

Association Between Mitral Valve Disease and Myocarditis in COVID-19 Hospitalizations: A National Inpatient Sample Analysis

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Abstract

Background: Myocarditis has emerged as a complication of COVID-19 infection. However, its relationship to pre-existing cardiac conditions, such as mitral valve disease (MVD), still needs to be elucidated. This study aimed to assess the development of myocarditis in COVID-19 patients and to determine whether the presence of MVD was an associated factor.

Methods: A retrospective cohort study utilizing the 2021 National Inpatient Sample database examined adult hospitalizations for COVID-19, categorizing patients into four groups based on COVID-19 and MVD status. Statistical analysis included survey weights for national estimates, including Rao-Scott χ^2 tests for categorical variables and linear regression for continuous variables. Two models using logistic regression were created to assess the relationship between COVID-19, myocarditis, and MVD. Model 1 adjusts for individual comorbidities, while

Model 2 uses the Elixhauser comorbidity score for overall comorbidity assessment.

Results: Out of approximately 1 million hospitalizations, 600,873 weighted hospitalizations were included. Patients with concomitant COVID-19 and MVD demonstrated greater comorbidity burden. In model 1, MVD was not significantly associated with myocarditis (OR 1.97, 95% CI 0.82-4.76; $p = 0.13$). In Model 2, MVD was independently associated with increased odds of myocarditis (OR 3.14, 95% CI 1.36-7.27; $p = 0.008$). Higher Elixhauser scores increased myocarditis risk, whereas older age and female sex had lower odds.

Conclusions: This study suggests a potential association between MVD and myocarditis among hospitalized COVID-19 patients after adjustment for overall comorbidity burden. Findings are limited by reliance on ICD-10 coding and the low incidence of myocarditis, which may affect statistical stability.

Keywords: COVID-19, SARS-CoV-2, myocarditis, mitral valve disease, cardiovascular risks

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Introduction

Since the emergence of the COVID-19 pandemic, it has been evident that SARS-CoV-2, the virus responsible, affects more than solely the respiratory system. Myocarditis, an inflammatory condition of the myocardium, has emerged as a severe complication and has been increasingly recognized as a significant contributor to morbidity and mortality among patients infected with this virus. (1) The exact mechanism is multifactorial and remains under investigation, though it is hypothesized to involve direct viral invasion, immune-mediated injury, or microvascular damage. (1,2)

The adverse effects of MVD, including primary and secondary mitral regurgitation, on the outcome of the patients are largely unknown, but it could elevate cardiac stress and hemodynamic instability, increasing the likelihood of myocardial injury. The existence of pre-existing cardiovascular disease may be a predisposing factor for a worse prognosis by increasing cardiac stress and hemodynamic derangement. (3,4) Autopsy findings have revealed the presence of the virus in cardiac tissue of deceased COVID-19 patients, supporting the hypothesis of direct myocardial infection as a contributing factor to cardiac damage. (4) The goal of the study is to assess the relationship between MVD and the incidence of myocarditis in COVID-19 hospitalized patients.

Estimates of myocarditis incidence following SARS-CoV-2 infection vary, with pooled analyses indicating a prevalence of approximately 1% to 7%, influenced by disease stage and diagnostic criteria. (5) Additionally, studies indicate a heightened risk of myocarditis following COVID-19 compared to other viral respiratory infections. (6)

Methods

Study Setting and Design

This retrospective cohort study used the 2021 National Inpatient Sample (NIS), one of several databases and software tools produced by the Healthcare Cost and Utilization Project (HCUP). It comprises data from around 7 million hospital stays per year and forecasts approximately 35 million hospitalizations across the United States. (7)

Patients

The patients admitted with a diagnosis of COVID-19 were identified using ICD-10 codes and stratified into COVID-19-positive and COVID-19-negative groups. Further classification was performed based on the presence or absence of MVD.

Data Collection

The study utilized specific ICD-10 codes to identify patients within the sample:

U07.1 for hospitalized COVID-19 cases; I51.4 for myocarditis; and I34.0, I34.1, I34.2, I34.8, and I34.9 for non-rheumatic MVD. Patient infection statuses were accurately classified by cardiac conditions, including myocarditis, identified by ICD-10 code I51.4. While administrative coding facilitates large-scale analyses, it lacks clinical validation,

such as biomarkers, imaging, or histopathology. Validation studies indicate only moderate diagnostic accuracy of ICD-10 myocarditis coding, showing positive predictive values ranging from 30% to 75%, which raises concerns about the potential for misclassification bias. (8)

The following variables were extracted using the NIS Data Elements Descriptions, provided by HCUP: mortality during hospitalization (DIED), uniform patient disposition coding (DISPUNIFORM), sex indicator (FEMALE), hospital stratum (NIS_STRATUM), length of stay (LOS), race/ethnicity (RACE), and median household income based on ZIP code (ZIPINC_QRTL). These variables were incorporated into the analysis to control for demographic and hospital-level factors.

