ORIGINAL RESEARCH

Incidence and Impact of Acute Pericarditis in Hospitalized Patients With COVID-19

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BACKGROUND: Acute pericarditis (AP) is considered a cardiovascular complication in patients with COVID-19. We aimed to assess the incidence, associated complications, and clinical impact of AP on hospitalized patients with COVID-19.

METHODS AND RESULTS: In this retrospective cohort study, *International Classification of Diseases, Tenthth Revision, Clinical Modification* (*ICD-10*) codes were used to identify patients with COVID-19 with or without AP in the National Inpatient Sample 2020 database. We compared outcomes between AP and non-AP groups before and after propensity-score matching for patient and hospital demographics and relevant comorbidities. A total of 211 619 patients with a primary diagnosis of COVID-19 were identified, including 983 (0.46%) patients who had a secondary diagnosis of AP. Before matching, patients with COVID-19 with AP were younger (59.93±19.24 years old versus 64.29±16.82 years old) and more likely to have anemia (40.5% versus 19.9%), cancer (6.7% versus 3.6%), and chronic kidney disease (29.3% versus 19.6%) (all *P*<0.05). After matching, patients with COVID-19 with AP (n=980), when compared with the matched non-AP group (n=2936), had higher rates of mortality (21.3% versus 11.1%, *P*<0.001), cardiac arrest (5.0% versus 2.6%, *P*<0.001), cardiogenic shock (4.2% versus 0.5%, *P*<0.001), ventricular arrhythmia (4.7% versus 1.9%, *P*<0.001), acute kidney injury (38.3% versus 28.9%, *P*<0.001), acute congestive heart failure (14.3% versus 4.8%, *P*<0.001), and longer length of stay (7.00±10.00 days versus 5.00±7.00 days, *P*<0.001) and higher total charges ($75066.5±$130831.3 versus $44824.0±$63660.5, *P*<0.001).

CONCLUSIONS: In hospitalized patients with COVID-19, AP is a rare but severe in-hospital complication and is associated with worse in-hospital outcomes.

Key Words: acute pericarditis ■ COVID-19 ■ in-hospital complications ■ mortality

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See Editorial by Alder.

The global pandemic of COVID-19 caused by severe acute respiratory syndrome-coronavirus 2 has challenged health care services worldwide.[1] The infection not only caused respiratory complications but also resulted in extrapulmonary syndromes and risks to other systems, including the cardiovascular system.[2] Cardiovascular complications linked with COVID-19 include myocarditis, myocardial infarction, cardiac arrest, and atrial fibrillation.[3–6]

Most COVID-19 reports have focused on myocardial involvement, whereas studies on pericardial disease, including acute pericarditis (AP), have been less common.[7–9] AP is the most common inflammatory heart disorder, and includes infectious and noninfectious forms.[10] Although the number of case reports suggesting the coexistence of AP and COVID-19 is increasing, the incidence and effects of AP on the prognosis of patients with COVID-19 are unclear.[11,12] Therefore, using

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CLINICAL PERSPECTIVE

What Is New?

- Hospitalized patients with COVID-19 had a low incidence (0.46%) of the complication of acute pericarditis.
- Hospitalized patients with COVID-19 with acute pericarditis had higher in-hospital mortality rates than did those without acute pericarditis.
- Hospitalized patients with COVID-19 with acute pericarditis had worse outcomes including a longer length of stay, higher health care costs, and a higher likelihood of cardiac arrest, cardiogenic shock, and acute kidney injury.

What Are the Clinical Implications?

- Future studies should focus on developing risk stratification tools for targeting patients with COVID-19 at high risk of developing acute pericarditis and assess the effect of early treatment on improving outcomes in hospitalized patients with COVID-19.
- Our study provides valuable insight into the complex relationship between acute pericarditis and COVID-19 and will help guide future clinical studies.
- Clinical trials are necessary to investigate the potential of using corticosteroids as first-line therapy for acute pericarditis in hospitalized patients with COVID-19 because of their benefit in treating severe COVID-19, and because the frequency of acute kidney injury in this group may contraindicate nonsteroidal anti-inflammatory drugs and colchicine use.

Nonstandard Abbreviations and Acronyms

ACHF	acute congestive heart failure
AKI	acute kidney injury
AP	acute pericarditis
NIS	National Inpatient Sample

the latest data from the National Inpatient Sample (NIS), we aim to investigate the incidence, associated adverse events, and impact of AP on hospitalized patients with COVID-19.

METHODS

The authors declare that all supporting data are available within the article and its supplemental material. Using the NIS 2020 database, we examined the association between AP and COVID-19 outcomes. The NIS database includes >7 million hospital stays each year and, since 2016, has used the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes for all in-hospital diagnoses.[13] Beginning in 2020, COVID-19-related hospitalizations can be identified by the *ICD-10-CM* diagnosis code of "U071" (2019 novel coronavirus disease) in the NIS database. The *ICD-10-CM* codes used in this study are shown in Tables S1. Research using the NIS does not require Institutional Review Board approval or patient consent, given the deidentified nature of the database.

Study Population and Covariates

All patients in the 2020 NIS database with the primary diagnosis of COVID-19 were identified. Patients without a discharge status were excluded from this study. We selected the following variables as covariates: patient and hospital demographics (age, sex, race, geographic location, household income, primary payer, and hospital type, region, and bed size), common cardiovascular comorbidities (hypertension, hyperlipidemia, diabetes, smoking, obesity, chronic obstructive pulmonary disease, chronic kidney disease, anxiety, depression, obstructive sleep apnea, anemia, and cancer), and autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, and inflammatory bowel disease).

We divided patients who had COVID-19 into 2 groups: those who had AP as a comorbidity (n=983) and those who did not have AP (n=210636). The detailed patient selection process is shown in Figure 1. To assess the correlation between waves of COVID-19 infections and AP, we analyzed monthly trends of AP during the COVID-19 hospitalization waves in 2020. We evaluated the incidence of COVID-19-related AP before and after June 2020 to assess the potential effect of corticosteroid treatment after preliminary results from the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial were released on June 16, 2020.[14]

Outcomes

The primary outcomes were the rates of in-hospital mortality and severe in-hospital complications, including cardiogenic shock, cardiac arrest, ventricular arrhythmias (including ventricular tachycardia, ventricular flutter, and ventricular fibrillation), acute congestive heart failure (ACHF), acute respiratory failure, and acute kidney injury (AKI). Hospital length of stay (LOS) and total admission charges were also examined.

