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Letter to the Editors-in-Chief

In-hospital fatality and venous thromboembolism during the first and second COVID-19 waves at a center opting for standard-dose thromboprophylaxis

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Coronavirus disease 2019 (COVID-19) emerged as a potentially life-threatening disease characterized by multiorgan involvement, high rate of venous thromboembolism (VTE), primarily among hospitalized patients, and substantial fatality particularly among the elderly [1–3]. Unanswered questions include whether an early thromboprophylaxis, as for example in the outpatient setting, may reduce these risks [4], if selected hospitalized patients may benefit from therapeutic-dosed anticoagulation (against the use of a standard thromboprophylaxis) [5]; and if post-discharge VTE prevention is necessary [6]. In the absence of firm evidence from phase 3 trials, international guidance and expert consensus vary widely, particularly concerning the timing and dosage of in-hospital thromboprophylaxis [7]. Data comparing the first and the second COVID-19 wave are still sparse and likely influenced by the change in our medical approach to disease management and prevention of thromboembolic complications [8].

In this study, we described the characteristics and course of patients admitted to the Internal Medicine Ward of the Magenta Hospital (Italy), where an institutional COVID-19 clinical protocol was implemented in March 2020 to guide decisions of the medical personnel concerning the use of specific medications and respiratory support. In particular, the suggestion to opt for standard thromboprophylaxis regimen in all medical patients (not requiring admission to an intensive care unit) remained unchanged during the first and in the second COVID-19 waves, based on lacking evidence from interventional studies. The scheme for thromboprophylaxis consisted of enoxaparin 40 mg once daily, reduced to 20 mg once daily in case of patients with severe renal insufficiency (estimated glomerular filtration rate < 30 ml/min) and increased to 60 mg once daily in obese patients (Body Mass Index >30 kg/m2). The diagnosis of SARS-CoV-2 infection was confirmed by reverse-transcriptase–polymerase-chain-reaction assays performed on nasopharyngeal swab specimens. Patients aged 17 years or younger, on therapeutic-dose antithrombotic therapy upon admission, with a previous VTE, or still hospitalized at the time of data analysis were excluded from this study. By doing so, we included patients who were hospitalized up to 4 December 2020, allowing a two-week follow-up until the updated data collection. The end of follow-up was the date of discharge, transferral to another hospital, or death.

In this retrospective analysis, we focused on the in-hospital incidence of VTE (acute deep vein thrombosis, DVT, and pulmonary embolism, PE), as well as on in-hospital death. The diagnostic pathway of VTE, including compression ultrasound followed by computed tomography pulmonary angiography, was left to the attending physician. While no systematic imaging screening was performed, the suspicion of VTE was raised in the presence of signs or symptoms or in patients with an otherwise unexplainable clinical worsening or in the presence of a significant increase of D-dimer levels, e.g. more than two folds from admission. Electronic medical charts were accessed to retrieve clinical information into a pseudo-anonymized database. The ethical approval for this study and the need for written informed consent were not required due to local regulations in light of the retrospective nature of the study. In-hospital incidences were accompanied by the corresponding 95% confidence interval (95% CI). The first and the second waves were compared by fitting univariate and multivariable logistic regression models: conditioning variables were chosen based on their clinical relevance and lack of collinearity. In line with current literature and recommendations, no inferential analysis was performed to compare the groups with respect to baseline characteristics and biomarkers levels. JASP served for statistical analysis.

A total of 476 patients have been admitted: 316 between 21 February 2020 and 5 April 2020 (first wave) and 160 between 15 October 2020 and 4 December 2020 (second wave). The demographic and baseline characteristics are summarized in Table 1. No clinically relevant differences were observed concerning age, sex, and prevalence of cardiovascular risk factors. The distribution of commonly tested biomarkers also appeared comparable over time. The use of metilprednisolone 1 mg/kg/day was routinely used in all patients requiring Continuous Positive Airway Pressure: 130 (41.1%) in the first wave and 98 (61.3%) in the second wave. Other specific medications intended to mitigate the course of COVID-19 were differently used in the first and in the second wave. In particular, remdesevir was used in only 7 (4.4%) patients from the second wave, whereas tocilizumab was used in only 7 (2.2%) patients from the first wave. The routine use of plaquenil and ritonativ/lopinavir was abandoned in the second wave.

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Table 1
Baseline characteristics and in-hospital incidence of events in COVID-19 patients during the first and second 2020 wave.

