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ORIGINAL ARTICLE

COVID-19–associated venous thromboembolism: risk of recurrence and major bleeding

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Abstract

Background: Complications under anticoagulant treatment in patients with COVID-19-associated venous thromboembolism (VTE) have not been consistently reported.

Objectives: This study aimed to compare the 90-day rates of VTE recurrences and major bleeding in patients with COVID-19-associated VTE versus those with VTE without COVID-19.

Methods: We used the RIETE registry to compare the 3-month outcomes in patients with COVID-19-associated VTE versus those with VTE without COVID-19.

Results: The study included 1,747 patients with COVID-19-associated VTE and 8,711 with VTE without COVID-19. Patients with COVID-19-associated VTE were more likely to be hospitalized at baseline and to present with pulmonary embolism. During the first 90 days, 123 patients (1.17%) developed VTE recurrences, and 266 (2.54%) experienced major bleeding. Patients with COVID-19-associated VTE had a similar rate of VTE recurrences (0.9% vs 1.2%) but a higher rate of major bleeding (4.6% vs 2.1%; $P < .001$) than those without COVID-19. Multivariable analysis adjusted for competing risks showed that patients with COVID-19-associated VTE had an increased risk of major bleeding (subhazard ratio, 1.395; 95% confidence interval, 1.037-1.877). The 30-day mortality after major bleeding was 26.3% in patients with COVID-19-associated VTE and 17.7% in those without COVID-19.

Conclusion: Patients with COVID-19-associated VTE had a 5-fold higher rate of major bleeding than VTE recurrences during the first 90 days of anticoagulation. In VTE patients without COVID-19, both rates were similar. These findings highlight the importance of carefully monitoring and optimizing anticoagulation in these patients.

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KEYWORDS
anticoagulants, COVID-19, hemorrhage, pulmonary embolism, venous thromboembolism

Essentials

- Complications of anticoagulation in COVID-19-venous thromboembolism (VTE) have not been reported.
- Patients with COVID-19-VTE versus patients with VTE without COVID-19 from the RIETE registry were included.
- In COVID-19-associated VTE, the risk of major bleeding far outweighed the risk of VTE recurrences.
- COVID-19–associated VTE had increased rates of hemoptysis, retroperitoneal, or muscular bleeding.

1 | INTRODUCTION

Patients with COVID-19 infection are at an increased risk of developing thrombotic events, mainly venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) or pulmonary embolism (PE), but also arterial thrombosis. This risk is particularly high in patients hospitalized in *intensive care units* (ICU) [1–4]. COVID-19-associated VTE shows distinctive features when compared with non–COVID-19 associated VTE, including higher D-dimer levels and a higher presence of peripheral PE, suggesting a mechanism of *in situ* pulmonary thrombosis [5–8].

In patients with COVID-19-associated VTE, current guidelines recommend prescribing anticoagulant therapy with similar therapeutic strategies than in VTE patients without COVID-19 infection [9–11]. The recommended duration of treatment is 3 to 6 months, and a recent study suggests that COVID-19 should be considered a transient risk factor for VTE [9,12]. Another recent study showed that among 233 patients with COVID-19-associated VTE the risk of recurrence was low (1.25 per 1000 person-months) [13]. However, to date, there are no studies comparing the risk for VTE recurrences and major bleeding during anticoagulation in patients with COVID-19-associated VTE versus those without COVID-19 infection.

2 | METHODS

2.1 | Patient selection

We used data from the Registro Informatizado de la Enfermedad Tromboembólica (RIETE) registry, which prospectively gathers information on patients with acute symptomatic, objectively confirmed VTE (ClinicalTrials.gov NCT02832245). The design and conduct of the RIETE registry have been previously reported [14]. Since March 2020, the registry has been updated to include information on COVID-19 infection: date of infection confirmation and diagnostic tests. All patients provided informed consent for participation in the registry. Consecutive patients diagnosed with acute VTE (DVT, PE, or both) between March 1, 2020, and June 30, 2022, were considered for inclusion in this study. COVID-19-associated VTE was defined as a VTE event that occurred after a confirmed COVID-19 infection in the prior 30 days. Patients with incidentally found VTE and those with only superficial vein thrombosis were excluded. All patients were followed up for at least 90 days or until death if it occurred earlier. Symptomatic PE was confirmed with a positive computerized tomography (CT) of the pulmonary arteries or a high probability lung scintigraphy. DVT was confirmed using a compression ultrasound or CT of the extremities.