Statistical Analysis

The STATA Statistics software (College Station, TX) with the Complex Samples module was used to account for the survey design of the NIS. Survey weights, stratification, and clustering variables were used to generate nationally representative estimates and adjust for the complex sampling design of the database. Hospitalizations were classified into four mutually exclusive categories based on the presence of MVD and COVID-19 infection status:

COVID-negative/MVD-negative (COVID-/MVD-), COVID-negative/MVD-positive (COVID-/MVD+), COVID-positive/MVD-negative (COVID+/MVD-), and COVID-positive/MVD-positive (COVID+/MVD+).

Statistical analysis accounted for hospital-level clustering, stratification, and discharge weights with categorical variables reported as weighted frequencies and percentiles. We compared groups using the Rao-Scott weighted χ^2 test and analyzed continuous variables with survey-weighted, complex-sample-adjusted linear regression, specifically in pairwise comparisons among the four defined groups.

To further assess the relationship between comorbidities, COVID-19, MVD, and myocarditis, an analysis based on COVID-19 status was performed. Categorical variables between groups were evaluated using a design-adjusted Wald test, and pairwise comparisons of continuous variables utilized a survey-adjusted Wald test of linear differences between group coefficients.

To evaluate the association between MVD and myocarditis, survey-weighted multivariable logistic regression models were developed among COVID-19 hospitalizations. In all analyses, statistical signifi-

cance was established as a two-sided p-value of less than 0.05. Due to the low amount of missing data, we performed a comprehensive case analysis. Odds Ratios (OR) and 95% confidence intervals (95% CI) were provided where indicated.

Two models were specified:

Model 1: Adjusted for demographic characteristics and individual cardiovascular comorbidities, including hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD).

Model 2: Adjusted for demographic characteristics and overall comorbidity burden using the Elixhauser comorbidity score. This approach reduces model overfitting and collinearity that may arise when multiple individual comorbidities are included in a rare-event model.

Complex survey methods enabled thorough weighted analyses reflecting the sampling design. The association between COVID-19 and MVD and myocarditis was assessed using a survey-weighted multivariable logistic regression model. In this model, myocarditis was the dependent variable, while COVID-19 status and MVD status, age, sex, and Elixhauser comorbidity score were included as covariates. Results were reported as adjusted odds ratios (OR) with corresponding 95% confidence intervals (CI). Adjusted predictive margins were derived from the multivariable model for COVID-19 status, MVD status, and combined COVID-19/MVD exposure groups. This improved clinical interpretability by providing adjusted predictive probabilities of myocarditis.

Ethical Considerations

This study utilized a de-identified, publicly available dataset, the National Inpatient Sample. Therefore, this study was exempt from full institutional review board (IRB) and the requirement for informed consent in accordance with federal regulations and the Declaration of Helsinki.

Results

Study Characteristics

The weighted study cohort included a total of 600,873 hospitalized patients, equally divided into four mutually exclusive groups based on COVID-19 and MVD status:

COVID−/MVD− (275,894), COVID−/MVD+ (5,250), COVID+/MVD− (316,149), and COVID+/

MVD+ (3,580). The corresponding unweighted counts were 55,179, 1,050, 63,230, and 716, respectively. **Table 1** demonstrates the baseline characteristics across the COVID-19/MVD strata.

Patients with MVD were older in both COVID-negative and COVID-positive cohorts. The mean age was 59.35 years in the COVID−/MVD− group, 72.61 years in the COVID−/MVD+ group, 63.02 years in the COVID+/MVD− group, and 71.62 years in the COVID+/MVD+ group ($p<0.00001$). Median age was similar, with the oldest patients observed in the MVD group. Comorbidity burden, measured by the Elixhauser score, was also substantially higher in patients with MVD. The mean Elixhauser score was 3.61 in COVID−/MVD−, 6.06 in COVID−/MVD+, 3.84 in COVID+/MVD−, and 6.10 in COVID+/MVD+ hospitalizations ($p<0.00001$).

Gender Distribution and Demographics

Sex distribution differed significantly across the four groups ($p<0.00001$). Female patients accounted for 55.4% of the COVID−/MVD− group, 57.1% of the COVID−/MVD+ group, 47.8% of the COVID+/MVD− group, and 53.6% of the COVID+/MVD+ group.

Race distribution showed significant differences ($p<0.00001$), with White patients comprising the largest proportions across all groups: 69.1% in COVID−/MVD−, 78.7% in COVID−/MVD+, 65.5% in COVID+/MVD−, and 76.0% in COVID+/MVD+. Black and Hispanic patients were followed, with smaller proportions from Asian/Pacific Islander, Native American, and other racial categories.

The median household income quartiles varied significantly among the four groups (overall $p<0.00001$), indicating differences across income categories. Geographic disparities were also significant ($p<0.00001$), pointing to regional variations in hospitalizations among the study groups.

