Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Intensified thromboprophylaxis in COVID-19 critically ill patients: Is it enough?

Dear editor

We read with great interest the review article by Skevaki et al.[1], who analyzed laboratory characteristics of COVID-19 patients. They show that SARS-CoV-2 infection causes systemic disease, involving multiple organs and systems, including hyperactivation of the immune system and the clotting system. Indeed, initial reports of venous thrombotic events (VTE) in critically ill patients with SARS-CoV-2 have yielded prevalences of more than 40% [2–4], prompting the empirical use of intensified thromboprophylaxis regimens. The aim of our study was to determine the prevalence of VTE in critically ill COVID-19 patients using such an intensified thromboprophylaxis protocol as recommended by French guidelines[5]. The protocol consisted in curative dose enoxaparin for very high-risk patients (*i.e.* high flow nasal oxygen / mechanical ventilation (HFNO/VM) with a body mass index $\geq$ 30 kg/m^2 and other thrombotic risk factors), and enoxaparin 4000UI/12 h for high-risk patients (*i.e.* all other patients with HFNO/VM) [5], and to determine clinical and biological factors associated with VTE.

All consecutive patients admitted to the medical ICU of our hospital with severe ARDS due to SARS-Cov2 between February and May 2020 were consecutively included. Venous doppler ultrasonography of femoral and jugular veins was performed weekly by an intensivist in all patients and before each central venous catheter insertion, until ICU discharge. Angio CT-scans were performed only as clinically indicated. Clinical and biological variables, as well as anticoagulant therapies were recorded daily from ICU admission to ICU discharge. Patients were followed until hospital discharge or day 60. To account for the competing risks between death and VTE, we used a cause-specific hazard model to assess the risk of VTE during the study period (SAS 9.4). We tested variables at ICU admission and variables collected daily as time-dependent covariates. The impact of time-dependent VTE on patient survival was tested using a Cox model. Variables collected at time t-1 were used to model event occurring at time t.

Among 134 ARDS COVID-19 patients included, median age was 59.5 [51; 69], and 100 (74.6%) were male. At ICU admission, 105 (78.4%) patients were considered at high risk and received high prophylactic heparin doses, and 24 (17.9%) patients were considered at very high risk and received curative heparin doses. During ICU stay, 74 (56.1%) patients required invasive mechanical ventilation, 73 (54.5%) required vasopressors and 43 (32.6%) received renal replacement therapy. A VTE occurred in 21 (15.6%) patients, including 15 pulmonary embolisms and 6 deep venous thrombosis (**Table 1**). In multivariate analysis, the only variable associated with a VTE was the presence of a central vein catheter (cause specific hazard ratio 5.2 [95% confidence interval 1.52; 17.83], $p<0.01$) (**Table 2**). In univariate analysis, levels of fibrinogen, fibrin monomers and D-dimers were not associated with the occurrence of a VTE. Compared to high dose thromboprophylaxis, curative anticoagulation before VTE was not significantly associated with prevention of VTE risk (CSHR 2.16 [95%CI 0.87–5.39], $p=0.1$). All-cause 60-day mortality was 41% (55/134), and VTE was not related to mortality after adjusting on comorbidities and SOFA score at ICU admission (HR=1.7 [95%CI 0.8; 3.5], $p=0.17$).

Even when using a high dose prophylaxis or curative anticoagulant therapy, VTE occurred in 16% of cases, suggesting that other mechanisms than coagulation may concur to thromboembolic events. Endothelial damage leading to activation of tissue factor and platelets [6], hypofibrinolysis [7], and proinflammatory cytokines that foster microvascular injuries and thrombus formation are thought to be implicated in the thrombotic process. However, the single center design of this study and its small sample size preclude from any definitive conclusion. We suspect that multiple intricated pathways lead to VTE and that multimodal thromboprophylaxis strategies in COVID-19 patients should require further evaluation.

Ethics approval and consent to participate

This observational cohort study was conducted using data from the French prospective OUTCOMEREA database. The OUTCOMEREA database, has been approved by the French Advisory Committee for Data Processing in Health Research and the French Informatics and Liberty Commission (CNIL, registration no. 8999262). The database protocol was submitted to the Institutional Review Board of the Clermont-Ferrand University Hospital (Clermont-Ferrand, France), who waived the need for informed consent (IRB no. 5891).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contribution

Conception and design of the study: NA, DF, JFT.
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Table 1
Characteristics of the study population at ICU admission.

