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Postacute elevation of D-dimer levels in severe acute respiratory syndrome coronavirus 2-positive nonhospitalized patients with mild symptoms

Rebecca Folkman[a], Habiba Kamal[a,b], Marcus Ahl[a,b], Adrian Szum[c], Maria Magnusson[d,e] and Soo Aleman[a,b]

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[a]Department of Infectious Diseases, Karolinska University Hospital, [b]Department of Medicine Huddinge, Karolinska Institutet, [c]Department of Radiology, [d]Department of Hematology, Karolinska University Hospital and [e]Clinical Chemistry and Blood Coagulation Research, MMK, Department of Pediatrics, CLINTEC, Karolinska Institutet, Stockholm, Sweden

Correspondence to Rebecca Folkman, Department of Infectious Diseases Huddinge, I73, Karolinska University Hospital, 141 86 Stockholm, Sweden. Tel: +46 70 171 34 32; e-mail: Rebecca.folkman@sll.se

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Introduction

Several studies about the clinical course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have shown that increased activation of the hemostatic system is common in hospitalized patients with coronavirus disease 2019 (COVID-19) and that the risk of thrombosis is high [1]. Elevated levels of D-dimer have been associated with increased morbidity and mortality [2]. Data are though scarce, about D-dimer levels in nonhospitalized cases of mild COVID-19 [3,4]. We aimed, therefore, to investigate the results of D-dimers tests in patients with mild COVID-19 and assess the clinical outcomes.

Method

This cohort included 126 consecutive nonhospitalized patients with COVID-19, positive for the SARS-CoV-2 test in reverse transcriptase PCR assay from nasopharyngeal swab tests between 2 March and 27 April 2020. They were followed up until September 2020 at the Department of Infectious Diseases, Karolinska University Hospital, Sweden. No patients were vaccinated against SARS-CoV-2 during the study.

Serial D-dimer tests were analyzed by the Siemens INNOVANCE D-dimer assay (Siemens Healthineers, Erlangen, Germany) on the instrument Sysmex CS5100 (Siemens Healthineers) and reported in mg/l FEU, as part of the research project. Age-dependent reference interval was used [5]. Extended coagulation tests, including fibrinogen, fibrin, antithrombin, activated partial thromboplastin time (aPTT), and Prothrombin Time-International Normalized Ratio (PT/INR), were analyzed according to the routine method. Computed tomography pulmonary angiography (CTPA) and 6 min walk test (6MWT) were performed, according to the discretion of the responsible physician, and based on symptom and test results. Two patients were excluded because of failed test results; thus, 124 remained. The study has been approved by the Central Ethics Committee of Sweden.

Results

Baseline characteristics at the time of testing are shown in Table 1. The first D-dimer tests were taken at a median of 3.3 months (IQR 3.0–3.5) after the debut of symptoms. According to the age group, elevated D-dimer levels were

Table 1 Baseline characteristics at initial testing and laboratory data of 124 patients with diagnosed severe acute respiratory syndrome coronavirus 2 infection and mild symptoms, categorized by elevated or nonelevated D-dimer levels

Patient characteristics	All patients	Patients with elevated D-dimer levels	Patients with normal D-dimer levels
Total number [*n* (%)]	124	15 (12%)	109 (88%)
Age, median (IQR) (years)	49.6 (44.7–56.2)	50.0 (47.7–54.3)	49.6 (44.6–56.3)
Age [*n* (%)]			
18–39 years	19 (15.3)	1 (6.7)	18 (16.5)
40–49 years	45 (36.3)	7 (46.7)	38 (34.9)
50–59 years	41 (33.1)	4 (26.7)	37 (33.9)
60–69 years	14 (11.3)	2 (13.3)	12 (11.0)
>70 years	5 (4.0)	1 (6.7)	4 (3.7)
Sex			
Men [*n* (%)]	64 (51.6)	9 (60.0)	55 (50.5)
Comorbidity [*n* (%)]			
Diabetes mellitus	3 (2.4)	0	3 (2.8)
Hypertension	15 (12.1)	2 (13.3)	13 (11.9)
Cardiovascular disease	7 (5.6)	0	7 (6.4)
Chronic lung disease	7 (5.6)	0	7 (6.4)
Cancer	1 (0.8)	0	1 (0.9)
Liver disease	1 (0.8)	1 (6.7)	0
Obesity (BMI >30 kg/m^2)[a]	6 (5.9)	1 (7.1)	5 (5.7)
Present smoker	0	0	0
Positive SARS-COV-2 antibodies [*n* (%)]	107 (86.3)	13 (86.7)	94 (86.2)
Hemoglobin count, median (IQR) (g/l)	138.0 (128.3–148.0)	139.0 (128.0–153.0)	138.0 (129.5–147.0)
Leucocyte count [median (IQR)]	5.5 (4.7–6.5)	6.0 (4.9–7.1)	5.5 (4.6–6.4)
Lymphocyte count [median (IQR)]	1.7 (2.4–2.1)	1.7 (1.3–2.1)	1.7 (1.4–2.1)
Albumin [median (IQR)] (g/l)	40.0 (38.0–41.0)	39.0 (37.7–40.0)	40.0 (38.0–42.0)
Ferritin [median (IQR)] (μg/l)	120.5 (64.0–244.5)	124.0 (79.0–287.0)	118.0 (62.0–242.0)
Lactate dehydrogenase, median (IQR) (μkat/l)	3.3 (3.0–3.6)	3.4 (3.0–3.6)	3.1 (3.0–3.5)
Elevated troponin level (>15 ng/l) [*n* (%)]	1 (0.8)	0	1 (0.9)
Elevated CRP level (>3 mg/l) [*n* (%)]	16 (12.9)	3 (20)	13 (11.9)
Elevated NT-proBNP level (≥155 ng/l) [*n* (%)]	6 (4.8)	1 (6.7)	5 (4.6)

