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ORIGINAL ARTICLE

Bleeding risk in hospitalized patients with COVID-19 receiving intermediate- or therapeutic doses of thromboprophylaxis

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Abstract

Introduction: Some local protocols suggest using intermediate or therapeutic doses of anticoagulants for thromboprophylaxis in hospitalized patients with coronavirus disease 2019 (COVID-19). However, the incidence of bleeding, predictors of major bleeding, or the association between bleeding and mortality remain largely unknown.

Methods: We performed a cohort study of patients hospitalized for COVID-19 that received intermediate or therapeutic doses of anticoagulants from March 25 to July 22, 2020, to identify those at increased risk for major bleeding. We used bivariate and multivariable logistic regression to explore the risk factors associated with major bleeding.

Results: During the study period, 1965 patients were enrolled. Of them, 1347 (69%) received intermediate- and 618 (31%) therapeutic-dose anticoagulation, with a median

duration of 12 days in both groups. During the hospital stay, 112 patients (5.7%) developed major bleeding and 132 (6.7%) had non-major bleeding. The 30-day all-cause mortality rate for major bleeding was 45% (95% confidence interval [CI]: 36%-54%) and for non-major bleeding 32% (95% CI: 24%-40%). Multivariable analysis showed increased risk for in-hospital major bleeding associated with D-dimer levels >10 times the upper normal range (hazard ratio [HR], 2.23; 95% CI, 1.38–3.59), ferritin levels >500 ng/ml (HR, 2.01; 95% CI, 1.02–3.95), critical illness (HR, 1.91; 95% CI, 1.14–3.18), and therapeutic-intensity anticoagulation (HR, 1.43; 95% CI, 1.01–1.97).

Conclusions: Among patients hospitalized with COVID-19 receiving intermediate- or therapeutic-intensity anticoagulation, a major bleeding event occurred in 5.7%. Use of therapeutic-intensity anticoagulation, critical illness, and elevated D-dimer or ferritin levels at admission were associated with increased risk for major bleeding.

KEYWORDS
anticoagulants, COVID-19, death, hemorrhage, prognosis

1 | INTRODUCTION

The coronavirus disease of 2019 (COVID-19) is a viral illness caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). A number of studies found several hemostatic abnormalities, including intravascular coagulopathy, in patients infected by COVID-19.[1-4] Additionally, critical illness and immobility predispose these patients to develop venous thromboembolism (VTE).[5-10] Based on a recent systematic review and meta-analysis, the overall incidence of VTE in hospitalized patients with COVID-19 was estimated at 17% (95% confidence interval [CI]: 13.4%–20.9%), and the incidence of major bleeding was 3.9% (95% CI: 1.2–7.9).[11] Multiple ongoing randomized controlled trials are currently evaluating the role of a group of antithrombotic regimens in patients with COVID-19. In most trials, the intensity of antithrombotic therapy is proportional to the expected VTE rates. More intensive therapies (including parenteral intermediate-dose or fully therapeutic doses of anticoagulants) are being considered in trials of hospitalized patients.

A key to understanding the net benefit from escalated-dose empiric anticoagulation is the potential risk reduction for thrombosis versus the risk of bleeding. While some research has focused on the thrombotic event rates, the true hemorrhagic event rates, predictors of major bleeding events, or the association between bleeding and mortality remain largely unknown.

The RIETE (Registro Informatizado de Enfermedad TromboEmbólica) Registry is an ongoing, multicenter, international, observational registry of consecutive patients with objectively confirmed acute VTE (ClinicalTrials.gov identifier: NCT02832245).[12] Since March 25, 2020, the Steering Committee of RIETE agreed to take advantage of the existing platform of RIETE investigators to build two new registries of hospitalized patients with COVID-19 aimed to identify those at increased risk for VTE or for bleeding. We recently published the results of the first study, where we tried

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Essentials

- The risk of bleeding in COVID-19 patients with high-intensity thromboprophylaxis is unknown.
- Bleeding risk in COVID-19 patients with intermediate/therapeutic anticoagulation was evaluated.
- Major bleeding occurred in 5.7% patients and was associated with a higher risk of death.
- D-dimer, ferritin, intensive care unit admission, and full anticoagulation were associated with major bleeding.

