Original Article

Incidence, predictors and outcomes associated with acute pulmonary embolism in patients hospitalized with pneumonia: Insights from the National Inpatient Sample

CS Kwok, AI Qureshi, Y Lin, F Liu, E Holroyd, GYH Lip, A Bradaric & JA Borovac

Abstract

Background: The prevalence of acute pulmonary embolism (PE) among patients hospitalized with pneumonia and its association with adverse outcomes remain uncertain.

Methods: Data from the US National Inpatient Sample between 2016 to 2020 was used to determine the proportion of patients with chief diagnosis of pneumonia that had concomitant PE and to examine the relationship between PE and in-hospital outcomes such as mortality, mechanical ventilation, thrombolysis, length of stay (LoS), and inpatient costs.

Results: A total of 13,956,485 patients with a diagnosis of pneumonia were included and 2.6% had a concomitant diagnosis of PE. The median LoS for patients with PE was 7 days, compared to 5 days for those without PE. The median hospitalization cost was higher for patients with a diagnosis of PE compared to those without PE ($16,917 vs. $10,656). The strongest factors associated with a diagnosis of PE were other venous thromboembolism (Odds Ratio (OR) 11.65, 95%CI 11.42-11.88, p<0.001), arterial thrombosis (OR 2.64, 95%CI 2.40-2.89, p<0.001), previous venous thromboembolism (OR 1.72, 95%CI 1.68-1.77, p<0.001), cardiac arrest (OR 1.69, 95%CI 1.62-1.77, p<0.001) and cancer (OR 1.45, 95%CI 1.42-1.48, p<0.001). Co-diagnosis of PE was associated with greater in-hospital mortality (OR 1.50, 95%CI 1.46-1.54), mechanical ventilation (OR 1.12, 95%CI 1.10-1.15), thrombolysis use (OR 6.69, 95%CI 6.31-7.09), and major bleeding (OR 1.48, 95%CI 1.39-1.57).

Conclusions: A diagnosis of PE occurs in 2.6% of patients hospitalized with a principal diagnosis of pneumonia. Having concomitant PE was associated with greater risks of in-hospital mortality, increased use of mechanical ventilation and thrombolysis, extended hospital stay, and higher inpatient costs.

Keywords

pneumonia; pulmonary embolism; mortality; cost; length of stay

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Introduction

Pneumonia is a common acute respiratory infection that affects the alveoli and distal airways.[1] It is an important cause of admissions to hospitals as there were estimated to be more than 20 million pneumonia-associated hospitalizations in the United States between 2001 and 2014.[2] In addition, patients with pneumonia are at greater risk of mortality compared to the general population as the 30-day mortality was 18.5% in an analysis of a general population-based cohort in the United Kingdom which also reported a 4.6-fold increase in mortality for pneumonia cases compared to the general population.[3] It has been suggested that in patients with pneumonia there is an elevated risk of cardiovascular mortality which may be due to an associated risk of thrombosis-related vascular disease.[4]

A systematic approach to pulmonary embolism (PE) diagnosis in patients with pneumonia should be implemented in clinical practice. Since tachypnoea and hypoxia are hallmarks of both conditions, perhaps chest X-ray would be the reasonable first-line investigation to determine pulmonary infiltrates, followed by B-type natriuretic peptide (NT-pro BNP) testing and scrutinized analysis of electrocardiogram that might further prompt bedside echocardiography for the signs of right heart strain. This would ultimately lead to computed tomography pulmonary angiogram (CTPA) testing which is mandatory for the definitive confirmation of PE, however, streamlined decision to CTPA could be made if a clinical suspicion of PE is high, based on patient' history and leading signs and symptoms. This is important from a clinical perspective since

Supplementary Table 1. Codes for data analysis and their sources

Variable	Source	ICD-10 code
Viral pneumonia	I10_DX1/40	J09, J10, J11, J12
Bacterial pneumonia	I10_DX1/40	J13, J14, J15
Other pneumonia	I10_DX1/40	J16, J17, J18
Any pneumonia	I10_DX1/40	J09-J18
Pulmonary embolism	I10_DX1/40	I26*
Mechanical ventilation	I10_DX1/40 I10_PR1/25	Z99.11 5A1935Z, 5A1945Z, 5A1955Z
Previous stroke	I10_DX1/40	Z86.73, I69*
Previous myocardial infarction	I10_DX1/40	I25.2
Hypertension	I10_DX1/40	I10*, I11*, I12*, I13*, I15*, I16*
Hyperlipidemia	I10_DX1/40	E78.0*, E78.1, E78.2, E78.3, E78.4*, E78.5
Diabetes mellitus	I10_DX1/40	E08*, E09*, E10*, E11*, E13*
Anemia	I10_DX1/40	D64.9
Any cancer	I10_DX1/40	C00*-C96*
Liver diseases	I10_DX1/40	K70-K77
Pneumonia	I10_DX1/40	J12-J18
Atrial fibrillation or flutter	I10_DX1/40	I48*
Smoking (tobacco use)	I10_DX1/40	Z72.0
Alcohol misuse	I10_DX1/40	F10.1
Previous heart failure	I10_DX1/40	I50.22, I50.23, I50.32, I50.33, I50.42, I50.43, I50.812, I50.813
COVID-19	I10_DX1/40	U07.1
Chronic lung disease	I10_DX1/40	J40* – J47*
Chronic kidney disease	I10_DX1/40	N18*
Dementia	I10_DX1/40	F01*, F02*, F03*
Obesity	I10_DX1/40	E66.0, E66.1, E66.2, E66.8, E66.9
Other venous thrombosis	I10_DX1/40	I81*, I82*

timely diagnosis of PE among these patients would likely impact patient management and their outcomes.