2.2 | Outcomes

The primary efficacy outcome was the rate of VTE recurrences within the first 90 days, and the primary safety outcome was major bleeding. In patients with suspected VTE recurrences, the diagnosis was confirmed using a CT scan, V/Q lung scintigraphy, compression ultrasound, or pulmonary arteriography. VTE recurrence in the same location as previous episode was defined if the progression of VTE to a new territory was demonstrated. Major bleeding was defined as any bleeding event that was overt and required a transfusion of 2 units or more of blood, or was retroperitoneal, spinal, intracranial, intrathecal, intrapericardial, or intraocular or was fatal. This is the definition we use in the RIETE registry, which closely resembles the definition of the International Society on Thrombosis and Haemostasis [13]. Outcomes were defined by local investigators.

2.3 | Statistical analysis

Quantitative variables were expressed as mean and standard deviation or median and interquartile range, and qualitative variables were presented through the frequency distribution. Analysis of qualitative variables was carried out using the chi-squared test, and the Mann–Whitney *U*-test was used for the quantitative variables. Normality was assessed with Kolmogorov–Smirnov test. The hazard ratio (HR) and 95% CI were calculated. A Cox regression analysis with nonparametric proportional hazards adjustment was performed for the sensitivity analysis based on cancer, sex, age, hospitalization, ICU admission, year of diagnosis (2020, 2021, and 2022), recent

TABLE 1 Baseline characteristics, VTE risk factors, presentation, treatment and outcomes of patients with COVID-19-associated VTE and VTE nonrelated to COVID-19.

Variables	COVID-19-associated VTE (%) (*n* = 1,747)	VTE nonrelated to COVID-19 (%) (*n* = 8,711)	*P* value
Demographics			
Sex (male), *n* (%)	1,109 (63.5%)	4,538 (52.1%)	**<.001**
Median age (interquartile range)	65 (54-75)	66 (53-77)	.253
Obesity, *n* (%)	361 (29.7%)	1,936 (30.1%)	.818
Patients admitted at VTE diagnosis, *n* (%)	1,058 (62.1%)	2,519 (30.6%)	**<.001**
Patients in the ICU at diagnosis, *n* (%)	352 (34.5%)	540 (22.2%)	**<.001**
Required in-hospital therapy, *n* (%)	564 (91.4%)	3,635 (64.5%)	**<.001**
Concomitant use of corticosteroids, *n* (%)	322 (20.8%)	693 (9%)	**<.001**
Recent major bleeding, *n* (%)	31 (1.8%)	237 (2.7%)	**.022**
Anemia, *n* (%)	492 (28.2%)	2,435 (28.1%)	.959
Platelet count <100.000/uL, *n* (%)	37 (2.1%)	245 (2.8%)	.095
Risk factors for VTE			
Active cancer, *n* (%)	153 (8.8%)	2,012 (23.1%)	**<.001**
Prior VTE, *n* (%)	74 (4.2%)	999 (11.5%)	**<.001**
Recent surgery (prior 2 mo), *n* (%)	53 (3.0%)	846 (9.7%)	**<.001**
Recent immobilization (prior 2 mo), *n* (%)	1,168 (66.9%)	2,202 (25.3%)	**<.001**
Initial VTE presentation			
Isolated PE, *n* (%)	1480 (84.7%)	4,779 (54.9%)	**<.001**
Isolated DVT, *n* (%)	322 (18.4%)	4,323 (49.6%)	**<.001**
Of these, distal DVT, *n* (%)	123 (38.2%)	856 (19.8%)	**<.001**
Concomitant PE and DVT, *n* (%)	142 (8.1%)	1,034 (11.9%)	**<.001**
In patients with PE			
Main pulmonary arteries involved, *n* (%)	52 (4.7%)	491 (12.9%)	**<.001**
Only subsegmental PE, *n* (%)	196 (11,2%)	415 (4,8%)	**<.001**
SBP levels <90 mm Hg, *n* (%)	46 (2.7%)	159 (2%)	.065
Heart rate >110 bpm, *n* (%)	196 (16.8%)	593 (13.2%)	**.002**
sPESI >1, *n* (%)	648 (52.4%)	2741 (54.6%)	.165
Treatment received			
Initial therapy			
• Low molecular weight heparin	1,532 (87.7%)	6,943 (79.7%)	**<.001**
o Enoxaparin	1,178 (76.9%)	4,881 (70.3%)	**<.001**
o Bemiparin	283 (18.5%)	1,291 (18.6%)	.894
o Tinzaparin	51 (3.3%)	570 (8.2%)	**<.001**
o Other low molecular weight heparin	20 (1.3%)	201 (2.9%)	**.001**
• Unfractionated heparin	96 (5.5%)	374 (4.3%)	.031

