Assessment of Factor VIII Activity and D-Dimer Levels in the Post-COVID Period

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Abstract

Changes in the hemostatic system during COVID infection lead to hypercoagulability. Numerous studies have evaluated hemostatic abnormalities in COVID patients during acute infection, in the period of hospitalization. However, the hemostatic status following hospital discharge has not been sufficiently assessed. Considering the importance of FVIII and D-dimer levels as markers for the assessment of thrombosis, our study aimed to evaluate changes in these markers, as well as the influence of patient's age and clinical presentation of COVID infection on those hemostatic markers in the post-COVID phase. This prospective study (July 2020 to December 2022) included 115 COVID patients, 68 (59%) with asymptomatic/mild and 47 (41%) with moderate/severe clinical presentation. Patient follow-up included laboratory evaluation of FVIII and D-dimer levels at 1, 3, and 6 months following the COVID infection. Three months after the COVID infection, elevated FVIII was recorded in 44% of younger versus 65% of older individuals, $p = 0.05$, respectively, and 30 versus 57% ($p = 0.008$) 6 months post–COVID infection. With a focus on clinical presentation, a higher number of patients with moderate/severe COVID had elevated FVIII activity, but a statistically significant difference was observed only for the 6 months (32% mild vs. 53% moderate/severe, $p = 0.041$) post-infection time point. Following a COVID infection, an increase in FVIII activity suggests a continued hypercoagulable state in the post-COVID period and correlates with elevated D-dimer levels. This increase in FVIII is more pronounced in patients with moderate/severe clinical picture and those patients older than 50 years.

Keywords

- hypercoagulability
- venous thrombosis
- infectious diseases
- factor VIII

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Introduction

Alterations of the hemostatic system during COVID infection lead to hypercoagulability accompanied with increased levels of plasma coagulation factors.[1–4] Several studies investigated the changes of plasma coagulation factors in COVID patients with most reporting high levels of fibrinogen, von Willebrand factor (VWF) antigen, and factor VIII (FVIII) activity.[5–10] COVID patients admitted to the intensive care unit (ICU) showed increased fibrinogen levels and markedly increased FVIII activity (up to 460 U/dL).[5] von Meijenfeldt et al demonstrated significant increases in plasma levels of fibrinogen, VWF, and FVIII in patients who required respiratory support, in comparison to those who required minimal or no respiratory support.[6] Studies that investigated the severity of clinical picture and levels of plasma coagulation factors showed that patients with concomitant increases in FV and FVIII activity had higher venous thromboembolism (VTE) rates compared with those with normal activity of plasma coagulation factors.[7] In addition, a study comparing hemostatic changes during hospitalization and after discharge in the follow-up period of 4 months showed increased factor V, VWF, and fibrinogen during hospitalization, with normalization observed during follow-up. On the other hand, FVIII activity was elevated during hospitalization and remained significantly higher in follow-up period, when compared with healthy controls.[8]

When focusing on D-dimer changes, the main initial coagulation abnormality during COVID infection is elevated D-dimer levels, a well-recognized nonspecific marker of hypercoagulability. Several studies have shown that severely ill patients have high or very high levels of D-dimers, describing a state of hypercoagulability that is in some cases accompanied by the development of the most severe coagulopathy, such as disseminated intravascular coagulation (DIC).[9–11] The initial data showing higher frequency of VTE in seriously ill COVID patients were presented as preliminary reports from China and focused on a relatively small number of patients.[10] Subsequently, colleagues from Europe reported a higher frequency of thromboembolic events, mainly venous thromboses, in patients with COVID who had pneumonia and were treated in ICU. The prevalence of VTE among COVID patients was shown to vary between 2.6 and 35%.[12–14] We recently showed the prevalence of VTE among our COVID patient population as 23% in patients with thrombophilia and 20% among those without thrombophilia.[15]

To date numerous studies have evaluated hemostatic changes in COVID patients with acute infection during hospitalization, while hemostatic status of COVID patients after hospital discharge in the post-COVID phase has not yet been sufficiently assessed. Considering the importance of FVIII and D-dimers as markers for thrombotic risk assessment, our study aimed to evaluate the changes in these markers, as well as the influence of patient's age and clinical presentation of COVID infection on these hemostatic markers in the post-COVID phase.

