Observational Study

Medicine

OPEN

Relationship between elevated homocysteine levels and the degree of white matter lesions in stroke patients

Xingying Wu, MM[a], Yanni Du, MM[a], Na Wei, MM[a], Leiqiang Pan, MM[b], Chuanyu Cao, MM[a,*]

Abstract

This study explores the relationship between elevated homocysteine (Hcy) levels and white matter lesion (WML) severity in stroke patients, aiming to clarify Hcy role in stroke pathology and support clinical treatment and prevention strategies for cerebrovascular diseases. A retrospective analysis was conducted on 200 stroke patients from Guyuan People's Hospital (2022–2024). Hcy levels were measured using a Beckman AU5800 analyzer, and WML severity was assessed via magnetic resonance imaging using the Fazekas scale. Carotid intima-media thickness (cIMT) was measured by ultrasound. The mean Hcy level was significantly higher in the moderate to severe WML group (16.2 ± 5.3 µmol/L) compared to the mild group (11.4 ± 3.8 µmol/L, $P < .001$), showing a positive correlation with WML severity. The moderate to severe group also had significantly higher left and right cIMT ($P < .001$). Logistic regression identified age, hypertension, diabetes, Hcy levels, and right-sided cIMT as independent predictors of moderate to severe WML. Receiver operating characteristic curve analysis indicated high diagnostic value for both Hcy levels and right-sided cIMT, with combined use improving assessment accuracy. Elevated Hcy levels and increased right-sided cIMT are independent risk factors for moderate to severe WML in stroke patients. Combining these measures improves assessment accuracy and highlights the need for targeted interventions. Future research should investigate Hcy and cIMT mechanisms and interventions to enhance clinical application.

Abbreviations: AF = atrial fibrillation, cIMT = carotid intima-media thickness, Hcy = homocysteine, MRI = magnetic resonance imaging, ROC = receiver operating characteristic, WML = white matter lesions.

Keywords: carotid intima-media thickness, Fazekas scale, homocysteine, MRI, stroke, white matter lesions

1. Introduction

Cerebral infarction, a significant neurological disorder threatening human health, presents with complex pathological processes and severe consequences that cannot be ignored.[1–3] The core pathological feature focuses on the acute or chronic occlusion of cerebral blood vessels, leading to a sharp decrease in blood supply to local brain tissues and resulting in ischemic necrosis.[4–6] This process not only directly damages the structure and function of brain tissues but also often accompanies a series of neurological dysfunctions, such as hemiplegia, aphasia, and cognitive impairment, severely impacting patients' quality of life and prognosis.[2,7]

In recent years, with the rapid development of neuroimaging technology, especially the widespread application of high-resolution magnetic resonance imaging (MRI), scientists have been able to observe the microstructural changes in the brains of stroke patients in greater detail.[8–10] Among these changes, white matter lesions (WML) have emerged as a significant imaging finding and have become a research hotspot.[11,12] As a critical area responsible for information transmission in the brain, the degeneration of white matter not only reflects abnormalities in the brain's microvascular system, such as compromised blood-brain barrier integrity, reduced vascular dilation function, and hardened vessel walls, but also indicates damage to the myelin sheath, which insulates nerve fibers. These pathological changes are particularly prominent in cerebral small vessel disease, which is closely related to various neurological disorders, including stroke and vascular dementia, and significantly contribute to the poor prognosis of stroke patients.[13–16]

Homocysteine (Hcy), a nonessential amino acid, has metabolic abnormalities closely linked to the development and progression of various cardiovascular and cerebrovascular diseases.[17–19] Numerous studies have confirmed that elevated plasma homocysteine levels are independent risk factors for atherosclerosis, stroke, and cognitive decline.[20–23] This finding reveals the potential role of homocysteine in endothelial cell dysfunction, suggesting that high homocysteine levels may

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Neurology, Guyuan People's Hospital Affiliated to Ningxia Medical University, Guyuan, Ningxia, China, [b] Department of Radiology, Guyuan People's Hospital Affiliated to Ningxia Medical University, Guyuan, Ningxia, China.

