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RESEARCH ARTICLE

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Contribution of genotypes in Prothrombin and Factor V Leiden to COVID-19 and disease severity in patients at high risk for hereditary thrombophilia

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Abstract

Thrombotic and microangiopathic effects have been reported in COVID-19 patients. This study examined the contribution of the hereditary thrombophilia factors Prothrombin (FII) and Factor V Leiden (FVL) genotypes to the severity of COVID-19 disease and the development of thrombosis. This study investigated FII and FVL alleles in a cohort of 9508 patients (2606 male and 6902 female) with thrombophilia. It was observed that 930 of these patients had been infected by SARS-CoV-2 causing COVID-19. The demographic characteristics of the patients and their COVID-19 medical history were recorded. Detailed clinical manifestations were analyzed in a group of cases ($n = 4092$). This subgroup was age and gender-matched. FII and FVL frequency data of healthy populations without thrombophilia risk were obtained from Bursa Uludag University Medical Genetic Department's Exome Databank. The ratio of males (31.08%; 27.01%) and the mean age (36.85 ± 15.20; 33.89 ± 14.14) were higher among COVID-19 patients compared to non-COVID-19 patients. The prevalence of FVL and computerized tomography (CT) positivity in COVID-19 patients was statistically significant in the thrombotic subgroup ($p < 0.05$). FVL prevalence, CT positivity rate, history of thrombosis, and pulmonary thromboembolism complication were found to be higher in deceased COVID-19 patients ($p < 0.05$). Disease severity was mainly affected by FVL and not related to genotypes at the Prothrombin mutations. Overall, disease severity and development of thrombosis in COVID-19 are mainly affected by the variation within the FVL gene. Possible FVL mutation should be investigated in COVID-19 patients and appropriate treatment should be started earlier in FVL-positive patients.

KEYWORDS
COVID-19, Factor V Leiden, Prothrombin, thrombophilia

1 | INTRODUCTION

Thrombophilia is a coagulation condition characterized by an increased risk of thrombosis, either from hereditary or acquired causes.[1] It arises from a defect in the coagulation pathway or abnormalities in the fibrinolytic system.[2] While acquired thrombophilia occurs as a result of secondary diseases such as surgery, obesity, infection, smoking, antiphospholipid antibody syndrome, and cancer.[2] Hereditary thrombophilia occurs due to Prothrombin mutation (FII), Factor V Leiden (FVL) mutation, antithrombin 3 deficiency, and protein C or S deficiency.[3] The FVL mutation is the most common genetic form of hereditary thrombophilia. FII-related thrombophilia is the second most common genetic cause of thrombophilia. The history, physical examination, laboratory, and imaging findings are important in clinical diagnosis. Genetic testing is recommended for confirming the diagnosis in families with known mutations, differential diagnosis, relapse risk assessment, and for asymptomatic patients.[3] FVL G1691A and FII G20210A mutations are widely studied in genetic analysis because they are the most common hereditary thrombophilia factors.

COVID-19 is a disease that causes endothelial damage and microvascular abnormalities.[2] Severe COVID-19 is characterized by a

marked pro-inflammatory response and procoagulant activity, leading to life-threatening thromboembolic complications.[4–6] Multiple cohort studies have shown an increased risk of thromboembolism in COVID-19, and the risk is higher in COVID-19 patients hospitalized in the intensive care unit (ICU) due to severe pneumonia.[7,8] Again, thrombotic and microangiopathic effects of the SARS-CoV-2 virus have been reported in COVID-19 patients.[9] However, the genetic factors that may cause it are still not fully explained.[10]

Hereditary thrombophilia has a heterogeneous clinic.[3] This situation is similar in patients with COVID-19. While some survive the disease without attacks of thromboembolism, some show very severe hypercoagulability. The severe clinical course in elderly patients, sudden death at a young age, similar clinical findings in consanguineous patients, venous thromboembolism (VTE), microangiopathic thrombus, and distal extremity circulatory disorders in patients were similar to patients with hereditary thrombophilia. This suggested an association between inherited thrombophilia factors and COVID-19.

