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Research Article

Evaluation of Antiplatelet/Anticoagulant Use and Prognosis in Primary Thrombophilia Patients with COVID-19

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Objective: This study is aimed to investigate the relationship between inherited thrombophilia and COVID-19 symptoms and the outcomes of treatment strategies.

Materials and Methods: This descriptive and retrospective study included patients who were followed up for thrombophilia in a training and research hospital. Data from 121 patients who had COVID-19 infection and those who met the inclusion criteria were collected through retrospective examination of medical records and telephone interviews using a data collection form developed by the researchers. The data obtained from the study was evaluated using descriptive and comparative statistical methods.

Results: Among the patients diagnosed with COVID-19, 11.6% had severe clinical presentations requiring intensive care support. During COVID-19 infection, mostly no drug was preferred for treatment (51.2%), and the most preferred drug was acetylsalicylic acid (ASA) (33.1%). A total of 13 thromboembolic events occurred in 12 patients who were included in the study during and after COVID-19 infection. No thromboembolic events occurred in patients using warfarin or new-generation oral anticoagulants during COVID-19. There was no significant difference in thromboembolism complications among patients who did not use any medication, those who used ASA/clopidogrel, and those who used low molecular weight heparin during COVID-19 infection. The most common gene mutation in the study was plasminogen activator inhibitor-1 (PAI-1) mutation, and there was no statistically significant difference between PAI-1 gene mutation and new thrombotic events (p=0.988).

Conclusion: COVID-19 infection was found to cause bilateral lung involvement with diffuse microthrombi in patients with genetic thrombophilia. No new thromboembolic events occurred in patients with thrombophilia using warfarin or new-generation oral anticoagulants.

Keywords: Coronavirus, Hereditary thrombophilia, Coagulation, Anticoagulation, Thrombosis

1. INTRODUCTION

Patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are more likely to develop venous, cerebrovascular, and coronary thrombi, especially if they have severe coronavirus illness (COVID-19). Although further research is needed, the pathophysiology is complicated and likely involves proinflammatory cascades, coagulopathy, and neutrophil extracellular traps (1). The dysregulated connection between innate immunity and coagulation is sometimes called immuno-thrombosis (2, 3). Through the angiotensin-converting enzyme 2 (ACE2) receptor, the SARS-CoV-2 virus directly infects endothelial cells. This causes viral inclusion bodies to form in the lungs, liver, small intestines, and kidneys, as well as the loss of endothelial glycocalyx proteins and a drop in heparanase-2 levels. As a result, the patient progresses from normal hemostasis to an antifibrinolytic state (4).

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Inherited thrombophilia diaseas are rare diseases characterized by prolonged bleeding time resulting from deficiencies in protein cofactors and enzymes that play a role in blood clotting.

Classical inherited thrombophilia includes loss-of-function variants in the genes that encode the natural anticoagulant proteins, antithrombin (AT), protein C (PC), and protein S (PS), and gain-of-function mutations in the genes encoding factor V (factor V Leiden (FVL)) and prothrombin (FII) (previous nomenclature G20210A). Rarer congenital thrombophilias have been described in the literature, such as genetically determined increased homocysteine levels, coagulation factors (VIII and IX), and hypodysfibrinogenemia. Venous thromboembolic disease (VTD) is a multifactorial disease resulting from the interaction between environmental, clinical, and biological risk factors (5,6). Each thrombophilic abnormality significantly increases the risk of thrombosis, especially if combined with additional factors such as COVID-19 (7). For prevention, several antithrombotic medicines have been proposed as potential therapy for COVID-19-associated thrombosis. Many of these drugs also have pleiotropic anti-inflammatory or antiviral effects. The growing awareness and mechanistic understanding of COVID-19 patients' prothrombotic state drives efforts toward more stringent diagnostic screening for thrombotic complications and the early administration of antithrombotic drugs to prevent and treat thrombotic complications (8). This study is aimed to investigate the association between inherited thrombophilias and COVID-19 manifestations and outcomes of treatment strategies.