* Correspondence: Chuanyu Cao, No. 225, Jiulong Road, Southwest New District, Yuanzhou District, Guyuan City, Ningxia 756000, China (e-mail: ccy1234560730@163.com).

How to cite this article: Wu X, Du Y, Wei N, Pan L, Cao C. Relationship between elevated homocysteine levels and the degree of white matter lesions in stroke patients. Medicine 2025;104:14(e41984).

Received: 19 August 2024 / Received in final form: 8 February 2025 / Accepted: 11 March 2025

http://dx.doi.org/10.1097/MD.0000000000041984

impair vascular integrity by inducing oxidative stress, promoting inflammatory responses, and interfering with nitric oxide synthesis, thereby accelerating vascular hardening and exacerbating the degree of white matter lesions.

However, despite the preliminary validation of these associations, research on the specific mechanisms linking elevated homocysteine levels and white matter lesions remains insufficient, especially within the context of stroke.[24] The quantitative relationship and dynamic evolution between the 2 need further elucidation. Therefore, exploring the impact of elevated homocysteine levels on the degree of white matter lesions in stroke patients will not only provide new insights into the pathological mechanisms of stroke but also offer scientific evidence for developing more precise prevention and treatment strategies.[25,26]

To investigate the relationship between elevated homocysteine levels and the degree of white matter lesions in stroke patients. By analyzing the impact of elevated homocysteine levels on the severity of white matter lesions, the study seeks to further elucidate its pathological mechanisms in stroke patients. The hypothesis of this study is that there is a positive correlation between elevated homocysteine levels and the degree of white matter lesions, meaning that as homocysteine levels increase, the severity of white matter lesions worsens. This hypothesis is based on existing literature on the relationship between homocysteine and vascular lesions. To validate this hypothesis, the study will retrospectively analyze the clinical data of stroke patients, measure their blood homocysteine levels, and assess the degree of white matter lesions through cranial MRI. Statistical analysis will be used to explore the relationship between elevated homocysteine levels and the degree of white matter lesions, providing reference data for the clinical treatment of stroke patients and advancing comprehensive prevention strategies for cerebrovascular diseases.

2. Materials and methods

2.1. Selection of study subjects and data collection

This study was approved by the Ethics Committee of Guyuan People's Hospital Affiliated to Ningxia Medical University. This retrospective study selected stroke patients treated in the neurology department of Guyuan People's hospital between 2022 and 2024. A total of 200 patients with detailed clinical data were included, all of whom were diagnosed through cranial MRI. Stroke is defined and classified as follows: stroke is defined as an acute neurological deficit resulting from a vascular cause, classified into ischemic stroke (cerebral infarction) and hemorrhagic stroke based on cranial MRI findings. Ischemic stroke is characterized by the presence of focal cerebral infarction due to arterial occlusion, while hemorrhagic stroke is defined by the presence of intracerebral or subarachnoid hemorrhage. In this study, only patients diagnosed with ischemic stroke (cerebral infarction) were included.

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) age 40 years and above. (2) Diagnosed with cerebral infarction through cranial MRI. (3) Complete medical records, including blood lipid levels, blood uric acid, Hcy, and carotid artery ultrasound results.

Exclusion criteria: (1) nonvascular white matter lesions. (2) Malignant tumors, dementia, and psychiatric disorders. (3) Incomplete data or cases that did not meet the study requirements.

2.3. Measurement of study indicators

(1) Hcy levels: measured using blood samples and quantitatively analyzed with a Beckman AU5800 fully automated biochemical analyzer.[27] Blood samples were collected within 24 to 72 hours after stroke onset to minimize the influence of acute-phase fluctuations.

(2) Degree of WML: WML severity was assessed via cranial MRI using the Fazekas scale. The scoring criteria evaluate both periventricular and deep white matter lesions, assigning separate scores to each region. However, for analysis, patients were classified based on the highest score among these regions, with WML severity categorized as mild (1 point) or moderate-to-severe (≥2 points). This approach provides a comprehensive assessment while ensuring consistency in severity classification.[28] MRI was performed within 3 to 7 days after stroke onset to ensure stable lesion visualization while reducing the impact of acute ischemic changes.