Length of Stay and Mortality

Length of stay and in-hospital mortality varied significantly across groups ($p<0.00001$). The mean length of stay was 5.42 days for COVID−/MVD−, 5.83 days for COVID−/MVD+, 8.68 days for COVID+/MVD−, and 9.63 days for COVID+/MVD+. Median lengths of stay were 3, 4, 5, and 6 days, respectively. In-hospital mortality rates were 2.7% for COVID−/MVD−, 2.2% for COVID−/MVD+, 11.5% for COVID+/MVD−, and

15.2% for COVID+/MVD+ overall ($p<0.00001$). Notably, the COVID+/MVD+ group had a higher mortality rate (15.2%) compared to the COVID+/MVD- group (11.5%), with a pairwise p -value of 0.003.

Discharge outcomes

Markers of illness severity and resource utilization were significantly higher in COVID-positive hospitalizations, especially among those with MVD. Respiratory failure was notably more frequent in COVID patients, with similar rates in both COVID-positive groups (50.8% versus 48%, $p=0.22$). Mechanical ventilation was needed in 3.1%, 3.6%, the necessity of this intervention was supported by the finding that COVID-positive hospitalizations were greater than COVID-negative hospitalizations, with no significant difference between the COVID+/MVD- and COVID+/MVD+ groups (10.1% versus 10.5%, $p=0.76$).

Acute renal failure rates significantly varied across patient groups, with 17.6% in COVID-/MVD-, 22.7% in COVID-/MVD+, 27.6% in COVID+/MVD-, and 33.8% in COVID+/MVD+ ($p<0.00001$), indicating higher severe complications in those with both COVID-19 and MVD. Myocarditis, while rare, also showed variation: 0.1% in COVID-/MVD-, 0.0% in COVID-/MVD+, 0.3% in COVID+/MVD-, and 0.8% in COVID+/MVD+ ($p<0.00001$). The COVID+/MVD+ group had higher unadjusted odds of myocarditis compared to COVID+/MVD- (OR 3.31, 95% CI 1.47-7.45; $p=0.0038$), though the overall incidence remained low at 1%, suggesting a limited clinical impact at the population level.

Analysis based on COVID-19 status

Analysis of COVID-19 status indicated that affected individuals were generally older, predominantly male, and required longer hospital stays, as summarized in **Table 2**. Significant differences were observed in clinical factors such as respiratory failure and mechanical ventilation needs. However, the Elixhauser comorbidity score revealed no considerable differences, suggesting that while individual comorbidities may differ, the overall burden is similar across groups.

Multivariable Regression Analysis

Survey-weighted multivariable logistic regression was utilized to investigate the relationship between MVD and myocarditis in COVID-19 hospitaliza-

tions, as presented in **Table 3**.

In Model 1, MVD was associated with increased odds of myocarditis but was not statistically significant (OR 1.97, 95% CI 0.82-4.76; $p=0.13$), while CAD and CHF were strongly associated (OR 6.19, 95% CI 3.68-10.44; $p<0.001$; OR 4.44, 95% CI 2.77-7.13; $p<0.001$, respectively). Conversely, CKD (OR 0.59, 95% CI 0.39-0.90; $p=0.014$), COPD (OR 0.49, 95% CI 0.28-0.87; $p=0.015$), and HTN (OR 0.58, 95% CI 0.37-0.93; $p=0.024$) were associated with lower odds of myocarditis, as was increasing age (OR 0.97, 95% CI 0.96-0.98; $p<0.001$).

In Model 2, the Elixhauser comorbidity score MVD was associated with higher odds of myocarditis (OR 3.14, 95% CI 1.36-7.27; $p=0.008$), along with a one-point increase in the Elixhauser score (OR 1.16, 95% CI 1.09-1.23; $p<0.001$). Conversely, older age (OR 0.98; $p<0.001$) and female sex (OR 0.65; $p=0.007$) correlated with lower odds of myocarditis. Interestingly, the relationship between MVD and myocarditis varied across the models. In Model 1, adjusting for individual comorbidities revealed no significant association, whereas Model 2, which adjusted for overall comorbidity burden, indicated a statistically significant association. This variability may stem from collinearity issues, over-adjustment, or low event rates contributing to instability. Hence, these results should be viewed cautiously as hypothesis-generating rather than confirmatory. These associations are shown in the forest plot of adjusted odds ratios for myocarditis (**Figure 1**).

Sensitivity analyses for secondary outcomes showed that, after adjustment, MVD was associated with lower odds of in-hospital mortality (OR 0.55, 95% CI 0.44-0.70; $p<0.00001$), acute renal failure (OR 0.42, 95% CI 0.34-0.52; $p<0.00001$), respiratory failure (OR 0.77, 95% CI 0.66-0.91; $p=0.0017$), and mechanical ventilation (OR 0.49, 95% CI 0.37-0.64; $p<0.00001$).

Multivariable analyses reveal that COVID-19 significantly increases odds of myocarditis (aOR 4.23, 95% CI 2.97-6.02, $p<0.001$), and MVD also correlates with higher odds of myocarditis (aOR 2.35, 95% CI 1.04-5.34, $p=0.041$).

