RESEARCH PAPER

Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios in Cerebral Small Vessel Disease: A Systematic Review of White Matter Hyperintensity Burden and Drug Delivery Implications

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ABSTRACT
Cerebral small vessel disease (CSVD) affects the small arteries, arterioles, capillaries and venules of the brain, and white matter hyperintensity (WMH) is the imaging marker seen most often. Conventional vascular risk factors do not fully explain why the extent of white matter damage differs so widely between patients, and systemic inflammation has been put forward as part of the missing explanation. The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are attractive candidates because both come free with a routine full blood count. We systematically reviewed the evidence linking these two ratios to the degree or burden of WMH in CSVD and related cerebrovascular conditions. Scopus was searched for observational studies published between 2016 and 2026, selection followed the PRISMA 2020 statement, eligibility was framed with the PECOS structure, and methodological quality was judged with the Joanna Briggs Institute checklists. Of 223 records identified, eight studies met the criteria. Six reported a higher NLR alongside a greater degree or burden of WMH, with adjusted odds ratios ranging from about 1.4 for moderate-to-severe overall WMH to 2.2 for severe total CSVD burden, and one large biobank analysis linked NLR to segmented WMH volume and to microstructural injury. Two studies found no independent association once vascular and metabolic confounders were controlled for, or in the setting of acute ischaemic stroke. Associations were more consistent for periventricular than for deep lesions. Evidence on PLR was much thinner: one study reported higher values in severe WMH, another found no relationship with total CSVD burden, and the remaining six did not treat PLR as a main exposure. NLR therefore rests on a broader and steadier evidence base than PLR, though neither is ready to stand alone. Beyond risk stratification, these markers may help identify the patients in whom inflammation-directed treatment, delivered across an already permeable blood-brain barrier, would be worth testing.

Keywords: cerebral small vessel disease; white matter hyperintensity; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; systemic inflammation; blood-brain barrier; targeted drug delivery.

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INTRODUCTION

Cerebral small vessel disease (CSVD) is the umbrella term for the disorders that affect the small arteries, arterioles, capillaries and venules of the brain. It sits behind a substantial share of lacunar stroke, intracerebral haemorrhage, gait disturbance, cognitive decline and vascular dementia, and it shows itself on imaging as white matter hyperintensity (WMH), lacunes, cerebral microbleeds, enlarged perivascular spaces and brain

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atrophy.[1,2] Of these, WMH is the marker encountered most often, appearing as a hyperintense lesion on T2 and fluid-attenuated inversion recovery sequences. A heavier WMH burden tracks a greater risk of cognitive decline and dementia, chiefly through executive function, processing speed, attention and memory, so grading the lesion load carries really clinical and prognostic weight.[3,4]

The vascular risk factors behind CSVD have been recognised for decades: advancing age, hypertension, diabetes, dyslipidaemia, smoking and impaired renal function all contribute through atherosclerosis, vessel stiffening and disturbed perfusion. What these factors do not explain is why the extent of white matter damage varies so much from one patient to the next. Some patients carry a heavy WMH burden on a modest risk profile, while others accumulate risk factors without comparable damage.[5,6] That gap has pushed attention towards mechanisms beyond conventional vascular injury, and inflammation is the one that has attracted most interest.

The biological case is reasonable. Inflammation increases leucocyte adhesion and vascular permeability, raises thrombotic activity and damages the neurovascular unit, which together produce chronic hypoperfusion and injury to the white matter.[7] Against this background the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) have been proposed as simple proxies for that process. NLR captures the balance between the innate inflammatory response and the adaptive immune response; PLR reflects platelet involvement alongside inflammation and thrombotic activity.[7,8] Both are derived from a full blood count that has already been taken, cost nothing extra, and are available within minutes, which is precisely the appeal.

A growing body of work has tested the idea. An analysis of more than thirty-six thousand UK Biobank participants found NLR associated with WMH volume and with several indices of white matter microstructural injury after confounders were taken into account.[9] Hospital-based studies have reported that a raised NLR accompanies heavier CSVD burden and poorer cognitive performance,[8] and a recent meta-analysis of fifteen studies and almost sixty-three thousand subjects linked higher NLR to the presence of CSVD, to total CSVD burden and to larger WMH volume.[10] That same meta-analysis found considerable heterogeneity, however, and the association with WMH severity shifted once studies at high risk of bias were removed. Work in acute ischaemic stroke has likewise failed to find a consistent independent association with most CSVD imaging markers after adjustment.[11]

Evidence on PLR is thinner and less settled. Studies in CSVD have found no significant relationship between PLR and severe total CSVD burden, while work in other vascular populations has reported associations with clinical outcomes without demonstrating a specific correlation with white matter lesion scores.[8] Whether PLR carries an association of comparable strength to NLR therefore remains open.

Several things could account for the disagreement between studies. Populations differ; disease phase differs, since NLR and PLR both rise as part of the acute stress response; the timing of blood sampling differs; and WMH has been graded in at least five different ways, from the Fazekas scale to automated volumetry, microstructural indices, lesion phenotypes and composite CSVD burden scores.[9,12,13] Direct comparison across such varied approaches is not straightforward, which is why a systematic appraisal is needed rather than another individual cohort.

