Cohort Study

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Outcomes of viral myocarditis in patients with and without COVID-19: a nationwide analysis from the United States

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Background: Cardiovascular complications contribute to 40% of coronavirus disease 2019 (COVID-19) related deaths. The viral myocarditis associated with COVID-19 accounts for significant morbidity and mortality. How COVID-19 myocarditis compares to other viral myocardites is unknown.

Methods: The authors conducted a retrospective cohort study using the National Inpatient Sample database to identify adult patients hospitalized for viral myocarditis in 2020 and to compare outcomes between those with and without COVID-19. The primary study outcome was in-hospital mortality. Secondary outcomes included in-hospital complications, length of stay, and total costs.

Results: The study population included 15 390 patients with viral myocarditis, of whom 5540 (36%) had COVID-19. After adjustment for baseline characteristics, patients with COVID-19 had higher odds of in-hospital mortality [adjusted odds ratio (aOR) 3.46, 95% CI 2.57–4.67], cardiovascular complications (aOR 1.46, 95% CI 1.14–1.87) including cardiac arrest (aOR 2.07, 95% CI 1.36–3.14), myocardial infarction (aOR 2.97, 95% CI 2.10–4.20), venous thromboembolism (aOR 2.01, 95% CI 1.25–3.22), neurologic complications (aOR 1.82, 95% CI 1.10–2.84), renal complications (aOR 1.72, 95% CI 1.38–2.13), and hematologic complications (aOR 1.32, 95% CI 1.10–1.74), but lower odds of acute heart failure (aOR 0.60, 95% CI 0.44–0.80). The odds of pericarditis, pericardial effusion/tamponade, cardiogenic shock, and the need for vasopressors or mechanical circulatory support were similar. Patients with COVID-19 had longer length of stay (7 days vs. 4 days, $P < 0.01$) and higher total costs ($21,308 vs. $14,089, $P < 0.01$).

Conclusions: Among patients with viral myocarditis, COVID-19 is associated with higher in-hospital mortality and cardiovascular, neurologic, renal, and hematologic complications compared to non-COVID-19 viruses.

Keywords: complications, COVID-19, in-hospital mortality, viral myocarditis

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HIGHLIGHTS

- How coronavirus disease 2019 (COVID-19) myocarditis compares to other viral myocardites is unknown.
- COVID-19 myocarditis is associated with higher in-hospital mortality than non-COVID-19 viral myocardites.
- COVID-19 myocarditis is associated with higher cardiovascular, neurologic, renal, and hematologic complications than non-COVID-19 viral myocardites.
- Hispanics and other racial minorities with COVID-19 myocarditis had higher in-hospital mortality than Whites.

Introduction

The severe acute respiratory syndrome coronavirus responsible for coronavirus disease 2019 (COVID-19) caused a global pandemic that began in 2020[1,2]. The extremely contagious virus has driven research by physicians worldwide to understand the virus' profound impact across many susceptible human tissues. Myocardial injury, evidenced by elevated troponin, is a prominent feature of the disease, occurring in 20–30% of hospitalized patients, and cardiovascular complications contribute to ~40% of all COVID-19-related deaths[3]. Myocarditis has been reported

in 1.4–7.2% of cases by autopsy[4] and results from the hyper-inflammatory and hypercoagulable state induced by COVID-19 in combination with direct viral cytotoxicity[5,6]. However, 60–80% of patients who recover from COVID-19 have cardiac magnetic resonance imaging evidence of myocarditis at a median of 70 days from symptomatic infection[7].

How the outcomes following COVID-19 myocarditis compare to those following myocarditis from other viral etiologies is unknown. We conducted a retrospective cohort study to assess the outcomes of COVID-19 myocarditis in comparison to other viral myocardites using the National Inpatient Sample (NIS) database.

Methods

Data source

Data were abstracted from the NIS database, which is part of the Healthcare Cost and Utilization Project (HCUP) family of databases sponsored by the Agency for Healthcare Research and Quality[8]. The NIS is the largest publicly available fully de-identified all-payer inpatient healthcare database in the United States. The 2020 NIS data are derived from administrative claims submitted by hospitals to statewide organizations in 48 U.S. states and the District of Columbia and have reliable and verified patient linkage numbers that can be used to track patients across hospitals within each state while adhering to strict privacy guidelines. The NIS database contains both patient and hospital-level information from ~1000 hospitals and represents ~20% of all U.S. hospitalizations, covering over 7 million unweighted hospitalizations each year. When weighted, the NIS extrapolates to the national level ~35 million hospitalizations each year. Up to 40 discharge diagnoses and 25 procedures are collected for each patient using the International Classification of Diseases, Ninth Revision (ICD-9) codes[9] until September 2015 and the International Classification of Diseases, Tenth Revision (ICD-10) codes[10] from October 2015 through December 2020. This study was exempt from the requirements of the Creighton University Institutional Review Board because the NIS is a publicly available database with de-identified data, Supplemental Digital Content 1, http://links.lww.com/MS9/A151.

Study population and patient selection

We queried the NIS database from January through December 2020 to identify hospitalizations in which adult patients (age ≥ 18 years) had a diagnosis of viral myocarditis [ICD-10, Clinical Modification (ICD-10-CM) I40×, I41, B33.22, J10.82, J11.82, B26.82, and I51.4 in any diagnosis field]. Hospitalizations with missing baseline demographic or hospital characteristic data were excluded. Hospitalizations that met inclusion criteria were stratified into two cohorts based upon the presence or absence of COVID-19 (ICD-10-CM U07.1). All ICD-10 diagnosis and procedure codes used in this study can be found in Table S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A152. The key findings and a detailed flow diagram are presented in Figures 1 and 2, respectively.

