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Racial disparities in COVID-19 associated pulmonary embolism: A multicenter cohort study

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ABSTRACT

Background: Thromboembolism is a recognized component of severe coronavirus disease 2019 (COVID-19) disease. However, research into racial disparities in COVID-19-related pulmonary embolism is limited.

Materials and methods: In this retrospective cohort study, we examined adults diagnosed with COVID-19 between January 20 and September 30, 2020, using a multicenter electronic health record dataset of over 73 million patients (TriNetX), mostly in the USA. The main study outcomes were development of pulmonary embolism or mortality within 30 days of COVID-19 diagnosis. Secondary outcome analysis included hospitalization, mechanical ventilation, and ICU admission within 30 days of diagnosis, as well as lab values within 0–1 days of diagnosis. Sociodemographic and clinical variables were used to create balanced cohorts via propensity matching.

Results: 346,953 patients were identified, with 56.0% non-Hispanic white and 14.7% non-Hispanic black; the mean age was 47.6 years. 3879 patients developed PE, with 2036 (1.30% of 157,049) white and 1088 (2.16% of 50,376) black patients. After propensity matching, black race was associated with higher mortality (risk ratio 1.890 [95% CI 1.727–2.067]) and PE (RR 1.537 [1.380–1.711]; $p < 0.0001$). Both races had higher mortality with COVID-associated PE than COVID or PE alone (RR 1.575–1.627 and 3.000–5.389 respectively; $p < 0.0001$). Black patients with COVID-19 and PE had a higher rate of mortality compared to white patients (RR 1.397 [1.059–1.844]; $p = 0.0174$).

Interpretation: Black race was associated with higher risk of pulmonary embolism and mortality after COVID-19. Additionally, black patients with COVID-19 and PE had a higher mortality compared to white patients.

1. Introduction

Coronavirus disease 19 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide with a global pandemic stage since March 2020, continuing to increase in the United States. Since the beginning of the pandemic, increasing data has highlighted racial disparities in the prevalence of COVID-19 in the United States [1] [2]. Thromboembolic events including pulmonary embolism (PE) are an increasingly recognized complication of COVID-19 [3–6]. Autopsy studies report widespread microthrombosis and endothelial injury within COVID-19-affected lung [7], with these features more prominent in COVID-19 compared to other pulmonary infections [8]. Pulmonary embolism itself is a leading cause of cardiovascular death and morbidity [9], with pre-COVID studies showing an increased incidence of thromboembolic disease in black individuals [10,11].

Thus far, most published data on COVID-19 and PE consist of case series or single-center studies often with a focus specifically on critically ill patients. Differences in clinical characteristics and outcomes based on factors like age, gender, ethnicity, or pre-existing clinical comorbidities may not be fully reflected in these smaller data sets, emphasizing the importance of examining the effects of race on thromboembolic disease

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in the context of the COVID-19 pandemic in large patient cohorts. Therefore, we aimed to examine the effects of race on the event rate and outcomes of PE in patients with COVID-19 disease using a large multicenter global geographically and demographically diverse dataset, balancing their demographics and pre-existing conditions using propensity matching.

2. Methods

This retrospective observational cohort study used the TriNetX COVID-19 Research Network, a federated global research network [12]. This network provides aggregated real-time data from the electronic health records (EHRs) of approximately 73 million patients over 56 health care organizations (HCOs), with the majority of these contained within the United States. Each HCO consists of an integrated health care system, encompassing patients in emergency, inpatient, and outpatient care settings. Datasets from each HCO are processed by TriNetX as either de-identified or limited data. Within each HCO, patients are counted once, even if they received care at multiple locations within the HCO. As the TriNetX network uses aggregated counts of de-identified data without protected health information, it received a waiver from Western IRB.