Materials and Methods

Institutional approval for the study was granted by the Local Research Ethics Committee (number 1391/2) in accordance with the internationally accepted ethical standards. Each patient signed the informed consent form. This study took place in the period from July 2020 to December 2022.

Patients

With regard to the inclusion criteria, the study participants who were confirmed to have COVID-19 infection related to nasopharyngeal swab using SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) were eligible for the study, regardless of hospital or home treatment. In relation to the exclusion criteria, younger than 18 years, pregnant women, and patients with active malignancy were not eligible for the study. With regard to the type of treatment, patients with mild clinical presentation were home treated for 7 to 14 days, while those patients with moderate or severe clinical presentation were hospitalized for 10 to 30 days.

Index for COVID-19 classification in relation to the WHO clinical progression scale[16] was used as the criteria to establish the clinical severity of COVID-19. Ambulatory mild disease was defined as patients who were asymptomatic, with viral RNA detected, as well as for patients with a mild clinical presentation. Hospitalized patients with moderate clinical presentation were classified as those with pneumonia who required oxygen delivery by mask or nasal prongs, while hospitalized patients with severe clinical presentation were defined as patients with acute respiratory distress syndrome (ARDS) who needed intubation and mechanical ventilation. They were followed up for 6 months after acute COVID infection. The data related to age, gender, body mass index (BMI), comorbidities, previous thrombosis, thrombosis related to COVID infection, clinical presentation of COVID infection, and objectively diagnosed severe post-COVID complications (pericarditis, pulmonary fibrosis, and cardiac disease) were collected. For COVID patients who were hospitalized, discharge list and medical documentation were used, while in those who had home treatment, the anamnestic data, laboratory, and COVID-related medical reports were collected. All thrombotic events were defined as COVID-related thrombotic event developed during the acute infection or in the subsequent 6-month period. Thrombotic events were documented using color Doppler or computed tomographic scan. In total, 25 patients developed thrombosis, 2 patients were presented with asymptomatic deep venous thrombosis (DVT), and 1 was presented with arterial thrombosis of the upper limb.

Methods

COVID patients were followed up for 1, 3, and 6 months after the resolution of COVID infection. For all patients, the laboratory evaluation of hemostatic parameters included the measurement of FVIII activity and D-dimers. Whole blood was collected using sterile, atraumatic venipuncture into two Vacutainer citrate tubes (Vacutest Kima, containing

1/10 volume sodium citrate stock solution at 0.129 mmol/L). For each study participants, two samples were collected and processed to obtain platelet-poor plasma, with aliquots stored at −80 °C until testing. Factor VIII:C was measured using the one-stage clotting assay with IL test reagents (Instrumentation Laboratory, Milan, Italy), using IL Coagulometers ACL 6000 (Instrumental Laboratory). Factor VIII:C activity above 1.5 IU/mL was considered as elevated.[17] Measurement of D-dimer was performed using the Innovance D-dimer (Siemens Healthcare Diagnostics) immunoturbidimetric assay for the quantitative determination of cross-linked fibrin degradation products (D-dimer) in human plasma using BCS Siemens coagulometer. D-dimer results were expressed in mg/L FEU (fibrinogen equivalent units) with the cut-off value for discrimination of VTE of 0.5 mg/L FEU in patients younger than 50 years. In those who were older than 50 years, adjusted D-dimer level was used. During the scheduled follow-ups, the general condition and possible changes related to the appearance of a thrombotic event were recorded for each patient. In case of symptomatic thrombotic events during the follow-up, the FVIII and D-dimer results in the period of acute thrombosis were not included in the statistical analyses. Taking into account the stability of samples at −80 °C (up to 3 months), the analyses were performed in batches of at least 30 patient-samples with the mandatory normal and low abnormal controls for FVIII and control 1 (low) and control 2 (upper range) for D-dimer. The overall reproducibility median coefficient of variation% for FVIII:C was <11%. Coefficients of variation for D-dimer were 4.3% for control 1 and 2.2% for control 2.

Statistics

The Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, Illinois, United States) was used for statistical analysis. Distributions of measured FVIII and D-dimer values were analyzed. Nonparametric test (Mann–Whitney *U*-test) was used for relation of FVIII activity and D-dimer levels in each follow-up period following the COVID infection. For bivariate correlation analysis of FVIII activity and D-dimer levels (each measured after first, third, and sixth months post–COVID infection), the Spearman tests were used, and results are shown as correlation factor R-square (R^2). Continuous values (FVIII, D-Dimer, age, BMI) were represented as median value with interquartile range. The probability (*p*-value) of less than 0.05 was considered as statistically significant, except for the Spearman test of correlations where *p*-value of less than 0.01 was considered statistically significant.

