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Associations Between Adrenal Insufficiency and Cardiovascular Outcomes in Patients Hospitalized with Takotsubo Cardiomyopathy: Insights from the Nationwide Readmissions Database (2019)

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Abstract

Background/Objectives: Patients with adrenal insufficiency (AI) are at an increased risk of adverse events (AEs) during cardiovascular hospitalization. However, the association between AI and takotsubo cardiomyopathy (TCM) remains unclear. We investigated the association between AI and cardiovascular outcomes in patients with TCM. Methods: We analyzed data on patients with TCM included in the 2019 Nationwide Readmissions Database to compare in-hospital outcomes between patients with and without AI. The primary outcome measure was inpatient mortality. Secondary outcomes included the odds of all-cause 90-day readmission, acute kidney injury (AKI), mechanical ventilation use, vasopressor use, cardiogenic shock, length of stay (LOS), and total hospitalization charges (THC). Multivariate regression models were used to adjust for confounding variables. Results: Among 30,987 cases, 0.59% (n = 183) had concomitant AI. AI was associated with higher odds of in-hospital mortality (adjusted odds ratio [aOR] 3.32, 95% confidence interval [CI] 1.43–7.74, $p = 0.005$), cardiogenic shock (aOR 5.28, 95% CI 3.16–8.82, $p < 0.001$), mechanical ventilation use (aOR 3.20, 95% CI 1.78–5.74, $p < 0.001$), AKI (aOR 1.96, 95% CI 1.11–3.48, $p = 0.021$), vasopressor use (aOR 4.59, 95% CI 1.56–13.47, $p = 0.006$), longer LOS (6.84 vs. 3.67 days, $p < 0.001$), and higher THC ($97,419 vs. $54,574, $p < 0.001$). Additionally, AI was associated with lower odds of all-cause 90-day readmissions (aOR 0.44, 95% CI 0.25–0.79, $p = 0.006$). Conclusions: Among patients with TCM, AI was associated with higher odds of fatal and non-fatal adverse events. Further studies are required to confirm these findings and better understand how to improve outcomes in this high-risk population.

Keywords: takotsubo cardiomyopathy; adrenal insufficiency; national readmission database

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1. Introduction

Takotsubo cardiomyopathy (TCM) is a reversible form of cardiomyopathy primarily observed in postmenopausal women. TCM, often referred to as broken heart syndrome, stress cardiomyopathy, or apical ballooning syndrome, was first documented in Japan in

1990. It represents 1–2% of patients with acute coronary syndrome, with an overwhelming female predominance (89.8%) and a mean age of 66.8 years [1]. TCM has attracted significant attention in the field of cardiovascular diseases. Despite various proposed hypotheses, no specific etiology has been identified to explain its occurrence in this population. Contemporary literature suggests that the neurocardiac axis plays a crucial role in TCM pathophysiology.

Adrenal insufficiency (AI) is characterized by an inadequate production of glucocorticoids, primarily cortisol, which are essential for the body's response to stress. Cortisol plays a pivotal role in modulating the cardiovascular system by maintaining vascular tone and regulating catecholamine sensitivity. Cortisol deficiency may disrupt this balance and has been associated with cardiovascular manifestations. Emerging evidence suggests a link between AI and TCM. While TCM is often associated with acute stressors that lead to a surge in catecholamines, the absence of adequate cortisol may exacerbate the myocardial response to these catecholamines, resulting in transient left ventricular dysfunction, a characteristic of TCM. Reports of TCM in patients with AI highlight their potential relationship [2,3]. Patients with adrenal insufficiency are particularly vulnerable during periods of physiological stress, as inadequate glucocorticoid dose adjustment may lead to life-threatening complications, including adrenal crisis.

Given the limited data on TCM outcomes in patients with AI, we analyzed a comprehensive national administrative claims database to better understand the clinical outcomes in this specific patient population. We hypothesized that the presence of AI would be associated with poor cardiovascular outcomes in these patients.

