Original Article

Increased risk of pulmonary embolism and deep vein thrombosis with COVID-19 pneumonia in comparison to influenza pneumonia: insights from the National Inpatient Sample database

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily a respiratory virus causing coronavirus disease 2019 (COVID-19) pneumonia, induces a hypercoagulable state. Previous studies comparing the prevalence of venous thromboembolism (VTE) in patients with COVID-19 pneumonia and those with influenza pneumonia revealed a higher risk of pulmonary embolism (PE) and deep vein thrombosis (DVT) associated with COVID-19 pneumonia. However, these studies have not adequately accounted for the severity and acuity of the presenting viral pneumonia.

Methods: In this retrospective study, we rigorously adjusted for critical illness using a nationally representative dataset to investigate whether COVID-19 pneumonia is independently linked to a higher risk of PE and DVT.

Results: After comprehensive multivariate adjustment, our findings demonstrated that patients with COVID-19 pneumonia maintained significantly higher odds of developing acute inpatient PE [adjusted odds ratio (aOR): 2.48; 95% confidence interval (CI): 2.16–2.86; P<0.01] and DVT (aOR: 1.66; 95% CI: 1.41–1.96; P<0.01) during the early pandemic compared to patients with influenza pneumonia. Furthermore, we identified congenital heart disease and malnutrition as novel risk factors for acute PE in COVID-19 patients.

Conclusions: Our study suggests that the higher prevalence of acute inpatient PE over DVT in patients with COVID-19 pneumonia may support a "thrombus *in situ*" mechanism of SARS-CoV-2-mediated pulmonary thrombosis. Consequently, clinicians should maintain a high index of suspicion for PE, even in the absence of DVT, among patients with COVID-19 pneumonia and should follow evidence-based guidelines for diagnosis and management.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), principally a respiratory virus causing coronavirus disease 2019 (COVID-19) pneumonia, results in a hypercoagulable state (1). Numerous observational studies have linked acute COVID-19 pneumonia with an increased risk of venous thromboembolism (VTE), including pulmonary embolism (PE) and lower extremity deep vein thrombosis (DVT) (2-7). However, it is unclear if this finding is due to intrinsic viral characteristics such as vascular tropism or a product of the inflammatory state associated with critical illness. Clinically, we sought to answer this question by comparing the inpatient prevalence of acute PE and acute lower extremity DVT among patients hospitalized with COVID-19 pneumonia versus patients hospitalized with influenza pneumonia using a large, nationally representative sample. Influenza pneumonia was selected as a comparator viral pneumonia because it has a similar clinical course and has been associated with an increased risk of myocardial infarction (MI), ischemic stroke, and VTE (3-5).

Previous studies comparing the prevalence of VTE in patients with COVID-19 pneumonia and patients with influenza pneumonia have shown that COVID-19 pneumonia is associated with a higher risk of PE and DVT; however, these studies do not adjust for the severity and acuity of the respective viral pneumonia (6,7). Therefore, we designed our study to compare the risk of acute PE and DVT after extensive adjustment for critical illness to investigate whether COVID-19 pneumonia continues to be associated with a higher risk of PE and DVT when compared with influenza pneumonia. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1674/rc).

Highlight box

Key findings

- Patients with coronavirus disease 2019 (COVID-19) pneumonia face a higher risk of pulmonary embolism (PE) and deep venous thrombosis when compared to those with influenza pneumonia.

What is known, and what is new?

- Even after accounting for illness severity and traditional risk factors, this elevated risk persists.
- Additionally, congenital heart disease and malnutrition are emerging risk factors for PE in COVID-19 patients, and the prevalence of PE is higher than deep venous thrombosis, suggesting a "thrombus in situ" mechanism.

What is the implication and what should change now?

- This emphasizes the importance for clinicians to remain vigilant for PE, even in the absence of deep venous thrombosis, and to follow evidence-based guidelines for diagnosis and management.

