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Hereditary Thrombophilia Profile and Clinical Results of Our Eastern Black Sea Region Pulmonary Embolism Patients: Descriptive Research

Doğu Karadeniz Bölgesi Pulmoner Emboli Hastalarımızın Herediter Trombofili Profili ve Klinik Sonuçları: Tanımlayıcı Araştırma

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ABSTRACT Objective: The frequency and clinical implications of mutations causing hereditary thrombophilia are unclear. We aimed to investigate the frequency and clinical implications of gene mutations causing hereditary thrombophilia in patients with pulmonary embolism. **Materials and Methods:** The study included patients with pulmonary embolism who were investigated for hereditary thrombophilia. Data were collected retrospectively. **Results:** 107 (3.2%) of 3,340 patients with pulmonary embolism were found to have hereditary thrombophilia. Of the patients, 54 (50.5%) were female and 53 (49.5%) were male. MTHFR 677 was found in 37 (19.8%), factor V Leiden in 34 (18.2%), MTHFR1298 in 31 (16.6%), prothrombin 20210 in 13 (7.0%), AFAS in 12 (6.4%), AT III deficiency was present in 4 (2.1%), protein C resistance in 1 (0.5%), protein C deficiency in 1 (0.5%), and protein S deficiency in 1 (0.5%). The most common mutation was MTHFR 677 (22-33%) in women and factor V Leiden (22-32%) in men. MTHFR 677 was the most frequently observed mutation regardless of gender. The coexistence of pulmonary embolism and deep vein thrombosis (DVT) (34%), presence of acute DVT (31.3%), concomitant arterial thrombosis (30.6%), and recurrence of pulmonary embolism (25.6%) were higher in factor V Leiden deficiency than in other mutations. The highest heterozygosity rate was found in factor V Leiden. **Conclusion:** In our study, hereditary thrombophilia was detected in 3.2% of the pulmonary embolism patient population. The most common genetic mutations in our region are MTHFR 677 and factor V Leiden.

Keywords: Thrombophilia; pulmonary embolism; thrombosis

ÖZET Amaç: Herediter trombofiliye nedeni mutasyonların sıklığı ve klinik yansımaları net değildir. Pulmoner embolili hastalarda herediter trombofiliye neden olan gen mutasyonlarının sıklığı ve klinik yansımalarının araştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Çalışmaya, herediter trombofili araştırılan pulmoner embolili hastalar dâhil edildi. Veriler retrospektif toplandı. **Bulgular:** 3.340 pulmoner embolili hastasının 107'sinde (%3,2) herediter trombofili saptandı. Hastaların 54'ü (%50,5) kadın, 53'ü (%49,5) erkekti. Hastaların 37'sinde (%19,8) MTHFR 677, 34'ünde (%18,2) faktör V Leiden, 31'inde (%16,6) MTHFR1298, 13'ünde (%7,0) protrombin 20210, 12'sinde (%6,4) AFAS, 4'ünde (%2,1) AT III eksikliği, 1'inde (%0,5) protein C rezistansı, 1'inde (%0,5) protein C eksikliği, 1'inde (%0,5) protein S eksikliği mevcuttu. Kadınlarda en sık gözlenen mutasyon MTHFR 677 (%22-33), erkeklerde faktör V Leiden (%22-32) idi. MTHFR 677 cinsiyet ayrımı yapılmaksızın en sık gözlenen mutasyondu. Faktör V Leiden eksikliğinde, pulmoner emboli ve derin ven trombozu (DVT) birlikteliğinin (%34), akut DVT varlığının (%31,3), eşlik eden arteriyel trombozun (%30,6), pulmoner emboli nüksünün (%25,6) diğer mutasyonlardan daha yüksek olduğu gözlendi. En yüksek heterozigotluk oranı faktör V Leiden'de bulundu. **Sonuç:** Çalışmamız ile pulmoner emboli hasta popülasyonununda herediter trombofili %3,2 oranında saptanmıştır. Bölgemizde en sık rastlanan genetik mutasyonlar MTHFR 677 ve faktör V Leiden'dir.

