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Authors

Hajra, Adrija
Malik, Aaqib
Bandyopadhyay, Dhruvajyoti
[et al.](#)

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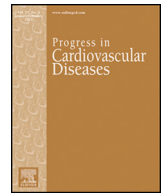
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Impact of COVID-19 in patients hospitalized with stress cardiomyopathy: A nationwide analysis



Adrija Hajra ^a, Aaqib Malik ^b, Dhrubajyoti Bandyopadhyay ^{b,*}, Akshay Goel ^b, Ameesh Isath ^b, Rahul Gupta ^c, Suraj Krishnan ^d, Devesh Rai ^e, Chayakrit Krittanawong ^f, Salim S. Virani ^g, Gregg C. Fonarow ^h, Carl J. Lavie ⁱ

^a Department of Internal Medicine, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA

^b Department of Cardiology, Westchester Medical Center, New York Medical College, Valhalla, NY, USA

^c Department of Cardiology, Lehigh Valley Heart Institute, Lehigh Valley Health Network, Allentown, PA, USA

^d Department of Internal Medicine, Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA

^e Department of Cardiology, Sands–Constellation Heart Institute, Rochester Regional Health, Rochester, NY, USA

^f Department of Cardiology, NYU Langone Health, New York, USA

^g Michael E. DeBakey Veterans Affairs Medical Center, Section of Cardiovascular Research, Baylor College of Medicine, Houston, TX, USA

^h Ahmanson–UCLA Cardiomyopathy Center, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

ⁱ John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, USA

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ABSTRACT

Stress cardiomyopathy was noted to occur at a higher incidence during coronavirus disease of 2019 (COVID-19) pandemic. This database analysis has been done to compare the in-hospital outcomes in patients with stress cardiomyopathy and concurrent COVID-19 infection with those without COVID-19 infection. The National Inpatient Sample database for the year 2020 was queried to identify all admissions diagnosed with stress cardiomyopathy. These patients were then stratified based on whether they had concomitant COVID-19 infection or not. A 1:1 propensity score matching was performed. Multivariate logistic regression analysis was done to identify predictors of mortality. We identified 41,290 hospitalizations for stress cardiomyopathy, including 1665 patients with concurrent diagnosis of COVID-19. The female preponderance was significantly lower in patients with stress cardiomyopathy and COVID-19. Patients with concomitant COVID-19 were more likely to be African American, diabetic and have chronic kidney disease. After propensity matching, the incidence of complications, including acute kidney injury (AKI), AKI requiring dialysis, coagulopathy, sepsis, cardiogenic shock, cases with prolonged intubation of >24 h, requirement of vasopressor and inpatient mortality, were noted to be significantly higher in patients with COVID-19. Concomitant COVID-19 infection was independently associated with worse outcomes and increased mortality in patients hospitalized with stress cardiomyopathy.

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List of abbreviations

AKI	Acute kidney injury
aOR	Adjusted odds ratio
COVID 19	Coronavirus disease of 2019
CV	Cardiovascular
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CABG	Coronary artery bypass graft
CI	Confidence interval
CHF	Congestive heart failure
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation

HCUP	Healthcare Cost and Utilization Project
HMO	Health Maintenance Organization
HD	Hemodialysis
HTN	Hypertension
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IABP	Intra-aortic balloon pump
IFN γ	Interferon-gamma
IL1B	Interleukin 1B
IQR	Interquartile range
LOS	Length of hospital stay
MI	Myocardial infarction
NIS	Nationwide Inpatient Sample
PE	Pulmonary embolism
PCI	Percutaneous coronary intervention
SNF/NH/IC	Skilled nursing facility/nursing home/ intermediate care
TNF α	Tissue necrosis factor alpha

* Corresponding author.

E-mail address: drdhrubajyoti87@gmail.com (D. Bandyopadhyay).