This large, comprehensive study aims to evaluate the possible association between FVL G1691A, FII G20210A mutations, and COVID-19 disease predisposed to hypercoagulability.

2 | MATERIALS AND METHODS

This retrospective, cross-sectional research was conducted in 24 medical genetic centers in Turkey and Northern Cyprus between January 2017 and December 2020.

FII and FVL frequency data of healthy populations without thrombophilia risk were obtained from Bursa Uludag University Faculty of Medicine Medical Genetic Department's Exome Databank.

A total of 9508 cases of hereditary thrombophilia factors with different clinical indications were included. Thrombophilia test indications were determined as: Idiopathic or recurrent VTE; the first episode of VTE at a "young" age (< 40 years); family history of VTE (especially a first-degree relative with thrombosis at a young age); venous thrombosis in an unusual vascular site (cerebral, hepatic, mesenteric, or renal vein thrombosis); pulmonary thromboembolism (PTE); and habitual abortion.

Prothrombin gene (FII; rs1799963; G20210A), FVL (FV-Leiden; rs6025; G1691A) hereditary thrombophilia factors were evaluated to provide a common data set in all centers.

Exclusion criteria were as follows: patients who applied to medical genetics clinics, whose thrombophilia genetic factors were not studied, and whose electronic medical data records could not be accessed.

Patient data and COVID-19 medical history were obtained from files and the hospital's electronic medical records.

Participants were divided into two groups: Participants who were polymerase chain reaction (PCR) and/or CT-positive were classified as COVID-19 group and participants who were never tested or only had negative test results were classified as non-COVID-19 group.

A randomized age-gender-matched group was formed to evaluate the patients in detail (COVID-19 $n = 372$; non-COVID-19 $n = 3720$; total patients $n = 4092$). The clinical features, PCR positivity, computerized tomography (CT) findings showing COVID-19-compatible lung involvement, familial and individual thrombosis histories, and genetic mutations predisposed to hereditary thrombophilia were compared with medical history related to COVID-19 disease. The history of thrombosis in patients was PTE, deep vein thrombosis, cerebrovascular disease, and disseminated intravascular coagulation.

Patients whose radiological examination findings were compatible with COVID-19 disease were classified as CT-positive. The patients were not vaccinated because the vaccine was not yet available at the time of the study.

2.1 | Statistical analyses

Data were analyzed using Statistical Package for the Social Sciences 22.0 IBM. Categorical variables were expressed as percentage frequency and continuous variables as mean ± standard deviation. The χ^2 test was used for categorical variables, and the independent t-test was used for continuous variables in group comparisons. A value of $p < 0.05$ was considered statistically significant.

3 | RESULTS

FII and FVL frequency data of healthy populations from Bursa Uludag University Faculty of Medicine Medical Genetic Department's Exome Databank were demonstrated in Supporting Information: 1. The descriptive information of 9508 cases who underwent the thrombophilia test is shown in Table 1.

There were 6902 females and 2606 males as participants in the study. The mean age was 34.18 ± 14.27. The prevalence of the FVL mutation detected in the study group was higher than FII. Only 5.49% of the participants had a positive family history of hereditary thrombophilia factors. PCR test was positive in 9.23%, and CT was positive in 2.42%. COVID-19 was detected in 930 patients (9.8%) by PCR and/or CT status. Of the 9508 cases, 8578 (90.2%) had no proven laboratory or clinical signs of COVID-19 (non-COVID-19) (Table 2).

The mean age and the proportion of male individuals were higher in the COVID-19 group (36.85 ± 15.20 and 31.08, respectively) resulting a statistical significance ($p < 0.001$ and $p = 0.008$, respectively). The prevalence of FII was higher (8.71%) and statistically significant ($p = 0.008$), and FVL was lower (16.45%) but not significant ($p = 0.11$) in the COVID-19 group. The reason for the high prevalence of FII was the FII heterozygous individuals. There was no significant difference ($p \geq 0.05$) between the two groups in terms of family history (Table 2).

