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Characteristics and Factors Associated With Mortality in Patients With Coronavirus Disease 2019 and Pneumothorax

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Abstract

Objective: To describe the incidence, clinical characteristics, and factors associated with mortality in patients hospitalized for coronavirus disease 2019 (COVID-19) in whom pneumothorax developed.

Patients and Methods: This study was a retrospective analysis conducted using a large administrative database of adult patients hospitalized for COVID-19 in the United States from February 1, 2020, to June 10, 2021. We characterized the clinical features of patients in whom pneumothorax developed and the factors associated with mortality and stratified pneumothorax by the timing of the initiation of invasive mechanical ventilation (IMV) and by the time of hospital admission (early versus late).

Results: A total of 811,065 adult patients had a positive test result for severe acute respiratory syndrome coronavirus 2, of whom 103,858 (12.8%) were hospitalized. Pneumothorax occurred in 1915 patients (0.24% overall and 1.84% among hospitalized patients). Over time, the use of steroids and remdesivir increased, whereas the use of IMV, pneumothorax rates, and mortality decreased. The clinical characteristics associated with pneumothorax were male sex; the receipt of IMV; and treatment with steroids, remdesivir, or convalescent plasma. Most patients with pneumothorax received IMV, but pneumothorax developed before the initiation of IMV and/or early during hospitalization in majority. Multivariable analysis revealed that pneumothorax increased the risk of death (adjusted hazard ratio [aHR], 1.15; 95% CI, 1.06-1.24). In patients who did not receive IMV, pneumothorax led to nearly twice the mortality (aHR, 1.99; 95% CI, 1.56-2.54). Increased mortality was also noted when pneumothorax occurred before IMV (aHR, 1.37; 95% CI, 1.11-1.69) and within 7 days of hospital admission (aHR, 1.60; 95% CI, 1.29-1.98).

Conclusion: The overall incidence of pneumothorax in patients hospitalized for COVID-19 was low. Pneumothorax is an independent risk factor for death.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged as a global pandemic on March 11, 2020, and has resulted in, to date, over 50 million cases and an more than 800,000 deaths in the United States.[1] Coronavirus disease 2019, an infectious disease caused by the SARS-CoV-2 virus, was the leading cause of death in the United States in 2021.[2] The overall mortality rate was 1.6%,[3] but the rate increased from 4% to 23% in those with severe disease[4] (ie, among hospitalized patients) and increased to approximately 80% in those who received invasive mechanical ventilation (IMV).[4]

Pneumothorax is an increasingly reported complication of COVID-19 and may be a marker of the severity of the disease. Radiologically, architectural distortion of the lung parenchyma with the formation of cysts has been shown in lungs with COVID-19, which may predispose such patients to the development of pneumothorax.[5] Clinically, patients with pneumothorax have been shown to have inferior gas exchange and worse respiratory mechanics than those who do not have pneumothorax.[6,7] The development of

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pneumothorax in patients with COVID-19 with severe respiratory illness may also be associated with increased mortality.[8-10]

Management strategies, knowledge, and treatment evolve as we learn more about SARS-CoV-2. For instance, clinical trials, such as the A randomised trial of treatments to prevent death in patients hospitalised with COVID-19 and Adaptive COVID-19 Treatment Trial trials, that emerged within the initial year of the pandemic reported improved mortality and outcomes with treatment with dexamethasone and remdesivir and are used as the standard of care.[11,12] Early proning and noninvasive ventilation (NIV) were increasingly employed to delay or avoid IMV.[13] The waves of the disease, characterized by a high incidence of cases lasting weeks until the infection rates troughed, also stressed on resources such as staffing, supplies, and space; furthermore, new variants of the virus emerged.[4] These factors may alter the clinical course of the disease, development of pneumothorax, and outcomes of COVID-19.

To date, little is known about the incidence, characteristics associated with the development of pneumothorax, and factors associated with poor outcomes in patients with COVID-19 and pneumothorax. Even lesser is known about how these changed over the course of the pandemic. Most information stems from small case series, populations limited to critical illnesses or the use of IMV, reports from early stages of the pandemic when the knowledge of SARS-CoV-2 and its management options were limited, or series outside the United States.

The purpose of this study was to examine patients hospitalized for COVID-19 in whom pneumothorax developed and describe the incidence of pneumothorax, clinical characteristics of the development of pneumothorax, and factors associated with inpatient mortality. We further stratified the cohort by the receipt of IMV, timing of pneumothorax, and wave of the pandemic. The study was conducted using a retrospective cohort analysis of a large, nationally representative dataset in the United States.