(3) Carotid intima-media thickness (cIMT): measured using a GE VIVID E80 ultrasound diagnostic instrument, with bilateral cIMT values recorded. All measurements were performed by an experienced technician to ensure accuracy, and the instrument was calibrated regularly to maintain measurement reliability.[29] cIMT was measured at the common carotid artery, approximately 1 cm proximal to the carotid bifurcation, using B-mode ultrasound. The internal carotid artery was not included in the measurement to ensure standardization and reproducibility. cIMT assessment was conducted within 3 to 7 days after stroke onset, in parallel with MRI evaluation, to provide a comprehensive assessment of vascular status.

2.4. Imaging and scoring methods

Cranial MRI examinations were performed using 1.5 T or 3.0 T high-field MRI scanners provided by SIEMENS AERA or SIEMENS VIDA, including standard axial scans such as T1-weighted images, T2-weighted images, and FLAIR sequences. Fazekas scale scoring was independently conducted by 2 experienced neurologists using a double-blind method to ensure objectivity. A third neurologist reviewed the scores in case of disputes.

2.5. Statistical analysis

Data analysis was performed using SPSS 25.0 statistical software. For normally distributed quantitative data, results are expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared between groups using independent *t* tests. Non-normally distributed quantitative data are expressed as median (M) and interquartile range (P25, P75), with group comparisons conducted using rank-sum tests. Categorical data are expressed as frequency (n) and percentage (%), with group comparisons conducted using $\chi 2$ tests. Additionally, binary logistic regression analysis was used to identify independent risk factors for moderate to severe white matter lesions. Receiver operating characteristic (ROC) curve analysis was employed to assess the diagnostic efficacy of Hcy levels and cIMT in predicting the severity of white matter lesions, including calculations of sensitivity and specificity.

3. Results

3.1. Basic characteristics of study subjects

This retrospective study included 200 stroke patients admitted to the neurology department of Guyuan People's hospital from 2022 to 2024. All patients were diagnosed via cranial MRI. According to the Fazekas scale, patients were divided into the mild WML group (112 cases, score of 1) and the moderate-to-severe WML group (88 cases, score ≥ 2). The average age of patients in the mild group was significantly lower than in the moderate-to-severe group (62.4 years *vs* 70.1 years). There were significant differences in clinical characteristics such as gender, hypertension, diabetes, and coronary heart disease between the 2 groups ($P < .05$). Detailed data are shown in Table 1.

3.2. Analysis of Hcy levels

The average Hcy level in the moderate-to-severe WML group was significantly higher than in the mild group (16.2 ± 5.3 μmol/L *vs* 11.4 ± 3.8 μmol/L, $P < .001$), indicating a significant correlation between elevated Hcy levels and the severity of WML. Specific data are presented in Table 2.

3.3. Comparison of cIMT

In the moderate-to-severe WML group, the measurements of both left and right cIMT were significantly higher than those in the mild group, possibly reflecting the potential role of vascular lesions in WML. Detailed data are shown in Table 3.

3.4. Regression analysis of independent risk factors

Binary logistic regression analysis revealed that age, hypertension, diabetes, Hcy levels, and increased right cIMT were independent predictors of moderate-to-severe WML. Specific data are presented in Table 4.

3.5. Application of ROC curve analysis

ROC curve analysis demonstrated the diagnostic value of Hcy levels and right cIMT in assessing the severity of WML, with the combined use of both indicators showing better evaluation efficiency. This is illustrated in Fig. 1.

4. Discussion

This study investigates the relationship between elevated Hcy levels and the degree of WML in 200 stroke patients through a retrospective analysis. The results indicate that Hcy levels in the moderate-to-severe WML group are significantly higher than in the mild group, with a positive correlation between Hcy levels and WML severity. Additionally, cIMT is closely associated with WML severity, particularly the right cIMT. Binary logistic regression analysis revealed that higher Hcy levels and thicker right cIMT are independent risk factors for moderate-to-severe WML, consistent with previous research findings.

4.1. Age, gender, hypertension, and diabetes as independent risk factors

Our study identified age as a significant independent risk factor for moderate-to-severe WML, consistent with previous research linking aging to cerebral small vessel disease. Age-related endothelial dysfunction, impaired cerebrovascular autoregulation, and increased prevalence of hypertension and diabetes likely contribute to the progression of WML.

