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Outcomes Among Heart Failure Patients Hospitalized for Acute Pulmonary Embolism and COVID-19 Infection: Insight From the National Inpatient Sample

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Outcomes among heart failure patients hospitalized for acute pulmonary embolism and COVID-19 infection: Insight from the National Inpatient Sample

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Abstract

There is paucity of data regarding the outcomes of hospitalized acute pulmonary embolism (PE) patients with heart failure (HF) and Coronavirus Disease 2019 (COVID-19) infection. We utilized the 2020 National Inpatient Sample (NIS) Database in conducting a retrospective cohort study to investigate the outcomes of hospitalized acute PE patients with HF and COVID-19, looking at its impact on in-hospital mortality, thrombolysis, and thrombectomy utilization as well as hospital length of stay (LOS). A total of 23,413 hospitalized acute PE patients with HF were identified in our study, of which 1.26% ($n = 295/23,413$) had COVID-19 infection. Utilizing a stepwise survey multivariable logistic regression model that adjusted for confounders, COVID-19 infection among acute PE patients with HF was found to be an independent predictor of overall in-hospital mortality (adjusted odds ratio [aOR]: 2.77; 95% confidence interval [CI], 1.15–6.67; $p = 0.023$) and thrombolysis utilization (aOR: 5.52; 95% CI, 2.57–11.84; $p \leq 0.001$) compared to those without COVID-19. However, there were comparable rates of thrombectomy utilization and LOS among acute PE patients with HF regardless of the COVID-19 infection status. On subgroup analysis, patients with HF with reduced ejection fraction was found to be associated with increased risk for in-hospital mortality (aOR: 3.89; 95% CI, 1.33–11.39; $p = 0.013$) and thrombectomy utilization (aOR: 4.58; 95% CI, 1.08–19.41; $p = 0.042$), whereas both HF subtypes were associated with increased thrombolysis utilization. COVID-19 infection among acute PE patients with HF was associated with higher over-all in-hospital mortality and increased thrombolysis utilization but had comparable hospital LOS as well as thrombectomy utilization.

KEYWORDS
acute pulmonary embolism, COVID-19, heart failure

INTRODUCTION

Acute pulmonary embolism (PE) is a significant cause of morbidity and mortality especially among those with comorbid heart failure (HF).[1] The coexistence of acute PE and HF may cause aggravation of both conditions which has significant therapeutic implications and detrimental effects on survival.[2] The interaction between HF and acute PE is bidirectional. A previous study by Piazza et al.[3] showed that the same risk factors for the development of coronary artery disease leading to ischemic cardiomyopathy including obesity, hypertension, hyperlipidemia, diabetes, and smoking also predisposes a person to develop venous thrombosis leading to acute PE. On the other hand, acute PE may cause significant right ventricular (RV) dysfunction which could lead to decreased left ventricular (LV) filling and subsequently reduce LV output.[4–6] Coronavirus Disease 2019 (COVID-19) has brought about global concern due to its associated increase in morbidity and mortality especially among those with concurrent pre-existing medical diseases such as chronic cardiovascular diseases.[7–9] Further, previous literature demonstrated that COVID-19 infection increases the risk for acute decompensation among those with pre-existing HF through induction of a severe inflammatory reaction leading to increased metabolic demand, coagulopathy, direct myocardial injury, and cardiac arrhythmias causing worsening of cardiac dysfunction.[10] Moreover, COVID-19's procoagulopathic mechanism increases the risk for the development of acute PE among infected patients leading to increased morbidity and mortality.[11] Due to this increased risk for venous thromboembolism (VTE), there is potential for increased utilization of certain procedures such as thrombolysis[12] and thrombectomy,[13] especially in severe disease. Although previous studies [1,14] suggest that acute PE patients with HF have poor outcomes, there is paucity of data regarding the impact of COVID-19 in this population. With this, we aim to investigate the outcomes among hospitalized acute PE patients with comorbid HF and concomitant COVID-19 infection by utilizing a large nationwide database.

