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MARKERS OF PROTHROMBOTIC STATE OF PATIENTS RECOVERED AFTER COVID-19

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Background. *In recent period the attention of scientists and doctors was focused mainly on methods of COVID-19 treatment. However, clinical course of coronavirus disease strongly affects blood coagulation with the tendency for venous and arterial thrombosis, leading to long-term imbalance between coagulation and anticoagulation systems, which can cause serious danger for health of post-COVID-19 (PCD) patients.* ***Objective.*** *In our work we focused on the analysis of the molecular markers of hemostasis system activation in blood plasma of patients recovered after COVID-19.* ***Methods.*** *Blood plasma samples of 191 seropositive patients recovered from COVID-19 were analysed. The patients were divided into a high-risk group (HRG, n = 163) and a non-risk group (NRG, n = 28) according to WHO recommendations. Patients were examined in a recovery time scale of 1-30; 31-60 days and more than 2 months. Blood plasma samples of seronegative healthy volunteers were collected as the reference group (n = 19). The concentration of soluble fibrin (SF) and D-dimer was measured with sandwich ELISA, generation of activated protein C (PC) and prethrombin-1 (Pre-1) level with assay using specific chromogenic substrates, and fibrinogen concentration with spectrophotometric method after initiation of coagulation by Ancistron-H.* ***Results.*** *Concentration of fibrinogen, SF and Pre-1 were increased in a blood plasma of patients of NRG and HRG groups in comparison to the reference group. Increasing of fibrinogen and Pre-1 concentrations correlated with COVID-19 stage. The fibrinogen and SF concentrations remained high more than 2 months after recovery in HRG group and elevated after 2 months after recovery in NRG group. D-dimer and protein C levels were elevated in 8% and 11% of PCD patients respectively.* ***Conclusions.*** *Long-term prethrombotic state was more expressed in HRG group of PCD patients. Monitoring of the main coagulation markers can indicate the risk of intravascular thrombus formation in PCD patients. SF, Pre-1 and elevated fibrinogen concentrations were selected as useful thrombosis markers in PCD patients.*

K e y w o r d s: coagulation, thrombosis, COVID-19 patients, D-dimer, soluble fibrin, fibrinogen, protein C.

Coronavirus disease 2019 (COVID-19) strongly affects blood coagulation [1, 2]. The main complications of COVID-19 are thrombosis, pulmonary intravascular coagulopathy and disseminated intravascular coagulation [3-6]. Studies of COVID-19 patients demonstrate that elevated circulating D-dimer levels are associated with increased mortality rate. At the beginning of the pandemic, the determination of the level of D-dimer became the main parameter for assessing the risk of thrombosis [7]. Nevertheless, increasing D-dimer level occurs in both thrombosis and bleeding complications [8]. Such parameters of hemostasis are increasing fibrinogen and factor VIII levels [9, 10], manifestation of soluble fibrin monomer complexes [11] or prothrombin fragment F1+2 [12, 13]. These coagulation factors can be informative markers for the assessment of the hemostasis system state during COVID-19. Nevertheless, other parameters such as the international normalized ratio (INR), Activated

Partial Thromboplastin Time (APTT), platelet count/ aggregation level or protein C (PC) levels were not reported to have major diagnostic values [4, 8, 9, 14].

Thus, studying hemostasis disorders during COVID-19 are important for both patients' survival and for understanding of the mechanisms of interaction between coagulation and inflammation during this pathology.

In recent days the attention of scientists and doctors was focused mainly on methods of COVID-19 treatment. However such strong activation of coagulation that is observed during the pathology can lead to long-term imbalance between coagulation and anticoagulation systems, which can cause serious danger for health of post-COVID-19 (PCD) patients.

That is why we focused on the analysis of blood coagulation system of PCD patients. We selected soluble fibrin (SF), fibrinogen (FB), D-dimer, Protein C (PC) and prethrombin-1 (Pre-1) as the markers of activation of blood coagulation. These parameters of coagulation system were chosen as a direct result of processes in hemostasis system, that are highly sensitive to activation of blood coagulation system and reflect different directions of its action (Fig. 1).

Therefore, the aim of study was the analyzing of the molecular markers of hemostasis system activation in blood plasma of patients recovered after COVID-19. We compared selected parameters of PCD patient of two groups according to risk factors, according to time scale after recovery and in keeping with COVID-19 stages in high-risk group patients.

Materials and Methods

Cohorts. PCD patients (58 male and 133 female) signed the informed consent form and took part of the study. At the time of blood collection, patients recovered from COVID-19 and were seropositive and PCR-negative.

