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Sex Differences in Thrombosis and Mortality in Patients Hospitalized for COVID-19

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Gender-specific differences in thrombosis have been reported in hospitalized patients with COVID-19. We sought to investigate the influence of age on the relation between gender and incident thrombosis or death in COVID-19. We identified consecutive adults aged ≥18 years hospitalized with COVID-19 from March 1, 2020, to April 17, 2020, at a large New York health system. In-hospital thrombosis and all-cause mortality were evaluated by gender and stratified by age group. Logistic regression models were generated to estimate the odds of thrombosis or death after multivariable adjustment. In 3,334 patients hospitalized with COVID-19, 61% were men. Death or thrombosis occurred in 34% of hospitalizations and was more common in men (36% vs 29% in women, p <0.001; adjusted odds ratio [aOR] 1.61, 95% confidence interval [CI] 1.36 to 1.91). When stratified by age, men had a higher incidence of death or thrombosis in younger patients (aged 18 to 54 years: 21% vs 9%, aOR 3.17, 95% CI 2.06 to 5.01; aged 55 to 74 years: 39% vs 28%, aOR 1.63, 95% CI 1.28 to 2.10), but not older patients (aged ≥75 years: 55% vs 48%; aOR 1.20, 95% CI 0.90 to 1.59) (interaction p value: 0.01). For the individual end points, men were at higher risk of thrombosis (19% vs 12%; aOR 1.65, 95% CI 1.33 to 2.05) and mortality (26% vs 23%; aOR 1.41, 95% CI 1.17 to 1.69) than women, and gender-specific differences were attenuated with older age. Associations between thrombosis and mortality were most striking in younger patients (aged 18 to 54 years, aOR 8.25; aged 55 to 74 years, aOR 2.38; aged >75 years, aOR 1.88; p for interaction <0.001) but did not differ by gender. In conclusion, the risk of thrombosis or death in COVID-19 is higher in men compared with women and is most apparent in younger age groups. **(Am J Cardiol 2022;170:112−117)**

Patients hospitalized with COVID-19 are at risk for thrombotic complications, including deep vein thrombosis (DVT), pulmonary embolism (PE), ischemic stroke, and myocardial infarction (MI).[1−3] Thrombosis occurs in 16% to 31% of patients hospitalized with COVID-19 and is associated with critical illness and all-cause mortality.[1,2,4] Older age and male gender are established risk factors for severity of illness and mortality associated with COVID-19.[5−11] However, the influence of age on gender-specific differences in COVID-19 is unknown. Age-dependent gender-specific differences in outcomes have been reported in cardiovascular diseases before the COVID-19 pandemic. In patients with acute MI, for example, younger but not older women have excess in-hospital mortality compared with men of the same age.[12,13] In community cohorts, women of reproductive age have higher risks of venous thrombosis and lower risks of arterial thrombosis compared with age-matched men.[13−15] This study aimed to investigate the influence of age on the relation between gender and incident thrombosis or death in patients hospitalized with COVID-19, after accounting for differences in demographics, clinical comorbidities, and disease presentation.

Methods

The study was approved by the New York University (NYU) Grossman School of Medicine institutional review board. Consecutive adults aged ≥18 years with COVID-19 admitted to NYU Langone Health, a large health care system in New York, between March 1, 2020, and April 17, 2020, were identified. All patients were required to have a positive nucleic acid amplification test for SARS-CoV-2 during hospitalization and a diagnosis of COVID-19. Patient demographics and clinical comorbidities were determined through a systematic query of the electronic health record, as previously described.[1]

Thrombotic events of interest included those occurring in both the venous and arterial circulation. Venous thromboembolism (VTE) was defined as DVT or PE, and arterial thrombosis was defined as ischemic stroke, myocardial infarction, or other systemic thromboembolism. Events were identified using an open-source natural language processing tool to search clinical documentation and radiology reports.[16] Additional thrombotic events were identified through a query of the relevant International Classification Of Diseases, 10th Revision codes, and review of echocardiography reports. All suspected thromboses were confirmed

