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Neurovascular health insights: a powerful tool to understand and prognose neurocognitive decline

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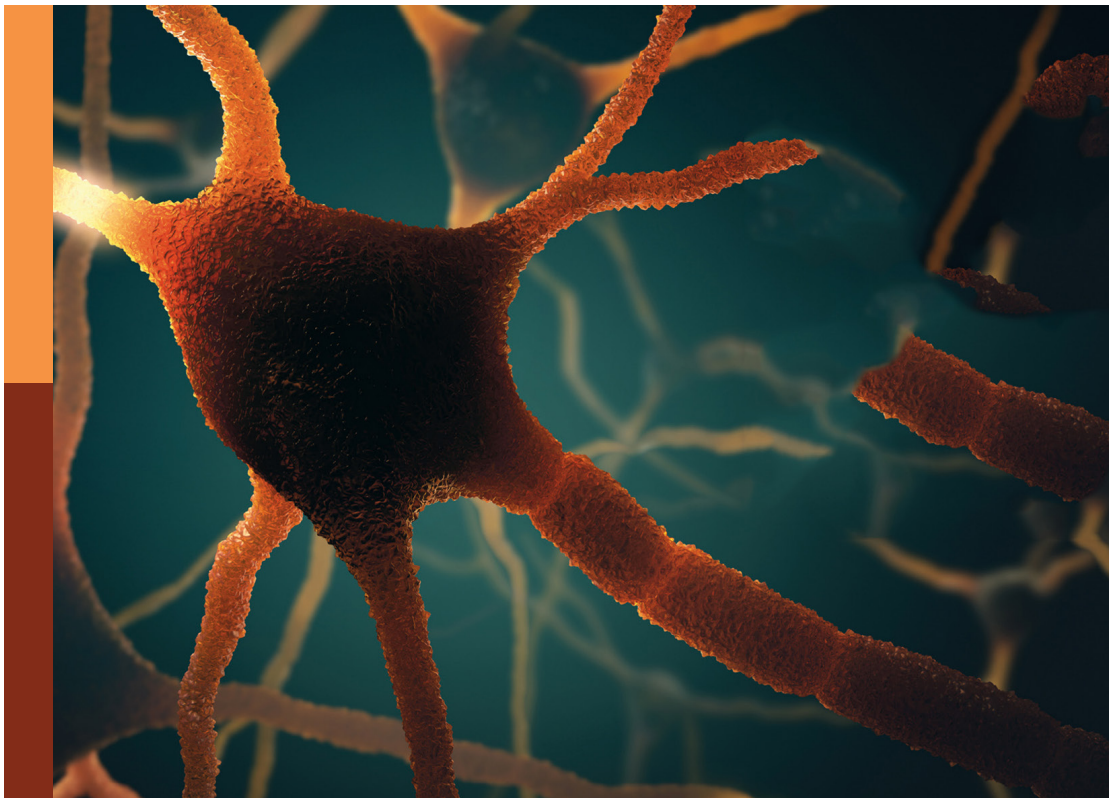

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Neurovascular health insights: a powerful tool to understand and prognose neurocognitive decline

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Editorial: Neurovascular health insights: a powerful tool to understand and prognose neurocognitive decline

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Editorial on the Research Topic
Neurovascular health insights: a powerful tool to understand and prognose neurocognitive decline

As societies age, the global prevalence of dementia is expected to reach 139 million by 2050, with an estimated cost of $2.8 trillion by 2030 alone. However, dementia is neither an inevitable nor an unavoidable condition, up to 40% of cases can be prevented or delayed by addressing established risk factors (Long et al., 2023). Neurovascular health plays a pivotal role in the etiology, progression, and outcomes of neurocognitive decline. Impaired neurovascular coupling, characterized by reduced endothelial vasodilatory capacity (Rudnicka-Drożak et al., 2022) and diminished oxygen and glucose delivery to neurons due to decreased cerebral blood flow (Kisler et al., 2017), has been implicated in the onset and progression of dementia. Understanding the intricate interplay between vascular factors and neurodegenerative mechanisms is crucial for addressing the global burden of cognitive disorders. Advancing our understanding of neurovascular health brings us closer to mitigating cognitive decline through early detection, targeted interventions, and personalized care.

Cerebral small vessel disease (CSVD) is increasingly acknowledged as a critical contributor to neurocognitive decline, particularly in aging populations. From 2008 to 2030, nearly 5,000 publications on CSVD have appeared in 790 journals across 84 countries. Yan et al. conducted a bibliometric analysis and network visualizations of these literatures, providing insights into future research prospects. Their analysis identified magnetic resonance imaging (MRI) segmentation and enlarged perivascular spaces in the Basal ganglia as recent research interest, based on keywords co-occurrence analysis and burst graph emergence detection. MRI segmentation may enhance the diagnostic capabilities for CSVD and inspire the exploration of therapeutic targets. However, the diagnostic significance of enlarged perivascular spaces in CSVD remains unrecognized, necessitating further research into lesion differentiation and the development of quantitative methods to assess disease burden accurately.

Leveraging on its high spatial resolution, MRI uniquely visualizes subtle brain changes associated with neurocognitive decline. It is revealing that alterations in white matter integrity and cortical thinning, are crucial for understanding early-stage cognitive impairment due to vascular pathology. By integrating structural and functional imaging techniques, MRI provides a comprehensive understanding of how vascular risk factors contribute to neurocognitive decline. This facilitates the identification of biomarkers for early intervention before dementia. Zhang et al. reviewed advancements in multimode MRI, including structural MRI (sMRI), diffusion tensor imaging, resting-state fMRI, and magnetic resonance spectroscopy, in assessing vascular cognitive impairment not dementia (VCIND). They concluded that MRI not only elucidate the neurobiological mechanisms of vascular cognitive impairment (VCI) but also aids in distinguishing VCI from VCIND. Unlike MRI, Li et al. found EEG, featured by high temporal resolution, offers more precision in discriminating VCIND from healthy controls. They also demonstrated that combining EEG and sMRI using machine learning outperformed unimodal approaches in differentiating various stages of VCI. Their research highlights the possibility for early clinical diagnosis of VCI, enabling timely intervention that may delay or even reverse neurocognitive decline (Gorelick et al., 2011).

To gain deeper insight into vascular contributions to neurocognitive decline, Lim et al. examined clinical cases of post-stroke cognitive decline, focusing on brain structure, function, and metabolism. This 6-year study analyzed multimodal MRI and 18F-florbetaben PET data from 11 post-stroke cognitive decline and 10 matched non-decline controls. However, no difference was observed between the two groups on the CVSD features, including the proportion of moderate-to-severe white matter hyperintensities (WMHs) as well as the number of lacunes and microbleeds. In the decliner group, WMH volume showed a marked association with neurocognitive scores. A similar phenomenon occurred in amyloid PET characteristics, where subthreshold PET standardized uptake value ratios negatively correlated with both final neurocognitive scores and changes over time. WMH-induced white matter tract damage and amyloid pathology lead to neural network deficits that eventually trigger neurocognitive decline (Coenen et al., 2023), consistent with their study. These findings hint that neurovascular involvement in neurocognitive decline may result from multiple interacting factors.

Despite early CVSD lesions, especially before the neurocognitive decline onset, which may be evident on imaging, these changes always lag behind neurovascular lesions. Beyond imaging techniques, emerging biomarkers offer a foundation for assessing the risk and progression of neurocognitive decline. Wang Q. et al. explored the association between C677T polymorphism and neurocognitive decline in a cross-sectional study. C677T mutation is a key enzyme in homocysteine metabolism, causing high homocysteine levels, a known contributor to neurovascular injury (Hassan et al., 2004). Their study found C677T polymorphism as a genetic marker linked to elevated homocysteine levels, aggravating white matter damage and neurocognitive decline in CSVD. Likewise, Wang H. et al. explored insulin resistance as a potential mechanism underlying neurocognitive decline, highlighting its role as another contributor to neurovascular injury. They demonstrated the relationship between the triglyceride-glucose index and neurocognitive decline, emphasizing its utility as a metabolic risk indicator. Moreover, Zhao et al. confirmed baseline serum ferritin as an independent risk factor for neurocognitive decline following mild ischemic stroke and transient ischemic attack, supporting its inclusion in the predictive model of post-stroke cognitive trajectories. Their findings offer novel perspectives into understanding neurovascular health in neurocognitive decline, contributing to advancements in early detection and treatment strategies.

Collectively, these studies seek to improve patient outcomes through facilitating early diagnosis and implementing effective intervention to slow neurocognitive decline. Not just the aforementioned biomarkers, but demographics, health status, etc., also play a crucial role in determining neurocognitive decline outcomes. Wei et al. successfully developed and validated a predictive model integrating age, race, stroke, cardiovascular disease, and blood urea nitrogen to estimate 5-year mortality in neurocognitive decline patients. Their model serves as a valuable tool for prognostic evaluation and personalized care planning. Furthermore, Miranda et al. identified frailty—a state of vulnerability often linked to aging—as a mediator of poor outcomes following ischemic stroke. Their findings reveal that frailty accounted for 28% of the effect of age on disability or mortality, suggesting that mitigating frailty could enhance post-stroke recovery.

These studies highlight the significant role of neurovascular health in neurocognitive decline, emphasizing early detection and intervention. Multimodal imaging, biomarkers, and predictive models offer valuable insights into vascular contributions, aiding in personalized risk assessments. The identification of metabolic and genetic risk factors, along with the impact of frailty, underscores the need for comprehensive approaches to prevention and treatment. As dementia prevalence rises, integrating these findings into clinical practice can help delay or prevent cognitive impairment. Future research should focus on refining these diagnostic tools and intervention strategies to improve patient outcomes and quality of life.

Author contributions

MX: Writing – original draft, Writing – review & editing. MN: Conceptualization, Supervision, Writing – review & editing. BW: Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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Multimodal magnetic resonance imaging on brain structure and function changes in vascular cognitive impairment without dementia

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Vascular cognitive impairment not dementia (VCIND) is one of the three subtypes of vascular cognitive impairment (VCI), with cognitive dysfunction and symptoms ranging between normal cognitive function and vascular dementia. The specific mechanisms underlying VCIND are still not fully understood, and there is a lack of specific diagnostic markers in clinical practice. With the rapid development of magnetic resonance imaging (MRI) technology, structural MRI (sMRI) and functional MRI (fMRI) have become effective methods for exploring the neurobiological mechanisms of VCIND and have made continuous progress. This article provides a comprehensive overview of the research progress in VCIND using multimodal MRI, including sMRI, diffusion tensor imaging, resting-state fMRI, and magnetic resonance spectroscopy. By integrating findings from these multiple modalities, this study presents a novel perspective on the neuropathological mechanisms underlying VCIND. It not only highlights the importance of multimodal MRI in unraveling the complex nature of VCIND but also lays the foundation for future research examining the relationship between brain structure, function, and cognitive impairment in VCIND. These new perspectives and strategies ultimately hold the potential to contribute to the development of more effective diagnostic tools and therapeutic interventions for VCIND.

KEYWORDS

vascular cognitive impairment not dementia, multimodal, magnetic resonance imaging, brain structure, brain function

Introduction

Vascular cognitive impairment (VCI) is a recognized disease primarily caused by cerebrovascular diseases (Corriveau et al., 2016; Rundek et al., 2022). VCI-non-dementia (VCIND) is the mildest stage of VCI and the most common type among elderly individuals, with a diagnosis rate of 2.4% in the population aged 65 years and above. It is also associated with an increased risk of mortality (Rockwood et al., 2000). Patients with VCIND may experience impairments in multiple or single cognitive domains, such as visual–spatial and executive abilities, memory, attention, language, abstract thinking, calculation, and orientation (Sun, 2018; van der Flier et al., 2018). The progression of VCIND can be insidious and slow, often accompanied by cognitive impairments in multiple brain regions (Li et al., 2023). Existing evidence suggests that the progression of VCIND can be delayed or even reversed through early detection and intervention (Gorelick et al., 2011).

With the continuous development of multimodal magnetic resonance imaging (MRI) techniques, including structural MRI (sMRI), diffusion tensor imaging (DTI), resting-state functional MRI (rs-fMRI), and hydrogen proton magnetic resonance spectroscopy (^{1}H-MRS), it is possible to obtain brain structural, functional, and metabolic changes to evaluate or predict abnormal changes in the brain structure and function in VCIND, thereby providing assistance for the study of central mechanisms in VCIND (Gorelick et al., 2011).

VCIND study of brain structure

SMRI

SMRI is a non-invasive clinical imaging technique commonly used to examine the anatomical structure of the brain, as well as to identify diseases through examining morphological changes (Figure 1) (Frisoni et al., 2010; Vemuri and Jack Jr, 2010). Tan et al. (2023) conducted a study using gray matter density analysis to investigate differences in gray matter volume between healthy controls and patients with subcortical ischemic vascular dementia (SIVD), including those with normal cognition, VCIND, and vascular dementia (VaD). The results showed that, in the SIVD-VCIND group, there was a positive correlation between gray matter total volume, right temporal superior gyrus, middle frontal gyrus, anterior cingulate gyrus, bilateral orbital medial gyrus, and Boston Naming Test scores, as well as a positive correlation between gray matter total volume, right superior frontal gyrus, right middle frontal gyrus, and overall cognitive function. These findings reveal the relationship between structural imaging changes caused by SIVD-VCIND and cognitive impairment, providing valuable evidence for understanding the pathogenesis of subcortical VCI and aiding in the early diagnosis of SIVD-VCIND and early warning of SIVD-VaD. Zhao et al. (2022) investigated the value of brain sMRI combined with APOE-ε4 genotype for the early diagnosis and progression of VCIND in elderly patients. It was found that the VCIND group had significantly higher white matter (WM) volume (WMV), WM hyperintensity (WMH), and Fazekas scores compared to the normal control group. Logistic regression analysis results showed that patients with higher WMV, WMH, and Fazekas scores had a higher probability of developing VCIND. The follow-up results of VCIND showed that, compared to the non-dementia group, the dementia group had significantly higher WMV, WMH, and Fazekas scores. These results suggest that widespread injury caused by white matter lesions can lead to VCIND. Zhang et al. (2022) investigated the application of MRI combined with neuropsychological assessment based on artificial intelligence technology in cognitive function impairment in patients with neurovascular diseases. The patients were divided into control, VCIND, VaD, and Alzheimer's disease (AD) groups. All patients underwent MRI, neuropsychological evaluations, and examinations, and an improved fuzzy c-means (FCM) clustering algorithm was proposed for MRI processing. The study found that the segmentation accuracy (SA) and similarity index of the improved FCM algorithm were higher than those of the standard FCM algorithm, bias-corrected FCM algorithm, and rough FCM algorithm. In terms of activities of daily living (ADL), the VCIND group and VD group were higher than the control group, indicating a negative correlation between hippocampal volume and ADL. In conclusion, the improved FCM algorithm has higher segmentation effectiveness and SA in MRI of neurovascular diseases. Additionally, the distribution, quantity, WM lesions, and hippocampal volume of lacunar infarction are associated with cognitive function impairment in patients with cerebrovascular diseases.

DTI

DTI is an advanced MRI technique that measures the directionality and magnitude of water molecules diffusion in neural tissue to reflect the microstructural integrity of WM tracts (Douglas et al., 2015; Antkowiak et al., 2021). The commonly reported DTI indices include fractional anisotropy (FA) and mean diffusivity (MD), which represent the degree of directionality and average diffusivity of water, respectively (Mayo et al., 2019; Dorsman et al., 2020; Kimura et al., 2020). Qin et al. (2021) applied DTI technique to investigate the changes in the microstructure of default mode network (DMN) WM in patients with VCIND and its role in cognitive dysfunction. Compared to healthy elderly individuals, patients diagnosed with subcortical VCIND showed abnormal WM integrity in several key hubs of the DMN. The severity of DMN WM microstructural damage was significantly associated with cognitive impairment. The integrity of DMN in patients with subcortical VCIND was significantly compromised, and the disruption of DMN connectivity could explain the impairments in attention, language, and executive functions, suggesting that the WM integrity of DMN may serve as a neuroimaging indicator for VCIND. In their study, Zhou et al. (2011) focused on using DTI histogram analysis to detect WM damage in patients with VCIND, and they aimed to investigate the correlation between DTI histogram measurements and cognitive impairment in these patients. To conduct their research, the researchers recruited both VCIND patients and cognitively normal individuals as a control group. They analyzed and compared the MD and FA histograms of WM and normal appearing WM (NAWM) for each subject. The results of their analysis revealed that the VCIND group exhibited decreased FA values throughout the brain when compared to the control group. This finding suggests that there is a widespread disruption of WM integrity in VCIND patients. Additionally, significant differences were observed in the FA and MD histogram patterns between the VCIND group and the control group for both WM and NAWM. To further investigate the relationship between DTI measurements and cognitive impairment, the researchers examined the neurocognitive results, measured as z-scores, and found significant

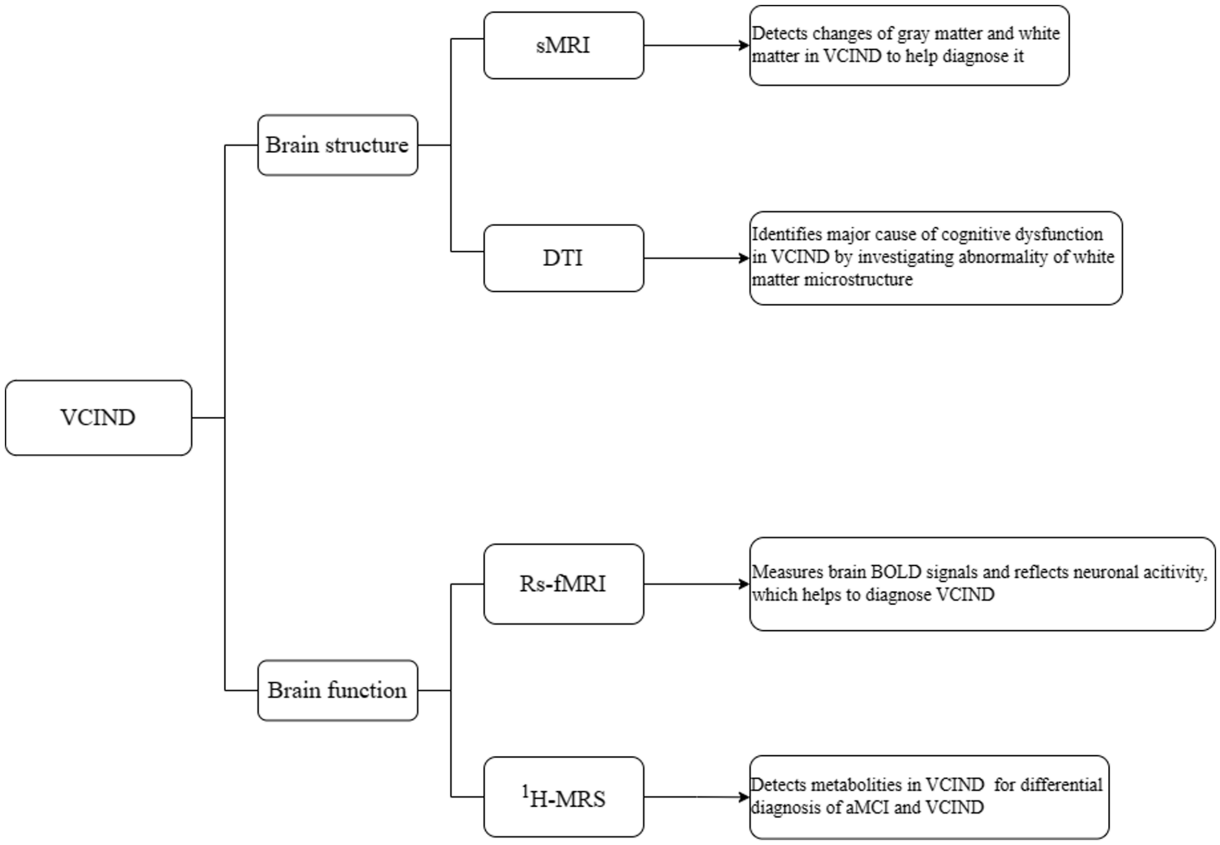

FIGURE 1
Multimodal MRI of brain structure and function in VCIND.

correlations with various DTI histogram measurements. Specifically, the average FA peak position, average MD, and average MD peak position of WM were all significantly correlated with the neurocognitive results. Similarly, the average FA peak height, average MD, and average MD peak position of NAWM were also significantly correlated with the neurocognitive outcomes. These findings suggest that the severity of WM and NAWM damage, as indicated by DTI histogram measurements, may be closely related to the level of cognitive impairment in VCIND patients. Overall, the findings of this study indicate that DTI histogram analysis can provide valuable insights into the extent and patterns of WM damage in VCIND patients. Furthermore, the study highlights the potential role of DTI histogram analysis in enhancing our understanding of the pathophysiology of VCIND and its association with cognitive impairment. Chen et al. (2018) conducted DTI examinations on 24 patients with SIVD, including 13 cases of VCIND and 11 cognitively normal individuals. They found widespread reduction in FA and increase in MD values in the WM areas of the VCIND group, primarily in the corpus callosum, bilateral internal capsule/radiation of the corona radiata/thalamus posterior region/frontal–parietal subcortical pathway, and the right inferior/superior longitudinal fasciculus. The distribution of areas with decreased FA and lower local diffusion homogeneity (LDH) values showed slight differences. There was a positive correlation between the values of WM, FA ($r = 0.653$, $p = 0.001$), and LDH ($r = 0.617$, $p = 0.001$) levels and the cognitive test results in patients with SIVD. On the other hand, there was a negative correlation between the WMMD ($r = -0.597$, $p = 0.002$) value and the cognitive test scores in patients with SIVD. These findings indicate that abnormal WM microstructure is an important factor contributing to cognitive dysfunction in patients with SIVD, and DTI parameters may serve as potential biomarkers for detecting VCIND in SIVD (Figure 1).

VCIND study of brain function

Rs-fMRI

FMRI measures the blood oxygen level-dependent (BOLD) signal in the brain, which is determined by the levels of oxygenated and deoxygenated hemoglobin and reflects neuronal activity (Li et al., 2018; Ryan et al., 2023). Rs-fMRI measures low-frequency BOLD signals. It estimates the brain's BOLD signal in awake participants when they are not performing any specific tasks (Azeez and Biswal, 2017; Wei et al., 2022). Wang et al. (2019) divided patients with brain injuries into two groups: those with white matter lesions and VCIND (WMLs-VCIND) and those with WMLs-VaD. Rs-fMRI data were collected and it was found that the overall functional connectivity strength was lowest in WMLs-VaD patients and highest in normal control participants. Both the WMLs-VCIND group and the WMLs-VaD group exhibited a decrease in small-world characteristics compared to the normal control group. Furthermore, the small-world properties were significantly correlated with the Montreal Cognitive Assessment scores. This

suggests a potential constructive reorganization of brain networks after brain injury and provides new insights into the role of small-world characteristics (a small-world network is a form that lies between random networks and regular networks, with relatively shorter average path lengths and higher clustering efficiency) in cognitive impairment following brain damage. Sun et al. (2011) conducted a study in which they obtained rs-fMRI data from patients with SIVD who met the criteria for VCIND, as well as a control group of SIVD patients without cognitive impairment. They utilized a time-correlation method to investigate the synchronized low-frequency fMRI signal fluctuations to assess connectivity within the brain. Comparing the VCIND patients to the control group, the researchers discovered decreased FCin regions such as the left middle temporal gyrus, left anterior cingulate gyrus/left middle frontal gyrus, right caudate nucleus, right middle frontal gyrus, and left medial orbital gyrus/paracentral lobule. On the other hand, they observed increased connectivity in certain regions like the right inferior temporal gyrus, left middle temporal gyrus, left precentral gyrus, and left superior parietal lobule. These findings revealed alterations in the neural activity patterns during resting-state in VCIND patients. The changes in connectivity observed in VCIND patients are likely associated with subcortical WM lesions, which disrupt both direct and indirect fiber bundle connections in the brain's WM. These lesions also impact cortical FC and are influenced by decreased perfusion due to small vessel disease. Overall, the simplicity and non-invasiveness of this method suggest its potential as a valuable tool in understanding the underlying mechanisms of VCIND. Shi et al. (2020) divided participants into three groups: the group with lacunar infarction and VaD (LA-VaD), the group with lacunar infarction and VCIND (LA-VCIND), and the normal control group. They used independent component analysis and Granger causality analysis to study changes in resting-state networks (RSN). The functional connectivity strength of the networks varied between the normal control group, the LA-VCIND group, and the LA-VaD group. The effective connectivity between RSNs was compensated by the increase or decrease in effective connectivity changes in these three groups. The composition of resting-state networks continuously changed with the progression of the disease. This indicates that the human brain compensates for specific functional changes at different stages (Figure 1).

^{1}H-MRS

MRS can be used in conjunction with conventional MRI to characterize the tissues of living animals (Rhodes, 2017). Unlike MRI, MRS does not produce images but rather generates spectra, where different peaks can be distinguished and attributed to different chemical groups and metabolites, enabling non-invasive quantification of metabolites (van de Weijer and Schrauwen-Hinderling, 2019). Depending on the acquisition method, several low molecular weight metabolites can be detected, such as N-acetyl aspartate (NAA), choline-containing compounds (Cho), creatine and phosphocreatine (Cr), myo-inositol (mI), and glutamate (Glu) (Baruth et al., 2013; Harris et al., 2017). NAA represents the integrity of neurons and axons, and a decrease in its content may indicate neuronal tissue loss or damage. Alterations in Cho levels can indicate cellular proliferation, changes in cell membrane phospholipid turnover, or inflammation (Oz et al., 2014), while Cr concentration is often considered constant, it's important to note that differences in Cr concentration may also occur. MI has regulating functions in osmotic pressure, cell nutrition, antioxidant effects, and the production of surfactants. Glu is a key metabolite due to its role as the primary excitatory neurotransmitter in the central nervous system. Quantifying Glu levels using ^{1}H MRS offers insights into neuronal and synaptic integrity and the metabolic processes associated with glutamatergic neurotransmission.

^{1}H-MRS is the most abundant atomic nucleus in human body, so the application of ^{1}H-MRS is the most extensive. Chen et al. (2016) conducted hydrogen proton ^{1}H-MRS examinations on patients with multiple-domain amnestic mild cognitive impairment (M-aMCI) and VCIND. They measured levels of NAA, Glu, mI, Cho, and creatine (Cr). Compared to the normal control group, the NAA/Cr ratio in all regions of interest was significantly reduced in both the M-aMCI and VCIND groups. The Glu-Cr ratio in the posterior cingulate gyrus was significantly lower in the M-aMCI group compared to VCIND. The mI-Cr ratio in the frontal white matter was significantly higher in the VCIND group compared to M-aMCI. These results suggest that ^{1}H-MRS is an effective method for differentiating between M-aMCI and VCIND. Liu et al. (2014) used two-dimensional chemical shift imaging proton MRS to evaluate and characterize the metabolic markers of aMCI and VCIND patients compared to normal control subjects. The NAA/Cho ratio in the bilateral white matter of frontal lobe (FLWM), left occipital lobe white matter, and right dorsal thalamus (DT) was significantly lower in VCIND patients compared to normal control or aMCI patients. Furthermore, compared to the control group, VCIND patients exhibited decreased NAA/Cr values in the bilateral DT and FLWM. In addition, aMCI patients showed increased mI in the right posterior cingulate gyrus, and VCIND patients showed increased Cho in the left FLWM. These findings may contribute to the clinical differentiation of these two diseases (Figure 1).

Limitations

There are two limitations in the current research. Firstly, the heterogeneity of results may be caused by differences in image quality, magnetic field strength, characteristics of participants (age, gender, education, etc.), and analysis methods in different studies. Secondly, some studies have small sample sizes. In the future, larger samples and more comprehensive and homogeneous evaluation indicators can be used for in-depth analysis of VCIND. It is believed that as research continues to deepen, multimodal MRI will make greater progress in the diagnosis and treatment of VCIND.

Summary

In summary, various multimodal MRI methods, such as sMRI, DTI, rs-fMRI, and ^{1}H-MRS examination methods focus on different aspects in VCIND, but all can reveal the correlation between cognitive impairment and structural and functional changes in the brain. MRI has been widely applied in the exploration of VCIND, and various MRI techniques can detect structural and functional changes in the brain, assisting in early diagnosis and providing imaging evidence for clinical treatment to delay further cognitive deterioration and improve patient survival. SMRI can observe extensive damage to white matter lesions that can lead to VCIND. DTI can indicate whether the white matter fibers of the

DMN are intact, which may be a neuroimaging marker for VCIND, while parameters such as FA and MD can serve as potential biomarkers for detecting VCIND. Rs-fMRI suggests that the composition of the brain's resting-state networks changes continuously with disease progression, indicating that the brain compensates for specific functional changes at different stages. MRS can differentiate between aMCI and VCIND by evaluating metabolic markers in brain tissue.

Author contributions

QZ: Conceptualization, Data curation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. XL: Resources, Validation, Visualization, Writing – review & editing. SG: Conceptualization, Resources, Visualization, Writing – review & editing. SY: Methodology, Resources, Validation, Visualization, Writing – review & editing. AL: Methodology, Software, Validation, Visualization, Writing – review & editing. ZW: Resources, Validation, Visualization, Writing – review & editing. SH: Software, Validation, Visualization, Writing – review & editing. YH: Validation, Visualization, Writing – review & editing. XL: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DC: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Validation, Visualization, Writing – review & editing. JY: Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

QZ and JY were employed by Shenzhen Frontiers in Chinese Medicine Research Co., Ltd. AL was employed by Sanofi-Aventis China Investment Co., Ltd and is currently employed by Servier (Beijing) Pharmaceutical Research & Development CO. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

VCIND	vascular cognitive impairment not dementia
VCI	vascular cognitive impairment
VaD	vascular dementia
^{1}H-MRS	hydrogen proton magnetic resonance spectroscopy
MRI	magnetic resonance imaging
sMRI	structural MRI
fMRI	functional MRI
DTI	diffusion tensor imaging
rs-fMRI	resting-state fMRI
MRS	magnetic resonance spectroscopy
SIVD	subcortical ischemic vascular dementia
WMV	white matter volume
WMH	white matter hyperintensity
FA	fractional anisotropy
MD	mean diffusivity
DMN	default mode network
AD	Alzheimer's disease
FCM	fuzzy c-means
SA	segmentation accuracy
ADL	activities of daily living
NAWM	normal appearing WM
LDH	local diffusion homogeneity
BOLD	blood oxygen level-dependent
WMLs	white matter lesions
LA	lacunar infarction;
RSN	resting-state networks
NAA	N-acetyl aspartate, Cho, choline-containing compounds
Cr	creatine and phosphocreatine
mI	myo-inositol; Glu, glutamate
aMCI	amnestic mild cognitive impairment
M-aMCI	multiple-domain aMCI
FLWM	white matter of frontal lobe
DT	dorsal thalamus

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Association between the triglyceride glucose index and cognitive impairment and dementia: a meta-analysis

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Background: The triglyceride and glucose (TyG) index is an alternative index of insulin resistance (IR). We aimed to clarify the relationship between the TyG index and cognitive impairment and dementia.

Methods: We conducted a comprehensive search of the PubMed, Cochrane Library, and Embase databases until February 2023 to identify relevant studies. Random-effects models were used to pool effect sizes, and the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE) was used to assess the quality of the evidence.

Results: Ten studies were included, with seven of which investigated the relationship between the TyG index and cognitive impairment and three exploring the association between the TyG index and dementia. When the TyG index was described as a categorical variable, it was positively associated with the risk of cognitive impairment (OR = 2.32; 95% CI 1.39–3.87) and dementia (OR = 1.14, 95% CI 1.12–1.16). The association of the TyG index with the risk of cognitive impairment (OR = 3.39, 95% CI 1.67–6.84) and dementia (OR = 1.37, 95% CI 1.03–1.83) remained significant for per 1 unit increment in the TyG index. The GRADE assessment indicated a very low certainty for cognitive impairment. Low certainty and moderate certainty were observed for dementia when the TyG index was analyzed as a categorical variable and as a continuous variable, respectively.

Conclusion: The TyG index is associated with an increased risk of cognitive impairment and dementia. Further prospective research is warranted to confirm these findings.

Systematic review registration: https://www.crd.york.ac.uk/, Protocol registration number: CRD42023388028.

KEYWORDS

triglyceride and glucose index, cognitive impairment, dementia, insulin resistance mild cognitive impairment, insulin resistance triglyceride and glucose index, insulin resistance

Introduction

As the global population ages, cognitive impairment has emerged as a pressing public health concern. Age-related dementia is projected to affect 150 million individuals by 2050 (Iadecola et al., 2019). Mild cognitive impairment (MCI) often precedes dementia, imposing substantial treatment costs and significantly diminishing patients' quality of life. Therefore, identifying

simple risk factor are imperative for the cognitive impairment and dementia screening and early diagnosis.

Insulin resistance (IR) has long been recognized as an important risk factor for the development of neurodegeneration and cognitive impairment (Cui et al., 2022). The triglyceride and glucose (TyG) index, as an applicable indicator of IR (Guerrero-Romero et al., 2010), is highly likely to be closely associated with cognitive impairment and dementia, as shown by many previous studies. For instance, Weyman-Vela et al. found that a high TyG index was strongly associated with MCI in older adults (Weyman-Vela et al., 2022). A prospective cohort study conducted by Sun et al. also proposed that the TyG index may be used as a simple surrogate marker for early detection of Alzheimer's disease (AD; Sun et al., 2022). However, as far as we know, there is no existing meta-analysis to systematically assess the relationship between the TyG index and cognitive impairment and dementia. As a result, we aimed to conduct a systematic meta-analysis to evaluate the association between the TyG index and cognitive impairment and dementia.

Methods

Protocol and registration

We registered our protocol (registration number: CRD42023388028) at PROSPERO (International Prospective Register of Systematic Reviews)[1] system. We reported our results by following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Supplementary Table S1).

Literature search

We conducted a careful search of all studies that reported the relationship between the TyG index and cognitive impairment and dementia in PubMed,[2] Cochrane Library[3] and Embase[4] until the end of February 2023. The search terms were "Cognitive Dysfunction" OR "Cognitive Impairment" OR "Cognitive Disorder" OR "Mild Cognitive Impairment" OR "Cognitive Decline" OR "Mental Deterioration" OR "Dementia" AND "TyG index" OR "triglyceride glucose index" OR "triacylglycerol glucose index." The detailed search strategy is presented in Supplementary Table S2.

Study selection

Two of our authors (MJ. Z and Q.L.) independently conducted the literature search and imported all relevant literature into Endnote X9 software (Tomson Reuters, New York, NY, United States). Duplicated documents were automatically and manually removed. The titles and abstracts of all articles were first screened, and content-related studies were read in full text to identify the included studies. In cases where no article or other information was available, we contacted the corresponding author for the information. The final included studies were determined by consensus between the two authors or resolved by the third reviewer (X. L.) if differences remained after consultation.

The Inclusion criteria were as follows: (1) Types of participants: adult (age > 18 years); (2) exposure and comparator: high TyG index versus low TyG index; (3) Outcomes: cognitive impairment or dementia; (4) types of studies: retrospective or prospective cohort, case–control and cross-sectional studies; and (5) the studies provided odds ratio (OR)/relative risk (RR)/hazard ratio (HR) and corresponding 95% confidence interval (CI) for the association between TyG Index and cognitive impairment and dementia.

Studies that meet any of the following criteria were excluded: (1) protocols, reviews, conference abstracts or animal studies; (2) studies that lacked a clear definition for cognitive impairment or dementia; (3) studies that used regression coefficients, SE, β or other methods for the statistical analysis; (4) studies for which relevant data could not be obtained completely; and (5) studies with unavailable data even after contacting the corresponding author for further information.

Data extraction and quality assessment

We extracted the following information from the included studies: (1) first author's last name; (2) publication year; (3) country or region; (4) study design; (5) participants' characteristics (source, mean age, sex, etc.); (6) outcome; (7) diagnosis; (8) categories of TyG; (9) hazard ratio (HR) or odds ratio (OR) from the most adjusted model (with 95% confidence interval (CI)); (10) follow-up period; and (11) adjustments.

The Newcastle Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the included case–control and cohort studies, and studies with more than six stars were considered high-quality, with a total score of 9 stars. The included cross-sectional studies were assessed by Joanna Briggs Institute's (JBI) critical appraisal checklist, which helps us to evaluate the quality by sampling method, size, diagnosis, measurement, and analysis. We assessed the quality and strength of evidence by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (Atkins et al., 2004). GRADEPro GDT[5] was used to provide evidence analysis tables.

Statistical analysis

Most of the included studies reported the results with ORs, while a minority calculated HRs as the results. Therefore, we treated HRs as ORs because the incidence of cognitive or dementia is considered low (Shigesi et al., 2019) and finally used summary ORs and their corresponding 95% CIs as a general indicator of the association between the TyG index and cognitive impairment and dementia.

The formula of TyG: $\ln\left[\frac{\text{triglycerides}\,(\text{mg/dL}) \times \text{fasting glucose}\,(\text{mg/dL})}{2}\right]$. For the studies in which the TyG index was described as a categorical variable,

1 http://www.york.ac.uk/ast/crd
2 https://pubmed.ncbi.nlm.nih.gov/
3 http://www.cochranelibrary.com
4 https://www.embase.com/
5 https://gradepro.org

we compared the effect size of the highest TyG group to that of the lowest group, while we standardized the TyG index as per 1 unit in the studies that described the TyG index as a continuous variable. We summarized the effect size and conducted a subgroup analysis using RevMan software, version 5.4.1 (The Cochrane Collaboration 2016, Nordic Cochrane Center Copenhagen, Denmark) in a random-effects model, which followed Der Simonian and Laird's generic inverse variance method (Xu et al., 2019).

We used I^2 to explore the inconsistency across the findings of the included studies and Tau^2 was reported as the variance of the true effect size. Since the number of studies we included for each outcome was less than 10, potential publication bias was not assessed.

Given the limited number of included studies, we only performed a subgroup analysis of the five studies that assessed the association between the TyG index and cognitive impairment, stratified by mean age, type of study design, sample size, body mass index (BMI), diagnosis and adjustment for confounders. Stata software (Version 16.0, Stata Corp LP, College Station, Texas, United States) was used to conduct sensitivity analyses.

Results

Literature search

We retrieved a total of 196 related studies in these three databases (PubMed = 148; Cochrane Library = 34; Embase = 14), and the overall inclusion flow of the studies is presented in Figure 1. After excluding 14 duplicate records, we screened the titles and abstracts of the remaining 182 articles, and ultimately, 16 articles were included for full-text review. Six of these articles were excluded for the following reasons: (1) they were without target data ($n = 3$); (2) it was focused on other outcomes ($n = 1$); (3) it was focused on other exposures ($n = 1$); and (4) it was a conference abstract ($n = 1$). The detailed reasons for exclusion for each of these studies are shown in Supplementary Table S3. We finally established the inclusion of seven cohort studies (Faqih et al., 2021; Guo et al., 2021; Hong et al., 2021; Li et al., 2022; Sun et al., 2022; Teng et al., 2022; Wang et al., 2022), one case–control study (Jiang et al., 2021) and two cross-sectional studies (Tong et al., 2022; Weyman-Vela et al., 2022).

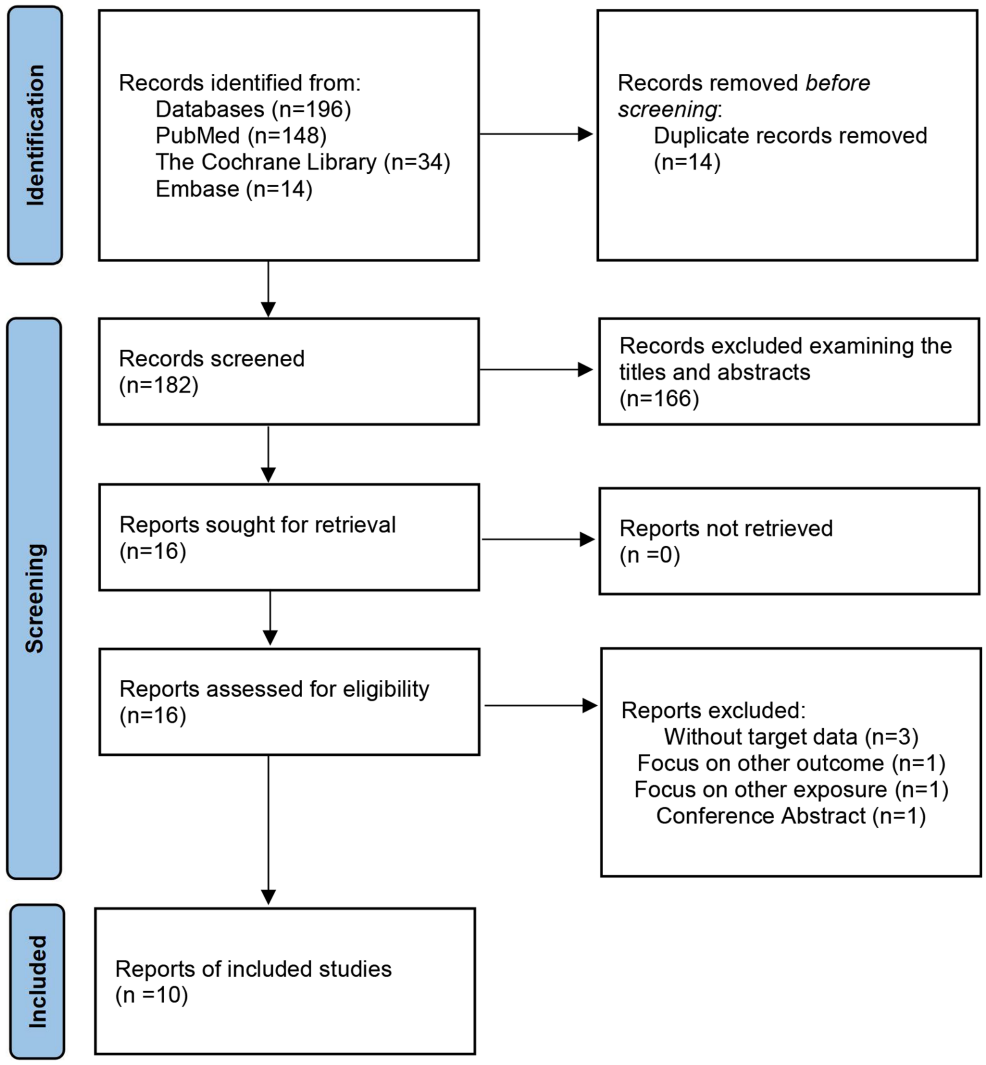

FIGURE 1
Flow chart of the study selection process for the meta-analysis for the association between TyG index and cognitive impairment and dementia.

Study characteristics and quality evaluation

Table 1 summarizes the basic characteristics of the included studies according to their outcomes. The studies were published between 2021 and 2022 and included a total of 8,443,279 participants ranging in age from 58.2 to 80.5 years old. Only one study was conducted in North America (Weyman-Vela et al., 2022), while the remaining studies were conducted in Asia. Two of the included studies (Tong et al., 2022; Weyman-Vela et al., 2022) were cross-sectional studies, and the rest were cohort studies, which improved the credibility of our results. Among the studies, seven reported the association between the TyG index and cognitive impairment (Guo et al., 2021; Jiang et al., 2021; Li et al., 2022; Teng et al., 2022; Wang et al., 2022; Weyman-Vela et al., 2022), while the remaining four studies' endpoints can be classified as "dementia" (Faqih et al., 2021; Hong et al., 2021; Sun et al., 2022; Tong et al., 2022). Cognitive impairment was mainly diagnosed by the Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE), while the diagnosis of dementia was mostly based on the ICD-10. Each study adjusted for confounders that may influence the stability of the results.

The JBI checklist for quality assessment of the two cross-sectional included studies is presented in Figure 2A, which shows that the quality was high in terms of sample representativeness, sample size, method, statistical analysis, and confounding factors. However, the criteria for the subgroup analysis were unclear. The NOS scores ranged from 7 to 9 (Figure 2B), suggesting that the quality of our included studies was acceptable.

Association between the TyG index and cognitive impairment

Seven studies with 7,709 participants were included in the analysis between the TyG index and cognitive impairment. The summary OR was 2.32 (95% CI 1.39–3.87, $p < 0.001$, $\tau^2 = 0.26$, highest vs. lowest), suggesting that a high TyG index was associated with a 132% higher risk of cognitive impairment (Figure 3A). Similarly, when the TyG index was analyzed as a continuous variable, we found that every unit of increasing TyG index may be associated with a 239% higher risk of cognitive impairment (OR = 3.39, 95% CI 1.67–6.84, $p = 0.001$, $\tau^2 = 0.38$; Figure 3B).

Association between the TyG index and dementia

Three cohort studies with 8,435,570 participants were included for the association between the TyG index and dementia. TyG may be associated with the risk of dementia (OR = 1.14, 95% CI 1.12–1.16, $p = 0.34$, $\tau^2 = 0$) in the categorical analysis (Figure 4A). In studies analyzing the TyG index as a continuous variable, a 1.37 times higher risk of dementia may be associated with each increased unit of the TyG index, with OR = 1.37 (95% CI 1.03–1.83, $p = 0.77$, $\tau^2 = 0$) (Figure 4B).

Sensitivity analysis and publication bias

A sensitivity analysis was performed by omitting one study at a time and revealed that the pooled results remained consistent in the association between the TyG index and cognitive impairment or dementia (Supplementary Figure S1), further supporting the validity of our main results. As we included a limited number of studies (fewer than 10 for each outcome), an analysis of publication bias was not performed.

Subgroup analyses

Heterogeneity was not evident among the age-stratified subgroups, and similar results were shown in the sample-size-stratified groups and whether the model was adjusted for cholesterol (Table 2), suggesting that these three factors may be potential sources of heterogeneity.

GRADE assessment

The GRADE assessment revealed a very low level of certainty regarding the association between the TyG index and cognitive impairment due to significant heterogeneity observed in both the categorical analysis ($p < 0.001$) and the continuous analysis ($p = 0.001$). Moreover, the lack of serious risk of bias warranted a downgrade. On the other hand, the GRADE assessment indicated a moderate level of certainty regarding the association between the TyG index and dementia when analyzed as a continuous variable (Supplementary Table S4).

Discussion

Major findings

Our study found that a higher TyG index was significantly associated with an increased risk of cognitive impairment and dementia. When the TyG index was regarded as a categorical variable, the risk of cognitive impairment and dementia in the high TyG index group was 2.32 and 1.14 times higher than that in the low TyG index group, respectively. For each additional unit of the TyG index, the risk for cognitive impairment and dementia increased by 3.39 and 1.37, respectively. To the best of our knowledge, this is the first meta-analysis of the association between the TyG index and cognitive impairment and dementia.

To account for the potential impact of various factors on cognitive impairment, we conducted a subgroup analysis. Currently, cognitive impairment is typically diagnosed using assessment scales such as the MMSE and the MoCA. The use of different scales across studies could potentially affect our results. However, our analysis showed a high level of within-group heterogeneity, particularly in the subgroup using the MMSE (76%), indicating that the diagnostic method for cognitive impairment is not the primary source of heterogeneity in our results. Nonetheless, given the limited number of studies included, it is worth further exploring whether diagnostic methods may impact the relationship between the TyG index and cognitive impairment.

In groups with a mean age older than 60 years, a sample size of less than 1,000, and adjusted cholesterol levels, there was more than a threefold greater risk of cognitive impairment associated with a higher TyG index. This is consistent with the higher incidence of cognitive impairment in elderly individuals (Pais et al., 2020). The within-group

TABLE 1 Characteristics of included studies in the meta-analysis of TyG and risk of cognitive impairment and dementia.