Statistical Analysis

We used mean and SD to express continuous variables and percentages to express categorical variables. We
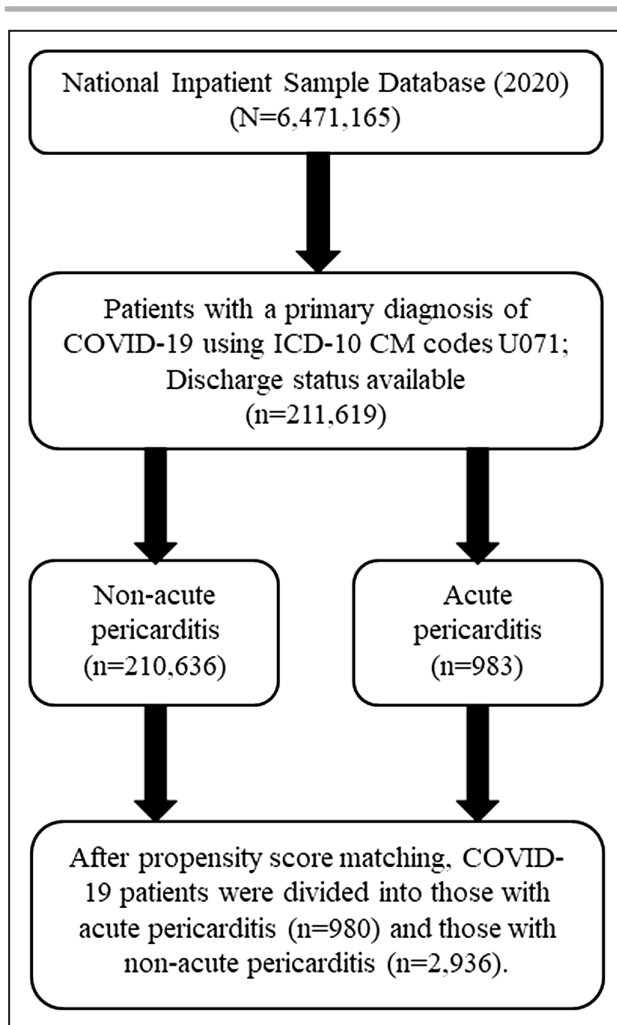
Figure 1. Flow chart of the selection process for the final patient sample used in this study.
Inclusion criteria were applied to the National Inpatient Sample 2020 database. All eligible patients were matched 1:3 based on propensity scoring to generate the acute pericarditis versus nonacute pericarditis comparison cohorts. *ICD-10-CM* indicates *International Classification of Diseases, Tenth Revision, Clinical Modification*.

also provided the median and interquartile range for the LOS and total charges. Continuous variables were tested with a *t* test, and categorical variables were tested with a χ^2 test. *P* values ≤0.05 were considered significant. All data analysis and statistical processes were performed using R statistics software (version 3.6.1, R Development Core Team).

To reduce selection bias in the unmatched cohort, we conducted a propensity-score matching analysis in a 1:3 target ratio to match patients from the AP group and the non-AP group. A multivariate logistic regression model was built and used to adjust for patient and hospital demographics (age, sex, race, geographic location, household income, primary payer, and hospital

type, region, and bed size) and common cardiovascular comorbidities as mentioned above. This statistical method was consistent with the methodology used in previous studies.[15]

Finally, we compared in-hospital outcomes between the 2 groups before and after covariate adjustment to demonstrate the impact of AP on in-hospital outcomes of COVID-19.

To further explore the relationship between COVID-19 and AP, we extracted data on all patients with the primary diagnosis of AP in the NIS database. We classified these patients into COVID-19 and non-COVID-19 groups based on their COVID-19 status. We performed a similar propensity-score matching analysis in a 1:3 target ratio to match patients from the COVID-19 group and the non-COVID-19 group using the abovementioned variables. The in-hospital outcomes were compared between the 2 groups before and after matching.

RESULTS

Comparison of Hospitalized Patients With COVID-19 With and Without AP
Baseline Characteristics
The COVID-19 cohort in this study included 211 619 patients; of those, 983 (0.46%) had AP, leaving 210 636 in the cohort of patients with COVID-19 without AP. Baseline characteristics are provided in Table 1.

Before matching, patients in the AP cohort were younger than those in the non-AP cohort (59.93±19.24 versus 64.29±16.82 years, respectively; *P*<0.001) and had higher rates of comorbidities including anemia, cancer, chronic kidney disease, systemic lupus erythematosus, and systemic sclerosis. In contrast, a higher proportion of patients in the non-AP group had hypertension, obesity, hyperlipidemia, anxiety, depression, and obstructive sleep apnea. No differences were seen in the distribution of chronic obstructive pulmonary disease, diabetes, rheumatoid arthritis, Sjogren syndrome, and inflammatory bowel disease (Table 1).

Various differences were seen in socioeconomic factors, including race, patient location, primary payer, hospital type, and hospital size, in both groups before matching (Table 1). More patients in both groups were White (40.3% AP and 50.9% non-AP). The analysis of hospital type and bed size suggested that most patients in both groups were admitted at urban teaching hospitals and clinics with a large bed size.

After matching, the non-AP (n=2936) and AP (n=980) groups were well matched for all baseline characteristics (*P*>0.05; Table 1). All baseline variables