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by a manual review of the medical record. In-hospital mortality or discharge to hospice was determined for all patients. Owing to the potential for multiple contributing causes in critically ill patients with multi-organ dysfunction, adjudication of the cause of death was not performed. Fatal thrombosis was defined as any arterial or venous thrombosis that occurred in a patient who subsequently died in hospital. Given the competing risk of death, we evaluated the composite end point of death or thrombosis in our primary analyses. Critical illness was defined as mechanical ventilation or transfer to the intensive care unit during hospitalization for COVID-19.

Categorical data are shown as frequencies and proportions and compared by chi-square tests. Continuous data are expressed as median (interquartile range) and compared by Mood's test. The incidence of thrombosis and in-hospital mortality was evaluated in subgroups by age and gender. Multivariable logistic regression models were generated to estimate the odds of thrombosis, death, or both by age subgroup and gender, adjusted for race/ethnicity, body mass index (BMI), smoking, clinical comorbidities including hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, a history of MI, heart failure, atrial fibrillation, peripheral artery disease, known cerebrovascular disease, chronic obstructive pulmonary disease, kidney disease, any history of malignancy, and initial D-dimer concentration at the time of hospital presentation.[1,17] Multivariable logistic regression models were also generated to assess risk factors associated with thrombosis in gender-stratified cohorts, adjusted for demographics and covariates as previously described. The influence of age on the relation between gender and incident thrombosis or death was evaluated by adding an interaction term for age subgroup (18 to 54, 55 to 74, and ≥75 years) and gender to the multivariable logistic regression models. Statistical analyses were conducted using R Studio Software Version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). Two-tailed p values <0.05 were considered statistically significant.

Results

In 3,334 patients admitted with COVID-19, 2,014 (61%) were men. Patient characteristics by age and gender are listed in Table 1. A greater proportion of women were of Black race compared with men. Across all age groups, men had a higher prevalence of coronary artery disease than women. In patients ≥55 years of age, smoking was more common in men. Women had lower median BMIs compared with men in patients aged <55 years (Table 1).

The composite end point of death or thrombosis occurred in 34% patients hospitalized with COVID-19 and was more common in men than women (36% vs 29%, p <0.001). After adjusting for age, race/ethnicity, BMI, smoking,

Table 1
Baseline characteristics of men and women hospitalized with COVID-19 infection by age group

