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ORIGINAL ARTICLE

Incidence of pulmonary embolism in COVID-19 infection in the ED: ancestral, Delta, Omicron variants and vaccines

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Abstract

Purpose This retrospective review examines the incidence of pulmonary embolism (PE) during computed tomography pulmonary angiography (CTPA) exams performed in the emergency room setting of a tertiary care center over dominant periods of the ancestral, Delta, and Omicron variants of COVID-19.

Materials/methods Demographic information, patient comorbidities and risk factors, vaccination status, and COVID-19 infection status were collected from patient's charts. Incidence of PE in COVID positive patients was compared between variant waves. Subgroup analysis of vaccination effect was performed.

Results CTPA was ordered in 18.3% of COVID-19 positive patients during the ancestral variant period, 18.3% during the Delta period and 17.3% during the Omicron wave. PE was seen in 15.0% of the ancestral COVID-19 variant cohort, 10.6% in the Delta COVID cohort and 9.23% of the Omicron cohort, reflecting a 41% and 60% increased risk of PE with ancestral variants compared to Delta and Omicron periods respectively. The study however was underpowered and the difference in rate of PE did not reach statistically significance ($p = 0.43$ and $p = 0.22$). Unvaccinated patients had an 2.75-fold increased risk of COVID-associated PE during the Delta and Omicron periods ($p = .02$) compared to vaccinated or recovered patients.

Conclusion Vaccination reduces the risk of COVID-19 associated PE. Patients infected with the Delta and Omicron COVID-19 variants may have a lower incidence of pulmonary embolism, though a larger or multi-institution study is needed to prove definitively.

Keywords Pulmonary embolism · COVID-19 · Ancestral · Delta · Delta variant · Omicron · Omicron variant · Blood clots · Computed-tomography angiography · Emergency department

Introduction

The coronavirus disease 19 (COVID-19) pandemic has led to millions of deaths worldwide, and although infection with COVID-19 predominantly involves the respiratory system, other organ systems can also be affected [1]. Prothrombic coagulation abnormalities and resulting thromboembolism, such as pulmonary embolism (PE), are a known complication of COVID-19 infection, which has been attributed to direct viral toxicity, endothelial cell damage, and dysregulation of the immune system [2, 3]. PEs in patients infected with COVID-19 have been found to be clinically different from PEs in patients without COVID-19 infection. For example, autopsy studies have found thrombosis and microangiopathy in the small vessels and capillaries of patients who succumbed to COVID-19 infection, suggesting that the PEs in these patients may in fact represent pulmonary thrombosis instead of embolism [2]. Additionally, PEs in COVID-19 positive patients are associated with a higher risk of morbidity and mortality [4]. Since the inception of the pandemic, multiple new variants have emerged with the most significant subsequent waves in the USA caused by the Delta (B.1.617.2) and Omicron (B.1.1.529) variants [5]. The Delta variant is estimated to be about 60% more transmissible than earlier variants and is associated with an increased rate of hospitalization and morbidity during hospitalization [6–9]. The Omicron variant was found to be 70% more transmissible than the Delta variant, causing milder symptoms than previous strains with high transmission

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rates, vaccine breakthrough, and antibody resistance [10]. Additional characteristics that make these variants clinically unique continue to be studied. Based on our experience in a tertiary care center, we hypothesize that the incidence of PE, as diagnosed with a computed tomography pulmonary angiography (CTPA) exam, in emergency department (ED) patients is lower in those infected with the Delta and Omicron COVID variants, as compared to the ancestral COVID variants. To our knowledge this is the first such comparison. Additionally, we evaluate the influence of vaccination on COVID-19 associated PE.

Methods

Time period selection

State health department data [11] showing rates of ED COVID-19 infection were reviewed to identify dominant periods of infection for the ancestral, Delta, and Omicron variant waves between November 15–December 29, 2020 (ancestral variants), August 10–September 23, 2021 (Delta), and January 1–February 18, 2022 (Omicron) were selected (Fig. 1). Data from the US Centers for Disease Control was accessed to assess regional variant prevalence which ranged from 98.2 to 99.8% during of the sampled Delta wave and 94.7–98.9% during the Omicron wave [5], in lieu of individual PCR genetic analysis which was not available.