Table 1. Baseline Characteristics

Variables	Unmatched cohort			Propensity-matched cohort		
	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	P value	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	P value
N	210 636	983		2936	980	
Age, mean (SD)	64.29 (16.82)	59.93 (19.24)	<0.001	60.46 (19.08)	60.03 (19.18)	0.54
Sex, n (%)			0.96			0.87
Male	111 229 (52.8)	516 (52.5)		1551 (52.8)	514 (52.4)	
Female	99 399 (47.2)	467 (47.5)		1385 (47.2)	466 (47.6)	
Unknown	8 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Race and ethnicity, n (%)			<0.001			0.98
White	107 236 (50.9)	396 (40.3)		1178 (40.1)	395 (40.3)	
Black	37 642 (17.9)	292 (29.7)		873 (29.7)	291 (29.7)	
Hispanic	42 256 (20.1)	180 (18.3)		547 (18.6)	179 (18.3)	
Asian or Pacific Islander	6581 (3.1)	31 (3.2)		86 (2.9)	31 (3.2)	
Native American	2126 (1.0)	5 (0.5)		14 (0.5)	5 (0.5)	
Other	8385 (4.0)	44 (4.5)		117 (4.0)	44 (4.5)	
Unknown	6410 (3.0)	35 (3.6)		121 (4.1)	35 (3.6)	
Patient location, n (%)			<0.001			0.99
"Central" counties of metro areas of ≥1 million population	66 463 (31.6)	359 (36.5)		1064 (36.2)	357 (36.4)	
"Fringe" counties of metro areas of ≥1 million population	48 936 (23.2)	242 (24.6)		739 (25.2)	242 (24.7)	
Counties in metro areas of 250 000–999 999 population	39 346 (18.7)	182 (18.5)		532 (18.1)	182 (18.6)	
Counties in metro areas of 50 000–249 999 population	18 683 (8.9)	69 (7.0)		205 (7.0)	69 (7.0)	
Micropolitan counties	20 005 (9.5)	65 (6.6)		190 (6.5)	65 (6.6)	
Nonmetropolitan or micropolitan counties	16 378 (7.8)	60 (6.1)		181 (6.2)	59 (6.0)	
NA	825 (0.4)	6 (0.6)		25 (0.9)	6 (0.6)	
Mean household income, n (%)			0.71			0.97
$1–$42 999	71 045 (33.7)	340 (34.6)		1037 (35.3)	337 (34.4)	
$43 000–$53 999	57 326 (27.2)	279 (28.4)		813 (27.7)	279 (28.5)	
$54 000–$70 999	45 435 (21.6)	195 (19.8)		575 (19.6)	195 (19.9)	
$71 000 or more	33 530 (15.9)	153 (15.6)		458 (15.6)	153 (15.6)	
Unknown	3300 (1.6)	16 (1.6)		53 (1.8)	16 (1.6)	
Primary payer, n (%)			0.003			0.99
Medicare	109 153 (51.8)	491 (49.9)		1471 (50.1)	490 (50.0)	
Medicaid	25 350 (12.0)	154 (15.7)		437 (14.9)	153 (15.6)	
Private including HMO	58 265 (27.7)	255 (25.9)		759 (25.9)	255 (26.0)	
Self-pay	7163 (3.4)	27 (2.7)		86 (2.9)	27 (2.8)	
No charge	517 (0.2)	4 (0.4)		15 (0.5)	4 (0.4)	
Other	9786 (4.6)	47 (4.8)		155 (5.3)	47 (4.8)	
Unknown	402 (0.2)	5 (0.5)		13 (0.4)	4 (0.4)	
Hospital type, n (%)			<0.001			0.89
Rural	24 605 (11.7)	60 (6.1)		168 (5.7)	60 (6.1)	
Urban nonteaching	40 431 (19.2)	155 (15.8)		470 (16.0)	155 (15.8)	
Urban teaching	145 600 (69.1)	768 (78.1)		2298 (78.3)	765 (78.1)	
Hospital region, n (%)			0.21			0.71
Northeast	37 206 (17.7)	195 (19.8)		550 (18.7)	194 (19.8)	
Midwest	49 003 (23.3)	210 (21.4)		646 (22.0)	209 (21.3)	
South	88 137 (41.8)	416 (42.3)		1284 (43.7)	415 (42.3)	
West	36 290 (17.2)	162 (16.5)		456 (15.5)	162 (16.5)	

(Continued)

Table 1. Continued

Variables	Unmatched cohort			Propensity-matched cohort		
	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	*P* value	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	*P* value
Hospital bed size, n (%)			<0.001			0.77
Small	54 032 (25.7)	206 (21.0)		649 (22.1)	206 (21.0)	
Medium	60 827 (28.9)	258 (26.2)		753 (25.6)	257 (26.2)	
Large	95 777 (45.5)	519 (52.8)		1534 (52.2)	517 (52.8)	
Comorbidities, n (%)						
Smoking	56 403 (26.8)	233 (23.7)	0.03	722 (24.6)	232 (23.7)	0.59
Hypertension	87 811 (41.7)	244 (24.8)	<0.001	728 (24.8)	244 (24.9)	0.98
Diabetes	85 215 (40.5)	396 (40.3)	0.94	1183 (40.3)	396 (40.4)	0.98
Hyperlipidemia	88 516 (42.0)	373 (37.9)	0.01	1080 (36.8)	373 (38.1)	0.50
Obesity	59 658 (28.3)	247 (25.1)	0.03	719 (24.5)	247 (25.2)	0.68
Anxiety	26 946 (12.8)	103 (10.5)	0.03	300 (10.2)	103 (10.5)	0.84
Depression	24 010 (11.4)	91 (9.3)	0.04	285 (9.7)	91 (9.3)	0.75
OSA	21 686 (10.3)	77 (7.8)	0.01	237 (8.1)	77 (7.9)	0.88
Chronic kidney disease	41 324 (19.6)	288 (29.3)	<0.001	850 (29.0)	286 (29.2)	0.92
COPD	30 966 (14.7)	141 (14.3)	0.79	402 (13.7)	141 (14.4)	0.62
Anemia	41 838 (19.9)	398 (40.5)	<0.001	1202 (40.9)	395 (40.3)	0.76
Cancer	7506 (3.6)	66 (6.7)	<0.001	211 (7.2)	66 (6.7)	0.69
SLE	1130 (0.5)	20 (2.0)	<0.001	48 (1.6)	18 (1.8)	0.78
Rheumatoid arthritis	4289 (2.0)	25 (2.5)	0.31	67 (2.3)	24 (2.4)	0.86
Systemic sclerosis	151 (0.1)	4 (0.4)	0.001	8 (0.3)	3 (0.3)	1
Sjogren syndrome	355 (0.2)	1 (0.1)	0.91	4 (0.1)	1 (0.1)	1
IBD	1153 (0.5)	4 (0.4)	0.71	12 (0.4)	4 (0.4)	1

COPD indicates chronic obstructive pulmonary disease; HMO, health maintenance organization; IBD, inflammatory bowel disease; NA, not available; OSA, obstructive sleep apnea; and SLE, systemic lupus erythematosus.

in this study had standard mean differences <0.1 between 2 groups (Figure 2).

