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Original article

Characteristics of the Hemostasis Mechanism in Patients with Sars-Cov-2 Viral Infection

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SUMMARY

Introduction/Aim. During the SARS-CoV-2 pandemic, there was a significant number of cases accompanied by thrombosis. The precise pathophysiological mechanism remains unclear. The importance of the fibrinolytic mechanism in maintaining physiological hemostasis led us to explore its potential contribution to COVID-19-induced thromboembolism. This study aimed to identify changes in the hemostasis at the time of admission of SARS-CoV-2-positive patients to the hospital and their influence on the disease outcome.

Methods. The presented prospective study included 60, rt-PCR-confirmed patients hospitalized in the Covid units of the Clinical Center of Vojvodina. Platelet number, platelet aggregability, aPTT, PT, fibrinogen, D-dimer, and Euglobulin Clot Lysis Time (ECLT) were determined from blood samples. Participants were classified as those with preserved and suppressed primary hemostasis, those with physiological and increased thrombin activity, those with preserved and decreased fibrinolytic activity, and those with positive and negative disease outcomes.

Results. Forty-four positive outcomes were observed (73.3%), while a negative outcome, including thromboembolic complications and death was present in 16 subjects (26.7%). Unconditional logistic regression revealed a mild negative influence of all investigated parameters on the disease outcome. For ECLT, OR was 1.084 with 95%CI 1.023 – 1.160. The multivariate regression model showed that of all the investigated parameters, only ECLT was a significant predictor for negative outcome with a level of $p < 0.001$.

Conclusion. The global assessment of the fibrinolytic mechanism is a useful predictor of disease outcome in SARS-CoV-2-positive patients at the moment of their admission to hospital.

Keywords: **SARS-CoV-2, Covid-19, hemostasis, fibrinolysis**

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INTRODUCTION

During the SARS-CoV-2 pandemic, there was a significant number of cases accompanied by various degrees of hemostatic mechanism disorders, manifested as disseminated intravascular coagulation and venous and arterial thrombosis. The precise pathophysiological mechanism of thrombosis in Covid remains unclear but it has been debated that all three components of Virchow's triad, coupled with inflammation and inadequate immune response, play a significant role, leading to endothelial dysfunction, hypercoagulability, and disturbed blood flow (1, 2). To this very day, great importance was given to coagulation in the pathogenesis of venous thromboembolism, however, the fibrinolytic system was generally overlooked. Needless to say, the same happened in SARS-CoV-2 infection.

The importance of the fibrinolytic system and its role in maintaining physiological hemostasis led us to explore its potential contribution to the pathophysiology of COVID-19-induced thromboembolism. The fibrinolytic system represents an integral part of hemostasis with the main function in the enzymatic degradation of fibrin clots guided by local plasminogen conversion into plasmin. Researchers have shown that alveolar sacs represent a profibrinolytic area of the human organism in a physiological state. On the other hand, the greatly depleted activity of plasminogen activator was found in various pulmonary pathologies leading to fibrin accumulation (3). The same was observed in numerous inflammatory states (4, 5). It is debated that the rise of plasminogen activator inhibitor-1 (PAI-1) in lungs and plasma leads to fibrinolysis suppression. Knowing that the primary site of action for SARS-CoV-2 are lungs guided us to assess the fibrinolytic mechanism in patients infected by the pathogen and try to utilize this information to predict the outcome regarding the risk of thrombus formation. Also, some data show that the fibrinolytic mechanism's sole phenotype greatly affects hemostasis disorders in COVID-19 (6).

The aim of the paper was to predict the outcome of the disease utilizing basic hemostasis laboratory panels used in routine diagnostics of SARS-CoV-2 infected patients, their sole predictive value, and their combined effect on the outcome.

PATIENTS AND METHODS

General study design

Research was conducted as a prospective study which included 60, rt-PCR (real-time polymerase chain reaction)-confirmed, patients hospitalized in COVID units of the Clinical Center of Vojvodina, excluding patients in intensive care units. Patients aged 18 and older who gave written consent to participate in the study were included. Patients younger than 18 years, cases non-confirmed by rt-PCR, patients with a previous medical history of thromboembolism and active malignancy, and patients using anticoagulant therapy were excluded from the research (Figure 1). Samples were collected at the moment of hospitalization, before any therapeutic or invasive diagnostic action.

Data were received from patients' medical history and results of analyses of specimens of the whole blood and citrate plasma. All patients gave their consent for the use of their medical records in this research. Also, the research was approved by the Ethics Committee of the Clinical Centre of Vojvodina.