Within the TriNetX network, we queried adult patients (≥18 years) diagnosed with COVID-19 from January 20 to September 30, 2020. Data queries were conducted on March 16–17, 2021, using codes adhering to the International Classification of Diseases, 10th Revision (ICD-10); Logical Observation Identifiers Names and Codes (LOINC); Current Procedural Terminology (CPT); and RxNorm. Data collection included demographic characteristics (age, gender, reported race and ethnic group, decedent status); COVID-19 status via specific terminology (ICD-10 B34.2, B97.29, J12.81, U07.1, U07.2 and exclusion of 079.89; positive results for LOINC 94309-2, 94315-9, 94316-7, 94500-6, 94533-7, 94534-5, 94559-2, 94505-5, 95506-3, 94507-1, 94508-9); and diagnosis of pulmonary embolism (ICD-10 I26, Z86.711, I27.82). Clinical comorbidities included hypertension, diabetes, obesity, chronic obstructive pulmonary disease, cerebral infarction, systemic connective tissue disorders, reduced mobility, pregnancy, neoplasm, nicotine dependence, use of systemic contraceptives, and prior hospitalization (respectively ICD-10 I10, E08-E13, E66.9, J44, I63, M30-36, Z74.0, Z33, C00-D59, F17; RxNorm HS200; CPT 1013659). Homelessness (Z59) was also included as a socioeconomic covariate. Outside of mortality, other clinical outcomes included hospital admission (CPT 1013659), intensive care unit admission (CPT 1013729) and mechanical ventilation (ICD-10 5A19). Analyzed laboratory outcomes included lymphocyte count, leukocyte count, platelet count, erythrocyte sedimentation rate, C-reactive protein, serum ferritin, oxygen saturation rate, D-dimer in fibrinogen equivalent units (FEU), and procalcitonin (respectively LOINC 731-0, 9015, 9020, 9066, 9063, 9042, 9075, 48065-7, 33959-8).

We compared characteristics of COVID-19 positive patients by race (non-Hispanic black vs. non-Hispanic white). To adjust for potential confounder variables and to facilitate comparison between cohorts, we performed propensity score matching [13]. Selected variables were identified using diagnosis codes and focused on demographics and common clinical comorbidities linked to pulmonary embolism, as detailed in the previous section [9]. A logistic regression model including demographic and comorbidity status for each patient generated a propensity score. Matching was then performed using greedy nearest neighbor matching with a caliper of 0.1 pooled standard deviations. Differences between groups before and after propensity matching were reported as standardized differences with corresponding p-values. A standardized mean difference of 0.1 or less was interpreted as a negligible difference in the mean or proportion of a covariate between the compared groups [14].

Clinical outcomes of interest consisted of development of mortality, intensive care unit admission, mechanical ventilation, and pulmonary embolism within an observation window of 0–30 days after diagnosis of COVID-19, unless stated otherwise. Laboratory values of interest included a range of hematologic and inflammatory serum markers as well as oxygen saturation level; these values were obtained from a narrower window of 0–1 days after index event to capture biomarkers at time of COVID-19 diagnosis.

Categorical measures are presented as percentages, while continuous measures are presented as means with standard deviations. For comparisons of clinical outcomes between groups, relative risk ratios were calculated with corresponding 95% confidence intervals. For comparison of means of laboratory values, two-tailed *t*-tests were obtained. Two-sided p-values of <0.05 were used to determine statistical significance. For selected outcomes, Kaplan-Meier curves and log-rank tests were also calculated. All analyses were performed using browser-based features within the TriNetX network, with the platform based on R software version 3.4.4 (The R Project for Statistical Computing, Vienna, Austria).

3. Results

A total of 346,953 patients with COVID-19 were identified, 3879 of which developed pulmonary embolism within 30 days of COVID-19 diagnosis (1.18%). Of these patients, there were 157,049 white and 50,376 black patients with COVID-19; there were 2036 white and 1088 black patients who developed PE after COVID-19. The overall mean age was 47.6 ± 19.1 years, and 54.7% were female (Table 1). Compared to COVID-19 patients without PE, COVID-19 patients with PE were older, more likely to be male, and more likely to have medical comorbidities including hypertension, diabetes, obesity, reduced mobility, neoplasm, and prior hospitalization. The geographical distribution of these patients within the US is presented in Fig. 1 and Table 2; the distributions of white and black patients were significantly different (χ^2 15,291.4; $p < 0.0001$), with a higher proportion of black COVID-19 patients in the South compared to white patients.

Before propensity matching, blacks with COVID-19 were younger and more likely to be female than whites (Table 3). Black COVID-19 patients had higher prevalence of diabetes, hypertension, and obesity, as well as a higher likelihood of homelessness. White patients had a higher prevalence of neoplasms. After propensity matching, two cohorts of 50,162 black and white patients were analyzed. The cohorts showed improved balance in demographic and clinical characteristics, as shown by standardized mean differences being reduced to <0.10 in all selected variables (Table 3).

Within these matched cohorts, blacks with COVID-19 had a higher mortality rate at 30 days (RR 1.890, $p < 0.0001$), as well as higher rates of hospitalization, ICU care and mechanical ventilation within 30 days of COVID-19 diagnosis (Table 4). Additionally within the matched cohorts, blacks had a higher risk of developing PE (RR 1.537, $p < 0.0001$). The incidence curve for development of mortality and pulmonary embolism for black and white patients is presented in Fig. 2, with a significant difference for both outcomes between blacks and whites at 30 days (χ^2 152.33 for mortality with $p < 0.0001$; χ^2 of 193.12 for PE with $p < 0.0001$).