Patient and hospital characteristics

For each hospitalization, we extracted baseline patient demographic and clinical characteristics as well as hospital characteristics. Demographic variables included age, biological sex, race/ethnicity (White, Black, Hispanic, other), insurance status (Medicare, Medicaid, private, self-pay), median household income, along with data on the type of admission (elective/nonelective, weekend/weekday). NIS combines 'race' and 'ethnicity' into 1 data element (RACE). If both 'race' and 'ethnicity' were coded, ethnicity was preferred over race in assigning the HCUP value for 'RACE'[11]. For the purpose of this analysis, three racial groups with small sample sizes (Asian/Pacific Islanders, Native Americans, and 'other race') were combined into a single 'Other' group to facilitate the analysis. The other three HCUP race/ethnicity groups (White, Black, and Hispanic) were analyzed separately. 'White' refers to non-Hispanic White patients, 'Black' refers to non-Hispanic Black patients, and 'Hispanic' refers to Hispanic patients of all races and origins.

Hospital characteristics included location/teaching status (rural, urban nonteaching, urban teaching), bed size (small, medium, large), and the region of the United States in which the facility was located (Northeast, Midwest, South, West). Estimated median household incomes are Zone Improvement Plan code-specific, updated annually, and classified into four quartiles indicating the poorest to wealthiest populations. Bed-size categories are based on inpatient beds and are specific to the hospital's location and teaching status. A more detailed explanation of all the variables in the NIS, including the specific dollar amounts in each category of median household income and the number of hospital beds in each category, is available online (https://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp).

Clinical characteristics included relevant individual comorbidities, and the severity of comorbid conditions was defined using the Charlson Comorbidity Index and Elixhauser Comorbidity Score, both of which are widely-used, well-validated scores to quantify comorbidity burden in retrospective studies including those using NIS data[12,13]. Two authors (M.I. and H.A.) independently verified the ICD-10 codes corresponding to each comorbidity (Table S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A152), and any disagreements regarding inclusion or exclusion of ICD codes were resolved with a third author (A.A.).

Study outcomes

The primary outcome was all-cause in-hospital mortality. Secondary outcomes included cardiovascular, neurologic, renal, and hematologic complications, and the need for palliative care consultation. The definition of each complication can be found in Table S2, Supplemental Digital Content 1, http://links.lww.com/MS9/A152. We also evaluated hospital length of stay (LOS), total hospital costs (inflation-adjusted to 2020 U.S. dollars[14]), and discharge disposition, as well as independent predictors of in-hospital mortality in patients with COVID-19 myocarditis. The ICD-10 codes corresponding to each of the in-hospital outcomes were identified with the same process used to identify comorbidity codes (Table S1, Supplemental Digital Content 1, http://links.lww.com/MS9/A152).

Statistical analysis

Hospitalizations for viral myocarditis were stratified into two cohorts by the presence or absence of COVID-19. Categorical variables were compared using the Pearson χ^2-test, while continuous variables were compared using the Mann–Whitney U

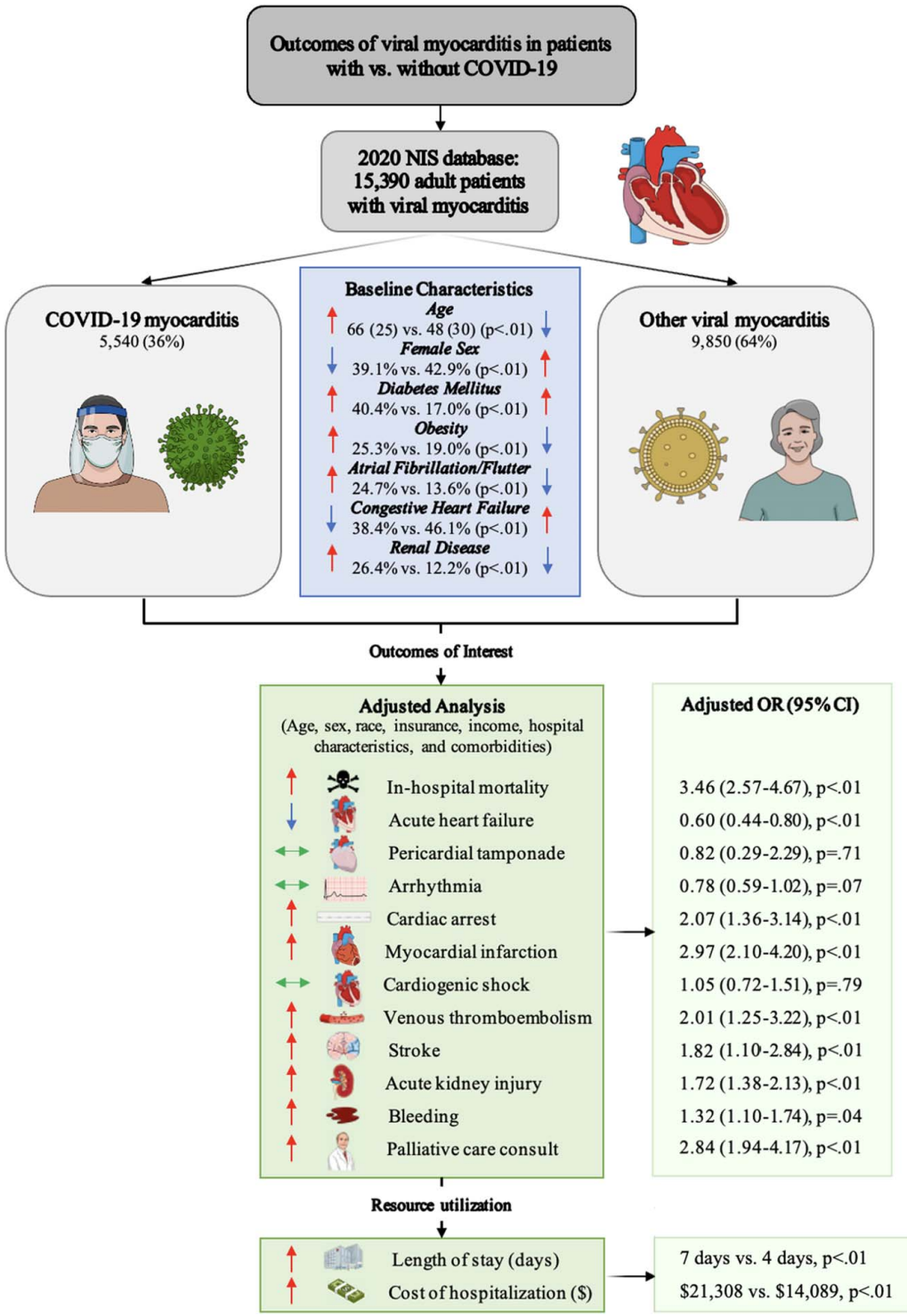

Figure 1. Summary of clinical outcomes of coronavirus disease 2019 myocarditis versus other viral myocardites after adjustment for baseline characteristics. Reported numbers represent national-level estimates. NIS, National Inpatient Sample.

test. We reported categorical variables as percentages and continuous variables as medians with an interquartile range.