First Author, Year, Country	Source of participants	Participant	Study design/ sample size	Mean age (years), Male (%)	Mean BMI, kg/ m^2	Outcome/ diagnosis	Categories of TyG	OR/HR (95% CIs)	Follow-up period	Adjustments
Cognitive impairment										
Guo, 2021, China	Second Affiliated Hospital of Nantong University	Patients with CSVD	Retrospective cohort study/275	67.7, 54.5	24.5	VCI/MoCA: ≤26	<8.78 ≥8.78 Continuous variable	Ref 4.09 (2.18, 7.68) 2.42 (1.37, 4.29)	NR	Age, education level, LDL-C, homocysteine, SUA, and CSVD
Jiang, 2021, China	Second Affiliated Hospital of Nantong University	Patients with CSVD	Retrospective cohort study/280	67.6, 57.9	25	VCI/MoCA: ≤26	3.57 3.89 4.09 4.38	Ref 2.69 (1.17, 6.16) 2.54 (1.12, 5.75) 4.67 (1.79, 12.16)	NR	Age, sex, BMI, diabetes, hypertension, education level, HDL-C, LDL-C, Hs-CRP, HbAlc, IL-34 level, mRS, BI
Li, 2022, China	Jidong Cognitive Impairment Cohort Study	General population	Prospective cohort study/1,774	53.5, 48.0	25	Cognitive impairment/MMSE[a]	7.46 8.06 8.47 9.09	Ref 1.17 (0.85, 1.62) 1.31 (0.93, 1.83) 1.51 (1.06, 2.14)	4 years	Age, sex, BMI, educational level, smoking status, alcohol consumption, physical activity, history of hypertension, TG
Teng, 2022, China	Hebei General Hospital	Patients with T2D	Retrospective cohort study/308	71.0, 48.7	25	Cognitive impairment/MMSE[b]	18.39 28.96 39.58 Continuous variable	Ref 1.75 (0.93, 3.30) 3.30 (1.69, 6.45) 2.24 (1.44, 3.50)	5 years	Age, sex, education level, hypertension, history of stroke, SBP, HbA1c, HDL-C, insulin or metformin use, serum tHcy
Wang, 2022, China	China Health and Retirement Longitudinal Study	General population	Prospective cohort study/4,420	58.9, 46.7	NR	Cognitive impairment/WRT and MST: the slope of cognitive decline <0	Male: Q1 Q2 Q3 Q4 Female: Q1 Q2 Q3 Q4	Ref 1.13 (0.88, 1.45) 1.01 (0.79, 1.29) 1.11 (0.87, 1.42) Ref 1.09 (0.85, 1.40) 1.09 (0.85, 1.41) 1.32 (1.03, 1.71)	4 years	Age, sex, BMI, education level, marriage, residence, leisure time social activity, health insurance status, alcohol consumption, smoking status, hypertension, diabetes
Weyman-Vela, 2022, Mexico	Inhabitants from durango	General population	Cross-sectional study/135	72.8, 18.5	28.7	MCI/MMSE: 20–30	Continuous variable	2.97 (1.12, 14.71)	NA	Age, sex, WC, education level, occupation, physical activity

(Continued)

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TABLE 1 (Continued)

First Author, Year, Country	Source of participants	Participant	Study design/ sample size	Mean age (years), Male (%)	Mean BMI, kg/ m^2	Outcome/ diagnosis	Categories of TyG	OR/HR (95% CIs)	Follow-up period	Adjustments
Tong, 2022, China	The First Affiliated Hospital of Harbin Medical University	Patients with T2D	Cross-sectional study/517	58.0, 54.4	25.3	MCI/National Institute on Aging-Alzheimer's Association criteria	Continuous variable	7.37 (4.72, 11.50)	NA	Age, sex, smoking status, drinking consumption, duration of diabetes, education level, TG, HbA1c, diabetic nephropathy, fatty liver, insulin or statins use
Dementia										
Hong, 2021, Korea	National Health Screening program	General population	Retrospective cohort study/ 8,433,046	45.0, 55.7	23.5	All-cause dementia/ ICD-10 for dementia	Male: 7.92 8.51 8.91 9.52 Female: 7.68 8.23 8.6 9.16	Ref 1.04 (1.02, 1.05) 1.07 (1.05, 1.09) 1.14 (1.12, 1.16) Ref 1.04 (1.02, 1.05) 1.07 (1.05, 1.09) 1.14 (1.12, 1.16)	7.21 years	Age, sex, BMI, smoking status, alcohol consumption, physical activity, low income, hypertension, TG
Sun, 2022, China	Framingham Heart Study Offspring cohort	General population	Prospective cohort study/2,170	63.0, 46.7	28.1	AD/NINCDS-ADRDA	7.62 8.48 8.89 10.55 Continuous variable	Ref 1.52 (0.93, 2.48) 1.69 (1.03, 2.77) 1.48 (0.86, 2.54) 1.39 (1.02, 1.88)	13.8 years	Age, sex, BMI, education level, smoking status, physical activity, SBP, CVD, antihypertensives, hypoglycemic therapy, lipid-lowering therapy
Faqih, 2021, Saudi Arabia	KAMC-J	General population	Retrospective cohort study/354	80.5, 46.3	NR	AD/ICD-10 for dementia	Continuous variable	1.2 (0.99, 3.1)	4 months	Age, sex, BMI, co-morbidities, insulin use, HbA1c

BMI, body mass index; TyG, triglyceride and glucose index; OR, odds ratio; HR, hazards ratio; CI, confidence interval; NA, not appliable; NR, not reported; AD, Alzheimer's disease; LDL-C, low density lipoprotein cholesterol; SUA, serum uric acid; CVSD, cerebral small-vessel disease; VCI, vascular cognitive impairment; MoCA, Montreal Cognitive Assessment; TG, total cholesterol; HDL-C, high density lipoprotein cholesterol; Hs-CRP, high-sensitivity C-reactive protein; HbA1c, hemoglobin A1c; mRS, modified Rankin Scale; BI, Barthel Index; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure; WRT, word recall test; MST, mental status test; CVD, cardiovascular disease; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association; T2D, type 2 diabetes; MCI, mild cognitive impairment; WC, waist circumference; KAMC-J, King Abdulaziz Medical City, Jeddah.

[a]: ≤17 for illiterate individuals, ≤20 for primary school graduates, ≤24 for junior high school graduates or above.

[b]: ≤17 for illiterate, ≤20 for patients with1-6 years of education, ≤24 for patients with 7 or more years of education.

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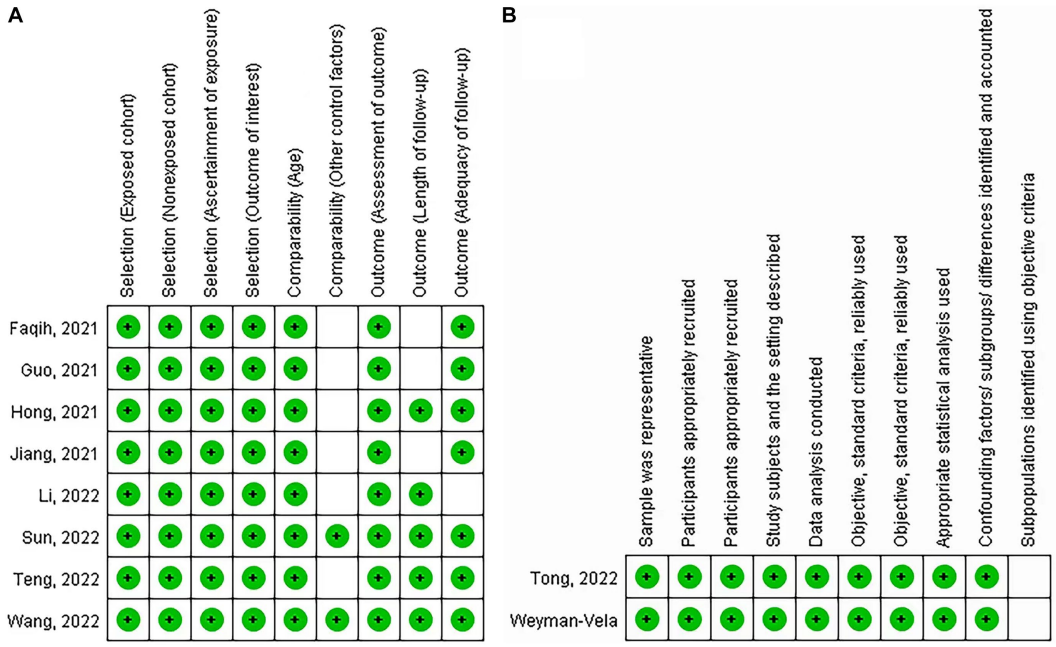

FIGURE 2
(A) The quality asessment of the included studies. Newcastle Ottawa Quality Assessment Scale for the case–control and cohort studies and **(B)** Joanna Briggs Institute's critical appraisal checklist for cross-sectional studies. Each green pattern represents a score.

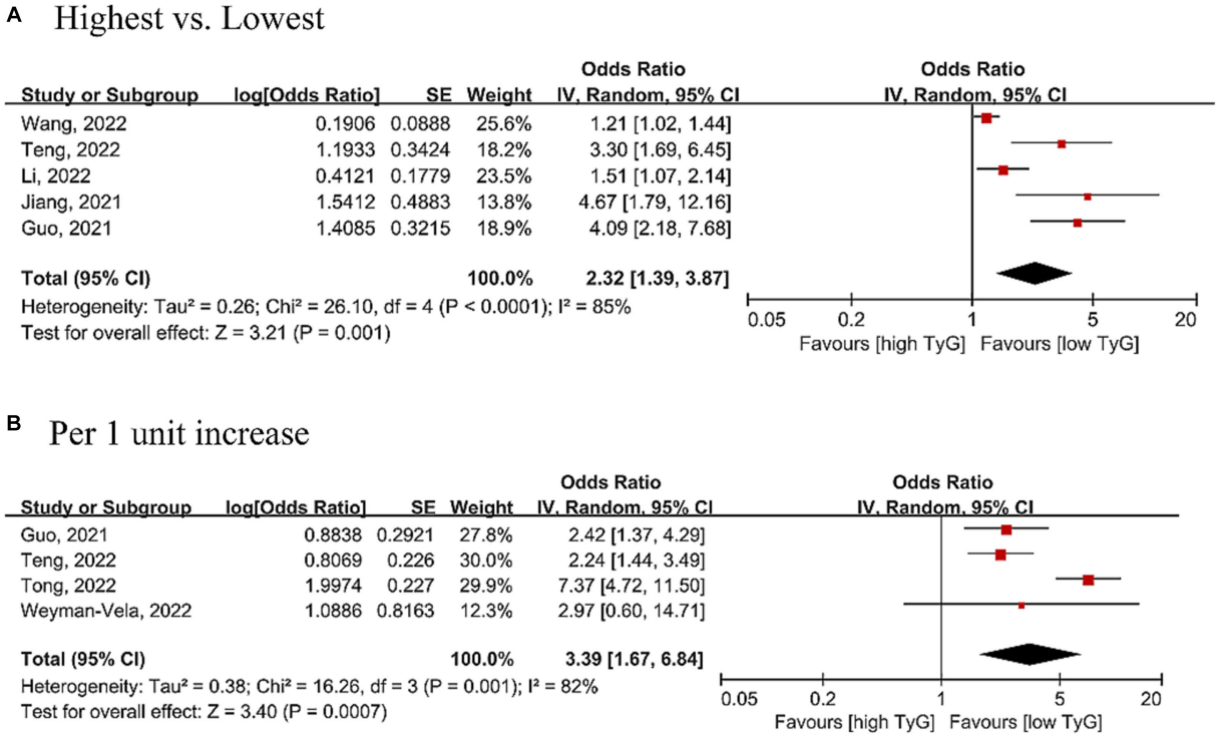

FIGURE 3
Forest plot of the association between the triglyceride-glucose index [**(A)** Analyzed as categorical variable; **(B)** analyzed as continuous variable] and the risk of cognitive impairment. The black midline indicates the line of no effect. The diamond indicates the pooled estimate. Red boxes are relative to study size, and the black transverse lines indicate the 95% confidence interval around the effect size estimate.

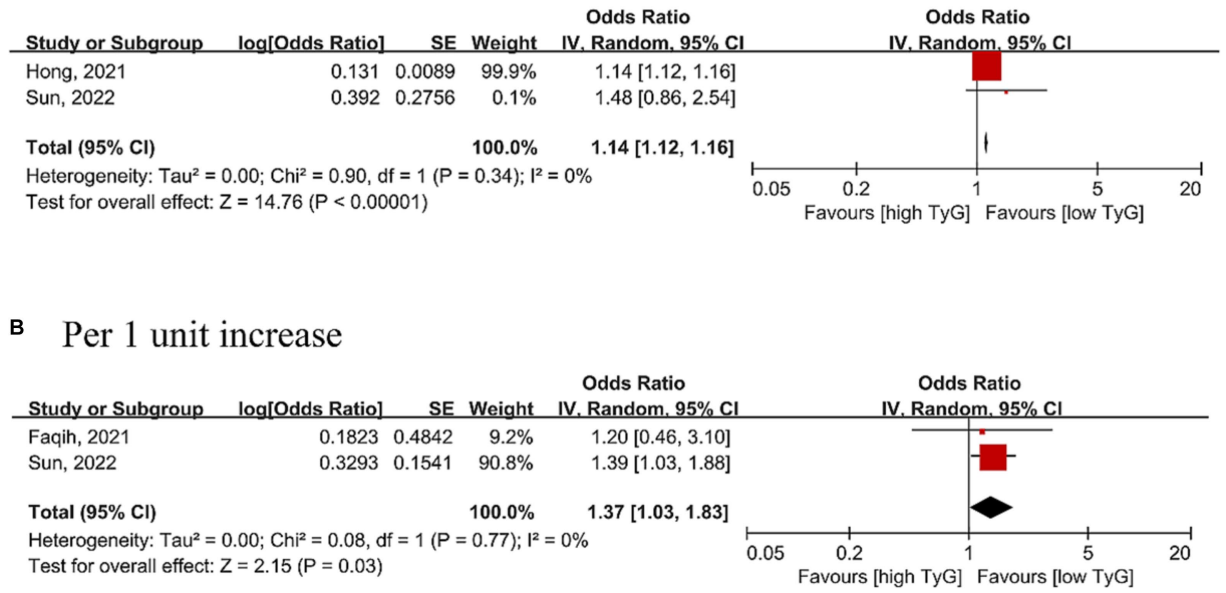

FIGURE 4
Forest plot of the association between the triglyceride-glucose index [**(A)** Analyzed as categorical variable; **(B)** analyzed as continuous variable] and the risk of dementia. The black midline indicates the line of no effect. The diamond indicates the pooled estimate. Red boxes are relative to study size, and the black transverse lines indicate the 95% confidence interval around the effect size estimate.

heterogeneity in these subgroups was small, suggesting that age and adjustment for high cholesterol were the primary sources of heterogeneity in our final results.

Moreover, a cohort study that enrolled 1,674 individuals showed that people who used statins were approximately 50% less likely to develop cognitive impairment or dementia than those who did not use statins (HR = 0.52; 95% CI 0.34–0.80; Cramer et al., 2008). Another study, the Sydney Memory and Aging Study (Samaras et al., 2020), found that the incidence of dementia was significantly higher in diabetes patients who did not receive metformin than in those who did (OR = 5.29, 95% CI 1.17–23.88). These findings suggest that hypoglycemic and hypolipidemic drugs may decrease the risk of cognitive impairment and dementia as well as affect the measurement of the TyG index. Therefore, we acknowledge that these factors may affect our results, and they should be considered in future studies. However, only a few included studies stated that they have adjusted for these factors. Due to the limited number of studies included in our analysis, we were unable to perform a subgroup analysis of these factors to explore whether they might affect our final results, so further investigation is necessary.

Potential mechanism

Among the underlying mechanisms associated with the TyG index and cognitive impairment, IR may be one of the reasons that cause cognitive impairment independently or in combination with other pathologies.

First of all, IR may contribute to cognitive impairment uniquely. Prolonged IR can hinder insulin from crossing the blood–brain barrier (Arnold et al., 2018), thereby reducing insulin levels in the brain and then reducing the levels of insulin-degrading enzymes that break down amyloid-β (Aβ). As a hallmark of AD, Aβ is known to form insoluble extracellular plaques (Cole and Frautschy, 2007). So low insulin level can lead to its accumulation and potentially impair cognitive function (Ghasemi et al., 2014). In addition, low insulin levels or insulin insensitivity can result in the long-term inhibition (LTD) of excitatory synaptic transmission by regulating the endocytosis of 3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors (Huang et al., 2010), which can reduce hippocampal synaptic plasticity, leading to memory loss or, even worse, neurodegenerative diseases.

Secondly, IR may also combine with other pathologies to promote the incidence of cognitive impairment. Previous studies have shown that patients with type II diabetes (T2D) have a higher risk of AD (Biessels et al., 2006; Luchsinger et al., 2007; Kopf and Frölich, 2009), which is characterized by IR, indicating that there may be a common pathological mechanism between T2D and AD. They are both protein misfolding disorders associated with protein aggregate deposition due to misfolding of protein structures (Chiti and Dobson, 2006), with Aβ depositing in the brain of AD patients and pancreatic amyloid peptides (IAPP) in the pancreas of T2D patients. A study hypothesized that IAPP and Aβ can interact through 'cross-seeding' to enhance the deposition of misfolded protein aggregates (Moreno-Gonzalez et al., 2017), which may explain the high incidence of comorbidities in AD and T2D.

Several studies have notably linked IR to reduced brain perfusion (Cui et al., 2017; Hoscheidt et al., 2017). In a small case–control study, individuals with type 2 diabetes exhibited significantly lower cerebral blood flow (CBF) compared to healthy controls. Additionally, a moderate correlation emerged between IR, as assessed by the HOMA-IR index, and decreased perfusion in posterior brain regions, particularly the posterior cingulate cortex and precuneus, as revealed by MRI. Since hypoperfusion is known to be associated with the

TABLE 2 Subgroup analysis of TyG index and cognitive impairment.

Items		Number of studies	Effect size (95%CI)	$p^*_{h\,(\%)}$
Result of primary analysis		5	2.32 [1.39, 3.87]	85
Mean age	<60 years	2	1.28 [1.06, 1.55]	19
	≥60 years	3	3.86 [2.55, 5.84]	0
Sample size	<1,000	3	3.86 [2.55, 5.84]	0
	≥1,000	2	1.28 [1.06, 1.55]	19
BMI	<25	1	4.09 [2.18, 7.68]	–
	≥25	3	2.60 [1.27, 5.30]	74
	NR	1	1.21 [1.02, 1.44]	-
Diagnosis	MoCA	2	4.26 [2.52, 7.21]	0
	MMSE	2	2.11 [0.99, 4.51]	76
	Others	1	1.21 [1.02, 1.44]	–
Adjustment for confounders				
Gender	Yes	4	1.95 [1.20, 3.17]	80
	No	1	4.09 [2.18, 7.68]	–
Cerebrovascular disease	Yes	2	3.70 [2.34, 5.85]	0
	No	3	1.62 [1.03, 2.56]	76
Hypertension	Yes	4	1.95 [1.20, 3.17]	80
	No	1	4.09 [2.18, 7.68]	–
Diabetes	Yes	2	2.18 [0.59, 8.11]	86
	No	3	2.61 [1.32, 5.17]	79
Cholesterol	Yes	3	3.86 [2.55, 5.84]	0
	No	2	1.28 [1.06, 1.55]	19
Medication use	Yes	1	3.30 [1.69, 6.45]	-
	No	4	2.13 [1.23, 3.67]	85
Physical activity	Yes	1	1.51 [1.07, 2.14]	-
	No	4	2.79 [1.24, 6.27]	88

*p for within-group heterogeneity (TyG index was analyzed as a categorical variable). TyG, triglyceride and glucose index; CI, confidence interval; BMI, body mass index; SBP, systolic blood pressure; NR, not report.

development and advancement of neuropathologies, IR may contribute to cognitive impairment through its involvement in hypoperfusion.

Clinical implications

Our study found a link between an elevated TyG index and the risk of cognitive impairment and dementia. The TyG index values can be easily obtained in clinical practice by measuring plasma glucose and TG levels. Several studies have suggested that the TyG index has the potential to serve as an indicator of cognitive impairment.

In a study by Jiang et al. (2021), the diagnostic performance of the TyG index for vascular cognitive impairment (VCI) was evaluated using ROC curve analysis. The optimal threshold was determined to be 3.94, with an area under the curve (AUC) of 0.727 (95% CI 0.636–0.779). Similarly, Teng et al. (2022) identified an optimal cutoff point of 9.015 for the TyG index in diagnosing cognitive impairment, with an AUC of 0.671. However, it is important to note that these studies were primarily preclinical and had limitations such as small sample sizes, limited generalizability to different races and regions, and study design. Therefore, further research is needed to fully understand the predictive value of the TyG index in dementia or Alzheimer's disease.

Limitations

We acknowledge that there were some limitations in our study. First, the number of included studies was limited, future studies are needed to further validate our findings. Second, the majority of included studies were conducted in Asia, with only one study from Mexico. Therefore, the influence of geographical and racial factors on our results cannot be fully excluded, and further studies from diverse populations are needed to validate our results. Third, potential confounding variables such as sex, age, diabetes, hypertension, genetic factors, and others may affect our results. For example, the apolipoprotein E (APOE) ε4 allele is one of the most significant risk factors for cognitive impairment, accounting for about 5% of the variance in lifetime cognitive decline (Davies et al., 2014). Meanwhile, ApoE is involved in lipid transport and lipoprotein metabolism to mediate lipid distribution or redistribution in tissues and cells, affecting the plasma triglyceride level and then the TyG index level (Getz and Reardon, 2018). Thus, if the APOE genotypes

in each of the included articles can be analyzed, it could be better to understand the relationship between TyG and cognitive impairment or dementia. Moreover, the TyG index was calculated from TG and plasma glucose, hypoglycemic and hypolipidemic drugs will affect the measurement of the TyG index. However, due to the data limitations, we cannot exclude the potential effect. Fourth, some of the included studies were cross-sectional in design. However, only two of the included studies (Tong et al., 2022; Weyman-Vela et al., 2022) were cross-sectional studies, and excluding them did not affect the final results (Supplementary Figure S1B). Finally, the data restriction precludes us from conducting an exposure-response analysis. More importantly, despite there are thousands of publicly published papers reporting the relationship between AD and T2D, observations from clinical studies are highly controversial and failed to elucidate a clear pathology pathway for an increased risk of dementia in patients with T2D (Salas and De Strooper, 2018). As a result, we need to pay more attention to the studies with different results and make rational analyses, to facilitate broader scientific consensus.

Conclusion

In conclusion, our study showed that an elevated TyG index is associated with the risk of cognitive impairment and dementia. However, given the limitations of the included articles, additional studies are needed to explore the generality of the association of TyG with cognitive impairment and dementia. The GRADE assessment showed very low certainty for cognitive impairment, and low (categorical variable) or moderate (continuous variable) certainty for dementia with TyG index. Despite some limitations, our findings provide important insights into the association between the TyG index and cognitive impairment and dementia and highlight the need for further research in this area.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HW: Writing – original draft. QL: Writing – original draft. YW: Writing – original draft. MZ: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2023.1278730/full#supplementary-material

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Glossary

MCI	Mild cognitive impairment
IR	Insulin resistance
TyG	Triglyceride and glucose
AD	Alzheimer's disease
OR	Odd ratio
RR	Relative risk
HR	Hazard ratio
CI	Confidence interval
NOS	Newcastle Ottawa Quality Assessment Scale
JBI	Joanna Briggs Institute's
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
BMI	Body mass index
MoCA	Montreal Cognitive Assessment
MMSE	Mini-Mental State Examination
Aβ	Amyloid-β
LTD	Long-term inhibition
T2D	Type II diabetes
CBF	Cerebral blood flow
VCI	Vascular cognitive impairment
AUC	Area under the curve
APOE	Apolipoprotein E

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To what extent does frailty mediate the association between age and the outcomes of brain reperfusion following acute ischemic stroke?

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Objective: We evaluated the extent to which frailty mediated the association between age, poor functional outcomes, and mortality after acute ischemic stroke when patients were treated with brain reperfusion (thrombolytic therapy and/or thrombectomy).

Materials and methods: This retrospective cohort study included patients diagnosed with ischemic stroke who had undergone intravenous cerebral reperfusion therapy and/or mechanical thrombectomy. We created a mediation model by analyzing the direct natural effect of an mRS score > 2 and death on age-mediated frailty according to the Frailty Index.

Results: We enrolled 292 patients with acute ischemic stroke who underwent brain reperfusion. Their mean age was 67.7 ± 13.1 years. Ninety days after the stroke ictus, 54 (18.5%) participants died, and 83 (28.4%) lived with moderate to severe disability (2 < mRS < 6). In the mediation analysis of the composite outcome of disability (mRS score > 2) or death, frailty accounted for 28% of the total effect of age. The models used to test for the interaction between age and frailty did not show statistically significant interactions for either outcome, and the addition of the interaction did not significantly change the direct or indirect effects, nor did it improve model fit.

Conclusion: Frailty mediated almost one-third of the effect of age on the composite outcome of disability or death after acute ischemic stroke.

KEYWORDS

stroke, frailty, thrombolytic therapy, thrombectomy, brain reperfusion

Introduction

Frailty occurs in approximately one-quarter of all patients (Taylor-Rowan et al., 2019) and is common in older people and is associated with increased mortality, long-term hospitalization, and disability (Mathers et al., 2000; Kwon et al., 2012; Makizako et al., 2015; Miranda et al., 2022). Frailty is defined as a state of heightened risk of adverse health, which is a by-product of the accumulation of age-related health conditions [deficit accumulation model (Rockwood et al., 2002)], and as a biological syndrome characterized by common factors, including weight loss, exhaustion, slow mobility, limited physical activity, and weakness [frailty phenotype model (Fried et al., 2001)].

Sobolewski et al. (2020) suggested that patients who experienced a stroke and are ≥80 years of age can be safely treated with cerebral reperfusion in routine practice. Similarly, Furlan et al. (2021) observed that cerebral reperfusion was a viable treatment for ischemic stroke that did not increase mortality in elderly or very elderly patients. The elderly patients in this Latin American study had worse functional results at hospital discharge and 90 days after stroke. However, the results also reaffirmed the benefits of thrombolytic therapy in stroke patients in this age group. Age was an independent risk factor for disabilities; however, the mortality rate of older patients in this cohort was more strongly related to comorbidities than age.

Additionally, Winovich et al. (2017) observed that frailty was a risk factor for decreased survival and worse recovery after ischemic stroke among people aged ≥65 years. In support of this, Evans et al. (2020) reported that clinical frailty was independently associated with 28-day post-stroke mortality and attenuated improvements in stroke severity following thrombolysis. Furthermore, Miranda et al. (2022) identified frailty as a predictor of acute ischemic stroke outcomes in older adults and reported that it may provide additional prognostic information beyond the determination of stroke severity at hospital admission and facilitate shared decision-making for patients with acute stroke.

However, to the best of our knowledge, the extent to which frailty mediates the effects of age on stroke outcomes has not yet been studied. This information could contribute to our knowledge of the mechanisms underlying the association between aging and poor post-stroke outcomes. Furthermore, from a public health perspective, this would help estimate the stroke-related disability and death that could be avoided through the prevention of frailty among older adults. Therefore, this study aimed to evaluate the extent to which frailty mediates the association among age, poor functional outcomes, and mortality after acute ischemic stroke in patients treated with brain reperfusion (thrombolysis and/or thrombectomy).

Methods

Study design, setting, and participants

This was a retrospective cohort study of patients diagnosed with ischemic stroke who had undergone intravenous cerebral reperfusion therapy and/or mechanical thrombectomy. Data were collected from patients who visited the Botucatu Stroke Unit between June 2012 and September 2020. All patients were treated during the acute phase of stroke.

The study included participants who had an ischemic stroke confirmed by neuroimaging, were > 18 years old, had no history of stroke, and had undergone cerebral reperfusion therapy. Individuals were excluded if they presented with other neurological diseases, hemorrhagic stroke confirmed using computed tomography or magnetic resonance imaging, or stroke mimics. All patients were admitted to the hospital [details removed] within the first 48 h of ictus or were referred to the hospital [details removed] in severe cases or in cases of clinical instability that required intensive care support. Patients were followed up at the cerebrovascular disease outpatient clinic 90 days after admission.

Data collection

All participants were managed at the stroke unit of [details removed] and evaluated by the research team within 72 h of admission. Following the clinical protocol for stroke management at the study institution, the patients were followed up for 90 days through in-person consultations at the cerebrovascular disease outpatient clinic or, if needed, by telephone. Baseline data were collected through direct interviews with patients and their informants, and electronic medical records. This information included sociodemographic data (age, sex, and race), Frailty Index, stroke characteristics (injury site, time from onset of symptoms to hospital arrival, whether patients underwent thrombolytic and/or thrombectomy treatments, and the timing of treatment relative to the ictus), National Institutes of Health Stroke Scale (NIHSS) score at admission, and the patients' baseline functional status 1 week before the ictus, as classified by the modified Rankin Scale (mRS). We also collected data on the presence of a range of comorbidities (e.g., systemic arterial hypertension, diabetes, dyslipidemia, hypothyroidism, previous myocardial infarction, heart failure, kidney failure, and prior stroke) that were used to construct the Frailty Index (Mitnitski et al., 2001).

Study variables

Exposure variable

In this study, the exposure of interest was patient age, which was treated as a continuous variable in our regression models.

Mediator variable

Frailty, as measured by the Frailty Index, was the mediating variable of interest in this study. The Frailty Index is a tool commonly used to assess frailty in epidemiologic studies and is based on the deficit accumulation theory (Rockwood and Mitnitski, 2007). This index is calculated as a ratio of at least 30 diseases, disabilities, symptoms, and abnormal laboratory parameters, which, in this model, are collectively referred to as "deficits." For example, if an individual has four of 40 such deficits, that person Frailty Index would be 0.1. We created a Frailty Index that included 31 variables (Supplementary appendix 1) following the standard procedure recommended for the creation of such indices (Searle et al., 2008). Each deficit represented by those variables was assigned a score of 1 point when present and 0 otherwise. In our regression analyses, the Frailty Index was treated as a continuous variable as recommended by developers (Mitnitski et al., 2001).

Outcome measures

Two outcomes were assessed: overall mortality and disability, which were measured using the modified Rankin Scale (mRS) score 90 days after stroke ictus. The mRS is an ordinal scale that ranges from 0 (no symptoms) to 6 (death). We used modified Rankin Scale (mRS) scores ranging from 3 to 6 to assign a composite outcome of disability or death (Cincura et al., 2009; Baggio et al., 2014).

Covariates

The following covariates were used as potential confounders following the disjunctive cause criterion (VanderWeele, 2019): sex, race, stroke severity according to the NIHSS score at admission (recorded as a continuous variable), and smoking status (never smoked, former smoker, or current smoker). Other comorbidities were not included as potential confounders because they had already been used to construct the Frailty Index. The outcomes were not categorized by intravenous thrombolysis (IVT), endovascular therapy (EVT), or mixed because of similar NIHSS scores between the groups.

Statistical analyses

We performed descriptive analyses of participants' baseline characteristics using absolute numbers and proportions for categorical variables. For continuous variables, we used mean and standard deviation (SD) for normally distributed variables or medians and interquartile ranges (IQR) otherwise (Lang and Altman, 2015). For baseline comparisons involving categorical variables, we used the Chi-square test when the expected numbers in each cell of the contingency tables were ≥ 5, and Fisher's exact test otherwise. For comparisons comprising continuous variables, we used Welch's *t*-test for normally distributed variables, and the Wilcoxon Rank Sum test otherwise (Norman and Streiner, 2014).

We performed regression-based causal mediation analysis (Vanderweele, 2015) using the regmedint (Yoshida et al., 2022) R package. In those models, age was the exposure of interest, frailty was the mediator, mRS > 2 and mortality 90 days after the stroke were the outcomes of interest in separate analyses, and sex, race, NIHSS score at admission, and smoking status were the covariates used for adjustment for possible confounding. We also tested for interactions between the exposure (age) and the mediator (frailty) and evaluated multicollinearity by examining variation inflation factors of the regression models (Fox, 2016).

Through the mediation analyses described above we were able to estimate the total effect, the natural direct effect and the natural indirect effect of age on mRS and mortality, as well as the proportion of the total effect of age on those outcomes that was mediated through frailty (Vanderweele, 2015). The total effect corresponds to the effect of changing one unit of the individual's exposure (age) on the outcome. The natural direct effect corresponds to the effect of changing the individual's exposure (age) in one unit, while holding the value of the mediator (frailty) constant at the value that would be observed under the specific level of the exposure variable. The natural indirect effect is the effect of changing the mediator value in one unit while holding the exposure the individual's exposure constant. The proportion mediated is calculated by dividing the natural indirect effect by the total effect and determines the proportion of the total effect of the exposure (age) on the outcome that is mediated by the mediator (frailty).

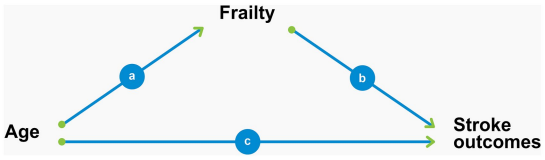

FIGURE 1
Graphical representation of frailty as a mediator of the association between age and stroke outcomes.

Figure 1 shows the graphical representation of the mediation model and may facilitate the understanding of the mediation analyses performed in this study. The path represented by *c* in that figure corresponds to the natural direct effect described above and stands for the regression coefficient of the age variable calculated by means of a logistic regression of the study outcomes (mRS > 2 and mortality) on age with adjustment for the mediator (frailty) and for confounding due to the other study covariates (sex, race, smoking status, and NIHSS score at admission). The path represented by *b* represents the regression coefficient of the mediator (frailty) in the same logistic regression described above. As to path *a*, it represents the regression coefficient of the linear regression of the mediator (frailty) on the exposure (age) adjusted by the same covariates described previously. The natural indirect effect calculated through the mediation analyses represent the joint effect of paths *a* and *b* together. Finally, the total effect of age on the outcomes represents the joint effect of paths *a*, *b*, and *c*, and is calculated through a logistic regression of the outcomes on age with adjustment for the same covariates but without the mediator.

We did not perform imputation procedures for missing data, which were excluded from the analyses. All statistical analyses were performed using the R software 4.1.2 (R Core Team, 2022). We used a two-tailed alpha level of 0.05 to define statistical significance.

Results

Figure 2 shows a flowchart of the selection of the participants for this study. A total of 292 participants were included. Their mean age was 67.7 ± 13.1 years, and the majority were white men. Table 1 shows the baseline demographic and clinical characteristics of participants.

Ninety days after the stroke ictus, 54 (18.5%) participants died, and 83 (28.4%) lived with moderate to severe disability (2 < mRS < 6). In the mediation analysis of the composite outcome of disability or death (mRS score > 2), frailty accounted for 28% of the total effect of age (Table 2). Importantly, the natural direct effect of age on this outcome remained statistically significant, indicating that the association between age and the composite outcome of disability or death was not fully explained by frailty. Figure 3 shows the results of the regressions underlying the mediation analysis, which revealed that all paths in the mediation diagram were statistically significant and highlighted the strong association between frailty and composite disability/death outcomes. None of the values of the variation inflation factors in our statistical models were above 3. Hence, we are confident that multicollinearity did not bias our results.

Mediation analysis for mortality outcomes showed that 33% of the total effect of age was mediated through frailty, although this was not

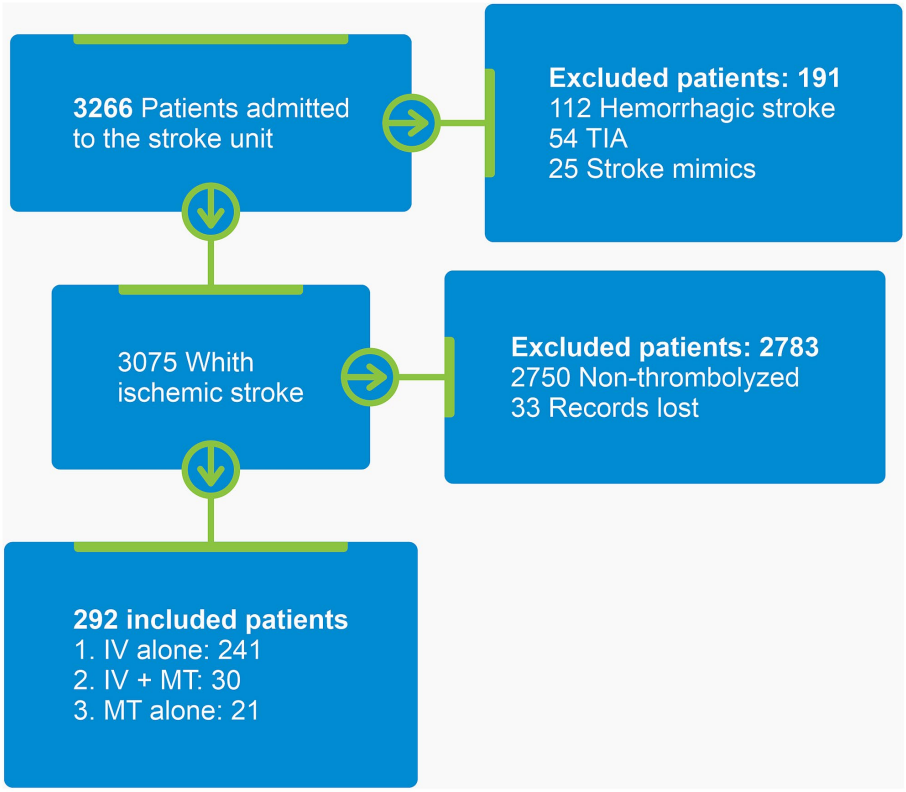

FIGURE 2
Participant selection flowchart. TIA, Transient ischemic attack; IV, Intravenous thrombolysis; MT, Mechanical thrombectomy.

statistically significant (Table 3). Interestingly, the direct effect of age on mortality was not significant in this model. In contrast, the natural indirect effect, that is, the effect of age on mortality mediated by frailty, remained statistically significant (Figure 4).

The models used to test for the interaction between age and frailty did not show statistically significant interactions for either outcome, and the addition of the interaction did not significantly change the direct or indirect effects nor improve the model fit (Vanderweele, 2015).

Discussion

To our knowledge, this is the first study to evaluate the extent to which frailty mediates the association between age and stroke outcomes. Our results suggest that, if frailty is prevented, approximately 28% of the impact of age on the composite outcome of disability or death can be avoided. Our sample was composed of young and elderly adults, predominantly white and male. The main risk factor was hypertension and diabetes and neurological severity ranged from mild to severe stroke. As is widely known, hypertension and diabetes are among the main causes of stroke (McFarlane et al., 2005), and the frequency of stroke type also differs in ethnic groups; white people have more frequency of large vessels and embolic strokes, while blacks have a higher frequency of small vessels and hemorrhagic strokes (Alter, 1994).

Unfortunately, owing to the limitations of the moderate sample size in our study, the confidence interval of the proportion of the effect of age on the mortality outcome mediated by frailty was wide, and this analysis did not reach statistical significance. Nevertheless, it is noteworthy that the effect of frailty on mortality remained significant, whereas that of age did not. This finding suggests that frailty may have a stronger relationship with the mortality outcome than age itself.

Indeed, for many diseases, frailty is a better predictor of clinical outcomes than age alone. Tan et al. (2022) observed that frail patients who experienced a stroke were more likely to be female and to have more comorbidities than those who were not frail. In addition, the authors showed that frailty was associated with poorer functional outcomes 90 days after endovascular therapy in patients aged ≥70 years. Another study performed at a UK comprehensive stroke center reported that pre-stroke frailty was prevalent in real-world patients eligible for thrombectomy and was an important predictor of poor outcomes. However, age was no longer a predictor of outcomes when adjusted for frailty (Joyce et al., 2022). Although higher frailty status increases the likelihood of poor outcomes and death after endovascular thrombectomy (Pinho et al., 2021; Tiainen et al., 2022), Evans et al. (2020) highlighted that the median NIHSS score improved significantly in non-frail individuals after thrombolysis. Notably, none of these studies evaluated the extent to which frailty mediates the association between age and stroke outcomes.

Our study has a few limitations. First, as discussed, our moderate sample size may not have provided sufficient power to detect a statistically significant proportion of the total effect of age on mortality mediated by frailty. Second, the observational nature of our data does not exclude the possibility of residual confounding involving the causal paths depicted in Figure 1. Importantly, our Frailty Index already included several comorbidities and participants'

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TABLE 1 Clinical and demographic characteristics of the study participants.

Characteristic	Proportion (*N* = 292)
Age, N (%)	
<50 years	26 (8.9)
50–59 years	50 (17.1)
60–69 years	85 (29.1)
70–79 years	69 (23.6)
≥80 years	62 (21.2)
Sex, N (%)	
Male	165 (56.5)
Female	127 (43.5)
Race, N (%)	
White	260 (89.0)
Black	32 (11.0)
Frailty index, median (Q1, Q3)	0.10 (0.03, 0.13)
Modified Rankin Scale, N (%)	
0	202 (69.2)
1	60 (20.5)
2	19 (6.5)
3	8 (2.7)
4	3 (1.0)
Initial NIHSS, median (Q1, Q3)	12.0 (7, 18)
Hypertension, *N* (%)	221 (75.7)
Diabetes, *N* (%)	87 (29.8)
Dyslipidemia, *N* (%)	56 (19.2)
Smoking, N (%)	
Never smoked	151 (51.7)
Former smoker	56 (19.2)
Current smoker	85 (29.1)
Previous myocardial infarction, *N* (%)	37 (12.7)
Atrial fibrillation, *N* (%)	29 (9.9)
Heart failure, *N* (%)	26 (8.9)
Previous ischemic stroke, *N* (%)	41 (14.0)
Previous acute ischemic attack, *N* (%)	14 (4.8)
Peripheral arterial disease, *N* (%)	6 (2.1)

Q, Quartile; NIHSS, National Institutes of Health Stroke Scale.

TABLE 2 Results of the mediation analysis* for the composite outcome of disability or death (modified Rankin Scale > 2) 90 days after the stroke ictus.

	OR (95% CI)	*p*
Total effect of age on mRS > 2	1.03 (1.02–1.05)	<0.01
NDE of age on mRS > 2	1.02 (1.00–1.04)	0.03
NIE of age on mRS > 2 mediated by frailty	1.01 (1.00–1.02)	0.01
Proportion mediated	27.7% (2.3–53.2%)	0.03

OR, odds ratio; CI: Confidence interval; mRS, modified Rankin Scale; NDE: Natural direct effect; NIE: Natural indirect effect; * Mediation analysis adjusted for sex, race, National Institutes of Health Stroke Scale score, and smoking status.

baseline functional status, which is the standard for the development of such an index (Searle et al., 2008). Hence, it was not appropriate to include these variables as covariates to adjust for confounding factors in the statistical models. Third, because of the retrospective nature of our data, our Frailty Index was limited to 31 variables and did not include the presence of geriatric syndromes such as falls and

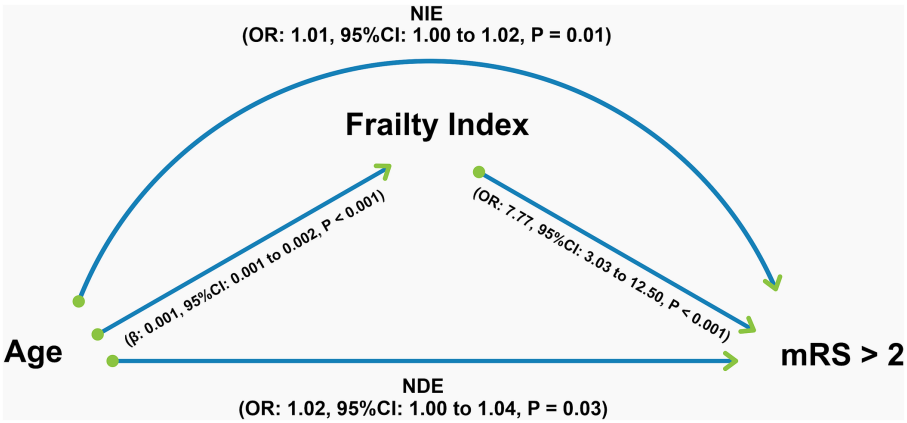

FIGURE 3
Graphical representation of the results of the mediation analysis for the composite outcome of disability or death (modified Rankin Scale >2) 90 days after the stroke ictus. All regressions underlying the mediation analysis, the coefficients of which are shown in the figure, were adjusted for sex, race, National Institutes of Health Stroke Scale score, and smoking status. NIE, natural indirect effect; NDE: Natural direct effect; OR: Odds ratio; CI: Confidence interval; mRS, modified Rankin Scale.

TABLE 3 Results of the mediation analysis* for the 90-day mortality outcome.

	OR (95% CI)	*p*
Total effect of age on mRS > 2	1.03 (1.00 to 1.06)	0.04
NDE of age on mRS > 2	1.02 (0.99 to 1.05)	0.19
NIE of age on mRS > 2 mediated by frailty	1.01 (1.00 to 1.02)	0.02
Proportion mediated	32.5% (0 to 72.6%)	0.11

OR, odds ratio; CI: Confidence interval; mRS, modified Rankin Scale; NDE: Natural direct effect; NIE: Natural indirect effect; * Mediation analysis adjusted for sex, race, National Institutes of Health Stroke Scale score, and smoking status.

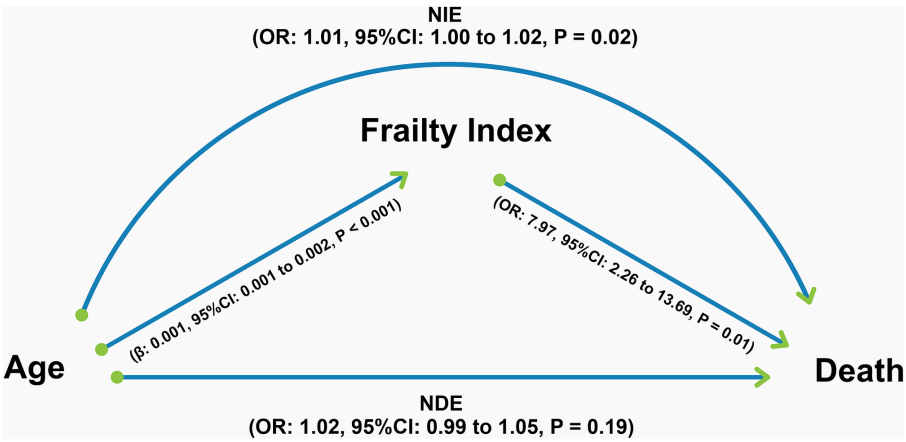

FIGURE 4
Graphical representation of the results of the mediation analysis for the 90-day mortality outcome. All regressions underlying the mediation analysis, the coefficients of which are shown in the figure, were adjusted for sex, race, National Institutes of Health Stroke Scale score, and smoking status. NIE, Natural indirect effect; NDE, Natural direct effect; OR, Odds ratio; CI, Confidence interval.

incontinence. Nevertheless, the guidelines for the creation of Frailty Indices state that at least 30 variables are required but do not impose the inclusion of any specific items (Rockwood and Mitnitski, 2007; Searle et al., 2008).