2. Materials and Methods

2.1. Materials, Methods, and Ethics Statement

We examined records from the Nationwide Readmissions Database (NRD) covering 1 year from 1 January 2019, to 31 December 2019. The NRD, which is part of the Healthcare Cost and Utilization Project overseen by the Agency for Healthcare Research and Quality in the US, contains publicly accessible, de-identified information. Accordingly, the need for institutional review board approval was eliminated [4,5]. Patients aged $\geq$18 years who were hospitalized primarily for TCM, as indicated by the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) code I51.81, were included in this study. The patients were categorized into two groups depending on AI status (ICD-10-CM codes E271, E273, E2740, E2749). In-hospital mortality was the primary outcome measure. The secondary outcomes included all-cause readmission within 90 days, acute kidney injury (AKI), mechanical ventilation use, vasopressor administration, cardiogenic shock, average hospital stay duration, and overall hospitalization expenses. Additionally, we identified baseline demographic and clinical characteristics using specific ICD-10-CM codes. These included the prevalence of type 1 and 2 diabetes, heart failure, dyslipidemia, hypertension, prior acute myocardial infarction (AMI), stroke, and hypothyroidism.

2.2. Study Population

Adult patients (>18 years) in the NRD diagnosed with TCM (ICD-10 Code I51.81, referring to Takotsubo Syndrome) in 2019 were selected. Patients with a secondary diagnosis of AI (ICD-10 codes E27.1 [Primary adrenocortical insufficiency], E27.2 [Addisonian crisis], and E27.4 [Other and unspecified adrenocortical insufficiency]) were selected. The patients were grouped according to age, as shown in Table 1.

Table 1. Study group description.

NRD 2019 data	TCM (n = 30,987)	
Group description	AI (n = 183)	No AI (n = 30,804)

NRD, Nationwide Readmissions Database; TCM, takotsubo cardiomyopathy; AI, adrenal insufficiency.

2.3. Statistical Analyses

The survey weights, strata, and clustering variables from the NRD were incorporated into the analysis to produce nationally representative estimates with accurate standard errors. The patient demographic profiles were summarized using descriptive statistical methods. We calculated both unadjusted odds ratios (uORs) and adjusted odds ratios (aORs) to examine the association between adrenal insufficiency and outcome measures. The uORs were determined using univariate logistic regression. Subsequently, we constructed multivariate logistic regression models to derive aORs, controlling for potential confounders, including age, sex, insurance coverage type, average household income by zip code, and comorbidity burden (assessed using the Deyo-modified Charlson Comorbidity Index [CCI]). For statistical comparisons between groups, continuous variables were analyzed using Student's *t*-test, while categorical variables were evaluated using the Rao–Scott chi-square test. All statistical analyses were performed using Stata version 18.0, with $p < 0.05$ considered statistically significant. Data were analyzed using Stata Corp. 2025. Stata Statistical Software: Release 18.0. College Station, TX, USA, StataCorp, LLC.

3. Results

3.1. Patient Characteristics

Among the 30,987 patients admitted with a primary diagnosis of TCM, 0.59% (183 patients) had a secondary diagnosis of AI. Patients with AI were younger (mean age: 66.1 years vs. 67.0 years) and had a significantly higher CCI (mean: 2.67 vs. 1.78, $p < 0.001$). Patients with AI were also more likely to have hypothyroidism (30% vs. 19%, $p = 0.017$), type 1 diabetes (1.9% vs. 0.37%, $p = 0.011$), type 2 diabetes (31% vs. 20%, $p = 0.018$), all-cause anemia (16.2% vs. 6.7%, $p < 0.001$), and heart failure (50.1% vs. 33.3%, $p = 0.001$) than those without AI. Hyperthyroidism, prior AMI, prior stroke, alcohol use, hypertension, dyslipidemia, tobacco use, and chronic obstructive pulmonary disease (COPD) did not differ between the groups. The baseline characteristics of patients with TCM stratified by the presence or absence of AI are shown in Table 2.

Table 2. Baseline characteristics and comorbidities of patients with TCM stratified by the presence vs. absence of AI.

