

## Coronavirus Pandemic

# Is venous thromboembolism a predictable marker in older patients with COVID-19 infection? A single-center observational study

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### Abstract

Venous thromboembolism (VTE) represents an important clinical complication of patients with SARS-CoV-2 infection, and high plasma D-dimer levels could suggest a higher risk of hypercoagulability. We aimed to analyse if laboratory exams, risk assessment scores, comorbidity scores were useful in predicting the VTE in SARS-CoV-2 patients admitted in internal medicine (IM). We evaluated 49 older adults with suspected VTE analysing history and blood chemistry, besides we calculated the Padua Prediction Score, the modified early warning scoring (MEWS) and the modified Elixhauser index (mEI). All patients underwent venous color-doppler ultrasounds of the lower limbs. Out of the 49 patients enrolled (mean age 79.3±14 years), 10 (20.4%) had deep vein thrombosis (DVT), and they were more frequently female (80% vs 20%,  $p = 0.04$ ). We could not find any association with the Padua Prediction Score, the MEWS, and the mEI. D-dimer plasma levels were also not associated with DVT. In elderly people hospitalized with SARS-CoV-2 infection hospitalized in IM, our data, although limited by the sample size, suggest that prediction and diagnosis of VTE is difficult, due to lack of precise biomarkers and scores.

**Key words:** COVID-19; elderly; venous thromboembolism; comorbidity score; D-dimer.

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### Introduction

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) dramatically spread throughout the world, involving more than 210 Countries with approximately 67 million confirmed global cases and more than 1,54 million fatal cases worldwide [1]. All clinical manifestations of SARS-CoV-2 disease are not completely understood, and multiple general and respiratory symptoms are reported, although varying in severity. Common, and confounding, symptoms include fever, cough, myalgia or fatigue, pneumonia and dyspnoea [2], so that they should be careful taken into account in order to prevent the progression of this disease towards severe and progressive respiratory failure due to the alveolar damage. There is a close association between this highly transmissible disease and elderly male patients

[3], and a recent meta-analysis evaluating more than 2,000 subjects concluded that most of the cases dying because of novel coronavirus 2019 (COVID) were elderly males and acute respiratory distress syndrome and shock were risk factors for death [4]. Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) may represent late complication in COVID-19 patients [5-7]. High plasma D-dimer and lactate dehydrogenase (LDH) levels, associated with prolonged coagulation times, could suggest a higher risk of hypercoagulability of SARS-CoV-2 [8]. It is always somewhat difficult to investigate incidence and prevalence of VTE, DVT and PE, probably because these diseases not always require hospitalization, and data from hospital databases are more likely to be obtained. Even in the United States (US), information on VTE incidence is limited because

there is no national surveillance system; however, it is estimated that in 2014 there were ~676,000 DVTs, 340,000 PEs, and 1,016,000 total events (US population: 319 million in 2014) [9]. In Europe, data from the PREFER in VTE registry, conducted between 2013 and 2015 in primary and secondary care across seven European countries, also had the majority of patients (79%) assessed in the hospital setting as inpatients or outpatients, and diagnosis of DVT and PE was found in 59.5% and 40.5%, respectively [10]. The incidence of venous thromboembolism (VTE), including both pulmonary embolism (PE) and possibly deep vein thrombosis (DVT) is increased in SARS-CoV-2 patients due to both a severe inflammatory syndrome and a procoagulant state, suggesting the definition of COVID-19 associated coagulopathy [11-15].

Different studies, conducted in several Countries, reported a lower prevalence of DVT and PE, ranging between 21% and 28% [16-19]. Even lower incidence rate of VTE than in ICUs has been reported for patients with SARS-CoV-2 infection admitted in internal medicine setting, ranging between 6.6 and 9.2% [20].

Thus, based on the limited available data regarding elderly patients admitted to internal medicine wards, the present study was aimed to evaluate clinical profile of COVID-19 patients with and without VTE.

