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Psychological distress, cancer-associated coagulopathy, and genetic vulnerability: Integrating psycho-oncology mechanisms in ischemic stroke risk

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Zhang B, Zheng Y, Tang Y, et al.
Psychological distress, cancer-associated coagulopathy, and genetic vulnerability: Integrating psycho-oncology mechanisms in ischemic stroke risk. *Psycho-Oncologie*. 2025; 19(4): 4260.
<https://doi.org/10.18282/po4260>

ARTICLE INFO

Received: 13 March 2025

Revised: 10 April 2025

Accepted: 16 April 2025

Available online: 16 December 2025

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Abstract: The relationship between Factor V gene polymorphism, immune biomarkers, and ischemic stroke (IS) remains insufficiently understood in Asian populations, and even less is known about how cancer-related physiological and psychological processes may jointly contribute to cerebrovascular vulnerability. This case-control study examined whether Factor V Leiden polymorphism, anticardiolipin antibody (ACA) levels, and cancer history were associated with IS risk in Chinese adults, while interpreting these associations through a psycho-oncological framework. Factor V genotypes were identified using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and ACA levels were measured using enzyme-linked immunosorbent assay (ELISA). Clinical variables, including hypertension and cancer/tumor history, were also evaluated. The GA and AA genotypes and the A allele of the Factor V gene were significantly associated with increased IS risk ($P < 0.05$). Hypertension and cancer/tumor occurrence were more prevalent in the IS group ($P < 0.001$). Although mean ACA levels did not differ between groups, cancer patients exhibited a higher likelihood of ACA positivity, consistent with immune activation in malignancy. Interpreted from a psycho-oncological perspective, cancer-related hypercoagulability may interact with chronic psychological distress characterized by sustained stress-system activation, emotional burden, and behavioral disruption to exacerbate inflammatory and coagulative instability, thereby heightening stroke susceptibility. These findings suggest that genetic predisposition, cancer-associated physiological changes, and psychological stress may collectively shape IS risk. Future research incorporating validated psychological assessments and stress-related biomarkers, alongside longitudinal follow-up, is needed to clarify the mechanistic role of psychological distress in cancer-associated stroke vulnerability.

Keywords: anticardiolipin antibodies; cancer; Factor V polymorphism; ischemic stroke; psychological distress; psycho-oncology

1. Introduction

Ischemic stroke (IS) is a leading source of morbidity and mortality in China [1–4]. Traditional risk factors alone fail to fully explain its rising incidence, particularly among individuals living with cancer [5,6]. Psycho-oncology research increasingly recognizes that cancer exerts not only physiological changes but also profound psychological effects [7]. Cancer patients frequently endure chronic stress, anxiety, depression, and anticipatory fear, all of which contribute to biological dysregulation

[7,8].

Psychological distress activates the hypothalamic–pituitary–adrenal (HPA) axis, alters cortisol rhythms, upregulates sympathetic activity, elevates inflammatory cytokines (e.g., IL-6, CRP), and promotes endothelial dysfunction [7,9]. These changes collectively enhance platelet activation and coagulation, forming a psychophysiological environment conducive to thrombosis [5,10]. Such mechanisms are particularly relevant in cancer populations, who already exhibit tumor-driven hypercoagulability, treatment-induced vascular injury, and immune dysregulation [5,9].

Inherited factors, such as the Factor V Leiden polymorphism, further modify coagulation dynamics by reducing the anticoagulant effect of activated protein C [4]. Although its prevalence is lower in Asian populations than in Caucasians, interaction with cancer-related stress biology may render genetically susceptible individuals more vulnerable to thrombotic events [11]. Likewise, autoantibodies such as anticardiolipin antibodies (ACA) common in malignancy due to immune activation serve as additional markers of thrombosis risk [5].

Despite substantial evidence linking psychological distress, cancer biology, and coagulation, these domains are rarely studied together [5,6]. This gap limits the field's understanding of how psychological states may biologically interact with inherited vulnerabilities to influence stroke risk [7].

This study therefore had two objectives:

- (1) to assess the association between Factor V polymorphism, ACA levels, cancer history, and IS; and
- (2) to interpret these biological findings through a psycho-biological model, proposing that cancer-related psychological distress may amplify prothrombotic pathways in genetically predisposed individuals [4,9].

