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ORIGINAL RESEARCH

Elevated Fibrinogen-to-Albumin Ratio Correlates with Incident Stroke in Cerebral Small Vessel Disease

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Purpose: We aimed to explore the association between fibrinogen-to-albumin ratio (FAR) and the risk of incident stroke (IS) in a cohort of cerebral small vessel disease (CSVD) patients.

Patients and Methods: Participants were screened from a prospective CSVD database. Clinical data, hematologic measures and imaging findings were collected. The primary outcome was IS during follow-up, with a secondary outcome of composite vascular events (CVE) including IS, myocardial infarction (MI), and vascular deaths. Univariate and multivariate COX proportional risk models, along with competing risk models, were employed to identify factors associated with outcomes. Restricted cubic spline (RCS) and subgroup analyses were conducted to assess the association between FAR and the risk of IS and CVE in CSVD patients.

Results: In the final analysis of 682 CSVD patients over a median observation period of 34.0 [24.0–53.0] months, there were 33 cases of IS (4.84%, 1.55/100 person-years), 4 incidents of MI (0.59%, 0.19/100 person-years), 15 non-vascular deaths (2.20%, 0.70/100 person-years), and 37 occurrences of CVE (5.43%, 1.74/100 person-years). Multivariate Cox regression analysis revealed a significant positive correlation between elevated FAR and both IS (HR 1.146; 95% CI 1.043–1.259; P=0.004) and CVE (HR 1.156; 95% CI 1.063–1.257; P=0.001) in CSVD patients. Multivariate competing risk model showed the similar results (IS: HR 1.16; 95% CI 1.06–1.27; P=0.001, CVE: HR 1.15; 95% CI 1.05–1.26; P=0.003). RCS analysis indicated a linear relationship between FAR and the risks of both IS (P for non-linearity =0.7016) and CVE (P for non-linearity =0.6475), with an optimal cutoff value of 8.69, particularly in individuals over 60 years of age.

Conclusion: Elevated FAR demonstrated an independent and linear association with IS and the development of CVE in CSVD patients.

Keywords: cerebral small vessel disease, incident stroke, fibrinogen-to-albumin ratio, inflammation

Introduction

Cerebral small vessel disease (CSVD) is a group of cerebrovascular disorders caused by a number of different etiologies affecting mainly small perforating arterioles, capillaries, and small veins. As defined by the updated Standards for Reporting Vascular Changes on Neuroimaging 2 (STRIVE-2), CSVD is characterized by neuroimaging markers, including recent small subcortical infarcts (RSSI), lacune of presumed vascular origin, white matter hyperintensities (WMHs) of presumed vascular origin, enlarged perivascular spaces (EPVS), cerebral microbleeds, cortical superficial siderosis, cortical cerebral microinfarcts, and cerebral atrophy.[1,2] Clinically, the recurrence of stroke events is not uncommon among patients with CSVD, with some patients even experiencing frequent recurrences. Previous studies have reported recurrence rates for specific CSVD types, such as lacunar infarction (LI) and cerebral autosomal dominant arteriopathy subcortical infarcts leukoencephalopathy (CADASIL), ranging from 2.7% to 7.3% of patients per year,[3–5]

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and some risk factors have been identified.[3,6–9] However, there remains a lack of clarity regarding the proportion and specific risk factors for incident stroke (IS) within a broader CSVD population defined by imaging markers of CVSD.

Longitudinal studies have shown that elevated systemic inflammatory markers present initially can forecast the severity and progression of CSVD. These markers affect the development of CSVD by impacting the permeability of the blood-brain barrier (BBB).[10,11] Fibrinogen to Albumin Ratio (FAR), a novel marker of systemic inflammation, has been linked to prognosis in various cancers, such as breast and hepatocellular carcinoma. Furthermore, FAR is associated with recurrence and outcomes after acute ischemic stroke (AIS) and hemorrhagic transformation (HT) following thrombolysis.[12–15] Despite these findings, there is a paucity of research on FAR's role in predicting outcomes in CSVD patients. Our study aims to address this gap by examining the relationship between FAR and the risk of IS and composite vascular events (CVE) in a broader CSVD population.

Methods

Patients Selection

Patients were screened from a hospital based CVSD database in the First Affiliated Hospital of Zhengzhou University from January 2017 to December 2022. The inclusion criteria of the database were as follows: (1) age≥18 years; (2) visible CSVD lesion on brain magnetic resonance imaging (MRI) meeting any of these:[1,2,16] 1) cerebral WMHs with a Fazekas score≥2; 2) Fazekas=1 with≥2 vascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, obesity and prior vascular events other than stroke, etc).; 3) RSSI (a recent infarction occurring within the past approximately 3 weeks located in the region of a single penetrating artery with a maximum axial diameter of no more than 20 mm and explaining the clinical symptoms).; 4) possible vasculogenic lacunar foci (penetrating arterial distribution 3–15 mm in diameter with cerebrospinal fluid signal); 5) enlarged perivascular space (EPVS, ≤3 mm in diameter along the vascular pathway); and 6) cerebral microbleeds foci (low signal on susceptibility-weighted imaging [SWI], ≤10 mm in diameter, no high signal on T1 and T2-weighted MRI for the corresponding lesion); (3) daily living ability (modified Rankin score≤2). Exclusion criteria: (1) large recent/old infarcts on diffusion weighted imaging (DWI) of the brain (middle cerebral artery region > 1/3, cerebellar hemisphere volume > 1/3, or Alberta Stroke Program Early CT-DWI (ASPECT-DWI) score less than 7); (2) patients with acute intracerebral hemorrhage or large vessel stenosis exceeding 50%; (3) dementia from diagnosed neurodegenerative diseases; (4) non-vascular white matter lesions; (5) history of cerebral vascular malformations, subarachnoid hemorrhage from cerebral aneurysms, or untreated aneurysm (>3mm in diameter); (6) diagnosis of mental disorders according to DSM-V diagnostic criteria; (7) intracranial occupancy, toxicity, metabolic or infectious, and demyelination-related disorders; and (8) suffering from severe organic diseases, such as malignant tumors, with an expected survival time of less than 5 years. In this study, we further excluded: (1) patients with incomplete demographic information, hematologic data, and imaging information; (2) patients who did not sign an informed consent form. The study was conducted with the approval of the Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Ethics Approval No. 2021-KY-1059-002.