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USD	United States dollar
UTI	Urinary tract infection
VT	Ventricular tachycardia
VF	Ventricular fibrillation

Introduction

The coronavirus disease of 2019 (COVID-19) pandemic has various cardiovascular (CV) manifestations, including myocardial injury, arrhythmias, cardiac arrests, heart failure, and coagulation abnormality.^{1,2} Cases of stress cardiomyopathy have also been reported in COVID-19 patients. The incidence of stress cardiomyopathy has drawn attention among clinicians for its significant effects on patient management and treatment.³ Since its clinical discovery, the pathogenesis of stress cardiomyopathy remains unclear. Systemic viral illnesses, including influenza, have been noted to be associated with stress cardiomyopathy, and cases have been reported in COVID-19-affected individuals, particularly patients with severe disease.⁴ But data are sparse regarding the baseline characteristics, risk factors associated with inpatient morbidity, and mortality in stress cardiomyopathy patients affected with COVID-19. We have conducted a population-based analysis using a large nationally representative database to compare the characteristics and outcomes of adult patients hospitalized with stress cardiomyopathy with and without concomitant COVID-19 in the United States (US). We also aimed to determine the clinical predictors of adverse outcomes in stress cardiomyopathy patients with COVID-19.

Methods

Data source

The Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) database is the largest all-payer inpatient dataset in the US and is available publicly. The NIS represents 95% of US hospitalizations from 44 states participating in HCUP and provides a stratified sample of 20% of discharges, including up to 8 million hospital discharges per year. The NIS database has been previously demonstrated to correlate well with other discharge databases in the US. In addition, it has been validated in various studies to provide reliable estimates of admissions within the US.⁵

Study population

We included hospitalizations with a diagnosis of stress cardiomyopathy based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code (I51.81) which has positive predictive value of 98% and identified patients with and without a concurrent diagnosis of COVID-19 based on ICD-10-CM code U07.1.⁶

Outcomes

The primary outcome of interest was in-hospital mortality in patients with stress cardiomyopathy with concurrent COVID-19 infection compared with those with stress cardiomyopathy without concurrent COVID-19 infection. Secondary outcomes included AKI as well as, AKI requiring dialysis, acute respiratory failure as well as, respiratory failure requiring intubation, need for mechanical circulatory support such as intra-aortic balloon pump (IABP) (and/or impella), extracorporeal membrane oxygenation (ECMO), length of stay (LOS) and hospitalization costs.

Statistical analysis

Statistical analyses were performed using Stata 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). The discharge weights provided by the Agency for Healthcare Research

and Quality were applied to obtain weighted numbers to calculate national estimates.

A 1:1 propensity score matching was performed to compare outcomes for patients with concomitant stress cardiomyopathy and COVID-19 and patients with stress cardiomyopathy without concomitant COVID-19 using a propensity score calculated based on a multivariable logistic regression model. Propensity score matching without a replacement was performed in a 1:1 nearest-neighbor fashion with a caliper width of 0.1 of the estimated propensity scores. Multivariate logistic regression models were generated to identify the independent predictors and were reported as adjusted odds ratio (aOR) with 95% confidence interval (CI). Categorical variables were expressed as percentages. Continuous variables were expressed as median and interquartile range. Categorical variables were compared using the Pearson chi-square test, while continuous variables were compared using the student's *t*-test. All reported *P* values are 2-sided, with a value of <0.05 considered significant.