There is also a question that has scarcely been asked. No disease-modifying treatment exists for CSVD, and if systemic inflammation genuinely contributes to white matter injury, then anti-inflammatory strategies become a plausible therapeutic direction. Any such attempt runs into two practical difficulties: choosing the patients whose disease is inflammatory in character, and getting a drug to a cerebral microvascular bed that lies behind the blood-brain barrier. We therefore carried out this systematic review to synthesize the evidence on NLR, PLR and the degree or burden of WMH in CSVD, to identify the methodological factors that explain the disagreement between studies, and to consider what these simple markers might offer for patient selection and for targeted delivery in a disease where the barrier itself is already leaking.

METHODS

Study design and registration

This work was conducted as a systematic review of observational studies and reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.[19] The review set out to evaluate the association between NLR, PLR and the degree or burden of WMH in patients with CSVD or a related cerebrovascular condition. The unit of analysis was the eligible primary article rather than patient-level data. Because the work draws only on already-published studies, individual ethical approval was not required. A protocol covering the search, selection, extraction and quality appraisal was agreed before screening began.

Review question and eligibility criteria

The review question was framed with the PECOS structure (Population, Exposure, Comparison, Outcome, Study design). The population was adults with CSVD or a related cerebrovascular condition; the exposure was NLR or PLR measured in peripheral blood; the comparators were high against low marker values, mild against severe WMH, or subjects with and without CSVD; and the outcomes were total or overall WMH, periventricular WMH, deep WMH, WMH volume, white matter microstructural injury, lesion phenotype, or a total CSVD burden score that included WMH as a component.

Studies were included if they (1) were primary research articles published between 2016 and 2026; (2) enrolled adults with CSVD, ischaemic stroke, single small subcortical infarction, non-disabling ischaemic

cerebrovascular events, or populations undergoing MRI for the assessment of WMH and CSVD markers; (3) measured NLR or PLR from peripheral blood; (4) reported the degree or burden of WMH in one of the forms listed above; (5) used an observational cross-sectional, retrospective, retrospective cohort, prospective cohort or longitudinal design; and (6) provided a retrievable abstract and full text with data matching the PECOS components. We excluded duplicates and articles outside the year range, articles without an abstract or retrievable full text, literature reviews, case reports, editorials, letters and other non-empirical publications, studies that did not measure either ratio as an exposure, studies that did not assess WMH or a CSVD imaging marker involving WMH, studies without extractable results for the association of interest, and studies whose neurological outcomes were unrelated to CSVD or white matter damage.

Information sources and search strategy

Scopus was searched with the assistance of Watase Uake Tools for articles published between 2016 and 2026. The search combined terms for the disease, the imaging outcome and the exposure: Cerebral Small Vessel White Matter, White Matter Hyperintensity, AGE, Systemic Inflammatory White Matter, Neutrophil Lymphocyte Ratio White Matter, Platelet Lymphocyte Ratio Cerebral, and Relationship of neutrophil/lymphocyte ratio with cerebral small vessel disease, applied combinatorially with Boolean operators. Restricting the search to a single database was a deliberate choice made to keep the indexing standard uniform, and its consequences are considered among the limitations.

Study selection

Records were de-duplicated before screening. Titles and abstracts were screened against the eligibility criteria, after which the full text of the remaining records was assessed. Disagreements were settled by discussion, with a senior reviewer consulted where consensus could not be reached. The selection process is summarised in the PRISMA 2020 flow diagram (Figure 1).

Data extraction and risk-of-bias assessment

Data were extracted into a standardised form. For each study we recorded the first author, year, country, setting, design, sample size and clinical condition of participants; the marker assessed, its method of calculation, the timing of blood sampling and whether it was analysed as a continuous or a categorical variable; the MRI protocol, the WMH grading method, lesion location and volume, microstructural parameters and the use of WMH within a composite CSVD burden score; and the reported effect estimates, confidence intervals, p values and adjusted results, together with the confounders and limitations acknowledged by each study.

Methodological quality was judged with the Joanna Briggs Institute (JBI) Critical Appraisal Checklists appropriate to each design.[20] Cross-sectional studies were appraised with the checklist for analytical cross-sectional studies and the remainder with the checklist for cohort studies. Each item was scored yes, no, unclear or not applicable, and items marked not applicable were excluded from the denominator. The appraisal covered subject selection, sample appropriateness, validity of the biomarker measurement, reliability of WMH assessment, identification and control of confounders, and the appropriateness of the statistical analysis; for cohort studies it also covered baseline comparability, adequacy of the observation period, completeness of follow-up and the handling of loss to follow-up. Studies meeting 80 per cent or more of applicable criteria were regarded as high quality, 60 to 79 per cent as moderate, and below 60 per cent as low. The results are shown in Table 2 and summarised graphically in Figure 2.

Synthesis methods

Given the variation in exposure definition, outcome definition, sample characteristics, analytical approach and effect measure, a formal meta-analysis was not appropriate and a narrative synthesis was used instead. Extracted data were tabulated and compared by biomarker, population, design, WMH measurement method, lesion location and direction of association, so that points of agreement and the sources of variation could be identified.

