Original Article

Prevalence and patient risk factors for pneumothorax in COVID-19 and in influenza pneumonia: a nationwide comparative analysis

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Background: Pneumothorax is a rare but deadly complication in patients who require mechanical ventilation. As with any condition associated with acute respiratory distress syndrome (ARDS), coronavirus disease 2019 (COVID-19) is known to be associated with pneumothorax. However, in the literature, comparative data on the risk factors for pneumothorax in COVID-19 and other diseases like influenza are limited. The aim of this study is to determine the prevalence and risk factors for pneumothorax in hospitalized COVID-19 patients and compare them with influenza pneumonia patients.

Methods: This study is a retrospective analysis of the National Inpatient Sample (NIS) 2020 database cohort. Univariate and multivariate logistic regression were used to identify the prevalence and risk factors for pneumothorax in COVID-19 patients and compared with the risk of pneumothorax in influenza patients.

Results: The NIS 2020 database includes 1,608,980 hospitalizations of COVID-19 patients, of which 22,545 [95% confidence interval (CI): 21,491–23,598] (1.4%) developed pneumothorax. On multivariate analysis, factors associated with pneumothorax in COVID-19 included patient age of 41–64 years; male sex; Hispanics, Native Americans, and other races; hospitals with large-bed size; privately owned hospitals; urban teaching hospitals; hospitals in the southern United States (US); stroke; malnutrition; chronic obstructive pulmonary disease (COPD); bronchiectasis; pulmonary fibrosis; liver disease; non-invasive and invasive ventilation; and extracorporeal membrane oxygenation (ECMO). Of 184,980 influenza patients, 1,630 (95% CI: 1,448–1,811) (0.88%) developed pneumothorax. The prevalence of pneumothorax was higher (1.4%) in COVID-19 patients compared to patients with influenza pneumonia (0.88%).

Conclusions: COVID-19 patients who develop pneumothorax have a poor prognosis. Several risk factors for the development of pneumothorax were identified. Patients with these risk factors should be prioritized in applying evidence-based guidelines to prevent pneumothorax.

Keywords: Coronavirus disease 2019 (COVID-19); pneumothorax; influenza

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Introduction

Pneumothorax, a rare but deadly complication in patients with coronavirus disease 2019 (COVID-19), is more common in patients requiring mechanical ventilation (1). Studies have demonstrated the incidence of pneumothorax in hospitalized COVID-19 patients is 1–2% (2-5).

The pathogenesis of pneumothorax in COVID-19 is multifactorial. A proposed mechanism is the distortion of lung parenchyma with cyst formation and reduced lung compliance from reticulation and fibrotic changes (6). Invasive mechanical ventilation (IMV) increases the risk of barotrauma, rupture of the alveoli, and introduction of air into the pleural cavity. In a spontaneously breathing patient with COVID-19, an increased respiratory rate, severe cough, and air hunger increase alveolar shear stress, contributing to the pathogenesis of pneumothorax. The development of pneumothorax is associated with increased mortality risk in COVID-19 patients (7-9).

Although many case series and reports discuss the epidemiology of pneumothorax in COVID-19 patients, few nationwide studies establish its prevalence, risk factors, and mortality. This study comparatively analyzes the prevalence, risk factors, and associated mortality of pneumothorax in COVID-19 and in influenza pneumonia, using the National Inpatient Sample (NIS) database of the United States (US). We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1454/rc).

Highlight box

Key findings

- Pneumothorax is a rare complication of coronavirus disease 2019 (COVID-19). It is an indicator of poor prognosis and is associated with increased mortality.

What is known, and what is new?

- Risk factors for pneumothorax in COVID-19 include factors such as increasing age, male gender, a history of stroke, liver disease, malnutrition, specific lung ailments, and additional underlying health conditions.
- The risk of pneumothorax is greater in COVID-19 compared to influenza pneumonia. Given the increased risk, it is advisable to prioritize preventive strategies for COVID-19 patients who exhibit the aforementioned risk factors.

What is the implication, and what should change now?

- Those receiving mechanical ventilation necessitate vigilant monitoring to detect potential pneumothorax development promptly. Timely identification and intervention in cases of pneumothorax can lead to reduced mortality rates in COVID-19 patients.

Methods

Data source

The study utilized the NIS 2020 dataset. The NIS is a part of a series of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) (10). It serves as the largest publicly available comprehensive inpatient database in the US, designed to generate regional and national estimates on various aspects of inpatient care, including utilization, access, cost, quality, and outcomes. Unweighted, it encompasses data from approximately 7 million hospital stays annually, which, when weighted, translates to approximately 35 million hospitalizations nationwide. The NIS encompasses all states participating in HCUP, representing more than 97 percent of the US population. The NIS constitutes a 20-percent stratified sample of discharges from community hospitals across the US. The current version's self-weighting design minimizes the margin of error for estimates, resulting in more robust and precise estimations compared to earlier iterations of the NIS. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was exempt from institutional review board approval as the NIS 2020 database is comprised of previously collected, de-identified data.

Patient selection and outcomes

Our study included adult patients (age 18 years and above) with COVID-19 [International Classification of Diseases, Tenth Revision (ICD-10) code U07.1] and influenza (ICD-10 code J09.X1, J10.00, J10.01. J10.08, J11.00, J11.08) who were hospitalized between January 1st, 2020, and December 31st, 2020. Patients who were transferred to another acute care hospital were excluded. This exception was necessary as pneumothorax and mortality may not have occurred in the same hospitalization. Socioeconomic and comorbidity risk factors for pneumothorax in COVID-19 patients and its associated mortality were identified in the same cohort. Primary outcomes were the prevalence of pneumothorax in COVID-19 patients and the socioeconomic and comorbidity risk factors demonstrated in these patients. Secondary outcomes were the comparison of COVID-19 patients with pneumothorax and those without

pneumothorax and the comparison of pneumothorax risk in influenza and in COVID-19.