Results

A total of 41,290 hospitalizations for stress cardiomyopathy were identified, of which 1665 patients (4%) had a concurrent diagnosis of COVID-19. Table 1 describes the baseline characteristics of patients admitted with COVID-19. Stress cardiomyopathy patients with COVID-19 had a mean age of 71 years compared to a mean age of 68 years in stress cardiomyopathy patients without COVID-19. Approximately, 12.3% of patients in the COVID-19 group were African American vs. 8.2% of patients without COVID-19. Before propensity matching, stress cardiomyopathy hospitalizations with COVID-19 had higher prevalence of diabetes mellitus (39.0 vs. 24.5%, *p*-value <0.001), chronic kidney disease (CKD) (23.1% vs. 15%, *p*-value <0.001), coagulopathy (22.2% vs. 9.5%, *p*-value <0.001). Around 5.4% of stress cardiomyopathy patients with COVID-19 had a smoking history (18.6% in patients without COVID-19, *p*-value <0.001). Approximately, 44.2% of stress cardiomyopathy patients with COVID-19 had a history of coronary artery disease (31.2% in patients without COVID-19, *p*-value <0.001). The cost of hospitalization was higher, and the LOS was longer in patients with COVID-19, with statistical significance. Table 2 shows the complications and outcomes of stress cardiomyopathy patients with and without COVID-19 infection. Inpatient mortality was higher in COVID-19 affected patients than patients without COVID-19 (33.9% vs. 7.3%, *p*-value <0.001). Incidence of acute kidney injury (AKI) (48.1% vs. 25.2%) and AKI leading to hemodialysis (6.6% vs. 2.2%), myocarditis (5.7% vs. 0.4%), respiratory failure with intubation of >24 h (25.5% vs. 15.8%), cardiogenic shock (16.5% vs. 7.0%), requirement of vasopressors (12.3% vs. 5.6%), sepsis (44.4% vs. 18.7%) is more in patients with COVID-19 compared to patients without COVID-19 with *p*-value of <0.001 (Table 2).

Propensity score matching was performed to create a more balanced population, with 1620 hospitalizations in each group. In a propensity score-matched population, stress cardiomyopathy patients with COVID-19 had a higher incidence of in-hospital mortality than stress cardiomyopathy patients without COVID-19 (33.6% vs. 13.6%, respectively; aOR 3.22, CI 2.19–4.72, *p* < 0.001). In addition, sepsis, respiratory failure, respiratory failure requiring prolonged intubation for >24 h, cases with prolonged intubation and length of stay were significantly higher in stress cardiomyopathy patients with COVID-19, even after propensity match.

There was an increase in the number of stress cardiomyopathy hospitalizations with concomitant COVID-19 throughout the year. The risk of in-hospital mortality was highest for those admitted earlier in the year, and decreased after the initial months, with another peak in the later part of the year (Fig. 1).

Predictors of mortality

On multivariable regression analysis, COVID-19 was found to be independently associated with mortality in patients admitted with stress cardiomyopathy (aOR 6.10, 95% CI 4.62–8.05, *p*-value <0.001).

Table 1
Baseline characteristics of patients with COVID-19 and stress cardiomyopathy before and after propensity match with complications of hospitalized patients.