In summary, almost one-third of the effect of age on the composite outcome of disability or death after acute ischemic stroke is mediated by frailty. Our study suggests that progress in frailty prevention may have the additional benefit of decreasing the effect

of age on negative stroke outcomes in patients undergoing cerebral reperfusion therapy. Furthermore, our findings suggest that beyond age, clinicians should consider their patient's frailty status when attempting to estimate the prognosis of patients with stroke undergoing reperfusion therapy. Future studies should examine the extent to which frailty, as defined by other diagnostic tools, mediate the association between age and stroke outcomes, and test whether integrating frailty assessments in decision algorithms regarding the deployment of reperfusion therapies leads to improved selection of patients for those therapies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Botucatu Medical School committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LAM: Conceptualization, Methodology, Project administration, Writing – original draft. GL: Conceptualization, Methodology, Writing – review & editing. PB: Writing – review & editing. NEF: Writing – review & editing. FW: Writing – review & editing. NCF: Writing – review & editing. PH: Writing – review & editing. JdS: Writing – review & editing. LCM: Writing – review & editing. SZ: Writing – review & editing. GP: Writing – review & editing. CF: Writing – review & editing. EV: Formal analysis, Writing – review & editing. RB: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1305803/full#supplementary-material

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Association between *MTHFR* C677T polymorphism and cognitive impairment in patients with cerebral small vessel disease: a cross-sectional study

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Objective: Cerebral small vessel disease (CSVD) is the most common vascular cause of cognitive impairment. This study aimed to explore the association between *MTHFR* C677T polymorphism and cognitive impairment in CSVD patients.

Methods: Demographic, medical, laboratory, cognitive evaluation, and *MTHFR* C677T polymorphism data were collected from CSVD patients admitted to our hospital between January 2019 and July 2023. Inclusion criteria for CSVD were based on the Standards for Reporting Vascular changes on Neuroimaging (STRIVE) criteria, with age ≥ 45 years. Binary logistic regression models were used to analyze risk factors associated with WMH and cognitive impairment.

Results: A total of 330 CSVD participants were recruited in this study, including 179 male and 151 female, with a median age of 64 years (interquartile range: 58–73 years). There were 185 patients (56.1%) with cognitive impairment, 236 patients (71.5%) with WMH, 89 patients (27.0%) with CMB, 87 patients (26.4%) with lacunes. All participants completed *MTHFR* polymorphism analysis, 149 cases (45.2%) of the CC genotype, 112 cases (33.9%) of the CT genotype and 69 cases (20.9%) of the TT genotype. Patients with TT genotype exhibited higher plasma homocysteine levels and more severe WMH and cognitive impairment ($p < 0.001$). Multivariable binary logistic regression model showed that WMH was significantly associated with age ($p = 0.019$), history of hypertension ($p = 0.011$), HHcy ($p = 0.019$) and *MTHFR* genotype ($p = 0.041$); while cognitive impairment was significantly associated with age ($p = 0.033$), history of hypertension ($p = 0.019$), HHcy ($p = 0.040$), *MTHFR* genotype ($p = 0.039$), WMH ($p = 0.041$), and lacunes ($p = 0.001$).

Conclusion: In this cross-sectional study, we investigated the association between *MTHFR* C677T polymorphism and cognitive function in CSVD patients. We found that *MTHFR* 677 TT genotype was an independent risk factor for the progression of WMH and cognitive impairment in CSVD patients.

KEYWORDS

cerebral small vessel disease, cognitive impairment, *MTHFR* C677T polymorphism, white matter hyperintensity, hyperhomocysteinemia

Introduction

Cerebral small vessel disease (CSVD) is a chronic progressive cerebrovascular disorder, involving lesions in intracranial small arteries, arterioles, capillaries, and small veins. CSVD is a prominent determinant of cognitive impairment in the elderly, accounting for approximately 50% of dementia cases worldwide (Wardlaw et al., 2019). The clinical manifestations of CSVD demonstrate significant heterogeneity, often lacking apparent clinical symptoms and being under-recognized in early stages. With the emergence and widespread application of neuroimaging techniques, CSVD can be increasingly identified based on its characteristic radiologic features, including white matter hyperintensities (WMH), cerebral microbleeds (CMBs), lacunar infarctions (Wardlaw et al., 2013).

With accelerating aging populations and rising incidence of cerebrovascular risk factors, the prevalence of CSVD continues to rise. However, its pathogenesis remains to be incompletely understood (Wardlaw et al., 2019). In addition to the well-recognized risk factors including blood–brain barrier (BBB) dysfunction, hypoperfusion, oxidative stress, and inflammation, hyperhomocysteinemia (HHcy) has been identified as a potential novel independent risk factor for CSVD (Hassan et al., 2004; Ji et al., 2020). HHcy can promote vascular endothelial damage by oxidative stress mechanisms, accelerate atherosclerotic plaque formation, exacerbate arteriosclerosis, and act synergistically with hypertension to increase the likelihood of stroke (Liu et al., 2017). Methylenetetrahydrofolate reductase (*MTHFR*) is a crucial enzyme in homocysteine metabolism, with over 10 recognized allelic variants. The most common variant is the C677T mutation, which reduces MTHFR enzyme activity and thermostability, constituting a major genetic basis for heightened homocysteine levels.

Although it is possible to identify CSVD manifestations through imaging, these radiological changes often lag behind the onset of lesions. Early detection and intervention before symptoms onset can significantly improve the prognosis of CSVD. Therefore, comprehensive analysis of CSVD risk factors and identification of relevant biomarkers has become particularly critical. Most current studies have focused on the association between CSVD and homocysteine levels, with limited attention to the relationship between *MTHFR* C677T polymorphism and cognitive impairment. Notably, homocysteine levels are susceptible to various external factors, including lifestyle and environmental influences, making it an unstable marker for early detection. Recent studies have indicated that the TT genotype is an independent risk factor for WMH (Li et al., 2022). A meta-analysis of 36 prospective studies demonstrated that WMH is associated with increased risk of cognitive impairment, serving as a neuroimaging marker for dementia (Hu et al., 2021).

Therefore, we collected clinical information and radiological data related to CSVD and assessed cognitive function using the MMSE. The purpose of this study was to explore the association between *MTHFR* C677T polymorphism and cognitive impairment in CSVD patients.

Materials and methods

Study design and participants

This single-center, retrospective, cross-sectional study was approved by the ethics committee of our hospital. All participants were recruited from the neurology departments of our institution from January 2019 to July 2023. Written informed consent was obtained from all participants. The sample size was calculated based on the 30.5% value of CSVD prevalence in Chinese population (Yang et al., 2023), with a confidence level of 95% and a margin error of 5%. The sample size required for this study was 330. Inclusion criteria for CSVD were based on the Standards for Reporting Vascular changes on Neuroimaging (STRIVE), with an age of 45 years or older. Exclusion criteria were: (1) history of large cerebral infarction or hemorrhage, (2) white matter lesions secondary to autoimmune diseases, inflammatory conditions, multiple sclerosis, or neoplasms, (3) chronic kidney disease and renal transplantation, (4) abnormal thyroid function, (5) impaired hepatic function or liver diseases, (6) recent use of methotrexate, B vitamins, folic acid, or antiepileptic agents.

Data collection

We collected demographic and medical information, including age, sex, smoking status, history of hypertension, diabetes mellitus, and hyperlipidemia. Hypertension was defined as self-reported hypertension, treatment with antihypertensive medication, systolic blood pressure $\geq$ 140 mmHg, or diastolic blood pressure $\geq$ 90 mmHg. Diabetes mellitus was defined as self-reported diabetes, use of oral antidiabetic drugs or insulin, fasting serum glucose $\geq$7.0 mmol/L or hemoglobin A1c (HbA1c) $\geq$6.5%. Hyperlipidemia was defined as fasting serum total cholesterol (TC) >5.2 mmol/L, low density lipoprotein cholesterol (LDL-C) >3.62 mmol/L, or use of lipid-lowering drugs. Smoking status was classified as current smoker (at least within the prior month) or non-current smoker. HHcy was classified as fasting plasma homocysteine $\geq$15 μmol/L. Venous blood samples, routinely drawn after an overnight fast, were analyzed for plasma TC, LDL-C, glucose, HbA1c and homocysteine.

MTHFR genotyping

Genomic DNA was extracted from peripheral blood leukocytes using a genomic DNA extraction kit (QIAGEN). The *MTHFR* C677T polymorphism was performed by polymerase chain reaction (PCR) with the following primers: forward 5'-TGAAGGAGAAGG TGTCTGCGGGA-3′, reverse 5'-AGGACGGTGCGGTGAGAGTG-3′.

Neuroimaging data collection

Imaging was performed using a 3.0 T Siemens scanner, included T1-weighted imaging, T2-weighted imaging, diffusion-weighted imaging (DWI), and magnetic resonance angiography (MRA) or computed tomography angiography (CTA). All neuroimaging data were independently evaluated by two experienced Neurologist. WMHs on MRI were visually assessed using the Fazekas scale (0–3): grade 0 = no lesions, grade 1 = focal damage, grade 2 = partial fusion of lesions and grade 3 = diffuse involving the entire area, with or without "U"-fiber involvement. CMBs were defined as homogeneous round or ovoid signal loss on SWI, 2 to 10 mm in diameter with blooming

effect. Lacunar infarctions were defined as focal deep infarcts 3 to 15 mm in size, mainly located in basal ganglia or white matter.

Cognitive function assessment

Cognitive function was assessed using the Mini-Mental State Examination (MMSE). The MMSE has a maximum score of 30 with higher scores denoting better cognitive performance. The MMSE cutoff points for cognitive impairment screening were 17 for illiterate, 20 for individuals with 1–6 years of education, and 24 for individuals with 7 or more years of education (Creavin et al., 2016).

Statistical analysis

All data were entered into Excel and analyzed using SPSS 26.0 software (IBM, Armonk, New York, United States). Continuous variables were described as means ± standard deviations or medians (interquartile ranges, IQR). Non-normally distributed continuous variables were compared using the Kruskal-Wallis H rank sum test. Categorical variables were expressed as constituent ratios or rates (%), and compared using Pearson chi-squared (X^2) test. The Spearman correlation analysis was employed to assess the association between WMH and cognitive impairment with various factors, accounting for non-normal distribution. Initial univariate binary logistic regression models were performed for each variable with WMHs. Then, multivariable binary logistic regression models were adjusted for age, hypertension, HHcy and *MTHFR* genotype. Finally, univariate and multivariable binary logistic regression analyses were performed for cognitive impairment with age, hypertension, HHcy, *MTHFR* genotype, WMHs, and lacunes as covariates. The results were expressed as odds ratio (OR) and 95% confidence interval (CI). p values <0.05 were considered statistically significant.

Results

Demographics in CSVD participants

A total of 330 CSVD participants were recruited in this study. The cohort consisted of 179 male and 151 female, with a median age of 64 years (interquartile range: 58–73 years). Among the participants, 154 (46.7%) were current smokers, 183 (55.5%) had a history of hypertension, 100 (30.3%) had diabetes mellitus, 136 (41.2%) had hyperlipidemia, 131 (39.7%) were HHcy, and 185 (56.1%) had cognitive impairment. Participants were categorized into three groups based on neuroimaging characteristics: the WMH group ($n = 236$, 71.5%), CMB group ($n = 89$, 27.0%) and lacunar infarctions group ($n = 87$, 26.4%). The WMH group had a significantly higher proportion of participants compared to the other two groups. Demographic parameters are shown in Table 1.

Association between *MTHFR* genotype and WMH in CSVD

All participants completed *MTHFR* polymorphism analysis. When categorized by genetic typing, there were 149 cases (45.2%) with the CC genotype, 112 cases (33.9%) with the CT genotype and 69 cases (20.9%) with the TT genotype. Notably, the proportion of TT genotype was lowest among the three genotype groups. Moreover, we confirmed that individuals with the TT genotype exhibited higher plasma homocysteine levels compared to those with the CC and CT genotypes ($p < 0.001$). No statistically differences were observed in terms of age, gender, smoking status, LDL-C, TC, history of hypertension, diabetes and hyperlipidemia. Importantly, there was a statistically significant difference among the three genotype groups in patients with WMH and cognitive impairment ($p < 0.001$), while no statistical difference was found in patients with CMB and lacunes (Table 2).

TABLE 1 Demographic characteristics of CSVD participants.

	Total (n = 330)	WMH (n = 236)	CMB (n = 89)	Lacunes (n = 87)
Age, y, median (interquartile range)	64 (58–73)	67 (60–73)	61 (51–69)	67 (59–73)
45–54	50 (47–51)	49.5 (47–51)	50 (48–51)	50 (48–51)
55–64	61 (59–63)	62 (59–63)	60 (59–61)	60 (59–61)
65–74	69 (67–72)	69 (67–72)	69 (66–70)	71 (67–72)
≥75	79 (76–82)	79 (76–84)	77 (76–79)	80 (76–82)
Sex, Male, n, (%)	179 (54.2)	131 (55.5)	45 (50.6)	49 (56.3)
Current smoker, n, (%)	154 (46.7)	109 (46.2)	42 (47.2)	44 (50.6)
Hypertension, n, (%)	183 (55.5)	146 (61.9)	44 (49.4)	46 (52.9)
Diabetes mellitus, n, (%)	100 (30.3)	74 (31.4)	33 (37.1)	25 (28.7)
Hyperlipidemia, n, (%)	136 (41.2)	98 (41.5)	38 (42.7)	36 (41.4)
TC, mmol/L, median (interquartile range)	4.39 (3.32–5.53)	4.35 (3.34–5.57)	4.42 (3.38–5.42)	4.30 (3.24–5.57)
LDL-C, mmol/L, median (interquartile range)	2.60 (1.65–3.60)	2.62 (1.73–3.59)	2.85 (1.57–3.73)	2.44 (1.52–3.76)
HHcy, (n, %)	131 (39.7)	113 (47.9)	31 (34.8)	32 (36.8)
Hcy, μmol/L, median (interquartile range)	11.85 (9.47–17.3)	14.25 (9.90–18.10)	10.6 (8.70–15.55)	11.7 (9.40–17.30)
Cognitive impairment, n, (%)	185 (56.1)	151 (64.0)	44 (49.4)	59 (67.8)

WMH, white matter hyperintensity; CMB, cerebral microbleeds; TC, total cholesterol; LDL-C, low density lipoprotein chesterol; Hcy, homocysteine; HHcy, hyperhomocysteinemia.

TABLE 2 Relationships between *MTHFR* genotype and CSVD.

	CC (n = 149)	CT (n = 112)	TT (n = 69)	p value
Age, y, median (interquartile range)	63 (58–72)	65 (55–73)	69 (59–74.5)	0.63*
Sex, male, *n*, (%)	80 (53.7)	62 (55.4)	37 (53.6)	0.958#
Current smoker, *n*, (%)	73 (49.0)	47 (42.0)	34 (49.3)	0.471#
Hypertension, *n*, (%)	77 (51.7)	63 (56.3)	43 (62.3)	0.332#
Diabetes mellitus, *n*, (%)	46 (30.9)	34 (30.4)	20 (29.0)	0.961#
Hyperlipidemia, *n*, (%)	62 (41.6)	45 (40.2)	29 (42.0)	0.962#
TC, mmol/ L, median (interquartile range)	4.41 (3.32–5.69)	4.41 (3.24–5.40)	4.19 (3.44–5.54)	0.891*
LDL-C, mmol /L, median (interquartile range)	2.62 (1.625–3.75)	2.52 (1.625–3.54)	2.63 (1.82–3.59)	0.898*
HHcy, (*n*, %)	34 (22.8)	40 (35.7)	57 (82.6)	<0.001#
Hcy, μmol /L, median (interquartile range)	10.1 (8.4–14.5)	13.15 (9.55–16.37)	18.1 (15.55–20.85)	<0.001*
Cognitive impairment, *n*, (%)	65 (43.6)	65 (58.0)	55 (79.7)	<0.001*
MRI features, n, (%)				
WMH				
0	58 (38.9)	28 (25.0)	8 (11.6)	<0.001#
1	33 (22.1)	43 (38.4)	27 (39.1)	
2	45 (30.2)	19 (17.0)	16 (23.2)	
3	13 (8.7)	22 (19.6)	18 (26.1)	
CMB	46 (30.9)	25 (22.3)	18 (26.1)	0.300#
Lacunes	39 (26.2)	27 (24.1)	21 (30.4)	0.642#

*, Kruskal-Wallis H rank sum test; #, Pearson chi-squared (X^2) test; WMH, white matter hyperintensity; CMB, cerebral microbleeds; Hcy, homocysteine; HHcy, hyperhomocysteinemia; CC, CC genotype; CT, CT genotype; TT, TT genotype; $p \leq 0.05$ was considered statistically significant.

Factors significantly associated with white matter damage

Spearman correlation analysis of relevant risk factors for WMH is shown in Table 3. A positive correlation was observed between the severity of WMH and age ($p < 0.001$), history of hypertension ($p < 0.001$), HHcy ($p < 0.001$), and *MTHFR* genotype ($p < 0.001$).

Univariate analysis of binary logistic regression model showed that WMH was significantly associated with age, history of hypertension, HHcy and *MTHFR* genotype. When included in the multivariable model, age (65–74 years, OR: 2.530, 95% CI: 1.213 to 5.279, $p = 0.013$; ≥75 years, OR: 2.860, 95% CI: 1.201 to 6.809, $p = 0.018$), history of hypertension (OR: 1.977, 95% CI: 1.170 to 3.341, $p = 0.011$), HHcy (OR: 2.201, 95% CI: 1.139 to 4.251, $p = 0.019$) and *MTHFR* TT genotype (TT genotype, OR: 2.706, 95% CI: 1.096 to 6.685, $p = 0.031$) remained significant (Table 4).

TABLE 3 Spearman correlation analysis of WMH in CSVD patients.

	ρ	p value
Age (y)	0.374	<0.001
Sex	0.068	0.220
Current smoker	0.050	0.365
Hypertension	0.224	<0.001
Diabetes mellitus	0.012	0.832
Hyperlipidemia	0.020	0.723
HHcy	0.305	<0.001
MTHFR genotype	0.193	<0.001

HHcy, hyperhomocysteinemia; $p \leq 0.05$ was considered statistically significant.

Factors significantly associated with cognitive impairment

Spearman correlation analysis of relevant risk factors for cognitive impairment is shown in Table 5. A positive correlation was observed between the cognitive impairment and age ($p < 0.001$), history of hypertension ($p < 0.001$), HHcy ($p < 0.001$), *MTHFR* genotype ($p < 0.001$), WMH ($p < 0.001$) and lacunes ($p = 0.01$).

Univariate binary logistic regression analysis showed cognitive impairment was significantly associated with age, hypertension history, HHcy, *MTHFR* genotype, WMH, and lacunes. When included in the multivariable model, age (65–74 years, OR: 2.219, 95% CI: 1.074 to 4.585, $p = 0.031$; ≥75 years, OR: 2.714, 95% CI: 1.185 to 6.214, $p = 0.018$), history of hypertension (OR: 2.009, 95% CI: 1.203 to 3.353, $p = 0.008$), HHcy (OR: 1.874, 95% CI: 1.030 to 3.408, $p = 0.040$), *MTHFR* TT genotype (TT genotype, OR: 2.786, 95% CI: 1.233 to 6.295, $p = 0.014$), WMH (Fazekas grade 2, OR: 2.518, 95% CI: 1.208 to 5.250, $p = 0.014$; Fazekas grade 3, OR: 3.067, 95% CI: 1.225 to 7.680, $p = 0.017$) and lacunes (OR: 2.875, 95% CI: 1.518 to 5.445, $p = 0.001$) remained significant (Table 6).

Discussion

CSVD represented a a progressively accumulating chronic injury process, which gradually affected patients' cognitive abilities,

TABLE 4 Binary logistic regression analysis of risk factors of WMH in CSVD patients.

variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age (y)				
45–54	Ref		Ref	
55–64	1.351 (0.722, 2.528)	0.347	1.522 (0.777, 2.979)	0.221
65–74	3.487 (1.743, 6.977)	<0.001	2.530 (1.213, 5.279)	0.013
≥75	4.185 (1.840, 9.518)	0.001	2.860 (1.201, 6.809)	0.018
p for trend		<0.001		0.019
Sex	1.196 (0.741, 1.930)	0.465		
Current smoker	0.935 (0.579, 1.509)	0.782		
Hypertension	2.499 (1.531, 4.080)	<0.001	1.977 (1.170, 3.341)	0.011
Diabetes mellitus	1.195 (0.704, 2.028)	0.510		
Hyperlipidemia	1.047 (0.643, 1.702)	0.855		
HHcy	3.879 (2.185, 6.885)	<0.001	2.201 (1.139, 4.251)	0.019
MTHFR genotype				
CC	Ref		Ref	
CT	1.912 (1.115, 3.280)	0.019	1.720 (0.968, 3.056)	0.064
TT	4.860 (2.168, 10.894)	<0.001	2.706 (1.096, 6.685)	0.031
p for trend		<0.001		0.041

CI, confidence interval; OR, odds ratio; HHcy, hyperhomocysteinemia; CC, CC genotype; CT, CT genotype; TT, TT genotype; $p \leq 0.05$ was considered statistically significant.

TABLE 5 Spearman correlation analysis of cognitive impairment in CSVD patients.

	ρ	*p* value
Age (y)	0.335	<0.001
Sex	0.082	0.139
Current smoker	0.045	0.417
Hypertension	0.238	<0.001
Diabetes mellitus	0.066	0.234
Hyperlipidemia	0.059	0.285
HHcy	0.306	<0.001
MTHFR genotype	0.269	<0.001
WMH	0.289	<0.001
CMB	−0.081	0.142
Lacunes	0.142	0.010

WMH, white matter hyperintensity; CMB, cerebral microbleeds; HHcy, hyperhomocysteinemia; $p \leq 0.05$ was considered statistically significant.

emotional states, and capabilities for daily living. This imposed substantial economic and social burdens on both the patients themselves and their families (Markus and Erik de Leeuw, 2023). In this cross-sectional study, we investigated potential associations between the *MTHFR* C677T polymorphism and cognitive function. Our findings indicated that the *MTHFR* 677 TT genotype independently conferred increased risk for both progression of WMH and cognitive impairment in CSVD patients.

Although WMH was the most common radiological manifestation of CSVD, its insidious symptom onset often led to underestimation of true prevalence. A prior study based on a Chinese population revealed that the prevalence of periventricular hyperintensity (PVH) was 72.1%, and deep white matter hyperintensity (DWMH) prevalence of 65.4% among CSVD patients (Yang et al., 2023). In our study, the proportion of participants with WMH was 71.5%, consistent with these previous findings. While variations existed across races and WMH definitions among research reports, a notably high WMH prevalence persisted (Yang et al., 2023). We observed a marked increase in cognitive impairment prevalence within the WMH subgroup, emphasizing the association between WMH and cognitive decline.

The linkage between the *MTHFR* gene and elevated homocysteine levels has been widely acknowledged, and the relationship between genetically-mediated HHcy and cerebrovascular diseases represented a major focus of current clinical research (Li et al., 2022). The *MTHFR* C677T mutation included three polymorphisms (wild-type CC, heterozygous CT, and homozygous TT). The CC genotype exhibited the highest frequency (45.2%) while the TT genotype was least frequent (20.9%). Patients with the TT genotype exhibited significantly higher plasma homocysteine compared to those with CC and CT genotypes ($p < 0.001$). Elevated homocysteine may promote inflammatory responses via increased pro-inflammatory and reduced anti-inflammatory cytokines, consequently impairing vascular endothelial structure and function, enhancing vascular permeability, disrupting the blood–brain barrier, and ultimately resulting in ischemic and hypoxic injury to both white and gray matter (Al Mutairi, 2020). For equivalent damage, the homocysteine concentration required for cerebral small vessel endothelial injury was lower than for large vessels, indicating greater small vessel sensitivity to homocysteine. This further confirmed more pronounced damage to small vessels from elevated homocysteine (Feng et al., 2013). Our findings corroborate this perspective, patients possessing the TT genotype displayed heightened severity of WMH pathology and cognitive

TABLE 6 Binary logistic regression analysis of risk factors of cognitive impairment in CSVD patients.

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Age (y)				
45–54	Ref		Ref	
55–64	1.164 (0.621, 2.181)	0.635	1.166 (0.580, 2.342)	0.667
65–74	3.934 (2.062, 7.503)	<0.001	2.219 (1.074, 4.585)	0.031
≥75	4.889 (2.329, 10.261)	<0.001	2.714 (1.185, 6.214)	0.018
p for trend		<0.001		0.033
Sex	1.391 (0.898, 2.153)	0.139		
Current smoker	1.199 (0.775, 1.855)	0.415		
Hypertension	2.667 (1.703, 4.176)	<0.001	2.009 (1.203, 3.353)	0.008
Diabetes mellitus	1.337 (0.829, 2.157)	0.234		
Hyperlipidemia	1.274 (0.818, 1.986)	0.284		
HHcy	3.823 (2.357, 6.202)	<0.001	1.874 (1.030, 3.408)	0.040
MTHFR genotype				
CC	Ref		Ref	
CT	1.787 (1.089, 2.934)	0.022	1.543 (0.873, 2.729)	0.136
TT	5.077 (2.598, 9.923)	<0.001	2.786 (1.233, 6.295)	0.014
p for trend		<0.001		0.039
MRI features				
WMH				
0	Ref		Ref	
1	2.275 (1.282, 4.035)	0.005	1.843 (0.936, 3.631)	0.077
2	3.103 (1.669, 5.771)	<0.001	2.518 (1.208, 5.250)	0.014
3	6.738 (3.070, 14.786)	<0.001	3.067 (1.225, 7.680)	0.017
p for trend		<0.001		0.41
CMB	0.693 (0.426, 1.130)	0.142		
Lacunes	1.957 (1.169, 3.276)	0.011	2.875 (1.518, 5.445)	0.001

CI, confidence interval; OR, odds ratio; HHcy, hyperhomocysteinemia; CC, CC genotype; CT, CT genotype; TT, TT genotype; WMH, white matter hyperintensity; CMB, cerebral microbleeds; $p \leq 0.05$ was considered statistically significant.

impairment compared to those harboring the CC and CT genotypes. However, we observed no statistically significant variations between genotypic groups regarding CMB and lacunar infarcts.

We further investigated factors associated with WMH, finding a significant positive correlation between the severity of white matter lesion severity and age, hypertension, homocysteine and *MTHFR* genotype ($p < 0.001$). Our results were consistent with other cohorts in showing that age and hypertension were independent risk factors for WMH (Yang et al., 2023). Hypertension can directly impair small arteries, precipitating atherosclerotic evolution, reflecting similar microvascular pathologies with CSVD. Concomitantly, it can induce lipoidosis, gradually compromising cerebral metabolism and elevating risk of cognitive impairment, with these consequences intensifying in conjunction with aging. The association between *MTHFR* C677T polymorphism and CSVD remained a topic of ongoing debate. Previous studies indicated robust associations between *MTHFR* C677T polymorphism and WMH volume (Rutten-Jacobs et al., 2016), and HHcy had been identified as a predictive factor for the severity of white matter lesions in elderly patients (Yu et al., 2020). However, Jeon et al. reported that despite the linkage between HHcy and small vessel disease (SVD), and the role of TT genotype as an important determinant of HHcy, the *MTHFR* C677T polymorphism was not related to SVD (Jeon et al., 2014). In this study, we observed age, hypertension, HHcy, TT genotype to be independent risk factors of WMH by multivariable logistic regression analysis. However, the association between the *MTHFR* C677T polymorphism and neuroimaging phenotypes of CSVD remains to be fully elucidated.

One previous study reported that WMH may increase the risks of vascular dementia by 73%, and consistently increased volume or severity of WMH shown to heighten dementia susceptibility (Hu et al., 2021). Remaining consistent with the perspective expressed above, our results demonstrated that CSVD patients with more severe WMH have a significantly increased risk of cognitive impairment. WMH may engender cognitive dysfunction through secondary demyelination and consequent neuronal loss (Wang et al., 2021). WMH were regarded as a crucial neuroimaging biomarker of cognitive impairment, and a more accurate assessment could be achieved through the measurement of WMH volume (Prins and Scheltens, 2015). Our study revealed a modest correlation between lacunar infarcts and cognitive impairment. Research

shown approximately 40% of lacunar infarcts patients exhibit varying degrees of vascular cognitive impairment (Ohlmeier et al., 2023). WMH and lacunar infarcts may exhibit synergistic effects on cognitive impairment; therefore, future investigations focused on elucidating the intricate interrelationships between neuroimaging biomarkers and cognitive function in CSVD are imperative.

Although HHcy has been identified as a potential risk factor for dementia (Miwa et al., 2016; Teng et al., 2022), homocysteine levels were influenced by a multitude of both external and internal factors, hence, the impact of homocysteine on cardiovascular disease may exhibit a diverse effects. Our study revealed that more pronounced cognitive impairment in individuals with HHcy and the *MTHFR* 677 TT genotype. This implies that CSVD patients may develop more substantial cognitive impairment under specific genetic backgrounds. Given the positive correlation between WMH burden and risk of cognitive impairment, we can speculate that *MTHFR* 677 TT genotype may aggravate WMH by elevating serum homocysteine levels, thereby heightening susceptibility to cognitive decline. However, as a cross-sectional study, we could not establish definitive causal relationships between the MTHFR 677 TT genotype, WMH, and cognitive dysfunction. Future longitudinal cohort studies will help elucidate the interrelationships among these factors.

Cognitive impairment resulted from the complex interplay of multiple factors. Apart from the MTHFR 677 TT genotype as an important genetic risk factor, other hazards warranted attention as well. For instance, hypertension could engender atherosclerosis, while aging exacerbated β-amyloid deposition—both processes were implicated in cognitive decline. Although incorporating common risk factors like age, sex, smoking, hypertension, dyslipidemia, and diabetes, our study provides limited assessments of the complex multifactorial etiology underlying cognitive impairment. Further large-scale multifactor investigations will be warranted to construct sophisticated predictive models that appraise the impacts and interactions of diverse risk elements on cognitive dysfunction, vital steps for forecasting and preventing neurological morbidity. Although non-genetic or mixed factors may have played essential roles in the pathogenesis of homocysteine-induced vascular changes, our research advised that high-risk individuals with HHcy undergo screening for associated genetic risks, so preemptive interventions can mitigate cognitive impairment risk.

This study has several limitations. Firstly, the cross-sectional design of our study, is unable to investigate causality. Secondly, the single-center study with a relatively limited sample size, which may introduce selection bias and constrain generalizability beyond the sampled population. Due to the limited sample size, conducting risk factor analyses for lacunar infarctions and cerebral microbleeds was not feasible. Thus, larger multi-center studies are needed to enhance generalizability. Moreover, cognitive impairment typically arises from multifactorial influences, yet this study exclusively focuses on *MTHFR* gene variations, while interactions with other risk factors or potential confounders require further investigation. Future investigations should implement a prospective cohort design, augment sample sizes, and evaluate the comprehensive effects of diverse risk determinants to bolster the credibility of study conclusions.

Conclusion

Through analyzing imaging characteristics, *MTHFR* C677T polymorphisms, and cognitive function in 330 CSVD patients, this study demonstrates the *MTHFR* 677 TT genotype as an independent genetic risk factor contributing to WMH and cognitive impairment in CSVD patients. These findings underscore the complex genetic underpinnings of CSVD, which may ultimately inform development of personalized preventative and therapeutic modalities for this condition. However, the cross-sectional design and limited sample size constrain generalizability and causal inferences, necessitating future large-scale, longitudinal investigations with a prospective cohort design to unravel the intricate pathogenic mechanisms underlying cognitive impairment in CSVD.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: China National GeneBank Database, CNP0005057.

Ethics statement

The studies involving humans were approved by the Affiliated Mindong Hospital of Fujian Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QW: Investigation, Methodology, Writing – original draft. CY: Formal analysis, Investigation, Methodology, Writing – original draft. ZZ: Conceptualization, Data curation, Supervision, Writing – review & editing. CC: Data curation, Investigation, Project administration, Supervision, Writing – review & editing. XZ: Data curation, Formal analysis, Investigation, Writing – original draft. XL: Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Machine learning based on the EEG and structural MRI can predict different stages of vascular cognitive impairment

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Background: Vascular cognitive impairment (VCI) is a major cause of cognitive impairment in the elderly and a co-factor in the development and progression of most neurodegenerative diseases. With the continuing development of neuroimaging, multiple markers can be combined to provide richer biological information, but little is known about their diagnostic value in VCI.

Methods: A total of 83 subjects participated in our study, including 32 patients with vascular cognitive impairment with no dementia (VCIND), 21 patients with vascular dementia (VD), and 30 normal controls (NC). We utilized resting-state quantitative electroencephalography (qEEG) power spectra, structural magnetic resonance imaging (sMRI) for feature screening, and combined them with support vector machines to predict VCI patients at different disease stages.

Results: The classification performance of sMRI outperformed qEEG when distinguishing VD from NC (AUC of 0.90 vs. 0,82), and sMRI also outperformed qEEG when distinguishing VD from VCIND (AUC of 0.8 vs. 0,0.64), but both underperformed when distinguishing VCIND from NC (AUC of 0.58 vs. 0.56). In contrast, the joint model based on qEEG and sMRI features showed relatively good classification accuracy (AUC of 0.72) to discriminate VCIND from NC, higher than that of either qEEG or sMRI alone.

Conclusion: Patients at varying stages of VCI exhibit diverse levels of brain structure and neurophysiological abnormalities. EEG serves as an affordable and convenient diagnostic means to differentiate between different VCI stages. A machine learning model that utilizes EEG and sMRI as composite markers is highly valuable in distinguishing diverse VCI stages and in individually tailoring the diagnosis.

KEYWORDS

machine learning, quantitative electroencephalogram, vascular cognitive dysfunction, structural magnetic resonance imaging, applications of support vector machine

1 Introduction

Vascular cognitive impairment (VCI) is a leading cause of chronic progressive cognitive impairment in the elderly population and is caused by cerebrovascular lesions and their associated risk factors (Biesbroek and Biessels, 2023). Vascular cognitive impairment (VCI) spans a spectrum including subjective cognitive decline (SCD), vascular cognitive impairment with no dementia (VCIND), and vascular dementia (VD). Today's research has shown that in people with vascular cognitive impairment (VCI), many subtle changes in the structure and function of the brain have taken place prior to the appearance of overt cognitive impairment and clinical deficits (Sang et al., 2020; Yang et al., 2022; Badji et al., 2023). Some of the most significant challenges at present are to identify brain disorders that show VCI in the early stages of the disease and, if possible, to identify those that may progress to VD. However, to date, the structural brain characteristics and electrophysiologic functional changes in different stages of VCI have not been quantitatively distinguished in any relevant study. Mechanical learning methods that combine neuroimaging features have been utilized in recent years for early VCI diagnosis, demonstrating significant potential (Lu et al., 2020; Li et al., 2021). However, there has been relatively little study on combined neuroimaging and neurophysiology. Due to the limitations of unimodal studies, a combined multimodal analysis that incorporates both neuroimaging and neurophysiology may offer a novel approach for identifying the structural and functional changes in the brains of VCI patients at different stages. This could potentially serve as a biomarker for identifying the various stages of VCI and pave the way to explore new therapeutic targets. This study aimed at investigating precision of sMRI and resting-state EEG in discriminating between different stages of VCI, and at integrating both techniques in discriminating between VCI, VCIND, and healthy elderly using a support vector machine classification.

2 Materials and methods

All participants with VCI in the study were patients who visited the Memory Clinic and the Ward of the Department of Neurology at Hongqi Hospital, Affiliated to Mudanjiang Medical College, from September 2021 to October 2022, with the primary complaint of memory loss. All participants without cognitive impairment were recruited from the general community or from physical examinations at memory clinics. All participants provided informed consent prior to their inclusion in the study. The detailed methodologies are described below and in **Figure 1**. The study was conducted in adherence with the guidelines laid out in the Declaration of Helsinki. The Ethical Review Committee of Hongqi Hospital, affiliated with Mudanjiang Medical College, approved the study (Ethics No. 2022011).

2.1 Inclusion and exclusion criteria

All participants were sorted into three groups after undergoing the Montreal Cognitive Assessment (MoCA) and the clinical dementia rating scale (CDR) with physician supervision. These groups consist of the NC group (n = 30), the VCIND group (n = 32), and the VD group (n = 21). For the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), a cutoff value of < 26 indicates cognitive impairment. Additionally, one point is added to the raw MoCA score if the participant's education level is < 12. All participants in the study were right-handed individuals of Han Chinese descent from northeastern China. Enrollment requirements for the NC group included: (1) absence of cognitive decline complaints; (2) a MoCA score of 26 or higher and a CDR score of 0; (3) no identification of symptoms or positive signs during the physical examination, and (4) no significant anomalies found in the head magnetic resonance imaging. Enrollment requirements for the VCIND group included (Sachdev et al., 2014): (1) a complaint or evidence of cognitive dysfunction from a knowledgeable source, with normal or slightly impaired ability to perform daily activities; (2) a MoCA score less than 26 and a CDR score equal to 0 or 0.5; and (3) an intracranial lesion visible on imaging, meeting VCI diagnostic criteria and clearly linked to cognitive decline. Enrollment requirements for the VD group included (Erkinjuntti, 1994): (1) significant cognitive impairment, reported by the patient or by an appropriate caregiver, affecting activities of daily living, (2) MoCA score < 22 and CDR score ≥ 1, and (3) cognitive impairment from VD confirmed by imaging evidence of intracranial pathology meeting diagnostic criteria and clearly associated with patient cognitive impairment. Exclusion criteria: (1) The participant has a history of heart or kidney disease, cancer, or other significant systemic illness. (2) The cognitive decline is unrelated to cerebrovascular disease. (3) The participant experiences progressive memory or cognitive decline without associated imaging changes. (4) The participant is unable to communicate due to severe impairment in hearing, vision, or speech; (5) The participant displays symptoms of depression and anxiety according to the Hamilton depression and anxiety inventory; (6) The participant has a history of mental illness or congenital developmental abnormalities; (7) The participant refuses or is unable to undergo brain MRI and EEG; (8) The participant experienced an acute cerebral infarction within the past three months.

2.2 Neuropsychological tests

All participants underwent a thorough neuropsychological evaluation, which assessed their verbal and visual situational memory, attention, executive function, visuospatial skills, and language proficiency. The evaluation utilized various specific tests, such as the Montreal Cognitive Assessment (MoCA), shape trails test (STT), shape trails test-A (STT-A), and shape trails test-B (STT-B). The STT consisted of two components: shape trails test-A (STT-A) and shape trails test-B (STT-B). All neuropsychological assessments were performed under the guidance of a specialist physician in neurology.

2.3 Acquisition of EEG data

Electroencephalography (EEG) data were collected early in the morning, between 8:00 and 9:30 a.m., with patients awake,

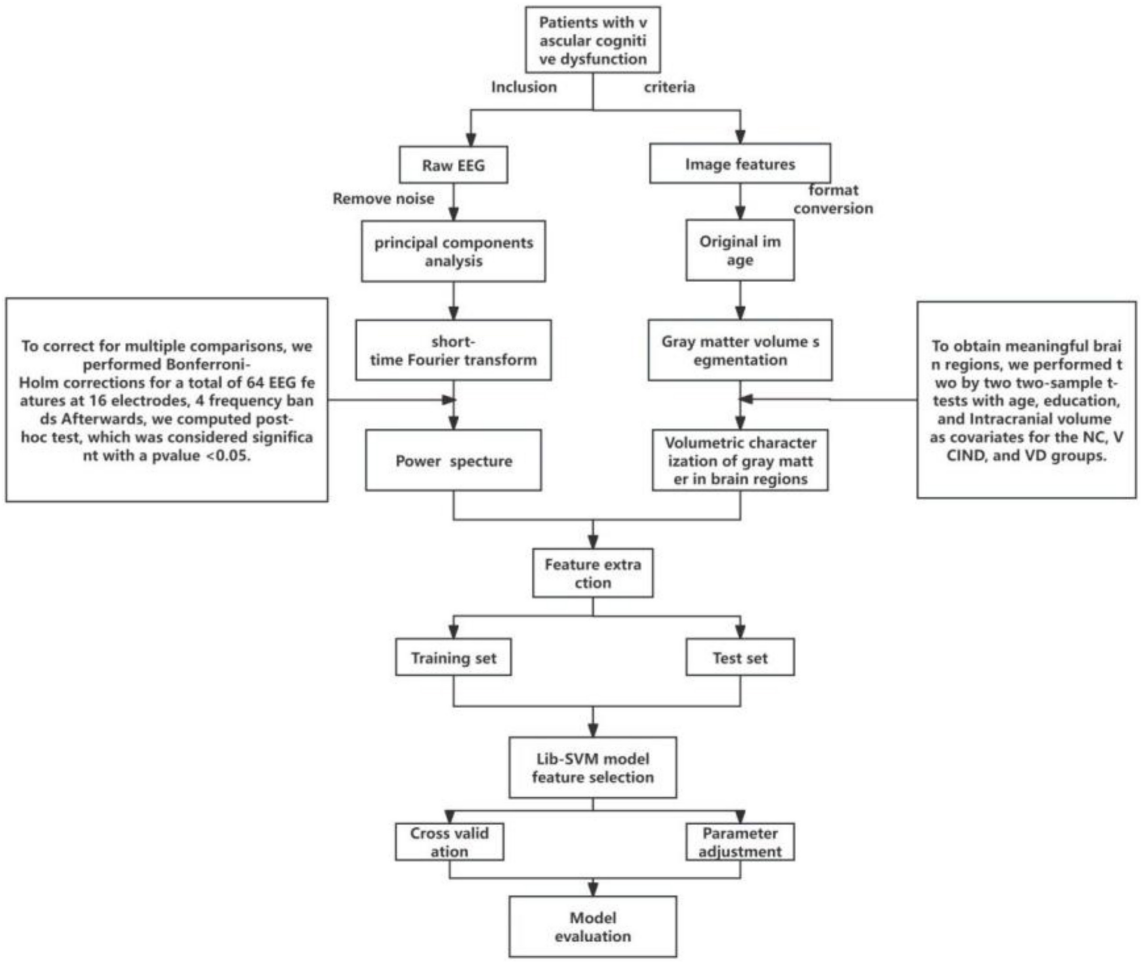

FIGURE 1
Data processing flow chart.

fasted, and in a quiet, closed-eye state. All EEG data were recorded on the same digital EEG system (NicoletOne^{TM} EEG system, Natus Neurology Inc.), and a uniform signal acquisition standard was used to eliminate bias caused by different EEG equipment and parameters. Standardization of signal acquisition was used to eliminate bias caused by different EEG equipment and parameters. We collected data by placing a total of 16 electrodes (including Fp1, Fp2, F7, F8, F3, F4, C3, C4, T3, T4, T5, T6, P3, P4, O1, and O2) according to the international 10–20 standard lead system at a sampling rate of 250 Hz, with the input impedance set to Z > 100 MΩ, and collected the EEG signals for at least 30 min.

2.4 EEG data processing

(1) We used the EEGLAB toolkit[1] based on matlab2019b[2] to localize electrodes, reject useless electrodes, and perform mean-based data re-referencing for all EEG data. (2) Select low frequency 1HZ high frequency 30HZ to filter and save the file; (3) Two or more EEG experts visually analyze the data and remove bad segments and artifacts; (4) Run the EEGLAB independent component analysis (ICA) toolbox to analyze the data for principal components and remove ICA-unusable components; (5) Extraction of EEG power spectra in each frequency band based on short-time Fourier transform. (6) Finally, 64 qEEG features (16 channels, 4 frequency bands) were extracted for each patient, and we performed multivariate analysis of covariance (MANCOVA) with age, sex, and education as covariates for the NC, VCIND, and VD groups, followed by multiple comparisons to control for error rates at the level of statistical significance (using Bonferroni-Holm correction), and after Bonferroni-Holm correction, *post-hoc* tests were performed and significance was determined at $p < 0.05$.

2.5 Nuclear magnetic resonance data acquisition

Magnetic resonance imaging (MRI) data acquisition for all subjects was performed on a Philips Achieva 3.0T MRI machine, using an 8-channel head coil, performing routine cranial transverse T1WI sequence scans. Scanning parameters: FOV = 256 mm × 256

1 https://sccn.ucsd.edu/eeglab/download.php
2 https://matlab.vmecum.com/

mm^2, slice thickness = 1 mm, GAP = 0, number of slices = 192, TR/TE/TI = 7/3.2/1,100 ms, 7° flip angle, matrix = 256 × 256.

2.6 Magnetic resonance data processing

We used MRIcron, SPM12 and DPABI software package to analyze the NMR data and calculate the gray matter volume of the whole brain voxel. All of the above were run on MatLab (R2019b). The main steps were as follows: (1) MRIcron software was used to convert the MRI data DICOM files of all participants into NIfTI files; (2) the NIfTI files were imported into CAT12 in SPM12 for segmentation; (3) quality checks were performed, and the segmented gray matter image was smoothed; (4) the smoothed data were imported into DPABI for statistical analysis and image presentation (all gray matter structures were partitioned using Anatomical Automatic Labeling). (5) Using DPABI, the significant brain regions obtained from the Voxel-based morphometry (VBM) analysis were set as regions of interest (ROI), and the gray matter volumes of the ROI were obtained.

2.7 Machine learning feature filtering

In this study, a support vector machine (SVM) model is constructed and the algorithm consists of two main steps: training of the SVM classifier and evaluation of the model. We divided the 83 samples into a training set and a test set at a ratio of 8:2 to ensure the generalization performance of the model. In the model of the NC group with the VCIND group, 24 NC participants and 26 patients of the VCIND group were randomly selected as the training set to build the SVM model, and the remaining 12 were used as the test set; in the NC group and VD group model, 24 NC participants and 17 VD group patients were selected at random as the training set to build the SVM model, and the remaining 10 were used as the test set; and in the VCIND group and VD group model, 26 VCIND patients and 17 VD patients were selected at random as the training set, and the remaining 10 patients were used as the test set. In this study, we performed quantitative electroencephalogram (qEEG) power spectrum analysis and VBM analysis on the test sets of the NC group vs. VCIND group, the NC group vs. VD group, and the VCIND group vs. VD group, and we selected statistically significant ($p < 0.05$) data obtained from two-way comparisons as categorical features (qEEG power spectra and volume of brain area corresponding to gray matter atrophy).

Then the LibSVM toolbox[3] in MATLAB is used for support vector machine classification, the model has two key parameters: the kernel function and the regularization parameter, to optimize the model's performance, we chose the radial basis function as the kernel function and used the grid search method in quintuple cross-validation to determine the regularization parameter. We used the model on the training set to predict the diagnostic results on the test set and evaluated the predictive ability of the model using the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC-ROC). This approach helps to prevent overfitting of the model on the training set and thus allows for a more accurate assessment of the generalization ability of the model.

3 https://www.csie.ntu.edu.tw/$\sim$cjlin/libsvm/

2.8 Data analysis

SPSS version 21 was used to analyze all clinical and demographic data between groups. Count data are presented as case numbers (proportion), and Fisher's exact test was used to analyze participant demographics. Normally distributed data are presented as mean ± standard deviation, whereas non-normally distributed data are presented as M (Q1, Q3). Normally distributed data were analyzed by one-way analysis of variance (ANOVA), and the least significant difference was used for *post-hoc* testing. Non-normally distributed data were tested using the Kruskal-Wallis H test, an independent-samples non-parametric test ($p < 0.05$ was regarded as statistically significant). All MRI image data were analyzed using DPABI. Age, sex, education level, and total brain volume were used as covariates, and the permutation test was used to correct for multiple comparisons to analyze gray matter atrophy changes in participants.

3 Results

3.1 Demographic and clinical characteristics

The study included 83 subjects, and Table 1 displays their demographic characteristics. The three patient groups differed significantly in age, education level, history of hypertension, and level of cognitive impairment ($P < 0.05$).

3.2 Results of sMRI

To reduce confounding, we used patient age, sex, education, and intracranial volume as covariates and corrected for multiple comparisons using the permutation test to analyze changes in gray matter atrophy between participants. In our study, VBM analysis showed significant differences only in gray matter in the Putamen_L, Caudate_L, and Thalamus_R regions when comparing the NC group with the VCIND group (as shown in Figure 2 and Table 2), but differences in more extensive gray matter atrophy were seen when comparing the VCIND group with the VD group and the NC group with the VD group. In the comparison between the VCIND group and the VD group, it showed atrophy in 18 relevant brain regions including Fusiform_L, Cerebelum_6_L, Cerebelum_4_5_R, Fusiform_R, Lingual_R, Cerebelum_4_5_L, Cerebelum_6_R, and so on (as shown in Figure 3 and Table 2); while the comparison between NC and VD groups showed atrophy of 25 brain regions including Thalamus_L, Thalamus_R, Fusiform_L, Olfactory_L,

TABLE 1 Sample demographic and clinical characteristic.