Gender differences were also observed, which may be influenced by hormonal factors, vascular structure, and metabolic risks. Estrogen may provide vascular protection in premenopausal women, while postmenopausal hormonal decline could accelerate WML progression. Additionally, men are more prone to early atherosclerosis, which could contribute to differences in cIMT and stroke risk profiles.

Hypertension and diabetes, both identified as independent risk factors, are well-established contributors to WML. Chronic hypertension leads to small vessel remodeling, reduced cerebral perfusion, and blood-brain barrier dysfunction, accelerating WML formation. Similarly, diabetes is associated with

Table 1

Comparison of clinical characteristics between 2 patient groups.

Group	Gender (male/female)	Age (years)	Hypertension (n, %)	Diabetes (n, %)	Coronary Heart Disease (n, %)	Hcy (μmol/L)
Mild group (n = 112)	68/44	62.4 ± 9.8	42 (37.5%)	15 (13.4%)	10 (8.9%)	11.4 ± 3.8
Moderate-severe group (n = 88)	64/24	70.1 ± 10.3	56 (63.6%)	32 (36.4%)	18 (20.5%)	16.2 ± 5.3
t/*Z*	2.679	3.124	2.961	2.783	3.123	3.352
P-value	.023	<.001	<.001	<.001	.027	<.001

Table 2

Comparison of carotid intima-media thickness (cIMT) between 2 patient groups.

Group	Left cIMT (mm)	Right cIMT (mm)
Mild group (n = 112)	0.92 ± 0.16	0.93 ± 0.18
Moderate-severe group (n = 88)	1.05 ± 0.22	1.08 ± 0.20
P-value	<.001	<.001

Table 3

Logistic regression analysis of risk factors for moderate-severe white matter hyperintensities.

Variable	Wald	OR (95% CI)	*P*-value
Age	45.321	1.084 (1.057–1.112)	<.001
Hypertension	15.673	2.583 (1.593–4.188)	<.001
Diabetes	8.342	2.456 (1.332–4.527)	.004
Hcy	11.624	1.069 (1.031–1.108)	<.001
Right cIMT	6.728	3.157 (1.529–6.514)	.009

CI = confidence interval, Hcy = homocysteine, OR = odds ratio.

Table 4

ROC curve analysis of Hcy and right cIMT for assessing the severity of white matter hyperintensities.

Indicator	Optimal cutoff	Sensitivity (%)	Specificity (%)	AUC (95% CI)	*P*-value
Right cIMT	1.05	67.5	72.3	0.721 (0.675–0.767)	<.001
Hcy	14.5	70.3	74.1	0.737 (0.691–0.783)	<.001
Combined cIMT & Hcy	–	75.6	78.4	0.783 (0.741–0.825)	<.001

AUC = area under the curve, CI = confidence interval, Hcy = homocysteine, ROC = receiver operating characteristic.

