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Association between Serum Innate Immunity-related Inflammatory Markers and MRI Features of Cerebral Small Vessel Disease: A Systematic Review and Meta-analysis

Shenglong Wu and Bing Zhu

Department of Radiology, Hainan Women and Children's Medical Center, Haikou, Hainan, China

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ABSTRACT

Cerebral small vessel disease (CSVD) is a microvascular disorder associated with endothelial dysfunction, blood–brain barrier disruption, and chronic immune inflammation. However, the relationships between circulating inflammatory markers and magnetic resonance imaging (MRI) features of CSVD remain unclear.

A systematic search of PubMed, Embase, Web of Science, Cochrane Library, CNKI, and Wanfang databases was conducted from inception to December 2025. Observational studies evaluating associations between serum inflammatory markers and MRI-defined CSVD features, including white matter hyperintensities (WMH), lacunar infarction (LI), and cerebral microbleeds (CMB), were included. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects models.

Eighteen studies were included. Elevated interleukin-6 (IL-6) levels were significantly associated with LI (OR=1.53, 95% CI: 1.11–2.11) and CMB (OR=1.28, 95% CI: 1.06–1.55). Increased high-sensitivity C-reactive protein (hs-CRP) levels were significantly associated with WMH (OR=2.19, 95% CI: 1.18–4.07), LI (OR=1.97, 95% CI: 1.21–3.20), and CMB (OR=1.67, 95% CI: 1.37–2.04). Elevated fibrinogen (FIB) levels were significantly associated with WMH (OR=1.48, 95% CI: 1.21–1.80). In contrast, conventional C-reactive protein showed no significant association with CSVD imaging markers.

This meta-analysis demonstrates that elevated IL-6, hs-CRP, and FIB levels are associated with MRI features of CSVD, supporting the involvement of innate immune inflammation in CSVD pathophysiology. These markers may reflect chronic cerebral microvascular injury and endothelial dysfunction. However, causal relationships cannot be established, and further prospective studies are required.

Keywords: Cerebral small vessel disease; Inflammatory factors; MRI characteristics; Meta-analysis; Systematic review

INTRODUCTION

Cerebral small vessel disease (CSVD) is a group of cerebrovascular diseases centered on lesions of small arteries, arterioles, capillaries, and venules in the brain. The total number and volume of these lesions may be associated with various conditions such as cognitive impairment, gait abnormalities, and emotional disorders.

Corresponding Author: Bing Zhu, PhD;
Department of Radiology, Hainan Women and Children's Medical Center, Haikou, Hainan, China. Tel: (+86 018) 6898 56202, Fax: (+86 018) 6898 56202, Email: zbwxn-yy@163.com

Without timely intervention, it may seriously affect patients' quality of life.[1,2] In the clinical assessment of CSVD, magnetic resonance imaging (MRI), leveraging its high-resolution advantage, can clearly visualize characteristic structural abnormalities, including recent subcortical small infarcts, white matter hyperintensities (WMH), lacunar infarction (LI), enlarged perivascular spaces, cerebral microbleeds (CMB), and brain atrophy. Thus, it is universally recognized as the gold standard for the diagnosis and evaluation of CSVD.[3] However, due to the characteristics of CSVD, such as complex etiology, insidious onset, and significant symptomatic heterogeneity, there exists substantial heterogeneity and a lag between imaging abnormalities and clinical manifestations. Moreover, with advancing age, CSVD-related imaging changes are prevalent in the elderly population, but most of these changes are physiological or subclinical. Not all individuals with imaging abnormalities will progress to symptomatic CSVD patients with definite clinical manifestations. Therefore, accurately predicting the risk of progression from subclinical imaging abnormalities to symptomatic CSVD has become a research focus in the current field. From a pathological perspective, the pathogenesis and progression of CSVD involve not only endothelial dysfunction, but also the blood-brain barrier (BBB) disruption, white matter injury, and immune-inflammatory responses.[4] Increasing evidence indicates that systemic inflammatory markers can predict the severity and progression of CSVD.[5] Systemic inflammation is mainly characterized by elevated serum inflammatory factors in the peripheral circulation, whereas central neuroinflammation is featured by microglial activation. Although these two processes differ in location and regulatory pattern, they form a mutually reinforcing vicious cycle across the BBB: systemic inflammation impairs BBB integrity, facilitating the infiltration of inflammatory factors and immune cells into the brain; in turn, mediators released from local central inflammation can enter the peripheral circulation and further amplify systemic inflammation. Such an immune-inflammatory response mediated by the interplay between systemic and local inflammation directly affects the progression and prognosis of CSVD.[6] Additionally, previous studies have suggested a potential association between inflammatory biomarkers and MRI-detected white matter hyperintensities.[7] Given that serum inflammatory factors are a class of biomarkers with convenient detection and easy popularization, the specific association patterns between serum inflammatory factor levels and various MRI characteristics of CSVD remain unclear to date. Clarifying this correlation is expected to provide reliable biological indicators for the early screening of CSVD, and it holds significant theoretical and practical significance for improving the clinical prevention and treatment system of CSVD. Based on this, the present study intends to adopt the method of systematic review and meta-analysis to comprehensively retrieve relevant domestic and international clinical studies, systematically integrate research data on the correlation between serum inflammatory factor levels and various MRI characteristics of CSVD, aiming to clarify their association patterns and provide evidence-based medical evidence for the risk prediction and early intervention of CSVD.

MATERIALS AND METHODS

Literature Retrieval Strategy

This meta-analysis was conducted and reported in strict accordance with the PRISMA 2020 statement.