The coexistence of PE and pneumonia is not uncommon diagnosis in the emergency care setting.[5] Moreover, pneumonia is one of the illnesses for which PE is most often mistaken because of the overlap in their clinical presentation.[6] A study of 794 patients with PE suggested that co-existing pneumonia occurred in 5% of patients and pneumonia was more common in those with fever and elevated C-reactive protein (CRP).[7] However, a retrospective study of patients with a diagnosis of PE and community-acquired pneumonia found that pulmonary infiltrates, high fever and high levels of CRP can deceive the physician to suspect pneumonia instead of PE.[8] A systematic review of the literature on misdiagnosis of PE found that respiratory infection including pneumonia was one of the most commonly diagnosed conditions instead of PE.[9] Nevertheless, there is a scarcity of studies and reports that looked at the incidence of PE in patients with pneumonia and its association with clinical outcomes.

The objective of this study was to determine the prevalence of PE diagnosis among inpatients with pneumonia and to examine which factors might be associated with a PE in the large nationwide cohort of patients from the United States. We further investigated the in-hospital mortality, need for mechanical ventilation and thrombolysis, bleeding events, length of stay, and inpatient cost associated with PE in patients with a principal diagnosis of pneumonia. Finally, we examined these clinical outcomes across different pneumonia subgroups such as those caused by viruses, bacteria, and other.

Methods

This manuscript was prepared in accordance with the recommendations of the STROBE guidelines.[10] The National Inpatient Sample (NIS) is a dataset which can be analyzed without the requirement of institutional review board approval.[11]

Previous venous thrombosis/embolism	I10_DX1/40	Z86.71
Arterial thrombosis	I10_DX1/40	I74*
Tachycardia	I10_DX1/40	I47*, R00.0
Hypotension	I10_DX1/40	I95*
Cardiac arrest	I10_DX1/40	I46.2, I46.8, I46.9
Thrombolysis	I10_PR1/25	3E03017, 3E03317, 3E04017, 3E05017, 3E05317, 3E06017, 3E06317, 3E07017, 3E07317, 3E08017, 3E08317, 3E04317
Anticoagulation	I10_DX1/40	Z79.01
Major bleeding	I10_DX1/40 I10_PR1/25	I60*, I61*, I62*, I69.0, I69.1, I69.2, K92.0, K92.1, K92.2, K25.0, K25.1, K25.2, K25.4, K25.5, K25.6, K26.0, K26.1, K26.2, K27.0, K27.1, K27.2, K27.4, K27.5, K27.6, K28.0, K28.1, K28.2, K28.4, K28.5, K28.6 30243N0, 30243N1, 30243P0, 30243P1, 30243H0, 30243H1, 30240N0, 30240N1, 30240P0, 30240P1, 30240H0, 30240H1, 30230H0, 30230N0, 30230N1, 30230P0, 30230P1, 30233N0, 30233N1, 30233P0, 30233P
Age	NIS Core	AGE
Female sex	NIS Core	FEMALE
Month of admission	NIS Core	AMONTH
Weekend admission	NIS Core	AWEEKEND
Discharge weight	NIS Core	DISCWT
Discharge disposition	NIS Core	DISPUNIFORM
Elective admission	NIS Core	ELECTIVE
Length of stay	NIS Core	LOS
Primary expected payer	NIS Core	PAY1
Race	NIS Core	RACE
Year	NIS Core	YEAR
Rural	NIS Core	PL_NCHS
ZIP income quartile	NIS Core	ZIPINC_QRTL
In-hospital mortality	NIS Core	DIED
Total charge	NIS Core	TOTCHG
Cost	-	Total charge x charge-to-cost ratio
Hospital bed size	NIS Hospital	HOSP_BEDSIZE

Study design, setting, and participants

We conducted a retrospective cohort study using data from the NIS from 2016 to 2020. The NIS is the largest publicly available all-payer inpatient healthcare databased designed to produced estimates of inpatient utilization, access, cost, quality and outcomes.[12] The NIS approximates a 20% stratified sample of all discharges from United States hospitals, excluding rehabilitation and long-term acute care hospitals. The sampling strategy has been designed to produce precise estimates that reduce the margin of error while protecting patient confidentiality. There are approximately 7 million hospital stays for each year which can be weighted to produce national estimates of hospitalizations. The NIS underwent a transition from International Classification of Disease 9th (ICD-9) to International Classification of Disease 10th revision (ICD-10) codes in 2015. In order to avoid any issues related to differences in coding for ICD-9 and ICD-10 we used the NIS dataset from 2016 to 2020.

We included hospital admissions with a diagnosis of pneumonia based on ICD-10 code of J09 to J18 in any diagnostic code and determined the proportion of patients with ICD-10 codes I26 as PE. Hospital admissions of patients with missing values for age, sex and discharge status were excluded as well as patients who were under the age of 18 years. The estimated admissions were multiplied by a factor of 5 in order to provide national estimates as there is 20% stratified sampling of all discharges from United States community hospitals in the NIS.

