



# Alcohol Use Disorder is Associated with an Increased Risk for Respiratory Failure among Patients with Takotsubo Cardiomyopathy

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## Abstract

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**BACKGROUND:** While takotsubo cardiomyopathy (TCM) was initially considered a benign disease, recent studies have demonstrated poor cardiovascular outcomes. It is important to determine the predictors of these outcomes for appropriate risk stratification and to decrease the overall disease burden. Physical stressors (e.g., acute neurologic disorder and lung disorder) and pre-existing heart failure have been associated with worse outcomes. Alcohol abuse has been associated with cardiomyopathy and may also exacerbate pre-existing heart conditions.

**AIM:** We aimed to determine the impact of alcohol abuse on patients with TCM.

**METHODS:** We identified 11,221 patients from the 2009 to 2012 National Inpatient Sample, of which 10,622 had TCM alone and 599 had TCM and alcohol use disorder (AUD). Our outcomes of interest were overall mortality, need for mechanical hemodynamic support (MHS), acute respiratory failure, sudden cardiac arrest, cardiogenic shock, stroke, and atrial fibrillation. All clinical characteristics were defined per the International Classification of Diseases 9<sup>th</sup> revision codes. Logistic regression was used to estimate the odds ratios of the outcomes in patients with concomitant TCM and AUD, compared to those with TCM without AUD while adjusting for confounders.

**RESULTS:** The mean age of the sample was 60.5 ± 11 for TCM with AUD and 56.0 ± 11 for TCM alone. There was no significant difference between the two groups in the rates of atrial fibrillation (10.4% vs. 8.5%; p = 0.134), cardiogenic shock (5.9% vs. 4.8%; p = 0.3), use of MHS (2.6% vs. 1.7%; p = 0.165), overall in-hospital mortality (4.0% vs. 3.7%; p = 0.691), stroke (1.6% vs. 1.3%; p = 0.593), and sudden cardiac arrest (2.7% vs. 3.5%; p = 0.24). Rates of acute respiratory failure (17.7% vs. 25.2%; p < 0.0001) were significantly higher in patients with TCM with AUD compared to those with TCM alone. After adjusting for significant cofounders, the odds ratio for respiratory failure among patients with concomitant TCM and AUD was 1.36 (95% CI: 1.11–1.66) compared to those with TCM without AUD.

**CONCLUSION:** Pre-existing AUD is associated with an increased risk for respiratory failure in a patient with TCM.

## Introduction

Takotsubo cardiomyopathy (TCM) or stress-induced cardiomyopathy is a transient reversible myocardial dysfunction thought to be secondary to exaggerated myocardial catecholamine exposure [1]. Predominantly seen in post-menopausal female in the setting of emotional or physical stressors, it is an increasingly recognized cause of inpatient hospitalization in recent years [1], [2].

Although, initially considered a benign condition, multiple observational studies have consistently demonstrated increased mortality and morbidity in patients with TCM [3]. Notably, up to 20% of these patients will go on to develop cardiogenic shock, up to 15% will develop a cardiac arrhythmia, and 4.5% will develop stroke. Finally, the in-hospital mortality rate can be as high as 5% [3], [4]. In relation, it is important to determine the predictors of poor outcomes in this patient population, to allow appropriate risk stratification, mitigate the risks, and improve overall outcomes.

Clinical factors such as older age, physical stressors, diabetes mellitus, and pre-existing heart failure have been associated with poor outcomes [4]. The impact of alcohol use on outcomes in patients with TCM has not been discussed. Oxidative stress and accelerated protein catabolism have been implicated in the pathogenesis of alcoholic cardiomyopathy [5], [6]. In addition, they might exacerbate pre-existing heart conditions which may delay recovery and lead poor outcomes in patients with TCM [5], [6]. We aim to determine the effects of alcohol use on outcomes among patients with TCM.

