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The relationship between thromboembolic conditions and hereditary thrombophilia in COVID-19 patients

Thromboembolic conditions and genetics in COVID-19

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Abstract

Aim: COVID-19 has spread rapidly worldwide, becoming a major cause of morbidity and mortality. This study investigates the relationship between this thrombosis-related disease and hereditary thrombophilia.

Methods: This single-center retrospective study included patients with hereditary thrombophilia (Factor V Leiden, Factor II, methylenetetrahydrofolate reductase gene (MTHFR) A1298C, plasminogen activator inhibitor-1 (PAI-1), and Factor XIII gene mutations) who presented to the emergency department during the pandemic. Demographic, clinical, and laboratory data were analyzed, with significance set at $P < .05$.

Results: A total of 203 cases were included. Thromboembolism (TE) was significantly higher in patients with Factor V and MTHFR A1298C mutations, while no such association was found for Factor II, Factor XIII, or PAI mutations. Homozygous mutations in any of the studied genes (Factor V, Factor II, Factor XIII, MTHFR A1298C, and PAI-1) were associated with a significantly higher incidence of TE compared to heterozygous or mutation-free cases. D-dimer levels and hospitalization rates were also elevated in TE cases.

In patients with positive COVID-19 polymerase chain reaction (PCR) tests, TE was significantly more frequent in those with MTHFR A1298C and Factor XIII mutations, a pattern not observed in PCR-negative cases. Homozygous mutations in any of the studied genes were again associated with increased TE risk in COVID-19-positive cases. Elevated D-dimer levels were particularly prominent in TE cases among COVID-19-positive patients. No significant differences were observed among other groups.

Conclusion: COVID-19 significantly increases thrombotic complications in patients with hereditary thrombophilia, highlighting the need for close monitoring in this population.

Keywords

thrombosis, hereditary, thrombophilia, COVID-19, genetics

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Introduction

COVID-19 disease, caused by SARS-CoV-2, emerged in Wuhan, China, in December 2019, and the World Health Organization declared it a pandemic in March 2020. The spectrum of COVID-19 disease is very wide; it can be asymptomatic or cause severe respiratory failure and even death.[1] Since its emergence, COVID-19 has caused both deaths and many complications, including thrombotic events, worldwide. It was confirmed that COVID-19 was reported in approximately 500 million cases and caused more than 6 million deaths in 2022.[2]

Hereditary thrombophilia is an inherited disease that causes thromboembolic (TE) events at young ages, leading to miscarriages and sudden deaths due to cerebral or coronary artery occlusion. Common mutations include Factor V Leiden, methylenetetrahydrofolate reductase gene (MTHFR) (C677T, A1298C), plasminogen activator inhibitor-1 (PAI-1) (4G-5G), and FXIII gene mutations, which are often the underlying cause in patients with hereditary thrombophilia. Few studies have examined the relationship between hereditary thrombophilia and increased thrombotic activity in COVID-19 patients.[3-5]

Prophylactic anticoagulant and antiplatelet treatment is started in patients with hereditary thrombophilia. However, venous or arterial TE events can still occur.[6,7] Studies report that COVID-19 disease could trigger thrombotic events in patients and may worsen the progression of the disease in patients with hereditary thrombophilia.[8,9] Again, in these studies, it is reported that the frequency of TE increases even in COVID-19 patients whose symptoms are mild enough to be followed up without hospitalization.[9]

Protein fragments originate from the breakdown of fibrin bonds in the final stage of coagulation. This protein fragment is D-dimer, and increased D-dimer levels in blood indicate that the coagulation and fibrinolytic systems are active.[10]

In our study, we aimed to investigate the effect of COVID-19 status on TE events in patients with hereditary thrombophilia and to contribute to the literature by doing so.

Materials and Methods

Study Setting and Study Population

This retrospective, single-center study was conducted in a tertiary education and research hospital. Patient data were retrieved from hospital records and the electronic medical system. The study population consisted of individuals with confirmed hereditary thrombophilia gene mutations (Factor V Leiden, Factor II, MTHFR, PAI-1, and Factor XIII) who presented to the hospital's genetics clinic and met the inclusion criteria. We monitored these patients during the COVID-19 pandemic.