METHODS

We utilized the National Inpatient Sample (NIS) database of the year 2020 to conduct a retrospective cohort study. Briefly, the NIS of the Health Care Utilization Project (HCUP) is sponsored by the Agency for Healthcare Research and Quality (AHRQ) and is the largest publicly available all-payer inpatient database in the United States that utilizes a survey design database of discharge data for inpatient hospital care from nonfederal, nonrehabilitation, acute care, and short-term hospitals. Additionally, it approximates about 20% of stratified samples of all discharges from US community hospitals. Further, the NIS is an annual sample of hospital discharges providing national estimates of the characteristics of the patients, diagnoses, and hospital-based procedures performed in US acute-care hospitals. All hospital discharges from the sample are recorded and weighed to ensure that they are nationally representative.

In our study sample of interest, all patients aged 18 and older who were admitted with a principal diagnosis of acute PE and with a HF comorbidity during the index hospitalization between January 2020 and December 2020 were included in the analysis. All eligible discharge records that had acute PE and HF as the diagnoses were identified using the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Patients were subsequently stratified according to the presence or absence of COVID-19 infection (see Supporting Information: Figure S1). Furthermore, another stratification for subgroup analysis based on HF ejection fraction was carried out: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). Moreover, comorbidities and other past medical history were obtained based on the hospital discharge records containing the ICD-10 CM codes for the patient's diagnoses during the index hospitalization and were subsequently recorded accordingly. (See Supporting Information: Table S1 for ICD-10-CM codes used in this study).

The main clinical outcome of interest in this study was to investigate the impact of COVID-19 infection on in-hospital mortality among hospitalized acute PE patients with comorbid HF. Secondary outcomes included other factors associated with in-hospital mortality, the influence of COVID-19 infection on thrombolysis and thrombectomy utilization rates, and length of stay among patients with acute PE and comorbid HF.

We utilized StataBE 17.0 (StataCorp.) in all data analyses performed in this study. The NIS is a large database that is based on a complex sampling design that includes stratification, clustering, and weighing of variables. This provides an analysis that produces nationally representative results, variance estimates, and p values. Continuous variables were presented as median and interquartile range (IQR). Categorical variables were presented as numbers and/or percentages. Proportions were compared using the χ^2 test, and continuous variables were compared using the Student t test. Moreover, we utilized Survey univariable and multivariable logistic and linear regression analysis to calculate both adjusted and unadjusted odds ratios (ORs) for the primary and secondary outcomes. Subsequently, outcomes were adjusted for potential patient and hospital level confounders, including age, gender, race, Charlson Comorbidity Index, median income, hospital bed size,

TABLE 1 Baseline characteristics of admitted acute pulmonary embolism patients with comorbid heart failure based on Coronavirus disease 2019 (COVID-19) infection status.