Notable covariates include increasing age, which slightly decreases myocarditis odds (aOR 0.97 per year, 95% CI 0.96-0.98, $p<0.001$); and female sex, associated with lower odds compared to male (aOR 0.61, 95% CI 0.46-0.80, $p<0.001$). In contrast, a higher Elixhauser comorbidity score was associated with increased odds of myocarditis (aOR 1.07 per point, 95% CI 1.05-1.08, $p<0.001$).

In the adjusted predictive margins shown in **Figure 2** and summarized in **Table 4**, the probability of myocarditis was particularly higher among patients with COVID-19 than those without COVID-19 (0.27% vs. 0.06%) and higher in patients with MVD compared to those without MVD (0.390% versus 0.167%). Among the combined exposure cohort groups, the adjusted predicted probability of myocarditis was found to be lowest in patients who had neither COVID-19 nor MVD (0.063%), intermediate in patients with MVD alone (0.147%) or COVID-19 alone (0.263%), and highest in patients with both COVID-19 and MVD (0.615%).

An interaction term between COVID-19 and MVD was examined for effect modification; however, the interaction model was excluded due to the low incidence of myocarditis as an outcome and the presence of sparse subgroup cells, leading to complete or near-complete separation. This situation rendered the parameters of logistic regression unstable, causing excessively large coefficients and unreliable standard errors. As a result, formal inference used a more stable main-effects survey-weighted model, and adjusted prediction margins illustrated the risk patterns across the combined COVID-19 and MVD groups. Results from the interaction model are available in **Supplementary Table 1**.

Discussion

Our study suggests that MVD may contribute to an increased likelihood of myocarditis among hospitalized COVID-19 patients, particularly when overall comorbidity burden is considered. Findings indicate that myocarditis occurred in 0.8% of COVID+/MVD+ hospitalizations compared to 0.3% among COVID+/MVD- patients. This association could link structural heart abnormalities exacerbated by SARS-CoV-2 infection. These findings should also be interpreted in the context of prior literature demonstrating variable incidence rates of COVID-19-associated myocarditis and the limitations of administrative data in accurately capturing this diagnosis. (9,10)

In MVD, particularly mitral regurgitation, the continuous volume overload can lead to left ventricular enlargement, thus increasing the risk of myocardial damage, particularly under the systemic inflammation caused by COVID-19. This phenomenon could be partly responsible for the higher incidence of myocarditis in patients with concurrent COVID-19 and MVD in our cohort.

Another study supports variable incidence rates of myocarditis in COVID-19 patients, emphasizing the

difficulty of capturing accurate diagnoses through administrative data. The interaction between SARS-CoV spike protein and angiotensin-converting enzyme 2 (ACE2) in cardiac tissues may lead to immunological activation and endothelial dysfunction, potentially heightening myocarditis risk. (2) The spike protein needs to be cleaved at the S1/S2 site and then the S2' site before binding to ACE2. (6) This spike protein cleavage process engages key proteases like TMPRSS2 and raises concerns about SARS-CoV-2 infecting the heart, although typical viral receptor presence does not always predict susceptibility.

The different clinical presentations of COVID-19 myocarditis have been described in the literature, from subclinical myocardial injury to fulminant myocarditis that may be missed without advanced imaging. (1) In MVD, even mild inflammation can lead to severe complications due to structural abnormalities and reduced myocardial reserve.

Our results are consistent with prior studies showing that cardiovascular comorbidities, particularly valvular and ischemic heart diseases, correlate with poorer outcomes in COVID-19, evidenced by longer hospital stays and higher mortality rates. (2,3,7) The study underlines significant differences in outcomes based on gender, ethnicity, and socioeconomic factors, calling for equitable healthcare reforms.

Model comparisons within the study suggest possible instability of the association between MVD and myocarditis. Model 1, containing individual comorbidities, may have been subject to multicollinearity and over-adjustment, particularly in view of the strong overlap between cardiovascular conditions. Model 2, using the Elixhauser score, offered a more parsimonious adjustment for comorbidity burden but may oversimplify disease heterogeneity. These discrepancies suggest cautious interpretation.

Biological plausibility for the inverse relationships between certain comorbidities (e.g., CKD, COPD, and hypertension) and myocarditis is lacking. Possible explanations include coding bias, competing risks, or reduced diagnostic intensity in critically ill patients with multiple comorbidities. Despite higher complication rates, MVD showed lower adjusted mortality, a paradox potentially due to residual confounding, selection bias, or management differences, and should not be considered protective.

Limitations

First, the study utilized administrative data from the NIS, which may present issues such as coding errors

and misclassification bias, particularly with ICD-10 codes potentially leading to incorrect identification of myocarditis.

Second, the NIS lacks comprehensive clinical details (e.g., lab values, imaging, and biomarkers) necessary for confirming myocarditis diagnoses and assessing disease severity.

Third, the cross-sectional nature of the data prevents establishing the temporal relationship between COVID-19 infection, myocarditis, and associated cardiac conditions.

Fourth, although we adjusted for a large number of comorbidities using both individual covariates and the Elixhauser comorbidity score, residual confounding may still exist. Patients with valvular heart disease have complex cardiovascular profiles, which may affect clinical outcomes.