Results

In total, 115 COVID patients, 86 females and 29 males, median age of 48 years, were included in this prospective study. Clinical characteristics of the study participants obtained results of hemostatic parameters measured during 1, 3, and 6 months post-COVID, data related to thrombotic complications in the post-COVID period, and other severe post-COVID complications such as pericarditis, pulmonary fibrosis, and the new or worsening pre-existing cardiac diseases are presented in ►Table 1.

Assessment of Changes in FVIII Activity and D-Dimer Levels during Follow-up for the Whole Study Group

Factor VIII activity and D-dimer levels during post-COVID phase are shown (►Fig. 1A, B). The highest activity of FVIII and D-dimer levels were observed during the first month after COVID infection. However, in the subsequent measurement at 3 and 6 months post-COVID infection, a decreasing trend was recorded with the same pattern for both FVIII activity and D-dimer levels. Statistically significant differences were observed between all measurements (except between third and sixth months) in relation to both hemostatic markers, with significantly higher number of patients with elevated D-dimer levels outlier of maximum (►Fig. 1B).

Assessment of Changes in FVIII Activity and D-Dimer Levels during Follow-up in Relation to the Patient's Age

During the first month post-COVID, equal number of patients had high FVIII activity regardless of age, with 63% younger versus 68% older patients, $p = 0.735$. In subsequent measurements, statistically significant difference was observed, considering that 3 months after COVID high FVIII was observed in 44% younger versus 63% older patients ($p = 0.05$) and 30% younger versus 57% older patients ($p = 0.008$) at the 6-month follow-up (►Fig. 2A).

Within 1 and 3 months of COVID infection, an equal number of patients had an elevated D-dimer level (64% younger vs. 63% older, $p = 0.919$, and 39 vs. 46%, $p = 0.571$, respectively). However, 6 months after COVID infection, 26% of younger patients compared with 46% of older patients had elevated D-dimer levels, $p = 0.04$ (►Fig. 2B).

Assessment of Changes in FVIII Activity and D-Dimer Levels during Follow-up in Relation to the Clinical Presentation of COVID Infection

During the post-COVID assessments, a higher number of patients with moderate/severe COVID infection had a high FVIII activity, with a statistically significant difference compared with those with mild presentation observed only in the 6-month follow-up (32% mild vs. 53% moderate/severe, $p = 0.041$; ►Fig. 3A). In case of D-dimer, an equal number of patients had an elevated D-dimer level across all follow-up measurements (61% mild vs. 66% moderate/severe, $p = 0.793$, at 1 month; 42 vs. 43%, $p = 0.855$, at 3 months; and 32 vs. 38, $p = 0.646$, at 6 months (►Fig. 3B).

Assessment of Correlation between the FVIII Activity and D-Dimer Levels and Occurrence of Thrombotic Events

The dynamics of changes in FVIII activity are positively correlated with the dynamics of changes in D-dimer levels and were observed in all measurement during follow-up period (►Table 2).

In total, 25 (21.6%) of COVID patients developed thrombotic events, with equal number of patients developing

Table 1 Clinical characteristics of COVID patients

Age, median (IQR)	48 (20.5)
Sex, F/M	86/29
BMI, median (IQR)	25.34 (6.7)
Overweight/Obese	43/19
Comorbid disease, *n* (%)	51 (44)
Previous thrombosis	13 (11.3)
COVID treatment, home/hospital	68/47
Clinical presentation of COVID infection,[a] *n* (%)	
Asymptomatic	6 (5)
Mild	62 (53.5)
Hospitalized moderate	44 (37.9)
Hospitalized severe	3 (2.6)
FVIII (IU/mL)	Median (IQR)
1 mo	1.85 (0.87)
3 mo	1.58 (1.1)
6 mo	1.47 (1.0)
D-dimer (mg/L)	Median (IQR)
1 mo	0.75 (0.92)
3 mo	0.45 (0.53)
6 mo	0.4 (0.37)
COVID-related thrombosis (total), *n* (%)	25 (21.6)
During acute COVID	12
Thrombosis localization	
DVT	4
PE	2
DVT/PE	3
UT	2
Arterial	1
Serious post-COVID complications	
Thrombosis after COVID	13
Thrombosis localization	
DVT	4
PE	4
Superficial	2
UT	3
Time to thrombosis (month), average (range)	2.4 (1–5)
Pericarditis	3
Pulmonary fibrosis	2
Cardiac diseases worsening[b]	5
The new cardiac diseases[b]	4