Variables and data sources

Data from the NIS were determined from diagnostic codes, procedure codes as well as variables from the NIS core and NIS hospital files. All variables used in the analysis are described in detail in **Supplementary Table 1.** Data were collected for age, sex, race, smoking, alcohol misuse, elective admission, weekend admission, season of admission, year of admission, rural status for hospital, hospital bed size, primary

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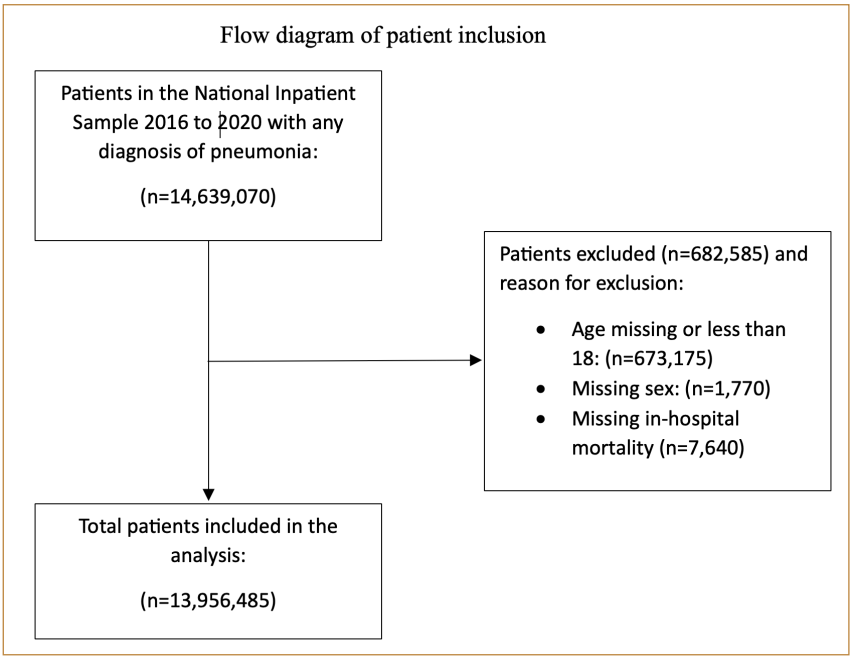

Figure 1. Flow diagram of patient inclusion for the analysis.

expected payer, income quartile based on ZIP code, obesity, hypertension, hyperlipidemia, diabetes mellitus, previous myocardial infarction, previous stroke, atrial fibrillation, previous heart failure, other non-PE venous thromboembolism, previous venous thromboembolism, arterial thrombosis, COVID-19 infection, chronic lung disease, chronic kidney disease, liver disease, anemia, cancer, dementia, tachycardia, hypotension, cardiac arrest, receipt of ventilation, receipt of anticoagulation, and receipt of thrombolysis. The outcomes were length of stay, major bleeding, in-hospital mortality and inpatient cost. Cost was defined by the total charge multiplied by the charge-to-cost ratio.

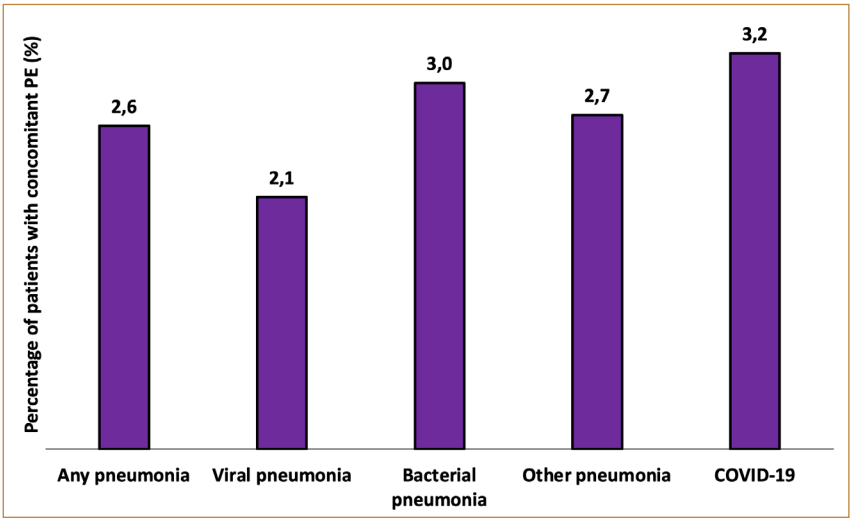

Figure 2. Proportion of patients (%) with concomitant diagnosis of acute pulmonary embolism stratified by the type of pneumonia.

