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Coagulation parameters and venous thromboembolism in patients with and without COVID-19 admitted to the Emergency Department for acute respiratory insufficiency

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ARTICLE INFO

Keywords:
Venous thromboembolism
COVID-19
Coagulation
D-dimer

ABSTRACT

Background: In the recent outbreak of COVID-19 pandemic, increased D-dimer levels and high rates of venous thromboembolic events were reported. We aimed to compare coagulation parameters on admission between COVID-19 patients and non-COVID-19 patients with acute respiratory insufficiency and to describe VTE diagnosed at entry.

Methods: In this single-centre, observational retrospective study consecutive patients admitted for fever and acute respiratory failure were included. Patients underwent laboratory tests, arterial blood gas, chest X-ray, point of care ultrasound (POCUS), limited compression ultrasonography of the lower limbs (L-CUS), chest CT-scan if necessary, and swab test for COVID-19.

Results: Of 324 patients, 50\% had COVID-19. COVID19 patients had significantly lower mean white blood cells, neutrophils, platelet count, and pCT values, and significantly higher CRP, LDH, and ferritin levels than non-COVID19 patients. D-dimer was increased in 86.5\% COVID19 patients and in 84.9\% non-COVID19 patients; mean values were similar (2185 ng/mL and 2814 ng/mL, respectively, \( p = \text{n.s.} \)). After multivariate analysis, results were unchanged (Odds Ratio 1.00 95\%CI: 0.99–1.00, \( p = 0.21 \)). PT and aPTT values were also similar between the two groups, fibrinogen levels were higher in COVID19 than in non-COVID19 patients (684 and 496 mg/dL, respectively, \( p < 0.0001 \)). Five patients had asymptomatic proximal deep vein thrombosis detected by L-CUS (3 COVID19) and 2 patients had symptomatic pulmonary embolism (both non-COVID19).

Conclusions: D-dimer levels were similarly increased in patients with and without SARS-CoV 2 related disease. There were few cases of asymptomatic deep vein thrombosis or symptomatic pulmonary embolism at first day of admission, similarly distributed between COVID19 patients and non-COVID19 patients.

1. Introduction

In late 2019, we observed the diffusion of a new severe acute respiratory syndrome, known as coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2). SARS-CoV 2, at first identified in China in the Wuhan district, rapidly became pandemic with a deep impact on mortality, society, economy and everyday life [1].

Interstitial pneumonia is known to be the most important clinical manifestation of COVID-19, leading to severe acute respiratory failure [2], but many other clinical manifestations were subsequently reported, including thrombotic and coagulation disorders. Different studies have reported high rates of venous and arterial thromboembolism in COVID-19 patients [3,4]; although it is currently unknown if this is due to the direct effect of SARS-CoV 2 virus or if it reflects the activation of the coagulation system in response to the severity of the acute inflammatory condition. An association between increased D-dimer values, decreased survival and increased need for critical care was described [5]. A Chinese study first highlighted that, in COVID-19 patients, elevated D-dimer levels at admission were significantly associated with an increased risk of in-hospital mortality [3]. Other haemostatic parameters alterations, such has prolonged PT time, were also linked to illness severity and need for ICU admission [5,6].

However, the described alterations of haemostatic parameters are...
not exclusively of COVID-19 and can be found in other settings of acutely ill medical patients, including heart failure, respiratory failure, stroke, infectious or inflammatory disease. Previous studies have consistently reported that the elevation of D-dimer levels in these patients is associated with an increased risk of venous thromboembolism [7].

Aim of this observational, retrospective study was to compare laboratory parameters, with particular focus on coagulation tests, between confirmed COVID-19 patients and patients presenting with acute respiratory insufficiency not related to COVID-19. The prevalence of venous thromboembolism upon admission was also documented.

2. Methods

We collected data of consecutive adult patients admitted to a single institution, the Emergency Department of the teaching hospital of Varese, in Italy, between March 1st and April 30th 2020. Patients included in the study were referred because of fever and respiratory symptoms or respiratory failure requiring hospitalization.

The Emergency Department was organized in 2 separate areas, one for suspected COVID19 patients and one for other diseases. All included patients were referred to the COVID19 area for acute respiratory insufficiency and immediately underwent laboratory testing, arterial blood gas testing, chest X-ray, point of care ultrasound (POCUS), limited compression ultrasonography of the lower limbs (L-CUS), and chest CT-scan, when necessary. Angio-CT scan was performed when pulmonary embolism was clinically suspected. Information on baseline characteristics, comorbidities, and concomitant use of anticoagulant therapies was collected.