IQR, interquartile range NT-pro BNP, N-terminal pro hormone B-type natriuretic peptide. [a]Available in 102 patients.

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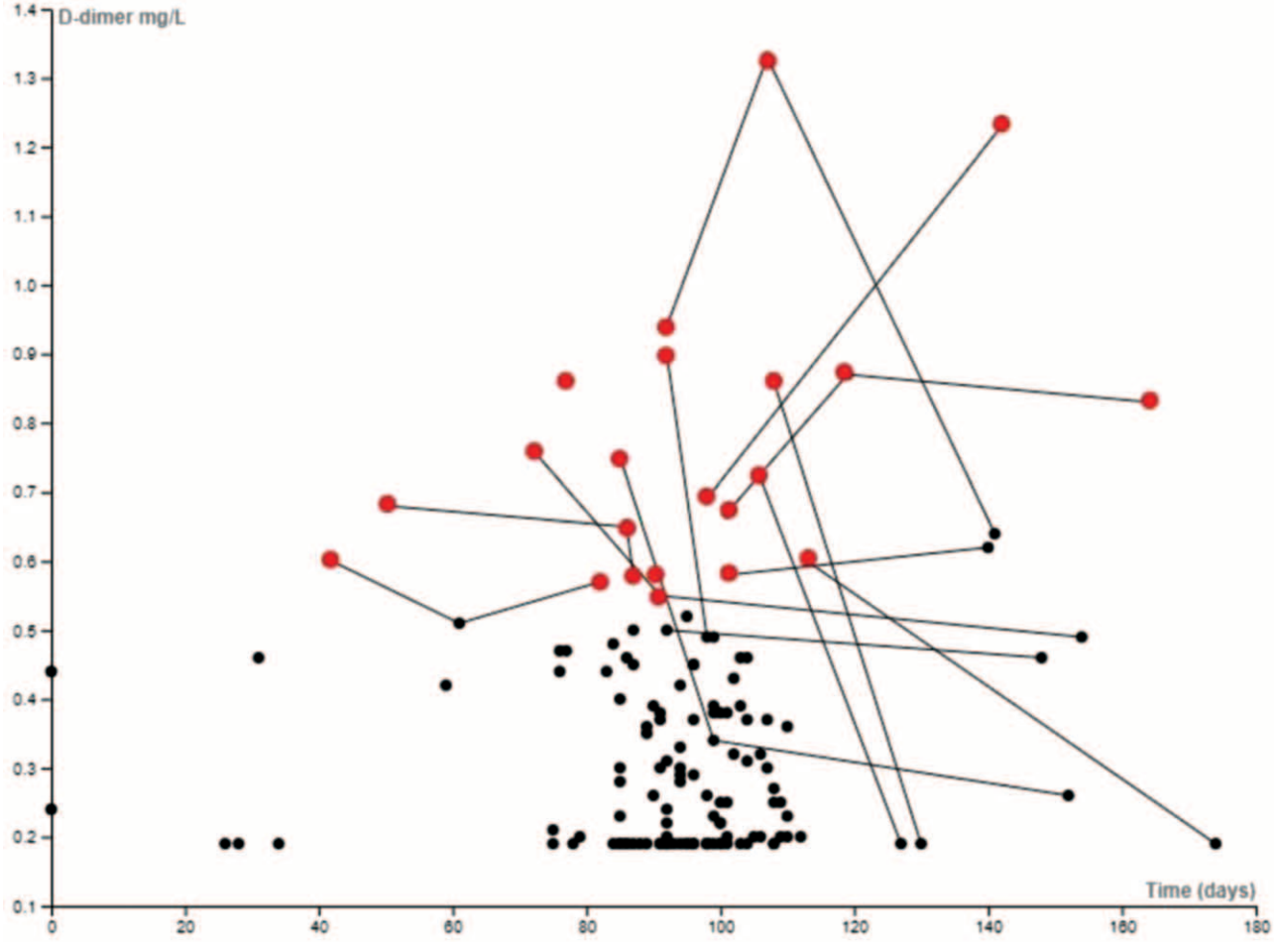
seen in 12% of the patients ($n = 15$) (Fig. 1, Supplementary Table 1, http://links.lww.com/BCF/A127). Thirteen patients (87%) underwent consecutive test/s with D-dimer, with nine patients (9/13, 69%) reaching normalization of values at the end of follow-up. An extended coagulopathy investigation was performed at consecutive D-dimer test in 12 patients with normal results. No patient had received anticoagulants.