RESULTS

Literature search results

The search identified 223 records. Twenty-four were removed before screening: one duplicate, fifteen marked ineligible by automation tools because they fell outside the 2016 to 2026 window, one that did not meet the journal tier requirement, and seven without an abstract. The remaining 199 records were screened on title and abstract, of which 184 were excluded as irrelevant to the review question. Full texts were sought for fifteen reports and six could not be retrieved. Of the nine reports assessed in full, one was excluded for not meeting the inclusion criteria. Eight studies entered the final qualitative synthesis (Figure 1).

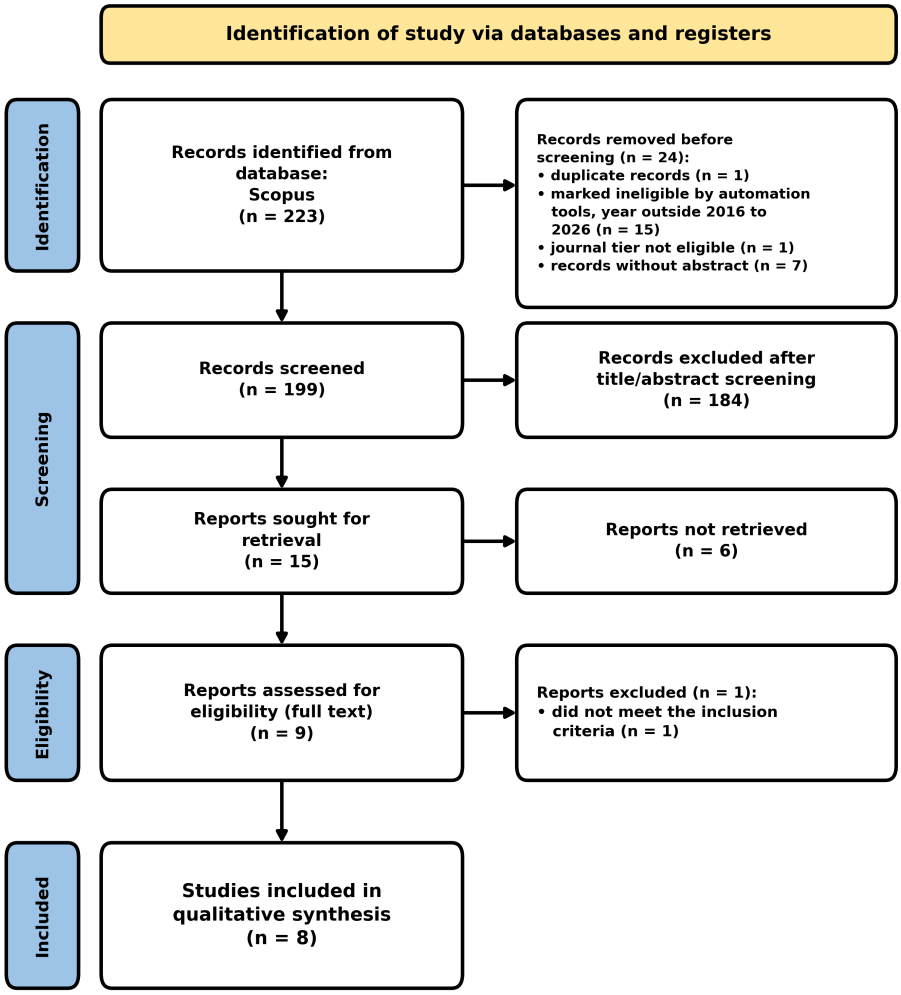

Figure 1. *PRISMA 2020 flow diagram of study identification, screening and inclusion. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.*

Characteristics of included studies

The eight included studies were published between 2023 and 2026 and came from Thailand, China, South Korea and the United Kingdom, the last through UK Biobank data. Designs comprised four analytical cross-sectional studies, one retrospective cohort, one multicentre prospective cohort, one hospital-based retrospective study and one population study with cross-sectional and longitudinal components. Sample sizes ranged from 148 to 36,411 participants. Populations spanned clinically defined CSVD, acute ischaemic stroke, single small subcortical infarction, non-disabling ischaemic cerebrovascular events, health check-up attendees and a population cohort. NLR was measured in every study; PLR was analysed directly in only two. The characteristics of the included studies are summarised in Table 1.