Methods

Data source

This retrospective study used the National Inpatient Sample (NIS) database from the years 2019 and 2020; this comprises hospitalizations in the United States (U.S.) from January 1st, 2019, to December 31st, 2020 (8). The NIS is maintained by the Healthcare Cost and Utilization Project (HCUP) and is the largest publicly available all-payer inpatient healthcare database designed to produce U.S. regional and national estimates of inpatient utilization, access, cost, quality, and outcomes. Unweighted, it contains data from approximately seven million hospital stays each year. Weighted, it estimates around 35 million hospitalizations nationally. The NIS is drawn from all states participating in HCUP, covering more than 97% of the U.S. population and approximates 20% of discharges from U.S. community hospitals (8). 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.

Study population and baseline demographics

Our study contained two populations: (I) patients 18 years of age and older who were hospitalized with a primary diagnosis of COVID-19 pneumonia between January 1st, 2020, and December 31st, 2020; and (II) patients 18 years of age and older who were hospitalized with a primary diagnosis of influenza pneumonia between January 1st, 2019 and December 31st, 2019. Exclusion criteria included patients who were transferred out of the index hospital to another acute care hospital and patients admitted with a diagnosis of acute trauma. This was necessary in order to minimize duplicates since the NIS database does not track patients after hospital discharge. The COVID-19 pneumonia population was identified using International Classification of Diseases, 10th Revision (ICD-10) codes U07.1 and J12.89 (other viral pneumonia), while excluding influenza pneumonia, ICD-10 codes J09, J10, and J11. Similarly, the influenza pneumonia population was identified using the corresponding ICD-10 codes (Table S1) during the year 2019. We felt that the advantage of using 2019 influenza data and 2020 COVID-19 data is that it lowers the likelihood of including patients who may have been coinfected. The following variables were extracted from the NIS database:

- Demographic characteristics: age, sex, and race;
- Medical comorbidities, Elixhauser comorbidity index, and venous thromboembolic risk factors were based on the Padua prediction score for VTE and literature analysis. These were extracted using ICD-10 codes.

Primary outcomes and statistical analysis

The two primary outcomes of this study were inpatient acute PE and inpatient acute lower extremity deep venous thrombosis, which were also determined using ICD-10 codes (Tables S1,S2).

Descriptive statistics were used to report the mean for continuous variables and the proportion for categorical variables within the baseline populations. Univariate logistic regression was used to compare baseline characteristics of the two populations (*Table 1*). Univariate logistic regression was also used to determine the unadjusted odds ratios (ORs) for the two primary outcomes, comparing patients with COVID-19 pneumonia and patients with influenza pneumonia. Risk factor analysis was performed for all listed baseline characteristics (*Table 1*) with respect to both primary outcomes to investigate association. In our multivariate model, we created a variable with influenza pneumonia as the reference and COVID-19 pneumonia as the predictor. Using this variable and other risk factors for VTE, we created two multivariate models—one for PE and another one for DVT. Variables with significant P values on the univariate model or those with important clinical relevance were used to construct a multivariate logistic regression model to determine if COVID-19 pneumonia is independently associated with PE and DVT when compared to influenza pneumonia (*Table 2*).

All analysis was carried out using Stata statistical software: release 17 (2021; StataCorp LLC, College Station, TX, USA). Stata's svy command and appropriate weights were used in all estimations. The overall fit was assessed using receiver operating characteristic (ROC) curves, and sensitivity analysis was performed using the evalue package. The study was exempt from institutional review board approval as the database uses previously collected de-identified data.

Results

Baseline characteristics

A total of 1,172,410 COVID-19 patients and 184,980 influenza patients were included in the study. At baseline, patients with COVID-19 pneumonia were older, had a higher proportion of males, and had more racial multiplicity, including larger populations of Blacks and Hispanics, than patients with influenza pneumonia. Patients with COVID-19 pneumonia also had lower Elixhauser comorbidity indices, lower prevalence of solid, hematologic, and metastatic malignancies, lower prevalence of previous VTE, and were less likely to be smokers. The only pre-existing risk factors for VTE that had an increased prevalence among patients with COVID-19 pneumonia were chronic estrogen use and known thrombophilia.