Characteristic	AI Group (n = 183)	Non-AI Group (n = 30,804)	*p*-Value
Sex, %			0.1
Male	5.9	10.0	
Female	94.1	90.0	
Age category (years), %			0.5
18–34	2.9	1.6	
35–65	40.2	38.5	
>65	56.9	60.0	
CCI Score, %			0.0009
0	13.9	24.8	
1	22.5	28.2	
2	17.8	21.1	
≥3	45.8	26.0	

Table 2. *Cont.*

Characteristic	AI Group (n = 183)	Non-AI Group (n = 30,804)	*p*-Value
Median household Income (USD), %			0.8
$1–49,000	25.2	23.8	
$50,000–64,999	22.2	27.7	
$65,000–85,999	29.6	27.2	
≥$86,000	23.0	21.3	
Insurance, %			0.4
Medicare	68.4	63.3	
Medicaid	6.2	8.5	
Private	22.5	25.5	
Self-pay	2.9	2.7	
Tobacco use, %	36.5	42.5	0.3
Diabetes type 1, %	1.9	0.4	0.01
Diabetes type 2, %	31.0	20.0	0.02
Heart failure, %	50.1	33.3	0.001
Hypothyroidism, %	30.0	19.0	0.02
Hyperthyroidism, %	2.9	0.9	0.09
Prior AMI, %	5.7	8.5	0.4
Prior stroke, %	8.9	6.5	0.4
Hypertension, %	41.0	44.0	0.6
Dyslipidemia, %	41.0	48.0	0.2

TCM, takotsubo cardiomyopathy; AI, adrenal insufficiency; CCI, Charlson Comorbidity Index; AMI, acute myocardial infarction.

3.2. Primary and Secondary Outcomes

In the unadjusted analysis, patients with AI had significantly higher odds of experiencing adverse outcomes than those without AI. Specifically, AI was associated with an increased in-hospital mortality (6.1% vs. 1.6%; uOR 3.91, 95% CI 1.77–8.63, $p = 0.001$), cardiogenic shock (24.2% vs. 5.0%; uOR 6.04, 95% CI 3.74–9.75, $p < 0.001$), and mechanical ventilation use (15.9% vs. 5.0%; uOR 3.57, 95% CI 2.05–6.24, $p < 0.001$). AKI was also more frequent in the AI group (24.2% vs. 10.8%; uOR 2.64, 95% CI 1.58–4.40, $p < 0.001$), as was vasopressor use (4.6% vs. 0.8%; uOR 5.56, 95% CI 1.98–15.65, $p = 0.001$). Interestingly, all-cause 90-day readmissions were significantly lower in the AI group (19.4% vs. 9.3%; uOR 0.43, 95% CI 0.24–0.77, $p = 0.004$) (Table 3).

After adjusting for baseline characteristics, AI remained independently associated with adverse in-hospital outcomes. The aORs indicated higher odds of in-hospital mortality (aOR 3.32, 95% CI 1.43–7.74, $p = 0.005$), cardiogenic shock (aOR 5.28, 95% CI 3.16–8.82, $p < 0.001$), and mechanical ventilation use (aOR 3.20, 95% CI 1.78–5.74, $p < 0.001$). Adjusted analyses also confirmed increased odds of AKI (aOR 1.96, 95% CI 1.11–3.48, $p = 0.021$) and vasopressor use (aOR 4.59, 95% CI 1.56–13.47, $p = 0.006$). Additionally, AI was associated with significantly lower odds of all-cause 90-day readmissions (aOR 0.44, 95% CI 0.25–0.79, $p = 0.006$) (Table 4, Figure 1).

Table 3. Unadjusted outcomes based on the presence vs. absence of AI.

Outcome	AI Group (%)	Non-AI Group (%)	Unadjusted Odds Ratio (uOR)	95% CI	*p*-Value
In-hospital mortality	6.1	1.6	3.91	1.77–8.63	0.001
Cardiogenic shock	24.2	5.0	6.04	3.74–9.75	<0.001
Mechanical ventilation use	15.9	5.0	3.57	2.05–6.24	<0.001
AKI	24.2	10.8	2.64	1.58–4.40	<0.001
Vasopressor use	4.6	0.8	5.56	1.98–15.65	0.001
90-day readmissions (all-cause)	9.3	19.4	0.43	0.24–0.77	0.004

CI, confidence interval; AI, adrenal insufficiency; AKI, acute kidney injury.

