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ORIGINAL ARTICLE HEMATOLOGY

Mean platelet volume as an effective biomarker for predicting high-risk patients of hereditary thrombophilia: A retrospective study

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ABSTRACT

OBJECTIVE: Literature shows evidence of the use of mean platelet volume (MPV) as a biomarker in thromboembolic conditions. It is recommended that genetic testing be performed selectively for hereditary thrombophilia. It might be useful to determine the priority of patients for genetic testing of hereditary thrombophilia through appropriate methods. We aimed to investigate the predictive value of MPV for high-risk patients of hereditary thrombophilia.

METHODS: The hematologic (MPV), biochemical (antithrombin III, protein S, protein C), molecular genetic test results (factor V Leiden [FVL], and prothrombin G20210A [PT]) obtained retrospectively from medical files of 263 patients categorized into high- versus low-risk for thrombophilia were statistically analyzed and the value of MPV in predicting high-risk patients was assessed by receiver operating characteristic (ROC) analysis.

RESULTS: The frequencies of high- versus low-risk patients were 45.2% and 54.8%, respectively. Significantly more high-risk patients (n=81) compared to low-risk patients had FVL (n=66) and PT mutations (n=80 vs. 34) (p<0.001). The MPV values in high-risk patients (mean=11.1 fl, range=7.8-13.6) were significantly higher than those in the low-risk patients (mean=8.6 fl, range=6-10.9) (p<0.001). The ROC curve analysis for MPV revealed a statistically significant area under the curve of 0.961 (95% confidence interval=0.931-0.981) at a cut-off point of 10.1 fl with a sensitivity of 89.1% and a specificity of 91.7% (p<0.001).

CONCLUSION: MPV might be used as an effective biomarker to screen and select patients for genetic thrombophilia testing. Large multicenter studies are needed for recommending the inclusion of MPV in future guidelines for hereditary thrombophilia.

Keywords: Antithrombin III; factor V Leiden; hereditary thrombophilia; mean platelet volume; prothrombin G20210A.

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Thrombophilia, derived from the Greek words "thrombus" for a blood clot and "philia" for affinity, describes an elevated tendency of blood clotting that leads to susceptibility to the formation of thrombosis in the vascular system [1]. Although an accurate estimate of the prevalence of hereditary thrombophilias is difficult due to the complexity of clinical presentation, methodological, and technical variations among reports, an estimate of 0.01%–7% in Caucasians was made based on epidemiologic data and established models [2]. Venous thromboembolic diseases, such as deep vein thrombosis (DVT), pulmonary embolism (PE), and venous thromboembolic events (VTE), are the most common thromboembolic events. The frequency of DVT and PE together represents 98% of all cases with VTE [3].

The function of platelets in the complex process of thrombus formation is essential and they have critical roles in both the arterial and venous thrombotic

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events. The size of the platelets which is most commonly measured as the mean platelet volume (MPV) is considered a potential reflection of the activity of platelets, including an increase in reactivity and aggregation and shortened time of bleeding. There is extensive research on the relationship between MPV and arterial thrombotic events. Although a significant impact of larger platelet size on incidence and clinical severity of thrombotic events has been proposed, there were conflicting findings in several studies [4–9].

MPV, an easy to obtain, a cost-effective, and reliable parameter is regarded as a convenient biomarker that can be calculated from routine blood tests [5, 10]. There were different cut-off values of MPV with variable diagnostic power for different clinical situations [8, 11–14]. Serial measurements of MPV indicating its trend might be useful in predicting risk of PE in patients with the first episode of acute proximal DVT [13]. Although no solid evidence has been consistently reported for the diagnostic or prognostic value of MPV in thromboembolic conditions, it can be speculated that it might be a useful tool for the initial estimation of thromboembolism risk [10]. In a recent meta-analysis, results that showed an association between higher values of MPV and both the occurrence and related mortality in PE suggested that it could be used as a predictor that was cheap and easy to test in clinical practice. The high heterogeneity observed in the pooling of MPV, on the other hand, made the authors who consider that MPV was better used as a tool for risk stratification that might be involved in the future guidelines [5].