Table 1. *Characteristics of the eight studies included in the review.*

Study (year)	Country	Design	Sample size	Outcome(s) assessed	Key finding
Tieachanpan et al. (2026)	Thailand	Retrospective cohort	299 acute ischaemic stroke	Fazekas deep and periventricular WMH; total SVD score	Highest NLR tertile not independently associated with severe deep or periventricular WMH after adjustment.
Wu et al. (2025)	China	Multicentre prospective cohort	513 single small	Overall, periventricular and	NLR associated with moderate-to-

Study (year)	Country	Design	Sample size	Outcome(s) assessed	Key finding
			subcortical infarction	deep WMH; functional outcome	severe overall and periventricular WMH; WMH mediated part of the effect on outcome.
Qiao et al. (2025)	United Kingdom	Population study, cross-sectional and longitudinal	36,411 (3,807 in longitudinal subset)	Segmented WMH volume; microstructural indices	NLR positively associated with WMH volume and with fractional anisotropy, mean diffusivity and ISOVF.
Yang et al. (2025)	China	Analytical cross-sectional	8,481 (1,526 CSVD, 6,955 controls)	Fazekas WMH; total CSVD burden 0 to 6	Baseline difference in NLR lost significance after adjustment for vascular and metabolic factors.
Zhao et al. (2025)	China	Hospital-based retrospective	148 CSVD inpatients	Total CSVD burden 0 to 4; cognitive function	NLR independently associated with severe CSVD burden; PLR not significant.
Cai et al. (2024)	China	Retrospective	667 (368 CSVD, 299 non-CSVD)	Total, periventricular and deep WMH; presence of CSVD	NLR independently associated with all three WMH outcomes; ROC cut-off 2.47 for CSVD.
Li et al. (2024)	China	Analytical cross-sectional	257 non-disabling ischaemic cerebrovascular events	Mild versus severe WMH (Fazekas); cognition	Both NLR and PLR higher in the severe WMH group.
Park et al. (2023)	South Korea	Analytical cross-sectional	610 adults aged over 40 years	White matter lesion phenotype classes; STRIVE markers	NLR higher in the class characterised by large periventricular lesions.

Abbreviations: CSVD, cerebral small vessel disease; ISOVF, isotropic compartment volume fraction; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; STRIVE, Standards for Reporting Vascular changes on Neuroimaging; SVD, small vessel disease; WMH, white matter hyperintensity.

How white matter hyperintensity was measured

The included studies graded WMH in five broadly different ways, and this turned out to matter for the comparison. Most applied the Fazekas scale to periventricular and deep lesions on a scale of zero to three, sometimes analysing the two locations separately and sometimes summing them into a total score of zero to six. Cai and colleagues split that total into mild and moderate-to-severe categories, while Li and colleagues divided patients at a Fazekas score of two, giving mild and severe groups. Zhao and colleagues and Yang and colleagues folded WMH into a composite CSVD burden score alongside lacunes, cerebral microbleeds and enlarged perivascular spaces. Qiao and colleagues segmented lesion volume automatically and added microstructural indices, and Park and colleagues classified lesions by number, size, distribution, the ratio of periventricular to deep involvement and lesion contrast. WMH was therefore reported as an ordinal score, a severity category, a continuous volume, a composite score and a lesion

phenotype, which is the single largest obstacle to pooling these data.

Risk-of-bias assessment

Methodological quality on the JBI checklists was generally good. Six of the eight studies met every applicable criterion and were graded high quality, while two fell into the moderate band (Table 2, Figure 2). Tieachanpan and colleagues met eight of eleven cohort criteria, the shortfall lying mainly in the length and completeness of follow-up, which is understandable in a retrospective single-centre design. Li and colleagues met six of eight cross-sectional criteria, having controlled for fewer confounders than the other studies and having used regression chiefly for the cognitive rather than the imaging outcome. Both were accepted with reservations, and their results are read here with that caveat attached. The broader limitation is not captured by the checklists at all: the predominance of cross-sectional and retrospective designs means the appraisal scores speak to internal conduct rather than to the strength of causal inference.

Table 2. *Joanna Briggs Institute critical appraisal of the eight included studies.*

Study (year)	JBI checklist	Items met	Percentage	Grade	Decision
Tieachanpan et al. (2026)	Cohort (retrospective)	8/11	72.7	Moderate	Accepted with reservations
Wu et al. (2025)	Cohort (prospective)	10/10*	100	High	Accepted
Qiao et al. (2025)	Analytical cross-sectional	8/8	100	High	Accepted
Yang et al. (2025)	Analytical cross-sectional	8/8	100	High	Accepted
Zhao et al. (2025)	Analytical cross-sectional	8/8	100	High	Accepted
Cai et al. (2024)	Analytical cross-sectional	8/8	100	High	Accepted
Li et al. (2024)	Analytical cross-sectional	6/8	75.0	Moderate	Accepted with reservations
Park et al. (2023)	Analytical cross-sectional	8/8	100	High	Accepted

Items scored yes counted as one; no and unclear counted as zero. Items marked not applicable were excluded from the denominator. High quality was set at 80 per cent or more of applicable criteria, moderate at 60 to 79 per cent, and low below 60 per cent. *Wu et al. were appraised against ten applicable items, one item being not relevant to the design. JBI, Joanna Briggs Institute.

