on the influence of mental disorders on TTC using statistical methods and a national database.

2. Methods

This study used data from the 2012 National Inpatient Sample (NIS): the largest all-payer inpatient care database in the United States. Only datasets from 2006 onwards were considered, as the TTC ICD-9 code was introduced in 2006. This database was chosen due to its nationwide coverage of cases, and the detailed diagnostic information it provides. TTC cases were identified using the ICD-9 code 492.83 to find all records with a primary or secondary diagnosis of TTC.

The author of this study completed the required HCUP data training requirements and completed a data use agreement. Under this agreement, direct distribution of the raw data by the author is not permitted, but can be accessed through HCUP instead. To support open science and enhance the reproducibility of this research, the Jupyter notebook containing the code used for analysis can be made available, and contains comprehensive comments to facilitate replication by other researchers.

Python (v3.12.2), pandas (v2.2.1), numpy (v1.26.4), scipy (v1.11.4), matplotlib (v3.8.4), and statsmodels (v0.14.1) were used for the analysis.

The data was cleaned to remove any rows with missing, invalid, unavailable, or inconsistent entries, encoded as ".", ".A", ".B", or ".C" as described in the NIS documentation. Manual inspection of the data revealed that some records contained negative numbers as entries, such as for 'age' and 'length of stay'. Only records containing valid entries – i.e. numeric and non-negative – were used in the analysis.

To maintain clarity and precision, mental disorders directly associated with TTC have been preserved as distinct categories based on their ICD-9 codes. Anxiety (300.xx), mood disorders (296.xx) and depression (309.xx) were selected, based on the existing literature comparing these three mental health conditions to TTC [16-18]. Two other categories of stress-related disorders were also individually preserved, given the stress-triggered genesis

of TTC: adjustment reaction (309.xx) and acute reaction to stress (308.xx). The remaining disorders were aggregated into broader categories for simplicity. Groups with low counts (n<10) were grouped into an 'other' category to comply with HCUP's data reporting guidelines.

To evaluate the association between each mental disorder and TTC, chi-squared tests were performed (given the categorical nature of the data) and reported with p-values. An additional overarching comparison was conducted to test if the presence of *any* mental disorder correlates with TTC using the chi-squared test. Sex disparities were also compared using the chi-squared test.

The mean ages of patients with and without TTC were compared with t-tests, given the continuous nature of age.

A logistic regression analysis was conducted using the Maximum Likelihood Estimation method with the statsmodel.api library. The model included an age-sex interaction term to account for the heightened risk of TTC among elderly women: a demographic consistently highlighted in the literature. To account for modifying variables such as seasonal variation [19], four confounding variables were also included to adjust for potential biases and improve the reliability of the data: sex, age, admission month and weekend admission.

The model adequacy was evaluated with the Pseudo R-Squared value, to gauge the model's explanatory power, and the log-likelihood value, to assess the goodness of fit between the model and the observed data. To ensure the predictors were independent and to check there was no multicollinearity, the Variance Inflation Factor (VIF) was computed for each predictor variable. Successful convergence of the model was also confirmed to ensure a stable solution had been reached.

This study's focus was accurately capturing the nuanced relationship between mental disorders and TTC incidence. Given the limited dataset size, performance metrics that rely on splitting the data into testing and training subsets – e.g. precision and accuracy – were not used, to ensure the full dataset was used for training, to preserve the integrity and comprehensiveness of the analysis.

A forest plot of the results was created using matplotlib to illustrate the odds ratios (ORs) with 95% confidence intervals (CIs) for the presence of specific mental disorders within the TTC cohort. To allow detailed interpretation, the exact numeric values of the ORs, CIs and p-values were also included in the plot.

Stratified analyses were implemented to further investigate the impacts of mental disorders on TTC incidence across different sex and age demographics, based on the substantial body of existing literature that has found disparities between sex and age demographics and TTC incidence. Within each demographic segment, the five mental disorders identified as having the most substantial impact on TTC, based on the results from the preliminary logistic regression, were examined. In segmenting the data for stratified analyses, age groups were deliberately chosen to delineate known high-risk age groups – postmenopausal and the elderly – while ensuring that all groups contained sufficient sample sizes (n>10). The five age strata were segmented as follows: 0-25, 26-39, 40-59, 60-79, and 80+ years.

This stratification resulted in relatively sparse subgroup datasets. To address the potential for overfitting from sample size limitations, a regularised logistic regression model with an elastic net approach was used. This method combines the L1 (lasso) penalty for feature selection and the L2 (ridge) penalty for multicollinearity. This was implemented using statsmodels.api's fit_regularized() function. ORs and 95% CIs derived from this approach were presented in a forest plot, with results indicating statistical significance ($p<0.05$) highlighted in red. To maintain interpretability, CIs that extended beyond 0.1 to 20 were truncated, to ensure the remaining data remained clearly visible. Counts of TTC occurrences and total patient numbers were reported at the subgroup level, while individual disorder totals were aggregated to comply with HCUP data guidelines.

