Thromboembolic Complications in COVID-19 Patients Hospitalized in Italian Ordinary Wards: Data from the Multicenter Observational START-COVID Register

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Keywords
► COVID-19
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Abstract
Background Coronavirus disease 2019 (COVID-19) infection causes acute respiratory insufficiency with severe interstitial pneumonia and extrapulmonary complications; in particular, it may predispose to thromboembolic disease. The reported incidence of thromboembolic complications varies from 5 to 30% of cases.

Aim We conducted a multicenter, Italian, retrospective, observational study on COVID-19 patients admitted to ordinary wards, to describe the clinical characteristics of patients at admission and bleeding and thrombotic events occurring during the hospital stay.

Results The number of hospitalized patients included in the START-COVID-19 Register was 1,135, and the number of hospitalized patients in ordinary wards included in the study was 1,091, with 653 (59.9%) being males and 71 years (interquartile range

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59–82 years) being the median age. During the observation, two (0.2%) patients had acute coronary syndrome episodes and one patient (0.1%) had an ischemic stroke; no other arterial thrombotic events were recorded. Fifty-nine patients had symptomatic venous thromboembolism (VTE) (5.4%) events, 18 (30.5%) deep vein thrombosis (DVT), 39 (66.1%) pulmonary embolism (PE), and 2 (3.4%) DVT + PE. Among patients with DVT, eight (44.4%) were isolated distal DVT and two cases were jugular thrombosis. Among patients with PE, seven (17.9%) events were limited to subsegmental arteries. No fatal PE was recorded. Major bleeding events occurred in nine (1.2%) patients and clinically relevant nonmajor bleeding events in nine (1.2%) patients. All bleeding events occurred among patients receiving thromboprophylaxis, more frequently when treated with subtherapeutic or therapeutic dosages.

**Conclusion**  Our findings confirm that patients admitted to ordinary wards for COVID-19 infection are at high risk for thromboembolic events. VTE recorded among these patients is mainly isolated PE, suggesting a peculiar characteristic of VTE in these patients.
when the patients were discharged, transferred to ICU, or died. The outcome was defined as being favorable when the patient was discharged, and severe when the patient was transferred to ICU or died. Thrombotic and bleeding events occurring during follow-up were recorded. Objective confirmation of thrombotic events was requested. The index event was objectively confirmed by compression ultrasonography, ventilation-perfusion lung scan, or computed tomographic pulmonary angiography. Major bleeding (MB) events were defined according to the International Society of Thrombosis and Haemostasis. Clinically relevant nonmajor bleeding (CRNMB) events were defined as those events that are not major but require any kind of medical intervention.

### Statistical Analysis
Descriptive analysis was performed. Continuous variables were expressed as median with interquartile range (IQR) or as mean plus or minus standard deviation. Categorical variables were expressed as frequencies and percentages. Preliminary statistical analysis was performed using Wilcoxon signed-rank test (continuous variables) or Fisher exact test (categorical data). A p-value <0.05 was considered statistically significant.

We used the SPSS version 26 software (SPSS Inc, Chicago, IL, United States) for Windows for data processing.

### Results

#### Patients
From March 1st and June 30th 2020, 1,135 patients hospitalized for COVID-19 infection were included in the START-COVID-19 Register; 1,091 patients hospitalized in ordinary wards were included in the study, 653 being males (59.9%) with a median age of 71 years (IQR 59–82 years). Characteristics of patients have been previously described. In brief, hypertension was present in 570 (52.2%) patients, the median Charlson’s index of the cohort was 3 (range 2–5), and 406 (37.2%) patients had no associated comorbidities. At admission, fever was present in 796 patients (73.0%), dyspnea in 581 (53.3%), and cough in 450 (41.2%).