Identification of variables

The NIS variables encompassed demographic characteristics of patients, comprising age, gender, insurance status, race, and income quartiles derived from zip codes. Additionally, hospital characteristics such as bed size (capacity), teaching status, and ownership were identified. Elixhauser Comorbidity Index variables, including complicated and uncomplicated hypertension, diabetes, solid cancer, chronic pulmonary disorders, liver disease, and rheumatoid arthritis/collagen vascular disorders were directly utilized. Further variables were extracted through ICD-10, Clinical Modification (ICD-10-CM) diagnosis codes (Table S1).

Statistical analysis

Descriptive analysis calculated the mean for continuous variables and the proportion for categorical variables. Initially, the distribution of socioeconomic factors, comorbidities, and complications among COVID-19 patients with and without pneumothorax was examined. Univariate logistic regression identified risk factors associated with pneumothorax in COVID-19 patients. Variables demonstrating significant P values (P<0.05) and those of particular clinical relevance were incorporated into multivariate logistic regression to determine independent predictors of pneumothorax in COVID-19. Univariate and multivariate logistic regression analyses were conducted to ascertain COVID-19 as a risk factor for pneumothorax, with influenza pneumonia serving as a reference. StataCorp. 2021, Stata Statistical Software: Release 17, StataCorp LLC (College Station, TX, USA), basic edition (BE) version was utilized for analysis. The Stata "SVY" command and appropriate weights were applied in all estimations. The overall model fit was assessed using receiver operating characteristic (ROC) curves. Sensitivity analysis was conducted using the E-value package. Additionally, survival analysis was performed, with length of stay serving as the time variable. Kaplan-Meier survival curves were generated for patients with and without pneumothorax.

Results

Patient characteristics and demographics

Of the 1,608,980 patients who tested positive for COVID-19 and were hospitalized in 2020, a cohort of 22,545 [95% confidence interval (CI): 21,491–23,598] (1.4%) developed a pneumothorax. Mean age of patients who developed pneumothorax was 64.5 years [standard deviation (SD): ±0.5 years]. Prevalence of pneumothorax increased with age. Prevalence in the 18–40 years of age group was 5.7%, 39.7% in the 41–64 years group, and highest at 52.1% in the age group >65 years. Of the COVID-19 patients in the pneumothorax cohort, 34% were females, and 66% were males. The type of insurance used included Medicare (49.8%), private insurance (27.2%), Medicaid (13.9%), self-pay (4%), and others (4.6%). Caucasians comprised 43.9% of the cohort, Hispanics 31.8%, African-Americans 12.9%, Native Americans 1.5%, and other origins 6.1%. Within the cohort, 36.6% were reported in the 0–25th percentile of the zip code income bracket, 26.9% in the 26th–50th percentile, 21.3% in the 51st–75th percentile, and 14.9% in the 76th–100th percentile. Patients were admitted to large-bed (50.8%), medium-bed (30%), and small-bed capacity hospitals (19%). Patients with pneumothorax were hospitalized in urban teaching hospitals (77.5%), in urban non-teaching hospitals (17.2%), and in rural hospitals (5.1%).

Geographically, 43.7% of the patients were hospitalized in the South, 20.1% in the West, 18% in the Midwest, and 18% in the Northeast. Non-profit private hospitals admitted 69.7% of the patients with pneumothorax, private hospitals 18.6%, and government hospitals 11.5% (*Table 1*).

Total hospitalization charges of pneumothorax patients were significantly higher than those of patients without pneumothorax. Average hospitalization cost of a patient with pneumothorax was $437,692 (95% CI: 415,842–459,542), compared to $87,081 (95% CI: 84,858–89,304) for a patient with no pneumothorax (*Table 2*).

Mortality was significantly higher in patients with pneumothorax at 68.7% compared to 13% in patients without pneumothorax (*Table 2*).

Risk factors and mortality associated with pneumothorax

Multivariate analysis indicated females were less likely to develop pneumothorax [adjusted odds ratio (aOR): 0.68, 95% CI: 0.63–0.73, P<0.001]. Age was a significant risk factor for the development of pneumothorax: highest in patients in the 41–64-year age group (aOR: 2.45, 95% CI: 2.15–2.79, P<0.001) followed by age group ≥65 years (aOR: 2.29, 95% CI: 2.01–2.60, P<0.001). Compared to private insurance, the odds of getting pneumothorax were lower

Table 1 Socioeconomic risk factors for pneumothorax in COVID-19 stratified into two groups: patients without pneumothorax and patients with pneumothorax