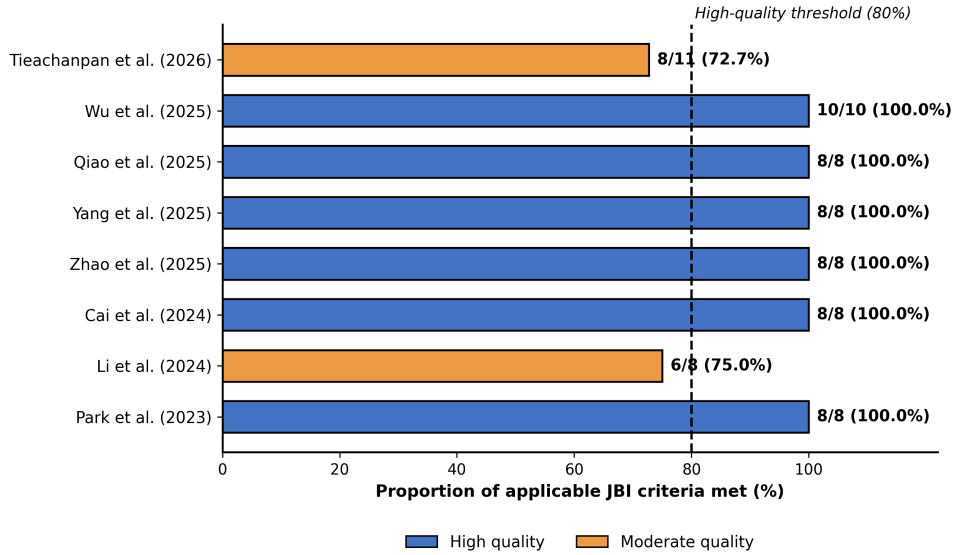

Figure 2. *Joanna Briggs Institute appraisal of the eight included studies, expressed as the proportion of applicable criteria met. The dashed line marks the 80 per cent threshold used to define high quality. JBI, Joanna Briggs Institute.*

Findings on NLR and white matter hyperintensity

NLR was the marker examined in every study, and six of the eight reported an association with at least one WMH outcome. The clearest signal came from Cai and colleagues, who studied 667 subjects and found NLR independently associated with the presence of CSVD (odds ratio 1.929, $p < 0.001$), with moderate-to-severe total WMH (odds ratio 2.136), with periventricular WMH (odds ratio 2.138) and with deep WMH (odds ratio 1.654); receiver operating characteristic analysis produced a cut-off of 2.47 with a sensitivity of 84.2 per cent and a specificity of 66.9 per cent for CSVD.[13] Wu and colleagues, working with 513 patients with single small subcortical infarction in a multicentre prospective cohort, found that each one-unit rise in NLR was associated with moderate-to-severe overall WMH (odds ratio 1.41, 95% CI 1.20 to 1.66) and with moderate-to-severe periventricular WMH (odds ratio 1.41, 95% CI 1.20 to 1.67), while the association with deep WMH disappeared under full adjustment (odds ratio 1.01, $p = 0.808$).[17]

The largest dataset came from Qiao and colleagues, who analysed 36,411 UK Biobank participants with automated segmentation of WMH on FLAIR and T1-weighted imaging. In a model adjusted for age, sex, brain volume, education, smoking, alcohol, hypertension, diabetes, stroke and low-density lipoprotein, NLR was positively associated with WMH volume (beta 0.0126, 95% CI 0.0031 to 0.0221), and also with fractional anisotropy, mean diffusivity and the isotropic compartment volume fraction, extending the relationship from visible lesions to microstructural injury.[9] Zhao and colleagues, in 148 CSVD inpatients, found NLR independently associated with severe total CSVD burden (odds ratio 2.246, $p = 0.002$) and correlated with the burden score (Spearman rho 0.246, $p = 0.003$).[8] Park and colleagues reported a median NLR of 1.7 in the lesion class characterised by large periventricular lesions, against 1.4 and 1.5 in the other two classes ($p = 0.003$), which suggests the association follows lesion distribution rather than lesion count alone.[16]

Two studies did not find an independent association. Yang and colleagues examined 8,481 health check-up participants and saw a small baseline difference in NLR between those with and without CSVD (1.79 against 1.77, $p = 0.005$), but this vanished after adjustment for age, sex, blood pressure, body mass index, comorbidity, smoking, alcohol and metabolic parameters (odds ratio 1.00, 95% CI 0.89 to 1.11, $p = 0.97$).[15] Tieachanpan and colleagues, in 299 patients with acute ischaemic stroke, found the highest NLR tertile unrelated to severe deep WMH (relative risk ratio 1.52, $p = 0.43$) or to severe periventricular WMH (relative risk ratio 0.87, $p = 0.74$) after adjustment; an apparent association with lobar microbleed burden also disappeared.[11] Both null results are informative rather than merely negative: one shows how much of the crude signal is carried by shared vascular risk, and the other shows what happens when blood is drawn during an acute event. The fragility of the signal under adjustment is, in other words, part of the finding. The NLR results are summarised in Table 3.