The majority of patients ($n = 12$, 80%) with elevated D-dimer levels did not have any symptoms associated with pulmonary embolism or deep vein thrombosis. One patient described dyspnea on physical exertion and underwent both CTPA and 6MWT with normal results. One patient experienced intermittent chest pain but CT investigation showed only signs of air trapping but no sign of thrombosis and normal 6MWT result. Another patient with intermittent chest pain, borderline elevated D-dimer at 0.5 mg/l and elevated N-terminal prohormone B-type natriuretic peptide (NT-proBNP) at 152 ng/l was investigated with echocardiography, showing normal condition. Altogether, seven patients (47%) underwent CTPA, with no sign of pulmonary arterial thrombosis. Five of these were performed with dual-energy CT angiography. A previous report using this method has shown signs of lung perfusion deficits in patients with severe COVID-19, which could indicate the presence of microthrombosis [6]. Seven patients underwent 6MWT, with only one investigation showing desaturation from 99 to 89% but subsequent CT angiography showed no sign of thrombosis.

Discussion

Our study has shown that elevated D-dimer during convalescence phase is not uncommon but no clinical sign of thrombosis was found. This is in line with a recent study in which elevated D-dimer in convalescent mild or severe COVID-19 was seen, despite normalization of other coagulation and inflammatory markers [7]. D-dimer is

Fig. 1



D-dimer levels in 124 patients with mild coronavirus disease 19 in the convalescent phase. The time from the debut of COVID-19 symptoms to the first, second, and third tests was in median 3.3 (IQR 3.0–3.5), 4.4 (IQR 3.3–4.9), and 5.0 (IQR 3.1–5.4) months, respectively. Normal D-dimer values according to age are shown in black dots and abnormal D-dimer values in red dots. COVID-19, coronavirus disease 2019; IQR, interquartile range.

formed when cross-linked fibrin is degraded and indicates activation of coagulation and fibrinolysis. D-dimer is used as a biomarker of thromboembolism and disseminated intravascular coagulation but can be elevated in various conditions, for example, inflammation, infection, obesity, cancer, cardiac disease, and increases with age [8]. In this study, age-adjusted cut-offs for D-dimer were used, the patients were middle-aged, and most of them healthy; despite this, elevated D-dimer were seen 3 months after mild COVID-19 symptoms in 12% of the patients.

The elevation of D-dimer in hospitalized patients with COVID-19, even without detectable thrombosis, has been suggested to be attributable to activation of the coagulation system via the SARS-CoV-2 virus, inflammation, and microthrombosis [9].

Reports of stroke in patients with mild COVID-19 have been described, raising the question of coagulopathy in even patients with mild course [10]. The role of coagulation activation and microthrombosis in long-term COVID-19 in the increasing number of patients reporting postacute COVID-19 symptoms is still unknown [11].

Some limitations of this study are lack of D-dimer data in the acute phase, and we cannot entirely rule out any microthrombosis in the lungs, because of technical limitations of the CTPA and screening for deep vein thrombosis was not performed.

Conclusion

Elevated D-dimer levels could be seen as frequent as in every tenth person 3 months after the debut of mild COVID-19 in our study but none were diagnosed with thrombosis at follow-up. Considering the high number of SARS-CoV-2-infected persons with mild COVID-19 around the world, this issue needs to be noticed and further explored.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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