METHODS

Data Source

In this retrospective cohort study, we used the Optum electronic, longitudinal database of deidentified COVID-19 health records consisting of multiple hospital networks from all regions in the United States, consisting of more than 90 million patients. The database contains deidentified inpatient and ambulatory, encounter-level information as well as data on procedures, prescriptions, and the administration of medication. The University of Texas Medical Branch institutional review board approved this study (IRB#, 20-0180). Written informed consent was not required because of the deidentified nature of the patient data.

Cohort

The study cohort included patients older than 18 years diagnosed with SARS-CoV-2 infection between February 1, 2020, and June 10, 2021, who were subsequently hospitalized within 14 days. Coronavirus disease 2019 was identified based on a positive laboratory test for SARS-CoV-2 (Supplemental Appendix 1, available online at http://www.mcpiqojournal.org) or the International Classification for Diseases, 10th revision (ICD-10), clinical modification, diagnosis code U07.1.

Outcomes

We collected information on patient demographic characteristics as well as clinical and medication history. The ICD-10, procedure coding system, codes were used to identify convalescent plasma (XW13325 and XW14325) and remdesivir (XW043E5 and XW033E5) administered during hospitalization. Steroids were identified using National Drug Codes, with the names of the products and therapeutic classes obtained from the 2019 RED BOOK Select database (RED BOOK Select Extracts, Truven Health Analytics). The primary outcome was inpatient mortality among patients with hospitalization for COVID-19. The main independent variable of interest was pneumothorax, which was

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TABLE 1. Characteristics of Patients Hospitalized for Coronavirus Disease 2019 and By Pneumothorax Status From February 2020 to June 2021 in the United States[a]

Characteristics	Category	Total	No pneumothorax, N (%) N=101,943	Pneumothorax, N (%) N=1915	*P* value
Age, mean (SD)			61.9 (17.8)	62.6 (15.3)	<.0001
Age (y)	18-50	24,616	24,268 (23.8)	348 (18.2)	<.0001
	51-64	29,416	28,782 (28.2)	634 (33.1)	
	65-80	31,493	30,803 (30.2)	690 (36)	
	≥80	18,333	18,090 (17.7)	243 (12.7)	
Sex	Women	50,921	50,268 (49.3)	653 (34.1)	<.0001
	Men	52,937	51,675 (50.7)	1262 (65.9)	
Race/ethnicity[b]	African American	19,509	19,245 (18.9)	264 (13.8)	<.0001
	Asian	2577	2506 (2.5)	71 (3.7)	
	Caucasian	61,461	60,379 (59.2)	1082 (56.5)	
	Hispanic	12,895	12,605 (12.4)	290 (15.1)	
	Other/missing	7416	7208 (7.1)	208 (10.9)	
Census bureau region	Midwest	45,962	45,214 (44.4)	748 (39.1)	<.0001
	Northeast	26,313	25,790 (25.3)	523 (27.3)	
	South	21,829	21,350 (20.9)	479 (25)	
	West	6574	6448 (6.3)	126 (6.6)	
	Unknown	3180	3141 (3.1)	39 (2)	
Comorbidity					
Smoking					<.0001
	Current	10,114	9931 (9.7)	183 (9.6)	
	Prior	29,395	28,853 (28.3)	542 (28.3)	
	Never	59,039	57,997 (56.9)	1042 (54.4)	
	Unknown	5310	5162 (5.1)	148 (7.7)	
DM	No	61,321	60,271 (73.3)	1050 (75.1)	.1472
	Yes	22,274	21,925 (26.7)	349 (24.9)	
HTN	No	33,392	32,814 (39.9)	578 (41.3)	.2913
	Yes	50,203	49,382 (60.1)	821 (58.7)	
Asthma	No	74,507	73,245 (89.1)	1262 (90.2)	.1911
	Yes	9088	8951 (10.9)	137 (9.8)	
CKD	No	74,105	72,855 (88.6)	1250 (89.3)	.4040
	Yes	9490	9341 (11.4)	149 (10.7)	
ESRD	No	80,488	79,134 (96.3)	1354 (96.8)	.3186
	Yes	3107	3062 (3.7)	45 (3.2)	
Stroke	No	52,735	51,876 (63.1)	859 (61.4)	.1884
	Yes	30,860	30,320 (36.9)	540 (38.6)	
CHF	No	68,368	67,172 (81.7)	1,196 (85.5)	.0003
	Yes	15,227	15,024 (18.3)	203 (14.5)	
Cancer	No	81,750	80,396 (97.8)	1,354 (96.8)	.0095
	Yes	1845	1800 (2.2)	45 (3.2)	
CAD	No	67,323	66,177 (80.5)	1146 (81.9)	.1883
	Yes	16,272	16,019 (19.5)	253 (18.1)	
Liver disease	No	77,611	76,336 (92.9)	1275 (91.1)	.0126
	Yes	5984	5860 (7.1)	124 (8.9)	
COPD	No	37,961	37,326 (81.4)	635 (81.3)	.9547
	Yes	8683	8537 (18.6)	146 (18.7)	
Body mass index (calculated as the weight	<30	48,975	47,947 (47)	1028 (53.7)	<.0001

