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Original Article

Peripheral blood diagnostic markers of chronic cerebral hypoperfusion

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Abstract: Objective: To investigate the efficacy of ischemia-modified albumin (IMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), brain-derived neurotrophic factor (BDNF), and visinin-like protein-1 (VILIP-1) in diagnosing chronic cerebral hypoperfusion (CCH). Methods: This retrospective study included 84 patients with suspected chronic cerebral ischemia admitted to Sichuan Provincial People's Hospital between February 2021 and April 2022. Arterial spin labeling (ASL) imaging and biological examinations were performed. According to the ASL perfusion imaging patterns, the patients were divided into a CCH group (n = 55) and a non-CCH group (n = 29). Serum markers of the two groups were compared, and correlation analysis was conducted between ischemic marker levels and cerebral blood flow (CBF) in the ischemic region, as measured by ASL. Receiver operating characteristic (ROC) curve analysis was used to evaluate the efficacy of each marker for diagnosing chronic cerebral ischemia. The Delong test was used to compare AUC size between groups. Results: Compared to the non-CCH group, the CCH group exhibited higher IMA levels and lower BDNF concentrations ($P < 0.05$). However, VILIP-1 and Lp-PLA2 concentrations were not significantly different between the two groups ($P > 0.05$). Moreover, IMA and BDNF levels were not correlated with CBF in the hypoperfused area. ROC curve analysis demonstrated that the cut-off values of 24.2915 U/mL and 6.714 ng/L for IMA and BDNF achieved a sensitivity of 83.6% and 41.8% and a specificity of 62.1% and 93.1%, respectively. Lastly, the areas under the curve for IMA and BDNF were 0.738 (95% confidence interval [CI], 0.627-0.848) and 0.631 (95% CI, 0.512-0.751), respectively. Conclusion: IMA and BDNF may have clinical value in the diagnosis of CCH.

Keywords: Chronic cerebral hypoperfusion, arterial spin labeling, diagnostic biomarkers

Introduction

Chronic cerebral hypoperfusion (CCH) lacks a universally accepted definition; however, it is characterized by chronically inadequate brain perfusion. CCH primarily involves structural cerebrovascular abnormalities and/or abnormal blood concentration and hemodynamic hypoperfusion. These conditions can be attributed to various reasons, leading to overall or regional cerebral hypoperfusion in both anterior and posterior circulations, failing to meet the metabolic needs of normal brain tissue [1]. Consequently, the affected individuals may experience chronic and fluctuating cerebral functional impairment syndromes without clear focal neurological signs [2, 3]. Epidemiological studies in China suggest that two-thirds of the population aged over 65 years have concurrent CCH, with incidence rates of 50% and 25% in those aged 50-65 years and 45-50 years, respectively [4]. Clinical manifestations of CCH are primarily nonspecific. Therefore, imaging examinations such as computed tomography (CT) and magnetic resonance (MR) perfusion imaging, are crucial in CCH diagnosis and can reveal locally or globally reduced perfusion. Furthermore, MR perfusion imaging with arterial spin labeling (ASL) can quantitatively analyze cerebral blood flow (CBF) and reflect the meta-

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bolic activity in brain tissues, thereby aiding in CCH diagnosis. However, imaging diagnosis of CCH is costly and carries the risk of contrast-induced nephropathy, with the patient having already reached the stage of decompensated cerebral ischemia at the time of imaging assessment. In contrast, serum examination is a more economical and convenient method, with relatively higher patient compliance. Hence, research exploring peripheral blood diagnostic markers for early CCH diagnosis is pivotal [4].

Previous studies have suggested that ischemia-modified albumin (IMA), lipoprotein-associated phospholipase A2 (Lp-PLA2), brain-derived neurotrophic factor (BDNF), and visinin-like protein-1 (VILIP-1) could be diagnostic biomarkers of coronary atherosclerotic heart disease and acute ischemic stroke [5-8]. However, their expression levels in patients with CCH remain unclear. Therefore, this study analyzed the expression levels of these four biomarkers in patients with CCH and their potential value in CCH diagnosis.

