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Peripheral Immune Dysregulation and Blood Biomarkers in Vascular Cognitive Impairment and Vascular Dementia

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ABSTRACT

Vascular cognitive impairment (VCI) and vascular dementia (VaD) are major clinical consequences of cerebrovascular injury, with cerebral small vessel disease (CSVD) serving as their most common structural substrate. Although neuroimaging and cognitive assessment remain central to diagnosis and follow-up, accessible blood-based tools for early risk identification and progression monitoring are still limited. Emerging evidence suggests that peripheral immune dysregulation contributes to CSVD progression through chronic inflammatory imbalance, endothelial dysfunction, blood-brain barrier vulnerability, and inflammation-coagulation coupling. Blood biomarkers have therefore attracted increasing interest, ranging from routine inflammatory proteins and blood cell–derived indices to markers related to endothelial activation, barrier injury, extracellular matrix remodeling, and neural injury. Current evidence indicates that most single biomarkers have limited specificity and variable reproducibility, whereas panel-based approaches may offer better translational potential. In this review, we summarize the biological rationale and clinical evidence for peripheral immune and blood biomarkers in VCI/CSVD, and propose a time-layer and panel-oriented framework to distinguish background risk markers, pathway-activity markers, and downstream injury markers. We further discuss key methodological issues, including disease heterogeneity, sampling windows, repeated measurements, medication effects, external validation, and model transportability. Overall, near-term clinical progress is more likely to come from parsimonious multimarker panels integrated with imaging progression and cognitive trajectories than from any single biomarker. Future studies should prioritize standardized sampling, longitudinal design, and multicenter validation to support risk stratification and biomarker-guided intervention research.

Keywords: Blood-brain barrier; Cerebral small vessel disease; Endothelial function; Peripheral immune homeostasis; Serum biomarkers; Vascular cognitive impairment

INTRODUCTION

Vascular cognitive impairment (VCI) is a spectrum of cognitive syndromes caused by cerebrovascular pathology, ranging from mild cognitive impairment to

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vascular dementia (VaD). Unlike typical Alzheimer disease (AD), which is often characterized by predominant episodic memory loss, VCI more commonly presents with early deficits in executive function, attention, and processing speed, reflecting disruption of frontal-subcortical circuits and white matter connectivity.[1–3]

Cerebral small vessel disease (CSVD) is the most common structural substrate of VCI. Its imaging manifestations include white matter hyperintensities (WMH), lacunar infarcts, cerebral microbleeds, enlarged perivascular spaces, and subcortical atrophy. Because CSVD is common, quantifiable, and suitable for longitudinal follow-up, it represents a useful intermediate phenotype linking peripheral biological changes to cognitive outcomes.[1,4–6]

At present, clinical evaluation of VCI/CSVD relies mainly on neuropsychological testing and neuroimaging. However, cognitive scales are influenced by educational background, culture, mood, and sensory status, and may be insensitive to slow or domain-specific decline. Imaging, in contrast, is effective for depicting accumulated structural damage, but it cannot directly reflect dynamic biological processes, such as immune-inflammatory activity, endothelial dysfunction, or microcirculatory instability.[2,4,7] In practice, patients with similar imaging burden often show substantial differences in cognition and progression rate, suggesting that conventional tools do not fully capture disease activity or biological vulnerability.[5–8]

Peripheral immune homeostasis dysregulation has increasingly been recognized as a potential link between systemic vascular risk and cerebral microvascular injury. Rather than representing simple inflammatory upregulation, it is better understood as a chronic imbalance between proinflammatory signaling and immune regulation or resolution, accompanied by endothelial activation, reduced blood-brain barrier (BBB) stability, and enhanced inflammation-coagulation coupling. These processes may contribute to microcirculatory hypoperfusion, white matter injury, and progression of CSVD.[3,6–9] In this context, serum or plasma biomarkers are attractive because they are accessible, repeatable, and potentially suitable for longitudinal monitoring. However, existing studies have often focused on single-marker associations and are strongly influenced by comorbidities, infection, medication exposure, and assay-platform variability, resulting in limited reproducibility and external generalizability.[7–11]

This gap is clinically important. Imaging is well suited to characterize cumulative lesion burden, but it is less informative for short-term changes in pathological activity. Likewise, cognitive assessment reflects clinical consequences rather than ongoing biology. For this reason, blood-based indicators may be valuable not only for early risk identification, but also for dynamic risk stratification, monitoring of progression, and individualized follow-up planning in VCI/CSVD.[8–11] Biomarkers reflecting systemic inflammatory tone, endothelial reactivity, BBB vulnerability, or microcirculatory disturbance may help identify patients entering a higher-risk phase before substantial structural progression becomes evident on imaging.[8,10,11]

From a translational perspective, biomarker research may also help explain the marked heterogeneity of VCI/CSVD. Some patients develop pronounced executive dysfunction despite modest imaging burden, whereas others retain relatively preserved cognition despite more extensive structural abnormalities.[5,6,8] This discrepancy suggests that clinical outcome is shaped by lesion burden, lesion distribution, network vulnerability, disease activity, and the host immune-vascular background. If peripheral immune dysregulation contributes to this heterogeneity, blood biomarker panels may help predict not only whether progression is likely to occur, but also which biological pathways may be driving it.[8–11]

VCI/CSVD should therefore not be viewed as a linear disorder explained by a single mechanism. Rather, it is a chronic and heterogeneous brain-network injury process influenced by aging, blood pressure variability, metabolic dysfunction, renal impairment, sleep disturbance, and coexisting neurodegenerative pathology, with different factors becoming more prominent at different stages.[2,4,6,12,13] Within this framework, peripheral immune dysregulation is important not because it explains the entire disease, but because it may act as a convergence point through which multiple systemic risks are translated into cerebral injury via endothelial, microcirculatory, and BBB-related pathways.[3,6–9] Interpreting serum biomarkers within a framework that integrates systemic biology, intermediate imaging phenotypes, and cognitive outcomes may therefore provide a more coherent basis for clinical translation.[8,10,11]

Another practical challenge in VCI/CSVD is the mismatch sometimes observed between imaging and clinical course. Some individuals show relatively stable imaging but continued functional decline, whereas others have imaging progression with only limited short-term clinical fluctuation.[5,8,14,15] These patterns may reflect differences in cognitive reserve, lesion location, network compensation, or ongoing pathological activity. Integration of biomarker information with lesion distribution, connectivity measures, and domain-specific cognitive trajectories may therefore help move assessment beyond a burden-centered model toward a framework that also captures disease activity and vulnerability.[6,8–11,15]

Compared with existing reviews, the present review has 2 specific aims. First, it organizes blood biomarkers in VCI/CSVD using a time-layer framework that distinguishes background inflammatory signals, pathway-activity markers, and downstream neural injury readouts, rather than treating all biomarkers as functionally equivalent. Second, it emphasizes a panel-based translational strategy oriented toward clinical deployment, with particular attention to repeated measurements, longitudinal imaging and cognitive endpoints, external validation, and real-world transportability. Accordingly, this review aims not only to summarize candidate biomarkers, but also to clarify which markers are closer to screening, prognostic stratification, or dynamic monitoring, and what methodological conditions are required for their future clinical use.