Laboratory confirmation of SARS-CoV-2 infection was performed at the Municipal noncommercial enterprise "Monastery city hospital"; Municipal Non-Commercial Enterprise "Husiatyn Communal District Hospital"; Municipal Non-Commercial Enterprise "Shumsk City Hospital"; Municipal Non-Commercial Enterprise "Ternopil Munici-

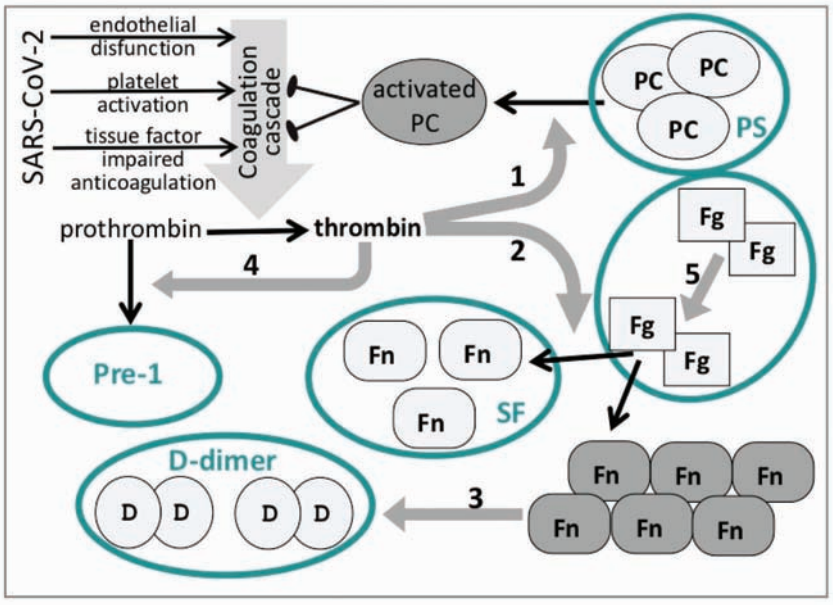

Fig. 1. Molecular markers of activation of coagulation cascade: protein C (PC); soluble fibrin (SF), D-dimer and prethrombin-1 (Pre1) fibrinogen. Pathophysiology of COVID-19 leads to the endothelial dysfunction, activation of platelets, exposition of tissue factor and impairment of anticoagulant system. These initiate coagulation cascade resulting in generation of thrombin. Further actions: 1 – thrombin activates PC and activated PC is being used, level of PC is decreasing; 2 – thrombin converts fibrinogen (FBg) to fibrin (FBn) and SF is formed; 3 – cross-linked fibrin clot is cleaved by fibrinolytic system and D-dimer appears as a result; 4 – thrombin converts prothrombin to Pre-1; 5 – inflammation causes the increase of fibrinogen concentration in bloodstream

pal City Hospital №2". Only laboratory-confirmed cases were included in the analysis.

Ethical committee approval. I. Horbachevsky TNMU (N59, 06/06/2020).

PCD patients were examined in a recovery time scale of 1-30; 31-60 days and more than 2 months. Patients were divided on non-risk group (NRG) n = 28; and high-risk group (HRG) n = 163. HRG patients had at least one of listed risk factors (Fig. 2): age over 65 years (n = 38), obesity with BMI > 25 (n = 132), diabetes mellitus (n = 19), cardiovascular disease (CVD, n = 83) including deep vein thrombosis, varicose veins, atherosclerosis, heart failure, arrhythmia, congenital heart disease, coronary heart disease, cardiomyopathy, multiple sclerosis, angina pectoris), respiratory diseases (RD, n = 18) including chronic bronchitis, bronchial asthma, diffuse pneumofibrosis, chronic obstructive pulmonary disease), rheumatoid arthritis (RA, n = 11) and high blood pressure (HBP, n = 81).

In HRG the coagulation parameters were compared separately in different COVID-19 Stages according to WHO classification [15]: mild, moderate, severe and critical. Healthy volunteers, seronegative reference group (RefG, n = 19) were used as reference group.

Because this was a comprehensive study involving multiple assays, not all patient plasma samples were analyzed in every test. Accordingly, the sample size (n) for each analysis is specified separately in the corresponding figure legend.