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TABLE 1. Continued

Characteristics	Category	Total	No pneumothorax, N (%) N=101,943	Pneumothorax, N (%) N=1915	*P* value
in kilograms divided by the height in meters squared)[c]					
	≥30	50,601	49,777 (48.8)	824 (43)	
	Unknown	4282	4219 (4.1)	63 (3.3)	
Treatment					
Steroids	No	44,936	44,465 (43.6)	471 (24.6)	<.0001
	Yes	58,922	57,478 (56.4)	1444 (75.4)	
Remdesivir	No	71,816	70,704 (69.4)	1112 (58.1)	<.0001
	Yes	32,042	31,239 (30.6)	803 (41.9)	
Convalescent plasma	No	94,949	93,376 (91.6)	1573 (82.1)	<.0001
	Yes	8909	8567 (8.4)	342 (17.9)	
IMV	No	86,182	85,706 (84.1)	476 (24.9)	<.0001
	Yes	17,676	16,237 (15.9)	1439 (75.1)	
Pneumothorax timing					
Early pneumothorax[d]	No		n/a	327 (17.1)	
	Yes		n/a	1588 (82.9)	
IMV + pneumothorax (N=1439)	Before IMV		n/a	1135 (78.8)	
	After IMV		n/a	304 (22.1)	
Length of stay in d, mean (SD)			8.2 (9.0)	25.8 (23.2)	<.0001
Mortality					
Inpatient death among all hospitalized	No	92,394	91,417 (89.7)	977 (51)	<.0001
	Yes	11,464	10,526 (10.3)	938 (49)	
Inpatient death among IMV (N=17,676)	No	10,127	9531 (58.7)	596 (41.4)	<.0001
	Yes	7549	6706 (41.4)	843 (58.6)	

[a]CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; IMV, invasive mechanical ventilation; n/a, not available; SD, standard deviation.
[b]Persons self-identifying as non-Hispanic ethnicity where categorized based on race (White, Black, Asian, other/unknown). Patients self-identifying as Hispanic ethnicity were included in the "Hispanic" group, regardless of race.
[c]For body mass index, when multiple observations were available, we recorded the value at the date closest to the diagnosis of coronavirus disease 2019.
[d]Early pneumothorax was defined as occurring in less than 7 days from the date of hospital admission.

defined based on the ICD-10, clinical modification, diagnosis code J93.X. Among the subset of patients with pneumothorax, we defined early pneumothorax as occurring within 7 days from hospital admission. The use of IMV was based on the ICD-10, procedure coding system, codes 5A1935Z, 5A1945Z, and 5A1955Z and the Current Procedural Terminology code 31500.

Statistical Analyses

The patient and clinical characteristics were summarized as frequencies and percentages or means and standard deviations and then compared using chi-square statistics or *t* tests, as appropriate. A logistic regression model with random effect for hospital network was used to determine the predictors of a patient being diagnosed with pneumothorax. We used time-dependent Nelson-Aalen cumulative hazard functions to assess the rate of inpatient mortality among patients with pneumothorax and those without pneumothorax. Multivariable Cox proportional hazard models with random effects for hospital network were used to estimate the hazard ratios for inpatient mortality accounting for the patient and clinical characteristics. Pneumothorax was included in the model as a time-dependent variable based on the date of onset. The patients were censored at the time of death, during hospital discharge, or at the

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end of the study period (June 24, 2021). The interaction between pneumothorax and mechanical ventilation was also tested. Additionally, we conducted subset analyses among the patients with pneumothorax to determine the effect of the timing of presentation (early or late or before or after mechanical ventilation) on inpatient mortality. Multivariable Cox proportional hazard models were used to model these effects. All the analyses were performed using SAS, version 9.4 (SAS, Inc.). A *P* value of <.05 was considered statistically significant.

