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Elevated high-sensitivity C-reactive protein levels are associated with intracranial arterial stenosis in elderly patients

Mimi Li[1], Shufen Liu[1] and Chunnuan Chen[1*]

Abstract

Background To determine the correlation between intracranial atherosclerotic stenosis and high-sensitivity C-reactive protein (hs-CRP) levels in elderly patients with cerebral infarction.

Methods We performed a retrospective assessment of acute minor ischemic stroke patients aged over 60 at our institution from January 2021 to May 2023. A thorough computed tomography angiography (CTA) assessment was conducted for each participant. The patients were classified into four categories according to the site of stenosis in the cerebral arteries: (1) intracranial atherosclerotic stenosis (ICAS), (2) extracranial atherosclerotic stenosis (ECAS), (3) combined intracranial and extracranial atherosclerotic stenosis (IEAS), and (4) non-arterial stenosis (NOAS). Multivariate logistic regression analysis was utilized to evaluate the relationship between intracranial atherosclerotic stenosis and hs-CRP levels. The predictive efficacy of hs-CRP for intracranial arterial stenosis was assessed utilizing the Receiver Operating Characteristic (ROC) curve.

Results The research comprised 203 participants in total. Among these, 73 individuals (34.96%) were categorized as having Intracranial Stenosis Atherosclerosis (ICAS). The hs-CRP levels in the ICAS group were markedly elevated ($P=0.011$), while no significant difference in hs-CRP levels was observed between the ECAS and NOAS groups ($P=0.080$). Hs-CRP levels were found to be independently correlated with intracranial arterial stenosis (OR 1.136, 95% CI 1.038–1.242, $P=0.006$) following multivariable analysis, as shown in Table 2. The upper quartile of hs-CRP was determined to be a statistically significant independent risk factor for intracranial stenosis (OR 3.779, 95% CI 1.519–9.402, $P=0.004$). The area under the curve (AUC) for hs-CRP was calculated to be 0.632 following the analysis of the ROC curve. The ideal cutoff value for hs-CRP was established at 3.96 mg/L, accompanied by a 95% confidence interval ranging from 0.555 to 0.710 ($P=0.001$). The sensitivity and specificity were 0.500 and 0.735, respectively.

Conclusions In elderly patients with acute minor ischemic stroke, elevated hs-CRP levels are significantly correlated with intracranial atherosclerosis stenosis, rather than extracranial atherosclerotic stenosis.

Keywords Stroke, Intracranial atherosclerosis stenosis, High-sensitivity C-reactive protein, Senile patients, Inflammation

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Background

Cerebral infarction is increasingly prevalent among the elderly due to rising life expectancy, making stroke a significant cause of disability and mortality [1–2]. Stenosis of both intracranial and extracranial arteries is the primary pathological basis of ischaemic stroke [3]. Arterial stenosis, a recognized risk factor for stroke, significantly elevates morbidity and mortality, thereby straining healthcare systems. Recent comprehensive epidemiological studies have underscored the significant prevalence of carotid atherosclerosis in China. A nationwide study involving over 10.7 million adults revealed a carotid plaque prevalence of 21.0% [4], characterized by significant geographic and demographic disparities, particularly among older individuals and in specific high-risk regions. A population-based study of 194,878 Chinese adults revealed a 36.27% prevalence of carotid plaque and a 0.40% prevalence of carotid stenosis, with the highest stenosis rates observed in northern cities [5]. These findings underscore the prevalence of carotid atherosclerosis and its potential role in stroke pathogenesis. A direct, precise, and cost-effective screening method to identify high-risk individuals is urgently required due to the substantial association between carotid plaque, carotid stenosis, and stroke risk. Employing this strategy may facilitate early intervention and augment stroke prevention initiatives.