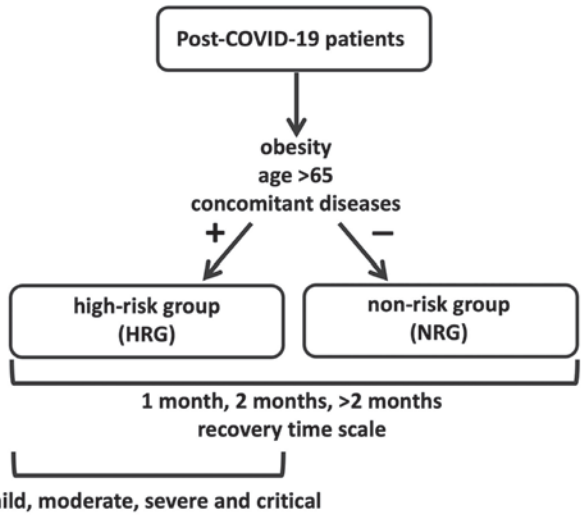

Fig. 2. Scheme of patients' division on groups and their analysis

Chemicals and proteins. Chromogenic substrates S2238 (H-D-Phe-Pip-Arg-pNA) and S2236 (p-Glu-Pro-Arg-pNa), thromboplastin and activator of protein C (PC) were purchased from (Siemens healthcare diagnostics products, Germany). Prothrombin activator (ecamulin) was purified from *Echis multisquamatis* venom according to the method of Solov'yev et al. [16]. Thrombin-like enzyme (Ancistron-H) was purified from the venom of *Agkistrodon halys halys* according to the method of Solov'yev et al. Monomeric fibrin desA was prepared from human fibrinogen as described in [17]. D-dimer was obtained by plasminolysis of cross-linked fibrin as described in [18]. Prethrombin-1 was obtained from prothrombin under the direct action of thrombin as it was described in [19].

Blood plasma. Citrated blood plasma samples were collected by I. Horbachevsky Ternopil Medical University, Ternopil, Ukraine. SARS-CoV-2 infection was diagnosed on the basis of the WHO guidance [15]. A confirmed case of COVID-19 was defined as a positive result on high-throughput sequencing or real-time polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens [20].

Protein C (PC) level. PC level was determined using the activator of PC (Siemens healthcare diagnostics products, Germany). The generation of activated PC was measured by chromogenic substrate assay using specific chromogenic substrate S2236 (p-Glu-Pro-Arg-pNa) [21]. The analysis was performed in 0.05 M Tris-HCl buffer pH 7.4, at 37°C. Chromogenic substrate concentration was 30 mM. The amount of p-nitroaniline that was generated from the chromogenic substrate under the action of PC was measured at 405-492 nm on a microtiter plate reader Multiscan EX (Thermo Fisher Scientific, Waltham, USA).

Results were presented as ratio of PC level in the blood plasma of patient to PC level in the blood plasma of healthy donor.

Fibrinogen. Fibrinogen concentration in the blood plasma was determined by the modified spectrophotometric method. Blood plasma (0.2 ml) and PBS (1.7 ml) were mixed in glass tubes. Coagulation was initiated by the addition of 0.1 ml of Ancistron-H (1 NIH/ml). The mixture was incubated for 30 min at 37°C. The fibrin clot was removed and redissolved in 5 ml of 1.5% acetic acid. The concentration of protein was measured using a spectrophotometer Optizen POP (Mecacys, Seongnam, South Korea) at 280-320 nm (ε = 1.5 $l \cdot g^{-1} \cdot cm^{-1}$) [22].

Soluble fibrin (SF). Soluble fibrin was detected using sandwich ELISA. Fibrin-specific monoclonal antibody I-3C was used as catch-antibody [23, 24]. Biotinilated monoclonal antibody II-4d that has epitope in NH_2-terminal fragment of γ-chain of D-region of fibrin(ogen) molecule was used as a tag-antibody [25]. As a substrate was used 0.03 % of 0.04 % o-phenylenediamine solution in 0.05 M potassium-phosphate buffer pH 6,0. Reaction was terminated by the addition of 0.1 ml of 2 M H_2SO_4. Optical density of the solutions determined at 492 nm using multiplate reader RT 2100C (Rayto, China). For the calibration curve for quantitative analysis we used samples of fibrin desA. Normal parameters of SF content in the developed test were calculated as 3 mkg/m.

D-dimer. D-dimer was detected using sandwich ELISA as described above for soluble fibrin with following exception: biotinilated D-dimer-specific monoclonal antibody III-3B that has epitope in NH2-terminal fragment of Bβ-chain of D-region of fibrin(ogen) molecule was used as the catch-agent. Concentration of D-dimer was measured using the calibration curve obtained for purified D-dimer. Normal parameters of D-dimer content in the developed test were calculated as 100 ng/ml [26].

Prethrombin-1 (Pre-1). The level of Pre-1 in blood plasma was measured using activators of prothrombin: thromboplastin as well as ecamulin. Ecamulin (prothrombin activator from *Echis multisqumatis* venom) is an enzyme that activates prothrombin, descarboxy-prothrombin and prethrombin-1 [27]. It's application makes possible to determine the total prothrombin level. On the other hand thromboplastin acts through the tissue factor pathway of coagulation and activates only functionally active carboxylated and uncleaved forms of prothrombin as it is in the "prothrombin time" test. Thrombin generation in both tests was measured by chromogenic substrate assay using thrombin-specific S2238 (H-D-Phe-Pip-Arg-pNA) [28].