	First wave (n = 316)	Missing	Second wave (n = 160)	Missing
Demographic and baseline characteristics				
Age, median (Q1–Q3)	72 (63–80)	0	72 (62–81)	0
Women, n (%)	99 (31.3)	0	53 (33.1)	0
Chronic heart failure, n (%)	56 (17.7)	0	27 (16.9)	0
Chronic obstructive pulmonary disease, n (%)	44 (13.9)	1	22 (13.8)	1
Diabetes mellitus, n (%)	71 (22.5)	14	36 (22.5)	1
Arterial hypertension, n (%)	184 (58.2)	14	87 (54.4)	1
Prior stroke, n (%)	17 (5.4)	0	8 (5.0)	1
Body mass index >30 kg/m^2, n (%)	40 (12.7)	0	22 (13.8)	1
Active cancer, n (%)	16 (5.1)	0	7 (4.4)	1
Pneumonia upon admission, n (%)	247 (78.2)	0	114 (71.3)	2
Acute respiratory distress syndrome, n (%)	92 (29.1)	0	74 (46.3)	3
Days on continuous positive airway pressure, median (Q1–Q3)	6 (3.8–4.9)	0	11 (7–17)	0
Days of hospitalization, median (Q1–Q3)	10 (7–17)	0	17 (8–27)	0
Biomarkers levels measured upon admission				
Creatinine (mg/dL), median (Q1–Q3)	0.89 (0.74–1.15)	41	0.98 (0.81–1.20)	1
D-dimer (μg/l), median (Q1–Q3)	526 (339–1563)	78	414 (244–1031)	20
Hemoglobin (g/dL), median (Q1–Q3)	12.9 (11.9–14.1)	24	13.9 (12.5–14.8)	1
White blood cells (per 10^9/L), median (Q1–Q3)	6.9 (5.2–9.6)	24	8.0 (5.5–10.2)	1
Platelet count (per 10^9/L), median (Q1–Q3)	215 (159–284)	24	198 (150–262)	1
C-reactive protein (mg/L), median (Q1–Q3)	9.8 (5.3–13.7)	165	8.0 (3.3–13.3)	3

During the second wave, a higher proportion of patients presented with acute respiratory distress syndrome (ARDS; 46.3% vs. 29.1%) and the median length of hospitalization was longer (17 days; [Q1–Q3 8–27] vs. 10 days [Q1–Q3 7–17]). Twelve (3.8%) patients in the first wave and 14 (8.8%) patients during the second wave underwent computed tomography pulmonary angiography. Of these, 5 (1.6%) and 7 (4.4%) were diagnosed with PE, respectively; Table 1. Eleven of 12 patients with PE had a concomitant upper- or lower-extremity DVT. A total of 316 compression ultrasounds were performed: 143 (45% of total) during the first wave and 114 (71%) during the second wave after a median of 5 (Q1–Q3 4–7) days and 7 (Q1–Q3 5–12) days, respectively. Of these patients, 121 (84.6% of ultrasounds) and 102 (89.5%) had no typical signs or symptoms of DVT and the exam was performed based on other clinical reasons. The in-hospital incidence of lower-extremity DVT was 8.5% and 13.1% in the two waves with a similar percentage of positive ultrasonography tests (16% of tests), but with a lower proportion of isolated distal DVT vs. proximal DVT being diagnosed in the first wave (3 distal DVT; 24 proximal DVT) than in the second wave (11 distal DVT; 10 proximal DVT); Table 2. Upper-extremity DVT was diagnosed in 5.7% of patients during the first wave and 10.0% of patients during the second wave, corresponding to a rate of positive ultrasound examinations of 12.6% and 14.0%, respectively. Overall, a total of 44 (13.9%; 95%CI 10.5%–18.2%) patients during the first wave and 29 (18.1%; 95%CI 12.9%–24.8%) patients during the second wave were diagnosed with DVT or PE.

In-hospital fatality was 24.7% during the first wave (n = 78) and 25.0% (n = 40) during the second wave for an OR of 1.02 (95%CI 0.67–1.58); Table 2. In a multivariable model conditioning for sex, chronic obstructive pulmonary disease, prior chronic heart failure, cancer, and time distribution the covariates "age" (OR 1.11 per year increase; 95% CI 1.10–1.15) and "ARDS diagnosis" (OR 3.05; 95%CI 1.84–5.04) correlated with the risk of in-hospital death. This could not been shown for time distribution (adjusted OR for the second vs. first wave 0.81; 95%CI 0.49–1.33).

Table 2
Clinical events during hospitalization.