(Continues)

TABLE 1 (Continued)

Variables	COVID-19-associated VTE (%) (*n* = 1,747)	VTE nonrelated to COVID-19 (%) (*n* = 8,711)	*P* value
• Direct oral anticoagulants	82 (4.7%)	1045 (12%)	**<.001**
• Fondaparinux	10 (0.6%)	192 (2.2%)	**<.001**
Long-term therapy			
• Low molecular weight heparin	480 (27.5%)	2,421 (28.0%)	.685
• Vitamin K antagonists	364 (20.8%)	2,055 (23.6%)	**.013**
• Direct oral anticoagulants	942 (53.9%)	4,503 (51.7%)	.089
Cava vein filter, *n* (%)	25 (1.4%)	220 (2.5%)	**.006**
90-d outcomes			
VTE recurrences	16 (0.9%)	107 (1,2%)	.269
After anticoagulation discontinuation	1 (6.2%)	9 (8.4%)	1
Major bleeding	80 (4.6%)	186 (2.1%)	**<.001**
After anticoagulation discontinuation	0 (0%)	4 (2.1%)	.11
Death	215 (12.3%)	576 (6.6%)	**<.001**

DVT, deep vein thrombosis; PE, pulmonary embolism; SBP, systolic blood pressure; sPESI; simplified pulmonary embolism severity index; VTE, venous thromboembolism.

immobilization, and initial VTE presentation. Since death can interfere with the occurrence of recurrences or bleeding generating an upward bias in the estimation of the cumulative incidence, competing risk analysis using Fine and Gray method was performed. A propensity score analysis using the variables hospital admission and ICU admission was also performed. A *P* value of < .05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0, IBM Corp. To plot the cumulative incidence curves and conduct competing risks regression analysis we used R Core Team (2021). R: a language and environment for statistical computing (https://www.R-project.org/).