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to identify patients at increased risk for VTE. The current study describes the results of a call to recruit data from hospitalized patients with COVID-19 that received higher than recommended doses of anticoagulants for VTE prophylaxis during their hospital stay. We hypothesized that in some patients the use of intermediate- or full-therapeutic doses of anticoagulants might be associated with unacceptably high rates of bleeding. Thus, in the current study we aimed to: (1) identify hospitalized patients at increased risk for bleeding while receiving higher than recommended doses of anticoagulants for VTE prophylaxis, and (2) evaluate the association between bleeding and 30-day mortality.

2 | METHODS

2.1 | Patients

For this study, we used the data from the RIETE-BLEEDING registry, in which the investigators enrolled consecutive patients hospitalized for COVID-19 (confirmed by positive polymerase chain reaction testing of a nasopharyngeal sample) who received intermediate

or therapeutic doses of anticoagulants for VTE prophylaxis between March 25 and July 22, 2020. The protocol was approved by the Ethics Committee of Hospital Germans Trias i Pujol (number PR(AG)213/2020), and then in all participating centers. The study was registered in ClinicalTrials.gov (NCT02832245). Unlike prior RIETE studies, the RIETE-BLEEDING study has distinctions for patient enrollment criteria compared to the original RIETE registry.[12] Unlike the original RIETE registry (which is still ongoing), the RIETE-BLEEDING study included only hospitalized patients with COVID-19 and excluded those with known acute VTE. This study analyzed data from 32 hospitals located in three countries (Spain, Italy, and the United States). Investigators monitored bleeding events appearing during hospital stay.

2.2 | Study design

There was no intervention planned. The main goals of this prospective study were to understand the incidence of in-hospital major and clinically relevant non-major bleeding events, and to identify the predictors of such bleeding events. Particularly, we were interested in assessing whether intermediate-dose and fully therapeutic anticoagulation are associated with distinct bleeding profiles. The minimum duration of prophylaxis to be included into the registry was 3 days. Only patients receiving higher-than-recommended doses of anticoagulants were recruited. In patients that switched regimens from intermediate to therapeutic doses (or vice versa) before reaching an outcome, we considered the regimen that was unchanged for at least 72 hours until completion of hospital stay, death, or bleeding events. Patients with prior VTE receiving anticoagulation and those receiving therapeutic doses of anticoagulants for other reasons (atrial fibrillation, mechanical valves, and so on) were excluded from the study.

This study used major bleeding as the primary endpoint, and clinically relevant non-major bleeding as secondary outcome. Major bleeding was defined as bleeding events that were overt and required a transfusion of two units or more of blood; were retroperitoneal, spinal, intracranial, intrathecal, intrapericardial, or intraocular; or were fatal.[12] This is the definition we use in the RIETE registry, and closely resembles the definition of the International Society on Thrombosis and Haemostasis. Non-major bleeding were those overt bleeds not meeting criteria for major bleeding but that required medical assistance.

2.3 | Variables of interest

Key data elements included: clinical characteristics (sex, age, body weight, mechanical ventilation, recent bleeding, concomitant therapy with antiplatelet or anticoagulant drugs), site of hospitalization (medical ward vs. intensive care unit [ICU]), laboratory tests (hemoglobin, platelet count, prothrombin time, fibrinogen levels, D-dimer, interleukin-6, ferritin, creatinine clearance) obtained at the moment of inclusion in the study, use of VTE prophylaxis (drugs, doses, duration), presence of bleeding during VTE prophylaxis, and 30-day all-cause mortality.