Databases, including PubMed, Embase, The Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), Chinese Biology Medicine (CBM), and Wanfang Database, were searched from January 1997 to December 2025. The search was conducted using a combination of subject terms and free-text terms. English and Chinese search terms were as follows: cerebral small vessel disease, CSVD, interleukin-6, IL-6, C-reactive protein, CRP, high-sensitivity C-reactive protein, hs-CRP, inflammation, magnetic resonance imaging, MRI, white matter hyperintensities, WMH, lacunar infarction, LI, cerebral microbleeds, CMB, etc. The PubMed search formula is set to: (cerebral small vessel disease [Title/Abstract] OR CSVD [Title/Abstract] OR CADASIL [Title/Abstract] OR sCVSD [Title/Abstract]) AND (MRI [Title/Abstract] OR Magnetic Resonance Imaging [Title/Abstract] OR WMH [Title/Abstract]) AND (Interleukin-6 [Title/Abstract] OR IL-6 [Title/Abstract] OR C-Reactive Protein [Title/Abstract] OR CRP [Title/Abstract] OR hs-CRP [Title/Abstract] OR Inflammation [Title/Abstract]) AND (white matter hyperintensities [Title/Abstract] OR WMH [Title/Abstract] OR lacunar infarction [Title/Abstract] OR LI [Title/Abstract] OR cerebral microbleeds [Title/Abstract] OR CMB [Title/Abstract]).

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Study participants presented with at least one MRI characteristic of CSVD, including LI, WMH, and CMB; (2) Study types were publicly published cohort studies, case-control studies, or cross-sectional studies; (3) Serum inflammatory factor levels were measured, and the independent association between serum inflammatory factors and a single MRI characteristic of CSVD was reported; (4) Extractable effect sizes (odds ratio [OR], β) with 95% confidence intervals (95% CI) were provided.

Exclusion criteria: (1) Duplicate publications; (2) Conference abstracts, reviews, systematic analyses, animal experiments, case reports, and master's theses; (3) Study participants with other cerebrovascular diseases; (4) The data could not be obtained; (5) Studies with poor quality, unclear or incomplete data, or data that could not be converted into effect sizes; (6) Literature not in Chinese or English.

According to the STRIVE criteria, the definitions of MRI features of CSVD are as follows:

WMH: Abnormal signal regions of variable shape within the white matter (excluding lesions in the subcortical gray matter or brainstem), usually punctate or patchy. They present as hyperintense on T2-weighted imaging (T2WI) or fluid-attenuated inversion recovery (FLAIR) sequences, and are isointense or hypointense on T1WI, without cavitation. They are most often distributed symmetrically in both cerebral hemispheres.

LI: Round or oval subcortical cavities filled with cerebrospinal fluid (CSF)-like signal, measuring 3–15 mm in diameter. The MRI signal intensity is consistent with CSF: hypointense on T1WI, hyperintense on T2WI, hypointense on FLAIR, isointense or hypointense on diffusion-weighted imaging (DWI), and isointense on T2*WI or susceptibility-weighted imaging (SWI). A peripheral hyperintense rim on FLAIR may occasionally be observed around the lesion.

CMB: Hemosiderin deposits formed by phagocytosis of leaked erythrocytes from damaged cerebral small vessels by macrophages. On T2*WI or other susceptibility-sensitive sequences, they typically appear as round or oval hypointense lesions with a diameter of 25 mm (occasionally up to 10 mm), accompanied by a corresponding blooming artifact.

Literature Screening and Data Extraction

Two reviewers independently screened the literature, extracted data, and cross-validated the results. In case of discrepancies, a third reviewer was consulted for arbitration. Missing data were supplemented by attempting to contact the corresponding authors. The following data were extracted: first author's name, year of publication, sample size, type of serum inflammatory factors, MRI characteristics, and key effect sizes.

Quality Assessment

The methodological quality of cohort studies or case-control studies was evaluated using the Newcastle-Ottawa Scale (NOS), which includes three domains: patient selection, comparability of study groups, and outcome assessment. Each study was scored on a scale of 0 to 9, with a score of ≥7 indicating high-quality studies, 5–6 indicating moderate-quality studies, and ≤4 indicating low-quality studies. For cross-sectional studies, the JBI Critical Appraisal Tool for Cross-Sectional Studies (developed by the Joanna Briggs Institute, Australia) was adopted, consisting of 10 items, with each item scored 0–2 points. A total score of ≥15 was considered high-quality, 10–14 as moderate-quality, and≤9 as low-quality.

Statistical Analysis

Meta-analysis was performed using RevMan 5.3 software. Based on the type of extractable effect sizes from the included studies, the odds ratio (OR) with 95% confidence interval (95% CI) was used as the primary effect size indicator. Heterogeneity was evaluated by the Q test and I^2 statistic. If $I^2 \leq 50\%$ and $p \geq 0.10$, no statistical heterogeneity was considered among the studies, and a fixed-effects model was adopted; otherwise, a random-effects model was used, and sensitivity analysis was performed via the stepwise exclusion method to assess the impact of each study on the overall results, thereby verifying the robustness of the meta-analysis findings. The significance level was set at $\alpha=0.05$.

Data from the included studies were transformed and extracted to establish a database.[8] For studies reporting β coefficients or OR with 95% CI, the effect size was calculated as: effect size=ln(OR)=β, and the SE of the effect size was computed as: SE = ln(upper 95% CI− lower 95% CI)/3.92.

RESULTS

Literature Search and Screening

A total of 1608 articles were initially retrieved (418 from PubMed, 233 from Embase, 262 from The

Cochrane Library, 368 from Web of Science, 121 from CNKI, and 206 from Wanfang Database). After screening against the inclusion and exclusion criteria, 18 articles were finally eligible for this meta-analysis. Figure 1 illustrates the study selection process.

Basic Characteristics of the Included Studies

A total of 18 studies were ultimately included in this meta-analysis, among which 3 were prospective cohort studies, 4 were case-control studies, and 11 were cross-sectional studies. Characteristics are summarized in Table 1.[5-22]

Quality Assessment

A total of 18 studies were included in this research. The Newcastle-Ottawa Scale (NOS) was adopted to assess the methodological quality of prospective cohort studies and case-control studies. Among these studies, 6 were identified as high-quality ones, while the quality of 1 study was not evaluated due to the unavailability of its full text. For the 11 cross-sectional studies, the Critical Appraisal Tool developed by the Joanna Briggs Institute (JBI) of Australia was used for quality assessment. Of these cross-sectional studies, 9 were classified as high-quality, whereas the quality of 2 studies was not assessed because their full texts could not be obtained. Details are presented in Table 1.