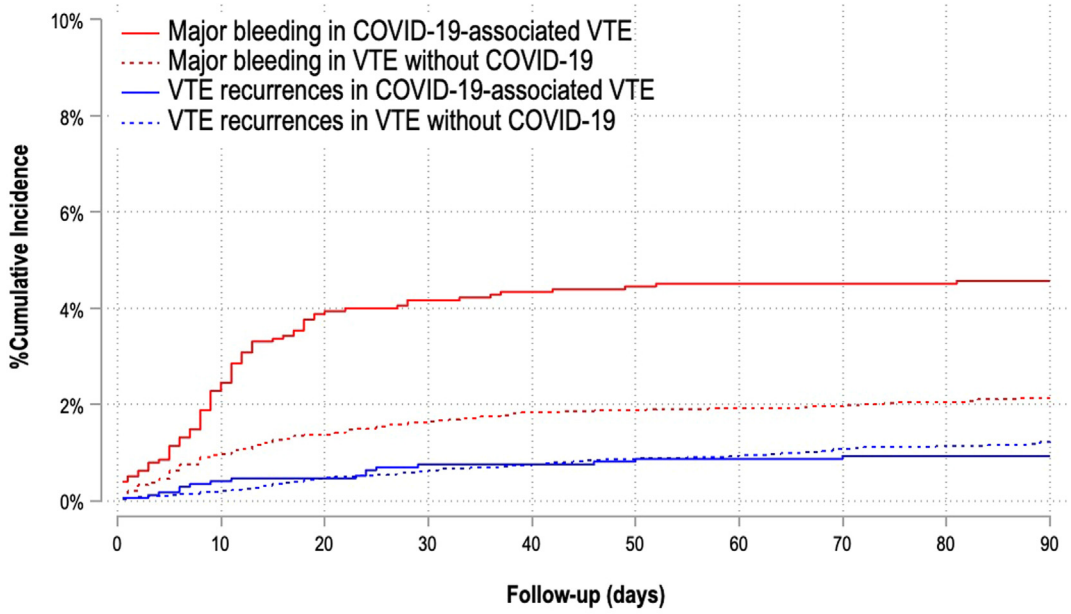
3 | RESULTS

During the study period, 10,458 patients with acute VTE were recruited. Of these, 1,747 (17%) had COVID-19-associated VTE, and 8,711 had VTE nonrelated to COVID-19. Patients with COVID-19-associated VTE were more likely to be male, to be in-hospital (particularly in the ICU) at VTE diagnosis, and to be receiving corticosteroids than those without COVID-19 (Table 1). However, they were less likely to have cancer or prior VTE. As for the initial VTE presentation, patients with COVID-19-associated VTE were more likely to present as PE, and to have peripheral PEs. Most patients in both subgroups received initial therapy with low molecular weight heparin and long-term therapy with direct oral anticoagulants.

During the first 90 days, 16 patients with COVID-19-associated VTE (0.9%) developed VTE recurrences and 80 (4.6%) had major bleeding (in the gastrointestinal tract 16, subcutaneous hematoma 14, retroperitoneal 14, muscular hematoma 10, hemoptysis 8, other sites 19). Among patients with VTE nonrelated to COVID-19, the percentages were 1.2% and 2.1%, respectively (Table 1). Patients with COVID-19-associated VTE had a similar rate of VTE recurrences than those without COVID-19 and a higher rate of major bleeding (relative risk [RR]: 2.14; 95% CI, 1.65-2.77) or death (RR: 1.86; 95% CI, 1.6-2.15) (Table 1 and Figure). Multivariable analysis of mortality, after adjusting for cancer, sex, age, hospitalization, ICU admission, year of diagnosis, recent immobilization, and initial VTE presentation revealed an HR of 1.489 (95% CI, 1.237-1.794).

After having major bleeding, the 30-day mortality was 26.3% in patients with COVID-19-associated VTE and 17.7% in those without COVID-19. Competing risk analysis of major bleeding, after adjusting for cancer, sex, age, hospitalization, ICU admission, year of diagnosis, recent immobilization, and initial VTE presentation revealed a subhazard ratio (SHR) of 1.395 (95% CI, 1.037-1.877) (Table 2).

Among patients who had major bleeding, those with COVID-19-associated VTE were more likely to develop hemoptysis (10% vs 1.1%, *P* = .001), retroperitoneal (17.5% vs 7.5%, *P* = .015) or muscular



	Day 7	Day 15	Day 30	Day 60	Day 90
Major bleeding (COVID & VTE)	26 (32.5%)	58 (72.5%)	73 (80%)	79 (98.7%)	80 (100%)
Major bleeding (no COVID)	66 (35.4%)	104 (55.9%)	144 (77.4%)	167 (89.8%)	186 (100%)
Recurrence (COVID & VTE)	6 (37.5%	8 (50%)	13 (81.2%)	15 (93.7%)	16 (100%)
Recurrence (no COVID)	13 (12.1%)	26 (24.2%)	55 (51.4%)	83 (77.5%)	107 (100%)

FIGURE Ninety-day rates of major bleeding and VTE recurrences (Fine and Gray regression). Recurrences and major bleedings at day 7, 15, 30, 60, and 90. VTE, venous thromboembolism.

bleeding (12.5% vs 3.2%, P = .008) than patients with non–COVID-19 VTE. Location of major bleeding in patients in both subgroups is detailed in Table 3.