RESULTS

During the study period, 811,065 adults had a SARS-CoV-2 positive test result and had complete data. Of these, 103,858 adult patients (12.8%) were hospitalized within 14 days of diagnosis. Pneumothorax occurred in 1915 (0.24%) of those with a COVID-19 diagnosis and 1.84% of patients hospitalized for COVID-19. Of patients with pneumothorax, 70% required tube thoracostomy, and nearly one third required the insertion of more than 1 chest tube.

Characteristics and Outcomes of Patients Hospitalized for COVID-19

Table 1 shows the characteristics of patients hospitalized for COVID-19. Overall, the average age was 62 years, the number of men and women was nearly equal, and over half were Caucasian. Smoking status, either current or prior smokers, accounted for 38% of the cohort and did not differ based on the pneumothorax status. With regard to treatment, 15.9% received IMV, few received convalescent plasma, one third received remdesivir, and over half received steroids. When we compared the characteristics based on the pneumothorax status, a higher proportion of pneumothorax cases occurred in those aged between 51 and 80 years and in men. Differences in race were observed overall and based on the pneumothorax status. For instance, similar proportions of Caucasians hospitalized based on the pneumothorax status were noted. African Americans accounted for 18.9% of hospitalizations for COVID-19 but represented only 13.8% of those with a pneumothorax diagnosis. However, Hispanics

TABLE 2. Odds Ratios of the Development of Pneumothorax Among Patients Hospitalized for Coronavirus Disease 2019 From February 2020 to June 2021 in the United States[a]

Variables	Odds ratio	95% CI
Age (y)		
18-50	ref	
51-64	1.36	1.20-1.53
65-80	1.35	1.19-1.52
≥80	0.91	0.78-1.06
Sex		
Women	ref	
Men	1.63	1.51-1.77
Race/ethnicity[b]		
Caucasian	ref	
African American	0.85	0.75-0.95
Asian	1.26	0.99-1.59
Hispanic	1.21	1.07-1.37
Other/unknown	1.40	1.21-1.62
Region		
West	ref	
Midwest	1.01	0.67-1.53
Northeast	1.04	0.66-1.64
South	1.60	1.05-2.43
Unknown	0.74	0.47-1.16
Comorbidity		
DM		
No	Ref	
Yes	0.90	0.82-0.98
Stroke		
No	Ref	
Yes	1.06	0.98-1.15
HTN		
No	Ref	
Yes	0.91	0.83-1.00
Asthma		
No	Ref	
Yes	1.03	0.90-1.17
CKD		
No	Ref	
Yes	0.95	0.83-1.08
CAD		
No	Ref	
Yes	0.82	0.73-0.91
Liver disease		
No	Ref	
Yes	1.20	1.05-1.38
COPD		
No	Ref	
Yes	0.98	0.88-1.09

Continued on next page

TABLE 2. Continued

Variables	Odds ratio	95% CI
Body mass index[c]		
<30	Ref	
≥30	0.72	0.66-0.78
Unknown	0.88	0.68-1.14
Treatment		
Steroids		
No	Ref	
Yes	2.02	1.83-2.22
Remdesivir		
No	Ref	
Yes	1.07	0.97-1.17
Convalescent plasma		
No	Ref	
Yes	1.81	1.62-2.04
IMV		
No	Ref	
Yes	2.38	2.18-2.58

[a]CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IMV, invasive mechanical ventilation; Ref, reference.

[b]Persons self-identifying as non-Hispanic ethnicity where categorized based on race (White, Black, Asian, other/unknown). Patients self-identifying as Hispanic ethnicity were included in the "Hispanic" group, regardless of race.

[c]For body mass index, when multiple observations were available, we recorded the value at the date closest to the diagnosis of coronavirus disease 2019.

and Asians comprised 12.4% and 2.5% of the cohort, respectively, and both represented higher proportions of pneumothorax cases (15.1% and 3.7%, respectively). With regard to treatment, a higher proportion of those with pneumothorax received IMV, remdesivir, convalescent plasma, and steroids compared with those who did not have pneumothorax. Among those with pneumothorax, more than 80% of cases occurred early, ie, within 7 days of hospital admission. Although majority received IMV during hospitalization, in more than three fourth of those with pneumothorax, pneumothorax developed before the initiation of IMV. On average, the patients with pneumothorax were hospitalized for longer (9 vs 23.2 days).

