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The Distribution of Hereditary Risk Factors in Patients with Pulmonary Thromboembolism without Identifiable Acquired Risk Factors

Tanımlanabilir Edinsel Risk Faktörleri Olmayan Pulmoner Tromboembolizmli Hastalarda Kalıtsal Risk Faktörlerinin Dağılımı

Savaş GEGİN[1]
0000-0001-7362-8710
Taner KARAKAYA[2]
0000-0002-3437-5324
Esra ARSLAN AKSU[3]
0000-0003-0448-1801
Burcu ÖZDEMİR[1]
0000-0003-4678-7729
Levent ÖZDEMİR[3]
0000-0002-3478-5454
Ahmet Cemal PAZARLI[4]
0000-0002-7094-837X

[1]Department of Chest Diseases, Samsun Education and Research Hospital, Samsun, Türkiye
[2]Department of Medical Genetics, Samsun University Faculty of Medicine, Samsun, Türkiye
[3]Department of Chest Diseases, Samsun University Faculty of Medicine, Samsun, Türkiye
[4]Department of Pulmonary Diseases, Tokat Gaziosmanpaşa University Faculty of Medicine, Tokat, Türkiye

Corresponding Author
Sorumlu Yazar
Ahmet Cemal PAZARLI
dracp60@gmail.com

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ABSTRACT

Aim: This study aimed to investigate the distribution of hereditary risk factors in patients with pulmonary thromboembolism (PTE) who have no acquired risk factors and to explore the relationship between genetic factors and the early mortality risk of embolism.
Material and Methods: Data from 295 patients diagnosed with PTE were examined retrospectively. Of these, 44 patients who had no acquired risk factors and were screened for hereditary risk factors, including factor V Leiden (FVL), prothrombin (PT) G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, MTHFR A1298C, plasminogen activator inhibitor (PAI) 4G/5G, factor XIII, antithrombin (AT) III, protein C, protein S, and activated protein C resistance (APCR), were included in the study.
Results: Of the patients, 14 (31.8%) were female and 30 (68.2%) were male, with a mean age of 46.5±17.3 years. Among the hereditary risk factors, the most common homozygous mutations were MTHFR A1298C (n=10, 22.7%), PAI 4G/5G (n=9, 20.5%), and FVL (n=5, 11.4%), while the most common heterozygous mutations were PAI 4G/5G (n=26, 59.1%), MTHFR A1298C (n=19, 43.2%), and MTHFR C677T (n=16, 36.4%). The heterozygous MTHFR A1298C mutation was detected in 10 (52.6%) patients with a history of recurrent PTE.
Conclusion: This study highlights the presence of genetic mutations such as PAI 4G/5G, MTHFR A1298C, MTHFR C677T, FVL, factor XIII, and PT G20210A in patients with PTE. The results show a high prevalence of genetic causes, especially in patients under 50 years of age with no acquired risk factors, no history of recurrent PTE or thrombophilia in any family member.
Keywords: Pulmonary thromboembolism; acquired risk factors; hereditary risk factors.