Abbreviations: BMI, body mass index; DVT, deep venous thrombosis; F/M, female/male; FVIII, factor VIII; IQR, interquartile range; PE, pulmonary embolism; UT, unusual thrombosis.
[a]Clinical presentation of COVID infection in relation to the WHO clinical progression scale[15]; cutoff (FVIII 1.5 IU/mL, D-dimer 0.5 mg/L).
[b]Hypertension, atrial fibrillation, congestive heart failure.

thrombosis, regardless of the acute or the post-COVID period (12 vs. 13). Based on the national protocol for COVID treatment, all hospitalized patients with a severe form of COVID-19 infection received a high prophylactic dose of low-molecular-weight heparin (LMWH), enoxaparin 40 mg subcutaneously twice a day, while patients with moderate disease received enoxaparin 40 mg once daily. Patients with mild clinical picture were advised to take aspirin, while those who were asymptomatic were advised to take only supplements. From 25 patients who developed thrombotic events, 1 was recorded as arterial thrombosis of the upper limb during acute COVID infection, which required emergency embolectomy. The remaining thrombotic events were venous thrombosis, mostly presented as DVT in 12, isolated PE in 5, DVT/PE in 3, and unusual thrombosis (abdominal and upper limb) in 4 patients. Two patients presented with asymptomatic DVT, with sudden elevated D-dimer level, which required the use of additional imaging diagnostics to confirm or exclude thrombotic event.

In the post-COVID period, 13 patients developed a thrombotic event, with 8 of these patients treated at home during COVID infection and did not receive any prophylaxis. The remaining five individuals who were hospitalized received LMWH prophylaxis during the hospitalization period, and very shortly after. The average time to thrombotic events was 2.4 months, with the first thrombotic event recorded 1 month post-COVID in three patients, 2 months post-COVID in five patients, 3 months post-COVID in three patients, and 4 and 5 months post-COVID in two patients.

Patients with thrombosis, regardless of the acute or the post-COVID period of thrombosis development, had significantly higher FVIII activity compared with those who did not develop thrombosis, during all follow-up periods. On the other hand, D-dimer levels were higher in patients with thrombosis, compared with those who did not develop thrombosis only at the time of the first follow-up (1 month; ►**Fig. 4A, B**).

Discussion

To our knowledge, this is the largest prospective study focusing on changes in FVIII activity and D-dimer levels in the post-COVID phase. To date, published studies have focused on the assessment of changes in the hemostatic system within the acute COVID infection and during hospitalization.[5–10] Our study included all patients regardless of hospital or home treatment, who were followed up during the period of 6 months post-resolution of COVID infection. However, it should be emphasized that a recently published similar study focused on the pediatric population. Specifically, this investigation of coagulation profile among children affected with COVID infection, 8 and 12 weeks post-COVID, showed that a higher proportion of children with the post-COVID condition, and specifically those with a more severe spectrum, had abnormal D-dimer levels compared with children who fully recovered.[18]

In our study, we recorded all objectively diagnosed severe complications in the post-COVID phase, including thrombotic complications, pericarditis, pulmonary fibrosis, and the new or worsening of preexisting cardiac diseases, including