Data Collection

We collected basic information (including gender, age, past medical history, smoking history, drinking history, etc)., laboratory information (including routine blood, blood lipids, fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), liver and kidney function, etc)., and imaging information from each patient. Hypertension was defined as systolic blood pressure (SBP)≥140 mmHg, diastolic blood pressure (DBP)≥90 mmHg or history of antihypertensive medication. Diabetes mellitus was identified as FBG>7.0 mmol/L or HbA1c>6.5% or former use of hypoglycemic drugs. Hyperlipidemia was defined as total cholesterol (TC) >5.0 mmol/L or low-density lipoprotein (LDL) cholesterol >3.62 mmol/L or prior lipid-lowering medication. History of smoking was defined as regular ongoing smoking or abstinence from smoking during the past 6 months. History of drinking was defined as ongoing regular use of alcohol or withdrawal from alcohol use within 6 months. FAR was defined as the ratio of fibrinogen to albumin (ALB).[17] For the collection of hematological indices, all patients were tested by blood collection on the morning of the second day after admission, making sure that the patients were in a fasting state and had fasted for not less than 8 hours.

Imaging Assessment

Due to the unavailability of SWI as a routine and obtainable sequence, this study primarily focused on evaluating certain CSVD imaging markers, including lacunar infarction (LI), WMHs, and EPVS from each patient's images. Conventional sequences included T1 and T2 scans, DWI and apparent diffusion coefficient (ADC), and fluid attenuated inversion recovery (FLAIR) sequences. Patients were examined by Siemens 3.0T superconducting MRI (Prisma, Verio and Skyra), following an imaging protocol that encompassed: Transverse DWI sequence with a 5mm slice thickness, repetition time (TR) of 4600ms, echo time (TE) of 80ms, b values 0 and 1000s/mm², and automated ADC map reconstruction. Transverse and sagittal T1-weighted imaging at 5mm slice thickness with TE of 2.5ms, transverse T2-weighted imaging at 5mm slice thickness with TE of 2.5ms, and transverse T2 FLAIR at 5mm slice thickness with TR of 6500ms and TE of 85ms.

LI was defined as the presence of at least one visible lacunar foci within the brain parenchyma. WMHs was classified into paraventricular and deep WMHs based on their location, whereas high-grade WMHs (HWMH) was defined as a Fazekas score ≥2 for paraventricular or deep WMHs.[18] EPVS were classified into centrum semiovale and basal ganglia region based on their locations, while high-grade EPVS (HPVS) was defined as the number of visible EPVS exceeded 10 in the basal ganglia region (counted on the side with the highest number).[19] The imaging information was evaluated by two neurologists who were unaware of the patient's clinical information, and when a disagreement existed, a third neurologist evaluated and ultimately reached a consensus.

Outcomes

In the study, we performed follow-up of CSVD patients by telephone or face-to-face clinic visits at 3, 6, 12, 24 months or over 36 months after discharge from the hospital routinely. All patients were followed from enrollment until the time of the terminal events, the last clinically documented visit, or the end of the last follow-up visit (September 30, 2023). The terminal events we focused on during the follow-up were whether the patient had IS, myocardial infarction (MI), or deaths after discharge from the hospital. The primary outcome of this study was IS (including ischemic or hemorrhagic stroke, lethal or non-lethal). Contacting patients by phone or face-to-face clinic visits, IS was confirmed by querying patients whether they had visited a healthcare facility for any new episode of limb or facial weakness or numbness, or vision, speech, and swallowing dysfunction lasting for more than 24 hours, and whether the diagnosis of stroke (ischemic stroke or cerebral hemorrhage) was already confirmed by a specialized healthcare facility. The secondary outcome was CVE that included the occurrence of IS, MI, and vascular deaths.[20] Vascular deaths referred to the deaths due to ischemic stroke, intracranial hemorrhage, MI, heart failure, or other unspecified nonvascular deaths that do not meet the criteria for lethal stroke, MI, or hemorrhage.[21]

Statistics Analysis

In our study, all analyses and visualizations performed using SPSS (version 26.0) and R (version 4.1.2) software. Missing values for continuous variables were imputed with the mean or median for continuous variables and the plurality method for categorical variables. Continuous variables were expressed as mean (standard deviation) or median (quartiles). Group differences were tested using *t*-tests or Mann–Whitney *U*-tests, as appropriate. Categorical variables were presented as number (rate), and differences were assessed using the chi-square test. Univariate and multivariate analyses were performed using the COX proportional risk model. Cumulative probability curves were plotted for the different groups with the Log rank test. Considering competing events, both univariate and multivariate analyses based on the competing risk model were conducted. Nelson-Aalen cumulative risk curves were generated using the cumulative incidence function (CIF), and Fine-Gray's test assessed significant differences in the risk function between variable groups. The "survminer" package determined the optimal cutoff point for continuous variables with Maximally Selected Rank Statistics (MSRS) identifying appropriate cutoff values. Restricted Cubic Spline (RCS) analysis explored the association between FAR and the risk of stroke recurrence and CVE in CSVD patients. Subgroup analysis of FAR associated with the risk of stroke recurrence and CVE was performed. Two-tailed P-value < 0.05 was considered significant.

Results

Baseline Characteristics

Of the 787 patients initially included in the prospective CSVD database spanning from January 2017 to December 2022, a total of 682 CSVD patients were enrolled in the final analysis after excluding 92 individuals due to insufficient clinical and imaging data, and 13 who declined to provide the informed consent (Figure 1). The patients' mean age was 61.0 ±11.1 years, and 260 (38.1%) were female. Further baseline information is presented in Table S1.

Outcomes

Over a median follow-up period of 34.0 [interquartile range, 24.0–53.0] months, 32 (4.69%) were lost to follow-up. The primary outcome, IS, occurred in 33 (4.84%, 1.55/100 person-years) patients, comprising 4 cases of intracerebral hemorrhage, 24 cases of ischemic stroke, and 5 cases with unidentified subtypes. Additionally, 4 (0.59%, 0.19/100 person-years) patients had MI, 15 (2.20%, 0.70/100 person-years) died from causes unrelated to stroke, and in total, 37 (5.43%, 1.74/100 person-years) experienced CVE.