Meta-analysis

Association between IL-6 Levels and WMH

Three studies reported the correlation between IL-6 and WMH. There was heterogeneity among the included studies (I^2=55%, p=0.11), thus a random-effects model was employed for the meta-analysis. The results showed that elevated IL-6 levels were not significantly associated with an increased risk of WMH (OR=1.59, 95% CI=1.00–2.54; p=0.05; Figure 2). Sensitivity analysis indicated that heterogeneity was completely eliminated after excluding the study by Fornage et al (2008) (I^2=0, p=0.72), with the pooled effect size suggesting a significant association (OR=2.22, 95% CI=1.31–3.76; p=0.003). Additionally, heterogeneity was also fully eliminated when the study by Li et al (2025) was excluded (I^2=0, p=0.41), and the pooled effect size also revealed a significant association (OR=1.25, 95% CI=1.08–1.45; p=0.003). These findings demonstrated that both studies were the sources of heterogeneity.

Association between IL-6 Levels and LI

Four studies reported the correlation between IL-6 and LI. There was significant heterogeneity among the included studies (I^2=73%, p=0.01), and thus a random-effects model was adopted for the meta-analysis. The results showed that elevated IL-6 levels significantly increased the risk of LI (OR=1.53, 95% CI=1.11–2.11; p=0.009; Figure 3). Heterogeneity was completely eliminated after excluding the study by Hervella et al (2024) (I^2=0, p=0.51), with the pooled effect size still indicating a significant association (OR=1.75, 95% CI=1.36–2.24; p<0.001). These findings demonstrated that this study was the primary source of heterogeneity.

Table 1. Characteristics of patients included in the study

Reference	Country/ region	n	Study type	Type of serum inflammatory factors	CSVD MRI characteristics	Main effect sizes (OR, β)	Adjusted confounding factors	Field strength and sequences	Quality assessment
Staszewski J 2018 (1)[9]	Poland	123	Prospective cohort study	FIB	LI, WMH	OR	Age, gender, baseline lesion severity, and traditional vascular risk factors	1.5T, T2-weighted sequence, FLAIR sequence, and gradient-echo sequence	High
Van Dijk EJ 2005[10]	Netherlands	1033	Prospective cohort study	CRP	LI, WMH	OR	Age, sex, diabetes, smoking, body mass index, hypertension, and cholesterol/high-density lipoprotein ratio	1.5T, T1-weighted sequence, T2-weighted sequence, and proton density-weighted sequence	High
Yao H 2019[11]	Japan	259	Cross-sectional study	hs-CRP	WMH	OR	Age, gender, hypertension, diabetes, hyperlipidemia, chronic kidney disease, metabolic syndrome, smoking, drinking habits, and uric acid	1.5T, T1-weighted sequence, T2-weighted sequence, FLAIR sequence, and T2*-weighted sequence	High
Staszewski J 2018 (2)[12]	Poland	123	Prospective cohort study	hs-CRP, IL-6	LI, WMH	OR	Not adjusted	NR, T2-weighted FLAIR sequence	High

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Table 1. Continued...

Reference	Country/ region	n	Study type	Type of serum inflammatory factors	CSVD MRI characteristics	Main effect sizes (OR, β)	Adjusted confounding factors	Field strength and sequences	Quality assessment
Li X 2025[13]	China	88	Cross-sectional study	IL-6	LI, WMH	OR	Gender, age, smoking history, etc.	NR, 3D TOF-MRA	High
Lu QL 2017[14]	China	201	Case-control study	IL-6, hs-CRP	CMB	OR	Age, gender, and traditional risk factors	3.0T, SWI, GRE-T2WI, FLAIR, T1-weighted, T2-weighted	High
Lu QL 2016[15]	China	180	Case-control study	IL-6, hs-CRP	CMB	OR	NR	3.0T, SWI, FLAIR, T1-weighted, T2-weighted	High
Wada M 2011[16]	Japan	651	Cross-sectional study	FIB	LI, WMH	OR	Age, gender, smoking history, traditional factors	NR, axial T1-weighted, T2-weighted, FLAIR sequence	High
Fornage M 2008[17]	United States	2905	Cross-sectional study	IL-6, CRP	WMH	OR	Age, gender, smoking history, traditional factors	NR, sagittal T1-weighted localizer, axial T1-weighted, proton density-weighted, T2-weighted sequence	High
Hervella P 2024[18]	Spain	240	Case-control study	IL-6	LI	OR	Arterial hypertension, carotid atherosclerosis, white matter lesions	NR, T1-weighted, T2-weighted, DP-weighted, FLAIR sequence	High

Table 1. Continued...

Reference	Country/ region	n	Study type	Type of serum inflammatory factors	CSVD MRI characteristics	Main effect sizes (OR, β)	Adjusted confounding factors	Field strength and sequences	Quality assessment
Hoshi T 2005[19]	Japan	194	Cross-sectional study	IL-6, hs-CRP	LI	OR	Age, sex, BMI, smoking, hypertension, diabetes, hyperlipidemia, and drug use	1.5T, T1-weighted spin-echo sequence, T2-weighted spin-echo sequence, FLAIR sequence	High
Guo X 2021[20]	China	109	Cross-sectional study	hs-CRP, FIB	WMH	OR	NR	3.0T, T1-weighted sequence, FLAIR sequence, T2-weighted sequence	High
Gu Y 2018[21]	United States	508	Cross-sectional study	IL-6, CRP	CMB	OR	Age, gender, risk factors	1.5T, T1-weighted sequence, FLAIR sequence, proton density/T2-weighted dual-echo sequence	High
Qiao Y 2025[22]	United Kingdom	36411	Cross-sectional study	CRP	WMH	β	Age, gender, brain volume, Thomson's index, education level, smoking status, alcohol consumption, hypertension, diabetes, stroke, and low-density lipoprotein cholesterol	3.0T, FLAIR sequence, T1-weighted sequence, dMRI sequence	High

Table 1. Continued...

