https://doi.org/10.52645/MJHS.2025.2.03

UDC: 616.13/.14-005.6-037

RESEARCH ARTICLE

Development of a mathematical model for thrombosis risk prediction using serum biomarkers

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ABSTRACT

Introduction. Thrombosis is a frequently underdiagnosed condition associated with high mortality in neglected cases. Many factors, including geoheliophysical and biochemical ones, are responsible for thrombosis modulation. Routine investigations may sometimes be inconsistent and, thus, unreliable in a clinical setting.

Material and methods. Data were collected from patients treated in the Department of Vascular Surgery at the 'Timofei Moșneaga' Republican Clinical Hospital, Chișinău, Republic of Moldova. A total of 1,865 patients were initially included in the study. After applying rigorous inclusion and exclusion criteria, 263 eligible patients were identified, and their complete blood counts and biochemical reports were retrospectively analyzed.

Results. The analysis revealed increased mean values for absolute polymorphonuclear neutrophils, absolute monocytes, erythrocyte sedimentation rate (ESR), and glucose. The median values of these indicators, except for absolute polymorphonuclear neutrophils and ESR in female patients, were also elevated above normal ranges. Significant Pearson and Spearman correlations were identified among the analyzed indicators, and a binary logistic regression model was constructed using the most statistically significant variables.

Discussion. Usual mathematical models that outline thrombosis consider deep vein thrombosis without a sustainable arterial assessment. The sensitivity of our model is lower than that of the D-dimer, while the specificity is almost the same. Platelets and clotting tests are well-known, reliable indicators; however, novel contemporary augmentations to these may, in turn, increase the predictive capability of our model if applied. This study has its limitations due to the lack of variance in the variance inflation factors (VIF), preventing the evaluation of multicollinearity among the included biomarkers.

Conclusions. The mathematical model developed in this study shows potential for further clinical application; however, additional research, validation, and the incorporation of non-biochemical indicators may be necessary to enhance its predictive accuracy.

Keywords: thrombosis, biomarkers, models, theoretical.

Cite this article: Croitoru D, Trohin I, Pavlovschi E, Arnaut O, Cerevan E. Development of a mathematical model for thrombosis risk prediction using serum biomarkers. Mold J Health Sci. 2025;12(2):16-21. https://doi.org/10.52645/MJHS.2025.2.03.

Manuscript received: 12.02.2025

Accepted for publication: 22.05.2025

Published: 15.06.2025

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Key messages

What is not yet known about the issue addressed in the submitted manuscript

There are no mathematical models that can accurately predict thrombosis risk in a clinical setting; thus, the development of one is a mainstay task.

The research hypothesis

There are certain biomarkers that may be used to develop a mathematical model capable of predicting thrombosis risk.

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The novelty added by the manuscript to the already published scientific literature

The development of a new mathematical model that may become more reliable and sustainable over time.

Introduction

Thrombosis is defined as the formation of a blood clot that can obstruct the normal permeability of the circulatory system [1]. The mortality burden associated with thromboembolic events is substantial (25% fatal outcomes) [2].

Differences in thrombosis rates across regions are thought to be influenced by variations in plasma rheology and clotting factors, such as fibrinogen, and factor VII, which could potentially overshadow the impact of seasonality [3]. The interactions of the endocrine system and its array of pathologies are of utmost importance when considering the etiology of thrombosis. Conditions like hyperthyroidism, hypercortisolism (endogenous or exogenous), growth hormone excess, hyperprolactinemia, and pregnancy, which involve direct or indirect involvement of the hormonal system, are known to have a higher incidence of thrombosis [4].

In the past, erythrocytes were considered to play a passive role in thrombotic events. However, they are now recognized as active contributors. Erythrocytes can enhance blood viscosity, interact with vessel walls, and influence the spatial organization of platelets during aggregation [5]. This aggregation, a critical process in thrombosis, is driven by elevated levels of adenosine diphosphate (ADP) [6]. Leukocytes, especially monocytes, are renowned for their capacity to promote clot formation in an environment that has the components required for thrombosis to emerge [7]. Serum bilirubin has remarkable antioxidative and cytoprotective effects [8], which in turn warrants that its low concentrations will lead to increased venous thromboembolism events in an acute respiratory infection setting [9-10].