Anahtar Kelimeler: Trombofili; pulmoner emboli; tromboz

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Venous thromboembolism (VTE) is a common vascular disease. It results in 2 main clinical signs: deep vein thrombosis (DVT) and pulmonary embolism (PE). PE is one of the most common chest diseases emergencies, and patients are often presented with an accompanying risk factor.[1] Hypercoagulability is one of the major mechanisms in the etiology of VTE, which is an important cause of mortality and morbidity. Hypercoagulability is an increase in the clotting tendency of the blood and is called thrombophilia. Thrombophilia can be hereditary or acquired. When an acquired factor causing VTE cannot be found, the presence of an underlying hereditary thrombophilia must be investigated. The importance of the presence of hereditary thrombophilia is that VTE occurs at a younger age than the general population and has a repetitive characteristic. There is a high probability of a mutation related to coagulation factors in patients diagnosed with VTE who also have a family history of VTE and who have no acquired risk factors have been detected and this should be investigated.[2,3] Although there is no clear data about the prevalence of hereditary thrombophilia, it is thought to be responsible for approximately 25-50% of VTE cases. The most common hereditary mutations in the population are factor V Leiden and prothrombin *G20210A* gene mutations which carry a high risk for VTE. In studies conducted in our country, factor V Leiden mutation was found to be the most common mutation with a rate of 2-12% in healthy patients and 5-35% in patients with VTE.[3] Although the exact frequency of prothrombin *G20210A* gene mutation is unknown, it is reported as 3% in the whole population and approximately 6% in patients with VTE.[4] Apart from these mutations, there are many types of thrombophilia such as protein C, protein S, antithrombin III deficiency, hyperhomocysteinemia, plasminogen deficiency and factor XII deficiency.[5,6] The frequency and clinical reflections of these mutations, which can be seen in every period of life and cause life-threatening clinical problems, are not clear. A limited number of studies on this subject in our country have been conducted by examining a limited number of patient data and the existing data are not sufficient. Considering the necessity of lifetime use of anticoagulants, especially in some individuals with these mutations, it is seen that the need for more experience and literature knowledge is obvious.

In our study, by reviewing our 10-year patient data, it was aimed to contribute to the literature and our daily practice in an area with a lack of clear information by investigating the frequency of gene mutations causing hereditary thrombophilia, and whether there is a difference in the presence of mutations, clinical course of VTE, thrombus load, and the anatomically located regions.

MATERIAL AND METHODS

The study was initiated after the approval of the University's Clinical Research Ethics Committee with protocol number 2021/70, and date March 5, 2021. Patients who were diagnosed with PE in our chest diseases clinic between January 2010-December 2020 but were investigated for hereditary thrombophilia because no significant risk factor could be detected were included in the study. The study was prepared in accordance with the Helsinki Declaration. All authors reviewed and approved the article. Patient data were collected retrospectively using file records and hospital automation system (clinical course, radiological imaging, laboratory records, etc.). Demographic characteristics, clinical features, pregnancy and abortion history of the patient, the type of mutation detected, presence of family history, localization of VTE were recorded from the files of the patients with hereditary thrombophilia.

PE patients under 18 years of age and with significant acquired thrombophilia were not included in the study.

STATISTICAL ANALYSIS

In the analysis of the data, Shapiro-Wilk and Kolmogorov Smirnov tests were used to examine the suitability of the data for normal distribution. Kruskall-Wallis, Mann-Whitney U, student-t and chi-square tests were used for intergroup comparisons. General linner modelling; Wilcowon and Friedman tests were used in serial follow-up data. The data were expressed as percentage, mean (std deviation) and median (minimum-maximum). Chi-square test

was used to compare qualitative data. Categorical data were presented as frequency and percentage.