Table 3. *Studies reporting an association between the neutrophil-to-lymphocyte ratio and white matter hyperintensity or total cerebral small vessel disease burden.*

Study (year)	Comparison	Effect estimate	Outcome
Cai et al. (2024)	Continuous NLR; ROC cut-off 2.47	OR 2.136; OR 2.138; OR 1.654; sensitivity 84.2%, specificity 66.9%	Total, periventricular and deep WMH; presence of CSVD
Wu et al. (2025)	Per one-unit rise in NLR	OR 1.41 (1.20 to 1.66); OR 1.41 (1.20 to 1.67); deep WMH OR 1.01 (p = 0.808)	Moderate-to-severe overall and periventricular WMH
Qiao et al. (2025)	Continuous NLR, fully adjusted	Beta 0.0126 (0.0031 to 0.0221)	Segmented WMH volume and microstructural injury
Zhao et al. (2025)	Continuous NLR	OR 2.246 (p = 0.002); Spearman rho 0.246 (p = 0.003)	Severe total CSVD burden on MRI
Park et al. (2023)	Median NLR across lesion classes	1.7 versus 1.4 and 1.5 (p = 0.003)	Large periventricular lesion phenotype
Yang et al. (2025)	Continuous NLR, fully adjusted	OR 1.00 (0.89 to 1.11), p = 0.97	WMH and total CSVD burden (no association)
Tieachanpan et al. (2026)	Highest against lowest NLR tertile	RRR 1.52 (p = 0.43); RRR 0.87 (p = 0.74)	Severe deep and periventricular WMH (no association)

Confidence intervals are 95% throughout. Abbreviations: CSVD, cerebral small vessel disease; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; ROC, receiver operating characteristic; RRR, relative risk ratio; WMH, white matter hyperintensity.

Findings on PLR and platelet-related indices

PLR was treated as a main exposure in only two of the eight studies, and they disagreed. Li and colleagues, in 257 patients with non-disabling ischaemic cerebrovascular events, found a mean PLR of 126.31 in the severe WMH group against 119.02 in the mild group ($p = 0.006$), alongside a median NLR of 2.34 against 1.86 ($p < 0.001$).[18] Zhao and colleagues found no relationship between PLR and severe total CSVD burden (odds ratio 1.004, $p = 0.374$), even though NLR in the same cohort and the same model was significant.[8] The remaining six studies calculated PLR in passing or not at all. On this evidence PLR cannot be said to have been tested properly rather than to have failed, and the distinction matters for how the finding is read. Supporting work outside the included set suggests platelets are not irrelevant: the systemic immune-inflammation index, which folds platelets together with neutrophils and lymphocytes, has been associated with WMH volume, particularly in participants aged sixty and above,[22] and mean platelet volume has been linked to WMH in individuals without stroke.[23] The platelet contribution may simply show itself more clearly through activation indices than through a raw count ratio. The PLR findings are summarised in Table 4.

Table 4. *Studies reporting on the platelet-to-lymphocyte ratio and related platelet indices in relation to white matter hyperintensity.*

Study (year)	Marker	Effect estimate	Outcome
Li et al. (2024)	PLR (continuous)	Mean 126.31 versus 119.02 ($p = 0.006$)	Severe versus mild WMH (Fazekas 2 to 3 versus 0 to 1)
Zhao et al. (2025)	PLR (continuous)	OR 1.004 ($p = 0.374$)	Severe total CSVD burden (no association)
Nam et al. (2022) *	Systemic immune-inflammation index	Association strongest in participants aged 60 years and above	WMH volume
Choi et al. (2022) *	Mean platelet volume	Higher values associated with lesion presence	WMH in individuals without stroke

*Supporting studies cited in the discussion; these were not among the eight studies included in the synthesis and are listed here for context only. Abbreviations: CSVD, cerebral small vessel disease; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; WMH, white matter hyperintensity.

Overall pattern of association

Taken together, the direction of effect for NLR was consistent even where statistical significance was not. Six studies reported an association or a group difference for at least one WMH outcome, and the two null results came from a large cohort with unusually thorough confounder control and from a study conducted during acute stroke. Associations were reported more often for periventricular than for deep lesions, which recurred across three separate studies using different methods and is probably the most reproducible observation in this literature. Effect sizes for NLR clustered between odds ratios of roughly 1.4 and 2.2, and the proposed cut-offs ranged from 1.89 in the work of Wang and colleagues to 2.47 in that of Cai and colleagues, so no single threshold can yet be recommended.[13,14] The evidence base for PLR is too small to support any comparable statement.

DISCUSSION

This systematic review brought together eight studies on NLR, PLR and white matter hyperintensity in cerebral small vessel disease. The most consistent message is that a higher NLR accompanies a greater degree or burden of WMH, particularly for total lesion load, segmented volume and periventricular lesions.[9,13,17] The relationship is not universal, and the exceptions are instructive: it weakened to nothing when Yang and colleagues adjusted extensively for vascular and metabolic factors,[15] and it did not appear at all in the acute stroke setting studied by Tieachanpan and colleagues.[11] NLR, in other words, behaves less like an independent driver of white matter damage and more like a marker of how inflamed and vascularly unwell a patient is overall.

The biology is plausible enough. Neutrophils release proteolytic enzymes, free radicals and inflammatory mediators that can damage the blood-brain barrier, while lymphocytes support anti-inflammatory responses and tissue repair, so the ratio between them captures a shift in the balance of immune activity. That shift plausibly contributes to endothelial dysfunction, barrier leakage and chronic hypoperfusion, which are the accepted proximate mechanisms of white matter injury in CSVD.[6,7] The evidence extends beyond cell counts. Jickling and colleagues showed that progression of WMH volume tracks leucocyte gene expression involving endothelial dysfunction, inflammation, ischaemic response and impaired remyelination,[25] and Unger and colleagues found NLR associated with both WMH and enlarged perivascular spaces in a broader review of circulating immune cells.[26] These proposed links are summarised in Figure 3.