Univariate Analysis of Risk Factors for IS and CVE

In the univariate COX regression analysis, higher age (P=0.045), monocyte count (P=0.046), fibrinogen level (P=0.048) and higher FAR (P=0.001) were positively associated with IS in CSVD patients, Conversely, higher ALB (P=0.005) and a higher proportion of LI (P=0.013) were negatively correlated with IS in CSVD patients (Table 1). Additionally, higher age (P=0.005), monocyte count (P=0.013), fibrinogen level (P=0.018), higher FAR (P<0.001), higher paraventricular (P=0.027), deep (P=0.022) and total WMHs (P=0.010) were positively associated with CVE in CSVD patients, On the contrary, higher ALB (P=0.006), estimated glomerular filtration rate (eGFR) (P=0.011), a higher proportion of LI (P=0.014) and HWMHs (P=0.045) were negatively correlated with CVE in CSVD patients (Table 1).

In the univariate competing risk model, higher fibrinogen level (P=0.025), higher FAR (P=0.002) and a higher proportion of LI (P=0.014) were positively associated with IS. Conversely, higher ALB (P=0.013) was negatively correlated with IS (Table 2). Moreover, higher age (P=0.016), monocyte count (P=0.014), fibrinogen level (P=0.01), higher FAR (P<0.001), a higher proportion of LI (P=0.014) and HWMHs (P=0.046), higher paraventricular (P=0.044), deep (P=0.037) and total WMHs (P=0.022) was positively associated with CVE. Simultaneously, higher ALB (P=0.018) was negatively correlated with CVE (Table 2).

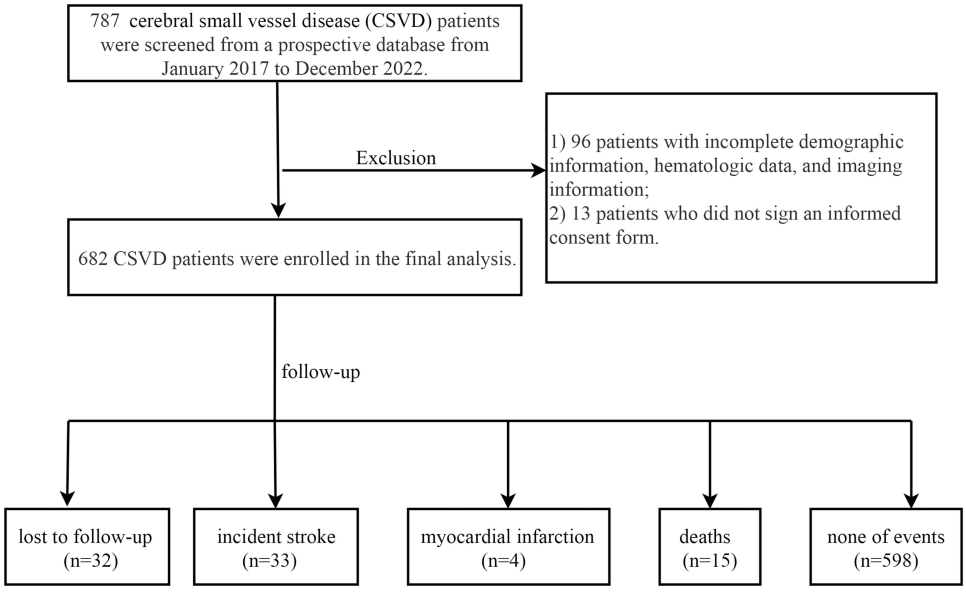

Figure 1 Patient screening flow chart.
Abbreviation: CSVD, cerebral small vessel disease.

Table 1 Univariate COX Regression Analysis of Risk Factors for Incident Stroke and Composite Vascular Events in Patients with Cerebral Small Vessel Disease

Variables	Incident Stroke			Composite Vascular Events		
	HR	95% CI	P-value	HR	95% CI	P-value
Demographic Information						
Age	1.035	1.001–1.071	**0.045**	1.048	1.014–1.084	**0.005**
Female	1.099	0.545–2.215	0.793	1.306	0.663–2.57	0.440
SBP	0.995	0.976–1.014	0.594	0.999	0.981–1.017	0.915
DBP	0.996	0.966–1.026	0.780	0.996	0.969–1.025	0.807
Hypertension	0.813	0.366–1.804	0.610	0.706	0.322–1.546	0.384
CHD	0.803	0.282–2.286	0.681	0.912	0.323–2.574	0.861
Diabetes	1.268	0.589–2.728	0.543	0.991	0.498–1.972	0.979
CVD	0.722	0.359–1.453	0.361	0.777	0.399–1.511	0.457
Smoking	2.256	0.871–5.843	0.094	2.092	0.873–5.015	0.098
Drinking	1.021	0.475–2.197	0.957	0.907	0.448–1.835	0.786
Hyperlipidemia	1.095	0.544–2.201	0.800	0.910	0.463–1.788	0.784
Laboratory Data						
WBC	1.129	0.977–1.305	0.099	1.136	0.993–1.301	0.064
PLT	1.002	0.997–1.008	0.382	1.002	0.997–1.007	0.549
Lymphocyte	0.797	0.409–1.554	0.505	0.754	0.4–1.423	0.384
Neutrophil	1.130	0.967–1.319	0.123	1.141	0.988–1.317	0.072
Monocyte	4.066	1.025–16.13	**0.046**	4.794	1.393–16.503	**0.013**
ALB	0.884	0.812–0.963	**0.005**	0.893	0.823–0.968	**0.006**
Fibrinogen	1.245	1.002–1.548	**0.048**	1.263	1.041–1.531	**0.018**
FBG	0.902	0.726–1.121	0.352	0.981	0.837–1.151	0.816
HbA1c	0.898	0.662–1.217	0.487	0.920	0.702–1.205	0.545
Homocysteine	0.999	0.957–1.043	0.952	1.005	0.968–1.043	0.801
TC	0.762	0.539–1.079	0.126	0.808	0.587–1.111	0.189
TG	0.878	0.579–1.331	0.539	0.878	0.592–1.302	0.518
HDL	0.387	0.113–1.322	0.130	0.554	0.183–1.673	0.295
LDL	0.800	0.536–1.194	0.275	0.846	0.583–1.226	0.376
eGFR	0.984	0.965–1.003	0.097	0.978	0.961–0.995	**0.011**
FAR	1.154	1.063–1.254	**0.001**	1.157	1.072–1.249	**0.000**
Imaging Features						
LI	0.412	0.204–0.831	**0.013**	0.437	0.226–0.846	**0.014**
HWMH	0.573	0.289–1.133	0.110	0.515	0.27–0.984	**0.045**
Location of WMHs						
Paraventricular	1.351	0.918–1.987	0.127	1.499	1.047–2.147	**0.027**
Deep	1.288	0.924–1.796	0.135	1.430	1.053–1.943	**0.022**
Total	1.193	0.976–1.458	0.085	1.275	1.059–1.535	**0.010**
Location of PVS						
Centrum semiovale	1.135	0.398–3.231	0.813	1.001	0.39–2.571	0.999
Basal ganglia	0.441	0.106–1.845	0.262	0.391	0.094–1.627	0.197
HPVS	0.757	0.381–1.502	0.426	0.665	0.349–1.266	0.214