## Methodology

This retrospective study was conducted in agreement with the Declaration of Helsinki of 1975, revised in 2013, and was approved by the local ethic committee. Ferrara is a province located in the north-east of Italy, the total population is about 350,000 individuals, including a high percentage of elderly subjects (~26% of total population is aged > 65 years, and nearly 1% > 90 years). The General and University Hospital (Azienda Ospedaliero-Universitaria ‘S.

Anna’), is provided with 626 beds and represents the hub and teaching hospital of the entire province. The annual flow of patients by the Emergency Department (ED) is approximately 90,000. The approach to the pandemic coronavirus outbreak was organized planning a specific COVID-dedicated hospital pathway, including multiple units: Emergency Department, Infectious Disease, Internal Medicine, Pulmonology, and Intensive Care, all open to receive admissions 24/24 and 7/7. This study included all patients consecutively admitted, from April 1 to 30, 2020, to the 48-bed COVID university internal medicine unit (Clinica Medica and Internal Medicine). Overall, 88 patients with confirmed SARS-CoV-2 infection (positive polymerase chain reaction, tested by nasopharyngeal swab) were consecutively admitted during the considered period. Of these, 49 patients were clinically suspected to suffer with VTE, having a Wells score greater than 1 [21]. We collected data on gender, age, clinical history, blood chemistry panel including C-reactive protein and D-dimer. Aim of this study is to evaluate the utility of D-dimer dosage and VTE and comorbidity predictive scores to predict the presence of VTE in patients with SARS-CoV-2 infection admitted to internal medicine wards.

## Statistical analysis

Patients were assessed by means of the Padua Prediction Score [22], representing the main clinical score able to assess the risk of thrombotic events, by the Modified Early Warning Scoring (MEWS) [23], a promising performance score able to predict in-hospital mortality [24], and by the modified Elixhauser index (mEI) [25-26], a comorbidity score associated with in-hospital mortality in Internal Medicine. All patients underwent venous color-doppler ultrasound of the lower limbs in order to identify the presence of DVT. A descriptive analysis was carried out, and results were

**Table 1.** Main characteristics of the internal medicine patients, admitted for SARS-Cov-2 infection and investigated for suspected deep vein thrombosis (DVT).

	<b>n = 49</b>	<b>Without DVT (N = 39)</b>	<b>With DVT (N = 10)</b>	<b>P</b>
Male (n(%))	24 (49%)	22 (56.4%)	2 (20%)	<b>0.04</b>
Female (n(%))	25 (51%)	17 (43.6%)	8 (80%)	
Age (years)	79.3 ± 14	78.4 ± 14.6	82.9 ± 11.4	0.345
D-dimer (mg/l)	2.99 ± 4.33	2.6 ± 4.14	4.55 ± 4.95	0.072
D-dimer >4 mg/dl (n(%))	17 (34.7%)	11 (28.2%)	6 (60%)	0.06
C-reactive protein (mg/dl)	7.3 ± 5.9	7.19 ± 6.03	7.71 ± 5.84	0.763
Padua Predicting score	4.25 ± 1.89	4 ± 1.6	5.1 ± 2.6	0.297
Padua Predicting Score ≥ 4 (n(%))	26 (53.1%)	20 (51.3%)	6 (60%)	0.622
Modified early warning scoring	1.88 ± 0.88	1.9 ± 0.9	1.8 ± 0.8	0.855
Modified Elixhauser index	21.88 ± 13.3	21.3 ± 12.6	24.1 ± 5.2	0.651

expressed as absolute numbers, percentages, or mean  $\pm$  SD. The univariate analysis defined the difference between patients with or without DVT, and Chi-square test, Student t test, and Mann–Whitney test were used as appropriately. Also, a logistic regression analysis was carried out in order to detect the independent parameters associated with the development of DVT. Development of DVT represented the dependent variable of our model, whilst scores, age and gender were considered the independent ones. All p-values were 2-tailed, and p-value  $< 0.5$  was considered significant. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, 2004) was used for statistical analyses.