Ecamulin and prothrombin indexes by the formulas. Results of prothrombin and ecamulin tests were presented as ecamulin and prothrombin indexes by the formulas (1), (2).

$$EI = An/Ap, \quad (1)$$

where EI – ecamulin index; An – the thrombin activity of a healthy control donor blood plasma in ecamulin test; Ap – the thrombin activity of a patient blood plasma in ecamulin test.

$$PI = An/Ap, \quad (2)$$

where PI – prothrombin index; An – the thrombin activity of a healthy control donor blood plasma in prothrombin test; Ap – the thrombin activity of a patient blood plasma in prothrombin test.

Calculation of the concentration of Pre-1 was performed according by the formula obtained from the calibration curve with the use of purified prethrombin-1 (3).

$$C = \frac{EI/PI - 0.9919}{0.141} - 0.1, \quad (3)$$

where C – Pre-1 concentration, μg/ml; EI – ecamulin index; PI – prothrombin index.

Statistical analysis. Data are presented as median with interquartile range. The box plots allowed us to assess whether the data distribution was normal. In the vast majority of groups, the data were not normally distributed; therefore, nonparametric statistical methods were used. Kruskal-Wallis Test was used to comparing groups. If a series of groups had differences in the Kruskal-Wallis Test, then for further detailed analysis they were used the Wilcoxon-Mann-Whitney (WMW) test using online calculator provided by Social Science Statistics (https://www.socscistatistics.com/). Data were considered significant when $P < 0.05$. Statistical analysis was performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). All assays were performed in a series of at least three replicates.

Results

Fibrinogen. Fibrinogen is one of the proteins of the acute phase of inflammation so it indicates the residual inflammatory process and also can be assumed as the risk-factor of intravascular thrombus formation [29].

The fibrinogen level was significantly increased in blood plasma of patients of NRG and HRG groups in comparison to the RefG. In blood plasma of HRG patients fibrinogen level was significantly higher than in NRG in 1.5 times (Fig. 3, *A*). In blood plasma of HRG patients fibrinogen level remains elevated for more than 2 months after recovery (Fig. 3, *B*). In blood plasma of NRG patients fibrinogen concentration was normal during the 1st month after recovery but unexpectedly grew up after 2nd month (Fig. 3, *B*).

The concentration of fibrinogen in blood plasma of HRG patients correlated with disease stage. In severe and critical patients it was more than 2 times elevated in comparison to the RefG (Fig. 4).

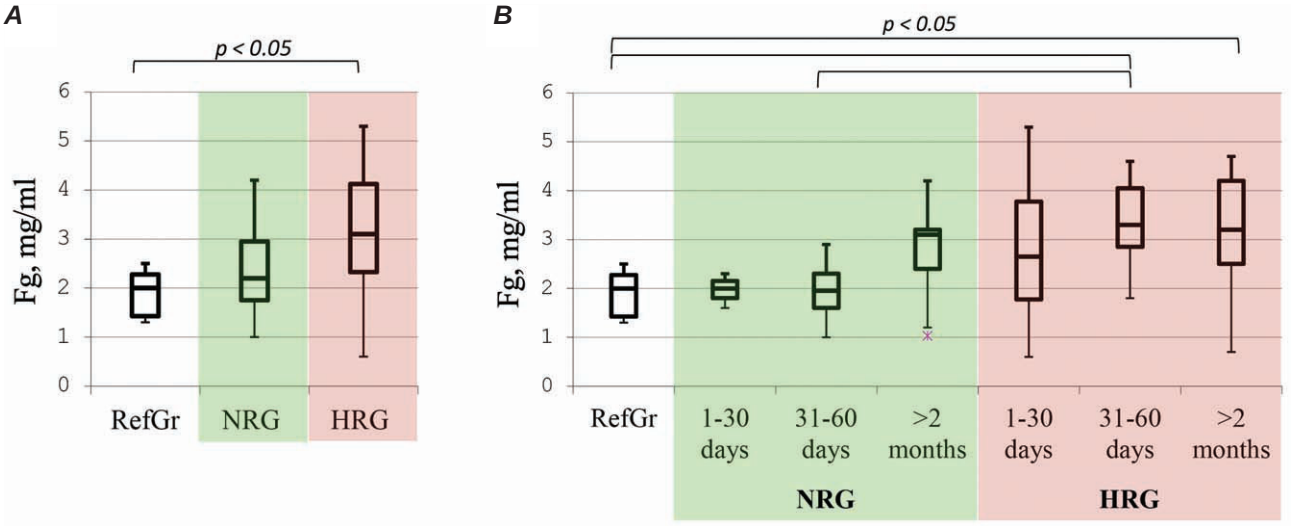

*Fig. 3. The fibrinogen level (Fg) in reference group (RefG, n = 19), non-risk group (NRG, n = 12) and high-risk group (HRG, n = 68) in general (**A**) and during recovery in NRG and HRG (**B**, 1 month, 2 month, >2 month). *P < 0.05 comparing to the RefG according to Wilcoxon-Mann-Whitney (WMW) test*