	NC (n = 31)	VCIND (n = 32)	VD (n = 21)	F	P
Sex (male)%	60.1	60.7	53	\	0.089
Age	54.84 ± 7.82	59.41 ± 7.35	60.67 ± 10.93	3.586	0.032*
Education	10.53 ± 3.35	8.91 ± 3.55	7.24 ± 3.37	5.829	< 0.01**
Hypertension	5	21	13	20.232	< 0.01**
Coronary heart disease	2	3	2	0.092	0.912
Atrial fibrillation	2	0	0	0.056	0.946
Diabetes	8	11	6	2.311	0.106
Valvular heart disease	0	2	2	0.659	0.520
Smoking	12	10	6	0.690	0.505
MoCA	26 ± 2.4	22 ± 1.3	18.5 ± 4.4	\	< 0.01**
STT-A	45.6 ± 27.1	132.5 ± 3.3	181.7 ± 90.05		0.028*
STT-B	76.1 ± 38.4	157 ± 2.0	200.5 ± 2.2	\	< 0.01**

NC, healthy controls; VCIND, vascular cognitive impairment with no dementia; VD, vascular dementia; *$p < 0.05$; **$p < 0.01$.

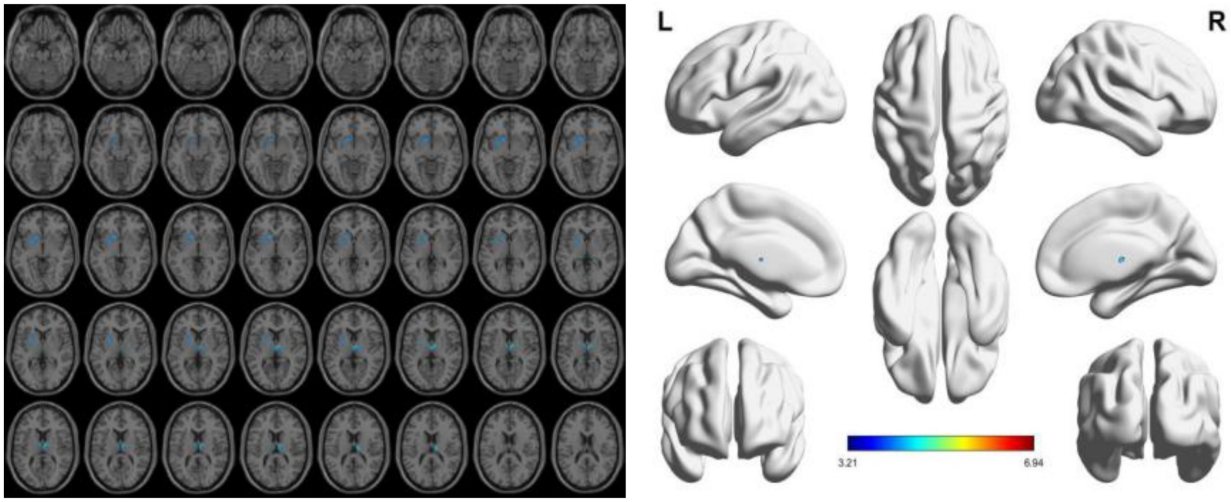

FIGURE 2
The presence of gray matter atrophy in the VCIDS group compared to the NC group, indicated in blue, with a statistically significant difference ($p < 0.05$).

Cerebelum_6_L, Cerebelum_4_5_R, Fusiform_R, and Lingual_R (as shown in Figure 4 and Table 2).

3.3 EEG analysis results

In our experiment, the VCIND group exhibited an increase in theta power in the O2 region and a decrease in beta power in the O1-O2 region compared to the NC group. Three EEG power spectra were statistically significant: the T3-O1 (Alpha1/Alpha2), O2 (Beta1), and O2 (Theta) waves. As for the comparison between the VD and VCIND groups, in addition to the power changes in the O1-O2 region, it also showed an increase in theta in the frontal and parietal lobes and a higher delta power in the F3-F4 region, where the theta difference was most pronounced, and there were a total of four power spectral features with statistically significant differences, namely F4 (delta), O1-O2 (theta), T4 (beta2), and O2 (theta/gamma);The comparison of the NC and VD groups revealed significant differences in six power spectra: P3 (Theta), F3 (Delta), O1 (Alpha2), P4 (Theta/gamma), O2 (Alpha1/Alpha2), and O1-O2 (Beta1). Refer to Figure 5 and Table 2 for more details.

3.4 Feature extraction and selection

Based on the results of the VBM analysis, we labeled voxels suggesting statistical significance, calculated the volume of brain regions in their areas, and analyzed them (see Table 2 for details). We believe that since some features are useless, irrelevant or redundant for classification, too many features can lead to "overfitting," so eliminating useless features and selecting meaningful ones not only simplifies the classification model, but also improves the classification accuracy. In the training set, we selected 3 power spectral features and 2 sMRI

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TABLE 2 Feature extraction and selection.

	NC (n = 31)	VCIND (n = 32)	VD (n = 21)	p
Intracranial volume	1,319.24 ± 136.50	1,331.75 ± 169.48	1,358.54 ± 151.86	0.667
Gray matter volume	549.41 ± 42.43	533.39 ± 54.83	494.82 ± 58.84	0.002**
White matter volume	470.39 ± 44.78	473.00 ± 62.44	428.33 ± 70.52	0.017*
Cerebelum_Crus2_L[bc]	2.70 ± 0.76	2.82 ± 0.76	2.37 ± 0.96	0.133
Cerebelum_8_L[c]	3.11 ± 1.03	3.18 ± 0.90	2.53 ± 1.07	0.051
Cerebelum_6_L[bc]	4.80 ± 0.48	4.71 ± 0.61	4.36 ± 0.63	0.023*
Fusiform_L[bc]	4.39 ± 0.43	4.24 ± 0.51	3.86 ± 0.52	0.001**
Thalamus_R[abc]	5.55 ± 0.47	5.57 ± 0.78	4.50 ± 0.82	0.000**
Thalamus_L[bc]	5.24 ± 0.40	5.30 ± 0.77	4.46 ± 0.95	0.000**
Cerebelum_6_R[bc]	4.60 ± 0.57	4.56 ± 0.62	4.10 ± 0.57	0.007**
Lingual_R[bc]	3.26 ± 0.36	3.22 ± 0.34	2.98 ± 0.37	0.013*
Cerebelum_4_5_R[bc]	4.74 ± 0.58	4.59 ± 0.71	4.39 ± 0.67	0.179
Cerebelum_4_5_L[bc]	4.26 ± 0.48	4.18 ± 0.63	3.91 ± 0.60	0.089
Fusiform_R[bc]	4.37 ± 0.54	4.26 ± 0.48	3.95 ± 0.59	0.021*
Lingual_L[bc]	3.41 ± 0.33	3.35 ± 0.34	3.16 ± 0.45	0.053
ParaHippocampal_R[bc]	4.43 ± 0.49	4.33 ± 0.46	4.03 ± 0.50	0.015*
Hippocampus_R[c]	4.97 ± 0.46	4.94 ± 0.49	4.30 ± 0.56	0.000**
Hippocampus_L[c]	5.10 ± 0.50	5.00 ± 0.56	4.40 ± 0.64	0.000**
Cingulum_Ant_L[bc]	3.82 ± 0.48	3.74 ± 0.51	3.47 ± 0.60	0.062
Olfactory_L[c]	5.43 ± 0.74	5.26 ± 0.69	4.83 ± 0.85	0.022*
Temporal_Inf_L[bc]	3.84 ± 0.39	3.81 ± 0.43	3.41 ± 0.58	0.002**
ParaHippocampal_L[bc]	4.11 ± 0.40	4.07 ± 0.41	3.87 ± 0.52	0.123
Amygdala_R[c]	5.74 ± 0.58	5.67 ± 0.61	5.16 ± 0.69	0.003**
Amygdala_L[c]	6.39 ± 0.67	6.29 ± 0.71	5.66 ± 0.88	0.002**
Rectus_R[bc]	4.26 ± 0.55	4.21 ± 0.55	3.86 ± 0.59	0.032*
Olfactory_R[bc]	5.49 ± 0.68	5.37 ± 0.69	4.99 ± 0.89	0.057
Vermis_4_5[bc]	3.36 ± 0.37	3.12 ± 0.44	3.11 ± 0.44	0.036*
Insula_L[c]	4.76 ± 0.53	4.72 ± 0.50	4.27 ± 0.69	0.006**
Putamen_L[a]	5.89 ± 0.65	5.94 ± 0.69	5.39 ± 1.12	0.038*
Caudate_L[a]	4.91 ± 0.70	5.06 ± 0.93	4.63 ± 1.30	0.288
Theta[abc]	0.23 ± 0.02	0.18 ± 0.02	0.31 ± 0.0	< 0.01**
Delta[bc]	0.41 ± 0.05	0.14 ± 0.03	0.26 ± 0.17	0.020*
Alpha2[c]	0.20 ± 0.01	0.21 ± 0.17	0.21 ± 0.29	0.023*
Theta/gamma[bc]	0.14 ± 0.12	0.24 ± 0.05	0.17 ± 0.10	0.044*
Alpha1/Alpha2[ac]	0.37 ± 0.28	0.17 ± 0.21	0.22 ± 0.17	0.032*
Beta1[ac]	0.23 ± 0.14	0.20 ± 0.08	0.30 ± 0.07	0.018*
Beta2[bc]	0.31 ± 0.22	0.11 ± 0.22	0.28 ± 0.12	0.007*

[a]Denotes relevant brain regions with significant gray matter atrophy or power spectra with significant differences in the comparison between the NC and VCIND groups.
[b]Denotes relevant brain regions with significant gray matter atrophy or power spectra with significant differences in the comparison between the VCIND and VD groups.
[c]Denotes relevant brain regions with significant gray matter atrophy or power spectra with significant differences in the comparison between the NC and VD groups.
*$p < 0.05$; **$p < 0.01$.

features that were statistically significant in the NC group compared with the VCIND group (see Table 2 for details, the upper right corner is labeled as a); 4 power spectral features and 11 sMRI features that were statistically significant in the VCIND group compared with the VD group (see Table 2 for details, the upper right corner is labeled as b); 6 power spectral features and 16 sMRI features that were statistically significant in the NC group compared with the VD group (see Table 2 for details, the upper right corner is labeled as c).

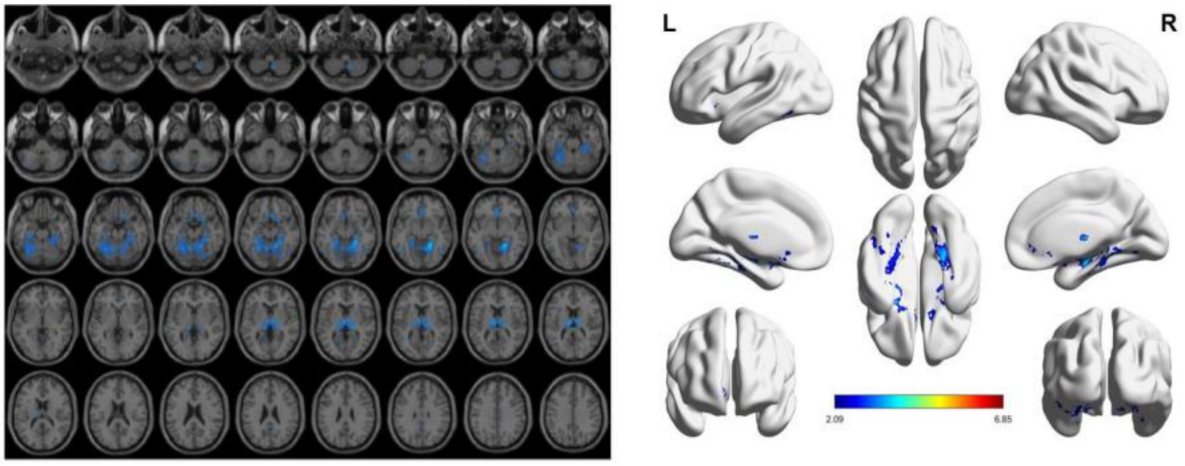

FIGURE 3
The presence of gray matter atrophy in the VD group compared to the VCIND group, indicated in blue, with a statistically significant difference ($p < 0.05$).

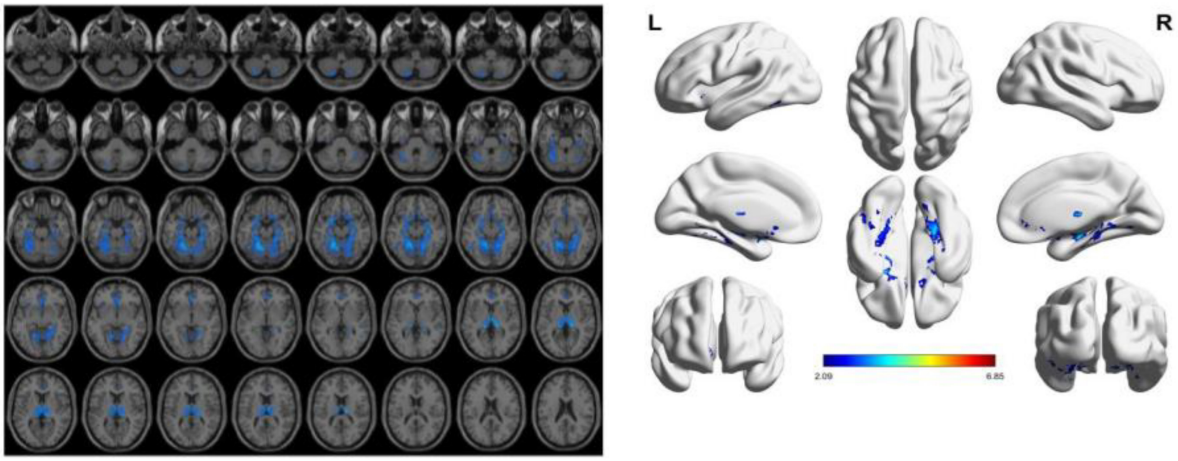

FIGURE 4
The presence of gray matter atrophy in the VD group compared to the NC group, indicated in blue, with a statistically significant difference ($p < 0.05$).

3.5 Machine learning models

Our study shows that sMRI has better classification ability than qEEG in distinguishing VD from cognitively normal people. The area under the ROC curve of the sMRI-based support vector machine learning model is AUC = 0.90, and the area under the ROC curve of the machine learning classification model based on the qEEG features is AUC = 0.82. The "composite marker" model that combines sMRI and qEEG achieves the best classification results, with an area under the ROC curve of AUC = 0.98 (Table 3 and Figures 6A–C). When distinguishing between VD and VCIND populations, sMRI demonstrated better classification ability than qEEG. The machine learning model based on sMRI had an area under the ROC curve of AUC = 0.80, while the machine learning classification model based on qEEG features had an AUC of only 0.64. The composite marker model, which combined sMRI and qEEG, achieved optimal classification results with an ROC curve AUC of 0.92 (Table 3 and Figures 6D–F). When using only sMRI or qEEG features to differentiate between VCIND patients and NC, both methods had poor classification ability, with an area under the ROC curve of 0.56 for sMRI features and 0.54 for qEEG features. However, the "composite marker" model, which combines both sMRI and qEEG features, achieved relatively good classification ability with an area under the ROC curve of 0.72 (Table 3 and Figures 6G–I).

4 Discussion

This study applies a machine learning method that combines sMRI with qEEG to compare the classification ability of single-mode markers of qEEG or sMRI and composite markers of qEEG+sMRI for VCIND and VD. We found that EEG performed well in differentiating between VD and NC, with an AUC score

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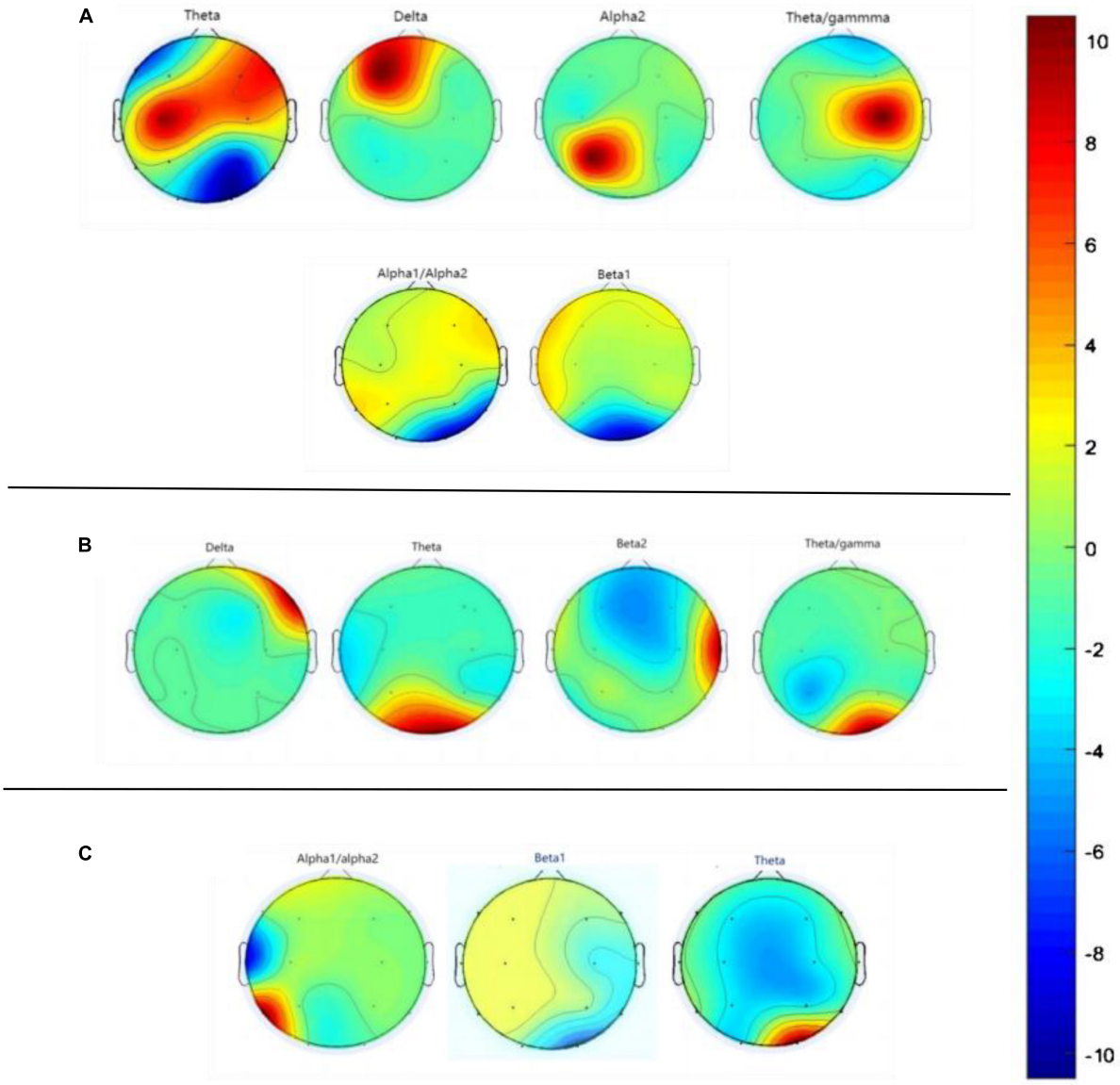

FIGURE 5
Graph **(A)** represents the difference in EEG power spectra between NC and VD groups, graph **(B)** represents the difference in EEG power spectra between VD and VCIND groups, and graph **(C)** labels the difference in EEG power spectra between VCIND and NC groups.

TABLE 3 **Projected results.**

	Feature	Accuracy%	Sensitivity%	Specificity%	AUC
VD vs. HC	sMRI	82.10	83.33	77.34	0.9
	qEEG	64.28	58.21	71.28	0.82
	sMRI+qEEG	86.28	88.31	79.79	0.98
VD vs. VCIND	sMRI	62.31	60.23	68.36	0.8
	qEEG	60.14	57.28	61.24	0.64
	sMRI+qEEG	84.10	82.35	74.38	0.92
VCIND vs. HC	sMRI	54.10	53.18	55.85	0.56
	qEEG	51.03	50.64	53.18	0.54
	sMRI+qEEG	73.85	69.24	70.01	0.72

NC, healthy controls; VCIND, vascular cognitive impairment with no dementia; VD, vascular dementia.

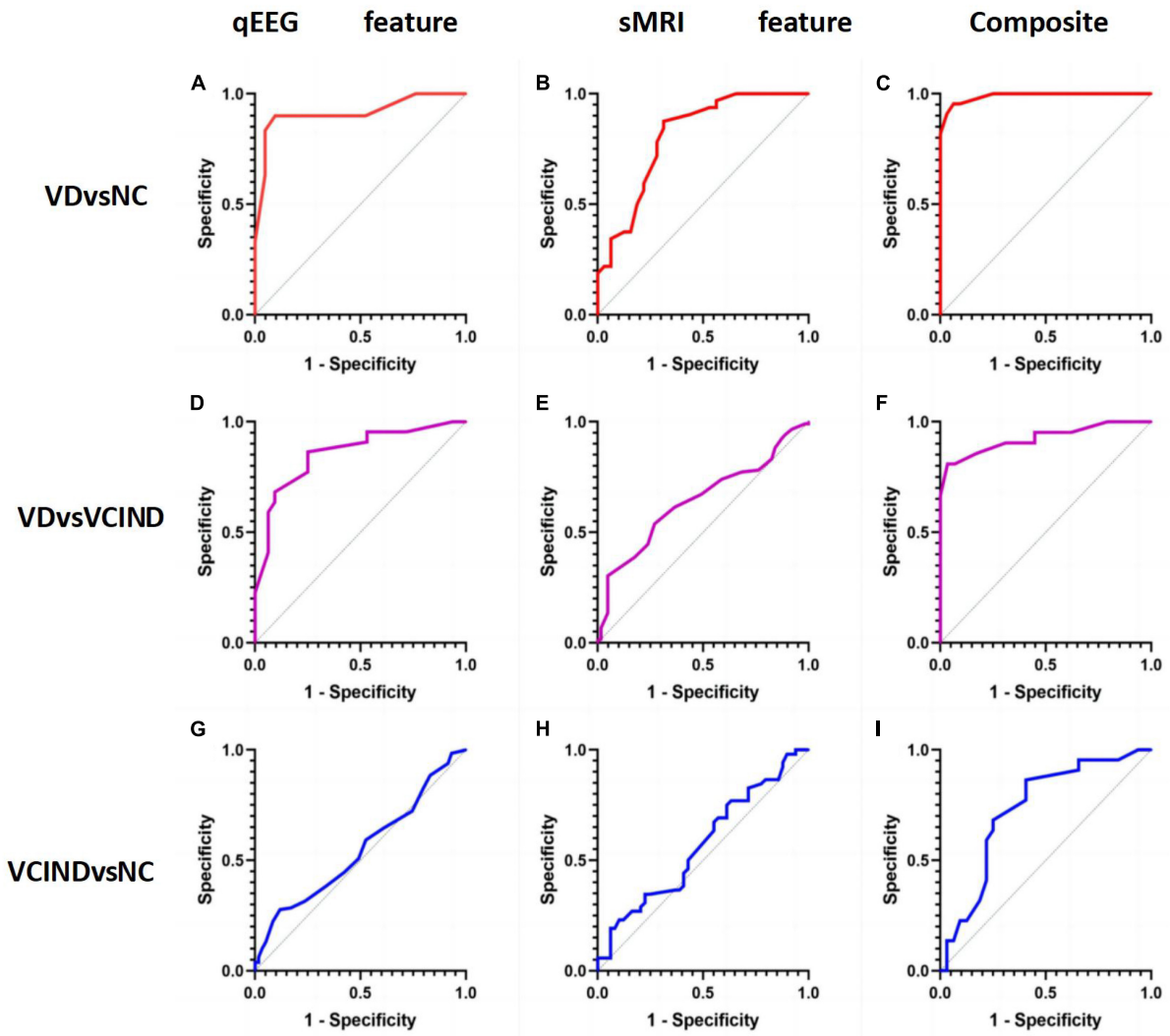

FIGURE 6
(A) shows the accuracy of distinguishing VD group from NC group by qEEG feature model in support vector machine machine learning model; **(B)** shows the accuracy of distinguishing VD group from NC group by sMRI feature model in support vector machine machine learning model; **(C)** shows the accuracy of distinguishing VD group from NC group by composite markers to distinguish the accuracy of VD group from NC group; **(D)** shows the accuracy of distinguishing VD group from VCIND group by qEEG feature model in support vector machine machine learning model; **(E)** shows the accuracy of distinguishing VD group from VCIND group by sMRI feature model in the support vector machine machine learning model; **(F)** shows the accuracy of distinguishing VD group from VCIND group by composite markers in the support vector machine machine learning model; **(G)** shows the accuracy of distinguishing VCIND group from NC group by qEEG feature model in the support vector machine machine learning model; **(H)** shows the accuracy of distinguishing VCIND group from NC group by sMRI feature model in the support vector machine machine learning model. **(H)** represents the accuracy of distinguishing VCIND group from NC group by sMRI feature model in the machine learning model of support vector machine. **(I)** shows the accuracy of distinguishing VCIND group from NC group by composite markers in the support vector machine machine learning model.

of 0.82. One of the strongest predictors was elevated theta power, and this effect was similarly demonstrated in several regions, such as P3, O1, and O2 electrodes. In contrast, the EEG model exhibited lower accuracy in classifying the VCIND group compared to the NC group, with an AUC score of only 0.54. The optimal EEG features for classification differed from those used to differentiate between VD-NC, mainly in the form of an increase in theta power at the O2 electrode and a decrease in Beta power in the O1-O2 region, as was also found in a previous study (Babiloni et al., 2021). Throughout history, fluctuations in theta power have been associated with learning and memory (Herweg et al., 2020). Theta power has been linked to the exchange of information between hippocampus, entorhinal, perirhinal, and parahippocampal cortices and the memory of constituent events (Mayes et al., 2007). Previous studies have confirmed that an increase in theta power correlates with the severity of vascular injury (Herweg and Kahana, 2018). Additionally, a decrease in beta power has been found to correlate with dementia (Giustiniani et al., 2023). The neurophysiologic changes associated with VCI are primarily characterized by damage to the neurovascular unit (NVU). The neurovascular unit (NVU) is a complex anatomical structure composed of blood-brain barrier-specialized endothelial cells surrounded by the basal lamina and interacting with neurons, astrocytes, microglia, pericytes, and extracellular matrix (Iadecola,

2017; Zanon Zotin et al., 2021; Rundek et al., 2022). Damage to the NVU in the early pathogenic stages may lead to impaired regulation of cerebral blood flow, vascular permeability, immune transport, and waste removal. Reduced perfusion flow to brain tissue and vascular risk factors, such as hyperlipidemia, hyperglycemia, and hyperuricemia, due to intracranial atherosclerosis, stenosis, and occlusion, have superimposed effects that significantly increase the production of pro-inflammatory molecules and cytokines. This leads to increased neuroinflammation, damage to axons, and consequent slowing of neural conduction, ultimately resulting in altered rhythms of electrophysiological activity in the brain (Torres-Simón et al., 2022). Previous studies have demonstrated that an increase in slow-wave activity (delta and theta) and a decrease in fast-wave activity (alpha and beta) reflects the loss of synaptic innervation during the progression of the disease (Musaeus et al., 2018). Our experiments have yielded similar results. Theta power is widely regarded as the most reliable predictor of patient status. An increase in theta is one of the earliest neurophysiological changes observed in mild cognitive impairment (Chino-Vilca et al., 2022). In our study, the most significant difference in theta was observed between the VCIND group and the NC in the posterior head region, specifically O1-O2. In addition to the posterior head region, the VD group with the VCIND group also showed increased theta power in the frontal and parietal lobes and higher delta power in the F3-F4 region. These changes may reflect broader cerebral cortex changes during the later stages of VCI. The delta power changes occur at a later stage.

In the present study, we also evaluated the early predictive value of qEEG and sMRI in patients with VCI. In the qEEG study, we found that increased theta power in the posterior head showed the best results in differentiating the VD-NC group, suggesting that theta power may be an early clinical manifestation of neurodegeneration, and Chen et al. (2008) also concluded that changes in theta power are associated with dysfunction of brain networks, and that the elevation of theta power in fMRI in corresponding brain regions is inversely proportional to the BOLD signal (Laufs, 2008), which further supports our view. In addition, animal studies have shown that theta waves are generated in the hippocampus and are associated with functional changes in the hippocampus (Fox et al., 1986). Accordingly, we propose that changes in theta power in the early stages of vascular cognitive impairment may be a marker of hippocampal impairment and disruption of functional brain network connectivity in patients with VCI. Cognitive impairment in VCI has long been reported in previous studies (Hajjar et al., 2015; Boomsma et al., 2022), mainly including executive function (Hajjar et al., 2009; Degen et al., 2016), visuospatial function (Degen et al., 2016), and situational memory (Song et al., 2020), and these cognitive alterations are inextricably linked to structural changes in the brain of VCI patients. In our experiments, the sMRI model outperformed EEG in distinguishing VD from NC and VCIND participants. Both achieved high classification accuracy with VD vs. HC: AUC = 0.9 and VD vs. VCIND: AUC = 0.8. However, sMRI performed poorly in distinguishing between VCIND and NC participants (AUC = 0). In the VCIND population, model features only included Putamen_L and Thalamus_R, indicating that extensive gray matter atrophy has not yet developed and structural changes in the brain are not yet evident. This is consistent with previous studies (Frantellizzi et al., 2020). The decrease in gray matter in the thalamic region among VCIND patients may be linked to a decline in executive function, as previously demonstrated by Cao et al. (2010). The VCIND group exhibited impairments in various cognitive domains, ranging from 17 to 66%, with the lowest rate in the Clock Plotting Trial and the highest in the STT-A. Additionally, there were significant reductions in regional cerebral blood flow (rCBF) bilaterally in the thalamus compared to NC. Our EEG model is comparable to previous studies in terms of classification rate (Al-Qazzaz et al., 2018; Torres-Simón et al., 2022), achieving approximately 85–90% accuracy in distinguishing between the VD and NC groups, but only 60% accuracy in distinguishing between the VCIND and NC groups. The better performance of sMRI in categorizing VD versus NC compared with resting-state EEG may demonstrate that anatomical information captured by sMRI features is more sensitive than the neurophysiological information provided by EEG. The study found that models using only EEG or sMRI features had low accuracy in distinguishing between VCIND and NC groups. However, the "composite marker" model, which combined both features, achieved a classification accuracy of 72%. This discovery could potentially lead to earlier detection and intervention in more patients with early, undetectable VCIND, ultimately reducing the growth rate of VD.

Our study combines qEEG with sMRI to build a support vector machine classification model, which not only highlights the advantages in early identification of patients with VCI, but also helps to explore biomarkers with significant differences between patients with VCI and normal subjects. The discovery of these biomarkers may help to understand the biological mechanisms of the disease and may also contribute to the search for potential therapeutic targets for VCI.

Our study has limitations. It is important to note that these limitations do not invalidate the results of our study. We did not follow the participants longitudinally, and we did not validate the predictive power of the "composite marker" model of EEG and sMRI for disease progression in patients with VCI. Future studies should expand the sample size, extract more accurate EEG and sMRI features, and conduct longitudinal studies to clarify the biological features related to the progression of patients with VCI. This will help establish a prediction model for the progression of VCI, accurately identifying and predicting the progression of patients with VCIND in the early stages when symptoms are not significant.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee, Hongqi Hospital, Mudanjiang Medical College. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZL: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. MW: Conceptualization, Investigation, Formal analysis, Visualization, Writing – original draft. CY: Funding acquisition, Resources, Writing – review & editing. ZW: Data curation, Visualization, Writing – original draft. JW: Data curation, Writing – original draft. LC: Data curation, Visualization, Writing – original draft. WZ: Funding acquisition, Resources, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A glimpse into the future: revealing the key factors for survival in cognitively impaired patients

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Background: Drawing on prospective data from the National Health and Nutrition Examination Survey (NHANES), our goal was to construct and validate a 5-year survival prediction model for individuals with cognitive impairment (CI).

Methods: This study entailed a prospective cohort design utilizing information from the 2011–2014 NHANES dataset, encompassing individuals aged 40 years or older, with updated mortality status as of December 31, 2019. Predictive models within the derivation and validation cohorts were assessed using logistic proportional risk regression, column-line plots, and least absolute shrinkage and selection operator (LASSO) binomial regression models.

Results: The study enrolled a total of 1,439 participants (677 men, mean age 69.75 ± 6.71 years), with the derivation and validation cohorts consisting of 1,007 (538 men) and 432 (239 men) individuals, respectively. The 5-year mortality rate stood at 16.12% ($n = 232$). We devised a 5-item column-line graphical model incorporating age, race, stroke, cardiovascular disease (CVD), and blood urea nitrogen (BUN). The model exhibited an area under the curve (AUC) of 0.772 with satisfactory calibration. Internal validation demonstrated that the column-line graph model displayed strong discrimination, yielding an AUC of 0.733, and exhibited good calibration.

Conclusion: To sum up, our study successfully developed and internally validated a 5-item nomogram integrating age, race, stroke, cardiovascular disease, and blood urea nitrogen. This nomogram exhibited robust predictive performance for 5-year mortality in individuals with CI, offering a valuable tool for prognostic evaluation and personalized care planning.

KEYWORDS

cognitive impairment, NHANES, mortality, nomogram, prospective studies

Introduction

Cognitive functioning encompasses a wide array of functions, spanning verbal and non-verbal memory, attention, executive functioning, language, and motor skills, where impairments often manifest across multiple cognitive domains, affecting language, computation, judgment, memory, and executive functioning. These deficits can lead to behavioral, emotional, and personality abnormalities, ultimately diminishing work capacity and daily task performance, imposing significant financial and psychological strains on families and society (Gavelin et al., 2021; Chehrehnegar et al., 2022; Huang et al., 2022).

The repercussions of cognitive impairment (CI) extend beyond individual health, impacting independence, productivity, and necessitating substantial social, medical, and financial resources. With increasing life expectancies, age-related cognitive decline emerges as a pressing challenge for older individuals globally, underscoring the critical public health importance of cognitive well-being (Hebert et al., 2013; Knapp and Wong, 2020). The early identification of high-risk individuals and timely interventions are pivotal in mitigating premature mortality among older persons with cognitive impairment. Therefore, the imperative lies in the development of mortality prediction models tailored to this demographic, an area where existing studies have been hindered by limited sample sizes, follow-up durations, and generalizability issues to the broader population of cognitively impaired individuals. Notably, a dearth of population-based research exists in constructing mortality risk prediction models for older individuals with cognitive impairment (Xing et al., 2023). Nomogram is a visual statistical prognostic tool that is widely used in clinical prognostic evaluation by calculating scores for potential predictors (Hu et al., 2021).

This study aims to establish and validate a 5-year all-cause mortality prediction map for older individuals with CI based on a nationally representative U.S. population, furnishing a valuable reference for averting and managing adverse outcomes in this demographic. Moreover, to enhance the elucidation of the objectives and theoretical model outlined in this paper, a conceptual framework (Figure 1) was developed. This framework serves to visually represent the relationships and key components under investigation, providing a structured overview of the study's aims and the hypothesized model being explored.

Methods

Study design and population

NHANES is an ongoing research project that provides estimates of the population's nutrition and health status in the United States (Pan et al., 2024). It uses a stratified, multi-stage probability design to recruit a representative sample of the American population. Data is collected through structured interviews at home, health screenings at mobile health centers, and laboratory sample analysis (Pan et al., 2023). This study analyzed data from the National Health and Nutrition Examination Survey (NHANES) from 2011 to 2014, which includes information on cognitive function. After screening, a total of 1,439 participants with CI were included. Figure 2 illustrates the flow chart of the study.

Assessment of cognitive performance

In the 2011–2014 NHANES survey, the assessment of cognitive function in participants aged 60 years or older was conducted through a series of tests. At the end of a private face-to-face interview at a mobile examination center (MEC interview) (Fillenbaum and Mohs, 2023), trained interviewers administered these tests. Three tests were used to evaluate cognitive function: the Consortium to Establish a Registry for Alzheimer's Disease Word List (CERAD W-L) subtest, which assesses immediate and delayed recall of new verbal information (Desai et al., 2022); the Animal Fluency Test (AFT), which measures categorical verbal fluency (Zhao et al., 2013); and the Digit Symbol Substitution Test (DSST), which evaluates processing speed, sustained attention, and working memory (Liu et al., 2021). These tests have been widely used in mass screening efforts and clinical studies (Walsh et al., 2022; Liang and Zhang, 2024). While cognitive assessments cannot replace a clinical diagnosis based on examination, they are valuable in study cognitive function in relation to various diseases and risk factors.

The CERAD W-L assesses immediate and delayed learning ability for new verbal information. This test involves three consecutive learning trials and a delayed recall test (Luck et al., 2018). During the learning trials, participants are asked to read aloud 10 unrelated words, presented one at a time. They are then asked to recall as many words as possible immediately after each presentation. The order of the words changes in each trial. Participants who cannot read are instructed to repeat each

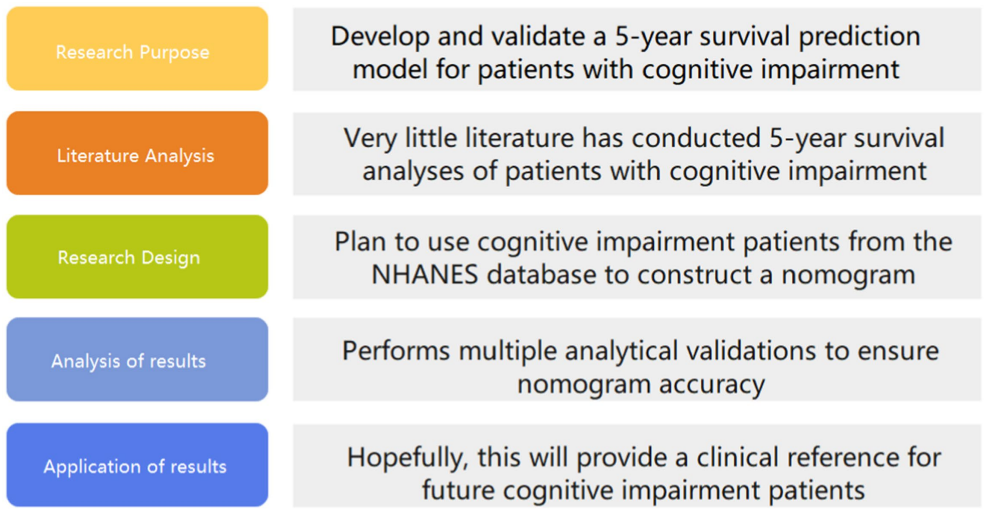

FIGURE 1
Framework diagram of the study.

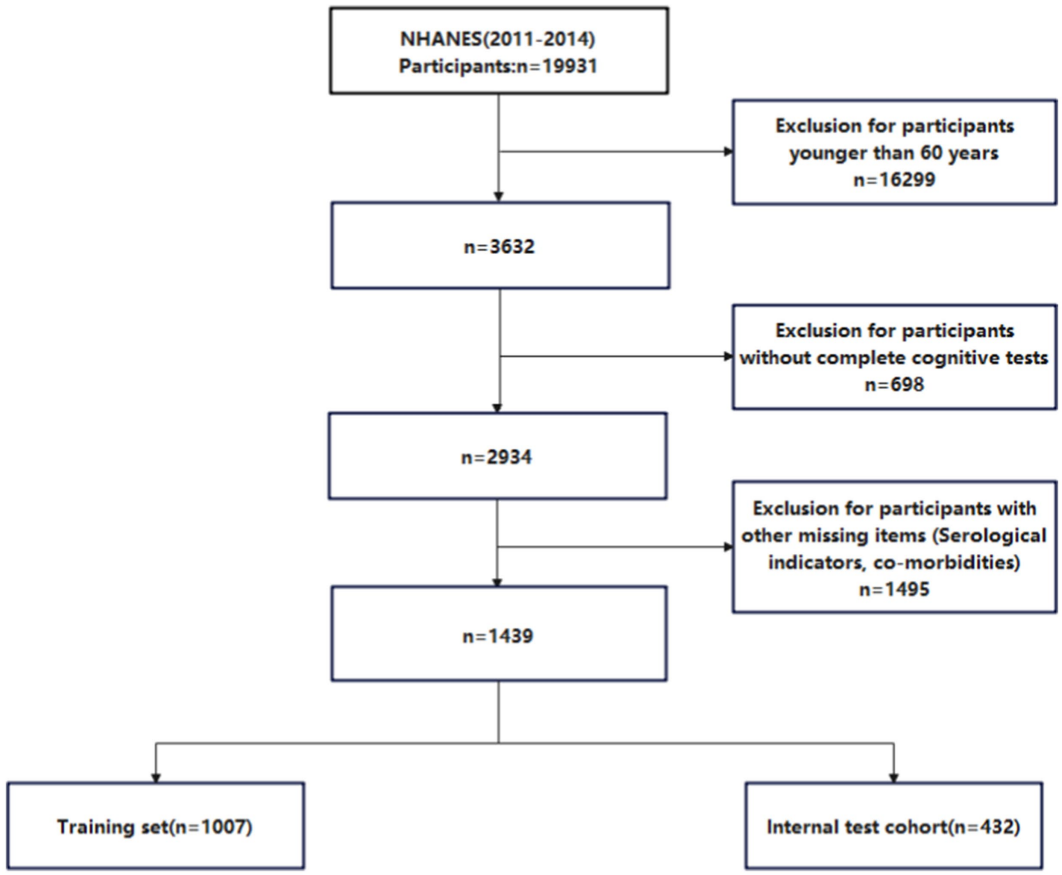

FIGURE 2
Low chart for participant screening.

word after it is read out by the interviewer. The delayed recall test takes place after the other cognitive exercises, approximately 8–10 min from the start of the word learning trials (Casagrande et al., 2021).

The AFT assesses categorical verbal fluency, a component of executive function. It requires awareness of animal names, regardless of cultural context, and is not dependent on formal education (Prince et al., 2003). The test has been shown to distinguish between individuals with CI and those with normal cognitive function. Participants are asked to name as many animals as possible in 1 min, and each named animal receives a point (Mcdonnell et al., 2020). NHANES participants first complete a practice test of naming three items of clothing. Those who cannot name three articles of clothing do not proceed with the Animal Fluency Test.

The DSST is a performance module of the Wechsler Adult Intelligence Scale (WAIS III). It is designed to assess processing speed, sustained attention, and working memory (Song et al., 2023). The exercise is conducted using a paper form that has a key at the top containing 9 numbers paired with symbols. Participants are given 2 min to copy the corresponding symbols into the 133 boxes that are adjacent to the numbers (Jiang et al., 2023). The score is calculated based on the total number of correct matches. In NHANES, a sample practice test is administered prior to the main test, allowing participants to familiarize themselves with the task. Participants who were unable to correctly match the symbols with the numbers during the pretest practice were not continued.

In this study, the cognitive scores ranges for CERAD, AFT, and DSST were 0–30, 3–40, and 0–105, respectively. Due to the absence of a gold standard for identifying CI using these three tests, we conducted a comprehensive analysis of previous studies (Timmers et al., 2019; Dong et al., 2020; Shi et al., 2023). To minimize the influence of age on cognitive function, participants were divided into three age groups: 60–69 years, 70–79 years, and 80 years or older. We utilized the lowest quartile of test scores in each group as the threshold for defining cognitive impairment. In these three age groups, the lowest quartiles of CERAD scores were 21, 20, and 17, respectively; for AFT, they were 13, 11, and 11; and for DSST, they were 33, 27, and 25. Therefore, participants with CI were identified based on these criteria.

Assessment of covariates

Standardized questionnaires were collected on participants' sociodemographic characteristics, smoking status, diabetes, hypertension, hypercholesterolemia, past diseases and aspirin use. Participants who smoke less than 100 cigarettes in their lifetime are classified as non-smokers, while those who previously smoked more than 100 cigarettes but did not quit are defined as current smokers (Pan et al., 2024). Former smokers were those who used to smoke more than 100 cigarettes but had already quit. Race/ethnicity is classified as Mexican American, other Hispanic, non-Hispanic white,

non-Hispanic black, and other races. Education level in our research is classified as lower than high school (less than 9th grade), high school [include 9-12th grade (general educational development or equivalent)], or college or above (some college or Associate's degree and college graduate or above) (Pan et al., 2023). Marital status is classified into three categories in our researchers, the first being married or living with partners, the second being married, divorced or separated, and the third being unmarried. Poverty income ratio (PIR) scores were defined as less 3, 1–3, and more than 3. It is calculated by dividing the household income by the poverty guidelines of a specific survey year (Song et al., 2023).

Statistical analysis

All statistical analyses were performed using R software (version 4.3.1). The data collected from the NHANES database were randomly divided into training and validation cohorts at a ratio of 7:3, and the variables were compared. Non-normal data were presented as median (interquartile ranges). For categorical variables, the chi-square test or Fisher's exact test was used in the univariate analysis, while the *t*-test or rank-sum test was used for continuous variables (Ning et al., 2023). In the training cohort, multivariate analysis was conducted using the least absolute shrinkage and selection operator (LASSO) logistic regression analysis to identify independent risk factors and construct a prediction nomogram for cognitive impairment. The performance of the nomogram was assessed using receiver operating characteristic (ROC) curve and calibration curve. Additionally, a decision curve analysis (DCA) was performed to determine the net benefit threshold of prediction. Results with a *p*-value of <0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 1,439 participants were recruited based on predefined criteria, with 1,007 individuals allocated to the development group and 432 to the validation group. Table 1 presents baseline characteristics, including demographics, biochemical indices, co-morbidities, duration of hypertension, and medication use.

Predictive model

The candidate predictors initially considered in the model encompassed gender, age, race, education level, marital status, smoking status, diabetes, cardiovascular disease, PIR, hyperlipidemia, high-density lipoprotein levels, depression, sleep disorders, stroke, aspirin usage, along with certain hematological indicators. Through LASSO regression analysis conducted in the training cohort, these predictors were streamlined to 5 key variables. The coefficient profile is depicted in Figure 3A, while Figure 3B showcases a cross-validated error plot of the LASSO regression model. The final model, characterized by regularization and parsimony, identified 5 variables as significant predictors: race, cardiovascular disease (CVD), age, stroke, and blood urea nitrogen (BUN). This refined model, exhibiting a cross-validated error within one standard error of the minimum, underscores the predictive strength of these specific variables in the context of the study.

Development of nomogram

The ultimate logistic model integrated 5 independent predictors (race, CVD, age, stroke, BUN) and was transformed into an easily interpretable nomogram, visually depicted in Figure 4. This column chart comprises 8 axes, with axes 2–6 corresponding to each prognostic factor incorporated in the final model. Each predictor is assigned a distinct weighted score within the nomogram. Axes 7 and 8 signify that as the total score increases, the 5-year risk of mortality in individuals with CI escalates accordingly.

Internal and external validation

Within the training cohort, the c-index value of 0.772 signifies that the model exhibits commendable discriminative capabilities, as illustrated in Figure 5A. The calibration curves, closely aligned with the diagonal, indicate a high level of concordance between the model's predictions and the observed outcomes, as depicted in Figure 6A. Transitioning to the internal test cohort, the model maintains its robust discriminative performance, boasting a c-index of 0.733, as showcased in Figure 5B. Furthermore, the calibration plots demonstrate that the model offers a well-fitted representation of CI in the elderly population, as highlighted in Figure 6B.

