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***Original Article*** / *Özgün Makale*

# Genes predisposing tunneled catheter thrombosis in hemodialysis patients

*Hemodiyaliz hastalarında tünelli kateter trombozuna yol açan genler*

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***ABSTRACT***

***Background:*** This study aims to investigate the association of genes predisposing thrombophilia with tunneled catheter thrombosis in hemodialysis patients.

***Methods:*** Between October 2018 and December 2020, we compared the frequencies of genetic polymorphisms causing thrombophilia, including prothrombin G20210A, factor V Leiden, *methylene tetrahydrofolate reductase (MTHFR)* C677T, *MTHFR* A1298C, plasminogen activator inhibitor (PAI), factor XIII V34L and clinical characteristics of 52 patients with a history of ≥2 tunneled catheter thrombosis occlusions within a year (Group 1; 24 males, 28 females; mean age: 62±8.9 years; range, 45 to 77 years), 52 patients who underwent their first tunneled catheter thrombosis insertion (Group 2; 29 males, 23 females; mean age: 63±15.2 years; range, 22 to 87 years), and 51 healthy controls (Group 3; 26 males, 25 females; mean age: 34±9.2 years; range, 19 to 54 years).

***Results:*** Groups 1 and 2 carried the *MTHFR* A1298C (p=0.048) and compound heterozygous *MTHFR* A1298C and C677T (p=0.048) polymorphisms more frequently than Group 3. However, subgroup analysis results were not statistically significant. The other polymorphisms were distributed similarly in all three groups. The *MTHFR* polymorphisms had a weak effect on tunneled hemodialysis catheter thrombosis in neural network analysis.

***Conclusion:*** Our study results indicated that there was a concomitance of *MTHFR* polymorphisms with hemodialysis-dependent chronic kidney disease. The *MTHFR* A1298C and compound heterozygous *MTHFR* polymorphisms may be associated with tunneled hemodialysis catheter thrombosis. Thrombophilia gene screening may be recommended in hemodialysis patients undergoing tunneled hemodialysis catheter thrombosis at least twice in a year.

***Keywords:*** Chronic kidney disease, genetic polymorphism, thrombophilia, thrombosis, tunneled hemodialysis catheter.

***ÖZ***

***Amaç:*** Bu çalışmada hemodiyaliz hastalarında tünelli kateter trombozu ile trombofiliye eğilim yaratan genlerin ilişkisi araştırıldı.

***Çalışma planı:*** Ekim 2018 - Aralık 2020 tarihleri arasında, trombofiliye neden olan genetik polimorfizmlerden protrombin G20210A, faktör V Leiden, *metilen tetra-hidrofolatredüktaz (MTHFR)* C677T, *MTHFR* A1298C, plazminojen aktivatör inhibitörü (PAI), faktör XIII V34L sıklıkları ve yılda ikiden fazla tünelli hemodiyaliz kateteri trombozu yaşayan 52 hastanın (Grup 1; 24 erkek, 28 kadın; ort. yaş: 62±8.9 yıl; dağılım, 45-77 yıl), ilk kez tünelli kateter tromboz girişimi yapılan 52 hastanın (Grup 2; 29 erkek, 23 kadın; ort. yaş: 63±15.2 yıl; dağılım, 22-87 yıl) ve 51 sağlıklı kontrolün (Grup 3; 26 erkek, 25 kadın; ort. yaş: 34±9.2 yıl; dağılım, 19-54 yıl) klinik özellikleri karşılaştırıldı.

***Bulgular:*** Grup 1 ve Grup 2'deki hastaların *MTHFR* A1298C (p=0.048) ve bileşik heterozigot *MTHFR* A1298C ve C677T (p=0.048) polimorfizmlerini, Grup 3'deki sağlıklı kontrollere kıyasla daha sık taşıdıkları saptandı. Ancak alt grup analiz sonuçları istatistiksel olarak anlamlı değildi. Diğer polimorfizmler, üç grupta benzer oranda dağılmaktaydı. Nöral ağ analizinde, *MTHFR* polimorfizmlerinin tünelli hemodiyaliz kateter trombozu üzerine zayıf etki gösterdiği saptandı.