## Methods

### Study design

This is a cross-sectional study that used the discharge data from the National Inpatient Sample (NIS)

database for the year 2009–2012. The NIS, Healthcare Cost and Utilization Project, agency for healthcare research and quality (AHRQ) is the largest all-payer inpatient database in the United States (US). The database contains a 20% stratified sample of all discharges from the US nonfederal short-term general hospitals, subspecialty hospitals, and public hospitals and is stratified based on the number of beds, ownership, hospital teaching status, US region, and state. Stratified random sampling ensures that the database is representative of the US population and accounts for 90% of all hospitalizations in the US after applying appropriate weights. The NIS includes information on demographic characteristics, hospital characteristics, up to 25 diagnostic and procedure codes based on the International Classification of Diseases 9<sup>th</sup> revision, Clinical Modification (ICD-9-CM), and outcomes based on patient discharge records. Each record represents a single hospitalization and thus, multiple records are possible for an individual with recurrent hospitalizations [7].

### Study population, variables, and outcomes

We identified patients aged 18–75 years from the 2009 to 2012 NIS with the discharge diagnosis of TCM using ICD-9-CM code 429.83 (Figure 1). The study group consisted of patients with a diagnosis of both TCM and alcohol use disorder (AUD), while the control group included – patients with a diagnosis of TCM without AUD in any of their discharge codes. AUD was identified using the ICD-9-CM codes 305.00–305.03 and 303.90–303.93 (supplementary Table 1). Demographics and primary prayer associated with each discharge diagnosis were identified from the NIS. Comorbidities were identified using the AHRQ comorbidity software. This software allows identification of comorbidities not related to the primary diagnosis that was present before admission [8]. Comorbidities chosen were those used in prior studies evaluating outcomes in patients with TCM [8], [9], [10]. The primary outcomes of interest included overall in-hospital mortality, atrial fibrillation, sudden cardiac arrest, cardiogenic shock, acute respiratory failure, stroke, and mechanical hemodynamic support (MHS). All clinical variables were defined by the ICD-9-CM codes (See supporting information for ICD-9-CM codes of these variables).

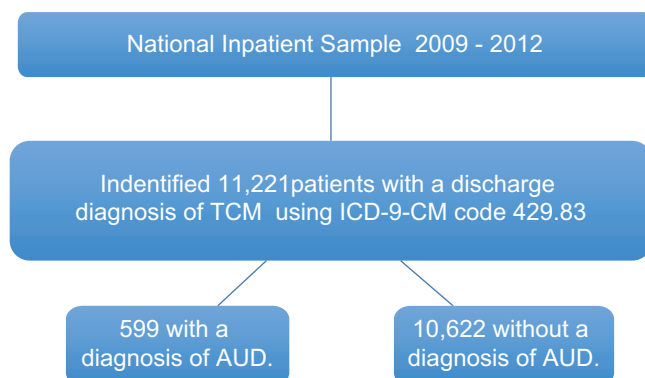


Figure 1: Selection of the patients

### Statistical analysis

All statistical analyses were performed using SPSS version 20. We compared baseline patient characteristics and outcomes between patients with concomitant TCM and AUD and those with TCM without AUD. Chi-square test of significance was used for categorical variables and independent sample t-test to compare for the continuous variable. Logistic regression analysis was used to estimate the adjusted odds ratios (aOR) the outcomes between these two groups patients. Covariates adjusted for were include age, sex, tobacco use, hypothyroidism, chronic kidney disease, obesity, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and coronary artery disease. Association of each outcome variable with AUD was reported as aOR with 95% confidence interval. A two-tailed  $p < 0.05$  was considered statistically significant.