The figure below exhibits the DCA curves associated with the nomogram. A high-risk threshold probability signifies the likelihood of notable disparities in the model's predictions when clinicians confront significant shortcomings while employing the nomogram for diagnostic and decision-making tasks. This study underscores that the nomogram yields considerable net advantages for clinical utilization based on its DCA curve representations (Figures 7A,B).

Discussion

Our study aimed to construct and validate a predictive model for 5-year mortality risk among patients with CI using data from the NHANES in the United States. The results underscored the importance of developing targeted prognostic tools for this vulnerable population. The model was built on a cohort of 1,439 participants aged 40 and above, revealing a 5-year mortality rate of 16.12% and highlighting significant health risks associated with CI in older adults. Our approach employed logistic proportional hazards regression and innovative techniques such as bar-line plots and LASSO binary regression models to enhance prediction accuracy. Central to our predictive model were five key variables: age, race, history of stroke, CVD, and BUN. Through rigorous statistical analysis, these factors were identified as critical predictors of mortality risk among CI patients. The resulting nomogram visually represents these predictive factors, demonstrating robust performance with an AUC of 0.772, indicating good discriminative ability. Internal validation further

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TABLE 1 Patient demographics and baseline characteristics.

Characteristic	Cohort		*p*-value
	Training cohort, *N* = 1,007	Internal test cohort, *N* = 432	
Male	538 (53.4%)	239 (55.3%)	0.508
Non-Hispanic White	362 (35.9%)	151 (35.0%)	0.718
Education level			0.305
Less than highschool	393 (39.0%)	182 (42.1%)	
High school	253 (25.1%)	93 (21.5%)	
More than highschool	361 (35.8%)	157 (36.3%)	
Marry status			0.610
Married	532 (52.8%)	217 (50.2%)	
Widowed/Divorced	356 (35.4%)	158 (36.6%)	
Other	119 (11.8%)	57 (13.2%)	
Poverty income ratio			0.986
<1.0	238 (23.6%)	102 (23.6%)	
1.0–3.0	519 (51.5%)	221 (51.2%)	
>3.0	250 (24.8%)	109 (25.2%)	
Smoke			0.775
Never smoker	503 (50.0%)	207 (47.9%)	
Ever smoker	361 (35.8%)	162 (37.5%)	
Current smoker	143 (14.2%)	63 (14.6%)	
Diabetes	308 (30.6%)	123 (28.5%)	0.422
Cardiovascular disease	200 (19.9%)	70 (16.2%)	0.103
Stroke	96 (9.5%)	42 (9.7%)	0.911
Hypertension	657 (65.2%)	280 (64.8%)	0.876
Hypercholesterolaemia	557 (55.3%)	233 (53.9%)	0.630
Depression	860 (85.4%)	367 (85.0%)	0.826
Sleep disorder	106 (10.5%)	50 (11.6%)	0.558
Use of aspirin	812 (80.6%)	347 (80.3%)	0.891
Age	69 (64, 76)	68 (64, 74)	0.062
Albumin	42.0 (40.0, 44.0)	42.0 (40.0, 44.0)	0.297
Alanine aminotransferase	19 (15, 25)	20 (16, 25)	0.194
Aspartate aminotransferase	23 (20, 27)	23 (20, 28)	0.797
Blood urea nitrogen	15 (12, 19)	14 (12, 19)	0.275
Serum Ca	2.35 (2.30, 2.40)	2.35 (2.30, 2.40)	0.548
Creatine Kinase	109 (74, 179)	104 (71, 168)	0.299
Alkaline phosphatase	67 (55, 82)	68 (57, 83)	0.304
Total cholesterol	185 (158, 215)	186 (158, 216)	0.715
Creatinine	86 (72, 103)	81 (68, 102)	0.087
Serum iron	14.0 (10.6, 17.7)	14.3 (10.7, 17.8)	0.678
Serum Phosphorus	1.20 (1.07, 1.32)	1.19 (1.07, 1.30)	0.380
Total bilirubin	10.3 (8.6, 13.7)	11.1 (8.6, 13.7)	0.164
Uric acid	5.60 (4.70, 6.63)	5.50 (4.58, 6.60)	0.153
Triglyceride	129 (89, 183)	121 (82, 179)	0.085
High density lipoprotein	50 (41, 61)	51 (43, 61)	0.163

Frequency (weighted percentages) was presented for categorical variables. Quantitative variables are expressed as median, 25th percentile and 75th percentile.

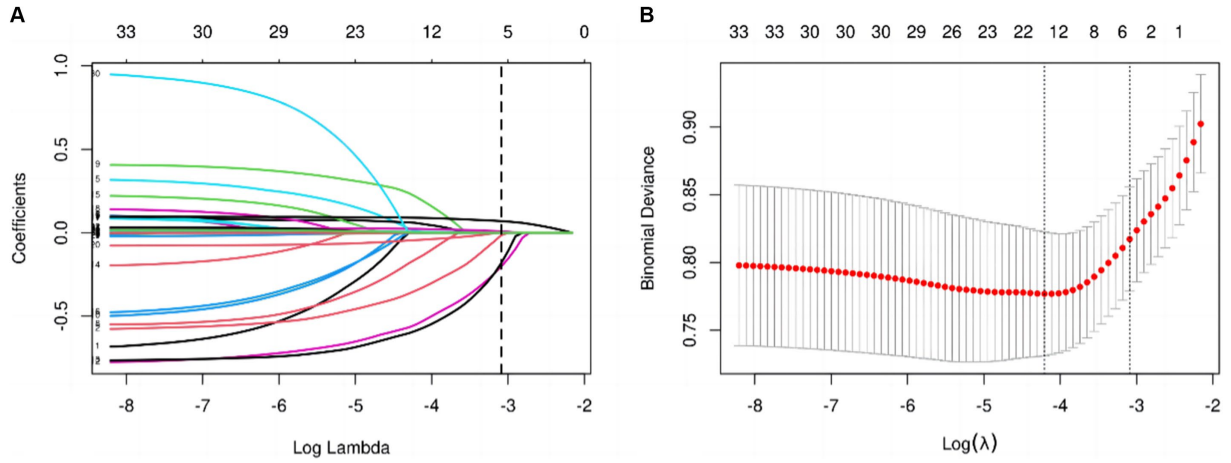

FIGURE 3
(A) LASSO regression coefficient path plot. **(B)** LASSO regression cross-validation plot.

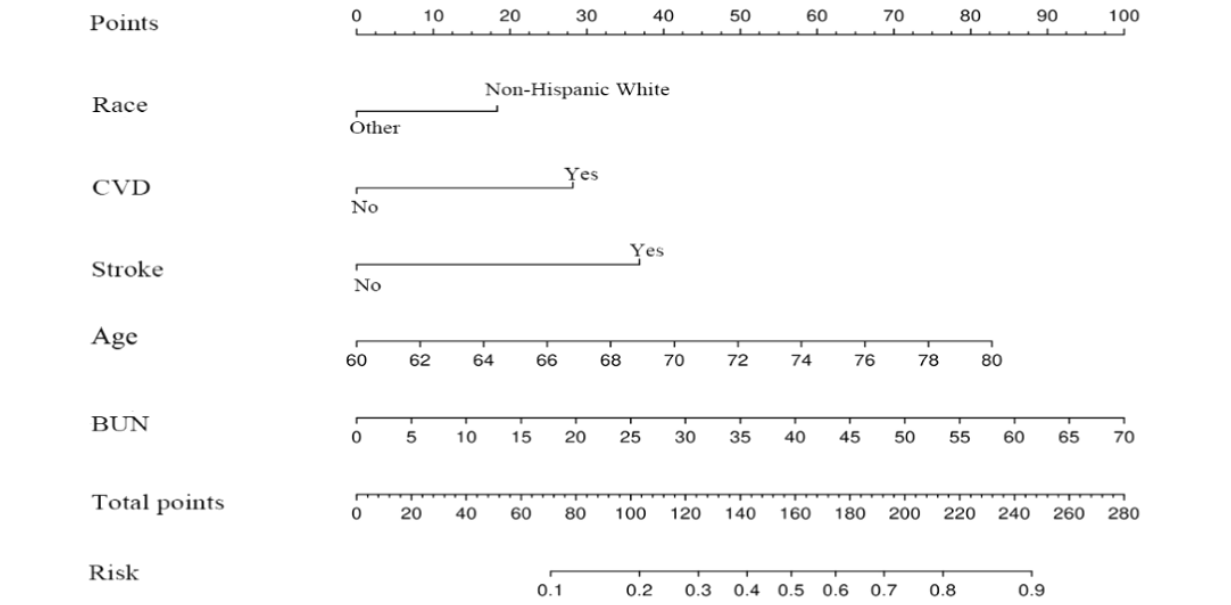

FIGURE 4
Nomogram prediction model.

confirmed the model's reliability with an AUC of 0.733 and satisfactory calibration, affirming its applicability in clinical settings. This nomogram not only enhances risk stratification but also facilitates targeted interventions aimed at improving outcomes for individuals with CI, thereby contributing to more effective healthcare management strategies. Future research could further refine the model's accuracy and explore additional factors to optimize its utility in clinical practice.

In recent years, nomograms have been increasingly used to diagnose and predict a variety of diseases, including cancer (Balachandran et al., 2015), myocardial infarction (Ye et al., 2023), and hypertension (Zhang et al., 2022). The utilization of nomograms serves to simplify the interpretation of pertinent risk factors, aiding both clinicians and patients in navigating the challenges posed by diseases. With the escalating numbers of individuals affected by Alzheimer's disease and hypertension, the development of a universal risk assessment tool tailored to this demographic becomes increasingly crucial. Despite this pressing need, previous research has not produced analogous nomograms. Hence, our study aimed to establish a prognostic nomogram encompassing demographic characteristics and standard laboratory parameters, furnishing essential insights to shape personalized intervention strategies and forecast 5-year mortality rates in patients with CI. A pivotal outcome of our investigation was the internal validation of our model. We observed that the nomogram exhibited a discriminative power exceeding 0.7 in predicting the five-year mortality rates of CI patients. Moreover, the predicted probabilities closely mirrored the actual probabilities along a

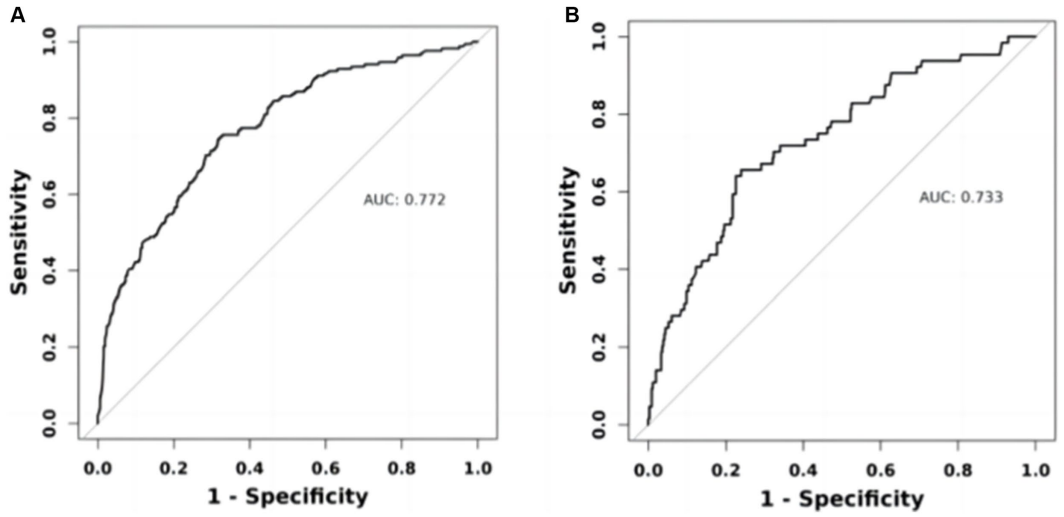

FIGURE 5
ROC curves of the nomogram prediction model. **(A)** Training set ROC curve. **(B)** Internal validation set ROC curve.

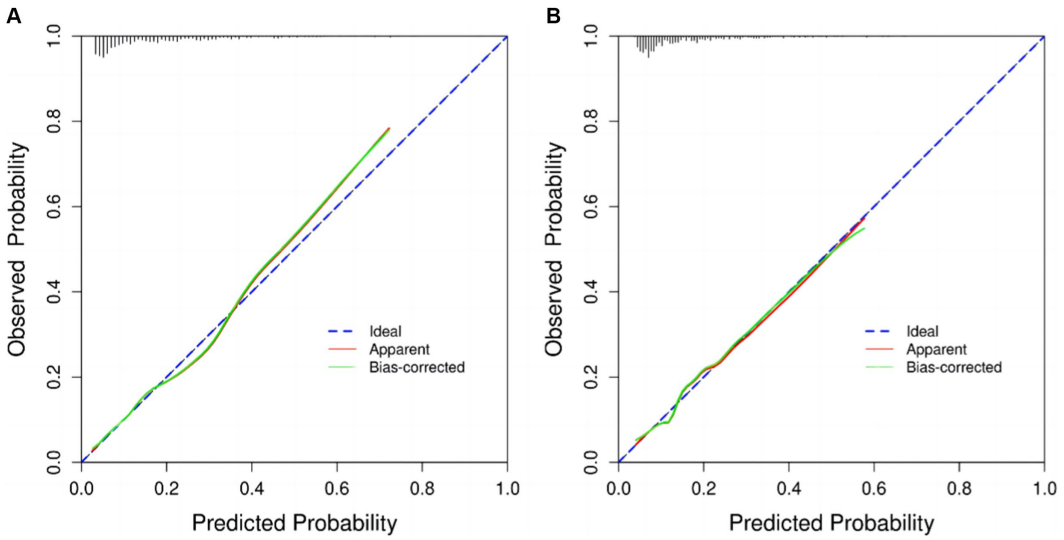

FIGURE 6
Calibration curves. **(A)** training cohort, **(B)** internal test cohort.

45-degree diagonal, underscoring the robustness and accuracy of our predictive model. These results serve to validate the efficacy and reliability of our prognostic tool.

According to our study, the mortality rate of older CI persons is positively correlated with age, which indicates that the older the age, the higher the mortality rate. Many studies have confirmed the effect of age on cognitive function, and although the mechanisms by which changes in brain structure and function occur with age are not clear, several studies (Schmeidler et al., 2019; Sprague et al., 2019) have shown that various brain functions are affected by a variety of factors, which can lead to cognitive decline. The rate of cognitive decline accelerates with age and can be detected already in middle age (45 to 55 years) (Kohler et al., 2023). In our study, in order to minimise age-related factors, we divided the included population into three different age groups and calculated the lowest quartile of cognitive test scores in each group. However, in our statistical analyses, we found that the effect of age on cognitive functioning could be observed despite the exclusion of some possible biases. Therefore, there is a need for routine screening of cognitive function in the older persons (Travis and Martin, 2020).

There is little research pointing to race on mortality in older CI patients, but studies on Alzheimer's disease (AD) point to race/ethnicity as a possible influence on life expectancy in AD patients. Schaffert evaluated 1,401 patients with AD, incorporating 21 predictors, and found that white patients with AD possessed less life expectancy (Schaffert et al., 2022). Mehta conducted a retrospective study in which 30,916 AD patients were followed for a mean of 2.4 years and concluded that African American and Latino Alzheimer's disease patients may have longer survival compared to white

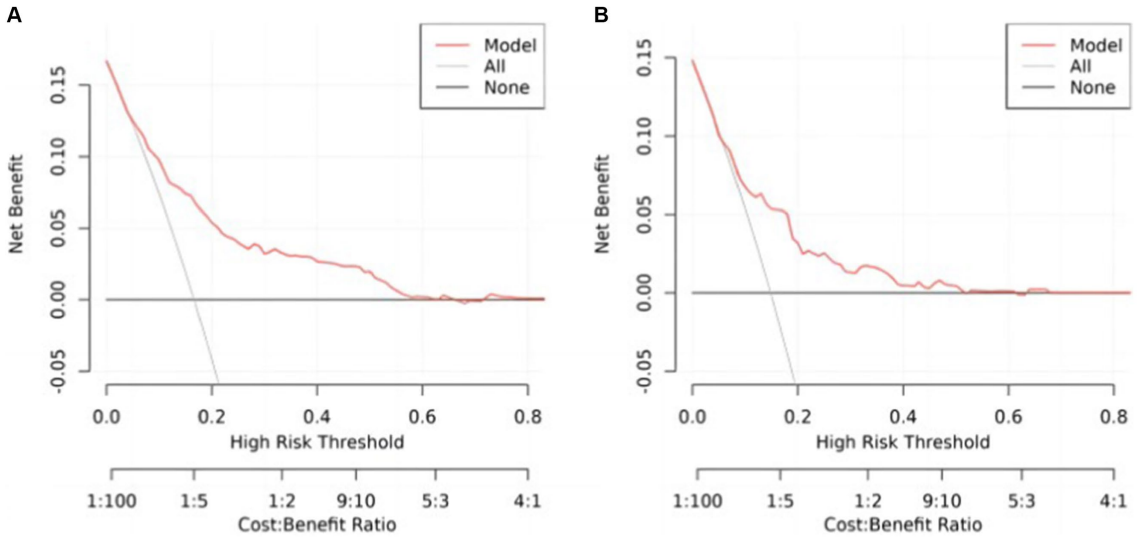

FIGURE 7
Decision curve analysis, **(A)** training cohort, **(B)** internal test cohort.

Alzheimer's disease patients (Mehta et al., 2008). The above studies are generally similar to our conclusions, reflecting that more care and attention should be given to the white population.

Several earlier studies have proposed that cardiovascular disease and older CI persons interact with each other and contribute to their respective development. Ren conducted a prospective study aimed at revealing the relevance of CI in patients with heart failure and its prognosis, and found that new-onset dementia was independently associated with an increased risk of all-cause mortality in patients with CVD (Ren et al., 2023). Yono prospectively recruited 585 hypertensive patients, assessed cognitive functioning at baseline, and prospectively identified CVD events, and concluded that the prevalence of cognitive dysfunction was higher in patients with CVD events than in those without (Yano et al., 2014). dysfunction was more prevalent than in patients without CVD events, Van provided insight into the causes of death in dementia patients through a national cohort study ($n = 59{,}201$), which found that, although the prevalence of CVD was low (18.7% in men and 19.2% in women), it was also one of the leading causes of death in dementia patients (van de Vorst et al., 2016). The above study and our prediction model remind us that patients with CVD combined with CI should be followed up in a targeted manner to prevent bad outcomes.

Stroke is also a risk factor for death in older persons with CI. Rist conducted a cross-sectional study including 10 countries and 6,080 patients and found that approximately 30% of ischaemic stroke survivors exhibited CI and that the risk of dementia was high over time, even in the absence of recurrent strokes, and should therefore be closely monitored for further cognitive decline (Rist et al., 2013). Gale designed a 20-year follow-up study of 921 older persons with CI and found that the relationship between cognitive function and risk of stroke death suggested that cerebrovascular disease is an important cause of cognitive decline (Gale et al., 1996).

Urea nitrogen is one of the main tests reflecting the conditions of renal function, which may be accompanied by renal insufficiency in most patients (Naz and Sulaiman, 2016). And the argument that chronic kidney disease (CKD) is associated with cognitive decline has been supported by some literature. Anatomically, both the kidney and the cranium are low vascular impedance systems that allow continuous, high volume blood perfusion (Tsai et al., 2017), which makes both vulnerable to damage from diseases that cause microvascular damage such as diabetes and hypertension. It has been demonstrated that patients with renal insufficiency are more prone to white matter injury, asymptomatic cerebrovascular haemorrhage and cranial microvascular haemorrhage (Wu et al., 2020). A German prospective study with a 2-year follow-up found an association between moderate - severe renal impairment and dementia (Hiramatsu et al., 2020). To some extent, CKD is closely related to cognitive decline. Meanwhile, BUN is also an easily accessible indicator that can prevent the decline of life expectancy in older persons with CI in advance.

Limitations

Although our study used a large, representative sample of older Americans, and the NHANES database offers significant advantages in terms of survey methodology and quality control, this article still has some limitations. Firstly, the cohort is based on a population from the U.S. Centers for Disease Control and Prevention, which may not be representative of the wider population, particularly those in low-income countries. Additionally, our model may include potential unmeasured confounders. Future studies should aim to externally validate our nomogram in different populations and settings.

Conclusion

To sum up, our study successfully developed and internally validated a 5-item nomogram integrating age, race, stroke, cardiovascular disease, and blood urea nitrogen. This nomogram exhibited robust predictive performance for 5-year mortality in individuals with CI, offering a valuable tool for prognostic evaluation and personalized care planning.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the National Center for Health Statistics Research Ethics Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LW: Writing – original draft. DP: Writing – original draft. SW: Data curation, Investigation, Writing – review & editing. HW: Data curation, Software, Writing – original draft. JW: Conceptualization, Methodology, Writing – original draft. LG: Writing – review & editing. YG: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Subthreshold amyloid deposition, cerebral small vessel disease, and functional brain network disruption in delayed cognitive decline after stroke

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Background: Although its incidence is relatively low, delayed-onset post-stroke cognitive decline (PSCD) may offer valuable insights into the "vascular contributions to cognitive impairment and dementia," particularly concerning the roles of vascular and neurodegenerative mechanisms. We postulated that the functional segregation observed during post-stroke compensation could be disrupted by underlying amyloid pathology or cerebral small vessel disease (cSVD), leading to delayed-onset PSCD.

Methods: Using a prospective stroke registry, we identified patients who displayed normal cognitive function at baseline evaluation within a year post-stroke and received at least one subsequent assessment. Patients suspected of pre-stroke cognitive decline were excluded. Decliners [defined by a decrease of ≥3 Mini-Mental State Examination (MMSE) points annually or an absolute drop of ≥5 points between evaluations, confirmed with detailed neuropsychological tests] were compared with age- and stroke severity-matched non-decliners. Index-stroke MRI, resting-state functional MRI, and 18F-florbetaben PET were used to identify cSVD, functional network attributes, and amyloid deposits, respectively. PET data from age-, sex-, education-, and apolipoprotein E-matched stroke-free controls within a community-dwelling cohort were used to benchmark amyloid deposition.

Results: Among 208 eligible patients, 11 decliners and 10 matched non-decliners were identified over an average follow-up of 5.7 years. No significant differences in cSVD markers were noted between the groups, except for white matter hyperintensities (WMHs), which were strongly linked with MMSE scores among

decliners (rho = −0.85, $p < 0.01$). Only one decliner was amyloid-positive, yet subthreshold PET standardized uptake value ratios (SUVR) in amyloid-negative decliners inversely correlated with final MMSE scores (rho = −0.67, $p = 0.04$). Decliners exhibited disrupted modular structures and more intermingled canonical networks compared to non-decliners. Notably, the somato-motor network's system segregation corresponded with the decliners' final MMSE (rho = 0.67, $p = 0.03$) and was associated with WMH volume and amyloid SUVR.

Conclusion: Disruptions in modular structures, system segregation, and inter-network communication in the brain may be the pathophysiological underpinnings of delayed-onset PSCD. WMHs and subthreshold amyloid deposition could contribute to these disruptions in functional brain networks. Given the limited number of patients and potential residual confounding, our results should be considered hypothesis-generating and need replication in larger cohorts in the future.

KEYWORDS

vascular cognitive impairment, neural network, connectome, small vessel disease, amyloid deposition

Introduction

Post-stroke cognitive impairment (PSCD) can be categorized as either early or delayed in onset (Mok et al., 2017). Early-onset PSCD typically occurs 3–6 months post-stroke, affecting about 20% of patients after their first stroke (Pendlebury and Rothwell, 2009; Mok et al., 2017). In contrast, delayed-onset PSCD is characterized by cognitive decline arising 1 year or more after an initially stable post-stroke period. The prevalence of PSCD varies, ranging from 4.4 to 23.9%, depending on the observation period (Mok et al., 2017). The causal factors for these two forms of PSCD seem to diverge; early-onset PSCD is believed to stem from a complex interplay between stroke lesion characteristics and brain resilience, whereas delayed-onset PSCD is primarily attributed to cerebral small vessel disease (cSVD) and, to a lesser extent, Alzheimer's disease (AD) pathology or recurrent stroke (Mok et al., 2017).

Although its incidence is relatively low, delayed-onset PSCD may provide valuable insights into "vascular contributions to cognitive impairment and dementia" (Snyder et al., 2015). The pattern of initial cognitive stability post-stroke, followed by later deterioration, suggests functional compensation but subsequent decompensation. cSVD, AD pathology, and stroke recurrence may underlie this decompensation process (Mok et al., 2017).

Network analysis has become instrumental in deciphering the functional architectures of the brain (Margulies et al., 2016; Bayrak et al., 2019). A strong correlation has been observed between the reduction in inter-hemispheric integration and intra-hemispheric segregation and multi-domain cognitive dysfunction in the acute stage of stroke (Siegel et al., 2016). The subsequent recovery of modularity has been linked to improvements in memory, attention, and language functions within the first year post-stroke (Siegel et al., 2018). However, a knowledge gap exists regarding delayed-onset PSCD and functional brain networks.

In this context, our study aimed to determine whether patients with delayed-onset PSCD differ from those without this condition regarding functional brain network attributes and whether such differences can be traced back to amyloid pathology or cSVD. We hypothesized that underlying amyloid pathology or cSVD might disrupt the compensation observed post-stroke, leading to delayed-onset PSCD. This disruption might manifest as a decrease in functional segregation.

Abbreviations: MMSE, Mini-mental state examination; DMN, Default mode network; SMN, Somatomotor network.

Materials and methods

This study received approval from the Seoul National University Bundang Hospital Institutional Review Board (Approval no. B-1606-352-301). Written informed consent was obtained from all eligible patients or their legally authorized representatives. All methods were performed in accordance with the relevant guidelines and regulations of the Seoul National University Bundang Hospital Ethics Committee and the Declaration of Helsinki.

Study design and participants

We conducted a nested case–control study within a pre-established stroke cohort (Figure 1) (Kim et al., 2014) of acute ischemic stroke patients admitted to SNUBH within a week of stroke onset and registered in a prospective stroke registry from February 2007 to May 2019. The selection process began with 442 participants demonstrating normal cognition within 12 months after stroke. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and further verified through the Korean-Vascular Cognitive Impairment Harmonization Standard-Neuropsychology Protocol (K-VCIHS-NP, Supplementary material) (Kang and Na, 2003; Yu et al., 2013).

From the initial cohort, 259 patients who underwent at least one follow-up neuropsychological assessment more than 6 months after the baseline evaluation were identified. We excluded individuals suspected of pre-stroke cognitive decline [Informant Questionnaire on Cognitive Decline in the Elderly, (IQCODE) score ≥3.6, $n = 47$], even if their baseline cognitive test scores were normal, and those who experienced

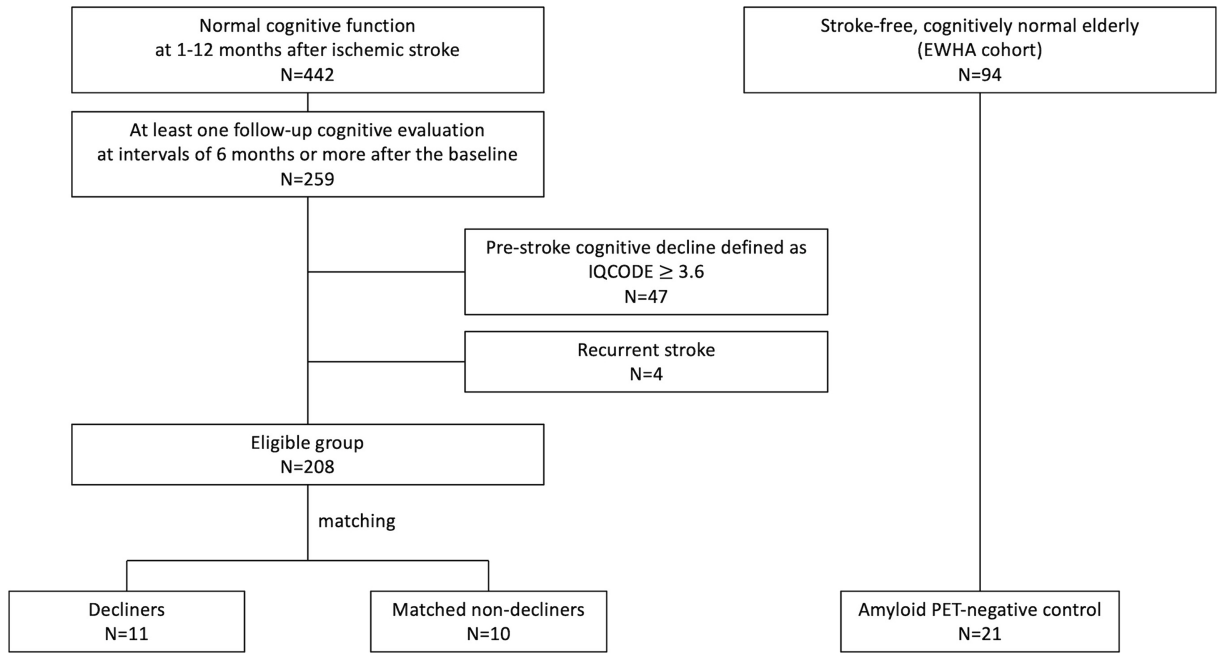

FIGURE 1
Enrollment flowchart.

a recurrent stroke ($n = 4$) (Figure 1). The baseline characteristics of these 208 eligible patients are detailed in Supplementary Table S1.

Delayed-onset decliners were defined as individuals exhibiting a decline of ≥3 points annually or a drop of ≥5 points between baseline and the last MMSE scores (Hensel et al., 2007). In contrast, non-decliners were defined by a decline of one point or less per year and an absolute decline of fewer than three points (Diener et al., 2008). A prior study indicated a reliable MMSE change ranging from 2 to 4 points over 1.5 years (1.3–2.7 points per year) (Hensel et al., 2007). A significant change in the MMSE for a 5-year follow-up was reported as four points (Tombaugh, 2005). Thus, we set a criterion for a considerable change as a difference in the absolute value of ≥5 points or a decline of ≥3 points annually. Those with a significant cognitive change were re-evaluated using the K-VCIHS-NP. Non-decliners were matched with decliners by age (±3 years) and initial stroke severity [National Institutes of Health Stroke Scale (NIHSS), ±2 points].

In the 18F-florbetaben PET analysis, we selected cognitively unimpaired individuals from the community-dwelling Ewha cohort. This cohort comprised 94 cognitively unimpaired adults aged 60 or above with normal cognitive function across all cognitive domains exceeding −1 SD based on age- and education-adjusted norms (Kang and Na, 2003). Of the 62 individuals with a negative 18F-florbetaben PET scan, we selected 21 stroke-free controls by matching the decliners' age, sex, and education. Additionally, we ensured that there were no differences in the proportion of apolipoprotein E (APOE) e4 carriers between the groups.

Data collection

We gathered data on demographics, risk factors, and index-stroke characteristics from the registry database (Kim et al., 2014). Magnetic resonance imaging (MRI) images were downloaded from our institution's Picture Archiving and Communication System. APOE genotyping was performed for patients who provided consent. The characteristics of stroke lesions, such as location, laterality, and multiplicity, were analyzed. Medial temporal lobe atrophy was assessed utilizing Scheltens' visual grade (Scheltens et al., 1992). cSVD markers, including white matter hyperintensities (WMHs), lacunes, and cerebral microbleeds, were evaluated according to the Standards for Reporting Vascular changes on nEuroimaging (STRIVE) protocol using index-stroke MRI images (Wardlaw et al., 2013). All neuroimaging parameters were scrutinized by an independent rater (EBK), who has extensive neuroradiological expertise and was blinded to patient allocations. A neurology specialist (JSL) subsequently confirmed the assessments.

WMH mapping

We produced a cumulative lesion map to provide a visual representation of WMH distributions. For the segmentation of WMHs on FLAIR sequences, we semi-automatically set regions of interest with the help of ImageQnA's lesion growth and shrinkage algorithms (Ryu et al., 2014). To ensure consistency in comparisons across various scans, we mapped the segmented WMHs onto a standardized template—Montreal Neurological Institute 152—utilizing a mesh-warping algorithm coupled with linear interpolation. By applying a customized MATLAB code, we generated a lesion frequency map, quantifying both the voxel count and its proportion relative to total brain volume (Ryu et al., 2014).

^{18}F-florbetaben PET

PET scans were performed exclusively on decliners, with comparative data from stroke-free controls (the Ewha cohort). The

brain amyloid plaque load (BAPL) score was used to assess amyloid positivity; scores two or three denoted the presence of amyloid deposits (Barthel et al., 2011). Additionally, standardized uptake value ratio (SUVR) values were calculated for quantitative comparisons between decliners and stroke-free controls. At 90 min after the bolus intravenous administration of ^{18}F-florbetaben (296 MBq, or 8 mCi), participants underwent a 20-min positron emission scan using dedicated PET/CT scanners (Biograph mCT40 or mCT64, Siemens Healthcare, Germany). A CT scan was used for attenuation correction, followed by an emission scan of the brain. PET images were reconstructed on a 400×400 image size with a $1 \times 1 \times 1.5$ mm voxel size. Using 24 subsets and six iterations, images were reconstructed with ordered subset expectation maximization. A post-reconstruction Gaussian filter (full width at half maximum of 2 mm) was applied. The PET image was co-registered with the T1-MRI image. The T1-coregistered PET image was then normalized to the Montreal Neurological Institute (MNI)-152 template using the transformation matrix calculated during T1-MRI segmentation. After normalization, the SUVR was calculated using the gray matter of the cerebellum as the reference region. Using 116 gray matter regions from the automated anatomical labeling (AAL) atlas, SUVR was extracted regionally (Tzourio-Mazoyer et al., 2002). We used the averaged value of the SUVR of the four brain regions from the AAL atlas (frontal, cingulate, lateral parietal, and lateral temporal cortex) to calculate the global SUVR value. This preprocessing was accomplished with SPM12 and MATLAB 2020a (Mathworks, Natick, MA, United States). The intervals between the index stroke and ^{18}F-florbetaben PET were 96.4 ± 18.0 months (mean ± standard deviation).

Resting-state functional MRI

The protocols and preprocessing steps for functional and structural MRI can be found in the Supplementary material. We assessed functional connectivity by determining Pearson's correlations between pairs of blood-oxygenation-level-dependent (BOLD) signals. Initially, we spatially averaged the BOLD signals of voxels within each of the 265 predefined brain regions from the Schaefer atlas (Schaefer et al., 2017).[1] This allowed us to compute correlations between pairs of the average BOLD time series, resulting in functional connectivity matrices. We then used this region-level connectivity data to explore brain network characteristics and system segregation measures, represented graphically through spring-embedded network plots.

Network analysis

We examined the functional network structure between decliners and non-decliners, focusing on the following: (1) conventional network attributes for global architectures, (2) system segregations of large-scale neural networks, and (3) spring-embedded graph layout for inter-network structure changes.

We evaluated the global network architecture using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). This includes measures of network integration (characteristic path length and global efficiency) and network segregation (modularity, clustering coefficient, and transitivity) (Wang et al., 2021). We calculated these measures with region-level functional connectivity matrices at various thresholds of network densities (0.05, 0.10, 0.15, 0.20). Each attribute was normalized against its null distribution, estimated by 100 iterations of random rewiring (Rubinov and Sporns, 2010). The characteristic path length was inverted, so lower values represent a worse function.

System segregation of large-scale networks quantifies a network module's functional isolation from others. We used the equation:

$$SysSeg = \frac{\overline{Z_w} - \overline{Z_b}}{\overline{Z_w}},$$

where $\overline{Z_w}$ is the mean Fisher z-transformed connectivity (r) within the same module and $\overline{Z_b}$ is the mean z-transformed (r) between nodes of one module and all nodes in other modules (Chan et al., 2014). The affected large-scale networks included visual network (VN), somatomotor network (SMN), dorsal attention network (DAN), ventral attention network (VAN), limbic network (LN), frontoparietal network (FPN), and default mode network (DMN) (Yeo et al., 2011). Codes for the analyses are available on GitHub.[2]

Spring-embedded graph layout visualized qualitative characteristics in brain network composition (Gordon et al., 2017). Attractive forces were applied between connected nodes, while repulsive forces were applied to all nodes. The nodes were iteratively moved until they reached equilibrium, resulting in a layout that captures the intrinsic topology of a network. Codes for the analyses are available on GitHub.[3]

Statistical analysis

Continuous variables were analyzed using Student's t-tests or Wilcoxon rank-sum tests, while categorical variables were examined using χ^2 or Fisher's exact tests. Associations between WMH volume, ^{18}F-florbetaben PET SUVR, and cognitive test scores were investigated using Pearson's correlation. Group-level differences (i.e., decliner vs. non-decliner) in associations between WMH volume and cognitive scores were tested using linear regression with interaction terms (i.e., groups × WMH volume). We used logistic regression analysis, adjusted for age, sex, and education levels, to compare amyloid deposition patterns between decliners and stroke-free controls expressed as Group (Decliner = 1, stroke-free control = 0) = $\beta_0 + \beta_1$ age + β_2 sex + β_3 education + β_4 SUVR (voxel level). In this voxel-wise PET image analysis, we used an uncorrected p value for exploratory

1 https://github.com/cocoanlab/cocoanCORE/blob/master/Canonical_brains/Schaefer/Schaefer_265_combined_2mm.nii

2 https://github.com/cocoanlab/cocoanCORE/blob/master/Network_analysis/system_segregation.m

3 https://github.com/cocoanlab/cocoanCORE/blob/master/Visualization/vis_network.m

purposes. All statistical analyses were performed using R version 4.0.5, with a two-sided p-value (< 0.05) set as the statistical threshold.

Results

Out of 208 eligible patients, 11 (5.3%) met the criteria for delayed-onset PSCD, and there were 10 matched non-decliners. The average follow-up duration was comparable for both groups: 75.1 months for decliners and 75.4 months for non-decliners. The baseline characteristics, including features of stroke lesions and medial temporal lobe atrophy, did not differ between the two groups. The APOE e4 allele was present in one decliner and two non-decliners (Table 1).

The median MMSE scores at baseline were similar for both groups (29 for decliners vs. 27 for non-decliners). However, decliners reduced 6.0 points over 5.1 years, while non-decliners showed no change over 5.4 years (Supplementary Figure S1). Domain-specific z-scores on detailed neuropsychological tests consistently decreased in decliners and remained stable in non-decliners (Table 1).

cSVD features: comparisons between decliners and non-decliners

There was no significant difference in the proportions of moderate-to-severe WMHs (Fazekas grade 2 or higher) and the volume of WMHs between decliners and non-decliners. Confluent WMHs, characterized by Fazekas grade 3, were observed in only one decliner (Table 1).

Within the decliner group, the WMH volume was significantly associated with changes in MMSE scores and final MMSE scores (rho = −0.85, $p < 0.01$; rho = −0.91, $p < 0.01$, respectively) (Supplementary Figure S2). However, no such correlation was detected within the non-decliners (rho = −0.04, $p = 0.92$; rho = −0.29, $p = 0.41$). This differential effect of WMH volume on changes in MMSE scores was confirmed in the linear regression with the interaction term (i.e., group × WMH volume). WMH volume was not significantly correlated with baseline MMSE scores (rho = −0.51, $p = 0.11$ for decliners, rho = −0.36, $p = 0.30$ for non-decliners). Mapping of WMHs from the index-stroke MRI revealed a more frequent presence of WMHs in the centrum semiovale in decliners than non-decliners (Supplementary Figure S3).

Decliners and non-decliners did not show significant differences in the presence and number of lacunes and microbleeds. Only one decliner exhibited three or more lacunes.

Amyloid PET characteristics: comparisons between decliners and stroke-free controls

Only one decliner exhibited amyloid PET positivity. Nonetheless, in the amyloid-negative decliners, the global SUVR value negatively correlated with both the final MMSE scores (rho = −0.67, $p = 0.04$) and changes in MMSE scores (rho = −0.58, $p = 0.08$) (Figure 2A). There was no significant correlation between the participants' age and the SUVR value (rho = 0.09, $p = 0.81$).

In comparison to stroke-free, age-matched amyloid-negative controls ($n = 21$), the amyloid PET-negative decliners ($n = 10$) exhibited topographical patterns of subthreshold amyloid deposition in the precentral, supplementary motor, superior medial frontal, paracentral lobule, superior and inferior parietal, and superior temporal pole regions. These patterns diverged from the typical AD pattern (Figure 2B).

Network characteristics: comparisons between decliners and non-decliners

When comparing the functional networks of decliners and non-decliners, we observed qualitative differences, as depicted in the spring-embedded graph (Figure 3).

In representative non-decliners (Patients 1 and 9), brain regions within the same canonical networks were closely linked and arranged (Figure 3A), similar to patterns observed in healthy participants. However, representative decliners (Patients 14 and 15) demonstrated disrupted and intermingled canonical brain modules (Figure 3B). These patterns remained broadly consistent across various thresholds of network densities and other participants (Supplementary Figures S4–6).

We compared conventional network attributes between groups to quantitatively assess the topological differences in the functional network (Figure 4A). While no significant differences were observed between the two groups across all thresholds of network densities, all network measures were numerically lower for decliners compared to non-decliners. The effect sizes for the differences in network attributes averaged across all thresholds varied from small to large: Cohen's $d = 0.70$, 0.32, 0.26, 0.36, 0.43 for inverted characteristic path length, global efficiency, modularity, clustering coefficient, and transitivity, respectively. Despite a lack of statistical significance due to the small sample size, we speculate that this consistent trend implies a relationship between decreased modular segregation and the resultant loss of communication efficiency with delayed PSCD, as substantiated by the spring-embedded graphs (Figure 3, Supplementary Figures S4, S5).

Among the conventional network attributes, modularity was significantly correlated with the final MMSE scores in decliners (rho = 0.65, $p = 0.03$; Figure 5A).

To examine the network-wise contribution of modular segregation to the delayed-onset PSCD, we calculated system segregation, which quantifies the relative difference between within-network and between-network connectivity. Despite no significant difference in system segregation between decliners and non-decliners (Figure 4B), the final MMSE scores in decliners displayed a strong but marginally significant association with system segregation for all canonical networks and DMN (rho = 0.59, $p = 0.06$; rho = 0.57, $p = 0.07$) and a significant association with system segregation for SMN (rho = 0.67, $p = 0.03$) (Figure 5B). This suggests the role of SMN functional specialization in delayed PSCD. The relationships between network attributes and other cognitive scores, except MMSE, were not significant (Supplementary Figure S7).

Associations among network attributes, WMH volume, and amyloid PET SUVR

We calculated correlations between network attributes, WMH volume, and subthreshold PET SUVR in amyloid-negative decliners ($n = 10$) and observed a strong negative correlation between both

TABLE 1 Comparisons between decliners and non-decliners.

	Decliners ($n = 11$)	Non-decliners ($n = 10$)	*P*	Stroke-free amyloid-negative controls ($n = 21$)	*P*
Baseline age, years	69.2 ± 3.63	66.7 ± 9.02	0.43	69.4 ± 4.77	0.90
Female, *n* (%)	6 (54.5)	1 (10.0)	0.06	12 (57.1)	0.89
Education, years	8.9 ± 5.8	10.9 ± 5.8	0.45	10.3 ± 3.6	0.39
Initial NIHSS (median, IQR)	3 (0, 3.5)	4.5 (2.0, 5.0)	0.11		
Baseline MMSE (median, IQR)	29 (28, 29)	27 (25, 28)	0.16	29 (28, 29)	0.55
Absolute changes in MMSE scores during follow-up (median, IQR)	−6.0 (−12.5, −6.0)	0 (−1.0, 1.0)	< 0.01		
Changes in z-scores of neuropsychological tests during follow-up					
Verbal learning test—delayed recall	−1.8 (−2.4; −1.1)	0.2 (−0.4; 0.9)	<0.01		
Boston naming test	−1.6 (−2.8; −1.3)	0.0 (−0.4; 0.6)	<0.01		
Rey complex figure test—copy	−1.8 (−4.9; −0.9)	0.0 (−0.8; 0.7)	0.02		
Semantic fluency	−1.0 (−2.4; −0.6)	0.0 (−0.5; 0.6)	0.03		
Phonemic fluency	−1.2 (−2.3; −0.8)	0.0 (−0.5; 0.4)	<0.01		
Digit symbol coding	−3.4 (−3.8; −1.4)	−0.3 (−0.9; 0.1)	<0.01		
Trail-making test—A	−0.7 (−2.3; 0.1)	0.4 (−0.8; 1.0)	0.12		
Trail-making test—B	−2.4 (−4.5; −0.8)	−0.1 (−0.9; 0.8)	0.02		
Intervals between index-stroke and last cognitive evaluations (months)	75.1 ± 24.6	75.4 ± 30.6	0.98		
Interval between baseline and last cognitive evaluations (months)	68.3 ± 26.8	67.8 ± 25.2	0.96		
APOE e4 carriers*	1 (9.1)	2 (20.0)	0.31	3 (14.3)	0.45
Index-stroke characteristics					
Left-sided	8 (72.7)	3 (30.0)	0.13		
Multiplicity	6 (54.5)	7 (70.0)	0.78		
Cortical involvement	6 (54.5)	3 (30.0)	0.49		
Chronic imaging variables					
Deep WMH, Fazekas grade 0–1/2/3	8 (72.7)/3 (27.3)/0 (0)	8 (80.0)/2 (20.0)/0 (0)	0.48		
Periventricular WMH, Fazekas grade 0–1/2/3	7 (63.6)/3 (27.3)/1 (9.1)	5 (50.0)/5 (50.0)/0 (0)	0.41		
WMH volume (% of brain parenchymal volume)	0.58 (0.33, 0.76)	0.52 (0.37, 0.98)	0.99		
Lacunes	2 (18.2)	4 (40.0)	0.53		
No. of lacunes, 0/1–2/3 or more	9 (81.8)/1 (9.1)/1 (9.1)	6 (60.0)/2 (20.0)/2 (20.0)			
Cerebral microbleeds	5 (45.5%)	3 (30.0%)	0.78		
No. of microbleeds, 0/1/2–4/5 or more	6 (54.5)/4 (36.4)/1 (9.1)/0 (0)	7 (70.0)/2 (20.0)/1 (10.0)/0 (0)			
Medial temporal lobe atrophy, Schelten's grade 0–1/2/3	6 (54.6)/4 (36.4)/1 (9.1)	7 (70.0)/3 (30.0)/0 (0)	0.61		
Amyloid positivity—BAPL 2 or more	1 (9.1%)	n/a		0 (0%)	
Amyloid retention—global SUVR (mean, SD)	1.29 (0.16)	n/a			

Numbers denote mean ± standard deviations or frequencies (proportions) as appropriate. *APOE genotyping was unavailable in five participants (two decliners, two non-decliners, and one stroke-free amyloid-negative control) due to a lack of consent for genetic screening. NIHSS, National institutes of health stroke scale; MMSE, Mini-mental state examination; WMH, White matter hyperintensities; BAPL, Brain amyloid plaque load; SUVR, Standardized uptake value ratio.