Methods

Platelet number analysis was conducted on a Sysmex automated hematology analyzer from a whole blood specimen with EDTA as an anticoagulant. Platelet aggregability testing was conducted on a multiplate analyzer that uses impedance aggregometry. A whole blood specimen with lithium heparin as an anticoagulant was used for the determination of basal platelet aggregability by using the TRAP (thrombin receptor activating peptide) test.

Coagulation testing was performed from the samples of citrated plasma on a Siemens BCS-XP analyzer, including activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, and D-dimer determination.

For the assessment of the global functionality of the fibrinolytic mechanism, we used the euglobulin clot lysis time test (ECLT), according to Mc Farlane and Pilling (7). This method was based on the initial dilution of citrate plasma with distilled water, and further acidification of plasma with an acetic acid solution, which led to precipitation of the

euglobulin fraction of plasma. The precipitate obtained was resuspended in borate buffer by the addition of 0.025 M $CaCl_2$ solution until coagulation, after which the coagulum was incubated in a water bath at 37 °C, and lysis time in minutes was recorded.

Data analysis and statistics

According to the results of performed laboratory analyses, the patients were classified as follows: 1. Based on the assessment of primary hemostasis functionality: in subjects with preserved and suppressed primary hemostasis functionality. 2. Based on D-dimer values in subjects with physiological or insignificantly elevated levels of thrombin activity stimulation (D-dimer values up to 1000 ng /ml) and subjects with significantly elevated thrombin activity levels (D-dimer values greater than 1000 ng/ml). 3. Based on the value of ECLT, in subjects with preserved (ECLT value up to 240 min.) and suppressed global functionality of the fibrinolytic mechanism (ECLT value longer than 240 min.).

Concerning the outcome of the disease, patients were classified into two groups: patients with cured SARS-CoV-2 infection without thrombotic complications (positive outcome group) and patients who had died and/or patients with arterial or venous thrombotic complications combined as negative outcome group.

The statistical program SPSS, version 24.0 was used for data entry and processing. For analysis and description of the structure of the research sample, descriptive statistical indicators were used: frequencies, percentages, medians, and others. The results were presented in the form of tables and figures. Within comparative statistics, to determine the differences between the examined groups, a Student's t-test for independent samples was used, or the appropriate non-parametric substitution of the Mann-Whitney test depending on the nature of the examined parameters and subgroup size. A value of $p < 0.05$ was considered statistically significant. Unconditional logistic regression was used to assess the impact of individual parameters on the risk of negative outcomes. Finally, to assess the mutual impact of the observed clinical parameters on the risk of negative outcome, multivariable regression analysis was conducted.

RESULTS

The selection of patients is presented in Figure 1. In the group of respondents, there were 36 males (60%) and 24 females (40%). The average age of respondents was 65 years, with the youngest respondent being 32, while the oldest respondent was 96 years old. Of the total subjects, 4 (6.7%) were diagnosed with symptomatic deep vein thrombosis or pulmonary thromboembolism, while death occurred in 12 patients, which is 20% of the total subjects. By grouping the subjects in terms of treatment outcomes, 44 positive outcomes were observed (73.3%), while a negative outcome, including thromboembolic complications and death, was present in 16 subjects (26.7%).

Primary hemostasis testing included an assessment of basal platelet aggregability performed by the TRAP test. Results of the test showed that 26 subjects in the positive outcome group vs 11 subjects in the negative outcome group (59.1% vs 68.8% $p < 0.001$) had increased platelet aggregability, with a statistically significant difference between the groups (Table 1).

Using non-conditional logistic regression, the assessment of the relative risk of a negative outcome in patients concerning platelets' aggregability examined at the time of admission to the hospital was

Table 1. *Differences regarding the investigated parameters of hemostasis between positive and negative outcome group*

Hemostasis parameter	*Positive outcome n (%)*	*Negative outcome n (%)*	*p*
Increased aggregability of thrombocytes	26 (59.1)	11 (68.8)	**p< 0.001**
Increased fibrinogen concentration	40 (90.9)	16 (100)	**p < 0.001**
Elevated D-dimer levels	15 (88.6)	39 (93.8)	**p < 0,001**
Suppressed fibrinolytic activity	15 (45.5)	20 (93.8)	**p < 0.001**

Table 2. *Risk of negative disease outcome by investigated hemostasis parameters*

