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# Systematic testing for venous thromboembolism in hospitalized patients with COVID-19 and raised D-dimer levels

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## ABSTRACT

*Background:* Hospitalized patients with COVID-19 and raised D-dimer levels have high rates of venous thromboembolism (VTE).
*Methods:* We used data from hospitalized patients with COVID-19 that were tested for pulmonary embolism (PE) or deep vein thrombosis (DVT) because of raised D-dimer levels. We aimed to identify patients at increased risk for VTE.
*Results:* From March 25 to July 5th, 2020, 1,306 hospitalized patients with COVID-19 and raised D-dimer levels underwent testing for VTE in 12 centers. In all, 171 of 714 (24%) had PE, and 161 of 810 (20%) had DVT. The median time elapsed from admission to VTE testing was 12 days, and the median time from D-dimer measurement to testing 2 days. Most patients with VTE were men (62%), mean age was 62 ± 15 years, 45% were in an intensive care unit. Overall, 681 patients (52%) received VTE prophylaxis with standard doses, 241 (18%) with intermediate doses and 100 (7.7%) with therapeutic doses of anticoagulants. On multivariable analysis, patients with D-dimer levels >20 times the upper normal range (19% of the whole cohort) were at increased risk for VTE (odds ratio [OR]: 3.24; 95%CI: 2.18–4.83), as were those with a platelet count <100,000/μL (OR: 4.17; 95%CI: 1.72–10.0).
*Conclusions:* Hospitalized patients with COVID-19 and D-dimer levels >20 times the upper normal range were at an increased risk for VTE. This may help to identify what patients could likely benefit from the use of higher than recommended doses of anticoagulants for VTE prophylaxis.

## 1. Introduction

Hospitalized patients with coronavirus disease 2019 (COVID-19) are at increased risk for venous thromboembolism (VTE). The proportion of patients developing objectively confirmed VTE in the literature ranges from 0% to 85% [1–15]. This large variability in incidence rates of VTE may be due to small study sizes, variable testing strategies, use of VTE prophylaxis, and other variables. Recent guidelines issued by the International Society of Thrombosis and Haemostasis (ISTH) and other societies recommend the use of standard-of-care objective testing to diagnose

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VTE based on clinical index of suspicion only, and against systematic screening using doppler ultrasonography of the lower limbs or chest CT-scan [16,17].

However, they note that clinicians should have a low threshold for testing in patients with a reasonable degree of clinical suspicion for VTE. Moreover, the preliminary ISTH guidance on the detection and treatment of coagulopathy in COVID-19 suggests that patients with raised D-dimer levels should be admitted to hospital [18] and some authors have advocated the use of screening programs, at least in patients with raised D-dimer levels [8,19,20].

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). Since March 25, 2020, the Steering Committee of RIETE agreed to prospectively incorporate new data elements related to patients with COVID-19 [21]. The current study describes the results of a call to recruit data from hospitalized patients with COVID-19 that underwent diagnostic tests for VTE (either deep vein thrombosis [DVT] or pulmonary embolism [PE]) because of raised D-dimer levels. Our aim was to identify what patients were at increased risk for VTE.

## 2. Methods

### 2.1. Patients

For this study, we retrospectively analyzed data from the RIETE-Testing registry, which collected information on hospitalized patients with COVID-19 and raised D-dimer levels (ClinicalTrials.gov identifier, NCT04380792). All patients or their healthcare proxies provided written or oral consent for participation in the registry in accordance with local ethics committee requirements. The study analyzed data from 12 hospitals located in 4 countries (Spain 8, Italy 2, United States and Germany 1 each). The study used the presence or absence of confirmed VTE as the primary endpoint. The RIETE investigators used medical record review to assess vital status. Unlike prior RIETE studies, the RIETE-Testing study has distinctions for patient enrollment criteria compared with the original RIETE registry [22]. Unlike the original RIETE registry (which is still ongoing), the RIETE-Testing study included only hospitalized patients with COVID-19, with or without confirmed VTE.