In-Hospital Complications

Before matching (Table 2), more patients with COVID-19 in the AP group had complications of cardiac arrest, cardiogenic shock, ventricular arrhythmia, AKI, and ACHF than did those in the non-AP group. These trends were observed after matching, with the AP group having a higher incidence of the same complications listed above (Table 2). Figure 3 presents the adjusted odds ratio for in-hospital complications after matching.

Mortality, LOS, and Total Cost

In the unmatched cohort, patients with AP had a higher in-hospital mortality rate (21.4% versus 11.0%, *P*<0.001), a longer LOS (7.00±10.00 days versus 5.00±6.00 days, *P*<0.001), and higher total charges ($74 978.0±130 424.0 versus $41 490.0±54 656.5, *P*<0.001) than did the non-AP group (Table 2). The significant differences in all 3 of the above variables remained after matching (Table 2).

Trends of AP Cases During COVID Hospitalization Waves

Because several waves of COVID infection and hospitalization occurred during 2020, we analyzed the monthly trend of AP cases and COVID-19 hospitalizations in 2020 (Figure 4). As expected, a rise in COVID-19 hospitalizations corresponded to a rise in COVID-19-related AP cases. The highest numbers of both COVID-19 cases and COVID-19-related AP cases were seen in November and December 2020. The highest incidence of COVID-19-related AP occurred in March, May, and August, and the lowest incidence occurred in September and October. The incidence of COVID-19-related AP decreased significantly after June 2020 when compared with before June 2020 (0.46% versus 0.51%, *P*<0.001).

Comparison of AP Cases With and Without COVID-19

To gain a better understanding of the impact of COVID-19 on AP, we studied patients with the diagnosis of AP with and without COVID-19. Of the 46 913
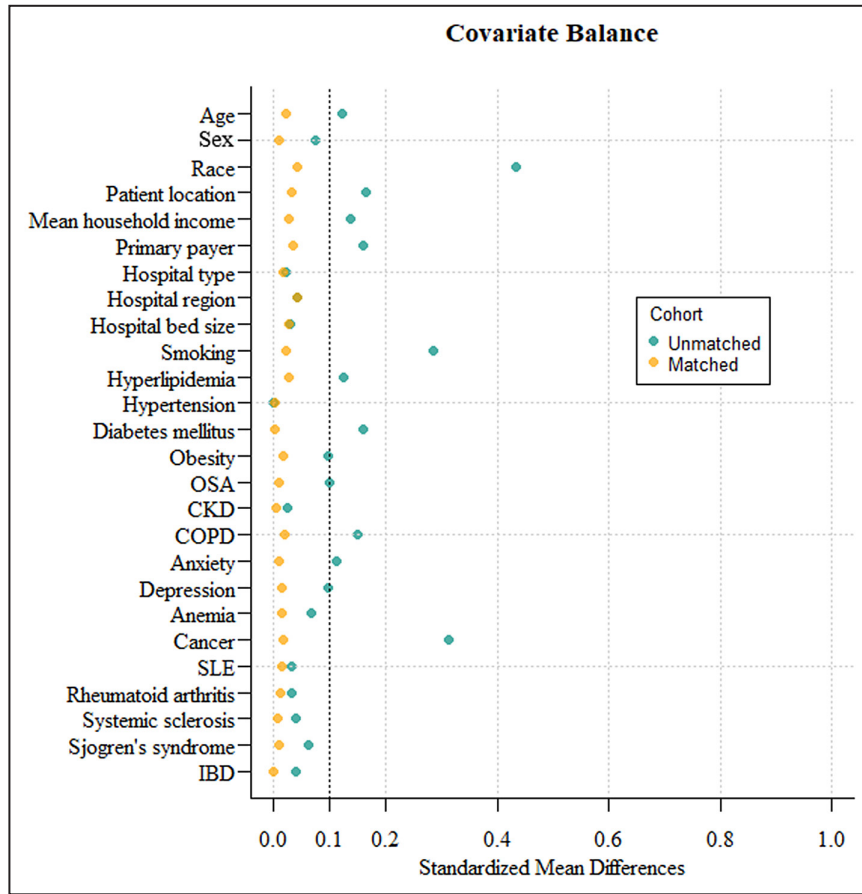
Figure 2. The standardized mean differences of covariates before and after propensity score matching between patients with COVID-19 with and without acute pericarditis.

The standardized mean difference was used to examine the balance of the covariate distribution between the matched acute pericarditis and the nonacute pericarditis groups. All standardized mean differences of covariate distributions in this study were <0.1, which was considered balanced. CKD indicates chronic kidney disease; COPD, chronic obstructive pulmonary disease; IBD, inflammatory bowel disease; OSA, obstructive sleep apnea; and SLE, systemic lupus erythematosus.

patients with AP, 3.96% (n=1860) were infected with COVID-19. The baseline characteristics of these patients are provided in Table S2.

Comparison of in-hospital outcomes (Table S3) showed that the group of patients with AP with COVID-19 had a higher rate of in-hospital mortality than did the non-COVID-19 group in both the unmatched (23.6% versus 7.3%, P<0.001) and the matched (23.7% versus 7.5%, P<0.001) groups. Compared with patients with AP without COVID-19, those with COVID-19 had higher rates of complications including cardiac arrest, AKI, and acute respiratory failure. In contrast, the non-COVID-19 group had higher rates of ACHF and cardiac tamponade than did the COVID-19 group. Compared with the non-COVID-19 group, the COVID-19 group had a longer LOS and higher total charges in both unmatched and matched groups (Table S3). There were no statistically significant differences in the incidence of cardiogenic shock and ventricular arrhythmia.

DISCUSSION

To our knowledge, this is the first study to examine the incidence and impact of AP in hospitalized patients with COVID-19. The incidence of AP in hospitalized patients with COVID-19 was low. However, when compared with the matched non-AP cohort of patients with COVID-19, those with AP had worse in-hospital mortality, higher risks of complications (cardiac arrest, cardiogenic shock, ventricular arrhythmia, AKI, and ACHF), longer LOS, and more hospitalization charges. Our findings also indicated in-hospital outcomes were significantly worse in patients who had AP that was complicated with COVID-19 than in AP patients without COVID-19.