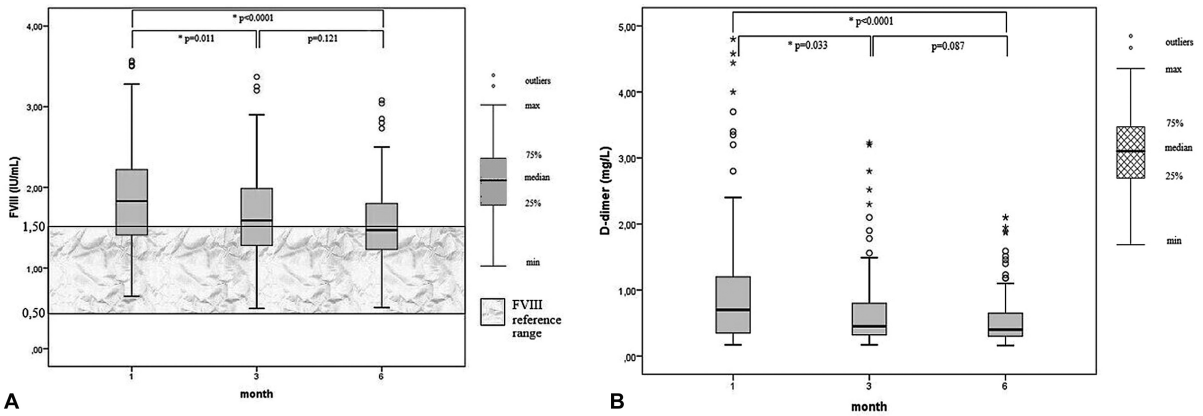

Fig. 1 Factor VIII activity and D-dimer levels during post-COVID follow-up. (**A**) Factor VIII activity (IU/mL); (**B**) D-dimer level (mg/L). *Statistically significant differences; month, months after COVID; boxplot schema represented by median value, max and min values, and outliers.

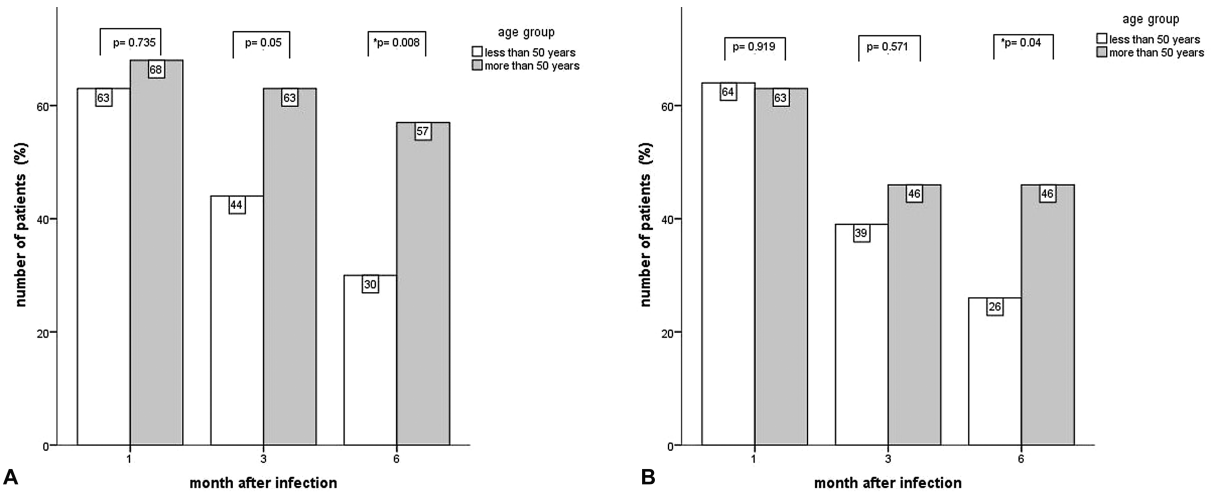

Fig. 2 Number of COVID patients with high FVIII activity (**A**) and D-dimer levels (**B**) in relation to the age (cutoff age value 50). Numbers of patients are presented as percentage of total number of patients with high FVIII or D-dimer. *Statistically significant differences.