## Results

Overall, of the 49 patients enrolled (mean age  $79.3 \pm 14$  years), only 10 (20.4%) had DVT developed within a period of  $8 \pm 7$  days. No fatal cases occurred and none of the enrolled patients required non-invasive or invasive ventilation. Table 1 summarizes the main results. Data analysis showed that DVT was more frequent in female patients (80% vs. 20%,  $p = 0.04$ ). No difference by age was found between the two groups, and no case of PE occurred. As for laboratory data, blood chemistry tests showed that D-dimer and C-reactive protein levels were not significantly different in the two groups analysed. As for the specific scores used, nor the Padua Prediction Score, nor the MEWS, nor the mEI were statistically different in subjects who suffered DVT and those who did not. The multivariate regression analysis did not detect any factor independently associated with the development of DVT.

## Discussion

The findings of this observational studies showed that in patients with SARS-CoV-2 infection hospitalized in Internal Medicine wards, VTE development seems to be unpredictable, when based on laboratory biomarkers and risk and/or comorbidity scores. We performed a review of the available studies enrolling patients hospitalized in similar settings and, after adding our results, we found that out of a total of 1,251 patients undergoing venous color-doppler ultrasound only less than 9% of patients developed VTE (Table 2). Gender analysis showed a higher risk for male patients (70% vs. 30%), and the majority of studies, dealing with a population with the mean age of  $68.5 \pm 7$  years, reported that the determination of D-dimer was useful. Our results did not agree with these last findings, showing that in patients with advanced age D-dimer determination seems to show low clinical value. This finding could have a clinical interest, since D-dimer has been shown to represent a marker of outcome. Demelo-Rodríguez *et al.* [31] in a cohort of 156 patients (65.4% male) hospitalized for SARS-CoV-2 pneumoniae and with DVT found that median D-dimer levels were higher and that the diagnostic power evaluated by the ROC curve was equal to 0.72. In addition, the increase in D-dimer levels has been reported as an important risk factor for mortality and potential biomarker of evolution towards a negative outcome. In a study analysing 191 Chinese patients from Wuhan, factors related to mortality included high D-dimer  $> 1 \mu\text{g/ml}$  at admission [40]. Similar results were confirmed in several clinical studies regardless of the hospitalisation setting [6, 41]. Zhou *et al.* [40]

**Table 2.** Venous thromboembolism (VTE) in medical patients admitted with SARS-CoV-2 infection (literature review).

	Authors (ref)	Patients n°	VTE diagnosis n° (%)	M/W	Mean age	Diagnostic
					(years)	value of D-dimer
<b>Case reports</b>	Davoodi [27]	1	1	0/1	57	Yes
	Griffin [28]	3	3	2/1	60	Yes
	Nauka [29]	1	1	1/0	48	Yes
<b>Clinical studies</b>	Cattaneo [2]	388	0	Not given	70	Not given
	Demelo-Rodríguez [31]	156	23 (14.7)	14/9	67	Yes
	Faggiano [32]	15	7 (46.7)	7/0	70	Yes
	Grillet [33]	100	23 (23)*	21/2	67	Yes
	Leonard-Lorant [34]	106	32 (30.3)**	25/7	64	Yes
	Lodigiani [18]	314	11 (3.5)	6/5	75	Yes
	Middeldorp [35]	123	6 (4.9)	Not given	60	Uncertain
	Artifoni [36]	71	23 (32.4)	11/5	64	Yes
	Zhang [37]	143	66 (46.2)	36/30	67	Yes
	Santoliquido [38]	84	10 (11.9)	7/3	72	Yes***
	Present study	49	10 (20.4)	2/8	79	No

\* only 6 patients were treated in non ICU; \*\* only 8 patients were treated in non ICU; \*\*\* only for patients with D-dimer level  $> 3 \mu\text{g/L}$ . DVT: deep vein thrombosis; M: men; PE: pulmonary embolism; W: women.

