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Full Length Article

Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy

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ABSTRACT

Background: Few data are available on the rate and characteristics of thromboembolic complications in hospitalized patients with COVID-19.

Methods: We studied consecutive symptomatic patients with laboratory-proven COVID-19 admitted to a university hospital in Milan, Italy (13.02.2020–10.04.2020). The primary outcome was any thromboembolic complication, including venous thromboembolism (VTE), ischemic stroke, and acute coronary syndrome (ACS)/myocardial infarction (MI). Secondary outcome was overt disseminated intravascular coagulation (DIC).

Results: We included 388 patients (median age 66 years, 68% men, 16% requiring intensive care [ICU]). Thromboprophylaxis was used in 100% of ICU patients and 75% of those on the general ward. Thromboembolic events occurred in 28 (7.7% of closed cases; 95%CI 5.4%–11.0%), corresponding to a cumulative rate of 21% (27.6% ICU, 6.6% general ward). Half of the thromboembolic events were diagnosed within 24 h of hospital admission. Forty-four patients underwent VTE imaging tests and VTE was confirmed in 16 (36%). Computed tomography pulmonary angiography (CTPA) was performed in 30 patients, corresponding to 7.7% of total, and pulmonary embolism was confirmed in 10 (33% of CTPA). The rate of ischemic stroke and ACS/MI was 2.5% and 1.1%, respectively. Overt DIC was present in 8 (2.2%) patients.

Conclusions: The high number of arterial and, in particular, venous thromboembolic events diagnosed within 24 h of admission and the high rate of positive VTE imaging tests among the few COVID-19 patients tested suggest that there is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory COVID-19 patients.

1. Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) causing coronavirus disease 2019 (COVID-19) has led to an unprecedented global health crisis. To date, > 185,000 COVID-19-related deaths have been confirmed. Case fatality rate has been estimated to be as high as 15% in some countries [1].

Clinical manifestations are absent or mild in a substantial proportion of subjects who test positive for SARS-CoV2. Bilateral pneumonia is the main finding in hospitalized patients and at least 5% initially present in serious condition, requiring advanced medical support or intensive care [1,2]. Bilateral pneumonia, systemic inflammation, endothelial dysfunction, coagulation activation, acute respiratory distress syndrome, and multiorgan failure have been described as key features of severe COVID-19 [3–8]. Signs of myocardial injury are present in at least one quarter of severe cases [2,9].
It has been postulated that the high mortality observed among COVID-19 patients may be partly due to unrecognized pulmonary embolism (PE) and pulmonary in situ thrombosis. Estimates of the risk of arterial and, in particular, venous thromboembolic complications are still preliminary and depend on local diagnostic and pharmacological preventive strategies [10,11].

Better understanding of COVID-19-related thromboembolic risk will help to optimize diagnostic strategies and guide the design and conduct of randomized controlled trials on VTE prevention. In this study, we described the rate and characteristics of venous and arterial thromboembolic complications in consecutive patients who have been admitted to a large academic hospital in Milan, Italy, since the beginning of the outbreak.

2. Methods

2.1. Setting and study population

In this retrospective cohort study, we included data from consecutive adult symptomatic patients with laboratory-proven COVID-19 who have been admitted to a large university hospital (Humanitas Clinical and Research Hospital, Rozzano, Milan, Lombardy, Italy) since February 2020. The study was approved by the institutional ethical committee and patients gave standard written consent to the use of their data.

2.2. Objectives

We aimed to describe the rate of venous and arterial thromboembolic complications in hospitalized patients with COVID-19.

2.3. Data collection

Electronic medical records served as source data for the collection of demographics, clinical, laboratory, treatment, and outcome data, which were extracted in an anonymized form by two physicians. Potential disagreements concerning the interpretation of the findings was done in collaboration with a third physician.