A subanalysis of hospitalized and nonhospitalized patients was performed (Table 4). Differences in mortality among COVID and non–COVID patients were consistent regarding the hospitalization status. However, competing risk analysis showed a higher risk of bleeding in hospitalized patients with COVID-19-associated VTE (SHR, 1.607; 95% CI, 1.099-2.348), with no differences in nonhospitalized patients (SHR, 1.061; 95% CI, 0.588-1.914). A propensity score analysis using the variables hospital admission and ICU admission is included in the Supplementary Materials.

4 | DISCUSSION

Our findings reveal that patients with COVID-19-associated VTE had a 5-fold higher rate of major bleeding than VTE recurrences during the first 90 days of anticoagulant therapy. One in every 4 patients (26.3%) who bled, died within the first 30 days. Thus, the clinical relevance of major bleeding in these patients should not be underestimated. In patients with VTE and without COVID-19, the rates of major bleeding and VTE recurrences were closer. The higher risk for major bleeding in patients with COVID-19 was confirmed on multivariable analysis, after adjusting for potential confounders, including year of COVID-19 diagnosis. Thus, COVID-19 might be an independent risk factor for major bleeding in these patients. This increased risk of bleeding in COVID-19 patients is only observed in hospitalized patients, most likely due to the inflammatory status of patients with more severe forms of the disease. To our knowledge, this is the largest study including patients with COVID-19-associated VTE, and the first

TABLE 2 Competing risks Fine and Gray regression.

Competing risks Fine and Gray regression					
Event: 90-d major bleeding					
Competing event: 90-d mortality					
Variables	**SHR**	**95% CI**	**z-value**	***P* (z)**	**Coefficient**
COVID-19 associated VTE	1.395	1.037-1.877	2.21	0.027	0.333

Variables included in the model: cancer, sex, age, hospitalization, ICU admission, year of diagnosis, recent immobilization and initial VTE presentation. CI, confidence interval; SHR, subhazard ratio; VTE, venous thromboembolism.

TABLE 3 Location of major bleeding in patients with COVID-19-associated VTE and VTE nonrelated to COVID-19.

Location of major bleeding	COVID-19-associated VTE (%) (n = 80)	VTE nonrelated to COVID-19 (%) (n = 186)	*P* value
Gastrointestinal, *n* (%)	16 (20%)	67 (36%)	**.010**
Hematoma, *n* (%)	14 (17.5%)	27 (14.5%)	.537
Intracranial, *n* (%)	8 (10%)	29 (15.6%)	.227
Retroperitoneal, *n* (%)	14 (17.5%)	14 (7.5%)	**.015**
Urinary, *n* (%)	2 (2.5%)	16 (8.6%)	.069
Muscular, *n* (%)	10 (12.5%)	6 (3.2%)	**.008**
Hemoptysis, *n* (%)	8 (10%)	2 (1.1%)	**.001**
Epistaxis, *n* (%)	2 (2.5%)	2 (1.1%)	.586
Hemopericardium, *n* (%)	0 (0%)	1 (0.5%)	1
Hemothorax, *n* (%)	1 (1.3%)	1 (0.5%)	.512
Menorrhagia, *n* (%)	0 (0%)	4 (2.2%)	.319
Other locations, *n* (%)	5 (6.3%)	17 (9.1%)	.433

VTE, venous thromboembolism.

comparing rates of VTE recurrences and major bleeding during the course of anticoagulation between COVID-19-associated VTE and non–COVID-19 VTE.