RESULTS

Between the specified dates, 3,340 patients were diagnosed with PE. Hereditary thrombophilia was investigated in 187 of these patients. While 107 (57.2%) of the patients had hereditary thrombophilia, 80 (42.8%) did not. The rate of thrombophilia among all patients with PE was 3.2%. 54 (50.5%) of the patients with thrombophilia were female and 53 (49.5%) were male. The mean age was 39.74±12.9 years in females and 43.74±13.8 years in males. There was no statistically significant difference between the 2 groups in terms of mean age (p=0.126). Demographic and clinical characteristics of the patients are shown in Table 1. Of the 107 patients, 37 (19.8%) had MTHFR 677, 34 (18.2%) had factor V Leiden, 31 (16.6%) had MTHFR 1298, 13 (7.0%) had prothrombin 20210, 12 (6.4%) had AFAS, 4 (2.1%) had AT III deficiency, 1 (0.5%) had protein C resistance, 1 (0.5%) had protein C deficiency, and 1 (0.5%) had protein S deficiency. Some patients had more than one mutation. The general distribution of mutations is shown in Figure 1, and the mutation distributions in both genders are shown in Figure 2.

The most common mutation observed in females was MTHFR 677 (22-33%), while it was factor V Leiden (22-32%) in males. In females, MTHFR 1298 (15-23%) mutation in the second and factor V Leiden (12-18%) mutation in the third frequency were observed. In males, MTHFR 1298 (16-24%) and MTHFR 677 (15-22%) mutations were observed in the second and third frequencies, respectively. MTHFR 677 was the most common mutation without gender discrimination.

TABLE 1: Demographic and clinical characteristics of patients with mutations.

	n (%)
Gender	
Female	54 (50.5%)
Male	53 (49.5%)
The average age	
Female	39.74±12.9
Male	43.74±13.8
Symptoms	
Dyspnea	61 (57.0%)
Chest pain	56 (52.3%)
Hemoptysis	12 (11.2%)
Syncope/presyncope	13 (12.1%)
Cough	11 (10.3%)
Palpitation	7 (6.5%)
Abortion story	8 (14.8%)
Family history	11 (10.3%)

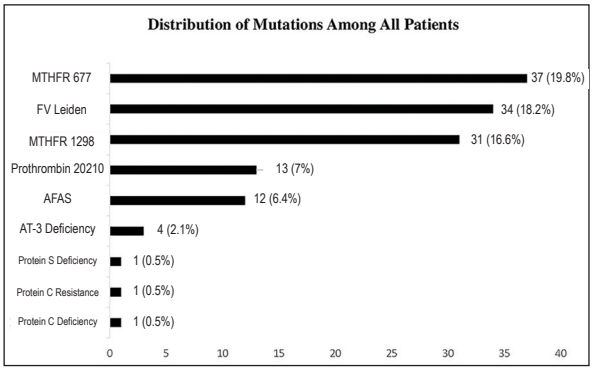

FIGURE 1: General distribution rates of mutations.
FV Leiden: Factor V Leiden; AT 3: Antithrombin 3; AFAS: Antiphospholipid syndrome.

When the distribution according to age was examined, it was determined that 49% of the mutations detected were between the ages of 18-40, 44% of them were between 41-60 age group. 7% of them were observed in the group over the age of 61 (Figure 3). In Figure 4, the distribution table of all mutations by age is given. Accordingly, all other mutations except the factor V Leiden mutation were found to be higher in the 18-40 age group, while the factor V Leiden mutation was found to be higher between 41-60 age group (55.9%).

The vast majority of detected gene mutations were heterozygous. The highest rate of heterozygosity was found in the factor V Leiden mutation. The highest homozygosity rate in all mutations was in the MTHFR 1298 mutation with a rate of 29% (n=9). Homozygosity rates of other mutations are given in Figure 5.

In patients with mutations, the PE+DVT coexistence (n=37) was 34.9%, the presence of acute DVT (n= 46) was 44.2%, the presence of chronic DVT (n=12) was 11.5%, the presence of proximal DVT (n=33) was 38.4%, the presence of distal DVT (n=16) was 18.6%, the presence of arterial thrombosis (n=5)