MATERIALS AND METHODS

This article is a narrative review based on a structured literature search, focusing on the role and translational potential of peripheral immune homeostasis dysregulation and serum biomarkers in VCI/CSVD. Literature sources included PubMed, Embase, Web of Science, and the Cochrane Library. The search covered studies published from database inception to January 2026 and was limited to English-language publications. In addition, high-quality reviews, consensus statements/guidelines, and key original studies were manually screened through reference lists to ensure that important evidence was not missed.

Search terms were organized into three modules: (1) diseases and phenotypes (VCI, VaD, CSVD, white matter hyperintensity, lacune, cerebral microbleeds, perivascular space); (2) mechanisms and pathways (systemic inflammation, immune homeostasis, endothelial dysfunction, blood-brain barrier, neurovascular unit, microcirculation, immunosenescence, inflammaging, thromboinflammation); and (3) biomarkers and strategies (biomarker, cytokine, chemokine, adhesion molecule, coagulation, platelet activation, MMP, NfL, GFAP, proteomics, extracellular vesicle, multi-marker panel, risk prediction model).

Eligible studies included cross-sectional association studies, longitudinal cohort studies, and mechanistic studies related to immune, endothelial, or BBB biology, with particular priority given to studies that included imaging and/or cognitive follow-up. We prioritized studies with relatively larger sample sizes, clear phenotypic definitions, adequate confounder adjustment, and repeated-measurement or external-validation designs. We excluded duplicate reports, conference abstracts without sufficient data, case reports, studies lacking clear biomarker or outcome definitions, and studies focused mainly on acute-phase fluctuations without clear relevance to VCI/CSVD progression.

Study selection was performed in 2 states, including title/abstract screening followed by full-text assessment. Because of substantial heterogeneity in populations, assay platforms, biomarker definitions, and study outcomes, no quantitative meta-analysis was performed. Given the narrative design and the marked heterogeneity of the included literature, no formal risk-of-bias tool was applied. Instead, evidence was weighted pragmatically according to study design hierarchy, sample size, phenotypic clarity, confounder control, repeated-measurement design, and external validation status. Evidence was synthesized using both a mechanistic framework and a clinical-use framework, with particular emphasis on the hierarchy of prevalent association, longitudinal prediction, incremental value, and external validation.

A pervasive challenge in VCI/CSVD biomarker research is the time dimension. Peripheral inflammatory and vascular-endpoint markers may be strongly influenced by acute events, such as stroke, infection, or hospitalization stress. Accordingly, this review prioritized evidence obtained during relatively stable phases and paid particular attention to sampling windows, repeated-measurement designs, and alignment with imaging and cognitive follow-up endpoints. Findings based only on cross-sectional differences without longitudinal

confirmation were treated as exploratory, whereas markers supported by external validation or multicenter replication were given greater interpretive weight.

In integrating evidence, we focused on 4 major sources of instability. First, disease-definition and population heterogeneity: definitions of VCI, VaD, post-stroke cognitive impairment, and CSVD-dominant cognitive impairment vary across studies, which can cause large between-study fluctuations in effect estimates.[1,5,10,11,14] Second, differences in sampling windows: short-term inflammatory elevation after acute events, hospitalization stress responses, and concurrent infection may distort immune and vascular-endpoint markers and cause event-reactive signals to be mistaken for chronic progression signals. Third, assay-platform and pre-analytical variables: different anticoagulants, processing delays, freeze-thaw cycles, platform sensitivity, and batch effects all influence comparability.[10,11] Fourth, outcome heterogeneity: some studies use cross-sectional imaging burden while others use longitudinal progression endpoints; some use global cognition while others use vascular-typical domains, such as executive function and processing speed, which directly affects interpretation.

Based on these considerations, this review does not equate statistical association with mechanistic causality or clinical usability. For markers supported mainly by cross-sectional evidence, we emphasize their likely position within mechanistic pathways and their value as research leads. For markers with longitudinal evidence, we further discuss gaps in external validation, threshold transportability, and model-level incremental value. This strategy is intended to align conclusions with the true maturity of the available evidence and to reduce over-interpretation.

Although no meta-analysis was performed, the evidence is organized around 3 clinically relevant questions: which patients are more likely to progress, which pathways are more likely to dominate progression, and which markers are closest to deployable status. This structure is intended to help readers identify evidence gaps in topic selection, modeling, and cohort design, and to provide clearer priorities for future multicenter validation research.

Conceptual Definitions and Study Population

VCI Spectrum and CSVD as a Quantifiable Intermediate Phenotype

In this review, "cognitive impairment" mainly refers to the vascular cognitive impairment spectrum (from mild VCI to VaD), with CSVD as the core structural substrate and quantitative carrier.[1,4,5] CSVD imaging phenotypes are used not only for baseline burden assessment but also for longitudinal progression endpoints, such as annual WMH growth, incident lacunes, and cumulative microbleeds, thereby supporting longitudinal validation and prediction analyses for serum biomarkers.[5,6,9] For cognitive outcomes, vascular-typical domains, such as executive function, attention, and processing speed, should be prioritized, and longitudinal outcomes, such as decline slopes or transition events (eg, progression from mild VCI to dementia), are more meaningful for translation.[2,5,6]

Mixed Pathology and Interpretive Boundaries

Mixed pathology, namely the coexistence of vascular lesions and AD-like neurodegenerative change, is common in older adults with cognitive impairment and may substantially affect the interpretation of peripheral inflammatory signals and neural injury biomarkers.[2,3,12] Ideally, biomarker studies should assess neurodegenerative burden and perform stratified analyses. When such information is unavailable, statistical adjustment and sensitivity analyses should at least be used to reduce confounding.[12,13] Accordingly, an elevation of a single inflammatory marker should not be interpreted directly as evidence of a vascular-specific mechanism; it is better considered a background risk signal or part of a broader biomarker panel.[12,13]

Priority of Evidence Type and Longitudinal Endpoints

Cross-sectional studies can reveal associations but do not support causal inference; longitudinal cohorts can assess predictive value; intervention studies, especially biomarker-stratified trials, come closest to causal validation.[10,11,14] VCI/CSVD biomarker research particularly requires a time-aware perspective, because transient post-event inflammatory elevations are not equivalent to chronic progression-driving signals. More informative designs involve stable-phase sampling, repeated measurements, alignment with imaging/cognitive follow-up, and use of progression endpoints (annual WMH growth, incident lacunes, cumulative microbleeds) plus cognitive decline slopes as external validation endpoints for biomarkers.[6,9–11]

Recommendations for Population Stratification (Reducing Heterogeneity and Improving Transportability)

To improve interpretability and generalizability of biomarker findings, stratification is recommended along 3 axes: (1) pathological source, including CSVD-dominant VCI, post-stroke cognitive impairment, and cognitive decline related to large-vessel disease[1,5,14]; (2) disease stage, including asymptomatic imaging burden, mild VCI, and VaD[1,2,5]; and (3) vulnerability discordance, ie, separate analyses of individuals with similar imaging burden but markedly different cognition to test whether immune homeostasis helps explain interindividual differences.[6,8,15] Such stratification may reduce confounding, improve pathway-level interpretability, and support pathway-dominant panel design.[8,11,15]

It should also be emphasized that endpoint selection in CSVD-related cognitive impairment is not merely a statistical issue, but also a mechanistic one. Cross-sectional global cognitive scores may be confounded by education, cognitive reserve, emotional state, and neurodegenerative burden.[2,5,12,13] By contrast, vascular-typical domains, such as executive function and processing speed, especially when modeled as decline slopes or transition events, are more closely aligned with CSVD-related pathways.[2,5,6,9] Similarly, in imaging, annual WMH progression, incident lacunes, and cumulative microbleeds generally reflect pathological activity better than a single baseline burden measure and may therefore serve as more informative external validation endpoints for biomarkers.[6,9–11]

In population stratification, treatment-exposure stratification should also be considered at the design stage. Intensified antihypertensive therapy, antiplatelet/anticoagulant treatment, lipid-lowering therapy, and certain anti-inflammatory drugs may all alter peripheral immune and vascular-endpoint biomarkers while also affecting imaging progression and cognitive outcomes.[10,14,16] Failure to record and appropriately control treatment exposure may overestimate or underestimate the independent predictive value of biomarkers. Cohorts that systematically record treatment intensity and adherence at baseline and during follow-up will have markedly stronger interpretability and translational value.