Socioeconomic risk factors	No pneumothorax, proportion % (95% CI)[†]	Pneumothorax, proportion % (95% CI)[†]	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
Age (in years)	63.2 (63–63.4)	64.5 (64.1–64.9)	1.00 (1.00–1.00)	<0.001*	1.00 (1.00–1.00)	<0.001*
Age categories (years)						
18–40	12.6 (12.3–12.8)	5.7 (5–6.4)	Reference	Ref		
41–64	35.6 (35.3–35.9)	39.7 (38.3–41.2)	2.45 (2.15–2.79)	<0.001*	NA	NA
≥65	49.8 (49.4–50.3)	52.1 (50.6–53.6)	2.29 (2.01–2.60)	<0.001*	NA	NA
Female sex	48.3 (48.1–48.6)	34 (32.6–35.5)	0.55 (0.51–0.58)	<0.001*	0.68 (0.63–0.73)	<0.001*
Insurance status						
Medicare	50.7 (50.2–51.3)	49.8 (48.2–51.4)	0.94 (0.88–1.01)	0.14	0.83 (0.76–0.91)	<0.001*
Medicaid	14.4 (14–14.9)	13.9 (12.8–15.2)	0.93 (0.84–1.03)	0.18	0.86 (0.77–0.96)	<0.001*
Private insurance	26.2 (25.7–26.7)	27.2 (25.7–28.7)	Reference	Ref	Reference	Ref
Self-pay	3.7 (3.5–4)	4 (3.3–4.7)	1.02 (0.86–1.21)	0.75	0.92 (0.77–1.10)	0.41
No charge	0.2 (0.1–0.3)	0.2 (0.1–0.6)	1.01 (0.56–1.83)	0.95	1.02 (0.57–1.81)	0.93
Other	4.3 (4.1–4.6)	4.6 (3.9–5.4)	1.02 (0.87–1.18)	0.78	0.85 (0.72–1.00)	0.05
Race						
Caucasians	50.9 (49.8–52)	43.9 (41.9–46)	Reference	Ref	Reference	Ref
African Americans	19.1 (18.4–20)	12.9 (11.7–14.2)	0.78 (0.70–0.86)	<0.001*	0.64 (0.58–0.72)	<0.001*
Hispanics	21.3 (20.4–22.4)	31.8 (29.8–33.9)	1.72 (1.59–1.86)	<0.001*	1.40 (1.28–1.53)	<0.001*
Asian or Pacific Islander	3.2 (3–3.4)	3.6 (3–4.2)	1.29 (1.09–1.52)	<0.001*	1.04 (0.87–1.24)	0.65
Native American	0.9 (0.8–1.1)	1.5 (1.1–2.1)	1.78 (1.36–2.34)	<0.001*	1.63 (1.25–2.13)	<0.001*
Others	4.2 (3.9–4.6)	6.1 (5.2–7)	1.66 (1.46–1.88)	<0.001*	1.36 (1.19–1.55)	<0.001*
Zip income quartile						
0–25th percentile	33.9 (32.8–35.1)	36.6 (34.7–38.6)	Reference	Ref	Reference	Ref
26th to 50th percentile	27.1 (26.3–27.8)	26.9 (25.3–28.6)	0.92 (0.85–1.00)	0.05	0.95 (0.87–1.04)	0.35
51st to 75th percentile	22.2 (21.5–22.9)	21.3 (20–22.8)	0.89 (0.81–0.96)	<0.001*	0.87 (0.80–0.96)	<0.001*
76th to 100th percentile	16.6 (15.7–17.5)	14.9 (13.5–16.5)	0.83 (0.75–0.92)	<0.001*	0.87 (0.78–0.97)	0.01*
Hospital bed size						
Small	23.8 (22.8–24.9)	19 (17.4–20.8)	Reference	Ref	Reference	Reference
Medium	29 (28–30)	30 (28–32.2)	1.29 (1.17–1.43)	<0.001*	1.18 (1.07–1.31)	<0.001*
Large	47 (45.9–48.2)	50.8 (48.5–53.1)	1.35 (1.23–1.48)	<0.001*	1.26 (1.14–1.38)	<0.001*
Hospital type						
Rural	9.3 (8.8–9.8)	5.1 (4.4–6)	Reference	Ref	Reference	Ref
Urban non-teaching	18.6 (17.8–19.4)	17.2 (15.6–18.9)	1.66 (1.42–1.95)	<0.001*	1.28 (1.07–1.52)	<0.001*
Urban teaching	72 (71.1–72.9)	77.5 (75.6–79.3)	1.93 (1.68–2.22)	<0.001*	1.48 (1.27–1.73)	<0.001*

Table 1 (*continued*)

Table 1 (*continued*)

Socioeconomic risk factors	No pneumothorax, proportion % (95% CI)†	Pneumothorax, proportion % (95% CI)†	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
Hospital region						
Northeast	18.4 (17.4–19.4)	18 (16.1–20.1)	Reference	Ref	Reference	Ref
Midwest	22.2 (21.3–23.1)	18 (16.5–19.7)	0.82 (0.73–0.94)	<0.001*	1.05 (0.93–1.18)	0.41
South	41 (39.9–42.2)	43.7 (41.1–46)	1.08 (0.96–1.21)	0.17	1.38 (1.23–1.54)	<0.001*
West	18.2 (17.3–19.2)	20.1 (18.3–22)	1.12 (0.99–1.27)	0.07	1.00 (0.88–1.13)	0.94
Hospital control						
Government, non-federal	12 (11.3–12.7)	11.5 (10.1–13.1)	Reference	Ref	Reference	Ref
Private, not-profit	73.3 (72.4–74.3)	69.7 (67.6–71.8)	0.98 (0.87–1.11)	0.84	1.12 (0.99–1.26)	0.06
Private, invest-own	14.5 (13.8–15.3)	18.6 (16.9–20.5)	1.32 (1.15–1.52)	<0.001*	1.35 (1.18–1.56)	<0.001*

†, no pneumothorax =1,586,435 (95% CI: 1,548,916–1,623,954); pneumothorax =22,545 (95% CI: 21,491–23,598). *, statistically significant P value <0.05. COVID-19, coronavirus disease 2019; CI, confidence interval; OR, odds ratio; NA, not applicable.

Table 2 Comorbidity risk factors for pneumothorax and associated mortality

Comorbidity risk factors	No pneumothorax, proportion % (95% CI)	Pneumothorax, proportion % (95% CI)	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
Stroke	1.2 (1.2–1.3)	3.3 (2.8–3.9)	2.69 (2.28–3.10)	<0.001*	1.28 (1.04–1.58)	0.02*
Chronic kidney disease	20.7 (20.4–21)	18.5 (17.4–19.7)	0.87 (0.80–0.94)	<0.001*	0.76 (0.68–0.85)	<0.001*
Heart failure	16.4 (16.1–16.6)	15.7 (14.7–16.9)	0.95 (0.88–1.03)	0.26	NA	NA
Ischemic heart disease	18 (17.7–18.2)	15.3 (14.2–16.1)	0.82 (0.76–0.89)	<0.001*	0.81 (0.74–0.89)	<0.001*
Paralysis	0.6 (0.6–0.7)	1.2 (1–1.6)	1.93 (1.50–2.48)	<0.001*	0.95 (0.69–1.30)	0.66
HIV/AIDS	0.6 (0.5–0.6)	0.5 (0.3–0.8)	0.86 (0.57–1.29)	0.48	NA	NA
Uncomplicated diabetes mellitus	14.7 (14.5–14.9)	12.3 (11.3–13.4)	0.81 (0.74–0.89)	<0.001*	0.81 (0.73–0.90)	<0.001*
Complicated diabetes mellitus	26.3 (26–26.5)	31.3 (29.9–32.7)	1.27 (1.19–1.36)	<0.001*	0.96 (0.89–1.03)	0.31
Uncomplicated hypertension	38 (37.8–38.3)	37.1 (35.6–38.6)	0.96 (0.90–1.02)	0.20	0.92 (0.85–1.00)	0.05
Complicated hypertension	27.1 (26.8–27.4)	26.1 (24.8–27.5)	0.95 (0.88–1.01)	0.15	0.82 (0.73–0.92)	<0.001*
Solid cancer	2.7 (2.7–2.8)	2.7 (2.3–3.3)	1.00 (0.83–1.20)	0.94	NA	NA
Overweight and obesity	25.6 (25.2–26.1)	26 (24.6–27.5)	1.02 (0.95–1.09)	0.57	NA	NA
Malnutrition	15.3 (15–15.7)	33 (31.2–34.7)	2.70 (2.51–2.91)	<0.001*	1.52 (1.40–1.64)	<0.001*
Primary immunodeficiency	0.1 (0.1–0.1)	0.1 (0.08–0.3)	1.38 (0.69–2.74)	0.35	NA	NA