Routine hemoleukogram, which measures parameters such as red blood cell count, white blood cell count, and hemoglobin levels, remains a valuable tool in the assessment of deep vein thrombosis (DVT). These routine measurements are essential for identifying patients at risk of pre-thrombotic or thrombotic conditions [11]. While advanced biomarkers, including D-dimers, selectins, microparticles, and inflammatory cytokines, demonstrate high accuracy in thrombosis evaluation, their utilization is often restricted to private healthcare settings due to their high cost. This financial barrier poses significant challenges for many healthcare systems globally, limiting the accessibility of these biomarkers in routine clinical practice [12].

Current mathematical models for assessing thrombosis risk, such as the Wells score, demonstrate limited performance. Their efficiency varies significantly, ranging from 0.5% to 23.4%, depending on the expertise of the specialist applying the model [13]. Additionally, these models perform poorly in critically ill patients, further limiting their reliability in high-risk populations [14].

The aim of this study was to develop a mathematical model for thrombosis diagnosis using serum biomarkers, particularly in patients lacking imaging data.

Material and methods

Study population. The study was conducted in the Department of Vascular Surgery at the *Timofei Moșneaga* Republican Clinical Hospital (RCH) in Chișinău, Republic of Moldova. In 2019, a total of 1,865 patients were admitted to the department for various vascular conditions, including atherosclerosis, atherothrombosis, thrombosis, and thromboembolism. The department primarily relies on a combination of biochemical laboratory investigations and imaging studies as the cornerstone of its clinical research and diagnostic methodologies.

Inclusion and exclusion criteria. To minimize systemic bias, reduce the risk of incomplete data inputs, and ensure consistency in data collection, stringent inclusion and exclusion criteria were established for the study population. Only patients who underwent a complete blood count (CBC) and biochemical investigation during the inpatient stage (on the first day of hospital admission) and tested negative for methicillin-resistant *Staphylococcus* (MRS) antibodies were included. A comprehensive range of comorbidities and conditions were considered exclusion criteria to ensure the reliability and objectivity of the biochemical results. The excluded conditions included hepatic and splenic disorders, oncological and infectious conditions, hematological disorders, autoimmune and dermatological conditions, vascular and cardiac conditions, gastrointestinal and endocrine disorders, and additional exclusions such as trauma, open wounds, systemic diseases requiring artificial grafts or stoma implants, post-thrombotic or post-inflammatory syndromes, chronic obstructive pulmonary disease (COPD), and patients receiving anticoagulant therapy. The exclusion criteria were carefully designed to reduce confounding variables and ensure high-quality biochemical data. It should be mentioned that the controls were confirmed to be patients who did not have thrombosis, using the same investigations as the patients with confirmed thrombosis (imaging and laboratory methods).

Statistical Data. A total of 263 patients included in the final study cohort were systematically documented and organized using Microsoft® Excel® 2013 (15.0.4569.1504). The data were collected retrospectively. The dataset encompassed a broad range of demographic, clinical, and laboratory parameters, including: demographic information (age, gender); clinical features (affected limb region: upper or lower limbs, type of thrombosis: arterial or venous, and season of occurrence); hematological parameters (white blood cell count [WBC], red blood cell count [RBC], hemoglobin

[HGB], hematocrit [HCT], mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH], mean corpuscular hemoglobin concentration [MCHC], platelet count [PLT], red cell distribution width – coefficient of variation [RDW-CV], and differential counts [absolute and relative values] of neutrophils, lymphocytes, monocytes, eosinophils, and basophils); inflammatory markers (erythrocyte sedimentation rate [ESR]; biochemical parameters (urea, aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], creatinine, total bilirubin, conjugated bilirubin, unconjugated bilirubin, glucose, albumin, and total protein); coagulation profiles (Quick prothrombin, international normalized ratio [INR], fibrinogen levels, activated partial thromboplastin time [aPTT], and thrombin time [TT]. This comprehensive collection of variables ensured a robust dataset for the subsequent analysis, enabling a thorough investigation of potential associations between the data.

Statistical Methods. The data were analyzed using IBM SPSS Statistics (version 26.0.0.0). The Shapiro-Wilk and Kolmogorov-Smirnov tests were applied to assess the normality of the data distribution. For normally distributed data, a one-sample t-test was performed with a t-value of 1.97 and a 95% confidence interval (CI). For non-normally distributed data, the one-sample Wilcoxon signed-rank test was utilized. Descriptive statistics, including mean values, standard deviations, medians, and minimum and maximum values, were calculated to summarize the data. Pearson and Spearman correlation coefficients were determined to evaluate relationships between the studied variables. Binary logistic regression analysis was conducted to identify, using mathematical methods, biochemical markers with potential predictive value for thrombosis events. An algorithm was developed using the statistically significant biomarkers identified in the analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

The mean age of the patients was 59.21±13.50 years while the median was 62 years, ranging in the interval of 23-90 years. Based on gender distribution, the study included 164 male patients (62.4%) and 99 female patients (37.6%). Among these, 74 patients (28.1%) presented during the winter season, 57 (21.7%) during spring, 72 (27.4%) during autumn, and 60 (22.8%) during summer. Of the total participants, 143 patients had thrombosis, while 120 served as controls.