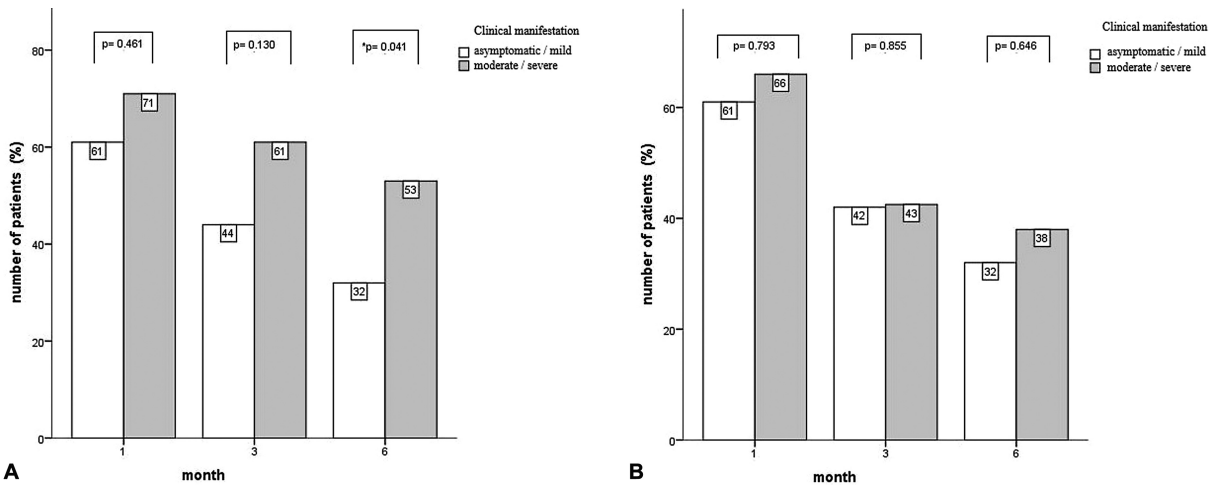

Fig. 3 Number of COVID patients with high FVIII activity (**A**) and D-dimer levels (**B**) in relation to the clinical presentation of COVID infection (asymptomatic/mild versus moderate/severe). Number of patients presented as percentage of total number of patients with high FVIII or D-dimer. *Statistically significant differences.

Table 2 Correlation of factor VIII and D-dimer

			FVIII			D-dimer		
			m1	m3	m6	m1	m3	m6
FVIII	m1	R^2		0.489	0.328	0.132	0.082	0.050
		p		**<0.0001**	**<0.0001**	**<0.0001**	**0.002**	**0.019**
	m3	R^2	0.489		0.733	0.102	0.158	0.162
		p	**<0.0001**		**<0.0001**	**0.001**	**<0.0001**	**<0.0001**
	m6	R^2	0.328	0.733		0.099	0.144	0.157
		p	**<0.0001**	**<0.0001**		**0.002**	**<0.0001**	**<0.0001**
D-dimer	m1	R^2	0.132	0.102	0.099		0.615	0.440
		p	**<0.0001**	**0.001**	**0.002**		**<0.0001**	**<0.0001**
	m3	R^2	0.082	0.158	0.144	0.615		0.681
		p	**0.002**	**<0.0001**	**<0.0001**	**<0.0001**		**<0.0001**
	m6	R^2	0.050	0.162	0.157	0.440	0.681	
		p	**0.019**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	

Abbreviations: FVIII, factor VIII; R^2, R-square.

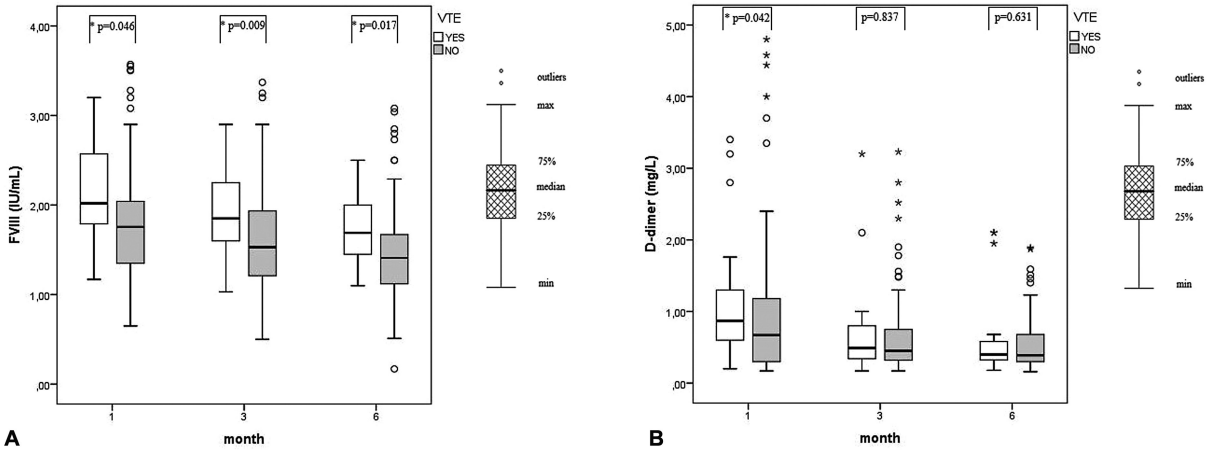

Fig. 4 FVIII activity (**A**) and D-dimer levels (**B**) among COVID patients with and without VTE occurrence. *Statistically significant differences; month, months after COVID; boxplot schema represented by median value, max and min values, and outliers.