D-dimer assays were not centrally provided: levels were compared according to each hospital's practice. Because the different D-dimer assays may use different detection antibodies and detection methods, and often different calibrators,[13-15] we requested that participating centers provide information on the different D-dimer manufacturers, units, and normal cut-off values. Then, we compared D-dimer levels across the different centers according to how many times they exceeded the upper limit of normality in each center. Therapeutic-dose prophylaxis included enoxaparin 1 mg/kg twice daily or 1.5 mg/kg once daily or equivalent doses of other anticoagulants including any low-molecular-weight heparin, unfractionated heparin, or direct oral anticoagulants. Intermediate-dose prophylaxis was defined as weight adjusted, double-dose prophylaxis, or any dosage greater than the standard dose and lower than the therapeutic dose.

2.4 | Statistical analysis

The study reported categorical data as proportions and continuous data as mean and standard deviation (SD) or median (interquartile range [IQR]) days. We used unpaired two-tailed t-tests or the Mann-Whitney U test (for those variables found not to follow a normal distribution) for comparisons in the distributions of continuous variables, and chi-squared or Fisher's exact tests to compare the categorical data between the two groups. We compared demographics, patients' disposition status (hospitalized in a medical ward or in an ICU), blood tests, and pharmacological VTE prophylaxis according to the occurrence of bleeding complications.

Then, we performed a multivariable analysis through a logistic regression model trying to identify independent predictors for major bleeding during admission. The risk for major bleeding was evaluated using competing risk models, with mortality (not due to bleeding) as the competing risk. Covariates entering into the model were selected by a significance level of $P < .10$ on univariable analysis or by a well-known association reported in the literature. We built a prognostic score assigning points to each independent variable according to regression coefficients beta, rounding to the nearest integer or a multiple of it. We assigned a risk score to each patient by adding up points for each independent variable. We conducted statistical analyses using SPSS (IBM SPSS Statistics for Windows, Version 25.0: IBM Corp.).

3 | RESULTS

From March 25 to July 22, 2020, a total of 1965 hospitalized patients with COVID-19 in 32 hospitals from three countries were evaluated (Table 1). Of these, 1347 patients (69%) received VTE prophylaxis at intermediate doses, and 618 (31%) received therapeutic doses

(Table 2). Most patients (65%) were men, mean age was 68±14 years, and 40% were in the ICU. Among patients receiving intermediate doses, the most commonly used drugs were: enoxaparin (75%), bemiparin (15%), and biosimilars of enoxaparin (8.8%). Only 21 patients (1.6%) received direct oral anticoagulants. Among patients receiving therapeutic doses, the most commonly used drugs were: enoxaparin (77%), biosimilars of enoxaparin (9.1%), and bemiparin (8.7%). Median duration of prophylaxis with intermediate doses was 12 days (IQR, 7–19 days), and median duration with therapeutic doses also was 12 days (IQR, 7–20 days).

During hospital stay, 112 patients (5.7%) developed major bleeding (in the gastrointestinal tract 28, orotracheal 15, hematoma 12, muscular 9, abdominal 8, intracranial 7, genitourinary 7, alveolar 5, other sites 21), 132 (6.7%) had non-major bleeding (orotracheal 31, gastrointestinal 18, alveolar 16, hematoma 16, genitourinary 14, other 37), and 50 patients who bled died within the first 30 days after bleeding. Interestingly, there was a large variability in the major

bleeding rates across different centers, ranging from 1.1% to 14% (Table 1).

Patients developing major or non-major bleeding were more likely to be in the ICUs than in medical wards, and to have higher levels of D-dimer, interleukin-6, or ferritin than those that did not bleed (Table 3). There were no differences in mean levels of platelet count, fibrinogen, or creatinine clearance. Among patients receiving intermediate doses of anticoagulants, the rate of major bleeding was 4.4%, and non-major bleeding 5.4%. Among those receiving therapeutic doses, the rates were 8.6% and 9.5%, respectively. Both rates were higher in patients receiving therapeutic doses than in those on intermediate doses (hazard ratio [HR]: 2.05; 95% CI: 1.39–3.03; and 1.85; 95% CI: 1.28–2.63, respectively). As for the 30-day mortality rate, 50 of 112 patients (45%; 95% CI: 36%--54%) with major bleeding died, compared to 42 of 132 (32%; 95% CI: 24%--40%) with non-major bleeding, and 306 of 1721 (18%; 95% CI: 16%--20%) that did not bleed.