Hemostasis parameters	Positive outcome n (%)	Negative outcome n (%)	Odds ratio* **(95% CI)**	Odds ratio† **(95% CI)**
Physiologic aggregability of thrombocytes	18 (40.9)	5 (31.1)	1.0 (Reference)	1.0 (Reference)
Suppressed aggregability of thrombocytes	26 (59.1%)	11 (68.8%)	1.00 (0.998-1.002)	1.075 (1.012-1.136)
Physiologic fibrinogen concentration	4 (9.1%)	0 (0%)	1.0 (Reference)	1.0 (Reference)
Hyperfibrinogenemia	40 (90.9%)	16 (100%)	1.927 (0.926-4.011)	1.093 (1.025-1.165)
Physiologic D-dimer level	5 (11.4%)	1 (6.3%)	1.0 (Reference)	1.0 (Reference)
Increased D-dimer level	39 (88.6%)	15 (93.8%)	1.00 (1.00-1.00)	1.067 (1.007-1.131)
Physiologic ECLT	24 (54.5%)	1 (6.3%)	1.0 (Reference)	1.0 (Reference)
Prolonged ECLT	20 (45.5%)	15 (93.8%)	1.015 (1.007-1.022)	1.084 (1.023-1.160)

*Crude OR; † OR adjusted for age and sex; ECLT- euglobulin clot lysis time

performed. The adjustment was made for the age and sex of the subjects, and the results indicate a mild influence of TRAP on negative outcome risk (OR 1.075; 95%CI 1.012 - 1.136) (Table 2). Observing the results of the risk assessment for the occurrence of a negative outcome of the disease concerning the examined parameter of primary hemostasis, we noted that increased aggregability of thrombocytes had an impact on the risk of the negative outcome in a way that it increased the risk by about 7%.

The concentration of D-dimer was elevated in 39 vs 15 patients (93.8% vs 88.6% $p < 0.001$) comparing negative and positive outcome groups, showing statistical significance for the measured parameter, as well as fibrinogen values observed in positive and negative outcome group, showing 16 vs 40 (100% vs 90.9% $p < 0.001$) patients with increased values, respectively (Table 1). Non-conditional logistic regression was also applied to the parameters of the coagulation mechanism to estimate their potential influence on a risk for negative outcome. The adjustment was made for the age and sex of the subjects, and the results indicate a mild influence of each examined parameter on the negative outcome of the disease, for fibrinogen (OR 1.093; 95%CI 1.025 - 1.165) and for D-dimer (OR 1.067; 95%CI 1.007 - 1.131) (Table 2).

The assessment of the fibrinolytic activity by using ECLT showed a statistically significant difference in the prevalence of pathological values between the examined groups with $p < 0.001$, where 20 patients in the negative outcome group vs 15 patients in the positive outcome group (93.8% vs 45.5%) had suppressed fibrinolytic activity (Table 1).

In the next phase of statistical processing, by using unconditional logistic regression, the assessment of the relative risk of a negative outcome in patients concerning the fibrinolytic mechanism examined at the time of admission to hospital was performed. Logistic regression was adjusted for the age and sex of the subjects. Given the uniformity of the study group in terms of criteria for inclusion in the study, which relate to factors that affect the functionality of the fibrinolytic mechanism, we did not have to adjust the analysis for other potential confounding factors. ECLT tested by non-conditional logistic regression showed a mild effect of this parameter on the risk for the negative outcome of the disease itself (OR 1.084; 95%CI 1.023-1.160) (Table2).

To examine the combined influence of individual examined parameters, their mutual interaction, effect, and contribution to the outcome of the disease, a multivariable model of logistic regression was used. Observing the model of a multivariate regression analysis, we can see that the model is a good predictor of the outcome (Adjusted R square 0.447) at a statistically significant level ($p < 0.001$), suggesting that the presented regression model can predict 44.7% variance of the outcome. The multivariate regression model showed that taking into account the contribution of each individual measured parameter of primary hemostasis, coagulation, and fibrinolytic mechanism, their interaction, and their effect on disease outcome, only ECLT was isolated as a statistically significant predictor for negative outcome with a level of $p < 0.001$ (Table 3).

Table 3. *Multivariant regression model for the influence of investigated parameters on the prediction of negative disease outcome*

Predictor	*p*	*95% CI Low*	*High*
Platelets	.774	-.013	.010
Fibrinogen	.435	-.058	.133
D-dimer	.913	.000	.000
TRAP	.848	.000	.000
ECLT	**.000**	.002	.003

ECLT- euglobulin clot lysis time

DISCUSSION

This study aimed to identify potential changes in the functionality of the hemostasis mechanism at the time of admission of SARS-CoV-2-positive patients to hospital treatment and their influence on the disease outcome.