The tendency for associations to appear more often in periventricular than in deep white matter deserves more attention than it usually receives. It recurred in the work of Wu and colleagues, in the lesion phenotype analysis of Park and colleagues and, weaklier, in that of Cai and colleagues, and it suggests that the two locations should be

treated as separate outcomes rather than summed. Periventricular lesions sit close to the ependymal surface and to the venous drainage territory, and they have long been suspected of a different pathogenesis from deep lesions. If systemic inflammation acts preferentially there, then studies that report only a combined Fazekas score may be diluting a real signal, which would help explain some of the inconsistency in this literature.

The clinical consequences are not confined to imaging. Wu and colleagues found that overall and periventricular WMH mediated between 24 and 36 per cent of the relationship between NLR and functional outcome,[17] and Zhao and colleagues reported a mediating effect of total CSVD burden on the relationship between NLR and cognitive impairment.[8] Hou and colleagues likewise found raised NLR in patients with CSVD and cognitive impairment.[21] These mediation findings matter because they connect a blood test, a radiological finding and a patient-level outcome in a single chain, which is more than most biomarker studies in this field manage.

PLR presents a different problem. Only two of the eight studies tested it as a primary exposure and they reached opposite conclusions, so the honest reading is that PLR remains untested rather than disproved. The supporting evidence on the systemic immune-inflammation index and on mean platelet volume suggests platelets do participate,[22,23] but perhaps through activation state rather than through a count-based ratio. A study designed specifically to test PLR, in a population with high inflammatory and thrombotic activity, would settle the question far more efficiently than another cohort in which PLR is calculated as an afterthought.

Heterogeneity between studies had identifiable sources rather than being simply unexplained. Population was one: acute stroke raises both ratios as part of the stress response, which makes them poor proxies for a chronic process. Outcome definition was another, given the five distinct grading approaches described above. Lesion location was a third. Age and blood pressure appear to modify the relationship, with Nam and colleagues finding the inflammation and WMH association mainly in older participants,[22] and Woldstad and colleagues finding an association between an inflammatory score and lesion burden only in normotensive individuals.[24] And the extent of confounder adjustment was decisive, as the contrast between Cai and Yang shows most plainly.

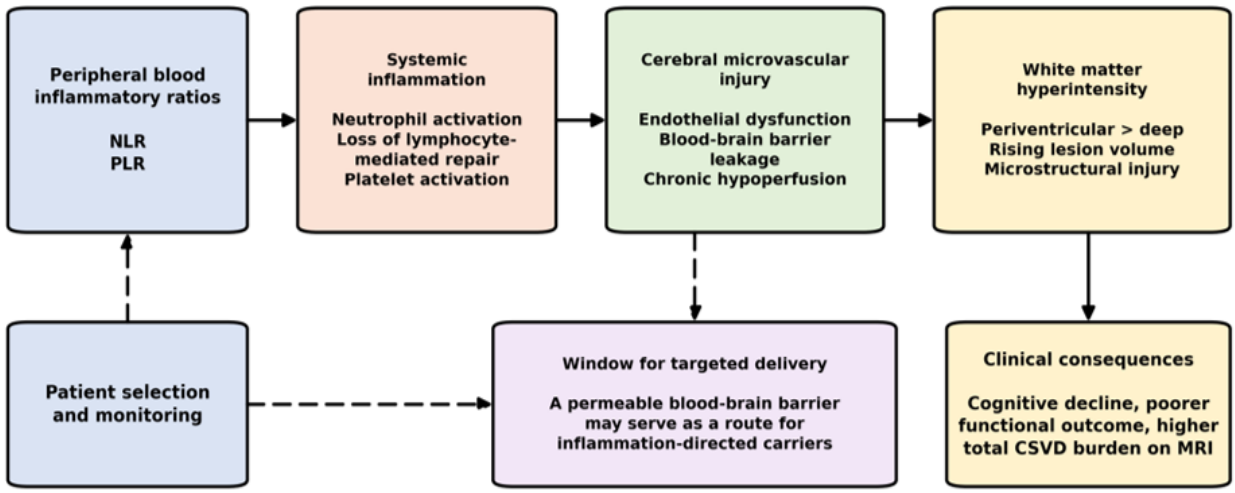

Figure 3. *Conceptual model of how raised peripheral inflammatory ratios relate to white matter hyperintensity in cerebral small vessel disease, through systemic inflammation, endothelial dysfunction, blood-brain barrier leakage and chronic hypoperfusion, together with the implications for patient selection and targeted delivery. CSVD, cerebral small vessel disease; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. The diagram is a schematic summary and is not drawn to scale.*

Implications for drug targeting and delivery

There is still no disease-modifying pharmacotherapy for CSVD. What has been tried has concentrated on endothelial function, barrier integrity and cerebral perfusion rather than on inflammation itself,[6,27] and the demonstration that agents such as isosorbide mononitrate and cilostazol can be given tolerably over months in patients with lacunar stroke at least establishes that long-term intervention in this population is feasible.[28] If systemic inflammation contributes to white matter injury, as this synthesis suggests it does, an anti-inflammatory approach becomes worth considering. The obstacle is delivery. Prolonged systemic anti-inflammatory therapy carries well-recognised infective and metabolic costs, and access to the cerebral microvasculature and the perivascular compartment is restricted by the blood-brain barrier.