2.4. Outcomes

The primary outcome was a composite of venous and arterial thromboembolic events, encompassing VTE and other cardiovascular events. VTE included pulmonary embolism (PE) and deep vein thrombosis (DVT) diagnosed by accepted imaging tests. During the period considered for the present analysis, no VTE screening strategy among COVID-19 patients was in place at the study site: VTE imaging tests were performed in subjects with signs or symptoms of DVT or with an unexplained clinical worsening of the respiratory function, primarily assessed using the PaO2/FIO2 ratio, or a rapid increase of D-dimer levels. Two-point compression ultrasonography (CUS) was used on the intensive care unit (ICU); whole-leg ultrasound was performed in symptomatic patients on the general ward. Cardiovascular events included acute coronary syndrome/myocardial infarction and ischemic stroke, as reported by the treating physicians in the medical charts.

Secondary outcome was overt disseminated intravascular coagulation (DIC). We reviewed the electronic medical charts and patients’ laboratory findings (platelet count, D-dimer, prothrombin time, fibrinogen level) of all COVID-19 patients to retrospectively calculate the International Society on Thrombosis and Haemostasis (ISTH) score for overt DIC, which was considered present if the score was 5 or greater [12].

2.5. Statistical methods

We described the characteristics of our study population using counts and percentages for categorical variables. We used appropriate measures of central tendency and dispersion to describe continuous variables. The rate of events was accompanied by 95% confidence interval (95%CI) and calculated for closed cases, defined as patients discharged, or dead, or (for analysis on thromboembolic complications) diagnosed with a thromboembolic event. Cumulative rates were calculated for the whole study population, including patients still hospitalized. A univariate logistic regression was performed to ascertain the effect of age on the likelihood that patients died during hospitalization: the probability of death across age was depicted visually. Missing values have been reported for each variable, if any. JASP v.0.11.1 and SPSS v. 25.0 served for data analysis.

3. Results

We extracted data from 388 consecutive patients with laboratory-proven COVID-19 admitted between 13.02.2020 and 10.04.2020. The median age was 66 (Q1-Q3 55–85) years and 264 (68%) were men. A total of 375 (97%) patients were tested for SARS-CoV2 before or on the day of initial hospital admission. Eight (2.1%) patients were tested during the first week of hospitalization and six (1.5%) between week 2–4 of hospitalization. Patients admitted to hospital during the very first days of the outbreak belonged to the latter group.

A total of 61 (16%) patients required intensive care; the remaining 327 patients were admitted to general wards. Of 61 patients who required intensive care, 30 (49%) were initially admitted to a general ward for a median of 4 (Q1-Q3 3–6) days; the median length of stay in the ICU was 12 (Q1-Q3 8–15) days. Table 1 summarizes the baseline characteristics of the study population, including the overall duration of hospitalization.

We recorded a total of 92 in-hospital deaths, corresponding to an in-hospital mortality rate of 26% among closed cases. Deaths occurred after a median of 7 (Q1-Q3 4–12) days from hospital admission. Fig. 1 depicts the probability of in-hospital death across age (Odds Ratio 1.10 per year increase, 95%CI 1.07–1.13). Variations in D-dimer levels among survivors and non-survivors are displayed in Table 2.

3.1. Use of thromboprophylaxis

All ICU patients received thromboprophylaxis with low-molecular-weight heparin: the dosage was weight-adjusted in 17 patients and therapeutic in two patients on ambulatory treatment with direct oral anticoagulants. A total of 246 (75%) patients admitted to general wards received initial in-hospital thromboprophylaxis: a prophylactic dosage was used in 133 (41%) patients, 67 (21%) were treated with intermediate-dosage thromboprophylaxis, and 74 (23%) received therapeutic-dose anticoagulation, including 22 who continued ambulatory treatment for atrial fibrillation or prior VTE.