Patient selection and clinical data acquisition

IRB approval was obtained for retrospective review of all CTPA exams performed in the emergency room setting acquired during these time periods, identified via an internal radiology report search engine (mPower, Nuance Communications Inc, Burlington MA, USA) via querying the desired dates, ER setting, and imaging exam code. All CTPA reports were reviewed by board certified radiologists for the presence or absence of acute PE. Demographic information (age, sex), patient co-morbidities and risk factors (active malignancy, current anti-coagulation, recent surgery, history of prior PE, recent deep venous thrombosis or hypercoagulable state), vaccination status, and COVID-19 infection status, obtained during the same encounter as the CTPA exam, were collected from the patients' charts. A patient was considered vaccinated if they had received two doses of any vaccine or had a documented case of COVID-19 previously. Additionally, the ER provider note was reviewed for additional COVID-19 infection status information. Patients were considered positive for COVID-19 infection with any form of positive test within 30 days prior to or 5 days after the CT as well as report of a recent positive outside test in the clinical

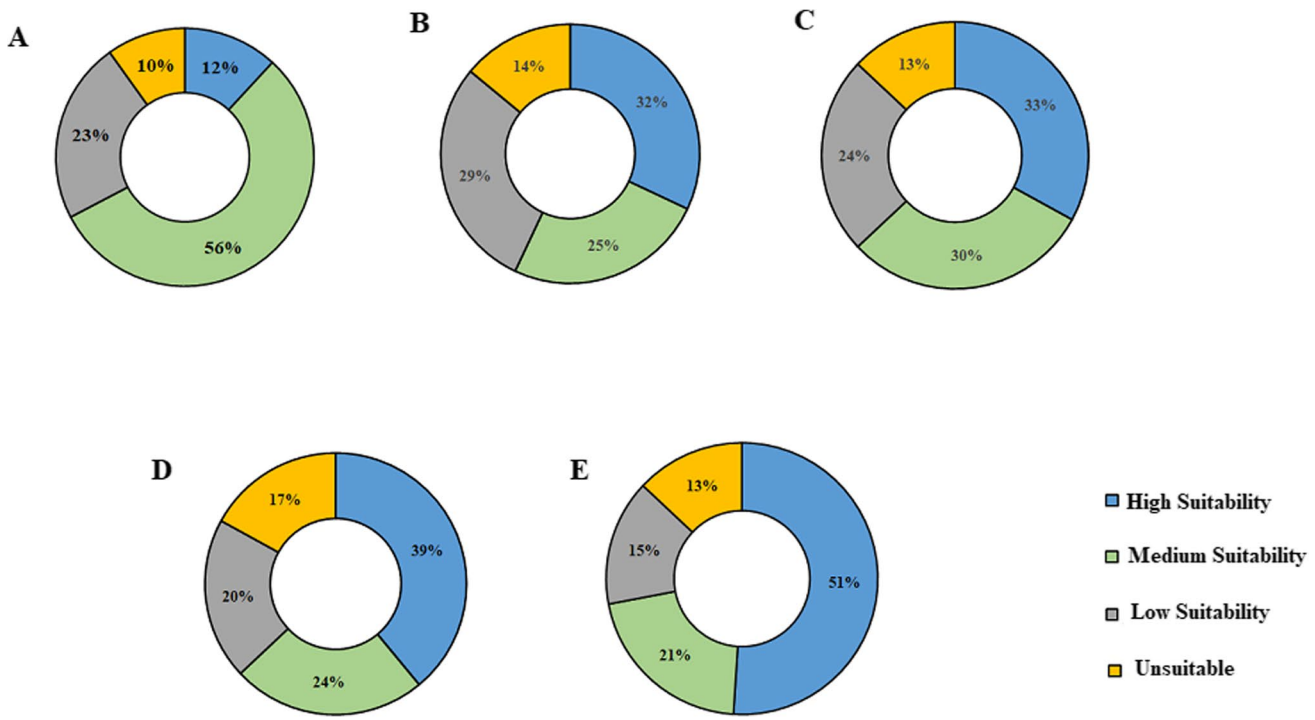

Fig. 1 COVID positive case counts in the state of Utah, obtained from https://coronavirus.utah.gov/case-counts/ Accessed 3/1/2022. Superimposed orange bars indicate the time ranges selected for the ancestral cohort (11/15–12/29/2020), Delta variant cohort (8/10–9/23/2021), and Omicron variant cohort (1/1/2022–2/18/2022)

note. CTPAs were only ordered for those patients with a clinical suspicion for acute PE and there was no protocol for CTPA screening in our ED during the study periods. To provide contextual reference between the three periods, ED-visit coding data was accessed to determine the total number of visits and COVID-19 diagnoses in the ED during each period. ED diagnoses were produced via Epic Systems electronic health record report query that utilized COVID-19 associated International Classification of Diseases, tenth edition (ICD-10) codes (U07.1, J12.82).

Data analysis

