LETTER TO THE EDITOR

Second wave of the COVID-19 pandemic: D-dimer levels are not so high anymore

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Dear Editor,

Italy was the first European country to be hit by the coronavirus disease 2019 (COVID-19) pandemic in the beginning of 2020. During that first wave, it was soon noticed that many patients hospitalized for COVID-19 had extremely high levels of D-dimer, with values often in the range of thousands and high incidence of venous thromboembolism (VTE) [1]. For instance, we reported that, among patients hospitalized for COVID-19 in the Internal Medicine wards of our University Hospital in Rome, Italy, during a random week of the month of April 2020, the mean D-dimer level was 4108 ± 7098 ng/ml [2]. Very high levels of D-dimer have been consistently reported by many other authors in various countries [3]. Based on this, D-dimer has become the laboratory hallmark of COVID-19-induced coagulopathy and the biomarker used to discriminate between patients at high and low risk of thrombotic complications in both the international literature and the clinical practice [4].

Since October 2020, Italy is facing a severe second wave of the COVID-19 pandemic. However, we have been under the impression that, compared to the first phase, D-dimer levels are now substantially lower. To confirm this impression, we conducted a retrospective analysis comparing 247 consecutive patients hospitalized in dedicated Internal Medicine wards at our University Hospital during the first wave of the COVID-19 pandemic (between March and May 2020) and 142 consecutive patients hospitalized in the same Internal Medicine wards during the second wave of the COVID-19 pandemic (between October and December 2020). D-dimer levels were assessed by using a latex agglutination test. We found that the mean D-dimer level during the first pandemic phase was 3585.0 ± 7172.2 ng/ml, while it was 1748.1 ± 3417.5 ng/ml during the current second phase ($P = 0.02$) (Table 1).

Why is this happening? One possibility is that the patients that we are treating during the second pandemic wave in Italy are less severely ill than those that we saw during the first phase of the COVID-19 pandemic. However, this does not seem to be the case. Indeed, as shown in Table 1, patients in the second wave are older than those in the first wave and are more often affected by hypertension, diabetes, and ischemic cardiovascular diseases (including coronary artery disease, previous stroke, and peripheral artery disease). Also, the levels of the prototypical inflammatory marker C-reactive protein (CRP) are not different between the two groups (93.2 ± 77.6 vs 74.1 ± 67.4 mg/l, $P = 0.07$), while with cell count is higher among patients in the second pandemic wave (6943.5 ± 3187.4 vs 8811.2 ± 3767.4 cells/mmc, $P = 0.001$). In addition, we have calculated that the mean quick COVID-19 severity index (qCSI), a score that predicts critical respiratory illness in patients admitted to the hospital with COVID-19 [5], is higher now than among patients hospitalized during the first wave of the pandemic (4.4 ± 4.3 and 2.1 ± 3.3, respectively, $P < 0.001$). Taken together, these data do not support the hypothesis that D-dimer levels are lower because patients are less severely ill.

Another possible explanation is that now many patients receive early treatment with anticoagulants and steroids at home, before being hospitalized. This might change D-dimer dynamics and affect serum levels at the time of hospital admission. Indeed, D-dimer is a plasmin-derived soluble degradation product of cross-linked fibrin and its generation requires the sequential activity of three enzymes, including thrombin being inactivated by the action of heparin bound to antithrombin [6]. Therefore, on one side, heparin administration may reduce D-dimer production through thrombin inhibition and, on the other, steroid use could limit endothelial damage and the release of intrinsic pathway coagulation

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Table 1 Comparison between patients during the first and second pandemic wave