Table 2 (*continued*)

Table 2 (*continued*)

Comorbidity risk factors	No pneumothorax, proportion % (95% CI)	Pneumothorax, proportion % (95% CI)	Unadjusted		Adjusted	
			OR (95% CI)	P value	OR (95% CI)	P value
Nicotine abuse	6.4 (6.3–6.6)	4.3 (3.7–4.9)	0.64 (0.55–0.75)	<0.001*	0.75 (0.64–0.88)	<0.001*
Substance abuse	2.4 (2.3–2.4)	2 (1.6–2.4)	0.84 (0.68–1.04)	0.11	0.66 (0.53–0.83)	<0.001*
Tuberculosis	0.01 (0.01–0.02)	0.06 (0.02–0.2)	3.35 (1.05–10.6)	0.04*	2.28 (0.62–8.36)	0.21
Long term steroid or immunomodulators	13.1 (12.9–13.3)	13.6 (12.6–14.7)	1.04 (0.95–1.14)	0.33	NA	NA
Asthma	7.8 (7.7–8)	6.2 (5.5–6.9)	0.77 (0.69–0.87)	<0.001*	0.97 (0.85–1.10)	0.69
COPD	1.7 (1.7–1.8)	3.5 (3–4)	2 (1.70–2.34)	<0.001*	1.83 (1.52–2.20)	<0.001*
Cystic fibrosis	0.02 (0.01–0.02)	0.04 (0.01–0.1)	1.98 (0.49–7.97)	0.33	1.26 (0.33–4.79)	0.72
Obstructive sleep apnea	8.1 (7.9–8.3)	6.7 (6–7.5)	0.81 (0.72–0.92)	<0.001*	0.79 (0.69–0.90)	<0.001*
Bronchiectasis	0.3 (0.2–0.3)	1.1 (0.8–1.4)	3.57 (2.69–4.75)	<0.001*	2.04 (1.47–2.83)	<0.001*
Pneumoconiosis	0.06 (0.05–0.07)	0.1 (0.05–0.2)	2.04 (0.93–4.47)	0.07	1.08 (0.39–2.96)	0.87
Pulmonary fibrosis	0.6 (0.6–0.7)	2.3 (1.9–2.8)	3.53 (2.88–4.34)	<0.001*	1.84 (1.44–2.35)	<0.001*
Lung cancer	0.5 (0.4–0.5)	0.7 (0.5–1.1)	1.58 (1.13–2.22)	<0.001*	1.35 (0.92–1.99)	0.12
Primary pulmonary hypertension	0.01 (0.01–0.02)	0.06 (0.02–0.2)	3.98 (1.23–12.8)	0.02*	3.31 (0.78–14)	0.10
Secondary pulmonary hypertension	2.4 (2.3–2.5)	3.2 (2.7–3.8)	1.34 (1.13–1.58)	<0.001*	1.01 (0.84–1.22)	0.88
Liver disease	5.3 (5.2–5.4)	12.4 (11.4–13.5)	2.50 (2.27–2.76)	<0.001*	1.38 (1.24–1.54)	<0.001*
Rheumatoid arthritis or collagen vascular disease	2.9 (2.8–2.9)	3 (2.5–3.6)	1.05 (0.88–1.26)	0.54	NA	NA
HFNC/BIPAP/CPAP	5.9 (5.6–6.2)	19.6 (18.1–21.2)	3.86 (3.56–4.19)	<0.001*	1.82 (1.66–1.98)	<0.001*
Intubation	9.4 (9.2–9.6)	64 (62.1–65.7)	17 (15.7–18.3)	<0.001*	13.6 (12.5–14.7)	<0.001*
ECMO	0.1 (0.1–0.1)	3.2 (2.5–4)	21.9 (17.5–27.3)	<0.001*	7.24 (5.16–10.1)	<0.001*
Cardiac arrest	2.4 (2.3–2.5)	16.6 (15.5–17.9)	7.85 (7.21–8.54)	<0.001*	NA	NA
Death	13 (12.8–13.2)	68.7 (67.3–70.1)	14.65 (13.7–15.6)	<0.001*	NA	NA
Total charges (in dollars)	87,081 (84,858–89,304)	437,692 (415,842–459,542)		<0.001*	NA	NA
Elixhauser Comorbidity Index categories						
≤3	49.6 (49.2–50.1)	28.4 (27–30)	Reference	Ref	NA	NA
4–6	38.8 (38.4–39.1)	53.7 (52.2–55.2)	3.51 (3.41–3.60)	<0.001*	NA	NA
>6	11.5 (11.2–11.7)	17.7 (16.5–18.9)	7.60 (7.33–7.88)	<0.001*	NA	NA
Mean Elixhauser	3.6 (3.6–3.7)	4.6 (4.5–4.7)	1.19 (1.18–1.20)	<0.001*	NA	NA

*, statistically significant P value <0.05. CI, confidence interval; OR, odds ratio; HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; COPD, chronic obstructive pulmonary disease; HFNC, high flow nasal cannula; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation; NA, not applicable.