Significant laboratory differences within 0–1 days of COVID-19 diagnosis between the groups included platelet count in blacks with COVID, as well as higher inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and ferritin) and lower oxygen saturation rate (Table 5). An apparent increase in mean D-Dimer in black patients nearly reached statistical significance (t-value 1.957; $p = 0.0506$).

Within patients with COVID-19 and PE, there were 1088 blacks with COVID-19 associated PE (2.16% of total black COVID-19 patients) and 2036 whites (1.30% of total white COVID-19 patients). The event rate of pulmonary embolism was greater in blacks than whites within all COVID-19 patients in unmatched cohorts (RR 1.666; $p < 0.0001$); however, there was no significant difference in subsets of hospitalized or ICU-admitted COVID-19 patients (Table 6).

We also compared 30-day mortality rates for COVID-19 with PE to either entity alone (e.g., "COVID-19 without PE" and "PE without

Table 1
Baseline characteristics of all COVID-19 patients, COVID-19 patients with PE, and COVID-19 patients without PE.

Parameters		All COVID-19 patients (n = 346,953)	COVID-19 patients with PE (n = 3879)	COVID-19 patients without PE (n = 338,345)	Standardized mean difference
Age (in years)		47.6 ± 19.1	60.4 ± 16.2	47.4 ± 19.0	0.74*
Gender	Male	45.10%	52.6%	45.0%	0.15*
	Female	54.70%	47.4%	54.8%	0.15*
Race	White	56.00%	54.0%	55.8%	0.04
	Black	14.70%	24.3%	14.5%	0.25*
	Asian	2.00%	1.4%	2.0%	0.05
	Native American	0.80%	1.2%	0.8%	0.04
	Other	26.20%	18.8%	26.5%	0.19*
Comorbidities and other conditions	Diabetes	12.60%	28.0%	12.2%	0.4*
	Hypertension	24.20%	46.2%	23.4%	0.49*
	COPD	4.00%	11.2%	3.6%	0.29*
	CKD	5.50%	12.7%	5.1%	0.27*
	Obesity (BMI > 30)	11.50%	19.2%	11.0%	0.23*
	CVA	2.00%	4.9%	1.9%	0.17*
	Neoplasm	16.30%	26.0%	15.8%	0.25*
	Connective tissue disorders	1.40%	2.7%	1.3%	0.1*
	Reduced Mobility	1.00%	2.9%	0.8%	0.15*
	Homelessness	0.6%	1.3%	0.6%	0.07
	Pregnancy	2.6%	1.3%	2.6%	0.1*
	Use of systemic contraceptives	6.1%	2.8%	6.1%	0.16*
	Nicotine dependence	7.0%	10.3%	6.8%	0.13*
	Prior Hospitalization	8.4%	24.6%	7.9%	0.47*

* Significant mean difference of ≥0.10.

