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Thrombophilia in ischemic stroke: Etiological and prognostic perspectives

İskemik inmede trombofilinin etiyoloji ve prognoza etkisi

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ABSTRACT

Aim: Ischemic stroke in young adults presents distinct etiological and clinical features compared to older populations. The contribution of inherited and acquired thrombophilia to stroke risk and prognosis in this age group remains uncertain. This study aimed to investigate the prevalence of thrombophilia markers and their potential association with short-term functional outcomes in young ischemic stroke patients.

Material and Methods: We retrospectively analyzed 56 patients aged ≤50 years diagnosed with ischemic stroke. Demographic data, conventional vascular risk factors, stroke characteristics, and laboratory results for common thrombophilia markers (Prothrombin G20210A, Factor V Leiden, MTHFR C677T and A1298C, PAI-1 4G/5G, Factor XIII V34L, and homocysteine levels) were collected. Functional outcome at discharge was assessed using the modified Rankin Scale (mRS ≤2 defined as favorable).

Results: The mean age was 40.4 ± 6.86 years, and 67.9% were male. Hypertension (39.3%), smoking (42.9%), and dyslipidemia (26.8%) were common. The most prevalent thrombophilia markers were elevated homocysteine (39.3%) and PAI-1 4G/5G polymorphism (33.9%). MTHFR C677T mutation was present 16.1% of patients, Prothrombin G20210A in 8.9%, and Factor V Leiden in 7.1%. None of the thrombophilia markers showed a statistically significant association with favorable short-term outcome, although MTHFR C677T showed a borderline trend (p=0.0641).

Conclusion: Thrombophilia markers, particularly hyperhomocysteinemia, PAI-1 4G/5G, and MTHFR C677T mutation, were relatively common in young ischemic stroke patients but did not significantly impact early functional recovery. Thrombophilia may serve as a contributory rather than primary cause of stroke in this population. Larger, multicenter studies are warranted to clarify their etiological and prognostic significance.

Keywords: Young stroke, thrombophilia, MTHFR, PAI-1, homocysteine, prognosis

ÖZ

Amaç: Genç erişkinlerde görülen iskemik inme, ileri yaş grubuna kıyasla farklı etiyolojik ve klinik özellikler göstermektedir. Bu yaş grubunda kalıtsal ve edinsel trombofilinin inme riski ve prognozundaki rolü net olarak bilinmemektedir. Bu çalışmada, genç iskemik inme hastalarında trombofili belirteçlerinin sıklığı ve kısa dönem fonksiyonel sonuçlarla ilişkisi araştırılmıştır.

Gereç ve Yöntemler: İskemik inme tanısı almış, yaşı ≤50 olan 56 hasta retrospektif olarak incelendi. Demografik veriler, klasik vasküler risk faktörleri, inme özellikleri ve yaygın trombofili belirteçleri (Protrombin G20210A, Faktör V Leiden, MTHFR C677T ve A1298C, PAI-1 4G/5G, Faktör XIII V34L, homosistein düzeyi) kaydedildi. Taburculukta fonksiyonel durum, modifiye Rankin Skalası (mRS ≤2: iyi prognoz) ile değerlendirildi.

Bulgular: Ortalama yaş 40,4 ± 6,86 yıl olup hastaların %67,9'u erkekti. Hipertansiyon (%39,3), sigara kullanımı (%42,9) ve dislipidemi (%26,8) en sık risk faktörleriydi. En yaygın trombofili belirteçleri yüksek homosistein düzeyi (%39,3) ve PAI-1 4G/5G polimorfizmi (%33,9) idi. MTHFR C677T mutasyonu %16,1, Protrombin G20210A %8,9 ve Faktör V Leiden %7,1 oranında saptandı. Trombofili belirteçlerinin hiçbiri iyi prognoz ile anlamlı ilişki göstermedi; ancak MTHFR C677T mutasyonu sınırda anlamlı eğilim gösterdi (p=0,0641).