#### Thrombotic Complications
During the observation, two (0.2%) patients had acute coronary syndrome episodes and 1 patients (0.1%) had stroke; no other arterial thrombotic events were recorded. Fifty-nine patients had VTE (5.4%), 18 (30.5%) patients had deep vein thrombosis (DVT), 39 (66.1%) patients had pulmonary embolism (PE), and 2 (3.4%) patients had DVT + PE. Two patients (0.2%) had superficial vein thrombosis (+ Table 1). Among patients with DVT, eight (44.4%) were isolated distal DVT and two cases were jugular thrombosis. Among patients with PE, seven (17.9%) events were limited to subsegmental arteries. No fatal PE was recorded. PE was diagnosed by CT angiography in 25 cases and by CT scan in 9 cases, and no information was available for 7 cases.

Characteristics of patients with VTE are reported in – Table 2, they presented on the whole a significantly lower number of comorbidities with respect to patients without VTE, even if the median Charlson comorbidity index was similar to patients without VTE. Instead, among VTE patients, median D-dimer levels were significantly higher. The mortality rate was low among patients who had VTE during hospital stay (2 out of 59 patients, 3.4%) with respect to patients without VTE (198 out of 1,032 patients, 19.2%).

At the time of admission, 70.5% of patients of the entire cohort received thromboprophylaxis, mainly with prophylactic doses of enoxaparin. The percentage of treatment was similar among patients who develop and patients who did not develop VTE (p-value = 0.4).

#### Bleeding Complications
During hospital stay, nine (1.2%) patients had MB events and nine (1.2%) patients CRNMB events. All bleeding events occurred among patients treated with antithrombotic drugs. MBs and CRNMBs occurred more frequently among patients treated with subtherapeutic/therapeutic dosage with respect to patients treated with prophylactic dosage (5 [3.1%] and 6 [3.7%] vs. 4 [0.7%] and 3 [0.5%], respectively).

### Discussion
The principal finding of our study is the confirmation of the rate of thrombotic events reported among patients admitted to ordinary wards for COVID-19 infection. Our results are consistent with those reported by other authors in hospitalized medical patients who are not critically ill, frequency ranging from 5.8 to 9.2%,8,9 In particular, in an Italian single-center retrospective cohort study, the proportion of COVID-19 patients with VTE was found to be 6.6% in ward patients. The thrombotic events reported are mainly VTE, in particular PE. Our data are in keeping with these findings. In our cohort, 66.1% of VTE events were PE, with a large number of episodes confined to segmental and subsegmental arteries, whereas

| Event                                      | N (%)  |
|--------------------------------------------|--------|
| Venous thromboembolism                     | 59 (5.4) |
| Deep vein thrombosis                       | 18 (30.5) |
| Pulmonary embolism                         | 39 (66.1) |
| Proximal artery                            | 8 (20.5) |
| Segmentary artery                          | 22 (56.4) |
| Subsegmentary artery                       | 7 (17.9) |
| Not available                               | 2 (5.1) |
| Deep vein thrombosis + Pulmonary embolism  | 2 (3.4) |
| Superficial vein thrombosis                | 2 (0.2) |
| Stroke                                     | 1 (0.1) |
| Acute coronary syndrome                    | 2 (0.2) |
one-fifth of the episodes involved the main or lobar arteries. None of the events was fatal. Isolated DVT was present in 30% of patients with VTE, and 8 out of 18 (44.4%) DVT cases were limited to the distal veins, this frequency being consistent with that found by other authors as was that of PE and overall DVT. The mortality rate of VTE patients was impressively lower with respect to that recorded among patients who did not develop VTE during the hospital stay. This unexpected result could be explained by the lower number of comorbidities detected among this group of patients. As a matter of fact, the number of total comorbidities is significantly lower among patients with VTE with respect to patients without, and a trend of lower incidence of diseases associated with higher mortality (coronary artery disease, atrial fibrillation, heart failure, peripheral obstructive arterial disease, cerebrovascular disease, and cancer) is detected among patients without VTE.