When we assessed the patient characteristics and the outcomes of the hospitalized patients based on the waves of the pandemic (Supplemental Table 1, available online at http://www.mcpiqojournal.org), changes were noted, mainly in treatment, with the use of remdesivir and steroids increasing significantly (from 0.3% to 44.1% and 30.6% to 61.4%, respectively). When the overall trends were assessed over time, we excluded wave 4 because the study period may have ended before all patient outcomes were resolved. The use of IMV decreased from 21.3% in wave 1 to 15% by wave 2 and then remained steady. The rates of pneumothorax remained stable overall, but the proportion of patients with pneumothorax who did not receive IMV or in whom pneumothorax developed before the initiation of IMV increased. The overall mortality rate of the COVID-19 cohort was 11%. The mortality among all the hospitalized patients with COVID-19 decreased, whereas the mortality among those with pneumothorax and those who received IMV was stable over time.

Risk Factors for the Development of Pneumothorax

As shown in Table 2, the factors associated with increased odds of the development of pneumothorax among the patients hospitalized for COVID-19 were male sex and an age of 51-80 years. Treatment with steroids, convalescent plasma, and IMV showed an increased odds ratio of being associated with pneumothorax. The receipt of remdesivir showed no difference in the incidence of pneumothorax.

Risk of Death in Patients Hospitalized for COVID-19

Table 3 presents the multivariate analysis of the characteristics associated with inpatient death among patients hospitalized for COVID-19. The most significant risk factors associated with inpatient death were increasing age and the receipt of IMV. In patients in whom pneumothorax developed, the hazard ratio of inpatient death was 1.15 (95% CI, 1.06-1.24). Patients who received remdesivir and steroids had a lower hazard ratio of inpatient death.

A step-wise multivariate analysis (Figure 1) was conducted to show the impact of comorbidities, demographic characteristics, and the use of IMV on mortality in those with pneumothorax. Patient demographic characteristics and comorbidities had the highest effect on increasing mortality, whereas the receipt of IMV and medications attenuated this effect.

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Effect of Pneumothorax and Mortality

We also assessed the effect of the interactions between pneumothorax and IMV and the effect of the timing of pneumothorax on mortality. The risk of death was double when we compared patients who had never received IMV and had pneumothorax with those who received IMV at some point during their hospitalization (adjusted hazard ratio [aHR], 1.99; 95% CI, 1.56-2.54). Among patients who received IMV, the presence of pneumothorax increased the risk of death by 9% (aHR, 1.09; 95% CI, 1.0-1.19) (Figure 2). However, when we assessed the timing of pneumothorax—both before the initiation of IMV or during early stages (within 7 days of admission)—we found an increased hazard ratio of death after adjusting for all the variables in Table 1 ([aHR, 1.37; 95% CI, 1.11-1.69] and [aHR, 1.60; 95% CI, 1.29-1.98], respectively) (Figure 3).

DISCUSSION

In summary, we characterized and described outcomes among patients hospitalized for SARS-CoV-2 infection and pneumothorax in a large US cohort. The rate of pneumothorax was less than 2%. The risk factors for pneumothorax were age and male sex. Treatment with steroids, convalescent plasma, and IMV were also shown to increase the hazard ratio for pneumothorax, but this association may reflect the severity of the disease rather than a causal relationship. Pneumothorax is associated with an increased risk of death, especially when it develops early and/or before the initiation of IMV, which occurred in most of these patients.

Pneumothorax and Sex

An interesting finding was the increased proportion (more than two third) of pneumothorax cases noted among men with COVID-19, also seen in multiple previous reports.[6,7,14-16] However, a similar proportion (77%) of pneumothorax cases among men was observed before SARS-CoV-2 infection.[17] Although the reasons for this are unknown, the hypotheses include an increase in the prevalence of the consumption of tobacco and the anthropometric characteristics of men.[17,18]

Pneumothorax in Spontaneously Breathing Patients

We noted that more than 80% of the pneumothorax cases occurred in patients who had never received IMV or in patients before the initiation of IMV. The reasons for this phenomenon are unclear. The increased use of positive pressure via the expanded use of NIV[6,7,9,19,20] and the prolonged duration of NIV before the initiation of IMV[21] have both occurred during the pandemic and have also been shown to increase the incidence of barotrauma.[15] Unfortunately, the use of NIV could not be ascertained using our data, and it is unclear whether NIV, as a risk factor for pneumothorax, accounted for the increased rates of pneumothorax.

Similar to our study, other reports found that up to half of pneumothorax cases occurred while the patient was not receiving IMV.[14,15,19,20] One of the largest studies of pneumothorax in patients with COVID-19 reported that pneumothorax occurred while using simple low-flow supplemental oxygen (31%) or no-oxygen therapy (5%).[15] Palumbo et al[22] found that just under half of cases of pneumothorax occurred while using simple oxygen. These reports may suggest a pathophysiology beyond that caused solely by positive-pressure ventilation.