Statistical analysis

Statistical analysis was performed on Stata 13.0 (College Station, TX, USA). The cohort was stratified by the presence or absence of PE and descriptive statistics were performed with median and interquartile range for continuous variables and percentage for categorical variables. The median test on Stata was used to determine if there were any statistical difference for categorical variables and the Chi^2 test was used to determine if there were any statistical differences for continuous variables. The proportion of patients with PE in the group with any pneumonia, viral pneumonia, bacterial pneumonia, other pneumonia and among patients with COVID-19 co-diagnosis with pneumonia was determined. The proportion of patients with in-hospital mortality, mechanical ventilation and thrombolysis according to PE and no PE was also determined. Multivariable logistic regression was used to determine the factors associated with PE with adjustments for all baseline non-COVID, non-treatment and non-outcome variables. Multiple logistic regressions were used to determine the independent odds of in-hospital mortality, mechanical ventilation, thrombolysis and major bleeding. Multiple linear regression was used to determine the association between PE and both length of stay and cost after adjustments for baseline variables. A sensitivity analysis was performed to determine the proportion of patients with PE and the association between PE and outcomes according to different subgroups of patients with viral pneumonia, bacterial pneumonia, other pneumonia, and co-existing diagnosis of COVID-19 for those admissions in 2020. In order to reduce the chance of type 1 error related to adjustments for multiple variables in the logistic and linear regressions, we applied the Bonferroni correction. As we adjusted for 33 variables, the p-value for statistical significance was 0.0015.

Results

A total of 13,956,485 patients with a principal pneumonia diagnosis were included in the final analysis (**Figure 1**). The proportion of patients with a diagnosis of PE according to type of pneumonia is shown in **Figure 2**. The overall rate of PE in any pneumonia diagnosis was 2.6% which was lowest in the group with viral pneumonia (2.1%) and greatest in the group with COVID-19 (3.2%) and bacterial pneumonia (3.0%).

Table 1 shows the baseline characteristics of the patients hospitalized with a diagnosi of pneumonia with and without PE. Patients with a diagnosis of PE were younger (median age 65 *vs.* 70 years, p<0.001) and were less proportionately female (46.6% *vs.* 50.0%, p<0.001). There were more patients with a diagnosis of PE who were black (17.7% *vs.* 14.1%)

Table 1. Characteristics and outcomes for patients with any pneumonia diagnosis stratified according to presence or absence of pulmonary embolism.

Variable	Patients with no PE (N=13,597,985)	Patients with PE (N=358,500)	Total population (N=13,956,485)	p-value
Median age [IQR]	70 [58 to 80]	65 [52 to 76]	70 [58 to 80]	<0.001
Female sex	50.0%	46.6%	49.9%	<0.001
Race				<0.001
White	70.0%	69.3%	69.9%	
Black	14.1%	17.7%	14.2%	
Hispanic	9.9%	8.0%	9.9%	
Asian or Pacific Islander	2.6%	1.7%	2.6%	
Native American	0.7%	0.6%	0.7%	
Other	2.8%	2.8%	2.8%	
Smoking	1.0%	1.0%	1.0%	0.32
Alcohol misuse	1.8%	1.9%	1.8%	0.30
Elective	5.3%	5.0%	5.3%	0.001
Weekend admission	25.5%	24.9%	25.5%	<0.001
Season of admission				<0.001
Spring	26.4%	24.7%	26.4%	
Summer	19.9%	23.0%	20.0%	
Fall	22.1%	25.2%	22.2%	
Winter	31.6%	27.2%	31.5%	
Year				<0.001
2016	17.8%	16.3%	17.8%	
2017	19.1%	17.0%	19.0%	
2018	19.5%	18.2%	19.5%	
2019	18.8%	18.2%	18.8%	
2020	24.8%	30.4%	25.0%	
Rural hospital	19.7%	19.1%	19.7%	<0.001
Hospital bed size				<0.001
Small	23.8%	20.0%	23.7%	
Medium	29.8%	29.0%	29.8%	
Large	46.4%	51.0%	46.5%	
Primary expected payer				<0.001
Medicare	65.3%	53.3%	65.0%	
Medicaid	12.2%	16.5%	12.4%	
Private insurance	16.7%	22.5%	16.9%	
Self-pay	3.0%	4.4%	3.1%	
No charge	0.2%	0.4%	0.3%	
Other	2.4%	2.9%	2.4%	
ZIP income quartile				0.021
1st-25th	33.2%	33.6%	33.2%	
26th-50th	27.4%	26.9%	27.4%	
51st-75th	22.4%	22.6%	22.4%	
76th-100th	17.0%	16.9%	17.0%	
Obesity	16.6%	17.6%	16.6%	<0.001
Hypertension	69.4%	58.8%	69.1%	<0.001
Hyperlipidemia	39.0%	30.6%	38.8%	<0.001
Diabetes mellitus	35.1%	25.3%	34.9%	<0.001
Previous myocardial infarction	6.6%	4.4%	6.6%	<0.001
Previous stroke	10.6%	7.3%	10.5%	<0.001
Atrial fibrillation	25.2%	19.7%	25.0%	<0.001
Previous heart failure	21.2%	16.0%	21.1%	<0.001