Note: P-value <0.05 was considered meaningful. Significant values are in bold.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CVD, cerebrovascular disease; WBC, white blood cell; PLT, platelet; ALB, albumin; FBG, fasting blood glucose; HbA1c, Glycation Hemoglobin; TC, Total cholesterol; TG, Triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LI, Lacunar infarction; WMHs, white matter hyperintensities; PVS, perivascular space; HWMH, high-grade white matter hyperintensities; HPVS, high-grade perivascular space; FAR, fibrinogen to albumin ratio; HR, hazard ratio; CI: confidence interval.

Multivariate Analysis of Risk Factors for IS and CVE

In the multivariate COX regression analysis, higher FAR (Hazard Ratio[HR] 1.146; 95% confidence interval [CI] 1.043–1.259; P=0.004) was positively associated with IS in CSVD patients independently after adjusting for age, LI and monocyte count,

Table 2 Univariate Competing Risk Model of Risk Factors for Incident Stroke and Composite Vascular Events in Patients with Cerebral Small Vessel Disease

Variables	Incident Stroke			Composite Vascular Events		
	HR	95% CI	P-value	HR	95% CI	P-value
Demographic Information						
Female	0.93	0.46–1.90	0.9	0.78	0.39–1.54	0.5
age	1.03	1.00–1.07	0.079	1.05	1.01–1.09	**0.016**
SBP	0.99	0.98–1.01	0.5	1	0.98–1.01	0.9
DBP	1	0.97–1.03	0.8	1	0.97–1.02	0.8
Hypertension	1.22	0.55–2.72	0.6	1.41	0.64–3.10	0.4
CHD	1.25	0.44–3.53	0.7	1.1	0.39–3.07	0.9
Diabetes	0.78	0.36–1.69	0.5	1.01	0.51–2.02	>0.9
CVD	1.34	0.66–2.70	0.4	1.24	0.64–2.43	0.5
Smoking	0.44	0.17–1.13	0.088	0.47	0.20–1.13	0.093
Drinking	0.97	0.46–2.07	>0.9	1.1	0.55–2.22	0.8
Hyperlipidemia	0.92	0.46–1.85	0.8	1.12	0.57–2.19	0.7
Laboratory Data						
WBC	1.13	0.97–1.32	0.13	1.14	0.99–1.31	0.077
PLT	1	1.00–1.01	0.4	1	1.00–1.01	0.6
Lymphocyte	0.81	0.41–1.58	0.5	0.76	0.40–1.45	0.4
Neutrophil	1.13	0.96–1.33	0.2	1.14	0.98–1.32	0.081
Monocyte	3.99	0.96–16.5	0.056	4.76	1.37–16.6	**0.014**
ALB	0.89	0.81–0.97	**0.013**	0.9	0.82–0.98	**0.018**
Fibrinogen	1.25	1.03–1.51	**0.025**	1.26	1.06–1.51	**0.01**
FBG	0.9	0.71–1.13	0.4	0.98	0.83–1.16	0.8
HbA1c	0.9	0.68–1.17	0.4	0.92	0.74–1.14	0.4
Homocysteine	1	0.95–1.05	>0.9	1	0.96–1.05	0.8
TC	0.76	0.51–1.14	0.2	0.81	0.57–1.15	0.2
TG	0.88	0.63–1.23	0.5	0.88	0.65–1.19	0.4
HDL	0.38	0.13–1.10	0.075	0.55	0.20–1.53	0.3
LDL	0.8	0.50–1.30	0.4	0.85	0.56–1.30	0.5
eGFR	0.98	0.97–1.00	0.13	0.98	0.96–1.00	0.016
FAR	1.15	1.06–1.26	**0.002**	1.16	1.07–1.26	**<0.001**
Imaging Features						
LI	2.39	1.20–4.77	**0.014**	2.26	1.18–4.33	**0.014**
HWMH	1.72	0.87–3.40	0.12	1.93	1.01–3.67	**0.046**
Location of WMHs						
Paraventricular	1.32	0.88–1.99	0.2	1.48	1.01–2.17	**0.044**
Deep	1.27	0.90–1.78	0.2	1.42	1.02–1.98	**0.037**
Total	1.18	0.96–1.45	0.12	1.27	1.04–1.55	**0.022**
Location of PVS						
Centrum semiovale	0.89	0.32–2.52	0.8	1.02	0.40–2.62	>0.9
Basal ganglia	2.24	0.53–9.45	0.3	2.54	0.61–10.7	0.2
HPVS	1.33	0.67–2.65	0.4	1.53	0.80–2.92	0.2

Note: P-value <0.05 was considered meaningful. Significant values are in bold.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CVD, cerebrovascular disease; WBC, white blood cell; PLT, platelet; ALB, albumin; FBG, fasting blood glucose; HbA1c, Glycation Hemoglobin; TC, Total cholesterol; TG, Triglycerides; LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; LI, Lacunar infarction; WMHs, white matter hyperintensities; PVS, perivascular space; HWMH, high-grade white matter hyperintensities; HPVS, high-grade perivascular space; FAR, fibrinogen to albumin ratio; HR, hazard ratio; CI: confidence interval.