ÖZ

Amaç: Bu çalışmada edinilmiş risk faktörü olmayan pulmoner tromboemboli (PTE) hastalarında kalıtsal risk faktörlerinin dağılımının araştırılması ve genetik faktörler ile emboli kaynaklı erken mortalite riski arasındaki ilişkinin araştırılması amaçlanmıştır.
Gereç ve Yöntemler: PTE tanısı almış 295 hastanın verileri geriye dönük olarak incelendi. Bunlardan edinilmiş risk faktörü olmayan ve faktör V Leiden (FVL), protrombin (PT) G20210A, metilentetrahidrofolat redüktaz (MTHFR) C677T, MTHFR A1298C, plazminojen aktivatör inhibitörü (PAI) 4G/5G, faktör XIII, antitrombin (AT) III, protein C, protein S ve aktive protein C direnci (APCR) dahil olmak üzere kalıtsal risk faktörleri açısından taranan 44 hasta çalışmaya dahil edildi.
Bulgular: Hastaların 14'ü (%31,8) kadın ve 30'u (%68,2) erkek olup, yaş ortalaması 46,5±17,3 yıl idi. Kalıtsal risk faktörleri arasında en sık görülen homozigot mutasyonlar MTHFR A1298C (n=10, %22,7), PAI 4G/5G (n=9, %20,5) ve FVL (n=5, %11,4) iken, en sık görülen heterozigot mutasyonlar PAI 4G/5G (n=26, %59,1), MTHFR A1298C (n=19, %43,2) ve MTHFR C677T (n=16, %36,4) idi. Tekrarlayan PTE öyküsü olan 10 (%52,6) hastada heterozigot MTHFR A1298C mutasyonu tespit edildi.
Sonuç: Bu çalışma, PTE'li hastalarda PAI 4G/5G, MTHFR A1298C, MTHFR C677T, FVL, faktör XIII ve PT G20210A gibi genetik mutasyonların varlığını vurgulamaktadır. Sonuçlar, özellikle edinilmiş risk faktörü olmayan, tekrarlayan PTE öyküsü olmayan veya herhangi bir aile üyesinde trombofili olmayan 50 yaş altı hastalarda genetik nedenlerin yüksek prevalansta olduğunu göstermektedir.
Anahtar kelimeler: Pulmoner tromboemboli; edinilmiş risk faktörleri; kalıtsal risk faktörleri.

INTRODUCTION

Pulmonary thromboembolism (PTE) has a multifactorial pathogenesis and, with its increasing incidence and decreasing mortality rate, is currently a common cause of cardiovascular mortality. It typically presents as a complication of deep vein thrombosis (DVT). In addition to acquired factors such as, active cancer, advanced age, major trauma, surgery, pregnancy, and immobilization, genetic factors like factor V Leiden (FVL), prothrombin (PT) G20210A, antithrombin (AT) III, protein C, and protein S deficiencies play a significant role in the development of PTE (1). The coexistence of multiple prothrombotic disorders increases the risk of developing PTE, both in the presence and absence of acquired risk factors (2). Although the true prevalence of hereditary factors in the development of PTE is not clearly known, studies have shown that the rate of thrombophilia detection varies between 10%-50%, depending on the characteristics of the selected population. In studies conducted in Türkiye on hereditary thrombophilia, the frequency of thrombophilia was found to be 15.1% in healthy populations, while it was 41.6% in patients with PTE. Frequently, commonly identified mutations include FVL, PT G20210A, factor VIII elevation, AT III, protein C, and protein S deficiency (3).

Understanding the distribution of hereditary thrombophilias in PTE patients and their impact on the disease plays a crucial role in disease management, risk classification, and determining personalized treatment options. Therefore, it is recommended to investigate hereditary thrombophilia in patients under 50 years old who develop PTE without acquired risk factors, patients who develop PTE for the first time with a family history of PTE or thrombophilia, those with a history of recurrent PTE, patients with PTE in atypical locations, those with a history of warfarin-induced skin necrosis, patients with unexplained multiple miscarriages, those with a history of neonatal thrombosis, and young patients with arterial ischemia caused by paradoxical embolism (right-to-left shunt) (4).

This study aimed to investigate the distribution of hereditary risk factors in patients with PTE without identifiable acquired risk factors and to explore the relationship between genetic factors and the risk of PTE.

MATERIALS AND METHODS

The data of 295 patients diagnosed with PTE through pulmonary angiography or ventilation-perfusion scintigraphy at Samsun Education and Research Hospital Chest Diseases Clinic between July 2021 and July 2024 were retrospectively analyzed. Genetic screening for hereditary risk factors was performed in 51 patients who had no acquired risk factors and for whom genetic testing was recommended according to the PTE diagnosis and treatment consensus report (3). The data of 7 patients were unavailable, thus, 44 patients were included in the study.