A multivariate logistic regression analysis was conducted to adjust for potential confounders, including age, sex, race, insurance, income, hospital location and teaching status, bed size, region, type of admission, Elixhauser and Charlson index scores, and relevant comorbidities (Table S3, Supplemental Digital Content 1, http://links.lww.com/MS9/A152). Adjustment variables were selected *a priori* based on their clinical significance that may directly influence in-hospital outcomes. The results from this

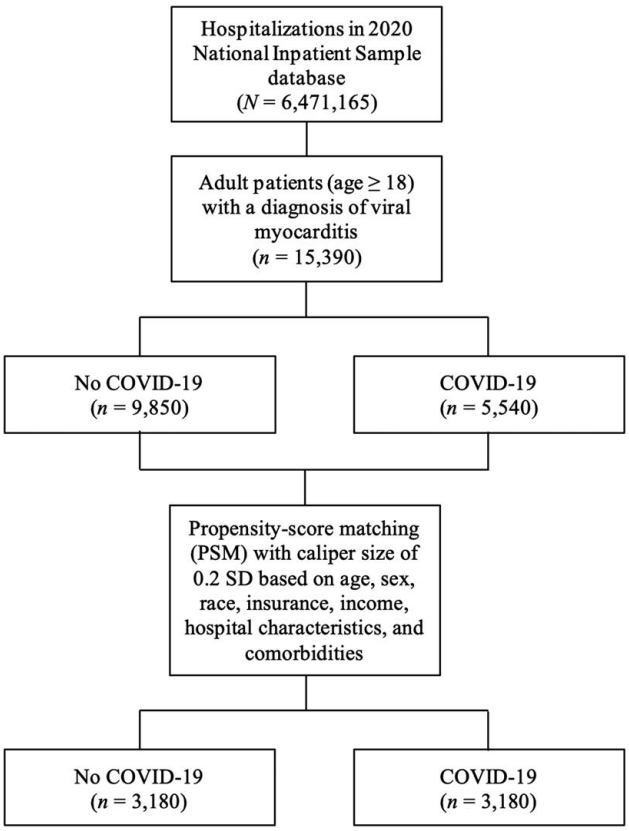

Figure 2. Study flow diagram showing inclusion and exclusion criteria. Hospitalization counts represent national-level estimates.

model are presented as adjusted odds ratios (aORs) with 95% CIs. The multivariate regression model was also used to determine independent predictors of all-cause in-hospital mortality in patients with COVID-19 myocarditis using relevant demographic and clinical variables shown in Tables 1 and 2.

A secondary analysis was performed using propensity score matching methodology to match viral myocarditis hospitalizations in patients with COVID-19 to those without COVID-19 in a 1:1 ratio. Each COVID-19 case was propensity-matched to a control using the nearest neighbor technique, with a caliper width of 0.2 (Figure S1). The propensity score was calculated from the same variables used in the multivariate regression model (Table S3, Supplemental Digital Content 1, http://links.lww.com/MS9/A152) using PSMatch2 order[15].

In accordance with the HCUP data use agreement, variables that contained a small number of observed (i.e. unweighted) hospitalizations (< 11) were not reported to avoid the risk of person identification or data privacy violation[16]. A two-tailed *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using Stata version 17 (StataCorp, College Station) software, accounting for the NIS sampling design, and were weighted using sampling weights provided with the NIS database to estimate national-level effects per HCUP-NIS recommendations[17]. The research reported in this paper adhered to HCUP-NIS guidelines[17]. Data were analyzed in March 2023.

Table 1

Demographic and hospital characteristics stratified by COVID-19 status

	Unmatched			Propensity-matched[a]		
	No COVID-19 (*n* = 9850)	COVID-19 (*n* = 5540)	*P*	No COVID-19 (*n* = 3180)	COVID-19 (*n* = 3180)	*P*
Demographic characteristics						
Age (years)	48 (33–63)	66 (52–77)	< 0.01	59 (44–72)	59 (45–71)	0.82
18–64	77.0	46.5	< 0.01	60.4	60.8	0.09
65–74	13.2	24.5		18.9	22.3	
75–84	7.6	18.1		15.6	11.2	
85 +	2.2	10.9		5.2	5.7	
Biological sex						
Male	57.1	60.9	< 0.01	61.6	59.3	0.36
Female	42.9	39.1		38.4	40.7	
Race/ethnicity						
White	61.7	45.5	< 0.01	50.9	52.7	0.82
Black	17.1	21.5		20.9	19.0	
Hispanic	13.0	23.3		19.8	19.3	
Other	8.1	9.7		8.3	9.0	
Insurance						
Medicare	26.7	54.1	< 0.01	41.4	41.7	0.98
Medicaid	20.3	14.8		16.4	16.4	
Private insurance	45.7	26.8		35.5	35.7	
Self-pay	7.3	4.2		6.8	6.3	
Income quartile						
I	25.2	30.7	< 0.01	27.8	26.3	0.92
II	26.9	27.7		27.8	28.9	
III	23.3	21.8		21.9	22.5	
IV	24.7	19.9		22.5	22.3	
Hospital characteristics						
Location/teaching status						
Rural	4.2	7.4	< 0.01	3.9	4.4	0.92
Urban nonteaching	14.1	14.6		15.4	15.1	
Urban teaching	81.8	78.0		80.7	80.5	
Bed size						
Small	16.4	19.0	< 0.01	18.4	17.3	0.86
Medium	25.6	31.1		28.1	29.2	
Large	58.0	49.9		53.5	53.5	
Region						
Northeast	22.9	26.2	0.24	25.6	25.5	0.83
Midwest	22.5	22.5		23.3	22.5	
South	34.2	34.2		34.4	33.2	
West	20.4	17.1		16.7	18.9	
Elective admission	3.6	3.1	0.45	3.3	3.5	0.87
Weekend admission	24.4	27.3	0.08	25.3	25.2	0.95