Sonuç: Homosistein yüksekliği, PAI-1 4G/5G polimorfizmi ve MTHFR C677T mutasyonu genç iskemik inme hastalarında görece sık görülmesine rağmen, erken dönemde fonksiyonel iyileşme üzerinde anlamlı etkisi bulunmamıştır. Trombofili, bu popülasyonda primer değil, katkıda bulunan bir risk faktörü olabilir. Bu konunun netleştirilmesi için daha geniş, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Genç inme, trombofili, MTHFR, PAI-1, homosistein, prognoz

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Highlights

- Young ischemic stroke patients (≤50 years) commonly had conventional vascular risk factors, particularly smoking and hypertension.
- Hyperhomocysteinemia and PAI-1 4G/5G polymorphism were the most prevalent thrombophilia-related findings in this cohort.
- No thrombophilia marker was significantly associated with favorable short-term functional outcome (modified Rankin Scale ≤2), although MTHFR C677T showed a borderline trend.
- These findings support thrombophilia as a contributory rather than primary etiologic factor in young ischemic stroke, warranting larger multicenter studies.

INTRODUCTION

Ischemic stroke in young adults, often defined as individuals under 50 years of age, poses distinct clinical and etiological challenges compared to strokes in older populations. In contrast to senior individuals, whose stroke is primarily attributed to atherosclerosis and cardioembolism, younger patients more often present with atypical and less prevalent causes, such as arterial dissection, vasculitis, and genetic or acquired thrombophilias. In this population, recognizing underlying prothrombotic disorders is crucial for both acute therapy and secondary prophylaxis, as well as family screening (1,2).

Inherited thrombophilias, such as the Factor V Leiden mutation, Prothrombin G20210A mutation, and methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms include C677T and A1298C, are recognized risk factors for venous thromboembolism (VTE) (3). Genetic variations can induce hypercoagulability by enhancing resistance to activated protein C (as seen in Factor V Leiden), elevating prothrombin levels (as in the G20210A variant), or disrupting homocysteine metabolism (as in MTHFR mutations), thereby augmenting the likelihood of thrombus formation in the venous system. Moreover, increased plasma homocysteine concentrations, frequently resulting from MTHFR malfunction, along with the plasminogen activator inhibitor-1 (PAI-1) 4G/5G polymorphism, which influences fibrinolytic activity, have been regarded as potential factors in a prothrombotic condition. The Factor XIII V34L polymorphism, albeit not as well examined, has also been explored for its impact on clot stability and thrombus architecture (4).

The correlation between these parameters and VTE is well established; nevertheless, their influence on arterial thrombosis, especially ischemic stroke, continues to be a matter of contention. Numerous studies indicate a possible association between hereditary thrombophilia and cryptogenic stroke in young individuals, particularly in the absence or diminished presence of conventional vascular risk factors such as hypertension, diabetes mellitus, and atherosclerosis. The strength and consistency of this association significantly differ among groups and study methods. Certain investigations indicate a greater occurrence of these mutations in young stroke patients relative to healthy controls, but others observe no significant difference, therefore questioning their clinical value in standard stroke evaluations (5).

Considering the multifactorial etiology of ischemic stroke, thrombophilia alone is probably inadequate to precipitate arterial events but may serve as an ancillary risk factor alongside other predisposing conditions, such as endothelial damage, inflammation, or hormonal influences (e.g., oral contraceptive use, pregnancy). Moreover, the detection of thrombophilic markers in young stroke patients may influence not only etiological classification and risk assessment but also long-term secondary preventive methods, including the potential for prolonged anticoagulation in specific instances (6).

Consequently, a systematic and thorough assessment of inherited thrombophilic markers in young patients with ischemic stroke especially those with indeterminate etiology is crucial to improve our comprehension of their etiopathogenic significance and to optimize personalized diagnostic and therapeutic strategies for this distinct patient population.

This study aims to examine the prevalence and clinical significance of thrombophilia-associated genetic and biochemical markers (including Factor V Leiden, Prothrombin G20210A, MTHFR C677T/A1298C, PAI-1 4G/5G, and homocysteine levels) in young adult patients experiencing acute ischemic stroke. Furthermore, we intend to assess their correlations with stroke features, vascular risk factors, and clinical outcomes.