Based on the available literature on the use of MPV as a biomarker in thromboembolic conditions and the recommendations on the conditions for thrombophilia genetic testing, we determined a need for identifying the patients with priority for genetic testing. Thus, we hypothesized that the MPV would be higher in patients at high risk for hereditary thrombophilia and could be used as a biomarker for selecting the patients for genetic testing. To the best of our knowledge, the literature lacks any studies that explored our hypothesis in a heterogeneous group of patients with thromboembolic. Therefore, in this study, we aimed to investigate the significance of MPV in patients with hereditary thrombophilia and analyze its predictive value for identifying high-risk patients for hereditary thrombophilia.

Highlight key points

- MPV has been considered a valuable biomarker for predicting occurrences of several thromboembolic conditions.
- MPV can be used as an effective biomarker to screen and select patients with genetic thrombophilia.
- MPV testing may be added to the testing algorithms for hereditary thrombophilia in the future.

MATERIALS AND METHODS

Study Design and Patient Population

The patient population in this retrospective study consisted of adults with hereditary thrombophilia who were admitted to the Department of Hematology, School of Medicine, Umraniye Training and Research Hospital between January 2018 and April 2021 for medical management and follow-up purposes. The study, which was designed in line with the Declaration of Helsinki and Ethical Standards, was approved by the Institutional Ethics Committee (Umraniye Training and Research Hospital, Date: 19.02.2020, Number: 54132726-000-4638) which waived the need for signed informed consent due to the retrospective collection of data from existing medical records in the archives of our hospital.

The data from medical files of patients who were admitted to our department for thromboembolic events, such as DVT, PE, and habitual abortion and had a confirmed diagnosis of hereditary thrombophilia based on molecular genetic and biochemical test results were included in the study. The patients with an acquired thrombophilia etiology and medical files that lacked relevant data were excluded from the study. Data regarding test results were only retrieved when they were performed in our institutional hematology, biochemistry, and molecular genetics laboratories to minimize procedural bias that could be introduced during laboratory techniques used in different settings.

Methodology

The demographic data, consisting of age, gender, and smoking status obtained from the hospital medical records of all patients were noted.

The MPV values that were tested on the admittance day of all patients were recorded. The laboratory results of biochemical tests and molecular genetic thrombophilia panel recorded were composed of testing for antithrombin III deficiency (AT), protein C deficiency (PC),

Table 1. Comparison of demographic and clinical parameters between low- versus high-risk patient groups

	Low-risk group (n=144)	High-risk group (n=119)	p
Age (years) mean±SD	40.0±11.9	38.2±10.6	0.186
Gender (%)			
Male	22.2	23.5	0.917
Female	77.8	76.5	
Smoking, yes (%)	41.0	39.5	0.907
Factor V Leiden, yes (%)	45.8	68.1	<**0.001**
Heterozygote	100.0	51.9	<**0.001**
Homozygote	0	48.1	
Prothrombin G20210A, yes (%)	23.6	68.4	<**0.001**
Heterozygote	100.0	73.8	**0.002**
Homozygote	0	26.2	
Antithrombin, median (minimum–maximum)	0.3 (0.2–0.4)	0.3 (0.1–0.4)	**0.011**
Protein C, median (minimum–maximum)	67.0 (24.0–140.0)	68.0 (22.0–165.0)	0.331
Protein S, median (minimum–maximum)	62.0 (17.0–139.0)	65.0 (26.0–147.0)	0.403
MPV, median (minimum–maximum)	8.6 (6.0–10.9)	11.1 (7.8–13.6)	<**0.001**

*: Pearson Chi-square/Fisher's exact test. Descriptive statistics presented as (%); **: Mann–Whitney U-test. Descriptive statistics presented as median (minimum–maximum); ***: Independent samples t-test. Descriptive statistics presented as mean±SD. SD: Standard deviation; MPV: Mean platelet volume.

protein S deficiency (PS), factor V Leiden (FVL), and prothrombin G20210A (PT) mutations as recommended previously [15, 16].

The patients were grouped into high-risk and low-risk categories based on the results of tests for hereditary thrombophilia in accordance with the guidelines [16]. The patients who were homozygotes or double heterozygotes for FVL and/or PT mutations were categorized into the high-risk group. The heterozygote carriers of FVL or PT mutations were considered in the low-risk group.