Table 2.   In-Hospital Outcomes

Variables	Unmatched cohort			Propensity-matched cohort		
	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	P value	COVID-19 without acute pericarditis	COVID-19 with acute pericarditis	P value
n	210 636	983		2936	980	
Outcomes						
Death, n (%)	23 246 (11.0)	210 (21.4)	<0.001	325 (11.1)	209 (21.3)	<0.001
Cardiac arrest, n (%)	4437 (2.1)	49 (5.0)	<0.001	75 (2.6)	49 (5.0)	<0.001
Cardiogenic shock, n (%)	799 (0.4)	41 (4.2)	<0.001	14 (0.5)	41 (4.2)	<0.001
Ventricular arrhythmia, n (%)	3652 (1.7)	46 (4.7)	<0.001	57 (1.9)	46 (4.7)	<0.001
AKI, n (%)	52 770 (25.1)	375 (38.1)	<0.001	849 (28.9)	375 (38.3)	<0.001
ARF, n (%)	117 535 (55.8)	518 (52.7)	0.05	1564 (53.3)	518 (52.9)	0.85
ACHF, n (%)	8308 (3.9)	140 (14.2)	<0.001	141 (4.8)	140 (14.3)	<0.001
LOS, d						
Median (IQR)	5.00 (6.00)	7.00 (10.00)	<0.001	5.00 (7.00)	7.00 (10.00)	<0.001
Mean (SD)	7.43 (8.03)	11.89 (14.07)	<0.001	8.05 (8.85)	11.90 (14.08)	<0.001
Total charge, $						
Median (IQR)	41 490 (54657)	74 978 (130424)	<0.001	44 824 (63661)	75 067 (130831)	<0.001
Mean (SD)	78 063 (147908)	178 424 (367509)	<0.001	91 539 (188695)	178 758 (368009)	<0.001

ACHF indicates acute congestive heart failure; AKI, acute kidney injury; ARF, acute respiratory failure; IQR, interquartile range; and LOS, length of stay.

The first reported study on infection-related pericarditis was published in 1933.[16] Viral infections have been documented as the most common cause of AP in the general population.[17] Yet, pericardial disease studies on coronaviruses are limited to case reports and small prospective studies.[12,18,19] In our study, we identified 983 (0.46%) patients with AP in the COVID-19 in-hospital group. The low incidence is consistent with findings from previous prospective studies.[18,20] However, small retrospective studies have suggested a high incidence of pericardial disease (up to 90.7%) in critically ill patients with COVID-19 in the intensive care unit.[21–23] The different study populations could explain the variations in the reported incidence of AP since our cohort was unselected hospitalized patients with COVID-19, including both intensive care unit and
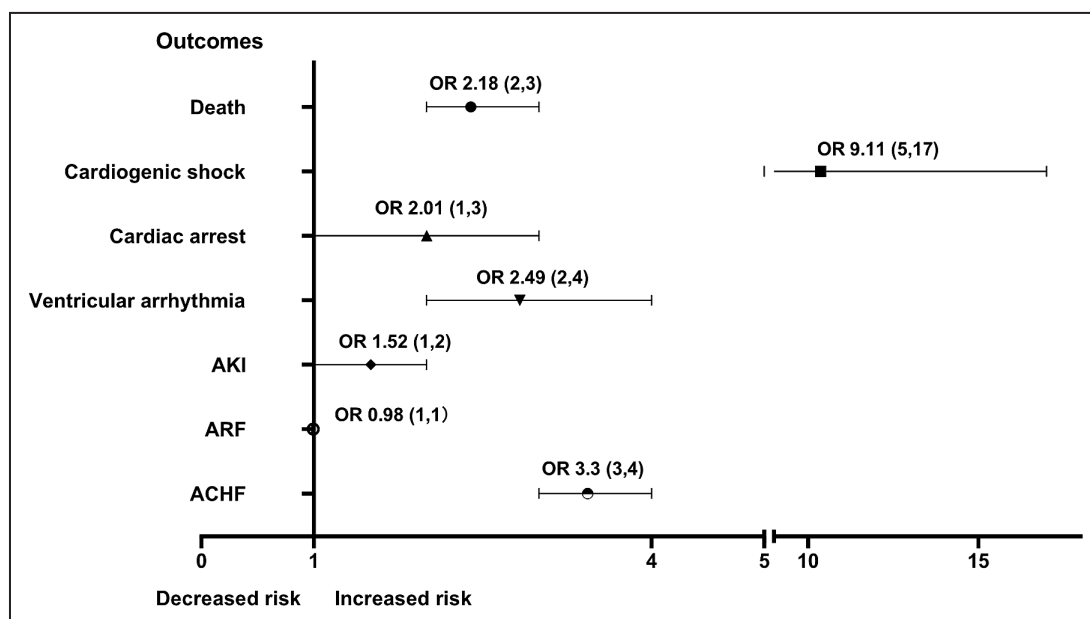

Figure 3.   Forest plot graph showing adjusted odds ratio for in-hospital outcomes after propensity score matching.
ACHF indicates acute congestive heart failure; AKI, acute kidney injury; ARF, acute respiratory failure; and OR, odds ratio.
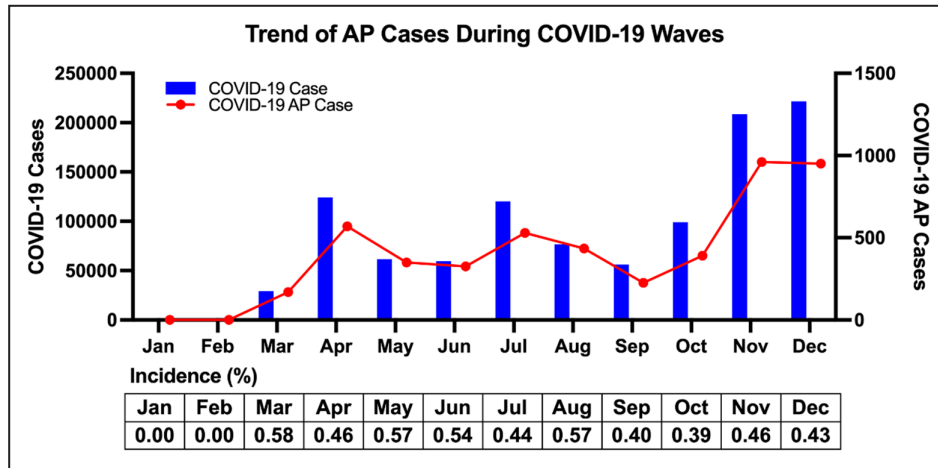
Figure 4. Monthly trends of COVID-19-related acute pericarditis and COVID-19 hospitalizations in 2020 in the United States.
The monthly trends of COVID-19-related acute pericarditis and COVID-19 hospitalizations show a similar wave pattern. AP indicates acute pericarditis.

non–intensive care unit settings, and may be more representative of the incidence of AP in the general hospitalized COVID-19 population.