There are numerous clinical markers indicating a high acuity of illness among patients with COVID-19 pneumonia, including higher rates of vasopressor use, renal replacement therapy, and intubation with mechanical ventilation (in contrast to patients with influenza pneumonia who had more use of non-invasive positive-pressure ventilation). Similarly, patients with COVID-19 pneumonia had significantly longer hospital stays and higher inpatient mortality.

There was no difference in pre-admission antiplatelet use between the two groups. With respect to in-hospital

Table 1 Baseline characteristics of patients with COVID-19 pneumonia versus patients with influenza pneumonia

Baseline characteristics	COVID-19 pneumonia	Influenza pneumonia	P value
Age (years)	64.4	64.2	<0.001
Sex			
Female	45.5	52.8	<0.001
Male	54.4	47.1	<0.001
Race			
White	49.7	67.6	Reference
Black	18.6	14.6	<0.001
Hispanic	22.5	10.9	<0.001
Asian/Pacific Islander	3.5	2.8	<0.001
Native American	1.0	0.9	<0.001
Other	4.4	2.8	<0.001
Length of stay (days)	8.8	6.9	<0.001
Elixhauser comorbidity index	3.8	4.2	<0.001
Iatrogenic modulators of VTE risk			
Anticoagulation use	9.2	10.4	<0.001
Antiplatelet use	16.2	16.8	0.10
Estrogen use	2.9	1.7	<0.001
Tobacco use	5.3	21.8	<0.001
Medical comorbidities			
Thrombophilia	1.7	0.4	<0.001
Prior VTE	4.0	4.8	<0.001
Chronic kidney disease	20.9	22.4	<0.001
Congestive heart failure	17.7	30.3	<0.001
Congenital heart disease	0.2	0.4	<0.001
Leukemia or lymphoma	1.4	3.5	<0.001
Solid tumor, non-metastatic	2.1	3.6	<0.001
Metastatic cancer	0.9	1.8	<0.001
Paralysis	1.1	1.2	0.058
Chronic neurological disease	17.3	16.5	0.02
Connective tissue disease	3.0	5.2	<0.001
Chronic malnutrition	15.9	18.0	<0.001
Obesity	29.0	19.3	<0.001
Diabetes mellitus	28.2	21.4	<0.001
Previous hip or knee replacement	0.1	0.02	0.07

Table 1 (*continued*)

Table 1 (*continued*)

Baseline characteristics	COVID-19 pneumonia	Influenza pneumonia	P value
In-hospital complications and interventions			
Vasopressors	3.1	2.1	<0.001
Intubation	12.6	10.0	<0.001
Renal replacement therapy	5.5	5.0	0.01
HFNC/BiPAP/CPAP	7.7	9.6	<0.001
Cardiac arrest	3.2	1.4	<0.001
Acute MI	1.9	2.6	<0.001
Acute stroke	0.3	0.3	0.48
Acute liver failure	1.5	1.7	0.02
Severe sepsis	5.0	8.9	<0.001
Septic shock	8.8	8.8	0.93
Acute blood loss anemia	0.3	0.5	0.001
In-hospital mortality	16.6	5.4	<0.001

Data are presented as mean or percentage. COVID-19, coronavirus disease 2019; VTE, venous thromboembolism; HFNC, high flow nasal cannula; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; MI, myocardial infarction.

Table 2 Prevalence of PE and DVT among patients with COVID-19 pneumonia versus patients with influenza pneumonia with unadjusted and aORs

Primary outcomes	COVID-19 pneumonia (%)	Influenza pneumonia (%)	Unadjusted		Adjusted[†]	
			OR (95% CI)	P value	OR (95% CI)	P value
PE	3.1	1.2	2.54 (2.22–2.92)	<0.001	2.48 (2.16–2.86)	<0.001
Lower extremity deep venous thrombosis	1.9	1.0	1.80 (1.59–2.21)	<0.001	1.66 (1.41–1.96)	<0.001