Statistical Analysis

The high-risk and low-risk group patients were statistically compared. Statistical analyses were performed using the Jamovi project (2022), Jamovi (version 2.2.2.5 and JASP (version 0.16.1) software (retrieved from https://jasp.stats.org), and MedCalc statistical software trial version (MedCalc Software bvba, Ostend, Belgium, http://www.medcalc.org; 2015). The descriptive statistics with mean, median, standard deviation, frequency, minimum, and maximum values were used to describe the categorical and numerical data. Quantitative data were assessed for normal distribution using the Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson–Darling tests, and comparisons between groups were performed using the independent samples t-test, while the Kruskal–Wallis H-test was used for variables without normal distribution. Pearson's Chi-square, Fisher-Freeman-Halton, and Fisher's exact tests were used to analyze the categorical variables with normal distribution, while the Dwass-Steel-Critchlow-Fligner test was used to analyze the differences between groups for non-parametric tests. Receiver operating characteristic (ROC) analysis was performed for determining the power of MPV value in predicting the high-risk patients. A p-value below 0.05 was considered as statistically significant.

RESULTS

Demographic and clinical data of 263 eligible patients with a mean age of 39.2±11.3 years were used in the study. The majority of patients (n=203, 77.2%) were female and the male patients constituted only 22.8% (n=60) of the study population. The rate of smoking among patients was 40.3% (n=116). The mean values of AT, PC, and PS were 0.3 g/dl (0.1–0.4), 67% (22%–165%), and 64% (17–147), respectively. The mean MPV value in the studied population was 9.9 fl and ranged between 6 and 13.6 fl.

TABLE 2. Receiver operating characteristic analysis for predictive value of mean platelet volume for high-risk patients

	AUC	Sensitivity	Specificity	Cut-off	95% CI	p
MPV	0.961	89.1	91.7	>10.1	0.931–0.981	<**0.001**

ROC: Receiver operating characteristic; AUC: Area under the ROC curve; MPV: Mean platelet volume; CI: Confidence interval.

Among all the patients in the study, 45.2% (n=119) were in the high-risk, while the remaining 54.8% (n=144) were in low-risk groups. No differences in the mean age, smoking status, and gender distribution were found between the high- versus low-risk patient groups (p>0.05). Significantly more patients from high-risk group (n=81, 68.1%) compared to low-risk patients had FVL (n=66, 45.8%) and PT mutations (n=80 vs. 34, 68.4% vs. 23.6%) (p<0.001 for both mutations). The frequencies of heterozygote FVL and PT mutations in the low-risk group (100% for both mutations) were significantly higher than those in the high-risk group (51.9% and 72.5%, respectively) (p<0.001 for both). The AT level in high-risk group (mean=0.3 g/dl, range=0.1–0.4) was significantly lower than that in low-risk patients (mean=0.3 g/dl, range=0.2–0.4) (p=0.011). The values of serum PS and PC levels did not show any significant differences between the high- versus low-risk groups (p=0.403 and p=0.331, respectively). The MPV values in the high-risk patients (mean=11.1 fl, range=7.8–13.6) were significantly higher than those in the low-risk patients (mean=8.6 fl, range=6–10.9) (p<0.001) (Table 1).

When we analyzed the relationships between the MPV and smoking, FVL, and PT mutations, no statistically significant associations were found. Moreover, no significant correlations were present between AT levels and MPV in none of the risk groups (p>0.05 for all).

The ROC curve analysis for MPV revealed a statistically significant area under the curve of 0.961 (95% confidence interval=0.931–0.981) at a cut-off point of 10.1 fl with a sensitivity of 89.1% and a specificity of 91.7% (p<0.001) (Table 2 and Fig. 1).

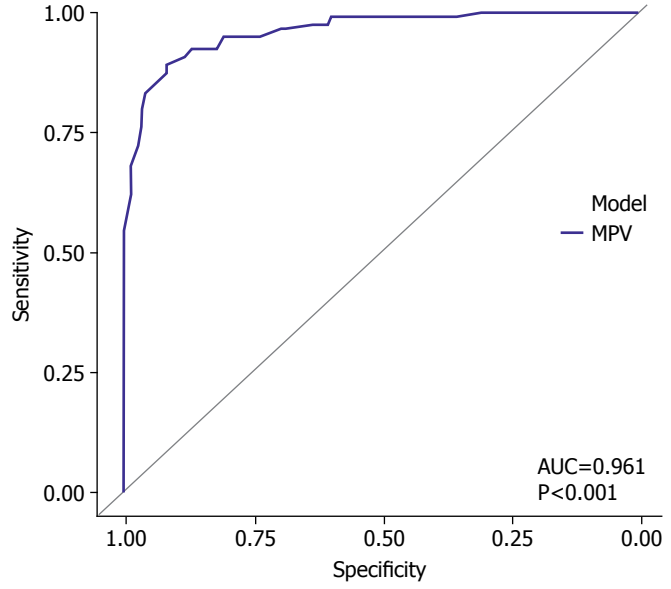

FIGURE 1. ROC curve for predictive value of MPV for high-risk patients.