In our study, four cases of symptomatic venous thromboembolism were diagnosed, making up 6.7% of the total number of subjects included. This does seem like a very low number of thrombotic complications; however, the total number of negative disease outcomes must be borne in mind. Namely, at the time of data collection and inclusion of respondents in the study, autopsies of persons deceased from COVID-19 were not performed. In a review of the literature and published scientific articles of the countries and health centers where autopsies were performed, autopsy findings speak in favor of an extremely high incidence of thrombotic complications in persons with a negative outcome of the disease. Thus, the work of Wichmann et al. (7) showed that the majority of deaths are due to deep vein thrombosis and pulmonary thromboembolism. In the paper of Edler et al. (8), over 40% of deaths were attributed to deep vein thrombosis, and an additional 25% of autopsies showed the presence of microthrombi in the vasculature of various tissues and organs, while a study by Elsoukkary et al. (9) states that pulmonary thromboembolism and/or deep vein thrombosis were found in as many as 88% of deaths at autopsy. For this reason, we decided to consider the group of subjects with a negative outcome (including venous thrombosis and death) as a representative group for monitoring the parameters of the hemostasis mechanism in relation to the group with a positive outcome.

TRAP is a sensitive parameter of basal platelet functionality that is also influenced by the patient's platelet count. Antiplatelet therapy with acetylsalicylic acid does not affect this parameter, so its possible use did not jeopardize the validity of the data obtained. Considering the great variability of this parameter and the impossibility of comparing different methods of determining platelet aggregability, there are conflicting data regarding the degree of aggregation in patients with SARS-CoV-2 virus infection. The study of Heinz C. et al. showed that platelet aggregability had no significant effect on disease outcomes (10). However, although this study was performed on an identical aggregometer as ours, there is a limit in terms of the number of subjects of only 27 where the subjects were recruited from intensive care units. However, the same study using Multiplate for aggregometry assessment showed statistically significantly lower platelet aggregability in patients compared with healthy controls.

The results of our study showed significantly higher fibrinogen concentrations in patients with negative disease outcomes compared to patients with positive outcomes, while univariate non-conditional logistic regression showed a slight contribution of fibrinogen concentration to disease outcome (OR 1.093; 95 % CI 1.025 - 1.165). In patients with COVID-19, there is an increase in the concentration of fibrinogen and VWF within the defense mechanisms of the host organism. The cohort study of Di Micoo et al. showed a statistically significant increase in fibrinogen concentration at the time of admission to hospital in the group of patients ending up with developed acute respiratory distress syndrome (ARDS) (11). Our study showed a statistically significant difference in D-dimer levels between groups of patients with a negative outcome compared to survivors, with a very mild effect of D-dimer on the disease outcome measured by unconditional logistic regression (OR 1.067 95% CI (1.007 - 1.131). Sampling in our study was performed at the time of hospitalization and we assume that at that moment the inflammation and endothelial dysfunction did not reach their full extent. The study of Zhang L. et al. showed that high levels of D-dimer at the time of admission can be used as a predictor of in-hospital mortality (12). Similarly, the cohort study of Naymagon L et al. showed that elevated D-dimer levels had been a good predictor of the outcome although they cannot be used as an isolated parameter

but rather in conjunction with other diagnostic tests (13).

Finally, for global assessment of the fibrinolytic mechanism, we determined the euglobulin clot lysis time. Given the undeniable importance of the fibrinolytic mechanism in maintaining the hemostasis mechanism's physiological functionality and numerous pathophysiological mechanisms by which its dysfunction contributes to thrombosis, we considered that its determination in SARS-CoV-2 viral infection may have significance and indicate a possible risk.