***Sonuç:*** Çalışma sonuçlarımız *MTHFR* polimorfizmlerinin hemodiyaliz bağımlı kronik böbrek yetmezliği ile birlikteliğini gösterdi. *MTHFR* A1298C ve bileşik heterozigot *MTHFR* A1298C ve C677T polimorfizmleri tünelli hemodiyaliz kateteri trombozu ile ilişkili olabilir. Trombofili genlerinin taraması yılda ikiden fazla tünelli hemodiyaliz kateter trombozu yaşayan hemodiyaliz hastalarında önerilebilir.

***Anahtar sözcükler:*** Kronik böbrek yetmezliği, genetik polimorfizm, trombofili, tromboz, tünelli hemodiyaliz kateteri.

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Preserving dialysis access patents in chronic kidney disease (CKD) patients is vital. While some patients with arteriovenous fistulas (AVFs) or tunneled hemodialysis catheters (THC) can undergo dialysis for a long time, others quickly lose their access for dialysis. They require recurrent interventions for access thrombosis, and they experience serious complications, such as deep vein thrombosis (DVT) and pulmonary embolism (PE). The patient is lost, when effective dialysis cannot be performed. Therefore, the patency of dialysis access prolongs the lifespan and improves the quality of life of CKD patients.

Genetic polymorphisms most commonly considered responsible for hemodialysis (HD) access thrombosis or occlusion are *methyltetrahydrofolate reductase (MTHFR)*, factor V, and other coagulation factors, hem-oxygenase 1, matrix metalloproteinases, transforming growth factor-beta1, tumor necrosis factor-alpha, vascular endothelial growth factor-A, and genes involved in the renin-angiotensin-aldosterone system.[1]

In our clinical practice, we observe that some CKD patients have recurrent THC thrombosis. In the present study, we aimed to investigate the association of common genetic polymorphisms predisposing thrombophilia with THC thrombosis in HD patients.

## PATIENTS AND METHODS

This prospective cross sectional study was conducted at Manisa Celal Bayar University Faculty of Medicine, Department of Cardiovascular Surgery between October 4th, 2018 and December 31st, 2020. We compared the frequencies of common thrombophilia-causing genetic polymorphisms, including prothrombin G20210A (factor II), factor V Leiden, *MTHFR* C677T, *MTHFR* A1298C, PAI, and factor XIII V34L, as well as demographic and clinical characteristics of 52 patients with a history of ≥2 THC occlusions within a year (Group 1; 24 males, 28 females; mean age: 62±8.9 years; range, 45 to 77 years), 52 patients who underwent their first THC insertion (Group 2; 29 males, 23 females; mean age: 63±15.2 years; range, 22 to 77 years), and 51 healthy controls (Group 3; 26 males, 25 females; mean age: 34±9.2 years; range, 19 to 54 years). The THC insertion indication was determined by the nephrologists. When catheter disfunction occurs, they apply thrombolytic therapy at first. If it fails, the nephrologists consult the patient to cardiovascular surgery clinic for a new THC insertion. All CKD patients in our study were consulted to cardiovascular surgery clinic due to acute HD requirement. Most of the patients in Group 1 had multiple prior failed arteriovenous access with no available options. Some of the patients in Group 2 had immature AVF. The MAHURKAR™ 14.5-Fr dual lumen catheter (Covidien, Mansfield, MA, USA) was inserted from the right jugular vein in most of HD patients. In patients whose right jugular vein was occluded, the left jugular vein used as the second option. The authors planned to include minimum 40 participants for each group according to *priori* samples size computations. All patients who applied to the hospital with a history of ≥2 THC occlusions within a year during the study period were included in the study and the number of other groups was planned equal to Group 1. Patients with active and former catheter infection were excluded from the study.

Comorbid diseases such as hypertension, diabetes mellitus, hyperlipidemia, obesity, peripheral artery disease (PAD), rheumatic disease, CKD etiology, also history of DVT, PE, familial thrombophilia, consanguinity, smoking, alcohol use, antiplatelet or anticoagulant drug use were investigated.