	Men 18-54 (n=634)	Women 18-54 (n=364)	P value	Men 55-74 (n=943)	Women 55-74 (n=527)	P value	Men >74 (n=437)	Women >74 (n=429)	P value
Age, years	45 (38-50)	42 (33-49)	0.001	64(60-69)	65 (61-70)	0.09	82 (78-86)	83 (79 -87)	0.05
Race									
White	199 (31%)	122 (34%)	0.53	413 (44%)	204 (38%)	0.07	258 (59%)	248 (58%)	0.77
Black	69 (11%)	75 (21%)	<0.001	135 (14%)	118 (22%)	<0.001	44 (10%)	68 (16%)	0.014
Hispanic	286 (45%)	139 (38%)	0.039	214 (23%)	158 (30%)	0.0025	76 (17%)	71 (17%)	0.81
Asian	34 (5%)	29 (8%)	0.14	76 (8%)	40 (7%)	0.82	33 (8%)	26 (6%)	0.46
Other	280 (44%)	120 (33%)	<0.001	241 (26%)	121 (23%)	0.30	74 (17%)	69 (16%)	0.81
Unknown	46 (7%)	14 (4%)	0.04	69 (7%)	25 (5%)	0.07	22 (5%)	13 (3%)	0.19
Comorbidities									
BMI, kg/m	30 (27-35)	32 (27 -38)	0.003	29 (33- 26)	29 (26 -35)	0.13	26 (23 -29)	26 (23 -30)	0.22
Chronic obstructive pulmonary disease	30 (5%)	33 (9%)	0.01	71 (8%)	77 (15%)	<0.001	64 (15%)	80 (19%)	0.14
Coronary artery disease	40 (6%)	9 (2%)	0.01	222 (24%)	71 (14%)	<0.001	164 (38%)	111 (26%)	<0.001
Current smoker	40 (6%)	32 (9%)	0.18	265 (28%)	108 (21%)	0.002	170 (39%)	119 (28%)	<0.001
Diabetes Mellitus	185 (29%)	96 (26%)	0.38	404 (43%)	235 (45%)	0.55	169 (39%)	157 (37%)	0.58
Hyperlipidemia	115 (18%)	61 (17%)	0.06	424 (45%)	231 (44%)	0.72	231 (53%)	223 (52%)	0.85
Hypertension	182 (29%)	94 (26%)	0.09	567 (60%)	310 (59%)	0.66	253 (58%)	270 (63%)	0.04
Congestive heart failure	20 (3%)	9 (2%)	0.67	65 (7%)	39 (7%)	0.80	69 (16%)	77 (18%)	0.45
Myocardial infarction	16 (3%)	5 (<1%)	0.32	64 (7%)	31 (6%)	0.57	39 (9%)	40 (9%)	0.93
Peripheral vascular. disease	16 (3%)	12 (3%)	0.61	79 (8%)	30 (6%)	0.08	60 (14%)	46 (11%)	0.21
Cerebrovascular disease	9 (1%)	10 (3%)	0.22	54 (6%)	32 (6%)	0.88	57 (13%)	50 (12%)	0.60
Renal disease	29 (5%)	23 (6%)	0.30	123 (13%)	64 (12%)	0.68	80 (18%)	75 (17%)	0.82
Malignancy	7 (1%)	10 (3%)	0.09	51 (5%)	40 (8%)	0.12	52 (12%)	34 (8%)	0.07
Atrial fibrillation	4 (<1%)	2 (<1%)	1	56 (6%)	31 (6%)	1	74 (17%)	63 (15%)	0.42
D-Dimer at hospital presentation	300 (202-490)	277 (202-502)	0.003	403 (255-769)	362 (223- 659%)	0.12	493 (317- 975)	575 (328-1113)	0.20