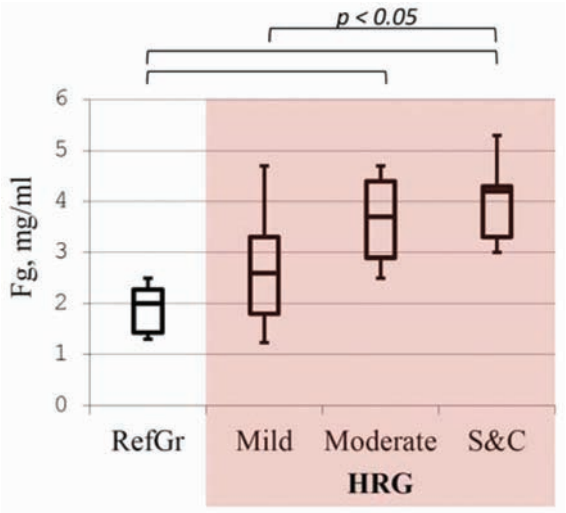

Fig. 4. The fibrinogen level (Fg) in high-risk group (HRG) according to COVID-19 stages (mild n = 38, moderate n = 13, S&C n = 14). S&C – severe and critical

Soluble fibrin. During the conversion of fibrinogen to fibrin, thrombin mediates the cleavage of a pair of fibrinopeptide A producing fibrin monomer, which form not only fibrin clot, but also soluble complexes with fibrinogen molecules [30]. SF is a direct result of thrombin action so it is sensitive and specific marker of intravascular coagulation in particular during COVID-19 [11, 31].

SF was detected in blood plasma of both groups (HRG, NRG) of patients (Fig. 5, *A*), it's concentration was significantly higher than in blood plasma of RefG patients. SF concentration remained high for a long time after the recovery in blood plasma of HRG patients (Fig. 5, *B*). In the case of NRG patients, SF concentration was close to the reference range during the 1st month after recovery, but was significantly elevated in 3.3 times after the 2nd month (Fig. 5, *B*).

Elevation of SF concentration in blood plasma of HRG patients was independent on COVID-19 stages (Fig. 6). It should be noted that 94% of patients with respiratory diseases and 96% of patients with heart disease had elevated concentrations of SF.

Prethrombin-1. Pre-1 appears as a result of down-regulation of procoagulant potential of blood coagulation system by prothrombin autolysis by thrombin. It indicates the appearance of active thrombin into the bloodstream [27, 32]. The Pre-1 concentration was shown to be high in blood plasma of both NRG and HRG groups of patients (Fig. 7, *A*).

We demonstrated a tendency of Pre-1 concentration dropping down after 2 months after recovery in blood plasma of both HRG and NRG patients. However, in blood plasma of NRG patients it still was high in 2 months after the recovery (Fig. 7, *B*). In blood plasma of HRG patients Pre-1 level was increased accordingly to COVID-19 stages and in blood plasma of severe and critical group patients was 6.6 times higher comparatively to the patients of mild group (Fig. 8).

D-dimer. D-dimer is a product of lysis of cross-linked fibrin clot by plasmin so it indicates work