Data was collated using Microsoft Excel (Redmond WA, USA). Statistical analysis was performed using the statistical software Stata (StataCorp LLC, College Station TX, USA). A power calculation was performed, assuming equal cohorts of 75 patient encounters (representing COVID + patients with a CTPA exam) and an incidence of PE of 15% within the ancestral COVID cohort and 10% within the Delta and Omicron COVID-19 cohort, yielding a power of 0.10. A 95% confidence interval for each cohort incidence was calculated from the standard error. A Fischer exact test was determined to be appropriate for the size of our data set to compare the relative incidences of PE. A chi-squared test was used to determine statistical significance.

Results/discussion

There were 6918 ED patient encounters and 403 COVID-19 diagnoses coded between 11/15/2020 and 12/29/2020, of these 283 encounters included a CTPA exam. There were 8829 ED patient encounters between 8/10/2021 and 9/23/2021, of which 349 included a CTPA exam (Fig. 2). Notwithstanding vaccination status, the demographic information and patient co-morbidities between these cohorts were similar (Table 1). Of these cohorts, there were 80 patients with ancestral COVID-19 variants infection who underwent CTPA, and 12 were positive for PE. Of the 66 patients with presumed Delta COVID-19 variant infection who underwent CTPA, 7 were positive for PE (Table 1). The rate of PE was 15.0% (95% *CI* [8.9, 25.2]) in the ancestral COVID-19 variants cohort and 10.6% (95% *CI* [5.2,21.3]) in the Delta COVID variant cohort, reflecting a 41% increased risk of PE with Ancestral variants compared to Delta variant (*RR* 1.41, 95% *CI* [0.59,3.38]), though not statistically significance ($p = 0.43$). The rate of PE in COVID-positive patients receiving CTPA during the Omicron period was slightly lower than the Delta period with PE discovered in 12 of 130 COVID-19 positive cases or 9.23% (95% 4.3–14.2%)

Table 1 Demographic information, COVID infection status and CTPA results of patients evaluated in the ER during the selected time ranges for whom a CTPA was ordered

ER patients who received a CTPA chest for evaluation of PE	Ancestral 11/15–12/29/2020	Delta 8/10–9/23/2021	Omicron 1/1–2/18/2022
Number of patients (*n*)	283	349	420
Percent female	61%	56%	56%
Age (avg)	51 yr	52 yr	51 yr
Vaccinated (% of pts)	n/a	56%	85%
COVID + (*n*)	80	66	128
PE + (*n*)	42	48	51
COVID + and PE + (*n*)	12	7	12