## Results

### Baseline demographics

We identified 11,221 patients with a discharge diagnosis of TCM. Among these patients, 599 (5.3%) had AUD and 10,622 (94.6%) did not have AUD. The study sample was mostly female (86.6%, Table 1). The mean age of patients with AUD was significantly lower compared to patient without AUD ( $56.01 \pm 11$  vs.  $60.47 \pm 11$ ;  $p < 0.0001$ ). There were no significant racial differences between both groups. The prevalence of tobacco use disorder (45.9% vs. 19%;  $p < 0.0001$ ) was significantly

Table 1: Baseline characteristics of study participants by alcohol use disorder status

Demographics	TCM ALONE (10,622)	TCM + AUD (599)	p-value
Age (years), mean (SD)	60.47 (11)	56.01 (11)	<0.0001
Sex			<0.0001
Female (n, %)	9297 (87.4)	427 (71.3)	
Male (n, %)	1335 (12.6)	172 (28.7)	
Race			0.159
White (n, %)	7629 (81.0)	447 (83.4)	
Black (n, %)	725 (7.7)	45 (8.4)	
Hispanic (n, %)	552 (5.9)	20 (3.7)	
Asian or Pacific Islander (n, %)	187 (2.0)	5 (0.9)	
Native America (n, %)	68 (0.7)	5 (0.9)	
Other (n, %)	261 (2.8)	14 (2.6)	
Primary prayer			<0.0001
Medicare (n, %)	5093 (48.0)	207 (34.7)	
Medicaid (n, %)	999 (9.4)	110 (18.4)	
Private insurance (n, %)	3649 (34.4)	169 (28.3)	
Self-pay (n, %)	522 (4.9)	77 (12.9)	
No charge (n, %)	45 (0.4)	4 (0.7)	
Other (n, %)	308 (2.9)	30 (5.0)	
Comorbidities			
Tobacco use disorder (n, %)	2023 (19)	275 (45.9)	<0.0001
VHD (n, %)	82(0.8)	3(0.5)	0.457
Hypothyroidism (n, %)	1527 (14.4)	62 (10.4)	0.006
CKD (n, %)	850 (8.0)	20 (3.3)	<0.0001
Obesity (n, %)	1136 (10.7)	28 (4.7)	<0.0001
CHF (n, %)	2856 (26.9)	172 (28.7)	0.32
COPD (n, %)	2116 (19.9)	140 (23.4)	0.039
Hyperlipidemia (n, %)	3882 (36.5)	117 (19.5)	<0.0001
Diabetes (n, %)	2640 (24.8)	112 (18.7)	0.001
Hypertension (n, %)	6380 (60.0)	339 (56.6)	0.097
CAD (n, %)	3660 (34.4)	182 (30.4)	0.043

AUD: Alcohol use disorder; CAD: Coronary artery disease; CKD: Chronic kidney disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; SD: Standard deviation; TCM: Takotsubo cardiomyopathy; VHD: Valvular heart disease.

higher in patients with AUD, while the prevalence of chronic kidney disease (3.3% vs. 8%;  $p < 0.0001$ ), obesity (4.7% vs. 10.7%;  $p < 0.0001$ ), hyperlipidemia (19.5% vs. 36.5%;  $p < 0.0001$ ), diabetes mellitus (18.7% vs. 24.8%;  $p = 0.001$ ), and hypothyroidism (10.4% vs. 14.4%;  $p = 0.006$ ) were significantly lower (Table 1).

## Outcomes

There was no significant difference between the two groups in the rates of atrial fibrillation (10.4% vs. 8.5%;  $p = 0.134$ ), cardiogenic shock (5.9% vs. 4.8%;  $p = 0.3$ ), use of MHS (2.6% vs. 1.7%;  $p = 0.165$ ), overall in

**Table 2: Outcomes in patients with alcohol use disorder compared to those without alcohol use disorder**

Outcomes	TCM alone	TCM+AUD	p-value
Overall mortality (n, %)	425 (4.0)	22 (3.7)	0.691
Mechanical hemodynamic support (n, %)	275 (2.6)	10 (1.7)	0.165
Atrial fibrillation (n, %)	1109 (10.4)	51 (8.5)	0.134
Respiratory failure (n, %)	1880 (17.7)	151 (25.2)	<0.0001
Cardiac arrest (n, %)	287 (2.7)	21 (3.5)	0.240
Cardiogenic shock (n, %)	623 (5.9)	29 (4.8)	0.300
Stroke (n, %)	172 (1.6)	8 (1.3)	0.593

TCM: Takotsubo cardiomyopathy; AUD: Alcohol use disorder.  $p < 0.05$  means statistical significant. Rates of sudden cardiac arrest and acute respiratory failure was significantly higher in patients with alcohol use disorder.