WMH volume and PET SUVR with SMN system segregation (rho = −0.76, $p < 0.01$; rho = −0.78, $p < 0.01$; respectively) (Supplementary Table S2). The WMH volume showed marginal associations with the system segregation of all large-scale networks (rho = −0.60, $p = 0.07$) and FPN (rho = −0.61, $p = 0.06$). Similarly, amyloid PET SUVR showed marginal associations with system

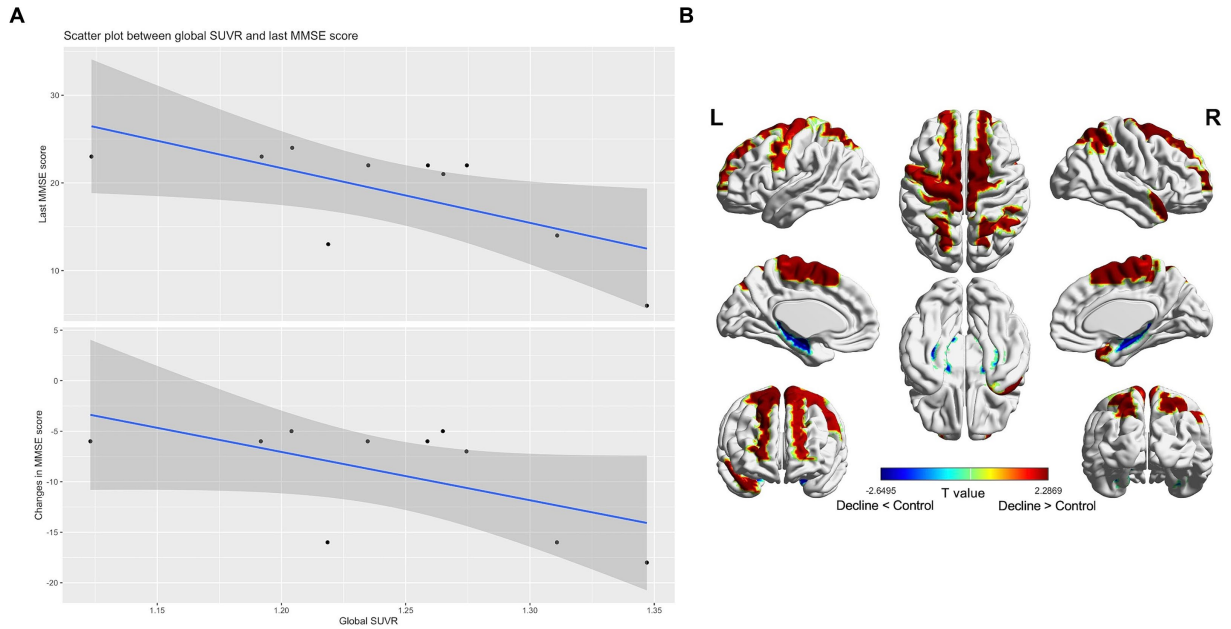

FIGURE 2
Subthreshold amyloid in patients with amyloid PET-negative delayed-onset post-stroke cognitive impairment ($n = 10$). In amyloid-negative individuals, the standard uptake value ratios were negatively correlated with the last cognitive scores and cognitive changes during follow-up **(A)**. T static map showing the difference in the topographical pattern of subthreshold amyloid deposition between the amyloid PET-negative decliners and the stroke-free, age-matched amyloid-negative controls ($n = 21$). The red color is the area where the standard uptake value ratios of the decliners increased compared to the control (thresholded by uncorrected $p < 0.05$) **(B)**.

segregation across all canonical networks (rho = −0.62, $p = 0.06$), DAN (rho = −0.62, $p = 0.06$), VAN (rho = −0.57, $p = 0.09$), and FPN (rho = −0.57, $p = 0.08$).

Discussion

We found that approximately 5% of stroke survivors who initially exhibited normal cognitive function developed delayed cognitive impairment around 6 years post-stroke. This cognitive decline significantly correlates with network characteristics such as modularity and system segregation. Furthermore, a significant association was observed between WMH volume and cognitive changes among decliners. Notably, among the amyloid-negative decliners, a substantial inverse correlation was found between the global SUVR of ^{18}F-Florbetaben PET and final MMSE scores. These results suggest that our hypothesized interrelationship between cSVD, amyloid pathology, and functional segregation as a compensatory mechanism after stroke may influence delayed PSCD.

Our findings indicate that underlying WMHs and subthreshold amyloid pathology might jointly contribute to delayed-onset PSCD. If either amyloid pathology or WMHs operate independently, symptoms only appear when the severity of either pathology surpasses a particular threshold. In our study, confluent WMHs were seen in only one decliner, and WMH volume was not exceedingly high (median = 0.58 in decliners and 0.52 in non-decliners, as a percentage of brain parenchymal volume) (Ryu et al., 2016). Likewise, while only one decliner displayed amyloid PET positivity, there was a substantial correlation between the SUVR value and cognitive scores, even at subthreshold levels. Previous research has suggested that subthreshold amyloid pathology potentially impacts delayed cognitive decline if it interacts with vascular pathology (Kapasi and Schneider, 2016). Patients with delayed-onset PSCD in our study exhibited significant deposition in the precentral gyrus, supplementary motor area, superior medial frontal cortex, paracentral lobule, superior and inferior parietal lobules, and superior temporal pole. This contrasts with the initial sites of amyloid accumulation in typical AD patients: the medial frontal, medial parietal, and lateral temporal–parietal lobes (Grothe et al., 2017). It has been reported that amyloid deposition in cases of cerebral amyloid angiopathy (CAA) is relatively increased in the occipital region (Charidimou et al., 2018). Considering this, it seems unlikely that the delayed-onset PSCD patients in our study are concurrently exhibiting typical early-stage AD or CAA. Nonetheless, due to the limited number of patients, the statistical interpretation of regional amyloid deposition patterns should be approached cautiously. Considering these points, along with the conflicting results reported in previous studies regarding the impact of amyloid pathology on the delayed onset of PSCD (Wollenweber et al., 2016; Liu et al., 2018) it may result from a complex interaction of multiple factors rather than a single independent influence.

We hypothesize that WMHs and amyloid pathology may contribute to delayed cognitive decline by altering the intracerebral network environment. Previous studies have indicated that WMH-induced white matter tract damage and amyloid pathology can result in neural network dysfunction, which, in turn, can negatively impact cognitive function (Taylor et al., 2017; Crockett et al., 2021; Coenen et al., 2023). Recent studies have also shown that amyloid pathology compromises white matter tract integrity (Collij et al., 2021). Our results are consistent with these findings, showing that the WMH volume

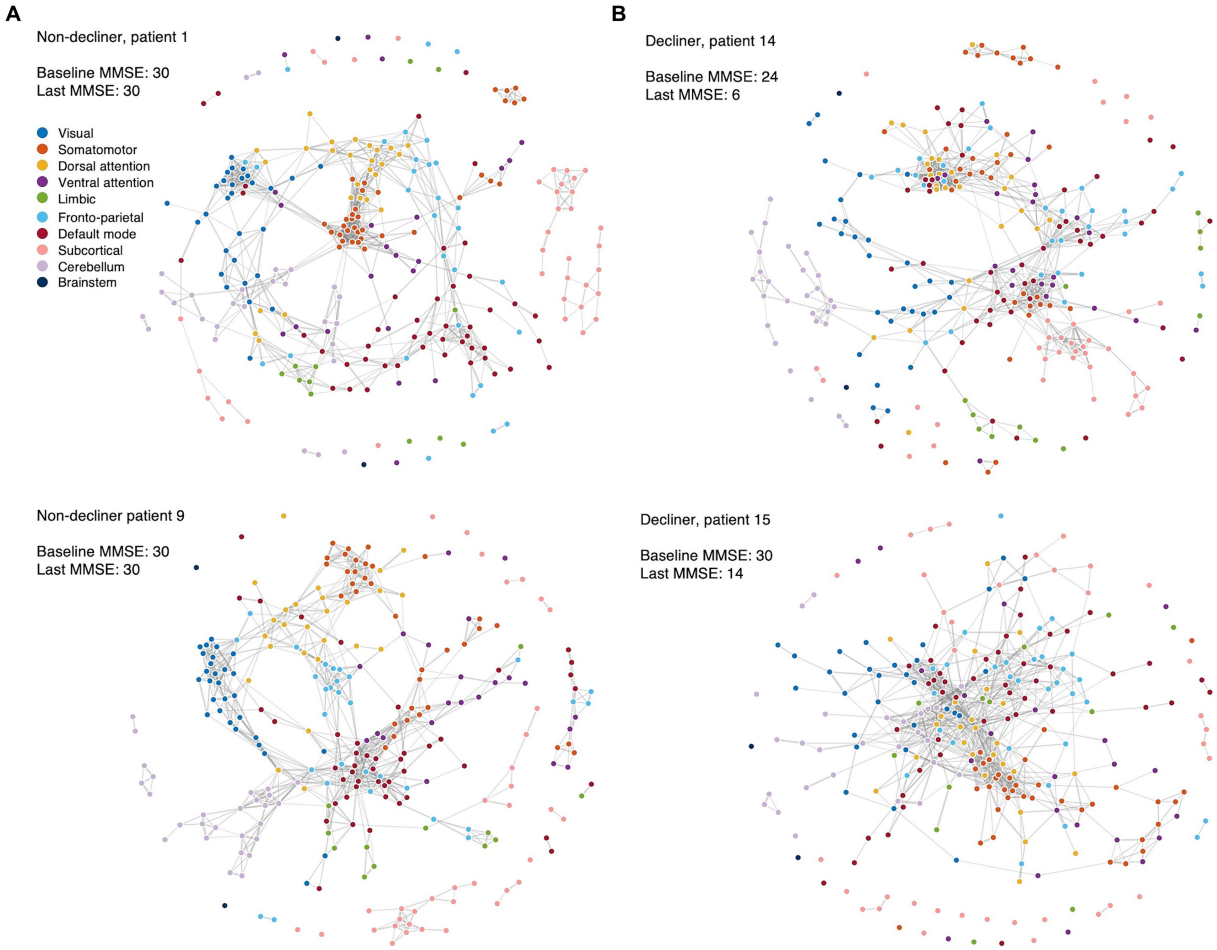

FIGURE 3
Spring-embedded graphs for the functional network compositions in the representative patients. The nodes correspond to different brain regions, with colors representing the corresponding canonical functional brain networks. The edges represent the functional connections between brain regions after thresholding. The spring-embedded graph plots present the functional brain network compositions for representative non-decliners **(A)** and decliners **(B)** at the threshold of network densities of 0.025. The plots show that the brain regions with the same canonical network were closely linked and arranged with each other **(A)**. However, representative decliners (demonstrated disrupted and intermingled canonical brain modules) **(B)**. The groups of strongly connected nodes are pulled together in the plot. Disconnected nodes are also visualized as dots without lines. Blue: visual, orange: somatomotor, yellow: dorsal attention, purple: ventral attention, green: limbic, light blue: frontoparietal, red: default mode, pink: subcortical, light purple: cerebellum, dark blue: brainstem.

and subthreshold PET SUVR are associated with decreased SMN system segregation. Although the decliners did not show statistically significant differences in conventional network attributes compared to the non-decliners, likely due to the small sample size, there were consistent trends indicating that these network attributes were less favorable in the decliners in both group comparisons and correlation analyses.

Previous studies suggested a pathophysiological link between neural network segregation, WMHs, and amyloid pathology, pointing to these factors as potential culprits for cognitive decline (Mok et al., 2016, 2017). For example, disruptions of functional segregation following a stroke could lead to global cognitive dysfunction (Siegel et al., 2018). Patients with higher WMH scores exhibited increased shortest path lengths, decreased clustering coefficient values, and reduced node efficiency, which significantly correlated with lower total Montreal Cognitive Assessment (MoCA) scores (Wang et al., 2022). In line with this, our results showed that modularity was negatively associated with cognitive outcomes and lower in the decliners than non-decliners. This finding is further supported by the low clustering coefficient and transitivity observed in the decliners and the decreased system segregation across all canonical networks (Figure 4). Our results also suggest that the functional structures of each canonical network may intermingle with each other, as seen in the spring-embedded graphs (Figure 3) (Gordon et al., 2017).

When we examined specific canonical networks, the system segregation of the SMN was significantly associated with cognitive outcomes in the decliners (Figure 5B). The SMN is related to somatosensory and action functions and is thus crucial for interacting with the surrounding environment. In old age, the relative contribution of SMN to the dynamic functional state of the resting brain decreases (Zhang et al., 2021), and a decline in the within-network connectivity of the SMN has been associated with poor cognitive performances (Geerligs et al., 2014). Previous studies have also suggested that disruption of sensorimotor networks due to WMH may contribute to overall cognitive deficits in older adults with cerebral small vessel disease (Crockett et al., 2021). Furthermore, the connectivity of the SMN in stroke patients significantly contributes to multitasking learning (Siegel et al., 2016).

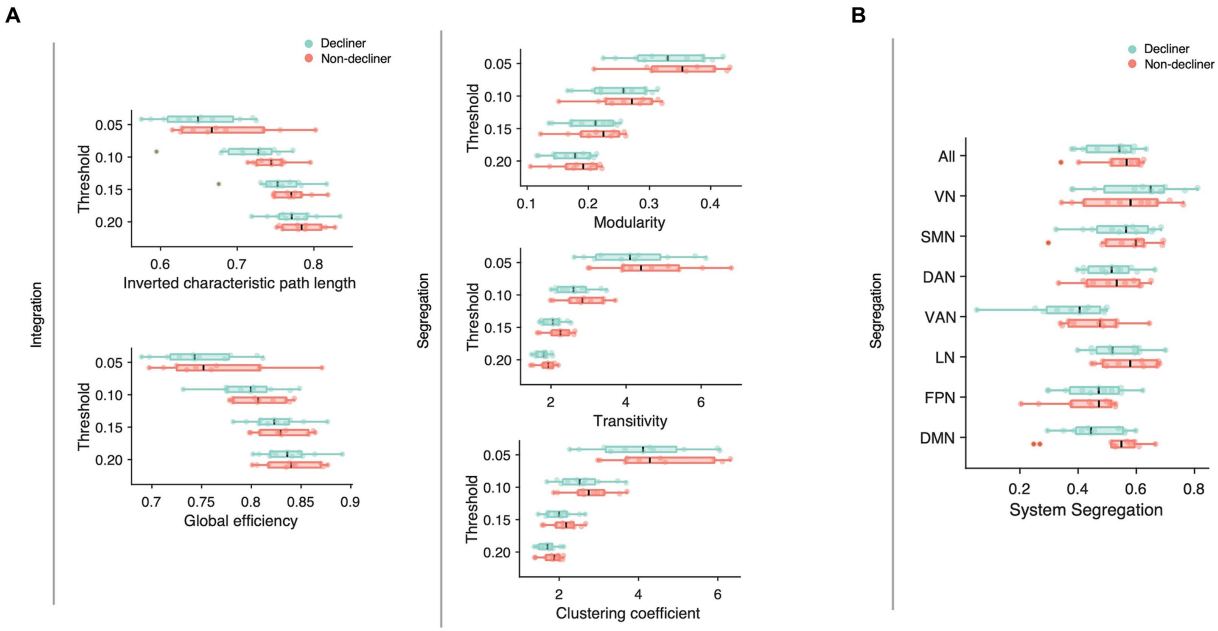

FIGURE 4
(A) Network attributes at multiple thresholds were compared between decliners (cyan) and non-decliners (magenta). Decliners showed lower scores in all attributes than non-decliners, but the differences were not statistically significant. Characteristic path length was inverted so that the lower value represents poorer functions to make them align with other attributes and thus help comparisons. **(B)** System segregation for different functional brain networks was compared between decliners and non-decliners. VN, visual network; SMN, somatomotor network; DAN, dorsal attention network; VAN, ventral attention network; LN, limbic network; FPN, frontoparietal network; DMN (default mode network).

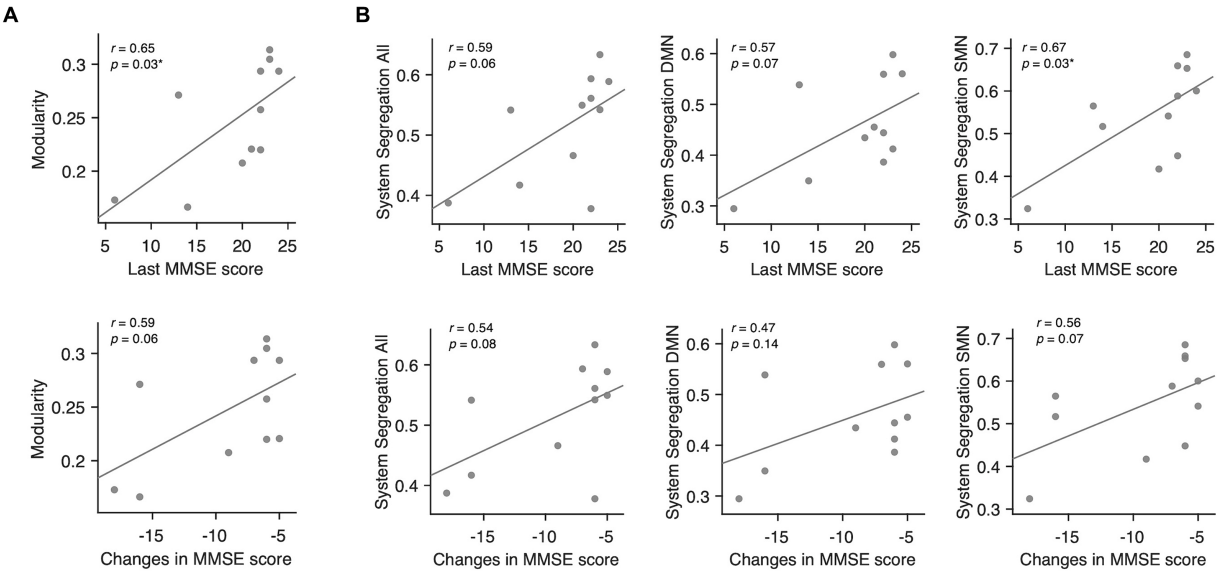

FIGURE 5
Associations between modularity, system segregation, and MMSE scores in delayed decliners. **(A)** Scatter plots for the associations between modularity averaged across all thresholds and the MMSE scores in delayed decliners, including the final MMSE score and the change in MMSE score over time. Modularity showed a significant association with the final MMSE score. **(B)** Scatter plots for the associations between system segregation across all networks, DMN, SMN, and the MMSE scores in delayed decliners, specifically the final MMSE score and the change in MMSE score over time. System segregation of the SMN showed a significant association with the final MMSE score.

Using a prospective stroke registry database, we identified 208 patients who had experienced a mild stroke but initially demonstrated normal cognitive function (Ryu et al., 2016). Over an average follow-up of 75 months, 5.3% (11 of 208) exhibited delayed onset PSCD. This rate is consistent with a previous study by Mok et al. (2016) wherein approximately 4.4% of 919 patients displayed delayed-onset dementia over a 2.6-year follow-up period (Mok et al., 2016). We found commonalities in our cohort's baseline characteristics, and Mok et al.'s: mean age was 69.1 ± 10.6 vs. 68.6 ± 11.4; and female participants were 39.9 vs. 42.8% (Mok et al., 2016). However,

neuroimaging characteristics of delayed decliners differed. Mok et al. (2016) found that confluent WMHs and three or more lacunes predicted post-stroke delayed-onset dementia. In contrast, only one decliner had these traits in our study. These discrepancies are likely attributed to the unique profiles of decliners in each study; our decliners were younger (69.2 vs. 76.2 years), had more years of education (8.9 vs. 4.1), and scored higher on the baseline MMSE (29 vs. 20) compared to Mok et al. (2016) decliners. These observations suggest that factors influencing delayed-onset PSCD may differ depending on the population of interest.

Our study has limitations. Despite the substantial number of stroke patients followed for over 6 years, the sample size was limited due to the low rate of cognitive decline in a single-center study. Furthermore, many variables, such as lesion location and size, were not closely matched between the groups, potentially leading to residual confounding. As a result, this study should be viewed as hypothesis-generating, with a need to validate the findings in larger-scale studies. Additionally, due to research funding limitations, we could not collect ^{18}F-Florbetaben PET data for the non-decliners in the study. Despite these limitations, we aimed to shed light on the characteristics and mechanisms underlying the worsening of cognition in patients with delayed-onset PSCD. This aim was achieved by including matched non-decliners and stroke-free elderly controls and obtaining functional MRI data.

In conclusion, after an almost 6-year observation period, the volume of WMHs, the presence and degree of subthreshold amyloid deposition, and alternations in functional brain networks emerged as possible factors in understanding delayed cognitive decline following stroke. Our findings suggest that delayed-onset PSCD may result from a complex interaction of multiple factors rather than a single cause. Understanding the stroke connectome and dynamic changes in brain networks during the acute and chronic phases of stroke holds promise for predicting cognitive changes during recovery and understanding how preventive therapy may be individually tailored.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Seoul National University Bundang Hospital (SNUBH) Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

J-SL: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. J-JL: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Data curation. GK: Writing – review & editing, Data curation. H-RK: Writing – review & editing, Visualization, Formal analysis, Data curation. DS: Writing – review & editing, Data curation. K-JL: Writing – review & editing, Data curation. MB: Writing – review & editing, Data curation. EK: Writing – review & editing, Data curation. BK: Writing – review & editing, Data curation. SK: Writing – review & editing, Data curation. W-SR: Writing – review & editing, Data curation. JC: Writing – review & editing, Visualization, Formal analysis, Data curation. D-EK: Writing – review & editing, Data curation. PG: Writing – review & editing. C-WW: Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization. H-JB: Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

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Conflict of interest

H-JB reports grants from: AstraZeneca, Bayer Korea, Bristol Myers Squibb Korea, Chong Kun Dang Pharmaceutical Corp., Dong-A ST, Jeil Pharmaceutical Co., Ltd., Korean Drug Co., Ltd., Samjin Pharm, Takeda Pharmaceuticals Korea Co., Ltd., and Yuhan Corporation. Additionally, outside the submitted work, personal fees from Amgen Korea, Bayer, Daiichi Sankyo, JW Pharmaceutical, Hanmi Pharmaceutical Co., Ltd. Otsuka Korea, SK Chemicals, and Viatris Korea. P-B Gorelick reports receiving honoraria as a Data Safety and Monitoring Board member for an industry study of blood pressure lowering in heart failure and cognitive maintenance.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2024.1430408/full#supplementary-material

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A bibliometric analysis of cerebral small vessel disease

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Background: Cerebral small vessel disease (CSVD) is a significant contributor to both stroke and dementia. While numerous studies on CSVD have been published, herein, we have conducted a bibliometric examination of the literature on CSVD, revealing its hot spots and emerging patterns.

Methods: We used the Web of Science Core Collection as our primary database and conducted a literature search from January 2008 to January 2023. CiteSpace, VOSviewer, online bibliometric platform, and R-bibliometrix were employed to conduct bibliometric analysis and network visualization, including the number of publications, countries, institutions, journals, citations, authors, references, and keywords.

Results: A total of 4891 publications on CSVD were published in 790 journals by 19,066 authors at 3,862 institutions from 84 countries. The United States produced the most written works and had a significant impact in this field of study. The University of Edinburgh had the highest publication count overall. The journal with the most publications and co-citations was *Stroke*. Wardlaw, Joanna was the most prolific author and commonly cited in the field. The current areas of research interest revolved around "MRI segmentation" and "Enlarged perivascular spaces in the basal ganglia."

Conclusion: We conducted a bibliometric analysis to examine the advancements, focal points, and cutting-edge areas in the field of CSVD to reveal potential future research opportunities. Research on CSVD is currently rapidly advancing, with a consistent rise in publications on the topic since 2008. At the same time, we identified leading countries, institutions, and leading scholars in the field and analyzed journals and representative literature. Keyword co-occurrence analysis and burst graph emergence detection identified *MRI segmentation* and *Basal ganglia enlarged perivascular spaces* as the most recent areas of research interest.

KEYWORDS

cerebral small vessel disease, CiteSpace, bibliometrics, VOSviewer, hot spots and frontiers

1 Introduction

Cerebral small vessel disease (CSVD) refers to a collection of abnormal processes that impact the small blood vessels in the brain, including arteries, arterioles, venues, and capillaries (Pantoni, 2010). The primary features of CSVD include alterations to vessel walls leading to thickening, stiffening, and eventual occlusion of small vessels. The typical radiological and pathological signs of CSVD are lacunar infarcts, white matter lesions, cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVS), and brain atrophy (Wu et al., 2022). Lacunar infarcts are caused by blockage of small arteries in the brain, leading to small subcortical infarcts.

White matter lesions likely reflect ischemia and eventually lead to demyelination and axonal loss in the white matter tracts supplied by the diseased small vessels (Chen and Song, 2019). Cerebral microbleeds represent focal leakages of blood plasma and erythrocytes from diseased small vessels. EPVS signify enlarged fluid-filled canals surrounding small penetrating vessels and reflect altered interstitial fluid drainage (You et al., 2021). Brain atrophy results from the cumulative effects of ischemia and neuronal loss caused by CSVD. Furthermore, CSVD is a major cause of not only lacunar ischemic strokes but also intracerebral hemorrhage, which account for 20–30% of all ischemic strokes (Wardlaw et al., 2019) and cerebral hemorrhage (Francis et al., 2019). In addition to acute events, CSVD is associated with insidious neurological decline including cognitive, gait, and urinary impairment that includes the syndrome of vascular cognitive impairment (Horsburgh et al., 2018). With the global increase of the aging population, the burden of CSVD and resulting disabilities are expected to rise substantially in the coming decades (Arba et al., 2017). Therefore, to compile compelling evidence and provide valuable insights for the early diagnosis, prevention, and treatment of CSVD, we conducted the following bibliometric analysis.

Bibliometric analysis is the study of the structure, quantity, and impact of academic literature. This analysis can be conducted on individual researchers, specific fields of research, institutions, or countries. It involves the use of mathematical and statistical techniques to extract and analyze information from published academic literature. The aim of bibliometric analysis is to identify trends, patterns, and patterns of academic research. This analysis has important implications for the evaluation of research output, academic performance, and resource allocation (Chen and Song, 2019; Wu et al., 2022). Hence, we employed CiteSpace and VOSviewer to conduct a bibliometric analysis of the research on small vessel disease from 2008 to 2023 with the following objectives: (1) reveal the general information of CVSD over the past 15 years; (2) uncover the intractable problems and research hot spots related to CVSD; and (3) construct a knowledge graph in this field to provide valuable insights for future related research.

2 Methods

2.1 Data source and search strategy

A systematic search strategy was used to retrieve publications on CSVD from the Web of Science Core Collection (WoSCC) database between January 1, 2008 and January 1, 2023. Access to more than 21,000 journals in the fields of science, social sciences, and humanities is available through the WoSCC (You et al., 2021). We selected this database because of its multidisciplinary scope and citation indexing, which enables identification of the most impactful publications on CSVD. This database enabled us to identify publications related to the occurrence, causes, genetic factors, symptoms, identification, and treatment of CSVD. WoSCC is a recognized online database considered most suitable for bibliometric analysis (You et al., 2021). The search strategy was as follows: TI = (cerebral small vessel disease). The retrieval time was from January 2008 to January 2023. We limited the document types to "article" and "review." Only papers published in English were searched. Because the set time span does not include the literature for the 11 months after January 2023, the data for 2023 is not complete, and the research analysis does not represent the whole year. The flowchart for the selection of publications is shown in Figure 1.

2.2 Data extraction and analysis

Complete data and referenced sources from all files in the WoSCC were obtained in either txt or BibTeX form and subsequently transferred to CiteSpace 6.1.R3, 64-bit (Drexel University, Philadelphia, PA, USA); VOSviewer 1.6.18 (Leiden University, The Netherlands); or R (Version 4.0.2), per the specific software needed for analyzing and displaying the information. CiteSpace was developed by Professor Chaomei Chen for visual analysis of bibliometrics. By analyzing a vast amount of reference data in a specific research area using co-occurrence and co-citation techniques, the CiteSpace software can provide an objective and quantitative analysis as well as predict future research frontiers and trends (Chen and Song, 2019). In this research, CiteSpace was used to analyze the dual-map overlap of journals and the cluster view and burst detection of cited literature. The parameters were set as follows: time span (2008–2023), years per slice (1), pruning (Minimum Spanning Tree and Pruning Sliced Networks), selection criteria (top $N = 50$), and others followed the default. VOSviewer 1.6.17 was used to identify productive co-cited authors, keywords, and related knowledge maps. The bibliometrics packages in R were used to analyze the trends of annual publications and the citations of the publications. The URL https://bibliometric.com/was used to analyze the changing trend of the annual publication quantity in the top 10 countries and the geographic distribution map of different countries.

3 Results

3.1 The annual growth trend of publications

A total of 4891 publications on CVSD were retrieved from the WoSCC, including 4,056 articles and 835 reviews. The papers were written by 19,066 authors from 3,862 organizations across 84 countries, published in 790 journals, and cited 103,885 references from 8,783 journals. Dynamic changes on the number of publications during the past decade reflected the overall development trend in the field, with an average annual growth rate of 2.53%. As shown in Figure 2, the output of publications grew steadily from 2008 to 2022, especially in the last 2 years, although the average number of citations remained low. The average citation frequency of each article was 31.63, and the mean citation reached a peak in 2013, with a total of 164 articles and 7.1 mean citation, indicating that publications in 2013 might have contained groundbreaking or influential research findings.

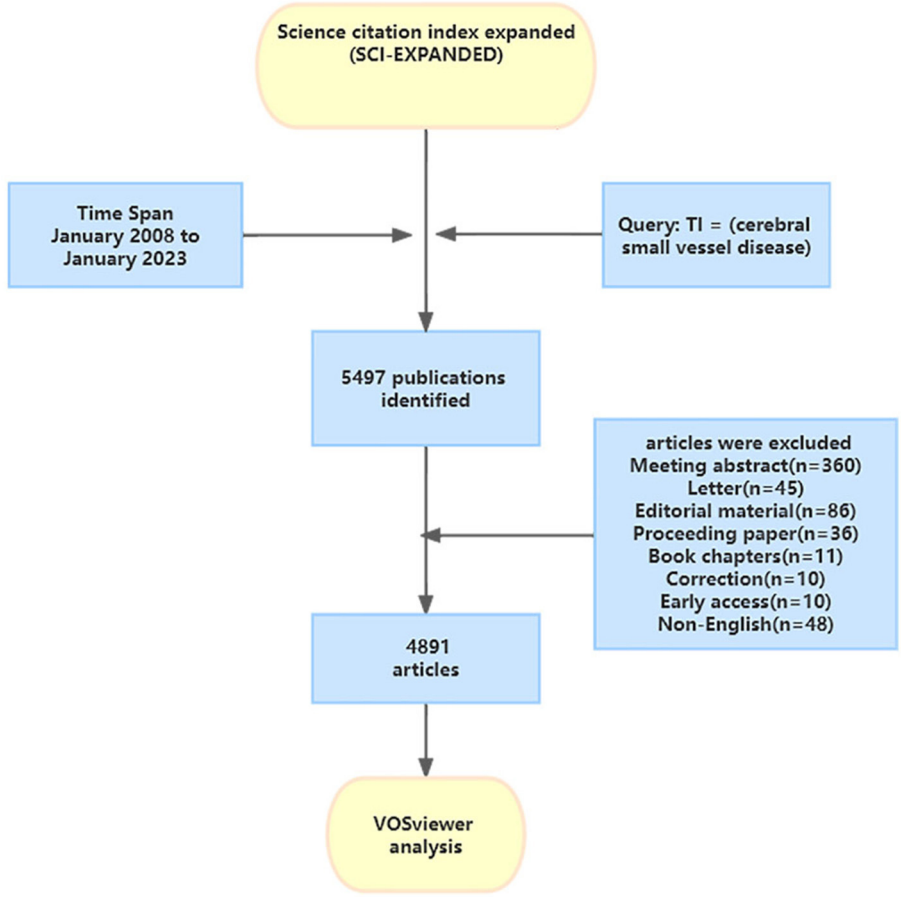

FIGURE 1
Flowchart for including and excluding literature studies.

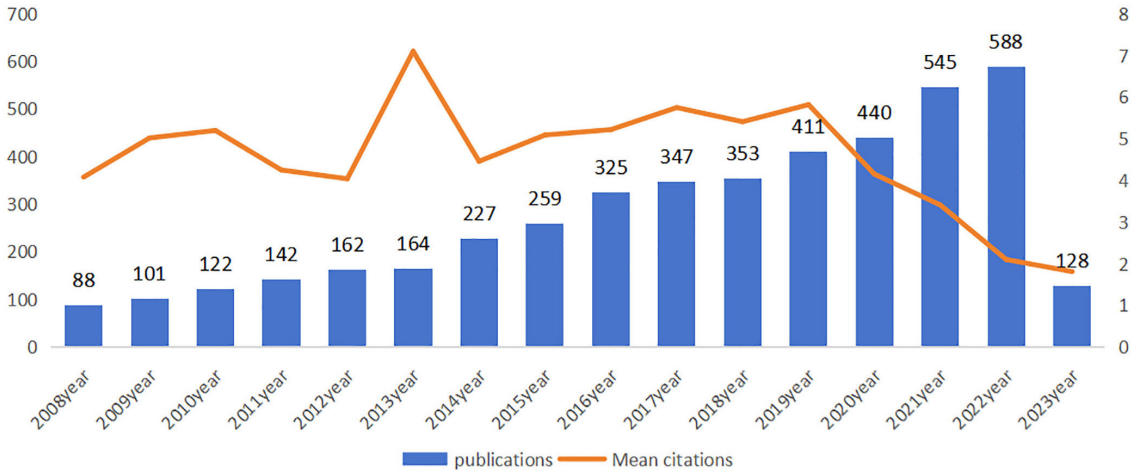

FIGURE 2
Number of annual publications and mean citation relating to CVSD from 2008 to 2023.

TABLE 1 Summary of the leading 10 nations and organizations.

Rank	Country	Number of publications	Number of citations	Average citation	Rank	Institution	Number of publications	Number of citations	Average citation	Country
1	USA	1,182	52,342	44.28	1	University of Edinburgh	221	13,906	62.92	England
2	China	973	18,686	19.20	2	Harvard Medical School	195	5,115	26.23	USA
3	Netherlands	563	31,217	55.45	3	Massachusetts General Hospital	138	6,708	48.61	USA
4	England	532	26,731	50.25	4	University of Cambridge	138	5,183	37.56	England
5	Germany	408	20,031	49.10	5	Capital Medical University	132	1,407	10.66	China
6	France	330	18,186	55.11	6	Univ med ctr Utrecht	119	4,864	40.87	Netherlands
7	Japan	314	7,360	23.44	7	Radboud University Nijmegen	116	4,335	37.37	Netherlands
8	Italy	264	13,280	50.30	8	Leiden University	115	4,526	39.36	Netherlands
9	South Korea	253	6,125	24.21	9	Maastricht University	94	3,727	39.65	Netherlands
10	Canada	252	14,555	57.76	10	Fudan University	92	1,084	11.78	China

3.2 Distribution of countries and institutions

The top 10 most productive countries and institutions in the CVSD field are presented in Table 1, including their publication count (NP), total citations (NC), and the average number of citations (AC). The United States (USA) led in publications with 1,182 papers (24.16%) and 52,342 citations, followed by China with 973 papers (19.89%) and the Netherlands with 563 papers (11.51%). It is important to mention that China's NC and AC were lower than the other top 10 productive countries, despite China being ranked second in NP.

In Figure 3A, the yearly publication count of the top 10 most productive nations is presented, indicating a rapid increase in publications related to CVSD. We utilized the Biblioshiny software to examine data and create visual representations to investigate international collaboration. The complexity of cooperation among various nations is illustrated in Figure 3B. As shown in Figure 3C, the international collaboration map among countries indicates that the USA collaborated most closely with China and England. VOSviewer analyzed the citation relationship between countries (Figure 3D). Countries that had at least 30 publications were considered. Out of the 48 countries and regions that reached this level, the leading five with the highest Total Link Strength (TLS) were the United States (TLS = 1,395), United Kingdom (TLS = 1,028), The Netherlands (TLS = 895), Germany (TLS = 888), and France (TLS = 728). The most influential institutions are outlined in Table 1. The institution with the highest NP and AC values was the University of Edinburgh (NP = 221). VOSviewer was used to analyze the citation connections among institutions (Figure 4). Institutions with at least 25 citation connections were considered for inclusion. Out of the 115 that qualified, the top five institutions with the highest TLS scores were the Massachusetts General Hospital (TLS = 54), Harvard Medical School (TLS = 44), University of Edinburgh (TLS = 34), University of Cambridge (TLS = 25), and Capital Medical University (TLS = 3).

3.3 Authors and co-cited authors

Table 2 displays the top 10 authors and co-cited authors who have made significant contributions to the field of CVSD. Wardlaw, Joanna was the most productive author, with 116 articles and 9,178 citations. The most co-cited author was also Wardlaw, Joanna, with a TLS of 10,176. A minimum of 30 publications per author was required, and 34 authors were chosen for co-authorship analysis using VOSviewer. According to the co-authorship analysis (Figure 5), the authors were categorized into five different clusters. The largest group of authors, with 10 individuals, was the red cluster with the most co-authorships.

3.4 Journals and co-cited journals

Stroke published the most articles (291, 36.8%) out of the journals analyzed, indicating that it is a leading journal in

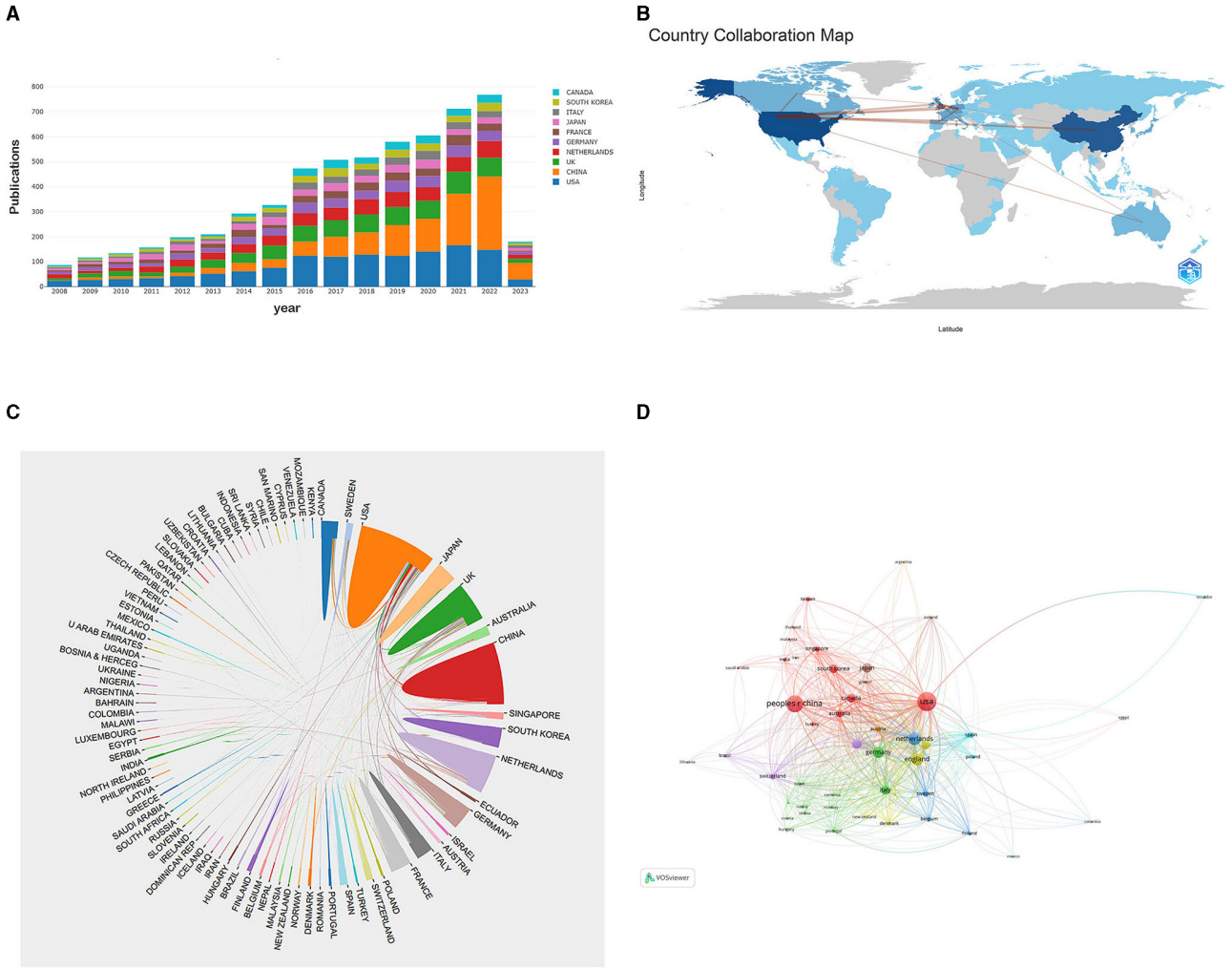

FIGURE 3
(A) The changing trend of the annual publication quantity in the top 10 countries from 2008 to 2023. **(B)** Geographic distribution map of different countries in the CVSD field. **(C)** The cross-country collaborations visualization map. **(D)** Network visualization showing the relationship between countries.

publishing research related to CSVD, followed by *Neurology* (156, 19.4%). Among the top 10 journals, *Neurology* holds the highest impact factor (IF = 10.1). The influence of the top 10 most co-cited journals is determined by how frequently they are cited. Table 3 shows that *Stroke* had the highest number of citations (23,217), suggesting its rigorous acceptance standards and commitment to publishing influential research that contributes to the advancement of knowledge and practice in the field. The second-most prolific journal was *Neurology*. We visually analyzed the collaboration of published journals using VOSviewer (Figure 6A). *Stroke*, *Neurology*, and the *Journal of Cerebral Blood Flow and Metabolism* had more times of co-citation and a greater influence than other journals. We also analyzed the change pattern in the annual occurrence frequency of journals (Figure 6B). The number of publications in *Stroke* has always been leading and is gradually widening the gap with other journals. The number of publications in *Frontiers in Neurology* increased rapidly from 2018 to 2022. In Figure 6C, the dual-map overlay of journal publishing research is presented. Citing journals on the left and cited journals on the right, the curve is the citation line, which completely shows the context of the citation. The more papers the journal publishes, the longer the vertical axis of the CVSD; the more authors they are, the longer the horizontal axis of the CVSD (Figure 6C). Three main citation paths were identified. The blue paths indicate that the studies published in Molecular/Biology/Genetics journals and Health/Nursing/Medicine journals are usually cited in the studies published in Molecular/Biology/Immunology journals. The pink paths represent that studies published in the Molecular/Biology/Genetics/Health/Nursing/Medicine/Psychology/Education/Social journals are typically cited in the studies published in Medicine/Medical/Clinical journals. The green paths represent that the studies published in Molecular/Biology/Genetic/Health/Nursing/Medicine/Psychology/Education/Social journals are usually

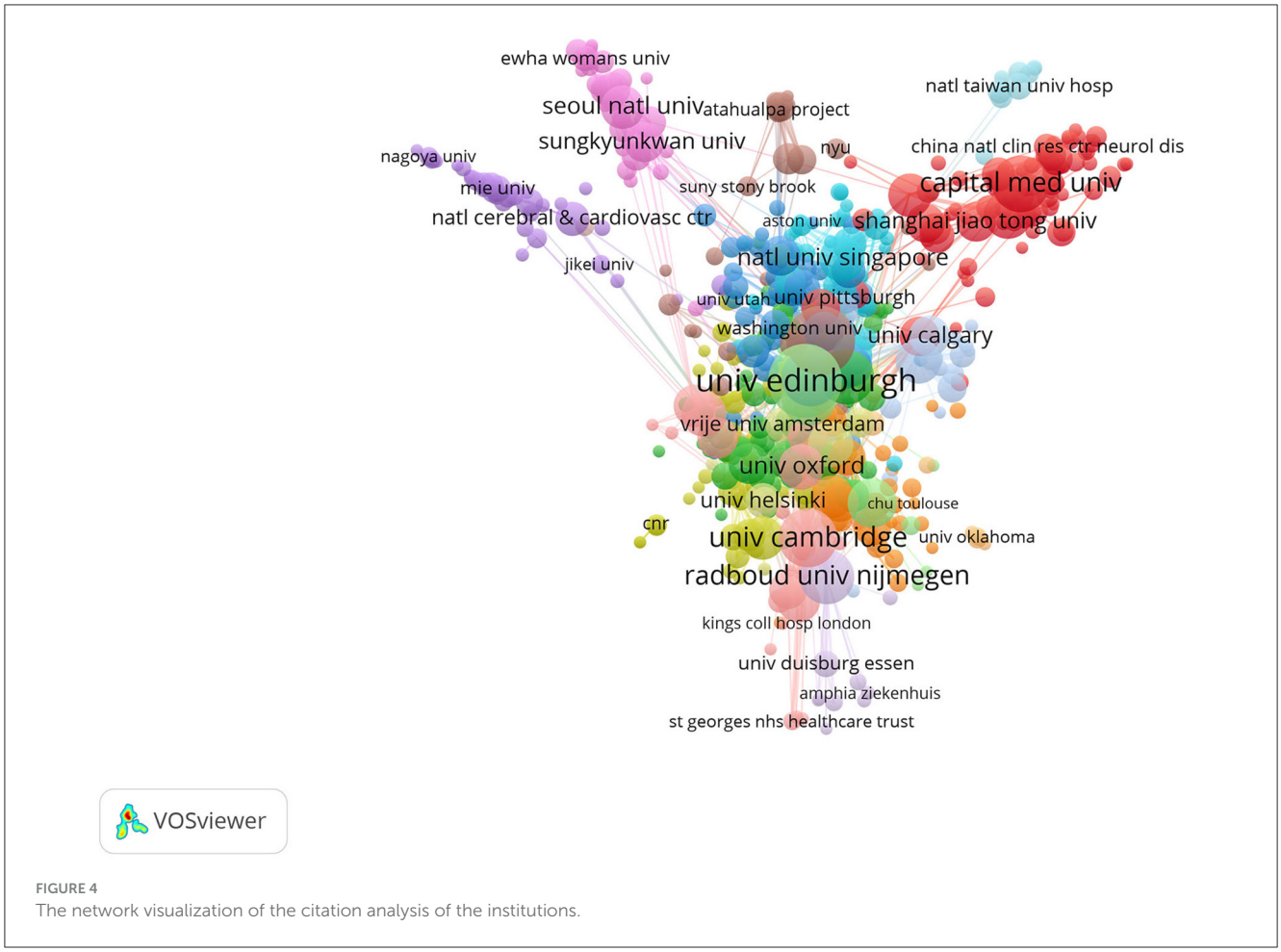

FIGURE 4
The network visualization of the citation analysis of the institutions.

TABLE 2 Top 10 authors and co-cited authors of CSVD publications.

Rank	Author	Publications	Citations	Average citation	Co-citations author	Citations	Total link strength
1	Wardlaw, Joanna M.	116	9,178	79.12	Wardlaw, Joanna M.	3,477	10,176
2	Greenberg, Steven M.	99	7,433	75.08	Pantoni, L	1,758	6,476
3	Charidimou, Andreas	94	4,676	49.74	Charidimou, A	1,527	7,032
4	Markus, Hugh S.	89	3,975	44.66	Fazekas, F	1,376	5,168
5	Viswanathan, Anand	86	5,453	63.41	Greenberg, SM	1,061	5,247
6	De Leeuw, Frank-Erik	77	3,355	43.57	Joutel, A	772	1,771
7	Dichgans, Martin	66	5,223	79.14	Smith, EE	659	3,634
8	Duering, Marco	64	2,463	38.48	Debette, S	618	3,035
9	Duering, Marco	60	3,531	58.85	Vermeer, SE	616	2,820
10	Biessels, Geert Jan	59	3,576	60.61	Schmidt, R	569	2,931

cited in the studies published in Neurology/Sports/Ophthalmology journals.