3.2. Thromboembolic complications

Thromboembolic events occurred in 28 of 362 closed cases for a rate of 7.7% (95%CI 5.4%–11.0%) among closed cases, corresponding to a cumulative rate of 21.0%. Eight events occurred in ICU patients (16.7%); 95%CI 8.7%–29.6%) corresponding to a cumulative rate of 27.6%. Twenty events occurred in patients on the general ward (6.4%; 95%CI 4.2%–9.6%) corresponding to a cumulative rate of 6.6% (Table 3). We reported a detailed description of all thromboembolic events in Table 4.

Forty-four patients underwent VTE imaging tests and 16 were positive (36% of tests, 4.4% of total patients). Ten (63%) of 16 events were pulmonary embolism; 33% of CTPE were positive. In 8 (50%) of 16 patients with VTE, the VTE event was diagnosed within 24 h of hospital admission. Nine (56%) of these 16 patients were not receiving any anticoagulant treatment. One patient diagnosed with sub-segmental PE that occurred during anticoagulant prophylaxis had a D-dimer level (323 ng/mL) within the normal range, whereas the
remaining 15 patients had values comprised between 1620 and 40,905 ng/mL. None of the patients diagnosed with acute PE or DVT had a history of VTE.

Ischemic stroke was diagnosed in 9 (2.5%) patients: 3 were on the ICU and 6 of those on the general ward. One patient developed both stroke and acute PE. In 6 (67%) patients, stroke was the primary reason for hospitalization. Acute coronary syndrome/myocardial infarction was diagnosed in four (1.1%) patients, of whom 3 were on the ICU and one of those on the general ward. This represented the primary reasons for hospitalization in 3 (75%) patients.

### 3.3. Disseminated intravascular coagulation

A total of 8 (2.1%) patients met the laboratory criteria for overt DIC. Six (75%) patients were men, one (13%) was required intensive care, four (50%) had solid or hematological cancer. No bleeding complications were recorded. Two (25%) patients had thromboembolic events (DVT, ischemic stroke); Table 4. Seven (88%) patients with overt DIC died during hospitalization.

### 4. Discussion

We performed a comprehensive analysis of the rate, timing, and characteristics of venous and arterial thromboembolic complications among consecutive COVID-19 patients admitted to a large university hospital in Milan, Italy. Our results indicate that thromboembolic complications may represent an integrating part of the clinical picture of COVID-19 and be already present at the time of initial hospital admission. Their incidence, however, may have been highly underestimated due to the low number of specific imaging tests performed. It remains unclear whether increased intensity of thrombosis prophylaxis in selected patients may provide clinical benefit in patients without confirmed acute VTE. Interventional and management trials should be conducted to improve the prevention, diagnosis, and treatment of thrombotic complications in these patients.

Previously, coagulation and cardiac biomarkers have been described to be elevated in COVID-19 patients: they reflect an inflammatory status characterized by coagulation activation and endothelial dysfunction, and are predictors of death [2–7,9]. We showed that, despite the use of anticoagulant prophylaxis, the rate of venous and arterial thromboembolic complications in hospitalized COVID-19 patients was remarkable, approximately 8%. Indeed, this already high
The observed rate of thrombotic events is in line with recent preliminary analyses, although the severity of patients and the use of thromboprophylaxis across studies were heterogeneous and may have influenced the estimates. In a recent Dutch paper, symptomatic VTE was diagnosed in 28 (15% of total; cumulative rate 27%) of 184 patients receiving thromboprophylaxis during intensive care and mainly consisted of PE (n = 25) [10]. In the Dutch study, only a minority of patients experienced arterial thrombotic events (n = 3). According to a Chinese study, the prevalence of VTE was 25% with routine VTE screening, although details on the type and timing of screening were not provided [11]. These values appear much higher than the rate of symptomatic VTE events observed in thromboprophylaxis trials, not exceeding 3% in patients not receiving anticoagulant therapy and < 1% on thromboprophylaxis [13], but in line with what observed in patients with sepsis or shock [14,15]. A recent analysis from a French group showed that the rate of thromboembolic complications in 150 COVID-19 patients with ARDS was much higher (11.7%) than what observed in a historical control group of non-COVID-19 ARDS patients (2.1%) despite anticoagulation [16].