in patients with Medicare (aOR: 0.83, 95% CI: 0.76–0.91, P<0.001) and Medicaid (aOR: 0.86, 95% CI: 0.77–0.96, P<0.001). In comparison to Caucasian patients, African Americans were at a lower risk of having a pneumothorax (aOR: 0.64, 95% CI: 0.58–0.72, P<0.001), but Hispanics, Native Americans, and patients belonging to other races had a higher risk with the highest risk in Native Americans (aOR: 1.63, 95% CI: 1.25–2.13, P<0.001). Regarding median household income of the patient's zip code of residence, patients with the highest zip code quartile income had the lowest possibility of pneumothorax: 51st–75th percentile (aOR: 0.87, 95% CI: 0.80–0.96, P<0.001) and 76th–100th percentile (aOR: 0.87, 95% CI: 0.78–0.97, P=0.01) In contrast to small-bed hospitals the risks of getting pneumothorax were higher in medium-bed hospitals (aOR: 1.18, 95% CI: 1.07–1.31, P<0.001) and highest in large-bed hospitals (aOR: 1.26, 95% CI: 1.14–1.38, P<0.001). The odds of pneumothorax were higher in urban non-teaching (aOR: 1.28, 95% CI: 1.07–1.52, P<0.001) and urban teaching hospitals (aOR: 1.48, 95% CI: 1.27–1.73, P<0.001) than in rural hospitals. Southern hospitals' patients had higher odds of pneumothorax (aOR: 1.38, 95% CI: 1.23–1.54, P<0.001) than hospitals in the Northwest. Compared to government non-federal hospitals, a higher likelihood of pneumothorax was seen in private invest-own hospitals (aOR: 1.35, 95% CI: 1.18–1.56, P<0.001) (*Table 1*).

Patients with a history of stroke (aOR: 1.28, 95% CI: 1.04–1.58, P=0.02), malnutrition (aOR: 1.52, 95% CI: 1.40–1.64, P<0.001), chronic obstructive pulmonary disease (COPD) (aOR: 1.83, 95% CI: 1.52–2.20, P<0.001), bronchiectasis (aOR: 2.04, 95% CI: 1.47–2.83, P<0.001), pulmonary fibrosis (aOR: 1.84, 95% CI: 1.44–2.35, P<0.001), liver disease (aOR: 1.38, 95% CI: 1.24–1.54, P<0.001), and positive pressure ventilation, including high flow nasal cannula (HFNC), bilevel positive airway pressure (BiPAP) and continuous positive airway pressure (CPAP) (aOR: 1.82, 95% CI: 1.66–1.98, P<0.001) were more likely to develop pneumothorax. Further, the odds were extremely high in intubated (aOR: 13.6, 95% CI: 12.5–14.7, P<0.001) and extracorporeal membrane oxygenation (ECMO) patients (aOR: 7.24, 95% CI: 5.16–10.1, P<0.001) (*Table 2*).

Interestingly, the likelihood of developing pneumothorax was low in nicotine abuse (aOR: 0.75, 95% CI: 0.64–0.88, P<0.001), substance abuse (aOR: 0.66, 95% CI: 0.53–0.83, P<0.001), and obstructive sleep apnea (OSA) [aOR: 0.79, 95% CI: 0.69–0.90, P<0.001] (*Table 2*).

In patients with pneumothorax, the risks of having a cardiac arrest were very high (aOR: 7.85, 95% CI: 7.21–8.54, P<0.001), and the odds of mortality due to any cause were extremely high (aOR: 14.65, 95% CI: 13.7–15.6, P<0.001) (*Table 2*).

Patients with a higher Elixhauser comorbidities score had higher risks of developing pneumothorax, with the highest risk when the Elixhauser comorbidities score was >6 (aOR: 7.60, 95% CI: 7.33–7.88, P<0.001). Patients with a pneumothorax had a higher probability of having higher mean Elixhauser comorbidities scores than patients without pneumothorax (aOR: 1.19, 95% CI: 1.18–1.20, P<0.001) (*Table 2*).

The prevalence of pneumothorax showed an upward trend with increasing severity of COVID-19. Among patients with asymptomatic COVID-19, the prevalence was 0.3%, while in those with lower respiratory tract infection without pneumonia, it was 0.8%. In COVID-19 pneumonia cases, the prevalence was 1.7%, and in patients with COVID-19 acute respiratory distress syndrome (ARDS), it significantly increased to 9% (Table S2).

Likewise, mortality rates attributed to pneumothorax also increased with severity. In patients with asymptomatic COVID-19, the mortality rate was 38%, while it 54% in those with lower respiratory tract infection without pneumonia. Among COVID-19 pneumonia cases, the mortality rate increased to 70%, and in patients with COVID-19 ARDS, it reached 76% (Table S2).

The odds of mortality in COVID-19 patients who developed pneumothorax were higher (aOR: 5.51, 95% CI: 4.87–6.23, P<0.001) (Table S3).

Comparison with influenza

Influenza pneumonia was seen more frequently in female patients and in patients of minority races and ethnicities. Compared to COVID-19 patients, certain comorbidities were more frequently observed in influenza patients, such as chronic kidney disease (CKD), smoking, and malnutrition. Conversely, comorbidities such as uncontrolled diabetes mellitus (DM) and complications such as vasopressor therapy, cardiac arrest, and overall mortality were higher in COVID-19 patients. Of 184,980 influenza patients, 1,630 (95% CI: 1,448–1,811) (0.88%) developed pneumothorax as compared to 1.4% of COVID-19 patients. After adjusting for confounding variables, COVID-19 pneumonia had higher odds of pneumothorax than influenza pneumonia (aOR: 2.07, 95% CI: 1.73–2.49. On sensitivity analysis, this yielded an E-value (point estimate 3.55, CI 2.85) (*Tables 3,4*).