In this framework, the biological results serve not only as independent clinical findings but as supportive evidence for a broader psycho-oncological mechanism

2. Materials and methods

2.1. Study subjects

Approved by the Ethics Committee of People's Hospital Affiliated to Chongqing Three Gorges Medical College, this study enrolled 180 patients diagnosed with ischemic stroke (IS) based on clinical presentation and imaging findings. During the same period, 145 healthy individuals without a history of IS were recruited from the hospital's physical examination center to serve as the control group. All participants were unrelated Han Chinese.

Clinical data and blood samples were collected after written informed consent was obtained. Although psychological variables were not directly assessed, the clinical and biological information gathered in this study provides a basis for interpreting stroke susceptibility within a psycho-biological framework, particularly in relation to cancer history and coagulation-related markers.

2.2. Inclusion criteria and exclusion criteria

IS patients were eligible if they met diagnostic criteria for acute ischemic stroke according to the 2018 Chinese Guidelines for the Diagnosis and Treatment of Acute IS and had not undergone intravenous thrombolysis or interventional therapy. Individuals with prior IS were included if neurological impairment was clinically documented.

Control participants were age- and sex-matched individuals with no history of stroke, confirmed by imaging, and no recent cardiovascular events such as myocardial infarction or angina.

Exclusion criteria for both groups included autoimmune disease, blood disorders, thyroid dysfunction, traumatic or drug-induced IS, vasculitis, cerebrovascular malformations, intracranial hemorrhage, recent severe cardiac events, hepatic, renal, or pulmonary insufficiency, coagulation abnormalities, and refusal to participate.

2.3. Gene polymorphism analysis

Following aseptic preparation, 2 mL of fasting venous blood was collected in EDTA tubes. Samples were aliquoted and stored at -80°C . Genomic DNA was extracted using the TSINGKE TSP201-200 kit (Thermo Fisher, USA). PCR primers and single-base extension primers were designed based on SNP information from the NCBI database and synthesized by Shanghai Tianhao Biotechnology Co., Ltd. Factor V polymorphisms were analyzed using PCR-RFLP.

This genetic information contributes to understanding how inherited coagulation vulnerability may interact with cancer-related physiological and psychological processes in stroke risk.

2.4. ACA investigation

IgA, IgG, and IgM anticardiolipin antibody (ACA) levels were measured using enzyme-linked immunosorbent assay (ELISA), with binding indices calculated according to standard protocols described previously [12]. ACA was evaluated as a marker of immune and coagulative activity that may intersect with stress-related inflammatory mechanisms in cancer patients.

2.5. Statistical analysis

Statistical analyses were conducted using SPSS 19.0. Continuous variables were compared using the t-test, and categorical variables were analyzed using the χ^2 test. A P-value < 0.05 was considered statistically significant.

Given that psychological data were not collected, the statistical approach focused on biological and clinical indicators, which were subsequently interpreted within a psycho-oncology framework during discussion.

3. Results

3.1. Demographic characteristics and stroke risk factors

Table 1 presents the demographic variables and major stroke-related risk

factors for the ischemic stroke (IS) and control groups. No significant differences were observed in age, sex distribution, BMI, smoking status, drinking history, or diabetes mellitus (all $P > 0.05$).

Two variables differed significantly between groups.

- First, hypertension was substantially more prevalent in the IS group (30.6%) compared with controls (16.5%) ($P < 0.001$).
- Second, cancer/tumor history occurred more frequently in IS patients (9.4%) than in controls (3.8%) ($P < 0.001$).

These findings reinforce the biological relevance of vascular and oncological risk factors while also supporting the psycho-biological perspective in which chronic cancer-related distress, inflammation, and neuroendocrine activation may interact with vascular vulnerabilities to elevate stroke risk.

Table 1. Demographic characteristics and risk factors comparison between the ischemic stroke group and the control group.

characteristics	ischemic stroke group (N = 180)	control group (N = 315)	P
Age	65.8 ± 8.8	64.6 ± 9.2	> 0.05
Men	126 (70.0%)	226 (71.7%)	> 0.05
BMI	25.8 ± 2.0	24.9 ± 1.5	> 0.05
Smokers	78 (43.3%)	129 (41.0%)	> 0.05
Drinking history	30 (16.7%)	60 (19.5%)	> 0.05
Hypertension	55 (30.6%)	52 (16.5%)	< 0.001
Diabetes mellitus	25 (13.9%)	45 (14.3%)	> 0.05
Cancer/Tumor	17 (9.4%)	12 (3.8%)	< 0.001

BMI, body mass index.