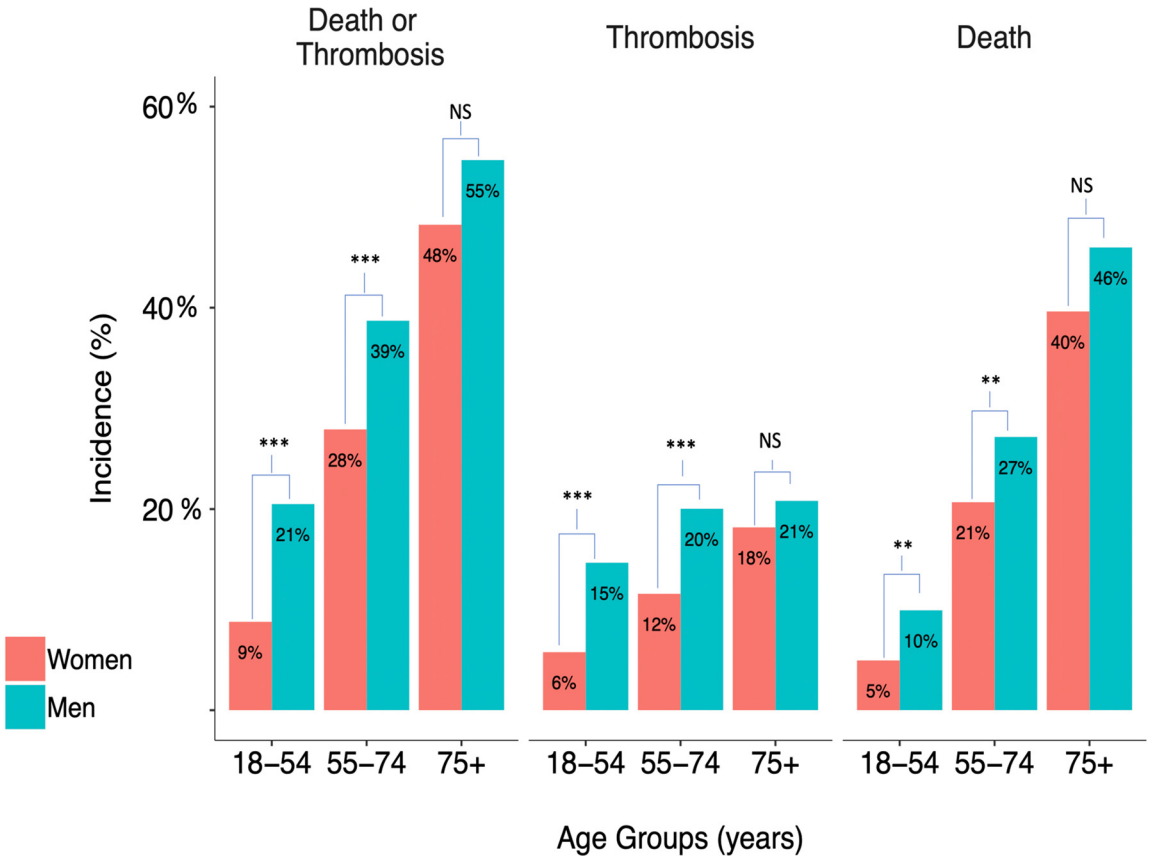

Figure 1. Incidence of Events in Men and Women Hospitalized with COVID-19 Infection.

clinical comorbidities, and initial D-dimer concentration, men were 65% more likely to develop death or thrombosis than women (adjusted odds ratio [aOR] 1.65, 95% confidence interval [CI] 1.32 to 2.05). When stratified by age, men had a greater risk of death or thrombosis than women in patients aged 18 to 54 years (21% vs 9%, p <0.001; aOR 3.17, 95% CI 2.06 to 5.01) and 55 to 74 years (39% vs 28%, p <0.001 aOR 1.63, 95% CI 1.28 to 2.10), but not older adults aged ≥75 years (55% vs 48% p = 0.07; aOR 1.20, 95% CI 0.90 to 1.59; p for interaction = 0.01; Figures 1 and 2).

A greater proportion of men hospitalized with COVID-19 had an in-hospital thrombotic event compared with women (19% vs 12%, p <0.001; aOR 1.65, 95% CI 1.33 to 2.05). A consistent gender-specific increased risk in men was observed for both venous (8% vs 4%, p <0.001; aOR 1.84, 95% CI 1.30 to 2.65) and arterial (12% vs 9%, p = 0.006; aOR 1.45, 95% CI 1.13 to 1.87) thrombosis. When evaluated by subtype of thrombosis, the incidence of MI, DVT, and PE was higher in men compared with women (Supplementary Figure 1). When analyzed by age, men had a greater risk of any thrombosis than women in younger cohorts (aged 18 to 54 years: 15% vs 6%, aOR 3.85, 95% CI 2.22 to 6.94; aged 55 to 74 years: 20% vs 12%, aOR 1.65, 95% CI 1.18 to 2.33), but not older cohorts (aged ≥75 years: 21% vs 18% p = 0.37; aOR 1.08, 95% CI 0.75 to 1.56; p for interaction = 0.01) (Figures 1 and 2). Similar findings were observed for VTE and arterial thrombotic events, with younger, but not older men having significantly higher risk of VTE (aged 18 to 54 years: 8% vs 3%, aOR 2.66, 95% CI 1.51 to 4.93; aged 55 to 74 years: 10% vs 5%, aOR 1.43, 95% CI 1.10 to 1.89; aged >75 years: 3% vs 3%, aOR) and arterial thrombosis (aged 18 to 54 years: 9% vs 3%, aOR 3.78, 95% CI 1.79 to 8.78; aged 55 to 74 years: 17% vs 12%, aOR 1.46, 95% CI 0.98 to 2.23; aged >75 years: 13% vs 18%, aOR 1.11, 95% CI 0.76 to 1.64) than women (Supplementary Figures 2 and 3). Gender-specific risk factors for any thrombosis in patients with COVID-19 are listed in Supplementary Table 1. In women, but not men, older age was an independent risk factor for thrombosis. Coronary artery disease and elevated initial D-dimer concentrations were associated with increased odds for thrombosis in both men and women (Supplementary Table 1).