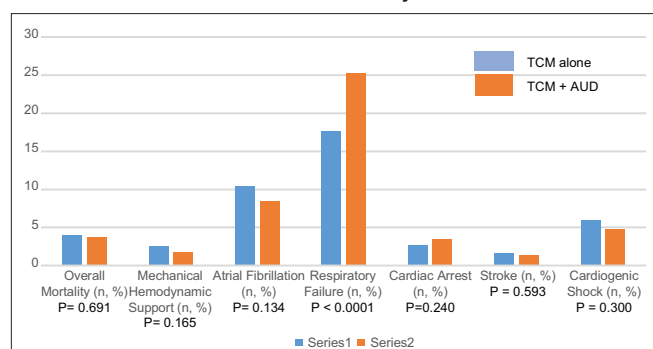
hospital mortality (4.0% vs. 3.7%;  $p = 0.691$ ), stroke (1.6% vs. 1.3%;  $p = 0.593$ ), and sudden cardiac death (2.7% vs. 3.5%;  $p = 0.24$ ). Rates of acute respiratory failure (25.2%, vs. 17.7%;  $p < 0.0001$ ) were significantly higher in patients with AUD compared to those without AUD (Table 2 and Figure 2). After adjusting for covariates (Table 3), the

**Table 3: Adjusted odds ratios and 95% confidence intervals for outcomes among those with alcohol use disorder compared to those without**

Outcomes	TCM	aOR (95% CI)	TCM+AUD	p-value
Overall mortality	1.0		0.81 (0.52–1.26)	0.34
AF	1.0		1.21 (0.89–1.65)	0.22
Cardiac arrest	1.0		1.13 (0.71–1.78)	0.61
Cardiogenic shock	1.0		0.73 (0.50–1.08)	0.13
MHS	1.0		0.59 (0.31–1.11)	0.10
Respiratory failure	1.0		1.34 (1.11–1.66)	0.003
Stroke	1.0		0.72 (0.35–1.48)	0.36

AUD: Alcohol use disorder; CI: Confidence interval; AF: Atrial fibrillation; MHS: Mechanical hemodynamic support. Adjusted covariates include age, sex, tobacco use, hypothyroidism, chronic kidney disease, obesity, chronic obstructive pulmonary disease, diabetes mellitus, hyperlipidemia, and coronary artery disease.

odds ratio for acute respiratory failure (aOR 1.36; 95% CI: 1.11–1.66) in patients with AUD compared to those without AUD remained significant. The association for the other outcomes was attenuated when adjusted for covariates.



**Figure 2: Proportion of outcomes by alcohol use disorder status.** The vertical axis represents percentage of outcomes, while the horizontal axis, the specified outcomes, and corresponding p-values. TCM: Takotsubo cardiomyopathy, AUD: Alcohol use disorder

## Discussion

In this study, we investigated the association between concomitant TCM and AUD compared to TCM without AUD and outcomes. We found a significant association between concomitant TCM and AUD and acute respiratory, with an estimated 36% increased risk, compared to those with TCM without AUD. There was no apparent association between concomitant TCM and AUD, and atrial fibrillation, stroke, sudden cardiac death, use of MHS, cardiogenic shock, or overall inpatient mortality. To our knowledge, this is the first study to evaluate the effects of AUD on TCM outcomes.