ROC: Receiver operating characteristic; MPV: Mean platelet volume.

DISCUSSION

To the best of our knowledge, this is the first study that investigated the value of MPV for predicting the patients that were at high risk for hereditary thrombophilia. The mean value of MPV in low-risk patients (8.6 fl) was found to be significantly lower than that of the high-risk patients (11.1 fl). ROC analysis results showed that a cut-off value of 10.1 fl for MPV was significant in predicting the high risk of hereditary thrombophilia with an 89.1% sensitivity and a 91.7% specificity in the study population.

Previous studies reported various cut-off values of MPV with different diagnostic power in predicting thrombotic events. A cut-off value of 13.3 fl for MPV was reported to predict DVT with a 98.1% sensitivity and 77.6% specificity and an inverse correlation was found between the MPV and DVT risk [6]. An MPV lesser than 10.8 fl was found to be related to increased risks of VTE, DVT, and PE diagnoses in a study conducted on patients admitted to the ER [7]. The mean MPV value in recurrent pregnancy loss patients in the high-risk group (8.7 fl) was found to be significantly higher than that of the low-risk group (8.1 fl) [17]. Similarly, Erdem et al. [18] found that the mean MPV in

recurrent pregnancy loss patients in the high-risk group (9.1 fl) was significantly higher than those of the intermediate- (8.7 fl) and low-risk (8.4 fl) groups. A cut-off value of 7.9 fl for MPV with a sensitivity of 70.6% and a specificity of 65.7% was found to be significantly higher in patients with portal vein thrombosis [11]. The predictive cut-off value of MPV for PE was found to be 8.5 fl with a sensitivity of 80% and a specificity of 60% [12]. Controversially, Sharma et al. [8] found a tendency for higher MPV values in splanchnic vein thrombosis patients that did not reach statistical significance levels. A cut-off value of 9 fl was determined to predict the development of pre-eclampsia in a retrospective study [14]. Lipinska et al. [10] found a 9.6 fl cut-off point of MPV to estimate a probability risk of PE with 69.2% sensitivity and 71.8% specificity. Our results which showed a mean MPV value of 8.6 fl in low-risk group patients were similar to the studies by Aynioglu et al. [17] and Erdem et al. [18]. In the present study, we showed that MPV higher than 10.1 fl had sensitivity and specificity values of 89.1% and 91.7% in predicting the high-risk thrombophilia. However, the mean MPV value in the high-risk group of the current study (11.1 fl) was higher than those reported by Aynioglu et al. [17] and Erdem et al. [18]. We suspect that the difference in mean MPV values in the high-risk group of patients between studies might be due to the heterogeneities of the studies. Hence, although variances depending on the clinical characteristics of the patient groups, MPV might be a predictive factor for thromboembolic events in risky groups.

The etiopathogenesis of thrombophilia broadly consists of inherited and acquired components [19]. The most commonly detected hereditary thrombophilias are usually related with genes coding for proteins in the coagulation cascade [20–24]. In hypercoagulated states due to hereditary thrombophilia, such as prothrombotic allele of PIA2, FVL, FII20210A, 677MTHFR, PLA1/A2, and 4G/4GPAI-1, a significant platelet activation was detected secondary to the changes in the surface roughness and morphology of the platelets [25, 26]. The close association was observed between higher MPV values and recurrent pregnancy loss in patients with either homozygous FVL or PT mutations or was double heterozygotes for FVL and PT mutations [17, 18]. On the contradictory, no effect of thrombophilia mutations on MPV was found in ischemic stroke patients [27]. Those findings reinforce the probable association between an increased MPV value and the presence of an allele carrying a thrombophilic mutation.