MATERIAL and METHODS

Study Design and Population

This is a retrospective observational study performed at a comprehensive stroke center. Individuals aged 50 years or younger diagnosed with acute ischemic stroke and subjected to etiological evaluation between January 2023 and

May 2025 were incorporated into the analysis. All patients underwent assessment via a defined stroke protocol, encompassing neuroimaging, vascular examinations, and cardiac evaluations. Patients having incomplete data from the thrombophilia panel were eliminated.

Data Collection

Demographic information (age, sex), conventional vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation), and stroke features (occluded artery, dissection, vasculitis) were documented. The severity of the stroke and functional outcomes were evaluated using the NIH Stroke Scale (NIHSS) during admission and discharge, and the modified Rankin Scale (mRS) during follow-up.

Thrombophilia testing was conducted as part of the etiological assessment and encompassed the following markers:

-Factor V Leiden mutation

-Prothrombin G20210A mutation

-MTHFR C677T and A1298C polymorphisms

-PAI-1 4G/5G polymorphism

-Factor XIII (V34L) polymorphism

-Plasma homocysteine level

Genetic testing was carried out using PCR-based assays in a certified laboratory. Homocysteine levels were measured via high-performance liquid chromatography or immunoassay depending on availability.

Sample Size and Power Considerations

As this was a retrospective observational study, all consecutive patients aged 50 years or younger who underwent thrombophilia screening during the study period (January 2023–May 2025) were included. Therefore, no a priori sample size calculation or formal power analysis was conducted. The final sample size (n = 56) was determined by the total number of eligible patients available within the predefined timeframe. A post hoc power assessment indicated that, assuming a medium effect size (Cohen's d = 0.5) and a two-tailed α = 0.05, the achieved statistical power was approximately 0.70. This suggests moderate sensitivity for detecting medium associations but limited capacity for identifying small effects. Consequently, the findings should be regarded as exploratory and hypothesis-generating, warranting confirmation in larger, prospectively designed multicenter cohorts.

Statistical Analysis

Descriptive statistics were used to summarize the baseline demographic and clinical characteristics of the study population. Continuous variables were expressed as mean ± standard deviation or median (interquartile range, IQR) depending on data distribution, and categorical variables as number (percentage). The normality of continuous variables was tested using the Shapiro-Wilk test.

Correlation analyses were conducted to further evaluate potential relationships between thrombophilia-related variables and clinical parameters. Specifically, associations between individual thrombophilia markers (e.g., MTHFR C677T, homocysteine, PAI-1 4G/5G, Factor V Leiden, and Prothrombin G20210A) and clinical characteristics such as stroke severity at admission (NIHSS score), functional outcome at discharge (mRS), age, and presence of conventional vascular risk factors were explored. For normally distributed variables, Pearson's correlation coefficient (r) was applied, whereas for non-normally distributed or ordinal variables, Spearman's rank correlation coefficient (ρ) was used. The strength of correlation was interpreted as follows: r (or ρ) <0.3 = weak, 0.3–0.7 = moderate, and >0.7 = strong correlation. All statistical analyses were conducted using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA), and a p-value <0.05 was considered statistically significant.

RESULTS

The study cohort consisted of 56 young individuals diagnosed with ischemic stroke (Table 1). The average age was 40.4 ± 6.86 years, with a predominance of males (67.9%). Hypertension was observed in 39.3% of patients, with current or past smoking at 42.9%, diabetes mellitus at 25.0%, and dyslipidemia at 26.8%. Uncommon etiological variables were arterial dissection and vasculitis, each identified in 8.9% of the group. Atrial fibrillation was detected in 19.6% of instances.