Detailed clinical information of 372 patients in the COVID-19 group was obtained and compared with 3720 age-gender-matched non-COVID-19 participants (Table 3).

The frequency of FII mutation was higher in the COVID-19 patient group ($p < 0.001$). The frequency of FVL mutation was

TABLE 1 The descriptive information of individuals included in the study

	Individuals included in the study (*n* = 9508)
The mean age (*X* ± SD)	34.18 ± 14.27
Gender, *n* (%)	
Female	6902 (72.59)
Male	2606 (27.41)
Prevalence, *n* (%)	
FII	632 (6.65)
FVL	1864 (19.60)
FII, *n* (%)	
Normal	8876 (93.35)
Heterozygous	588 (6.18)
Homozygous	44 (0.46)
FVL, *n* (%)	
Normal	7644 (80.40)
Heterozygous	1661 (17.47)
Homozygous	203 (2.14)
Familial history of thrombosis, *n* (%)	
Absent	8986 (94.51)
Present	522 (5.49)
PCR test, *n* (%)	
None or negative	8630 (90.77)
Positive	878 (9.23)
CT findings, *n* (%)	
None or negative	9278 (97.58)
Positive	230 (2.42)

Abbreviations: CT, computerized tomography; FII, Prothrombin gene; FVL, Factor V Leiden; PCR, polymerase chain reaction.

TABLE 2 Comparison of COVID-19 and non-COVID-19 groups

	COVID-19 (*n* = 930)	Non-COVID-19 (*n* = 8578)	*p* value
The mean age (*X* ± SD)	36.85 ± 15.20	33.89 ± 14.14	**<0.001**
Gender, *n* (%)			
Female	641 (68.92)	6261 (72.99)	**0.008**
Male	289 (31.08)	2317 (27.01)	
Prevalence, *n* (%)			
FII	81 (8.71)	551 (6.42)	**0.008**
FVL	153 (16.45)	1711 (19.95)	**0.011**
FII, *n* (%)			
Normal	849 (91.29)	8027 (93.58)	**0.008**
Heterozygous	74 (7.96)	514 (5.99)	**0.018**
Homozygous	7 (0.75)	37 (0.43)	>0.05
FVL, *n* (%)			
Normal	777 (83.55)	6867 (80.05)	**0.011**
Heterozygous	136 (14.62)	1525 (17.78)	**0.016**
Homozygous	17 (1.83)	186 (2.17)	>0.05
Familial history of thrombosis, *n* (%)			
Absent	890 (95.70)	8096 (94.38)	>0.05
Present	40 (4.30)	482 (5.62)	

Note: *p* values in bold indicate statistically significant ($p < 0.05$).
Abbreviations: CT, computerized tomography; FII, Prothrombin gene; FVL, Factor V Leiden; PCR, polymerase chain reaction.

lower in the COVID-19 patient group ($p = 0.001$). When the familial history of thrombosis was evaluated between both groups, the number of cases in the COVID-19 group was lower ($p = 0.001$) (Table 3). The age-gender-matched COVID-19 patient group was divided into two subgroups according to the history of thrombosis (Table 4).

The mean age of COVID-19 patients with thrombosis was found to be higher than COVID-19 patients without thrombosis ($p < 0.001$), and there was no significant gender difference in either subgroup. The incidence of FVL mutation detected in COVID-19 patients with thrombosis was significantly higher than in COVID-19 patients without thrombosis ($p = 0.004$). In terms of FII mutation, the situation was the opposite ($p = 0.037$). COVID-19-related lung involvement (CT positivity) was higher in patients with thrombosis than in COVID-19 patients without thrombosis ($p = 0.017$); interestingly, the opposite relationship was found in PCR positivity ($p = 0.031$). This correlation was inversely proportional to PCR positivity and directly proportional to CT positivity (Table 4).