TABLE 1 Prevalence of bleeding events and use of therapeutic doses of anticoagulants for VTE prophylaxis in the participating centers

Hospitals	N	Major bleeding	Non-major bleeding	Therapeutic doses
Patients, N	1965	112 (5.7%)	132 (6.7%)	618 (31%)
Universitario La Paz	205	24 (12%)	13 (6.3%)	58 (28%)
Universitario Clínico San Carlos	196	9 (4.6%)	7 (3.6%)	100 (51%)
Universitario de Fuenlabrada	193	20 (10%)	14 (7.2%)	114 (59%)
Universitari Germans Trias i Pujol	183	2 (1.1%)	4 (2.2%)	37 (20%)
Universitario Fundación Jiménez Díaz	150	0	1 (0.7%)	21 (14%)
General Universitario Gregorio Marañón	143	22 (15%)	37 (26%)	43 (30%)
Cantoblanco	127	0	5 (3.9%)	27 (21%)
Azienda Ospedaliera Universitaria, Parma	109	0	1 (0.9%)	21 (19%)
Universitario Infanta Sofía	81	2 (2.5%)	1 (1.2%)	27 (33%)
Universitario de Salamanca	78	6 (7.7%)	10 (13%)	45 (58%)
Clínica Universitaria de Navarra	74	0	2 (2.7%)	12 (16%)
Complejo Hospitalario de Pontevedra	56	1 (1.8%)	0	7 (12%)
Universitari Sagrat Cor	51	7 (14%)	8 (16%)	13 (25%)
Universitari Clínic de Barcelona	45	3 (6.7%)	4 (8.9%)	13 (29%)
Universitario del Sureste	41	0	0	2 (4.9%)
Galdakao	36	0	0	9 (25%)
Universitari Vall d'Hebron	33	2 (6.1%)	1 (3.0%)	29 (88%)
Universitario Gran Canaria Dr. Negrín	30	5 (17%)	11 (37%)	9 (30%)
Universitario Rey Juan Carlos	26	0	0	6 (23%)
Evanston NorthShore University	23	0	2 (8.7%)	6 (26%)
Massachusetts General	17	0	0	0
Hospital del Mar, Barcelona	16	3 (19%)	2 (12%)	6 (37%)
Universitario Reina Sofía, Córdoba	11	0	0	1 (9.1%)
Universitario de Guadalajara	8	2 (25%)	0	0
General Universitario de Elche	9	0	5 (56%)	3 (33%)
Buon Consiglio Fatebenefratelli	8	0	1 (12%)	6 (75%)
Other	16	4 (25%)	3 (19%)	3 (19%)

Abbreviation: VTE, venous thromboembolism.