Characteristics	1st pandemic wave (n = 247)	2nd pandemic wave (n = 142)	P-value
Demographic and clinical characteristics			
Mean age, years ± SD	65.3 ± 15.4	71.4 ± 14.0	0.47
Men, n (%)	160 (65.0%)	83 (58.0%)	0.21
Hypertension, n (%)	115 (46.5%)	88 (61.9%)	0.003
Diabetes, n (%)	32 (12.9%)	32 (22.5%)	0.01
Ischemic cardiovascular diseases, n (%)	29 (11.7%)	31 (21.8%)	0.007
VTE, n (%)	4 (1.6%)	3 (2.1%)	0.72
COPD, n (%)	20 (8.0%)	10 (7.0%)	0.70
Laboratory and clinical results during hospitalization			
Mean D-dimers, ng/ml ± SD	3585.0 ± 7172.2	1748.1 ± 3417.5	0.02
Mean C-reactive protein, mg/L ± SD	93.2 ± 77.6	74.1 ± 67.4	0.07
Mean leukocytes, cell/mmc ± SD	6943.5 ± 3187.4	8811.2 ± 3767.4	0.001
Mean PaO2/FiO2, ratio ± SD	292.2 ± 84.6	284.1 ± 77.6	0.16
Time from symptoms to D-dimer measurement, days ± SD	7.2 ± 4.0	4.9 ± 4.2	< 0.001
qCSI, mean ± SD	2.1 ± 3.3	4.4 ± 4.3	< 0.001
Deaths, n (%)	39 (15.7%)	20 (14.0%)	0.65
Hospital length in subject who died, days ± SD	14.5 ± 11.4	16.2 ± 14.3	0.30
Pre-admission therapy			
Anticoagulant, n (%)	14 (5.6%)	60 (42.2%)	< 0.00001
Steroids, n (%)	7 (2.8%)	54 (38.0%)	< 0.00001
Anticoagulant AND steroids, n (%)	2 (0.8%)	31 (21.8%)	< 0.00001
Anticoagulant OR steroid, n (%)	19 (7.7%)	83 (58.4%)	< 0.00001

factors. Although there is not a general consensus on the use of anticoagulants and steroids out of the hospital [7, 8], it is common knowledge that these medications are often prescribed to individuals with SARS-COV-2 infection by general practitioners and physicians working in the home-care system. As presented in Table 1, 42.2% of the patients that were hospitalized during the second wave of the COVID-19 pandemic had received some type of anticoagulant therapy at home, before being admitted to the hospital. There were also many patients that had received treatment with steroids at home (38.0%). In total, the percentage of patients that had received either an anticoagulant or a steroid at home, before hospitalization, was 58.4%. This is a relevant difference, compared to the first phase of the COVID-19 pandemic, when still there was great uncertainty about the appropriateness of the use of anticoagulants and steroids even in patients hospitalized for COVID-19. At that time, the use of such medications at home was virtually absent, or at least much lower than now. Obviously, it would be important to consider also the time between the onset of symptoms and hospitalization, because patients who stayed at home for a longer period of time before being hospitalized might have been exposed to an increased risk of VTE, due to reduced mobility and acute infection. Also, these patients might have received anticoagulants at home for a longer period of time,

with an effect on the D-dimer levels measured at the time of hospitalization. Nonetheless, one could hypothesize that patients who were able to manage the disease at home for a long period of time had a milder form of the disease, compared to those who required prompt hospitalization. For all these reasons, it is difficult to determine the actual effect of home treatment on the levels of D-dimer that were measured at the time of hospital admission.

Our observation that D-dimer levels in patients hospitalized for COVID-19 are lower now than during the first wave of the pandemic may lead to interesting considerations. One is that there is a discrepancy between D-dimer levels and disease severity. Indeed, as shown in Table 1, patients hospitalized during the second wave of the pandemic had similar PaO2/FiO2 ratio, similar mortality rate, and even higher qCSI, compared to patients hospitalized between March and May 2020. This might indicate that D-dimer is not a reliable prognostic marker of disease severity, as its levels do not correlate with the risk of developing critical respiratory illness, in contrast with the established notion that the degree of D-dimer elevation is associated with a greater likelihood of respiratory failure and mortality in COVID-19 patients. Another consideration is that lower D-dimer levels might facilitate the use of D-dimer as diagnostic marker of VTE. Indeed, the mean D-dimer values that we measured during

the first wave of the pandemic were above the thresholds recently proposed to identify COVID-19 patients with VTE, while the mean values measured during the second wave are substantially below these thresholds [9, 10]. Taken together, these findings suggest that, while D-dimer remains a powerful negative diagnostic and predictive marker, its thresholds for the management of COVID-19 are not yet established.

In conclusion, we report a significant reduction of D-dimer levels, when patients hospitalized during the second phase of the COVID-19 pandemic are compared to patients that were hospitalized in the beginning of 2020. Although the cause of this phenomenon remains to be elucidated, we believe that this finding deserves attention, in consideration of the important role that D-dimer has assumed as diagnostic and prognostic biomarker in patients affected by COVID-19.

Declarations

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