Reference	Country/ region	n	Study type	Type of serum inflammatory factors	CSVD MRI characteristics	Main effect sizes (OR, β)	Adjusted confounding factors	Field strength and sequences	Quality assessment
Liu H 2021[23]	China	420	Cross-sectional study	FIB	WMH	OR	NR	3.0T, FLAIR sequence	High
You CJ 2018[24,a]	China	170	Cross-sectional study	FIB	WMH	OR	Vascular risk factors	NR	NR
Wei CC 2017[25,a]	China	186	Case-control study	FIB	WMH	OR	NR	NR	NR
Mitaki S 2016[26,a]	Japan	519	Cross-sectional study	hs-CRP	WMH	OR	Traditional cardiovascular factors	NR	NR

[a]The full text cannot be obtained, but there is data research in the abstract.

BMI: body mass index; CMB: cerebral microbleeds; CRP: C-reactive protein; CSVD: cerebral small vessel disease; dMRI: diffusion magnetic resonance imaging; DP: density proton; FIB: fibrinogen; FLAIR: fluid-attenuated inversion recovery; GRE-T2WI: gradient-echo T2-weighted imaging; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin-6; LI: lacunar infarction; MRI: magnetic resonance imaging; NR: not reported; OR: odds ratio; SWI: susceptibility-weighted imaging; TOF-MRA: time-of-flight magnetic resonance angiography; WMH: white matter hyperintensities.

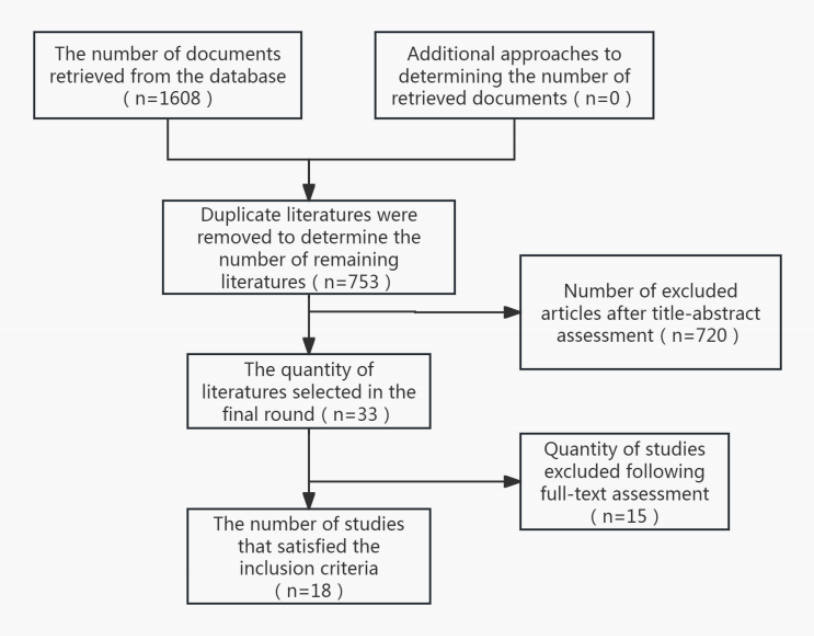

Figure 1. Literature retrieval flow chart.

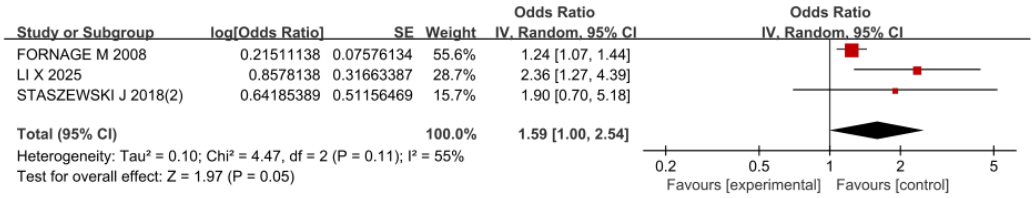

Figure 2. Forest plot of the correlation between IL-6 and WMH. CI: confidence interval; IL-6: interleukin-6; IV: inverse variance; OR: odds ratio; SE: standard error; WMH: white matter hyperintensities.

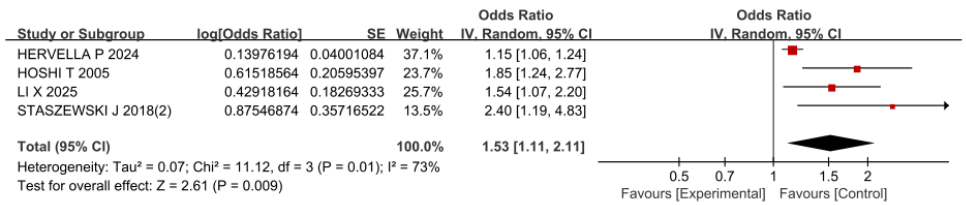

Figure 3. Forest plot of the correlation between IL-6 and LI. CI: confidence interval; IL-6: interleukin-6; IV: inverse variance; LI: lacunar infarction; OR: odds ratio; SE: standard error.

Association between IL-6 Levels and CMB

Two studies reported the correlation between IL-6 and CMB. No significant heterogeneity was observed among the included studies (I^2=23%, p=0.25); thus, a fixed-effects model was adopted for the meta-analysis. The results showed that elevated IL-6 levels significantly increased the risk of CMB (OR=1.28, 95% CI=1.06–1.55; p=0.01; Figure 4).

Association between hs-CRP Levels and WMH

Three studies reported the correlation between hs-CRP and WMH. No significant heterogeneity was detected among the included studies (I^2=0%, p=0.53); thus, a fixed-effects model was adopted for the meta-analysis. The results showed that elevated hs-CRP levels significantly increased the risk of WMH (OR=2.19, 95% CI=1.18–4.07; p=0.01; Figure 5).

Association between hs-CRP Levels and LI

Three studies reported the correlation between hs-CRP and LI. No significant heterogeneity was observed among the included studies (I^2=26%, p=0.26); thus, a fixed-effects model was adopted for the meta-analysis. The results showed that elevated hs-CRP levels significantly increased the risk of LI (OR=1.97, 95% CI=1.21–3.20; p=0.01; Figure 6).

Association between hs-CRP Levels and CMB

Two studies reported the correlation between hs-CRP and CMB. No significant heterogeneity was observed among the included studies (I^2=0%, p=0.62); thus, a fixed-effects model was adopted for the meta-analysis. The results showed that elevated hs-CRP levels significantly increased the risk of CMB (OR=1.67, 95% CI=1.37–2.04; p<0.001; Figure 7).