3. Results and Discussion

After preprocessing to ensure the validity of the data, 13,911 records were removed due to inconsistent or missing data. The resulting dataset comprised a total of 7,283,057 records from the 2012 NIS database. 5059 (=0.069%) of these records included a primary or secondary diagnosis of TTC.

Mental disorder	**χ^2**	**p-value**
Schizophrenia and other psychotic disorders	36.40	<0.001*
Episodic mood disorders	5.50	0.0191
Anxiety, dissociative and somatoform disorders	683.98	<0.001*
Acute reaction to stress	132.89	<0.001*
Adjustment reaction	10.04	0.00153
Depressive disorder	258.56	<0.001*
Drug- and alcohol-related disorders	83.47	<0.001*
Dementias	0.07	0.789
Personality and behavioural disorders	18.10	<0.001*
Disorders of childhood and adolescence	7.79	0.00525
Other mental disorders	1.40	0.236

Figure 1 - Chi-squared analysis comparing the incidence of TTC across various mental disorder categories. The table presents the chi-squared statistic values (to 2 decimal places) and the corresponding p-values. p-values lower than 0.001 are rounded

A chi-squared analysis to compare the presence of any mental disorder with TTC produced a significant result ($\chi^2=373.86$, $p<0.001$), with TTC present in 0.095% (2413/2,528,263) of patients with mental disorders compared to 0.056% (2646/4,749,735) in those without.

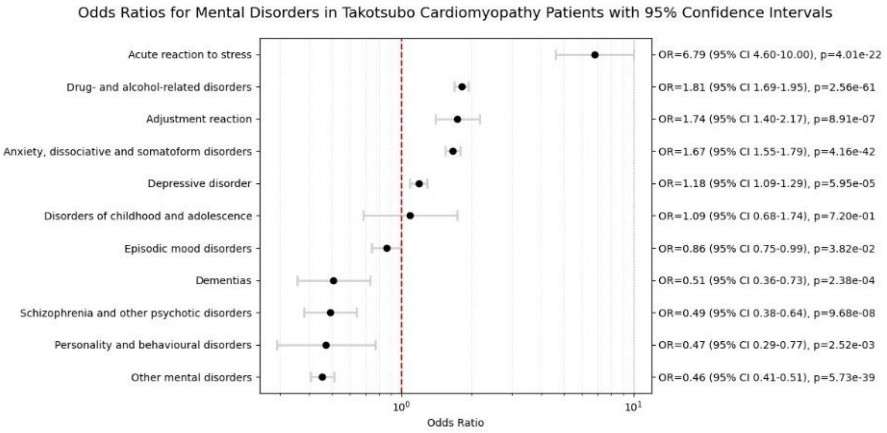

Figure 1 – Forest plot presenting odds ratios (ORs) for mental disorders in Takotsubo Cardiomyopathy with 95% confidence intervals (CIs). Points represent ORs, and horizontal lines represent CIs. ORs>1 indicate increased risk of TTC, and ORs<1 indicate decreased risk. The dashed line at OR=1 represents no effect. P-values<0.05 are considered statistically significant

Disparities between male and female patients were also significant (χ^2=1704.21, p<0.001), with TTC present in 0.10% (4370/4,198,501) of female patients, compared to 0.022% (689/3,079,497) of male patients.

A t-test comparing ages between patients with and without TTC also showed significant association (t=46.9, p<0.001), with the mean age of patients with TTC at 66.8 years (SD = ±13.9), compared to 48.6 years (SD = ±27.6) for those without TTC. These findings align with the prevailing evidence in the existing literature.

The VIF for all mental disorder variables was between 1.00 and 1.15, indicating low levels of multicollinearity.

Figure 3 shows that the group with the highest TTC risk is male patients over 80 (with a statistically significant, narrow CI), which contradicts current literature that does *not* link depression to TTC [16]. This highlights the importance of stratified analyses in uncovering specific demographic risks.

Figure 2 suggests that certain mental disorders may have a stronger association with TTC. In particular: acute reaction to stress (e.g. separation anxiety), drug- and alcohol-related disorders, adjustment reaction (e.g. post-traumatic stress disorder), anxiety, dissociative and somatoform disorders, and depressive disorders. One of the prevailing pathophysiological theories of TTC is the catecholamine surge theory [20], which posits that the surge in plasma catecholamines (e.g. adrenaline) that occurs after acute stress results in catecholamine-induced cardiotoxicity [21]. Catecholamines have been found to be involved in stress reactions [22], which may explain the underlying mechanisms between stress, anxiety and TTC.