The age-gender-matched COVID-19 patient group was divided into two subgroups according to deceased and recovery status (Table 5).

The mean age of deceased patients was found to be higher than the mean age of patients with cured COVID-19 ($p < 0.001$), and no significant difference was found between the two groups in terms of gender.

The frequency of FVL mutation detected in COVID-19 patients who died was higher than in those who recovered, and no FII mutation was detected in the deceased group. The incidence of thrombosis medical history was found to be statistically significantly higher in patients who died compared to those who recovered ($p < 0.001$). In the evaluation made in terms of thrombotic events, the frequency of PTE was higher in patients who died.

The frequency of COVID-19 CT positivity was higher in the deceased patient group. There was no significant difference in PCR positivity between the groups.

TABLE 3 Descriptive information of age-gender-matched groups ($n = 4092$)

	COVID-19 ($n = 372$)	Non-Covid-19 ($n = 3720$)	p value
The mean age ($X \pm SD$)	41.14 ± 15.40	40.65 ± 14.47	>0.05
Gender, n (%)			
Male	120 (32.26)	1200 (32.26)	>0.05
Female	252 (67.74)	2520 (67.74)	
Prevalence, n (%)			
FII	52 (13.98)	278 (7.47)	**<0.001**
FVL	49 (13.17)	752 (20.22)	**0.001**
FII, n (%)			
Normal	320 (86.02)	3442 (92.53)	**<0.001**
Heterozygous	47 (12.63)	257 (6.91)	**<0.001**
Homozygous	5 (1.34)	21 (0.56)	>0.05
FVL, n (%)			
Normal	323 (86.83)	2968 (79.78)	**0.001**
Heterozygous	45 (12.10)	675 (18.15)	**0.003**
Homozygous	4 (1.08)	77 (2.07)	>0.05
Familial history of thrombosis, n (%)			
Present	6 (1.61)	211 (5.67)	**0.001**
Absent	366 (98.39)	3509 (94.33)	

Note: p values in bold are statistically significant ($p < 0.05$).
Abbreviations: CT, computerized tomography; FII, Prothrombin gene; FVL, Factor V Leiden; PCR, polymerase chain reaction.

TABLE 4 Descriptive information of age-gender-matched COVID-19 patients according to the presence of thrombosis medical history

COVID-19 patients	Thrombosis medical history present ($n = 67$)	Thrombosis medical history absent ($n = 305$)	p value
The mean age ($X \pm SD$)	47.96 ± 18.89	39.64 ± 14.12	**<0.001**
Gender, n (%)			
Male	28 (41.79)	92 (30.16)	>0.05
Female	39 (58.21)	213 (69.84)	
Prevalence, n (%)			
FII	4 (5.97)	48 (15.74)	**0.037**
FVL	16 (23.88)	33 (10.82)	**0.004**
PCR, n (%)			
Positive	58 (86.57)	287 (94.10)	**0.031**
Negative	9 (13.43)	18 (5.90)	
CT ($n = 247$), n (%)			
Positive	35 (63.64)	87 (45.31)	**0.017**
Negative	20 (36.36)	105 (54.69)	

Note: p values in bold are statistically significant ($p < 0.05$).
Abbreviations: CT, computerized tomography; FII, Prothrombin gene; FVL, Factor V Leiden; PCR, polymerase chain reaction.