3.2. Factor V Leiden polymorphism and genetic susceptibility

Three Factor V Leiden genotypes GG, GA, and AA were identified in both groups. As shown in **Table 2**, GA and AA genotypes were significantly more common among IS patients compared with controls. Likewise, the A allele frequency was higher in the IS group ($P < 0.05$).

Table 2. Comparison of genotype and allele frequency between the ischemic stroke group and the control group.

FV Leiden	Control group (N = 315)		Ischemic stroke group (N = 180)		OR (95%CI) ^a	P ^a
	N	Percentage (%)	N	Percentage (%)		
GG	312	99	168	93.3	1.00 ^{REF}	
GA	2	0.6	7	3.9	6.50 (1.34–31.64)	0.021
AA	1	0.3	5	2.8	9.29 (1.08–80.14)	0.043
G	626	99.4	343	95.3	1.00 ^{REF}	
A	4	0.6	17	4.7	7.76 (2.59–23.24)	< 0.001

OR, odds ratio; CI, confidence interval; a Adjusted for sex and age by logistic regression model.

After adjusting for age and sex, both heterozygous (GA) and homozygous (AA) carriers demonstrated significantly increased odds of IS. These results suggest that Factor V Leiden polymorphism contributes to stroke susceptibility in this population.

Within a psycho-biological framework, this genetic vulnerability may interact with stress-related inflammatory activation, cancer-induced hypercoagulability, and psychological distress, collectively lowering the threshold for thrombotic events.

3.3. Anticardiolipin antibody (ACA) levels and positivity rates

There were no significant differences in anticardiolipin antibody (ACA) levels between the ischemic stroke (IS) group and the control group. Mean IgG levels were 0.72 ± 0.24 in the IS group and 0.68 ± 0.20 in controls ($P > 0.05$). IgM levels were 0.42 ± 0.15 in IS patients versus 0.38 ± 0.13 in controls ($P > 0.05$). IgA levels showed a similar pattern: 0.56 ± 0.19 in the IS group and 0.58 ± 0.20 among controls ($P > 0.05$).

ACA positivity rates also did not differ between groups. In IS patients, IgG positivity occurred in 10% of cases, IgM positivity in 2.2%, and IgA positivity in 1.1%. Corresponding rates in the control group were 8.9%, 2.9%, and 1.3%, respectively (all $P > 0.05$). Overall ACA positivity was similar in both groups 13.3% among IS patients and 13.1% among controls.

Although ACA patterns were not independently associated with stroke in this cohort, these findings remain biologically relevant when viewed within the context of cancer-driven immune dysregulation and stress-related inflammatory activation.

3.4. Comparison between ACA-positive and ACA-negative IS patients

Among the 180 patients with ischemic stroke, 24 were ACA-positive and 156 were ACA-negative. No significant differences were observed between these groups in age, sex distribution, hypertension prevalence, or smoking history (all $P > 0.05$).

However, a notable finding emerged: cancer or tumor history was significantly more common among ACA-positive IS patients. Fifteen of the 24 ACA-positive individuals (62.5%) had a cancer/tumor diagnosis, compared with only three of the 156 ACA-negative patients (1.9%) ($P < 0.001$). This strong association highlights the interplay between malignancy and immune activation.

From a psycho-oncological standpoint, cancer-related immune dysregulation often coexists with chronic psychological stress, which can intensify inflammatory pathways, modulate autoantibody expression, and increase coagulative instability. These interactions may help explain the elevated cancer incidence observed among ACA-positive stroke patients, despite the absence of direct psychological measurements.

4. Discussion

4.1. Biological risk factors and their psycho-biological relevance

The present study confirmed several established biological risk factors for ischemic stroke (IS), including hypertension and cancer history. Hypertension is a major vascular determinant of stroke risk, primarily through mechanisms such as endothelial injury, increased arterial stiffness, and microvascular remodeling. These pathways are well-characterized physiologically and have psycho-biological relevance [13]. Stress-related neuroendocrine activation can exacerbate blood

pressure variability, impair endothelial recovery, and accelerate atherosclerotic progression, thereby amplifying the impact of hypertension on cerebrovascular vulnerability [14,15].

Cancer history was significantly more common among patients with IS, reinforcing the role of malignancy as a prothrombotic condition. Tumors release procoagulant factors, promote platelet activation, and induce chronic inflammation, while chemotherapy and radiotherapy can damage vascular endothelium. Importantly, these effects coincide with the psychological distress that many cancers patients experience. Psychological stress activates inflammatory cytokines, elevates cortisol, and disrupts autonomic regulation, changes that can further increase the underlying hypercoagulability. Thus, cancer functions not only as a risk factor for stroke but as a context in which psychological distress may biologically potentiate thrombosis risk [5,6].