confirmed the stratification power of D-dimer risk in predicting a negative outcome of SARS-CoV-2 infection. Rodriguez-Sevilla *et al.* [41] conducted a retrospective study to evaluate the predictive value of D-dimer to assess computed tomography pulmonary angiography (CTPA) for diagnosis of pulmonary embolism (PE) in patients with COVID-19 pneumonia during their hospitalization. They studied 52 patients with a confirmed diagnosis of COVID-19 pneumonia and suspected PE. At the time of admission, D-dimer levels were not different among patients that developed PE [(median (P5–P75) 2350 (1070–10500) mcg/L) and those who did not [3030 (650–12415) mcg/L], ( $p = .87$ ), however authors found significant differences in the highest values of D-dimer before performing CTPA only in patients with PE [14,240 (5140–31550) mcg/L,  $P = .007$ ]. Authors calculated Positive Predicted Value (PPV), Negative Predicted Value (NPV), Positive Likelihood Ratio (LR+), and (LR–) values to predict the diagnosis of PE and suggested that D-dimer of 2000 mcg/L could be the best cut-off point of sensitivity for patients with PE: sensitivity, 1.00; PPV, 0.60; specificity, 0.44; and, NPV, 1.00; LR–, 0. By the use of this threshold there were zero negative false cases and 18 (35%) positive false cases. In our study mean D-dimer was higher than 2 mg/L in both groups with and without VTE. Artifoni *et al.* suggested that D-dimers monitoring could improve risk estimate of venous thromboembolism [36]. The negative predictive value of D-dimer for venous thromboembolism was clinically relevant when the level was  $< 1.0 \mu\text{g/ml}$  while patients with high levels ( $\geq 3.0 \mu\text{g/ml}$ ) had a particularly high risk of venous thromboembolism. Relationship between VTE and SARS-CoV-2 infection could be attributed to haemostatic changes, increased D-dimer levels, excess thrombin generation, and early fibrinolysis shutdown due to endothelial activation, severe hypoxemia and direct local vascular and endothelial injury causing microvascular clot formation and angiopathy [42]. However, the important vascular prothrombotic activation present in these patients induces a significant increase in D-dimer levels regardless of the development of the thrombotic process [43]. Ageing could be considered a major risk factor for predicting worse outcome in SARS-CoV-2 patients [44]. Although the patients enrolled in our study were older than those from any other study, and had high comorbidity burden, no case of PE developed. There were no fatal cases. With regard to risk and/or comorbidity assessment, although comorbidity is related with negative outcomes in hospitalized patients with SARS-CoV-2 infection [45], widely used scores,

such as Padua Predicting Score, MEWS and mEI, are not useful to predict the risk of VTE in these patients. On the usefulness of score, such as Padua Predicting Score, to predicting the risk of VTE in medical patients with SARS-CoV-2 infection contradictory data are reported in the literature [37–38]. We are aware that the present study, evaluating a small sample of patients, does not allow to draw any definite conclusion. The main limitations of our study were the low profile risk of enrolled patients, the small sample size and the study design, being a single centre and retrospective. However, our data suggest that in elderly hospitalized because of SARS-CoV-2 infection, VTE prediction and diagnosis could be difficult, due to lack of precise biomarkers and scores. We cannot rule out the possibility that, as in the elderly population in general, in elderly subjects with SARS-CoV-2 infection, correct D-dimer cut-off levels should be used in order to improve the performance of non-invasive diagnostic tests [46]. Furthermore, available literature data support the existence of a clear gender-specific effect in the clinical outcome of patients with SARS-CoV-2, characterised by significantly higher mortality in men [47].

## Conclusions

D-dimer is a useful when physicians need to rule-out test for avoiding imaging in several clinical settings [48], however its plasma levels are increased in venous thromboembolism, but also in many other conditions including inflammation, cancer, pregnancy, trauma, and sepsis [49]. The latter are frequently encountered in subjects admitted to internal medicine units making difficult its evaluation in COVID-19 patients admitted to internal medicine wards. In conclusion, a high level of clinical attention should always be maintained, especially in very elderly subjects, and heparin treatment should always be considered in patients with SARS-Cov-2, given its association with significantly lower mortality, even when the model is adapted to age and gender [50]. Further studies are needed to clarify the role of the relationship between clinical conditions, D-dimer and different hospital settings.