We showed that the majority of thrombotic complications were venous and primarily represented by (isolated) PE. Consistently, the proportion of positive CTPA out of total CTPA performed (33%) appeared higher than that of positive CUS (21%) out of total CUS performed. As indirect as this evidence is, one may postulate that in case of suspected PE, the execution of CUS may be logistically more feasible and give less useful information and delay CTPA testing. It has been suggested that the use of higher prophylaxis dosages may improve the outcome of COVID-19 patients [10,17]. The results of our analysis suggest that a lower threshold of suspicion to perform VTE imaging tests may be reasonable, even upon admission or in the very early phases of COVID-19. We observed at least half of thromboembolic events were diagnosed within the first 24 h of admission and, therefore, not preventable by in-hospital thromboprophylaxis, which would have been otherwise inadequately dosed in the presence of acute VTE.

Routine thromboprophylaxis is not recommended in ambulatory patients with acute medical illness or respiratory symptoms [18]. It has been postulated that the administration of low-molecular-weight heparin during the earlier phases of SARS-CoV2 infection may exert a positive effect not only in terms of thrombosis prevention, but also reducing systemic and pulmonary inflammation, and limiting viral invasion [7,17,19–21]. In several countries, a number of patients is being managed on an ambulatory basis, also for logistical reasons. The burden of thromboembolic complications in these patients is unknown. Our data, which represent conditional probabilities and should therefore be carefully interpreted, suggest that this may represent an underestimated, large-scale issue requiring rapid answers. A randomized controlled trial, the OVID trial, is being planned to study whether prophylactic-dose enoxaparin (vs. no treatment) may reduce early all-cause mortality and unplanned hospitalizations in adult symptomatic ambulatory COVID-19 patients with no other indications to receive anticoagulation.

We acknowledge limitations to our study. This was a retrospective analysis conducted at a large university hospital, therefore possibly not reflecting the management strategies and diagnostic facilities at other non-academic institutions. Patients included in this analysis were diagnosed at one of the “red zones” where the European outbreak started. This may have influenced not only patients’ outcome, as no global experience on the disease was available yet, but also the execution and frequency of imaging tests during hospitalization. From this perspective, we could not confirm whether thromboembolic events contributed to mortality.

### Table 2

| Group         | Setting             | Days 1–3 | Days 4–6 | Days 7–9 |
|---------------|---------------------|----------|----------|----------|
| Survivors     | Total               | n = 215  | n = 163  | n = 121  |
|               | ICU                 | 353 (236–585) | 389 (246–685) | 529 (303–1138) |
|               | General ward        | 615 (456–1005) | 605 (370–824)  | 3137 (1486–6571) |
| Non-survivors | Total               | n = 70   | n = 38   | n = 22   |
|               | ICU                 | 869 (479–2103) | 943 (611–2618) | 1494 (633–620) |
|               | General ward        | 1022 (615–3681) | 1301 (961–28,397) | 7746 (2914–12,578) |

The analysis was restricted to closed cases. D-dimer levels are presented as median (Q1–Q3) and expressed in ng/mL. ICU, intensive care unit.