### Investigation of genetic polymorphisms

Blood samples were obtained from admitted CKD patients in the cardiovascular surgery department for HD catheter insertion and from healthy volunteers. The blood samples were transferred to

**Table 1. Demographic characteristics of the groups**

| | Group 1 (n=52) | | | Group 2 (n=52) | | | Group 3 (n=51) | | | *P* value for pairwise comparison | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | n | % | Mean±SD | n | % | Mean±SD | *p* | I→II | I→III | II→III |
| Age (year) | | | 62±8.9 | | | 63±15.2 | | | 34±9.2 | <0.001† | 0.913 | <0.001 | <0.001 |
| BMI (kg/m$^2$) | | | 27±4.3 | | | 25±5 | | | 24±3.3 | 0.010† | 0.155 | 0.007 | 0.442 |
| Sex | | | | | | | | | | 0.625‡ | | | |
| Male | 24 | 46.2 | | 29 | 55.8 | | 26 | 51.0 | | | NS | NS | NS |
| Female | 28 | 53.8 | | 23 | 44.2 | | 25 | 49.0 | | | NS | NS | NS |

SD: Standard deviation; BMI: Body mass index; † One-way analysis of variance; ‡ Pearson chi-square Test. NS: Not significant.

the ethylenediaminetetraacetic acid blood tube, and the deoxyribonucleic acid (DNA) was separated using an isolation kit. The separated DNA samples were replicated through a polymerase chain reaction stage in an ABI PRISM™ 3130 genetic analyzer (Applied Biosystems, USA). A DNA sequence analysis was performed, and thrombophilia genes were investigated using the BigDye™ Terminator Cycle Sequencing Ready Reaction kit (ThermoFisher Scientific, MA, USA). Common gene polymorphisms related to thrombophilia were investigated.

### Statistical analysis

*A priori* computation for required sample size based on chi-square test made by using G*Power version 3.1.9.7 program (Heinrich-Heine-Universität, Düsseldorf, Düsseldorf, Germany). When given $\alpha$=0.05, power =0.95, effect size =0.50, 40 patients were sufficient for each group.

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median ($25^{th}$-$75^{th}$ percentiles), while categorical data were expressed in number and frequency. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

Normality was evaluated using the Kolmogorov-Smirnov test, while variance homogeneity was evaluated using the Levene test. For comparing quantitative data of three independent groups, one-way analysis of variance (Robust Test: Brown-Forsythe) was used as a parametric test, and the Fisher Tukey's honestly significant difference (HSD) and Games-Howell tests were used for *post-hoc* analyses. The Kruskal-Wallis test was used to compare non-normally distributed quantitative data, with the Monte Carlo simulation technique results, and the Dunn's test was used for *post-hoc* analyses. The Pearson chi-square and Fisher-Freeman-Holton tests were used to compare categorical variables among the groups, with the Monte Carlo simulation technique.

Logistic regression, simple (native) Bayes classification, and neural network (multilayer perceptron-Radial basis) analyses were used to identify the most significant variable causing THC thrombosis. Neural network analysis was the most successful model among these methods. A gradient descent was used for the optimization algorithm, the hyperbolic tangent was used as the hidden layer activation function, and Softmax was used as the

**Table 2. Patient characteristics and comorbidities**

| | Group 1 (n=52) | | | | Group 2 (n=52) | | | | Group 3 (n=51) | | | | | *P* value for pairwise comparison | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | Median | IQR | n | % | Median | IQR | n | % | Median | IQR | *p* | I→II | I→III | II→III |
| Catheter insertions | | | 4 | 3-5 | | | 1 | 1-1 | | | 0 | 0-0 | <0.001* | <0.001 | <0.001 | <0.001 |
| Duration of hemodialysis (year) | | | 3.5 | 2-8 | | | 1 | 1-2 | | | 0 | 0-0 | <0.001* | <0.001 | <0.001 | <0.001 |
| Obesity | $16^{III}$ | 30.8 | | | $13^{III}$ | 25.0 | | | 5 | 9.8 | | | 0.030† | NS | 0.008 | 0.042 |
| Hypertension | $28^{II..III}$ | 53.8 | | | $17^{II}$ | 32.7 | | | 5 | 9.8 | | | <0.001† | 0.029 | <0.001 | 0.005 |
| Diabetes mellitus | $28^{III}$ | 53.8 | | | $26^{III}$ | 50.0 | | | 0 | 0.0 | | | <0.001† | NS | <0.001 | <0.001 |
| Hyperlipidemia | 5 | 9.6 | | | $15^{I}$ | 28.8 | | | 0 | 0.0 | | | <0.001† | 0.013 | NS | 0.005 |
| Peripheral artery disease | $6^{III}$ | 11.5 | | | 4 | 7.7 | | | 0 | 0.0 | | | 0.038‡ | NS | 0.039 | NS |
| Rheumatic disease | 1 | 2.0 | | | 1 | 1.9 | | | 0 | 0.0 | | | 0.999‡ | NS | NS | NS |
| History of familial thrombophilia | 1 | 1.9 | | | 2 | 3.8 | | | 0 | 0.0 | | | 0.999‡ | NS | NS | NS |