Table 4. Adjusted outcomes based on the presence vs. absence of AI.

Outcome	Adjusted Odds Ratio (aOR)	95% CI	*p*-Value
In-hospital mortality	3.32	1.43–7.74	0.005
Cardiogenic shock	5.28	3.16–8.82	<0.001
Mechanical ventilation use	3.20	1.78–5.74	<0.001
Acute kidney injury (AKI)	1.96	1.11–3.48	0.021
Vasopressor use	4.59	1.56–13.47	0.006
90-day readmissions (all-cause)	0.44	0.25–0.79	0.006

AI, adrenal insufficiency; aOR, adjusted odds ratio; CI, confidence interval; AKI, acute kidney injury.

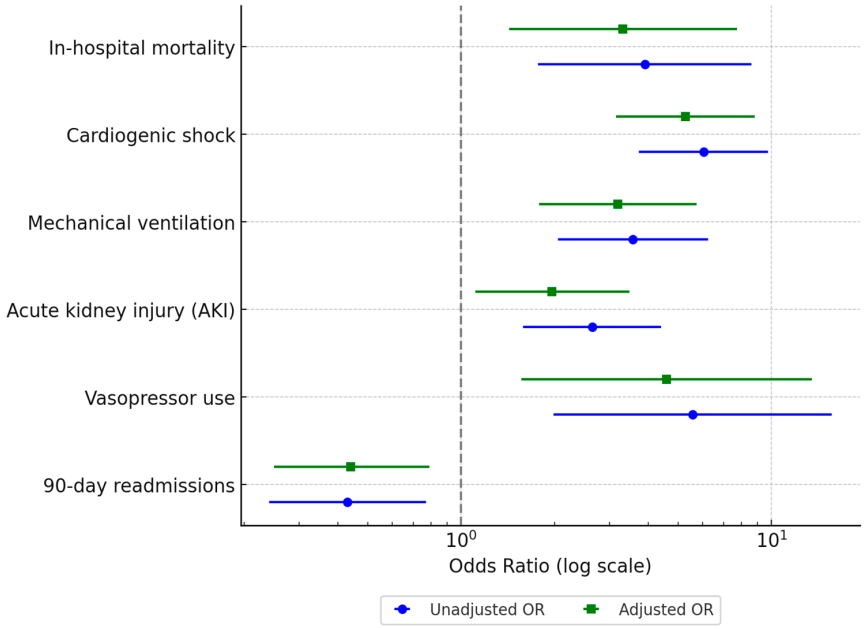

Figure 1. Forest plot of key hospital outcomes among patients admitted with TCM stratified by the presence or absence of AI. Adrenal insufficiency was independently associated with higher odds of in-hospital mortality, cardiogenic shock, mechanical ventilation, acute kidney injury, and vasopressor use. The 90-day hospital readmission remained low. All associations remained statistically significant after adjusting for age, comorbidities, and the Charlson Comorbidity Index. TCM, takotsubo cardiomyopathy; AI, adrenal insufficiency.

3.3. Length of Stay and Hospital Charges

Among patients with TCM, the mean hospital length of stay (LOS) was 6.84 days for patients with AI vs. 3.67 days for those without AI ($p < 0.001$). The adjusted LOS was significantly longer in patients with AI compared to those without AI (adjusted LOS increase: 2.73 days, 95% CI 1.39–4.06 days, $p < 0.001$). The mean total hospital charges were $97,419 and $54,574 for patients with and without AI, respectively ($p < 0.001$). The adjusted total charges were significantly higher in patients with AI than in those without AI (adjusted charge increase: $39,323, 95% CI $14,083–$64,563, $p = 0.002$).