Association between CRP Levels and WMH

Three studies reported the correlation between CRP and WMH. High heterogeneity was observed across studies (I^2=91%, p<0.001), so a random-effects model was adopted for the meta-analysis. The results demonstrated no significant correlation between elevated CRP levels and the risk of WMH occurrence (OR=1.00, 95% CI: 0.85–1.18; p=0.99; Figure 8). Leave-one-out sensitivity analysis showed that the overall conclusion remained consistent after excluding any individual study, with no significant association detected, and high heterogeneity persisted. Although the OR values fluctuated around 1 after the exclusion of single studies, all results were statistically nonsignificant, indicating that the present findings were robust and reliable. The detailed outcomes of the sensitivity analysis are presented in Table 2.

Association between FIB Levels and WMH

Six studies reported the correlation between FIB and WMH. Severe heterogeneity was observed among the included studies (I^2=95%, p<0.001); thus, a random-effects model was adopted for the meta-analysis. The results showed that elevated FIB levels significantly increased the risk of WMH (OR=1.48, 95% CI=1.21–1.80; p<0.001; Figure 9). A sensitivity analysis was performed using the one-by-one exclusion method to verify the correlation between FIB levels and WMH. The results demonstrated that after excluding any single study, the heterogeneity of the pooled results remained unchanged. Moreover, except for the study by Liu et al (2021), elevated FIB levels were still significantly associated with the risk of WMH (p<0.05), indicating that the pooled results were relatively stable. Details of the sensitivity analysis are presented in Table 3. The funnel plot (Figure 10) suggests the presence of publication bias in the analysis of the association between FIB and WMH.

Association between FIB Levels and LI

Two studies reported the correlation between FIB and LI. No significant heterogeneity was observed among the included studies (I^2=0%, p=0.41); thus, a fixed-effects model was adopted for the meta-analysis. The results showed that elevated FIB levels were not significantly associated with the risk of LI (OR=1.02, 95% CI=1.00–1.04; p=0.07; Figure 11).

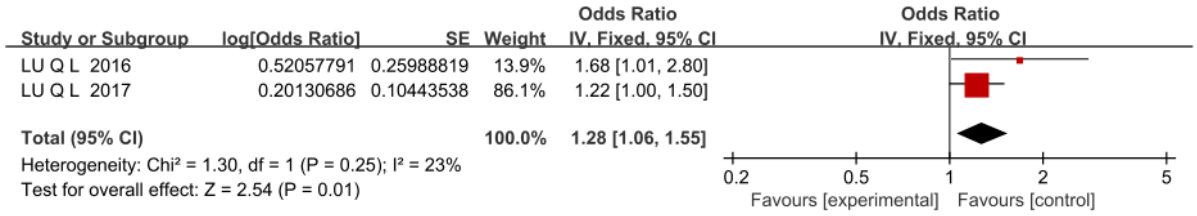

Figure 4. Forest plot of the correlation between IL-6 and CMB. CI: confidence interval; CMB: cerebral microbleeds; IL-6: interleukin-6; IV: inverse variance; OR: odds ratio; SE: standard error.

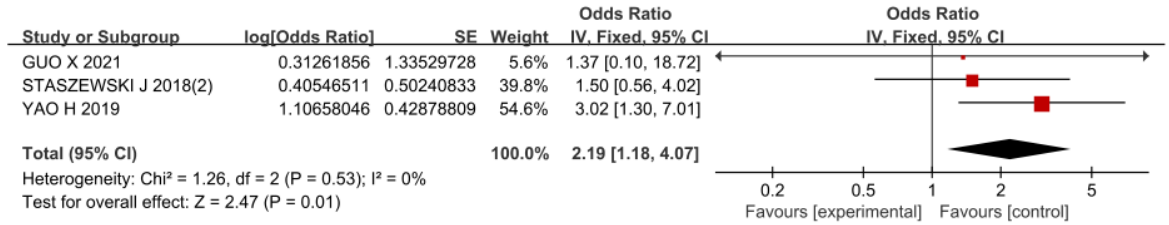

Figure 5. Forest plot of the correlation between hs-CRP and WMH. CI: confidence interval; hs-CRP: high-sensitivity C-reactive protein; IV: inverse variance; OR: odds ratio; SE: standard error; WMH: white matter hyperintensities.

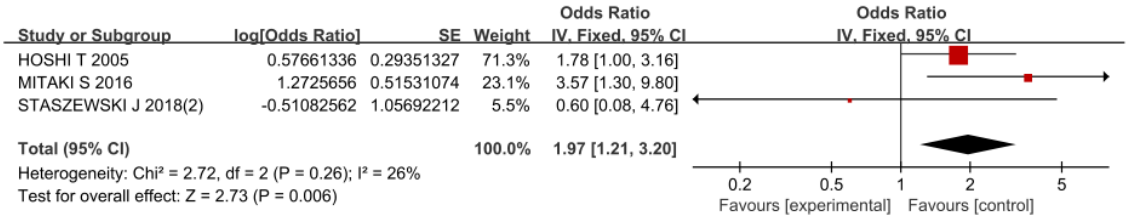

Figure 6. Forest plot of the correlation between hs-CRP and LI. CI: confidence interval; hs-CRP: high-sensitivity C-reactive protein; IV: inverse variance; LI: lacunar infarction; OR: odds ratio; SE: standard error.

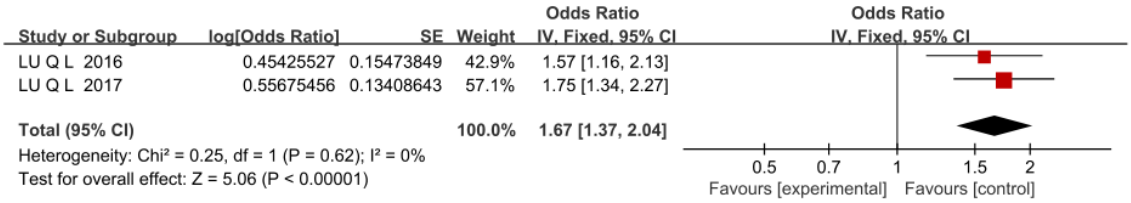

Figure 7. Forest plot of the correlation between hs-CRP and CMB. CI: confidence interval; CMB: cerebral microbleeds; hs-CRP: high-sensitivity C-reactive protein; IV: inverse variance; OR: odds ratio; SE: standard error.