[†], adjusted for all covariates P<0.05: age, sex, race, length of stay, pre-hospital anticoagulation use, estrogen use, tobacco use, Elixhauser comorbidity index as well specific chronic diagnoses such as: thrombophilia, previous VTE, chronic kidney disease, congestive heart failure, congenital heart disease, leukemia or lymphoma, metastatic and non-metastatic cancer, chronic neurologic disease, connective tissue disease, chronic malnutrition, obesity, and diabetes mellitus. Also adjusted for in-hospital complications: vasopressors, intubation, renal replacement therapy, HFNC/BiPAP/CPAP, cardiac arrest, acute MI, acute liver failure, severe sepsis, acute blood loss anemia, and mortality. PE, pulmonary embolism; DVT, deep vein thrombosis; COVID-19, coronavirus disease 2019; OR, odds ratio; VTE, venous thromboembolism; HFNC, high flow nasal cannula; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; MI, myocardial infarction.

complications, there were no differences in the prevalence of acute stroke or septic shock. Most complications were more prevalent in the COVID-19 group, except for a few, such as MI, severe sepsis, and the need for non-invasive ventilation.

Differential risk of acute PE and its risk factors

After multivariate adjustment, patients with COVID-19 pneumonia maintained significantly higher odds of developing acute inpatient PE when compared to patients with influenza pneumonia [adjusted OR (aOR): 2.48; 95% confidence interval (CI): 2.16–2.86; P<0.001]. On sensitivity analysis, this was associated with an expectation value (E-value) of 4.39 and an E-value (CI) of 3.74, indicative of a strong association.

Both male sex and black race (OR: 1.16; 95% CI: 1.14–1.18; P<0.001) were associated with a higher risk

of PE among patients with COVID-19 pneumonia when compared to patients with influenza pneumonia. As expected, traditional risk factors for VTE, including estrogen-based hormonal therapy, known thrombophilia, malignancies, and paralysis, had a stronger risk association for PE among patients with COVID-19 pneumonia. With respect to chronic comorbidities, congestive heart failure, congenital heart disease, connective tissue disease, chronic malnutrition, and obesity were all associated with higher risk for PE among patients with COVID-19 pneumonia. The higher acuity of care characterized by dependence on vasopressors, intubation, or non-invasive positive pressure ventilation was a stronger risk factor for PE among patients with COVID-19 pneumonia when compared to patients with influenza pneumonia.

Differential risk of acute lower extremity DVT and its risk factors

After multivariate adjustment, patients with COVID-19 pneumonia had a significantly higher risk of DVT (aOR: 1.66; 95% CI: 1.41–1.96; P<0.001) when compared to patients with influenza pneumonia. On sensitivity analysis, this yielded an E-value of 2.70 and an E-value (CI) of 2.1.

Both male sex and black race (OR: 1.17; 95% CI: 1.07–1.27; P<0.001) were associated with a higher risk of DVT among patients with COVID-19 pneumonia when compared to patients with influenza pneumonia. As expected, traditional risk factors for VTE, including estrogen-based hormonal therapy, known thrombophilia, prior VTE, malignancies, and paralysis, had a stronger risk association for DVT among patients with COVID-19 pneumonia. Tobacco use was associated with slightly lower odds of PE and DVT. With respect to chronic comorbidities, chronic kidney disease, congestive heart failure, congenital heart disease, chronic neurologic disease, connective tissue disease, diabetes mellitus, chronic malnutrition, and obesity were all associated with higher risk for DVT among patients with COVID-19 pneumonia. The higher acuity of care characterized by dependence on vasopressors, intubation, non-invasive positive pressure ventilation, or renal replacement therapy was a stronger risk factor for DVT among patients with COVID-19 pneumonia when compared to patients with influenza pneumonia.