IQR: Interquartile range; NS: Not significant; * Kruskal Wallis Test, † Pearson chi-square Test, ‡ Fisher Freeman Halton.

output layer activation function. The mini-batch method was used for the selection of training data.

## RESULTS

We compared CKD patients with recurrent THC thrombosis (≥2 times in a year) with beginners of HD who had their first THC and 51 healthy controls. Group 3 had the lowest mean age, and a lower body mass index. The sex distribution was similar among the three groups (Table 1). Regarding comorbidities, obesity and diabetes were more frequently observed in Groups 1 and 2 than in Group 3. Hypertension and PAD were more common in Group 1 than in Groups 2 and Group 3. The groups were similar in terms of rheumatic diseases (Table 2).

Groups 1 and 2 had similar CKD etiologies. Diabetes was the most common etiology (n=18 in Group 1 and n=17 in Group 2). Diabetes was followed by polycystic kidney disease and then hypertension. Other etiologies were kidney stones, postrenal occlusions, drug-induced nephrotoxicity, nephritis, eclampsia, congestive heart failure, and multiple myeloma.

The median duration of HD treatment in Groups 1 and 2 were 3.5 years (range, 2 to 8) and

**Table 3. The frequencies of common genetic polymorphisms causing thrombophilia**

| | Group 1 (n=52) | | Group 2 (n=52) | | Group 3 (n=51) | | | *P* value for pairwise comparison | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | *p* | (I→II) | (I→III) | (II→III) |
| MTHFR A1298C | | | | | | | | | | |
| Normal | 19 | 36.5 | 19 | 36.5 | 29[I,II] | 56.9 | | NS | 0.039 | 0.039 |
| Heterozygote | 22 | 42.3 | 28 | 53.8 | 18 | 35.3 | 0.048† | NS | NS | NS |
| Homozygote | 11 | 21.2 | 5 | 9.6 | 4 | 7.8 | | NS | NS | NS |
| MTHFR C677T | | | | | | | | | | |
| Normal | 25 | 48.1 | 23 | 44.2 | 27 | 52.9 | | NS | NS | NS |
| Heterozygote | 24 | 46.2 | 21 | 40.4 | 17 | 33.3 | 0.441† | NS | NS | NS |
| Homozygote | 3 | 5.8 | 8 | 15.4 | 7 | 13.7 | | NS | NS | NS |
| Compound heterozygote MTHFR | 16 | 30.8 | 15 | 28.8 | 6 | 11.8 | 0.048† | NS | 0.019 | 0.031 |
| Factor II (G2021A) | | | | | | | | | | |
| Normal | 48 | 92.3 | 48 | 92.3 | 49 | 96.1 | | NS | NS | NS |
| Heterozygote | 4 | 7.7 | 4 | 7.7 | 2 | 3.9 | 0.772‡ | NS | NS | NS |
| Homozygote | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | | NS | NS | NS |
| Factor V (Leiden) | | | | | | | | | | |
| Normal | 47 | 90.4 | 47 | 90.4 | 47 | 92.2 | | NS | NS | NS |
| Heterozygote | 3 | 5.8 | 5 | 9.6 | 4 | 7.8 | 0.576‡ | NS | NS | NS |
| Homozygote | 2 | 3.8 | 0 | 0.0 | 0 | 0.0 | | NS | NS | NS |
| PAI | | | | | | | | | | |
| 4G/4G | 8 | 15.4 | 8 | 15.4 | 14 | 27.5 | | NS | NS | NS |
| 4G/5G | 33 | 63.5 | 32 | 61.5 | 28 | 54.9 | 0.528† | NS | NS | NS |
| 5G/5G | 11 | 21.2 | 12 | 23.1 | 9 | 17.6 | | NS | NS | NS |
| Factor XIII (V34L) | | | | | | | | | | |
| Normal | 34 | 65.4 | 30 | 57.7 | 39 | 76.5 | | NS | NS | NS |
| Heterozygote | 16 | 30.8 | 22 | 42.3 | 11 | 21.6 | 0.106‡ | NS | NS | NS |
| Homozygote | 2 | 3.8 | 0 | 0.0 | 1 | 2.0 | | NS | NS | NS |