In 125 cases (87.41%), the lower limbs were affected, whereas the upper limbs were affected in 18 cases (12.59%). Regarding vascular involvement, the arterial system was implicated in 63 cases (44.06%), while the venous system was affected in 80 cases (55.94%).

The Shapiro-Wilk and Kolmogorov-Smirnov tests demonstrated that the data followed a normal distribution, except for hematocrit, relative polymorphonucleated neutrophils, and relative lymphocytes.

The one-sample t-test indicated that all parameters, except for relative eosinophils and conjugated bilirubin, were statistically significant, with n = 263, t = 1.97, and a 95% confidence interval (CI). The one-sample Wilcoxon signed-rank test was applied to relative eosinophils, where the sample median (MDN = 1.40) differed from the hypothesized population median (2.5), n = 263, Z = -7.818, 95% CI, r = 0.482. Similarly, the test for conjugated bilirubin demonstrated a sample median (MDN = 0) differing from the hypothesized population median (3.0), n = 263, Z = -8.432, 95% CI, r = 0.519, confirming their statistical significance.

Mean values for absolute polymorphonucleated neutrophils, absolute monocytes, erythrocyte sedimentation rate (ESR) in both male and female patients, and glucose were elevated above normal values (Table 1). Additionally, the median values for absolute monocytes, ESR in male patients, and glucose were also above normal values (Table 1).

The strongest Pearson and Spearman correlations (Table 2) are detailed. It is important to note that these values do not necessarily reflect the patient's condition during thrombosis events or in controls. Instead, they aim to identify potential bias factors in the diagnostic process. While such elevations are commonly associated with pathological states, they do not appear to directly correlate with the severity of the condition.

Table 1. Indicators above normal statistical values

Indicator	Mean±SD	Median value	Minimum	Maximum	Normal range
NEUT#	5.35±2.43	4.88	1.45	20.11	2-5 x 10^3/µL
MONO#	0.69±0.52	0.63	0.17	7.7	0.09-0.6 x 10^3/µL
ESR_{total}	16.87±28.89	12	1	445	2-10 mm/h
$ESR_{male\ gender}$	17.89±35.45	12	1	445	2-10 mm/h
$ESR_{female\ gender}$	15.19±11.72	12	2	65	3-12 mm/h
Glucose	5.98±2.07	5.6	1.47	20.71	3.5-5.5 mM/L

Note: NEUT# – absolute polymorphonucleated neutrophils; MONO# – absolute monocytes; ESR – erythrocyte sedimentation rate; SD – standard deviation.

Considering the statistical significance of the b-values derived from the binary logistic regression model and the predictive capability for thrombosis events, as indicated by a Nagelkerke R^2 value of 0.203, a mathematical model has been developed. This model includes a constant and the following statistically significant variables: platelets (PLT), mean platelet volume (MPV), and thrombin time (TT). The following mathematical model may be applied:

$$b = 4.854 - 0.009\ x\ PLT - 0.461\ x\ MPV + 0.096\ x\ TT\ .$$

Once the b-values are determined, the thrombosis chance (TC) is calculated using the following formula: $TC = \frac{e^b}{1+e^b}$.

The specificity of this model was 55.8%, while its sensitivity was 76.9%. The negative predictive value (NPV) was 67%, and the positive predictive value (PPV) was 67.48%.