2. MATERIALS AND METHODS

Before starting the study approval was obtained from the local ethics committee (E-71522473-050.01.04-651) and the Scientific Research Platform of the Ministry of Health of the Republic of Türkiye (2020-10-21T15_38_25). Two thousand seventy-nine patients who were diagnosed with thrombophilia between the dates of June 2017 and October 2020 were analyzed retrospectively referring to Sakarya University Training and Research Hospital Genetic Diseases Research Outpatient Clinic. Among the evaluated patients, 1856 patients who did not have COVID-19 during the COVID-19 pandemic were excluded from the study. Inclusion criteria for the study were patients who were between the age of 18 and 90, and those who had applied to the genetic diseases research outpatient clinic due to any thrombotic event, and the ones who had a coronavirus infection during the COVID-19 pandemic. Patients with no gene mutation predisposing to thrombosis during gene screening or who did not have a COVID-19 history and were pregnant, and breastfeeding were excluded from the study. Two hundred twelve patients who met the current criteria were called to inquire whether they used anticoagulant treatment before, during, and after the COVID-19 treatment. Ninety patients who could not be reached by phone or who refused to participate in the study were excluded from the study, and 121 patients, who were evaluated by age, gender, disease severity, gene mutation causing thrombosis, use of anticoagulants, use of antiaggregants, a new thrombotic event during and after COVID-19 infection were recorded by questioning.

2.1. Statistical analysis

Data analysis was performed using SPSS-22 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z). The variables were investigated using visual (histograms, probability plot) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are typically distributed. Frequency tables interpret categorical variables. The continuous variables were expressed as

mean and standard deviation. Categorical features and relationships between groups were assessed using an appropriate chi-square test. The statistically significant two-tailed p-value was considered as <0.05.

3. RESULTS

The study included 121 COVID-19 patients who had previously performed gene mutation analysis for thrombophilia in the hospital and had positive results in any parameter. Twenty patients (16.5%) were male. Patients in the study group had a mean age of 39.3±10.2. The clinical course of patients 14 (11.6%) were severe and required intensive care support. The mutation analysis results of MTHFR C677T, PAI, MTHFR A1298C, Factor 5 Leiden, Factor 13, and Factor 2 are summarized in Table 1

Table 1.

Baseline clinical characteristics of the patients

	Results (n=121)
Age	39.3±10.2
Gender, male, n (%)	20 (16.5)
Disease severity, n (%) *Critical patients* *Non-critical patients*	 14 (11.6) 107 (88.4)
MTHFR C677T mutation *Homozygous* *Heterozygous* *Absent*	 6 (5) 53 (43.8) 62 (51.2)
Plasminogen activator inhibitör-1 mutation *Homozygous* *Heterozygous* *Absent*	 31 (25.6) 58 (47.9) 32 (26.4)
MTHFR A1298C mutation *Homozygous* *Heterozygous* *Absent*	 15 (12.4) 54 (44.6) 52 (43.0)
Factor 5 Leiden mutation *Homozygous* *Heterozygous* *Absent*	 1 (0.8) 10 (8.3) 110 (90.9)
Factor 13 mutation *Homozygous* *Heterozygous* *Absent*	 4 (3.3) 32 (26.4) 85 (70.2)
Factor 2 mutation *Homozygous* *Heterozygous* *Absent*	 - 5 (4.1) 116 (95.9)

Peripheral arterial disease (38.0%) was the most common accompanying chronic complication, and abortus was the most common thrombotic event (54.5%). Before the COVID-19 infection, prophylaxis of coagulation was mostly not preferred (57.0%), and the most frequently preferred drug for prophylaxis was acetylsalicylic acid (ASA)/clopidogrel (28.9%). Also, during COVID-19 infection, no drug was preferred for treatment (51.2%), and the most preferred drug was ASA/clopidogrel (33.1%) (Table 2).

During and after the COVID-19 infection of the patients included in the study, six patients had minor ischemic stroke (AMIS), three had new abortion, two had cerebrovascular accident (CVA), one had pulmonary thromboembolism, and one had acute critical leg ischemia; a total of 13 thromboembolic events developed in 12 patients.

Among the patients with a positive thrombophilia panel, patients with and without a new thromboembolic event during COVID-19 infection were compared in terms of pulmonary involvement, and bilateral pulmonary involvement was significantly higher in the group with the event (66.7% vs 28.4% respectively, p=0.007) (Figure 1).

Table 2.