### Table 3

| Intensive care unit | Thromboembolic events | General ward | Total |
|---------------------|-----------------------|--------------|-------|
|                     | n | % of closed cases (n = 48) | % of imaging tests performed* | n | % of closed cases (n = 314) | % of imaging tests performed* | n | % of closed cases (n = 362) | % of imaging tests performed* |
| At least one thromboembolic event | 8 | 16.7% (95%CI 8.7%–29.6) | – | 20 | 6.4% (95%CI 4.2%–9.6) | – | 28 | 7.7% (95%CI 5.4%–11.0) | – |
| VTE                  | 4 | 8.3% | 22% | 12 | 3.8% | 46% | 16 | 4.4% | 36% |
| PE (± DVT)           | 2 | 4.2% | 25% | 8 | 2.5% | 36% | 10 | 2.8% | 33% |
| Isolated pDVT        | 1 | 2.1% | 7%  | 3 | 1.0% | 44% | 4 | 1.1% | 21% |
| Isolated dDVT        | 0 | –    | –   | 1 | 0.3% | 13% | 1 | 0.3% | 13% |
| Catheater-related    | 2 | 2.1% | 50% | 0 | –    | –   | 1 | 0.3% | 50% |
| Thromboembolic events | 3 | 6.3% | –   | 6 | 1.9% | –   | 9 | 2.5% | –   |
| ACS/MI               | 1 | 2.1% | –   | 3 | 1.0% | –   | 4 | 1.1% | –   |

ACS, acute coronary syndrome; DVT, deep vein thrombosis; MI, myocardial infarction; pDVT, proximal deep vein thrombosis; dDVT, distal DVT; PE, pulmonary embolism; VTE, venous thromboembolism.
Table 4
Description of patients with thrombotic events.

| Sex | Age | Cancer | Thromboprophylaxis at diagnosis | D-dimer | Setting | Thromboembolic event | AC therapy | Outcome |
|-----|-----|--------|---------------------------------|---------|---------|-----------------------|------------|---------|
| F   | 45  | –      | No                              | 1620    | General ward | Proximal DVT | Enoxaparin 80 mg bid | Discharged |
| F   | 64  | –      | No                              | 2371    | General ward | Great saphenous vein thrombosis, junction thrombosis | Nadroparin 5700 IU bid followed by enoxaparin 40 mg bid | Discharged |
| M   | 71  | –      | Yes (P)                         | 1842    | ICU      | Distal DVT       | Fondaparinux 7.5 mg qd | Hospitalized |
| M   | 68  | –      | Yes (I)                         | 4199    | General ward | Smaller saphenous vein thrombosis, junction thrombosis | Fondaparinux 2.5 mg qd | Discharged |
| M   | 55  | –      | Yes (P)                         | 1915    | ICU      | Subclavian-axillary catheter-related DVT | Fondaparinux 7.5 mg qd | Discharged |
| M   | 73  | –      | Lung small-cell carcinoma       | 5542    | General ward | Proximal DVT; overt DIC | Nadroparin 5700 IU bid | Discharged |
| M   | 86  | –      | Yes (P)                         | 2270    | General ward | Bilateral segmental PE | Nadroparin 5700 IU bid followed by cava filter placement after major bleeding | Dead |
| M   | 75  | –      | –                               | 323     | General ward | Multiple subsegmental PE | Enoxaparin 60 mg bid | Hospitalized |
| F   | 67  | –      | Pancreas carcinoma               | 2563    | General ward | Unilateral lobar PE | Nadroparin 5700 IU bid | Dead |
| F   | 78  | –      | No (Aspirin)                    | 40,950  | General ward | Bilateral PE, proximal DVT | Enoxaparin 8000 IU qd followed by edoxaban 60 mg qd | Discharged |
| M   | 78  | –      | —                               | 37176   | General ward | Bilateral segmental PE | Enoxaparin 4000 IU bid | Discharged |
| M   | 75  | –      | Lung small-cell carcinoma       | 4523    | ICU      | Inferior vena cava thrombosis with clot in right atrium and suspected PE | Nadroparin 9500 IU bid | Discharged |
| M   | 59  | –      | Yes (P)                         | 3123    | ICU      | Bilateral PE, subclavian and jugular DVT | Enoxaparin 60 mg bid | Discharged |
| M   | 55  | –      | None                            | 3636    | General ward | Bilateral lobar PE | Enoxaparin 90 mg bid | Discharged |
| M   | 67  | –      | Metastatic lung carcinoma       | 8608    | General ward | Stroke, PE | Local lysis and mechanical thrombectomy; PE: enoxaparin 60 mg bid | Discharged |
| M   | 71  | –      | Yes (P)                         | 408     | General ward | NSTEMI | Prasugrel followed by clopidogrel + indobufen + enoxaparin 40 mg bid | Discharged |
| F   | 82  | –      | Metastatic breast cancer        | 3000    | General ward | NSTEMI | Aspirin | Dead |
| M   | 65  | –      | –                               | 3187    | ICU      | NSTEMI | Aspirin + enoxaparin 40 mg qd (negative coronary angiogram) | Discharged |
| M   | 78  | –      | Larynx carcinoma                | 340     | General ward | STEMI | None | Dead |
| M   | 67  | –      | Yes (I)                         | 6435    | ICU      | Stroke (no atrial fibrillation) | Aspirin | Discharged |
| F   | 76  | –      | Yes (T)                         | 677     | General ward | Stroke (no atrial fibrillation) | Aspirin + nadroparin 5700 IU bid | Discharged |
| M   | 64  | –      | No (Aspirin)                    | 280     | General ward | Stroke (no atrial fibrillation) | Clodiagrel + nadroparin 3800 IU qd | Hospitalized |
| M   | 69  | –      | No (Aspirin)                    | 249     | ICU      | Stroke (atrial fibrillation) | Mechanical thrombectomy, aspirin followed by therapeutic-dose heparin (AF) | Hospitalized |
| M   | 57  | –      | Yes (P)                         | 6071    | ICU      | Stroke (no atrial fibrillation), necrotizing meningocencephalitis | Therapeutic-dose unfractionated heparin | Hospitalized |
| F   | 73  | –      | Yes (Acroromucarol INR 1.2)     | 1158    | General ward | Stroke (atrial fibrillation) | Systemic thrombolysis, therapeutic-dose nadroparin | Discharged |
| F   | 75  | –      | Lung carcinoma                  | 61,000  | ICU      | Stroke, DIC | Nadroparin 5700 IE | Dead |

