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Original Research Report

Pre-existing Psychiatric Illness is Associated With Increased Risk of Recurrent Takotsubo Cardiomyopathy

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Background: *The increased prevalence of psychiatric illness among patients with takotsubo cardiomyopathy (TC) has been previously described.* **Objectives:** *We sought to assess the effect of pre-existing psychiatric illness on clinical outcomes following the diagnosis of TC.* **Methods:** *Adults diagnosed with TC at Vanderbilt University Medical Center between 1999 and 2015 were included in the study. Medical records were retrospectively reviewed to identify any pre-existing mood, anxiety, or schizophrenia-spectrum illness before TC presentation. Multivariable logistic regression was used to test for independent association of pre-existing psychiatric illness with 30-day mortality and recurrent TC; Cox proportional hazard analysis was used to evaluate for association with long-term mortality.* **Results:** *Among 306 patients diagnosed with TC during the study period, 114 (37%) had a pre-existing psychiatric illness. In all, 43 (14%) and 88 (29%) patients died within 30 days of index diagnosis and as of last medical record review, respectively. Of the 269 who survived their index hospitalization, 19 (7%) had a confirmed recurrent episode of TC. In multivariable analyses, pre-existing psychiatric illness was not associated with increased 30-day (P = 0.320) or long-term (P = 0.621) mortality. Pre-existing psychiatric illness was associated with higher risk of recurrent TC (odds ratio = 7.44, 95% CI: 2.30–24.01, P < 0.001).* **Conclusions:** *Pre-existing psychiatric illness was associated with an increased risk of recurrent TC. No significant association was noted between pre-existing psychiatric illness and survival.*

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Key words: Takotsubo, Stress cardiomyopathy, Psychiatric illness, Survival, Recurrence.

INTRODUCTION

Takotsubo cardiomyopathy (TC), also known as stress cardiomyopathy, is commonly recognized as transient left ventricular dysfunction that may mimic acute coronary syndrome but is without angiographic evidence of obstructive coronary artery disease.[1] TC has been increasingly associated with pre-existing psychiatric illness. Higher burden of pre-existing psychiatric comorbidity has been identified in patients with TC compared to healthy controls and patients

with a history of myocardial infarction or chronic heart failure.[2,3] Nevertheless, there is no strong consensus on the true spectrum of psychiatric illness in TC or the association of individual psychiatric diagnoses with this disorder. A number of studies have indicated that anxiety, but not mood disorders, may be associated with a higher risk of TC.[4,5]

Additionally, little remains known about any association of pre-existing psychiatric disease with clinical outcomes. We sought to assess the prognostic significance of pre-existing psychiatric illness for survival and recurrent cardiomyopathy after an index diagnosis of TC.

METHODS

Population and Study Design

After obtaining Institutional Review Board approval, we performed a retrospective observational study of all adult patients diagnosed with TC at Vanderbilt University Medical Center between 1999 and 2015. TC was defined using the following Mayo Clinic Criteria: transient abnormality in left ventricle wall motion beyond the perfusion territory of a single epicardial coronary artery, absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture, presence of new electrocardiographic abnormalities or elevation in cardiac biomarkers, and the absence of pheochromocytoma or myocarditis.[1]

Demographic and clinical data were collected by manual review of the electronic health record (EHR). Problematic alcohol use was defined as current consumption of more than 2 alcoholic drinks per day, self-report of current alcohol abuse, or a positive answer to a CAGE question at the time of index diagnosis. Overall burden of medical comorbidity was estimated using the Charlson comorbidity index.[6] The clinical context for each TC case was reviewed to distinguish among physical, emotional, and unidentified stressors. The presence of chest pain, shortness of breath, and syncope/presyncope was recorded when present at the time of TC presentation. Pattern of wall motion abnormality was reviewed from echocardiography; midventricular, basal, and focal wall motion abnormality were defined as atypical variants of TC.

Pre-existing mood, anxiety, or schizophrenia-spectrum illness and use of psychotropic medications, including antidepressants, antipsychotics, and anxiolytics, at the time of TC presentation were identified by expert review of EHR. For subjects with sufficient documentation of psychiatric history, pre-existing medical record diagnoses were manually reviewed per Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria.[7] Antidepressants were classified as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and other antidepressant agents including monoamine oxidase inhibitors, tricyclic antidepressants, bupropion, and mirtazapine. Antipsychotics included typical and atypical antipsychotic agents. Categorized anxiolytic agents included benzodiazepines and buspirone.

Duration of follow-up was calculated as the time between index discharge and last clinical encounter with a health care provider. Mortality was assessed by review of the EHR and Social Security Death Index as of January 14, 2016. The designated outcomes of the study were 30-day mortality following index diagnosis in addition to overall mortality and recurrent TC as of last medical record review.