The bleeding risk has been an issue of concern in COVID-19 patients, particularly at the beginning of the pandemic [15,16]. Observational studies reported a higher risk for major bleeding in patients with COVID-19 receiving intermediate or therapeutic doses of thromboprophylaxis during hospital admission [15–18]. Similarly to our findings, a recent observational study comparing 79 patients with COVID-19-associated PE to 150 patients with PE without COVID-19 revealed that COVID-19 patients had a higher risk of bleeding and a low risk of recurrence [19]. Our study reveals that in patients with COVID-19-associated VTE, the rate of major bleeding is much higher than the rate of VTE recurrences. Thus, anticoagulant therapy should be carefully chosen and checked, and treatment duration should be optimized in these patients.

Our study has several limitations that need to be discussed. First, since RIETE is an observational study, treatment choice was made by the attending physicians (there is no adjudication committee). Second, due to the characteristics of the registry, some information regarding VTE infection, specifically antiviral treatment, and symptoms onset was missing. Third, we decided to include all patients with COVID-19-associated VTE, whether they were hospitalized due to COVID-19 infection or home; these populations and their expected outcomes might be different. Fourth, sociocultural aspects of health care (which include structural racism for example) were not included in the study and might impact in the results, due to the social determinants of health impacts in health outcomes.

5 | CONCLUSION

Patients with COVID-19-associated VTE had a 5-fold higher rate of major bleeding than VTE recurrences during the first 90 days of anticoagulation. In VTE patients without COVID-19, both rates were closer. Since one in every 4 patients who bled died within the first 30 days, physicians taking care of patients with COVID-19 associated VTE should periodically monitor these patients during anticoagulation. These findings require external validation.

TABLE 4 Subanalysis of hospitalized and nonhospitalized patients.

Variables	Hospitalized COVID-19-associated-VTE vs VTE without COVID-19	Nonhospitalized COVID-19-associated-VTE vs VTE without COVID-19
Univariate analysis		
Recurrences	HR 0.733 (95% CI, 0.384-1.1401)	HR 0.309 (95% CI, 0.0756-1.268)
Major bleeding	HR 1.975 (95% CI, 1.392-2.802)	HR 1.247 (95% CI, 0.726-2.142)
Death	HR 1.472 (95% CI, 1.205-1.798)	HR 1.616 (95% CI, 1.192-2.190)
Multivariable analysis (Cox regression)		
Major bleeding	HR 1.607 (95% CI, 1.072-2.408)	HR 1.061 (95% CI, 0.595-1.892)
Death	HR 1.633 (95% CI, 1.292-2.064)	HR 1.478 (95% CI, 1.065-2.051)
Competing risk analysis (Fine and Gray regression)		
Major bleeding	SHR 1.607 (95% CI, 1.099-2.348)	SHR 1.061 (95% CI, 0.588-1.914)

Multivariable: Cox regression analysis adjusted for cancer, sex, age, hospitalization, ICU admission, year of diagnosis (2020, 2021, 2022), recent immobilization and initial VTE presentation. Competing risk analysis: Fine and Gray analysis using death as competing risk after adjusting for cancer, sex, age, year of diagnosis, recent immobilization and initial VTE presentation.

CI, confidence interval; HR, hazard ratio; SHR, subhazard ratio; VTE, venous thromboembolism.

APPENDIX

Members of the RIETE Group

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AUTHOR CONTRIBUTIONS

P.D.R., R.A.B, L.J.P., F.G.V., and M.M. conceptualized the study. P.D.R., R.A.B, L.J.P., and M.M. provided the methodology. P.D.R., R.A.B, L.J.P., and M.M validated the study. P.D.R., R.A.B, L.J.P., F.G.V., A.B.R., A.V., I.F., G.V., A.L.R., M.M., and the RIETE Investigators investigated the study; P.D.R., R.A.B, and M.M. curated the data., P.D.R., R.A.B, L.J.P., and M.M. prepared the original draft. P.D.R., R.A.B, L.J.P., F.G.V., A.B.R., A.V., I.F., G.V., A.L.R., M.M., and the RIETE Investigators reviewed and edited the manuscript. M.M. supervised the study. M.M. administered the project. All authors have read and agreed to the published version of the manuscript.

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RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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