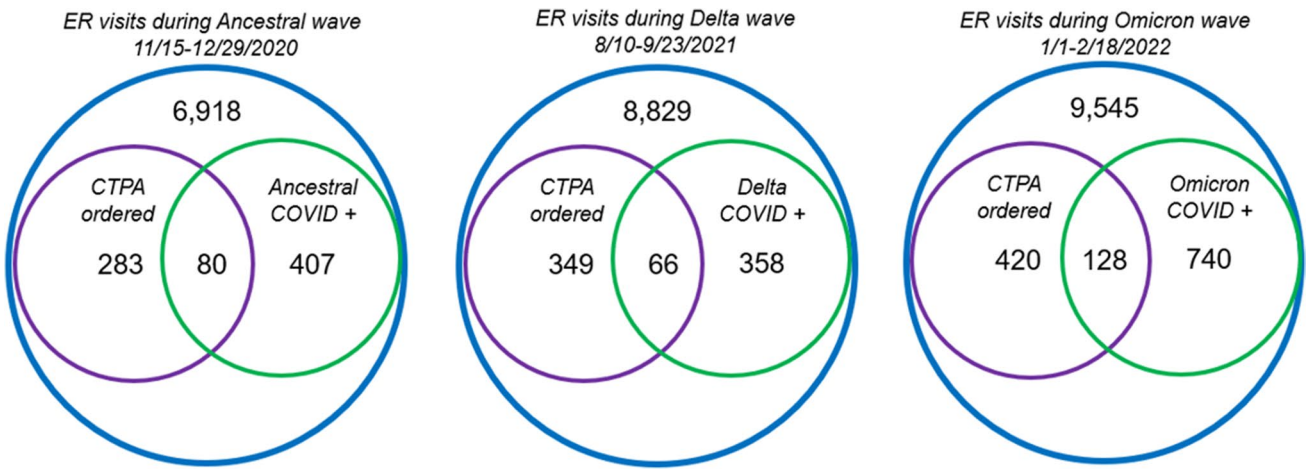

Fig. 2 Venn diagram depicting the total number of ER visits within the selected time ranges, and of those visits the number involving COVID + patients and/or a CTPA exam

Table 2 Rate of pulmonary embolism in COVID positive patients, as compared between the ancestral, Delta, and Omicron variant cohorts. *P*-value was obtained from a chi-squared test

	Ancestral	Delta	Omicron
Rate of COVID + PE	15.0% (8.9–25.2%) (reference)	10.65 (5.2–21.3%) $p = .43$	9.23% (4.23–14.2%) $p = .22$

and came closer to significance relative to ancestral variants (*RR* 1.60, 95% *CI* 0.76–3.89, $p = 0.22$) (Table 2).

In order to assess for possible changes in CTPA ordering habits or other clinical practice changes between the two time periods, the rate of CTPA use and incidence of PE as a fraction of total COVID-19 diagnoses in the ED was determined. CTPA was ordered in 18.3% of COVID-19 positive patients during the ancestral variants wave, 18.3% during the Delta wave, and 17.3% for the Omicron wave. PE was seen in 1.94% of all COVID-19 positive ED visitors during the Delta wave and 1.6% during the Omicron wave compared to 2.97% of all COVID-19 positive ED visitors during the ancestral wave, also reflecting an increased risk of PE with ancestral variants (ancestral vs Delta *RR* 1.53, 95% *CI* 0.61, 3.85, $p = 0.36$ and ancestral vs Omicron *RR* 1.81, 95% *CI* 0.82–4.01, $p = 0.14$), though neither reached statistical significance (Table 3).

Our results for the incidence of PE in COVID-19 infections are congruent with previous reports summarized in the meta-analysis of PE incidence in COVID-19 positive patients by Suh et al. [2]. Reported incidences for PE in non-ICU patients averaged 10.4% (95% *CI* 5.1–20.2) for the ancestral variants in that analysis.