Previously, a study from Turkiye, which was similar to ours in that the researchers included 394 patients with either venous or arterial thrombosis, reported a mean age of 45.49±15.08 years with the majority of the patients (51.3%) female. The frequencies of FVL homozygotes and heterozygotes in the study were 3% and 17%, respectively [28]. In our study, the mean age of the patients was 39.2±11.3 years and females constituted 77.2% of the patients. The frequencies of FVL heterozygotes and homozygotes in our study were 73.5% and 26.5%, respectively. Although the study populations in both studies were heterogeneous with both the arterial and venous thrombosis cases and differed from most of the studies in the literature in that regard, in addition to the similar ethnic background sharing due to the same geography of the sampled populations, the differences in FVL mutation frequencies could be interpreted as an effect of the differences in the mean age and gender distribution between the two studies.

Up to date, most of the studies that investigated the use of MPV in thromboembolic diseases as a predicting factor have been focused on the diagnosis and prognosis of the diseases. For instance, Diaz et al. [29] found evidence that high MPV was an independent risk factor for mortality after a VTE event. On the contrary, Braester et al. [3] were not able to demonstrate a significant predictive value of high MPV in early diagnosis of VTE in patients that presented to the ER. The authors discussed several reasons for the discrepant results among similar studies and suggested that the anticoagulant in the blood sample tubes and the type of the automated analyzer were as critical as the blood sampling procedure and the co-existing diseases in the patients. We share the concerns of Febra and Macedo about all the technical aspects of MPV measurement starting from the venipuncture, sampling tube anticoagulant, storage conditions, to the type of automated analyzer [12].

Hereditary thrombophilia screening should be focused on after the patient has been comprehensively evaluated for the prothrombic state. The careful selection of the patient for genetic thrombophilia testing was suggested to limit medical costs and the emotional burden of uncertainties to the patients and act in opposition to a universal, indiscriminate, and population screening [1]. As an easy-to-measure and readily available parameter for clinical detection, MPV has been considered a valuable biomarker for predicting occurrences of several thromboembolic conditions. Moreover, the use of MPV as a risk stratification method for

enhancing diagnostic accuracy, minimizing early mortality, and comparing various therapeutic approaches was suggested in a meta-analysis on the significant relationship between MPV and PE prediction [30].

The association between the increased risk of arterial and VTE and homozygous states of FVL and prothrombin G20210A mutations might be questioned. Previous animal studies showed that homozygosity of FVL mutation in mice was a significant factor for the increased risk of arterial thrombosis and atherosclerosis [31]. They thought that non-platelet-derived plasma FVL led to accelerated thrombosis. Nevertheless, the effect of MPV on this speculative issue was unclear. In clinical studies, the heterozygous and homozygous states of FVL and prothrombin G20210A were not analyzed as two separate groups [16, 27]. Hence, we have difficulty to obtain comparative data about MPV in patients with heterozygous and homozygous states of FVL and prothrombin G20210A. Prospective studies are needed to clarify such controversial issues.

In the present study and different from most of the previous papers, our research did not focus on finding a direct diagnostic or prognostic relationship between MPV and thromboembolic diseases. We determined a need to identify the patients who would benefit from molecular testing and evaluated MPV values in the risk-stratified patient population. Our results not only provided evidence for an association between higher MPV values and high-risk hereditary thrombophilia but also a 10.1 fl cut-off value of MPV that would predict the existence of high-risk hereditary thrombophilia in a patient were calculated.

There are several strengths and limitations of the present study that should be addressed. The retrospective study design might have caused a bias in selection; however, the inclusion of patient files was performed consecutively to minimize that potential bias. Second, our sample size was small and from a single center, which might limit the generalizability of the results. It is mandatory to conduct an external study to validation of our results. The measurement of MPV, as mentioned frequently in previous literature, has inherent disadvantages and is non-standardized, so calculating a cut-off point for MPV in ROC analysis might not be valid for others. Moreover, no robust analyses of various cut-off values were conducted to observe potential variations among them. An accurate interpretation of the current results would only be done after either universal test standardization or the establishment of conditions for different methods and automated analyzers used for MPV testing. Nevertheless, in the present study population, the procedure of testing was sustained as standard for all the patients in the study population as the laboratory conditions, hematological, biochemical, and molecular genetic techniques, and procedures were the same starting from obtaining and storing the samples to the same devices and automated analyzer used for tests. We are confident that minimal test requirements for MPV in all patients were met as emphasized in detail previously [32]. Future studies, preferably cohorts with a larger sample size that involves data regarding participant characteristics, such as surgical/medical history, comorbid conditions, anticoagulants used during blood sampling, detection time of MPV, and automated analyzer specifications, are warranted to verify the results of the present study.