### 2.2. Study design

The investigators enrolled patients hospitalized for COVID-19 (confirmed by positive polymerase chain reaction testing of a nasopharyngeal sample or from tracheal aspirate in intubated patients) who had raised D-dimer levels between March 25 and July 5th, 2020. All patients with raised D-dimer levels during the study period were systematically investigated for VTE diagnosis, irrespectively of the presence or absence of VTE suspicion criteria. Testing included either lower limb venous compression ultrasonography (CUS) for deep vein thrombosis (DVT), or ventilation-perfusion (V/Q) scintigraphy or contrast-enhanced, helical chest computerized tomography (CT) for pulmonary embolism (PE). The time interval between obtaining blood samples for measuring D-dimer levels to VTE testing had to be $< 3$ days. Patients diagnosed with VTE prior to hospitalization for COVID-19, and those who developed VTE after hospital discharge were not included in the analysis. The major outcome was objectively confirmed VTE (PE, DVT, or both).

### 2.3. Variables of interest

Key data elements included: clinical characteristics (gender, age, body weight, mechanical ventilation), site of hospitalization (medical ward vs. an intensive care unit [ICU]), laboratory tests on the day of screening (platelet count, prothrombin time, D-dimer, fibrinogen, ferritin, creatinine), use of VTE prophylaxis (drugs, doses, duration) and the presence or absence of VTE on objective tests.

D-dimer testing was not centrally provided: levels were compared according to each hospital's practice. Cut-off levels to define raised D-dimer were established by the Department of Clinical Chemistry at each participating site. Since the different D-dimer assays use different detection antibodies, different detection methods and often different calibrators [23–26], we requested the participating centers to provide information on the different 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 centre.

### 2.4. Statistical analysis

The study reported categorical data as proportions and continuous data as mean and standard deviation (SD) or median (inter-quartile range). We compared demographics, laboratory tests, pharmacological VTE prophylaxis, and 30-day mortality according to patients' disposition status: hospitalized in a medical ward or in an intensive care unit (ICU). 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 between medical ward and ICU patients, and chi-squared or Fisher's exact tests to compare the categorical data between the two groups. The risk to develop VTE was assessed with Cox proportional hazard model. We selected the following covariates in regression models for adjustment: sex, age, body weight, hospital status (in medical ward or ICU), platelet count, fibrinogen levels, D-dimer levels and use of VTE prophylaxis. Finally, we calculated the association between D-dimer levels (given as multiples of upper normal range) and VTE diagnosis (either DVT or PE). We calculated and compared the c-statistics, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio and negative likelihood ratio of different multiples of the upper normal range of D-dimer. We conducted statistical analyses with the use of SPSS (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

## 3. Results

From March 25 to July 5th, 2020, 1,306 hospitalized patients with COVID-19 and raised D-dimer levels were tested for VTE: 639 underwent helical CT-scan, 75 ventilation perfusion lung-scan and 810 lower limb CUS (218 were screened for both, PE and DVT). In all, 171 of 714 patients undergoing chest CT-scan or V/Q lung scan (24%) had confirmed PE, and 161 of 810 patients undergoing CUS (20%) had confirmed DVT. The rates of PE and DVT largely varied among participating centers, as did the proportion of patients with D-dimer levels above 10 times the upper limit of normality (Table 1). In general, the highest rates of VTE were found in those centers where a highest proportion of patients had D-dimer levels above 10 times the upper normal limit, and vice versa.

The median time elapsed from COVID-19 diagnosis to testing for VTE was 16 days (interquartile range [IQR]: 7–22) in patients testing positive for VTE and 11 days (IQR: 5–19) in those testing negative. The median time elapsed from hospital admission to testing was 14 days (IQR: 7–21) in patients with VTE and 10 days (IQR: 5–19) in those without VTE. The median time from D-dimer measurement and testing was 2 days. Most patients (62%) were men, mean age was $62 \pm 15$ years, 45% were in the ICU and 39% were on mechanical ventilation.