Note: Data presented as median (IQR) or %.
[a]Propensity-matched based on age, sex, race, insurance, income, hospital location and teaching status, bed size, region, type of admission, Elixhauser and Charlson index scores, and relevant comorbidities.
IQR, interquartile range.

Results

Patient and hospital characteristics

In 2020, an estimated 15 390 hospitalizations in the United States met inclusion criteria, of which an estimated 5540 (36%) had COVID-19 (Figure 2).

Table 2

Clinical characteristics stratified by COVID-19 status

	Unmatched			Propensity-matched[a]		
	No COVID-19 ($n=9850$)	COVID-19 ($n=5540$)	P	No COVID-19 ($n=3180$)	COVID-19 ($n=3180$)	P
Elixhauser comorbidity index	3 (2–5)	5 (3–6)	< 0.01	4 (2–6)	4 (3–6)	0.64
Charlson comorbidity index	1 (1–3)	2 (1–4)	< 0.01	2 (1–3)	2 (1–3)	0.74
0	21.6	13.7	< 0.01	16.5	16.7	0.80
1	29.9	23.3		27.8	25.5	
2	19.5	21.6		20.6	21.9	
≥ 3	29.0	41.4		35.1	36.0	
Individual comorbidities						
Diabetes mellitus	17.0	40.4	< 0.01	30.0	28.9	0.67
Hypertension	45.8	65.7	< 0.01	60.1	60.7	0.82
Dyslipidemia	31.3	40.4	< 0.01	37.1	39.6	0.36
Nicotine/tobacco use	35.2	22.0	< 0.01	23.4	26.3	0.25
Alcohol abuse	4.2	3.2	0.20	3.8	3.8	1.00
Drug abuse	10.4	2.2	< 0.01	2.7	3.0	0.73
Obesity	19.0	25.3	< 0.01	24.1	25.0	0.69
Coronary artery disease	24.5	26.3	0.27	25.9	27.8	0.44
Peripheral vascular disease	6.8	4.6	0.02	4.4	5.2	0.53
Atrial fibrillation/flutter	13.6	24.7	< 0.01	21.1	19.8	0.56
Congestive heart failure	46.1	38.4	< 0.01	46.1	44.7	0.61
Renal failure	12.2	26.4	< 0.01	20.1	18.7	0.52
Dialysis dependent	1.3	4.0	< 0.01	2.0	2.0	1.00
Liver disease	10.1	9.9	0.91	11.5	10.5	0.59
Chronic pulmonary disease	17.1	19.9	0.05	21.1	20.3	0.72
Obstructive sleep apnea	7.5	7.5	0.97	7.9	9.6	0.27
Coagulopathy	12.4	22.3	< 0.01	18.6	17.3	0.57
Cancer	4.5	2.6	0.01	4.1	3.8	0.77
Malnutrition	4.0	6.3	< 0.01	5.7	5.7	1.00
Dementia	1.1	10.0	< 0.01	3.0	2.0	0.28
Depression	12.0	9.9	0.08	11.2	11.2	1.00
Previous history						
Myocardial infarction	6.2	5.6	0.50	6.1	6.4	0.81
Stroke/TIA	3.2	4.8	0.01	3.9	3.6	0.77
Cardiac arrest	1.1	0.8	0.41	0.8	0.8	1.00
PCI	2.7	5.3	< 0.01	5.2	4.9	0.79
CABG	1.2	4.1	< 0.01	2.7	2.5	0.86
ICD	2.0	0.8	< 0.01	0.8	1.1	0.56
PPM	0.9	2.1	< 0.01	1.4	1.6	0.82

Note: Data presented as median (IQR) or %.

[a]Propensity-matched based on age, sex, race, insurance, income, hospital location and teaching status, bed size, region, type of admission, Elixhauser and Charlson index scores, and relevant comorbidities.

CABG, coronary artery bypass grafting; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; PCI, percutaneous coronary intervention; PPM, permanent pacemaker; TIA, transient ischemic attack.

Patients with COVID-19 were more likely to be older (66 years vs. 48 years, $P < 0.01$), male (60.9 vs. 57.1%, $P < 0.01$), non-White (54.5 vs. 38.3%, $P < 0.01$), and living in the lowest median household income neighborhoods quartile (30.7 vs. 25.2% $P < 0.01$) compared to those without COVID-19. COVID-19 patients were more likely to have higher Elixhauser (5 vs. 3, $P < 0.01$) and Charlson (2 vs. 1, $P < 0.01$) comorbidity index scores, which was mainly driven by their higher likelihood of having diabetes mellitus, hypertension, dyslipidemia, obesity, atrial fibrillation/flutter, renal failure dependent on dialysis, coagulopathy, malnutrition, and dementia (all $P < 0.01$). COVID-19 patients were also more likely to have a history of stroke/transient ischemic attack, percutaneous coronary intervention, coronary artery bypass grafting, and permanent pacemaker (all $P < 0.05$). A history of implantable cardioverter-defibrillator, nicotine/tobacco use, drug abuse, peripheral vascular disease, congestive heart failure, and cancer were less likely in patients with COVID-19 (all $P < 0.05$). Baseline characteristics of the unmatched and matched cohorts stratified by COVID-19 status are shown in Tables 1 and 2.