Finally, the findings are not generalizable to those with mild or outpatient COVID-19 infections and may be underestimated because studies focus solely on hospitalized patients and have moderate ICD-10 diagnostic accuracy for myocarditis, which may skew the true incidence. (10)

Conclusions

This study suggests a possible association between

MVD and the risk of myocarditis in COVID-19-positive hospitalized patients. However, given the low absolute incidence and reliance on administrative data, results should be interpreted with caution.

There is a recommendation for enhanced cardiovascular screening, including echocardiography, particularly for COVID-19 patients with pre-existing valvular diseases such as MVD. Further research is needed to determine if early interventions can reduce significant complications like myocarditis and mortality.

Our results emphasize the necessity of proactive, interdisciplinary management strategies for high-risk populations during pandemics that include specialists in infectious disease, cardiology, and health policy to improve prognosis.

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Abbreviations and acronyms:

ACE2	Angiotensin-Converting Enzyme 2	LOS	Length of Stay
AMA	Against Medical Advice	MVD	Mitral Valve Disease
CI	Confidence Interval	NIS	National Inpatient Sample
COVID-19	Coronavirus disease 2019	OR	Odds Ratio
HCUP	Healthcare Cost and Utilization Project	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
ICD-10	International Classification of Diseases, 10th Revision	SNF	Skilled Nursing Facility
IQR	Interquartile range	SPSS	Statistical Package for the Social Sciences

Table 1. Baseline characteristics of groups stratified according to COVID-19 status and mitral valve disease

Demographics	COVID- / MVD-	COVID- / MVD+	COVID+ / MVD-	COVID+ / MVD+	p-value
Age	59.35 (0.09) 62.0 (42.0, 75.0)	72.61 (0.42) 75.0 (65.0, 83.0)	63.02 (0.07) 65.0 (52.0, 77.0)	71.62 (0.56) 74.0 (62.0, 84.0)	<0.001
Sex (Female), n (%)	152,890 (55.4)	3,000 (57.1)	151,185 (47.8)	1,920 (53.6)	<0.001
Socioeconomic factors, income quartile					<0.001
- 76th-100th percentile, n (%)	89,065 (32.3)	2,095 (39.9)	89,470 (28.3)	1,150 (32.1)	
- 51st-75th percentile, n (%)	73,745 (26.7)	1,405 (26.8)	84,710 (26.8)	940 (26.3)	
- 26th-50th percentile, n (%)	57,145 (20.7)	935 (17.8)	71,570 (22.6)	805 (22.5)	
- 0-25th percentile, n (%)	52,215 (18.9)	745 (14.2)	66,315 (21.0)	635 (17.7)	
Race					<0.001
- White, n (%)	190,670 (69.1)	4,130 (78.7)	207,039 (65.5)	2,720 (76.0)	
- Black, n (%)	35,050 (12.7)	530 (10.1)	43,075 (13.6)	370 (10.3)	
- Hispanic, n (%)	26,930 (9.8)	255 (4.9)	35,650 (11.3)	245 (6.8)	
- Asian/Pacific Islander, n (%)	7,075 (2.6)	80 (1.5)	9,010 (2.8)	80 (2.2)	
- Native American, n (%)	485 (0.2)	0 (0.0)	545 (0.2)	15 (0.4)	
- Other races, n (%)	6,920 (2.5)	75 (1.4)	8,255 (2.6)	60 (1.7)	
Urbanicity					<0.001
- Central metro counties ≥ 1 million, n (%)	84,925 (26.1)	1,070 (20.4)	855 (23.9)	83,000 (26.3)	
- Fringe metro counties ≥ 1 million, n (%)	116,455 (35.8)	2,335 (44.5)	1,405 (39.2)	112,715 (35.7)	
- Metro counties: 250000-999999, n (%)	69,235 (21.3)	1,095 (20.9)	760 (21.2)	67,380 (21.3)	
- Metro counties: 50000-249999, n (%)	21,080 (6.5)	280 (5.3)	250 (7.0)	20,550 (6.5)	
- Micropolitan counties, n (%)	22,200 (6.8)	285 (5.4)	205 (5.7)	21,710 (6.9)	
- Non-metro/non-micropolitan counties, n (%)	9,515 (2.9)	170 (3.2)	100 (2.8)	9,245 (2.9)	
Comorbidity burden					
- Elixhauser score	3.61 (0.01) 3.0 (2.0, 5.0)	6.06 (0.07) 6.0 (4.0, 8.0)	3.84 (0.01) 4.0 (2.0, 5.0)	6.1 (0.08) 6.0 (4.0, 8.0)	<0.001
- Hypertension, n (%)	154,545 (56.0)	4,315 (82.2)	190,785 (60.3)	2,770 (77.4)	<0.001
- Diabetes, n (%)	73,750 (26.7)	1,495 (28.5)	105,895 (33.5)	1,135 (31.7)	<0.001
- Chronic kidney disease, n (%)	48,815 (17.7)	1,690 (32.2)	58,600 (18.5)	1,110 (31.0)	<0.001
- Congestive heart failure, n (%)	54,040 (19.6)	3,255 (62.0)	53,800 (17.0)	1,830 (51.1)	<0.001
- Coronary artery disease, n (%)	64,540 (23.4)	2,610 (49.7)	72,295 (22.9)	1,665 (46.5)	<0.001
- Chronic obstructive pulmonary disease, n (%)	40,420 (14.7)	1,150 (21.9)	47,050 (14.9)	740 (20.7)	<0.001