Other non-pulmonary embolus venous thromboembolism	2.6%	26.4%	3.2%	<0.001
Previous venous thromboembolism	5.7%	10.1%	5.9%	<0.001
Arterial thrombosis	0.2%	0.9%	0.2%	<0.001
Chronic lung disease	44.8%	35.3%	44.6%	<0.001
Chronic kidney disease	25.6%	16.2%	25.3%	<0.001
Liver disease	6.4%	7.8%	6.4%	<0.001
Anemia	12.4%	13.3%	12.4%	<0.001
Cancer	12.5%	22.3%	12.8%	<0.001
Dementia	11.2%	7.3%	11.1%	<0.001
COVID-19 infection	8.9%	10.9%	9.0%	<0.001
Tachycardia	7.4%	10.9%	7.5%	<0.001
Hypotension	6.9%	7.9%	6.9%	<0.001
Cardiac arrest	2.0%	4.1%	2.1%	<0.001
Mechanical ventilation	12.7%	20.3%	12.9%	<0.001
Anticoagulation	11.4%	14.3%	11.5%	<0.001
Thrombolysis	0.3%	3.0%	0.3%	<0.001
Median length of stay [IQR]	5 [3-9]	7 [4-14]	5 [3-9]	<0.001
Major bleeding	3.5%	5.8%	3.5%	<0.001
In-hospital mortality	7.9%	13.7%	8.0%	<0.001
Median cost [IQR]	$10,656 [6,300 to 20,227]	$16,917 [9,197 to 36,225]	$10,768 [6,348 to 20,540]	<0.001

and having private insurance (22.5% *vs.* 16.7%). There was a greater proportion of patients with other non-pulmonary venous thromboembolism (26.4% *vs.* 2.6%, p<0.001), previous venous thromboembolism (10.1% *vs.* 5.7%, p<0.001), and cancer (22.3% *vs.* 12.5%, p<0.001) among those with a diagnosis of PE. There was a lower proportion of patients with comorbidities such as arterial hypertension (58.8% *vs.* 69.4%, p<0.001), hyperlipidemia (30.6% *vs.* 39.0%, p<0.001), diabetes mellitus (25.3% *vs.* 35.1%, p<0.001), atrial fibrillation (19.7% *vs.* 25.2%, p<0.001), previous heart failure (16.0% *vs.* 21.2%, p<0.001), chronic lung disease (35.3% *vs.* 44.8%, p<0.001) and chronic kidney disease (16.2% *vs.* 25.6%, p<0.001) in the group with PE. COVID-19 disease was present in 8.9% of patients with no diagnosis of PE compared to 10.9% of patients with a diagnosis of PE. Patients with a diagnosis of PE were more likely to receive both mechanical ventilation (20.3% *vs.* 2.0%, p<0.001) and thrombolysis (3.0% *vs.* 0.3%, p<0.001) (**Figure 3**). The length of stay for patients with a diagnosis of PE was a median of 7 days (IQR 4 to 14) compared to 5 days (IQR 3 to 9) without a diagnosis of PE. We observed greater rates of major bleeding (5.8% *vs.* 3.5%, p<0.001) and in-hospital mortality (13.7% *vs.* 7.9%) for patients with a diagnosis of PE compared to no diagnosis of PE. Median cost was more than $6,000 higher with concomitant PE diagnosis compared to no diagnosis of PE ($16,917 *vs.* $10,656).

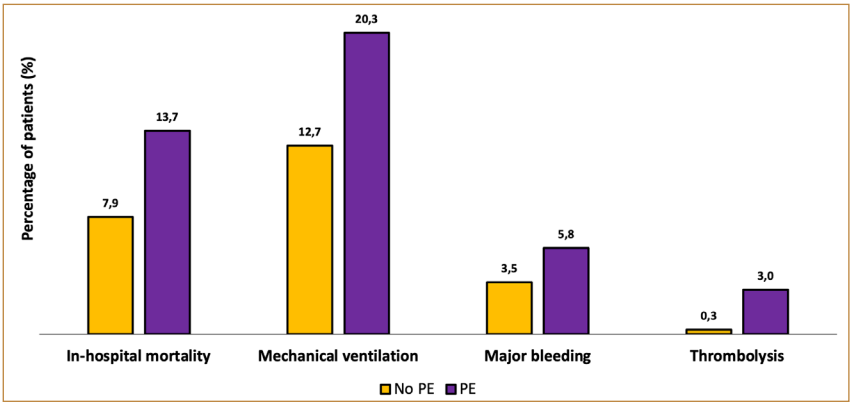

Figure 3. Crude rates (%) of in-hospital outcomes such as mortality, mechanical ventilation, major bleeding, and thrombolysis, according to the presence or absence of P

Multivariate regression analysis

The independent factors associated with a diagnosis of PE are shown in **Table 2**. The strongest factors associated with a diagnosis of PE were other venous thromboembolism (OR 11.65, 95%CI 11.42-11.88, p<0.001), arterial thrombosis (OR 2.64, 95%CI 2.40-2.89, p<0.001), previous venous thromboembolism (OR 1.72, 95%CI 1.68-1.77, p<0.001), cardiac arrest (OR 1.69, 95%CI 1.62-1.77, p<0.001) and cancer (OR 1.45, 95%CI 1.42-1.48, p<0.001). Factors which were associate with reduced odds of a diagnosis of PE were Asian or Pacific Islander race (OR 0.65, 95%CI 0.61-0.69, p<0.001), chronic kidney disease (OR 0.67, 95%CI 0.66-0.69, p<0.001), Hispanic

race (OR 0.69, 95%CI 0.67-0.71, p<0.001), diabetes mellitus (OR 0.75, 95%CI 0.74-0.77, p<0.001).