Finally, the presence of mixed pathology does not make VCI/CSVD biomarker research meaningless; rather, it shifts the design emphasis from excluding confounding to identifying contributions. In real-world populations, vascular and neurodegenerative pathology often coexist. Thus, a more clinically relevant question is whether peripheral immune and vascular-endpoint biomarkers can still predict CSVD imaging progression or decline in vascular-typical cognitive domains in the context of mixed pathology.[12–15] Such questions are closer to real-world clinical scenarios and more likely to produce broadly useful risk-stratification tools.

Peripheral Immune Homeostasis Dysregulation: Evidence and Biological Features

Peripheral immune homeostasis dysregulation may manifest as innate immune activation with inflammatory amplification, adaptive immune imbalance with failure of immune regulation, a chronic low-grade inflammatory background driven by immune-metabolic coupling, and a lowered response threshold caused by immunosenescence.[16–19] Through endothelial and BBB pathways and effects on microcirculation, these changes can translate systemic inflammatory stress into cerebral microvascular injury and white matter connectivity degeneration, thereby driving CSVD progression and a VCI phenotype characterized predominantly by executive dysfunction and slowed processing speed.[18–20]

When discussing immune homeostasis, it is important to emphasize that homeostasis is dynamic rather than static. Under persistent stimuli, such as metabolic burden, blood pressure fluctuation, aging, or infection exposure, dysregulation may not appear as persistently elevated inflammatory markers, but more often as a lowered activation threshold, delayed recovery, or a sustained mild shift between proinflammatory and anti-inflammatory/resolution mechanisms.[16,17,19] In this sense, the peripheral immune abnormalities observed in VCI/CSVD may resemble a chronic, low-grade, fluctuating deviation rather than a classic acute inflammatory pattern, with clinical relevance mainly through their long-term effects on microvascular endothelial function, BBB stability, and microcirculatory regulation.[18–20]

This understanding has direct methodological implications for biomarker research. A single measurement may capture only random fluctuation at one time point and may not represent the individual's long-term immune state.[10,11,17] Likewise, even when a single proinflammatory factor differs statistically, it may not adequately reflect the overall direction of homeostatic drift.[10,11,17] Compared with simply asking

whether one marker is elevated, greater emphasis should be placed on multivariate patterns, stability or trajectory under repeated measurement, ratios or pathway scores between proinflammatory and immune-regulatory/resolution markers, and their temporal relationships with imaging progression and cognitive decline slopes.[10,11,18]

Innate Immunity: Inflammatory Initiation and Maintenance of Vascular Wall Inflammation

Neutrophil activation and neutrophil extracellular trap (NET) formation can injure the endothelium, promote platelet adhesion and the coagulation cascade, facilitate microthrombus formation, and contribute to microcirculatory hypoperfusion, while also potentially worsening BBB permeability changes.[16,20,21] In CSVD/VCI research, indices such as the neutrophil-to-lymphocyte ratio (NLR) are often associated with WMH burden or cognitive-domain performance, but they are highly sensitive to infection, stress, and the post-stroke time window. Interpretation therefore requires careful separation of stable-phase observations from post-event states and control for recent infection, medication exposure, and other confounders.[10,14,21]

The monocyte-macrophage axis is crucial for the maintenance of chronic vascular-wall inflammation. A shift toward proinflammatory phenotypes can increase mediator release, promote leukocyte adhesion and migration, and cause sustained endothelial activation and reduced vascular reactivity, thereby contributing to functional microvascular injury and WMH progression.[16,18,20] The complement system, an amplifier of innate immunity, is cross-coupled with coagulation and may participate in vascular-wall inflammation and thrombogenic tendency; however, complement signals are strongly influenced by infection, autoimmune background, and renal function, and require strict stratification and adjustment before independent associations with CSVD progression can be evaluated.[17,20,22] Inflammasome pathways (eg, NLRP3) may link metabolic abnormalities, oxidative stress, and inflammatory mediator release, and may represent an important node connecting metabolic risk, immune activation, and vascular injury.[17–19,22] However, their translational relevance still requires longitudinal validation and stronger clinical evidence.

It is also important to frame innate immune abnormalities in CSVD not merely as an enhanced inflammatory background, but as part of a structure-function coupling injury process in small vessels. Penetrating arteries and microvessels are anatomically and hemodynamically vulnerable. Once chronic inflammation disrupts endothelial homeostasis, local vasomotor regulation, barrier function, and perfusion reserve may all be persistently affected.[18,20,23] In this process, neutrophil-related signals, proinflammatory monocyte phenotypes, complement amplification, and inflammasome activation may collectively sustain a low-grade but chronic vascular-wall stress state, gradually converting potentially reversible functional abnormalities into visible structural injury on imaging.[18,20,23]

Functional Pathways of Innate Immunity: Microvascular Reactivity and Perfusion Vulnerability

The association between innate immune abnormalities and CSVD is not expressed only through inflammatory intensity. Chronic low-grade inflammation may also alter microvascular reactivity and vascular-wall remodeling. By reducing endothelial nitric oxide bioavailability and weakening vasomotor regulation, low-grade inflammation can make microcirculation more prone to decompensation under blood pressure fluctuations or metabolic stress, thereby creating perfusion vulnerability.[18,23,24] This functional vulnerability may appear on imaging as slow WMH progression and clinically as slowing of processing speed preceding more obvious memory impairment.[5,6,24] Joint analysis of perfusion/vascular reactivity indicators with immune biomarkers may therefore build a stronger mechanistic loop and improve interpretability of progression prediction.[6,18,24]

From an evidence-evaluation perspective, current innate immunity studies are limited by heavy reliance on cross-sectional designs and insufficient control for recent infection, stroke timing, and medication exposure, making it difficult to distinguish acute inflammatory responses from chronic progression-driving background.[10,11,14] To improve translational value, future work should prioritize stable-phase longitudinal studies with repeated measurements and imaging follow-up endpoints, and should model innate immune indices jointly with perfusion or vascular reactivity markers to test whether they provide independent predictive gain beyond traditional risk factors and baseline imaging burden.[9–11,24]

Adaptive Immunity: Imbalanced Regulation, Failed Immune Control, and Insufficient Resolution