Patient characteristics	With COVID	Without COVID	*p* Value
Number of patients	295	23,118	
Age at index admission, years (IQR)	68 (57–81)	71 (60–81)	0.683
Women, no. (%)	180 (61.02)	11,215 (48.51)	**0.051**
Race/ethnicity, no. (%)			
White	145 (49.15)	15,080 (65.23)	**0.012**
Black	95 (32.20)	5622 (24.32)	0.143
Hispanic	35 (11.86)	1135 (4.91)	**0.011**
Asian or Pacific Islander	5 (1.69)	240 (1.04)	0.622
Native American	0 (0)	116 (0.5)	0.584
Others	10 (3.39)	409 (1.77)	0.361
Comorbidities no. (%)			
Hypertension	10 (3.39)	450 (1.95)	0.431
Hyperlipidemia	150 (50.85)	11,270 (48.75)	0.752
Diabetes Mellitus	30 (10.17)	2825 (12.22)	0.633
Obesity	75 (25.42)	6646 (28.75)	0.561
COPD	40 (13.56)	5116 (22.13)	0.112
CAD	115 (38.98)	8588 (37.15)	0.771
CKD, stages 1–4	50 (16.95)	6258 (27.07)	0.084
ESRD	10 (3.39)	835 (3.61)	0.931
Tobacco use	0 (0)	250 (1.08)	0.422
In-hospital procedures no. (%)			
Thrombolysis			
Overall	40 (13.56)	650 (2.81)	**<0.001**
HFrEF	52 (17.65)	724 (3.13)	**<0.001**
HFpEF	24 (8)	571 (2.47)	0.081
Thrombectomy			
Overall	10 (3.39)	391 (1.69)	0.302
HFrEF	17 (5.88)	365 (1.58)	**0.030**
HFpEF	0 (0)	414 (1.79)	0.504
Charlson Comorbidity Index score, no. (%)			
1	60 (20.34)	3216 (13.91)	0.151
2	95 (32.2)	5063 (21.9)	0.062
3	140 (47.46)	14,839 (64.19)	**0.012**
Median annual income in patient's zip code, US$, no. (%)			
$1–$49,999	120 (40.68)	7673 (33.19)	0.221
$50,000–$64,999	45 (15.25)	6207 (26.85)	**0.053**
$65,000–85,999	65 (22.03)	5047 (21.83)	0.971
≥$86,000	65 (22.03)	3810 (16.46)	0.244

(Continues)

TABLE 1 (Continued)

Patient characteristics	With COVID	Without COVID	*p* Value
Insurance type, no. (%)			0.875
Medicaid	138 (46.67)	13,469 (58.26)	0.201
Medicare	79 (26.67)	4913 (21.25)	0.472
Private	59 (20)	3176 (13.74)	0.323
Uninsured	10 (3.33)	955 (4.13)	0.831
Hospital characteristics			
Hospital region, no. (%)			
Northeast	108 (36.67)	3731 (16.14)	**<0.001**
Midwest	79 (26.67)	5313 (22.98)	0.631
South	59 (20)	10,063 (43.53)	**0.011**
West	49 (16.67)	4011 (17.35)	0.922
Hospital bed size, no. (%)			0.152
Small	49 (16.67)	4510 (19.51)	0.691
Medium	108 (36.67)	6420 (27.77)	0.271
Large	138 (46.67)	12,188 (52.72)	0.501
Location and teaching status of the hospital, no. (%)			0.751
Rural	0 (0)	1628 (7.04)	0.131
Urban nonteaching	20 (6.67)	3861 (16.7)	0.142
Urban teaching	275 (93.33)	17,632 (76.27)	**0.031**
Mortality, no. (%)	30 (10.17)	1052 (4.55)	**0.035**

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

hospital location, and teaching status, insurance type, and comorbidities. Additionally, survey multivariate linear regression analysis was used for the secondary outcome of hospital length of stay to adjust for possible patient and hospital level confounders as above. Variables were tested for collinearity, ORs, and beta coefficients with 95% confidence intervals were provided as appropriate. A $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

There was a total of 161,468 hospitalizations with a principal diagnosis of acute PE identified in the NIS database in the year 2020, of which 14.78% ($n = 23,865/161,468$) had a diagnosis of HF including 12,350 HFrEF and 11,515 HFpEF during the index hospitalization. Of these, 23,413 met our inclusion criteria. Table 1 summarizes the baseline characteristics of the study population. Patients with concomitant COVID-19 infection accounted for 1.26% ($n = 295/23,413$) of the total study population. Further, the median age for those with and without COVID-19 were 68 years old (IQR: 57–81 years) and 71 years old (IQR: 60–81 years), respectively. Compared to patients admitted without COVID-19 infection, admitted acute PE patients with comorbid HF and concomitant COVID-19 infection were more likely to be female (180 [61.02%] vs. (vs) 11,215 [48.51%], $p = 0.051$) or of the Hispanic ethnicity (35 [11.86%] vs. 1135 [4.91%], $p = 0.011$). Further, the study population with COVID-19 had a lower proportion of Caucasians (145 [49.15%] vs. 15,080 [65.23%], $p = 0.012$) compared to those without COVID-19. Moreover, regardless of COVID-19 status, the study population was similar in terms of median annual income, insurance type, characteristics of admitting hospitals and prevalence of hypertension, hyperlipidemia, diabetes mellitus, obesity, chronic obstructive pulmonary

TABLE 2 Multivariable logistic regression table of factors associated with inpatient mortality among patients admitted with acute pulmonary embolism and comorbid heart failure.