Table 2. Pearson and Spearman correlations between the biochemical markers

Pearson correlations	Value	Spearman correlations	Value
NEUT% x LYMPH%	-0.950**	NEUT% x LYMPH%	-0.952**
NEUT# x LYMPH%	-0.644**	QP x INR	-0.923**
QP x INR	-0.617**	NEUT# x LYMPH%	-0.671**
MCH x RDW-CV	-0.540**	NEUT# x BASO%	-0.542**
NEUT% x LYMPH#	-0.476**	NEUT% x BASO%	-0.516**
BASO# x BASO%	0.766*	HGB x HCT	0.831**
RBC x HCT	0.803**	RBC x HCT	0.838**
EO# x EO%	0.883**	EO# x EO%	0.908**
TotalBil x UnconjBil	0.909**	TotalBil x UnconjBil	0.919**
WBC x NEUT#	0.942**	WBC x NEUT#	0.935**

Note: * Statistical significance at $p < 0.05$; ** Statistical significance at $p<0.01$; NEUT% – relative polymorphonucleated neutrophils; LYMPH% – relative lymphocytes; BASO% – relative polymorphonucleated basophils; EO% – relative polymorphonucleated eosinophils; NEUT# – absolute polymorphonucleated neutrophils; LYMPH# – absolute lymphocytes; BASO# – absolute polymorphonucleated basophils; EO# – absolute polymorphonucleated eosinophils; RBC – red blood cells; WBC – white blood cells; HGB – hemoglobin; HCT – hematocrit; QP – Quick prothrombin; INR – international normalized ratio; MCH – mean corpuscular hemoglobin; RDW-CV – red cell distribution width (coefficient of variation); TotalBil – total bilirubin; UnconjBil – unconjugated bilirubin

Discussion

Previous models for thrombosis evaluation were primarily developed to assess deep vein thrombosis (affecting the upper or lower limbs) and pulmonary embolism, without adequately addressing arterial thrombosis [15-17]. In this research, a new model has been proposed that integrates both arterial and venous thrombosis, providing a comprehensive framework for the empirical management of patients. The proposed model relies on widely available and inexpensive biomarkers, making it particularly suitable for resource-limited settings where advanced imaging or specialized tests are not accessible. However, its specificity (55.8%) limits its standalone utility in clinical practice.

The widely used screening test of D-dimers has a high incidence of false-positive results due to its low specificity. As a result, its application may introduce a significant range of systematic errors, despite its clinical utility [18]. Our score is generally less sensitive than D-dimers; however, given their similar specificity, it could serve as an additional confirmatory tool for patients who cannot undergo this test.

Elevated absolute polymorphonucleated basophil values have been associated with increased mortality in patients with coronary artery disease (CAD), suggesting their potential role as a pro-thrombotic marker [19].

Platelets, the primary circulating elements responsible for clot formation [20], are expected to fluctuate during thrombosis events, reflecting their critical role in the coagulation process.

Although platelets are the key players in primary hemostasis, they can also contribute to secondary hemostasis through mediators found in their granules, including alpha, dense, and lysosomal granules. Additionally, cytosolic factors can sustain the coagulation cascade, further enhancing biochemical interactions at this level [21]. These molecules may serve as potential predictive biomarkers for future algorithm development [22-23].

Mean platelet volume (MPV) has been shown to reduce thrombosis risk in multiple regression analysis, consistent with the findings of this study [24]. However, this contrasts with classical high-evidence studies that identify elevated mean platelet volume as a risk factor for thrombosis [25]. MPV has been found to have low significance in predicting thrombosis in COVID-19 patients [26], while demonstrating good sensitivity and specificity in assessing thrombosis recurrence in conditions such as antiphospholipid syndrome (APS) [27]. However, in a retrospective study, MPV was found to be less effective compared to D-dimers [28].

Thrombin time (TT) reflects the ability of fibrinogen to convert into fibrin. An elevated TT may indicate fibrinogen deficiency, dysfunction, or disruption of other coagulation factors [29]. A study conducted in Japan states that TT, when enhanced by clot waveform analysis (CWA), may provide valuable insights into hemostatic abnormalities in patients without deficiencies in other clotting components [30]. This novel global coagulation assessment tool may also mitigate the influence of certain drugs due to its biophysical nature [31-32]. However, both activated partial thromboplastin time (aPTT) and TT are known for their inherent variability and limited diagnostic utility in thrombotic events. Individually assessed biomarkers are often deemed unreliable in thrombosis diagnosis [33]. A significant portion of false-negative results may be attributed to the depletion of key thrombogenic elements–platelets, fibrinogen/fibrin, protein C, and protein S–which directly impact Quick prothrombin (PT) and aPTT [34]. Notably, a widely recognized scoring system requires platelet count, D-dimer levels, PT, and fibrinogen values to predict the onset of disseminated intravascular coagulation (DIC) [35].

It can be hypothesized that enhancing current standard methods for thrombosis assessment may improve the specificity and sensitivity of the proposed mathematical model. However, this study did not evaluate variance inflation factors (VIF) to assess multicollinearity among the included biomarkers.