4 | DISCUSSION

Thrombotic complications, especially PTE, observed in SARS-CoV-2 infection, which carries a high risk of thrombosis, are the cause of high mortality in patients.[11] It is important to monitor the prognosis in patients with COVID-19 and to identify patients at high risk of thrombosis in the post-COVID period. Although there are studies in the literature trying to reveal the relationship between COVID-19 hereditary thrombophilia factors,[12–16] there is no study examining the relationship between hereditary thrombophilia and COVID-19 in patients with high thrombosis risk. Demonstrating this relationship may facilitate the follow-up of COVID-19 patients in terms of clinical progression and enable appropriate treatment to be initiated in the early period. If patients with a predisposition to hereditary thrombosis suffer from COVID-19, early intervention will reduce the long-term mortality of patients due to thrombosis. In this study, a large group of patients at high risk for hereditary thrombophilia was evaluated, and the possible relationship between common hereditary thrombophilic gene mutations (FVL and FII) and COVID-19 was examined.

FVL mutation frequency varies between different geographical regions and ethnicity. The healthy population frequency of FVL is 2%–15%, 7.5%, 12.1%, and 8.4% in Caucasians, Greece, Cyprus, and Turkey, respectively.[17–19] The healthy population frequency of FII is 4.5% and 1.2% in Greece and Turkey, respectively. Recent meta-analysis study in Turkey, the frequency of FVL is 7.9% in the healthy population and 22.8% in VTE patients.[20] In addition, the frequency of FII mutations in the healthy population is 2.3% and 6.2% in the history of thrombosis.[21] This study group is the largest cohort (healthy = 2378, history of thrombosis = 9508) and previous findings support the present results. The FII and FVL mutation frequencies in the patient group with a predisposition to thrombophilia were higher than the population frequency obtained from Databank. In addition, the frequencies of the patient group who had COVID-19 were higher than the other two groups. These data thought a relationship between COVID-19 and hereditary thrombophilia factors.

Researchers demonstrated that the male and elderly population had a significantly higher disease positivity rate.[13,22,23] Despite the high number of females in the present study group, the rate of contracting COVID-19, a history of medical thrombosis, and mortality were higher in males. In addition, these individuals have an increased risk of thrombosis with age.[13,24] In the present study, the mean age was 34.18 ± 14.27. However, the mean age of the patients in the COVID-19 group, the COVID-19 thrombosis medical history group, and the deceased COVID-19 group gradually increased. Thus, it was observed that age was a factor affecting the severity of the disease. Ultimately, the present findings supported and strengthened previous research.

TABLE 5 Descriptive information of age-gender-matched COVID-19 patients by recovery/deceased status

COVID-19 patients	Deceased COVID-19 (n = 11)	Recovery status COVID-19 (n = 361)	p value[a]
The mean age ($X \pm SD$)	63.18 ± 18.71	40.47 ± 14.81	**<0.001**
Gender, n (%)			
Male	4 (36.36)	116 (32.13)	>0.05
Female	7 (63.64)	245 (67.87)	
Prevalence, n (%)			
FII	0 (0.00)	52 (14.40)	**<0.001**
FVL	4 (36.36)	45 (12.47)	**0.021**
History of thrombosis, n (%)			
Present	7 (63.64)	60 (16.62)	**<0.001**
Absent	4 (36.36)	301 (83.38)	
Thrombosis clinic, n (%)			
PTE	6 (54.55)	27 (7.48)	**<0.001**
DVT	1(9.09)	18 (4.99)	>0.05
PCR, n (%)			
Positive	10 (90.91)	335 (92.80)	>0.05
Negative	1(9.09)	26 (7.20)	
CT (n = 247), n (%)			
Positive	10 (90.91)	112 (47.46)	**<0.001**
Negative	1 (9.09)	124 (52.54)	

Note: p values in bold are statistically significant ($p < 0.05$).
Abbreviations: CT, computerized tomography; DVT, deep vein thrombosis; FII, Prothrombin gene; FVL, Factor V Leiden; PCR, polymerase chain reaction; PTE, pulmonary thromboembolism.
[a]Fisher's exact test.