Variable	aOR	95% CI	*p* Value
COVID-19	2.77	1.15–6.67	**0.023**
Age	1.01	0.99–1.02	0.314
Charlson Comorbidity Index	1.17	1.10–1.25	**<0.001**
Comorbidities			
Hyperlipidemia	0.48	0.35–0.66	**<0.001**
CAD	0.60	0.43–0.84	**0.003**
Diabetes	0.78	0.46–1.32	0.355
Obesity	0.39	0.26–0.60	**<0.001**
CKD Stage 1-4	0.94	0.65–1.37	0.748
ESRD	1.18	0.62–2.25	0.610
COPD	0.51	0.34–0.76	**<0.001**

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ESRD, end-stage renal disease.

disease (COPD), coronary artery disease, chronic kidney disease, as well as tobacco use.

In-hospital mortality based on the patient's COVID-19 status

The overall mortality rate among patients admitted for acute PE with HF was 4.55% ($n = 1065/23{,}413$). Among those with concomitant COVID-19 infection, the mortality rate was significantly higher at 10.17% ($n = 30/295$, $p = 0.035$). Further, there was a significantly higher rate of in-hospital mortality among HFrEF (1790 [14.71%] vs. 624 [5.13%]; $p = 0.012$) but not among HFpEF (451 [4%] vs. 425 [3.77%]; $p = 0.951$) patients with COVID-19 infection.

On univariate and multivariate analyses that adjusted for patient and hospital level confounders, concomitant COVID-19 infection was found to be an independent predictor of overall in-hospital mortality (aOR: 2.77; 95% CI, 1.15–6.67; $p = 0.023$). Moreover, a higher Charlson Comorbidity Index was significantly associated with increased inpatient mortality among patients admitted for acute PE with known HF (aOR: 1.17; 95% CI, 1.10–1.25; $p \leq 0.001$) (see Table 2). Interestingly, our analysis showed that the utilization of either thrombolysis (aOR: 2.68; 95% CI, 1.37–5.25; $p = 0.004$) or thrombectomy (aOR: 3.39; 95% CI, 1.62–7.11; $p \leq 0.001$) increased the risk for in-hospital mortality in the study population (see Supporting Information: Table S2). In terms of HF subtypes, COVID-19 infection independently increased the risk for in-hospital mortality among admitted acute PE patients with concomitant HFrEF (aOR: 3.89; 95% CI, 1.33–11.39; $p = 0.013$) but not for those with HFpEF (see Table 3).

TABLE 3 Adjusted odds ratio for in-hospital mortality among hospitalized acute pulmonary embolism patients with heart failure and concomitant Coronavirus disease 2019 (COVID-19) infection stratified by heart failure subtype.

	aOR[a]	95% CI	*p* Value
Overall	2.77	1.15–6.67	**0.023**
Heart failure subtype			
HFrEF	3.89	1.33–11.39	**0.013**
HFpEF	1.52	0.18–12.75	0.704

Note: Bold values are statistically significant $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a]Adjusted for age, gender, race, Charlson comorbidity index, median annual income, insurance type, hospital location, hospital bed size, hospital teaching status, hyperlipidemia, hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease (stages 1–4), end-stage renal disease, tobacco use.