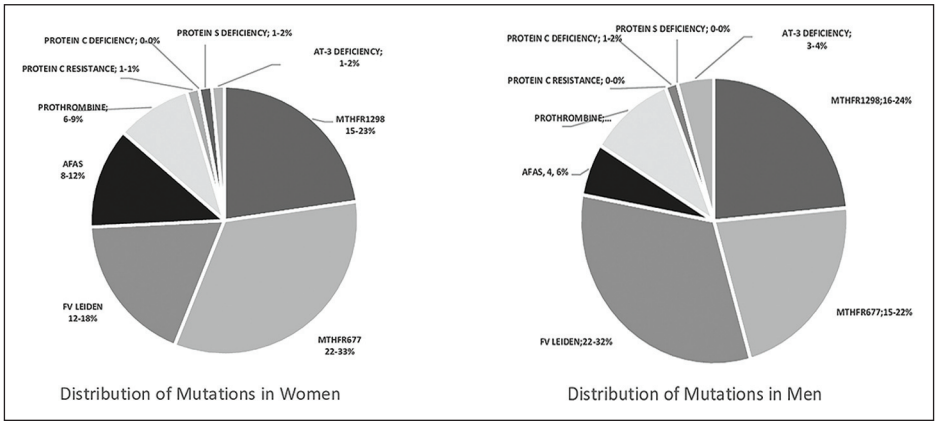

FIGURE 2: Distribution of mutations in both genders.
FV Leiden: Factor V Leiden.

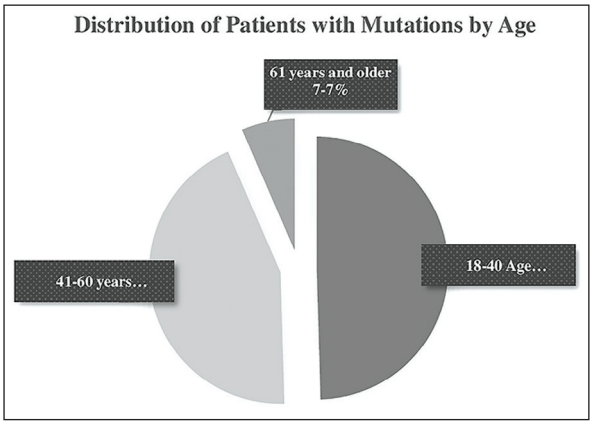

FIGURE 3: Distribution of patients with mutations by age.

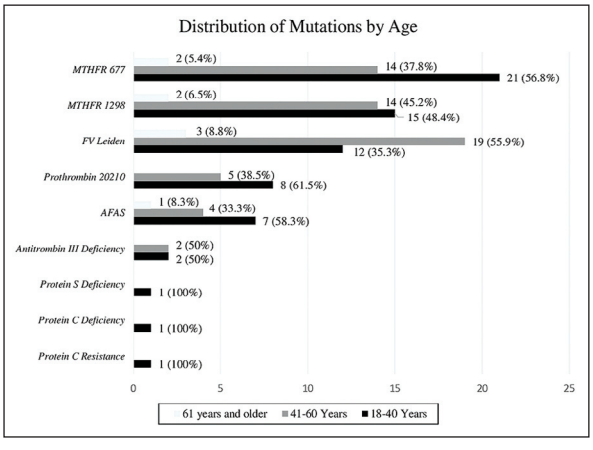

FIGURE 4: Distribution of mutations by age.
FV Leiden: Factor V Leiden.

was 4.7%, the PE or DVT recurrence (n=30) was 28.6% and the development of CTEPH (n=3) was 2.8%. When the mutations were compared among themselves, it was observed that in factor V Leiden deficiency, the association of PE and DVT (34%), the presence of acute DVT (31.3%), concomitant arterial thrombosis (30.6%) and PE recurrence (25.6%) developed at higher rates than other mutations (Figure 6). The percentages of thrombotic events according to the homo or heterozygosity rates of the mutations are given in Figure 7.

When the thrombus load was examined according to the mutations, the highest rate of bilateral PE was observed in MTHFR677 with 58.8%, while the highest mutation rate in the main pulmonary arteries was found in patients with the prothrombin 20210 mutation with 44.4%. Comparison of other thrombus locations and parenchymal findings is given in Table 2.