Overall, 681 patients (52%) had received VTE prophylaxis with low-molecular-weight heparin (LMWH) or direct oral anticoagulants (DOACs) at standard doses, 241 (18%) at intermediate doses, and 100 (7.7%) at therapeutic doses (Table 2). Moreover, 86 patients (6.6%) received unfractionated heparin, 7 (0.5%) vitamin K antagonists and 6 (0.5%) received fondaparinux. In 186 patients (14%) there was no available information on the drugs, doses and/or duration.

There were no differences in the clinical characteristics (sex, age, body weight) of patients with- or without VTE, but patients with VTE were more likely to be in an ICU than in a medical ward, and more likely

**Table 1**
Screening testing and D-dimer technique characteristics in the participating centers.

| | N | PE testing | | DVT testing | | D-dimer levels 10 x upper normal range |
|---|---|---|---|---|---|---|
| | | N | Positive | N | Positive | |
| Patients, N | 1,306 | 714 | 171 (24%) | 810 | 161 (20%) | 486 (37%) |
| Massachusetts General | 302 | 195 | 21 (11%) | 147 | 24 (16%) | 117 (39%) |
| Gregorio Marañón, Madrid | 233 | 81 | 18 (22%) | 195 | 38 (19%) | 110 (47%) |
| La Paz, Madrid | 193 | 189 | 60 (32%) | 41 | 12 (29%) | 117 (61%) |
| IFEMA, Madrid | 156 | 35 | 9 (26%) | 156 | 2 (1.3%) | 14 (9.0%) |
| Vall d'Hebrón, Barcelona | 118 | 18 | 9 (50%) | 118 | 30 (25%) | 36 (31%) |
| Universitario Salamanca | 100 | 95 | 18 (19%) | 7 | 2 (29%) | 19 (19%) |
| 12 de Octubre, Madrid | 92 | 75 | 17 (23%) | 49 | 13 (27%) | 42 (46%) |
| Azienda Ospedaliera Parma | 51 | 2 | 0 | 49 | 25 (51%) | 11 (22%) |
| Germans Trias, Badalona | 20 | 0 | – | 20 | 9 (45%) | 8 (40%) |
| General de Catalunya | 17 | 16 | 14 (87%) | 4 | 3 (75%) | 10 (59%) |
| Azienda Ospedaliera Ravenna | 13 | 4 | 3 (75%) | 13 | 0 | 0 |
| Klinikum Dresden | 11 | 4 | 2 (50%) | 11 | 3 (27%) | 2 (18%) |

***Abbreviations:*** PE, pulmonary embolism; DVT, deep vein thrombosis.

were on mechanical ventilation (Table 3). There were no significant differences in mean levels of platelet count, prothrombin time, fibrinogen, ferritin or creatinine clearance between patients with- or without VTE, but patients with VTE were more likely to have D-dimer levels above 10- or even 20 times the upper normal level than those without VTE (Table 3). The proportion of patients with confirmed DVT, PE or VTE (both DVT or PE) progressively increased as the levels of D-dimer (given as multiples of the upper normal range) also increased (Fig. 1). Patients receiving standard doses of VTE prophylaxis had similar rates of PE (odds ratio [OR]: 0.87; 95%CI: 0.56–1.37) or DVT (OR: 0.94; 95%CI: 0.55–1.66) than those on intermediate doses, but had lower rates of PE (OR: 0.32; 95%CI: 0.19–0.55) or DVT (OR 0.28; 95%CI: 0.15–0.51) than those receiving therapeutic doses (Table 2).