	First wave (n = 316)	Second wave (n = 160)
Lower-extremity DVT, n (% of patients)	27 (8.5)	21 (13.1)
(Iliaco)-femoro-popliteal, n	15	8
Popliteal, n	9	2
Isolated distal, n	3	11
Upper-extremity DVT, n (% of patients)	18 (5.7)	16 (10.0)
Axillary vein (bilateral), n	5	4
Axillary vein (unilateral), n	6	10
Subclavian vein (unilateral), n	1	2
Subclavian vein (bilateral), n	0	0
Catheter-related, n	8	1
PE, n (% of total; % of CT pulmonary angiogram)	5 (1.6; 41.7)	7 (4.4; 50.0)
Central or lobar, n	2	2
Segmental, n	3	4
Subsegmental, n	0	1
Any VTE (DVT or PE), n (; 95% CI)	44 (13.9; 10.5–18.2)	29 (18.1; 12.9–24.8)
Death, n (%; 95% CI)	78 (24.7; 20.3–28.9)	40 (25.0; 18.9–32.2)

PE, pulmonary embolism; DVT, deep vein thrombosis; VTE, venous thromboembolism; 95% CI, 95% confidence interval.

Our results are in line with data from two Italian provinces indicating a stable trend in COVID-19-related fatality [9]. These appear in contrast with a more recent analysis of data from eight Dutch hospitals, which showed a 50%-reduced risk for overall fatality and a similar incidence of VTE [8]. In our cohort, the demographic and baseline characteristics of patients admitted in spring and autumns appeared surprisingly similar and characterized by older patients with a median age of 72 years. However, the proportion of patients requiring Continuous Positive Airway Pressure increased from 41% in the first wave to 61% in the second wave, consistently with that of Acute Respiratory Distress Syndrome (29% to 46%, respectively). This may partly explain why no apparent improvement in patient survival could be observed.

The rate of VTE events in our study is similar to what reported in other cohorts of COVID-19 patients [2] and, considering the routine use of thromboprophylaxis, much higher than what observed in patients with medical illnesses without COVID-19 [10]. Nonetheless, this likely represents an underestimation of the actual rate, which remains unknown and largely depends on the number of imaging tests been performed. For instance, in the Dutch study 21% of patients in the first wave and in 38% in the second wave underwent computed tomography pulmonary angiography, which represent much higher values compared to what observed (3.8% and 8.8%, respectively) in this cohort. A more frequent use of imaging testing was associated with more subsegmental PE events been diagnosed. In the Dutch cohort, 24% of patients with PE in the first wave and 38% in the second wave were diagnosed with a subsegmental PE event. In this cohort, the percentage was overall much lower with only one subsegmental PE event (8%) been diagnose. It remains unclear in whom an acute PE should be excluded, how accurate computed tomography pulmonary angiography is for the detection of small emboli and whether their detection has clinical relevance in this setting. Moreover, the strategy of performing a compression ultrasound as a first-line imaging test if a PE is suspected may be useful in other settings to reduce the number of computed tomography pulmonary angiography, but not efficient if the pathophysiological mechanism of disease accounts for pulmonary thrombosis secondary to local inflammation and pneumonia.

It is clear that the available risk assessment models fall short to identify patients for whom an anticoagulant prophylaxis is indicated. A number of randomized controlled studies overcoming the intrinsic limitations of observational studies are ongoing to study the impact of non-standard thromboprophylaxis regimens in this setting [5]. At the same time, the so far unsatisfactory results of available trials showed that only corticosteroids appear to improve survival among COVID-19 patients [11,12], leaving vaccination as the sole hope to prevent deaths globally and minimize the burden of disease.

In conclusion, in this retrospective study we observed no major clinical differences between the first and the second COVID-19 wave in terms of baseline characteristics, biomarker levels upon admission, parameters of severity, and fatality among patients admitted to the same institution and receiving standard-dose thromboprophylaxis. We ascribe the higher incidence of VTE observed during the second wave to longer length of in-hospital stay and more diagnostic tests been performed, the latter as the result of a greater awareness [13] for thromboembolic complications.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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References

[1] C. Lodigiani, G. Iapichino, L. Carenzo, M. Cecconi, P. Ferrazzi, T. Sebastian, N. Kucher, J.D. Studt, C. Sacco, A. Bertuzzi, M.T. Sandri, S. Barco, C.-T. F. Humanitas, Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy, Thromb. Res. 191 (2020) 9–14.

[2] L. Roncon, M. Zuin, S. Barco, L. Valerio, G. Zuliani, P. Zonzin, S.V. Konstantinides, Incidence of acute pulmonary embolism in COVID-19 patients: systematic review and meta-analysis, Eur. J. Intern. Med. 82 (2020) 29–37.

[3] F. Bompard, H. Monnier, I. Saab, M. Tordjman, H. Abdoul, L. Fournier, O. Sanchez, C. Lorut, G. Chassagnon, M.P. Revel, Pulmonary embolism in patients with COVID-19 pneumonia, Eur. Respir. J. (2020) 56(1).