Meanwhile, a higher FAR (HR1.156; 95% CI 1.063–1.257; P=0.001) were positively correlated with CVE independently after adjusting for age, LI, monocyte count, eGFR and HWMHs (Table 3). Using the "survminer" package, an optimal cutoff value of 8.69 for FAR was obtained (Figure S1). Consequently, FAR > 8.69 was classified as the high group, and FAR ≤ 8.69 as the low

Table 3 Multivariate Analysis of Risk Factors for Incident Stroke and Composite Vascular Events in Patients with Cerebral Small Vessel Disease

Variables	Incident Stroke			Composite Vascular Events		
	HR	95% CI	P-value	HR	95% CI	P-value
COX proportional-hazards model						
Model 1*				**Model 3#**		
FAR	1.146	1.043–1.259	**0.004**	1.156	1.063–1.257	**0.001**
Model 2*				**Model 4#**		
ALB	0.919	0.845–1.000	0.051	0.935	0.861–1.016	0.112
Fibrinogen	1.259	0.926–1.712	0.141	1.302	0.992–1.709	0.057
Competing risk model						
Model 5&				**Model 7※**		
FAR	1.16	1.06–1.27	**0.001**	1.15	1.05–1.26	**0.003**
Model 6&				**Model 8※**		
ALB	0.91	0.83–0.99	**0.032**	0.94	0.86–1.03	0. 2
Fibrinogen	1.30	1.03–1.63	**0.026**	1.30	1.06–1.60	**0.012**

Notes: *Adjusting for age, LI and monocyte.#Adjusting for age, LI, monocyte, eGFR and HWMH. &Adjusting for LI. ※Adjusting for age, LI, monocyte, eGFR and HWMH. P-value <0.05 was considered meaningful. Significant values are in bold.

Abbreviations: ALB, albumin; eGFR, estimated glomerular filtration rate; LI, Lacunar infarction; WMHs, white matter hyperintensities; HWMH, high-grade white matter hyperintensities; FAR, fibrinogen to albumin ratio; HR, hazard ratio; CI, confidence interval.

group. The cumulative probability curves indicated that the group with FAR > 8.69 in CSVD patients had a significantly elevated risk of IS (P=0.0043) and CVE (P=0.00052) compared to the group with FAR ≤ 8.69. (Figure 2A and B).Furthermore, in the univariate competing risk model, higher FAR was positively associated with IS (HR 1.16; 95% CI 1.06–1.27; P=0.001) after adjusting for LI, and higher FAR was negatively correlated with CVE (HR 1.15; 95% CI 1.05–1.26; P=0.003) after adjusting for age, LI, monocyte count, eGFR, and HWMHs (Table 3). Additionally, Nelson-Aalen cumulative risk curves demonstrated that CSVD patients in the FAR > 8.69 group still had a higher risk of IS (P=0.006) and CVE (P<0.001) compared with the FAR ≤ 8.69 group after correction for competing events (Figure 2C and D).

Risk of IS and CVE with FAR Through RCS Analysis

RCS analysis was employed to flexibly model and visualize the relationship between FAR and the risk of IS and CVE in CSVD patients (Figure 3). FAR demonstrated a linear association with the risk of IS (P for non-linearity = 0.7016). Specifically, when FAR > 8.69, the risk of IS increased with the rising FAR (P = 0.0041) (Figure 3A). Similarly, a linear relationship was observed between FAR and the risk of CVE (P for non-linearity = 0.6475). In cases where FAR > 8.69, the risk of CVE increased with the rise of FAR (P = 0.0048) (Figure 3B).

Subgroup Analysis

In subgroup analysis, an interaction was noted between the FAR and gender (P=0.04), age (P=0.005), and history of cerebrovascular disease (P=0.011). In comparison to the low FAR group (FAR≤8.69), the high FAR group (FAR>8.69) was associated with a significantly increased risk of IS among patients aged >60 years (adjusted HR 3.825; 95% CI 1.553–9.425). Similarly, interactions were identified between the FAR and age (P<0.001), hypertension (P=0.009), cerebrovascular disease (P=0.005), and history of hyperlipidemia (P=0.019). The high FAR group was linked to a significantly elevated risk of CVE among those aged >60 years (adjusted HR 3.118; 95% CI 1.257–7.736) compared with the low FAR group (Figure 4).

Comparison of Baseline Information Between FAR>8.69 and FAR≤8.69 Groups

Compared with the FAR≤8.69 group, the FAR >8.69 group had higher age (P<0.001), shorter time of follow-up (P=0.003), a higher proportion of diabetes mellitus (P=0.005), higher WBC count (P<0.001), neutrophil count (P<0.001), and monocyte count (P<0.001), lower ALB (P<0.001), higher fibrinogen level (P<0.001), higher HbA1c (P=0.014), lower eGFR (P=0.005),