DISCUSSION

Although genetic risk factors vary according to the population selected among PTE risk factors, they constitute 10-50%. The incidence of hereditary thrombophilia in patients with PTE in different regions of our country is 7.9-8.6%.[7-9] In our study, 3.2% of 3,340 patients diagnosed with acute PTE in the Eastern Black Sea region had hereditary thrombophilia disorder within 10 years. When the literature is examined, factor V Leiden mutation and G20210A prothrombin mutation (PTM) are the most common genetic causes of thrombophilia.[10-12] Factor

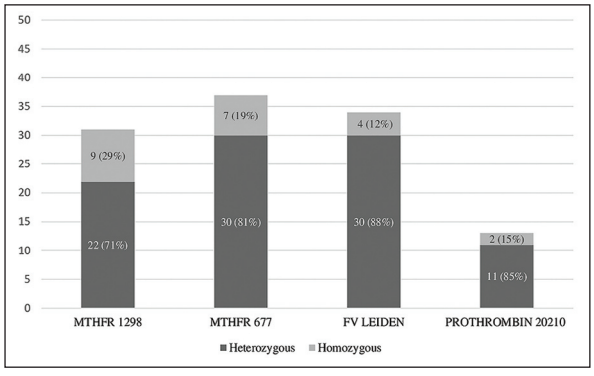

FIGURE 5: Homozygous-heterozygous ratios of mutations.
FV Leiden: Factor V Leiden.

V Leiden and *PTM* gene mutations account for 50-60% of hereditary hypercoagulability. Defects in protein S, protein C, and antithrombin (previously known as antithrombin III) are responsible for most of the remaining cases.

While the factor V Leiden mutation is found to be 2-5% in the general healthy population, it is found to be 12-18% in VTE patients, and the prothrombin G20210A mutation is found to be 2% in the general population, while it is found in 5-8% of VTE patients.[10] Our aim in presenting these data is to reveal the hereditary thrombophilia profile in PTE pa-

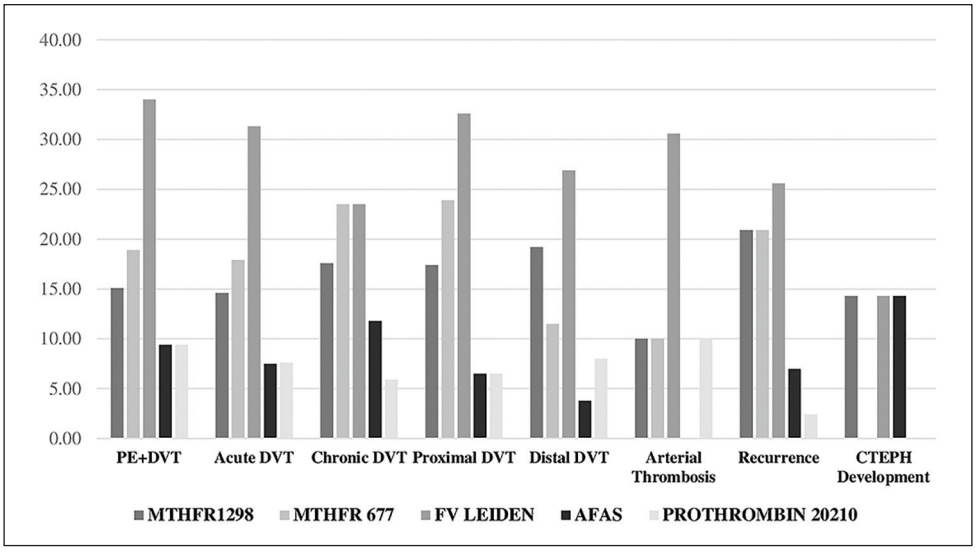

FIGURE 6: Distribution percentages of thrombotic events by mutations.
PE: Pulmonary embolism; DVT: Deep vein thrombosis; FV Leiden: Factor V Leiden.