Screening for hereditary risk factors was conducted in patients under 50 years of age who developed PTE without acquired risk factors (n=24), patients with a history of recurrent PTE (n=19), and patients with a family history of PTE or thrombophilia who developed PTE for the first time (n=1). Patients with incomplete data were excluded from the study (n=7).

Demographic data, comorbid conditions, PTE risk status, and hereditary risk factors of the patients were recorded. Acquired risk factors were questioned as advanced age, nephrotic syndrome, obesity, long-term travel, major surgery (pelvic abdominal), immobility due to sitting (e.g. prolonged car or air travel), cancer, congestive heart failure, myocardial infarction, stroke, oral contraceptive use, hormone replacement therapy, chemotherapy, central venous catheter, spinal cord injury, polycythemia vera, pregnancy/puerperium, and trauma. PTE risk classification was performed according to the 2019 European Society of Cardiology (ESC) Guidelines (5), categorizing patients into low, intermediate (intermediate-low, intermediate-high), and high risk groups (Figure 1). The hereditary risk factors examined included FVL, PT G20210A, methylenetetrahydrofolate reductase (MTHFR) C677T, MTHFR A1298C, plasminogen activator inhibitor (PAI) 4G/5G, factor XIII, AT III, protein C, protein S, and activated protein C resistance (APCR).

The levels of protein C, protein S, and AT III were measured after the acute phase of pulmonary embolism. The levels of protein C and protein S were measured two weeks after discontinuing warfarin treatment, while the levels of AT III were measured 48 hours after the initiation or discontinuation of low-molecular-weight heparin/heparin therapy (3).

Ethical approval for the study was obtained from the Samsun University Non-Interventional Clinical Research Ethics Committee (Date: 10.07.2024, No: 2024/13/7).

Statistical Analysis

All data were analyzed using the IBM SPSS v.23 for Windows program. Frequencies and percentages of categorical variables, as well as means and standard deviations of numerical variables, were calculated. The assumption of normal distribution was made using the Kolmogorov-Smirnov test.

Early mortality risk		Indicators of risk			
		Haemodynamic instability[a]	Clinical parameters of PE severity and/or comorbidity: PESI class III–V or sPESI ≥I	RV dysfunction on TTE or CTPA[b]	Elevated cardiac troponin levels[c]
High		+	(+)[d]	+	(+)
Intermediate	Intermediate-high	–	+[e]	+	+
	Intermediate-low	–	+[e]	One (or none) positive	
Low		–	–	–	Assessment optional; if assessed, negative

Figure 1. Pulmonary thromboembolism risk classification

RESULTS

Of the 44 patients included in the study, 14 (31.8%) were female and 30 (68.2%) were male, with a mean age of 46.5±17.3 years. Comorbidity was detected in 28 (63.6%) of the patients. The most common comorbidities were DVT (n=16, 36.4%) and hypertension (n=8, 18.2%). Nineteen patients (43.2%) were classified as low-risk, while 6 (13.6%) were classified as high-risk (Table 1).

The most common homozygous mutations among the hereditary risk factors were MTHFR A1298C (n=10, 22.7%), PAI 4G/5G (n=9, 20.5%), and FVL (n=5, 11.4%), while the most common heterozygous mutations were PAI 4G/5G (n=26, 59.1%), MTHFR A1298C (n=19, 43.2%), and MTHFR C677T (n=16, 36.4%). The distribution of mutations was shown in Table 2 and Figure 2.

In PTE patients under 50 years old without acquired risk factors, the most common heterozygous mutation identified was PAI 4G/5G (n=17, 70.8%), while in patients with a history of recurrent PTE, the most common heterozygous mutation was MTHFR A1298C (n=10, 52.6%, Table 3).