Comprehensive research conducted in recent decades has emphasised the pivotal role of inflammatory mediators in the progression of atherosclerosis [6]. Among them, High-sensitivity C-reactive protein (hs-CRP), an acute-phase inflammatory biomarker, has been shown to significantly increase during the acute phase of atherosclerosis and to actively engage in all stages of atherogenesis [7]. Elevated hs-CRP levels have been associated with an increased risk of stroke in numerous prospective epidemiological studies [8]. The correlation between elevated hs-CRP levels and different types of arterial pathology, such as intracranial artery plaques, intracranial artery stenosis, extracranial carotid artery plaques, and extracranial carotid artery stenosis, continues to be contentious [9–10]. Research indicates that elevated hs-CRP levels are prevalent in patients with intracranial artery stenosis and may act as a predictor of stroke risk and adverse outcomes in this demographic [11–13]. In contrast, other studies indicate that after controlling confounding variables, the relationship between hs-CRP levels and intracranial artery stenosis loses its statistical significance [14]. Likewise, some studies have shown that patients with extracranial carotid artery stenosis have markedly elevated hs-CRP levels compared to controls [15, 16], while others contend that increased hs-CRP does not independently heighten the risk of ischemic events in these patients [17]. This study seeks to clarify the relationship between intracranial and extracranial artery stenosis and hs-CRP levels in elderly patients with a history of cerebral infarction, considering the conflicting findings.

Methods

Study design

Participants were retrospectively selected from a cohort of patients diagnosed with acute minor cerebral infarction at our facility from January 2021 to May 2023. The inclusion criteria were: (1) Patients with acute cerebral infarction scoring 3 or lower on the National Institutes of Health (NIH) Stroke Scale; (2) age over 60; (3) assessed using computed tomography angiography (CTA); (4) hospitalized within 7 days of stroke onset. The exclusion criteria for subjects included: (1) infections, hepatic insufficiency, renal disease, and malignancies; (2) incomplete laboratory data and neuroimaging; (3) strokes of other specified etiologies, such as rheumatic heart disease, atrial fibrillation, patent foramen ovale, subacute arterial endocarditis, Moyamoya disease, arteriovenous malformation, syphilitic vasculitis, immune vasculitis, arterial dissection, radiation stenosis, hematological disorders, fibromuscular dysplasia, and arteritis, among others.

The Institutional Ethics Committee of the Second Affiliated Hospital of Fujian Medical University sanctioned our study in compliance with the Declaration of Helsinki.

Assessment of arterial stenosis and grouping strategy

Vascular imaging was conducted for all enrolled participants using a Siemens AG dual-source computed tomography (CT) scanner to evaluate both intracranial and extracranial arterial stenosis. The examined intracranial arteries comprised the middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), basilar artery (BA), the intracranial segment of the internal carotid artery (I-ICA; C4–C7), and the intracranial portion of the vertebral artery (I-VA; V4) [18]. The assessed extracranial arteries comprised the common carotid artery (CCA), external carotid artery (ECA), extracranial segment of the internal carotid artery (E-ICA; C1), and the extracranial portions of the vertebral artery (V1–V3) [19].

Two experienced investigators, blinded to clinical data, independently evaluated the degree of arterial stenosis. The severity of stenosis was assessed using standardized criteria from the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) [18] study and the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [19]. Participants were classified into four groups based on CTA findings: (1) Intracranial atherosclerotic stenosis (ICAS) group: Individuals exhibiting ≥ 50% stenosis in any intracranial artery.

(2) Extracranial carotid atherosclerotic stenosis (ECAS) group: Patients exhibiting ≥ 50% stenosis in extracranial arteries absent concurrent intracranial stenosis.(3) Group with combined intracranial and extracranial atherosclerotic stenosis (IEAS): Patients exhibiting ≥ 50% stenosis in both intracranial and extracranial arteries.(4) Non-cerebral atherosclerotic stenosis (NCAS) group: Individuals lacking substantial stenosis in both intracranial and extracranial arteries.

The identification of responsible vessels was based on a thorough evaluation incorporating clinical and imaging criteria. This assessment encompassed patient history, neurological manifestations, stroke subtype categorization per the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria, infarct localization on Magnetic resonance imaging (MRI) or CT, and associated CTA results.

Clinical and demographic information

A team of experienced and trained neurologists collected demographic data and clinical information. A documented history of hypertension diagnosis, or a systolic blood pressure of 140 mmHg or higher and/or a diastolic blood pressure of 90 mmHg or higher, were all criteria for the definition of hypertension [20]. A fasting glucose level more than 7.0 mmol/L, a random glucose level more than 11.1 mmol/L, or the requirement for continuous hypoglycemic therapy indicates a diagnosis of diabetes mellitus [21]. Patients with a smoking history comprise individuals who had ceased smoking within the last six months or who had smoked a minimum of five cigarettes daily for over twelve months.

