Journal of Thrombosis and Thrombolysis (2020) 50:211–216
https://doi.org/10.1007/s11239-020-02146-z

Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors

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Published online: 25 May 2020

Abstract
Coagulopathy in COVID-19 is a burning issue and strategies to prevent thromboembolic events are debated and highly heterogeneous. The objective was to determine incidence and risk factors of venous thromboembolism (VTE) in COVID-19 inpatients receiving thromboprophylaxis. In this retrospective French cohort study, patients hospitalized in medical wards non-ICU with confirmed COVID-19 and adequate thromboprophylaxis were included. A systematic low limb venous duplex ultrasonography was performed at hospital discharge or earlier if deep venous thrombosis (DVT) was clinically suspected. Chest angio-CT scan was performed when pulmonary embolism (PE) was suspected. Of 71 patients, 16 developed VTE (22.5%) and 7 PE (10%) despite adequate thromboprophylaxis. D-dimers at baseline were significantly higher in patients with DVT ($p < 0.001$). Demographics, comorbidities, disease manifestations, severity score, and other biological parameters, including inflammatory markers, were similar in patients with and without VTE. The negative predictive value of a baseline D-dimer level < 1.0 µg/ml was 90% for VTE and 98% for PE. The positive predictive value for VTE was 44% and 67% for D-dimer level ≥ 1.0 µg/ml and ≥ 3 µg/ml, respectively. The association between D-dimer level and VTE risk increased by taking into account the latest available D-dimer level prior to venous duplex ultrasonography for the patients with monitoring of D-dimer. Despite thromboprophylaxis, the risk of VTE is high in COVID-19 non-ICU inpatients. Increased D-dimer concentrations of more than 1.0 µg/ml predict the risk of venous thromboembolism. D-dimer level-guided aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies.

Keywords Venous thromboembolism · Pulmonary embolism · D-dimer · COVID-19

Highlights

- The incidence of venous thromboembolism (VTE) in non-ICU COVID-19 patients with thromboprophylaxis is unknown.
- Consecutive COVID-19 inpatients had systematic venous duplex ultrasonography at discharge.
- Of the 71 patients included, 16 developed VTE (22.5%) and 7 pulmonary embolisms (PE) (10%). The negative predictive value of baseline D-dimer level < 1.0 µg/ml was 90% for VTE, 98% for PE.
- D-dimer level-guided aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies.

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Introduction

Since the first cases reported in Wuhan in December 2019, coronavirus disease 2019 (COVID-19) has contributed to significant mortality worldwide [1]. Coagulopathy is frequently reported [1, 2] and elevated D-dimer is a significant poor prognosis factor [3, 4]. Moreover, some authors have suggested a particularly high frequency of thromboembolic events, including fatal pulmonary embolism [5]. Use of heparin was associated with reduced mortality in COVID-19 patients, suggesting that thromboembolism prophylaxis is critical in the management of COVID-19 [6–8]. The International Society of Thrombosis and Haemostasis has recommended systematic pharmacological thromboprophylaxis in all patients who require hospital admission for COVID-19 [9]. However, the incidence of venous thromboembolism in patients hospitalized for COVID-19 is unclear, particularly under thromboprophylaxis. Whether some clinico-biological parameters could predict venous thromboembolism risk and guide thromboprophylaxis management is also unknown. The objectives of the study were to determine the frequency and to identify predictive factors of venous thromboembolism in COVID-19 inpatients receiving pharmacological thromboprophylaxis.

Methods

Study population

In this retrospective cohort study, all consecutive patients with confirmed COVID-19 hospitalized for more than 48 h in two French centers (Nantes University Hospital and Châteaubriant Hospital) were screened between March 25, 2020 and April 10, 2020. Inclusion criteria were age > 18 years and adequate thromboprophylaxis and available low limb venous duplex ultrasonography. Exclusion criteria were previous anticoagulation and contraindication to thromboprophylaxis. A confirmed case of COVID-19 was defined as a positive result on real-time reverse-transcriptase–polymerase-chain-reaction assay of nasopharyngeal swab specimens for SARS-CoV-2 or typical pattern on chest CT-scan [10]. Thromboprophylaxis was considered adequate if it was implemented within 24 h of hospital admission, included daily administration of weight-appropriate enoxaparin following institutional recommendations (40 mg/day for BMI < 30 kg/m^2, 60 mg/day for BMI 30 to 40 kg/m^2 and 40 mg twice daily for BMI > 40 kg/m^2) and covered the whole hospital stay.