Hospitalized patients with COVID-19 with AP had a higher mortality rate and incidence of complications, including cardiac arrest, cardiogenic shock, ventricular arrhythmia, and ACHF, than did those without AP. Similarly, previous reports found that patients with COVID-19 with increased cardiovascular risks presented with worse clinical outcomes.[24,25] Although the interaction between severe acute respiratory syndrome-coronavirus 2 and AP remains unclear, several mechanisms have been proposed. First, infection can trigger an overactive immune response, such as a cytokine storm, which could cause deterioration in pericardial structure and function. Pathological studies suggested that higher expression levels of cytokines were correlated with viral loads, and thus more severe infections.[26] This suggests that patients with AP may have a more severe overactive immune response than non-AP patients. These chain reactions could accelerate disease progression and lead to poor outcomes. Moreover, acute respiratory distress syndrome and hypoxia caused by viral infections and inflammation can lead to pericardial damage.[18,27,28] With all these possible pathways to disease progression, a worse clinical outcome in patients with COVID-19 with AP would be expected. Although patients with COVID-19 with AP experienced worse outcomes than those without pericarditis, they had a lower incidence of cardiac tamponade and ACHF than did the non-COVID pericarditis group. This observation suggests that AP could serve as an indicator of a broader immune response, rather than being the primary underlying issue itself.

In the outcome analysis, we found a higher incidence of AKI in the AP-COVID-19 group. This finding may be attributed to various pathophysiological events. First, the pericardial effusion caused by AP, if it overwhelmed the pericardial capacity to stretch and thus restrict the cardiac chamber size, could lead to hemodynamic compromise with reduced cardiac output and systemic hypotension, thereby triggering AKI.[29] The diagnosis and management of AP could also contribute to AKI.[30] At the diagnosis stage, the complication of AP in patients with COVID-19 could mimic acute coronary syndrome. To differentiate acute coronary syndrome from pericarditis, coronary angiography with contrast dye may be used, which could cause contrast-induced AKI.[31] From a management perspective, as the first-line therapy indicated for AP, nonsteroidal anti-inflammatory drugs could induce AKI.[32] Additionally, inflammatory events secondary to AP and viral infection can directly attack the kidneys and lead to AKI.[33]

Hospitalized patients with COVID-19 with AP have higher health care costs and a longer LOS as compared with patients with COVID-19 without AP. Similar findings have been reported in previous studies of patients with COVID-19 with other cardiovascular comorbidities.[34,35] Although it is implicit that treating AP in addition to COVID-19 alone may result in higher costs generated from diagnosing and treating this condition, having more complications may have an exponential rather than linear effect on costs, as more comorbidities may reflect a more complex clinical condition and a sicker population. Furthermore, we found that the patients with COVID-19 with AP have unique demographic and socioeconomic features when compared with the non-AP group. We found a higher proportion of Black patients in the COVID-19 group with AP. The exact reason is unknown, but this finding is consistent with that in a previous study of the American

Heart Association's COVID-19 Cardiovascular Disease Registry.[36] Further analysis from the same study identified that Black patients with COVID-19 and cardiovascular diseases had higher mortality and morbidity. Patients with AP and COVID were seen more frequently in urban teaching hospitals or institutions with more beds, a finding also consistent with data from a previous study.[37] Higher rates of patients with AP and COVID in urban areas may reflect the demographics in the area and could also reflect a higher sensitivity for this diagnosis in teaching institutions and in hospitals with more resources. Overall, these findings may provide insight for additional financial support, resource allocation, and policy making.

The monthly trends of COVID-19-related AP and COVID-19 hospitalizations show similar wave patterns. The incidence of COVID-19-related AP decreased significantly after June 2020 compared with before June 2020 (0.46% versus 0.51%, $P<0.001$). The use of corticosteroids may partially explain this finding. After the release of the dexamethasone trial (RECOVERY trial)[38] data in June 2020, several meta-analyses[39,40] and randomized control trials[38,41,42] showed the benefits of corticosteroids in hospitalized patients with COVID, making low-dose dexamethasone the standard treatment for patients with COVID-19 who required respiratory support. Glucocorticoids[43] are usually used as second-line therapy for AP in patients who cannot tolerate or who do not respond to aspirin/nonsteroidal anti-inflammatory drugs and colchicine. The use of low-dose dexamethasone in patients with severe COVID-19 may result in a lower incidence of AP. This raises the question of whether corticosteroids could be used as first-line therapy for AP in hospitalized patients with COVID-19 because of their potential benefits for severe COVID-19 and because of the high AKI incidence in COVID-19-AP patients, which may contraindicate the use of nonsteroidal anti-inflammatory drugs. Clinical trials are needed to determine the optimal treatment approach for this patient group.

There are several strengths in our study. We have demonstrated, for the first time, the higher rates of mortality and higher incidences of complications in hospitalized patients with COVID-19 with AP. The findings will offer important information for optimizing diagnostic guidelines and management plans for patients with COVID-19 with AP. Also, the current retrospective study was conducted in a nationwide database with a large number of registries, which enhanced the power of our findings.

The present study has limitations. First, data extractions may be biased through the use of *ICD-10-CM* codes for selection. Moreover, the comorbidities identified with *ICD-10-CM* codes did not indicate the level of the severity of disease. Second, using the NIS database, we cannot acquire additional important information including treatment plan, multimodality imaging results, laboratory data, diagnostic features, and long-term outcomes (eg, recurrence of pericarditis) for analyzing patients with COVID-19 with AP. Third, although baseline characteristics were matched in both groups, we can only minimize the biased effects of confounding factors. Certain unidentified confounding factors still exist. Fourth, whether AP in hospitalized patients with COVID-19 is simply a marker for severe systemic inflammation or a relatively independent process cannot be ascertained in the current study because of the lack of laboratory data. Fifth, data on AP patients treated as outpatients, which may represent a significant group, are lacking in the NIS database. Sixth, we were unable to evaluate the effect of the COVID-19 variant (such as the Alpha variant that emerged at the end of 2020) or vaccination (which became available in December 2020) because this information was unavailable. Lastly, the use of retrospective data and diagnosis with *ICD-10-CM* codes may contribute to the underestimation of AP reported in the NIS database.