TABLE 2 Drugs and daily doses used for thromboprophylaxis

	Major bleeding	Non-major bleeding	No bleeding	All
Patients, N	112	132	1721	1965
Intermediate doses,	59 (4.4%)	73 (5.4%)	1,215 (90%)	1347
Enoxaparin 60 mg	27 (4.8%)	29 (5.1%)	510 (90%)	566
Enoxaparin 80 mg	19 (5.0%)	30 (7.9%)	332 (87%)	381
Enoxaparin 100 mg	5 (7.8%)	3 (4.7%)	56 (87%)	64
Bemiparin 5000–7500 IU	2 (1.0%)	6 (3.0%)	189 (96%)	197
Biosimilars enoxaparin 60 mg	2 (3.3%)	1 (1.7%)	57 (95%)	60
Biosimilars enoxaparin 80 mg	2 (3.6%)	3 (5.5%)	49 (91%)	55
Biosimilars enoxaparin 100 mg	0	0	3 (100%)	3
Apixaban 5 mg	2 (15%)	1 (7.7%)	10 (77%)	13
Edoxaban 30 mg	0	0	2 (100%)	2
Rivaroxaban 10 mg	0	0	4 (100%)	4
Rivaroxaban 15 mg	0	0	2 (100%)	2
Duration of prophylaxis				
Median days (IQR)	13 (7–22)	14 (9–23)	12 (7–18)	12 (7–19)
Therapeutic doses,	53 (8.6%)	59 (9.5%)	506 (82%)	618
Enoxaparin 120 mg	26 (8.8%)	35 (12%)	236 (79%)	297
Enoxaparin 160 mg	17 (11%)	16 (11%)	117 (78%)	150
Enoxaparin 200 mg	2 (7.7%)	1 (3.8%)	23 (88%)	26
Biosimilars enoxaparin 120 mg	4 (10%)	4 (10%)	32 (80%)	40
Biosimilars enoxaparin 160 mg	3 (19%)	2 (12%)	11 (69%)	16
Bemiparin 10 000–12 500 IU	1 (1.8%)	1 (1.8%)	52 (96%)	54
Tinzaparin 10 000–14 000 IU	0	0	15 (100%)	15
Edoxaban 60 mg	0	0	4 (100%)	4
Rivaroxaban 20 mg	0	0	11 (100%)	11
Dabigatran 220 mg	0	0	5 (100%)	5
Duration of prophylaxis				
Median days (IQR)	13 (7–19)	11 (7–20)	12 (7–20)	12 (7–20)

Abbreviations: IQR, interquartile range; IU, international units.

3.1 | Prediction of major bleeding

On multivariable analysis, patients admitted in the ICU (HR: 1.91; 95% CI: 1.14–3.18; P = .014), those with D-dimer levels above 10 times the upper normal range (HR: 2.23; 95% CI: 1.38–3.59; P = .001), with ferritin levels >500 ng/ml (HR: 2.01; 95% CI: 1.02–3.95; P = .044) and those receiving therapeutic doses of anticoagulants (HR: 1.43; 95% CI: 1.01–1.97; P = .039) were associated with major bleeding (Table 4). Patients who developed major bleeding (HR: 2.25; 95% CI: 1.39–3.63; P = .001) were at increased risk to die within the first 30 days.

A prognostic score to predict the risk for major bleeding was built assigning one point to each variable. Using this score, there were 376 patients (19%) at very low risk (0 points), 593 (30%) at low risk (1 point), 495 (25%) at intermediate risk (2 points), and 501 (25%) at high risk for bleeding (3–4 points), as shown in Table 5. The proportions of patients for each category that developed major bleeding were: 0.5%, 2.4%, 5.9%, and 13.4%, respectively (Figure 1). The

proportions of patients that developed non-major bleeding were: 1.6%, 2.4%, 8.5%, and 14.0%, respectively. The c-statistics were: 0.74 (95% CI: 0.70–0.79) for major bleeding and 0.72 (95% CI: 0.68–0.77) for non-major bleeding.

4 | DISCUSSION

Our study, obtained from a large prospective study of patients hospitalized for COVID-19 receiving higher than recommended doses of anticoagulants for VTE prophylaxis, reveals that 1 in every 18 (5.7%) suffered major bleeding, and 1 in every 15 (6.7%) had non-major bleeding. This is important because the 30-day mortality rate in patients with major bleeding (45%) was more than 2-fold higher than in those that did not bleed (18%), and major bleeding was a significant predictor of 30-day mortality, after adjusting for potential confounders. Because the use of therapeutic doses of anticoagulants was a predictor for major bleeding, early

TABLE 3 Clinical characteristics of the patients, according to the development of bleeding events