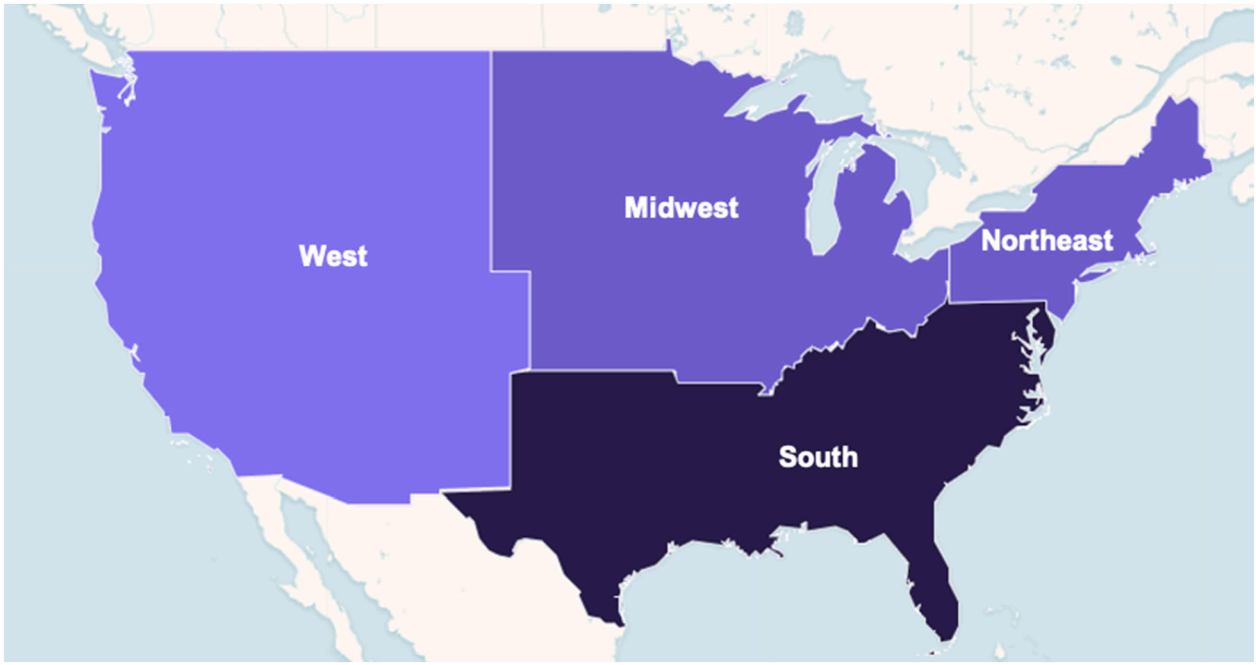

Fig. 1. Regional categorization of COVID-19 patients, as determined by HCO from which patients were counted. The "West" region also includes the states of Alaska and Hawaii.

Table 2
Geographical distribution of COVID-19 patients in the TriNetX database.

US regions	All patients	White patients	Black patients
Northeast	39,431 (11.3%)	16,044 (10.2%)	8526 (16.9%)
Midwest	46,300 (13.3%)	31,025 (19.7%)	7646 (9.19%)
South	115,890 (33.2%)	50,801 (32.3%)	28,482 (56.4%)
West	107,413 (30.8%)	53,613 (34.1%)	4674 (9.3%)
Outside US	30,171 (8.7%)	–	–
Unknown	9512 (2.7%)	5889 (3.7%)	1196 (2.4%)

COVID-19"), for all patients as well as black or white cohorts. To avoid possible confounding effects from undiagnosed COVID-19 in the "PE without COVID-19" group, we created a cohort of patients diagnosed with PE from January 1 – June 30, 2019, predating the COVID-19 pandemic. To avoid immortal time bias, we measured mortality from the event of COVID-19 diagnosis in the "COVID-19 without PE" group and from the event of PE diagnosis for the "COVID-19 with PE" and "PE without COVID-19" groups. The groups in these comparisons were also matched by demographic and clinical characteristics, with outcomes analyzed after propensity matching. For all groups after matching, the 30-day mortality rate within patients with both COVID-19 and PE was

Table 3
Baseline patient characteristics of black and white patients with COVID-19.

		Unmatched cohorts			Matched cohorts		
		Black COVID-19 (n = 50,376)	White COVID-19 (n = 157,049)	Standard mean difference	Black COVID-19 (n = 50,162)	White COVID-19 (n = 50,162)	Standard mean difference
Age (mean years ± standard deviation)		47.1 ± 17.9	50.2 ± 20	0.17*	47.1 ± 17.9	47.8 ± 18.4	0.03
Gender	Male	40.1%	45.7%	0.11*	40.2%	40.5%	0.006
	Female	59.8%	54.3%	0.11*	59.8%	59.5%	0.02
Comorbidities and other conditions	Diabetes	18.0%	12.5%	0.17*	18.5%	18.9%	0.01
	Hypertension	34.3%	28.3%	0.13*	34.0%	33.9%	0.002
	COPD	4.5%	5.6%	0.05	4.5%	4.2%	0.02
	CKD	8.7%	6.3%	0.09	8.6%	8.6%	0.0003
	Obesity (BMI > 30)	16.3%	12.9%	0.1*	16.2%	16.4%	0.007
	CVA	3.2%	2.4%	0.05	3.1%	3.0%	0.009
	Neoplasm	17.2%	21.8%	0.12*	17.2%	16.3%	0.02
	Connective tissue disorder	1.7%	1.7%	0.002	1.7%	1.5%	0.02
	Reduced mobility	1.8%	1.1%	0.06	1.7%	1.7%	<0.0001
	Homelessness	1.5%	0.5%	0.1*	1.2%	1.3%	0.006
	Pregnancy	3.2%	2.5%	0.04	3.2%	3.3%	0.007
	Use of systemic contraceptives	8.2%	7.3%	0.03	8.2%	7.5%	0.03
	Prior Hospitalization	13.0%	10.3%	0.08	12.8%	12.8%	0.002
	Nicotine dependence	8.9%	8.8%	0.002	8.8%	8.7%	0.004

* A significant mean difference of ≥0.10.

Table 4
30-day clinical outcomes of black and white patients with COVID-19. P value of 0.05 or lower is bolded as statistically significant.