CONCLUSIONS

In the current large retrospective cohort of hospitalized patients with COVID-19 infection, AP was not common. Nevertheless, it was associated with excess mortality, longer LOS, higher health care charges, and a greater chance of cardiac arrest, cardiogenic shock, ventricular arrhythmia, AKI, and ACHF. Our findings suggest that optimizing a diagnosis algorithm, especially focused on the early detection, prevention, and treatment of AP, should be considered during admission and monitoring of patients with COVID-19. Future studies should be aimed at developing and assessing risk stratification tools to target patients with COVID-19 with a high risk of developing AP and investigate whether early AP treatment can improve outcomes in hospitalized patients with COVID-19. Moreover, the underlying mechanism of crosstalk between COVID-19 and AP should be studied to increase our current understanding of the pathogenesis of both diseases, which may improve the current clinical protocol and give insight into new therapeutics.

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Supplemental Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. International Classification of Disease, 10th edition, Clinical Modification

(ICD-10-CM) Codes Used for Comorbidities and Complications.

Comorbidities/Complications	ICD-10-CM Code
Acute pericarditis	I30, I312-I314, I318, I319, I32
COVID-19	U071
Comorbidities	
Smoking	F17-F17299, Z720, Z87891
Hypertension	I10, I15-I159
Diabetes mellitus	E10-E109, E11-E119, E13-E139
Hyperlipidemia	E780-E785
Obesity	Z683-Z6839, Z684-Z6845, E66-E669
Anxiety	F064, F40-F409, F41-F419
Depression	F32-F329, F33-F339, F341
OSA	G473-G4739
CKD	N18-N189
COPD	J41-J418, J42, J43-J439, J44-J449
Anemia	D50-D59, D60-D64
Cancer	C00-C969, D00-D099
SLE	M32
Rheumatoid arthritis	M05, M06

Systemic sclerosis	M34
Sjögren's syndrome	M35.0
IBD	K50, K51
Complications	
Cardiac arrest	I46-I469
Cardiogenic shock	R570
Ventricular arrhythmia	I472, I490-I4902
Acute kidney injury	N17-N179
Acute respiratory failure	J960-J9622
ACHF	I5021, I5031, I5041, I5023, I5033, I5043
Cardiac tamponade	I319

ACHF, acute congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, Coronavirus disease 2019; IBD, inflammatory bowel disease; ICD-10-CM codes: International Classification of Diseases, 10th edition, Clinical Modification codes; OSA, obstructive sleep apnea; SLE, systemic lupus erythematosus

Table S2. Baseline Characteristics.

Variables	Unmatched Cohort			Propensity-Matched Cohort		
	Acute Pericarditis without COVID-19	Acute Pericarditis with COVID-19	*P* Value	Acute Pericarditis without COVID-19	Acute Pericarditis with COVID-19	*P* Value
n	45,053	1,860		5,554	1,856	
Age, (mean (SD))	61.52 (19.37)	59.15 (19.42)	<0.001	59.18 (20.82)	59.17 (19.43)	0.99
Sex, n (%)			0.01			0.86
Male	22,092 (49.0)	980 (52.7)		2,939 (52.9)	977 (52.6)	
Female	22,956 (51.0)	880 (47.3)		2,615 (47.1)	879 (47.4)	
Unknown	5 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Race, n (%)			<0.001			0.99
White	27,694 (61.5)	768 (41.3)		2,283 (41.1)	768 (41.4)	
African American	8,602 (19.1)	500 (26.9)		1,494 (26.9)	499 (26.9)	
Hispanic	4,662 (10.3)	383 (20.6)		1,155 (20.8)	380 (20.5)	
Asian/ Pacific Islander	1,328 (2.9)	59 (3.2)		186 (3.3)	59 (3.2)	
Native American	242 (0.5)	11 (0.6)		36 (0.6)	11 (0.6)	
Other	1,416 (3.1)	87 (4.7)		261 (4.7)	87 (4.7)	
Unknown	1,109 (2.5)	52 (2.8)		139 (2.5)	52 (2.8)	
Patient location, n (%)			<0.001			0.99
"Central" counties of metro areas of >=1 million population	14,139 (31.4)	720 (38.7)		2,184 (39.3)	716 (38.6)	
"Fringe" counties of metro areas of >=1 million population	11,455 (25.4)	433 (23.3)		1,292 (23.3)	433 (23.3)	

Counties in metro areas of 250,000-999,999 population	8,973 (19.9)	334 (18.0)		967 (17.4)	334 (18.0)	
Counties in metro areas of 50,000-249,999 population	3,832 (8.5)	137 (7.4)		411 (7.4)	137 (7.4)	
Micropolitan counties	3,729 (8.3)	118 (6.3)		353 (6.4)	118 (6.4)	
Non-metropolitan or micropolitan counties	2,684 (6.0)	104 (5.6)		298 (5.4)	104 (5.6)	
NA	241 (0.5)	14 (0.8)		49 (0.9)	14 (0.8)	
Mean household income, n (%)			<0.001			0.98
$1-$42,999	13,393 (29.7)	642 (34.5)		1,910 (34.4)	640 (34.5)	
$43,000-$53,999	11,706 (26.0)	504 (27.1)		1,508 (27.2)	504 (27.2)	
$54,000-$70,999	10,036 (22.3)	386 (20.8)		1,163 (20.9)	384 (20.7)	
$71,000 or more	9,164 (20.3)	299 (16.1)		875 (15.8)	299 (16.1)	
Unknown	754 (1.7)	29 (1.6)		98 (1.8)	29 (1.6)	
Primary payer, n (%)			<0.001			0.99
Medicare	24,424 (54.2)	908 (48.8)		2,717 (48.9)	908 (48.9)	
Medicaid	6,916 (15.4)	333 (17.9)		1,023 (18.4)	333 (17.9)	
Private including HMO	10,766 (23.9)	455 (24.5)		1,318 (23.7)	455 (24.5)	
Self-pay	1,626 (3.6)	64 (3.4)		200 (3.6)	64 (3.4)	
No charge	140 (0.3)	10 (0.5)		33 (0.6)	10 (0.5)	
Other	1,126 (2.5)	82 (4.4)		240 (4.3)	80 (4.3)	
Unknown	55 (0.1)	8 (0.4)		23 (0.4)	6 (0.3)	
Hospital type, n (%)			0.68			0.81