In a retrospective study, clinical, laboratory, and CT findings were compared in 60 critically ill COVID-19 patients. Notably, the CT findings were compatible with COVID-19 in 100% (10/10) of all patients who died. The proportion of deceased patients with negative CT result was significantly lower than the proportion of deceased patients whose CT result was compatible with COVID-19.[25] In a study that supported the previous study and examined postmortem COVID-related pulmonary involvement, the presence of platelet-rich fibrin thrombus in the small arterial vessels of the lung tissues of patients who died due to COVID-19 was evaluated as a cause of mortality, indicating widespread thrombosis.[26] Increased inflammatory and procoagulant markers were associated with severe hypoxemia and major thrombotic events, emphasizing fibrinolytic suppression in the microcirculatory system and micro- and macrovascular thrombosis in severe COVID-19.[11,27] In the present study, the thrombosis medical history was found to be inversely proportional to PCR positivity, and directly proportional to CT positivity. In addition, CT positivity was statistically significant in deceased patients. Previous studies support the present findings.[11,14,25–28]

COVID-19 could lead to severe consequences such as adult respiratory syndrome, sepsis, coagulopathy, and death.[24] Coagulopathy was observed in nearly 50%–75% of COVID-19 patients with severe complications.[29,30] Many studies have found associations between hereditary thrombophilia factors (FVL, PAI-1, etc.) and thromboembolic disease, which is common in severe novel coronavirus pneumonia (NCP; COVID-19) and often associated with death,[13,31] while other have not.[15] In a study of autopsy patients, investigators found no association with inherited thrombophilia factors (FII and FVL) in patients with thromboembolism.[12]

In the present study, the frequency of thrombosis detected in the COVID-19 patient group was higher than in the non-COVID-19 group. FVL mutation affects thrombosis, but thrombosis is not associated with FII mutation. FVL hereditary thrombophilia has been shown to predispose to thrombosis in SARS-CoV-2 infected patients and poses an additional risk for the prothrombotic nature of COVID-19 disease. The present findings strengthened the observations made by Xie et al.[13] In addition, in this study, PTE thrombosis was diagnosed more frequently in COVID-19 patients who died, similar to the literature.[12]

The presence of thrombosis medical history in patients who died due to COVID-19 was high. Also, the frequency of FVL mutation was higher in COVID-19 patients who died as an additional risk factor for mortality. As a result, the presence of FVL hereditary thrombophilia in patients who died due to COVID-19 can be considered a significant risk factor for thrombosis and mortality.

There is no study in the literature examining cases of COVID-19 thrombophilia and familial features of the disease. In this study, the number of familial thrombosis cases detected in the COVID-19 group was lower than in the non-COVID-19 group. This result suggests other genetic factors that may play a role in familial cases of COVID-19. Undefined genetic risk factors for thrombotic events may affect the outcome of COVID-19. Exome analysis may be a useful tool for identifying these factors. This research is significant in that it is the first study in the literature to examine in terms of COVID-19 familial characteristics.

5 | CONCLUSION

In conclusion, thrombosis has increased in critically severe patients infected with COVID-19 and especially treated in ICUs. This retrospective study investigated the relationship between COVID-19 and hereditary coagulation factors FII and FVL. Advanced age, male gender, and positive CT were associated with COVID-19 severity. The frequency of FVL mutation detected in COVID-19 patients with a history of thrombosis was higher than in COVID-19 patients without a history of thrombosis. The FVL mutation was high, also in patients who died. FVL mutation can be regarded as a significant risk factor for a more severe course of COVID-19 infection and morbidity and mortality.

Therefore, the presence of FVL mutation can be considered as a prognostic factor affecting the severity of the disease. Based on these data, possible FVL mutation should be investigated in COVID-19 patients and appropriate treatment should be started earlier in FVL-positive patients.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are available upon request.

ETHICS STATEMENT

The multicenter research was approved by institutional ethics review boards. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Cukurova University, Fac. of Medicine/2020-102/07.08.2020 and Near East University, Faculty of Medicine YDU/2021/88-1294). Informed consent was obtained from all patients and parents.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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