	Major bleeding	Non-major bleeding	No bleeding	All patients
Patients, N	112	132	1721	1965
Clinical characteristics,				
Male sex	75 (67%)	96 (73%)[*]	1100 (64%)	1271 (65%)
Mean age (years±SD)	67±12	65±13[†]	69±15	68±14
Mean body weight (kg±SD)	80±17	82±17	80±18	80±18
Admitted in ICUs	84 (75%)[‡]	108 (82%)[‡]	597 (35%)	789 (40%)
Recent (<30 days) major bleeding	2 (1.8%)	4 (3.1%)[*]	13 (0.76%)	19 (1.0%)
Blood tests				
Anemia	34 (30%)	58 (44%)[†]	525 (31%)	617 (31%)
Platelet count (mean/µl ± SD)	221±100	225±102	232±114	231±112
Platelet count <100 000/µl	8 (7.1%)	9 (6.8%)	74 (4.3%)	91 (4.6%)
Fibrinogen levels (mean mg/dl ± SD)	671±290	688±273	669±231	670±238
Fibrinogen levels <1000 mg/dl	95 (87%)	107 (88%)	1466 (91%)	1668 (90%)
Prothrombin time (mean seconds ± SD)	13.8±4.3[‡]	14.8±8.2[*]	16.8±14.5	16.4±13.8
Prothrombin time >13.5 seconds	35 (32%)[*]	49 (38%)	669 (42%)	753 (41%)
D-dimer levels >upper normal limit	103 (96%)[*]	125 (98%)[‡]	1508 (90%)	1736 (91%)
D-dimer levels >10 x upper limit	74 (69%)[‡]	78 (61%)[‡]	567 (34%)	719 (38%)
Ferritin levels (ng/mL±SD)	1430 ± 1227[†]	1455 ± 1282[†]	1130±1064	1173±1097
Ferritin >500 ng/mL (N=1545)	85 (88%)[‡]	93 (80%)[*]	930 (70%)	1108 (72%)
IL-6 levels (mean pg/mL±SD)	497±975[†]	479±1032[†]	156±349	206±516
IL-6 levels >300 pg/mL (N=1028)	17 (24%)[†]	25 (30%)[‡]	91 (10%)	133 (13%)
CrCl levels (mean mL/min±SD)	70±54	74±57	67±59	68±58
CrCl levels <60 mL/min	52 (46%)	52 (39%)	805 (47%)	909 (46%)
Concomitant therapies				
Antiplatelets	19 (17%)	20 (15%)	263 (15%)	302 (15%)
VTE prophylaxis				
Intermediate doses	59 (53%)[‡]	73 (55%)[‡]	1215 (71%)	1347 (69%)
Therapeutic doses	53 (47%)[‡]	59 (45%)[‡]	506 (29%)	618 (31%)
Duration (median days, IQR)	13 (7–21)	13 (8–21)	12 (7–19)	12 (7–19)
30-day mortality				
Yes	50 (45%)[‡]	42 (32%)[‡]	306 (18%)	398 (20%)

Abbreviations: CrCl, creatinine clearance; ICUs, intensive care units; IL-6, interleukin-6; IQR, interquartile range; SD, standard deviation.

Comparisons between patients with versus without bleeding events:

[*]$P <0.05$;

[†]$P <0.01$;

[‡]$P <0.001$.

identification of high-risk subgroups for bleeding is of clinical relevance.

In our study, there was a large variability in the major bleeding rates across different centers, ranging from 1.1% to 14%. These differences may likely be due to differences in the admission in the ICUs or in medical wards, D-dimer levels, and in the proportion of patients receiving intermediate or therapeutic doses of VTE prophylaxis. However, the rates of major bleeding in our cohort compare well with those in previous studies, ranging from 1.9% to 11%.[16-22] A study of 355 hospitalized patients with COVID-19 also found that those

receiving therapeutic anticoagulation had remarkably higher rates of major bleeding than those with no anticoagulation (11% vs. 2%) or standard doses only (4%).[17] Another study found that the rate of bleeding events was high in patients receiving (sub)therapeutic doses of anticoagulants,[18] and the doses of anticoagulants were the strongest determinant of the risk for bleeding. A recent study comparing the bleeding risk in patients with critical COVID-19 and other respiratory viral illnesses found that therapeutic-intensity anticoagulation was associated with a higher risk for major bleeding than standard VTE prophylaxis.[23]