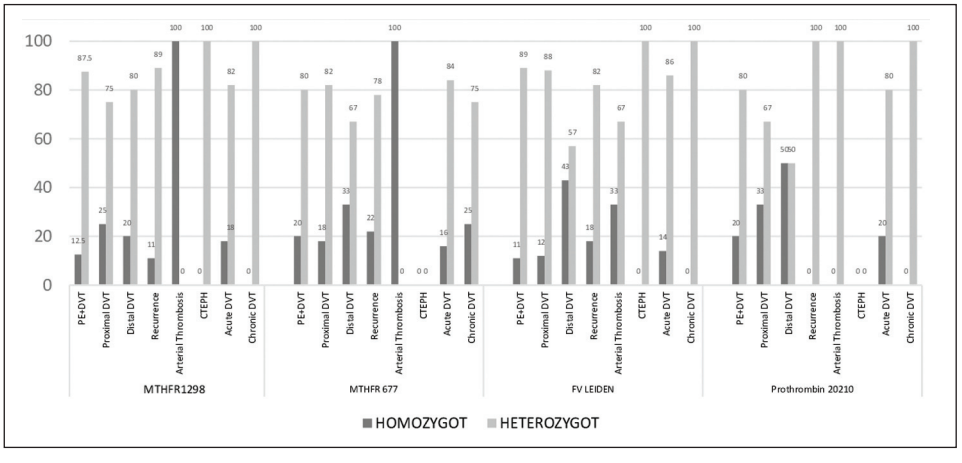

FIGURE 7: Percentage of thrombotic events according to homo-heterozygosity ratios of mutations.
DVT: Deep vein thrombosis.

TABLE 2: Thrombus burden and radiological findings by mutations.

Radiological findings	MTHFR1298	MTHFR677	Factor V Leiden	Prothrombin 20210
Bilateral PE	15 (55.6%)	20 (58.8%)	12 (40.0%)	5 (41.7%)
Thrombus in main PA	4 (17.4%)	6 (21.4%)	10 (41.7%)	4 (44.4%)
Thrombus in lober PA	15 (65.2%)	21 (75.0%)	15 (62.5%)	7 (77.8%)
Thrombus in segmentary PA	17 (73.9%)	18 (64.3%)	20 (83.3%)	9 (100%)
Thrombus in subsegmentary PA	9 (39.1%)	10 (35.7%)	10 (41.7%)	4 (44.4%)
Parenchymal infarct	0 (0.0%)	0 (0.0%)	2 (5.9%)	0 (0.0%)
Mosaic perfusion	1 (3.2%)	3 (8.1%)	0 (0.0%)	0 (0.0%)
Pleural effusion	5 (16.1%)	3 (8.1%)	5 (14.7%)	1 (7.7%)
Consolidation	0 (0.0%)	0 (0.0%)	3 (8.8%)	1 (7.7%)
Graund glass	1 (3.2%)	2 (5.4%)	1 (2.9%)	1 (7.7%)
Atelectasis	6 (19.4%)	7 (18.9%)	11 (32.4%)	3 (23.1%)

PE: Pulmonary embolism; PA: Pulmonary artery.

tients who are referred from the surrounding provinces or applied directly to our institution, which is a tertiary reference hospital in the Eastern Black Sea part of the Turkish gene pool. In our study, 3,340 patients were diagnosed with PTE during the retrospective 10-year period, and hereditary thrombophiliawas investigated in 187 (5.5%) of these patients according to risk factors. The patient group recommended to screen for thrombophilia as a risk factor in a patient with PE is still under discussion. Essentially, thrombophilia research should be performed if the test result will change the treatment plan. In addition, testing is not recommended in people with major temporary risk factors such as major surgery and trauma.[13] Considering that it may be a risk factor in our study, positive test results was obtained in 57.2% (107 patients) of the group whose thrombophilia panel was studied. In our study, the most common genetic mutations were found to be MTHFR 677 in 37 (19.8%) of 107 patients, factor V Leiden in 34 (18.2%), and MTHFR1298 in 31 (16.6%). In a study by Ridker et al., in which the distribution of factor V Leiden in patients with VTE was examined by ethnicity, the incidence of the said mutation was found to be similar in Caucasian men and women (5.53% vs. 4.85%, p=0.5).[14] Mitrus et al., on the other hand, found that congenital thrombophilia associated with the G1691A mutation of the factor V Leiden gene is more common in males than females.[15] In their study, Nefic et al. found that there was no statistically significant difference between men and women in terms of MTHFR 677 and MTHFR 1,298 carriers.[16] In our study, the most common mutation was MTHFR 677 (22-33%) in women and factor V Leiden (22-32%) in men.