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### Authors' Contributions

All authors: (i) gave substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (ii) drafted the article and revised the article critically for important intellectual content; (iii) gave final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

### References

- COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). Available: <https://coronavirus.jhu.edu/map.html> Accessed 10 August 2020.
- Pascarella G, Strumia A, Piliago C, Bruno F, Del Buono R, Costa F, Scarlata S, Agrò FE (2020) COVID-19 diagnosis and management: a comprehensive review. *J Intern Med* 288: 192-206.
- Sun ZH (2020) Clinical outcomes of COVID-19 in elderly male patients. *J Geriatr Cardiol* 17: 243-245.
- Qiu P, Zhou Y, Wang F, Wang H, Zhang M, Pan X, Zhao Q, Jing Liu J (2020) Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: a systematic review and meta-analysis. *Aging Clin Exp Res* 32: 1869-1878.
- Yin S, Huang M, Li D, Tang N (2020) Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. *J Thromb Thrombolysis* 51: 1107-1110.
- Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS, China Medical Treatment Expert Group for Covid-19 (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med* 382: 1708-1720.
- Contini C, Caselli E, Martini F, Maritati M, Torreggiani E, Seraceni S, Vesce F, Perri P, Rizzo L, Tognon M (2020) COVID-19 Is a Multifaceted Challenging Pandemic Which Needs Urgent Public Health Interventions. *Microorganisms* 8: 1228. doi: 10.3390/microorganisms8081228.
- Lippi G, Favaloro EJ (2020) D-dimer is associated with severity of coronavirus disease 2019: a pooled analysis. *Thromb Haemost* 120: 876-878.
- Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Chaffin Jordan L, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Shane Loop M, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee et al (2019). Heart Disease and Stroke Statistics – 2019 Update: report from the American Heart Association. *Circulation* 139: e56-e528.
- Cohen AT, Gitt AK, Bauersachs R, Fronk EM, Laeis P, Mismetti P, Monreal M, Willich SN, Bramlage P, Agnelli G, on behalf of the prefer in VTE scientific steering committee and the PREFER in VTE investigators (2017) The management of acute venous thromboembolism in clinical practice. Results from the European PREFER in VTE Registry. *Thromb Haemost* 117: 1326-1337.
- Miesbach W, Makris M (2020) COVID-19: Coagulopathy, Risk of Thrombosis, and the Rationale for Anticoagulation. *Clin Appl Thromb Hemost* 26: 1076029620938149.
- Ramacciotti E, Macedo AS, Biagioni RB, Caffaro RA, Lopes RD, Guerra JC, Orsi FA, Marques MA, Tafur AJ, Caprini JA, Nicolaides A, Carter CA, Filho CC, Fareed J (2020) Evidence-based practical guidance for the antithrombotic management in patients with coronavirus disease (COVID-19) in 2020. *Clin Appl Thromb Hemost* 26: 1076029620936350.
- Schulman S (2020) Coronavirus Disease 2019, Prothrombotic Factors, and Venous Thromboembolism. *Semin Thromb Hemost* 46: 772-776.
- Tal S, Spectre G, Kornowski R, Perl L (2020) Venous Thromboembolism Complicated with COVID-19: What Do We Know So Far? *Acta Haematol* 143: 417-424.
- Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Gianni D, Douketis JD, Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication (2020) Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 18: 1859-1865.
- Cui S, Chen S, Li X, Liu S, Wang F (2020) Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. *J Thromb Haemost* 18: 1421-1424.
- Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 191: 145-147.
- Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, Kucher N, Studt JD, Sacco C, Alexia B, Sandri MT, Barco S, Humanitas COVID-19 Task Force (2020) Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res* 191: 9-14.
- Poissy J, Goutay J, Caplan M, Parmentier E, Duburcq T, Lassalle F, Jeanpierre E, Rauch A, Labreuche J, Susen S, Lille ICU Haemostasis COVID-19 Group (2020) Pulmonary embolism in patients with COVID-19: awareness of an increased prevalence. *Circulation* 142: 184-186.