The interesting point is that the same barrier is already dysfunctional in this disease. Increased permeability is not merely a consequence of CSVD but potentially a route into it, and carrier systems that exploit endothelial adhesion molecules upregulated during inflammation, or that use neutrophils and monocytes as transport vehicles, could in principle concentrate an agent at the affected microvascular bed at doses well below those needed systemically. Nanoparticle and liposomal formulations built on these principles have been explored in other neuroinflammatory conditions and have not, to our knowledge, been evaluated in small vessel disease. We put this forward as a direction worth pursuing rather than as a conclusion the present data support, since none of the included studies examined treatment of any kind.

This is where a cheap haematological ratio earns its place. Any trial of an inflammation-directed agent in CSVD will need a way of enriching the population for patients whose white matter damage is genuinely inflammatory, because including patients whose lesions are driven mainly by haemodynamic or amyloid-related mechanisms would dilute the treatment effect towards nothing. NLR is inexpensive, reproducible and available in essentially every hospital laboratory, which makes it an obvious candidate for enrichment and for serial monitoring. The evidence assembled here suggests the idea is worth testing; it also shows plainly that NLR is not ready for the task, given that thresholds vary between 1.89 and 2.47, that the association fails in acute illness, and that single measurements are vulnerable to transient influences. Serial measurement in a defined chronic population, tied to quantitative imaging endpoints, is the step that would have to come first.

Study limitations

Several limitations deserve emphasis. The evidence came predominantly from cross-sectional and retrospective designs, so the temporal ordering of raised biomarker values and lesion formation cannot be determined and no causal claim is available. NLR and PLR were almost always measured once, although both fluctuate with infection, physiological stress, medication, comorbidity and acute stroke. The included populations were weighted heavily towards East Asia, with a single European dataset, which limits generalisability. Grading of WMH was not uniform, ranging from ordinal Fazekas scores to automated volumetry and composite burden scores, and this variation is precisely why a quantitative meta-analysis was not attempted. Longitudinal evidence connecting change in either ratio with WMH progression is very scarce, and few studies examined NLR and PLR within the same multivariable model, which is what would be needed to judge their relative contributions. Finally, the search was confined to a single database, so relevant work indexed elsewhere may have been missed, and only articles with retrievable full text were assessed. The findings should therefore be read as indicative rather than definitive.

Clinical implications

For clinicians, the practical appeal of NLR is that it arrives unbidden with every full blood count and costs nothing extra. A raised value in a patient with vascular risk factors may reasonably prompt closer attention to white matter burden on imaging and to cognitive screening, particularly where periventricular lesions are already visible. It cannot replace MRI or clinical assessment, and it should not be used as a standalone test: the discriminative performance reported in the included studies was modest on its own and improved when NLR was combined with other indicators, as in the multimarker model that reached an area under the curve of 0.816.[14] Interpretation must also account for age, hypertension, infection, systemic inflammatory disease, medication and the phase of illness at which blood was drawn. Positioned within a multimarker assessment that includes vascular, metabolic and imaging components, NLR may add useful precision; positioned alone, it will mislead.

CONCLUSION

This review of eight studies indicates that a higher neutrophil-to-lymphocyte ratio is associated with a greater degree or burden of white matter hyperintensity in cerebral small vessel disease. The signal is strongest for total WMH, segmented lesion volume and periventricular lesions, weaker and less consistent for deep lesions, and it disappears both under thorough confounder adjustment and in the acute stroke setting. Evidence on the platelet-to-lymphocyte ratio is too sparse to support a conclusion in either direction, since only two studies tested it directly and they disagreed. Neither ratio is fit to serve as a standalone marker of lesion severity. What they may offer instead is a cheap and widely available means of identifying the patients in whom inflammation contributes materially to white matter damage, and therefore the patients in whom inflammation-directed treatment, delivered across a blood-brain barrier that is already permeable, would be most worth testing. Prospective longitudinal studies with serial biomarker measurement, quantitative imaging, separate reporting of periventricular and deep lesions, and both ratios analysed within the same multivariable model are needed before any of this can move from proposition to practice.

Ethics statement

This systematic review used secondary data from previously published articles and did not involve any identifiable patient data; individual ethical approval was therefore not required.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

MAFFS and MYA conceived and designed the review. MAFFS conducted the literature search, study selection and data extraction. AKB and JB supervised the screening and adjudicated disagreements. AWS and YAF carried out

the quality appraisal and verified the extracted data. MYA supervised the work throughout and revised the manuscript critically. All authors interpreted the data, drafted and revised the manuscript, and approved the final version.

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