Unadjusted in-hospital outcomes

The estimated overall in-hospital mortality rate was 15.5% (95% CI 14.1–16.9%), with statistically higher rates in patients with COVID-19 compared to those without (30.8 vs. 6.9%, $P < 0.01$). Patients with COVID-19 were more likely to experience cardiovascular complications (66.7 vs. 53.2%, $P < 0.01$) including arrhythmias (41.3 vs. 31.6%, $P < 0.01$), cardiac arrest (8.4 vs. 3.8%, $P < 0.01$), myocardial infarction (15.8 vs. 6.6%, $P < 0.01$), need for vasopressors (10.4 vs. 5.2%, $P < 0.01$), venous thromboembolism (6.7 vs. 2.7%, $P < 0.01$), neurologic complications (6.1 vs. 2.1%, $P < 0.01$), renal complications (50.3 vs. 27.5%, $P < 0.01$), hematologic complications (14.9 vs. 9.7%, $P < 0.01$), and palliative care consultation (14.3 vs. 3.6%, $P < 0.01$), and less likely to experience acute heart failure (16.3 vs. 24.6%, $P < 0.01$). Patients with and without COVID-19 had similar rates

Table 3

Primary and secondary in-hospital outcomes stratified by COVID-19 status

	Unmatched			Propensity-matched[a]		
	No COVID-19 ($n=9850$)	COVID-19 ($n=5540$)	*P*	No COVID-19 ($n=3180$)	COVID-19 ($n=3180$)	*P*
Death	6.9	30.8	< 0.01	12.1	24.8	< 0.01
Complications						
Cardiovascular	53.2	66.7	< 0.01	60.4	66.3	0.04
Acute heart failure	24.6	16.3	< 0.01	25.6	19.2	< 0.01
Pericarditis	2.9	1.8	0.06	2.0	2.5	0.55
Pericardial effusion/tamponade	1.5	1.0	0.22	1.3	1.1	0.79
Arrhythmia	31.6	41.3	< 0.01	39.6	36.2	0.19
Cardiac arrest	3.8	8.4	< 0.01	5.2	8.3	0.03
Myocardial infarction	6.6	15.8	< 0.01	8.5	17.1	< 0.01
Cardiogenic shock	11.1	10.3	0.49	13.1	12.3	0.68
Need for vasopressor	5.2	10.4	< 0.01	6.9	8.1	0.15
Need for MCS	4.0	2.7	0.15	4.4	3.0	0.11
Venous thromboembolism	2.7	6.7	< 0.01	3.1	6.5	< 0.01
Neurologic	2.1	6.1	< 0.01	2.7	6.2	< 0.01
Renal	27.5	50.3	< 0.01	36.9	44.7	< 0.01
Hematologic	9.7	14.9	< 0.01	10.3	14.4	0.04
Palliative care consultation	3.6	14.3	< 0.01	5.5	11.3	< 0.01
Discharge disposition						
Routine	68.2	33.9	< 0.01	58.2	43.4	< 0.01
Transfer to Short-term Hospital	6.1	4.2		5.0	3.9	
Transfer to SNF or ICF	7.0	18.6		9.0	15.9	
Home Health Care	10.2	12.3		14.8	11.6	
Resource utilization						
LOS (days)	3 (2–7)	8 (4–16)	< 0.01	4 (2–8)	7 (3–15)	< 0.01
Hospital cost ($)	12 869 (7828– 24 905)	23 025 (11 223– 54 570)	< 0.01	14 089 (8512– 28 290)	21 308 (10 334– 50 551)	< 0.01

Note: Data presented as median (IQR) or %.

[a]Propensity-matched based on age, sex, race, insurance, income, hospital location and teaching status, bed size, region, type of admission, Elixhauser and Charlson index scores, and relevant comorbidities.

ICF, intermediate care facility; IQR, interquartile range; LOS, length of stay; MCS, mechanical circulatory support; SNF: skilled nursing facility.

of pericarditis (1.8 vs. 2.9%, $P=0.06$), pericardial effusion-/tamponade (1.0 vs. 1.5%, $P=0.22$), cardiogenic shock (10.3 vs. 11.1%, $P=0.49$), and need for mechanical circulatory support (2.7 vs. 4.0%, $P=0.15$). COVID-19 patients had a longer hospital LOS (8 days vs. 3 days, $P<0.01$) and higher total costs ($23 025 vs. $12 869, $P<0.01$). For hospitalizations in which patients were discharged alive, those with COVID-19 were discharged at greater rates to a skilled nursing facility as opposed to home ($P<0.01$). In-hospital outcomes stratified by COVID-19 status are shown in Table 3 and Figure 3.

Adjusted and matched in-hospital outcomes

After adjustment, patients with COVID-19 had higher odds of in-hospital mortality (aOR 3.46, 95% CI 2.57–4.67, $P<0.01$), cardiovascular complications (aOR 1.46, 95% CI 1.14–1.87, $P<0.01$) including cardiac arrest (aOR 2.07, 95% CI 1.36–3.14, $P<0.01$), myocardial infarction (aOR 2.97, 95% CI 2.10–4.20, $P<0.01$), venous thromboembolism (aOR 2.01, 95% CI 1.25–3.22, $P<0.01$), neurologic complications (aOR 1.82, 95% CI 1.10–2.84, $P<0.01$), renal complications (aOR 1.72, 95% CI 1.38–2.13, $P<0.01$), hematologic complications (aOR 1.32, 95% CI 1.10–1.74, $P=0.04$), and palliative care consultation (aOR 2.84, 95% CI 1.94–4.17, $P<0.01$), but lower odds of acute heart failure (aOR 0.60, 95% CI 0.44–0.80, $P<0.01$). Differences in arrhythmia (aOR 0.78, 95% CI 0.59–1.02, $P=0.07$) and need for vasopressors (aOR 1.39, 95% CI 0.92–2.10, $P=0.11$) between patients with and without COVID-19 were no longer significant. The odds of pericarditis (aOR 0.86, 95% CI 0.43–1.73, $P=0.68$), pericardial effusion-/tamponade (aOR 0.82, 95% CI 0.29–2.29, $P=0.71$), cardiogenic shock (aOR 1.05, 95% CI 0.72–1.51, $P=0.79$), and need for mechanical circulatory support (aOR 0.60, 95% CI 0.31–1.12, $P=0.11$) remained similar between patients with and without COVID-19.