	Unmatched cohorts				Matched cohorts			
	Black COVID-19 (n = 50,376)	White COVID-19 (n = 157,049)	Risk ratio (95% CI)	p-Value	Black COVID-19 (n = 50,162)	White COVID-19 (n = 50,162)	Risk ratio (95% CI)	p-Value
Mortality	1360 (2.700%)	2653 (1.689%)	1.598 (1.498, 1.705)	**<0.0001**	1351 (2.693%)	715 (1.425%)	1.89 (1.727, 2.067)	**<0.0001**
Hospitalization	5464 (10.846%)	8577 (5.461%)	1.986 (1.923, 2.051)	**<0.0001**	5407 (10.779%)	2885 (5.751%)	1.874 (1.794, 1.957)	**<0.0001**
ICU admission	1971 (3.913%)	2815 (1.792%)	2.183 (2.063, 2.310)	**<0.0001**	1947 (3.881%)	972 (1.938%)	2.003 (1.857, 2.161)	**<0.0001**
Mechanical ventilation	1519 (3.015%)	2607 (1.660%)	1.816 (1.706, 1.934)	**<0.0001**	1507 (3.004%)	798 (1.591%)	1.888 (1.735, 2.056)	**<0.0001**
Pulmonary embolism	1088 (2.160%)	2036 (1.296%)	1.666 (1.548, 1.792)	**<0.0001**	833 (1.661%)	542 (1.08%)	1.537 (1.380, 1.711)	**<0.0001**

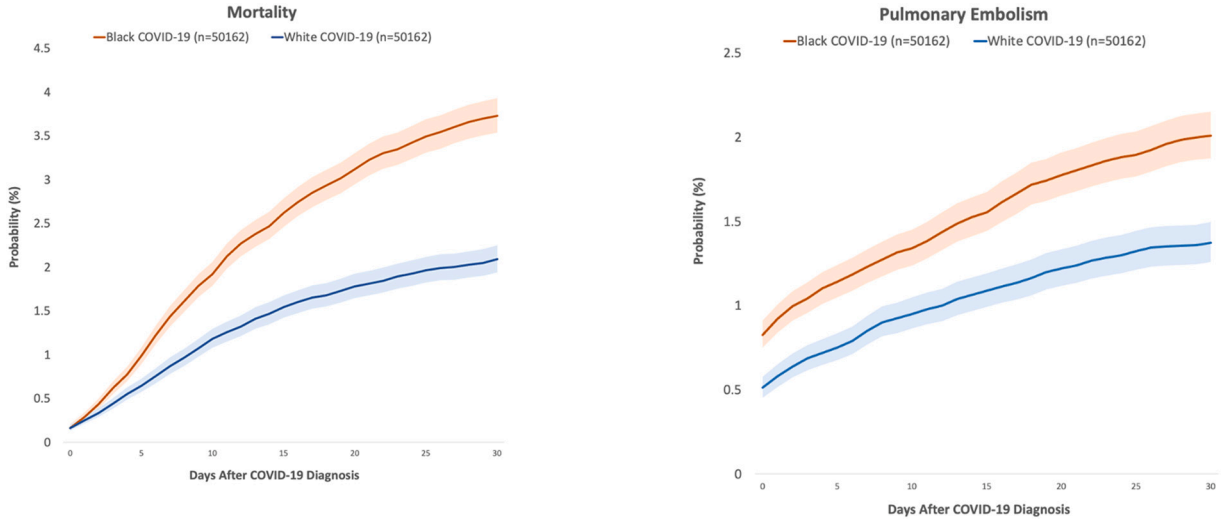

Fig. 2. Incidence of (a) mortality and (b) pulmonary embolism within 0–30 days of COVID-19 diagnosis, comparing black and white patients with COVID-19. Shaded areas represent 95% confidence intervals.
Mortality: Log-rank test χ^2 152.33, $p < 0.0001$.
Pulmonary embolism: Log-rank test χ^2 193.12, $p < 0.0001$.

Table 5
Selected lab values at 0–1 days after COVID-19 diagnosis, after propensity matching. P value of 0.05 or lower is bolded as statistically significant.