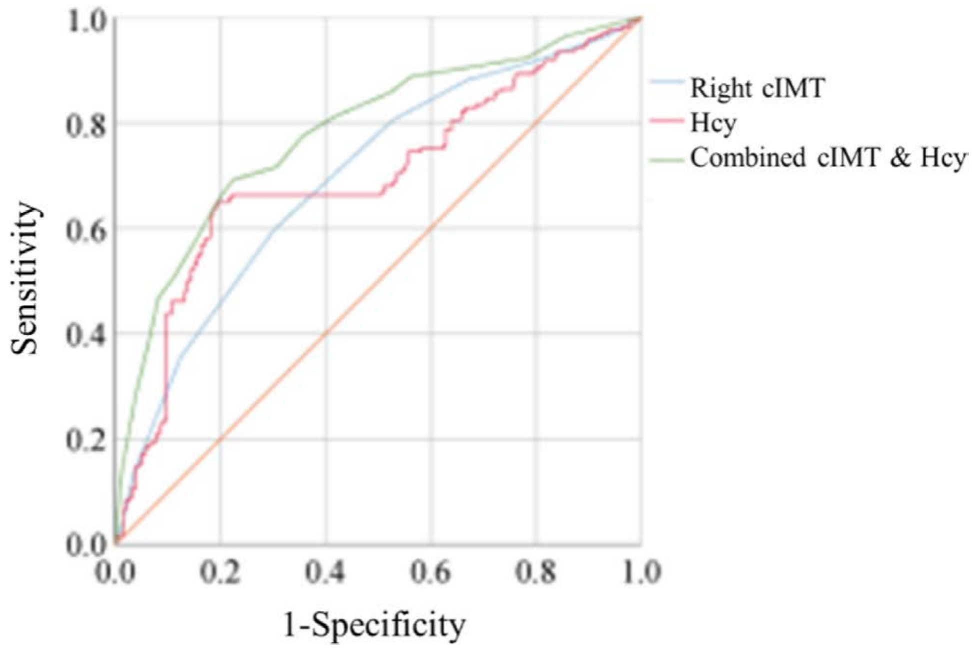

Figure 1. ROC curve diagram for assessing the severity of white matter lesions (WML) using right cIMT and Hcy. cIMT = carotid intima-media thickness, Hcy = homocysteine, ROC = receiver operating characteristic.

microvascular damage and oxidative stress, further exacerbating white matter degeneration.

These findings highlight the need for early identification and management of these risk factors to mitigate WML progression and cerebrovascular complications. Future studies should explore their combined effects on stroke outcomes.

4.2. Homocysteine and white matter lesions

Hcy, a sulfur-containing amino acid, is widely recognized as a significant risk factor for cardiovascular and cerebrovascular diseases. Elevated Hcy levels can cause endothelial dysfunction, leading to vascular sclerosis and atherosclerosis, thereby increasing the risk of stroke and cognitive impairment.[30,31] Our study found that Hcy levels were significantly higher in the moderate-to-severe WML group, consistent with Vermeer et al.'s findings, which demonstrated a close association between high Hcy levels and WML. Additionally, Hu et al.'s research also indicated that elevated Hcy levels are significant risk factors for Alzheimer disease and other cognitive disorders.

Hcy exhibits toxic effects on endothelial cells, and high levels of Hcy can cause endothelial cell damage, inhibit the release of endothelial nitric oxide, and subsequently lead to endothelial dysfunction.[32] Furthermore, Hcy can exacerbate vascular damage through oxidative stress and inflammatory responses.[33] These mechanisms may explain the relationship between elevated Hcy levels and WML. Our study further confirms this, finding that Hcy levels are an independent risk factor for moderate-to-severe WML.

4.3. Carotid intima-media thickness and white matter lesions

Carotid intima-media thickness (cIMT) is a critical indicator of atherosclerosis, and its thickening is closely associated with the risk of both cardiovascular and cerebrovascular diseases.[34] In this study, we observed that both left and right cIMT were significantly higher in the moderate-to-severe WML group compared to the mild group, with the relationship between right cIMT and WML severity being particularly pronounced.

Several studies have previously shown that increased cIMT correlates significantly with WML volume,[35] and Franki I et al found a strong association between increased cIMT and the severity of periventricular WML.[36] Our findings corroborate these results and highlight the role of vascular health in the progression of WML. The greater predictive value of right cIMT for WML severity in our study is noteworthy. It is known that the right carotid artery may be more prone to atherosclerotic changes, potentially influencing cerebral perfusion and contributing to WML development.

Regarding the differences between left and right cIMT, previous studies suggest that the left cIMT is often thicker in untreated hypertensive patients, possibly due to the left common carotid artery's origin from the aortic arch, which may be more influenced by hemodynamic changes.[37,38] However, our study indicates that the right cIMT may be more closely related to WML severity, which aligns with the findings of Lee et al., who suggested that right cIMT could independently predict cardiovascular events. This could reflect individual variations in hemodynamic conditions, including differences in blood flow dynamics between the carotid arteries, and potentially points to regional vascular differences that impact the progression of WML. Moreover, the right side's involvement could also be linked to asymmetries in intracranial small vessel disease, underscoring the complex interplay between vascular health and white matter integrity.