Chronic complications and antiaggregant/anticoagulant drugs of choice before and during COVID-19

	Results (n=121)
Chronic diseases, yes (%)	
Diabetes mellitus	11 (9.1)
Hypertension	16 (13.2)
COPD	10 (8.3)
ASCVD	7 (5.8)
Chronic renal failure	1 (0.8)
Peripheral arterial disease	46 (38.0)
Cerebrovascular disease	15 (12.4)
History of abortus	66 (54.5)
History of pulmonary thromboembolism	7 (5.8)
History of deep vein thrombosis	3 (2.5)
Anticoagulant/antiaggregant drugs of choice before COVID-19, n (%)	
ASA/Clopidogrel	35 (28.9)
Warfarin	4 (3.3)
Low molecular weight heparin	9 (7.4)
Novel Oral Anticoagulants	4 (3.3)
Absent	69 (57.0)
Anticoagulant/antiaggregant drugs of choice during COVID-19, n (%)	
ASA/Clopidogrel	40 (33.1)
Warfarin	4 (3.3)
Low molecular weight heparin	11 (9.1)
Novel Oral Anticoagulants	4 (3.3)
Absent	62 (51.2)

The frequency of newly developing thromboembolic events was compared according to the thrombophilia gene mutation, and no significant difference was found in any of the subgroups (Table 3).

No new thromboembolic events occurred in patients using warfarin (n=4) and new-generation oral anticoagulants (n=4) during Covid-19 infection. Complications of thromboembolism developed in 4 (6.5%) patients who did not use any drugs (n=62), 6 (15.0%) patients who used ASA/ Clopidogrel (n=40), and 2 (18.2%) patients who used low molecular weight heparin (n=11) and no significant difference was observed between the groups (Figure 2).

Figure 1.

Comparison of bilateral pulmonary involvement of COVID-19 in cases with new thrombotic events