Characteristics	Before Matching			After Matching		
	Without COVID-19	With COVID-19	P Value	Without COVID-19	With COVID-19	P Value
Age, median IQR, years	39,625	1665		1620	1620	
Age groups	68 (58–77)	71 (61–78)	0.0391	72 (61–81)	71 (61–78)	0.1094
18–59	10,785	380.00	0.1057	345	370	0.0300
60–69	10,355	405.00		375	390	
70–79	10,750	540.00		415	525	
>79 years	7735	340.00		485	335	
Female	32,040	1035	<0.001	1085	1030	0.3584
Caucasian race	3250	205	0.0113	255	200	0.2017
African American race	2425	325	<0.001	305	295	0.8303
Hispanics	2015	125	0.0552	130	115	0.6599
Atrial fibrillation	6535	330	0.1058	340	315	0.5984
Diabetes mellitus	9690	650	<0.001	660	620	0.4938
Hypertension	25,955	1110	0.6534	1070	1075	0.9297
Chronic kidney disease	5930	385	<0.001	390	375	0.7819
CHF	18,590	830	0.2811	845	800	0.4582
Peripheral vascular disease	3375	110	0.2317	110	110	0.9999
Dementia	2310	190	<0.001	220	185	0.3744
COPD	12,480	525	0.9891	480	515	0.5495
Valvular heart disease	1035	145	0.3796	150	145	0.8847
Arrhythmias	14,645	640	0.5790	675	625	0.4128
Liver disease	3520	190	0.1114	205	180	0.5403
Hypothyroidism	7205	245	0.1059	280	240	0.3767
Anemia	2155	115	0.2572	165	110	0.0947
Cancer	3665	75	0.002	60	75	0.5651
Rheumatological disorders	2195	70	0.2954	55	70	0.5174
Weight loss	5910	250	0.9606	280	230	0.2729
Coagulopathy	3770	370	<0.001	300	340	0.4387
Obesity	5155	345	0.0001	260	335	0.1122
Smoking history	7385	90	<0.001	95	90	0.8610
Coronary artery disease	17,510	520	<0.001	540	520	0.7393
Prior stroke	3870	180	0.5245	205	180	0.5230
Prior PCI	1915	80	0.9810	55	80	0.3277
Prior CABG	600	25	0.9850	15	25	0.4742
Alcohol	2420	20	0.0002	20	20	0.9999
Prior MI	4615	135	0.0537	200	135	0.0868
Discharge						
Routine	20,380	425	<0.001	655	420	<0.001
SNF/NH/IC	7515	390		380	380	
Home healthcare	7375	220		280	210	
Length of stay, median (IQR), days	4 (2–8)	8 (4–16)	<0.001	5 (2–9)	8 (4–16)	<0.001
Weekend admission	9560	470	0.0862	330	460	0.0196
Elective admission	2540	35	0.0049	85	35	0.0468
Hospital location and teaching status						
Prior CABG	600	25	0.9850	15	25	0.4742
Alcohol	2420	20	0.0002	20	20	0.9999
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Weekend admission	9560	470	0.0862	330	460	0.0196
Elective admission	2540	35	0.0049	85	35	0.0468
Hospital location and teaching status						
Rural	2380	105	0.3293	100	100	0.9599
Urban non-teaching	6470	220		230	220	
Urban teaching	30,775	1340		1290	1300	

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Table 1 (continued)

Characteristics	Before Matching			After Matching		
	Without COVID-19	With COVID-19	P Value	Without COVID-19	With COVID-19	P Value
Hospital region						
Northeast	8265	380	0.0235	320	375	0.2712
Midwest	9235	490		570	470	
South	13,535	450		385	445	
West	8590	345		345	330	
Insurance						
Medicare	24,610	1040	0.1626	1070	1015	0.1769
Medicaid	4745	175		220	175	
Private including HMO	8090	340		260	325	
Self-pay	1175	40		30	40	
Median household income (%)						
0–25th percentile	9830	415	0.6795	405	405	0.8133
26–50th percentile	10,510	475		445	450	
51–75th percentile	9770	420		445	415	
76–100th percentile	8775	325		275	320	
Total hospital cost USD median IQR	14,892 (9152–28,180)	25,887 (11438–56,742)	<0.001	18,753 (9396–34,557)	25,864 (11206–56,327)	0.0013
Hospital bed size						
Small	7515	315	0.4478	270	295	0.4633
Intermediate	10,770	400		340	390	
Large	21,340	950		1010	935	

CABG- coronary artery bypass graft, CHF- congestive heart failure, COVID 19- coronavirus disease 2019, CKD- chronic kidney disease, COPD- chronic obstructive pulmonary disease, HMO- health maintenance organization, MI- myocardial infarction, PCI- percutaneous coronary intervention, SNF/NH/IC- skilled nursing facility/nursing home/ intermediate care.

Additionally, arrhythmias (aOR 1.56, CI 1.33–1.84, p-value <0.001), coagulopathy (aOR 2.55, 95% CI 2.06–3.15, p-value <0.001), and liver disease (aOR 2.59, 95% CI 2.086–3.23, p-value <0.001) were found to be independently associated with increased odds of mortality in stress cardiomyopathy patients with concurrent COVID-19 infection (Table 3).