Eligible participants were adults (≥18 years) with a prior diagnosis of hereditary thrombophilia who were admitted to the emergency department during the pandemic, with complete clinical data available. Exclusion criteria included age under 18, pregnancy, incomplete records, absence of hospital admission during the pandemic, uncertain thrombophilia diagnosis, history or active treatment of malignancy, unknown outcomes, or unavailable medical history. We confirmed COVID-19 infection using real-time polymerase chain reaction (RT-PCR) testing of nasopharyngeal swab samples.

Data Collection

We evaluated patients' hospital admission during the pandemic period, COVID-19 RT-PCR test results, TE status, TE type, hospitalization status, and outcomes.

The radiologist diagnosed deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE); cerebrovascular accident (CVA) was diagnosed by a neurologist and radiologist, and acute myocardial infarction (AMI) was evaluated and diagnosed by a cardiologist.

All patients included in the study had at least two doses of the BioNTech-Pfizer or CoronaVac vaccine. All hospitalized patients were started on prophylactic enoxaparin 40 mg/day.

Ethical Approval

This study was approved by the Ethics Committee of Basaksehir Çam and Sakura City Hospital (Date: 02.09.2021, Decision No: 2021.09.200).

Statistical Analysis

Statistical analysis was performed using the SPSS 26.0 for Windows statistical program (IBM Inc., Chicago, IL, USA). Descriptive data were presented as numbers, percentages, means, standard deviations, medians, minimums, and maximums. The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnov Test. Pearson's chi-square test and Fisher's Exact test were used to compare categorical data. We used the t-test to compare two independent numerical data sets and the Kruskal-Wallis test to compare three numerical data sets. Post Hoc analysis was also used to compare the three numerical data sets with each other.

Results were considered significant at $P < .05$, with a 95% confidence interval.

Reporting Guidelines

This study is reported in accordance with the STROBE guideline.

Results

We included 203 cases in our study. The study population had a mean age of 40.2 ± 12.3 years, with a nearly equal gender distribution (47.8% male and 52.2% female). Regarding genetic mutations, Factor V Leiden was absent in most patients (81.8%), while 3.0% were homozygous and 15.3% were heterozygous carriers. Factor II mutation was absent in 91.6% of cases, with 2.0% homozygous and 6.4% heterozygous mutations. For MTHFR A1298C, 47.8% showed no mutation, whereas 14.8% were homozygous and 37.4% heterozygous. PAI-1 mutation was absent in 43.3% of patients, while 15.8% were homozygous and 40.9% were heterozygous. Factor XIII mutation analysis revealed that 30.0% had the 5G/5G genotype, 20.7% were homozygous (4G/4G), and 49.3% were heterozygous (4G/5G).

During the COVID-19 pandemic, 48.3% of patients tested positive, while 51.7% were negative. Homozygous mutations were present in 46.3% of cases. Mortality was observed in only 1.0% of patients, whereas hospitalization was required in 46.3%.

Thrombosis was found in 17.7% of the cases (acute TE during the pandemic period). When these thrombosis conditions were classified, DVT was observed in 38.9%, PTE in 36.1%, CVA in 11.1%, and AMI in 13.9% of patients. Laboratory findings showed a mean platelet count of 280.39 ± 96.65 $\times 10^3/mm^3$, prothrombin time of 12.38 ± 4.66 seconds, activated partial thromboplastin time of 24.46 ± 11.83 seconds, international normalized ratio (INR) of 1.04 ± 0.62, and D-dimer levels averaging 1319.34 ± 2115.79 µg/L.

We evaluated the relationship between demographic, clinical, and laboratory data by TE status, and found no correlation between TE status and age, gender, or mortality. When the mutation states

were examined, TE was found to be significantly higher in cases with Factor V Leiden and MTHFR A1298C mutations. However, no relationship was detected in cases with Factor II, Factor XIII, or PAI mutations. Again, TE was significantly higher in cases with homozygous mutations in any of these genes, including Factor V Leiden, Factor II, Factor XIII, MTHFR A1298C, and PAI-1, than in cases with no mutations or heterozygous mutations. Hospitalization was significantly higher in patients in the non-TE group. When the relationship between laboratory data and TE were examined, D-Dimer was found to be significantly higher in cases with TE. There was no significant correlation between other laboratory results and TE (Supplementary Table 1).