Adaptive immunity is more likely to shape the long-term low-grade inflammatory background. A proinflammatory shift in T-cell subset balance (such as T_H17/T_{reg} imbalance) may promote sustained endothelial activation, enhance adhesion and migration, and disturb BBB homeostasis, thereby contributing to white matter connectivity injury and decline in cognitive domains.[17–19,25] The role of B cells and humoral immunity in vascular inflammation is an emerging direction, but current evidence is scattered and susceptible to comorbidity effects, requiring more rigorous phenotypic stratification and causal-inference-oriented study designs.[17,19,25]

From a homeostasis perspective, the key issue is not simply the elevation of proinflammatory factors, but insufficient immune regulation and impaired inflammation resolution. A chronic shift in the balance between proinflammatory and anti-inflammatory/resolution systems may maintain higher inflammatory tension even in the absence of infection, thereby lowering vascular and BBB tolerance to mild inflammatory stimuli.[16–19,25] Accordingly, panel design and evidence appraisal should focus more on ratio relationships and pathway scores than on isolated proinflammatory markers alone.[17–19] Chronic vascular brain injury may therefore be associated less with marked elevation of a single factor than with persistent imbalance between inflammatory and regulatory signals, altered subset distribution, or abnormal response patterns to external stimuli.[17–19,25]

Adaptive immunity is also tightly linked with immunosenescence and metabolic abnormalities. In older adults, prolonged antigen exposure and metabolic load may reduce regulatory capacity and delay inflammatory recovery, thereby increasing endothelial and BBB sensitivity to mild inflammatory stimuli.[19,26] This suggests that age, metabolic comorbidity, and medication background are not only confounders requiring adjustment but may also be effect modifiers that determine the clinical significance of adaptive immune markers.[19,26]

Immune-metabolic Coupling, Hemodynamic Amplification, and Immunosenescence

Metabolic abnormalities can promote endothelial dysfunction and accelerate small-vessel injury through insulin resistance, adipokine imbalance, and chronic low-grade inflammation.[18,19,26] CSVD is also closely related to blood pressure variability: chronic inflammation reduces the buffering capacity of the vascular wall, while blood pressure fluctuations further aggravate endothelial injury and oxidative stress, forming a hemodynamic-inflammatory positive feedback loop.[23,24,26] Immunosenescence and inflammaging provide an age-related low-grade inflammatory background, and their lowered activation threshold indicates that biomarker thresholds and interpretation should be age-stratified to avoid misclassifying age-related inflammatory upshift as disease-specific signals.[19,26]

From a systems-biology viewpoint, peripheral immune homeostasis dysregulation in VCI/CSVD is likely characterized by low amplitude, long duration, and networked behavior rather than persistent high activation of a single inflammatory axis.[16–19] In real-world settings, this means that it is more common to observe mild fluctuations across multiple markers at different time points that collectively indicate impaired recovery capacity or a lowered homeostatic threshold, rather than a single marker being persistently and markedly abnormal.[27] Such a state may be hard to detect with 1-time testing during resting conditions but may manifest as vascular-endpoint imbalance under triggers, such as blood pressure fluctuation, metabolic stress, infection, or sleep disturbance, thereby promoting microcirculatory dysregulation and progressive white matter injury.[28] Future biomarker studies may therefore benefit from incorporating concepts such as within-subject variability and post-stress response patterns, which may prove more informative than single absolute values.

In addition, peripheral immune status and intracerebral pathology may interact bidirectionally. Although this review emphasizes translation from peripheral signals to brain injury, cerebral microvascular injury, white matter connectivity degeneration, and chronic neuroinflammation may also feed back onto peripheral immune status through neuroimmune regulation and humoral signaling.[28–30] This bidirectionality complicates causal interpretation in cross-sectional studies and further highlights the importance of longitudinal design, repeated measurement, and temporal analysis. For VCI/CSVD biomarker research, this is not merely a limitation; it also suggests that biomarkers should be modeled as process signals rather than simple etiological labels.

At the clinical-translation level, the concept of

peripheral immune homeostasis dysregulation also naturally supports panel-based and stratified strategies. If progression is driven by multiple pathways, no single marker is likely to represent overall risk stably. In contrast, a multilayer panel covering systemic inflammatory background, vascular-endpoint response, and neural injury readouts is more likely to maintain consistent performance across populations and disease stages.[5–8,31] This concept underlies the tripartite research strategy emphasized below: multi-marker panels, longitudinal endpoints, and external validation.

Mechanistic Integration: How Peripheral Immunity Drives CSVD Progression and Cognitive Decline

Endothelial Dysfunction and Neurovascular Unit (NVU) Injury

The vascular endothelium is the key portal through which peripheral immune signals are translated into brain injury. Inflammatory mediators and immune-cell adhesion/migration can induce endothelial activation, impair vasomotor responses, and reduce microvascular reactivity, thereby disrupting cerebral perfusion and neurovascular coupling.[18,20,23,27] The neurovascular unit (NVU), composed of endothelial cells, pericytes, smooth muscle cells, glial cells, and related elements, can amplify systemic inflammatory stress into local microcirculatory dysfunction when its function becomes dysregulated, providing a basis for WMH progression and subcortical network disconnection.[23,24,27]

BBB Breakdown and White Matter Connectivity Degeneration (Stage Dependence and Nonlinearity)

BBB disruption allows peripheral inflammatory mediators to enter the brain more readily, inducing glial responses and neuroinflammation and promoting chronic injury to white matter myelin and axons.[20,27,28] BBB-related signals may show stage dependence and nonlinearity: a mild permeability change at an early stage may not produce obvious increases in blood biomarkers, whereas after acute events, transient inflammatory responses may mask chronic progression signals.[10,11,28] Therefore, longitudinal repeated measurement and stable-phase sampling are critical for distinguishing short-term stress responses from chronic progression signals.

Inflammation-coagulation Crosstalk and Microthrombi/Hypoperfusion

Inflammation promotes coagulation and platelet activation, and coagulation feeds back to amplify inflammation, forming a positive loop that can lead to microthrombi and microhypoperfusion, thereby accelerating chronic ischemic white matter injury.[20,22,27,29] This pathway suggests that coagulation- and platelet-related biomarkers may be closer to vascular core mechanisms. However, interpretation is highly dependent on antiplatelet and anticoagulant medication background, which must be systematically documented and accounted for through adjustment or stratification.[10,14,29]

Network Mechanisms and Interindividual Differences: VCI Dominated by Connectivity Injury

VCI resulting from CSVD can be viewed as a network disease. White matter disconnection impairs frontal-subcortical circuits, making executive dysfunction and slowed processing speed particularly prominent.[2,5,6,30] Peripheral immune homeostasis dysregulation may help explain cognitive differences at a similar imaging burden by worsening hypoperfusion, amplifying neuroinflammation, accelerating disconnection, and reducing compensatory capacity.[8,18,27,30] Biomarkers that show stable correspondence with annual WMH progression, diffusion tensor imaging (DTI)-based white matter microstructural decline, and slopes of cognitive decline are therefore more likely to have translational value and to generalize to external cohorts.[6,9,10,30]

Taken together, peripheral immune dysregulation, endothelial/NVU dysfunction, BBB disruption, and inflammation-coagulation crosstalk should not be viewed as isolated modules, but as interacting components of a mutually reinforcing pathological network. Chronic low-grade inflammation may impair endothelial reactivity and blood-flow regulation; increased perfusion vulnerability may render tissue more susceptible to hypoperfusion injury; reduced BBB stability may facilitate entry of peripheral inflammatory mediators into the brain, further amplifying neuroinflammation and white matter degeneration; and coagulation/platelet pathways may act as vascular amplifiers by promoting microthrombi and perfusion insufficiency.[18,20,23,27,29] This integrated model is consistent with the chronic, cumulative, and progressive nature of CSVD and may help explain why single-pathway biomarkers often fail to capture individual risk adequately.[6,8,18,27]

The spatial distribution of CSVD-related injury may further determine the strength of association between peripheral immune signals and cognitive outcomes. The same total WMH burden may have very different cognitive consequences depending on whether lesions involve key frontal-subcortical pathways or more diffuse, relatively noncritical tracts.[5,6,30] Thus, variability in biomarker-cognition associations may partly reflect lesion-location effects rather than biomarker instability per se.[6,30,31] Future validation studies that incorporate lesion distribution and network involvement into prediction models may substantially improve the interpretability and predictive performance of biomarkers.