It should be borne in mind that systemic levels of fibrinolytic components are not always a good indicator of local fibrinolytic status, but as COVID-19 is a systemic disease affecting various tissues and organs, we thought that the application of global assessment of fibrinolytic mechanism can be a significant indicator for thromboembolic risk. Although insufficiently specific and sensitive, the performed test is easily accessible to clinical laboratories and provides valuable information on the functionality of the patient's fibrinolytic mechanism with a short turnaround time. The results of our study showed significantly suppressed fibrinolytic activity in patients with negative disease outcome in comparison with patients with a positive outcome, while univariate unconditional logistic regression showed a slight influence of decreased fibrinolysis on the risk for poor outcome (OR 1.084 95% CI 1.023 - 1.160). To date, several studies have been published focusing on the functionality of the fibrinolytic mechanism in individuals with SARS-CoV-2 viral infection. Although heterogeneous in terms of the selection criteria, recruitment moment, as well as the choice of diagnostic methods for the assessing the fibrinolytic activity, a majority of those showed dysfunction of the fibrinolytic mechanism in patients with SARS-CoV-2 viral disease. Thus, the study of Wright F. et al. (14) using thromboelastography in patients with COVID-19 placed in intensive care units showed suppression of the fibrinolytic mechanism and suggested it to be a good predictor of venous thromboembolism in further course of the disease. Another study by Bachler M. et al. (15) was able to demonstrate the suppression of the fibrinolytic mechanism in patients with SARS-CoV-2 using the ClotPro analyzer system, which operates on the principle of whole blood viscoelastography. A study by Blasi A. et al. (16) showed that despite the use of anticoagulant therapy, there is a constant presence of increased thrombin activity in patients with a suppressed fibrinolytic mechanism.

Awareness of the complex interactions between various components of the hemostatic mechanism led us to apply of multivariate logistic regression model, in which we included all examined parameters to assess their interaction, exclude individual bias in the study, and try to get a more precise picture of their sole contribution to the disease outcome. By final adjustment, the results of multivariate logistic regression showed that our model was primarily a good predictor of the outcome (Adjusted R square 0.447) at a statistically significant level ($p < 0.001$), arguing that the presented regression model could predict 44.7% outcome variances. After the performed statistical processing, the euglobulin clot lysis time showed statistical significance ($p < 0.001$) and proved to be the most relevant predictor of disease outcome.

CONCLUSION

Based on the gained results, we can assume that the global assessment of the fibrinolytic mechanism is a useful predictor of disease outcome in SARS-CoV-2 positive patients at the moment of their admission to hospital treatment, and that is why it can be used as a practical tool for stratification of risk for the negative outcome of the disease.

Note

The results of this scientific work are part of a doctoral dissertation.

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Karakteristike mehanizma hemostaze kod bolesnika sa SARS-CoV-2 virusnom infekcijom

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SAŽETAK

Uvod/Cilj. Tokom SARS-CoV-2 pandemije zabeležen je značajan broj slučajeva praćenih trombozom. Precizan patofiziološki mehanizam nastanka tromboze u okviru ove bolesti nije do sada razjašnjen. Značaj fibrinolitičkog mehanizma u održavanju fiziološke hemostaze naveo nas je da ispitamo njegov potencijalni doprinos tromboembolijskim komplikacijama kovid 19 infekcije. Ova studija imala je za cilj da identifikuje promene u mehanizmu hemostaze kod osoba koje su prilikom prijema na bolničko lečenje bile pozitivne na SARS-CoV-2, kao i njihov značaj za ishod bolesti.

Metode. Prikazana prospektivna studija obuhvatila je 60 rt-PCR pozitivnih osoba hospitalizovanih u kovid jedinicama Kliničkog centra Vojvodine. Iz uzoraka krvi bolesnika određeni su broj i agregabilnost trombocita, aPTT, PT, fibrinogen, D-dimer i ECLT (engl. *Euglobulin Clot Lysis Time* – ECLT). Bolesnici su podeljeni na one sa očuvanom i suprimiranom primarnom hemostazom, one sa fiziološkom i povišenom trombinskom aktivnošću i one sa očuvanom i smanjenom fibrinolitičkom aktivnošću. Takođe, izvršena je podela ispitanika na osnovu ishoda bolesti (na one kod kojih je ishod bio pozitivan i one kod kojih je ishod bio negativan).

Rezultati. Zabeležena su 44 pozitivna ishoda (73,3%), dok je negativan ishod, uključujući tromboembolijske komplikacije i smrt, zabeležen kod 16 (26,7%) ispitanika. Nekondicionalna logistička regresija pokazala je blagi negativan uticaj svih ispitivanih parametara na ishod bolesti. OR za ECLT bio je 1,084, sa 95%CI 1,023–1,160. Multivarijantni regresioni model pokazao je da je među svim ispitivanim parametrima ECLT jedini značajan prediktor za negativan ishod (sa nivoom $p < 0,001$).

Zaključak. Procena globalne funkcionalnosti fibrinolitičkog mehanizma predstavljala je koristan prediktor ishoda bolesti kod osoba koje su prilikom prijema na bolničko lečenje bile pozitivne na SARS-CoV-2.

Ključne reči: **SARS-CoV-2, kovid 19, hemostaza, fibrinoliza**