The high prevalence of isolated PE (66.1%) found in our cohort is somewhat surprising, as it is in contrast with approximately 20% that was reported in different cohorts of VTE patients without COVID-19 infection. We speculate that pulmonary vessel occlusions that are seen in COVID-19 patients are due to the development of local thrombi rather than arising from peripheral veins. A huge number of patients who require hospitalization in the widespread of the pandemic end up limiting the diagnosis of VTE, in particular in those with few or no symptoms. Whenever a systematic leg veins ultrasonography has been performed, a relevant rate of (mainly) asymptomatic episodes has been reported. Therefore, we cannot exclude that an underdiagnosis of VTE in our patients has occurred.

In our cohort, 70.5% of patients received thromboprophylaxis, in the great majority enoxaparin at prophylactic dosage. We confirmed the presence of COVID-19-associated coagulopathy, with elevated median D-dimer levels, higher levels among patients suffering from thrombotic complications. The role of heparin treatment in reducing mortality has been reported by several studies; on the contrary, a clear role in the thromboembolism prevention has not been demonstrated.

We acknowledge the limitations of our study. First, it is a retrospective observational study, and no standardized diagnostic procedure for the detection of thrombotic events was indicated by the study protocol. The severity of patients enrolled, as indicated by the elevated number of patients with fatal outcomes, may have determined underdiagnosis of thrombotic events particularly in the case of pauci- or asymptomatic episodes. The strength of the study lies in

### Table 2 Characteristics of patients with and without venous thromboembolism

| Characteristic                              | No. of patients with VTE | No. of patients without VTE | p-Value |
|--------------------------------------------|---------------------------|-----------------------------|---------|
| Patients                                   | 59                        | 1,032                       |         |
| Males                                      | 37 (62.7)                 | 616 (59.7)                  | 0.7     |
| Median age (IQR), years                    | 69 (58–79)                | 71 (59–82)                  | 0.6     |
| Body mass index median (IQR)               | 26.8 (25.2–30.1)          | 26.0 (24.0–29.1)            | 0.3     |
| Hypertension                               | 20 (33.9)                 | 550 (53.3)                  | 0.005   |
| Atrial fibrillation                        | 2 (3.4)                   | 81 (8.0)                    | 0.3     |
| Venous thromboembolism                     | 3 (5.1)                   | 33 (3.3)                    | 0.4     |
| Coronary artery disease                    | 3 (5.1)                   | 107 (10.5)                  | 0.3     |
| Heart failure                              | –                         | 22 (2.1)                    | –       |
| Peripheral arterial disease                | –                         | 16 (1.6)                    | –       |
| Cerebrovascular disease                    | 2 (3.4)                   | 63 (6.1)                    | 0.5     |
| Neurological disease                       | 7 (11.9)                  | 138 (13.4)                  | 0.8     |
| Chronic obstructive pulmonary disease      | 4 (6.8)                   | 108 (10.5)                  | 0.5     |
| Rheumatologic disease                      | –                         | 21 (2.0)                    | –       |
| Diabetes mellitus                          | 12 (20.3)                 | 178 (17.2)                  | 0.6     |
| Cancer                                     | 4 (6.8)                   | 137 (13.3)                  | 0.2     |
| Renal failure (eGFR < 30 mL/min)<          | 4 (14.8)                  | 92 (14.7)                   | 1.0     |
| Charlson score, median (IQR)               | 3 (2–4)                   | 3 (2–5)                     | 0.3     |
| No comorbidities                           | 34 (57.6)                 | 372 (36.3)                  | 0.001   |
| Median D-dimer (mg/dL) (IQR)               | 1,668 (505–4,385)         | 779 (407–1,611)             | 0.03    |
| Prothrombin time ratio, median (range)     | 1.2 (1.1–1.3)             | 1.1 (1.0–1.2)               | 0.1     |
| Thromboprophylaxis                         | 45 (76.3)                 | 724 (70.1)                  | 0.4     |

Abbreviations: eGFR, estimated glomerular filtration rate; IQR, interquartile range; VTE, venous thromboembolism.