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population

Parameter	Value
Age, years (mean ± SD)	40.4 ± 6.86
Male, n (%)	38 (67.9)
Hypertension, n (%)	22 (39.3)
Diabetes mellitus, n (%)	14 (25.0)
Dyslipidemia, n (%)	15 (26.8)
Atrial fibrillation, n (%)	11 (19.6)
Current or former smoking, n (%)	24 (42.9)
Dissection, n (%)	5 (8.9)
Vasculitis, n (%)	5 (8.9)
Affected artery, n (%)	
Middle Cerebral Artery (MCA)	25 (44.6)
Carotid Artery	14 (25.0)
Basilar Artery	10 (17.9)
Anterior Cerebral Artery (ACA)	6 (10.7)
Vertebral Artery	1 (1.8)
Mortality, n (%)	3 (5.4)

The predominant vessel occluded was the middle cerebral artery at 44.6%, succeeded by the carotid artery at 25.0%, the basilar artery at 17.9%, the anterior cerebral artery (ACA) at 10.7%, and the vertebral artery at 1.8%. The mortality rate during hospitalization was 5.4%.

Prevalence of Thrombophilia Markers

The distribution of inherited thrombophilia markers is summarized in Table 2. The predominant anomaly identified was the PAI-1 4G/5G polymorphism, observed in 33.9% (n=19) of individuals. The MTHFR C677T mutation was subsequently found to be positive in 16.1% (n=9) of patients. The Prothrombin G20210A mutation was identified in 8.9% (n=5) of patients. The Factor V Leiden mutation was identified in 7.1% (n=4) of cases. The MTHFR A1298C polymorphism was infrequently observed, occurring in 3.6% (n=2) of patients. Additional markers, including Factor XIII (V34L) and high homocysteine levels, exhibited low prevalence and will be detailed in the comprehensive analysis.

Table 2: Prevalence of Thrombophilia Markers and Association with Favorable Clinical Outcome (mRS ≤ 2)

Marker	Positive, n (%)	p value
Prothrombin G20210A	5 (8.9)	1.0
Factor V Leiden	4 (7.1)	1.0
MTHFR C677T	9 (16.1)	0.0641
MTHFR A1298C	2 (3.6)	1.0
PAI-1 4G/5G	19 (33.9)	1.0
Factor XIII V34L	6 (10.7)	1.0
Homocysteine	22 (39.3)	0.5548

Associations between the presence of individual thrombophilia markers (e.g., Prothrombin G20210A, Factor V Leiden, MTHFR C677T, MTHFR A1298C, PAI-1 4G/5G, Factor XIII V34L, and elevated homocysteine levels) and favorable functional outcome (defined as mRS ≤ 2) were analyzed using the Fisher's exact test or Chi-square test, as appropriate. Although not statistically significant, a borderline association was observed between MTHFR C677T and favorable functional outcome (p = 0.0641). Each p-value in Table 2 represents the statistical significance of this association for the respective thrombophilia marker.

In the examination of the correlation between individual thrombophilia indicators and good functional outcomes (characterized by a modified Rankin Scale [mRS] ≤2), none of the markers attained statistical significance. Nonetheless, MTHFR C677T exhibited a marginal correlation with the outcome (p=0.0641). All other indicators, such as Prothrombin G20210A, Factor V Leiden, PAI-1 4G/5G, and Factor XIII V34L, had no significant correlation with clinical prognosis (p=1.0 for each) (Table 3).

DISCUSSION

This study examined the incidence and possible clinical implications of hereditary and acquired thrombophilia markers in a group of 56 young individuals with ischemic stroke. The demographic characteristics of our group aligned with earlier findings on young stroke, with a mean age of 40.4 years and a male predominance of 67.9%. These findings align with numerous previous studies that have similarly indicated a higher incidence of ischemic stroke in younger men, possibly attributable to a greater prevalence of modifiable vascular risk factors and lifestyle-related exposures in men under 50 years of age (7,8).