TABLE 4 Univariate and multivariable analyses for major bleeding. Results expressed as hazard ratio and 95% confidence intervals

	Major bleeding	
	Univariate	Multivariable
Clinical characteristics		
Male sex	1.11 (0.74–1.67)	–
Age ≥65 years	0.93 (0.63–1.38)	–
Body weight ≤80 kg	0.95 (0.62–1.45)	–
Admitted in ICU	4.88 (3.15–7.56)	1.91 (1.14–3.18)[*]
Recent major bleeding	1.98 (0.45–8.67)	–
Blood tests		
Anemia	0.95 (0.63–1.44)	–
Platelet count <100,000/μL	1.64 (0.77–3.48)	–
Prothrombin time >13.5 sec	0.64 (0.43–0.95)	0.86 (0.56–1.33)
D-dimer >10 x upper limit	4.01 (2.63–6.10)	2.23 (1.38–3.59)[†]
Ferritin >500 ng/mL	2.94 (1.59–5.44)	2.01 (1.02–3.95)[*]
IL-6 levels >60 pg/mL	1.95 (1.17–3.27)	–
CrCl levels <60 mL/min	1.01 (0.69–1.48)	–
Concomitant therapies		
Anticoagulants	0.82 (0.51–1.33)	–
Antiplatelets	1.14 (0.69–1.90)	–
VTE prophylaxis		
Intermediate doses (Ref.)	Ref.	Ref.
Therapeutic doses	2.05 (1.39–3.01)	1.43 (1.01–1.97)[*]
Duration ≤12 days	1.16 (0.79–1.70)	1.61 (0.91–2.63)
Outcomes		
No bleeding (Ref.)	–	–
Major bleeding	–	–
Non-major bleeding	–	-

Abbreviations: CrCl, creatinine clearance; ICU, intensive care unit; IL-6, interleukin-6; Ref., reference; sec, seconds; VTE, venous thromboembolism.

[*]P <0.05;
[†]P <0.01;
[‡]P <0.001.

One in every 3 patients (38%) in our cohort had D-dimer levels above 10 times the upper normal range, and their rate of major bleeding was high (74 of 719 patients, 10%). Because patients with COVID-19 and raised levels of D-dimer also are at increased risk for VTE,[24] we suggest that these patients should be carefully evaluated to decide what doses of anticoagulants would be optimal. Certainly, not all D-dimer assays are the same: the different assays use different detection antibodies, different detection methods, and often different calibrators, and this may lead to confusion.[13-15] This is the reason we compared levels across centers based on times above the upper normal limits.

TABLE 5 Proportion of patients developing bleeding complications according to the prognostic score

Risk	Points	Patients, N	Major bleeding	Non-major bleeding
Any	Any	1,965	112 (5.7%)	132 (6.7%)
Very low	0	376	2 (0.5%)	6 (1.6%)
Low	1	593	14 (2.4%)	14 (2.4%)
Intermediate	2	495	29 (5.9%)	42 (8.5%)
High	3–4	501	67 (13.4%)	70 (14.0%)
c-statistics (95% CI)			0.74 (0.70–0.79)	0.72 (0.68–0.77)

Notes:: The score assigns 1 point for each of the following: ICU admission, D-dimer >10 times over the upper limit, ferritin >500 ng/mL and use of therapeutic anticoagulation
Abbreviations: CI, confidence intervals; ICU, intensive care unit.

Our study has a number of limitations that should be considered. First, patients receiving standard doses of prophylaxis were not included in the study, and no possible comparison between doses could be performed. This will be the aim of a number of ongoing clinical trials, specifically designed to answer this question. Second, because it was a non-interventional study, treatment strategies were conditioned by the clinical practice and protocols of each center. Third, the study was aimed to ascertain the bleeding event rates and to identify risk factors for bleeding, not the possible beneficial effect of anticoagulation on survival or thrombotic events. Fourth, our predictive model only applies to patients receiving higher than standard doses of thromboprophylaxis, and requires external validation.