*Available for 653 patients.
the multicentric design and the accuracy and completeness of follow-up for all patients enrolled.

In conclusion, we confirmed that patients admitted to ordinary wards for COVID-19 infection are at high risk for thromboembolic events. VTE recorded among these patients in ordinary wards for COVID-19 infection are at high risk for thrombophilia: data from the multicenter observational START-COVID Register. Int Emerg Med 2022;17(04):1013–1021

Authors Contribution
D.P., W.A., and R.M. were involved in study design, data collection and interpretation, writing and critical review, and final approval of the manuscript. E.A. was involved in data analysis and interpretation, and final approval of the manuscript. W.A., P.P., and G.P. revised the draft of the manuscript critically for important intellectual content. All other authors were involved in data collection and interpretation, writing, and final approval of the manuscript.

Conflict of Interest
None declared.

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References
1 Grasselli G, Greco M, Zanella A, et al; COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 2020;180(10):1345–1355
2 Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18(04):844–847
3 Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–147
4 Pizzi R, Gini G, Caiano L, et al. Coagulation parameters and venous thromboembolism in patients with and without COVID-19 admitted to the emergency department for acute respiratory insufficiency. Thromb Res 2020;196:209–212
5 Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood 2020;136(04):489–500
6 Goshua G, Pine AB, Mezlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. Lancet Haematol 2020;7(08):e575–e582
7 Middeldorp S, Coppens M, van Haaps TF, et al. Incidence of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost 2020;18(08):1995–2002
8 Lodigiani C, Iapichino G, Carenzo L, et al; Humanitas COVID-19 Task Force. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9–14
9 Antonucci E, Poli D, Tosetto A, et al; START-Register. The Italian START-Register on anticoagulation with focus on atrial fibrillation. PLoS One 2015;10(05):e0124719
10 Poli D, Antonucci E, Ageno W, Prandoni P, Palareti G, Marcucci RSTART-COVID Investigators. Low in-hospital mortality rate in patients with COVID-19 receiving thromboprophylaxis: data from the multicenter observational START-COVID Register. Int Emerg Med 2022;17(04):1013–1021
11 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JC. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42(02):377–381
12 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(05):373–383
13 Schulman S, Kearon CSubcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(04):692–694
14 Kaatz S, Ahmad D, Spyropoulos AC, Schulman SSSubcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13(11):2119–2126
15 Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv 2018;2(22):3198–3225
16 Santoliquido A, Porfidia A, Nesci A, et al; GEMELLI AGAINST COVID-19 Group. Incidence of deep vein thrombosis among non-ICU patients hospitalized for COVID-19 despite pharmacological thromboprophylaxis. J Thromb Haemost 2020;18(09):2358–2363
17 Palareti G, Cosmi B, Antonucci E, et al; DULCIS investigators. Duration of anticoagulation after isolated pulmonary embolism. Eur Respir J 2016;47(05):1429–1435
18 Palareti G, Antonucci E, Dentali F, et al. Patients with isolated pulmonary embolism in comparison to those with deep venous thrombosis. Differences in characteristics and clinical evolution. Eur J Intern Med 2019;69:64–70
19 Cattaneo M, Bertinato EM, Birocchi S, et al. Pulmonary embolism or pulmonary thrombosis in COVID-19? Is the recommendation to use high-dose heparin for thromboprophylaxis justified?. Thromb Haemost 2020;120(08):1230–1232
20 Giorgi-Pierfranceschi M, Paoletti O, Pan A, et al. Prevalence of asymptomatic deep vein thrombosis in patients hospitalized with SARS-CoV-2 pneumonia: a cross-sectional study. Intern Emerg Med 2020;15(08):1425–1433
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