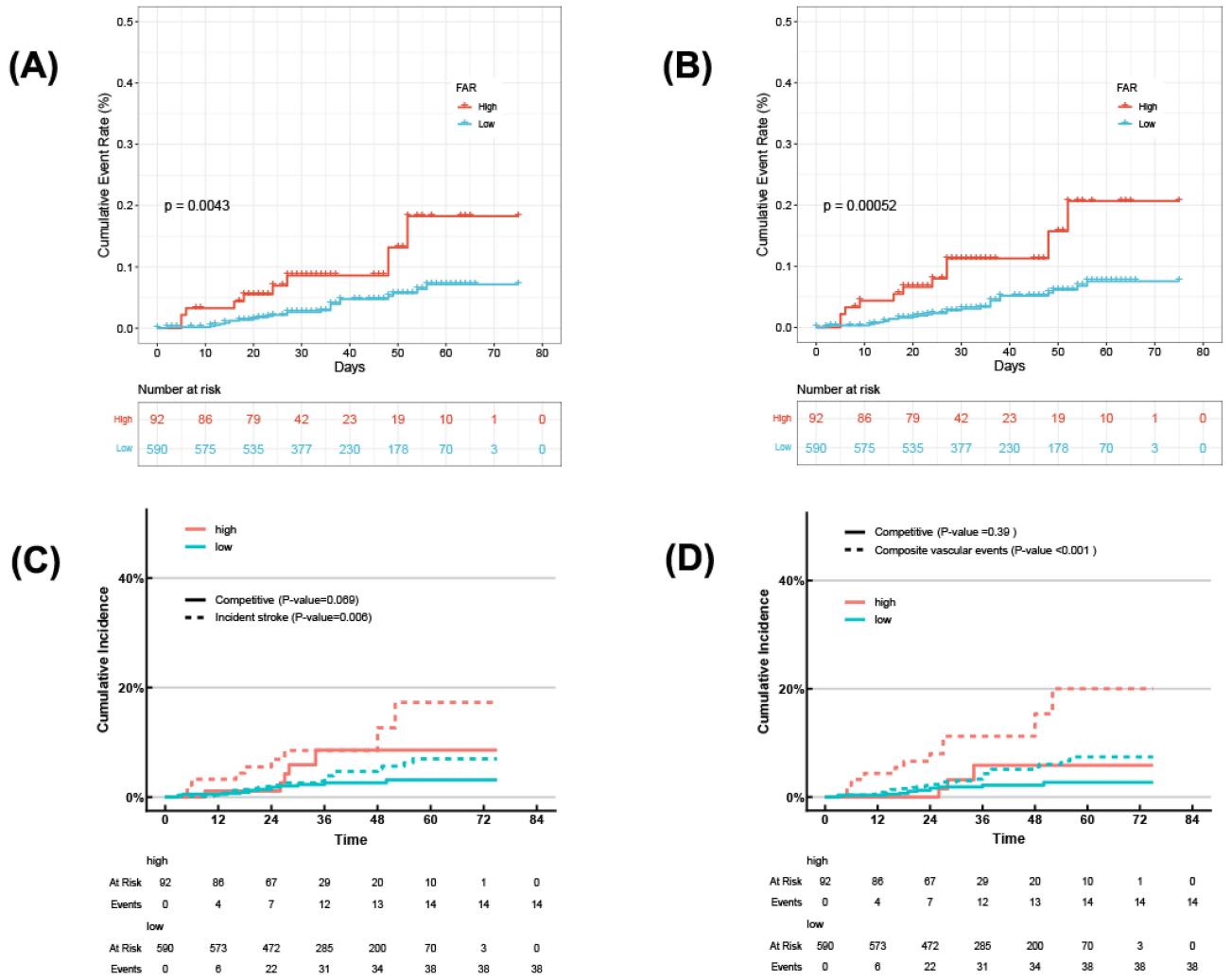

Figure 2 As the cumulative probability curves shown, compared with the FAR≤8.69 group, there was a higher risk of incident stroke (P=0.0043) (**A**) and CVE (P=0.00052) (**B**) In the FAR>8.69 group in CSVD patients, Nelson-Aalen cumulative risk curves shown that CSVD patients in the FAR >8.69 group still had a higher risk of incident stroke (P=0.006) (**C**) and CVE (P<0.001) (**D**) compared with the FAR≤8.69 group after correction for competing events. P-value <0.05 was considered meaningful.
Abbreviations: CSVD, cerebral small vessel disease; CVE, Composite vascular events; FAR, the ratio of fibrinogen to albumin.

and a higher proportion of CVE (P=0.01) and IS (P=0.011) (Table S1). There was a higher incidence of IS (3.52/100 vs 1.28/100 person-years; rate ratio, 2.764 [95% CI, 1.13–6.158]) and CVE (4.32/100 vs 1.39/100 person-years; rate ratio, 3.118 [95% CI, 1.39–6.53]) in the FAR>8.69 group compared with the FAR≤8.69 group.

Discussion

Our study established an independent association between elevated FAR and the risk of IS and CVE in patients with CSVD. Employing 8.69 as the optimal cutoff value, RCS analysis revealed a linear relationship: as FAR exceeded 8.69, the risk of IS and CVE in CSVD patients increased proportionally, with a more pronounced effect observed in individuals aged over 60 years.

In our study, 33 participants experienced IS, with an incidence rate of 4.84% (1.55 per 100 person-years). Previous investigations predominantly focused on specific subsets of CSVD patients, such as LI and CADASIL. In the Secondary Prevention of Small Subcortical Strokes (SPS3) study, the risk of recurrent stroke among patients assigned to receive aspirin alone was 2.7% per year.[3] Yasuhiro et al reported an incidence of 4.43 per 100 patient-years in a group of patients with lacunar stroke with single antiplatelet therapy.[4] Another study detected incident lacunes in approximately 7.3% of patients per year in a group diagnosed with CADASIL.[5] CADASIL, being a distinct subtype, inherently carries a higher