MTHFR: Methylene tetrahydrofolate reductase; PAI: Plasminogen activator inhibitor; NS: Not significant; † Pearson chi-square test, ‡ Fisher Freeman Halton. test

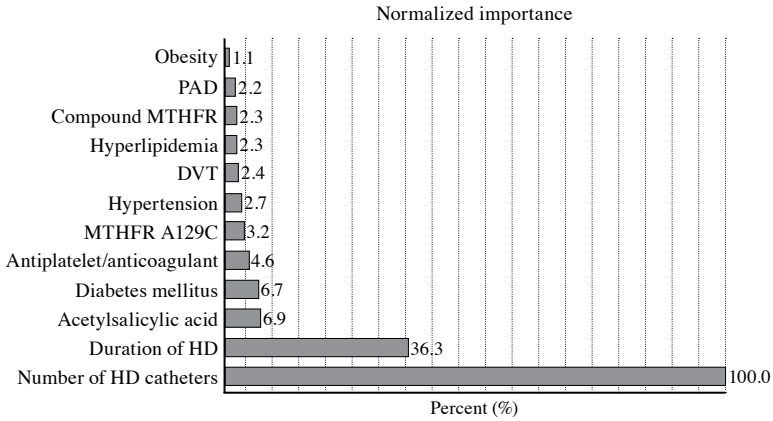


**Figure 1.** Factors effecting tunneled hemodialysis catheter thrombosis, Neural Network (Multilayer Perceptron), Hidden layer activation function: Hyperbolic tangent, Output layer activation function: Softmax, Dependent Variable: Groups,

PAD: Peripheral artery disease; MTHFR: Methylene tetrahydrofolate reductase; DVT: Deep vein thrombosis; HD: Hemodialysis.

1 year (range, 1 to 2), respectively. The median inserted catheter numbers in Groups 1 and 2 were four (range, 3 to 5) and one (range, 1 to 1), respectively.

A history of PE (p=0.31), smoking (p=0.54), alcohol use (p=0.1), consanguinity (p=0.9), and familial thrombophilia (p=0.9) were similar in all three groups. However, the history of DVT was higher in Group 1 (p=0.001).

The *MTHFR* A1298C (p=0.048) and compound heterozygous *MTHFR* A1298C and C677T (p=0.048) polymorphisms were more frequently observed in Groups 1 and 2 than in Group 3. Despite a significant difference in overall comparisons among the three groups, the subgroup analysis between Group 1 and Group 2 did not show a statistically significant difference in terms of *MTHFR* polymorphisms frequency. Other polymorphisms were similarly distributed among the groups (Table 3).

The neural network analysis showed that *MTHFR* A129C and compound *MTHFR* polymorphisms had a weak effect on the HD catheter thrombosis. The most important variables affecting catheter thrombosis were the frequency of HD catheter insertions and the duration of HD treatment, as well as the presence of diabetes. The other variables contributing HD catheter thrombosis were antiplatelet drug usage, hypertension, history of DVT, hyperlipidemia, PAD, and obesity (Figure 1).

## DISCUSSION

It is important to ensure safe and durable HD access for CKD patients, for which AVFs are ideal. However, THC are needed in patients who have no options for the AVF. Approximately 23 to 28% of patients with CKD continue long-term HD via THC. Of note, THC have specific complications, such as bacteremia and sepsis, occlusion due to fibrin sheath formation or catheter lumen thrombosis, and central vein narrowing or occlusion.[2,3] The one- and three-year patency rates of THC are 60 to 77% and 44 to 51%, respectively,[4] with low long-term patency rates.[5]

The patency of dialysis access is directly related to patient survival. In a recent study from Croatia, the one- and two-year survival rates of patients using a THC were 91% and 77%, respectively. In patients with an AVF, the one- and two-year patient survival were 97% and 95%, respectively.[6] Long-term patient survival with the THC was significantly lower than that of patients who underwent HD via the AVF or a grafted AVF.[7]

Most studies have shown that primary catheters have longer patency than secondary or multiple catheter interventions,[2] which is similar to our findings. In addition, the catheters inserted in the right internal jugular vein survive the longest, followed by catheters inserted in the left internal jugular vein and the femoral region.[2,3]

We experienced that some patients required repetitive catheter interventions despite adequate care and suffered from occluded AVFs and central veins. We thought that if we could detect the genetic thrombophilia, THC thrombosis could be prevented by early anticoagulant intake, improving the survival of CKD patients with genetic thrombophilia.