Atherosclerosis (AS) remains a central pathway connecting inflammation, endothelial dysfunction, and thrombosis. Factors such as oxidized low-density lipoprotein (LDL) deposition, foam cell formation, and plaque instability contribute to cerebral artery occlusion. Smoking, dyslipidemia, and genetic predisposition exacerbate these pathways. Psychosocial factors, including chronic stress and depression, also accelerate atherosclerotic progression by increasing inflammatory markers and impairing vascular repair, suggesting that psychological distress may modulate classical vascular mechanisms [16,17]. Together, these findings highlight the necessity of viewing biological risk factors for stroke in an integrated psychobiological model, where stress physiology interacts dynamically with vascular, oncological, and metabolic pathways [7].

4.2. Psychological distress as a mechanistic contributor to stroke vulnerability in cancer patients

Beyond physiological pathways, cancer patients frequently experience significant psychological burden, including anxiety, fear of recurrence, depressive symptoms, and chronic stress. Psycho-oncology research indicates that these emotional experiences have measurable biological consequences that impact vascular risk [11,17,18].

Persistent psychological distress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels and glucocorticoid resistance [19–21]. Chronic cortisol dysregulation impairs endothelial function, increases oxidative stress, and enhances systemic inflammation, accelerating atherosclerotic processes and promoting thrombosis [20]. Stress-induced autonomic imbalance marked by heightened sympathetic tone and diminished vagal activity can lead to blood pressure fluctuations, vasoconstriction, and platelet activation, thus raising stroke susceptibility [22,23].

Behavioral consequences of distress, such as reduced physical activity, impaired sleep, emotional fatigue, and diminished treatment adherence, further worsen cardiovascular risk factors [24], including hypertension, obesity, and glucose dysregulation. Psychological distress also elevates pro-inflammatory cytokines, such as IL-6 and CRP, contributing to endothelial injury, plaque instability, and

hypercoagulability [25].

In the context of cancer, these psychological mechanisms interact with malignancy-related biological changes. Cancer creates a prothrombotic environment through systemic inflammation, immune dysregulation, and treatment-related vascular injury. When combined with the heightened emotional stress common in oncology populations, the psycho-biological burden may substantially elevate stroke risk [26].

Therefore, psychological distress is not merely a secondary concern but constitutes a core mechanistic contributor to thrombotic vulnerability in cancer patients. Interventions like stress-reduction programs, psychological counseling, and early distress screening may provide both emotional and biological benefits, potentially reducing stroke risk by modulating inflammation, autonomic balance, and endocrine stability.

4.3. Genetic vulnerability and its interaction with cancer-related and psychological pathways

The study identified a significant association between the Factor V Leiden GA and AA genotypes and increased IS risk. Although historically considered less relevant in Asian populations, our findings suggest that genetic hypercoagulability may still play an important role, particularly when interacting with acquired risk factors [27].

Cancer-related hypercoagulability including tumor-derived procoagulants, cytokine activation, endothelial injury, and treatment toxicity may synergize with Factor V polymorphism to lower the threshold for thrombus formation. From a psycho-biological perspective, chronic psychological distress can further amplify this risk by increasing inflammation, disrupting immune regulation, and activating coagulation pathways. Thus, genetic predisposition may influence thrombotic outcomes differently based on levels of emotional and biological stress

These findings underline the importance of integrating genetic, oncologic, and psychological factors into a comprehensive model of stroke vulnerability. Individuals with Factor V Leiden who also experience cancer-related distress may represent a subgroup at particularly elevated risk. Future research should investigate whether stress-related biomarkers (e.g., cortisol, heart rate variability, IL-6) moderate or mediate the association between genetic vulnerability and thrombotic events. [11]

In summary, the interplay between inherited coagulation deficiencies, cancer biology, and psychological distress supports a multidimensional model of stroke susceptibility. Larger studies incorporating systematic psychological assessments and longitudinal follow-up are necessary to clarify these interactions and strengthen psycho-oncology-informed approaches to stroke prevention in cancer populations

5. Conclusion

This study examined how genetic, immunological, and oncological factors contribute to ischemic stroke (IS) risk in a Chinese population and interpreted these findings through a psycho-oncological lens. Hypertension, cancer history, and Factor

V Leiden polymorphism emerged as significant contributors to stroke susceptibility, underscoring the complex biological landscape in which cerebrovascular events occur. Within this framework, cancer-related hypercoagulability driven by tumor-derived procoagulants, systemic inflammation, immune disruption, and treatment-associated vascular injury provides a physiological foundation for increased thrombotic vulnerability.