Conclusions

This study proposes a simple and cost-effective model for thrombosis risk prediction based on platelets, MPV, and thrombin time. While the model shows promise for clinical application, further validation, refinement, and the integration of advanced biomarkers are needed to enhance its predictive accuracy and clinical applicability.

Competing interest

None declared.

Contribution of authors

DC designed the study, collected, and analyzed the data. IT critically revised the manuscript and analyzed the data. EP critically evaluated the results and assessed their applicability. OA designed the protocol for patient' eligibility. EC critically revised the manuscript.

Ethics approval

No approval was required for this study.

Funding

The authors declare no external funding.

Provenance and peer review

Not commissioned, externally peer-reviewed.

References

1. Ashorobi D, Ameer MA, Fernandez R. Thrombosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2025 Feb 2]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430/
2. Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res. 2016;118(9):1340-7. doi: 10.1161/CIRCRESAHA.115.306841.
3. Fröhlich M, Sund M, Russ S, et al. Seasonal variations of rheological and hemostatic parameters and acute-phase reactants in young, healthy subjects. Arterioscler Thromb Vasc Biol. 1997;17(11):2692-2697. doi: 10.1161/01.atv.17.11.2692.
4. Squizzato A, Gerdes VE, Ageno W, et al. The coagulation system in endocrine disorders: a narrative review. Intern Emerg Med. 2007;2(2):76-83. doi: 10.1007/s11739-007-0026-X.
5. Byrnes JR, Wolberg AS. Red blood cells in thrombosis. Blood. 2017;130(16):1795-1799. doi: 10.1182/blood-2017-03-745349.
6. Abe H, Endo K, Shiba M, et al. Correlation between platelet thrombus formation on collagen-coated beads and platelet aggregation induced by ADP. Transfus Apher Sci. 2020;59(1):102560. doi: 10.1016/j.transci.2019.06.001.
7. Noubouossie DF, Reeves BN, Strahl BD, et al. Neutrophils: back in the thrombosis spotlight. Blood. 2019;133(20):2186-2197. doi: 10.1182/blood-2018-10-862243.
8. Ziberna L, Martelanc M, Franko M, et al. Bilirubin is an Endogenous Antioxidant in Human Vascular Endothelial Cells. Sci Rep. 2016;6:29240. doi: 10.1038/srep29240.
9. Sutton SS, Magagnoli J, Cummings T, et al. Serum Bilirubin Levels and Risk of Venous Thromboembolism among Influenza Patients: A Cohort Study. Clin Appl Thromb Hemost. 2024;30:10760296241275138. doi: 10.1177/10760296241275138.
10. Duman H, Özyurt S, Erdoğan T, et al. The role of serum bilirubin levels in determining venous thromboembolism. J Vasc Surg Venous Lymphat Disord. 2019;7(5):635-639. doi: 10.1016/j.jvsv.2019.02.002.
11. Tural K, Kara F, Avcı S, et al. Can complete blood cell count parameters predict deep vein thrombosis? Acta Clin Croat. 2020;59(4):661-666. doi: 10.20471/acc.2020.59.04.12.
12. Anghel L, Sascău R, Radu R, et al. From classical laboratory parameters to novel biomarkers for the diagnosis of venous thrombosis. Int J Mol Sci. 2020;21(6):1920. doi: 10.3390/ijms21061920.
13. Trihan JE, Adam M, Jidal S, et al. Performance of the Wells score in predicting deep vein thrombosis in medical and surgical hospitalized patients with or without thromboprophylaxis: the R-WITT study. Vasc Med. 2021;26(3):288-296. doi: 10.1177/1358863X21994672.
14. Girardi AM, Bettiol RS, Garcia TS, et al. Wells and Geneva scores are not reliable predictors of pulmonary embolism in critically ill patients: a retrospective study. J Intensive Care Med. 2020;35(10):1112-1117. doi: 10.1177/0885066618816280.
15. Sermsathanasawadi N, Chaivanit T, Suparatchatpun P, et al. A new pretest probability score for diagnosis of lower limb deep vein thrombosis in unselected population of outpatients and inpatients. Phlebology. 2017;32(2):107-114. doi: 10.1177/0268355516630469.
16. Shen JH, Chen HL, Chen JR, et al. Comparison of the Wells score with the revised Geneva score for assessing suspected pulmonary embolism: a systematic review and meta-analysis. J Thromb Thrombolysis. 2016;41(3):482-492. doi: 10.1007/s11239-015-1250-2.
17. Constans J, Salmi LR, Sevestre-Pietri MA, et al. A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost. 2008;99(1):202-207. doi: 10.1160/TH07-08-0485.
18. Pulivarthi S, Gurram MK. Effectiveness of D-dimer as a screening test for venous thromboembolism: an update. N Am J Med Sci. 2014;6(10):491-9. doi: 10.4103/1947-2714.143278.
19. Pizzolo F, Castagna A, Olivieri O, et al. Basophil blood cell count is associated with enhanced factor II plasma coagulant activity and increased risk of mortality in patients with stable coronary artery disease: not only neutrophils as prognostic marker in ischemic heart disease. J Am Heart Assoc. 2021;10(5):e018243. doi: 10.1161/JAHA.120.018243.