Discussion

To the best of our knowledge, this is the first analysis of nationwide data to report the characteristics and outcomes of patients with stress cardiomyopathy and concomitant COVID-19 infection. Stress

Table 2

Complication of hospitalized patients with Takotsubo cardiomyopathy with or without COVID-19.

Complications	Before Matching			After Matching		
	Without COVID-19	With COVID-19	P Value	Without COVID-19	With COVID-19	P Value
AKI	9990	800	<0.001	595	780	0.0042
AKI leading to HD	855	110	<0.001	100	105	0.8667
UTI	4605	235	0.1529	250	225	0.5556
Sepsis	7425	740	<0.001	465	715	<0.001
DVT	910	85	0.0015	65	80	0.5769
PE	735	50	0.1369	45	50	0.8069
Stroke in-hospital	1075	25	0.1786	60	25	0.0678
Cardiogenic shock	2785	275	<0.001	205	265	0.1772
Cardiac arrest	1700	145	0.0002	80	145	0.0364
VT	2340	90	0.6967	110	90	0.5011
VF	765	15	0.1775	25	15	0.4805
Bleeding requiring transfusion	2025	145	0.0029	120	130	0.7442
Death	2895	565	<0.001	220	545	<0.001
Vasopressors	2205	205	<0.001	130	200	0.0572
Prolonged intubations >24 h	5710	625	<0.001	345	600	<0.001
Respiratory failure	13,910	945	<0.001	605	930	<0.001
Resp failure with intubation >24 h	6265	425	<0.001	365	420	<0.001
ECMO utilization	80	5	0.6986	5	5	0.999
Impella	165	10	0.6131	0	10	0.1572
IABP	250	15	0.5480	20	15	0.7055
CABG	100	0	0.3576	NA	NA	NA
PCI	1140	30	0.2459	35	30	0.7639
Tamponade	105	10	0.2577	5	10	0.5621
Acute heart failure	1335	5	0.0020	40	5	0.0185
Myocarditis	155	95	<0.001	5	90	0.0185
HTN crises	1705	25	0.0122	45	25	0.2767

AKI- acute kidney injury, COVID 19- coronavirus disease 2019, CABG- coronary artery bypass graft, DVT- deep vein thrombosis, ECMO- extracorporeal membrane oxygenation, HD- hemodialysis, HTN- hypertension, IABP- intra-aortic balloon pump, MI- myocardial infarction, PCI- percutaneous coronary intervention, PE- pulmonary embolism, UTI- urinary tract infection, VT- ventricular tachycardia, VF- ventricular fibrillation,