Protein C and protein S levels were assessed in 26 patients, while AT III and APCR were assessed in 16 patients. The mean AT III level was 103.3±20.2%, with one patient having a low level of 78%. The mean protein S level was 80.2±40.6%, and it was found to be low in 4 patients. The mean protein C level was 102.2±26.3%, and it was found to be low in 2 patients. The mean APCR was 0.88±0.1. APCR deficiency was not observed (Table 4).

In PTE patients with low risk, the most common mutations were MTHFR A1298C and PAI 4G/5G (n=15, 78.9%). The most common mutation was PAI 4G/5G both in intermediate-low risk patients (n=11, 91.7%) and in intermediate-high risk patients (n=5, 71.4%), while MTHFR A1298C (n=5, 83.3%) was the most common mutation in high-risk patients (Table 5).

Table 1. Demographic features (n=44)

Age (years), mean±SD	
Overall	46.5±17.3
Female	56.7±18.7
Male	41.8±14.7
Gender, n (%)	
Female	14 (31.8)
Male	30 (68.2)
Comorbidity and Risk Factors, n (%)	
Deep vein thrombosis	16 (36.4)
Hypertension	8 (18.2)
Ischemic heart disease	4 (9.1)
Diabetes	3 (6.8)
COPD	3 (6.8)
Asthma	2 (4.5)
Cerebrovascular disease	1 (2.3)
Pulmonary Thromboembolism Risk, n (%)	
Low Risk	19 (43.2)
Intermediate Risk	19 (43.2)
intermediate-low risk	12 (27.3)
intermediate-high risk	7 (15.9)
High Risk	6 (13.6)

SD: standard deviation, COPD: chronic obstructive pulmonary disease

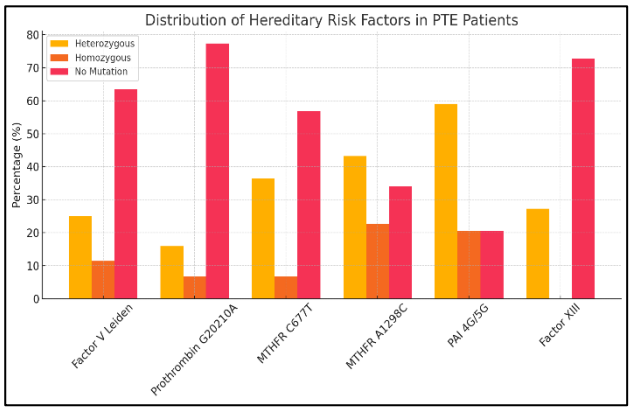

Figure 2. Distribution of hereditary risk factors in patients

Table 2. Distribution of hereditary risk factors (n=44)

Factor V Leiden, n (%)	
Heterozygous	11 (25.0)
Homozygous	5 (11.4)
No mutation	28 (63.6)
Prothrombin G20210A, n (%)	
Heterozygous	7 (15.9)
Homozygous	3 (6.8)
No mutation	34 (77.3)
MTHFR C677T, n (%)	
Heterozygous	16 (36.4)
Homozygous	3 (6.8)
No mutation	25 (56.8)
MTHFR A1298C, n (%)	
Heterozygous	19 (43.2)
Homozygous	10 (22.7)
No mutation	15 (34.1)
PAI 4G/5G, n (%)	
Heterozygous	26 (59.1)
Homozygous	9 (20.5)
No mutation	9 (20.5)
Factor XIII, n (%)	
Heterozygous	12 (27.3)
Homozygous	0 (0.0)
No mutation	32 (72.7)