Discussion

The primary finding of our study is that patients hospitalized with COVID-19 pneumonia have a significantly increased risk of acute inpatient PE and lower extremity deep venous thrombosis when compared to patients hospitalized with influenza pneumonia. More importantly, even after adjusting for the higher acuity of illness observed among COVID-19 patients during the early pandemic, the risk of PE and lower extremity DVT remains significantly elevated. To our knowledge, this study utilizes the largest sample of patients with COVID-19 and influenza pneumonia and is the first study to comprehensively adjust for the higher acuity of illness observed during the early pandemic.

Secondly, we identified congenital heart disease and malnutrition as novel risk factors for acute PE in COVID-19 patients.

At baseline, the overall population of patients with COVID-19 pneumonia had a lower burden of medical comorbidities when compared to patients with influenza pneumonia, as signified by the mean Elixhauser Comorbidity Indices. There are two primary exceptions; patients with COVID-19 pneumonia had a higher prevalence of obesity and diabetes mellitus. Existing literature demonstrates that obesity is independently associated with a 6.2-fold increased risk of VTE outside of COVID-19 pneumonia (9). Similarly, diabetes mellitus has also been independently associated with a significantly increased risk of VTE (aOR: 1.74; 95% CI: 1.21–2.51; P<0.001) (10). With respect to traditional VTE risk factors, patients with COVID-19 pneumonia had a lower prevalence of solid, hematologic, and metastatic malignancies, previous VTE, and tobacco use when compared to patients with influenza pneumonia. One possible explanation for the lower odds of VTE in tobacco users is residual confounding, as tobacco users are generally younger, and PE and DVT were more common in older patients. Our analysis did not show any risk modification effect of tobacco use. We did note an increased prevalence of chronic estrogen use and known thrombophilia among patients with COVID-19 pneumonia. In summary, while the prevalence of obesity, diabetes mellitus, estrogen use, and known thrombophilia likely contributed to the burden of in-hospital PE and DVT in patients with COVID-19 pneumonia, we found an independent risk of PE and DVT with COVID-19 pneumonia after multivariate adjustment.

In our risk factor analysis (*Table 3*), most of our findings were as expected. Known VTE risk factors were associated with a higher risk of PE and DVT among patients with COVID-19 pneumonia when compared to patients

Table 3 Determining risk factors for acute PE and DVT in patients with COVID-19 pneumonia