The 30-day mortality rate in patients with VTE was significantly higher than in those without VTE (OR: 1.63; 95%CI: 1.10–2.43). When separately analyzed however, the mortality rate was non-significantly higher in patients with PE than in those without PE (OR: 1.46; 95%CI: 0.87–2.42), or in patients with DVT than in those without DVT (OR: 1.64; 95%: 0.99–2.67).

On multivariable analysis, patients with D-dimer levels above 20 times the upper normal range were at an increased risk for VTE (OR: 3.24; 95%CI: 2.18–4.83), as were those with a platelet count <100,000/μL (OR: 4.17; 95%CI: 1.72–10.0) (Table 4). Patients with D-dimer levels above 10 times the upper normal range were not at a significantly higher risk for VTE (OR: 1.45; 95%CI: 0.97–2.18).

Finally, we calculated the association between D-dimer levels (given as multiples of upper normal range) and VTE diagnosis. As it could be expected, the sensitivity of D-dimer levels to detect VTE progressively decreased as the threshold value increased, and the specificity increased (Table 5). The cut-point associated with the best AUC value was 10 times higher the upper normal range (c-statistics: 0.67; 95%CI: 0.63–0.70).

**Table 2**
Drugs and daily doses, according to the three categories (standard, intermediate or therapeutic).

| | ICUs | Medical wards | All patients |
|---|---|---|---|
| All patients, N | 578 | 727 | 1,305 |
| Standard doses | 170 (29%)[‡] | 511 (70%) | 681 (52%) |
| Enoxaparin 40 mg | 159 (28%) | 485 (67%) | 644 (49%) |
| Bemiparin 3,500 IU | 1 (1.2%) | 17 (2.1%) | 25 (1.7%) |
| Certoparin 3,000 IU | 2 (0.3%) | 5 (0.69%) | 7 (0.54%) |
| Tinzaparin 2,500–4,500 IU | 0 | 1 (0.1%) | 1 (0.1%) |
| Apixaban 5 mg | 0 | 3 (0.4%) | 3 (0.2%) |
| Rivaroxaban 10 mg | 1 (0.2%) | 0 | 1 (0.1%) |
| Duration of prophylaxis | | | |
| Median days (inter-quartile range) | 18 (12–27) | 8 (4–15) | 10 (5–19) |
| **Intermediate doses** | **131 (23%)[‡]** | **108 (15%)** | **241 (18%)** |
| Enoxaparin 60–100 mg | 123 (21%) | 94 (13%) | 217 (17%) |
| Bemiparin 5,000–7,500 IU | 2 (0.3%) | 6 (0.8%) | 8 (0.6%) |
| Apixaban 10 mg | 5 (0.9%) | 6 (0.8%) | 11 (0.8%) |
| Edoxaban 30 mg | 0 | 1 (0.1%) | 1 (0.1%) |
| Rivaroxaban 10 mg | 0 | 1 (0.1%) | 1 (0.1%) |
| Certoparin 8,000 IU | 1 (0.2%) | 0 | 1 (0.1%) |
| Duration of prophylaxis | | | |
| Median days (inter-quartile range) | 16 (10–30) | 10 (5–16) | 13 (7–22) |
| **Therapeutic doses** | **63 (11%)[‡]** | **37 (5.1%)** | **100 (7.7%)** |
| Enoxaparin 120–240 mg | 57 (9.9%) | 25 (3.4%) | 82 (6.3%) |
| Bemiparin 10,000–12,500 IU | 4 (0.7%) | 3 (0.4%) | 7 (0.5%) |
| Tinzaparin 10,000–14,000 IU | 0 | 6 (0.8%) | 6 (0.5%) |
| Apixaban 20 mg | 1 (0.2%) | 1 (0.1%) | 2 (0.1%) |
| Edoxaban 60 mg | 1 (0.2%) | 0 | 1 (0.1%) |
| Rivaroxaban 20–30 mg | 0 | 2 (0.3%) | 2 (0.2%) |
| Duration of prophylaxis | | | |
| Median days (inter-quartile range) | 20 (11–28) | 10 (5–20) | 17 (7–27) |
| **Unfractionated heparin** | 69 (12%)[‡] | 17 (2.3%) | 86 (6.6%) |
| **Vitamin K antagonists** | 2 (0.3%) | 5 (0.7%) | 7 (0.5%) |
| **Fondaparinux** | 4 (0.7%) | 2 (0.3%) | 6 (0.5%) |
| **Other/no data** | 139 (24%) | 47 (6.5%) | 186 (14%) |