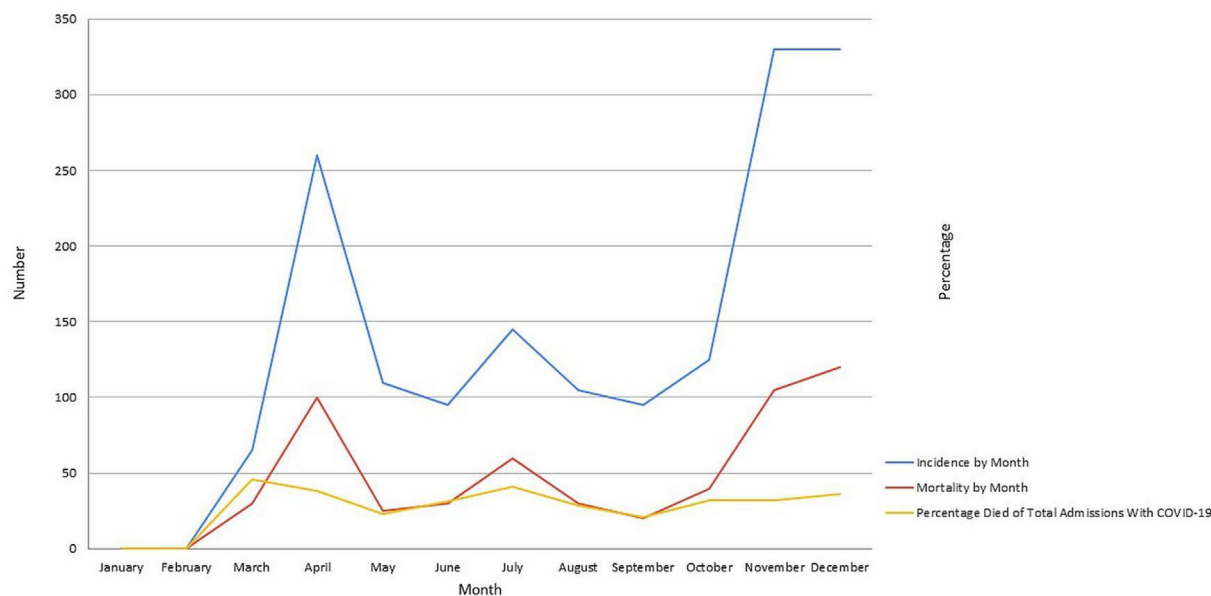


Fig. 1. Incidence by month, mortality by month and percentage died of total admissions with COVID-19. COVID-19- coronavirus disease of 2019.

cardiomyopathy is known to be more common in female patients.⁷ Interestingly, we found a lower number of female patients with stress cardiomyopathy in the COVID-19 affected group. Stress cardiomyopathy, previously known as Takotsubo cardiomyopathy, is caused by intense emotional or physical stress leading to rapid deterioration of cardiac function.^{8,9} Various possible mechanisms like sympathetic nervous system stimulation, estrogen deficiency, and excess deposition of extracellular matrix have been found to contribute to the pathogenesis of stress cardiomyopathy. COVID-19, complicated with multiorgan failure, shock, and profound hypoxia with adult respiratory distress syndrome, is hypothesized to trigger stress cardiomyopathy due to catecholamine surge. Direct myocardial injury in COVID-19 is also postulated to contribute to the pathogenesis of stress cardiomyopathy.¹⁰ Patients with COVID-19 have elevated levels of proinflammatory cytokines such as interleukin 1B (IL1B), interferon-gamma (IFN γ), and tumor necrosis factor alpha (TNF α). The cytokine storm, and physical and chemical stressors with postmenopausal status, could also contribute to the development of stress cardiomyopathy.^{4,11,12} A recent study by Zuin et al. showed an increased incidence of stress cardiomyopathy during the pandemic compared to control groups.¹³ Generalized increases in psychological distress, cytokine storm, increased sympathetic responses in patients with COVID-19, and microvascular dysfunction may result in this increased incidence.^{13,14} In our study, stress cardiomyopathy patients with COVID-19 had an increased incidence of respiratory failure requiring intubation, indicating that physiological stress is associated with worse outcomes in stress cardiomyopathy patients.

In this large, national, propensity-matched analysis, we found COVID-19 to be an independent predictor of in-hospital mortality,

Table 3
Predictors of mortality after multivariate analysis.

Variable	Odds Ratio	Lower Limit	Upper Limit	P Value
COVID 19	6.102	4.624	8.054	<0.001
Age	0.659	0.545	0.798	<0.001
CKD	1.237	1.000	1.529	0.0500
Coagulopathy	2.548	2.062	3.149	<0.001
Weight loss	1.435	1.157	1.778	0.0010
Arrhythmias	1.566	1.332	1.841	<0.001
Liver disease	2.597	2.086	3.233	<0.001
Cancer	2.117	1.678	2.67	

COVID 19- coronavirus disease 2019, CKD- chronic kidney disease.

with a higher rate of adverse clinical outcomes and increased healthcare resource utilization in patients hospitalized with stress cardiomyopathy. In our study, concomitant COVID-19 infection resulted in approximately a two and a half times higher mortality in patients with stress cardiomyopathy. In our study, the inpatient mortality of stress cardiomyopathy patients with concurrent COVID-19 infection was 33.64%. Recent studies have shown that, in general, stress cardiomyopathy has in-hospital mortality of 3.5–10.6%, comparable to that of acute coronary syndromes.¹⁵ Undoubtedly, our study has highlighted the significantly worse prognosis of stress cardiomyopathy in the setting of COVID-19 infection.