Nasopharyngeal and oropharyngeal swab was collected on the day of admission or in the morning of the day after. Specimen analysis was carried out with reverse-transcriptase polymerase chain reaction (RT-PCR) method. The swab was repeated after 48 h when laboratory and imaging tests were highly suspicious for COVID19.

Routinely performed laboratory tests on the day of admission at the Emergency Department included complete blood count, D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, lactate dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin (pCT), ferritin, creatinine, and liver function [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)].

All data were collected in an electronic database. The registry was approved by the Ethics Committee and no informed consent was requested. All information was anonymized.

2.1. Statistical analysis

Descriptive analysis was carried out to compare baseline characteristics, comorbidities, laboratory test results and the prevalence of concomitant proximal deep vein thrombosis at L-CUS or the incidence of symptomatic pulmonary embolism between COVID19 patients and controls without COVID19. The same variables were also compared between patients with normal and increased D-dimer levels.

Descriptive analysis was carried out to compare baseline characteristics, comorbidities, laboratory test results and the prevalence of concomitant proximal deep vein thrombosis at L-CUS or the incidence of symptomatic pulmonary embolism between COVID19 patients and controls without COVID19. The same variables were also compared between patients with normal and increased D-dimer levels. Absolute and relative frequencies in the case of discrete variables, with mean and standard deviation for continuous variables were reported. p-Value for mean and Chi-square test were used for comparison, a p value of < 0.05 was considered significant. For D-dimer levels, we reported both the mean values and the proportion of patients with levels above the cut-off of 500 ng/mL provided by the manufacturer (Innovance D-dimer, Siemens).

To explore the association between D-dimer and COVID-19, a multivariate logistic regression model was applied adjusted for potential confounding variables (age, sex, and comorbidities). Furthermore, adjusted p-values were calculated for comparison between normal and increased D-dimer levels. The analyses were performed with the SAS v9.4 software.

Table 1
Baseline characteristics.

| Characteristic | COVID-19 n (%) | Non-COVID-19 n (%) | p-Value |
|---------------|---------------|-------------------|---------|
| N             | 162           | 162               |         |
| Age Mean (SD) | 68.3 (14.2)   | 73.9 (14.2)       | 0.001   |
| Male gender   | n (%)         | 95 (58.6)         | 95 (58.6) | 0.99 |
| Comorbidities | Cardiovascular n (%) | 45 (27.8) | 86 (53.1) | < 0.0001 |
|               | Hypertension n (%) | 89 (54.9) | 102 (63.0) | 0.14 |
|               | Diabetes n (%) | 32 (19.8) | 40 (24.7) | 0.29 |
|               | Chronic respiratory disease n (%) | 21 (13.0) | 43 (26.7) | 0.002 |
|               | Chronic renal failure n (%) | 19 (11.8) | 35 (21.6) | 0.02 |
|               | Cancer n (%) | 13 (8.0) | 35 (21.6) | 0.001 |

3. Results

A total of 324 consecutive patients were enrolled, 162 of whom were objectively diagnosed with COVID19. Of the remaining patients, the large majority had bacterial pneumonia. COVID19 patients were significantly younger than controls, and significantly fewer had history of cardiovascular diseases, chronic respiratory failure, renal failure, and cancer than controls (Table 1).

A total of 5 patients, 3 with COVID19, had asymptomatic proximal deep vein thrombosis diagnosed by LCUS and 2 patients (both non-COVID19) had objectively documented symptomatic pulmonary embolism. Baseline characteristics and laboratory values at entry are described in Table 2. None of the patients was receiving prophylactic LMWH at entry, whereas two patients were on oral anticoagulant treatment with a DOAC for atrial fibrillation.

3.1. Laboratory parameters

COVID19 patients had significantly lower levels of white blood cells, neutrophils, lymphocytes, platelets, and pCT than controls (Table 3). Conversely, CRP, LDH, fibrinogen, ferritin, and transaminase levels were significantly higher in COVID19 patients than controls.

D-dimer was increased in 86.5% COVID19 patients and in 84.9% non-COVID19 patients. Neither mean D-dimer levels nor PT and aPTT levels differed between COVID19 patients and controls (Table 3). After multivariate analysis, the results were unchanged (Odds Ratio 1.00 95%CI: 0.99–1.00, p = 0.21).

Patients with elevated D-dimer levels were significantly older and had significantly higher levels of white blood cells, neutrophils, neutrophils/lymphocyte ratio, CRP, pCT, LDH, and fibrinogen than patients with normal D-dimer levels (Table 4).

4. Discussion

In this single-center, observational study carried out in patients with COVID-19 we found no significant difference in the prevalence of venous thromboembolism between COVID19 patients and controls, with a slightly more pronounced frequency of asymptomatic deep vein thrombosis. The prevalence of venous thromboembolism upon admission was also documented.