hypertension, atrial fibrillation, and congestive heart failure. Among patients who developed pericarditis and pulmonary fibrosis, a markedly elevated level of FVIII was maintained, in all measurements, and this increase correlates with increased D-dimer levels. In the group of patients with new or worsening of preexisting cardiac diseases, we observed the same pattern of changes in FVIII and D-dimer as was recorded in patients without severe post-COVID complications.

The main finding of our study is that the highest FVIII activity and D-dimer levels were recorded during the first month following COVID infection, which then gradually decreased and reached the lowest value 6 months after infection. However, in the group of patients with moderate/severe clinical presentation and those older than 50 years, a higher number of patients maintained elevated FVIII activity and D-dimer levels during follow-up. Considering the correlation between FVIII activity and D-dimer levels, increased FVIII activity could consequently lead to the maintenance of elevated D-dimer values. This was in fact observed in our patient population, with 57% of patients older than 50 years having elevated FVIII activity, while 46% of those patients had elevated D-dimer levels. In contrast, in younger patients, an increase in FVIII activity was observed in 30% of patients, while D-dimer levels were elevated in 26% of the same patients.

A higher number of patients with a moderate/severe clinical picture (53%) maintain high FVIII activity, contrary to 32% of those with mild clinical presentation. Subsequent measurement of D-dimer levels in both groups showed the same decreasing tendency.

Inflammation is likely the cause of elevated D-dimer levels during acute COVID infection and may also represent a sign of acute lung damage, where D-dimer levels track the severity of disease progression and inflammation.[3] Elevated values of D-dimers in the post-COVID phase in our patients should be

considered as part of hemostatic changes related to the increase in FVIII activity. Taking into consideration the role of FVIII in the hemostatic system and the established correlation with D-dimer levels in our subjects, we hypothesize that maintenance of elevated D-dimer levels correlated with the increase in FVIII activity, a factor that was strongly influenced by age, especially in patients who had D-dimer levels as outliers of maximum.

Mechanism underlying elevated FVIII activity is unclear but may involve sustained activation of the endothelium[19] and may explain the pronounced hypercoagulability that can be maintained several months after the patient becomes negative for the SARS-CoV-2 virus. Related to recently published study, COVID-recovered patients have a higher risk of VTE events compared with noninfected patients from the general population during the same follow-up period. Authors concluded that during the first months after COVID-19 infection, Hazard Ratio (HR) for DVT was 2.55 with a higher risk of incident PE with HR of 3.16.[20] The results of our study indicate an equal risk for the development of thrombosis both in the acute and in the post-COVID phase. Therefore, monitoring of FVIII could be a useful tool in assessing hypercoagulability and possible risk of thrombosis, especially in patients with specific clinical risk factors that predispose to thrombosis (e.g., the presence of thrombophilia, obesity, varicose veins, previous thromboembolism, malignancy diseases).[15]

Limitations of our study include a relatively small sample size, in addition to the selection bias present due to the significant difference between patients in relation to the clinical presentation of the COVID infection, and the type of the treatment. This could have impacted the results of investigated markers especially during the first month post-infection. Also, we did not have an age-matched control group that would be useful in interpreting the obtained results and differentiation from "normal" to age-related elevated FVIII and D-dimer levels. Despite the limitations, our study shows valuable data related to the patterns of changes in hemostatic markers among patients in the post-COVID phase.

Conclusion

Results from our study showed that after COVID infection, an increase in FVIII activity suggests a continued hypercoagulable state in the post-COVID period and correlates with elevated D-dimer levels. This increase in FVIII activity is more pronounced in patients with moderate/severe clinical picture and those older than 50 years.

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Conflict of interest

MK, MTB, MM, DB, BB and VI have no conflicts of interest BT: National research project funding: the Ministry of Education, Science and Technological Development, Serbia; Travel/accomodation support: COST (European Cooperation in Science and Technology)- CA15120.

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