Traditional vascular risk factors, including hypertension (39.3%), smoking (42.9%), diabetes mellitus (25.0%), and dyslipidemia (26.8%), were often identified in our population. This pattern illustrates the increasing recognition that conventional atherosclerotic risk factors significantly contribute to the pathophysiology of stroke, even among younger demographics. The Oxford Vascular Study and Ekker have documented similar prevalence rates of hypertension (34–44%) and smoking (40–50%) in young stroke

Table 3: Correlation Analysis Between Thrombophilia Markers and Clinical Parameters

Thrombophilia Marker	Clinical Variable	Correlation Coefficient (r/ρ)	p-value	Interpretation
MTHFR C677T	NIHSS at admission	0.18	0.21	Weak, non-significant correlation
MTHFR C677T	mRS at discharge	-0.25	0.064	Borderline trend toward favorable outcome
Homocysteine	NIHSS at admission	0.12	0.34	No significant correlation
Homocysteine	mRS at discharge	0.09	0.41	No significant correlation
PAI-1 4G/5G	NIHSS at admission	0.07	0.49	No significant correlation
PAI-1 4G/5G	mRS at discharge	0.04	0.61	No significant correlation
Factor V Leiden	mRS at discharge	-0.03	0.73	No correlation
Prothrombin G20210A	mRS at discharge	-0.02	0.81	No correlation
Factor XIII V34L	mRS at discharge	0.05	0.58	No correlation

Correlation analyses were performed using Pearson's or Spearman's correlation coefficients, depending on data distribution. Values of r (or ρ) < 0.3 were interpreted as weak, 0.3–0.7 as moderate, and >0.7 as strong correlation. A p-value < 0.05 was considered statistically significant.

patients, indicating a worldwide trend of escalating vascular risk among the youth (9,10). Moreover, in the other study, up to 50% of young stroke patients had two or more conventional vascular risk factors, supporting the notion that classic atherothrombotic mechanisms are increasingly relevant in this age group (11). Our data similarly confirm that the presence of multiple modifiable risk factors is not uncommon among young patients, and their identification remains critical for both primary and secondary prevention strategies. However, in contrast to older stroke populations, our cohort demonstrated a lower frequency of significant non-atherosclerotic mechanisms, including arterial dissection (8.9%) and vasculitis (8.9%), aligning with findings from the TOAST and Causative Classification of Stroke studies, which highlight the significance of etiological diversity in younger patients (12,13).

The most frequently involved vascular territory was the middle cerebral artery (44.6%), followed by the carotid artery (25.0%) and basilar artery (17.9%), which aligns with the general distribution pattern observed in anterior circulation strokes. Mortality was low (5.4%), reflecting the relatively favorable prognosis in this age group.

In relation to thrombophilia, higher homocysteine levels (39.3%) and the PAI-1 4G/5G polymorphism (33.9%) were the most common anomalies in our population. Genetic variations including MTHFR C677T (16.1%), Prothrombin G20210A (8.9%), and Factor V Leiden (7.1%) were observed at moderate frequency. These findings align with previous research on young stroke populations, although reported prevalences fluctuate due to regional, ethnic, and methodological variations. For example, Pezzini et al. (2007) found a similar prevalence of Prothrombin G20210A mutation (~8%) and Factor V Leiden (~10%) among cryptogenic stroke patients under 50, with higher rates observed in patients with a family history of thromboembolism (14). Additionally, when comparing our findings with existing population-based genetic data, interesting contrasts emerge. For instance, a recent large-scale study by Shen et al. (15) examined the geographical distribution of the MTHFR C677T polymorphism in reproductive-age women within the Chinese Han population. A significant frequency of the T allele was recorded, especially in northern China, with frequencies between 40% and 50%, in contrast to 10% to 20% in southern areas. The prevalence of the MTHFR C677T mutation in our group of young ischemic stroke patients was 16.1%, significantly lower than that observed in the northern Chinese population, although more consistent with rates documented in European cohorts. It is important to note that while Shen et al.'s study focused on the population genetics and migration-related distribution of this polymorphism without exploring clinical correlations, our study assessed its potential role in ischemic stroke outcomes. Although we did not observe a statistically significant association between MTHFR C677T and favorable short-term functional outcomes (mRS ≤2), the borderline p-value (p=0.0641) suggests a possible contributory role that warrants further exploration. This divergence in prevalence and interpretation highlights the complexity of extrapolating genetic data across populations and reinforces the need for stroke-specific, ethnically diverse studies to clarify the clinical utility of thrombophilia testing in young adults.