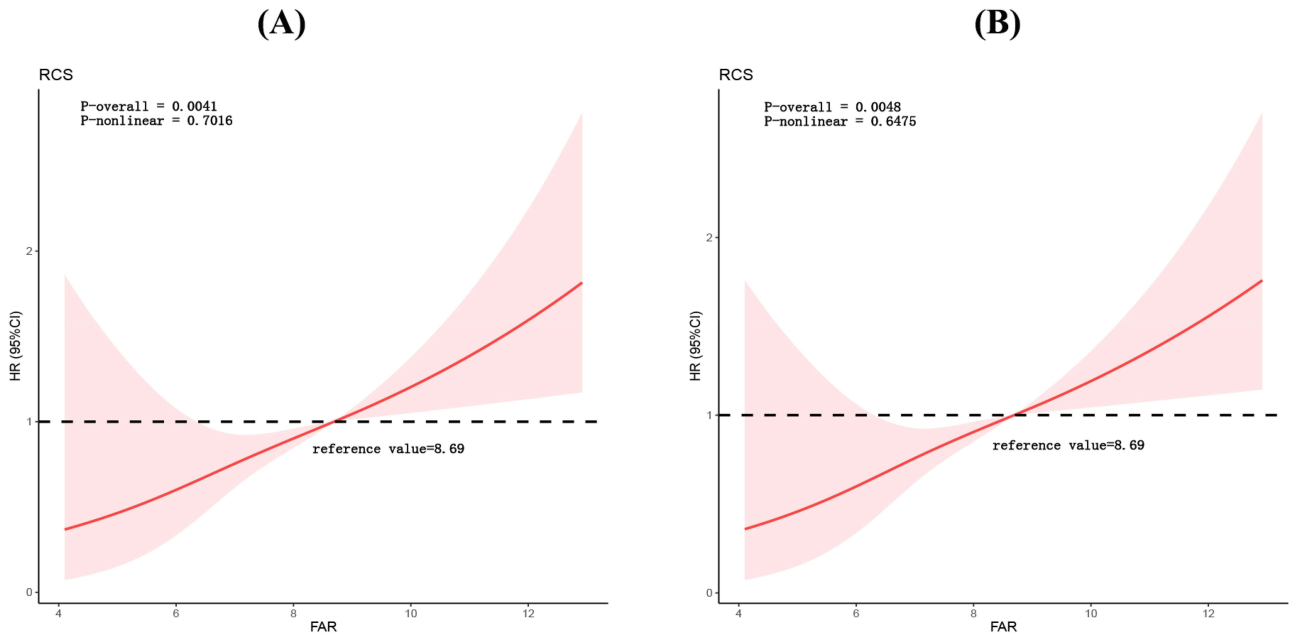

Figure 3 Restricted cubic spline analysis was used to flexibly model and visualize the relationship between FAR and the risk of incident stroke (**A**) and CVE in CSVD patients (**B**). P-value <0.05 was considered meaningful.
Abbreviations: CSVD, cerebral small vessel disease; CVE, Composite vascular events; FAR, the ratio of fibrinogen to albumin.

risk of recurrence, whether symptomatic or asymptomatic, and can even present with frequent silent acute microinfarcts on imaging.[22] Our study indicates a lower IS occurrence rate, potentially attributed to the diverse population, including patients with isolated conditions such as WMHs and EPVS. Moreover, hypertension, diabetes mellitus, and orthostatic hypotension were identified as risk factors for IS in previous studies. However, IS-related risk factors remain to be clarified to avoid the potential exposure to future terminal events in the general CSVD patients. We therefore excluded patients with lesions of macrovascular origin and other causes such as nonvascular lesions, degenerative disorders, metabolic, toxic, and malignant neoplasms to ensure that the overall CSVD population was represented.

In our study, we observed a significant association between FAR, an emerging inflammation indicator, and both IS and CVE in patients with CSVD. This association remained robust even after adjusting for competitive events, underscoring its stability. In previous investigations, FAR has demonstrated notable associations with prognosis in various medical conditions. Studies have linked FAR to prognostic indicators in different cancers, severity in obstructive sleep apnea, acute coronary artery disease, development of cardiac autonomic neuropathy in diabetic patients, and ischemic retinal vein occlusion[12,14,23–26] In the realm of cerebrovascular disease, Ruan Y et al conducted a study involving 256 consecutive stroke patients with comorbid hypertension (HT) and 256 age- and sex-matched non-HT stroke patients. Their analysis revealed that a high FAR was independently associated with an increased risk of hemorrhagic transformation (HT) after acute ischemic stroke (AIS).[27] Similarly, leveraging data from the third Chinese Stroke Registry (CNIS-III) survey, Wang X et al found that elevated FAR (>11.44) heightened the risk of short- and long-term poor functional Outcomes, encompassing disability and all-cause mortality, in patients with AIS.[28] Furthermore, Wang X et al revealed that FAR ≥0.077 on admission may be an independent predictor of death/disability at 3 months after lacunar stroke by analyzing 393 patients with acute lacunar stroke.[29] These findings collectively underscore the utility of FAR in both small and large cerebrovascular diseases, providing valuable insights into its prognostic significance across diverse cerebrovascular conditions.

There is a compelling correlation between vascular inflammatory markers (eg, adhesion molecules, von Willebrand factor [VWF]) and CSVD.[11] Elevated chronic inflammatory markers are posited as essential for the risk and progression of CSVD, influencing vascular endothelial cell damage, neurovascular unit alterations, and white matter integrity decline. Endothelial cell destruction-induced dysfunction can lead to BBB breakdown, increasing permeability and allowing