20. Linnemann B, Bauersachs R, Grebe M, Klamroth R, Müller O, Schellong S, Lichtenberg M (2020) Venous thromboembolism in patients with COVID-19 (SARS-CoV-2 infection) - a position paper of the German Society of Angiology (DGA). *Vasa* 49: 259-263.
21. Wells PS, Anderson DR, Bormanis J, Guy F, Mitchell M, Gray L, Clement C, Robinson KS, Lewandowski B (1997) Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 350: 1795-1798.
22. Barbar S, Noventa F, Rossetto V, Ferrari A, Brandolin B, Perlati M, De Bon E, Tormene D, Pagnan A, Prandoni P (2010) A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. *J Thromb Haemost* 8: 2450-2457.
23. Hammond NE, Spooner AJ, Barnett AG, Corley A, Brown P, Fraser JF (2013) The effect of implementing a modified early warning scoring (MEWS) system on the adequacy of vital sign documentation. *Aust Crit Care* 26:18-22.
24. Wang L, Lv Q, Zhang X, Jiang B, Liu E, Xiao C, Yu X, Yang C, Chen L (2020) The utility of MEWS for predicting the mortality in the elderly adults with COVID-19: a retrospective cohort study with comparison to other predictive clinical scores. *PeerJ* 8: e10018. doi: 10.7717/peerj.10018.
25. Fabbian F, De Giorgi A, Maietti E, Gallerani M, Pala M, Cappadona R, Manfredini R, Fedeli U (2017) A modified Elixhauser score for predicting in-hospital mortality in internal medicine admissions. *Eur J Intern Med* 40: 37-42.
26. De Giorgi A, Di Simone E, Cappadona R, Boari B, Savriè C, López-Soto PJ, Rodríguez-Borrego MA, Gallerani M, Manfredini R, Fabbian F (2020) Validation and comparison of a modified elixhauser index for predicting in-hospital mortality in Italian internal medicine wards. *Risk Manag Healthc Policy* 13: 443-451.
27. Davoodi L, Jafarpour H, Taghavi M, Razavi A (2020) COVID-19 presented with deep vein thrombosis: an unusual presenting. *J Investig Med High Impact Case Rep* 8: 2324709620931239.
28. Griffin DO, Jensen A, Khan M, Chin J, Chin K, Saad J, Parnell R, Awwad C, Patel D (2020) Pulmonary embolism and increased levels of d-dimer in patients with coronavirus disease. *Emerg Infect Dis* 26: 1941-1943.
29. Nauka PC, Oran E, Chekuri S (2020) Deep venous thrombosis in a non-critically ill patient with novel COVID-19 infection. *Thromb Res* 192: 27-28.
30. Cattaneo M, Bertinato EM, Birocchi S, Brizio C, Malavolta D, Manzoni M, Muscarella G, Orlandi M (2020) Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified? *Thromb Haemost* 120: 1230-1232.
31. Demelo-Rodríguez P, Cervilla-Muñoz E, Ordieres-Ortega L, Parra-Virto A, Toledano-Macias M, Toledo-Samaniego N, García-García A, García-Fernández-Bravo I, Ji Z, de-Miguel-Diez J, Alvarez-Sala-Walther LA, Del-Toro-Cervera J, Galeano-Valle F (2020) Incidence of asymptomatic deep vein thrombosis in patients with COVID-19 pneumonia and elevated D-dimer levels. *Thromb Res* 192: 23-26.
32. Faggiano P, Bonelli A, Paris S, Milesi G, Bisegna S, Bernardi N, Curnis A, Agricola E, Maroldi R (2020) Acute pulmonary embolism in COVID-19 disease: Preliminary report on seven patients. *Int J Cardiol* 313: 129-131.
33. Grillet F, Behr J, Calame P, Aubry S, Delabrousse E (2020) Acute pulmonary embolism associated with covid-19 pneumonia detected by pulmonary CT angiography. *Radiology* 296: E186-E188.
34. Leonard-Lorant I, Delabranche X, Severac F, Helms J, Pauzet C, Collange O, Schneider F, Labani A, Bilbault P, Molière S, Leyendecker P, Roy C, Ohana M (2020) Acute pulmonary embolism in covid-19 patients on CT angiography and relationship to d-dimer levels. *Radiology* 296: E189-E191.
35. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Müller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N (2020) Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 18: 1995-2002.
36. Artifoni M, Danic G, Gautier G, Gicquel P, Boutoille D, Raffi F, Néel A, Lecomte R (2020) Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. *J Thromb Thrombolysis* 50: 211-6. doi: 10.1007/s11239-020-02146-z. [Epub ahead of print]
37. Zhang L, Feng X, Zhang D, Jiang C, Mei H, Wang J, Zhang C, Li H, Xia X, Kong S, Liao J, Jia H, Pang X, Song Y, Tian Y, Wang B, Wu C, Yuan H, Zhang Y, Li Y, Sun W, Zhang Y, Zhu S, Wang S, Xie Y, Ge S, Zhang L, Hu Y, Xie M (2020) Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: prevalence, risk factors, and outcome. *Circulation* 142:114-28.
38. Santoliquido A, Porfidia A, Nesci A, De Matteis G, Marrone G, Porceddu E, Cammà G, Giarretta I, Fantoni M, Landi F, Gasbarrini A, Pola R; GEMELLI AGAINST COVID-19 Group, D'Alfonso ME, Lo Monaco MR (2020) Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. *J Thromb Haemost*. 18: 2358-2363
39. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 395: 1054-1062.
40. Tang N, Li D, Wang X, Sun Z (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost* 18: 844-847
41. Rodríguez-Sevilla JJ, Rodó-Pin A, Espallargas I, Villar-García J, Molina L, Pérez Terán P, Vázquez Sanchez A, Masclans JR, Jiménez C, Millan Segovia R, Zuccarino F, Salar A, Rodríguez-Chiaradía DA (2020) Pulmonary embolism in patients with COVID-19 pneumonia: the utility of D-dimer. *Arch Bronconeumol* 56:758-759.
42. Marchandot B, Sattler L, Jesel L, Matsushita K, Schini-Kerth V, Grunebaum L, Morel O (2020) COVID-19 related coagulopathy: a distinct entity? *J Clin Med* 9: 1651.
43. Yu B, Li X, Chen J, Ouyang M, Zhang H, Zhao X, Tang L, Luo Q, Xu M, Yang L, Huang G, Liu X, Tang J (2020) Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis. *J Thromb Thrombolysis* 50: 548-557.
44. Susen S, Tacquard CA, Godon A, Mansour A, Garrigue D, Nguyen P, Godier A, Testa S, Levy JH, Albaladejo P, Gruel Y; GIHP and GFHT (2020) Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. *Crit Care* 24: 364.
45. De Giorgi A, Fabbian F, Greco S, Di Simone E, De Giorgio R, Passaro A, Zuliani G, Manfredini R, and the OUTcome and COMorbidity Evaluation of INTERNAL MEDICINE COVID19 (OUTCOME-INTMED-COV19) Study Collaborators (2020)