Mechanistic integration also warns against pathway substitution effects. In some patients, endothelial dysfunction and perfusion vulnerability may dominate; in others, BBB vulnerability and chronic neuroinflammatory amplification may be more important.[23,24,27,28] If study samples include heterogeneous pathway-dominant subtypes but models include only a single pathway marker, overall effects may appear weak and between-study results may be inconsistent.[31,32] Panel-based strategies and pathway-stratified analyses are valuable precisely because they can identify such same-disease, different-mechanism patterns and provide pathological subtyping cues for subsequent stratified intervention studies.

Finally, peripheral immune markers, vascular-endpoint markers, and neural injury readouts may represent signals at different temporal layers of disease. Systemic inflammation and endothelial activation may reflect earlier risk background and pathological activity; BBB and matrix-remodeling markers may be closer to ongoing white matter injury; and neurofilament light (NfL)/glial fibrillary acidic protein (GFAP)-like neural injury markers may reflect downstream injury burden.[16,27,28,33,34] This time-layer perspective suggests that future panel development should aim not only for higher AUC but also for clearer functional positioning of markers across stages of the disease course, enabling more rational deployment for screening, stratification, and monitoring.

Progress in Novel Serum Biomarkers: Evaluation by Clinical Use and Evidence Level

Evidence Evaluation Framework: From "Statistically Significant" to "Deployable"

To have translational value, a biomarker should answer at least 4 questions: (1) Is it stably associated with CSVD burden or VCI (prevalent association)? (2) Can it predict CSVD imaging progression or the rate of cognitive decline (longitudinal prediction)? (3) Does it provide incremental value when added to clinical plus imaging models (eg, calibration, risk reclassification, decision-curve benefit)? (4) Is it transportable across independent cohorts or multicenter studies (external validation and threshold transferability)?[8,10,11,31] Statistical significance alone is insufficient for clinical translation; effect size, reproducibility, external generalizability, and added value for longitudinal endpoints should be emphasized.[10,11,31]

Two common interpretive errors should be avoided when evaluating serum biomarkers. First, statistical significance should not be equated with clinical usability. Second, mechanistic plausibility should not be equated with predictive effectiveness.[31,32] Biomarkers with real translational potential should demonstrate mechanistic relevance, reproducibility, and predictive gain simultaneously.[8,31,32] Accordingly, this review uses the sequence of prevalent association, longitudinal prediction, incremental value, and external validation. Markers with strong cross-sectional associations but insufficient longitudinal evidence are classified as exploratory; markers with some longitudinal support but no external validation are classified as promising but not deployable; only markers or panels that retain stable performance in external cohorts and clearly improve clinical/imaging models approach clinical deployment.[10,11,31,32] For practical interpretation, the biomarkers discussed below are also considered in 3 translational tiers: near-term candidates, emerging markers, and exploratory markers, according to accessibility, mechanistic relevance, longitudinal support, and external validation status.

In practice, evidence maturity can be refined along 3 additional dimensions. The first is biological stability: physiological variability, sensitivity to pre-analytical factors, and repeatability under repeated measurement. The second is clinical stability: whether the direction and magnitude of effects remain broadly consistent across age groups, comorbidity profiles, and medication backgrounds, and whether major center-to-center differences are present. The third is model stability: whether the marker consistently provides incremental value across different models and whether calibration and net benefit are preserved in external validation. Only when stability is progressively established at all 3 levels does a biomarker move closer to deployable status.

The value of negative results also deserves attention. A marker that appears mechanistically plausible but fails to show clear incremental value in longitudinal or external validation does not necessarily imply the pathway is unimportant; more often it indicates suboptimal sampling windows, assay platform choices, variable expression forms (absolute value vs ratio/score), or endpoint definitions.[28,31,32,35] Reviews and study designs should therefore treat negative findings as information for pathway optimization rather than simple failure evidence.

For panel development, we recommend a "few but stable" principle. Rather than constructing high-dimensional models with many markers in a single-center cohort, it is often preferable to build a minimal viable panel using a small number of accessible, reproducible, and mechanistically complementary markers and then iteratively validate and refine the panel in external cohorts. This strategy is more consistent with real-world deployment logic and facilitates subsequent threshold calibration and cross-platform harmonization.

Biomarkers for Screening and Risk Prediction

Systemic Inflammatory Proteins (hs-CRP, Fibrinogen, etc.)

Systemic inflammatory proteins are mature, low-cost assays suitable for large cohorts and real-world datasets. Studies suggest associations with vascular risk-factor burden, CSVD phenotypes, and cognitive outcomes.[33,34,36] However, these markers are nonspecific and are strongly influenced by infection, obesity, liver and kidney function, and medication exposure. A more reasonable translational strategy is to use these markers as background variables or model-base markers for low-cost preliminary screening and coarse risk stratification, followed by the addition of more mechanism-directed markers for refined stratification.[31,33,37]

Although systemic inflammatory proteins are often criticized for low specificity, this does not mean their value in VCI/CSVD biomarker systems is limited. Their strengths are accessibility, low cost, and ease of replication across centers. In multilayer panels, the task of first-layer markers is not to pinpoint a specific pathological pathway but to rapidly identify populations with an overall elevated risk and provide a stratified starting point for subsequent, more mechanism-directed testing.

Blood Cell–derived Inflammatory Indices (NLR, PLR, SII, etc.)

Blood cell–derived indices reflect an imbalance in immune-cell proportions and systemic inflammatory tension and are frequently associated with WMH burden or cognitive-domain outcomes.[33,35,38] However, thresholds are not standardized and the meaning of elevation is stage-dependent: elevations after acute events often reflect tissue injury and stress responses, whereas elevations during stable phases may better indicate chronic low-grade inflammatory tension.[36,39] These indices are also influenced by anemia, infection, cancer, and medications.[31,35] They are best modeled as continuous variables (or by quantiles) and require external threshold-transferability studies. They are generally more suitable as panel components than as stand-alone diagnostic markers.