Table 3 shows the odds of adverse outcomes and regression coefficient for length of stay and cost associated with a diagnosis of PE compare to no diagnosis of PE after adjustments for baseline variables. Overall, a diagnosis of PE was associated with increased odds of in-hospital mortality (OR 1.50, 95%CI 1.46-1.54), mechanical ventilation (OR 1.12, 95%CI 1.10-1.15), thrombolysis (OR 6.69, 95%CI 6.31-7.09), and major bleeding (OR 1.48, 95%CI 1.39-1.57). A diagnosis of PE was further linked to an increase in both LoS (coef 1.51, 95%CI 1.43-1.58) and hospital inpatient cost (coef 4917, 95%CI 4630 to 5204). PE diagnosis in patients with viral pneumonia was associated with greatest odds of mechanical ventilation (OR 1.44, 95%CI 1.36-1.52), thrombolysis (OR 9.67, 95%CI 8.39-11.15) and major bleeding (OR 1.57, 95%CI 1.46-1.68).

Length of stay and total hospitalization costs

PE diagnosis was associated with both increase in length of stay (coefficient 1.51) and cost (coefficient 4917). Interestingly, patients with COVID-19 co-diagnosis had the lowest increase in odds of in-hospital mortality (OR 1.32, 95%CI 1.23-1.41) compared to other types of pneumonia. Length of stay was longest and cost was greatest for patients with bacterial pneumonia (coefficient 3.26 and 12.84, respectively).

Discussion

This study reports several key findings. First, we show, in a large nationwide sample, that 2.6% of inpatients with the main admission diagnosis of pneumonia had a co-diagnosis of PE. When patients were stratified according to pneumonia type, those with COVID-19 had the highest prevalence of PE. Secondly, patients with a diagnosis of pneumonia who are found to have PE are generally younger and less comorbid than patients with pneumonia without PE, however, are more likely to have cancer, previous venous thromboembolism, and non-PE venous thromboembolism. Importantly, patients with a diagnosis of PE and co-existing pneumonia were significantly more likely to receive mechanical ventilation and thrombolysis and have longer length of stay and hospital cost. Finally, PE in patients with a diagnosis of pneumonia is independently associated with a 1.5-fold increase in adjusted odds of in-hospital mortality and there was a slight reduction in odds of mortality for patients with COVID-19. These findings altogether suggest that PE in patients with a diagnosis of pneumonia is not uncommon and associated with worse clinical outcomes.

There is a large scarcity of data reporting on the rate of PE in patients with pneumonia. A Japanese

Table 2. Table 2. Independent factors and variables associated with concomitant PE diagnosis among patients with pneumonia

Variable	Odds ratio (95%CI)	p-value*
Age (per year)	0.99 (0.99-0.99)	<0.001
Female	0.93 (0.91-0.94)	<0.001
Race *vs.* White		
Black	1.06 (1.04-1.08)	<0.001
Hispanic	0.69 (0.67-0.71)	<0.001
Asian or Pacific Islander	0.65 (0.61-0.69)	<0.001
Native American	0.80 (0.72-0.89)	<0.001
Other	0.85 (0.81-0.89)	<0.001
Alcohol misuse	0.84 (0.80-0.89)	<0.001
Elective	0.86 (0.83-0.89)	<0.001
Weekend admission	0.97 (0.95-0.99)	0.001
Season *vs.* Spring		
Summer	1.17 (1.15-1.20)	<0.001
Fall	1.17 (1.15-1.20)	<0.001
Winter	0.96 (0.94-0.98)	<0.001
Year *vs.* 2016		
2018	1.04 (1.02-1.07)	0.002
2019	1.06 (1.03-1.09)	<0.001
2020	1.31 (1.28-1.35)	<0.001
Rural hospital	1.05 (1.03-1.07)	<0.001
Hospital bed size *vs.* small		
Medium	1.09 (1.07-1.12)	<0.001
Large	1.10 (1.08-1.12)	<0.001
Primary expected payer *vs.* Medicare		
Medicaid	1.21 (1.17-1.24)	<0.001
Private insurance	1.15 (1.13-1.18)	<0.001
Self-pay	1.32 (1.26-1.37)	<0.001
No charge	1.69 (1.50-1.91)	<0.001
Other	1.15 (1.09-1.21)	<0.001
ZIP income quartile *vs.* 0-25th		
76th-100th	0.97 (0.94-0.99)	0.010
Obesity	1.14 (1.12-1.16)	<0.001
Hypertension	0.91 (0.90-0.93)	<0.001
Hypercholesterolemia	0.95 (0.94-0.97)	<0.001
Diabetes mellitus	0.75 (0.74-0.77)	<0.001
Previous myocardial infarction	0.86 (0.83-0.89)	<0.001
Previous stroke	0.84 (0.81-0.86)	<0.001
Atrial fibrillation	0.90 (0.88-0.92)	<0.001
Previous heart failure	0.94 (0.92-0.96)	<0.001
Other venous thromboembolism	11.65 (11.42-11.88)	<0.001
Previous venous thromboembolism	1.72 (1.68-1.77)	<0.001
Arterial thrombosis	2.64 (2.40-2.89)	<0.001
Chronic lung disease	0.78 (0.77-0.79)	<0.001
Chronic kidney disease	0.67 (0.66-0.69)	<0.001
Anemia	1.10 (1.08-1.12)	<0.001
Cancer	1.45 (1.42-1.48)	<0.001
Dementia	0.85 (0.82-0.87)	<0.001
Tachycardia	1.25 (1.21-1.28)	<0.001
Hypotension	1.06 (1.03-1.09)	<0.001
Cardiac arrest	1.69 (1.62-1.77)	<0.001

*Adjusted for all variables except for receipt of mechanical ventilation, thrombolysis, anticoagulation, length of stay, discharge disposition and total charge.