Hospital course and outcomes					
- Length of stay	5.42 (0.03) 3.0 (2.0, 6.0)	5.83 (0.23) 4.0 (2.0, 7.0)	8.68 (0.04) 5.0 (3.0, 10.0)	9.63 (0.52) 6.0 (3.0, 11.0)	<0.001
- Mechanical ventilation, n (%)	8,620 (3.1)	190 (3.6)	32,055 (10.1)	375 (10.5)	<0.001
- In-hospital mortality, n (%)	7,340 (2.7)	115 (2.2)	36,340 (11.5)	545 (15.2)	<0.001

Legend: The values are expressed as weighted frequencies (percentages) for categorical variables and as weighted means accompanied by standard errors (SE) for continuous variables. Group comparisons were conducted utilizing survey-adjusted Rao–Scott χ^2 tests for categorical variables and survey-weighted linear regression for continuous variables. The analyses addressed the intricate sampling design of the National Inpatient Sample (NIS), including stratification, clustering, and discharge-level weights.

Table 2. Baseline Characteristics stratified according to COVID-19 status

	COVID-19 Negative, n (%) or mean $\pm$ SE	COVID-19 Positive, n (%) or mean $\pm$ SE	Univariate OR (95% CI)	p-value
Age	59.6 $\pm$ 0.04	63.12 $\pm$ 0.03	1.010 (1.009 to 1.011)	<0.001
Length of stay (days)	5.43 $\pm$ 0.01	8.71 $\pm$ 0.02	1.057 (1.052 to 1.061)	<0.001
Elixhauser score	9.52 $\pm$ 0.02	9.59 $\pm$ 0.02	1.001 (0.999 to 1.003)	0.165
Sex (Female)	155,890 (55.5)	153,105 (47.9)	0.74 (0.73 to 0.75)	<0.001
COPD	41,570 (14.8)	47,790 (14.9)	1.01 (1.0 to 1.03)	0.081
Coronary artery disease	67,150 (23.9)	73,960 (23.1)	0.96 (0.95 to 0.97)	<0.001
Aortic stenosis	6,145 (2.2)	4,100 (1.3)	0.58 (0.56 to 0.6)	<0.001
Congestive heart failure	57,295 (20.4)	55,630 (17.4)	0.82 (0.81 to 0.83)	<0.001
Diabetes mellitus	75,245 (26.8)	107,030 (33.5)	1.38 (1.36 to 1.39)	<0.001
Acute renal failure	49,785 (17.7)	88,395 (27.6)	1.78 (1.75 to 1.8)	<0.001
Chronic kidney disease	50,505 (18.0)	59,710 (18.7)	1.05 (1.04 to 1.06)	<0.001
Dialysis	8,900 (3.2)	12,985 (4.1)	1.29 (1.26 to 1.33)	<0.001
Respiratory failure	33,545 (11.9)	162,460 (50.8)	7.62 (7.52 to 7.73)	<0.001
Malignancy	30,180 (10.7)	18,160 (5.7)	0.5 (0.49 to 0.51)	<0.001
Organ transplant	2,320 (0.8)	2,840 (0.9)	1.08 (1.02 to 1.14)	0.009
Hypertension	158,860 (56.5)	193,555 (60.5)	1.18 (1.17 to 1.19)	<0.001
Mechanical ventilation	8,810 (3.1)	32,430 (10.1)	3.49 (3.41 to 3.57)	<0.001
Mitral valve disease	5,250 (1.9)	3,580 (1.1)	0.6 (0.57 to 0.62)	<0.001

Myocarditis	185 (0.1)	835 (0.3)	3.98 (3.39 to 4.66)	<0.001
In-hospital mortality	7,455 (2.7)	36,885 (11.5)	4.79 (4.67 to 4.91)	<0.001
Race				<0.001
- White	194,800 (70.3)	209,759 (66.5)		
- Black	35,580 (12.8)	43,445 (13.8)		
- Hispanic	27,185 (9.8)	35,895 (11.4)		
- Asian or Pacific Islander	7,155 (2.6)	9,090 (2.9)		
- Native American	485 (0.2)	560 (0.2)		
- Other	12,045 (4.3)	16,610 (5.3)		
Primary payer				<0.001
- Medicare	136,650 (48.7)	161,395 (50.6)		
- Medicaid	55,295 (19.7)	53,770 (16.9)		
- Private	76,560 (27.3)	88,370 (27.7)		
- Self-pay	4,045 (1.4)	6,030 (1.9)		
- No charge	945 (0.3)	865 (0.3)		
- Other	6,995 (2.5)	8,315 (2.6)		
Median household income quartile				<0.001
- 0 to 25th percentile	52,960 (19.1)	66,950 (21.2)		
- 26th to 50th percentile	58,080 (20.9)	72,375 (22.9)		
- 51st to 75th percentile	75,150 (27.1)	85,650 (27.1)		
- 76th to 100th percentile	91,160 (32.9)	90,620 (28.7)		
Urbanicity				<0.001
- Large central metro	73,310 (26.2)	83,855 (26.4)		
- Large fringe metro	104,565 (37.4)	114,120 (35.9)		
- Medium metro	58,855 (21.1)	68,140 (21.4)		
- Small metro	17,675 (6.3)	20,800 (6.5)		
- Micropolitan	17,365 (6.2)	21,915 (6.9)		
- Not metro or micropolitan counties	7,660 (2.7)	9,345 (2.9)		