Cytokine/Chemokine Profiles: From Single Factors to Pathway Scores

Cytokine and chemokine profiles are more mechanism-oriented, but platform differences and batch effects are substantial, and single-factor findings are often unstable.[17,18,36] A more feasible strategy is to construct pathway scores or inflammatory signatures that integrate proinflammatory, chemotactic, and immune-regulatory factors into composite scores. This may reduce single-marker noise and better represent the concept of homeostatic dysregulation, thereby aligning more naturally with longitudinal progression endpoints.[17,18,36] A key next step is to identify a minimal standardized cytokine set that can be implemented on clinical platforms and then validated across multiple centers.[11,31,40]

Methodologically, emphasis should shift from identifying one "significant" cytokine to building pathway-level scores or inflammatory signatures. This approach reduces batch noise, better reflects the biology of system-level drift rather than point abnormalities in VCI/CSVD, and may provide much stronger longitudinal interpretability if pathway scores show stable correspondence with annual WMH progression or cognitive decline slopes.[6,9,10,36]

Endothelial Injury and BBB-related Biomarkers: Vascular Core Pathways

Endothelial Activation and Adhesion Molecules (VCAM-1, ICAM-1, etc.)

Adhesion molecules reflect endothelial activation and leukocyte adhesion/migration and thus provide an important window linking peripheral immune dysregulation to vascular-wall response.[20,23,37] Existing studies suggest associations with CSVD burden and cognitive-domain impairment and indicate relatively strong mechanistic relevance.[23,37] However, these signals may also reflect systemic vascular inflammation and renal function. They are therefore better used in panels and should be prioritized for validation in CSVD-dominant populations to test predictive gain and external transportability for outcomes, such as annual WMH growth and incident lacunes.[31,37]

BBB Permeability and Matrix-remodeling Molecules (e.g., MMP-Related Markers)

BBB- and matrix-remodeling-related markers are mechanistically aligned with barrier disruption, but results are often inconsistent.[27,28,38] Possible reasons include stage dependence, poor control of sampling windows, assay-platform variation, and noise amplification. Before translation, these markers require standardized sampling, repeated measurement, and longitudinal follow-up to verify whether they change with progression and whether they add predictive value beyond imaging models.[10,11,28,31,38]

In this review, BBB- and matrix-remodeling-related molecules, including matrix metalloproteinase (MMP)-related markers, are positioned primarily as upstream or intermediate indicators of barrier instability and tissue remodeling rather than as direct downstream neural injury readouts. This distinction is intended to reduce conceptual overlap with neural injury biomarkers, such as NfL and GFAP, which are discussed mainly as markers of injury burden and disease-course consequence.[27,28,30,38,42]

Proteomics Candidates and the Panelized "Discovery-Validation-simplification" Path

Proteomics provides a broad candidate pool but must pass through a disciplined chain of discovery, validation, external validation, and deployable simplification to avoid overfitting and poor transportability.[39,40] The ultimate goal is an accessible panel composed of a small number of stable markers that shows robust correspondence with imaging progression and cognitive decline slopes. Quality control, cross-platform consistency, and threshold-transferability testing are essential for real-world deployment.[11,31,39,40]

Compared with systemic inflammatory markers, biomarkers related to endothelial activation, BBB dysfunction, and matrix remodeling are closer to the pathological core of CSVD and may therefore better reflect vascular-pathway activity.[20,23,27,37,38] Their value lies not only in improving discrimination but also in helping answer which pathway is currently driving progression. For example, a panel pattern dominated by endothelial activation and coagulation abnormalities may indicate a vascular-endpoint inflammatory-coagulation pathway, while a pattern dominated by BBB/matrix-remodeling abnormalities may indicate a more active barrier-instability/white matter injury process.[27,29,37,38] Such pathway profiling is highly relevant for future stratified intervention studies.[8,31,40]

These markers may also have strong translational potential because they are easier to connect to intermediate imaging changes. Relative to background inflammatory markers, endothelial-activation and BBB-vulnerability signals are theoretically closer to the direct pathological processes of CSVD and may become abnormal before obvious new lesions appear on imaging.[23,27,28,37,38] If confirmed in longitudinal cohorts, they may become particularly useful in progression-warning scenarios.[9–11,31]

At the same time, over-mechanistic interpretation should be avoided. Endothelial-activation and BBB-related signals can also be affected by systemic vascular inflammation, renal dysfunction, metabolic abnormalities, and infection. Without careful confounder control, researchers may misattribute global systemic-state changes to CSVD-specific pathology.[40–44] Future studies should therefore focus on stable-phase, CSVD-dominant cohorts with clear comorbidity and medication documentation and use longitudinal progression endpoints plus external validation to strengthen inference.[42–44]

In panels, endothelial/BBB-pathway markers may provide actionable information, not just improved discrimination. If a patient exhibits a pattern dominated by endothelial activation and coagulation abnormalities, clinicians may place greater emphasis on hemodynamic stability, vascular risk management, and closer follow-up. If BBB/matrix-remodeling abnormalities dominate, this may indicate higher pathological activity and a need

for more frequent imaging reassessment and dynamic disease monitoring.[27–29,31,37,38,45] Such pathway-guided interpretation is highly relevant to future precision management.

Inflammation-coagulation Crosstalk and Platelet-related Biomarkers

This group of markers may capture microthrombotic and hypoperfusion pathways and may therefore offer strong interpretive value for CSVD progression, particularly annual WMH growth.[22,29,41] However, levels are strongly affected by antiplatelet and anticoagulant therapy, so medication exposure must be systematically recorded and adjusted for in analyses. If these markers still provide stable incremental prediction after medication control, they could become an important breakthrough in identifying vascular-specific and potentially modifiable mechanisms, and might help guide more precise follow-up and intervention strategies.[10,14,29,31,41]

Blood Biomarkers of Neural Injury (NfL, GFAP, etc.) and Extracellular Vesicles

Neural injury markers are better viewed as injury-burden readouts than upstream vascular-mechanism indicators. They are useful for disease-course monitoring and prognosis assessment and can reflect overall neural injury severity in mixed-pathology settings.[12,30,42] Extracellular vesicle/exosome-related approaches are innovative and may provide more source-specific molecular information, but standardization, batch effects, and quantitative consistency remain major barriers; in the short term, they are more suitable for mechanistic exploration and research stratification.[39,40,42] In VCI/CSVD translational pathways, neural injury markers are best positioned as the outcome-dimension component of a panel, jointly interpreted with vascular and immune markers to explain progression speed and cognitive decline slopes, rather than as a stand-alone basis for vascular subtyping.[30,31,42]

Multi-marker Panels and Multimodal Integration: Evaluation Standards for Deployable Models

A practical panel can be conceptualized as a 3-layer structure: layer 1 for systemic inflammatory background (routinely accessible markers), layer 2 for vascular-endpoint mechanisms (endothelial/coagulation/BBB-related markers), and layer 3 for brain injury readouts (neural injury biomarkers).[31,32,43] Model evaluation should extend beyond area under the curve (AUC) to include calibration, decision-curve analysis, and risk reclassification, and should include external validation and threshold-transferability testing. Interpretability should also be emphasized so that the model can be integrated into clinical pathways (eg, intensified risk-factor control, denser follow-up, or enrollment in stratified intervention trials). For example, a basic deployable panel may combine 1 or 2 routine inflammatory markers for background risk, 1 endothelial/coagulation/BBB-related marker for pathway activity, and 1 neural injury marker as a downstream injury readout, with the exact composition varying according to the intended use scenario and assay availability.[31,32,43,44]