In-hospital procedure and intervention utilization rates

For hospitalized acute PE patients with comorbid HF, the overall thrombolysis rates were 2.94% ($n = 688/23{,}413$). Among those with concomitant COVID-19 infection, the thrombolysis rates were noted to be significantly higher at 13.56% ($n = 40/295$) ($p \leq 0.001$). In terms of HF subtypes, there were significantly higher thrombolysis rates among those with HFrEF (2147 [17.65%] vs. 381 [3.13%], $p \leq 0.001$) and but not for those with HFpEF (901 [8%] vs. 278 [2.47%], $p = 0.081$). On the other hand, the overall thrombectomy rates among the study population is 1.71% ($n = 400/23{,}413$) and there are comparable overall thrombectomy rates among those with and without COVID-19 infection (793 [3.39%] vs. 395 [1.69%], $p = 0.302$). However, when stratified according to HF subtypes, those with HFrEF have significantly higher thrombectomy rates (717 [5.88%] vs. 193 [1.58%], $p = 0.030$) but not those with HFpEF (0 [0%] vs. 202 [1.79%], $p = 0.500$) (see Table 1).

On multivariate logistic regression analyses that adjusted for patient and hospital level confounders, concomitant COVID-19 infection among acute PE patients

TABLE 4 Adjusted odds ratio for thrombolysis and thrombectomy utilization rates among hospitalized acute pulmonary embolism patients with comorbid heart failure and concomitant Coronavirus disease 2019 (COVID-19) infection stratified based on heart failure subtype.

	Thrombolysis			Thrombectomy		
	aOR[a]	95% CI	*p* value	aOR	95% CI	*p* Value
Overall	5.52	2.57–11.84	**<0.001**	2.12	0.56–7.99	0.271
HFrEF	7.93	3.21–19.59	**<0.001**	4.58	1.08–19.41	**0.042**
HFpEF	4.53	1.30–15.82	**0.022**	No patients with COVID-19 with HFpEF had thrombectomy	–	–

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

[a]Adjusted for age, gender, race, Charlson comorbidity index, median annual income, insurance type, hospital location, hospital bed size, hospital teaching status, hyperlipidemia, hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease (stages 1–4), end-stage renal disease, tobacco use.

with comorbid HF was found to be an independent predictor of increased thrombolysis utilization rates (aOR: 5.52; 95% CI, 2.57–11.84; $p \leq 0.001$). Further, when stratified into HF subtypes, it showed that HFrEF and HFpEF were all independent predictors of increased thrombolysis utilization rates (see Table 4). On the other hand, our analyses showed that concomitant COVID-19 infection was not a predictor of increased thrombectomy rates among hospitalized acute PE patients with comorbid HF (aOR: 2.12; 95% CI, 0.56–7.99; $p = 0.271$). However, when stratified according to HF subtypes, although small in number, those with HFrEF had increased thrombectomy utilization rates (aOR: 4.58; 95% CI, 1.08–19.41; $p = 0.042$) but not HFpEF (see Table 4).

Total hospital length of stay based on the patients COVID-19 status

The median length of stay for hospitalized acute PE patients with comorbid HF and concomitant COVID-19 infection were 5 days (IQR: 3–8 days) in contrast to 4 days (IQR: 3–7 days) among those without COVID-19 infection. After adjusting for patient and hospital level confounders, our analysis showed that among admitted acute PE patients with comorbid HF, COVID-19 did not significantly increase the hospital length of stay (coefficient: 0.46, 95% CI −1.09 to 2.01; $p = 0.562$), even after stratifying for HF subtypes (see Table 5). Moreover, our analysis showed that the use of either thrombolysis (aOR: 1.31; 95% CI, 1.04–2.59; $p = 0.044$) or thrombectomy (aOR: 3.97; 95% CI, 1.85–7.11; $p = 0.013$) led to a longer LOS among patients in the study population (see Supporting Information: Table S2).

Please see Figure 1 for a summary of results.

TABLE 5 Adjusted coefficient table of length of stay among hospitalized acute pulmonary embolism patients with comorbid heart failure and Coronavirus disease 2019 (COVID-19) infection stratified based on heart failure subtype.