MTHFR: methylenetetrahydrofolate reductase, PAI: plasminogen activator inhibitor

Table 3. Distribution of mutations according to clinical features

	Age <50 Years (n=24)	**Recurrent PTE (n=19)**	**Familial PTE (n=1)**
Factor V Leiden, n (%)			
Homozygous	1 (4.2)	4 (21.1)	0 (0.0)
Heterozygous	8 (33.3)	3 (15.8)	0 (0.0)
Prothrombin G20210A, n (%)			
Homozygous	0 (0.0)	3 (15.8)	0 (0.0)
Heterozygous	5 (20.8)	2 (10.5)	0 (0.0)
MTHFR C677T, n (%)			
Homozygous	8 (33.3)	1 (5.3)	0 (0.0)
Heterozygous	2 (8.3)	8 (42.1)	0 (0.0)
MTHFR A1298C, n (%)			
Homozygous	5 (20.8)	4 (21.1)	0 (0.0)
Heterozygous	9 (37.5)	10 (52.6)	0 (0.0)
PAI 4G/5G, n (%)			
Homozygous	4 (16.7)	4 (21.1)	1 (100)
Heterozygous	17 (70.8)	9 (47.4)	0 (0.0)
Factor XIII, n (%)			
Homozygous	0 (0.0)	0 (0.0)	0 (0.0)
Heterozygous	8 (33.3)	4 (21.1)	0 (0.0)

MTHFR: methylenetetrahydrofolate reductase, PAI: plasminogen activator inhibitor, PTE: pulmonary thromboembolism

DISCUSSION

As a result of this study, a significant number of hereditary risk factors were identified in PTE patients without acquired risk factors. In particular, homozygous mutations were found as follows: MTHFR A1298C in 10 (22.7%) patients, PAI 4G/5G in 9 (20.5%) patients, FVL in 5 (11.4%) patients, and PT G20210A in 3 (6.8%) patients; while heterozygous mutations were most commonly observed in PAI 4G/5G (n=26, 59.1%), MTHFR A1298C (n=19, 43.2%), MTHFR C677T (n=16, 36.4%), Factor XIII (n=12, 27.3%), FVL (n=11, 25%), and PT G20210A (n=7, 15.9%). In the present study, the causes of hereditary thrombophilia were detected in 4 (15%) patients with protein S deficiency and 2 (7.6%) patients with protein C deficiency. Furthermore, it has been reported that genetic polymorphisms such as MTHFR (C677T, A1298C), FVL, and PT G20210A are considered risk factors for thromboembolism. However, certain genetic mutations like F13 V34L polymorphism may provide a protective role against thrombosis (6).

Many studies have been conducted on hereditary risk factors in patients with PTE. Rossi et al. (7) found that different types of hereditary thrombophilia significantly affected the incidence of symptomatic PTE, with AT III deficiency increasing the PTE risk when combined with the PT G20210A gene mutation, while it decreased the risk when combined with FVL. Similarly, Turan et al. (4) observed a high prevalence of genetic mutations such as FVL and protein S deficiency in patients with recurrent pulmonary embolism episodes, emphasizing the need for comprehensive screening of at-risk populations to conduct careful genetic testing. Komsa-Penkova et al. (8) highlighted that hereditary thrombophilias, such as FVL and PT G20210A, make individuals more susceptible to developing pulmonary embolism. Similarly, Brandimarti et al. (9) demonstrated the presence of multiple genetic mutations involved in the development of pulmonary embolism by examining thrombophilia-related specific genes in the post-mortem tissues of individuals who died from PTE.

Many studies with varying results have been conducted using retrospective and case-control designs to determine the frequency of genetic risk factors in identifying etiological causes. Most of these studies focused on screening for genetic risk factors in patients with acquired risk factors. In the present study, however, genetic risk factors were screened in patients with PTE who did not have identified acquired risk factors.