Statistical Analysis

Statistical analyses were performed using Stata Statistical Software: Release 14 (College Station, TX).[8] Descriptive statistics are expressed as median with interquartile ranges for continuous variables and frequencies (percentages) for categorical variables. Univariate analyses were performed using the Pearson chi-squared test and Wilcoxon rank sum test for categorical and continuous variables, respectively. Death and recurrence after index discharge are depicted using Kaplan-Meier plots. Multivariable logistic regression was used to test for independent association of pre-existing psychiatric illness with 30-day mortality and recurrent TC. Association between pre-existing psychiatric illness and long-term mortality following index discharge was assessed using a multivariable Cox proportional hazard model. Covariates included in the models were age, Charlson comorbidity index score, and mode of cardiomyopathy trigger. Results are expressed as odds ratios and hazard ratios with 95% CI. All tests were two-tailed and a $P \leq 0.05$ was considered statistically significant.

RESULTS

A total of 306 patients were diagnosed with TC during the study period. Baseline demographic and clinical features are depicted in Table 1. Further, 114 (37%) patients had a pre-existing mood, anxiety, or schizophrenia-spectrum illness at the time of index TC diagnosis, accounting for a total 151 diagnoses (Figure 1). A summary of psychotropic medication use among patients with pre-existing psychiatric illness is provided in Table 2.

In all, 43 (14%) and 88 (29%) patients died within 30 days of index diagnosis and as of last medical record review, respectively. Of the 269 patients who survived the index hospitalization, 19 (7%) had a confirmed recurrent episode of TC at a time interval ranging between 29 days and 15 years following initial diagnosis. Overall risk of TC recurrence was 5.8% per patient-year. Of the 19 patients with recurrent TC, 15 (79%) had pre-existing psychiatric illness (5 patients with mood-spectrum and anxiety-spectrum illness, respectively, in addition to 5 patients with concomitant mood-anxiety disorders). Risk of TC recurrence among patients without pre-existing psychiatric illness was 1.9% per patient-year compared to 11.4% per patient-year in patients with psychiatric comorbidity. Comparison of mortality and recurrent TC based on pre-existing psychiatric illness is provided in Figure 2.

In multivariable logistic regression and Cox proportional hazard analysis, pre-existing psychiatric illness was not associated with increased 30-day (odds ratio = 0.69; 95% CI: 0.33–1.44; $P = 0.320$) or long-term (odds ratio = 0.89; 95% CI: 0.56–1.41; $P = 0.621$) mortality. In a similar analysis controlling for age, Charlson comorbidity index scores, and mode of cardiomyopathy trigger, pre-existing psychiatric illness was associated with higher risk of recurrent TC (odds ratio = 7.44; 95% CI: 2.30–24.01; $P < 0.001$) (Table 3).

DISCUSSION

The primary findings of this study are that pre-existing psychiatric illness (particularly mood and anxiety-spectrum) in TC is common, is not associated with short-term or long-term survival, but does predict increased risk of TC recurrence.

There are scant data on predictors of recurrent TC, and, to our knowledge, this is the first study identifying the prognostic significance of pre-existing psychiatric illness. Although this finding requires confirmation in larger scale or prospective studies, it suggests that pre-existing psychiatric illness may be useful to stratify patients in regard to the risk of TC recurrence. Given an estimated 10% risk of cardiogenic shock and 4% risk of inpatient death with each

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TABLE 1. Baseline Demographic and Clinical Features

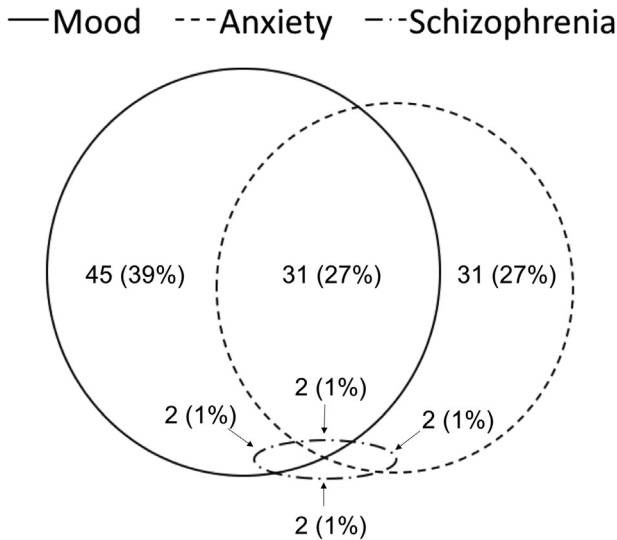|	N	No psychiatric illness (N = 192)	Pre-existing psychiatric illness (N = 114)	P value
Age (y)	306	69 (57–75)	60 (51–69)	<0.001[*]
Female (%)	306	149 (78%)	92 (81%)	0.522[†]
Race (% white)	306	161 (84%)	99 (87%)	0.480[†]
Insurance (% Medicaid)	304	16 (8%)	12 (11%)	0.513[†]
Education (% with college degree)	249	38 (25%)	24 (25%)	0.917[†]
Ongoing tobacco use (%)	299	30 (16%)	46 (41%)	<0.001[†]
Problematic alcohol use (%)	299	18 (10%)	15 (13%)	0.336[†]
Charlson comorbidity index	302	1 (0–3)	2 (1–3)	0.099[*]
Chest pain at presentation (%)	272	85 (50%)	48 (47%)	0.639[†]
Shortness of breath at presentation (%)	275	78 (46%)	49 (47%)	0.809[†]
Syncope or presyncope at presentation (%)	276	20 (12%)	13 (13%)	0.793[†]
Physical trigger (%)	306	115 (60%)	82 (72%)	0.034[†]
Atypical variant (%)	306	26 (14%)	21 (18%)	0.252[†]
Duration of hospitalization (d)	306	6 (3–12)	6 (3–10)	0.955[*]
Duration of follow-up (y)	277	0.1 (0–1.6)	0.2 (0–1.8)	0.594[*]