Importantly, these biological processes do not occur in isolation. Cancer patients often experience substantial psychological distress, including chronic stress, anxiety, and depressive symptoms, which can activate the hypothalamic–pituitary–adrenal axis, elevate inflammatory cytokines, and disrupt autonomic regulation. Such stress-related physiological changes may act synergistically with coagulation abnormalities and genetic predisposition, amplifying the risk of IS in vulnerable individuals. These findings support a psycho-biological model in which psychological distress serves as an additional and potentially modifiable layer of risk in cancer-associated stroke.

The study's limitations include a modest sample size, single-center design, and the absence of direct psychological assessments, which prevented empirical measurement of distress-related mechanisms. Future research should incorporate standardized psychological instruments, stress-biology biomarkers, and longitudinal follow-up to clarify how emotional, cognitive, and behavioral factors interact with cancer biology and genetic vulnerability to influence cerebrovascular outcomes.

Collectively, the results highlight the importance of integrating psychological screening, supportive care, and stress-management interventions into routine oncology practice. Psycho-oncology-informed approaches may not only improve emotional well-being but also mitigate biological pathways that contribute to stroke, offering a more holistic strategy for prevention and survivorship care among patients with cancer.

Author contributions: Conceptualization, BZ and YZ; methodology, YT; software, SZ; validation, SW, PF and GD; formal analysis, BZ and YZ; investigation, GD and PF; resources, BZ; data curation, BZ; writing—original draft preparation, BZ; writing—review and editing, GD; visualization, BZ; supervision, GD; project administration, GD. All authors have read and agreed to the published version of the manuscript.

Institutional review board statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Three Gorges Medical College (2023-065)

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Acknowledgments: We thank everyone in our experiment group for helping us in providing valuable feedback, advices and comments.

Conflict of interest: The authors declare no conflict of interest.