Data collection

Relevant data were extracted from electronic health records using a standardized form. The study was performed in accordance with French legislation (articles L.1121–1 paragraph 1 and R1121-2, Public health code) and Helsinki Declaration.

Outcome measures

All patients were systematically examined for deep-vein thrombosis by low limb venous duplex ultrasonography at hospital discharge or earlier if thrombosis was clinically suspected. Chest angio-CT scan was performed in case of suspicion of pulmonary embolism.

Statistical analysis

Data were expressed as number (percentage) or median (IQR), except otherwise indicated. Frequency comparisons were performed using Fischer Exact t test. Quantitative variables were compared using Mann–Whitney test. To estimate the correlation between two variables, a Spearman's test was used. Data were analyzed using GraphPad Prism version 5. All tests were two-sided, with p-values < 0.05 considered as statistically significant.

Results

Study population

Between March 25th and April 10th 2020, 133 COVID-19 inpatients were managed in the centers. Sixty-two patients were excluded: 1 died, 17 were transferred to intensive care unit, 5 were discharged early (< 48 h), 9 received oral anticoagulant, 21 were discharged without duplex ultrasonography, and 9 were not yet discharged. Seventy-one patients had a duplex ultrasonography before discharge (median [IQR] after admission: 13.0 [11.0–17.5] days) and were included in the study. The median age was 64 years (25th–75th percentile, 46–75 years). The majority of patients were males (61%). The most frequent comorbidities were hypertension in 41% of cases and diabetes in 20%. The median body mass index was 27.3 kg/m^2 (25th–75th percentile, 25.0–31.2 kg/m^2). Details of characteristics are reported in Table 1.

Venous thromboembolism events

Venous thromboembolism incidence was 22.5%. Deep venous thrombosis (DVT) was detected in 15 of 71

Table 1 Demographics, clinical, laboratory, radiographic characteristics at admission and treatment of the patients