Table 3. The association between pulmonary embolism and treatments and outcomes according to type of pneumonia.

Variable	Any pneumonia (N=13,956,485)	Viral pneumonia (N=2,664,825)	Bacterial pneumonia (N=2,394,615)	Other pneumonia (N=9,318,380)	COVID-19 in year 2020 (N=1,248,705)
In-hospital mortality	OR 1.50 (1.46-1.54)	OR 1.48 (1.39-1.57)	OR 1.51 (1.44-1.59)	OR 1.49 (1.44-1.54)	OR 1.32 (1.23-1.41)
Length of stay	OR 1.51 (1.43 to 1.58)	OR 1.89 (1.73 to 2.06)	OR 3.26 (3.01 to 3.51)	OR 1.11 (1.03 to 1.18)	OR 1.50 (1.29 to 1.71)
Cost	Coef 4917 (4630 to 5204)	Coef 8139 (7426 to 8852)	Coef 12843 (11771 to 13916)	Coef 3157 (2889 to 3426)	Coef 7363 (6408 to 8317)
Mechanical ventilation	OR 1.12 (1.10-1.15)	OR 1.44 (1.36-1.52)	OR 1.14 (1.09-1.19)	OR 1.10 (1.07-1.13)	OR 1.39 (1.31-1.49)
Thrombolysis	OR 6.69 (6.31-7.09)	OR 9.67 (8.39-11.15)	OR 5.21 (4.64-5.84)	OR 6.51 (6.04-7.01)	OR 9.25 (7.85-10.89)
Major bleeding	OR 1.4 (1.39-1.57)	OR 1.57 (1.46-1.68)	OR 1.29 (1.23-1.35)	OR 1.10 (1.07-1.13)	OR 1.53 (1.41-1.66)

*Adjusted for all variables except for anticoagulation, length of stay, discharge disposition and total charge.

retrospective analysis of claims data of in-hospital patients, not only those with pneumonia, reported that PE developed in 0.11% of hospitalizations.[13] In our current analysis of pneumonia patients which is derived from nationally representative data from the United States, we report a much greater rate of PE among inpatients with pneumonia.

There has been a recent public interest in PE events in patients with pneumonia because of COVID-19 pandemic. A study of 137 patients with SARS-Cov-2 infection and COVID-19 pneumonia who underwent CT examination reported a 24% cumulative incidence of PE.[14] Another study of 100 patients with contrast chest CT and severe clinical features of COVID-19 infection found that 23% had acute PE.[15] The association between COVID-19 and acute venous thromboembolism is also supported by several case studies.[16-18]

The factors which may be associated with PE in pneumonia are important to identify among patients who have both conditions. It is not surprising that non-PE venous thromboembolism was associated with PE as one study suggests that the prevalence of deep vein thrombosis in patients with PE was 45.4%.[19] Similarly patients with previous venous thromboembolism have a recurrent rate of approximately 7% at 6 months so it is not unexpected that previous venous thromboembolism is associated with PE.[20] Cancer is also associated with a 4- to 7-fold increase in risk of venous thromboembolism and PE is the second leading cause of death in these patients after the malignant disease itself.[21] The interesting observation in the current study was that the patients with DVT were more likely to be younger and less comorbid. It may be that patients that were older might be on anticoagulation for other reasons such as atrial fibrillation or receive prophylactic low molecular weight heparin but the exact reason for why patients with PE are less comorbid is unclear.

We show that PE in patients with a diagnosis of pneumonia is associated with worse in-hospital outcomes compared to pneumonia alone. This might be related to delay to optimal treatment which may also explain the prolonged hospital stay and increase in associated financial cost. In acute infections such as pneumonia there may be a window of opportunity to reverse disease progression to prevent mortality or serious complications. In the case of pneumonia, usually clinical symptoms such as chest pain, shortness of breath, cough, sputum and fever combined with signs such as hypoxia, tachypnea and crackles in the chest with an abnormal chest X-ray are enough to make the clinical diagnosis and initiate treatment. Non-response to treatment may prompt consideration of alternative or co-existing diagnosis such as PE. One prospective study in China suggest that for hospitalized patients with pneumonia and elevated D-dimer levels, PE should be considered for those of age 60 years or greater with coronary heart disease, chronic obstructive pulmonary disease, lower limb varicosity, chest pain, shortness of breath, hemoptysis, increased troponin levels, and low-grade fever.[22] More studies are needed to understand if there may be factors which can help in earlier identification of both conditions occurring together. Moreover, future investigations should determine the extent to which there may be a delay to establishing both diagnosis of PE and pneumonia and whether this had any impact on outcomes, however, this would require a more granular data to understand the timing of diagnoses, treatments and follow-up patient evaluation.