We have seen an increased incidence in TCM in recent years due to increased awareness and the wide availability of invasive coronary angiography [1]. While it was previously considered benign, recent studies have demonstrated rates of in-hospital complications similar to those in patients with acute coronary syndrome [11]. Ghadri *et al.* reported up to 15% rate of atrial fibrillation, 20% cardiogenic shock, and 6% sudden cardiac arrest in these patients [4]. Common predictors of these outcomes include a physical stressor, age >75 years, male sex, reduction in left ventricular systolic function on admission, high brain natriuretic peptide levels, and a troponin >10 times the upper reference limit [4]. In a recent study, Desai *et al.* demonstrated an increased risk of cardiac complications in obese patients with TCM compared to non-obese patients [12].

Acute respiratory failure as an in-hospital complication in TCM has not been well studied. Prior studies looking at in-hospital complications in patients with TCM have focused on cardiac complications such as cardiogenic shock, cardiac arrest, myocardial infarction, and arrhythmias [11]. In our study, we found an 18% rate of acute respiratory failure among patients with TCM, which is higher than that reported in other studies evaluating acute respiratory failure as a complication of TCM [8], [9], [12]. Desai *et al.*, while evaluating TCM complications in obese compared to non-obese patients, observed a 12% rate of acute respiratory failure, while Yassin *et al.* observed a 14% rate in another study evaluating the impact of atrial fibrillation on TCM [8], [12]. In our study, we found a 25% prevalence of acute respiratory failure in patients with concomitant TCM and AUD, compared to 17.7% in those without AUD.

While the exact pathogenesis of TCM is unclear, it is thought to be secondary to exaggerated myocardial catecholamine exposure [3]. Furthermore, studies have suggested that oxidative stress may also play a role through inducing left ventricular dysfunction by affecting calcium homeostasis and myocardial contractile function [10], [13]. Chronic alcohol use weakens the pulmonary immune system and makes the cells more susceptible to oxidative stress injury, increasing the risk for acute respiratory distress syndrome and

pneumonia[14],[15],[16]. Another plausible explanation for the higher risk of acute respiratory failure seen in patients with concomitant TCM and AUD is that patients with AUD have an increased risk of aspiration pneumonia, which can eventually lead to acute respiratory failure [17]. Furthermore, oxidant injury might explain acute respiratory failure seen in patients with TCM and increased susceptibility to such injury might explain why the rates are higher in patients with AUD.

### Limitations

Our study has some limitations related to the NIS database: (1) We identified patients with AUD using ICD-9-CM codes. We might have missed some patients with this condition in cases where the diagnosis was not coded. Furthermore, we were unable to quantify alcohol intake. (2) Information on laboratory and clinical data such as vital signs and left ventricular ejection fraction to determine the severity of TCM, was unavailable. This might play a role on the outcomes.

### Conclusion

Our study showed that the risk of acute respiratory failure was significantly higher among patients with concomitant TCM and AUD compared to those without AUD. Future studies are needed to replicate our findings and further clarify the impact of AUD on outcomes in patients with TCM.

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PMid:21659417

## Supplementary Table 1

International Classification of Disease 9th Revision –Clinical Modification Codes (ICD-9 CM) and Clinical Classifications Software and procedure (PR) codes used for Comorbidities and Complications not provided by NIS database

(The comorbidity codes provided by database: [https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/Table2-FY2010-V3\\_5.pdf](https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/Table2-FY2010-V3_5.pdf))

Comorbidities	ICD-9 CM/CCS/PR codes
Tobacco use disorder	305.1
Valvular heart disease	424.0, 424.1, 424.2, 424.3
Hypothyroidism	244.9
Chronic kidney disease	585.1–585.5
Obesity	278.0–278.03
Hypertension	401.9
Congestive heart failure	428.0
Chronic obstructive pulmonary disease	491, 492
Diabetes	250.00–250.03
Hyperlipidemia	272.4
Coronary artery disease	414.01
Complications	
Stroke	434.91
Atrial fibrillation	427.31
Cardiogenic shock	785.51
Cardiac arrest	427.5
Mechanical circulatory support (percutaneous ventricular assist device (Impella®), intra-aortic balloon pump)	PR 37.68, PR 37.61
Respiratory failure	518.81