Thus, while the left cIMT is often emphasized in vascular studies, our findings suggest that the right cIMT holds particular value in predicting WML severity. Further research is needed to explore the specific mechanisms underlying these differences and their potential implications for early intervention and risk stratification in stroke patients.

4.4. Value of combined analysis

Our study, through ROC curve analysis, found that both Hcy levels and right cIMT have value in assessing the severity of WML, with the combined evaluation being more effective. The sensitivity and specificity of the combined indicators were higher than those of single indicators, suggesting that in clinical practice, combined detection of Hcy levels and right cIMT can more accurately assess the severity of WML. Hcy and cIMT are easily accessible clinical indicators, thus their combined application holds significant clinical value.

Compared with previous studies, our study further clarifies the impact of Hcy and cIMT on the severity of WML in stroke patients. Previous studies have mostly focused on the relationship between Hcy and cIMT and WML in the general population or elderly population, while our study focuses on a specific population of stroke patients.[39] Muzurović E et al's study showed a close association between high Hcy levels and the occurrence of WML but did not further explore its role in stroke patients. Our study fills this research gap, providing evidence of the relationship between Hcy and cIMT and WML in stroke patients.

4.5. Clinical significance and future prospects

The results of this study have significant clinical implications. First, Hcy levels and right cIMT can serve as important indicators for assessing the severity of WML, helping clinicians to more accurately judge the patient's condition. Second, lowering Hcy levels may be an essential means of preventing and treating WML. Studies have shown that folic acid and vitamin B12 supplementation can effectively reduce Hcy levels, thereby reducing the risk of stroke. Future research should further explore the application effects of these interventions in stroke patients. Additionally, our study suggests that measuring cIMT is crucial for managing stroke patients. Regular monitoring of cIMT, especially right cIMT, can help in the early detection and intervention of WML, thereby improving patient prognosis. Previous studies link atrial fibrillation (AF) to WML via hypoperfusion and embolic mechanisms. Mayasi et al found AF-related anterior subcortical WML, while de Leeuw et al reported AF's association with periventricular WML.[40,41] Our study, however, identifies elevated Hcy and increased right cIMT as independent risk factors, highlighting the role of vascular pathology beyond cardiac influences. Future research should investigate the impact of interventions, such as antihypertensive and lipid-lowering treatments, on cIMT and their role in WML.

Despite revealing the impact of Hcy and cIMT on the severity of WML in stroke patients, our study has some limitations. First, as a retrospective study, it may have selection bias and information bias. Second, our study is a single-center study, and the results may not be generalizable, requiring further validation through multi-center, large-sample prospective studies. Additionally, our study only used the Fazekas scale to grade WML severity, and future studies could consider using more precise imaging measurement methods, such as imaging software or artificial intelligence technology, to further improve assessment accuracy.

5. Conclusion

In summary, our study systematically analyzes the relationship between Hcy levels and cIMT and the severity of WML in stroke patients, finding that high Hcy levels and thicker right cIMT are independent risk factors for moderate-to-severe WML, and the combined indicators can more accurately assess the severity of WML. This finding provides new perspectives for the diagnosis and treatment of cerebrovascular diseases, holding significant clinical value. Future research should further explore the mechanisms and interventions of Hcy and cIMT in different populations to improve the prognosis of stroke patients.

Acknowledgements

We would like to thank the participants of this study for sharing their experiences.

Author contributions

Conceptualization: Xingying Wu, Yanni Du, Chuanyu Cao.
Data curation: Xingying Wu, Yanni Du, Na Wei, Leiqiang Pan, Chuanyu Cao.
Formal analysis: Xingying Wu, Na Wei, Leiqiang Pan, Chuanyu Cao.
Investigation: Chuanyu Cao.
Methodology: Chuanyu Cao.
Writing – original draft: Xingying Wu, Yanni Du, Na Wei, Chuanyu Cao.
Writing – review & editing: Xingying Wu, Chuanyu Cao.