Data are presented as median (IQR) for continuous variables and number (percentage) of patients for categorical variables. *N* represents the number of patients with non-missing values. IQR = interquartile range.

[*] Wilcoxon rank sum test.

[†] Pearson chi-squared test.

FIGURE 1. Spectrum of Psychiatric Illness in Takotsubo Cardiomyopathy. A Total of 114 Patients Accounted for a total of 151 Mood, Anxiety, and Schizophrenia-Spectrum Diagnoses.

FIGURE 2. Kaplan-Meier Survival and Temporal Distribution of Recurrence in Patients Following Takotsubo Cardiomyopathy. Long-term Mortality Represents Cumulative Mortality from Index Diagnosis to the Date of Last Medical Record Review.

presentation of TC,[2] proper risk stratification may lead to more individualized prognostication and guide research into potential interventions aimed at reducing long-term morbidity and mortality in this patient population.
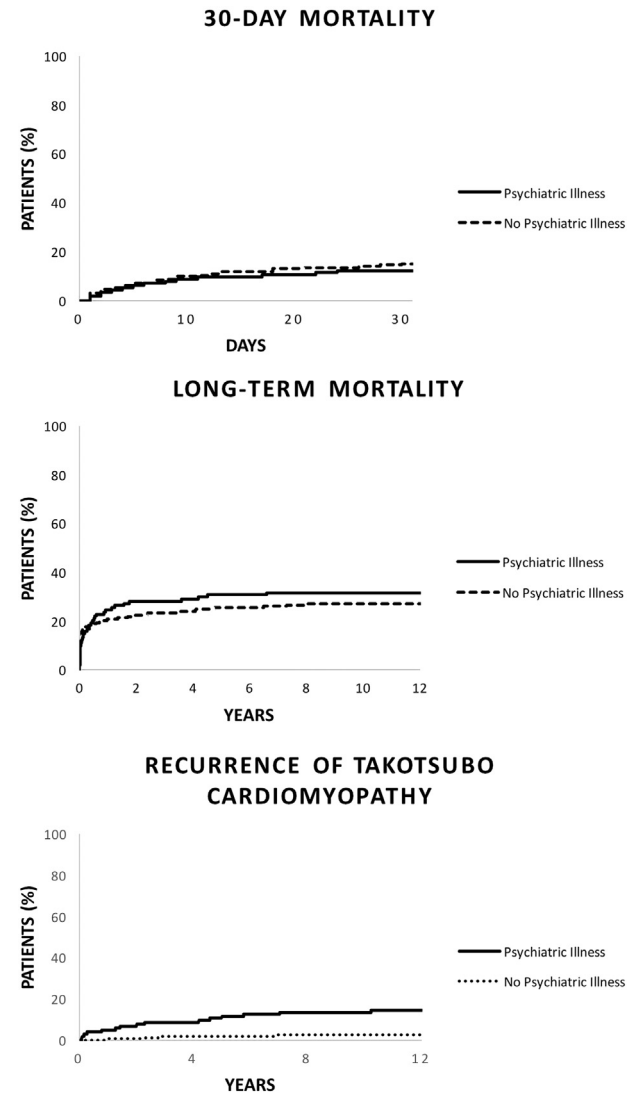
The appropriate management of psychiatric illness in TC is unclear. Insufficient statistical power precluded the study of an association between psychotropic use and TC recurrence. We chose to summarize the use of some common psychotropic agents among

TABLE 2. Psychotropic Use Among 114 Patients With Pre-existing Psychiatric Illness