	LOS		
	Coefficient[a]	95% CI	*p* Value
Overall	0.46	−1.09 to 2.01	0.562
HFrEF	0.54	−2.11 to 3.19	0.690
HFpEF	−0.30	−1.82 to 1.21	0.697

Abbreviations: CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LOS, length of stay.

[a]Adjusted for age, gender, race, Charlson comorbidity index, median annual income, insurance type, hospital location, hospital bed size, hospital teaching status, hyperlipidemia, hypertension, diabetes mellitus, obesity, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease (stages 1–4), end-stage renal disease, tobacco use.

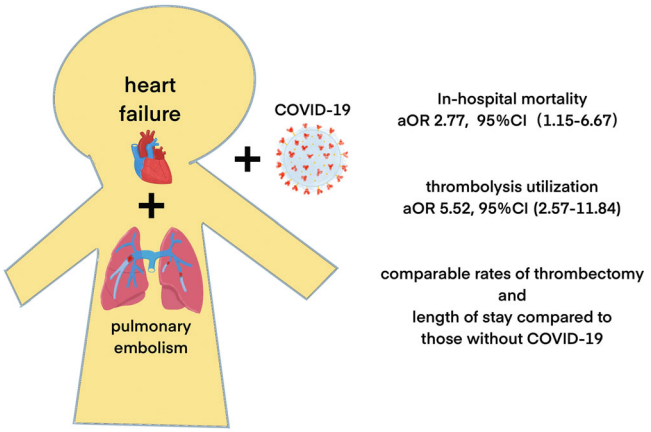

FIGURE 1 Summary of results showing the outcomes among heart failure patients hospitalized for acute pulmonary embolism and concomitant COVID-19 infection. aOR, adjusted odds ratio; CI, confidence interval.

DISCUSSION

To the best of our knowledge, this analysis is the first retrospective population cohort study utilizing a nationally representative database that investigated the outcomes among hospitalized patients with acute PE that had comorbid HF and concomitant COVID-19 infection. The investigated outcomes were overall in-hospital mortality, thrombolysis, and thrombectomy utilization rates as well as hospital length of stay. Our findings demonstrated that among hospitalized acute PE patients with HF, COVID-19 increased the risk for overall in-hospital mortality and thrombolysis utilization. However, there were comparable thrombectomy utilization rates as well as hospital LOS, regardless of COVID-19 infection status. On subgroup analysis, albeit small in size, our study demonstrated that HFrEF were associated with higher risk for in-hospital mortality and thrombectomy utilization. Additionally, there was increased thrombolysis utilization rates among hospitalized acute PE and HF patients with COVID-19, regardless of HF subtype. Finally, COVID-19 infection did not significantly increase the hospital LOS, even after stratifying for HF subtypes.