Comparisons between patients in the ICUs or in medical wards: [‡]$p < 0.001$.
***Abbreviations:*** ICUs, intensive care units; IU, international units.

## 4. Discussion

The optimal regimen for prevention of VTE in hospitalized patients with COVID-19 remains unknown. Findings from several ongoing randomized clinical trials will likely be informative on this issue. If the use of therapeutic doses of prophylaxis proves to be more effective than standard doses, they should be prescribed mostly to patients at increased risk. Our study reveals that among patients with COVID-19, raised D-dimer levels and a VTE outcome assessment, those with D-dimer levels above 20 times the upper normal range are at an increased risk (over 3-fold higher) for VTE. We also found thrombocytopenia to independently predict the risk for VTE, but less than 5% of patients in our cohort had a platelet count <100,000/μL. Patients with VTE were more likely to be in an ICU than in a medical ward, but this was probably due to the confounding influence of raised D-dimer levels.

In our cohort, one in every 6 patients (17%) had D-dimer levels above 20 times the upper normal range, and their rate of VTE was high (47% had PE, 42% had DVT). Since hospitalized patients with COVID-19 may also be at increased risk for bleeding, we suggest that those with D-dimer levels above 20 times the upper normal range could be candidates to receive higher than recommended doses of anticoagulants for VTE prophylaxis. 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 [23–26]. This is the reason why we compared levels across centers based on times above the upper normal limits.

**Table 3**
Clinical characteristics, blood tests, use of VTE prophylaxis and 30-day mortality rate according to the existence or absence of PE or DVT.

| | PE testing | | DVT testing | |
|---|---|---|---|---|
| | PE | No PE | DVT | No DVT |
| ***Patients, N*** | ***171*** | ***543*** | ***161*** | ***649*** |
| **Clinical characteristics** | | | | |
| Male gender | 105 (61%) | 322 (59%) | 116 (72%)* | 399 (61%) |
| Mean age (years±SD) | 65 ± 14 | 63 ± 16 | 62 ± 12 | 61 ± 14 |
| Mean body weight (kg±SD) | 80 ± 19 | 79 ± 19 | 85 ± 20* | 81 ± 19 |
| Admitted in ICUs | 88 (52%)† | 203 (37%) | 117 (73%)‡ | 272 (42%) |
| Mechanical ventilation | 75 (44%)* | 191 (35%) | 89 (61%)‡ | 234 (37%) |
| **Laboratory tests** | | | | |
| Platelet count (mean/μL±SD) | 269 ± 121 | 250 ± 126 | 266 ± 125 | 282 ± 144 |
| Platelet count <100,000/μL | 4 (2.3%)* | 41 (7.6%) | 7 (4.4%) | 32 (4.9%) |
| Fibrinogen (mean mg/dL±SD) | 670 ± 283 | 639 ± 239 | 620 ± 228 | 607 ± 234 |
| Prothrombin time (seconds±SD) | 13.1 ± 3.0 | 13.7 ± 4.4 | 13.6 ± 3.4 | 13.2 ± 3.1 |
| D-dimer levels >2 x upper limit | 162 (95%)† | 473 (87%) | 151 (94%)‡ | 549 (85%) |
| D-dimer levels >10 x upper limit | 114 (67%)‡ | 198 (36%) | 95 (59%)‡ | 194 (30%) |
| D-dimer levels >20 x upper limit | 70 (41%)‡ | 80 (15%) | 44 (27%)‡ | 60 (9.2%) |
| CrCl levels (mL/min) | 90.8 ± 58.8 | 96.6 ± 63.4 | 89.1 ± 60.6 | 91.4 ± 68.5 |
| Ferritin levels (ng/mL±SD) | 1,344 ± 2,219 | 1,115 ± 1,247 | 1,467 ± 2,064 | 1,138 ± 1,561 |
| **VTE prophylaxis** | | | | |
| Standard doses | 74 (43%)* | 292 (54%) | 71 (44%)* | 358 (55%) |
| Intermediate doses | 37 (22%) | 127 (23%) | 20 (12%) | 95 (15%) |
| Therapeutic doses | 33 (19%)‡ | 42 (7.7%) | 23 (14%)‡ | 32 (4.9%) |
| Other | 11 (6.4%) | 40 (7.4%) | 17 (11%) | 46 (7.1%) |
| Duration (median days, IQR) | 10 (4–18) | 12 (5–22) | 15 (8–21) | 11 (6–19) |