One explanation may be the phenomenon known as the Macklin effect, wherein an increase in the pulmonary interstitial pressure above the alveolar pressure along with sudden lengthening and shortening of the pulmonic vessels and associated bronchi prompts alveolar leakage along the vascular sheaths.[23] This can occur with increased work of breathing and coughing—predominant features of COVID-19. Another proposed mechanism involves a high respiratory drive, an excessive inspiratory effort, and uncontrolled transpulmonary pressures, causing self-inflicted lung injuries in patients; however, this phenomenon remains controversial.[24]

Pneumothorax Plus IMV and Mortality

Similar to our study, prior series of patients with COVID-19 have also shown that pneumothorax independently carries up to 3 times the risk of death.[6,7,16,25] Our a priori hypothesis was that the development of

TABLE 3. Hazard Ratios and 95% CI From Multivariable Cox Model for Inpatient Death Among Patients Hospitalized for COVID-19 From February 2020 to June 2021 in the United States[a]

Variables	Hazard ratio	95% CI
Age (y)		
18-50	Ref	
51-64	1.55	1.40-1.72
65-80	2.70	2.45-2.98
≥80	5.57	5.02-6.17
Sex		
Women	Ref	
Men	1.10	1.05 1.14
Race/ethnicity[b]		
Caucasian	Ref	
African American	0.86	0.81-0.92
Asian	0.84	0.73-0.98
Hispanic	0.83	0.77-0.90
Other/unknown	1.07	0.98-1.17
Region		
West	Ref	
Midwest	0.87	0.69-1.09
Northeast	0.92	0.72-1.17
South	1.01	0.80-1.27
Unknown	1.01	0.80-1.29
Comorbidity		
DM		
No	Ref	
Yes	1.00	0.96-1.05
Stroke		
No	Ref	
Yes	0.89	0.85-0.93
HTN		
No	Ref	
Yes	1.02	0.97-1.08
Asthma		
No	Ref	
Yes	0.87	0.81-0.94
CKD		
No	Ref	
Yes	1.20	1.13-1.27
CAD		
No	Ref	
Yes	1.07	1.02-1.13
Liver disease		
No	Ref	
Yes	1.21	1.13-1.31
COPD		
No	Ref	
Yes	1.13	1.07-1.19
Body mass index[c]		
<30	Ref	
≥30	0.94	0.90-0.98
Unknown	1.33	1.16-1.52
Treatment		
Steroids		
No	Ref	
Yes	0.84	0.80-0.88
Remdesivir		
No	Ref	
Yes	0.89	0.84-0.93
Convalescent plasma		
No	Ref	
Yes	1.10	1.03-1.17
IMV		
No	Ref	
Yes	3.62	3.44-3.80
Pneumothorax		
No	Ref	
Yes	1.15	1.06-1.24

[a]CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; IMV, invasive mechanical ventilation; Ref, reference.
[b]Persons self-identifying as non-Hispanic ethnicity were categorized based on race (White, Black, Asian, other/unknown). Patients self-identifying as Hispanic ethnicity were included in the "Hispanic" group, regardless of race.
[c]For body mass index, when multiple observations were available, we recorded the value at the date closest to the diagnosis of coronavirus disease 2019.

pneumothorax increases mortality, which is further increased while receiving IMV. Unexpectedly, our analysis in those who received IMV found that the effect of pneumothorax after adjusting for demographic characteristics and comorbidities was marginally significant in predicting death. However, for patients who did not receive IMV, the effect of pneumothorax on mortality was significant. This result differs from those of prior reports; however, those studies included patients who first received IMV and subsequently developed pneumothorax, or the studies did not mention the timing of pneumothorax relative to the initiation of IMV.[6,16] Rajdev et al[19] observed, among patients with COVID-19 hospitalized for pneumothorax or pneumomediastinum, increased mortality in those who received NIV vs in those who received IMV (80% vs 20%, respectively). We are unaware of any study that has evaluated the risk of pneumothorax or mortality specifically when

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pneumothorax develops before IMV. The reasons for the increased mortality in patients with pneumothorax who did not receive IMV may be a high mortality rate before the initiation of IMV; the underrecognition of pneumothorax, needing decompression; or the fact that IMV after the development of pneumothorax truly does not confer further increased risk of death in this population.

Comparison With Other Studies—Strengths

The largest prior US reports included less than 90 pneumothorax cases from New York.[6,7,25] A case series of patients with ARDS COVID-19, described by Wong et al,[7] reported outcomes only in those with pneumothorax. McGuinness et al[25] included patients with barotrauma who received IMV but did not distinguish pneumothorax from pneumomediastinum. A third of their cohort was still hospitalized and did not have an outcome at the time of publication. A study by Chopra et al[6] included only critically ill patients. Over two third of the cohort received IMV, and the timing of pneumothorax (before or after IMV) was not reported. None of these studies conducted multivariable analyses.