According to the study of Piazza et al. acute PE patients with HF have a higher overall mortality rate compared to those without HF, and PE was found to be an independent predictor of mortality among HF patients.[14] Moreover, patients with HF have a twofold greater risk of developing PE which increases further as systolic function declines.[15] This associated increase in mortality is likely secondary to a chronic reduced flow state secondary to low cardiac output, abnormalities of hemostasis as well as platelet and endothelial dysfunction. Further, central venous catheters as well as leads from implantable cardiac defibrillators (ICD) are common among HF patients which increases the risk for the development of upper extremity deep venous thrombosis.[16] Moreover, HF patients with LV systolic dysfunction, diastolic dysfunction, or a combination of both often have some degree of RV dysfunction. A sudden superimposed increase in RV afterload from acute PE leads to worsening RV dysfunction and subsequently reduced left-sided cardiac output,[17] thus, showing the intricate interaction between acute PE and HF. Previous studies demonstrated that COVID-19 infection increased the risk for mortality among those with acute PE and HF.[18,19] This was concurrent with the findings of our study which showed that concomitant COVID-19 infection significantly increased the risk for in-hospital mortality among hospitalized acute PE patients with comorbid HF. This significant increase in the in-hospital mortality among patients with concomitant COVID-19 infection is likely due to the implicating mechanisms of the SARS-CoV-2 virus causing increased risk for developing thrombosis as well as inciting cardiac injury in the setting of massive cytokine release and severe systemic inflammation with subsequent downstream pathophysiological effects.[20,21] COVID-19 infection increases the risk for developing arterial and venous thrombosis due to its procoagulant effect, with acute PE being the most common thrombotic manifestation.[22] Additionally, the mechanisms implicated in COVID-19 infection causing myocardial injury is through direct damage to the cardiomyocytes, systemic inflammation, and exaggerated cytokine response[23] leading to clinical entities including acute coronary syndrome, myocarditis, and the development or worsening of pre-existing HF. With this, COVID-19 negatively impacts the outcomes of hospitalized acute PE patients with HF as was evident in our study. Further, our analysis suggested that hospitalized acute PE patients with HFrEF have a higher risk for in-hospital mortality compared to those with HFpEF. This was concurrent with a previous study by Goyal et al.[24] which concluded that among COVID-19-infected patients, HFrEF confers an elevated risk for mortality compared to other HF subtypes. However, a study by Mehra et al.[25] demonstrated that there is an initial worsening of diastolic dysfunction in COVID-19 infection with subsequent worsening of systolic function in the latter stages due to the phenomenon of cytokine storm. This suggests that there could be some element of overlap between systolic and diastolic dysfunction along the course of COVID-19 infection which could be reflective of a more advanced HF, although more data is warranted to assess its impact on mortality. Interestingly, our study showed that hyperlipidemia, CAD, obesity, and COPD among hospitalized HF patient with acute PE was associated with reduced risk for mortality, which is clinically unsound, and are likely attributable to coding errors in the reporting of previous chronic comorbidities, especially among patients who are hospitalized with life-threatening conditions. Thus, caution should be exercised in interpreting these findings as these are speculative and hypothesis generating.

Several treatment strategies exist for patients with acute PE including the utilization of thrombolysis and thrombectomy which aim to decrease the burden of disease and improve survival.[26] This is especially important among patients with HF since these treatment options help improve elevated pulmonary artery pressures due to the obstructing pulmonary emboli, thereby offloading high RV pressure and thus improving systemic congestion. Further, these interventions would decrease RV afterload which increases LV preload and subsequently augment LV cardiac output. Moreover, previous studies suggested that COVID-19 is associated with a

prothrombotic state which increases the risk for VTE,[22,27] thus, effectively increasing the disease burden among those patients who are already at increased risk for the development of thrombotic events such as those with HF. Hence, the utilization of certain interventions such as thrombolysis and thrombectomy may be higher in this population since such interventions also depend on the severity of the acute PE and any underlying comorbidities.[28] Our findings demonstrated that concomitant COVID-19 infection among acute PE patients with comorbid HF, regardless of HF subtype, is an independent predictor of increased utilization of thrombolysis but not that of thrombectomy. Although both treatment strategies are effective in alleviating the burden of disease among acute PE patients, thrombolysis may be more easily accessible and performed compared to thrombectomy since the latter requires mobilization of specialized expertise,[28] which, during the early stages of the COVID-19 pandemic may not have been easily available in the setting of physician and medical staff shortages[29,30] as well as hospital protocols which entails stricter criteria for procedures to be conducted to limit spread of the infection, thus effectively limiting or delaying certain procedures to be done.[31,32] Interestingly, our study has shown that the utilization of either thrombolysis or thrombectomy led to an increase in the in-hospital mortality and longer LOS. However, caution should be used in interpreting these findings as these associations likely reflect the severity of the underlying condition precipitating the need for these interventions rather than as a direct consequence or complication of the procedure itself that led to an apparent increase in mortality and longer LOS.