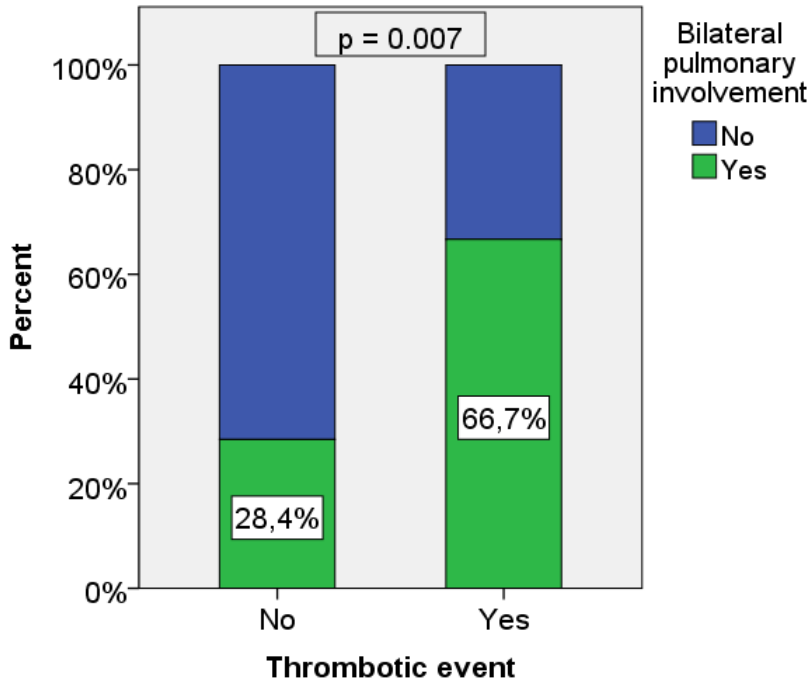


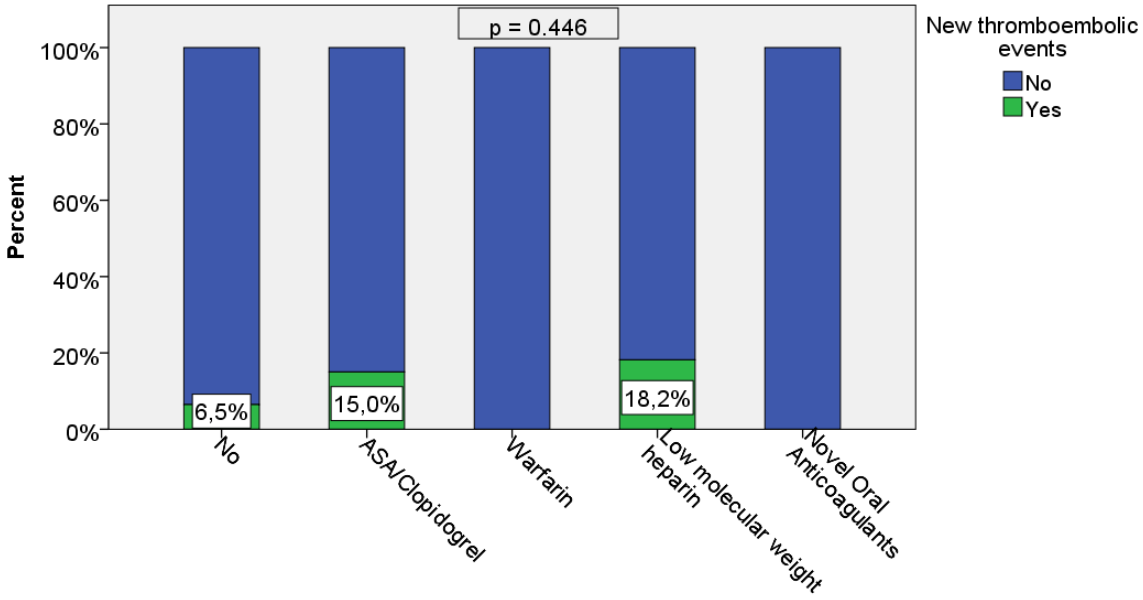
Table 1.

Comparison of new thromboembolic events according to thrombophilia gene mutation

	Homozygous	Heterozygous	Absent	P value
MTHFR C677T, n (%)	2 (33.3)	3 (5.7)	7 (11.3)	0.087
Plasminogen activator inhibitor-1, n (%)	3 (9.7)	6 (10.3)	3 (9.4)	0.988
MTHFR A1298C, n (%)	2 (13.3)	6 (11.1)	4 (7.7)	0.752
Factor 5 Leiden, n (%)	-	-	12 (10.9)	0.514
Factor 13, n (%)	-	3 (9.4)	9 (10.6)	0.781
Factor 2, n (%)	-	1 (20.0)	11 (9.5)	0.441

Figure 2.

Comparison of the frequency of new thromboembolic events by drug of choice



4. DISCUSSION

Many factors affect the development of thrombosis. Genetic diseases predisposing to thrombosis may trigger diseases with pathological thrombotic processes, such as COVID-19. This study's most common gene mutation was plasminogen activator inhibitor-1 (PAI-1) mutation with 89 cases. However, no significant statistical difference was found in this research regarding PAI-1 gene mutation and new thrombotic events (p = 0.988). When the frequency of newly developed thrombotic events was compared in patients with COVID-19, whose gene analyses were positive in the hospital with suspected genetic disease causing thrombosis, tall subgroups had no statistically significant difference. Still, a partially significant outcome was revealed in patients with MTHFR C677T gene mutation (p = 0.087). MTHFR C677T I is a gene mutation that causes high blood homocysteine levels. Homocysteine is a molecule that causes ischemic heart disease, peripheral arterial disease, ischemic stroke, and venous thrombosis. It achieves this effect by upregulating the angiotensin receptor and renin-angiotensin-aldosterone system components (9,10). Homocysteine has also been shown to play a role in the mechanism of action of SARS-CoV-2 infection by causing angiotensin II receptor activation (11-13). Therefore, although a partially significant difference was found, it may be said that genetic mutations associated with hyperhomocysteinemia are the most effective thrombophilias that stimulate the emergence of thrombotic complications of COVID-19 infection. More studies with higher sample sizes are needed to assess the effect of hyperhomocysteinemia during COVID-19 infection. Fox et al, (14) revealed diffuse microthrombi were detected in the pulmonary autopsies of COVID-19 patients with pulmonary involvement. In this study, the results of patients with gene mutations predisposing to thrombosis in genetic screening were presented, and patients with and without a new thromboembolic event during COVID-19 infection were compared regarding lung involvement. Bilateral lung involvement was significantly higher in the group with thromboembolic events (p = 0.007).