In panel and model development, calibration and clinical decision metrics are particularly important. For chronic progressive diseases such as VCI/CSVD, a model that systematically overestimates or underestimates risk may lead to inappropriate follow-up frequency or intervention intensity even if discrimination is acceptable.[32,43,44] Therefore, calibration curves, calibration intercept/slope, decision-curve analysis, and risk reclassification should be routinely reported to evaluate net clinical benefit.[32,43,44] Threshold transportability is another prerequisite for deployment: whether risk thresholds require recalibration across centers, assay platforms, and comorbidity spectra determines whether a model can move beyond the original single-center setting.[11,31,43,44]

Model interpretability is especially important in VCI/CSVD because management often involves long-term follow-up and multidisciplinary collaboration. If a model outputs only high-risk versus low-risk labels without pathway-level information, it is difficult to formulate specific management strategies.[31,44] In contrast, a panel that explicitly represents dimensions such as high systemic inflammatory background, active vascular-endpoint mechanisms, and rising neural injury readouts can be more easily cross-checked with imaging and clinical features and can better inform risk-factor management, imaging intervals, and potential intervention choices.[8,31,44]

At the statistical-modeling level, VCI/CSVD panel studies should address 2 frequently overlooked issues. The first is collinearity and information redundancy: systemic inflammation, endothelial activation, and coagulation markers may be strongly correlated, and

without variable selection or dimensionality reduction, apparent performance gains may not persist in external validation.[31,32,43,44] The second is inadequate sample size and event numbers: when endpoints are longitudinal progression events (eg, incident lacunes, cumulative microbleeds, or substantial cognitive decline), event counts are often limited, and too many variables can easily lead to overfitting.[10,11,31,46] Panel construction should therefore use predefined candidate-variable sets, robust internal validation, and transparent variable-selection procedures to improve reproducibility.[31,32,43–46]

At the deployment level, testing cost and workflow complexity also determine feasibility. Some high-dimensional proteomics models may perform well in research settings but have limited clinical utility if costs are high, platforms are specialized, and turnaround time is long.[47,48] A more realistic strategy is to establish a basic accessible panel first (eg, routine inflammatory markers plus a small number of vascular-endpoint markers and 1 neural injury marker), complete multicenter validation, and then explore whether more complex molecular assays are necessary in high-risk subgroups.[49,50] This layered deployment strategy balances innovation with implementability.[47,48]

Finally, multimodal integration does not mean that more modalities are always better. The integration of clinical, imaging, and biomarker data should be judged by stable incremental value and improved decision-making, not by model complexity alone.[31,32,43,44] In VCI/CSVD, a well-calibrated, interpretable model with a moderate number of markers that consistently identifies individuals at high progression risk is often more useful than a slightly higher-performing but opaque and difficult-to-replicate model.[31,43–46]

Clinical Translation and Methodological Challenges

The major obstacle in VCI/CSVD biomarker research is not a shortage of candidate markers but the lack of reproducibility, comparability, and deployability. First, application scenarios determine desirable marker properties: community screening emphasizes cost and accessibility; specialist stratification emphasizes mechanistic relevance; and follow-up monitoring emphasizes stability and sensitivity to change.[8,31,45] The same marker may require different thresholds in different scenarios, so risk stratification is generally preferable to rigid universal cutoffs, and transportability must be tested in external cohorts.[31,43,45]

Second, standardization is the prerequisite for reproducibility. Studies should harmonize serum versus plasma use, anticoagulant choice, sampling windows (stable-phase sampling preferred), storage conditions, and batch control. For multi-analyte assays, quality-control workflows and batch-correction strategies should be explicitly defined.[10,11,45] Third, confounding and causal interpretation must be addressed systematically: infection, metabolic comorbidities, renal function, autoimmune disease, and common cardio-cerebrovascular medications all alter immune profiles.[10,14,17,19,45] These factors should be systematically recorded and handled through stratification and sensitivity analysis. In addition, reverse causality should be considered, because established brain injury and neuroinflammation may themselves alter peripheral immune profiles. When appropriate, propensity-score methods and longitudinal mixed-effects models may help strengthen causal interpretation.[11,32,45]

Finally, selection bias and repeated measurement are especially important in chronic-disease biomarker research. Differences in composition between hospital-based and community-based cohorts can produce inconsistent effect estimates.[10,11,45] A stepwise path of community discovery, hospital validation, and multicenter external validation is recommended. Repeated measurements aligned with imaging follow-up should be incorporated whenever possible to test whether markers change with progression and thus better support chronic progression mechanisms.[9–11,45]

From both peer-review and implementation perspectives, VCI/CSVD biomarker research should further improve reporting transparency and reproducibility. Investigators should clearly report recruitment pathways, inclusion/exclusion criteria, recent infection or hospitalization history, medication use, and sampling windows so that readers can judge applicability to stable-phase CSVD populations.[10,11,45] For multi-marker models, variable-selection procedures, missing-data handling, internal validation strategies (eg, bootstrap or cross-validation), and external validation details should be reported to avoid the common problem of apparently excellent performance with poor reproducibility.[31,32,43–46] Because VCI/CSVD studies often involve long follow-up, primary and secondary endpoints should be prespecified, and preregistration or locked analysis plans should be considered to reduce bias from analytic flexibility.[10,11,45]

Future work should also avoid focusing only on new markers and should revisit the value of older accessible markers within new frameworks. Although many conventional markers lack pathway specificity, they may still play important roles in layered panels and stratified pathways.[31,33–35,46] Clinically influential solutions are often not those using the most cutting-edge assay, but those that achieve the best balance among cost, accessibility, stability, interpretability, and predictive gain as a minimal viable combination.[31,43–46]

From a real-world implementation perspective, inter-center workflow inconsistency is another major issue. Differences in blood-draw timing, fasting state, transport time, freezing conditions, assay platforms, quality-control procedures, and standard operating procedures (SOPs) can introduce non-biological heterogeneity in multicenter studies.[10,11,45] Thus, multicenter validation should establish unified pre-analytical and assay SOPs as far as possible and account for center or platform effects in statistical analyses.[31,43–46] This step often improves evidence quality more than simply increasing sample size.

Outcome standardization is equally critical. Cognitive assessment is influenced by evaluator training, test environment, and patient fatigue, while imaging endpoints are affected by scanner parameters, sequences, and reading methods.[5,6,9–11] If outcome measurement itself is noisy, true biomarker signals may be underestimated.[31,45,46] Future studies should therefore strengthen biomarker standardization and outcome standardization simultaneously rather than optimizing one while neglecting the other.[10,11,31,45]

At the reporting level, investigators should provide reproducible details, including sample-processing workflows, batch information, missing-data handling, variable-selection rules, internal and external validation procedures, and model formulas/scoring methods.[31,32,43–46] For teams planning follow-up studies or external validation, such details are often as valuable as significant findings themselves and better meet current standards for high-quality translational research.[43–46]