	Normal range	Total (n = 71)	VTE (n = 16)	No-VTE (n = 55)	p value
Demographics					
Age, year		64 (46.0–75)	61.0 (40.8–79.0)	64.0 (47.5–75.0)	0.92
Male sex		43 (60.6%)	11 (68.7%)	32 (58.2%)	0.56
BMI—kg/m^2		27.3 (25.0–31.2)	27 (25.5–29.1)	27.4 (24.2–32.3)	0.59
Underlying conditions					
Hypertension		29 (41)	3 (19)	26 (47)	0.35
Diabetes		14 (20)	0 (0)	14 (25)	0.029
Cancer		4 (6)	0 (0)	4 (7)	0.56
Current smoker		6 (9)	0 (0)	6 (12)	0.32
History of VTE		5 (7)	2 (13)	3 (5)	0.31
Surgery < 3 months		7 (10)	2 (13)	5 (9)	0.65
Time from illness onset to hospital admission, days		9.0 (5.0–11.0)	8.5 (7.0- 10.0)	9.5 (4.0- 12.0)	0.59
Physical examination					
Body temperature—°C		38.6 (37.9–39.1)	38.7 (38.5–39.4)	38.4 (37.8–39.1)	0.21
Fever		55 (79)	14 (93)	41 (75)	0.33
Respiratory rate > 24/min		46 (65)	8 (50)	35 (64)	0.40
Clinical suspicion of venous thrombosis		3 (4)	2 (12)	1 (2)	0.12
NEWS score		6 (4- 7)	8 (5–8)	4 (4- 7)	0.096
SOFA score		1 (1–2)	2 (1- 4)	1 (1- 2)	0.22
Laboratory findings					
White-cell count, $\times 10^{-9}$/L (N	4.0–10.0	6.36 (4.85–9.21)	5.96 (3.97–9.89)	6.56 (5.19–9.21)	0.34
Lymphocyte count, $\times 10^{-9}$/L	1.5–4.0	0.94 (0.72–1.28)	0.92 (0.75–1.25)	0.99 (0.72–1.29)	0.65
Platelet count, $\times 10^{-9}$/L	150–400	212 (162–248)	228 (183–260)	202 (160–243)	0.26
Serum creatinine, μmol/L	62–106	76.5 (60–91)	80 (51–89)	74 (60.5–91)	0.53
Aspartate aminotransferase, U/L	0–51	44.3 (30.5- 60.1)	39.7 (31.3–48.2)	45.6 (30.5–61.6)	0.33
Alanine aminotransferase, U/L	0–51	43.8 (23.7–68.8)	37.8 (19.8–66.4)	44.1 (27.4–70.0)	0.53
Lactate dehydrogenase, U/L	135–225	297 (233–411)	405 (260–550)	286 (231–380)	0.13
Creatine kinase, U/L	0–190	118 (41–197)	97.2 (44–262)	127 (44–201)	0.76
Serum ferritin, μg/L	30–400	798 (436–1821)	1354 (695–2271)	762 (400–1596)	0.12
> 300		42 (77)	11 (92)	31 (74)	0.56
Fibrinogen, g/L	2.0–4.0	4.9 (4.3–6.5)	5.2 (4.6–6.6)	4.8 (4.3–6.6)	0.58
D-dimer, μg/mL	< 0.5	0.79 (0.48–1.61)	1.63 (0.86–4.94)	0.67 (0.45–1.12)	0.0021
Prothrombin ratio	70–120	88 (79–95)	79 (71–99)	88 (82–94)	0.20
TCA ratio	0.8–1.2	1.00 (0.92–1.09)	1.01 (0.96–1.11)	1.00 (0.91–1.07)	0.43
Imaging features					
Time from illness onset to VDU, days		13.0 (11.0–17.5)	17.0 (11.0–22.0)	13.0 (10.0–16.3)	0.06
Chest-CT Scan		46 (64)	14 (88)	32 (58)	0.039
typical pattern of COVID-19		46 (100)	14 (100)	32 (100)	1
Treatments					
Prophylactic anticoagulation		70 (99)	16 (100)	54 (99)	1
Antibiotics		65 (92)	16 (100)	49 (89)	0.33
Antiviral treatment		29 (41)	7 (44)	22 (40)	0.78
Corticosteroïds		15 (21)	3 (20)	12 (22)	1
ICU admission		13 (18)	8 (50)	5 (9.1)	0.0008
Invasive mechanical ventilation		8 (11)	6 (37)	2 (4)	0.001

Data are median (IQR), n (%), or n/N (%). p values were calculated by Mann–Whitney U test, χ. test, or Fisher's exact test, as appropriate

VTE venous thromboembolism, *BMI* body mass index, *VDU* venous duplex ultrasonography, *ICU* Intensive care unit

patients (21.1%) including 2 (2.8%) symptomatic, 2 (2.8%) proximal and 5 (7.0%) distal. Isolated calf DVT was found in 7 patients (9.8%), with bilateral calf involvement in five (7.0%). Out of the 71 patients, 7 patients (9.8%) developed a pulmonary embolism (PE), among whom 5 had calf DVT, one proximal DVT and one no DVT. One patient died because of PE. Out of the 71 patients, 34 (48%) underwent angio-CT of whom 7 exhibited pulmonary embolism (21%), which was fatal in 1 case. Among patients with PE 5 (7%) had calf DVT, one (1.4%) proximal DVT and one (1.4%) no DVT. Demographics, disease manifestations, comorbidities and baseline COVID-19 severity were similar in patients with and without venous thromboembolism (Table 1). No significant differences were observed with regards to baseline complete blood counts, inflammatory markers hepatic or renal parameters.