20. Packham MA. Role of platelets in thrombosis and hemostasis. Can J Physiol Pharmacol. 1994;72(3):278-284. doi: 10.1139/y94-043.
21. Scridon A. Platelets and their role in hemostasis and thrombosis - from physiology to pathophysiology and therapeutic implications. Int J Mol Sci. 2022;23(21):12772. doi: 10.3390/ijms232112772.
22. Plăcintă G, Croitoru D. Aspecte fiziologice, fiziopatologice şi clinice în COVID-19 = Physiological, pathophysiological and clinical aspects in COVID-19. Mold J Health Sci. 2020;25(3):22-30.
23. Nieri D, Neri T, Barbieri G, et al. C-C motive chemokine ligand 2 and thromboinflammation in COVID-19-associated pneumonia: a retrospective study. Thromb Res. 2021;204:88-94. doi: 10.1016/j.thromres.2021.06.003.
24. Li J, Liang Y. Associations between mean platelet volume and risk of deep vein thrombosis: a mendelian randomization study and a retrospective study. Int J Gen Med. 2023;16:515-524. doi: 10.2147/IJGM.S401059.
25. Gasparyan AY, Ayvazyan L, Mikhailidis DP, et al. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17(1):47-58. doi: 10.2174/138161211795049804.
26. Erdem I, Ardic E, Yildirim I, et al. Is Mean platelet volume a predictive marker for the development of thrombosis in patients with COVID-19 infection? Kurume Med J. 2024;70(1.2):61-66. doi: 10.2739/kurumemedj.MS7012006.
27. Rupa-Matysek J, Gil L, Wojtasińska E, et al. The relationship between mean platelet volume and thrombosis recurrence in patients diagnosed with antiphospholipid syndrome. Rheumatol Int. 2014;34(11):1599-605. doi: 10.1007/s00296-014-2996-0.
28. Canan A, Halıcioğlu SS, Gürel S. Mean platelet volume and D-dimer in patients with suspected deep venous thrombosis. J Thromb Thrombolysis. 2012;34(2):283-7. doi: 10.1007/s11239-012-0746-2.
29. Ignjatovic V. Thrombin clotting time. Methods Mol Biol. 2013;992:131-138. doi: 10.1007/978-1-62703-339-8_10.
30. Wada H, Ichikawa Y, Ezaki M, et al. The reevaluation of thrombin time using a clot waveform analysis. J Clin Med. 2021;10:4840. doi: 10.3390/jcm10214840.
31. Wada H, Shiraki K, Matsumoto T, et al. A clot waveform analysis of thrombin time using a small amount of thrombin is useful for evaluating the clotting activity of plasma independent of the presence of emicizumab. J Clin Med. 2022;11(20):6142. doi: 10.3390/jcm11206142.
32. Matsumoto T, Wada H, Shiraki K, et al. The evaluation of clot waveform analyses for assessing hypercoagulability in patients treated with factor VIII concentrate. J Clin Med. 2023;12(19):6320. doi: 10.3390/jcm12196320.
33. Croitoru D, Pavlovschi E. The biochemical approach to thromboembolism: the relevance of molecular aspects. Mold J Health Sci. 2023;10(3):53-64. doi: 10.52645/MJHS.2023.3.07.
34. Levi M, Toh CH, Thachil J, et al. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. Br J Haematol. 2009;145(1):24-33. doi: 10.1111/j.1365-2141.2009.07600.x.
35. Toh CH, Hoots WK, SSC on Disseminated Intravascular Coagulation of the ISTH. The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. J Thromb Haemost. 2007;5(3):604-606. doi: 10.1111/j.1538-7836.2007.02313.x.