Legend: The values are expressed as weighted frequencies (percentages). Group comparisons were conducted via survey-adjusted Rao–Scott χ^2 tests. The analyses considered the complex sampling design of the National Inpatient Sample (NIS), including stratification, clustering, and discharge-level weights.

Table 3. Multivariable Logistic Regression for Myocarditis Among COVID-19 Hospitalizations

Variable	Model 1	Model 1 OR (95% CI)	Model 1 p-value	Model 2	Model 2 OR (95% CI)	Model 2 p-value
Mitral valve disease	Adjusted for age, sex, income, geography, and individual comorbidities	1.97 (0.82–4.76)	0.13	Adjusted for age, sex, and Elixhauser comorbidity score	3.14 (1.36–7.27)	0.008
Age		0.97 (0.96–0.98)	<0.001		0.98 (0.97–0.99)	<0.001
Sex (Female)		0.78 (0.57–1.06)	0.11		0.65 (0.48–0.89)	0.007
Elixhauser comorbidity score		—	—		1.16 (1.09–1.23)	<0.001
CHF		4.44 (2.77–7.13)	<0.001		—	—
CAD		6.19 (3.68–10.44)	<0.001		—	—
Hypertension		0.58 (0.37–0.93)	0.02		—	—
CKD		0.59 (0.39–0.90)	0.01		—	—
COPD		0.49 (0.28–0.87)	0.02		—	—

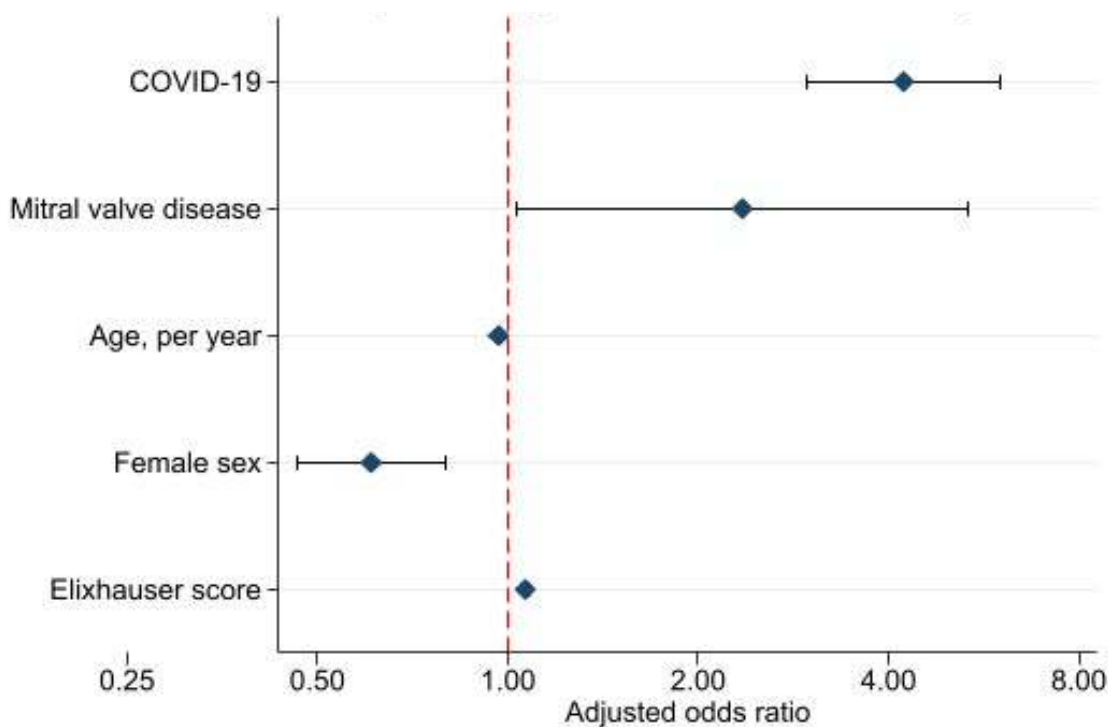
Legend: Model 1 was adjusted for age, sex, income, geographic region, and individual comorbidities. Model 2 was adjusted for age, sex, and Elixhauser comorbidity score, which replaced individual comorbidities to account for overall comorbidity burden. Odds ratios (OR) are presented with 95% confidence intervals (CI).