Conclusion

To the best of our knowledge, this is the first report that revealed a significant relationship between high MPV values and patients at high risk for hereditary thrombophilia, thus we suggest that MPV can be used as an effective biomarker to scan and select patients for genetic thrombophilia testing and recommend the addition of MPV testing in future guidelines considering the genetic testing algorithms for hereditary thrombophilia. The current data should be used as preliminary for future and larger studies.

Ethics Committee Approval: The Umraniye Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 19.02.2020, number: 54132726-000-4638).

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REFERENCES

1. Colucci G, Tsakiris DA. Thrombophilia screening revisited: an issue of personalized medicine. J Thromb Thrombolysis 2020;49:618–29.
2. Stevens SM, Woller SC, Bauer KA, Kasthuri R, Cushman M, Streiff M, et al. Guidance for the evaluation and treatment of hereditary and acquired thrombophilia. J Thromb Thrombolysis 2016;41:154–64.
3. Braester A, Stemer G, Khouri S, Raviv B, Barhoum M. Is there a predictive value of high mean platelet volume in early diagnosis of venous thromboembolism? Isr Med Assoc J 2021;23:635–8.
4. Ot S, Zafar L, Beg M, Siddiqui OA. association of mean platelet volume with risk factors and functional outcome in acute ischemic stroke. J Neurosci Rural Pract 2021;12:764–9. [CrossRef]