A multicenter research letter, recently published from the United Kingdom, on 1283 pneumothorax cases in patients hospitalized for COVID-19 during a similar time period used descriptive statistics to report the rates of pneumothorax and the use of oxygen, IMV, and steroids.[15] The incidence of pneumothorax was less than half of that reported in our study, and the researchers found a higher—nearly 3 times—risk of death with pneumothorax,[15] which did not change over the first half of the study period. The contribution of IMV or the timing of pneumothorax to death was not reported. A comparison of our results with that of this study is difficult because it failed to report the overall mortality, comorbidity, or trends over time. Additionally, the United States had disproportionate and early access to prevention, such as vaccinations and remdesivir, which were not readily available in the United Kingdom until recently, and these discrepancies may have affected the severity and outcomes of the disease, especially during the first 2 waves.

Study Strengths

This study is the largest cohort of pneumothorax in hospitalized patients with COVID-19 reported to date. We examined the trends of patient characteristics and outcomes related to the development of pneumothorax over time. Further, we provided additional information by reporting the timing of pneumothorax related to the course of hospitalization, which has not been previously reported. Reporting time trends is important as our understanding of prevention, treatment, and the disease itself evolves, which may alter the outcomes over time. For example, the incidence of vaccination, medications, treatment in the form of medications, proning, and the use of NIV and IMV significantly changed over time, and these changes may account for differences in outcomes.

Study Limitations

There are several limitations to our study. First, certain limitations are related to the retrospective, observational nature of the study. Second, administrative data cannot differentiate the types of barotrauma (pneumothorax vs pneumomediastinum); unilateral pneumothorax from bilateral pneumothorax; primary, spontaneous pneumothorax from secondary and iatrogenic pneumothorax; or pre-existing lung disease from COVID-19-related disease. Third, caution should be exercised while evaluating the potential effects of smoking status, which is found to be highly specific but less than 10% sensitivity, which has not changed over time with the use of administrative datasets.[26,27] Fourth, it is possible that undiagnosed pneumothorax cases and deaths attributed to these occurred, which might have led to the underreporting of the true rate of occurrence and attributable mortality. Further, we could neither stratify patients by the severity of respiratory parameters, such as oxygenation or lung mechanics, nor determine whether the best practices that may affect outcome, such as lung-protective ventilation strategies, were adhered to; however, prior reports examining this across the United States have shown adherence to these

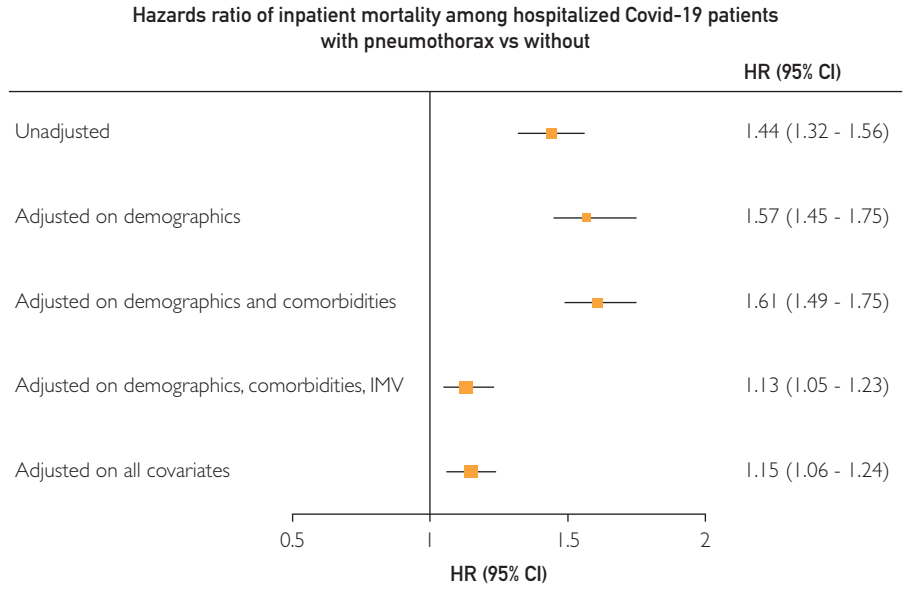

FIGURE 1. Forrest plot for hazard ratios and 95% CI for inpatient death among patients hospitalized for coronavirus disease 2019 from February 2020 to June 2021 in the United States. [a]COVID-19, coronavirus disease 2019; HR, hazard ratio; IMV, invasive mechanical ventilation. [a]HR adjusted for age, sex, race, region, comorbidities, and treatments received, as listed in Table 1.

best practices.[6,7] Additionally, 1 publication found no difference in the tidal volume or peak airway pressures in patients with COVID-19 who received IMV between those with barotrauma and those without barotrauma.[28] We attempted to control for these variables by comparing patients with pneumothorax with those without pneumothorax over the same time.