	Mean value in black COVID-19 (n = 40,147)	Number of patients with result	Mean value in white COVID-19 (n = 40,147)	Number of patients with result	T-value	p-Value
Platelets (K/dL)	269.97 ± 117.8	17,244	250.71 ± 105.7	11,980	14.331	**<0.0001**
D-Dimer (DDU ng/mL)	1346.9 ± 2971	768	992.7 ± 2026	322	1.957	0.0506
Erythrocyte sedimentation rate (U/L)	55.94 ± 33.0	1588	41.83 ± 28.8	747	10.035	**<0.0001**
C-reactive protein (mg/L)	80.97 ± 88.7	6608	74.16 ± 78.6	3902	3.962	**<0.0001**
Ferritin (ng/mL)	1155.6 ± 4301	5315	797.60 ± 2147	2610	4.014	**<0.0001**
Oxygen saturation (%)	85.33 ± 20.6	4722	86.64 ± 18.8	1912	−2.424	**0.0154**

Table 6
Comparison of 30-day event rates of pulmonary embolism in black and white patients with COVID-19, in different care settings. P value of 0.05 or lower is bolded as statistically significant.

	Race	Number of patients	(#) of COVID-19 patients with associated PE	(%) of COVID-19 patients with associated PE	Risk ratio (95% CI)	p-Value
All patients with COVID-19	Black	50,376	1088	2.16%	1.666 (1.548,	**<0.0001**
	White	157,049	2036	1.30%	1.792)	
	All	346,953	3879	1.18%	–	
Hospitalized patients with COVID-19	Black	6426	453	7.04%	0.978 (0.875,	0.7048
	White	10,508	757	7.20%	1.095)	
	All	24,520	1549	6.32%	–	
ICU patients with COVID-19	Black	2426	237	9.77%	1.016 (0.868,	0.8451
	White	3608	347	9.62%	1.188)	
	All	8710	772	8.86%	–	

higher than with either entity alone (RR 1.575–1.750, $p < 0.01$ compared to COVID-19 alone; RR 3.000–5.389, $p < 0.0001$ compared to pre-COVID PE; Table 7).

Before propensity matching, blacks with COVID and PE were younger and had a higher proportion of diabetes, hypertension, chronic kidney disease, homelessness, and prior hospitalization; whites had a higher proportion of COPD (Table 8). After propensity matching, there were two well-balanced cohorts of 1026 black and 1026 white patients with COVID-19 and PE. Black patients with COVID-19 and PE had a higher rate of 30-day mortality (RR 1.397; $p = 0.0174$); there was no significant difference in hospitalization, ICU admission, or mechanical ventilation (Table 8).

4. Discussion

This retrospective study used a large multicenter electronic health record dataset to investigate associations and clinical outcomes of COVID-19 and pulmonary embolism within non-Hispanic black and white patients. Patients with both COVID-19 and PE had an increased risk of 30-day mortality, compared to patients with only COVID-19 or patients with only PE before the COVID-19 pandemic. Compared to white patients, black patients had a higher proportion of comorbidities including hypertension, diabetes, and obesity. Black patients had a higher risk of developing PE compared to white patients, even after matching for common clinical comorbidities. Black patients also had a higher risk of 30-day mortality, hospitalization, ICU admission, and mechanical ventilation compared to whites, a finding also seen in other studies [15]. At time of COVID-19 diagnosis, black patients with COVID-19 presented in a more severe state of disease, as shown by higher inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate as well as lower oxygen saturation level. Additionally, we found an increased risk of 30-day mortality in black patients with COVID-19 and associated pulmonary embolism, compared to white patients; however, there was no significant difference in hospitalization, ICU admission, or mechanical ventilation (Table 9).

Racial differences in the prevalence and severity of COVID-19 have been noted as the pandemic has unfolded in the United States, with black patients representing the majority of COVID-19 cases and having higher rates of comorbidities [1], as well as higher prevalence and overall mortality rates [16]. Racial inequalities in general key health outcomes have long been known, with disproportionate effects falling upon African-American communities. Such disparities are wide-ranging, including prevalence of diabetes and obesity, mortality from cardiovascular disease, and overall life expectancy [17]. One possible explanation for the disparity in COVID-19 related outcomes is the higher rate of underlying comorbidities in black populations such as diabetes,

Table 7
30-day mortality rate in patients with COVID-19 and PE, compared to COVID-19 without PE and pre-COVID PE. P value of 0.05 or lower is bolded as statistically significant.