Table 4. Adjusted odds ratios and predictive probabilities of myocarditis by COVID-19 and mitral valve disease status

Status	Predicted % (95% CI)
COVID-19 Negative	0.064% (0.043% - 0.085%)
COVID-19 Positive	0.269% (0.225% - 0.313%)
MVD Absent	0.167% (0.141% - 0.193%)
MVD Present	0.390% (0.081% - 0.699%)
Negative COVID / Negative MVD	0.063% (0.042% - 0.083%)
Negative COVID / Positive MVD	0.147% (0.024% - 0.269%)
Positive COVID / Negative MVD	0.263% (0.220% - 0.307%)
Positive COVID / Positive MVD	0.615% (0.125% - 1.106%)

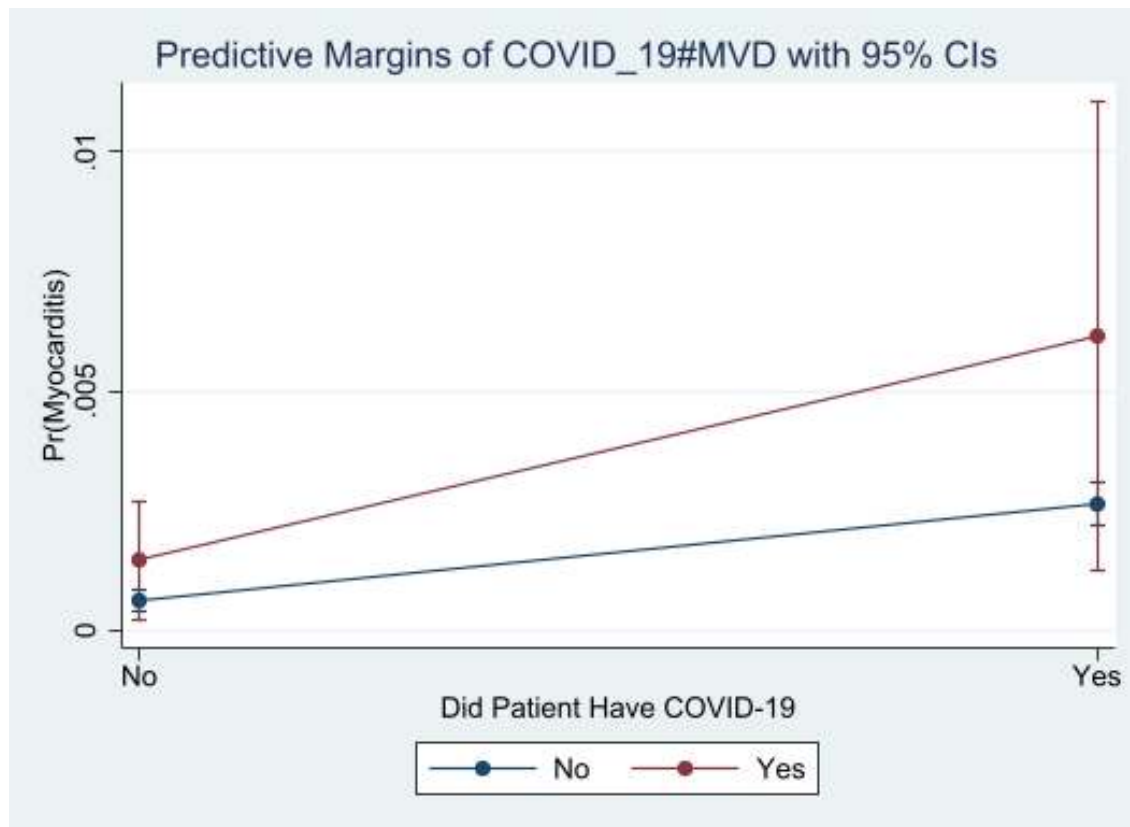
Legend: The values from a survey-weighted multivariable logistic regression model adjusted for age, sex, and Elixhauser comorbidity score are shown as adjusted odds ratios with 95% confidence intervals. Predictive margins reflect the adjusted predicted probabilities of myocarditis obtained from the same model. Survey analyses include stratification, clustering, and discharge weights. The interaction model of COVID-by-MVD was examined but ultimately dismissed due to sparse-event cells resulting in complete or near-complete separation and unstable estimations.

Figure 1. Forest plot of adjusted odds ratios for myocarditis



Legend: Adjusted odds ratios and 95% confidence intervals are shown for variables included in the multivariable model. The vertical line represents an odds ratio of 1.0. Values greater than 1 indicate higher odds of myocarditis.

Figure 2. Adjusted predicted probability of myocarditis by COVID-19 and MVD status



Legend: A survey-weighted multivariable logistic regression model adjusted for age, sex, and Elixhauser comorbidity score indicated that patients without either condition exhibited the lowest probability, while those with either condition showed increased risk, culminating in the highest probability among patients with both COVID-19 and MVD.

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