All-cause mortality was higher in men hospitalized with COVID-19 compared with women (26% vs 22%, p = 0.03, aOR 1.18, 95% CI 1.00 to 1.41). Gender differences in mortality were observed; however after multivariable adjustment, no significant age-gender interaction was observed (p for interaction = 0.30; Figures 1 and 2).

In patients with COVID-19 with thrombosis, outcomes were poor. Patients with thrombosis versus without had a higher incidence of critical illness (49% vs 23%, p <0.001, aOR 3.21, 95% CI 2.63 to 3.92) and in-hospital mortality (43% vs 21%, p <0.001, aOR 2.66, 95% CI 2.18 to 3.26; Table 2). The association between thrombosis and mortality was comparable in men (43% vs 22% without thrombosis; aOR 2.54, 95% CI 2.00 to 3.25) and women (44% vs 20%

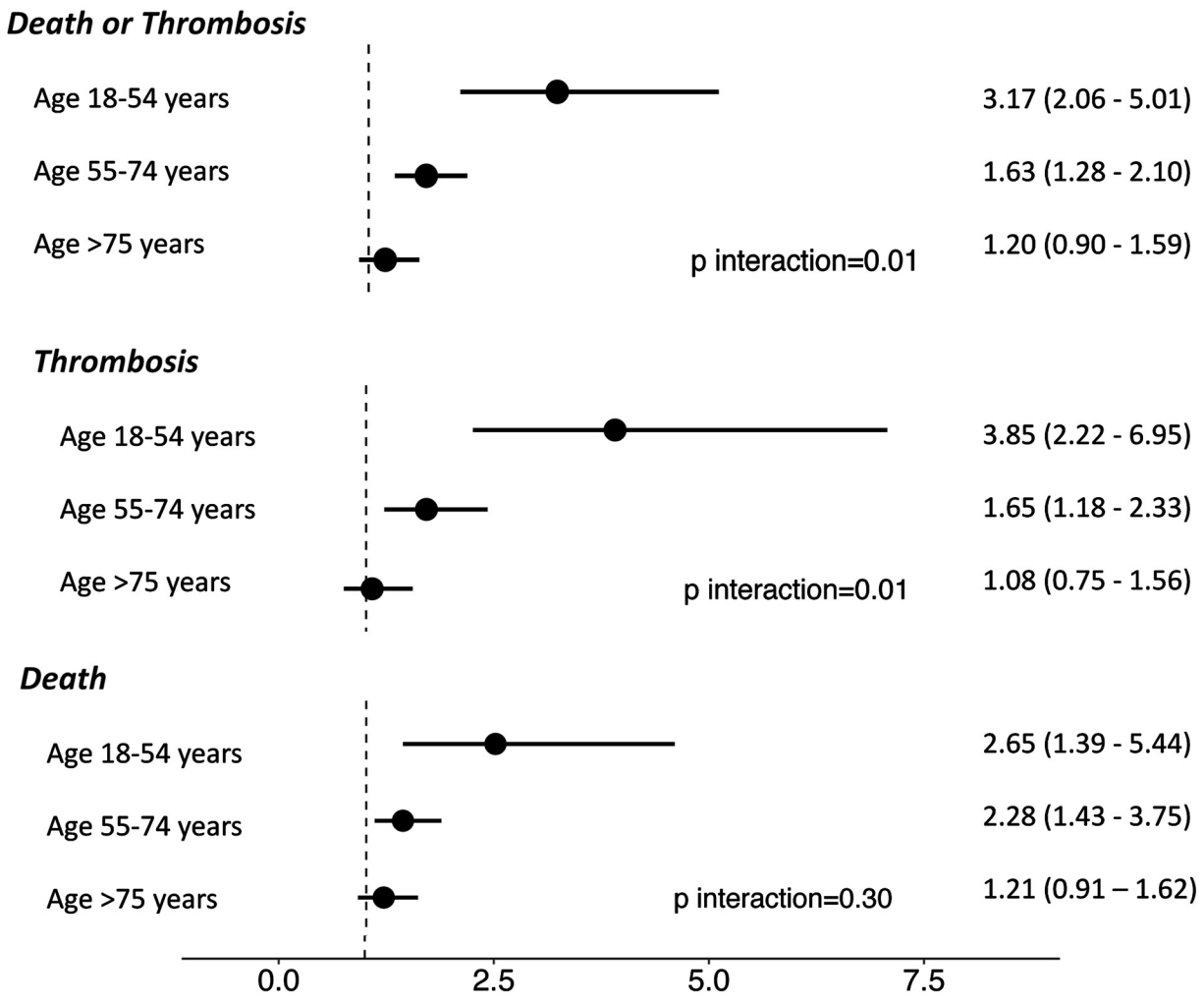

Figure 2. Adjusted Odds of Events in Men Relative to Women Hospitalized with COVID-19 by Age Group.

without thrombosis; aOR 3.02, 95% CI 2.08 to 4.37; p for interaction = 0.412; Table 2). The risk of mortality in patients with a thrombotic event was significant across all age groups (aged 18 to 55 years: 6% vs 2%, p <0.001, aOR 8.25, 95% CI 4.69 to 14.63; aged 54 to 75 years: 19% vs 9%, p <0.001, aOR 2.38, 95% CI 1.77 to 3.23; aged >75 years: 18% vs 10%, p <0.001, aOR 1.88, 95% CI 1.32 to 2.70); however, the association between thrombosis and death was most striking in younger patients (p for interaction p <0.001; Table 2).

Discussion

In this retrospective cohort of adults hospitalized with COVID-19, men had a higher risk of death or thrombosis than women, with gender differences most pronounced in the youngest patients and attenuated with older age. Gender differences were also observed in the