Comparison of patients with COVID-19 and PE, vs. patients with COVID-19 without PE					
		COVID-19 patients with associated PE	COVID-19 patients without PE	Risk ratio (95% CI)	p-Value
30-day mortality	Black (n = 1082)	96 (8.864%)	59 (5.448%)	1.627 (1.19, 2.225)	**0.002**
	White (n = 2037)	119 (5.842%)	68 (3.338%)	1.75 (1.307, 2.342)	**0.0001**
	All (n = 3878)	274 (7.065%)	174 (4.487%)	1.575 (1.309, 1.894)	**<0.0001**

Comparison of patients with COVID-19 and PE, vs. patients with PE before COVID-19					
		COVID-19 patients with associated PE	Patients with PE, before COVID-19	Risk ratio (95% CI)	p-Value
30-day mortality	Black (n = 1082)	97 (8.965%)	18 (1.664%)	5.389 (3.282, 8.848)	**<0.0001**
	White (n = 2021)	117 (5.789%)	39 (1.93%)	3.000 (2.099, 4.288)	**<0.0001**
	All (n = 3861)	273 (7.071%)	86 (2.227%)	3.174 (2.502, 4.028)	**<0.0001**

Table 8
Baseline characteristics of black and white patients with COVID-19 and associated PE, before and after propensity matching.

		Black COVID-19 patients with associated PE (n = 1088)	White COVID-19 patients with associated PE (n = 2036)	Standardized mean difference (SMD)	Black COVID-19 patients with associated PE (n = 1026)	White COVID-19 patients with associated PE (n = 1026)	Standardized mean difference (SMD)
		Unmatched cohorts			Matched cohorts		
Patient age (mean ± standard deviation)		57.5 ± 15.9	62.3 ± 16.0	0.3*	58.9 ± 15.9	59.0 ± 16.3	0.005
Gender	Male	47.0%	47.2%	0.005	45.6%	45.2%	0.009
	Female	53.0%	52.8%	0.005	54.4%	54.8%	0.009
Comorbidities and other conditions	Diabetes	44.5%	33.1%	0.23*	38.1%	40.5%	0.05
	Hypertension	68.6%	62.2%	0.14*	64.3%	65.2%	0.02
	COPD	18.8%	27.0%	0.2*	20.3%	20.3%	<0.0001
	CKD	25.5%	20.1%	0.13*	22.2%	21.6%	0.02
	Obesity (BMI > 30)	34.6%	31.9%	0.06	32.2%	35.2%	0.06
	CVA	12.2%	9.8%	0.08	11.0%	10.4%	0.02
	Neoplasm	37.5%	43.4%	0.12	37.9%	39.2%	0.03
	Connective tissue disorder	6.5%	6.6%	0.008	6.6%	6.4%	0.009
	Reduced mobility	11.0%	8.2%	0.09	8.4%	8.4%	<0.0001
	Homelessness	5.5%	3.0%	0.12*	3.5%	3.7%	0.01
	Pregnancy	1.9%	2.0%	0.004	2.2%	2.4%	0.01
	Use of systemic contraceptives	4.8%	3.9%	0.04	5.1%	4.8%	0.01
	Prior Hospitalization	54.0%	46.2%	0.16*	49.6%	48.2%	0.03
	Nicotine dependence	19.6%	19.6%	0.0006	17.2%	18.7%	0.04

* A significant mean difference of ≥0.10.

Table 9
Clinical outcomes of black and white patients with COVID-19 and associated PE. P value of 0.05 or lower is bolded as statistically significant.

		Unmatched cohorts				Matched cohorts			
		Black COVID-19 patients with associated PE (n = 1088)	White COVID-19 patients with associated PE (n = 2036)	Risk ratio (95% CI)	p-Value	Black COVID-19 patients with associated PE (n = 1026)	White COVID-19 patients with associated PE (n = 1026)	Risk ratio (95% CI)	p-Value
Outcomes at 30 days	Mortality	116 (10.662%)	140 (6.876%)	1.551 (1.226, 1.961)	**0.0002**	109 (10.624%)	78 (7.602%)	1.397 (1.059, 1.844)	**0.0174**
	Hospitalization	340 (31.25%)	615 (30.206%)	1.035 (0.927, 1.155)	0.5463	316 (30.799%)	336 (32.749%)	0.94 (0.828, 1.068)	0.343
	ICU admission	140 (12.868%)	244 (11.984%)	1.074 (0.884, 1.304)	0.4737	128 (12.476%)	139 (13.548%)	0.921 (0.736, 1.152)	0.4704
	Mechanical ventilation	92 (8.456%)	140 (6.876%)	1.23 (0.955, 1.583)	0.1087	87 (8.48%)	69 (6.725%)	1.261 (0.93, 1.709)	0.1338

hypertension, and obesity [18]. These comorbidities have been associated with higher risk of requiring hospitalization for COVID-19 infection [19] and have also been linked to higher risk for venous thromboembolism [20]. However, in our study, the higher mortality and pulmonary embolism rate persisted after propensity matching to control for these comorbidities.