5. Lin W, Wu Y, Lu X, Hu Y. Association between mean platelet volume and pulmonary embolism: a systematic review and meta-analysis. Aging (Albany NY) 2021;13:17253–73. [CrossRef]
6. Wang Z, Chen X, Wu J, Zhou Q, Liu H, Wu Y, et al. Low mean platelet volume is associated with deep vein thrombosis in older patients with hip fracture. Clin Appl Thromb Hemost 2022;28:10760296221078837.
7. Lippi G, Buonocore R, Cervellin G. The mean platelet volume is decreased in patients diagnosed with venous thromboembolism in the emergency department. Semin Thromb Hemost 2016;42:632–5.
8. Sharma S, Kumar N, Bihana I, Uppal V, Ahluwalia J, Naseem S, et al. Evaluation of platelet indices in patients with splanchnic vein thrombosis. Indian J Hematol Blood Transfus 2021;37:593–9. [CrossRef]
9. Oguz S. Relationship between first values of red cell distribution width, mean platelet volume, platelet distribution width and hospital mortality in acute deep venous thrombosis. J Coll Phys Surg Pakistan 2021;31:379–82. [CrossRef]
10. Lipinska A, Ledakowicz-Polak A, Krauza G, Przybylak K, Zielinska M. Complex calculation or quick glance? Mean platelet volume - new predictive marker for pulmonary embolism. Ther Clin Risk Manag 2018;14:2221–8. [CrossRef]
11. Aliosmanoglu I, Gul M, Oguz A, Basol O, Uslukaya O, Keles C. Can mean platelet volume be a new risk factor in portal venous thrombosis? Clin Appl Thromb Hemost 2013;19:433–6. [CrossRef]
12. Febra C, Macedo A. Diagnostic role of mean-platelet volume in acute pulmonary embolism: a meta-analysis and systemic review. Clin Med Insights Circul Respir Pulm Med 2020;14:1179548420956365.
13. Sevuk U, Bahadir MV, Altindag R, Baysal E, Yaylak B, Ay N, et al. Value of serial platelet indices measurements for the prediction of pulmonary embolism in patients with deep venous thrombosis. Ther Clin Risk Manag 2015;11:1243–9. [CrossRef]
14. Doğan K, Guraslan H, Senturk MB, Helvacioglu C, İdil S, Ekin M. Can platelet count and platelet indices predict the risk and the prognosis of preeclampsia? Hypertens Pregnancy 2015;34:434–42. [CrossRef]
15. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins–Obstetrics. ACOG Practice Bulletin No. 197: inherited thrombophilias in pregnancy. Obstet Gynecol 2018;132:e18–34. Erratum in: Obstet Gynecol 2018;132:1069. [CrossRef]
16. Turk Hematoloji Dernegi. Kalitsal Trombofili Tani ve Tedavi Kilavuzu. Ulusal Tedavi Rehberi 2011:73–98.
17. Aynıoglu O, Isık H, Sahbaz A, Harma MI, Isık M, Kokturk F. Can plateletcrit be a marker for recurrent pregnancy loss? Clin Appl Thromb Hemost 2016;22:447–52. [CrossRef]
18. Erdem HB, Ceylan AC, Kaya A, Bahsi T, Erdem ZS, Sahin I, et al. Positive correlation between platelet parameters and genetic markers of thrombophilia panel in recurrent pregnancy loss. Euras J Fam Med 2018;7:19–28.
19. Downes K, Megy K, Duarte D, Vries M, Gebhart J, Hofer S, et al. Diagnostic high-throughput sequencing of 2396 patients with bleeding, thrombotic, and platelet disorders. Blood 2019;134:2082–91. [CrossRef]
20. Koster T, Rosendaal FR, de Ronde H, Briët E, Vandenbroucke JP, Bertina RM. Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 1993;342:1503–6. [CrossRef]
21. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM. A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 1996;88:3698–703. [CrossRef]
22. Gandrille S, Borgel D, Sala N, Espinosa-Parrilla Y, Simmonds R, Rezende S, et al; Plasma Coagulation Inhibitors Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Protein S deficiency: a database of mutations--summary of the first update. Thromb Haemost 2000;84:918. [CrossRef]
23. Grundy C, Plendl H, Grote W, Zoll B, Kakkar VV, Cooper DN. A single base-pair deletion in the protein C gene causing recurrent thromboembolism. Thromb Res 1991;61:335–40. [CrossRef]
24. Marchant KK, Duncan A. Antithrombin deficiency. Arch Pathol Lab Med 2002;126:1326–36. [CrossRef]
25. Andreeva T, Komsa-Penkova R, Langari A, Krumova S, Golemanov G, Georgieva GB, et al. Morphometric and nanomechanical features of platelets from women with early pregnancy loss provide new evidence of the impact of inherited thrombophilia. Int J Mol Sci 2021;22:7778.
26. Todinova S, Komsa-Penkova R, Krumova S, Taneva SG, Golemanov G, Georgieva G, et al. PlA2 polymorphism in glycoprotein IIb/IIIa modulates the morphology and nanomechanics of platelets. Clin Appl Thromb Hemost 2017;23:951–60. [CrossRef]
27. Tasdemir S, Erdem HB, Sahin I, Ozel L, Ozdemir G, Eroz R, et al. Correlation with platelet parameters and genetic markers of thrombophilia panel (factor II g.20210G>A, factor V Leiden, MTHFR (C677T, A1298C), PAI-1, β-Fibrinogen, factor XIIIA (V34L), Glycoprotein IIIa (L33P)) in ischemic strokes. Neuromolecular Med 2016;18:170–6. [CrossRef]
28. Tasar PT, Karasahin O, Ozdemir O, Ceneli S, Turgut NH, Demirkan F. Demographic, clinical, and genetic evaluation of patients with suspected inherited thrombophilia. [Article in Turkish]. Van Med J 2019;26:103–8. [CrossRef]
29. Díaz JM, Boietti BR, Vazquez FJ, Waisman GD, Giunta DH, Rojas LP, et al. Mean platelet volume as a prognostic factor for venous thromboembolic disease. Rev Med Chil 2019;147:145–52. [CrossRef]
30. Lin WY, Lu X, Fan FJ, Hu Y. Predictive effect of mean platelet volume in patients with portal vein thrombosis: a meta-analysis of case-control studies. Curr Med Sci 2018;38:575–81. [CrossRef]
31. Eitzman DT, Westrick RJ, Shen Y, Bodary PF, Gu S, Manning SL, et al. Homozygosity for factor V Leiden leads to enhanced thrombosis and atherosclerosis in mice. Circulation 2005;111:1822–5. [CrossRef]
32. Arrachchillage DRJ, Laffan M. Can mean platelet volume (MPV) be used as a predictor of vascular disease? Problems and pitfalls. Semin Thromb Hemost 2017;43:599–608. [CrossRef]