Our study also has some strengths: to our knowledge ours is the first study to identify hospitalized patients with COVID-19 at increased risk for bleeding, using a large cohort of real-life patients (without exclusion criteria) from many centers. The strengths of the current study are the large sample of patients with prospective data collection from several hospitals, and standardized a priori implemented definitions for major bleeding and non-major bleeding. A plethora of ongoing randomized trials will be elucidating the role of a number of antithrombotic regimens with different intensities. Results of these trials should help clarify whether any of the antithrombotic regimens under investigation can safely mitigate thrombotic complications and improve patient outcomes. However, the majority of these trials excluded patients perceived to be at high risk of bleeding, such as those with a history of major bleeding, thrombocytopenia, or renal insufficiency. These patients were not excluded in our study.

In conclusion, 5.7% of hospitalized patients for COVID-19 receiving intermediate or therapeutic doses of anticoagulants for VTE prophylaxis suffered major bleeding, and 6.7% had non-major bleeding. Patients with major bleeding had a more than 2-fold higher mortality rate than those that did not bleed. Use of therapeutic-intensity anticoagulation, critical illness, and D-dimer and ferritin levels at admission were associated with increased hazards of major bleeding.
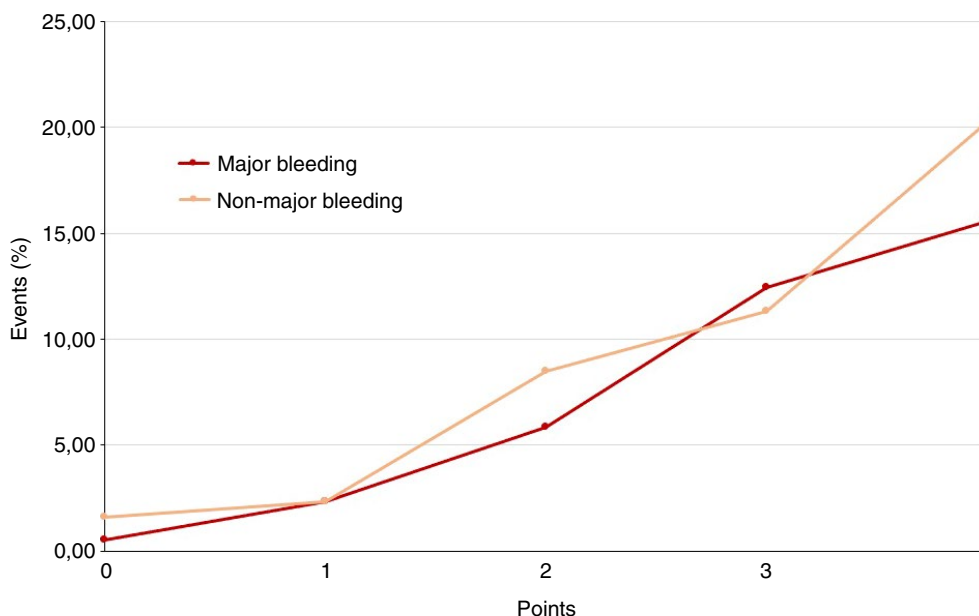
FIGURE 1 Percentage of patients developing major- or non-major bleeding events, according to points assigned in the prognostic score

CONFLICTS OF INTEREST

Dr. Bikdeli reports that he is a consulting expert, on behalf of the plaintiff, for litigation related to two specific brand models of IVC filters. The rest of authors state no conflicts of interest regarding this article.

AUTHOR CONTRIBUTIONS

P. Demelo-Rodríguez and M. Monreal designed research. All authors performed research. P. Demelo-Rodríguez, B. Bikdeli, D. Jiménez, and M. Monreal analyzed data and wrote the paper. The manuscript was reviewed by all authors and all of them approved the final version of the manuscript.

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APPENDIX

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