Blood tests

Fasting samples were collected within 24 h of admission. Serum concentrations of total triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), hemoglobin A1C (HbA1C), and homocysteine (HCY) were assessed using an automated analytical platform (Beckman LH 780 hematology analyzer: Beckman Coulter, Brea, CA, USA). Hs-CRP was analyzed using the Roche Modular P800 Analyzer (Basel, Switzerland).

Statistical analysis

Categorical variables were expressed as the count of subjects (percentage). Continuous data was presented as the mean ± standard deviation (SD) or the median with interquartile ranges, depending on the distribution of the data. The Chi-square test was employed to compare categorical data. Continuous variables were assessed utilizing one-way analysis of variance (ANOVA). The Wilcoxon test was utilized for non-parametric data. A multivariable logistic regression analysis was performed to assess the independent relationship between intracranial atherosclerotic stenosis (ICAS) and various risk factors. Due to the binary nature of the outcome variable, results are presented as odds ratios (ORs) along with their respective 95% confidence intervals (CIs). Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic accuracy of hs-CRP in ICAS. The discriminatory capacity of hs-CRP was assessed through the area under the curve (AUC), with elevated values signifying enhanced diagnostic efficacy. Sensitivity, specificity, and the optimal cut-off point were established utilizing Youden's index to enhance overall diagnostic efficacy. A p-value of less than 0.05 was deemed the criterion for statistical significance. All statistical analyses were performed using SPSS version 20.0. Before data collection, a sample size calculation was conducted utilizing an ANOVA model to guarantee sufficient statistical power for identifying significant associations.

Results

Of 298 consecutive elderly patients admitted with acute cerebral infarction, 95 were excluded based on the study criteria (Fig. 1). A total of 203 elderly patients, with a mean age of 72.62 ± 5.46 years and a male predominance of 61.1%, were included in the study. Among these, 60 patients (29.56%) were classified as having no arterial stenosis (NOAS), 73 (35.96%) as having intracranial atherosclerotic stenosis (ICAS), 47 (23.15%) as having both intracranial and extracranial atherosclerotic stenosis (IEAS), and 23 (11.33%) as having extracranial atherosclerotic stenosis (ECAS). Table 1 outlines the clinical characteristics of these four groups.

Relative to the NOAS group, low-density lipoprotein cholesterol (LDL-C) levels were significantly increased in the ICAS, ECAS, and IEAS groups ($p = 0.033$, $p = 0.006$, and $p = 0.001$, respectively). Total cholesterol (TC) levels were markedly increased in patients with ECAS and ICAS, with p-values of 0.048 and 0.049, respectively. Patients in the ICAS and IEAS groups exhibited elevated levels of hs-CRP, with statistically significant differences observed ($p = 0.011$ and $p = 0.004$, respectively). No substantial difference in hs-CRP levels was observed between the ECAS and NOAS groups ($P = 0.080$). No statistically significant differences were noted for additional characteristics.

The hypothesis posited that the prevalence of patients with intracranial atherosclerosis stenosis (including both ICAS and IEAS) would escalate with ascending quartiles of serum high-sensitivity C-reactive protein (hs-CRP) levels: Q1 ≤ 1.200 mg/L; 1.200 mg/L < Q2 ≤ 2.950 mg/L; 2.950 mg/L < Q3 ≤ 7.710 mg/L; Q4 > 7.710 mg/L. Statistical significance was observed exclusively between quartiles Q1 and Q4 ($\chi^2 = 8.337$, $P = 0.040$) (Fig. 2).