Kaplan-Meier survival estimates showed a clear

Table 3 Comparison between socioeconomic and comorbidity factors in COVID-19 and influenza pneumonia

Risk factors	COVID-19 pneumonia, proportion % (95% CI)	Influenza pneumonia, proportion % (95% CI)	Odds ratio (influenza pneumonia as reference) (95% CI)	P value
Age (in years)	64.4 (64.2–64.6)	64.2 (63–65.4)	0.99 (0.99–0.99)	<0.001*
Female sex	45.5 (45.2–45.8)	52.8 (52.1–53.5)	0.74 (0.72–0.77)	<0.001*
Race				
Caucasians	49.7 (48.5–50.9)	67.6 (66.4–68.9)	Ref	Ref
African Americans	18.6 (17.8–19.5)	14.6 (13.8–15.4)	1.73 (1.58–1.90)	<0.001*
Hispanics	22.5 (21.3–23.6)	10.9 (10–11.8)	2.80 (2.48–3.16)	<0.001*
Asian/Pacific Islander	3.5 (3.2–3.7)	2.8 (2.5–3.2)	1.66 (1.40–1.96)	<0.01*
Native American	1 (0.8–1.2)	0.9 (0.7–1.2)	1.47 (1.08–2.00)	<0.001*
Others	4.4 (4–4.8)	2.8 (2.4–3.3)	2.1 (1.75–2.53)	<0.001*
Chronic kidney disease	20.9 (20.6–21.2)	22.4 (21.7–23)	0.91 (0.87–0.95)	<0.001*
Nicotine dependence	5.3 (5.2–5.5)	21.8 (21.1–22.4)	0.20 (0.19–0.21)	<0.001*
Malnutrition	15.9 (15.5–16.2)	18 (17.4–18.6)	0.86 (0.81–0.90)	<0.001*
Vasopressor need	3.1 (2.9–3.4)	2.1 (1.9–2.4)	1.46 (1.25–1.71)	<0.001*
Intubation	12.6 (12.3–12.9)	10 (9.6–10.5)	1.29 (1.22–1.36)	<0.001*
Acute liver failure	1.5 (1.4–1.5)	1.7 (1.5–1.9)	0.87 (0.77–0.98)	0.02*
HFNC/BIPAP/CPAP	7.7 (7.4–8.1)	9.6 (9.1–10.2)	0.78 (0.72–0.85)	<0.001*
Cardiac arrest	3.2 (3–3.3)	1.4 (1.2–1.6)	2.29 (2.01–2.62)	<0.001*
Urinary ultrafiltration	5.5 (5.4–5.7)	5 (4.7–5.4)	1.10 (1.02–1.19)	0.01*
Heart failure	17.7 (17.4–17.9)	30.3 (29.6–31)	0.49 (0.47–0.51)	<0.001*
Paralysis	1.1 (1–1.1)	1.2 (1.1–1.4)	0.87 (0.76–1.00)	0.058
Other neurological disorders	17.3 (17–17.6)	16.5 (16–17.1)	1.05 (1.00–1.10)	0.02*
Metastatic cancer	0.9 (0.8–0.9)	1.8 (1.7–2)	0.47 (0.42–0.53)	<0.001*
Solid tumor without metastasis	2.1 (2.1–2.2)	3.6 (3.3–3.9)	0.58 (0.53–0.63)	<0.001*
Severe sepsis	5.5 (5.2–5.8)	8.9 (8.3–9.4)	0.60 (0.55–0.65)	<0.001*
Septic shock	8.8 (8.6–9)	8.8 (8.4–9.2)	1.00 (0.94–1.06)	0.93
Uncontrolled diabetes mellitus	28.2 (27.9–28.5)	21.4 (20.8–22)	1.44 (1.38–1.50)	<0.001*
Acute myocardial infarction	1.9 (1.8–2)	2.6 (2.4–2.9)	0.71 (0.64–0.78)	<0.001*
Obesity	29 (28.5–29.5)	19.3 (18.7–19.9)	1.70 (1.63–1.78)	<0.001*
COPD	1.9 (1.8–2)	2.8 (2.6–3.1)	0.66 (0.60–0.73)	<0.001*
Bronchiectasis	0.3 (0.3–0.4)	1.3 (1.1–1.4)	0.27 (0.24–0.32)	<0.001*
Pulmonary fibrosis	0.8 (0.7–0.8)	1.5 (1.3–1.7)	0.52 (0.46–0.59)	<0.001*
Liver disease	5.4 (5.2–5.5)	5.8 (5.4–6.1)	0.92 (0.86–0.99)	0.042*
ECMO	2.4 (2–2.9)	0.5 (0.4–0.6)	0.45 (0.33–0.62)	<0.001*
Elixhauser-comorbidity index score	3.8 (3.7–3.8)	4.2 (4.2–4.3)	0.90 (0.89–0.91)	<0.001*

Table 3 (*continued*)

Table 3 (*continued*)

Risk factors	COVID-19 pneumonia, proportion % (95% CI)	Influenza pneumonia, proportion % (95% CI)	Odds ratio (influenza pneumonia as reference) (95% CI)	P value
Mean length of stay (in days)	8.8 (8.7–8.9)	6.9 (6.7–7.1)	1.03 (1.02–1.03)	<0.001*
Composite complications	25 (24.6–25.4)	26.6 (25.9–27.4)	0.91 (0.88–0.96)	<0.001*
Mortality rate	16.6 (16.3–16.9)	5.4 (5.1–5.8)	3.45 (3.23–3.7)	<0.001*

*, statistically significant P value <0.05. COVID-19, coronavirus disease 2019; CI, confidence interval; HFNC, high flow nasal cannula; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation.