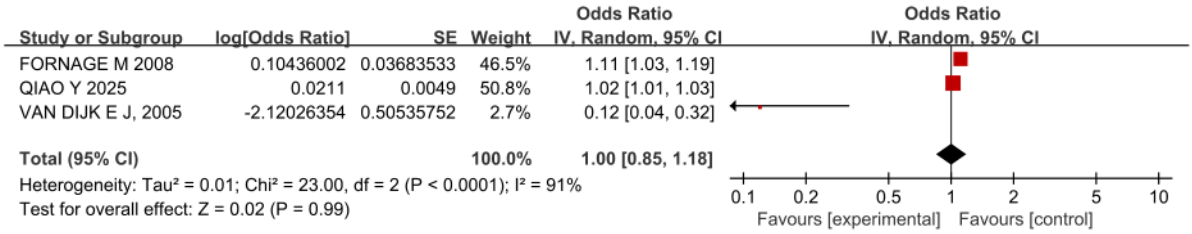

Figure 8. Forest plot of the correlation between CRP and WMH. CI: confidence interval; CRP: C-reactive protein; IV: inverse variance; OR: odds ratio; SE: standard error; WMH: white matter hyperintensities.

Table 2. Sensitivity analysis results

Elimination study	I^2, %	Heterogeneity *p*	OR (95% CI)	*p*
Fornage M 2008	94	<0.001	0.37 (0.05–3.02)	0.35
Qiao Y 2025	95	<0.001	0.39 (0.04–3.41)	0.39
Van Dijk EJ 2005	80	0.03	1.06 (0.97–1.14)	0.18

[a]CI: confidence interval; OR: odds ratio.

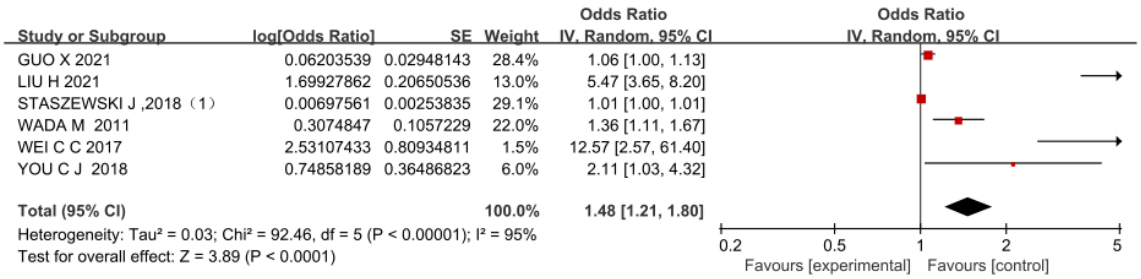

Figure 9. Forest plot of the correlation between FIB and WMH. CI: confidence interval; FIB: fibrinogen; IV: inverse variance; OR: odds ratio; SE: standard error; WMH: white matter hyperintensities.

Table 3. Sensitivity analysis results

Elimination study	I^2, %	Heterogeneity *p*	OR (95% CI)	*p*
Guo X 2021	96	<0.001	2.28 (1.27–4.09)	0.006
Liu H 2021	84	<0.001	1.12 (1.00–1.26)	0.060
Staszewski J 2018 (1)	95	<0.001	2.30 (1.30–4.05)	0.004
Wada M 2011	95	<0.001	1.51 (1.21–1.89)	0.0003
Wei CC 2017	95	<0.001	1.42 (1.17–1.71)	0.0003
You CJ 2018	95	<0.001	1.44 (1.18–1.76)	0.0004

CI: confidence interval; OR: odds ratio.

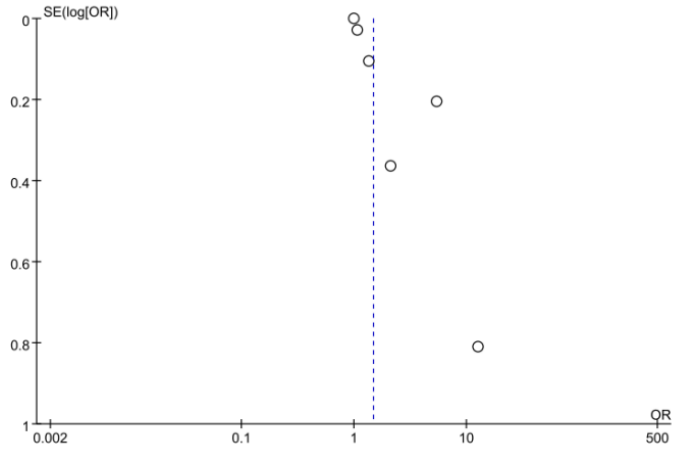

Figure 10. Funnel plot of the association between FIB and WMH. FIB: fibrinogen; OR: odds ratio; SE: standard error; WMH: white matter hyperintensities.

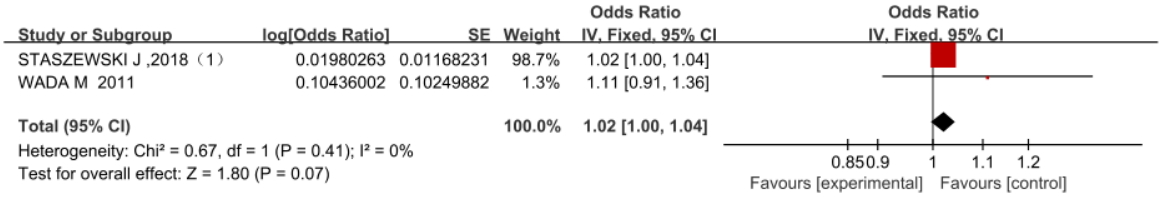

Figure 11. Forest plot of the correlation between FIB and LI. CI: confidence interval; FIB: fibrinogen; IV: inverse variance; LI: lacunar infarction; OR: odds ratio; SE: standard error.