During the Omicron wave, 85.2% of ED patients receiving CTPA were vaccinated compared to 56.3% during the Delta period. Vaccination had a protective effect on the risk of presenting to the ED with a COVID-19 associated PE, with 7/358 found to have a COVID-19-associated PE compared to 5/62 in the unvaccinated/unknown status population (relative risk (RR) for the unvaccinated 3.89 (95% *CI* 1.27–11.9, $p = 0.02$). This appears to be due to a reduction in Omicron infection rate as 59/62 (95.1%) of previously unvaccinated patients tested positive for COVID-19 compared to 69/358 (19.3%) vaccinated patients, though the testing result may have altered ED provider ordering behavior. The effect during the Delta wave was similar with 2/197 vaccinated patients found to have COVID-19-associated PE's compared to 5/153 unvaccinated patients, though not statistically significant (*RR* 3.2, 95% *CI* 0.62–16.1, $p = 0.17$). The combined vaccine effect during the Delta and Omicron waves was also significant (*RR* 0.36, 95% *CI* 0.15–0.87, $p = 0.02$). Once a patient had tested positive, there was not a significant protective benefit in the vaccinated group (Table 3).

Although there was an observed difference in incidence of PE in patients infected with the ancestral COVID-19 variants versus the Delta and Omicron COVID-19 variants, this finding did not reach statistical significance. However, this study is underpowered and the finding requires a larger multi-institution study or meta-analysis to further investigate this observation. Additionally, although the patient cohorts share similar demographic information and patient co-morbidities, this limited study does not control for these confounding variables which may affect the patients' inherent risk for PE, independent of COVID-19 infection. Regional reporting of variant prevalence, though between 94 and 99% dominant for each period, was used to select dominant periods for COVID-19 variants as individual PCR variant analysis was not available and, as such, we cannot be completely

Table 3 Subgroup analysis comparing the effect of vaccination on COVID-19 associated PE. Vaccination showed a significantly protective benefit primarily through preventing infection, but did not show a benefit in those patients testing positive (*RR* = relative risk for unvaccinated patients)

	Number	COVID +	COVID + %	COVID + and PE	Rate per CT	Rate per COVID +
Ancestral						
Vaccinated/recovered	n/a	n/a	n/a	n/a	n/a	n/a
Unvaccinated/unknown	283	80	28.3%	12	4.2%	15.0%
Omicron + Delta						
Vaccinated/recovered	555	85	15.32%	9	1.62%	10.59%
Unvaccinated/unknown	215	109	28.27%	10	4.65%	9.17%
Unvaccinated RR for COVID + PE in all CTPA patients				**2.75 (1.14–6.73)**		***p* = 0.02**
Unvaccinated RR for PE in COVID +				0.87 (0.37–2.1)		$p = 0.76$

Statistically significant results in bold

sure which variant an individual patient had. Additionally, the window of positive testing may range outside the dominant period; however, the interval between positive test and CTPA was 13.8 days for the ancestral sampling period, 8.9 days for Delta and 4.2 days for Omicron suggesting little spillover impact.

As demonstrated above, vaccination was an external intervention that does reduce the risk of COVID-19-associated PE and could explain the difference between rates of PE in the first wave and subsequent waves we compared. Furthermore, the detection of PE is dependent on the ED provider ordering a CTPA exam, and using total ED COVID-19 diagnoses is a crude method to control for changes in ordering habits that may have occurred over these different time periods of the COVID-19 pandemic. It is also possible that some ED diagnoses of COVID-19 were missed due to alternative ICD-10 coding; however, given the fairly large encompassing nature of the ICD-10 codes that were utilized, any missed cases are presumed to be small and likely non-significant.

Conclusion

We present a single institution study showing a difference in incidence of PE in ED patients infected with the ancestral COVID-19 variants and those infected with the Delta and Omicron COVID-19 variants. Though our findings do not reach statistical significance, they suggest that patients infected with the Delta or Omicron COVID-19 variants may have a lower incidence of pulmonary embolism. Vaccination with at least two doses does significantly reduce the risk of COVID-19 associated PE.

Declarations

Conflict of interest The authors declare no competing interests.

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