Some studies on genetic thrombophilia have investigated AVF patency, but few of them have examined HD catheter thrombosis, also most have focused on specific genes. Our study differs from others, as multiple genetic factors causing thrombophilia were simultaneously evaluated. In addition, patients' clinical characteristics, comorbidities, and medical history reports were examined. Among the investigated genetic polymorphisms, *MTHFR* A1298C and compound heterozygous *MTHFR* A1298C and C677T polymorphisms had a weak effect on THC thrombosis, while other polymorphisms did not have any effect.

The *MTHFR* enzyme provides remethylation of homocysteine to methionine. Approximately 40% of the population carries either C677T or A1298C polymorphism. The former causes a 30 to 70% decrease in enzyme activity by increasing the heat sensitivity when valine replaces alanine, whereas the latter causes a lesser decrease in enzymatic activity.[1,8] Consequently, plasma homocysteine levels increase, causing thrombophilia. *MTHFR* polymorphisms lead to early AVF thrombosis.[1,8,9] Homozygous carriers of the *MTHFR* C677T gene have increased risk of venous thromboembolism (VTE), PE, coronary artery disease, and cardiovascular events.[9,10] Nevertheless, some meta-analysis concluded that the effect of *MTHFR* C677T polymorphism on VTE was less than expected.[11-13] Dietary intake of folate and vitamin B12 creates a co-factor effect, compensating the effects of polymorphism.[9] The *MTHFR* polymorphisms are frequently observed in Asian and Caucasian populations, as well as in Türkiye. Therefore, there are controversial results among studies.[13]

In our study, *MTHFR* polymorphisms were observed more frequently in Group 1 and Group 2 compared to healthy population living in the same region. Although homozygous *MTHFR* A129C was more frequent in Group 1 in numbers, subgroup comparisons did not show a significant difference between Group 1 and Group 2. Small numbers of the groups may have prevented the exact statistical comparison.

In prothrombin G20210A (factor II) mutations, guanine at position 20210 in the 3'-untranslated region of the prothrombin gene is replaced by alanine, causing thrombophilia and increasing the risk of VTE by two or three times. It usually poses a significant risk in homozygous cases.[8] The incidence of this mutations is 2 to 3% in Europeans, and lower in other races.[12] In our study, there were heterozygous carriers more frequently in Groups 1 and 2 than in Group 3, without statistical significance.

The autosomal dominant factor V Leiden mutation is the most common polymorphism that causes inherited coagulopathy. Activated protein C (APC) limits coagulation by proteolytic inactivation of factors Va and VIIIa. This is a point mutation (G1691A) occurring when arginine at the 506$^{th}$ position is replaced by glutamine. Factor V develops resistance against APC inactivation, leading to increased thrombin levels, which causes thrombophilia. The risk of developing VTE in heterozygous individuals is three to eight times higher, while it is 50 to 80 times higher in homozygous individuals than in normal individuals.[1,8] The prevalence is high, particularly in Eastern Mediterranean countries and is low in Asian, American, and African populations. The incidences of factor V Leiden mutations in Europeans are 4 to 15%, and in Turks are 7.9 to 10.9%.[14]

A meta-analysis showed that 22% of VTE patients had factor V mutations compared to 7.6% of the controls.[15] A recent study from Iran investigated the effect of hereditary thrombophilia on THC thrombosis and factor V, protein C, protein S, and antithrombin III were evaluated.[16] They reported that genetic thrombophilia did not differ between those with and without catheter thrombosis. Some studies did not find any correlation between factor V Leiden mutation and AVF thrombosis, possibly due to the rarity in that region; many Eastern Mediterranean studies showed a relationship of AVF thrombosis with VTE.[15,17] In our study, the factor V polymorphism was similar in all groups and did not affect THC thrombosis. Two individuals in Group 1 were carriers of the homozygous factor V Leiden mutation.