DISCUSSION

CSVD is the most common cerebrovascular disease in the elderly population, typically with insidious onset and slow progression. It often has an insidious onset and progressive course and represents the leading cause of vascular dementia.[23-27] Different from large-vessel lesions, CSVD mainly involves the blood supply to deep white matter, basal ganglia, and other brain regions. The examination and research on terminal blood vessels face certain limitations in imaging, making the study of risk factors such as biomarkers particularly crucial. Currently, the diagnosis of CSVD mainly relies on cerebral imaging examinations, and it is generally recognized to be closely associated with MRI imaging characteristics. Noz et al[28] observed changes in WMH via MRI to assess the severity and progression rate of CSVD, and the results showed that the severity and progression rate of CSVD were correlated with changes in the expression of systemic inflammatory factors. An Atherosclerosis Risk in Communities study also indicated that individuals with higher CRP levels had more significant white matter structural abnormalities.[29] These findings all suggest that serum inflammatory factors have a certain association with MRI characteristics of CSVD, such as WMH. Clarifying the specific association strength and mechanism of action between serum inflammatory factors and CSVD MRI characteristics will provide an important theoretical basis for the early identification, disease assessment, and selection of therapeutic targets for CSVD. The IL-6, hs-CRP, CRP, and FIB included in the present study are all downstream markers of innate immune activation, and may reflect the activation status of immune–related inflammatory pathways to a certain extent.

The results of this meta-analysis showed that elevated levels of IL-6 and hs-CRP significantly increased the risk of LI and CMB. The BBB plays a pivotal role in the pathogenesis of CSVD. Among MRI markers such as WMH, perivascular spaces, and LI, CMB has the strongest correlation and highest sensitivity with BBB permeability.[30,31] IL-6 can impair

the integrity of the BBB and exacerbate increased BBB permeability.[32] Studies using in vitro BBB models have demonstrated that IL-6-mediated inflammatory stress may increase BBB permeability by downregulating tight junction proteins.[33] However, such evidence is derived from in vitro experiments rather than direct human in vivo data. Meanwhile, higher hs-CRP levels are associated with more severe cerebrovascular endothelial dysfunction, which in turn leads to abnormally increased BBB permeability.[34] Therefore, the abnormal release of IL-6 and the elevated level of hs-CRP can collectively induce blood–brain barrier dysfunction, thereby promoting the occurrence and progression of CMB. In addition, the overexpression of IL-6 is triggered by ischemia, hypoxia, and inflammation in the body, which stimulates the synthesis of proteins, thereby leading to thrombosis.[35,36] Meanwhile, elevated hs-CRP levels not only induce the release of a large number of inflammatory factors but also directly participate in the occurrence and development of carotid atherosclerosis, by aggravating vascular endothelial damage, promoting lipid deposition and plaque instability, the risk of plaque detachment.[37] If the detached plaque fragments or microthrombi formed by inflammation obstruct the lumens of perforating arteries in the deep brain with blood flow, they will cause small-scale infarction of brain tissue in the blood supply area due to ischemia and hypoxia, namely LI.

Innate immune inflammation serves as a key driver in the pathophysiological progression of CSVD. IL-6 and hs-CRP participate in the occurrence and development of CSVD through multiple mechanisms by synergistically activating innate immune pathways. As a pivotal pro-inflammatory cytokine in innate immunity, IL-6 contributes to persistent impairment of endothelial barrier function through JAK-mediated STAT3 phosphorylation and nascent protein synthesis.[38] Meanwhile, NF-κB, a key nuclear transcription factor, is widely involved in the regulation of inflammatory and immune responses. It can transcriptionally activate various inflammation–related genes, including IL-6, and further mediate IL-6-induced vascular endothelial dysfunction. In addition, IL-6 mediates the hepatic acute-phase response via the IL-6-CRP axis, inducing hepatocytes to synthesize and release hs-CRP and CRP. As major acute–phase proteins, the latter may activate the complement system, amplify local inflammatory cascades, and further exacerbate endothelial dysfunction.[39] Therefore, IL-6 and hs-CRP may synergistically regulate innate immune–mediated inflammatory responses, induce vascular endothelial dysfunction, and further disrupt BBB integrity with increased vascular permeability, ultimately leading to structural and functional damage to cerebral small vessels.

Furthermore, the results of this meta-analysis revealed that elevated FIB levels significantly increased the risk of WMH. Elevated FIB levels typically indicate an inflammatory state and activation of the fibrinolytic system in the body; they can not only exacerbate inflammatory responses but also increase blood viscosity, enhance coagulation function, promote platelet aggregation, and induce thrombosis. When thrombosis occurs in cerebral blood vessels, the thrombus obstructs cerebral vasculature, impairs blood supply to the white matter regions, and leads to local ischemia and hypoxia. Prolonged ischemia and hypoxia can cause myelin sheath damage and nerve fiber degeneration in the white matter, which subsequently manifests as WMH on imaging examinations.[40,41] However, high heterogeneity was observed among the included studies. Sensitivity analysis further demonstrated that significant heterogeneity persisted even after excluding any single study, yet the direction of the pooled effect size remained unchanged, indicating good robustness of the results. Nevertheless, since the sources of heterogeneity have not been fully elucidated, the interpretation of this finding requires prudent judgment. In addition, no significant correlation was found between FIB levels and the risk of LI. This may be due to the fact that the onset of LI is more dependent on the acute occlusion of small arteries. The pro-thrombotic effect of FIB might be masked by other strong risk factors (e.g., hypertension and diabetes mellitus), or its impact on the occlusion of perforating arteries is relatively weak, thus failing to exhibit a significant association.

The present study found that elevated IL-6 levels were not significantly associated with the risk of WMH. However, after excluding the studies contributing to heterogeneity, the heterogeneity was completely eliminated, and the pooled effect size indicated a significant association. This phenomenon might be attributed to the fact that prior to the exclusion of heterogeneity sources, the association between IL-6 levels and WMHs was already at a marginally significant level (p=0.05). At this point, the studies with high heterogeneity acted as key confounding factors, which directly offset the potentially significant association signals. After excluding these heterogeneous

studies, the effect sizes of the remaining studies were highly consistent in direction, thus amplifying the previously diluted marginally significant signals.