In the study by Turan et al. (4) evaluating hereditary thrombophilias in patients with PTE, FVL was identified in 19.1% of patients (18% heterozygous, 1.1% homozygous); PT G20210A in 3.4% (all heterozygous); MTHFR C677T in 58.4% (51.7% heterozygous, 6.7% homozygous); MTHFR A1298C in 53.3% (52.8% heterozygous, 0.9% homozygous); AT III deficiency in 1.1%; protein C deficiency in 5.7%; protein S deficiency in 13.6%; and APCR in 34.2%. In the study by Gurgey et al. (10) investigating FVL and PT G20210A mutations in 146 patients with thrombosis, FVL was identified in 30.8% of patients (26% heterozygous, 4.8% homozygous), PT G20210A in 6.8% (all heterozygous), and both FVL and PT G20210A mutations in 4.1% of patients. In the study by Kalkanlı et al. (11) evaluating FVL mutations in 61 patients with venous thrombosis, the FVL mutation was identified in 24.6% of patients (22.9% heterozygous, 1.6% homozygous). Results of the present study demonstrated, as observed in previous studies, that these mutations have a high prevalence. Notably, FVL and PT G20210A homozygous mutations were detected at a higher rate compared to the studies by Turan et al. (4), Gurgey et al. (10), and Kalkanlı et al. (11), whereas heterozygous mutations were identified at rates similar to those reported.

Table 4. Hereditary thrombophilia blood level

Hereditary Thrombophilia	Available
Protein C Deficiency, n (%) (n=26)	2 (7.6)
Protein S Deficiency, n (%) (n=26)	4 (15.0)
AT III Deficiency, n (%) (n=16)	1 (6.3)
APCR, n (%) (n=16)	0 (0.0)

AT: antithrombin, APCR: activated protein C resistance

Table 5. Distribution of mutations according to pulmonary thromboembolism risk

	Low (n=19)	Intermediate-Low (n=12)	Intermediate-High (n=7)	High (n=6)
Factor V Leiden, n (%)				
Homozygous	3 (15.8)	2 (16.7)	0 (0.0)	0 (0.0)
Heterozygous	4 (21.1)	3 (25.0)	2 (28.6)	2 (33.3)
Prothrombin G20210A, n (%)				
Homozygous	1 (5.3)	2 (16.7)	0 (0.0)	0 (0.0)
Heterozygous	2 (10.5)	3 (25.0)	2 (28.6)	0 (0.0)
MTHFR C677T, n (%)				
Homozygous	2 (10.5)	0 (0.0)	1 (14.3)	0 (0.0)
Heterozygous	6 (31.6)	6 (50)	2 (28.6)	2 (33.3)
MTHFR A1298C, n (%)				
Homozygous	3 (15.8)	3 (25.0)	2 (28.6)	2 (33.3)
Heterozygous	12 (63.2)	2 (16.7)	2 (28.6)	3 (50.0)
PAI 4G/5G, n (%)				
Homozygous	5 (26.3)	2 (16.7)	1 (14.3)	1 (16.7)
Heterozygous	10 (52.6)	9 (75.0)	4 (57.1)	3 (50.0)
Factor XIII, n (%)				
Homozygous	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Heterozygous	7 (36.8)	2 (16.7)	1 (14.3)	2 (33.3)

MTHFR: methylenetetrahydrofolate reductase, PAI: plasminogen activator inhibitor, PTE: pulmonary thromboembolism