In the secondary analysis using propensity matching with 6360 matched patients (3180 in each group), patients with COVID-19 had higher in-hospital mortality (24.8 vs. 12.1%, $P<0.01$), cardiovascular complications (66.3 vs. 60.4%, $P=0.04$) including cardiac arrest (8.3 vs. 5.2%, $P=0.03$), myocardial infarction (17.1 vs. 8.5%, $P<0.01$), venous thromboembolism (6.5 vs. 3.1%, $P<0.01$), neurologic complications (6.2 vs. 2.7%, $P<0.01$), renal complications (44.7 vs. 36.9%, $P<0.01$), hematologic complications (14.4 vs. 10.3%, $P=0.04$), palliative care consultations (11.3 vs. 5.5%, $P<0.01$), longer LOS (7 days vs. 4 days, $P<0.01$), and higher total costs ($21 308 vs. $14 089, $P<0.01$), but less acute heart failure (19.2 vs. 25.6%, $P<0.01$) compared to non-COVID-19 patients, confirming the findings of the multivariate regression analysis. The rates of pericarditis (2.5 vs. 2.0%, $P=0.55$), pericardial effusion/tamponade (1.1 vs. 1.3%, $P=0.79$), arrhythmia (36.2 vs. 39.6%, $P=0.19$), cardiogenic shock (12.3 vs. 13.1%, $P=0.68$), need for vasopressors (8.1 vs. 6.9%, $P=0.15$), and need for mechanical circulatory support (3.0 vs. 4.4%, $P=0.11$) were similar between COVID-19 and non-COVID-19 patients.

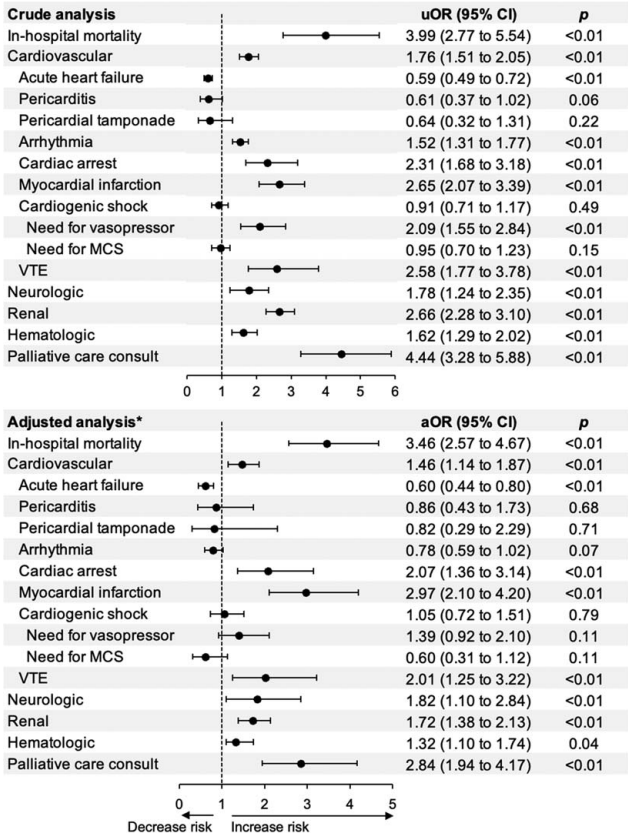

Figure 3. Forest plot showing crude and adjusted analyses for viral myocarditis outcomes in patients with vs. without coronavirus disease 2019. *Adjusted analysis based on age, sex, race, insurance, income, hospital location and teaching status, bed size, region, type of admission, Elixhauser and Charlson index scores, and relevant comorbidities. MCS, mechanical circulatory support; VTE, venous thromboembolism; uOR, unadjusted odds ratio; aOR, adjusted odds ratio.

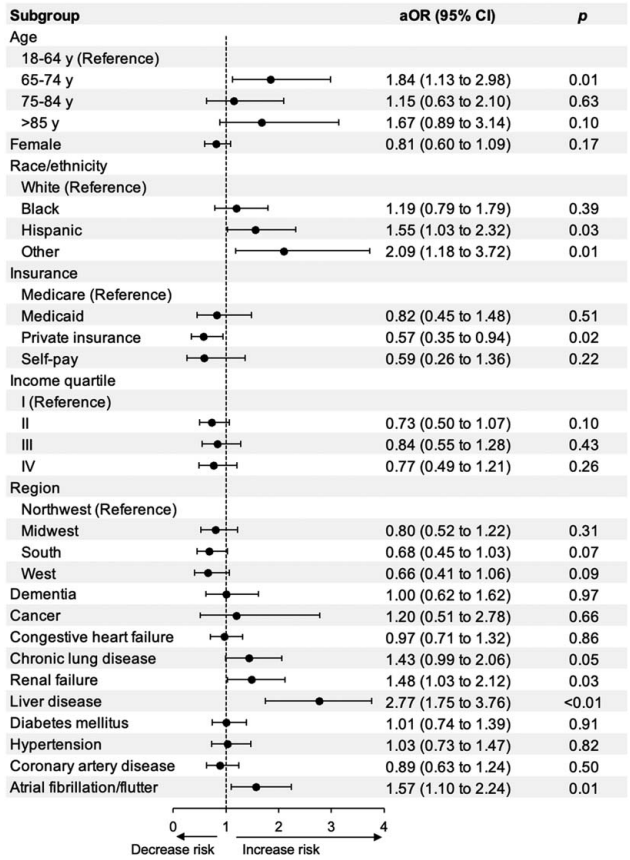

Figure 4. Forest plot showing predicators of in-hospital mortality in patients with coronavirus disease 2019 myocarditis. All odds ratios are adjusted for the other covariates listed. Odds ratios greater than 1 indicate greater odds of all-cause in-hospital mortality. aOR, adjusted odds ratio.