When thrombosis status was evaluated based on COVID-19 RT-PCR results, 28.6% of 98 patients with COVID-19 RT-PCR-positive results had TE, whereas 71.4% did not. TE was also observed in 7.6% of 105 patients who tested negative for COVID-19 RT-PCR, while 92.4% did not have TE. There was no significant relationship between age and TE presence, as well as COVID-19 status ($P > .05$). Among COVID-19 positive cases, TE was significantly higher in cases with MTHFR A1298C and Factor XIII mutations ($P = .007$ and $P = .015$, respectively). This was not the case for COVID-19-negative cases. Again, the presence of TE was found to be significantly higher in cases with homozygous mutations in any of the Factor V Leiden, Factor II, Factor XIII, MTHFR A1298C, and PAI-1 mutations than in cases with no mutations or heterozygous mutations ($P = .030$). This relationship was not detected for COVID-19 (-) cases. Among both the COVID-19 (+) and COVID (-) cases, hospitalization was significantly higher in cases with TE. In laboratory results, D-Dimer was significantly higher in cases with TE for both COVID-19 (+) and COVID (-) cases. This relationship was not significant in platelet (PLT), PT, activated partial thromboplastin time (aPTT), and INR values (Supplementary Table 2).

The association of cases with DVT, PTE, CVA, and AMI with gene mutations causing hereditary thrombophilia was examined, and no gene mutations were found to be associated with a specific TE type ($P > .05$ for all TE types).

In our study, the differences in D-dimer levels were examined according to the gene mutation types, and it was observed that the D-dimer level was significantly higher in cases with Factor XIII gene mutations ($P = .035$). In the post hoc analysis performed for this gene mutation, D-dimer level was found to be significantly higher in cases with homozygous gene mutation (4G/4G) as well as in cases with heterozygous gene mutation (4G/5G) compared to cases without Factor XIII gene mutation ($P = .010$ [95% CI: 266.91-1917.17] and $P = .038$ [95% CI: 40.75-1377.88] respectively). We did not observe this difference in D-dimer levels in cases with Factor V Leiden, Factor II, MTHFR A1298C, or PAI-1 mutations.

Cases were grouped according to COVID-19 RT-PCR results (+/-) and TE status (+/-), and the relationship between those statuses and D-dimer levels was examined. It was determined that D-dimer differed significantly according to COVID-19 results and TE status ($z = 51.89$; $P < .001$). According to the post hoc analysis results, it was observed that D-dimer was significantly higher in COVID-19 (+) and TE (+) cases than in other groups. There was no significant difference between the other groups (Supplementary Table 3).

Discussion

In our study, TE was found to be significantly higher in COVID-19 RT-PCR-positive cases with MTHFR A1298C and Factor XIII gene mutations compared to COVID-19-negative cases. This relationship was not detected in other hereditary thrombophilia gene mutations. Again, in cases with homozygous mutations in any of Factor V Leiden, Factor II, Factor XIII, MTHFR A1298C, and PAI-1 mutations, TE was found to be significantly higher than in cases with no mutations or heterozygous mutations.

There are studies investigating the relationship between thrombotic events and hereditary thrombophilia in cases of mortality due to COVID-19 disease.[5] Abdullaev et al. evaluated the relationship between FV (506R/Q), MTHFR (223A/V), F2 (20210G/A), PAI-1 (4G/5G) mutations and COVID-19. They reported that MTHFR 223A/V heterozygous and PAI-1 (4G/5G) genotypes were more frequent in cases with COVID-19 and thrombotic conditions, whereas the incidence of heterozygous FV (506R/Q), MTHFR (223A/V), and F2 (20210G/A) was lower. However, they reported that more patients were needed to reach a firm conclusion.[4,5] Again, in the studies by Khan S. and Han et al., it was reported that there is a strong relationship between PAI-1 and thrombotic complications of COVID-19.[3,11] In the study by Burlacu et al., hereditary thrombophilia was investigated in a COVID-19-positive male with stroke, and MTHFR A1298C, Factor XIII, angiotensin-converting enzyme (ACE) D/I, angiotensinogen (e3/e4), and angiotensinogen (AGT) M235T gene mutations were reported.[12] Cappadona et al. reported that COVID-19 has a poor prognosis in cases with MTHFR and methionine synthase (MTR) gene mutations.[13] Ponti et al. reported an increased incidence and severity of COVID-19 disease in patients with MTHFR gene mutations.[14]

In the study by de la Morena-Barrio et al., they examined the relationship between hereditary thrombophilia and thrombotic events due to COVID-19 and reported no interaction.[15] The results of this study differ from the results of the studies by Khan S, Han et al., and de la Morena-Barrio et al. However, they support the findings of Burlacu et al., Ponti et al., and Cappadona et al.