Rural	2,121 (4.7)	84 (4.5)		232 (4.2)	84 (4.5)	
Urban non-teaching	6,380 (14.2)	276 (14.8)		831 (15.0)	275 (14.8)	
Urban teaching	36,552 (81.1)	1,500 (80.6)		4,491 (80.9)	1,497 (80.7)	
Hospital Region, n (%)			0.36			0.98
Northeast	8,459 (18.8)	366 (19.7)		1,105 (19.9)	365 (19.7)	
Midwest	9,758 (21.7)	402 (21.6)		1,193 (21.5)	401 (21.6)	
South	18,118 (40.2)	761 (40.9)		2,247 (40.5)	759 (40.9)	
West	8,718 (19.4)	331 (17.8)		1,009 (18.2)	331 (17.8)	
Hospital Bed Size, n (%)			0.43			0.93
Small	8,187 (18.2)	360 (19.4)		1,064 (19.2)	358 (19.3)	
Medium	11,927 (26.5)	485 (26.1)		1,432 (25.8)	485 (26.1)	
Large	24,939 (55.4)	1,015 (54.6)		3,058 (55.1)	1,013 (54.6)	
Comorbidities, n (%)						
Smoking	16,270 (36.1)	431 (23.2)	<0.001	1,349 (24.3)	431 (23.2)	0.37
Hypertension	10,226 (22.7)	422 (22.7)	1.00	1,231 (22.2)	418 (22.5)	0.77
Diabetes mellitus	14,502 (32.2)	741 (39.8)	<0.001	2,164 (39.0)	738 (39.8)	0.56
Hyperlipidemia	19,547 (43.4)	692 (37.2)	<0.001	2,048 (36.9)	691 (37.2)	0.81
Obesity	9,039 (20.1)	448 (24.1)	<0.001	1,313 (23.6)	447 (24.1)	0.72
Anxiety	6,576 (14.6)	203 (10.9)	<0.001	619 (11.1)	201 (10.8)	0.74
Depression	5,318 (11.8)	165 (8.9)	<0.001	501 (9.0)	165 (8.9)	0.90
OSA	4,896 (10.9)	148 (8.0)	<0.001	460 (8.3)	148 (8.0)	0.71
Chronic kidney disease	14,239 (31.6)	567 (30.5)	0.32	1,666 (30.0)	567 (30.5)	0.67
COPD	9,020 (20.0)	267 (14.4)	<0.001	824 (14.8)	267 (14.4)	0.66
Anemia	21,179 (47.0)	813 (43.7)	0.01	2,404 (43.3)	812 (43.8)	0.75
Cancer	8,293 (18.4)	148 (8.0)	<0.001	448 (8.1)	148 (8.0)	0.94
SLE	1,072 (2.4)	36 (1.9)	0.25	95 (1.7)	36 (1.9)	0.58

Rheumatoid arthritis	1,199 (2.7)	40 (2.2)	0.20	108 (1.9)	40 (2.2)	0.64
Systemic sclerosis	300 (0.7)	7 (0.4)	0.17	20 (0.4)	7 (0.4)	1
Sjogren's syndrome	189 (0.4)	2 (0.1)	0.059	9 (0.2)	2 (0.1)	0.86
IBD	394 (0.9)	10 (0.5)	0.16	20 (0.4)	10 (0.5)	0.40

COPD, chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; HMO, health maintenance organization; IBD, inflammatory bowel disease; NA, not available; OSA, obstructive sleep apnea; SD, standard deviation; SLE, systemic lupus erythematosus

Table S3. In-Hospital Outcomes.

Variables	Unmatched Cohort			Propensity-Matched Cohort		
	Acute Pericarditis without COVID-19	Acute Pericarditis with COVID-19	*P* Value	Acute Pericarditis without COVID-19	Acute Pericarditis with COVID-19	*P* Value
n	45,053	1,860		5,554	1,856	
Outcomes						
Death, n (%)	3,298 (7.3)	439 (23.6)	<0.001	418 (7.5)	439 (23.7)	<0.001
Cardiac arrest, n (%)	1,352 (3.0)	110 (5.9)	<0.001	212 (3.8)	110 (5.9)	<0.001
Cardiogenic shock, n (%)	2,383 (5.3)	108 (5.8)	0.36	330 (5.9)	107 (5.8)	0.82
Ventricular arrhythmia, n (%)	2,617 (5.8)	119 (6.4)	0.31	372 (6.7)	119 (6.4)	0.71
AKI, n (%)	1,4513 (32.2)	795 (42.7)	<0.001	1,822 (32.8)	794 (42.8)	<0.001
ARF, n (%)	12,681 (28.1)	947 (50.9)	<0.001	1,517 (27.3)	946 (51.0)	<0.001
ACHF, n (%)	11,221 (24.9)	308 (16.6)	<0.001	1,469 (26.4)	308 (16.6)	<0.001
Cardiac tamponade	4,622 (10.3)	81 (4.4)	<0.001	556 (10.0)	81 (4.4)	<0.001
LOS (days)						
Median (IQR)	5.00 (7.00)	8.00 (12.00)	<0.001	5.00 (7.00)	8.00 (12.00)	<0.001
Mean (SD)	8.91 (13.78)	13.19 (14.76)	<0.001	9.20 (14.45)	13.13 (14.63)	<0.001
Total charge ($)						
Median (IQR)	70,949 (121,748)	94,761 (175,746)	<0.001	71,786 (127,005)	93,998 (174,178)	<0.001
Mean (SD)	157,032 (318,074)	207,620 (354,098)	<0.001	168,917 (332,264)	206,734 (353,520)	<0.001

ACHF, acute congestive heart failure; AKI, acute kidney injury; ARF, acute respiratory failure; COVID-19: Coronavirus disease 2019; IQR, interquartile range; LOS, length of stay; SD, standard deviation.