*On the day of thrombosis or closest available. AF, atrial fibrillation; bid, twice daily; DIC, disseminated intravascular coagulation; DVT, deep vein thrombosis; F, female; ICU, intensive care unit; INR, international normalized ratio; PE, pulmonary embolism; M, male; qd, once daily. Thromboprophylaxis dosage: (P) prophylactic; (I) intermediate (including weight-adjusted); (T) therapeutic.*
substantially to such a dramatic mortality and no autopsies were routinely performed in COVID-19 patients. Indeed, we showed that the D-dimer levels, a marker of inflammation and coagulation activation, rapidly increased in non-survivors during the course of hospitalization; overt DIC was present in 2% of COVID-19 patients and fatal in almost all cases.

5. Conclusions

Hospitalized patients with COVID-19 were characterized by substantial in-hospital mortality and a high rate of thromboembolic complications. Rapidly increasing D-dimer levels were observed in non-survivors, reflecting the inflammatory and procoagulant state of COVID-19. The high number of arterial and, in particular, venous thromboembolic events diagnosed within 24 h of admission and the high rate of positive VTE imaging tests among the few COVID-19 patients tested suggest that there is an urgent need to improve specific VTE diagnostic strategies and investigate the efficacy and safety of thromboprophylaxis in ambulatory COVID-19 patients.

Declaration of competing interest

Corrado Lodigiani received congress and travel payments from Bayer HealthCare, Daiichi-Sankyo and Boehringer Ingelheim, NovoNordisk, Takeda, and honoraria from Daiichi-Sankyo, Takeda, NovoNordisk, Boehringer Ingelheim, Bayer HealthCare, Aspen, Italfarmaco. Stefano Barco has received congress and travel payments from Daiichi-Sankyo and Bayer HealthCare, and honoraria from Bayer HealthCare and LeoPharma. The other authors do not disclose any potential conflict of interest. The present study was not funded.

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