Predictors of in-hospital mortality among patients with COVID-19 myocarditis

In a multivariate analysis, factors independently associated with increased in-hospital mortality in patients with COVID-19 myocarditis were age 65–74 years (aOR 1.84, 95% CI 1.13–2.98, $P = 0.01$) compared to 18–64 years, Hispanic (aOR 1.55, 95% CI 1.03–2.32, $P = 0.03$) and Other race (aOR 2.09, 95% CI 1.18–3.72, $P = 0.01$) compared to Whites, renal failure (aOR 1.48, 95% CI 1.03–2.12, $P = 0.03$), liver disease (aOR 2.77, 95% CI 1.75–3.76, $P < 0.01$), and atrial fibrillation/flutter (aOR 1.57, 95% CI 1.10–2.24, $P = 0.01$). Patients with private insurance had lower odds of in-hospital mortality (aOR 0.57, 95% CI 0.35–0.94, $P = 0.02$) compared to Medicare beneficiaries (Figure 4).

Discussion

This large all-payer national database study demonstrates three principal findings. First, COVID-19 myocarditis was associated with higher rates of in-hospital mortality, cardiovascular complications including cardiac arrest, myocardial infarction, and venous thromboembolism, neurologic complications, renal complications, and hematologic complications compared with other viral myocardites. Second, COVID-19 myocarditis was associated with lower rates of acute heart failure compared with other viral myocardites. Third, hospital LOS was longer and total costs were higher in patients with COVID-19 myocarditis compared with other viral myocardites.

In-hospital mortality and cardiovascular complications

Patients with COVID-19 myocarditis were found to have higher rates of mortality and cardiovascular complications, in particular myocardial infarction ($P < 0.01$), than those with non-COVID-19 myocarditis. A Sweden-based matched cohort analysis demonstrated increased myocardial infarctions among COVID-19 patients in the 2-week postdiagnosis period when compared to the control group (OR 6.61, 95% CI 3.56–12.20)[18]. A retrospective UK-based cohort found that the odds of death were nearly doubled when patients with COVID-19 had an acute myocardial infarction compared to those who did not (OR 2.39, 95% CI 1.31–4.40, $P = 0.05$), further concurring with the increased morality among COVID-19 patients cited in this paper[19]. The pathophysiology behind increased myocardial infarction in patients with COVID-19 may stem from the virus binding to the angiotensin-converting enzyme 2 receptor, a membrane-bound aminopeptidase expressed in cardiac myocytes, which leads

to altered immunological signaling resulting in myocardial damage[20]. Increased circulation of proinflammatory cytokines and chemokines in the presence of COVID-19, decreased oxygen availability and blood flow, and weakening of atherosclerotic plaque caps resulting in thrombogenesis also further contribute to myocardial infarction[20].

In a cohort study that focused on ST-elevation myocardial infarction among COVID-19 positive and negative patients, cardiac arrest was more frequent in COVID-19 positive patients than those who tested negative (23.1 vs. 5.7%, $P < 0.01$), which was further confirmed after adjustment for confounding factors (OR 4.85, 95% CI 2.04–11.51, $P < 0.01$)[21]. An observational study analyzed cardiac arrest both inside and outside of the hospital setting and found increased odds of cardiac arrest during hospitalization in COVID-19 positive patients (hazard ratio [HR] 1.48, 95% CI 1.09–2.01) and higher mortality within 30 days for out-of-hospital cardiac arrests in patients with COVID-19 versus without (HR 1.45, 95% CI 1.13–1.85)[22]. In addition, Girotra *et al.*[23] found that COVID-19 positive patients who suffered cardiac arrest had a lower likelihood of achieving return of spontaneous circulation (adjusted risk ratio [RR] 0.86, 95% CI 0.83–0.90, $P < 0.01$) and a lower likelihood of surviving to discharge (adjusted RR 0.65, 95% CI 0.60–0.71). Compression-only CPR was likely not effective in COVID-19 patients with cardiac arrest due to their impaired respiratory function[22]. The increased occurrence of cardiac arrest among COVID-19 patients is likely multifactorial, including worsening hypoxia, increased inflammation, coagulation abnormalities, acidosis, and arrhythmias (secondary to electrolyte abnormalities and medications)[24].

Increased thrombotic events in patients with COVID-19 are congruent with a prospective cohort study that found increased thrombotic complications (OR 2.6, 95% CI 1.1–6.1, $P = 0.03$) including pulmonary embolism (OR 6.2, 95% CI 1.6–23.4, $P < 0.01$) among acute respiratory distress syndrome patients who were COVID-19 positive compared to those who tested negative[25]. Increased venous thromboembolism rates can be attributed to the hyperinflammatory state, endothelial damage, COVID-19-induced hypoxia, and patient immobility, which promote thrombosis[26,27]. In addition, down-regulation of endogenous fibrinolytic activity and simultaneous up-regulation of procoagulant cytokine production contribute to hypercoagulability[5].

Despite having higher overall cardiovascular complications, patients with COVID-19 myocarditis had lower odds of acute heart failure (aOR 0.60, 95% CI 0.44–0.80, $P < 0.01$). This was also demonstrated in a retrospective cohort study by Priyadarshni *et al.*[28], who found that patients with COVID-19 had lower odds of developing heart failure compared to those with influenza (OR 0.49, CI 95% 0.46–0.52). This lower incidence of acute heart failure in COVID-19 patients could be explained by the respiratory compromise present among COVID-19 patients concealing the diagnosis of heart failure itself by masking prominent physical exam findings such as crackles[28]; length-time bias, as those who were critically ill with COVID-19 likely died prior to receiving a diagnosis of heart failure[28]; conservative fluid intake and possible early and aggressive use of diuretics in COVID-19 patients. In a retrospective observational study, a negative fluid balance approach encompassing diuretics (furosemide) and fluid restriction in COVID-19 patients resulted in improved oxygenation[29].