In hereditary thrombophilia, genetic predisposition to thromboembolic events usually begins at a young age and tends to recur. People have their first attacks spontaneously and at an early age by 70%. In the other 30% of the cases, there was a risk factor such as trauma, pregnancy, use of oral contraceptives, and previous surgery. The average age of thromboembolic events in individuals with a family history of thrombophilia is 30, and this age limit is 45 in the other population.[17] In our study, hereditary mutations were most common between the ages of 18-40 (49%), and this rate was only 7% over 61 years of age.

Although the most common mutation is MTHFR 677 and factor V Leiden mutations, *MTHFR* gene mutations are not a defined risk factor for VTE in the light of previous data as they are also high in the healthy population.[18-21] Similar to our study, a high rate of MTHFR mutation of 45.1% was detected in other data for Türkiye, while factor V Leiden, one of the strong risk factors, was 46.5% and *PT* gene mutation was 13.2%.[22]

On the other hand, in our study, in factor V Leiden deficiency, PE and DVT coexistence (34%), the presence of acute DVT (31.3%), concomitant arterial thrombosis (30.6%) and PE recurrence (25.6%) were observed to be higher than other mutations. In a

study conducted on DVT and PE patients, Martinelli et al. reported that isolated PE development was less in patients with factor V Leiden.[10] This result of our study supports the hypothesis that if PE is detected in patients with factor V mutation, it may be associated with DVT to a large extent.

The severity of thrombophilia also affects the risk of VTE. For example, while a single heterozygous mutation is considered mild, homozygous mutations or multiple heterozygous mutations are considered as severe thrombophilia.[23] The vast majority of gene mutations detected in our study were heterozygous. The highest homozygosity rate in all mutations was in the MTHFR 1298 mutation with a rate of 29%.[10] In our patients the highest rate of heterozygosity was found in the factor V Leiden mutation (88%).

Although there are studies on lower extremity veins in the literature, no study has been found in which the thrombus load in the pulmonary arteries according to mutations or the radiological lung parchyma findings due to PE have been compared.[24,25] In this respect, we believe that the data of our study is valuable.

The strengths of our study are that our data covers a long period of 10 years and that a large patient population such as 3,340 was screened. However, we think that the limitations of this study are that it is a retrospective study and the number of patients with thrombophilia is relatively low.

CONCLUSION

In conclusion, in this study, hereditary thrombophilia was identified as a risk factor in a large PE patient population in 3.2% of all patients, and in 57.2% of cases that are thought to be hereditary (young age, no significant risk factor, recurrent VTE, atypically located VTE, family history, unexplained miscarriages, etc.). The most common genetic mutations in the Eastern Black Sea region are MTHFR 677 and factor V Leiden mutations. Although there are previous similar descriptive studies, our study provides valuable regional data including a large pool of patients and contributes to the literature.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Olcay Ayçiçek, Funda Öztuna;* ***Design:*** *Olcay Ayçiçek, Mehmet Sönmez, Funda Öztuna;* ***Control/Supervision:*** *Funda Öztuna, Mehmet Sönmez;* ***Data Collection and/or Processing:*** *Olcay Ayçiçek, Kadir Çoban, Mehtap Pehlivanlar Küçük;* ***Analysis and/or Interpretation:*** *Olcay Ayçiçek, Mhmet Sönmez;* ***Literature Review:*** *Olcay Ayçiçek, Mehtap Pehlivanlar Küçük, Merve Özdoğan Algın;* ***Writing the Article:*** *Olcay Ayçiçek, Kadir Çoban, Merve Özdoğan Algın;* ***Critical Review:*** *Mehmet Sönmez, Funda Öztuna;* ***References and Fundings:*** *Funda Öztuna;* ***Materials:*** *Olcay Ayçiçek.*

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