An elevated risk for thromboembolic events in African-Americans has been seen before the COVID-19 pandemic, though the reasons are not fully understood [21,22]. Studies have shown a higher prevalence of PE in blacks, despite lower prevalence of transient risk factors like surgery and trauma and classic genetic predispositions such as mutations in factor V Leiden and prothrombin [21,23]. Other genetic factors may contribute to this disparity; for example, sickle cell trait (SCT) patients have higher risk for pulmonary embolism with or without associated deep venous thrombosis [24]. Additionally, studies have shown a higher D-Dimer in blacks with hypertension [25]. Higher D-Dimer in blacks has been associated with higher all-cause mortality, with underlying genetic explanation of *HBB* rs334 SCT locus as well as a variant of *F3* locus, encoding tissue factor within the extrinsic coagulation pathway [26]. Finally, an autopsy series of black COVID-19 decedents in Louisiana observed diffuse alveolar damage and specifically pulmonary microangiopathy in all patients [27]. These findings suggest that blacks may be in a higher baseline prothrombotic state due to phenotypic and epigenetic variants, leaving them more vulnerable to COVID-19-associated coagulopathy.

Social disparities in access to health care may also help explain our observation of increased rate of PE in blacks with COVID-19. Social determinants such as housing environment, access to healthcare and healthy foods, and socioeconomic status are closely interlinked to health outcomes. In communities where adverse social determinants already are linked to poorer health outcomes, the tasks of social distancing and other prevention measures for COVID-19 become even more difficult [28]. Besides possible differences in thrombotic predisposition, many blacks may be presenting at a later, more severe stage within the course of COVID-19 disease. This would also contribute to the worse clinical outcomes and higher inflammatory markers, such as D-Dimer, seen

within blacks with COVID-19 in our study. Finally, while we were unable to analyze patients by ZIP code or city, black and white COVID-19 patients did have a different overall geographic distribution with proportionally more black patients located in the Southeast US. Corresponding geographic differences in social environment and healthcare access may also contribute to the differences seen in our analyses.

Limitations of our study include dependence on medical records data and aggregate nature of our dataset. First, while our data represents a large and diverse cohort of COVID-19 and comparison patients, it is based on direct EMR data aggregation. Such data may have limitations in coding or data entry, although the aggregation methods in real-time fashion limit data collection errors at the point of the study investigators. As our dataset is compiled in a de-identified manner from multiple health centers, a small number of patients may have crossed from one HCO to another in the course of their COVID-19 management; however, this would affect all cohorts equally and would reflect only a small fraction of our cohort, given that each individual HCO in TriNetX is a large integrated system comprised of many healthcare centers. Additionally, inter-institutional differences in surveillance and treatment of PE may also be reflected within our observations. As this dataset tracks only patients seeking medical care, asymptomatic patients or patients unable to access health care could not be assessed. Due to the aggregate nature of our data, granular details such as severity of PE, severity of clinical comorbidities (e.g., degree of hypertension) or timing of symptoms could not be assessed. While we strived to control for clinical comorbidities and included homelessness as a socioeconomic variable, many socioeconomic details such as ZIP code of patient, type of health center, or patient income, were unavailable or limited within the de-identified nature of the TriNetX data; this limits our ability to assess the contribution of such socioeconomic factors to our findings. Finally, laboratory values were not performed for all patients within the cohort, and therefore the roles of some lab parameters may be undervalued.

Overall, we hope that these findings will help inform interventions to mitigate the impact of COVID-19 upon vulnerable communities. A greater understanding of potential underlying genetic and environmental factors can help identify those at more inherent risk for severe thromboembolic disease. With a more granular understanding of such factors, clinicians can improve surveillance and treatment strategies for COVID-19 associated coagulopathy, perhaps even including tailored anticoagulation regimens or differences in vaccine deployment. In addition, more detailed investigations into socioeconomic factors, such as differences in housing environment or ease of access to health care, can aid not just in fighting the COVID-19 pandemic but also in increasing overall health equity.

5. Conclusions

This multicenter retrospective cohort study demonstrated that black patients with COVID-19 have a higher risk of developing pulmonary embolism, compared to white patients. Additionally, black patients with COVID-19 and PE had a higher risk of 30-day mortality. Higher clinical suspicion for pulmonary embolism in black patients with COVID-19 may be warranted, especially in those who have other risk factors increasing pre-test probability for thromboembolism.

CRediT authorship contribution statement

Brandon Metra: Conceptualization; Methodology; Formal analysis; Writing – Original draft; Visualization
Ross Summer: Conceptualization; Writing – Review & editing
Sandra Elaine Brooks: Writing – Review & editing
Gautam George: Writing – Review & editing
Baskaran Sundaram: Conceptualization; Methodology; Writing – Review & editing; Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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