Figure 2 shows that only disorders of childhood and adolescence were not statistically significant (p=0.720). This aligns with the findings in Figure 3 that show wide confidence intervals and small sample sizes (n=42) in male and female patients under 25. This aligns with the existing literature showing high risk in postmenopausal and elderly demographics.

Figure 2 additionally shows that dementia, personality disorders and schizophrenia have a protective effect on TTC incidence. One pathophysiological explanation is that psychosis [23] and Alzheimer's [24] have both been associated with lower catecholamine levels, which aligns with the catecholamine surge theory. However, depressive disorders have also been associated with lower catecholamines levels [25], yet Figure 2 shows a positive link between depressive disorders and TTC.

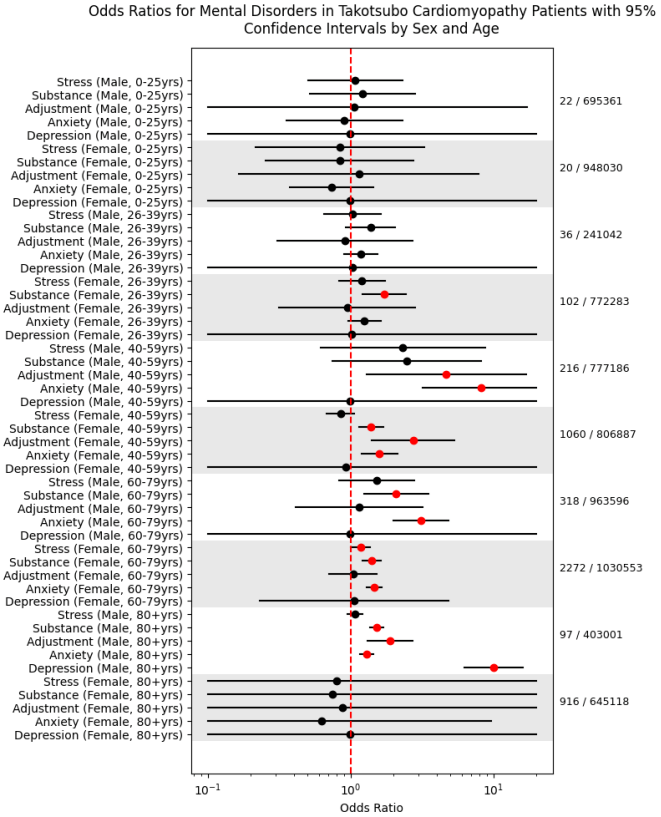

Figure 2 - Stratified forest plot for mental disorders in TTC. This plot displays ORs and 95% CIs for the top five mental disorders impacting TTC, stratified by sex and age. Each line represents a disorder's OR within specific demographics, with the point estimates (black dots for non-significant and red dots for significant results, p<0.05) denoting the ORs and the horizontal lines showing the CI range. The right column provides TTC counts and total patient numbers per subgroup. The dashed vertical line at OR=1 indicates no effect. ORs>1 suggest a higher TTC likelihood with the disorder, and ORs<1 suggest a lower likelihood. CIs outside the range of 0.1 to 20 were truncated for clarity

4. Conclusions

Summary: These results highlight the significant association between mental disorders and the incidence of TTC, with a significantly increased prevalence of TTC in patients with mental disorders compared to those without. There is a signification association between sex and TTC, with over a 400% increase in TTC incidence in female patients compared to male patients. There is a significant association between age and TTC, with a mean age nearly 20 years older in patients with TTC compared to those without. Age and sex demographics are affected differently by mental disorders, suggesting the need for personalised treatments. These findings suggest that stress management techniques and mental health treatment could be effective preventative treatment strategies in the management of TTC.

Critiques: using a large, nationally representative dataset enhances the generalisability of these findings. However, the use of a cross-sectional, not longitudinal, study limits the ability to infer causality from the observed data. Additionally, using the entire dataset to increase the training sample size limited the amount of validation that could be performed on the models. The analysis could have been improved by defining exclusion criteria for differential diagnoses of TTC such as myocardial infarction [7], e.g. by requiring coronary angiographic evidence of the absence of acute plaque rupture or obstructive coronary disease [26]. If the author had more time and compute power, sensitivity analyses and bootstrapping processes would have been implemented to measure the bias, variance and error of the models.

Clinical impact: future clinical trials could investigate these findings and further explore the causative mechanisms that link mental health disorders with TTC incidence. Developing novel treatments and interventions that target mental health could be effective in improving outcomes for patients with TTC.

5. References

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