Studies have also shown an association between the severity of COVID-19 infection with various complications, including AKI, sepsis, and organ failure.^{16,17} In our study, the incidence of complications including AKI, AKI requiring dialysis, respiratory failure with intubation of >24 h, cardiogenic shock, the requirement of vasopressors, and sepsis was higher in patients with stress cardiomyopathy and COVID-19 infection. These findings indicate the possible association of stress cardiomyopathy with the severity of COVID-19 infection. Studies have shown that patients with COVID-19 and stress cardiomyopathy have a higher incidence of CV risk factors, including diabetes, and an increased coagulopathy risk, as our study found.¹⁸ A study comparing patients with stress cardiomyopathy before the COVID-19 pandemic and during the pandemic showed increased LOS for affected patients with statistical significance, as noted in our study. This increased burden on the healthcare system is a matter of concern, and clinicians should be aware of this.¹⁹ Our findings validate that COVID-19 is associated with significantly increased morbidity and mortality in patients with stress cardiomyopathy. The findings of this analysis will help clinicians to be aware of the importance of early suspicion of deterioration of patients with concurrent stress cardiomyopathy and COVID-19. Early detection and aggressive management may change the outcome of patients suffering both an acute CV condition and viral infection.

Limitations

Our study has its inherent limitations. Firstly, it is a retrospective database analysis based on discharge diagnoses. We also do not have access to patient-level information and, thus, unmeasured confounding may affect these findings. The treatment guidelines and vaccination

policy for COVID-19 have emerged with time. We do not have the option to find out if any management guideline or vaccination status would have changed the outcome of patients included in this analysis. Cases are being reported with stress cardiomyopathy after COVID-19 treatment.²⁰ Studies have also shown an association between stress cardiomyopathy with COVID-19 vaccination.²¹ Also, one case of stress cardiomyopathy with a history of COVID-19 infection has been reported recently.²² More studies are required to understand the disease process better so that preventive measures can be taken in the future. Despite these limitations, NIS is a well-validated representation of the US population and with internal and external quality control measures. The large sample size of NIS data also compensates for residual confounders.

Conclusion

COVID-19 infection among patients hospitalized with stress cardiomyopathy is associated with significantly higher in-hospital mortality, adverse clinical outcomes, and use of in-hospital resources. In addition, advanced age, arrhythmia, liver disease, and coagulopathy were independent predictors of mortality in patients with stress cardiomyopathy hospitalized with concomitant COVID-19.

Author access to data

Publicly available National Inpatient Sample of the US.

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Ethical approval of studies and informed consent

Not applicable as it is a retrospective analysis of data.

CRediT authorship contribution statement

Adrija Hajra: Writing – original draft. **Aaqib Malik:** Conceptualization, Methodology, Data curation. **Dhrubajyoti Bandyopadhyay:** Conceptualization, Methodology, Data curation. **Akshay Goel:** Conceptualization, Methodology, Data curation. **Ameesh Isath:** Conceptualization, Methodology, Data curation. **Rahul Gupta:** Writing – original draft. **Devesh Rai:** Writing – original draft. **Salim S. Virani:** Writing – review & editing, Supervision. **Gregg C. Fonarow:** Writing – review & editing, Supervision. **Carl J. Lavie:** Writing – review & editing, Supervision.

Declaration of Competing Interest

Dr. Fonarow has served as a consultant for Abbott, Amgen, Bayer, Janssen, Medtronic, and Novartis.

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