Table 4 Comparison of risk of pneumothorax between COVID-19 and influenza pneumonia

Risk factors	Adjusted	
	OR (95% CI)	P value
COVID-19 pneumonia (influenza pneumonia as reference)	2.07 (1.73–2.49)	<0.001*
Age (continuous)	1.00 (1.00–1.00)	<0.001*
Female sex	0.73 (0.68–0.78)	<0.001*
Race		
Caucasians	Reference	Ref
African Americans	0.62 (0.56–0.69)	<0.001*
Hispanics	1.37 (1.25–1.50)	<0.001*
Asian or Pacific Islander	1.06 (0.89–1.27)	0.47
Native American	1.54 (1.19–2.00)	0.001*
Others	1.39 (1.22–1.59)	<0.001*
Insurance status		
Private insurance	Reference	Ref
Medicare	0.83 (0.76–0.91)	<0.001*
Medicaid	0.89 (0.79–1.00)	0.053
Self-pay	0.94 (0.78–1.13)	0.53
No charge	0.98 (0.53–1.81)	0.96
Other	0.81 (0.68–0.95)	0.01*
Zip income quartile		
0–25th percentile	Reference	Ref
26th to 50th percentile	0.93 (0.85–1.02)	0.15
51st to 75th percentile	0.85 (0.77–0.93)	0.001*
76th to 100th percentile	0.82 (0.73–0.92)	0.001*
Hospital bed size		
Small	Reference	Ref
Medium	1.20 (1.08–1.33)	<0.001*
Large	1.24 (1.12–1.36)	<0.001*
Hospital type		
Rural	Reference	Ref
Urban non-teaching	1.36 (1.14–1.63)	0.001*
Urban teaching	1.57 (1.34–1.85)	<0.001*
Hospital region		
Northeast	Reference	Ref
Midwest	1.03 (0.90–1.16)	0.63
South	1.41 (1.26–1.58)	<0.001*
West	1.01 (0.89–1.15)	0.80
Stroke	1.37 (1.13–1.65)	0.001*
Chronic kidney disease	0.69 (0.63–0.75)	<0.001*
Malnutrition	1.57 (1.45–1.71)	<0.001*
Nicotine use	0.74 (0.63–0.87)	<0.001*
COPD	1.62 (1.34–1.95)	<0.001*
Bronchiectasis	2.28 (1.67–3.1)	<0.001*
Pulmonary fibrosis	1.82 (1.43–2.30)	<0.001*
Chronic liver disease	1.37 (1.23–1.53)	<0.001*
HFNC/BIPAP/CPAP	1.68 (1.54–1.84)	<0.001*
Intubation	11.6 (10.6–12.7)	<0.001*
ECMO	7.42 (5.46–10.1)	<0.001*

Table 4 (*continued*)

Table 4 (*continued*)

*, statistically significant P value <0.05. COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HFNC, high flow nasal cannula; BIPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; ECMO, extracorporeal membrane oxygenation.

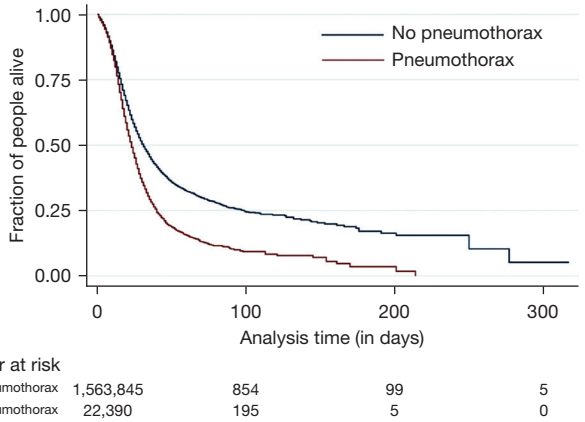

Figure 1 Kaplan-Meier survival estimates: the probability of survival was lower in patients who developed a pneumothorax. P value <0.001.

demarcation in mortality trajectories among COVID-19 patients with and without pneumothorax, especially during prolonged stays (*Figure 1*).

A trend of prevalence and mortality of COVID-19-induced pneumothorax was observed in 2020. Pneumothorax prevalence decreased from March to December 2020. However, the mortality rate remained consistent during the same period (Figures S1,S2).

Discussion

This nationwide study is one of the largest on the epidemiology of pneumothorax in COVID-19 patients. No existing literature compares pneumothorax in COVID-19 and influenza cases. Key findings were (I) the prevalence of pneumothorax in COVID-19 patients was 1.4%; (II) male sex and the elderly population with COVID-19 infection, and patients with stroke, malnutrition, COPD, pulmonary fibrosis, bronchiectasis, liver disease, or requiring non-invasive, IMV and ECMO were more likely to develop pneumothorax; (III) risk of pneumothorax was higher for COVID-19 patients than for those with influenza. Pneumothorax was associated with an increased risk of cardiac arrest and all-cause mortality. Although supporting several findings of earlier smaller studies, this study has highlighted some significant differences.

The prevalence of pneumothorax in this study (1.4%) was similar to a previous study by Malik *et al.* of 811,065 patients in which the incidence was 1.84% in COVID-19 hospitalized patients (11). Some previous large-scale studies observed a lower incidence. In a systematic review by Chong and colleagues, the overall incidence of pneumothorax in hospitalized COVID-19 patients was 0.3% (7). In a multi-center case-control study in Spain by Miró *et al.* of 71,904 COVID-19 patients initially assessed in the emergency department (ED), the incidence of pneumothorax was 0.06% (12). In a multi-center retrospective cohort study of 3,948 COVID-19 patients in US veteran affairs (VA) hospitals by Cates *et al.*, the incidence of pneumothorax was 0.6% (13). However, these studies do not describe the severity of the illness and the need for IMV or non-IMV (NIMV). In this study, pneumothorax is seen in a sicker patient population, and the previous studies may have included patients who were less critically ill. One retrospective study by McGuinness *et al.* assessed patients on mechanical ventilation, 9% of whom developed pneumothorax (14). Several early studies have reported an incidence of pneumothorax similar to this study (1–2%). However, the sample size of those studies was smaller (3,4,15).