In summary, COVID19 patients had significantly lower levels of white blood cells, neutrophils, lymphocytes, platelets, and pCT than controls (Table 3). Conversely, CRP, LDH, fibrinogen, ferritin, and transaminase levels were significantly higher in COVID19 patients than controls. D-dimer was increased in 86.5% COVID19 patients and in 84.9% non-COVID19 patients. Neither mean D-dimer levels nor PT and aPTT levels differed between COVID19 patients and controls (Table 3). After multivariate analysis, the results were unchanged (Odds Ratio 1.00 95%CI: 0.99–1.00, p = 0.21).

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admitted for acute respiratory failure at an Emergency Department, the prevalence of deep vein thrombosis at the time of admission was 1.5% and more than 85% of patients had elevated D-dimer levels. We found no difference in the prevalence of deep venous thrombosis and in the number of patients with increased D-dimer or in mean D-dimer values between patients with confirmed COVID19 and controls.

Previous studies have found inflammatory markers (such as CRP and ferritin), as well as other markers including LDH, transaminases, and D-dimer as independent predictors of disease severity and mortality in COVID-19 patients [1,2]. Consistently, we found significantly higher inflammatory markers, LDH and transaminases in COVID-19 patients than in controls reflecting the important degree of inflammation in response to the virus SARS-CoV 2. Yet, this higher inflammatory status did not result in differences in D-dimer levels between patients with COVID-19 and patients with other causes of acute respiratory failure, despite the clear association between inflammation and D-dimer elevation confirmed by our study. This apparent discrepancy can be explained by the fact that other concomitant conditions, such as venous stasis or a prothrombotic state associated with existing comorbidities such as cancer, can result in activation of coagulation, and, thus, in increased D-dimer levels.

Several trials have shown that acutely ill medical patients and intensive care patients are at increased risk of venous thromboembolism and require adequate thromboprophylaxis [8]. More recently, some studies have shown the role of D-dimer as an independent marker of this increased risk both during hospitalization and after hospital discharge in the medical population [7,9–11]. The high rate of COVID19 patients with elevated D-dimer levels found in our and previous studies confirms the need to consider these patients at high risk of VTE and to provide pharmacologic prophylaxis accordingly. Our results also stress the need to carefully assess the risk of venous thrombosis in every acutely ill medical patient, also by including D-dimer measurement to better define the risk profile as proposed by recent risk assessment models [11].

Other authors had speculated on a possible direct effect of SARS-CoV 2 on the coagulation system leading to coagulation disorders including thromboembolic events [12]. This effect is possibly mediated by a direct effect of the virus on the endothelium and may explain the high reported rates of thrombotic complications despite anticoagulant prophylaxis. Since COVID-19 patients were in most cases referred to the Emergency Department several days after the onset of symptoms and without receiving any form of prophylaxis at home, we expected to find high rates of venous thrombosis already at the time of admission, also in the light of the marked inflammatory and prothrombotic status at entry. The observed rate of venous thrombosis was low and was similar between COVID-19 patients and controls. Given the increased risk of venous thrombosis estimated in most study patients, prophylaxis with low molecular weight heparin was routinely prescribed unless absolutely contraindicated in all at-risk patients, with and without COVID19. Finally, D-dimer levels were increased in all, but two patients with objective diagnosis of deep vein thrombosis or pulmonary embolism at entry. Of interest, both patients were already receiving anticoagulant treatment with a direct oral anticoagulant and this could, at least in part, explain the normal D-dimer values.

This study has a number of limitations. First, false negative results in the diagnosis of SARS-CoV 2 using the PCR methodology can be expected and, thus, there is the possibility that some missed cases were included in the control group. However, uncertain cases were extensively studied using CT scan, repeat nasopharyngeal and oropharyngeal swab, and testing from bronchoalveolar lavage, if needed. Therefore, missed cases, if any, were likely a small minority. Second, angio-CT scan was not routinely performed in all patients with acute respiratory insufficiency and positive D-dimer, and we cannot exclude that some additional cases of patients with pulmonary embolism were undiagnosed. Since this was an observational study, the decision to perform angio-CT scan was left to the discretion of the treating physicians, and usually this was the case of patients without an alternative explanation of clinical symptoms and signs at entry. Third, we acknowledge the heterogeneity of the control population, which is represented by patients with bacterial pneumonia, but also acute heart failure, primary or metastatic lung cancer, and other inflammatory and infectious diseases, which not uncommonly coexisted. However, this population is representative of the population of acutely ill medical