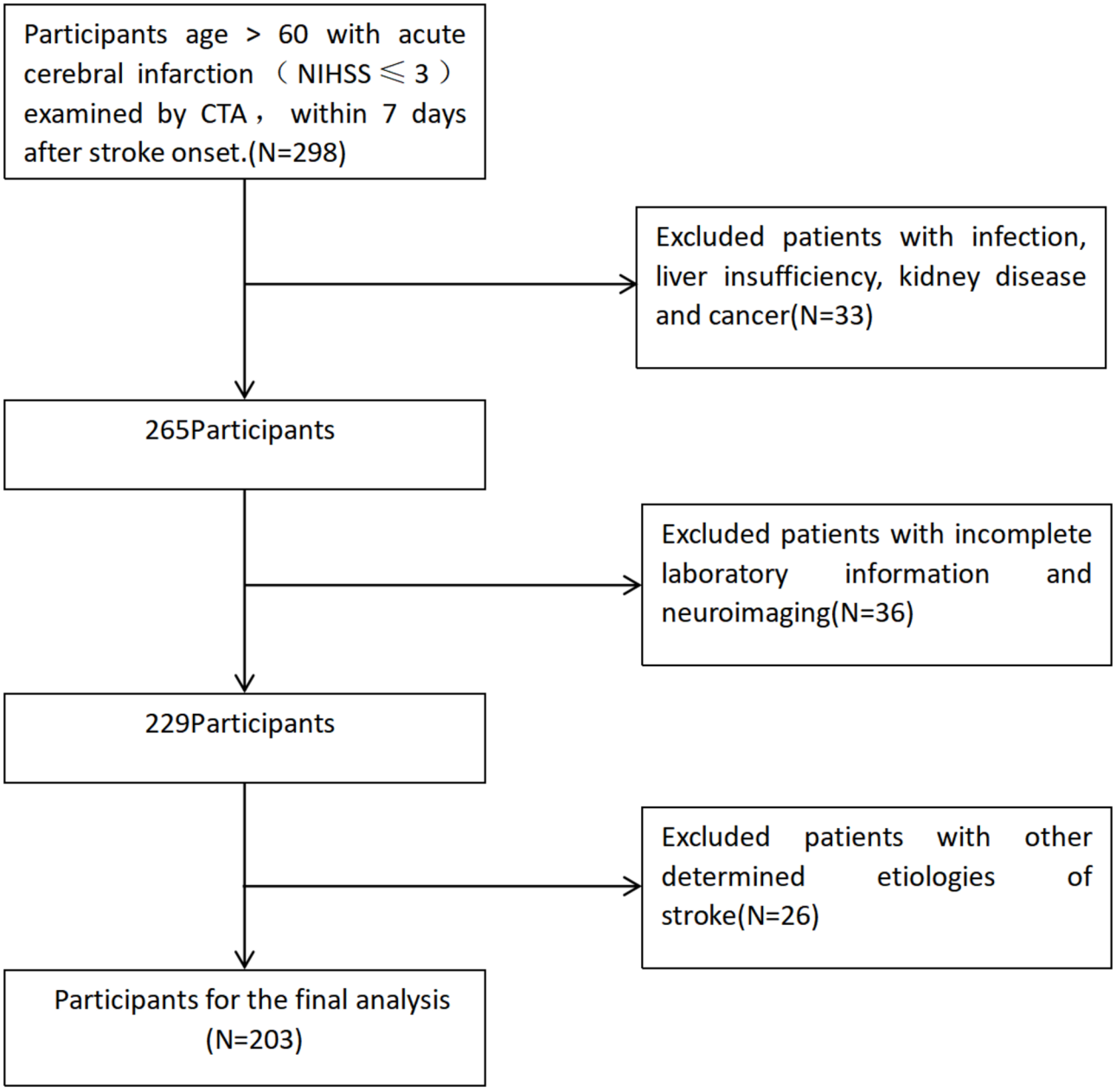

Fig. 1 Flow diagram of study cohort selection

Merge the IEAS group with the ICAS group to establish the Intracranial Arterial Stenosis group and combine the ECAS group with the NOAS group to create the control group. Utilizing clinical experience, the recognized risk factors were incorporated into a multivariate regression model analysis. After adjusting for other confounding variables, the level of hs-CRP was found to be independently associated with the incidence of intracranial arterial stenosis (OR 1.136, 95% CI 1.038–1.242, $p = 0.006$), as presented in Table 2. Moreover, the results indicated that a hs-CRP concentration exceeding 7.710 mg/L showed the strongest association with ICAS. The correlation was observed when quartiles of hs-CRP were included in the model (OR 3.779, 95% CI 1.519–9.402, $p = 0.004$), as demonstrated in Table 3.