Translational Pathway and Future Research Roadmap

To move biomarkers from research associations to clinical deployment, a 3-step strategy is recommended. Step 1 is accessible screening: use systemic inflammatory proteins and blood cell indices for low-cost preliminary screening and coarse risk stratification. Step 2 is mechanism-based fine stratification: add endothelial, coagulation, and BBB-related markers to form a mechanistically directed panel and identify high progression-risk and pathway-dominant subtypes. In this process, medication exposure should generally be treated not as a routine exclusion criterion, but as a key stratification variable and covariate, because antiplatelet, anticoagulant, antihypertensive, and lipid-lowering therapies are integral to real-world VCI/CSVD management and may influence both biomarker levels and clinical outcomes. Step 3 is longitudinal validation and intervention linkage: conduct multicenter external validation with annual WMH growth, incident lacunes, cumulative microbleeds, and slopes of cognitive decline as endpoints, and then use biomarker-driven enrichment designs or predictive stratification trials to test whether the panel predicts differential intervention benefit.[8–11,31,47] This roadmap emphasizes solving measurability and reproducibility first, then predictability and deployability, and ultimately interventional guidance.[31,43,47]

At the operational level, future multicenter research may adopt staged validation. In stage 1, community or health-check cohorts use basic clinical variables plus accessible inflammatory markers for initial screening to identify potentially high-risk individuals. In stage 2, neurological specialty cohorts add endothelial/coagulation/BBB markers and standardized MRI phenotyping to build mechanism-oriented panels. In stage 3, prospective longitudinal cohorts use annual WMH growth, incident lacunes/microbleeds, and cognitive decline slopes as primary endpoints for external validation and threshold calibration.[9–11,31,48] This staged strategy helps control cost while preserving study quality and improves the final model's real-world deployability.[4,48]

During preparation for intervention trials, the value of biomarker panels should extend beyond predicting who will worsen to exploring who is more likely to benefit from which intervention.[47,48] For example, some patients may be driven mainly by blood pressure variability and vascular-endpoint inflammation and may benefit more from intensified hemodynamic management, whereas others may show stronger BBB vulnerability or inflammation-resolution abnormalities and may be better candidates for future endothelial-protective or immunomodulatory strategies.[49–51] This pathway-based stratification approach may provide a

key bridge from risk assessment to precision intervention in VCI/CSVD.[8,31,47,48]

From the perspective of clinical workflow design, future biomarker applications can be divided into 3 scenarios. The first is community or health-check risk pre-screening, where the goal is to identify potentially high-risk individuals using low-cost, highly accessible markers; sensitivity and implementability are prioritized over pathway specificity.[52,53] The second is specialist outpatient mechanism stratification and follow-up planning, where endothelial/BBB/coagulation markers and standardized imaging are added to identify patients at high progression risk and optimize follow-up schedules.[54] The third is research/trial enrichment and predictive stratification, where panels are tested using strict SOPs and longitudinal endpoints to evaluate prediction of differential treatment response and support genuinely biomarker-driven intervention trials.[55] This scenario-specific strategy helps avoid the unrealistic expectation that one panel can solve all problems.

Future studies should also address threshold transferability and local calibration early. Even when a panel is statistically significant across centers, optimal thresholds and risk-category boundaries may differ due to population structure[56], comorbidity spectra, and assay-platform differences.[57] Local recalibration after external validation, rather than mechanical reuse of original thresholds, is likely essential for real-world performance.[43–46] This is especially important in chronic disease management such as VCI/CSVD because model outputs influence follow-up and management decisions.[31,47]

Finally, stronger linkage is needed between longitudinal cohorts and intervention trials. High-quality longitudinal cohorts should not only prove that biomarkers can predict progression, but also provide event-rate estimates, subtype distributions, endpoint definitions, and sample-size assumptions for future trials.[10,11,47,48] If this linkage is built early in study design, the efficiency of moving from observational association to interventional validation in VCI/CSVD biomarker research may improve substantially.[47–50]

Outlook: Biomarker-driven Stratified Interventions

If peripheral immune dysregulation makes a causal contribution to CSVD progression, stratified interventions aimed at restoring immune homeostasis, promoting inflammation resolution, or protecting the endothelium are theoretically attractive.[16–19,49] Trial designs may adopt enrichment approaches (selecting high progression-risk individuals to increase event rates) or predictive stratification approaches (comparing response differences to targeted interventions across pathway-defined subtypes).[47,49,50] A panel that predicts both imaging/cognitive progression and differential benefit from blood pressure variability control, endothelial protection, or antithrombotic strategies would markedly advance VCI/CSVD from risk assessment toward precision intervention.[24,29,47,58,59] Multi-omics integration may improve mechanistic interpretability, but cost, workflow complexity, and deployability must be carefully balanced; priority should be given to building and externally validating a minimal viable panel.[39,40,43,50]

A major challenge for future VCI/CSVD biomarker research is balancing complexity and deployability. Multi-omics integration and high-dimensional models have strong exploratory value but often fail to enter clinical practice without simplification and external validation.[39,40,50] Accordingly, the research pathway should be explicitly divided into a discovery layer (high-dimensional, multi-omics, mechanism exploration) and a deployment layer (low-dimensional, accessible, standardized), with transition achieved through candidate selection, model compression, and threshold calibration.[31,39,40,43,50] Only panels that maintain stable performance and clear interpretability across populations, centers, and platforms can become part of precision management in VCI/CSVD.[31,43,44,50]

Looking forward, the key task is not simply to discover more molecules but to establish an iterative evidence-accumulation system. Such a system should include standardized cohorts, harmonized pre-analytical procedures, reusable endpoint definitions, transparent reporting standards for models, and multicenter external validation networks.[10,11,31,43–46,50] Under this framework, novel markers identified by different teams can enter validation pipelines more efficiently instead of remaining isolated exploratory findings.[39,40,50]

At the same time, clinical implementation must balance scientific rigor and acceptability. For patients requiring long-term follow-up, excessively complex or costly testing is difficult to sustain and may reduce the practical value of biomarkers.[31,43,44,50] A more meaningful goal is to maximize mechanism coverage and predictive performance while minimizing panel complexity and improving assay accessibility and interpretability, so that biomarker tools genuinely

support clinical decision-making rather than remain research showcases.[31,43–46,60] This dual optimization of science and implementation will determine whether VCI/CSVD biomarker research can evolve from a conceptual framework into a routine management tool.

Limitations

This review has several limitations. First, it is a narrative review rather than a formal systematic review or meta-analysis, and although a structured search and explicit evidence-weighting strategy were used, some degree of selection and interpretive subjectivity remains. Second, the current evidence base is highly heterogeneous in terms of disease definitions, sampling windows, assay platforms, medication exposure, and outcome measures, which limits direct comparability across studies. Third, many candidate biomarkers are still supported mainly by cross-sectional associations rather than repeated-measurement longitudinal data or external validation. These limitations reinforce the need for standardized prospective cohorts, repeated measurements, and multicenter validation before broad clinical deployment.

CONCLUSION

Peripheral immune homeostasis dysregulation may contribute to CSVD progression and white matter connectivity injury through endothelial dysfunction, BBB disruption, and inflammation-coagulation crosstalk, resulting in a VCI phenotype characterized by executive dysfunction and slowed processing speed. Current serum biomarker evidence indicates that individual markers have limited specificity and inconsistent transportability across settings. A more promising direction is the development of parsimonious panel-based combinations integrated with CSVD imaging progression and slopes of cognitive decline to achieve stable incremental value and real-world applicability. Future work should prioritize standardized stable-phase sampling, repeated longitudinal measurements, transparent handling of medication exposure, and multicenter external validation. These steps are essential if biomarker research is to move from descriptive association toward deployable risk stratification and biomarker-guided intervention in VCI/CSVD.

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