4. Discussion

TCM remains a diagnosis of exclusion and is commonly identified in postmenopausal women presenting with acute coronary syndrome. Typical presentations include acute coronary syndrome and systolic dysfunction without evidence of epicardial coronary artery disease. Although various morphological patterns exist, the most typical presentation includes apical hypokinesis coupled with hyperkinesis in the basal segments. Typically, wall motion abnormalities extend beyond the perfusion territory of epicardial coronary arteries. Although various hypotheses have been proposed, no confirmatory evidence has been proposed to explain the pathophysiology of TCM. Catecholamine excess, microvascular

dysfunction, and impaired myocardial calcium handling have been widely discussed in the context of current research aimed at identifying their mechanistic etiologies. Although the concept of a catecholamine surge leading to TCM has been increasingly reported, AI has been associated with adrenergic receptor upregulation and increased catecholamine sensitivity, especially myocardial beta receptors, in the absence of cortisol, which can lead to increased sensitivity to normal or low catecholamine levels; however, these mechanisms cannot be directly evaluated in our dataset [2]. Additionally, the neuroendocrine feedback mechanism is impaired, resulting in excessive sympathetic stimulation in stressful situations. Cortisol is thought to exert cardioprotective effects; however, the extent to which cortisol deficiency contributes to myocardial injury in this population cannot be determined from our study. Cortisol exerts cardioprotective effects by regulating calcium homeostasis, thereby preventing the undue impact of catecholamine surges. However, this protective effect is abolished in the absence of cortisol, leading to myocardial injury and dysfunction [3].

TCM, long considered a stress-induced cardiomyopathy, increasingly intersects with systemic endocrine disorders, notably AI and polyendocrine autoimmune syndromes. In the present analysis, patients with TCM and concomitant AI demonstrated significantly worse clinical outcomes, including increased in-hospital mortality, incidence of cardiogenic shock, and need for vasopressors and mechanical ventilation. These findings are consistent with prior results showing a poor prognosis in endocrine-compromised critically ill populations [6,7].

AI disrupts the hypothalamic–pituitary–adrenal axis, impairing the physiological stress response. In TCM, acute sympathetic surges cause excessive catecholamine release, resulting in direct myocardial toxicity and transient systolic dysfunction [3]. In AI, cortisol deficiency leads to beta-adrenergic receptor upregulation, rendering the myocardium acutely sensitive even to physiologic levels of catecholamines—a phenomenon that may serve as a central mechanism in the development of TCM in patients with AI [8,9].

Cortisol also plays a role in calcium handling by modulating the sarco/endoplasmic reticulum calcium ATPase and L-type calcium channels. Deficiency results in dysregulated calcium influx, further predisposing the myocardium to stress-induced dysfunction and myocytolysis, both hallmarks of TCM.

The higher prevalence of autoimmune conditions—type 1 diabetes, hypothyroidism, and AI—among patients with TCM in this cohort suggests a potential shared autoimmune etiology, notably autoimmune polyendocrine syndrome type II (APS-2). APS-2 is characterized by autoimmune adrenalitis in conjunction with other organ-specific autoimmune diseases such as Hashimoto thyroiditis and type 1 diabetes [8,10]. This clustering reflects a broader immune dysregulation that may contribute to vascular inflammation, endothelial dysfunction, and enhanced myocardial vulnerability to stress, further implicating endocrinological abnormalities in the pathogenesis of TCM [9,10].

The presence of anemia in patients with AI and TCM may be a surrogate for chronic disease and glucocorticoid-mediated suppression of erythropoietin synthesis, compounding the metabolic stress on myocardial tissue; however, causality cannot be established in this dataset [11]. Similarly, hypothyroidism, another frequently coexisting autoimmune endocrinopathy, is associated with diastolic dysfunction and increased systemic vascular resistance, possibly potentiating myocardial strain during acute stress episodes [12].