Variables Median [Q1-Q3] or n (%)	All patients *n* = 134	VTE *n* = 21	Decedents without VTE *n* = 45	Survivors without VTE *n* = 68
Demographics				
Age, y	59.5 [51; 69]	52 [46; 63]	66 [58; 73]	58 [50; 68]
Male gender	100 (74.6)	18 (85.7)	31 (68.9)	51 (75)
Charlson score	1 [0; 4]	1 [0; 3]	3 [0; 4]	1 [0; 3]
Body mass index >30 Kg/m^2	51 (38.1)	10 (47.6)	16 (35.6)	25 (36.8)
Time from 1st symptoms to ICU admission, d	10 [7; 13]	10.5 [7.5; 14]	9 [7.5; 12]	10 [7; 13]
Severity at ICU admission				
SOFA score	5 [4; 7]	7 [5; 8]	7 [5; 11]	4 [3; 6]
Invasive mechanical ventilation	41 (30.6)	10 (47.6)	19 (42.2)	12 (17.6)
Biology at ICU admission				
Lymphocyte count, G/L	0.93 [0.62; 1.26]	1.07 [0.68; 1.36]	0.83 [0.58; 1.26]	0.97 [0.65; 1.28]
Neutrophil count, G/L	6.83 [4.61; 11.26]	8.10 [5.32; 13.46]	6.90 [4.27; 12.20]	6.71 [4.82; 10.90]
Platelets, G/L	232 [174; 308]	253 [178; 348]	211 [161; 280]	241 [170; 332]
C-reactive protein, mg/L	149 [76; 218]	149 [111; 244]	147 [95; 241]	147 [95; 241]
Fibrinogen, g/L	6 [4.9; 7.2]	6.1 [5.1; 8.5]	6.1 [5.2; 6.9]	5.7 [4.7; 7.2]
D-dimers, ng/mL	1055 [626; 2371]	2377 [744; 6563]	1025 [785; 1561]	777 [519; 1834]
Fibrin monomers, µg/L	3.5 [3.5; 3.5]	3.5 [3.5; 85.2]	3.5 [3.5; 29.2]	3.5 [3.5; 3.5]
Ferritin, µg/L	1376 [774; 2275]	1946 [1526; 4210]	1387 [751; 2711]	1159 [607; 1808]
ASAT, U/L	56 [37; 94.4]	62 [37; 121]	69 [42; 96]	45.5 [33; 78]
ALAT, U/L	47 [28; 64]	49 [34; 88]	41 [27; 61]	48.5 [30; 64]
LDH, U/L	434 [357; 568]	523 [424; 695]	511 [406; 694]	389 [330; 463]
Thromboprophylaxis at ICU admission				
High prophylactic dose	105 (78.4)	15 (71.4)	34 (75.6)	56 (82.4)
Curative dose	24 (17.9)	6 (28.6)	8 (17.8)	10 (14.7)
Outcomes				
ICU length of stay, d	8 [5; 17]	23 [16; 37]	9 [5; 21]	7 [5; 11]
Day-60 mortality	54 (40.3)	10 (47.6)	45 (100)	0

Abbreviation: VTE, Venous Thrombotic Event; SOFA, Sequential Organ Failure Assessment.

Table 2
Multivariate cause-specific Hazard model for the risk of venous thrombotic event and ICU death.

Variable	VTE		Death	
	csHR	*p*	*csHR*	*p*
Age, per year	0.97 (0.93; 1.02)	0.23	1.07 (1.04; 1.11)	<0.01
SOFA, per point	0.95 (0.83; 1.1)	0.51	1.23 (1.13; 1.35)	<0.01
Temperature < 36 °C	2.04 (0.64; 6.53)	0.23	1.56 (0.69; 3.53)	0.28
Central vein catheter	5.2 (1.52; 17.83)	<0.01	1.49 (0.64; 3.48)	0.36
Ferritin, per 1000 µg/L	1.05 (0.91; 1.2)	0.52	0.94 (0.85; 1.04)	0.22
LDH, per 1000 U/L	1.01 (0.21; 4.98)	0.99	2.77 (0.9; 8.59)	0.08

Abbreviation: VTE, Venous Thrombotic Event; csHR, cause specific hazard ratio; SOFA, Sequential Organ Failure assessment.

Declaration of Competing Interests

The authors declare that they have no competing interests

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2021.02.003.

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References

1. Chrysanthi Skevaki, C Fragkou Paraskevi, Chongsheng Cheng, Min Xie, Harald Renz. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. *J Infect* 2020;**81**(2):205–12. doi:10.1016/j.jinf.2020.06.039.
2. Julie Helms, Charles Tacquard, François Severac, Ian Leonard-Lorant, Mickaël Ohana, Xavier Delabranche, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intens Care Med* 2020;**46**(6):1089–98. doi:10.1007/s00134-020-06062-x.
3. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;**191**:145–7. doi:10.1016/j.thromres.2020.04.013.
4. Dominic Wichmann, Jan-Peter Sperhake, Marc Lütgehetmann, Stefan Steurer, Carolin Edler, Axel Heinemann, et al. Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020;**173**(4):268–77. doi:10.7326/M20-2003.
5. Sophie Susen, Charles Ambroise Tacquard, Alexandre Godon, Alexandre Mansour, Delphine Garrigue, Philippe Nguyen, et al. Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. *Crit Care* 2020;**24**(1):364. doi:10.1186/s13054-020-03000-7.
6. George Goshua, B Pine Alexander, Meizlish Matthew L, C-Hong Chang, Hanming Zhang, Parveen Bahel, et al. Endotheliopathy in COVID-19-associated co-

agulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol* 2020;**7**(8):e575–82. doi:10.1016/S2352-3026(20)30216-7.
7. Emmanuel Weiss, Olivier Roux, Jean-Denis Moyer, Catherine Paugam-Burtz, Larbi Boudaoud, Nadine Ajzenberg, et al. Fibrinolysis resistance: a potential mechanism underlying COVID-19 coagulopathy. *Thromb Haemost* 2020;**120**(09):1343–5. doi:10.1055/s-0040-1713637.

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