As COVID-19 pneumonia appears to be an enhancing risk factor for PE, it is interesting that COVID-19 co-diagnosis was associated with

lower adjusted odds of mortality compared to any pneumonia. This may be because many people were affected with COVID-19 with mild infection or co-diagnosis and admission to hospital for other reasons rather than life threatening chest infection. While there is a COVID-19 pneumonia code, we found that the 2020 NIS data did not have many patients that used this code so we used the COVID-19 diagnosis code.

Our findings bear some important clinical implications. First, it may be important to consider the possibility of PE in patients with pneumonia that clinically fail to respond to antibiotics and other initial measures such as oxygen therapy. There may be other clues such as transthoracic echocardiogram suggesting right ventricular dilatation, right heart systolic dysfunction, right ventricular strain, and tricuspid regurgitation suggesting pulmonary hypertension[23] and ECG abnormalities such as S1Q3T3 pattern, sinus tachycardia, electrical alternans, T wave inversions in V1-V3, and right bundle branch block.[24] Secondly, both pneumonia and PE may be treated but patients may also have underlying malignancy such as cancer which is a strong risk factors for PE. Finally, our study supports judicious use of thromboprophylaxis in patients who are hospitalized with pneumonia.

Future studies are need to better understand whether patient outcomes with pneumonia and PE could be improved. If there is no harm associated with missed initial diagnosis of PE in patients with pneumonia, then it may not be worthwhile to invest resources to try to promote more timely diagnosis. Moreover, if the harm is not avoidable because patients present typically with pneumonia without features of PE, changes to practice to support earlier diagnosis may not be beneficial. Nevertheless, this study suggests that PE in patients with pneumonia is associated with greater mortality, mechanical ventilation, thrombolysis, major bleeding, length of stay and cost. Therefore, it is important that clinicians are aware of the possibility of simultaneous diagnoses during hospital admission as well as the need to consider the possibility of PE when there are risk factors such as deep vein thrombosis or portal vein thrombosis, previous venous thromboembolism, arterial thrombosis, cardiac arrest, and cancer. There may also be the scope for education about the need to consider the possibility of PE when patients do not respond to initial treatment such as antibiotics and oxygen therapy.

It is notable that this study took place in the United States which has a unique multi-tiered healthcare system. As patients who had a private insurance had greater odds of diagnosis of PE, this may suggest that these patients may have better access to imaging compared to patients with Medicare.

These findings might support the use of CTPA for patients with pneumonia who are admitted to intensive care and patients who have type 1 respiratory failure with pneumonia, particularly those who fail to responds to initial therapy. We show that there is a high incidence of PE in patients with pneumonia and it may even be underestimated as not all patients undergo testing for PE. This is important as treatment such as anticoagulation or thrombolysis is available for PE that might improve the prognosis. For large PE anticoagulation is usually maintained for life now so anticoagulation would have important ongoing long-term benefits for patients once they have recovered from the initial event.

It is important to have more detailed information to determine if there was a missed opportunity related to delayed diagnosis of PE. It is also unanswered whether patients come to harm associated delayed diagnosis of PE when they are initially diagnosed with pneumonia. There may also be differences in pneumonia depending on whether they are viral, bacterial or other types of pneumonia.

This study has several limitations. First, pneumonia was based on ICD-10 codes and there was no indicator of severity of pneumonia or method to confirm diagnosis whether it was based on clinical suspicion with or without radiological and microbiological evidence to support the diagnosis. Second, not all cases of pneumonia had testing to exclude PE so some patients with mild PE may not be picked up on admission and we are not certain how many patients may have had undiagnosed PE and died in hospital with diagnosis of pneumonia. Third, observational studies may be at risk of confounding so we used robust multivariate-adjusted analysis to try to account for potential confounders. In addition, our study may be affected by confounding by indication as patients with both pneumonia and PE may have additional imaging like CTPA beyond that of chest X-ray in order to confirm both diagnoses. Therefore, patients with both imaging may be sicker and have worse outcomes. However, the purpose of this analysis is to evaluate what occurs in real-world setting rather than a study where patient consent to be a part of a study and undergo both imaging to ensure more robust diagnoses. Fourth, we have no understanding of the sequence of events within the admission whether pneumonia or PE was diagnosed first and second or both diagnoses were made at the same time. Another limitation is that the current study only determined pneumonia and pulmonary embolism based on ICD-10 codes and we cannot the exclude the possibility of misdiagnosis. The impact of this can be such that cases may be missed if not diagnosed during the hospital admission as well as those which may be wrongly classified as having pneumonia when it is actually something else such as pulmonary infarction. Also, our

study is limited because we do not have any information about the PE anatomical burden as subsegmental PEs may have less clinical impact than segmental or lobar artery PEs. An additional limitation is that the relationships observed in this national analysis applies on a national level and we do recognize that the results from individual hospitals may vary. Finally, this study is generalizable to the United States hospital settings and may not be representative of all patients with pneumonia which includes those from community settings as well as patients from other countries where there may be different patterns of pathogens causing pneumonia as well as different ethnic populations and healthcare services.

Conclusions

PE is not an uncommon finding in patients with a diagnosis of pneumonia which is associated with increase mortality, use of ventilation, thrombolysis, prolonged hospital stay and increased hospital inpatient cost.

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Conflict of Interest

The authors declare they have no conflict of interest.

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