Plasminogen activators (tissue plasminogen activator [t-PA] and urokinase plasminogen activator [u-PA]) catalyze the conversion of plasminogen to plasmin, which converts fibrin into degradation products. Plasminogen activator inhibitors (PAIs) regulate fibrinolysis by inhibiting t-PA and u-PA. The PAI polymorphism is common in Asians and Caucasians. The PAI gene may have four or five guanosine residues and the 4G/4G, 4G/5G, and 5G/5G genotypes. The 4G/5G polymorphism is associated with thrombophilia,[8,18] and has a higher incidence in the community, as seen in our study.[19] The 4G allele increases PAI-1 levels by increasing messenger ribonucleic acid (mRNA) transcription, causing a tendency for thrombosis.[18]

In a meta-analysis, the variants of PAI 4G/4G and 4G/5G were associated with the VTE risk compared to the variant PAI 5G/5G.[18] The PAI 4G/5G polymorphism has been associated with also

increased cardiovascular disease.[18-21] We found no association between the PAI polymorphism and THC thrombosis. Trimarchi et al.[21] reported that the 4G/5G variant may be associated with increased AVF thrombosis by polytetrafluoroethylene grafting.

Factor XIIIa turns soluble fibrin monomers into un-soluble polymers and stabilizes the fibrin clot by the formation of covalent cross-links between fibrin monomers. Factor XIII (Val34Leu) polymorphisms cause increased activity leading to early cross-link and thin fibrin formation, and prolonged clot lysis,[8] and provide protection against VTE.[22] This polymorphism is present in 25% of European Caucasians.[23] The relationship between factor XIII (Val34Leu) polymorphism and thrombosis is still unclear. The HuGe review[22] reported conflicting results with other studies,[24] and they found a protective effect against VTE, which became prominent in patients with high plasma fibrinogen levels.[22,25] In our study, Factor XIII (Val34Leu) polymorphism was observed similarly in both groups and had no effect on THC thrombosis.

In neural network analysis, the *MTHFR* polymorphism had a weak effect on THC thrombosis. The most important variable affecting THC occlusion was the number of times that the HD catheter was inserted, the number of years that the patient was on dialysis and presence of diabetes. Some patients in the study were taking antiplatelets or anticoagulants due to multiple accompanying comorbidities. These patients were not excluded from the study. Most of them were taking at least antiplatelets for cardiovascular risk reduction. We did not change patients drug therapy regulated by their nephrologists. Although acetylsalicylic acid seems to be a more effective variable than other antiplatelets/anticoagulants on THC thrombosis in neural network analysis, the difference was not statistically significant. The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline also suggests that low-dose aspirin may be used to maintain tunneled CVC patency in patients with a low bleeding risk, with low quality of evidence.[26] In our study, patients with CKD taking acetylsalicylic acid (100 mg/day) only were more common than those taking combined antiplatelet agents or anticoagulants.

Nonetheless, this study has some limitations. This study includes a small sample size, as we rarely run into the patients with recurrent tunneled catheter thrombosis. The study conducted in a single center. These results represent a racially homogenous population from a Turkish city. The patients were on HD program for varying lengths of time. Recurrent thrombosis may be also related to recurrent vascular damage due to multiple catheter insertion. Also, patients with *MTHFR* polymorphism in Group 2 may show recurrent thrombosis over time. Finally, patients who were taking antiplatelets or other anticoagulants were not excluded from the study.

In conclusion, our study results indicated that there was a concomitance of *MTHFR* polymorphisms with hemodialysis-dependent chronic kidney disease. Among the common genetic polymorphisms leading to thrombophilia, only *MTHFR* A1298C and compound heterozygous of *MTHFR* A1298C and *MTHFR* C677T polymorphisms showed a significant difference in overall comparisons of the three groups. Similarity in subgroup analysis may be originated from small numbers of the groups. Larger series may show the effect of *MTHFR* polymorphisms on tunneled hemodialysis catheters thrombosis more clearly. Genetic screening may be recommended in hemodialysis patients undergoing tunneled hemodialysis catheter thrombosis at least twice in a year.

**Ethics Committee Approval:** The study protocol was approved by the Manisa Celal Bayar University Medical Faculty Local Ethics Committee (approval number: 20478486-18832). The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Patient Consent for Publication:** A written informed consent was obtained from each patient.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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