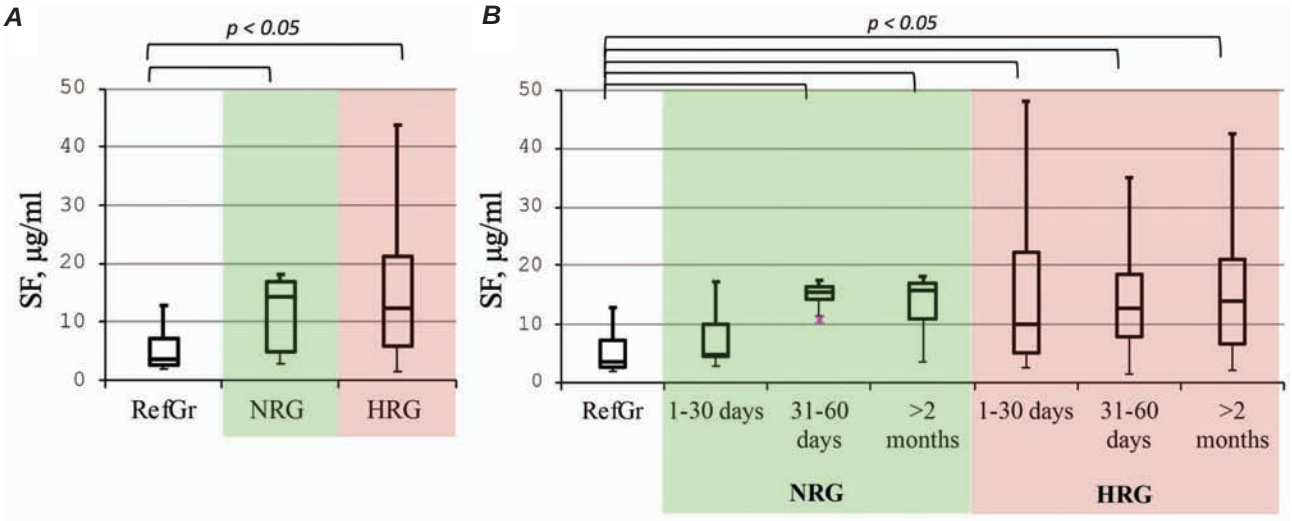

*Fig 5. The soluble fibrin (SF) level in reference group (RefG, n = 19), non-risk group (NRG, n = 28) and high-risk group (HRG, n=161) in general (**A**) and during recovery in NRG and HRG (**B**, 1 month, 2 month, >2 month). *P < 0.05 comparing to the RefG according to Wilcoxon-Mann-Whitney (WMW) test*

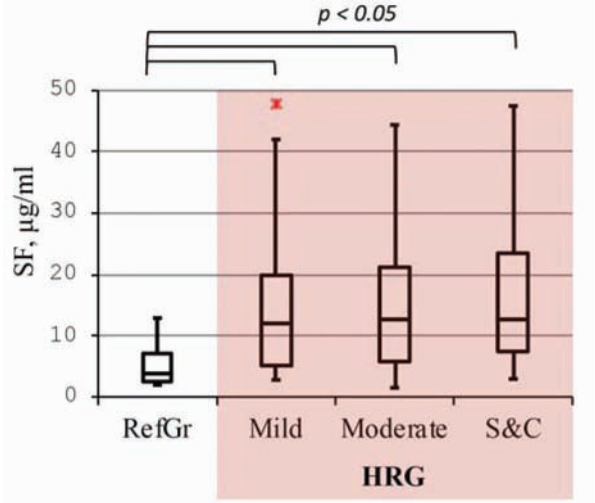

Fig 6. The soluble fibrin (SF) level in high-risk group (HRG) according to COVID-19 stages. (mild n = 56, moderate n = 67, S&C n = 38). S&C – severe and critical

of both coagulation and fibrinolysis. COVID-19 influences each of these systems, so D-dimer level may reflect the hemostasis response to SARS-CoV-2 infection [33, 34].

We did not find significant increase of D-dimer concentration in blood plasma of PCD patient. However, 15% of HRG patients had accumulation of D-dimer and it's concentration reached 1335 ng/ml. In particular high D-dimer level was found in 11 % and 27 % of patients with heart and respiratory diseases respectively. However, only 2 of 28 patients in NRG possessed elevated concentration of D-dimer.

Protein C. PC has anticoagulant action that is implemented mainly by factor Va and VIIIa cleavage. Also the strong anti-inflammatory action of PC occurs mainly through it's action on protease-activated receptor 1. That is why level of PC in blood plasma in the case acute inflammation is usually lower than normal [35].

Protein C level was decreased in blood plasma of 11% PCD patients in particular in 20% of NRG (during the second and third months after recovery) and in 9% of HRG patients (regardless of time after recovery). In blood plasma of HRG patients it's level significantly normalized after more than 2 months after recovery.

Discussion

We compared state of coagulation system of patients of NRG and HRG groups. In blood plasma of HRG patients fibrinogen concentration was significantly elevated and tendency to increasing of SF amount was also observed. The concentration of Pre-1 was high in both NRG and HRG groups. Number of patients with elevated level of D-dimer and decreased level of PC was slightly bigger in HRG. These findings indicated that pathological activation of blood coagulation system was typical for PCD patients of HRG and in a lesser degree for NRG patients.