Other complications and resource utilization

Patients with COVID-19 myocarditis had higher rates of non-cardiovascular complications as well. The odds of acute kidney injury (AKI) (aOR 1.72, 95% CI 1.38–2.13, $P < 0.01$) were significantly elevated. This finding was consistent with a prospective cohort study of U.S. veterans with COVID-19, who had an increased risk of AKI within 30 days (adjusted HR 1.94, 95% CI 1.86–2.04) and kidney disease of any type past 30 days (adjusted HR 1.35, 95% CI 1.30–1.39) compared to those without COVID-19[30]. Possible explanations for the higher incidence of AKI with COVID-19 include increased prevalence of hypertension and chronic kidney disease in COVID-19 patients, which are known risk factors for AKI in COVID-19 patients as demonstrated previously [hypertension (OR 2.58, 95% CI 1.71–3.89), chronic kidney disease (OR 2.14, 95% CI 1.33–3.42)][31]; aggressive diuretic use, which has been shown to be associated with a greater risk of AKI in COVID-19 patients (OR 1.79, 95% CI 1.27–2.53, $P < 0.01$)[32]; conservative fluid management, which is a known contributor to prerenal AKI due to intravascular volume depletion[33].

The increased odds of bleeding in COVID-19 patients (aOR 1.32, 95% CI 1.10–1.74, $P = 0.04$) are congruent with a combined matched cohort study and self-controlled case series based in Sweden[34]. Increased bleeding in COVID-19 patients is likely multifactorial: anticoagulant use may be higher in COVID-19 patients. In a study by Katsoularis *et al.*[34], COVID-19 patients on long-term anticoagulation were at a greater risk of bleeding (RR 2.37, 95% CI 1.79–3.14). Furthermore, Demelo-Rodriguez *et al.*[35]found that COVID-19 patients treated with therapeutic anticoagulation had higher risks of bleeding compared to those treated with low-dose anticoagulation (HR 1.43, 95% CI 1.01–1.97); COVID-19 induces a hyperinflammatory state. COVID-19 patients with a D-Dimer greater than 10 times normal (HR 2.23, 95% CI 1.38–3.59) as well as those with a ferritin level greater than 500 (HR 2.01, 95% CI 1.02–3.95) demonstrated increased risks of in-hospital bleeding[35]; endothelial damage, hypercoagulability, and a hyperinflammatory state lead to mild disseminated intravascular coagulation and a resultant consumptive thrombocytopenia and coagulopathy[5,28]. In addition, COVID-19 modifies capillaries of the pulmonary vasculature leading to platelet deformation and, in certain instances, an autoimmune phenomenon against platelets, further exacerbating thrombocytopenia[28].

The increased odds of stroke in COVID-19 patients (aOR 1.82, 95% CI 1.10–2.84, $P < 0.01$) are congruent with a population-based cohort study that showed a higher prevalence of ischemic stroke among COVID-19 patients in comparison to patients with viral influenza after adjustment for confounding factors[29]. Similar to our study, patients with COVID-19 were found to have increased risk factors for ischemic stroke such as diabetes mellitus, hypertension, and hypercholesterolemia[29]. In another study by Belani *et al.*[36], the presence of COVID-19 was significantly associated with acute ischemic stroke after adjustment for confounding factors such as age, sex, diabetes mellitus, hypertension, dyslipidemia, and atrial fibrillation (OR 3.9, 95% CI 1.7–8.9; $P < 0.01$). The pathogenesis of acute ischemic stroke in the setting of COVID-19 may be due to the virus binding to angiotensin-converting enzyme 2 receptors, which are found on both endothelial and epithelial cells, causing the release of inflammatory cytokines[37]. These cytokines, in combination with

a hypercoagulable state and COVID-19's impact on platelet aggregation and lipid metabolism, increase the risk of acute ischemic stroke[36].

Given the higher cardiovascular, neurologic, renal, and bleeding complications associated with COVID-19, the LOS was longer and total costs were higher in patients with COVID-19 myocarditis compared to other viral myocardites.

Limitations and strengths

Our study has several important limitations. First, in a retrospective NIS study using administrative claims codes, incorrect coding could lead to inaccurate data. Second, the retrospective nature of the study makes it subject to inherent selection bias. Third, detailed baseline characteristics such as echocardiographic findings and laboratory values were unavailable, which can lead to unmeasured bias. Fourth, the prescription and duration of medications could not be assessed in the NIS. Fifth, our outcomes were confined to mortality and complications during the index hospitalization.

However, the large NIS database allowed us to conduct the largest and most comprehensive study to date on COVID-19 myocarditis outcomes. The size of the dataset provided the power to characterize many outcomes with statistical significance. Furthermore, the use of multivariate regression and propensity score matching helped minimize bias.

Conclusion

Among patients with viral myocarditis, COVID-19 is associated with higher in-hospital mortality and cardiovascular, neurologic, renal, and hematologic complications compared to non-COVID-19 viruses. Hispanics and other racial minorities with COVID-19 myocarditis had higher in-hospital mortality than Whites. Further research is necessary to confirm these findings and identify the reasons for such racial disparities in the outcomes of COVID-19 myocarditis.

Ethical approval

This study was exempt from the requirements of the Creighton University Institutional Review Board (IRB) because the NIS is a publicly available database with de-identified data.

Consent

Consent was not required for this study.

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Author contribution

All authors contributed to this manuscript. M.I.: conceptualization, methodology, software, formal analysis, original draft, writing – review and editing; H.A. and D.H.: conceptualization, original draft, writing – review and editing; A.M.G., H.D.A., and A.A.: conceptualization, original draft, writing – review and editing, supervision.

Conflicts of interest disclosure

The authors have no conflict of interest to declare.

Research registration unique identifying number (UIN)

1. Name of the registry: NA.
2. Unique Identifying number or registration ID: NA.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

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