The ROC curve analysis was used to evaluate the predictive significance of hs-CRP for intracranial arterial stenosis. The results indicated that the AUC value of hs-CRP was 0.632, with an optimal cutoff of 3.96 mg/L (95% CI 0.555–0.710, $P = 0.001$), and the sensitivity and specificity were 0.500 and 0.735, respectively (Fig. 3).

Table 1 Clinical and demographic characteristics of participants

	ICAS	ECAS	IEAS	NOAS
	N = 73	*N* = 23	*N* = 47	*N* = 60
Age(years)	71.00(66.50–76.00)	73.00(69.00–77.00)	70.00(68.00–75.00)	74.00(69.00–77.00)
Gender(male)	36(49.32%)	14(60.87%)	32(68.09%)	42(70.00%)
Hypertension	54(73.97%)	12(52.17%)	36(76.60%)	37(61.66%)
Diabetes	25(34.25%)	11(47.82%)	15(31.91%)	15(25.00%)
Smoker	21(28.77%)	9(39.13%)	19(40.42%)	23(38.33%)
HbA1C(%)	5.90(5.25–7.95)	6.10(5.58–7.10)	5.80(5.20–6.70)	5.75(5.40–6.95)
HCY(umol/L)	10.72(8.20-12.58)	9.98(7.58–11.62)	11.10(9.57–14.60)	9.77(8.62–12.11)
hsCRP(mg/L)	3.98(1.29–9.93)*	2.72(0.56–8.81)	3.79(1.75–9.50)*	2.30(1.01–3.97)
TC(mmol/L)	5.00 ± 1.13	5.45 ± 1.04*	5.28 ± 1.15*	4.63 ± 1.24
HDL-C(mmol/L)	1.13 ± 0.30	1.31 ± 0.30	1.16 ± 0.32	1.21 ± 0.30
LDL-C(mmol/L)	3.22 ± 0.93*	3.51 ± 0.77*	3.46 ± 0.93*	2.87 ± 1.00
TG(mmol/L)	1.30(1.03–1.70)	1.40(0.91–1.81)	1.34(0.97–1.62)	1.18(0.85–1.67)