individual end point of thrombosis, with a nearly 2-fold excess risk of VTE and a 3-fold risk of arterial events in men compared with women. To our knowledge, this is the first study to explore age and gender differences in the incidence of thrombotic events or death in COVID-19. Our data provide compelling evidence that thrombosis, a potentially fatal complication of SARS-CoV-2 infection, may contribute to the observed gender differences in mortality from COVID-19.

Observations reported in this analysis are consistent with previous studies demonstrating gender differences in COVID-19 outcomes.[4] As of September 2021, men accounted for 57% of COVID-related deaths and 64% of intensive care unit admissions, according to dis-aggregated gender data available in 109 countries.[11,18] Similar to our findings, recent propensity-matched survival analysis showed that comorbid conditions could not fully explain observed gender differences in mortality, however, interaction testing by age subgroups was not performed.[9] To our knowledge, previous studies have not investigated the influence of age on the association between gender and clinical outcomes, including thrombosis.

We observed a significant age-gender interaction on the outcome of thrombosis or death during hospitalization for COVID-19. This observation cannot be explained by gender differences in traditional cardiovascular risk factors in our cohort, as younger women had a similar prevalence of cardiovascular risk factors compared with younger men. Differences in female sex hormones concentrations, including the systemic effects of estrogen, could account for

Table 2
Mortality by age group and gender in COVID-19 patients with and without thrombosis