D-dimer is a fibrin degradation product, reflecting pathological activation of hemostatic pathways in COVID-19 patients. In our study, the relationship between gene mutations and D-dimer levels was evaluated. We found that D-dimer was significantly higher in the presence of a Factor XIII mutation. This association was not seen in Factor V Leiden, Factor II, MTHFR A1298C, and PAI-1 mutations. In the cohort study by Köse et al., it was found that D-dimer was significantly higher in patients with Factor V Leiden mutation.[16] Chaireti et al. reported that D-dimer levels in patients with TE who had either homozygous or heterozygous Factor V Leiden mutations were significantly higher than in the control group (without the Factor V Leiden mutation).[17] According to the results of this study, unlike the literature, no significant relationship between Factor V Leiden mutation and D-dimer was found. We think that this may be due to the low number of patients with the Factor V Leiden mutation in our study.

Studies report that mortality in COVID-19 is associated with high D-dimer levels. We wanted to compare this relationship in patients with hereditary thrombophilia, but the low mortality rate in this study makes it difficult to conclude. Nevertheless, we found that the D-dimer level in cases with COVID-19 and with TE was significantly higher than in patients who tested negative for COVID-19 (Supplementary Table 3). Tang et al. reported that D-dimer levels in patients who died from COVID-19 were significantly higher than in those who survived.[18] According to Kampouri et al., D-dimer was significantly higher in COVID-19-positive cases with venous TE.[19] Brosnahan et al. reported that D-dimer levels in COVID-19-positive cases with TE are significantly higher than in COVID-19-negative cases with TE.[20] In this context, our study supports the literature data.

Limitations

The study has several limitations. The first is the risk of data loss and errors due to the retrospective nature of our study. Second, we followed up a small number of patients because cases were referred to other hospitals or transferred to other hospitals with similar conditions. Third, we did not have the opportunity to examine all gene mutations associated with hereditary thrombophilia. However, we do not think these limitations are sufficient to affect our study results.

Conclusion

Our study found that COVID-19 increased thrombotic complications in patients with hereditary thrombophilia. In addition, we believe anticoagulant and antiplatelet therapy in patients with hereditary thrombophilia can reduce both COVID-19-related and thrombotic complications.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Due to the retrospective design of the study, the requirement for informed consent was waived by the Ethics Committee.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest.

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None.

Author Contributions (CRediT Taxonomy)

Conceptualization: T.Ç., A.T., T.K., M.T.A., A.Ç., E.A., A.A.
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Writing – review & editing: A.T., H.C., A.Ç., E.A., A.A.

AI Usage Disclosure

The authors declare that no AI-assisted technologies were used.

Abbreviations

ACE: Angiotensin-converting enzyme
AGT: Angiotensinogen
AMI: Acute myocardial infarction
aPTT: Activated partial thromboplastin time
COVID-19: Coronavirus disease 2019
CVA: Cerebrovascular accident
DVT: Deep vein thrombosis
F2: Factor ii
FXIII: Factor xiii
INR: International normalized ratio
MTHFR: Methylenetetrahydrofolate reductase
MTR: Methionine synthase
PAI-1: Plasminogen activator inhibitor-1
PCR: Polymerase chain reaction
PLT: Platelet
PTE: Pulmonary thromboembolism
RT-PCR: Real-time polymerase chain reaction
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
STROBE: Strengthening the reporting of observational studies in epidemiology
TE: Thromboembolism

References

1. *Kimball A, Hatfield KM, Arons M, et al. Asymptomatic and presymptomatic SARS-CoV-2 infections in residents of a long-term care skilled nursing facility—King County, Washington, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(13):377-381. doi:10.15585/mmwr.mm6913e1*