Variables	Acute PE		Acute lower extremity DVT	
	OR (95% CI)[†]	P value	OR (95% CI)[†]	P value
Age	1.01 (1.01–1.01)	<0.001	1.01 (1.01–1.02)	<0.001
Female	0.77 (0.76–0.77)	<0.001	0.70 (0.69–0.71)	<0.001
Race				
White	Ref.	Ref.	Ref.	Ref.
Black	1.16 (1.14–1.18)	<0.001	1.17 (1.07–1.27)	<0.001
Hispanic	0.59 (0.58–0.61)	<0.001	0.96 (0.86–1.06)	0.47
Asian/Pacific islander	0.49 (0.46–0.51)	<0.001	0.82 (0.67–1.01)	0.07
Native American	0.70 (0.65–0.76)	<0.001	0.79 (0.56–1.10)	0.17
Other	0.79 (0.76–0.82)	<0.001	1.01 (0.85–1.19)	0.90
Iatrogenic modulators of VTE risk (pre-hospitalization)				
Anticoagulation use	2.15 (2.11–2.20)	<0.001	2.63 (2.58–2.68)	<0.001
Antiplatelet use	0.90 (0.88–0.91)	<0.001	0.91 (0.90–0.93)	<0.001
Estrogen use	1.28 (1.24–1.32)	<0.001	1.19 (1.15–1.23)	<0.001
Tobacco use	0.94 (0.92–0.95)	<0.001	0.76 (0.75–0.77)	<0.001
Medical comorbidities				
Elixhauser comorbidity index	1.26 (1.26–1.27)	<0.001	1.19 (1.19–1.20)	<0.001
Thrombophilia	7.36 (7.12–7.61)	<0.001	8.76 (8.48–9.06)	<0.001
Leukemia and lymphoma	1.39 (1.34–1.44)	<0.001	1.88 (1.82–1.94)	<0.001
Solid tumor, nonmetastatic	2.80 (2.75–2.84)	<0.001	2.83 (2.79–2.88)	<0.001
Metastatic cancer	3.64 (3.57–3.71)	<0.001	3.82 (3.75–3.89)	<0.001
Chronic kidney disease	0.83 (0.82–0.84)	<0.001	1.30 (1.28–1.32)	<0.001
Congestive heart failure	1.24 (1.22–1.25)	<0.001	1.24 (1.22–1.26)	<0.001
Congenital heart disease	2.28 (2.17–2.39)	<0.001	2.45 (2.32–2.58)	<0.001
Prior VTE	3.35 (3.28–3.41)	<0.001	3.81 (3.73–3.89)	<0.001
Paralysis	1.09 (1.05–1.13)	<0.001	1.70 (1.65–1.76)	<0.001
Previous hip/knee replacement	0.18 (0.17–0.19)	<0.001	0.25 (0.23–0.27)	<0.001
Chronic neurologic disease	1.15 (1.13–1.17)	<0.001	1.42 (1.40–1.45)	<0.001
Obesity	1.46 (1.44–1.48)	<0.001	1.34 (1.32–1.36)	<0.001
Chronic malnutrition	1.57 (1.55–1.59)	<0.001	1.94 (1.91–1.97)	<0.001
Connective tissue disease	1.22 (1.19–1.26)	<0.001	1.31 (1.28–2.35)	<0.001
Diabetes mellitus	0.81 (0.80–0.82)	<0.001	1.13 (1.11–1.14)	<0.001
In-hospital interventions and complications				
Vasopressors	2.84 (2.67–3.01)	<0.001	2.97 (2.78–3.18)	<0.001
Intubation	2.83 (2.77–2.89)	<0.001	2.66 (2.59–2.74)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Variables	Acute PE		Acute lower extremity DVT	
	OR (95% CI)[†]	P value	OR (95% CI)[†]	P value
HFNC/BiPAP/CPAP	1.81 (1.76–1.86)	<0.001	1.50 (1.46–1.56)	<0.001
Renal replacement therapy	0.86 (0.83–0.89)	<0.001	1.41 (1.36–1.46)	<0.001
Septic shock	2.56 (2.49–2.63)	<0.001	2.98 (2.90–3.06)	<0.001
Cardiac arrest	3.61 (3.49–3.72)	<0.001	2.33 (2.24–2.43)	<0.001
Acute MI	0.97 (0.93–1.00)	0.10	0.92 (0.89–0.95)	<0.001
Acute stroke	0.69 (0.66–0.72)	<0.001	1.05 (1.01–1.09)	0.01
Acute blood loss anemia	1.48 (1.42–1.55)	<0.001	1.82 (1.74–1.90)	<0.001
Acute liver failure	1.63 (1.56–1.69)	<0.001	1.84 (1.77–1.91)	<0.001
In-hospital mortality	3.08 (3.02–3.15)	<0.001	2.43 (2.37–2.49)	<0.001

[†], ORs for developing acute PE and DVT in patients with COVID-19 pneumonia versus patients with influenza pneumonia (reference) for each pre-specified variable. PE, pulmonary embolism; DVT, deep vein thrombosis; COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; ref., reference; VTE, venous thromboembolism; HFNC, high flow nasal cannula; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; MI, myocardial infarction.

with influenza pneumonia. This is congruent with the higher background risk of PE and DVT in patients with COVID-19 pneumonia, as demonstrated in our study—in other words, risk factors are likely additive to the higher intrinsic risk of PE and DVT in COVID-19 pneumonia. We observed two risk factors that were not reported in previous literature: congenital heart disease and chronic malnutrition. Possible mechanisms of increased PE risk (likely more so than DVT) in congenital heart disease may include alterations in pulmonary vasculature blood flow or epithelial characteristics; in any case, these are a heterogeneous group of diseases that require further analysis to elucidate the underlying mechanisms of thrombotic disease in COVID-19 pneumonia. The link between chronic malnutrition and thrombosis can likely be explained by alterations in the hepatic production of coagulant proteins (11).