Predictive value of D-dimer

D-dimer level at hospital admission, available in 65 of the 71 patients, was significantly higher in patients who developed venous thromboembolism during hospitalization (median: 1.63 µg/ml *vs* 0.63 µg/ml, p = 0.0021) (Fig. 1a). There was no correlation between D-dimer level and fibrinogen (p = 0.62). The negative predictive value of a baseline D-dimer level < 1.0 µg/ml was 90% for venous thromboembolism and 98% for pulmonary embolism (Fig. 1b). The positive predictive value for venous thromboembolism was 44% and 67% for D-dimer level ≥ 1.0 µg/ml and ≥ 3.0 µg/ml, respectively. D-dimer level kinetics, available in 8 out of 16 patients who developed venous thromboembolism and 7 out of 55 who did not develop venous thromboembolism (13%), are shown in Fig. 1c. Median time between admission and last D-dimer level assessment in these 15 patients was 9.0 days (IQR, 4.0–9.5 days). Taking into account the latest available D-dimer level prior to venous thromboembolism diagnosis

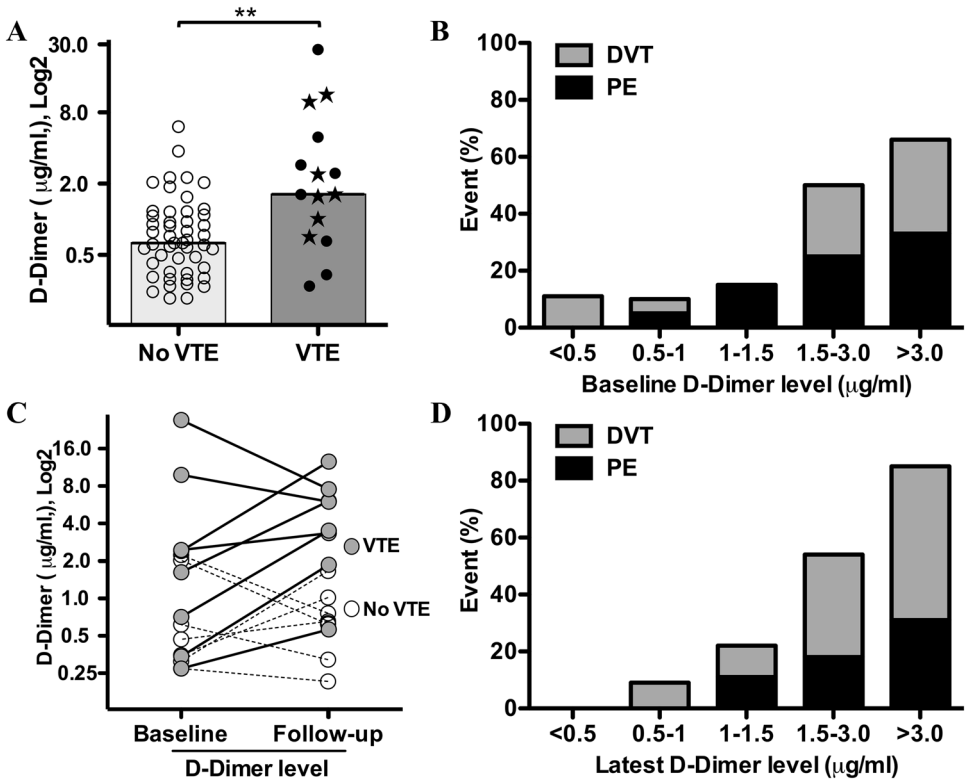

Fig. 1 correlation between D-dimer levels and venous thromboembolic events in the 65 COVID-19 patients who had a D-dimer level measurement on admission. (**a**, top left) Baseline (admission) D-dimer levels according to thromboembolism events. Stars represent pulmonary embolism. (**b**, top right) Risk of deep venous thrombosis and pulmonary embolism according to baseline D-dimer levels. (**c**, bottom, left) D-dimer levels kinetics between baseline and the latest value before the venous duplex ultrasonography in the 15 patients with D-dimer levels monitoring. 7 patients with no VTE, median [IQR] admission D-dimer: 0.62 [0.41–1.34], median [IQR] last-value: 0.66 [0.61–0.89]; 8 patients with VTE, median [IQR] admission D-dimer: 2.01 [0.62–4.30], median [IQR] last-value: 4.75 [2.98–6.42] (**d**, bottom, right) Risk of deep venous thrombosis and pulmonary embolism according to the latest D-dimer levels. *VTE* venous thromboembolic events, *DVT* deep venous thrombosis, *PE* pulmonary embolism. **p < 0.01

enhanced the predictive value of this marker: D-dimer level < 1.0 µg/ml had a 95% and 100% negative predictive value for venous thromboembolism and pulmonary embolism, respectively. Positive predictive values of a D-dimer level ≥ 1.0 µg/ml and ≥ 3.0 µg/ml to predict venous thromboembolism were 48% and 80%, respectively (Fig. 1d).