One study has been published investigating the possible correlation of thrombotic events with hereditary thrombophilia factors in patients who died of COVID-19 (15). The authors evaluated the mutations in FV 506R/Q, MTHFR 223A/V, F2 20210G/A and PAI-1 4G/5G. The results obtained by them show that the highest percentage was detected in pulmonary artery thrombosis, followed by pulmonary embolism. Additionally, the incidence of MTHFR 223A/V

heterozygous and PAI-1 4G/5G heterozygous genotypes was higher in patients with COVID-19 and thrombotic events, and that of FV 506R/Q and F2 20210G/A heterozygotes was lower. (15). The MTHFR gene encodes 5,10-methylenetetrahydrofolate reductase, which is involved in homocysteine metabolism. The severity of COVID-19 could be associated with HHcy and possibly with depleted folic acid in infected cells (16-19). HHcy was correlated with an increase in the incidence and severity of COVID-19 (20). In this study, while MTHFR and PAI were high, FV was low.

Low molecular weight heparin is the most commonly used anticoagulant to avoid thrombotic complications during severe COVID-19 infection (21). In this study, while the majority of patients (51.2%) did not use drugs, ASA/clopidogrel (33.1%) was the most preferred among drug users. The clinical severity of the disease differs in the cases since the patient group included in this study was a patient population with mutations detected in gene screening and who had COVID-19 infection. Previous research on the preventive role of chronic oral anticoagulation in COVID-19 hospitalized patients yielded conflicting results (22-28). Russo et al. 0) revealed no significant association among oral anticoagulants, neither with Novel Oral Anticoagulants (NOACs) nor vitamin K antagonists, and the severity of the disease regarding ARDS in hospitalized patients due to COVID-19 infection (22). As potential therapies for preventing thrombosis associated with COVID-19, antithrombotic drugs, including heparin, factor XII inhibitors, and fibrinolytic drugs, have been administered (29,30). One guide to thromboprophylaxis in COVID-19 recommends routine doses of thromboprophylaxis in the absence of contraindications in the hospital, increased intensity thromboprophylaxis in the intensive care unit, and consideration of anticoagulant thromboprophylaxis in patients with increased risk of venous thromboembolism post-hospital (31). In this study, although not statistically significant, no new thromboembolic event has developed in any of the patients using warfarin and new-generation oral anticoagulants. Very few publications have reported the results of patients with COVID-19 infection who have a genetic tendency to thrombosis. This study is one of the rare studies investigating the severity of the disease, the use of anticoagulants, and the effect of gene mutations on the disease in this group of patients. This study is limited by the retrospective design and the relatively small sample size of patients on anticoagulation therapy.

5. CONCLUSION

In conclusion, this study objectively evaluated the outcomes of patients with any gene mutation that causes thrombophilia who have had a COVID-19 infection retrospectively. This study also reveals that COVID-19 infection causes bilateral pulmonary involvement with diffuse microthrombi in patients with genetic thrombophilia. Especially high homocysteine levels in the blood are partially related to this thrombotic event. No new thrombotic events are developed in thrombophilia patients using warfarin and new-generation oral anticoagulants.

Congress:

The study was not presented at any scientific event.

Ethics Committee Approval:

This study was approved by the clinical research ethics committee of the Sakarya University. Date: 28.12.2020, number: 651.

Informed Consent:

Since the study had a retrospective design, consent could not be obtained from the patients.

Conflict of Interest:

None declared by the authors.

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Author Contributions:

Idea/Concept: Alper Erkin, Design: Alper Erkin, Ayşe Çelik Yılmaz, Data Collection/Processing: Alper Erkin, Ayşe Çelik Yılmaz, Analysis/ Interpretation: Alper Erkin, Ayşe Çelik Yılmaz, Literature Review: Cenk Sunu, Alper Erkin, Ayşe Çelik Yılmaz, Drafting/Writing: Cenk Sunu, Alper Erkin, Ayşe Çelik Yılmaz, Critical Review: Alper Erkin, Ayşe Çelik Yılmaz, Cenk Sunu

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