In their case-control study, Kupeli et al. (12) evaluated genetic risk factors for PTE in the Turkish population, including 80 PTE patients and 104 healthy individuals, and found no association between the presence or absence of acquired risk factors and genetic risk factors. Heterozygous FVL (14.2%), heterozygous PT G20210A mutation (15.2%), and homozygous MTHFR C677T (23.8%) were significantly higher among the patients. In a subgroup analysis comparing patients with and without acquired risk factors, the homozygous MTHFR C677T gene mutation (46.3%) was significantly higher in those without acquired risk factors, while the PAI 4G/5G gene mutation was high in both groups. In a case-control study by Oguzulgen et al. (13) with 143 PTE patients and 200 controls, it was found that the FVL mutation was significantly higher in the patient group (21%) compared to the control group (7.7%). However, no significant differences were observed between the patient and control groups for PT G20210A and PAI 4G/5G, leading to the conclusion that PAI is not a risk factor for PTE. In the subgroup analysis of 33 patients without acquired risk factors, no FVL or PT G20210A mutations were detected; in this subgroup, PAI was detected in 45.5% of patients, compared to 51.5% in the control group. In a case-control study conducted by Okumus et al. (14) with 191 PTE patients and 191 controls, FVL and protein C deficiency were found to be significantly higher in PTE patients compared to the control group, while no significant differences were found regarding protein S, AT activities, homocysteine levels, and PT G20210A mutations. In a case-control study conducted by Dölek et al. (15) with 270 DVT patients and 114 controls, FVL (DVT: 28.3%, control: 3.5%) and PT G20210A (DVT: 8.6%, control: 1.8%) were significantly higher in patients compared to the control group. Although MTHFR C677T (DVT: 49.8%, control: 39.5%) and MTHFR A1298C (DVT: 63.2%, control: 56.1%) gene mutations were higher in both groups, no significant difference was observed. In another case-control study conducted by Erkekol et al. (16) with 64 PTE patients and 64 controls, the FVL mutation was significantly higher in the patient group (26.9%), while no significant difference was observed for the PT G20210A mutation between the two groups. In the present study, heterozygous mutations of FVL, PT G20210A, MTHFR, and PAI 4G/5G were found at a high rate, similar to the case-control studies. However, unlike other studies, homozygous mutations, except for Factor XIII, were detected at a higher rate. This suggests that excluding acquired risk factors in this study to create a more isolated group for assessing genetic risk factors may have contributed to this difference, and that homozygous mutations, in addition to heterozygous mutations, could increase the risk of PTE.

In the literature review, no studies were found regarding the frequency of genetic risk factors stratified by the early mortality risk level of PTE. In Oguzulgen et al.'s (13) study, no acquired risk factors were found in 7 out of 32 high-risk patients, and genetic analysis in these patients revealed FVL in 6 cases and PT G20210A in 2 cases. In this study, unlike others, genetic risk factors were also evaluated based on the early mortality risk level of PTE. No correlation was observed between pulmonary embolism risk classes of 2019 ESC Guidelines and genetic factors. In low-risk patients, homozygous PAI 4G/5G was found in 26.3%, and heterozygous MTHFR A1298C was found in 63.2%. In intermediate-low risk patients, homozygous MTHFR A1298C was found in 25%, and heterozygous PAI 4G/5G was found in 75%. In intermediate-high risk patients, homozygous MTHFR A1298C was detected, and heterozygous PAI 4G/5G was found in 57.1%. In high-risk patients, homozygous MTHFR A1298C was found in 33.3%, and heterozygous PAI 4G/5G was found in 50%. It was thought that the reason why homozygous mutation was less common than homozygous mutation in high-risk patients was that the synergistic effect of heterozygous mutations was unknown.

The limitations of the study include a small sample size, a single-center and retrospective design, and the lack of a case-control design. Additionally, not all genetic factors were fully evaluated in PTE, and protein C, protein S, AT III, and APCR were not tested in all patients. This may have affected the results, preventing a full representation of the true picture. Another limitation is the failure to assess the combined effects of multiple genetic mutations or their interactions with acquired risk factors.

CONCLUSION

This study highlights the presence of genetic mutations such as PAI 4G/5G, MTHFR A1298C, MTHFR C677T, FVL, Factor XIII, and PT G20210A in patients with PTE. The results show a high prevalence of genetic causes, especially in patients under 50 years of age with no acquired risk factors, no history of recurrent PTE or thrombophilia in any family member. Future studies that integrate genetic screening into clinical practice, involve larger sample sizes in multicenter research, include a broader range of genetic tests, and examine the combined effects of multiple genetic mutations or their interactions with acquired risk factors could help identify high-risk individuals, facilitate targeted prevention measures, reduce disease incidence, and improve patient outcomes.

Ethics Committee Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Samsun University (10.07.2024, 13/7).

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