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

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Blood Coagulation and Fibrinolysis 2022, 33:285–287

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Received 27 August 2021 Revised 12 November 2021 Accepted 19 November 2021

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 permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

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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 (%):       | 124 (100%) | 119 (96%)                           | 5 (4%)                             |
| Age (years):            | 49.6 (44.7–56.2) | 50.0 (46.6–56.3) | 49.6 (44.7–56.2) |
| Sex:                    | 64 (51.6%) | 60 (50.5%)                           | 4 (3.3%)                           |
| Diabetes mellitus:      | 3 (2.4%) | 3 (2.6%)                             | 0 (0%)                             |
| Heart failure:          | 15 (12.1%) | 13 (11.5%)                           | 2 (1.6%)                           |
| Cardiovascular disease: | 7 (5.6%) | 7 (6.4%)                             | 0 (0%)                             |
| Chronic lung disease:   | 7 (5.6%) | 7 (6.4%)                             | 0 (0%)                             |
| Cancer:                 | 1 (0.8%) | 1 (0.8%)                             | 0 (0%)                             |
| Liver disease:          | 1 (0.8%) | 1 (0.8%)                             | 0 (0%)                             |
| Obesity (BMI >30 kg/m\(^2\)): | 6 (5.0%) | 7 (6.4%)                             | 5 (4.0%)                           |
| Positive SARS-CoV-2 antibodies (%): | 107 (86.3%) | 100 (88.3%) | 7 (5.7%) |
| Lymphocyte count (median (IQR)): | 138.0 (128.3–148.0) | 139.0 (128.0–153.0) | 138.0 (129.5–147.0) |
| Lymphocyte count (median (IQR)): | 5.5 (4.7–6.5) | 5.5 (4.7–6.5) | 5.5 (4.6–6.4) |
| Albumin (median (IQR)): | 40.0 (38.0–41.0) | 39.0 (38.0–41.0) | 40.0 (38.0–41.0) |
| C-reactive protein (median (IQR)): | 6.0 (4.9–7.1) | 6.0 (4.9–7.1) | 6.0 (4.9–7.1) |
| Ferritin (median (IQR)): | 124.0 (118.0–138.0) | 124.0 (118.0–138.0) | 124.0 (118.0–138.0) |
| Ferritin (median (IQR)): | 64.0 (44.5–91.0) | 64.0 (44.5–91.0) | 64.0 (44.5–91.0) |
| Lactate dehydrogenase (median (IQR)): | 3.3 (3.0–3.6) | 3.3 (3.0–3.6) | 3.3 (3.0–3.6) |
| Lactate dehydrogenase (median (IQR)): | 3.3 (3.0–3.6) | 3.3 (3.0–3.6) | 3.3 (3.0–3.6) |
| Elevated troponin level (%) (median (IQR)): | 1 (0.8%) | 1 (0.8%) | 0 (0%) |
| Elevated CRP level (%) (median (IQR)): | 16 (12.9%) | 16 (12.9%) | 0 (0%) |
| Elevated NT-proBNP level (%) (median (IQR)): | 6 (4.8%) | 6 (4.8%) | 0 (0%) |
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
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**

There are no conflicts of interest.

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