The co-occurrence relationships between institutions, authors, and publication sources are presented in a three-field plot (Figure 6D). The size of each node represented its frequency or importance, while the connections between nodes represented co-occurrence relationships between two indicators, with the thickness of the lines indicating the frequency or strength of the co-occurrence. The most co-occurrence relationship existed between the institutions "Harvard university" is predominantly associated with the author "Greenberg, Steven M." and the Journal of stroke and neurology. Notably, certain authors exhibited strong co-occurrence with specific institutions; for example, "Charidimou,

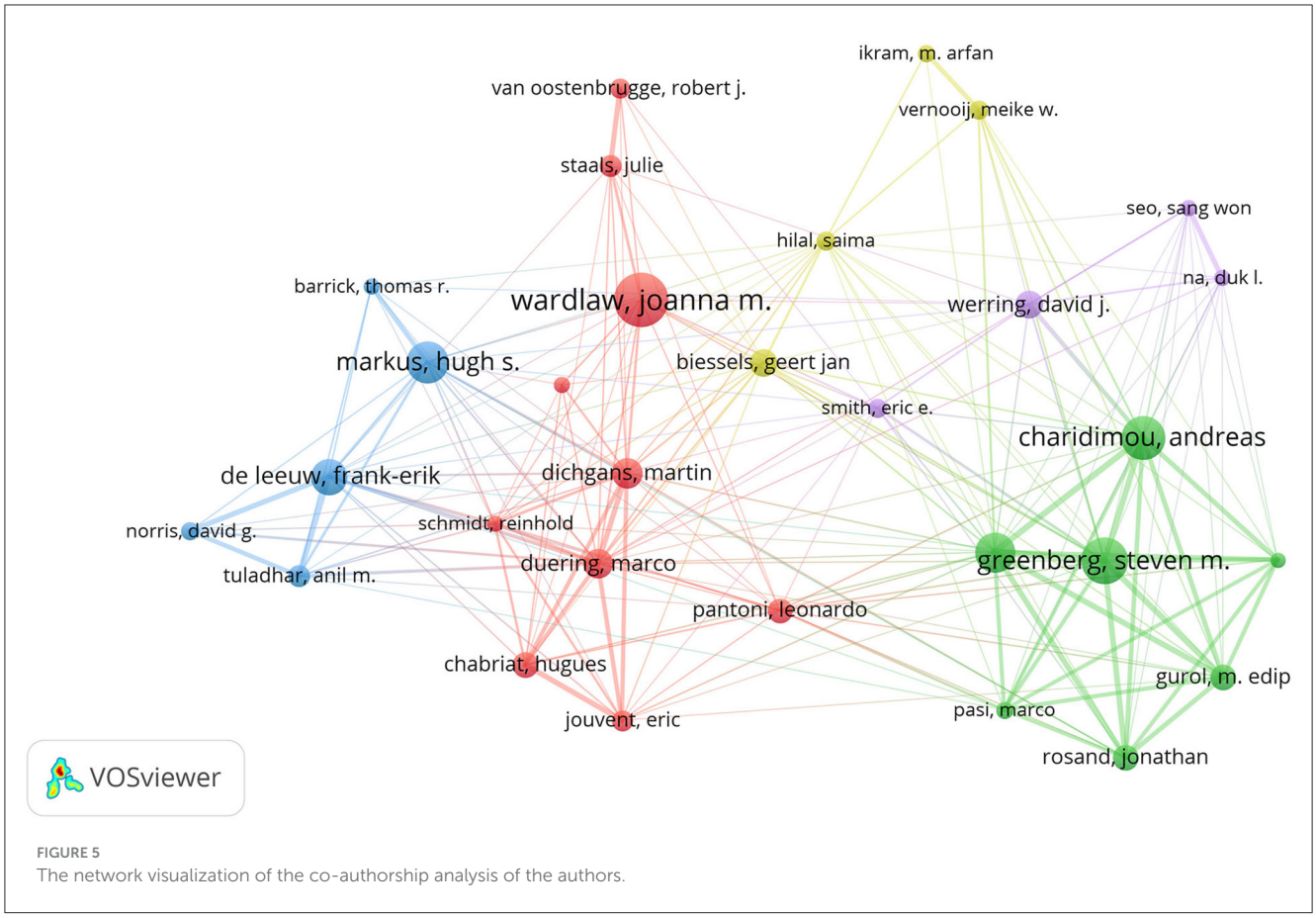

FIGURE 5
The network visualization of the co-authorship analysis of the authors.

TABLE 3 Top 10 journals and co-cited journals of CSVD publications.

Rank	Journal	Publications	IF (Journal Citation Reports, 2022)	Co-citations journal	Citations	IF (Journal Citation Reports, 2022)
1	Stroke	291	8.4	Stroke	23,217	8.4
2	Neurology	156	10.1	Neurology	16,194	10.1
3	Frontiers in Neurology	152	3.4	Lancet Neurol	7,570	48
4	Journal of Stroke & Cerebrovascular Diseases	132	2.5	Journal of Cerebral Blood Flow and Metabolism	4,401	1.6
5	Journal of Cerebral Blood Flow and Metabolism	124	6.3	Brainj Cerebr Blood F Met	4,288	0.5
6	Journal of Alzheimer's Disease	123	4	Ann Neurol	4,142	4.7
7	Frontiers in Aging Neuroscience	112	4.8	J Neurol Neurosur Ps	3,964	1.6
8	Journal of the Neurological Sciences	81	4.4	Neuroimage	3,865	5.7
9	PLOS One	70	3.7	Neurobiol Aging	3,024	5.9
10	International Journal of Stroke	69	6.7	Cerebrovascular Disease	2,843	1.9

Andreas" and "Viswanathan, Anand" were closely linked with Harvard University. With respect to journals, *Stroke* and *Neurology* contributed largely to all these authors' publications. These observations shed light on influential authors and institutions in this research domain and provide insights into potential future research directions.

3.5 Co-cited references and references burst

The top 10 documents that were cited the most are listed in Table 4. The paper titled "Neuroimaging standards for studying small vessel disease and its impact on aging

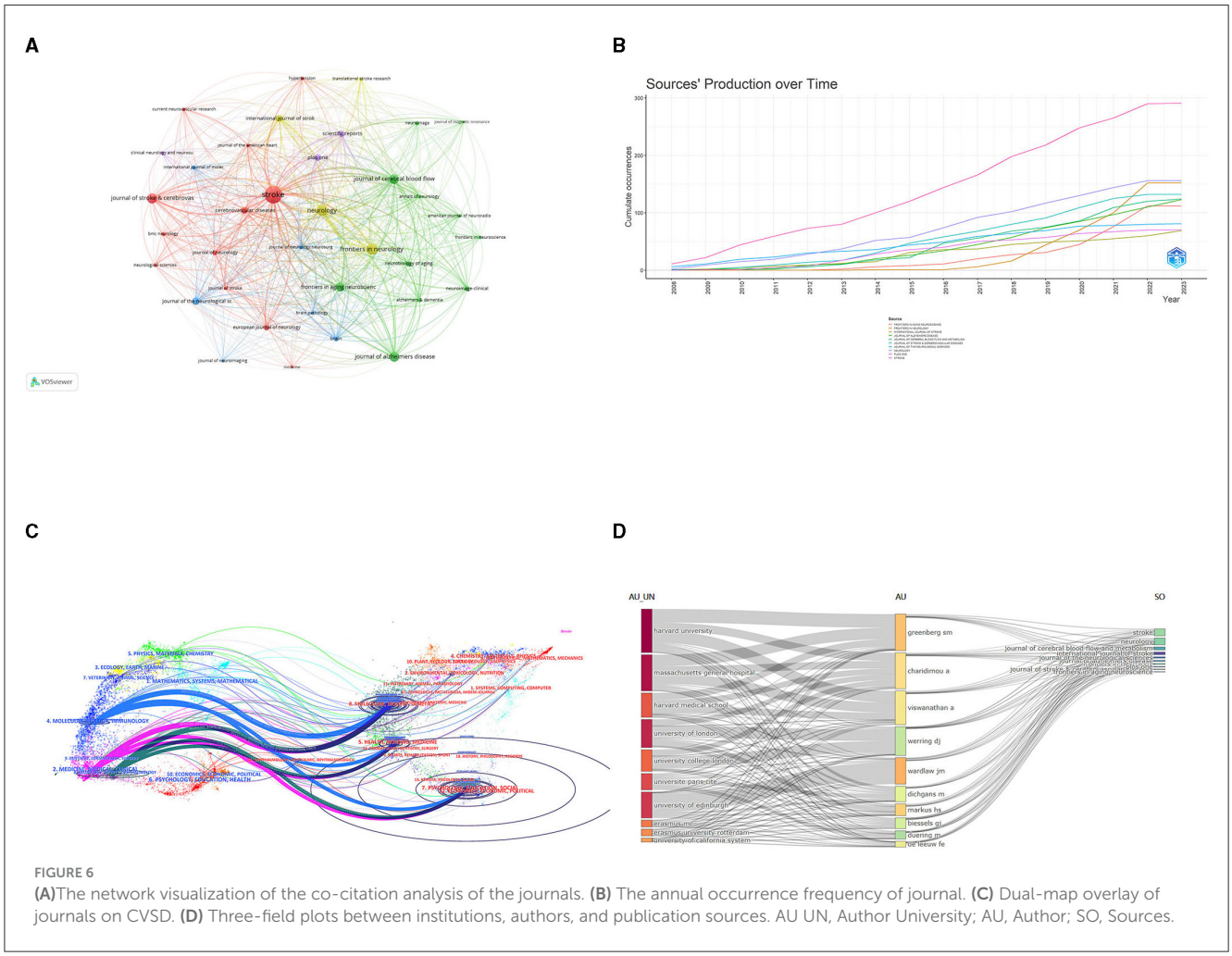

FIGURE 6
(A) The network visualization of the co-citation analysis of the journals. **(B)** The annual occurrence frequency of journal. **(C)** Dual-map overlay of journals on CVSD. **(D)** Three-field plots between institutions, authors, and publication sources. AU UN, Author University; AU, Author; SO, Sources.

and neurodegeneration" by Wardlaw et al. (2013a) is the most frequently referenced, with 3,276 citations. CiteSpace's clustering function was utilized to categorize co-cited references (Figure 7A), revealing the primary author and top 10 most-cited references. The literature that is cited most often and has the most significant bursts of citations is seen as the foundation for upcoming innovative research. This is illustrated in Figure 7B, which displays the top 25 bursts of citations in chronological order. The blue line indicates the observed time interval from 2008 to 2023, and the red color represents the duration of the burst, thus illustrating research hot spots and durations. The above paper authored by Wardlaw, Joanna achieved the highest citation strength for outbreaks (strength = 160.28). Nine articles focusing on the mechanism, pathology, and clinical features of CSVD were published starting in 2020.

3.6 Key topics of research hot-spots

To identify popular topics and assist scholars to better understand current scientific concerns, cluster analysis could be used to cluster the included keywords. Keyword co-occurrence and network cluster analysis are both available through CiteSpace. The hot spots of CSVD research are illustrated in Table 5 and Figure 8A, which display the most commonly used keywords. The most relevant terms in CSVD research were identified by the keyword co-occurrence clusters using the hierarchical cluster labeling method; the cluster modularity Q value is 0.8501, while the mean contour value S value is 0.9326. Typically, a Q value > 0.3 represents a significant clustering structure; if the average cluster contour value $S > 0.5$, the clustering is generally considered reasonable. If the S-value $>$ 0.7, the clustering result is considered convincing. This study identified 10 clusters of keywords, which includes "endothelial dysfunction" (cluster #1), "cerebral amyloid angiopathy" (cluster #2), "cerebral blood flow" (cluster #3), "cerebral small vessel disease" (cluster #4), "lesions" (cluster #5), "cerebral microbleeds" (cluster #6), "cerebrovascular disease" (cluster #7), "vascular dementia" (cluster #8), "magnetic resonance imaging" (cluster #9), and "blood pressure" (cluster #10) (Figure 8B). To depict the development of high-frequency keywords within each cluster, CiteSpace developed a keywords timeline viewer that could cluster keywords and take time into consideration. The viewer might also make it straightforward to identify the time frame for a specific subject and the development of this research area. Each stage and evolution path of the CSVD research's concentration could be intuitively understood, as shown in Figure 8C. This study formed 10 clusters of keywords, showcasing

TABLE 4 Top 10 co-cited references related to CVSD.

Paper	DOI	Total citations	TC per year	Normalized TC
Wardlaw et al. (2013a), Lancet Neurol	10.1016/S1474-4422(13)70124-8	3,276	297.82	41.97
Pantoni (2010), Lancet Neurol	10.1016/S1474-4422(10)70104-6	2,086	149	28.67
Greenberg et al. (2009), Lancet Neurol	10.1016/S1474-4422(09)70013-4	1,255	83.67	16.68
Iadecola (2013), Neuron	10.1016/j.neuron.2013.10.008	1,108	100.73	14.2
Wardlaw et al. (2013b), Lancet Neurol-A	10.1016/S1474-4422(13)70060-7	1,027	93.36	13.16
Sweeney et al. (2019), Physiol Rev	10.1152/physrev.00050.2017	939	187.8	32.26
Nation et al. (2019), Nat Med	10.1038/s41591-018-0297-y	751	150.2	25.8
Prins and Scheltens (2015), Nat Rev Neurol	10.1038/nrneurol.2015.10	656	72.89	14.32
Wardlaw et al. (2019), Lancet Neurol	10.1016/S1474-4422(19)30079-1	641	128.2	22.02
Mansour et al. (2018), Nat Biotechnology	10.1038/nbt.4127	621	103.5	19.13

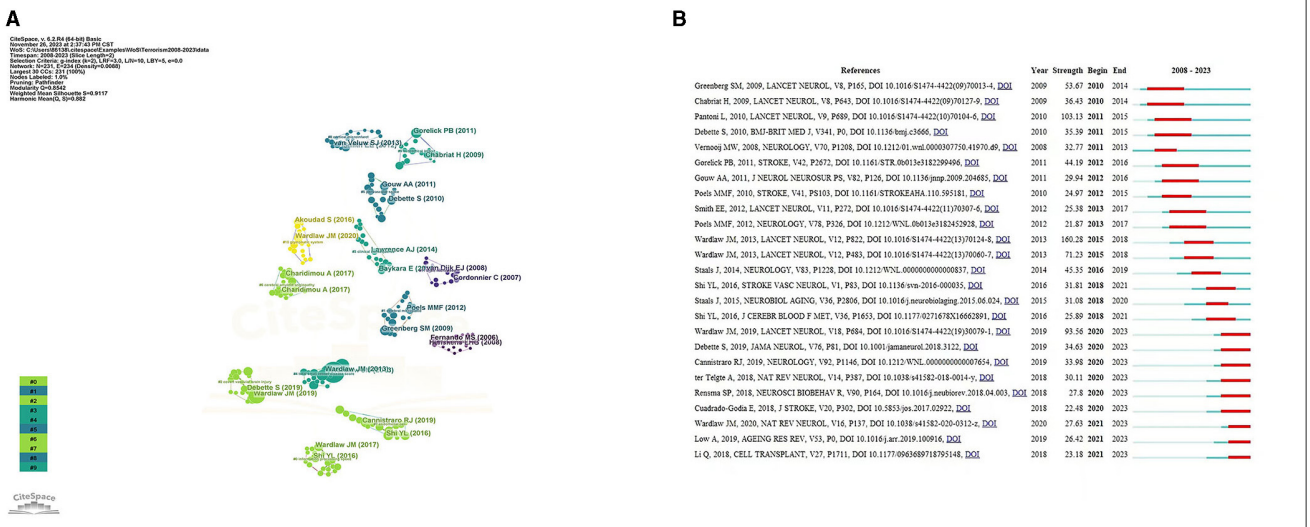

FIGURE 7
(A) References analysis to CVSD. **(B)** Top 25 References with the strongest citation bursts.

the knowledge structure and dynamic changes in the CVSD field to some extent. Table 6 contains a list of clusters in summary form.

According to the detection of emerging words with high frequency and fast growth rate within a period of time, keywords with high-burst intensity are an important indicator reflecting research hot spots, frontiers, and latest trends (Figure 9). Twenty-five new words were identified, with the term "white matter lesions" having the highest increase in citations at 37.48 in 2008. The keyword bursts among of them that lasted until 2023 included "cerebral small vessel disease," "segmentation," and "basal ganglia," which represented the hot spots in recent years.

4 Discussion

4.1 General information

This study examined the characteristics of articles in the CSVD field over the last 15 years to describe the current research and help guide future research. The number of publications per year was tracked to identify trends over the past 15 years. Highly cited articles, defined as those in the top percentile of citations, were noted as these tend to signify groundbreaking research. Productivity of countries was quantified by the number of CSVD publications across the time period. Specific research institutions and individual authors with extensive CSVD-focused portfolios

TABLE 5 The top 20 keywords associated with CSVD research.

Rank	Keyword	Count	Rank	Keyword	Count
1	Small vessel disease	1,370	11	Cognitive impairment	466
2	Stroke	1,058	12	White-matter hyperintensity	461
3	Cerebral small vessel disease	907	13	Magnetic resonance imaging	429
4	Dementia	868	14	Cerebral amyloid angiopathy	412
5	MRI	748	15	White-matter lesions	375
6	Alzheimer's-disease	657	16	Cerebral microbleeds	363
7	Small-vessel disease	566	17	Microbleeds	358
8	Risk-factors	565	18	Leukoaraiosis	354
9	Brain	559	19	Prevalence	342
10	Risk	514	20	Ischemic-stroke	329

were documented as leading producers. Using keyword analysis, prevalent research themes and hot topics were identified. Mapping these bibliometric parameters over time illustrated the evolution of global CSVD research. As shown in Figure 2, only 88 articles were published in 2008, suggesting that researchers were just beginning to understand CSVD. Since then, there has been a steady increase in the number of research papers focusing on CSVD, particularly in the past couple of years. This trend suggests that the study of CSVD is gaining more research interest and continues to be a popular research topic. The future trajectory remains positive. However, the number of mean citations is not smooth. The later the papers are published, the lower their times of being cited. The higher the mean citations, the more important the publication in the field. The mean citations peaked in 2013, suggesting that this was a pivotal year during which influential literature may have been published. Wardlaw et al. (2013a) paper titled "Neuroimaging standards for studying small vessel disease and its impact on aging and neurodegeneration" achieved the highest citation, and supported the correlation between the peaks in mean citations and the publication of seminal literature.

The analysis of countries showed that the USA made the highest contribution in terms of NP and NC, indicating that it is a top-performing and influential country in the field of CVSD research, with strong collaboration networks with China and England. Although the NP of China ranked second, the numbers of NC and AC were relatively low. These data suggest that China is experiencing a discrepancy between the number and standard of its publications. To tackle this problem, it is important to improve cooperation with various nations, particularly the United States, The Netherlands, and Germany, while also closely monitoring advancements in science and conducting thorough research to enhance the quality of publications. At the institutional level, the University of Edinburgh published the most articles in this field.

Wardlaw Joanna M., a researcher at the University of Edinburgh's Research Center for Stroke and Dementia, holds the record for the highest number of publications in this particular field of study. Among the top 10 most productive institutions, universities make up the main body, of which 40% were from The Netherlands and accounted for the largest proportion. In China, Capital Medical University and Fudan University are the most productive institutions in the CVSD field. In terms of research institutions, strengthening the cooperation between different institutions or teams is extremely important for future basic or clinical trials of CVSD. Wardlaw, Joanna turned out to be the most productive author in the CVSD field among the top 10 authors with high output. It is important to mention that Wardlaw is one of the top 10 authors frequently cited together, focusing on various articles related to the mechanisms, clinical importance, and neuroimaging criteria for small vessel disease (Arba et al., 2017; Francis et al., 2019; Horsburgh et al., 2018; Wardlaw et al., 2013a, 2019, 2013b). Furthermore, He participated in many clinical trials of CSVD (Blair et al., 2022; Markus et al., 2022) and was involved in the development of guidelines to provide evidence-based recommendations to assist with clinical decisions about CSVD management (Wardlaw et al., 2021). In this ESO Guideline on covert CVSD, he recommended patients with CSVD and hypertension to have their blood pressure well-controlled, as lower blood pressure targets may reduce CSVD progression; furthermore, he does not recommend antiplatelet drugs such as aspirin in CSVD. While the AC of Dishpans, martin was ranked first, but the gap is very subtle. Dishpans, Martin is a neurologist from the German Center for Neurodegenerative Disease. He is famous for his contributions to investigate the impact of lesion location in processing speed in age-related small vessel disease (Agirman et al., 2021; Duering et al., 2014). The VOSviewer software automatically categorized authors into distinct groups. The authors from the same clusters contributed excellent scientific works to their region. We also observed Charidimou, Andreas as a seconded TLS (Figure 5), whose research focused on cerebral amyloidosis and cerebral hemorrhage associated with CVSD (Castello et al., 2021; Charidimou et al., 2019; Scheumann et al., 2020). Wardlaw, Joanna was a bridge connection with other authors. The Boston criteria version 2.0 was established for the evaluation of cerebral amyloid angiopathy in a multicenter and retrospective study (Charidimou et al., 2022). Collaboration has always been an important requirement for the advancement of scientific discovery.

Among the top 10 journals with the highest productivity, *Stroke*, *Neurology*, and *Frontiers in Neurology* stood out as the most productive, specializing in CSVD. The number of publications

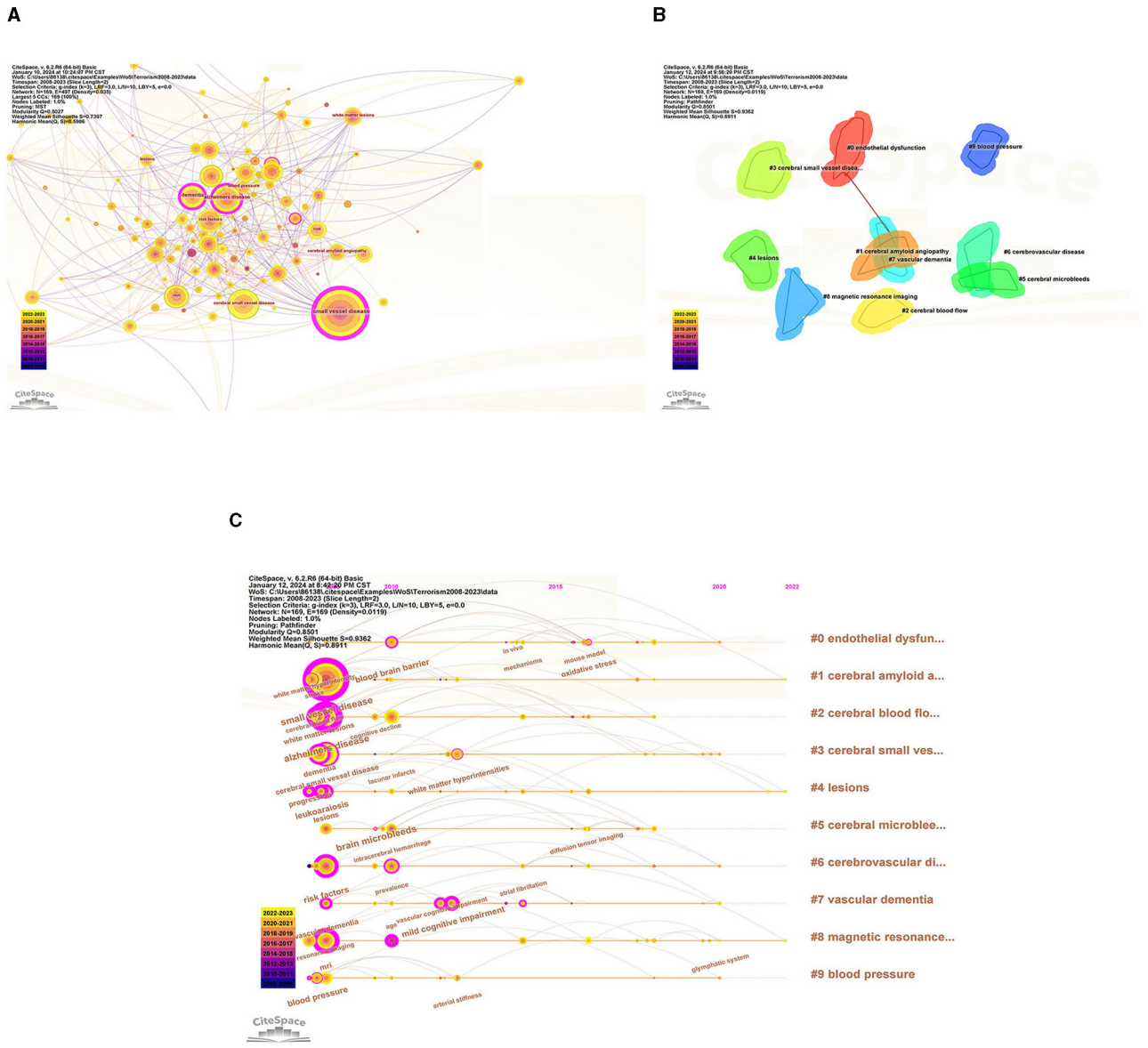

FIGURE 8
(A) The network map of keywords. **(B)** Clustered network of keywords. **(C)** The timeline view of keywords.

shows an increasing trend year by year, suggesting that CSVD is a relatively new and in-demand research field. In addition, the *Stroke* journal has gradually widened the gap with other journals, which likely indicates that research in the CSVD field is deepening and expanding, and academic collaboration may become more and more important to solve complex problems and improve the quality of research. More significant research findings are anticipated to be released in *Stroke* in the coming years, leading to an increase in both impact factor and scientific merit. Scientists must monitor this journal to track the advancement of CSVD and anticipate future developments. Moreover, analyzing the journal could assist researchers in expediting the research process by promptly determining the most suitable journals for submission. As shown in Figure 6C, the presence of these citation paths also highlights the importance of knowledge transfer across disciplines. Researchers in different fields often refer to and build upon each other's work, leading to the advancement and development of new ideas and approaches in various scientific domains. Overall, these identified citation paths provide insights into the interconnections of different fields of study, research trends, potential collaboration opportunities, and knowledge transfer across disciplines.

Analyzing co-citations is a useful way to evaluate the degree of connection among articles. In the professional field, the importance of an article is believed to increase with the frequency of its citations (Wu et al., 2021). Most of the top 10 cited references were published in top-ranked journals, and three articles were written by Wardlaw et al. (2013a,b, 2019); this result also confirmed the results of the author analysis. In 2013, Wardlaw, Joanna established the imaging criteria for CSVD for the first time, which have been referenced since then. Four out of the top 10 cited references focused on the

TABLE 6 Keyword cluster analysis.

Cluster ID	Size	Silhouette	Mean (year)	Top terms (LSI)
0	17	1	2014	Endothelial dysfunction; oxidative stress; blood brain barrier; microglia; magnetic resonance imaging
1	16	1	2011	Cerebral amyloid angiopathy; small vessel disease; white matter hyperintensity; cerebral small vessel disease; Alzheimer's disease
2	14	0.985	2011	Cerebral blood flow; Alzheimer's disease; cognitive impairment; white matter lesions; ischemic stroke
3	14	1	2013	Cerebral small vessel disease; white matter hyperintensities; white matter; lacunes; lacunar infarcts
4	13	0.921	2013	Lesions; progression; leukoaraiosis; dysfunction; infarcts
5	13	0.937	2014	Cerebral microbleeds; intracerebral hemorrhage; amyloid angiopathy; cortical superficial siderosis; cerebral amyloid angiopathy
6	13	0.976	2011	Cerebrovascular disease; risk factors; atrial fibrillation; prevalence; cerebral infarction
7	13	0.885	2013	Vascular dementia; vascular cognitive impairment; mild cognitive impairment; intracerebral hemorrhage; blood-brain barrier
8	12	0.931	2016	Magnetic resonance imaging; cerebral small vessel diseases; cognitive dysfunction; glymphatic system; perivascular spaces
9	12	1	2011	Blood pressure; arterial stiffness; lacunar stroke; risk; pulse-wave velocity

pathogenesis and clinical characteristics of CSVD. Understanding the pathology and clinical manifestations of disease can help people better recognize the disease, prevent it, treat it, and improve their quality of life. Three out of the top 10 references cited focused on the correlation between cognitive dysfunction and CSVD. The article titled "Blood-Brain Barrier: From Physiology to Disease and Back," focused on BBB transport physiology, endothelial and pericyte transporters, and perivascular and Para vascular transport. Additionally, it examines rare genetic neurological disorders that originate from defects in BBB-related cells, highlighting the connection between BBB dysfunction and neurodegeneration (Sweeney et al., 2019). Based on this, Wardlaw et al. found emerging targets for new therapies including brain barrier integrity, vascular reactivity, vascular compliance, perivascular inflammation, and myelin repair (Jian et al., 2020).

Citation bursts are citations that have been heavily cited by other researchers recently, indicating new trends in a particular area of study. The initial reference burst originated in 2010 because of studies that were published in 2014. Greenberg et al. (2009) have suggested a step-by-step manual for detecting CMBs and recommend potential future strategies for understanding the significance of these frequent abnormalities as indicators of, and contributors to, small-vessel brain disorders. Chabriat et al. (2009) summarized the knowledge of CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy)—the primary genetic factor leading to stroke and vascular dementia in adults. Both the above articles were published in *Lancet Neurol*. The strongest burst reference was the international neuroimaging standards for CSVD (Wardlaw et al., 2013a). There were nine article bursts from 2020 up to the present time (Bernal et al., 2020; Cannistraro et al., 2019; Cuadrado-Godia et al., 2018; Liu X. et al., 2018; Low et al., 2019; Ma et al., 2019; Rensma et al., 2018; Ter Telgte et al., 2018; Wardlaw et al., 2019), and the successful publication of these articles clarify the mechanism, pathology, and clinical manifestations of CSVD. Among them, new papers reporting vascular inflammation and endothelial dysfunction may be the driving force behind CSVD; however, the associations between systemic inflammation and CSVD remain inconclusive.

Keywords summarize the main concepts of an article and are typically seen as crucial markers that indicate the research focus and trending topics within a particular field (Yi et al., 2018). Analyzing the top 20 most frequent keywords reveals that "small vessel disease" and "Alzheimer's disease" were among them. In terms of different forms of coexisting disease in CSVD, Alzheimer's disease (AD) and small vessel disease often coexist (Gocke et al., 1970). Alzheimer's disease shares common risk factors such as high blood pressure and diabetes, and pathophysiological processes like oxidative stress, inflammation, mitochondrial dysfunction, and metabolic abnormalities with CSVD. Damage to the wall can cause microaneurysms to grow externally as a result of fibrosis and narrowing or blockage of the nearby lumen (Liu Y. et al., 2018). Pathologically, wall damage can lead to external expansion of microaneurysms due to fibrosis and proximal luminal stenosis or obstruction (Chou et al., 2021). Ultimately, dysfunction in the regulation of the affected small blood vessels causes a reduction in blood flow to the brain and long-term inadequate blood supply to the brain, while blockage of the artery results in sudden lack of blood flow, resulting in lacunar infarction (Tang and Liu, 2021). Severe stenosis and hypoperfusion involving multiple arterioles, mainly deep white matter, leading to incomplete ischemia, are seen on neuroimaging as "white matter hyperintensity" (WMH) (Wang et al., 2021). From the beginning, genetics have played a role in influencing the risk of developing AD. Early-onset AD has been linked to familial autosomal-dominant genes *PSEN1, PSEN2*, and the amyloid precursor protein (*APP*) gene (Lamb, 1997). Furthermore, multiple genetic indicators can influence both AD and CVSD. It is uncertain if these genes contribute to the development of CSVD and subsequently impact AD, or if they directly impact both CSVD and AD. The ε4 variant of the

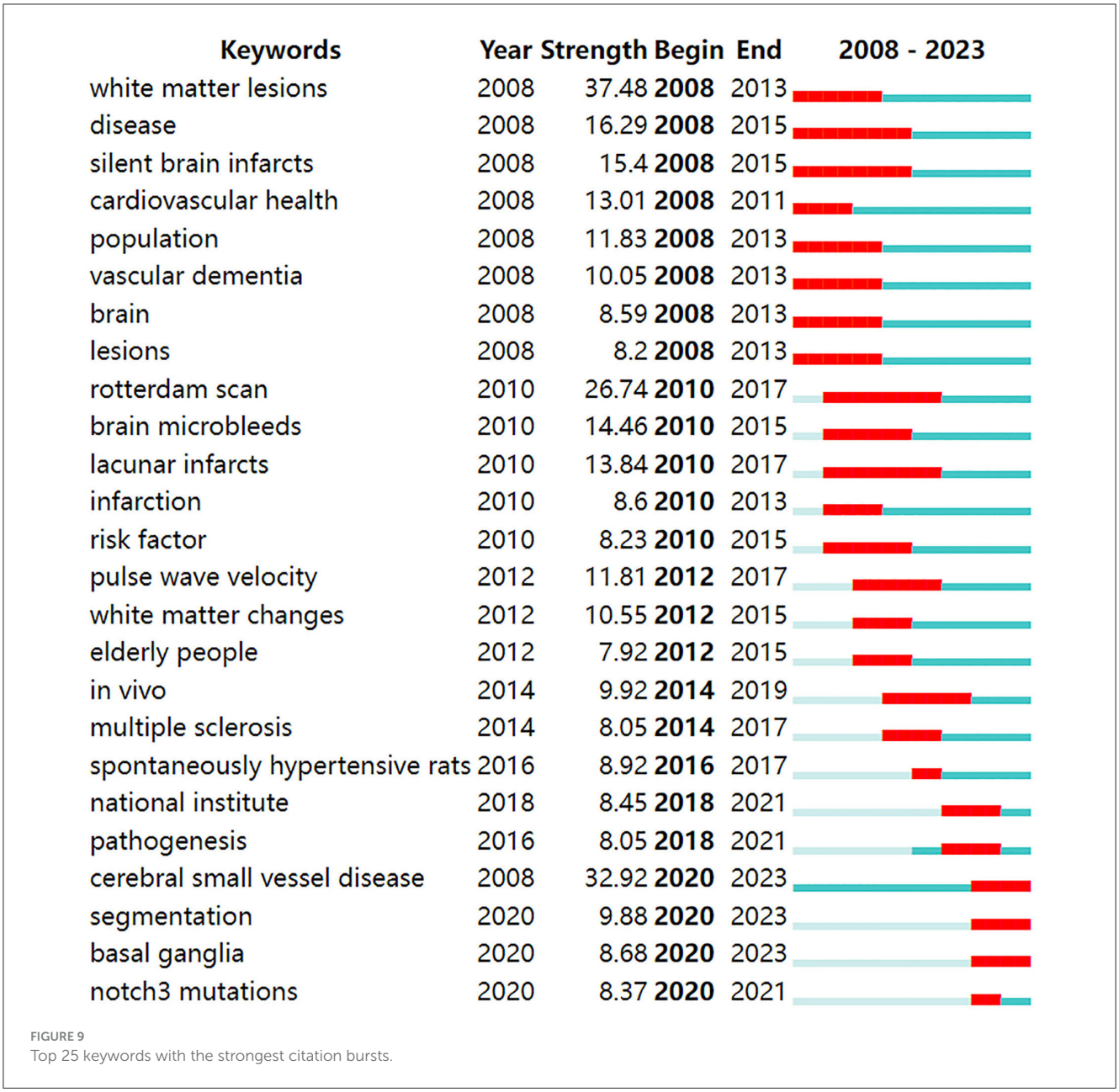

FIGURE 9
Top 25 keywords with the strongest citation bursts.

apolipoprotein E (*APOE*) gene increases the risk of both AD and CSVD (Kim et al., 2020).

The evolution and change of keywords over time reflect, to some extent, the development of hot spots and can guide future research directions. The research core themes can be distilled into the following characteristics by using four analyses: ① #2, # 7, and # 9 are disease research fields, mainly related to the sequel caused by CSVD, including keywords such as dementia, cognitive impairment, and lacunar stroke; ② #0 and #1 are pathological changes of CSVD, mainly including endothelial dysfunction, oxidative stress, and cerebral amyloid angiopathy; ③ #3, #4, #5, #6, and #8 are the markers on magnetic resonance imaging (MRI) and influence changes caused by CSVD, including leukoaraiosis, white matter, cerebral micro bleeds, cardiovascular spaces, and MRI.

Burst detection, which utilizes algorithms to identify significant changes in events, can be executed in CiteSpace. There are two characteristics associated with the burst: its strength and duration. Trending search terms have increased in popularity over time, indicating the level of interest from people. "Cerebral small vessel disease" lasted from 2008 until 2023, which means the people pay more attention to it. The keyword bursts among them that lasted from 2020 to 2023 included "cerebral small vessel disease," "segmentation," and "basal ganglia," which have represented the hot spots in recent years.

4.2 Research core themes

4.2.1 Clinical manifestation of CSVD

CSVD can present with different symptoms based on the underlying cause of the condition and the areas of the brain that are impacted. Individuals may present sudden onset stroke symptoms, progressive cognitive deterioration, dementia, gait disorder, sphincter dysfunctions, and psychiatric disorders (Del Bene et al., 2013; van der Flier et al., 2005; Rensma et al., 2020). Cognitive decline caused by CSVD presents with executive dysfunction, attention and memory decline, set-shifting disabilities, slower speed of information processing, decline of verbal fluency, and delayed recall. Symptoms of apathy, mood disorders, depression, and difficulties with daily activities were observed in the behavioral domain. Currently, the cause of cognitive impairment in CSVD is still unknown. It has been suggested that cognitive dysfunction in CSVD patients may be related to atherosclerosis and microvascular dysfunction (Rensma et al., 2020), which may affect cerebral blood perfusion, neurogenesis, and brain self-regulation, resulting in both neurological and cognitive dysfunction in CSVD patients (Rensma et al., 2020).

Additionally, lacunar infarctions make up 25% of total acute ischemic strokes. Although lacunar strokes may occasionally result from mechanisms of brain ischemia, such as cardiac embolism or carotid artery stenosis, most result from intrinsic diseases of the small deep perforating arteries (Bailey et al., 2012). Hypertension and diabetes mellitus are commonly linked to lacunar stroke (Wardlaw, 2005). The SPS3 trial (Secondary Prevention of Small Subcortical Strokes) is the largest study to date that enrolled cases of MRI confirmed lacunar stroke (Benavente et al., 2012). The SPS3 trial tested two randomized interventions: clopidogrel and aspirin vs. aspirin alone and two target levels of systolic blood pressure (Benavente et al., 2012). Dual antiplatelet therapy increased the incidence of major hemorrhage and mortality rate, and thus, the trial was stopped early. Furthermore, the risk of recurrent stroke was not significantly reduced by dual antiplatelet therapy. The SPS3 was also designed to test whether a systolic blood pressure target <130 mmHg compared with 130–149 mmHg would be associated with a reduction of all strokes (ischemic and hemorrhagic). Although there was a 19% decrease in all strokes that was not statistically significant, the authors found a significant decrease in intracerebral hemorrhage (Benavente et al., 2013). Recent research indicates that maintaining strict control over blood pressure may be advantageous for individuals who have experienced a lacunar stroke. Currently, antiplatelet monotherapy is recommended to prevent recurrent strokes after lacunar strokes, because dual antiplatelet therapy might increase major bleeding risk without providing additional stroke-reduction benefits. A recent trial called PICASSO (Prevention of Cardiovascular Events in Asian Patients with Ischemic Stroke at High Risk of Cerebral Hemorrhage) evaluated the efficacy and safety of cilostazol vs. aspirin. Cilostazol was found to be just as effective as aspirin in preventing cardiovascular events in the study; however, it did not lower the occurrence chance of a hemorrhagic stroke (Kim et al., 2018). A recent randomized controlled study found that individuals with minor ischemic stroke or high-risk transient ischemic attack had a reduced risk of major ischemic events but an increased risk of major hemorrhage at 90 days when treated with both clopidogrel and aspirin, compared to those treated with aspirin alone (Johnston et al., 2018).

4.2.2 The pathological changes of CSVD

The exact pathophysiological processes of CSVD remain unknown. We observed that the solid line of cluster#0 named "endothelial dysfunction" was initially believed to be an etiological contributor to CSVD, which halted in recent years on the timeline view. A previous study indicated that endothelial dysfunction is the key initiator for CSVD and its pathogenesis, predating BBB breakdown (Karlsson et al., 2012). Endothelial cells (ECs) act as a barrier between tissue and blood, controlling blood flow, managing transport of circulating components, and playing a role in inflammatory processes. Endothelial dysfunction-induced brain damage manifests in several ways *via* different mechanisms. The ECs control the local CBF by secreting vasodilatory mediators (NO and prostacyclin) or vasoconstrictors (endothelin) in response to chemical or mechanical stimulators which constitute the endothelial-dependent vasodilatory or vasoconstrictor response (Iadecola and Gottesman, 2019). The endothelial cells are also involved in creating the blood-brain barrier (BBB) by forming tight junctions (Iadecola and Gottesman, 2019). The reduction in NO synthesis in EC dysfunction can also lead to VCAM-1 expression, which is an adhesion molecule that is induced by proinflammatory cytokines (Liao, 2013).

"Oxidative stress" become a hot spot in 2006. Oxidative stress is a result of oxidant overproduction caused by NADPH oxidases, malfunction of antioxidant enzymes or decreased activity of these enzymes. The relationship between oxidative stress and endothelial dysfunction is bidirectional and interconnected: (1) Oxidative stress can directly damage endothelial cells, leading to dysfunction. Overproduction of ROS can lead to oxidative changes in lipids, proteins, and DNA in endothelial cells, disrupting their usual operation; and (2) Endothelial dysfunction can also contribute to oxidative stress. A dysfunctional endothelium produces fewer amounts of protective molecules like nitric oxide, which normally help counteract oxidative stress. This imbalance can further increase ROS production and exacerbate oxidative damage. As mentioned, hypertension and aging are considered the most important risk factors for CSVD. Some of the key features of CSVD have been described in mouse models of hypertension including reductions in CBF; impaired vasodilator capacity (e.g., NO-dependent responses, neurovascular coupling, and autoregulation); inward remodeling; and BBB disruption (De Silva and Miller, 2016). Angiotensin II, the primary active peptide in the renin-angiotensin system, seems to have a significant impact on these vascular irregularities, leading to an elevation in superoxide generation by Nox2-NADPH oxidase in cerebral vessels of rodents (De Silva and Miller, 2016).

Over the course of 15 years, "cerebral amyloid angiopathy" remained a focal point of ongoing interest and significance. Cerebral amyloid angiopathy is defined by the deposition of amyloid β (Aβ) in the walls of small arteries, arterioles, and capillaries of the leptomeninges, cerebral cortex, and cerebellar cortex, and it is the dominant cause of lobar intracerebral

hemorrhage. Aβ protein accumulation in capillaries affects BBB integrity, which leads to a loss of tight junction proteins and increased BBB permeability (Holland et al., 2008). Then, perivascular edema and extravasation of toxic plasma components caused by the disruption of BBB contributes to localized damage to brain parenchyma and EPVS (Hartz et al., 2012). Cerebral amyloid angiopathy also plays a role in causing cognitive decline as a separate symptom. The cause of cognitive decline related to cerebral amyloid angiopathy remains unknown; numerous research studies have suggested that cognitive decline and dementia may be attributed to diffuse brain microbleeds, micro-infarcts, hypoperfusion, and white matter hypoxia resulting from vessel changes linked to CAA, distinct from AD and Lewy body pathology (Shi and Wardlaw, 2016; Zhang et al., 2017).

4.2.3 CSVD markers on MRI and the influence changes caused by CSVD

The MRI features of CSVD mainly include recent small subcortical infarcts, lacunes, WMHs, EPVS, CMBs, and brain atrophy. Small vessel disease lesions are considered permanent, with WMHs representing demyelination, axon loss, and gliosis, lacunes being cavities replacing destroyed tissue, and microbleeds being fixed hemorrhages. Multiple longitudinal studies indicate progression of WMHs, with only few reported instances of slight reductions in WMH volume (Schmidt et al., 2016). Bilateral, mostly symmetrical hyperintensities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) MRI are characteristic features of white matter lesions accompanied with some hypointense difference from the cerebrospinal fluid (CSF) on T1-weighted MRI and low density on cerebral CT in most older individuals with or without cognitive decline. In addition to white matter, the hyperintense lesions are also located in subcortical gray matter structures, such as the basal ganglia and brainstem (Wardlaw et al., 2013b). The inclusion of hyperintensities in gray matter and brainstem as part of WMH is a topic of debate (Schmidt et al., 2011; Wardlaw et al., 2013b). Diffusion tensor (DT)-MRI and magnetization transfer (MT)-MRI were utilized more frequently to distinguish WMH from other types of brain lesions like lacuna and atrophy, to investigate their individual effect on dementia by providing quantitative data on the condition of the brain's white matter. CMBs are MR-visible small (generally 2–5 mm in diameter, but up to 10 mm) areas of signal void caused by perivascular collections of hemosiderin deposits that are foci of past hemorrhages resulting from small vessels involved in CAA or arteriolosclerosis (Shi and Wardlaw, 2016). Perivascular spaces (PVS), as also known as Virchow–Robin spaces, are extensions of the extracerebral fluid-filled spaces that follow the typical course of a vessel as it goes through gray or white matter (Aribisala et al., 2013). EPVS are predominantly located in the basal ganglia and show increased signal intensity equal to CSF on T2-weighted images, appear hypointense on T1-weighted and occasionally hypointense on FLAIR images without a hyperintense rim to be distinguished from old lacunar infarcts (Aribisala et al., 2013).

4.3 Research hotpots

4.3.1 MRI segmentation

Magnetic resonance imaging (MRI) segmentation is a process of dividing an MRI scan into different regions or segments based on the underlying anatomical characteristics. Segmentation is essential in a variety of medical uses, including diagnosing diseases, planning treatments, and monitoring progress. MRI segmentation aims to partition an image into meaningful regions that represent different tissues or structures such as organs, tumors, or blood vessels. This process can be performed manually by experts, but it is time-consuming and subjective. Therefore, automated or semi-automated techniques have been developed to assist in MRI segmentation. The neuroimaging features of CSVD include recent small subcortical infarct (RSSI), WMH, lacune, PVS, CMB, and brain atrophy. In recent years, samples of segmentation or detection have been made to automatically quantify the MRI manifestations of CSVD for better efficiency and reproducibility in research or clinical settings, and/or to associate these MRI features with possible clinical consequences for a better understanding of CSVD.

Clinically apparent RSSI, also called lacunar stroke, is defined as recent infarction (within the past few weeks) in the area supplied by a single perforating artery (Wardlaw et al., 2013b) that can be identified on MRI diffusion-weighted imaging (DWI) sequence as hyperintense lesions of up to 20 mm in diameter on axial sections. Early automated segmentation techniques for acute lesions on DWI typically relied on basic characteristics (such as intensity and edge details) that were not sufficiently reliable because of the large variations in lesion patterns (Prakash et al., 2006). With the increased application of deep-learning methods in recent studies, such as deep convolutional neural networks, high-level features of lesion patterns can be extracted that have achieved better performance than the traditional methods. The technique obtained a Dice similarity coefficient (DSC) of 79.13% and a lesion-wise precision, showing spatial agreement between the automatic segmentation results and the ground truth (Zhao et al., 2020). WMHs can be seen as bright spots on FLAIR and T2-weighted (T2w) MRI scans. Many approaches have been recently proposed for automatic segmentation of WMHs. Indeed, the performances of different WMH segmentation methods are generally not fully comparable because of the difference of subject characteristics and lesion load across studies. For example, the methods that achieved DSC of >0.80 were generally evaluated in stroke patients or patients with vascular dementia (Wardlaw et al., 2013a), where the patients tend to have larger lesion burden of WMH. In this regard, independent evaluations for different level of lesion load should be encouraged for a better generalizability of the segmentation performance. Lacunes can be seen as round or ovoid subcortical fluid-filled cavities in MRI with diameters of ~3–15 mm. Lacunes present as hypointensities in T1-weighted (T1w) and FLAIR images and hyperintensities in T2w images (approximate to the intensity of CSF). Few studies have suggested automated approaches for identifying lacunes, typically relying on intensity-based algorithms. CMBs can be identified as small (up to 10 mm) areas of signal void on MRI sequences such as T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted

images (SWI), and the SWI was reported to have better reliability and SE for CMB detection than T2*GRE (Cheng et al., 2013). Using automated detection techniques can reduce the burden on neuroradiologists and enhance the accuracy and speed of CMB identification. Supervised CMB detection methods using convolutional neural network (CNN) have advanced owing to the progress in deep-learning techniques. In a study with the largest benchmark data set available for CMB detection on SWI, Qi et al. (2016) applied 3D CNN and achieved an SE of 93.16%, precision of 44.31%, and FP/CMB of 1.17. When using 7T SWI instead of 1.5T/3T SWI, slightly better SE, FP/CMB, and much higher precision could be achieved. Automatic quantification methods for EPVS are significantly less developed than WMH and CMB. Dubost et al. (2019) developed an automated rating method of EPVS based on 3D regression fully CNN on 1.5T T2w image. Park et al. (2016) used manually delineated PVS masks as the ground truth for learning based on 7T MRI. Evaluation of brain shrinkage can be conducted in specific cerebral lobes, particular tissues, or distinct regions of the brain. In-depth evaluation of regional brain shrinkage typically involves segmenting brain tissues and specific structures using automated segmentation techniques, with statistical parametric mapping (SPM) being a widely used method for this purpose. Additionally, the methods include atlas-based (based on the accurate alignment of atlas priors), learning-based (based on an annotated training set), and algorithmic methods (relies on intensity information to a greater extent, e.g., region-based and deformable methods). Different methods may have their strengths and limitations for the segmentation of specific structures. In conclusion, MRI segmentation will be a research hot spot in the future of CSVD, and is currently undergoing rapid evolution to identify the best segmentation model for the imaging manifestations of CSVD. This approach could become a hot spot for future work and provide a stronger support for enhancing the diagnostic accuracy of CSVD and offer inspiration for exploring treatment targets.