*$p < 0.05$vsNOAS

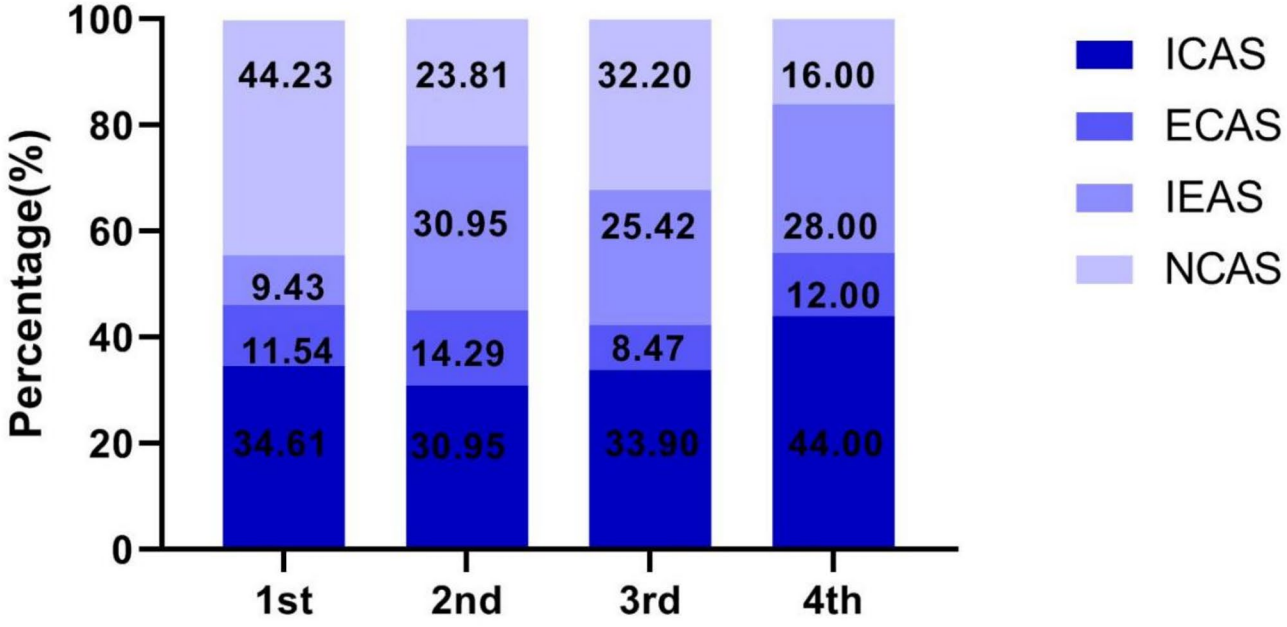

Fig. 2 Distribution of study groups based on hs-CRP levels

Discussion

Previous studies have demonstrated that serum biomarkers are among the most accessible and effective tools for diagnosing atherosclerotic arterial stenosis [22].

The development of intracranial atherosclerosis is anticipated to be a multifaceted process that may involve numerous factors [6]. A critical element in the development of arteriosclerosis is inflammation [23].

Hs-CRP is universally acknowledged as a non-specific acute-phase inflammatory mediator. Hepatocytes release a substantial amount of hs-CRP in response to cytokine signals, which are triggered by primary pro-inflammatory cytokines such as interleukin-6 (IL-6) [24].

Elevated hs-CRP levels actively promote vascular atherogenesis through the upregulation of chemokines and adhesion molecules [25]. Furthermore, meta-analyses of individual participant data have associated hs-CRP with an increased risk of stroke recurrence [26]. The Third China National Stroke Registry revealed that, particularly in patients with elevated hs-CRP levels, symptomatic intracranial or extracranial artery stenosis significantly enhances the risk of recurrent ischemic stroke, stroke, and composite vascular events within one year in individuals experiencing acute ischemic stroke or transient ischemic attack [27].

However, epidemiological studies examining the association between hs-CRP and intracranial artery stenosis have yielded conflicting results. Certain studies indicate a robust correlation between elevated hs-CRP levels and ICAS [8]. Conversely, another study indicated

Table 2 Crude and multivariate adjusted ORs for ICAS

	Crude			Adjusted		
	OR	**95%CI**	***P***	**OR**	**95%CI**	***P***
Age	0.953	0.905–1.004	0.069	0.942	0.888-1.000	0.048
Gender	0.630	0.352–1.137	0.122	0.880	0.398–1.946	0.752
Hypertension	2.082	1.140–3.800	0.017	2.390	1.188–4.806	0.015
Diabetes	1.096	0.602–1.996	0.764	0.797	0.357–1.779	0.580
Smoker	0.797	0.445–1.427	0.445	0.949	0.453–1.989	0.890
HbA1C(%)	0.957	0.861–1.063	0.411	0.915	0.796–1.051	0.210
HCY	1.017	0.971–1.065	0.473	1.026	0.979–1.076	0.276
TC	1.201	0.942–1.531	0.139	2.256	0.496–10.263	0.293
TG	1.032	0.735–1.449	0.857	0.685	0.372–1.261	0.224
HDL	0.371	0.145–0.955	0.040	0.117	0.022–0.628	0.012
LDL	1.347	0.998–1.820	0.052	0.676	0.132–3.459	0.638
Hs-CRP	1.123	1.035–1.218	0.005	1.136	1.038–1.242	0.006

*Combine the IEAS group with the ICAS group as the intracranial arterial stenosis group, and merge the ECAS group with the NOAS group as the control group

Table 3 Multivariate regression analyses for the association between ICAS and hs-CRP

Quartiles of hs-CRP Concentration(mg/L)	**Crude**			**Adjusted**		
	OR	**95%CI**	***P***	**OR**	**95%CI**	***P***
Q1(≤1.200)	Reference			Reference		
Q2(1.200–2.950)	2.049	0.894–4.694	0.900	2.072	0.835–5.141	0.116
Q3(2.950–7.710)	1.839	0.865–3.910	0.114	1.797	0.777–4.156	0.171
Q4(>7.710)	3.242	1.421–7.398	0.005	3.779	1.519–9.402	0.004