References

[1] Ma R, Xie Q, Li Y, et al. Animal models of cerebral ischemia: a review. Biomed Pharmacother. 2020;131:110686.
[2] Zhou J, Fangma Y, Chen Z, Zheng Y. Post-stroke neuropsychiatric complications: types, pathogenesis, and therapeutic intervention. Aging Dis. 2023;14:2127–52.
[3] Sweid A, Hammoud B, Bekelis K, et al. Cerebral ischemic and hemorrhagic complications of coronavirus disease 2019. Int J Stroke. 2020;15:733–42.
[4] Jurcau A, Simion A. Neuroinflammation in cerebral ischemia and ischemia/reperfusion injuries: from pathophysiology to therapeutic strategies. Int J Mol Sci . 2021;23:14.
[5] Przykaza L. Understanding the connection between common stroke comorbidities, their associated inflammation, and the course of the cerebral ischemia/reperfusion cascade. Front Immunol. 2021;12:782569.
[6] Yi Y, Liu Z, Wang M, et al. Penumbra in acute ischemic stroke. Curr Neurovasc Res. 2021;18:572–85.
[7] Sheppard SM, Sebastian R. Diagnosing and managing post-stroke aphasia. Expert Rev Neurother. 2021;21:221–34.
[8] Weiskopf N, Edwards LJ, Helms G, Mohammadi S, Kirilina E. Quantitative magnetic resonance imaging of brain anatomy and in vivo histology. Nat Rev Phys. 2021;3:570–88.
[9] van Veluw SJ, Arfanakis K, Schneider JA. Neuropathology of vascular brain health: insights from ex vivo magnetic resonance imaging – histopathology studies in cerebral small vessel disease. Stroke. 2022;53:404–15.
[10] Khan W, Egorova N, Khlif MS, Mito R, Dhollander T, Brodtmann A. Three-tissue compositional analysis reveals in-vivo microstructural heterogeneity of white matter hyperintensities following stroke. Neuroimage. 2020;218:116869.
[11] Tang Q, Li S, Yang Z, Wu M, Guo Y, Yin C. A narrative review of multimodal imaging of white matter lesions in type-2 diabetes mellitus. Ann Palliat Med. 2021;10:12867–76.
[12] Zivadinov R, Schweser F, Jakimovski D, Bergsland N, Dwyer MG. Decoding gray matter involvement in multiple sclerosis via imaging. Neuroimaging Clin N Am. 2024;34:453–68.