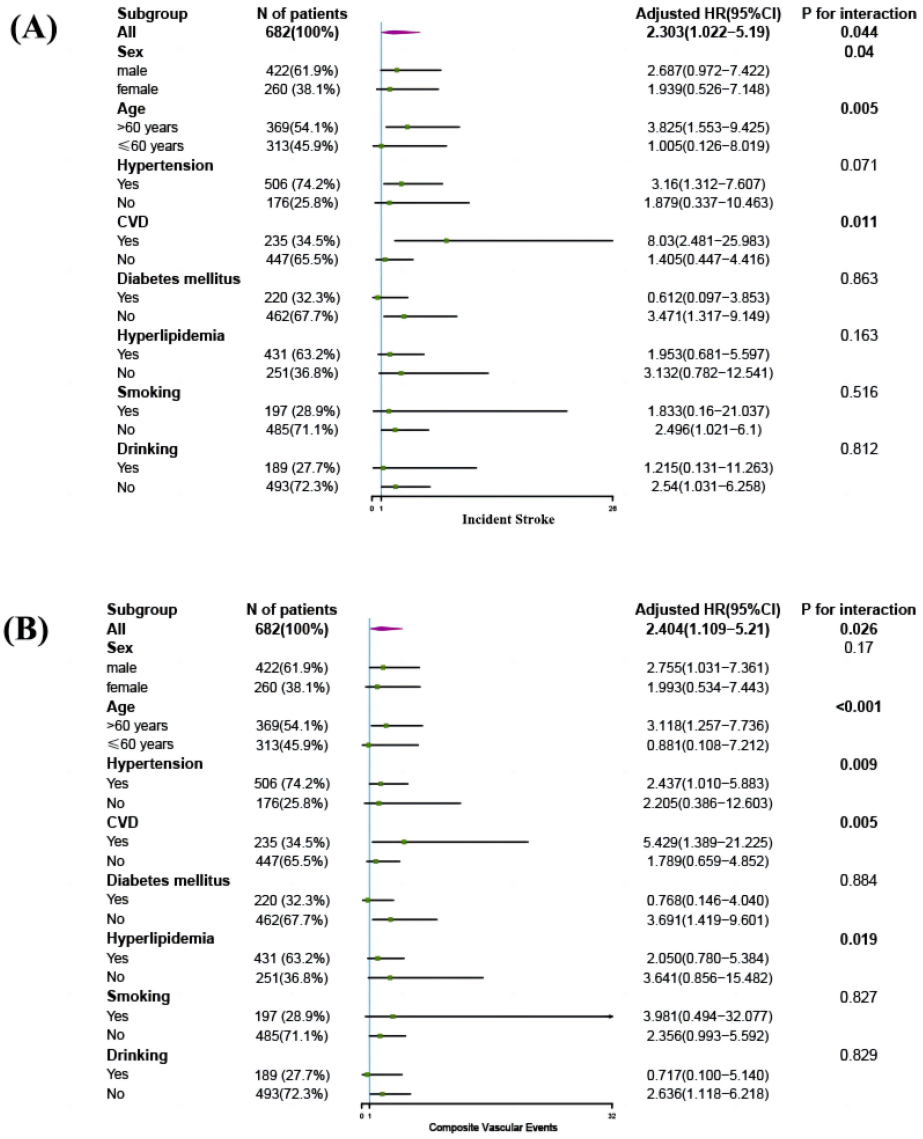

Figure 4 Subgroup analysis of the FAR associated with the risk of incident stroke (**A**) and composite vascular events (**B**). All HR were calculated with the low FAR group (FAR<8.69) as the reference groups, with models adjusted for age, LI and monocyte. P-value <0.05 was considered meaningful. Significant values are in bold.
Abbreviations: FAR, the ratio of fibrinogen to albumin; HR, hazard ratio; CI, confidence interval; LI, Lacunar infarction.

immune cells entry into the brain. This cascade contributes to changes in small blood vessel structure, thin-walled tissues, and perivascular spaces, collectively fostering CSVD development.[10,30] Several studies emphasize endothelial cell destruction and BBB leakage as initial pathologic hallmarks, suggesting inflammation as a potential driver of CSVD.[31,32] Consequently, focusing on inflammatory marker changes becomes crucial for early CSVD risk identification. Importantly, a notable study indicated an overall shift in blood protein patterns, characterized by increased fibrinogen and globulin levels and decreased albumin concentrations, as associated with subsequent vascular events (stroke, MI, or vascular death).[33] This highlights the potential value of FAR in predicting IS and CVE.

Fibrinogen and ALB, both synthesized by the liver, play distinct roles in the context of stroke and cardiovascular events. Fibrinogen is intricately linked to platelet aggregation, fibrin formation, and heightened plasma viscosity, serving as a marker for systemic inflammation.[34,35] Its involvement extends to disrupting endothelial cell integrity and increasing BBB permeability into the central nervous system, potentially leading to neuronal damage. This, in turn, triggers immune cell recruitment and the release of pro-inflammatory factors, culminating in a neuroinflammatory response.[36–38] Resch et al found that hyperfibrinogenemia was an independent risk factor for cardiovascular events in stroke survivors by

following up 625 first-time stroke patients (mean time 2 years).[39] Previous studies have shown that high levels of fibrinogen increase the risk of IS.[40] Conversely, ALB exhibits neuroprotective properties by reducing BBB permeability and engaging in anti-apoptotic, antioxidant, and anti-inflammatory processes. The enduring endothelium-protective and antioxidant effects of ALB contribute significantly to recovery from cerebral ischemia. Furthermore, ALB may inhibit fibrinogen activity, thus reducing fibrin accumulation and participating in processes such as the inhibition of platelet function and thrombosis.[41–46] In addition, ALB levels reflect the nutritional status of the body, and a low ALB level may indicate that the individual is malnourished with a higher likelihood of vascular events in the future, increasing the risk of stroke recurrence. The Results of a meta-analysis of 14 studies showed that a low plasma ALB level was independently associated with an increased risk of developing cardiovascular disease events.[47] In a study following 753 consecutive patients with acute ischemic stroke for one year, Zhang et al found that lower serum ALB levels were associated with an elevated risk of recurrence.[48] An intricate interplay was observed between fibrinogen and ALB, substantiating the role of FAR as a reflective measure of the body's inflammatory response.

Our study further elucidated a linear relationship between FAR and IS, as well as the incidence of CVE in patients with CSVD. The optimal cutoff value of 8.69 was identified through calculations, providing a practical benchmark for clinicians. In addition, the results of our subgroup analyses also revealed some specific populations in which IS and CVE occurred at high FAR levels, Based on the analysis of the robustness of the results, we concluded that high FAR levels could significantly affect IS and CVE in individuals aged more than 60 years. Studies showed that the plasma fibrinogen concentration increased with age, whereas there were no age-related changes in albumin synthesis rate and concentration.[49,50] This seemed to indicate that FAR levels may be higher in the body at a higher age, and this chronic inflammatory state was more likely to contribute to the development of vascular events.

Our study has a few limitations. Firstly, we only examined the relationship between baseline FAR and IS/CVE risk, neglecting trend changes in FAR, warranting further investigation. Secondly, as a single-center study, expanding the sample size and validating results in a multicenter population is crucial for broader applicability. Thirdly, our study was conducted exclusively in a Chinese population, necessitating validation in diverse populations to assess generalizability.

Conclusion

In Conclusion, our study revealed a significant and linear association between elevated FAR and the risk of IS, as well as the development of CVE in CSVD patients. Our findings suggested that as FAR surpassed 8.69, the risk escalated proportionally, with a particularly noteworthy impact observed among individuals aged over 60 years.

Data Sharing Statement

Data are available upon reasonable request from the corresponding author (E-mail address: xuyuming@zzu.edu.cn).

Ethical Approval and Informed Consent

Our study was approved by the Ethics Committee of the first Affiliated Hospital of Zhengzhou University (Ethics Review Number: 2021-KY-1059-002). All procedures carried out in studies involving human participants are consistent with the ethical standards of institutions and/or national research councils, as well as with the 1964 Helsinki Declaration and its subsequent amendments or similar ethical standards. All patients signed an Informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest related to this study.

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