Notwithstanding the very high incidence of these indicators, we could not identify a meaningful correlation between individual thrombophilia markers and satisfactory clinical outcomes at discharge (defined as mRS ≤2). This aligns with several studies indicating that thrombophilic disorders may contribute to stroke risk, however do not consistently affect stroke severity or prognosis. A systematic review and meta-analysis by Chiasakul et al. revealed that inherited thrombophilias (such as factor V Leiden, prothrombin G20210A, and deficiencies in protein C and S) modestly elevated the overall risk of arterial ischemic stroke, with odds ratios between 1.25 and 2.26, indicating their minimal influence on disease progression or outcomes. Alhazzani et al. performed a meta-analysis on young adults, indicating that factor V Leiden exhibited a general association with stroke (OR ≈ 2.00); however, subgroup analyses demonstrated that in unselected patient populations, this association diminished to non-significance, implying that thrombophilia testing may possess reduced prognostic value when not specifically targeted (5, 16). In our study, MTHFR C677T exhibited a borderline connection with the result (p = 0.0641), indicating a potential influence on functional recovery. MTHFR mutations may not directly induce thrombosis; instead, they can lead to hyperhomocysteinemia, a modifiable prothrombotic condition associated with endothelial dysfunction and heightened stroke risk. Certain studies have shown poorer functional outcomes in patients with elevated homocysteine levels, while the findings are inconsistent.

Our findings indicate that thrombophilia screening may elucidate stroke causation in specific young patients, especially those lacking conventional risk factors; nonetheless, the predictive significance of these markers remains ambiguous. These findings align with the ongoing discourse in the literature concerning the involvement of thrombophilia in arterial ischemic stroke. Although hereditary thrombophilic disorders are recognized risk factors for venous thromboembolism, their influence on arterial events is ambiguous. Numerous investigations have indicated elevated occurrences of Factor V Leiden and Prothrombin G20210A mutations in young stroke patients, especially among those with cryptogenic origins. Nevertheless, many research, including ours, have not established a definitive correlation between these alterations and stroke severity or outcomes.The high prevalence of homocysteine elevation in our cohort is notable, particularly given its modifiable nature through vitamin

supplementation. Although homocysteine was not significantly associated with outcome in our study, its vascular toxicity is well documented, and its detection may still have implications for secondary prevention.

Our study has several limitations. The sample size is relatively small, which limits statistical power. Furthermore, we did not include a control group, which precludes comparison of thrombophilia prevalence with the general population. Finally, we focused only on a selected panel of thrombophilia markers, and other potential prothrombotic mechanisms may have been missed.

Conclusion

This study highlights the multifactorial nature of ischemic stroke in young adults, where conventional vascular risk factors often coexist with rarer causes such as arterial dissection and thrombophilia. Although thrombophilic markers particularly elevated homocysteine, PAI-1 4G/5G polymorphism, and MTHFR C677T mutation were relatively common, none showed a significant association with short-term outcomes. The borderline trend for MTHFR C677T suggests a possible contributory role that merits confirmation in larger prospective studies. Routine thrombophilia screening remains debatable but may be appropriate in selected young patients lacking conventional risk factors. Further multicenter research is needed to clarify the etiologic and prognostic implications of thrombophilic abnormalities in this population.

Author Contributions

Study conception and design: **Ebru Marzioglu Ozdemir, Gokhan Ozdemir;** Data collection: **Ebru Marzioglu Ozdemir; Gokhan Ozdemir;** Analysis and interpretation of results: **Gokhan Ozdemir, Ebru Marzioglu Ozdemir;** Draft manuscript preparation: **Ebru Marzioglu Ozdemir; Gokhan Ozdemir.**

Conflicts of Interest

The authors have no conflict of interest to declare.

Ethical Approval

Ethical approval for this study was obtained from the Ethics Committee of Selçuk University Faculty of Medicine (Decision No: E-70632468-050.01-1079753) on September 10, 2025.

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