This study found that elevated hs-CRP levels significantly increased the risk of WMH, whereas no significant association was observed between elevated CRP levels and the risk of WMH. The underlying reason may be related to the difference in detection sensitivity between the two indicators: conventional CRP has low detection sensitivity and is mainly used for the evaluation of acute severe inflammation, which is poorly compatible with the pathological process of chronic low-grade inflammation associated with WMH. Therefore, compared with CRP, hs-CRP may be a more suitable biological indicator for reflecting the chronic inflammatory status related to the occurrence of WMH. Furthermore, the association analyses of FIB with LI and CRP with WMH showed that although the pooled ORs were slightly greater than 1, the differences were not statistically significant. Moreover, the effect sizes were extremely close to 1, suggesting that the actual clinical significance would be very limited even if a statistical association existed. Therefore, the present study does not support using FIB or CRP as independent predictive markers for LI or WMH.

Based on the above findings and mechanistic analyses, the pathophysiological roles of IL-6, hs-CRP, FIB, and CRP in CSVD remain incompletely understood and may involve multiple attributes. First, they may act as causal mediators that directly contribute to CSVD progression by damaging the endothelium, disrupting the blood–brain barrier, and promoting inflammation and thrombosis. Second, they may serve as surrogate markers that are passively elevated following tissue injury. Third, they may function as indicators of vascular risk burden, indirectly reflecting cumulative vascular damage associated with advanced age, hypertension, and atherosclerosis. Owing to the observational study design, the present study cannot establish causality; further validation via prospective cohort studies and mediation analyses is therefore warranted.

Within a broader framework of immune regulation, systemic inflammation in CSVD is not an isolated phenomenon but is closely linked to the immune dysregulation patterns widely investigated in allergy and immunology research. Allergic inflammation centered on Th2 cytokines (IL-4, IL-5, IL-13) can damage vascular endothelium by activating eosinophils and releasing oxidative stress products, sharing common pathological intersections with CSVD.[42] This suggests that systemic immune homeostasis imbalance may represent a shared upstream mechanism underlying both allergic inflammation and CSVD. More importantly, CSVD is highly prevalent in the elderly. With advancing age, overactivation of innate immunity and decline in adaptive immunity contribute to chronically mild elevations in pro-inflammatory factors such as IL-6 and hs-CRP, resulting in a state of systemic chronic low-grade inflammation. Inflammaging can directly exacerbate endothelial injury and BBB disruption, and may act synergistically with allergy-related Th2 immune deviation to amplify the inflammation–endothelial injury axis, ultimately promoting the initiation and progression of CSVD. Thus, the systemic inflammation observed in CSVD may essentially represent a complex immune dysregulation pattern shaped by the combined effects of immunosenescence, inflammaging, and allergic immune imbalance.

The present study has several limitations. First, significant heterogeneity existed among studies for some outcome indicators (e.g., the correlation between FIB and WMH), and sensitivity analysis failed to reduce such heterogeneity, which might have affected the stability and reliability of the pooled effect sizes. Second, the number of included studies was relatively small. This not only precluded the use of meta-regression to explore the sources of heterogeneity in the correlation between FIB and WMH, thereby limiting the generalizability of the conclusions, but also restricted the validation of the robustness of causal associations due to insufficient study quantity. Additionally, the included studies contained prospective cohort studies, which inherently have limitations such as inadequate adjustment for confounding factors and insufficient follow-up duration. Thus, prudence should be exercised when inferring causal relationships from the conclusions of this study. Third, the timing of inflammatory factor measurement varied across included studies, and some studies did not distinguish between acute and chronic phases, which may introduce heterogeneity. Fourth, the present study only included four peripheral inflammatory markers, which are insufficient to fully elucidate the complex immunopathological mechanisms of CSVD. Fifth, most studies did not differentiate between sporadic CSVD and CADASIL, limiting the generalizability of the conclusions. Sixth, the lack of a unified scoring scale for WMH may increase between-study heterogeneity. Seventh, some studies did not rigorously exclude

patients with autoimmune or chronic inflammatory diseases, which may confound cytokine levels; however, sensitivity analyses indicated that the core conclusions remained robust. Eighth, due to the objective limitations of the included original literature data, none of the studies clearly specified whether the MRI lesions were new or pre-existing, and some studies failed to report the spatial distribution characteristics of the lesions. Relevant stratified data were unavailable for extraction; thus, subgroup analyses of lesions with different onset statuses and lesion spatial distributions could not be performed, and only an overall correlation analysis was conducted in this study.

This meta-analysis demonstrated that elevated serum inflammatory factor levels were associated with an increased risk of MRI-detected features of cerebral CSVD. Specifically, IL-6 was significantly correlated with LI and CMB; hs-CRP showed significant associations with WMH, LI, and CMB; FIB exhibited a distinct specific correlation with WMH, while the role of CRP remains unclear.

The findings of the present study support that innate immunity–related inflammation is involved in the pathophysiological process of CSVD. Of note, MRI markers only reflect structural damage to cerebral small vessels, and their correlation with inflammatory factors cannot be directly equated with an active inflammatory process. It is worth emphasizing that this study only provides correlational evidence and cannot establish a causal relationship. To date, large-scale randomized controlled trials (RCTs) confirming the efficacy of anti-inflammatory or immunomodulatory therapies for CSVD remain lacking. Under a heterogeneous inflammatory background, therapeutic targets, dosages, and treatment durations have not been defined, and indiscriminate anti–inflammatory intervention may lead to adverse effects such as immunosuppression. Future large-scale RCTs are warranted to investigate the effects of targeted interventions such as anti-IL-6 therapy on CSVD lesion progression and clinical outcomes. Meanwhile, vessel-specific immunomodulatory strategies should be developed based on the pathological characteristics of CSVD to improve therapeutic precision and provide novel directions for the prevention and treatment of CSVD.

CONFLICT OF INTERESTS

The authors declared no conflict of interest.

STATEMENT OF ETHICS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

Not applicable.

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