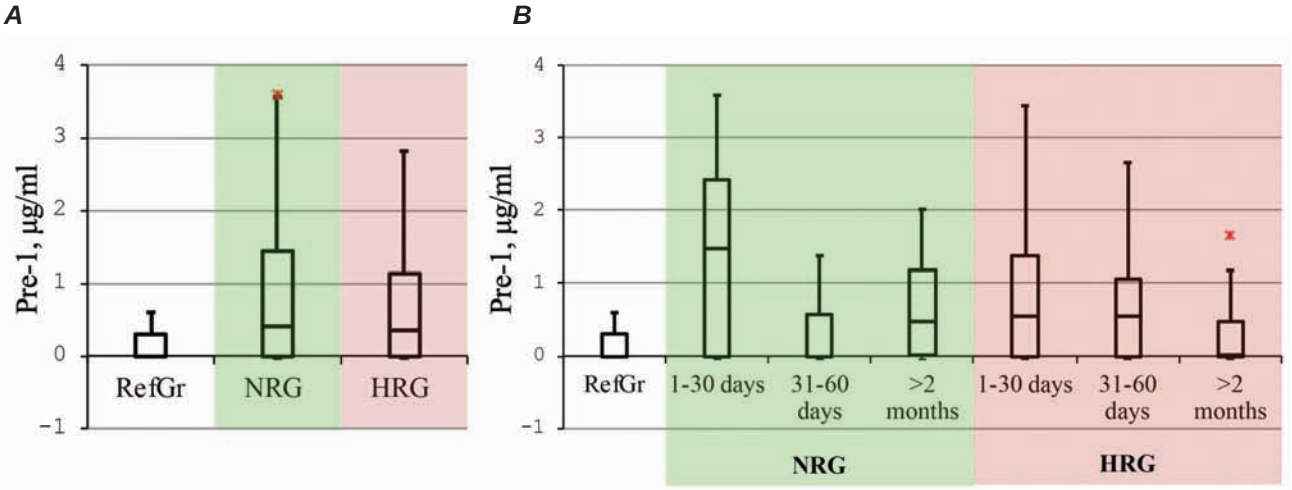

*Fig 7. The Prethrombin-1 (Pre-1) level in reference group (RefG, n = 19), non-risk group (NRG, n = 20) and high-risk group (HRG, n = 93) in general (**A**) and during recovery in NRG and HRG (**B**, 1 month, 2 month, >2 month)*

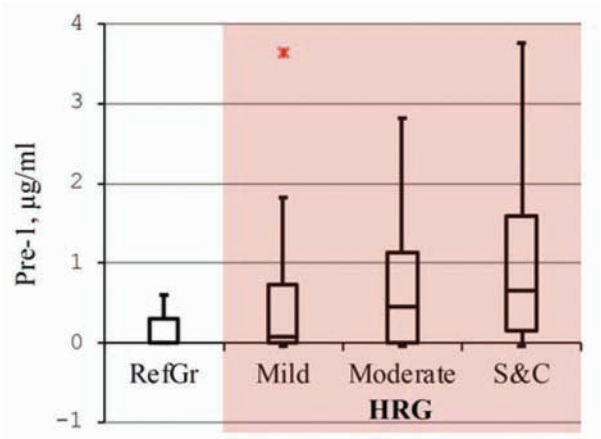

Fig 8. The Prethrombin-1 (Pre-1) level in high-risk group (HRG) according to COVID-19. (mild n = 44, moderate n = 30, S&C n = 19). S&C – severe and critical

Both SF and fibrinogen concentrations stay high during all time of measurement in HRG (more than 2 months). This indicated the long-lasting imbalance in hemostasis after the recovery from COVID-19.

As for NRG patients we observed normal fibrinogen concentration and moderate SF level on the 1st month after the recovery. However both of these parameters were significantly elevated after 2 months after recovery in NRG group. It indicated long-term effect of COVID-19 on blood coagulation system and can be assumed as the predisposition to intravascular thrombus formation.

At the same time, Pre-1 and PC levels had a tendency to normalization after 2 months after recovery in both NRG and HRG patients that can be assumed as slow but confident sign of stabilization of hemostasis system state.

On the background of the tendency to hypercoagulation, we did not find a significant increasing of the level of D-dimer in blood plasma of PCD patients. Taking into account that D-dimer is a product of plasmin hydrolysis of cross-linked clot. The finding can be a result of the altered fibrinolysis that was reported for COVID-19 [34, 36, 37]. This makes necessary to control hemostasis state of patients after recovery from COVID-19 to prevent thrombosis complications.

The data clearly demonstrated that the severity of past COVID-19 influenced the state of blood coagulation system of HRG patients. We showed acceleration of fibrinogen and Pre-1 concentrations with disease stages of PCD patients of HRG. As far as the fibrinogen is a protein of the acute phase of inflammation it's accumulation was obviously connected to the severity of COVID-induced inflammatory process. Pre-1, as a product of thrombin hyperactivity, indicated increased thrombin formation with increasing of disease severity [38, 39].

The results showed that activation of blood coagulation system was observed for patients with COVID-19 not only during infection and rehabilitation, but remained for a long period after recovery. This pathological activation was more expressed in blood plasma of patients with risk factors and se-

vere course of earlier COVID-19. We defined high concentrations of fibrinogen, SF and Pre-1 as the main markers of thrombosis risk in PCD patients. D-dimer level was significantly increased in some of studied samples that can be assumed as the additional parameter for the evaluation of the risk of intravascular thrombus formation.