[13] Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: a review. Adv Clin Exp Med. 2021;30:349–56.
[14] Markus HS, de Leeuw FE. Cerebral small vessel disease: recent advances and future directions. Int J Stroke. 2023;18:4–14.
[15] Mahammedi A, Wang LL, Williamson BJ, et al. Small vessel disease, a marker of brain health: what the radiologist needs to know. Am J Neuroradiol. 2022;43:650–60.
[16] Ren B, Tan L, Song Y, et al. Cerebral small vessel disease: neuroimaging features, biochemical markers, influencing factors, pathological mechanism and treatment. Front Neurol. 2022;13:843953.
[17] González-Lamuño D, Arrieta-Blanco FJ, Fuentes ED, et al. Hyperhomocysteinemia in adult patients: a treatable metabolic condition. Nutrients. 2023;16:135.
[18] McCaddon A, Miller JW. Homocysteine—a retrospective and prospective appraisal. Front Nutr. 2023;10:1179807.
[19] Zhou Q, Xu Z, Duan Y, Tang H, Zhang H, Liu H. MTHFR C677T, hyperhomocysteinemia, and their interactions with traditional risk factors in early neurological deterioration in Chinese patients with ischemic stroke. Heliyon. 2024;10:e31003.
[20] Lauriola M, D'Onofrio G, Ciccone F, et al. Relationship of homocysteine plasma levels with mild cognitive impairment, Alzheimer's disease, vascular dementia, psychobehavioral, and functional complications. J Alzheimers Dis. 2021;82:235–48.
[21] Smith AD, Refsum H. Homocysteine – from disease biomarker to disease prevention. J Intern Med. 2021;290:826–54.
[22] Cui L, Lu P, Li S, et al. Relationship among homocysteine, inflammation and cognitive impairment in patients with acute ischemic stroke and transient ischemic attack. Neuropsychiatr Dis Treat. 2021;17:3607–16.
[23] Wu JX, Xue J, Zhuang L, Liu C-F. Plasma parameters and risk factors of patients with post-stroke cognitive impairment. Ann Palliat Med. 2020;9:45–52.
[24] Rastogi A, Weissert R, Bhaskar SMM. Emerging role of white matter lesions in cerebrovascular disease. Eur J Neurosci. 2021;54:5531–59.
[25] Yuan Y, Cai X, Liu Y, Li N. Dose–response association between plasma homocysteine and white matter lesions in patients with hypertension: a case–control study. Hypertens Res. 2022;45:1794–801.
[26] Yu L, Yang L, Li Y, et al. Hyperhomocysteinemia can predict the severity of white matter hyperintensities in elderly lacunar infarction patients. Int J Neurosci. 2020;130:231–6.
[27] Brezovska Kavrakova J, Cekovska S, Tosheska Trajkovska K, et al. Homocystinemia and polymorphysm of the gene for methylentetrahydrofolate reductase (C677T) in patient with coronary artery disease. Clin Chim Acta. 2022;13:105.
[28] Pitkänen J, Koikkalainen J, Nieminen T, et al. Evaluating severity of white matter lesions from computed tomography images with convolutional neural network. Neuroradiology. 2020;62:1257–63.
[29] Li B, Liu S, Wang Y, et al. The influence of carotid atherosclerosis on surgical outcomes of patients with cervical spondylotic myelopathy: a retrospective study. Medicine (Baltimore). 2022;101:e28743.
[30] Moretti R, Giuffre M, Caruso P, Gazzin S, Tiribelli C. Homocysteine in neurology: a possible contributing factor to small vessel disease. Int J Mol Sci . 2021;22:2051.
[31] Lu ZH, Li J, Li XL, et al. Hypertension with hyperhomocysteinemia increases the risk of early cognitive impairment after first-ever ischemic stroke. Eur Neurol. 2020;82:75–85.
[32] Sun HJ, Wu ZY, Nie XW, Bian J-S. Role of endothelial dysfunction in cardiovascular diseases: the link between inflammation and hydrogen sulfide. Front Pharmacol. 2020;10:1568.
[33] Balint B, Jepchumba VK, Guéant JL, Guéant-Rodriguez R-M. Mechanisms of homocysteine-induced damage to the endothelial, medial and adventitial layers of the arterial wall. Biochimie. 2020;173:100–6.
[34] Huang Q, Liu Z, Wei M, et al. The atherogenic index of plasma and carotid atherosclerosis in a community population: a population-based cohort study in China. Cardiovasc Diabetol. 2023;22:125.
[35] Humayra S, Yahya N, Ning CJ, et al. Relationship between carotid intima-media thickness and white matter hyperintensities in non-stroke adults: a systematic review. Front Neuroanat. 2024;18:1394766.
[36] Franki I, Mailleux L, Emsell L, et al. The relationship between neuroimaging and motor outcome in children with cerebral palsy: a systematic review–Part A. Structural imaging. Res Dev Disabil. 2020;100:103606.
[37] Lindow A, Kennbäck C, Åkesson A, Nilsson PM, Weismann CG. Common carotid artery characteristics in patients with repaired aortic coarctation compared to other cardiovascular risk factors. Int J Cardiol Congenit Heart Dis. 2022;7:100319.
[38] Sendžikaitė S. Early Vascular Aging and Arterial Hypertension In Children After Correction of Coarctation of the Aorta. Vilniaus Universitetas; 2022.
[39] Muzurović E, Kraljević I, Solak M, Dragnić S, Mikhailidis DP. Homocysteine and diabetes: role in macrovascular and microvascular complications. J Diabetes Complications. 2021;35:107834.
[40] Mayasi Y, Helenius J, McManus DD, et al. Atrial fibrillation is associated with anterior predominant white matter lesions in patients presenting with embolic stroke. J Neurol Neurosurg Psychiatry. 2018;89:6–13.
[41] de Leeuw FE, de Groot JC, Oudkerk M, et al. Atrial fibrillation and the risk of cerebral white matter lesions. Neurology. 2000;54:1795–801.