CONCLUSION

In summary, the incidence of pneumothorax in patients hospitalized for COVID-19 is low. Most cases of patients with pneumothorax

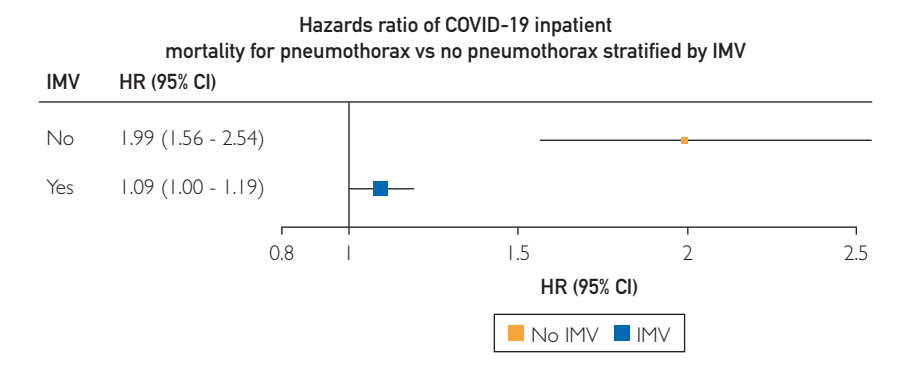

FIGURE 2. Forrest plot for hazard ratios and 95% CI among patients hospitalized for coronavirus disease 2019 with pneumothorax evaluating the effect of invasive mechanical ventilation from February 2020 to June 2021 in the United States. [a]COVID-19, coronavirus disease 2019; HR, hazard ratio; IMV, invasive mechanical ventilation. [a]HR adjusted for age, sex, race, region, comorbidities, and treatments received, as listed in Table 1.

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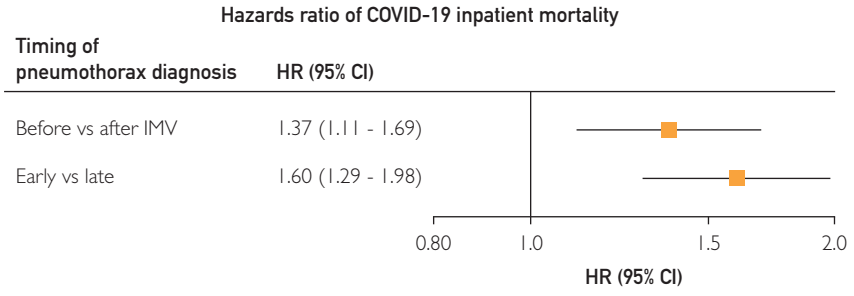

FIGURE 3. Forrest plot for hazard ratios and 95% CI among patients hospitalized for coronavirus disease 2019 with pneumothorax evaluating the effect of the timing of pneumothorax from February 2020 to June 2021 in the United States. [a]COVID-19, coronavirus disease 2019; HR, hazard ratio; IMV, invasive mechanical ventilation. [a]HR adjusted for age, sex, race, region, comorbidities, and treatments received, as listed in Table 1.

occurred early and before the initiation of IMV. The risk factors for the development of pneumothorax were an age of 50-80 years and male sex. Pneumothorax is an independent risk factor for death.

POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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Dr Nishi contributed to the conception and design; interpretation of data; draft of the article or revising it critically for important intellectual content; and final approval of the version to be published; guarantor of the paper. Drs Malik, Kaushik, and Heidelman contributed to the acquisition of data, analysis and interpretation of data, and final approval of the version to be published. Drs Polychronopoulou and Kuo contributed to the conception and design, analysis and interpretation of data, and final approval of the published version; Dr Sharma contributed to the conception and design, acquisition of data, or analysis and interpretation of data, drafted the article or revising it critically for important intellectual content; and final approval of the published version.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **aHR,** adjusted hazard ratio; **COVID-19, c**oronavirus disease 2019; **IMV,** invasive mechanical ventilation initiation; **NIV,** noninvasive ventilation; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2

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