*Combine the IEAS group with the ICAS group as the intracranial arterial stenosis group, and merge the ECAS group with the NOAS group as the control group

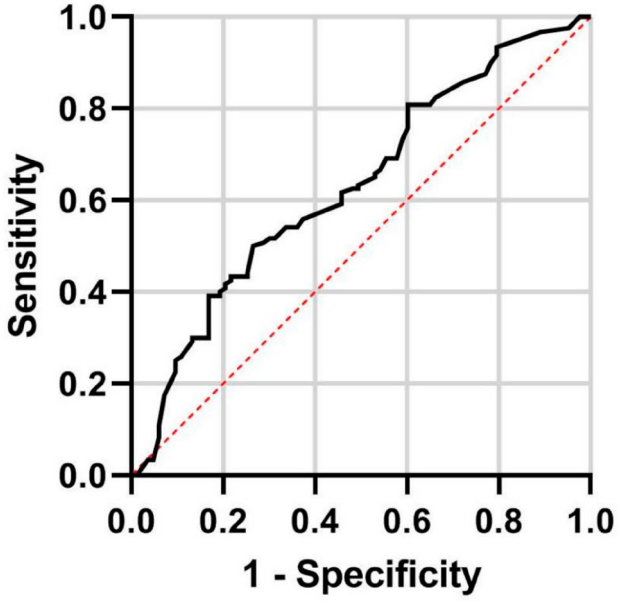

Fig. 3 Hs-CRP and intracranial atherosclerotic stenosis of ROC curve analysis

that elevated hs-CRP levels correlated with extracranial carotid artery stenosis, but not with ICAS [9].

Our research established that increased hs-CRP levels independently forecast stenosis in intracranial atherosclerosis. This result corresponds with the research conducted by Su et al. [28], which included 1,458 participants and revealed that elevated serum hs-CRP levels were linked to an increased risk of ICAS in both stroke patients and non-stroke individuals. Shimizu et al. [29] discovered that baseline hs-CRP concentrations did not demonstrate a significant correlation with ICAS, as assessed by Cox proportional hazard model analyses, despite increased hs-CRP levels in groups with arterial stenosis. A multitude of factors, including racial disparities, may have contributed to the incongruous results. Furthermore, it is essential to assess the likelihood of selection bias, the standards used to determine critical values of intracranial atherosclerotic stenosis, and the variability in sample size. Our study provides new perspectives on the current discourse by methodically assessing the relationship between hs-CRP and both intracranial and extracranial carotid artery stenosis within a single cohort. Unlike earlier studies that examined ICAS or ECAS separately, our results suggest that increased hs-CRP levels are independently correlated with ICAS, but not with ECAS. This observation is consistent with multiple previous studies [11–13, 17] and highlights an important distinction: the influence of systemic inflammation on atherosclerosis may differ based on the specific vascular territory involved.

It is widely acknowledged that the expression of hs-CRP can be induced by any type of tissue injury [24]. Consequently, distinguishing whether elevated hs-CRP levels indicate an acute-phase response or serve as a

biomarker for the atherothrombotic process can be challenging. Numerous prospective epidemiological studies have identified hs-CRP as a long-term risk factor for recurrent vascular events, irrespective of stroke severity [30]. Furthermore, evidence indicates that hs-CRP is preferentially expressed in diseased vessels. In our study, the elevation of hs-CRP was more pronounced in the ICAS group compared to other groups of stroke patients, suggesting that hs-CRP may serve as a marker for the progression of vascular atherogenesis.

Our findings indicate that hs-CRP may function as a predictive marker for ICAS risk, but not for ECAS, suggesting a significant divergence in the underlying pathophysiological mechanisms of intracranial and extracranial artery stenosis. Intracranial plaques are predominantly influenced by inflammatory processes [31], while extracranial plaques are typically lipid-rich and primarily affected by hemodynamic forces [32]. In ICAS, inflammation significantly contributes to the development of unstable, inflammation-associated plaques [31], while extracranial carotid atherosclerosis is more closely linked to lipid accumulation and mechanical stress [32]. This essential distinction may elucidate why hs-CRP levels do not significantly differ between ECAS and NOAS, as systemic inflammation may exert a less direct influence on extracranial plaque formation and ensuing stenosis.