### Table 3
Laboratory parameters in COVID-19 and non-COVID-19 patients.

|                      | COVID-19 | Non-COVID-19 | p value |
|----------------------|----------|--------------|---------|
|                      | Mean (SD)| Mean (SD)    |         |
| White blood cells    | 8.3 (5.3)| 11.4 (6.0)   | <0.0001 |
| Neutrophils          | 7.0 (5.3)| 8.7 (5.9)    | 0.006   |
| Lymphocytes          | 1.1 (1.2)| 1.3 (0.9)    | 0.09    |
| Neu/Lym ratio        | 9.6 (10.4)| 11.5 (19.3) | 0.29    |
| Platelets            | 213.4 (92.1)| 249.3 (114.0)| 0.002  |
| C reactive protein   | 113 (87.8)| 91 (98.2)    | 0.04    |
| Procalcitonin        | 2.2 (8.7)| 7.0 (20.1)   | 0.02    |
| LDH                  | 419.3 (193.9)| 297.8 (128.2)| <0.0001|
| PT                   | 1.23 (0.81)| 1.36 (0.93) | 0.16    |
| aPTT                 | 0.94 (0.20)| 0.98 (0.23) | 0.10    |
| Fibrinogen           | 684.9 (356.3)| 496.5 (172.0)| <0.0001|
| D-dimer              | 2185.9 (2460.5)| 2814.7 (2879.8)| 0.09    |
| ALT                  | 59.2 (39.9)| 53.3 (96.6) | 0.50    |
| AST                  | 45.8 (36.2)| 37.4 (52.7) | 0.10    |
| Creatinine           | 1.23 (0.66)| 1.40 (1.07) | 0.10    |
| Ferritin             | 1574.7 (2162.7)| 352 (324.2) | <0.0001|

SD, standard deviation.

### Table 4
Laboratory parameters in D-dimer positive and negative groups.

|                      | D-dimer < 500 ng/mL | D-dimer ≥ 500 ng/mL | p-Value |
|----------------------|---------------------|---------------------|---------|
|                      | Mean (SD)           | Mean (SD)           |         |
| Age                  | 64.6 (16.0)         | 72.9 (13.4)         | <0.0003 |
| Male gender          | 22 (73.3)           | 100 (55.6)          | 0.07    |
| White blood cells    | 7.1 (2.6)           | 10.3 (5.7)          | <0.0001 |
| Neutrophils          | 4.6 (1.8)           | 3.6 (5.5)           | <0.0001 |
| Lymphocytes          | 1.78 (2.4)          | 1.2 (0.9)           | 0.20    |
| Neu/Lym ratio        | 4.5 (4.1)           | 11.3 (15.6)         | <0.0001 |
| Platelets            | 208.7 (82.0)        | 241.3 (107.7)       | 0.11    |
| C reactive protein   | 52.5 (63.1)         | 105.5 (91.4)        | 0.0002  |
| Procalcitonin        | 2.59 (9.6)          | 4.54 (15.9)         | 0.45    |
| LDH                  | 287.6(102.6)        | 364.6 (182.9)       | 0.002   |
| PT                   | 1.39 (0.5)          | 1.29 (0.89)         | 0.60    |
| aPTT                 | 1.04 (0.26)         | 0.94 (0.20)         | 0.05    |
| Fibrinogen           | 498.7 (160.8)       | 582.8 (205.9)       | 0.04    |
| AST                  | 30.9 (17.1)         | 44.1 (53.8)         | 0.01    |
| ALT                  | 1.21 (0.95)         | 1.26 (0.79)         | 0.75    |
| Creatinine           | 883.8 (2206.1)      | 848.6 (1486.5)      | 0.94    |
patients who were recruited in most clinical studies carried out in this setting. Finally, we only performed limited CUS to detect proximal deep vein thrombosis and we cannot exclude that a number of thrombi located below the knee were not diagnosed at entry.

In conclusion, D-dimer levels, marker of poor prognosis and of increased risk of in-hospital and post-discharge venous thromboembolism, appear to be similarly increased in patients with fever and acute respiratory failure with and without SARS-CoV 2 related disease admitted to an Emergency Department. This was observed despite a statistically significant difference in the mean levels of inflammatory markers between the two groups. Given the known predictive role of D-dimer, these results suggest the importance of anticoagulant prophylaxis in all patients admitted for acute respiratory insufficiency, both with and without COVID19. Asymptomatic deep vein thrombosis detected by L-CUS or symptomatic pulmonary embolism at the time of admission were uncommon and similarly distributed between COVID19 patients and non-COVID19 patients.

Declaration of competing interest

None.

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