- Prediction of in-hospital mortality in Italian internal medicine wards patients with SARS-CoV-2 infection by comorbidity indexes: a single center study. *Eur Rev Med Pharmacol Sci* 24: 10258-10266.
46. Stals MAM, Klok FA, Huisman MV (2020) Diagnostic management of acute pulmonary embolism in special populations. *Expert Rev Respir Med* 14: 729-736.
  47. Capuano A, Rossi F, Paolisso G (2020) Covid-19 kills more men than women: an overview of possible reasons. *Front Cardiovasc Med* 7: 131.
  48. Righini M, Perrier A, DeMoerloose P, Bounameaux H (2008) D-Dimer for venous thromboembolism diagnosis: 20 years later. *J Thromb Haemost.* 6: 1059–71.
  49. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, Huisman MV, Humbert M, Jennings CS, Jiménez D, Kucher N, Lang IM, Lankeit M, Lorusso R, Mazzolai L, Meneveau N, Ni Ainle F, Prandoni P, Pruszczyk P, Righini M, Torbicki A, Van Belle E, Zamorano JL; ESC Scientific Document Group (2020) 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 41: 543–603
  50. Ayerbe L, Risco C, Ayis S (2020) The association between treatment with heparin and survival in patients with Covid-19. *J Thromb Thrombolysis* 50: 298-301.

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