2. *World Health Organization. WHO coronavirus (COVID-19) dashboard. Published 2024. Accessed June 4, 2025. https://covid19.who.int/*

3. *Khan SS. The central role of PAI-1 in COVID-19: thrombosis and beyond. Am J Respir Cell Mol Biol. 2021;65(3):238-240.*

4. *Badulescu OV, Sirbu PD, Filip N, et al. Hereditary thrombophilia in the era of COVID-19. Healthcare (Basel). 2022;10(6):993. doi:10.3390/healthcare10060993*

5. *Abdullaev A, Fevraleva I, Odilov A, et al. Thrombotic events and the profile of hereditary thrombophilia factors in COVID-19 patients. HemaSphere. 2021;5(Suppl 2):641.*

6. *Cui S, Chen S, Li X, Liu S, Wang F. Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia. J Thromb Haemost. 2020;18(6):1421-1424. doi:10.1111/jth.14830*

7. *Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with COVID-19 infection. Thromb Res. 2020;192:75-77. doi:10.1016/j.thromres.2020.05.025*

8. *Labò N, Ohnuki H, Tosato G. Vasculopathy and coagulopathy associated with SARS-CoV-2 infection. Cells. 2020;9(7):1583. doi:10.3390/cells9071583*

9. *Nauka PC, Oran E, Chekuri S. Deep venous thrombosis in a non-critically ill patient with novel COVID-19 infection. Thromb Res. 2020;192:27-28. doi:10.1016/j.thromres.2020.05.015*

10. *Gaffney PJ. Breakdown products of fibrin and fibrinogen: molecular mechanisms and clinical implications. J Clin Pathol Suppl (R Coll Pathol). 1980;14:10-17. doi:10.1136/jcp.33.suppl_14.10*

11. *Han M, Pandey D. ZMPSTE24 regulates SARS-CoV-2 spike protein–enhanced expression of endothelial PAI-1. Am J Respir Cell Mol Biol. 2021;65(3):300-308. doi:10.1165/rcmb.2020-0544oc*

12. *Burlacu A, Artene B, Crisan-Dabija R, Popa IV, Covic A. Is thrombophilic genetic profile responsible for an acute ischemic stroke in a COVID-19 male patient? Clin Appl Thromb Hemost. 2020;26:1076029620967107. doi:10.1177/1076029620967107*

13. *Cappadona C, Paraboschi EM, Ziliotto N, et al. MEDTEC students against coronavirus: investigating the role of hemostatic genes in the predisposition to COVID-19 severity. J Pers Med. 2021;11(11):1166. doi:10.3390/jpm11111166*

14. *Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-399. doi:10.1080/10408363.2020.1770685*

15. *Bravo-Pérez C, de la Morena-Barrio ME, de la Morena-Barrio B, et al. Molecular and clinical characterization of transient antithrombin deficiency: a new concept in congenital thrombophilia. Am J Hematol. 2022;97(2):216-225.*

16. *Kose M, Senkal N, Konyaoglu H, et al. The effect of hereditary thrombotic factors and comorbidities on the severity of COVID-19 disease. Eur Rev Med Pharmacol Sci. 2023;27(1):395-403.*

17. *Chaireti R, Jennersjö C, Lindahl TL. Thrombin generation and D-dimer concentrations in a patient cohort investigated for venous thromboembolism: relations to venous thrombosis, factor V Leiden and prothrombin G20210A. The LIST study. Thromb Res. 2009;124(2):178-184. doi:10.1016/j.thromres.2008.12.033*

18. *Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-847. doi:10.1111/jth.14768*

19. *Kampouri E, Filippidis P, Viala B, et al. Predicting venous thromboembolic events in patients with coronavirus disease 2019 requiring hospitalization: an observational retrospective study. Biomed Res Int. 2020;2020:9126148. doi:10.1155/2020/9126148*

20. *Brosnahan SB, Smilowitz NR, Amoroso NE, et al. Thrombosis at hospital presentation in patients with and without coronavirus disease 2019. J Vasc Surg Venous Lymphat Disord. 2021;9(4):845-852. doi:10.1016/j.jvsv.2020.11.004*

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