References

1. Casas JP, Hingorani AD, Bautista LE, Sharma P. Meta-analysis of genetic studies in ischemic stroke. *Arch Neurol*. 2004; 61(11): 1652. doi: 10.1001/archneur.61.11.1652
2. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack. *Stroke*. 2011; 42(1): 227-276. doi: 10.1161/STR.0b013e3181f7d043
3. Hankey GJ, Eikelboom JW, van Bockxmeer FM, Lofthouse E, Staples N, Baker RI. Inherited Thrombophilia in Ischemic Stroke and Its Pathogenic Subtypes. *Stroke*. 2001;32(8):1793-1799. doi: 10.1161/01.STR.32.8.1793
4. Juul K, Tybjaerg-Hansen A, Steffensen R, et al. Factor V Leiden: The Copenhagen City Heart Study and 2 meta-analyses. *Blood*. 2002; 100(1): 3-10. doi: 10.1182/blood-2002-01-0111
5. Demers M, Krause DS, Schatzberg D, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis. *Proceedings of the National Academy of Sciences*. 2012; 109(32): 13076-13081. doi: 10.1073/pnas.1200419109
6. Thålin C, Demers M, Blomgren B, et al. NETosis promotes cancer-associated arterial microthrombosis presenting as ischemic stroke with troponin elevation. *Thromb Res*. 2016; 139: 56-64. doi: 10.1016/j.thromres.2016.01.009
7. Bang OY, Chung JW, Lee MJ, et al. Cancer cell-derived extracellular vesicles are associated with coagulopathy causing ischemic stroke via tissue factor-independent way: The OASIS-CANCER study. *PLoS One*. 2016; 11(7): e0159170. doi: 10.1371/journal.pone.0159170
8. Gon Y, Okazaki S, Terasaki Y, et al. Characteristics of cryptogenic stroke in cancer patients. *Ann Clin Transl Neurol*. 2016; 3(4): 280-287. doi: 10.1002/acn3.291
9. Nakajima S, Kawano H, Yamashiro K, et al. Post-treatment plasma D-dimer levels are associated with short-term outcomes in patients with cancer-associated stroke. *Front Neurol*. 2022; 13. doi: 10.3389/fneur.2022.868137
10. Nam KW, Kim CK, Kim TJ, et al. Predictors of 30-day mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke. *PLoS One*. 2017; 12(3): e0172793. doi: 10.1371/journal.pone.0172793
11. Manso H, Krug T, Sobral J, et al. Variants in the inflammatory IL6 and MPO genes modulate stroke susceptibility through main effects and gene—Gene interactions. *Journal of Cerebral Blood Flow & Metabolism*. 2011; 31(8): 1751-1759. doi: 10.1038/jcbfm.2011.27
12. Lindqvist U, Rudsander Å, Boström Å, et al. IgA antibodies to gliadin and coeliac disease in psoriatic arthritis. *Rheumatology*. 2002; 41(1): 31-37. doi: 10.1093/rheumatology/41.1.31
13. Okereke OI, Manson JE. Psychosocial factors and cardiovascular disease risk. *Circ Res*. 2017; 120(12): 1855-1856. doi: 10.1161/CIRCRESAHA.117.311113
14. Arboix A, Roig H, Rossich R, Martí nez EM, García-Eroles L. Differences between hypertensive and non-hypertensive ischemic stroke. *Eur J Neurol*. 2004; 11(10): 687-692. doi: 10.1111/j.1468-1331.2004.00910.x
15. Chung JW, Oh MJ, Cho YH, et al. Distinct roles of endothelial dysfunction and inflammation in intracranial atherosclerotic stroke. *Eur Neurol*. 2017; 77(3-4): 211-219. doi: 10.1159/000460816
16. Arenillas JF, Álvarez-Sabín J, Molina CA, et al. Progression of symptomatic intracranial large artery atherosclerosis is associated with a proinflammatory state and impaired fibrinolysis. *Stroke*. 2008; 39(5): 1456-1463. doi: 10.1161/STROKEAHA.107.498600
17. Grau AJ, Aulmann M, Lichy C, et al. Increased cytokine release by leucocytes in survivors of stroke at young age. *Eur J Clin Invest*. 2001; 31(11): 999-1006. doi: 10.1046/j.1365-2362.2001.00923.x
18. Kostulas N, Pelidou SH, Kivisäkk P, et al. Increased IL-1 β , IL-8, and IL-17 mRNA expression in blood mononuclear cells observed in a prospective ischemic stroke study. *Stroke*. 1999; 30(10): 2174-2179. doi: 10.1161/01.STR.30.10.2174
19. Silverman MN, Sternberg EM. Glucocorticoid regulation of inflammation and its functional correlates: From HPA axis to glucocorticoid receptor dysfunction. *Ann N Y Acad Sci*. 2012; 1261(1): 55-63. doi: 10.1111/j.1749-6632.2012.06633.x
20. Sandrini L, Ieraci A, Amadio P, et al. Impact of acute and chronic stress on thrombosis in healthy individuals and cardiovascular disease patients. *Int J Mol Sci*. 2020; 21(21): 7818. doi: 10.3390/ijms21217818
21. Lei AA, Phang VWX, Lee YZ, et al. Chronic stress-associated depressive disorders: The impact of HPA Axis dysregulation and neuroinflammation on the hippocampus—A mini review. *Int J Mol Sci*. 2025; 26(7): 2940. doi: 10.3390/ijms26072940
22. Kotłęga D, Gołąb-Janowska M, Masztalewicz M, et al. The emotional stress and risk of ischemic stroke. *Neurol Neurochir Pol*. 2016; 50(4): 265-270. doi: 10.1016/j.pjnns.2016.03.006

23. Khalifa MA, Alardhi AS, Alharbi GFS, et al. Psychosocial stress and stroke risk: Meta-analysis of observational studies. *Front Neurol.* 2025; 16. doi: 10.3389/fneur.2025.1669925
24. Black PH, Garbutt LD. Stress, inflammation and cardiovascular disease. *J Psychosom Res.* 2002; 52(1): 1-23. doi: 10.1016/S0022-3999(01)00302-6
25. Beniwal SS, Calderón DC, Baweja T, et al. Inflammation in cardio-oncology and psychological disorders: Mechanisms, biomarkers, pain management, and therapeutic strategies. *Annals of Medicine & Surgery.* 2025; 87(7): 4229-4236. doi: 10.1097/MS9.0000000000003412
26. Woock M, Martinez-Majander N, Seiffge DJ, et al. Cancer and stroke: Commonly encountered by clinicians, but little evidence to guide clinical approach. *Ther Adv Neurol Disord.* 2022; 15. doi: 10.1177/17562864221106362
27. Margaglione M, D'Andrea G, Giuliani N, et al. Inherited prothrombotic conditions and premature ischemic stroke. *Arterioscler Thromb Vasc Biol.* 1999; 19(7): 1751-1756. doi: 10.1161/01.ATV.19.7.1751