In summary, in our study were all patients underwent low limb venous duplex ultrasonography and were with thromboprophylaxis, we found a high incidence of thromboembolic events (22.5%) and pulmonary embolism (10%).

In the MEDENOX trial, the incidence of venous thromboembolism in patients with acute medical illnesses was reduced to 5.5% with daily enoxaparin 40 mg injection (3.8% distal thrombosis, 1.7% proximal thrombosis, no pulmonary embolism) compared to 15% with placebo (9.4% distal, 4.9% proximal, 0.7% pulmonary embolism) [11]. In COVID-19, two retrospective cohort studies reported a high risk of thrombosis in patients hospitalized in intensive care units [12, 13], with a 25% incidence of venous thromboembolism without thromboprophylaxis [12]. Despite thromboprophylaxis in patients in intensive care, a cumulative incidence of 31% of symptomatic venous and/or arterial thrombosis was reported [13]. Our study was conducted in 2 medical units were all patients received optimal pharmacologic thromboprophylaxis. Our results highlight the high risk of venous thromboembolism, including pulmonary, suggesting that standard thromboprophylaxis is insufficient in COVID-19 inpatients, even if not requiring initial intensive care. Interestingly, D-dimers level measured at hospital admission predicted venous thromboembolism risk, whereas other conventional risk factors such as age or body mass index did not. The negative predictive value of D-dimer for venous thromboembolism was clinically relevant when the level was < 1.0 µg/ml while patients with high levels (≥ 3.0 µg/ml) had a particularly high risk of venous thromboembolism. Our data also suggest that D-dimers monitoring could improve risk estimate. The need for transfer to intensive care unit and/or for invasive mechanical ventilation was more frequent in patients who developed venous thromboembolism, although baseline clinical characteristics did not differ from patients who did not develop such event. This is consistent with the prognostic value of D-dimer levels in COVID-19 pneumonia, higher levels at admission being associated with critical presentation [4] and with higher mortality [3, 4]. Two studies demonstrated that systematic thromboprophylaxis reduces COVID-19 inpatients mortality for subjects hospitalized in medical wards [6, 7]. Whether this finding result from a reduction of fatal thrombotic events or from an anti-inflammatory of heparin effect is not known [14] but interestingly we found no correlation between fibrinogen and D-dimer levels in our study. Finally, the high frequency of thrombotic events could be explained by the host inflammatory reaction due to the direct involvement of endothelial cells by SARS-Cov2 [15].

Our study has some limitations. This was a retrospective study but it was a cohort of consecutive patients and screening for DVT was systematically performed. Second, this study was conducted in two hospital centers with limited sample size. As such this study may have included disproportionately more patients with poor outcomes.

In summary, venous thromboembolism is a key concern in patients with COVID-19 hospitalized in medical wards even under thromboprophylaxis. At admission, D-dimer < 1.0 µg/ml has an excellent negative predictive value for venous thromboembolism whereas the risk of thromboembolic events is strikingly high in patients with D-dimer level ≥ 3.0 µg/ml. D-dimer level-guided more aggressive thromboprophylaxis regimens using higher doses of heparin should be evaluated in prospective studies and may improve patients outcome.

Acknowledgments We want to thank Charlotte Biron, Jeanne Brochon, Marie Chauveau, Jérôme Connault, Colin Deschanvres, Cécile Durant, Dominique El Kouri, Alexandra Espitia-Thibault, Benjamin Gaborit, Nicolas Goffinet, Mohamed Hamidou, Ohian Joubert, Amal Kenzi, Paul Le Turnier, Maeva Lefebvre, Simon Ribes.

Author contributions MA, GD, GG, and PG collected and curated the data. MA, AN, and RL performed the analysis and wrote the manuscript. FR, DB, AN and RL critically reviewed the manuscript. All authors approved the final version.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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