Materials and methods

Study patients

This study obtained approval from the ethics committee of Sichuan Provincial People's Hospital (approval number: Ethics Review [Research] No. 55, 2022) and adopted a retrospective research design. Through the hospital's electronic medical record system, 84 patients suspected of having CCH and treated in the Department of Neurology between February 2021 and April 2022 were included. According to the ASL perfusion imaging patterns, which serve as the gold standard for CCH diagnosis, patients were divided into a CCH and a non-CCH group. Inclusion criteria were as follows: 1) age between 40 and 80 years, 2) presence of high-risk factors and clinical symptoms of CCH, 3) completion of ASL examination, and 4) availability of complete medical records and outcome evaluation data. Exclusion criteria were: 1) cerebral or myocardial infarction within the past 3 months; 2) connective tissue disease or vasculitis; 3) atrial fibrillation or valvular heart disease; 4) severe infection or organ dysfunction; 5) pregnancy; or 6) recent use of statins, aspirin, or clopidogrel within the last 3 months.

Clinical data collection

General characteristics and information related to vascular disease risk factors, such as age, sex, smoking habit, alcohol consumption, hypertension, and diabetes, were obtained from self-reported medical history. Laboratory examination results, including fasting blood glucose (FBG), glycated hemoglobin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), homocysteine (Hcy), and uric acid levels, and ApoA1/B, were also collected.

MR imaging (MRI) examination and image processing protocol

Enhanced ASL imaging was performed using a 3.0-T MRI scanner (Discovery MR750, GE Healthcare, Waukesha, WI, United States). During the procedure, patients were positioned supine, and head movements were restricted. The acquisition parameters for routine cranial MRI were as follows: (1) T1-weighted images: repetition time (TR) = 250.00 ms and echo time (TE) = 2.50 ms; (2) T2-weighted images: TR = 5744.40 ms and TE = 95.00 ms; (3) T2-weighted fluid-attenuated inversion-recovery images: TR = 10500.00 ms and TE = 94.00 ms; (4) 3D-ASL images: TR = 4300 ms, TE = 17.9 ms, field of view (FOV) = 300 mm × 300 mm, slice thickness = 4.0 mm, bolus duration (BD) = 800 ms, inversion time (TI) = 1800 ms, flip angle (FA) = 180°, and scan time = 5 min and 14 s. Additionally, the acquisition parameters for perfusion-weighted imaging were as follows: TR = 6000 ms, TE = 17.9 ms, FOV = 300 mm × 300 mm, slice thickness = 4.0 mm, excitation number = 1, BD = 800 ms, TI = 4000 ms, FA = 180°, and scan time = 3 min and 42 s. The raw images obtained from the MR perfusion scans were imported into MR Station software (Chengdu Zhongying Medical Technology Co., Ltd.) and processed to generate perfusion color maps, wherein red represented high perfusion and blue or black denoted low perfusion. The ASL images were assessed by two deputy chief physicians of the imaging department and one deputy chief physician of the neurology department to determine the presence of cerebral hypoperfusion areas and measure the CBF values in these areas. Normal CBF is approximately 50-55 mL/100 g of brain tissue/min (mL/100 g/min), with a reduction to 40 mL/100 g/min

resulting in brain dysbolism. In this study, ASL positivity was defined as CBF < 40 mL/100 g/min.

Peripheral blood biomarker examination

Enzyme-linked immunosorbent assay was performed to detect serum levels of IMA (zc-34490), Lp-PLA2 (zc-54155), BDNF (zc-34227), and VILIP-1 (zc-35325) using reagent kits purchased from ZCIBIO Technology Co., Ltd.

Classification of test results

In this study, our primary results were IMA, Lp-PLA2, BDNF, and VILIP-1 concentrations, while secondary measures included CBF, clinical symptoms, cerebrovascular disease risk factors, and study population characteristics.

Statistical analysis

All statistical data were analyzed using SPSS 26.0 software. Normally distributed measured data were presented as mean ± standard deviation ($x \pm s$) and compared between the two groups via independent sample *t*-tests, with the Pearson correlation test utilized for correlation analysis. Non-normally distributed measured data were expressed as medians and interquartile ranges (*M* [Q1, Q3]), and their between-group comparisons and correlation analysis were conducted using the Mann-Whitney *U* test and Spearman's rank correlation test, respectively. Categorical data were denoted as the number of patients and percentages and compared using the chi-square test. Moreover, receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) was calculated to analyze the diagnostic efficacy of the serum biomarkers for CCH. The Delong test was used to compare AUC size between groups. AUC values > 0.5 and differing significantly from 0.5 indicated diagnostic value of the indicator. The cut-off value was determined based on the point on the ROC curve where Youden's index was maximum. Finally, a *p*-value of < 0.05 was considered significant, and all tests were two-sided.