In this study, 66% of the patients who developed pneumothorax were males, which is consistent with the majority of studies in the literature (66–100%) (2,6,11-14,16). Possible causes include male anthropometric characteristics and the mechanical properties of the lungs in males (17,18). Studies have observed a risk of pneumothorax increasing with age, perhaps from underlying lung conditions like emphysema, interstitial lung disease (ILD)/pulmonary fibrosis, etc. Advancing age is a well-known risk factor for severe COVID-19, which is, in turn, linked to pneumothorax. Odds of pneumothorax were highest in patients aged 41–64 years, similar to the results in the studies by Malik *et al.* and Chong *et al.* (7,11). Native Americans, Hispanics, and patients of other origins had higher odds of pneumothorax, with the highest odds in Native Americans (63% higher than Caucasians). The odds of pneumothorax were lower for African Americans (36% lower than Caucasians). The exact reason for this is unclear, but the data may be confounded by differences in socioeconomic status and access to health care (19). These racial differences could also be due to the severity of COVID-19 in non-white races (20,21).

Large and urban hospitals demonstrated a higher likelihood of pneumothorax, presumably because they are referral centers for other hospitals and care for the sickest patients. Why hospitals in the South had a high prevalence of pneumothorax remains undetermined. The southern region also had a high number of COVID-19

patients. Racial and ethnic inequities in the region might have led to delays in access to health care. The association between higher-income zip codes and better outcomes highlights socioeconomic healthcare impacts in the US (20,21). Ironically, it is unclear why Medicare or Medicaid patients had lower odds of pneumothorax than private insurance. One potential reason is that Medicare and Medicaid place a strong emphasis on preventive care, facilitating the identification and management of underlying health conditions that could contribute to the risk of pneumothorax.

Literature on COVID-19 pneumothorax and stroke is sparse. Patients with stroke are at greater risk of developing pneumothorax. Smoking and physical inactivity are well-documented common risk factors for pneumothorax and stroke (22). Chronic liver disease was the single most predictive risk factor for severe COVID-19, according to the Centers for Disease Control and Prevention (CDC). Potential causes include coagulopathy and immune dysregulation in liver disease (23). The increased severity of COVID-19 in these patients may have increased the likelihood of pneumothorax. Malnutrition was associated with a higher risk of pneumothorax, which may result from poor healing which can produce prolonged air leakage in the pleural cavity (24,25). Pre-existing lung conditions can also be risk factors for pneumothorax. Chong *et al.* reported that 66.7% (6/9) of observational studies described the presence of pre-existing lung diseases such as asthma, bronchiectasis, COPD, and ILD among COVID-19 patients with pneumothorax (7). Our study confirmed an increased risk of pneumothorax in COPD, bronchiectasis, and pulmonary fibrosis patients. However, the data did not indicate an association between COVID-19 patients with pneumothorax and asthma, tuberculosis, cystic fibrosis, pneumoconiosis, primary and secondary pulmonary hypertension, or lung cancer. Mechanical and positive pressure ventilation increases the risk of pneumothorax due to increased barotrauma (26). Our study demonstrated this increased risk, as have previous study in which the risk of pneumothorax was significantly high in critically ill patients (27).

CKD, ischemic heart disease, uncomplicated DM, complicated hypertension, and substance abuse were associated with a lower risk of pneumothorax. Tobacco smoking is a major risk factor for pneumothorax (28). However, in our study, nicotine abuse was associated with lower odds of pneumothorax. The reason for this is unclear. Smokers may belong to a younger age group, which had a better outcome. OSA can increase the risk of pneumothorax, especially in patients on CPAP (29-31). However, in our study, OSA patients had a lower risk of pneumothorax. Although the exact cause is unclear, the NIS 2020 database does not differentiate patients with OSA on CPAP therapy and their compliance.

Influenza-related ARDS can cause diffuse alveolar damage and sub-pleural and intrapulmonary air cysts (32). However, no studies compare the risk and prevalence of pneumothorax in COVID-19 and influenza patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and influenza viruses share high infectivity, incidence, rapid onset, and mutability, along with similar signs, symptoms, and hematological parameters. While their chest computed tomography (CT) findings may overlap, they also exhibit distinct characteristics (33). In this study, the risk of pneumothorax was higher in patients with COVID-19 than in influenza patients. A higher degree of inflammation and changes in lung dynamics in COVID-19 could predispose the patients to develop a pneumothorax. The higher prevalence of pneumothorax in COVID-19 in 2020 could reflect fewer flu illnesses requiring hospitalization in that year.

Limitations

This study has several limitations. NIS is an administrative database. It relies on ICD-10 codes, which are inferior to manual chart review. It is an inpatient database and does not track patients post-discharge. If a patient was discharged alive but died at home or in a rehabilitation facility, that data will not be captured. NIS data lack laboratory investigations, imaging studies, and treatment; therefore cannot record the severity of illness during pneumothorax. Data on intensive care unit (ICU) admission, invasive and non-invasive ventilator settings, and duration of pneumothorax are not collected. Since no patients in the pneumothorax group had a lung transplant, an association could not be established. Implementation of ventilation techniques to mitigate barotrauma may have reduced the prevalence of pneumothorax over time. It is plausible that in the subsequent years, various COVID-19 variants, which are recognized for their impact on the disease's severity, may have also contributed to the incidence of pneumothorax. Unfortunately, NIS provides data through the year 2020. Although the prevalence of pneumothorax may have decreased, the risk factors remain unchanged. Lastly, this observational study cannot establish causality

between COVID-19 and pneumothorax. Some cases of pneumothorax might be coincidental with COVID-19 due to invasive or non-invasive ventilation or ECMO for ARDS due to COVID-19, but this is unlikely in this study due to the simultaneous presentation of COVID-19 and pneumothorax.

Conclusions

Pneumothorax, a rare complication of COVID-19, is a grave prognostic marker associated with a high mortality risk (14). Risk factors for the development of pneumothorax in COVID-19 include advancing age, male sex, stroke, liver disease, malnutrition, certain lung conditions, and additional comorbidities. Since the risk of pneumothorax was higher in COVID-19 than in influenza pneumonia, patients with COVID-19 and with the above-mentioned risk factors should be prioritized in applying strategies to prevent pneumothorax. COVID-19 patients, particularly those on mechanical ventilation, require close monitoring for potential pneumothorax development. Timely recognition and intervention can lower mortality rates in COVID-19 patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1454/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was exempt from institutional review board approval as the NIS 2020 database is comprised of previously collected, de-identified data.

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