A study by Darze et al.[33] showed that acute PE complicates the in-hospital outcomes among patients with HF, thus significantly increasing the hospital LOS. On the other hand, hospitalized COVID-19 patients may have varied LOS depending on multiple factors including the severity of the diagnoses during the index hospitalization.[34] This was concurrent with the findings of our study which suggested that concomitant COVID-19 infection is not an independent predictor of longer hospital LOS. However, our analysis is limited by its ability to infer the severity of acute PE, HF, and concomitant COVID-19 infection, since an asymptomatic or mild COVID-19 infection may not impact the overall prognosis of hospitalized acute PE patients with comorbid HF, hence will also have little to no impact in the hospital LOS.

Our study has several limitations owing to the use of an administrative data set and the cross-sectional nature of our study design which leads to the inability to capture patient-level data including the time to first medical contact, use of hospital anticoagulation, or time from presentation to thrombolysis or thrombectomy, all of which could confound the independent association of COVID-19 infection to the outcome of interest. Further, the use of this database limits the ability to identify information regarding the disease severity, indicator whether a condition is present on admission or not, and nonavailability of a disease state relevant to the outcome of interest. Moreover, due to the structure of the database itself, we are limited by the database's ability to identify the exact cause of death for each individual mortality and can only identify factors that might have contributed to the demise. Furthermore, the use of a large administrative database like NIS are prone to coding errors in terms of reporting previous chronic comorbidities, especially among hospitalized patients with life-threatening conditions, hence, caution should be exercised in interpreting findings such as what was seen in our study which showed that hyperlipidemia, CAD, obesity and COPD were associated with reduced HF development, as these are merely speculative and hypothesis generating. Additionally, the absence of radiographic, echocardiographic, and laboratory values limit the stratification of the severity of acute PE, HF as well as COVID-19 infection. Moreover, the ICD-10 code for COVID-19 was released on April 1, 2020 which potentially missed a significant amount of the total number of true COVID-19 cases. Further, caution should be exercised in interpreting the association of certain HF subtypes to the outcomes of interest including HFrEF in increased risk for in-hospital mortality and thrombectomy utilization since the sample size is small, thus, making it difficult to draw meaningful conclusions. Lastly, the study was limited to in-hospital events only, thereby certain outcomes that may have occurred after hospitalization could have been missed.

CONCLUSION

Our study demonstrated that hospitalized acute PE patients with HF and concomitant COVID-19 infection have higher risk for in-hospital mortality and increased thrombolysis utilization but had comparable thrombectomy utilization and hospital LOS compared to those without COVID-19 infection. Prospective studies with a larger sample size and with control of possible confounders are warranted to better delineate these associations.

AUTHOR CONTRIBUTIONS

Bruce Casipit: Conceptualization, methodology, software, validation, formal analysis, investigation, data

curation, writing—original draft, writing—review and editing, visualization, project administration. **Sahana Tito**: Conceptualization, methodology, validation, formal analysis, investigation, writing—review and editing, visualization, supervision. **Isaac Ogunmola**: Conceptualization, methodology, software, validation, formal analysis, investigation, writing—original draft, writing—review and editing, visualization, supervision. **Abiodun Idowu**: Conceptualization, methodology, software, validation, formal analysis, investigation, writing—original draft, writing— review and editing, visualization, supervision. **Shivaraj Patil**: Conceptualization, methodology, software, validation, formal analysis, investigation, writing—Original draft, writing—review and editing, visualization, supervision. **Kevin Lo**: Conceptualization, methodology, software, validation, formal analysis, investigation, writing—original draft, writing—review and editing, visualization, supervision. **Behnam Bozorgnia**: Conceptualization, methodology, validation, formal analysis, investigation, writing—review and editing, visualization, supervision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

BC has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

ETHICS STATEMENT

The authors declare that the work described does not involve experimentation on humans or animals. Further, the authors declare that the work described does not involve patients or volunteers. Since NIS is an administrative database that is commercially available and has deidentified data with no patient-level data for identification, an IRB approval was not indicated.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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