The results of the analysis in the present study revealed that, among patients hospitalized for TCM, those with AI were younger and had a significantly higher comorbidity burden. Additionally, among TCM hospitalizations, AI was associated with a higher prevalence of hypothyroidism, type 1 diabetes (1.9% vs. 0.37%, $p = 0.011$), type 2 diabetes, anemia, and heart failure. These findings align with those in existing literature suggesting that

patients with AI often present with complex metabolic and cardiovascular comorbidities, contributing to poorer outcomes [2,3]. Type 2 diabetes and hypothyroid disorders have shown independent worse outcomes in such scenarios, which can be explained partially by shared immunological patterns in AI, diabetes, and hypothyroidism as seen in type 2 polyglandular syndrome [10]. The occurrence of anemia in patients with AI can be attributed to impaired erythropoiesis [13]. Additionally, heart failure often manifests as a lack of vasomotor response, direct myocardial inhibition, and electrolyte imbalances [14,15].

Among patients hospitalized for TCM, AI was associated with increased in-hospital mortality, incidence of cardiogenic shock, need for vasopressors and mechanical ventilation, and AKI. These findings align with those of previous studies showing that AI was strongly associated with poor outcomes in critically ill patients [16–20]. Despite the higher in-hospital complication rates, the 90-day readmission rates in the AI group were unexpectedly lower in the present study. This could reflect a high in-hospital mortality rate, limiting subsequent readmissions, or more comprehensive outpatient follow-up care for patients with AI.

Economically, patients with AI experienced a significantly longer hospital LOS (6.84 vs. 3.67 days, $p < 0.001$) and higher hospital charges ($97,419 vs. $54,574, $p < 0.001$). The adjusted LOS was 2.73 days longer (95% CI 1.39–4.06 days, $p < 0.001$), and hospital charges were $39,323 higher (95% CI $14,083–$64,563, $p = 0.002$) for patients with AI compared to those without AI, respectively. These findings underscore the economic burden associated with managing stress-related cardiovascular diseases and the healthcare burden associated with AI, consistent with previous studies showing higher costs for patients with complex comorbidities [15,18–20].

This study has several limitations. First, the study relied on database analysis and diagnostic codes to retrospectively identify patients, which introduces the potential for diagnostic bias. Consequently, the population may have been under- or over-diagnosed. Second, owing to the presence of other covariates that may confound the outcomes, establishing causality is difficult. Third, recurrent hospitalizations of the same patient may be counted as separate cases, leading to an overrepresentation of the pathology. Fourth, it was not possible to confirm whether AI was a primary or secondary diagnosis, which may have influenced prognostic outcomes. Finally, AI severity could not be assessed as this information was not included in the database.

The substantially longer hospital LOS and increased charges observed in the AI group further reflect the complex hormonal interplay and multi-organ involvement of endocrine disorders in acute cardiac stress syndromes [21,22]. These findings reinforce the economic and clinical burden of undiagnosed or under-managed endocrine disorders in cardiology.

Interestingly, the lower 90-day readmission rate in the AI cohort may be partly explained by higher in-hospital mortality, or more likely, by more rigorous outpatient endocrine follow-up and corticosteroid supplementation initiated after index hospitalization, although this remains speculative and warrants prospective investigation.

It is difficult to determine whether there exists a temporal relationship between adrenal insufficiency and takotsubo cardiomyopathy, which further limits the ability to determine causality. In addition, the data that were available did not include information about glucocorticoid replacement therapy, adherence, or stress-dose adjustments, all of which could significantly impact the outcome of patients with adrenal insufficiency during times of acute stress. Consequently, mechanistic interpretations should be interpreted as hypothesis-generating rather than definitive.

5. Conclusions

Despite the abovementioned limitations, the results of this study highlight the significant association between poorer cardiovascular outcomes and longer hospital LOS in patients with AI linked to TCM. Further randomized controlled trials and other investigations in this population are essential to explore additional strategies for managing these patients and improving their health outcomes.

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Abbreviations

The following abbreviations are used in this manuscript:

ACS	acute coronary syndrome
AE	adverse events
AI	adrenal insufficiency
AKI	acute kidney injury
aOR	adjusted odds ratio
CI	confidence interval
LOS	length of stay
NRD	Nationwide Readmissions Database
TCM	takotsubo cardiomyopathy
THC	total hospitalization charges
uOR	unadjusted odds ratio

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