Pharmacologic agent	Subjects (%)
Antidepressants	
SSRI	46 (43%)
SNRI	15 (14%)
Other	17 (16%)
Antipsychotics	
Typical	1 (1%)
Atypical	14 (13%)
Anxiolytics	
Benzodiazepine	46 (43%)
Buspirone	3 (3%)

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

our patient population for descriptive purposes. Overall, there is no evidence to suggest that psychiatric illness in TC should be managed any differently than in the absence of this disorder. However, there are multiple reports of psychotropic agent withdrawal or overdose in addition to electroconvulsive therapy triggering TC in patients with psychiatric illness.[9–11] Careful management of psychotropic medications and understanding that cardiomyopathy may be triggered by electroconvulsive therapy is likely appropriate in

TABLE 3. Adjusted Odds Ratios for 30-d Mortality and Cardiomyopathy Recurrence in Addition to Hazard Ratios for Long-Term Mortality Following Takotsubo Cardiomyopathy

Characteristics	OR	95% CI	*P* value
30-d mortality			
Age (y)	1.00	0.98–1.03	0.604
Charlson comorbidity index (CCI)	1.21	1.05–1.40	0.010
Physical stress as takotsubo trigger	7.55	2.21–25.71	<0.001
Pre-existing psychiatric illness	0.69	0.33–1.44	0.320
	HR	**95% CI**	***P* value**
Long-term mortality			
Age (y)	0.99	0.97–1.01	0.186
Charlson comorbidity index (CCI)	1.14	1.02–1.26	0.016
Physical stress as takotsubo trigger	1.59	0.76–3.32	0.213
Pre-existing psychiatric illness	0.89	0.56–1.41	0.621
	OR	**95% CI**	***P* value**
Recurrent takotsubo cardiomyopathy			
Age (y)	1.00	0.96–1.04	0.897
Charlson comorbidity index (CCI)	1.01	0.76–1.34	0.968
Physical stress as takotsubo trigger	0.51	0.18–1.42	0.196
Pre-existing psychiatric illness	7.44	2.30–24.01	<0.001

HR = hazard ratio; OR = odds ratio.

the care of patients with ongoing psychiatric illness and a history of TC.

In addition to assessing the prognostic significance of psychiatric illness in TC, we attempted to evaluate potential demographic and clinical differences based on pre-existing psychiatric pathology. In univariate analyses, no significant difference was noted among the most common presenting symptoms of TC. Patients with pre-existing psychiatric illness were on average younger at the time of TC diagnosis, used tobacco in higher rates, and were more likely to present with TC triggered by a physical stressor. Younger age at index diagnosis of TC among patients with psychiatric illness could further support the association of psychiatric pathology with increased risk of TC. Relatively increased proportion of cases triggered by physical stressors may also support an inherent predisposition of patients with psychiatric illness toward TC even in the absence of acute emotional stressors.

Despite an increasing number of studies evaluating psychiatric illness in TC, overall knowledge and clinical application remains limited.[12,13] The relative rarity of TC poses a significant challenge to most research endeavors and is a large reason why several distinct mood, anxiety, and schizophrenia-spectrum diagnoses are often grouped together. In a number of relatively smaller studies, only anxiety-spectrum disorders were associated with increased risk of TC.[4,5] Larger-scale studies may help to better differentiate the association of different psychiatric illnesses with the occurrence of TC in addition to long-term prognosis. Regarding long-term management of psychiatric illness in patients with a history of TC, there is a great need for prospective studies that evaluate the role of pharmacological or behavioral therapy in potentially reducing the risk of recurrent cardiomyopathy.

Study Limitations

This study should be interpreted in the context of its limitations. The retrospective cohort design only allows for identification of association and cannot infer causation. Moreover, the size of our cohort limits statistical power to detect associations and constrains the number of covariates included in the multivariable analyses. Ongoing tobacco use, although associated with pre-existing psychiatric illness in univariate analyses, was not included in the multivariable analyses for recurrence or survival. This study is likely underpowered to detect a smaller association between psychiatric illness and long-term survival. Insufficient statistical power also limits the ability to analyze different psychiatric illnesses individually. There are potential biases related to follow-up duration, limitations of the EHR and Social Security Death Index in defining the cause of death, and incomplete ascertainment of pre-existing psychiatric illnesses or use of psychotropic medications at index diagnosis. In particular, most psychiatric diagnoses were obtained from review of medical history listings, and appropriate confirmation of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria was not feasible for all patients. We acknowledge that this may have led to the underdiagnosis or misdiagnosis of psychiatric illness in the cohort.

CONCLUSIONS

In this single institution cohort, pre-existing psychiatric illness was associated with an increased risk of recurrent TC. No significant association was noted between pre-existing psychiatric illness and survival. The prognostic significance of specific psychiatric disorders in TC and their appropriate management is unclear. There is a great need for larger scale and

prospective studies that evaluate prognostic indicators and long-term management strategies in patients with comorbid psychiatric illness and TC.

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