	Men & Women			Men			Women		
	No thrombosis (n=2801)	Thrombosis (n=533)	Adjusted Odds Ratio (95% Confidence Interval)	No thrombosis (n=1641)	Thrombosis (n=373)	Adjusted Odds Ratio (95% Confidence Interval)	No thrombosis (n=1160)	Thrombosis (n=160)	Adjusted Odds Ratio (95% Confidence Interval)
Overall	587 (21%)	230 (43%)	2.66 (2.18-3.26)	361 (22%)	159 (43%)	2.54 (2.00-3.25)	226 (20%)	71 (44%)	3.02 (2.08-4.37)
Age Group:									
18-55	48 (2%)	33 (6%)	8.25 (4.69-14.63)	37 (2%)	26 (7%)	6.01(3.15-11.52)	11 (1%)	7 (4%)	36.32 (7.08-217)
54-75	262 (9%)	103 (19%)	2.38 (1.77-3.23)	176 (11%)	80 (22%)	2.31 (1.64-3.26)	86 (7%)	23 (14%)	2.52 (1.35-4.65)
>75	277 (10%)	94 (18%)	1.88 (1.32-2.70)	148 (9%)	53 (14%)	2.01 (1.21-3.36)	129 (11%)	41 (26%)	2.03 (1.17-3.54)

favorable outcomes observed in younger women compared with men, but this requires further study.

Inflammation and sepsis can significantly increase risks of venous and arterial thrombosis.[19–23]. Gender differences in inflammation in response to COVID-19 have been reported,[24] but the impact of the inflammatory response on thrombotic outcomes in COVID-19 is unknown.[8] In addition, modulation of the renin-angiotensin-aldosterone axis, endothelial responses to inflammation, and coagulation profiles also vary by gender and age,[18,25,26] and may also contribute to differences in thrombotic risk.[21,27,28]

Consistent with previous studies, COVID-19 thrombosis was significantly associated with in-hospital mortality in men and women, and this relation was most pronounced in younger patients of both genders.[1] This may reflect competing risks of death from nonvascular causes in older patients with COVID-19. Alternatively, younger patients may be more likely to develop a large burden of thrombus associated with severe hemodynamic consequences in the setting of COVID-19.

This retrospective observational study has several important limitations. First, we were unable to account for unmeasured confounders associated with thrombosis, including recent surgery, trauma, thrombophilia, or immobility.[29] Although all patients in this cohort were hospitalized with COVID-19, we cannot exclude unmeasured gender differences in disease severity and immobility, a known risk factor for VTE. Even so, arterial thromboses were also more common in men than women, suggesting that immobility alone does not explain the observed differences in thrombotic risk associated with COVID-19. Second, we were unable to assess the use of prophylactic versus therapeutic anticoagulation during hospitalization. Patients in the study were admitted before widespread recognition of thrombotic risk in COVID-19, anticoagulation strategies for COVID-19 were not standardized at the time of this study, and gender differences in antithrombotic prescribing cannot be excluded. Similarly, our study does not report gender differences in steroid administration, and large population-based case-control studies have demonstrated that glucocorticoid use is associated with VTE.[30] However, patients in this study were enrolled before the discovery of risk reductions associated with immunosuppressive therapy, and steroids were not routinely prescribed.[31] Third, we were unable to account for missed diagnoses of thrombosis, which may have occurred without confirmatory diagnostic imaging. Thus, detection bias is a limitation of our study. Fourth, vascular causes of death were not adjudicated in the current analysis, and all-cause in-hospital mortality was reported instead. Finally, the incidence of out-of-hospital thrombosis could not be determined, and long-term mortality was not evaluated. Although practice patterns have changed significantly since the beginning of the pandemic, our study speaks to the natural history of untreated COVID-19 infection in unvaccinated patients.

In conclusion, men hospitalized with COVID-19 are at greater risk of thrombosis and death than women, and gender-specific differences are most pronounced in younger age groups. Outcomes of men and women with COVID-19-associated thrombosis are poor. Additional investigations of SARS-CoV-2 pathophysiology and host response are needed to inform the mechanisms of age and gender-

specific differences in cardiovascular outcomes and thrombotic risk in COVID-19.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.01.024.

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