4.3.2 Basal ganglia EPVS

CSVD is characterized by a range of markers that are clearly defined such as lacunes, WMHs, and CMBs. Currently, more attention is given to other markers such as EPVS. Vascular stiffness, inflammation, protein deposits, and disruption of the BBB—partly due to CSVD—decreases the clearance of solutes from the brain interstitial fluid (Brown et al., 2018). EPVS have been linked to various conditions such as head trauma, cerebrovascular accident, and idiopathic normal pressure hydrocephalus. EPVS are frequently found in the centrum semiovale and basal ganglia. Previous research has shown that age, high blood pressure, and WMHs are linked to an increased risk of basal ganglia enlarged perivascular spaces (BG-EPVS), indicating a potential connection to hypertensive arteriopathy (Charidimou et al., 2013). The potential mechanisms have been proposed. Increased intraluminal pressure may cause greater extravasation of fluid through the small arteries into PVS, which is supported by rat experiments in which sustained hypertension could cause increased permeability of endothelial cells and fluid-induced damage to the surrounding brain tissue (Gutierrez et al., 2013). Additionally, increased pulpability in these regions may result in the expansion of PVS due to their nearness to brain tissue (Gutierrez et al., 2013). However, the consequences of BG-EPVS are generally considered clinically silent; a few ongoing research studies have investigated the link between BG-EPVS and cognitive impairments (Hernández et al., 2013; Zhu et al., 2010). Nevertheless, the findings varied among the different research projects. The reason behind the connection between BG-EPVS and cognitive decline is still not fully understood, and it is speculated whether the connection is because of the direct impact of EPVS or the presence of CSVD markers such as WMH, CMB, and lacunes. Over a period of 5 years, Huijts et al. (2013) examined 189 individuals at high risk for cerebrovascular disease and discovered a correlation between the rise in BG-EPVS and a decline in cognitive processing speed. Interestingly, this connection was independent of age and high signal intensity in the white matter. However, Arba et al. (2018) found that the number of BG-EPVS was not associated with cognitive impairment. Additionally, recent research has shown a connection between BG-EPVS and gait disturbances (Yang et al., 2022). The exact pathophysiological processes responsible for the link between BG-EPVS and walking remain unclear. We hypothesized that an abundance of BG-EPVS could interfere with the operation of the basal ganglia, brain network, and brain environment, potentially resulting in difficulties with walking and balance. As mentioned above in the analysis, the prevalence of MRI segmentation has increased in recent years. Further work is needed to address the issue of lesion type discrimination and develop methods for quantifying disease markers in order to analyze accuracy results by disease load and inform a better the scope of their applicability.

5 Limitations

This study has some limitations. First, citation analysis favors English language journals, so our findings emphasize Western research. Manual screening of abstracts was not feasible which may have resulted in the inclusion of some irrelevant articles. Second, while WoSCC has a wider scope than databases like Scopus, PubMed, Cochrane, and Embase Library databases, it still has a bias toward English-language journals. A prior analysis found that over 95% of sources indexed in WoSCC publish in English. This potentially excluded relevant non-English publications and contributed to geographic biases, potentially only highlighting Western authors. Expanding the database sources could provide more diversity in the literature reviewed. Third, reliance on citation analyses introduces biases toward older, more established research areas and academics. Recently published innovative research is less likely to be highly cited initially compared to seminal work that has accumulated citations for decades. Finally, bibliometric software such as CiteSpace and VOSviewer cannot provide statistical functions, so it is impossible to understand the actual situation of publications in different countries.

Overall, while bibliometric analyses allow for broad mapping of research fields, they have limitations regarding representativeness. Combining database sources, expanding citation and publication timeframes, and implementing manual full-text reviews could

reduce biases, but likely at the expense of capturing a narrower slice of literature. Researchers must balance the strengths and limitations of these approaches when aiming to review and summarize evidence.

6 Conclusion

We analyzed the research progress, hot spots, and frontiers in this field; studied CSVD through bibliometric analysis; and revealed the future research prospects. Currently, research on CSVD is in a rapid development stage, and since 2008, publications related to CSVD have steadily increased. We also identified leading countries, institutions, and leading scholars in the field and analyzed journals and representative literature. Keyword co-occurrence analysis and burst graph emergence detection have identified "MRI segmentation" and "Basal ganglia enlarged perivascular spaces" as the most recent areas of research interest. The cause of CSVD remains unknown and requires additional investigation. Although this study utilized the most extensive database available, it is possible that it overlooked studies that were not included in the database. Subsequent evaluations could potentially explore various databases. In conclusion, bibliometric analysis provides objective insights into the research of CSVD and addresses further research opportunities and challenges.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

XY: Data curation, Investigation, Methodology, Visualization, Project administration, Writing – original draft. YZ: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – original draft. RH: Data curation, Formal analysis, Methodology, Validation, Writing – original draft. XC: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing. ML: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Development and internal validation of a nomogram for predicting cognitive impairment after mild ischemic stroke and transient ischemic attack based on cognitive trajectories: a prospective cohort study

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Introduction: Many predictive models for cognitive impairment after mild stroke and transient ischemic attack are based on cognitive scales at a certain timepoint. We aimed to develop two easy-to-use predictive models based on longitudinal cognitive trajectories to facilitate early identification and treatment.

Methods: This was a prospective cohort study of 556 patients, followed up every 3 months. Patients with at least two cognitive scales within 2.5 years were included in the latent class growth analysis (LCGA). The patients were categorized into two groups based on the LCGA. First, a difference analysis was performed, and further univariate and stepwise backward multifactorial logistic regression was performed. The results were presented as nomograms, and receiver operating characteristic curve analysis, calibration, decision curve analysis, and cross-validation were performed to assess model performance.

Results: The LCGA eventually included 255 patients, and the "22" group was selected for further subgroup analysis. Among them, 29.8% were included in the cognitive impairment trajectory. Model 1, which incorporated baseline Montreal Cognitive Assessment, ferritin, age, and previous stroke, achieved an area under the curve (AUC) of 0.973, and model 2, which incorporated age, previous stroke, education, and ferritin, with an AUC of 0.771. Decision curve analysis and cross-validation showed excellent clinical applicability.

Discussion: Here, we developed two simple and easy-to-use predictive models of post-stroke cognitive trajectories based on a LCGA, which are presented in the form of nomograms suitable for clinical application. These models provide a basis for early detection and prompt treatment.

KEYWORDS

cognitive trajectory, ferritin, mild stroke, nomogram, cognitive impairment, prediction model, latent class growth analysis

1 Introduction

Post-stroke cognitive impairment (PSCI) is a varying degree of cognitive decline associated with prior definite stroke symptoms caused by any reason (El Husseini et al., 2023). Some patients experience significant acute cognitive decline after a mild stroke and transient ischemic attack (TIA) (Pendlebury and Rothwell, 2019; Hua et al., 2023), with gradual improvement in some patients over several months (Cramer et al., 2023). However, during long-term follow-up, some patients progressively deteriorate (Pendlebury and Rothwell, 2019; El Husseini et al., 2023). Reversible causes of deterioration in cognitive function are a cause for concern. However, there is no consensus on the time frame of PSCI; despite this, 3–6 months is generally used as the cutoff point for diagnosing the disease (Mok et al., 2017). Most current studies analyzed cognitive function at a fixed time, such as 3, 6, and 12 months after stroke, as an outcome variable (Rost et al., 2022), which cannot comprehensively respond to the longitudinal changes in cognitive function after stroke. Therefore, we applied latent class growth analysis (LCGA) to automatically categorize patients into trajectory subgroups for trajectory analysis to provide a more comprehensive and objective depiction of cognitive function trends of patients with stroke.

There is no specific treatment for PSCI. However, many interventions exist, including medications (e.g., cholinesterase inhibitors) and non-pharmacological treatments (e.g., cognitive rehabilitation, transcranial magnetic stimulation, acupuncture, and remote ischemic conditioning) (El Husseini et al., 2023). These tools not only increase the financial burden but may also have certain side effects, making it important to recognize early whether cognitive deficits develop after stroke and TIA. The most widely accepted models are SIGNAL2 (Kandiah et al., 2016) and CHANGE (Chander et al., 2017). The SIGNAL2 model included age, education, acute cortical infarcts, white matter hyperintensity (WMH), chronic lacunae, global cortical atrophy, and intracranial large vessel stenosis, yielding an area under the curve (AUC) of 82.9%, sensitivity and specificity of 82.1% and 68.0% at 3–6 months (respectively), and of 64.7% and 79.17% at 12–18 months (respectively) (Kandiah et al., 2016). The CHANGE predictive model without intracranial stenosis, compared with SIGNAL2, had an AUC of 0.78 at 3–6 months. In addition, a study using a machine-learning predictive model for PSCI indicated that cortical infarcts, medial temporal lobe atrophy, initial stroke extent, stroke history, and strategic infarcts predicted PSCI, with an AUC of 79.19% (Lee et al., 2023). These studies all applied imaging and demographic data and did not include hematological indicators. Therefore, we further developed predictive models based on cognitive trajectories utilizing comprehensive and multivariate demographic, imaging, and clinically relevant data with the aim of early diagnosis and treatment.

2 Materials and methods

2.1 Study population

This prospective study was conducted at the First Hospital of the Jilin University. It consistently included individuals with mild stroke [National Institutes of Health Stroke Scale (NIHSS) score $\leq$ 6] and TIA from April 2019 to March 2022. A total of 556 individuals who met the criteria were enrolled and followed up every 3 months for 2.5 years. Two hundred and fifty-five patients with at least two cognitive scales were included in the trajectory analysis. The inclusion criteria were: (1) age 50–80 years, (2) onset of acute cerebral infarction and TIA definitively diagnosed within 2 weeks and NIHSS score $\leq$ 6, and (3) completed baseline cognitive scales. The exclusion criteria were: (1) presence of other diseases or drug applications affecting cognitive function before stroke, and (2) without follow-up data (Figure 1).

2.2 Ethics approval

The research was carried out following the World Medical Association Declaration of Helsinki and was approved by the First Hospital of Jilin University Ethics Committee. The procedures followed conformed to national and institutional guidelines, and written informed consent was obtained from all participants. This study was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn/; unique identifier: ChiCTR1900022675).

2.3 Cognitive assessment and definition of trajectory timepoints

We performed the first assessment of cognitive and neuropsychiatric function in patients who were relatively stable within 7–10 days after stroke/TIA onset, including the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA). For these assessment scales, we have obtained the copyright license. Subsequent cognitive assessments were performed every 3 months. These scales were completed by full-time evaluators with more than 5 years of experience, with one point added to the MMSE/MoCA score for $<$12 years of education. We used the MoCA, considered to have good sensitivity and specificity for assessing cognitive function after stroke (Salvadori et al., 2013), as the cognitive outcome. Overall cognitive function after stroke may not stabilize until 12 months after stroke onset (Rost et al., 2022), and therefore we used outcomes obtained every 3 months as a trajectory time point within 1 year, and every 6 months subsequently.

Follow-up data collected at 3–4 months post-stroke was assigned to the 3-month follow-up category, those collected at 5–7 months to the 6-month follow-up category, those collected at 8–10 months to the 9-month follow-up category, those collected at 11–15 months to the 12-month follow-up category, those collected at 16–21 months to the 18-month follow-up category, and those collected at 22–30 months to the 24-month follow-up category.

2.4 Study variables

We collected clinical data related to stroke and cognitive impairment at baseline, including sex, age, education, blood pressure, and risk factors associated with cerebrovascular

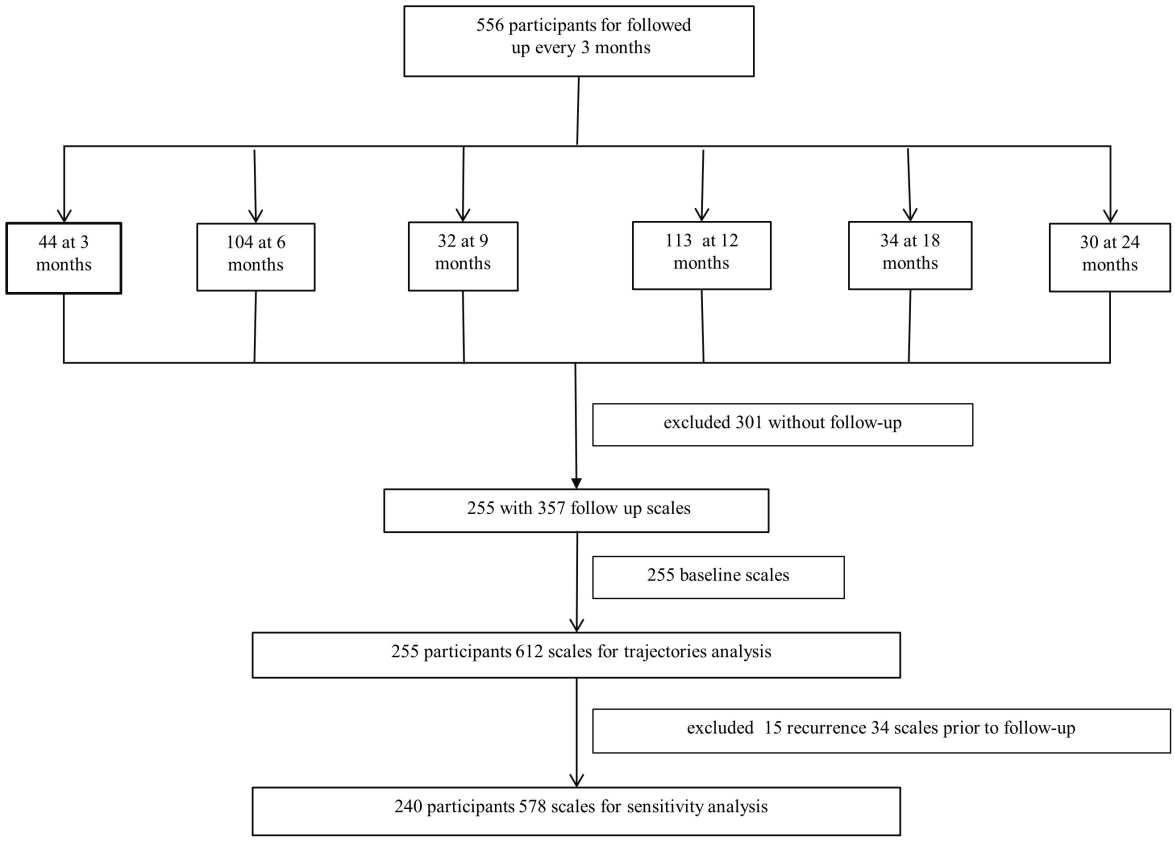

FIGURE 1
Participant selection flowchart.

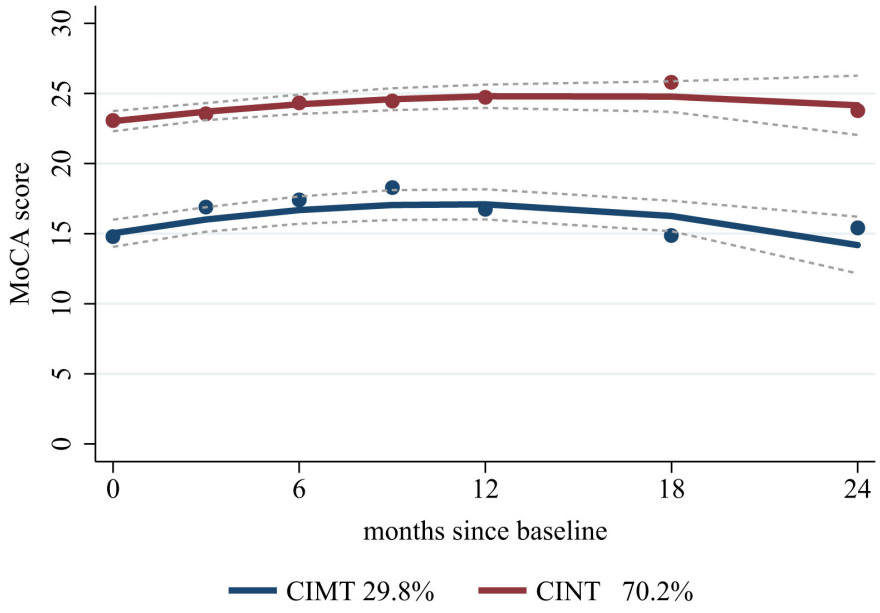

FIGURE 2
Cognitive trajectories graph. CIMT, cognitive impairment trajectory; CINT, cognitive intact trajectory; MoCA, Montreal Cognitive Assessment.

diseases such as smoking, alcohol consumption, hypertension, diabetes mellitus, cardiac disease, and previous stroke. We also gathered hematological indices such as glucose, lipids, uric acid, homocysteine, ferritin, and other iron metabolism indicators. Brain atrophy was defined as cerebral volume loss due to non-brain injury on brain magnetic resonance imaging (MRI). White matter

lesions on fluid-attenuated inversion recovery MRI, number of infarcts on diffusion-weighted MRI, and cervicocerebral arterial stenosis detected by ultrasound or magnetic resonance angiography were also recorded within 72 h of stroke/TIA onset. Smoking and drinking were categorized as current, previous, or never, with previous being more than 1 year of abstinence or occasional smoking/drinking. Hypertension and diabetes mellitus were defined as a previous medical history or meeting the diagnostic criteria during hospitalization. Heart disease and stroke were defined as a preexisting medical history. We used the Trial of Org 10172 in Acute Stroke Treatment (TOAST) as a criterion for stroke etiology classification (Adams et al., 1993), the NIHSS score to assess stroke severity (Kwah and Diong, 2014), and the Fazekas scale score, sum of deep white matter hyperintensity (DWMH), and periventricular hyperintensity (PVH) for white matter hyperintensities (Duering et al., 2023). Cervicocerebral arterial stenosis was defined as >50% stenosis. These definitions are consistent with previously unpublished research; since that study is not yet publicly available, we could not provide citations in this report. These definitions were developed based on our research needs and methodology to ensure consistency and comparability.

2.5 Statistical analysis

First, we constructed cognitive trajectories using LCGA based on cognitive scales and trajectory timepoints. Subsequently, we built a predictive model using a trajectory-based risk factor selection. Regarding sample size calculation, based on preliminary calculations, the event rate was 29.8%. Four variables were included in the final model, with the modeling requirement ($4 \times 10 = 40$), at least 40 patients with events and 94 without events should be included. Finally, we performed internal validation of the model. Measurement data were expressed as median and interquartile range, and count data were expressed as frequencies and percentages. Univariate logistic regression analyses were applied for comparisons between trajectory groups, and clinically or statistically significant univariate logistic regression variables were included in a stepwise backward multifactor logistic regression to build a predictive model for different trajectory groups and present the model as a nomogram. We then applied receiver operating characteristic (ROC) curves to evaluate the model's ability to discriminate patients in the cognitively impaired group, calibration to assess the probability consistency between the model-predicted and patients with actual cognitively impairment, and decision curve analysis (DCA) to quantify the net benefit at different threshold probabilities of cognitive impairment. Finally, we used 10-fold cross-validation for the internal validation of model performance. Relapsed patients were excluded from the sensitivity analysis. All missing values were numeric variables. Variables with more than 10% missing data were deleted, and the rest were imputed using the median. A second sensitivity analysis was conducted after excluding patients with imputed data. All statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY) and STATA15.0 (StataCorp, College Station, TX). A two-sided $P < 0.05$ denotes statistical significance.

3 Results

3.1 Latent class growth analysis

Based on the eligibility criteria, 255 patients were included in this study. We selected the "22" cognitive trajectories based on the low Akaike information criterion, Bayesian information criterion, high posterior probability (≥0.9), high entropy (>0.8), and >50 cases per trajectory (Mirza et al., 2016; Supplementary Table 1), in which 76 (29.8%) patients were included in the cognitive impairment trajectory (CIMT) and 179 (70.2%) patients were included in the cognitive intact trajectory (CINT). Regardless of baseline values, cognitive function showed a trend of initial improvement followed by gradual decline, reaching the highest value at 12 months after stroke, but the trajectory with cognitive impairment at baseline showed worse cognitive function at 24 months (Figure 2).

3.2 Population characteristics

The baseline characteristics are presented in Table 1. Compared with those in the CINT group, patients in the CIMT group were older (median: 63 vs. 60 years), less educated (median: 9 vs. 12 years), and had higher admission systolic blood pressure (SBP, median: 148.5 vs. 142.0 mmHg). While compared with those without previous stroke, patients with previous stroke had a 1.19-fold increased probability of cognitive decline [odds rate (OR) 2.19, 95% confidence interval (CI) 1.21–3.97, $P = 0.01$], and the probability of cognitive decline in patients with brain atrophy was 2.63 times higher (OR 3.63, 95% CI 1.95–6.76, $P < 0.001$). Similar findings were observed in NIHSS score, DWMH, Fazekas score, number of intracranial and cervicocerebral arterial stenoses, and cognitive assessment scales including MMSE and MoCA.

3.3 Nomogram development and validation

After careful consideration, we included indicators that are considered to potentially affect cognition in clinical practice and previous studies, including sex (Exalto et al., 2023) and number of infarcts (Ding et al., 2019), along with variables that showed statistical significance in the univariate logistic regression, into a multifactorial regression for further analysis. First, we included all the above indicators in model 1, and model 2 was built by excluding the cognitive mental scales (Table 2). The final model 1 included age, ferritin, previous stroke, and MoCA with the following equation:

$$\text{Logit (p)} = (0.1711434 \times [\text{age}]) + (0.0068815 \times [\text{ferritin}]) + (1.577801 \times [\text{previous\_stroke}]) - (0.8110665 \times [\text{MoCA}]) + 1.603149$$

whereas model 2 included age, ferritin, previous stroke, and educational years, with the following equation:

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TABLE 1 Baseline characteristics of the follow-up patients according to their cognitive trajectory.

Variables	Total	CIMT	CINT	Univariate logistic regression	
	n = 255	*n* = 76	*n* = 179	OR (95% CI)	*P*-value
Age	61 (56–68)	63 (59–70.75)	60 (55–67)	1.06 (1.02–1.1)	0.002**
Male	183 (71.8)	50 (65.8)	133 (74.3)	1.5 (0.84–2.69)	0.169
Educational years	12 (9–15)	9 (6–12)	12 (9–15)	0.84 (0.77–0.91)	<0.001***
Systolic pressure (mmHg)	143 (132–159)	148.5 (136.25–165)	142 (130–154)	1.01 (1–1.03)	0.026*
Diastolic pressure (mmHg)	85 (76–94)	87 (78–94.75)	84 (76–93)	1 (0.98–1.02)	0.818
Body mass index (kg/m^2)	24.51 (22.89–26.9)	24.5 (23.09–26.72)	24.61 (22.76–27.04)	0.99 (0.91–1.08)	0.831
Hypertension (%)	205 (80.4)	66 (86.8)	139 (77.7)	1.9 (0.9–4.03)	0.095
Diabetes (%)	107 (42)	33 (43.4)	74 (41.3)	1.09 (0.63–1.87)	0.758
Heart disease (%)	45 (17.6)	11 (14.5)	34 (19)	0.72 (0.34–1.51)	0.388
Previous stroke (%)	63 (24.7)	27 (35.5)	36 (20.1)	2.19 (1.21–3.97)	0.01**
Smoking				0.96 (0.72–1.27)	0.776
Never (%)	136 (53.3)	43 (56.6)	93 (52)		
Previous (%)	20 (7.8)	3 (3.9)	17 (9.5)		
Now (%)	99 (38.8)	30 (39.5)	69 (38.5)		
Alcohol				0.84 (0.61–1.15)	0.277
Never (%)	148 (58)	51 (67.1)	97 (54.2)		
Previous (%)	40 (15.7)	5 (6.6)	35 (19.6)		
Now (%)	67 (26.3)	20 (26.3)	47 (26.3)		
Diagnose				8.91 (1.17–67.78)	0.035*
TIA (%)	20 (7.8)	1 (1.3)	19 (10.6)		
Cerebral infarction (%)	235 (92.2)	75 (98.7)	160 (89.4)		
Brain atrophy (%)	55 (21.6)	29 (38.2)	26 (14.5)	3.63 (1.95–6.76)	<0.001***
NIHSS score	2 (1–3)	2 (1–3)	2 (1–3)	1.25 (1.04–1.5)	0.016*
PVH score	1 (1–2)	1 (1–2)	1 (1–2)	1.23 (0.86–1.78)	0.258
DWMH score	1 (0–1)	1 (1–2)	1 (0–1)	1.61 (1.15–2.25)	0.006**
Fazekas score	2 (1–3)	2 (2–4)	2 (1–3)	1.22 (1.01–1.47)	0.034*
TOAST				0.83 (0.65–1.06)	0.129
LAA (%)	83 (32.5)	32 (42.1)	51 (28.5)		
Cardioembolism (%)	3 (1.2)	1 (1.3)	2 (1.1)		
Small-vessel occlusion (%)	134 (52.5)	30 (39.5)	104 (58.1)		
Others (%)	35 (13.7)	13 (17.1)	22 (12.3)		
CASN	0 (0–0)	0 (0–0)	0 (0–0)	0.95 (0.64–1.41)	0.802
ICASN	0 (0–1)	0 (0–1)	0 (0–1)	1.52 (1.11–2.07)	0.009**
CCASN	0 (0–1)	0 (0–2)	0 (0–1)	1.21 (0.98–1.51)	0.082
FBG (mmol/L)	5.53 (5.02–6.81)	5.68 (4.98–6.99)	5.5 (5.03–6.69)	1.06 (0.92–1.23)	0.418
Total cholesterol (mmol/L)	4.49 (3.8–5.05)	4.55 (3.91–5.03)	4.41 (3.73–5.11)	1.15 (0.9–1.46)	0.271
Triglyceride (mmol/L)	1.48 (1.11–1.92)	1.64 (1.19–2.03)	1.45 (1.08–1.89)	1.18 (0.96–1.45)	0.124
HDL (mmol/L)	0.98 (0.87–1.16)	1.00 (0.88–1.16)	0.98 (0.87–1.16)	1.11 (0.35–3.49)	0.854
LDL (mmol/L)	2.74 (2.32–3.38)	2.89 (2.40–3.42)	2.69 (2.27–3.34)	1.2 (0.88–1.62)	0.254
Uric acid (μmol/L)	312 (266–372)	288 (259.75–344.5)	317 (270–382)	1 (0.99–1)	0.04*
Homocysteine (μmol/L)	11.9 (10–15.7)	13.09 (10.1–16.73)	11.7 (9.87–15.2)	1.02 (1–1.04)	0.138
Neutrophils (109/L)	4.31 (3.34–5.49)	4.3 (3.33–5.62)	4.33 (3.34–5.34)	1.14 (1–1.29)	0.045*

(Continued)

TABLE 1 (Continued)

Variables	Total	CIMT	CINT	Univariate logistic regression	
	n = 255	*n* = 76	*n* = 179	OR (95% CI)	*P*-value
Lymphocytes (109/L)	1.74 (1.41–2.23)	1.68 (1.33–2.14)	1.79 (1.44–2.26)	0.8 (0.53–1.2)	0.278
Monocytes (109/L)	0.45 (0.35–0.59)	0.47 (0.35–0.63)	0.45 (0.35–0.58)	2.23 (0.67–7.41)	0.191
Fe (μmol/L)	14.6 (11.9–18.1)	14.6 (11.38–16.65)	14.9 (12.2–19.3)	0.97 (0.92–1.02)	0.237
Ferritin (μg/L)	194.9 (130.8–274.8)	208.6 (155.93–313.35)	172 (120.8–255.4)	1 (1–1)	0.021*
TIBC (μmol/L)	47 (42.5–51)	46.7 (41.98–49)	47 (42.5–52.5)	0.96 (0.92–1)	0.061
MMSE	27 (24–29)	22 (19.25–24.75)	28 (26–29)	0.55 (0.47–0.63)	<0.001***
MoCA	21 (17–25)	15 (12–17)	23 (21–26)	0.51 (0.42–0.61)	<0.001***

Numeric variables are presented as median and interquartile range, and count data were expressed as frequencies and percentages (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$). CASN, carotid arterial stenosis number; CCASN, cervicocerebral arterial stenosis number; CIMT, cognitive impairment trajectory; CINT, cognitive intact trajectory; DWMH, deep white matter hyperintensities; FBG, fasting blood glucose; HDL, high-density lipoprotein; ICASN, intracranial arterial stenosis number; LAA, large-artery atherosclerosis; LDL, low-density lipoprotein; LMR, lymphocyte-to-monocyte ratio; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TIBC, total iron binding capacity; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

TABLE 2 Models based on cognitive trajectories.

	Model 1	Model 2
AUC (95% CI)	0.973 (0.957–0.988)	0.771 (0.707∼0.834)
	OR (95% CI)	OR (95% CI)
Age	1.187 (1.087∼1.295)***	1.086 (1.04∼1.134)***
Previous stroke	4.844 (1.58∼14.856)**	3.728 (1.852∼7.502)***
Ferritin	1.007 (1.002∼1.012)**	1.004 (1.001∼1.006)**
Educational years	–	0.801 (0.731∼0.877)***
MOCA	0.444 (0.349∼0.565)***	–

AUC, area under the curve; CI, confidence interval; MoCA, Montreal Cognitive Assessment; OR, odds ratio. **$P < 0.01$, ***$P < 0.001$.

$$\text{Logit (p)} = (0.0038726 \times [\text{ferritin}]) + (1.315809 \times [\text{previous\_stroke}]) - (0.2224969 \times [\text{educational\_years}]) + 0.0822759 \times [\text{age}]) - 4.861658).$$

Both models were represented as nomograms (Figure 3). The AUCs were estimated separately to assess the discriminative ability of the above models, yielding values of 0.97 (95% CI 0.96–0.99) for model 1 and 0.77 (95% CI 0.71–0.83) for model 2. Excluding patients with recurrent stroke, the AUC for model 1 reached 0.97 (95% CI 0.96–0.99) and 0.78 (95% CI 0.71–0.84) for model 2 (Supplementary Table 2 and Supplementary Figure 1), sensitivity analysis was also performed by excluding patients with missing data, yielding AUCs of 0.98 (95% CI 0.97–0.99) for model 1 and 0.78 (95% CI 0.72–0.85) for model 2 (Supplementary Table 3 and Supplementary Figure 2). The calibration plots overlapped with the ideal line, indicating that the predicted models sufficiently agreed with the actual observations (Figure 4). The threshold probabilities of standardized net gains in detecting cognitive impairment were determined by applying the nomogram based on DCA. The AUCs corresponding to the 10-fold internal validation were 0.97 and 0.75 for models 1 and 2, respectively.

4 Discussion

In this study, we built two cognitive trajectories to predict cognitive function trends after stroke and TIA, in which 29.8% of the patients were included in the CIMT group and 70.2% were included in the CINT group. A slow improvement in cognitive function occurred within the first 12 months after a mild ischemic event, followed by a decline, but patients with poorer cognitive function at baseline had worse cognitive levels at 24 months. Based on the aforementioned cognitive trajectories, we constructed predictive model1 of age, previous stroke, serum ferritin, MoCA with AUC of 0.973 (95% CI 0.957–0.988) and model 2 of age, previous stroke, serum ferritin, years of education with AUC of 0.771 (95% CI 0.707–0.834). Serum ferritin may play a role in the development of PSCI.

We observed an initial improvement followed by deterioration in cognitive function after stroke and TIA based on the two cognitive trajectories. Those with better cognitive function at baseline did not show a significant change at 24 months. However, those with poor cognitive function at baseline had worse cognitive function, in line with previous studies (El Husseini et al., 2023; Lo et al., 2023). This cognitive impairment over time may be because of stroke-induced structural disconnection (Pan et al., 2023), circuit disruption, inflammatory mediators caused by acute ischemia, and related complications (Pendlebury and Rothwell, 2019).

Current studies on cognitive impairment after stroke and TIA have applied inconsistent assessment scales (Lo et al., 2023). The Oxford Vascular Study applied an MMSE < 24 at baseline and follow-up as a diagnostic criterion (Pendlebury and Rothwell, 2019), while the Atherosclerosis Risk in Communities (ARIC) study employed 3- and 10-test batteries (Koton et al., 2022). We used the MoCA as the cognitive outcome, which has high sensitivity and specificity for evaluating cognitive function after stroke (Zietemann et al., 2018; El Husseini et al., 2023). We created two models because the cognitive assessment scales in model 1 were affected by many factors, such as the patient's medical conditions, and there was a certain degree of subjectivity. The first model included age, serum ferritin level, previous stroke, and MoCA, whereas the second model included age, ferritin level,

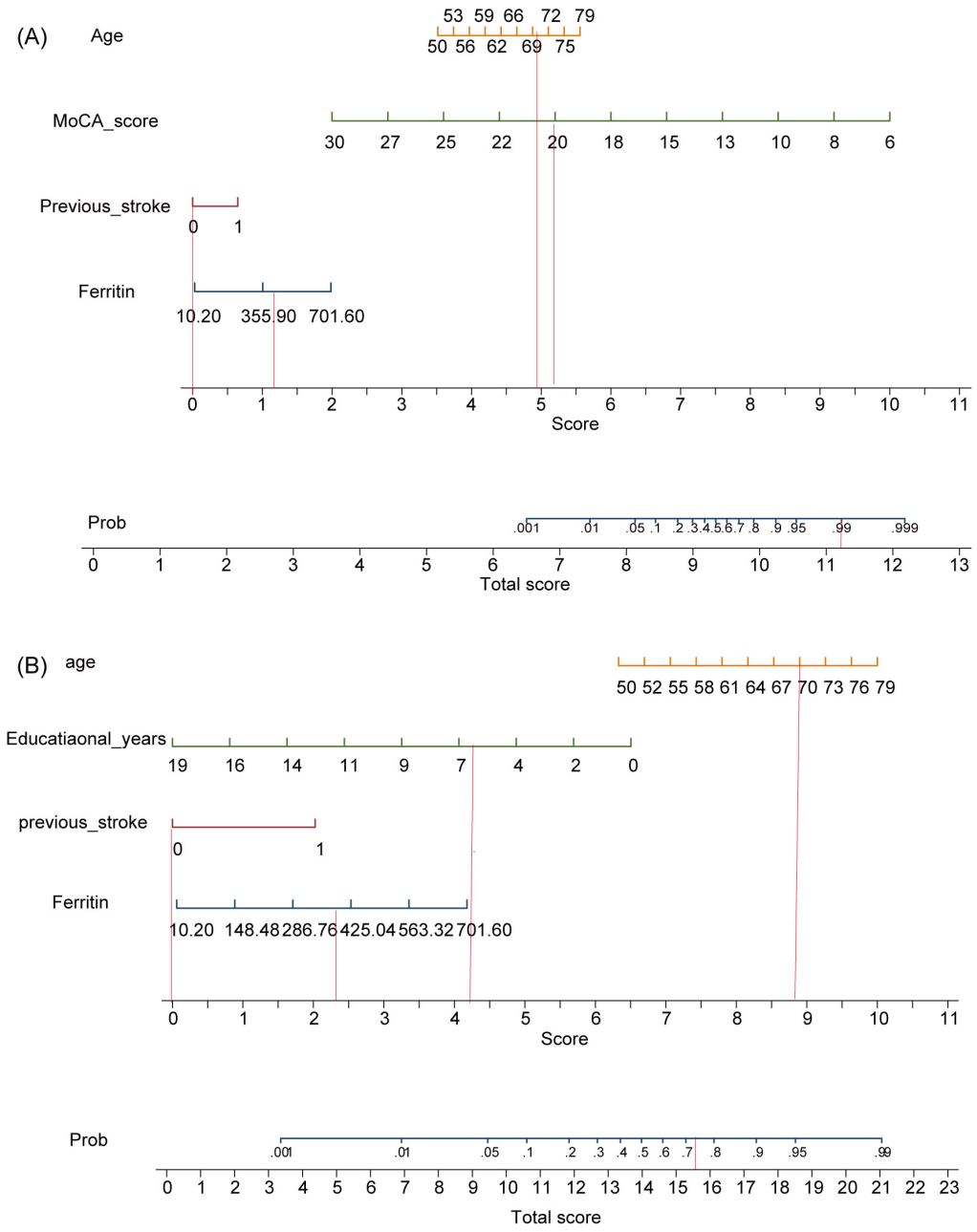

FIGURE 3
Model nomograms. **(A)** Model 1. **(B)** Model 2. MoCA, Montreal Cognitive Assessment. If a 70-year-old male patient with acute cerebral infarction, who had been educated for 6 years and had no previous history of stroke, was admitted to the hospital with a serum ferritin of 400 ng/ml and a MoCA score of 20, the probability of cognitive impairment in model 1 is 99%, while that in model 2 is 73%.

previous stroke, and educational years. We developed nomograms and internally validated two models. Both models exhibited good predictive performance and clinical utility, as assessed by their AUCs (0.973 and 0.771, respectively), calibration plots, and DCA. Compared with previously mentioned longitudinal data models, SIGNAL2 and CHANGE, our models incorporated more variables, resulting in two models that are simpler, easier to use, and more applicable in the clinical setting.

Models 1 and 2 both included age and previous stroke, and model 1 was significantly better than model 2, indicating that baseline cognitive function strongly predicted long-term cognitive function trajectory. Consistent with our findings, several large international longitudinal studies have indicated that age, previous stroke, stroke severity, low education, white matter lesions, and baseline cognitive function play important roles in PSCI (Pendlebury and Rothwell, 2019; Koton et al., 2022). Our previous exploration of the relationship between indicators of peripheral inflammation and cognitive deficits after stroke within 3–12 months also found that age, previous stroke, and limited education independently influenced cognitive function. These results further indicate the robustness of the models.

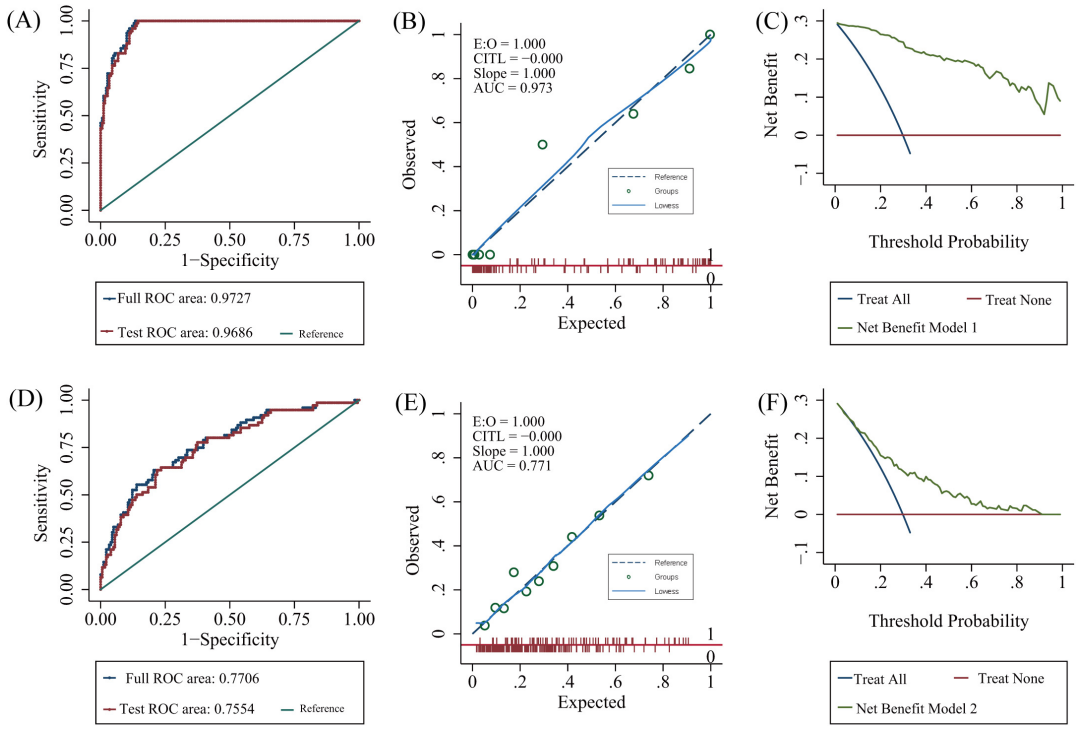

FIGURE 4
Model validation. Model 1: (**A**) 10-fold cross-validation, **(B)** calibration plots, **(C)** decision curve analysis. Model 2: **(D)** 10-fold cross-validation, **(E)** calibration plots, **(F)** decision curve analysis. AUC, area under the curve; ROC, receiver operating characteristic.

Interestingly, both models screened using multifactor logistic regression included serum ferritin levels. Ferritin is the site of intracellular iron storage in various organisms to avoid oxidative stress caused by an excess of free iron. Ferritin plays an important role in maintaining iron homeostasis (Zandman-Goddard and Shoenfeld, 2007; Zhang et al., 2021; Lee and Hyun, 2023; Shesh and Connor, 2023). Serum ferritin is a biomarker of iron loading of the organism (Ayton et al., 2023). Excessive iron loading in the body causes various diseases via Fenton's reaction. As more studies emerge, ferritin has been brought back into the spotlight. Along with being an iron storage protein and an acute-phase response protein that reacts to the inflammatory and autoimmune state of the body (Zhang et al., 2021; Mahroum et al., 2022), ferritin is also involved in Alzheimer's disease and neurodegenerative diseases in a different way (Sternberg et al., 2017; Ayton et al., 2023; Lee and Hyun, 2023). A clinical study demonstrated that cognitive dysfunction after cerebral hemorrhage is associated with elevated serum ferritin (Lan et al., 2021). Several clinical studies have demonstrated that elevated serum ferritin levels are associated with a higher risk of ischemic stroke (Ru et al., 2024) and stroke severity (Dávalos et al., 2000; Ru et al., 2024). The degree of stroke severity is strongly associated with PSCI (Koton et al., 2022). However, studies on serum ferritin and cognitive impairment after TIA and acute ischemic stroke are scarce.

Previous studies have used certain timepoints, e.g., 3–6 months (Kandiah et al., 2016; Chander et al., 2017) and 6–12 months (Dong et al., 2021; Gong et al., 2021) and thresholds, e.g., MoCA scores below 22 points (Wei et al., 2023) or 26 points (Zietemann et al., 2018) as endpoints. We applied all the available scale data from the follow-up patients, which can more comprehensively and objectively respond to cognitive changes. More indicators were included, which can reflect the real state of the patients as much as possible and respond to the true situation of the patients. Furthermore, the models were still excellent after excluding patients who had recurrence, which demonstrated their robustness.

We are the first to establish predictive models for cognitive impairment based on cognitive trajectories. However, our study has some limitations. First, this was a single-center study, and a large proportion of patients were lost during follow-up due to the COVID-19 pandemic and other reasons. We found that patients in the follow-up group had relatively better cognitive function, higher levels of literacy, a lower number of arterial stenoses in the head and neck, less severe WMH, and lower systolic blood pressure and serum homocysteine at admission compared to patients lost to follow-up (Supplementary Table 4). Second, we did not perform a systematic assessment of cognitive function prior to the ischemic event, although a detailed medical history was taken to rule out a possible prior cognitive impairment; in addition, because of the limited number of cases, we did not analyze patients with TIA and those with cerebral infarctions separately. Third, PSCI may be affected by stroke treatment methods and methods to improve intelligence, such as medication and cognitive rehabilitation. Many factors affect serum ferritin, including tumors and inflammation (Shesh and Connor, 2023), and we may not have adjusted for all of them. Serum ferritin was not followed up in parallel with cognition scales, which did not allow us to study the different roles played by serum ferritin at different times after stroke. Finally, because of the small number of endpoint variables, we did not categorize

the patients into a training and a validation set and did not carry out an external validation. However, we applied internal cross-validation and sensitivity analyses, and found the model to be stable. Additional studies are needed to validate our results.

Overall, we constructed two predictive models for cognitive impairment after mild ischemic stroke and TIA based on cognitive trajectories, and found that baseline cognitive assessments were important, and baseline serum ferritin were independent risk factors affecting cognitive trajectory. Further validation can be conducted in relevant clinical studies, and interventions targeting the reversible risk factor ferritin can be carried out in related basic research to assist in the early detection and timely treatment of PSCI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the First Hospital of Jilin University Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. LSh: Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. GZ: Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – review & editing. CW: Formal analysis, Investigation, Methodology, Visualization, Writing – review & editing. WZ: Formal analysis, Investigation, Methodology, Validation, Writing – review & editing. YS: Formal analysis, Investigation, Validation, Writing – review & editing. YW: Formal analysis, Investigation, Writing – review & editing. ZW: Formal analysis, Investigation, Writing – review & editing. LSu: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2025.1427737/full#supplementary-material

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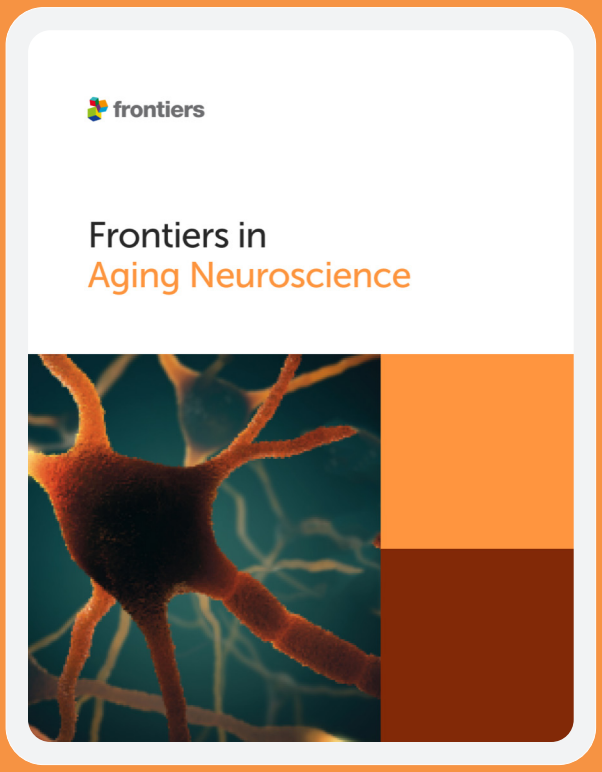

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