While hospitalized, patients with COVID-19 pneumonia had markers of high acuity illness characterized by more complications, longer hospital stays, and increased mortality. We believe that this finding likely stems from decreased host immunity to SARS-CoV-2 in the absence of widespread messenger RNA (mRNA) vaccine use during 2020, as well as intrinsic differences in virus characteristics (12). The acuity of illness is an important factor with respect to PE and DVT, as a higher acuity of illness and need for intensive care is independently associated with increased VTE risk regardless of the underlying disease process (13). Similarly, inflammatory and infectious diseases generally increase the risk of VTE (14,15). The strength of our analysis is that we adjusted for the acuity of illness and medical comorbidities and found that patients with COVID-19 pneumonia were at an independently high risk of VTE, and particularly acute PE, more so than lower extremity DVT. The higher risk of acute inpatient PE over lower extremity DVT in patients with COVID-19 pneumonia in comparison to patients with influenza pneumonia is a noteworthy observation.

These findings may support the "thrombus *in situ*" theory of SARS-CoV-2 affecting the pulmonary arteries and inducing pulmonary thrombosis rather than the traditional mechanism of peripheral deep venous clots embolizing to the pulmonary vasculature. Thrombotic disease in COVID-19 is likely due to two distinct mechanisms: (I) a hypercoagulable state leading to large-vessel thrombosis and thromboembolism; and (II) endothelial injury responsible for *in situ* microvascular thrombosis (16). Additionally, it has been proposed that SARS-CoV-2 directly infects endothelial cells, including pulmonary vasculature, causing inflammation and impairing the coagulation cascade (17,18). This mechanism of direct endothelial infection may explain the specific increase in PE risk among patients with COVID-19 pneumonia when compared to patients with influenza pneumonia.

Limitations

Our study has several limitations. First, the NIS is an administrative database that relies on ICD-10 codes for diagnosis. This may have underestimated the true prevalence of many risk factors, such as anticoagulant and antiplatelet use, medical comorbidities, and acute in-hospital complications due to under-coding. Moreover, there is a possibility of detection bias, as the ICD-10 code for COVID-19 pneumonia was created later in 2020, likely resulting in the under-reporting of COVID-19 pneumonia cases. Secondly, there remains a possibility of confounding bias in this retrospective study despite our thorough multivariate adjustment and sensitivity analysis. Thus, as with any observational study, association does not imply causation, and conclusions should be drawn cautiously. Thirdly, it is complicated to extrapolate data based on initial SARS-CoV-2 strains to currently evolving strains, including Omicron BA.5, as these may be accompanied by the possibility of modified thrombogenic properties. Lastly, our study utilizes data before widespread mRNA vaccine availability for COVID-19; we anticipate that host immune responses modulate thrombotic complications of COVID-19, including DVT and PE.

Conclusions

The primary finding of our study is that patients hospitalized with COVID-19 pneumonia have a significantly increased risk of acute inpatient PE and lower extremity deep venous thrombosis when compared to patients hospitalized with influenza pneumonia. More importantly, even after adjusting for the higher acuity of illness observed among COVID-19 patients during the early pandemic and for traditional risk factors of VTE, the risk of PE and DVT remains significantly elevated in this population. To our knowledge, this study utilizes the largest sample of patients with COVID-19 and influenza pneumonia and is the first study to comprehensively adjust for the higher acuity of illness observed during the early COVID-19 pandemic. In this study, we also discovered that congenital heart disease and malnutrition are emerging risk factors for acute PE in individuals with COVID-19. The higher occurrence of inpatient PE compared to lower extremity DVT in COVID-19 pneumonia patients suggests a possible "thrombus *in situ*" mechanism for SARS-CoV-2-induced pulmonary thrombosis. This highlights the need for clinicians to remain vigilant about the possibility of PE, even in the absence of DVT, in COVID-19 pneumonia patients. It is imperative to adhere to current evidence-based guidelines for the diagnosis and management of this condition (19).

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Footnote

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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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