The ROC analysis indicated that hs-CRP possesses moderate predictive capability for ICAS, with an AUC of 0.632, an optimal cutoff of 3.96 mg/L, a sensitivity of 50.0%, and a specificity of 73.5%. From both clinical and public health viewpoints, these findings highlight the potential value of hs-CRP as an adjunctive screening instrument for ICAS, especially in environments lacking access to advanced vascular imaging modalities, such as CTA or MRA. Due to its simplicity of measurement, affordability, and broad accessibility, hs-CRP screening may assist in identifying high-risk individuals who could benefit from additional vascular evaluation.

Limitations

This study possesses multiple limitations. Firstly, the evaluation of serum biomarkers was restricted to a singular time point, potentially failing to encompass temporal fluctuations. Secondly, while CTA was employed to assess the severity of stenosis, it is not regarded as the gold standard for these evaluations. Thirdly, being a cross-sectional study, this research identifies an association between hs-CRP and ICAS at a singular time point rather than establishing a causal relationship. The relationship between elevated hs-CRP and the progression of ICAS is ambiguous, raising the question of whether increased hs-CRP levels are a consequence of pre-existing ICAS. This highlights the necessity for longitudinal studies to investigate the potential causal connection between systemic inflammation and intracranial atherosclerosis. Moreover, selection bias may exist owing to the retrospective, single-center design, which constrains the generalizability of our results. The recruitment from a hospital setting may have led to an overrepresentation of individuals with more severe ICAS, potentially underestimating the prevalence among those with mild or asymptomatic conditions. Furthermore, since the study population was sourced from a singular center with restricted ethnic diversity, the results may not be entirely generalizable to wider populations. Future extensive, multicenter studies involving both hospitalized and community-based participants, as well as a more ethnically diverse cohort, are crucial to validate these findings and improve their generalizability.

Conclusions

Our findings demonstrate that increased hs-CRP levels are a significant predictor of intracranial atherosclerosis stenosis in elderly patients with cerebral infarction. Elevated hs-CRP levels seem to correlate more strongly with intracranial atherosclerosis than with extracranial atherosclerosis, underscoring the potential significance of hs-CRP as a biomarker for intracranial vascular pathology.

Abbreviations

Hs-CRP	High-sensitivity C-reactive protein
CTA	Computed tomography angiography
ICAS	Intracranial atherosclerotic stenosis
ECAS	Extracranial atherosclerotic stenosis
IEAS	Combined intracranial and extracranial atherosclerotic stenosis
NOAS	Non-arterial stenosis
ROC	Receiver Operating Characteristic
NIH	National Institutes of Health
CT	Computed tomography
MCA	Middle cerebral artery
ACA	Anterior cerebral artery
PCA	Posterior cerebral artery
BA	Basilar artery
I-ICA	Intracranial segment of the internal carotid artery
I-VA	Intracranial portion of the vertebral artery
CCA	Common carotid artery
ECA	External carotid artery
E-ICA	Extracranial segment of the internal carotid artery
WASID	Warfarin-Aspirin Symptomatic Intracranial Disease
NASCET	North American Symptomatic Carotid Endarterectomy Trial
TOAST	Trial of Org 10172 in Acute Stroke Treatment
MRI	Magnetic resonance imaging
TG	Total triglycerides
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
HbA1C	Hemoglobin A1C
HCY	Homocysteine
SD	Standard deviation
ANOVA	Analysis of variance
ORs	Odds ratio
CIs	Confidence intervals
AUC	Area under the curve
IL-6	Interleukin-6

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Author contributions
Mimi Li and Chunnuan Chen conceptualized the study, analyzed and interpreted the data, and drafted and revised the manuscript. Mimi Li and Shufen Liu analyzed and interpreted the data, drafted and revised the manuscript, did the statistical analysis, and prepared all the figures. Mimi Li did the interpretation of the data and revision of the manuscript. All authors contributed to the writing and revisions of the paper and approved the final version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Written informed consent form was obtained from all participants or their legal representatives. This study was approved by the Institutional Ethics Committees of Second Affiliated Hospital of Fujian Medical University(2019015), in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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