[4] S. Barco, R. Bingisser, G. Colucci, A. Frenk, B. Gerber, U. Held, F. Mach, L. Mazzolai, M. Righini, T. Rosemann, T. Sebastian, R. Spescha, S. Stortecky, S. Windecker, N. Kucher, Enoxaparin for primary thromboprophylaxis in ambulatory patients with coronavirus disease-2019 (the OVID study): a structured summary of a study protocol for a randomized controlled trial, Trials 21 (1) (2020) 770.

[5] T. Tritschler, M.E. Mathieu, L. Skeith, M. Rodger, S. Middeldorp, T. Brighton, P. M. Sandset, S.R. Kahn, D.C. Angus, M. Blondon, M.J. Bonten, M. Cattaneo, M. Cushman, L.P.G. Derde, M.T. DeSancho, J.L. Diehl, E. Goligher, B. Jilma, P. Juni, P.R. Lawler, M. Marietta, J.C. Marshall, C. McArthur, C.H. Miranda, T. Mirault, N. Morici, U. Perepu, C. Schorgenhofer, M. Sholzberg, A. C. Spyropoulos, S.A. Webb, R. Zarychanski, S. Zuily, G. Le Gal, International Network of VTCRNI-VTE, Anticoagulant interventions in hospitalized patients with COVID-19: a scoping review of randomized controlled trials and call for international collaboration, J. Thromb. Haemost. 18 (11) (2020) 2958–2967.

[6] Rashidi F, Barco S, Kamangar F, Heresi GA, Emadi A, Kaymaz C, Jansa P, Reis A, Rashidi A, Taghizadieh A, Rezaeifar P, Moghimi M, Ghodrati S, Mozafari A, Foumani AA, Tahamtan O, Rafiee E, Abbaspour Z, Khodadadi K, Alamdari G, Boodaghi Y, Rezaei M, Muhammadi MJ, Abbasi M, Movaseghi F, Koohi A, Shakourzad L, Ebrahimi F, Radvar S, Amoozadeh M, Fereidooni F, Naseari H, Movalled K, Ghorbani O, Ansarin K. Incidence of symptomatic venous thromboembolism following hospitalization for coronavirus disease 2019: prospective results from a multi-center study. Thromb. Res. 2020: 198: 135–138.

[7] P. Fontana, A. Casini, H. Robert-Ebadi, F. Glauser, M. Righini, M. Blondon, Venous thromboembolism in COVID-19: systematic review of reported risks and current guidelines, Swiss Med. Wkly. 150 (2020) w20301.

[8] F. Kaptein, M. Stals, M. Grootenboers, F. Klok, M. Huisman, Incidence of thrombotic complications and overall survival in hospitalized patients with COVID-19 in the second and first wave, Thromb. Res. 199 (2021) 143–148.

[9] M.E. Flacco, C. Acuti Martellucci, F. Bravi, G. Parruti, A. Mascitelli, L. Mantovani, S. Boccia, L. Manzoli, Severe acute respiratory syndrome coronavirus 2 lethality did not change over time in two Italian provinces, Open Forum Infect Dis 7 (12) (2020) (ofaa556).

[10] A.C. Spyropoulos, F.A. Anderson Jr., G. FitzGerald, H. Decousus, M. Pini, B. H. Chong, R.B. Zotz, J.F. Bergmann, V. Tapson, J.B. Froehlich, M. Monreal, G. J. Merli, R. Pavanello, A.G.G. Turpie, M. Nakamura, F. Piovella, A.K. Kakkar, F. A. Spencer, I. Investigators, Predictive and associative models to identify hospitalized medical patients at risk for VTE, Chest 140 (3) (2011) 706–714.

[11] P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, E. Elmahi, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L.C. Chappell, S.N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J.K. Baillie, R. Haynes, M.J. Landray, Dexamethasone in hospitalized patients with Covid-19 - preliminary report, N. Engl. J. Med. 384 (2021) 693–704.

[12] M. Edalatifard, M. Akhtari, M. Salehi, Z. Naderi, A. Jamshidi, S. Mostafaei, S. R. Najafizadeh, E. Farhadi, N. Jalili, M. Esfahani, B. Rahimi, H. Kazemzadeh, M. Mahmoodi Aliabadi, T. Ghazanfari, M. Sattarian, H. Ebrahimi Louyeh, S. R. Raeeskarami, S. Jamalimoghadamsiahkali, N. Khajavirad, M. Mahmoudi, A. Rostamian, Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial, Eur. Respir. J. (2020) 56(6).

[13] L. Roncon, M. Zuin, S. Barco, G. Zuliani, S.V. Konstantinides, Increased interest in acute pulmonary embolism in Italy during the COVID-19 pandemic: a google trends-based analysis, J. Thromb. Thrombolysis (2020), https://doi.org/10.1007/s11239-020-02336-9.

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