Limitations of the study. Several limitations of this study should be acknowledged. First, the study was observational and the assessment of patients at different recovery intervals did not allow us to establish individual longitudinal changes in hemostatic parameters. Therefore, the persistence of coagulation abnormalities over time should be interpreted with caution. Second, information regarding concomitant medications, particularly anticoagulant and antiplatelet therapy, as well as other factors potentially affecting hemostasis, was not considered when interpreting the observed changes in coagulation markers. Third, the study focused primarily on laboratory markers of coagulation and did not include systematic assessment of clinically confirmed venous or arterial thrombotic events.

Conclusions. Low risk patients with no preexisting comorbidities had less obvious pathological activation of blood coagulation system during first months after recovery; however, after two months and more we observed the increasing of fibrinogen and SF concentrations. During the follow up of PCD patients, the delayed thrombotic actions and the related factors should be part of the routine checkup of PCD patients.

We observed that the severity of COVID-19 directly influenced the state of blood coagulation system by increasing fibrinogen and Pre-1 concentrations. Hypercoagulation state was common for PCD who had additional risk factors (elderly or obese) and pre-existing comorbidities such as metabolic, respiratory, cardiovascular. Patients with risk-factors acquired increased concentrations of fibrinogen and SF that were observed during two months after recovery that suggests long-lasting prethrombotic state.

We concluded that it is obligatory to monitor the main coagulation markers that can indicate the risk of the intravascular thrombus formation in PCD patients.

Author contributions. Korda M.M. and Komisarenko S.V. conceived the study. Ivankiv Ya.I., Paliy S.M. and Voitovych A.I. collected blood plasma samples and patient information. Korolova D.S., Kostiuchenko O.P. and Chernyshenko T.M. developed the framework and determined hemostasis system parameters. Klymenko K.P. purified and obtained monoclonal antibodies. Shevchuk O.O., Chernyshenko V.O. and Platonova T.M. aided in the data analysis. Vari S.G. supervised the project. All authors discussed the results and contributed to the final manuscript.

Conflict of interest. The authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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МАРКЕРИ ПРОТРОМБОТИЧНОГО СТАНУ ПАЦІЄНТІВ, ЯКІ ОДУЖАЛИ ПІСЛЯ COVID-19

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Вступ. Останнім часом увага вчених та лікарів була зосереджена переважно на методах лікування COVID-19. Однак клінічний перебіг коронавірусної хвороби сильно впливає на згортання крові з тенденцією до венозного та артеріального тромбозу, що призводить до тривалого дисбалансу між системами згортання

та антизгортання, що може становити серйозну загрозу для здоров'я пацієнтів після COVID-19 (PCD). **Мета.** У нашій роботі ми зосередилися на аналізі молекулярних маркерів активації системи гемостазу в плазмі крові пацієнтів, які одужали після COVID-19. **Методи.** Були проаналізовані зразки плазми крові 191 серопозитивних пацієнтів, які одужали від COVID-19. Пацієнти були розділені на групу високого ризику (HRG, $n = 163$) та групу без ризику (NRG, $n = 28$) відповідно до рекомендацій ВООЗ. Пацієнтів обстежували за шкалою часу одужання 1-30; 31-60 днів та більше 2 місяців. У контрольній групі (n = 19) були зібрані зразки плазми крові серонегативних здорових добровольців. Концентрацію розчинного фібрину (SF) та D-димеру вимірювали за допомогою сендвіч-ELISA, генерацію активованого протеїну С (PC) та рівень претромбіну-1 (Pre-1) – за допомогою аналізу зі специфічними хромогенними субстратами, а концентрацію фібриногену – спектрофотометричним методом після ініціювання коагуляції за допомогою Ancistron-H. **Результати.** Концентрація фібриногену, SF та Pre-1 була підвищена у плазмі крові пацієнтів груп NRG та HRG порівняно з контрольною групою. Збільшення концентрацій фібриногену та Pre-1 корелювало зі стадією COVID-19. Концентрації фібриногену та SF залишалися високими більше 2 місяців після одужання в групі HRG та підвищеними через 2 місяці після одужання в групі NRG. Рівні D-димеру та протеїну С були підвищені у 8 та 11% пацієнтів з PCD відповідно. **Висновки.** Тривалий претромботичний стан був більш вираженим у групі HRG пацієнтів з PCD. Моніторинг основних маркерів коагуляції може вказувати на ризик утворення внутрішньосудинних тромбів у пацієнтів з PCD. SF, Pre-1 та підвищені концентрації фібриногену були обрані як корисні маркери тромбозу у пацієнтів з PCD.

Ключові слова: коагуляція, тромбоз, пацієнти з COVID-19, D-димер, розчинний фібрин, фібриноген, протеїн С.

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