Comparisons between patients with- or without VTE: *p < 0.05; †p < 0.01; ‡p < 0.001.
***Abbreviations:*** PE, pulmonary embolism; DVT, deep vein thrombosis; SD, standard deviation; ICUs, intensive care units; VTE, venous thromboembolism; IQR, inter-quartile range.

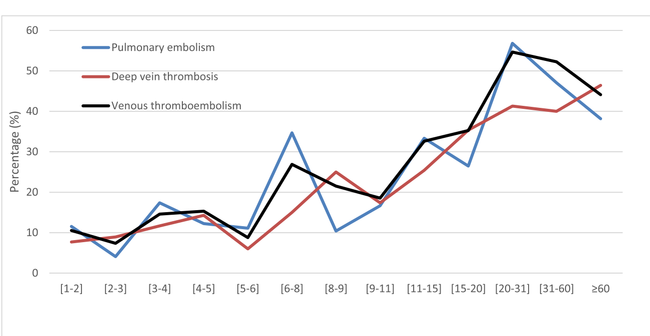


**Fig. 1.** Proportion of patients testing positive for DVT, PE or VTE, according to D-dimer levels.
***Abbreviations***: DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

In our study, 24% of patients tested for PE and 20% of those tested for DVT had positive findings. However, there was a large variability in the incidence rates in different centers (ranging from 1.3% to 87%). These differences may likely be due to differences in the intensity of the rise of D-dimer levels, admission in the ICUs or in medical wards, and in the proportion of patients receiving standard-, intermediate- or therapeutic doses of VTE prophylaxis.

**Table 4**
Univariate- and multivariate analyses for venous thromboembolism.

| | Venous thromboembolism | |
|---|---|---|
| | Univariate | Multivariate |
| Clinical characteristics | | |
| Male gender | 1.24 (0.93–1.67) | – |
| Age ≥65 years | 1.10 (0.83–1.46) | – |
| Body weight ≤80 kg | 0.93 (0.69–1.26) | – |
| Admitted in ICUs | 2.66 (1.99–3.56)[c] | 1.28 (0.90–1.83) |
| **Laboratory tests** | | |
| Platelet count <100,000/μL | 0.46 (0,21-1.02) | 4.17 (1.72–10.0)[b] |
| Fibrinogen >600 mg/dL | 1.12 (0.84–1.49) | – |
| Prothrombin time >13 s | 1.09 (0.81–1.48) | – |
| D-dimer levels >2 x upper limit | Ref. | Ref. |
| D-dimer levels >10 x upper limit | 1.97 (1.36–2.86)[c] | 1.45 (0.97–2.18) |
| D-dimer levels >20 x upper limit | 4.72 (3,28-6.81)[c] | 3.24 (2.18–4.83)[c] |
| Ferritin levels >1,000 ng/mL | 1.56 (1.14–2.13)[b] | 0.78 (0.56–1.08) |
| **VTE prophylaxis** | | |
| Standard doses | Ref. | Ref. |
| Intermediate doses | 1.24 (0.84–1.83) | 0.81 (0.51–1.27) |
| Therapeutic doses | 3.05 (1.92–4.84)[c] | 1.68 (0.99–3.06) |
| Other/not reported | 1.45 (1.01–2.07)[a] | 0.67 (0.36–1.09) |

Abbreviations*:* ICU, intensive care unit; VTE, venous thromboembolism; Ref., reference.
[a] p <0.05.
[b] p < 0.01.
[c] p < 0.001.

**Table 5**
Prognostic values of different multiples of the upper range of D-dimer to detect VTE.

| | 2 times | 5 times | 10 times | 20 times |
|---|---|---|---|---|
| Patients, N | 1,090 | 783 | 486 | 210 |
| c-statistics | 0.57 (0.53–0.60) | 0.64 (0.61–0.68) | 0.67 (0.63–0.70) | 0.62 (0.58–0.66) |
| Sensitivity | 95.7 (93.4–98.0) | 83.0 (78.7–87.3) | 63.3 (57.9–68.8) | 35.3 (29.9–40.7) |
| Specificity | 18.1 (15.7–20.5) | 45.5 (42.4–48.6) | 69.8 (66.9–72.7) | 89.4 (87.5–91.3) |
| PPV | 26.3 (23.7–28.9) | 31.8 (28.5–35.1) | 39.1 (34.8–43.4) | 50.5 (43.7–57.2) |
| NPV | 93.2 (89.6–96.7) | 89.7 (87.1–92.4) | 86.1 (83.7–88.5) | 81.9 (79.6–84.2) |
| PLR | 1.2 (1.1–1.2) | 1.5 (1.4–1.7) | 2.1 (1.8–2.5) | 3.3 (1.9–5.9) |
| NLR | 0.2 (0.1–0.4) | 0.4 (0.3–0.5) | 0.5 (0.5–0.6) | 0.7 (0.7–0.8) |

***Abbreviations:*** VTE, venous thromboembolism; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

Our study has a number of limitations that should be considered. First, we cannot know how many patients were truly asymptomatic, since hospitalized patients with COVID-19 often present with dyspnea, hypoxemia and acute respiratory distress syndrome. Second, some patients in our study underwent CT-scan, some V/Q scan and some CUS. Since patients were generally not subjected to both tests for PE and DVT, we do not know if patients with a negative test indeed did not have VTE, or did not have PE plus DVT. Third, local protocols (VTE prophylaxis, threshold for testing and choice of testing) may have resulted in major bias, as reflected by the wide ranges in VTE prevalence. Fourth, we did not include into the analysis concomitant diseases (such as cancer, chronic heart disease, chronic lung disease, anemia) or concurrent medications (antiplatelets, corticosteroids, …) that may also have influenced the risk for VTE. Finally, though only D-dimer levels above 20 times the upper normal range achieved significance on multivariable analysis, it had a lower c-statistics than levels above 10 times the upper range. Further studies are needed, with more patients, to ascertain what the optimal D-dimer threshold could be.

We conclude that hospitalized patients with COVID-19 and D-dimer levels above 20 times the upper normal limit had a 3-fold higher risk to develop VTE than those with less raised levels. This may help to identify what patients could likely benefit from the use of intermediate- or therapeutic doses of anticoagulants for VTE prophylaxis.

## 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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## Appendix 1

This article is original work that has not been previously published in any substantial part and is not under consideration for publication elsewhere. All authors have read and approved this manuscript. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. All authors had full access to all data and hold final responsibility for the decision to submit this manuscript for publication.

No author has any conflict of interest with regards to the manuscript.

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**RIETE-TESTING Registry Coordinating Center:** S & H Medical Science Service.

## *Appendix 2*

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