Results

Characteristics of the study population

A total of 84 patients (age, 46-78 [62.29 ± 8.21] years) with suspected CCH were included. Among them, 55 patients diagnosed with CCH based on the enhanced ASL imaging results were allocated to the CCH group, whereas 29 were categorized into the non-CCH group. **Table 1** presents the detailed characteristics of the study population grouped according to CCH diagnosis. The chief complaints of the patients with CCH were dizziness (*n* = 30, 54.5%), dizziness and headache (*n* = 15, 27.3%), headache (*n* = 7, 12.7%), and head distension (*n* = 3, 5.5%). Furthermore, more than half of the patients with CCH had multiple cerebral hypoperfusion areas (*n* = 34, 61.8%). Lastly, CBF in the hypoperfusion area ranged from 1.88 to 51.1 mL/100 g/min, with a mean CBF of 24.72 mL/100 g/min.

Comparison of cerebrovascular disease risk factors between the two groups

As shown in **Table 1**, the TC, LDL, HDL, and normal (N)-HDL levels in the CCH group were significantly higher than those in the non-CCH group ($P < 0.05$). However, no significant differences were observed in age, sex, smoking habit, alcohol consumption, hypertension, diabetes, ApoA1/B, and FBG, TG, N-HDL, HDL, uric acid, or Hcy levels between the two groups ($P > 0.05$).

Comparison of serum markers between the two groups

Compared to the non-CCH group, the CCH group demonstrated higher IMA and lower BDNF levels ($P < 0.05$), while VILIP-1 and Lp-PLA2 concentrations did not significantly differ between the two groups ($P > 0.05$; **Table 2**).

Correlation of abnormally expressed serum markers with CBF in the ischemic regions

As depicted in **Table 3**, correlation analysis suggested that CBF values in the ischemic brain region were not associated with IMA and BDNF levels. Similarly, the stratification of the patients in the CCH group according to CBF quartiles (**Table 4**) showed no significant difference in the serum IMA and BDNF concentrations between those with the lowest CBF (< 15.76 mL/100 g/min) and with highest CBF groups (> 32.28 mL/100 g/min).

ROC curve analysis of the diagnostic serum biomarkers for CCH

As illustrated in **Figure 1**, the ROC curve analysis revealed that a cut-off value of 24.2915 U/

Table 1. Comparison of the general information between the CCH and non-CCH groups

Characteristic	CCH group (*n* = 55)	Non-CCH group (*n* = 29)	*p*-value
Age (years)	63.35 ± 7.658	60.28 ± 8.964	0.110
Male	23/55	9/29	0.333
Smoking	13/55	2/29	0.057
Alcohol consumption	15/55	3/29	0.072
Hypertension	21/55	8/29	0.331
Diabetes	7/54	3/29	0.513
FBG level (mmol/L)	5.24 (4.95-5.75)	4.99 (4.6-5.92)	0.240
ApoA1/B	1.6 (1.3-1.9)	1.8 (1.25-2.1)	0.406
Hcy level (mmol/L)	12.4 (10.5-14.7)	11 (9.7-13.1)	0.182
Uric acid level (mmol/L)	312.15 ± 70.458	325.48 ± 65.034	0.401
TC level (mmol/L)	5.123 ± 0.944	4.375 ± 1.059	0.001
TG level (mmol/L)	1.67 (1.12-2.37)	1.44 (1.105-2.15)	0.463
LDL level (mmol/L)	3.219 ± 0.842	2.604 ± 0.849	0.002
HDL level (mmol/L)	1.457 ± 0.298	1.302 ± 0.27	0.019
N-HDL level (mmol/L)	3.666 ± 0.899	3.073 ± 1.029	0.008

CCH: chronic cerebral hypoperfusion; FBG: fasting blood glucose; Hcy: homocysteine; TC: total cholesterol; TG: triglycerides; LDL: low-density lipoprotein; HDL: high-density lipoprotein; N-HDL: normal high-density lipoprotein.

Table 2. Comparison of serum marker levels between the CCH and non-CCH groups

Serum marker	CCH group (*n* = 55)	Non-CCH group (*n* = 29)	*p*-value
VILIP-1 level (pg/mL)	71.852 ± 19.007	63.806 ± 20.786	0.078
BDNF level (ng/mL)	7.606 (6.076-8.897)	7.966 (7.184-8.944)	0.049
IMA level (U/mL)	27.581 (24.921-31.507)	23.417 (21.261-27.545)	< 0.001
Lp-PLA2 level (ng/mL)	303.475 (254.044-364.351)	278.588 (249.83-319.742)	0.119

CCH: chronic cerebral hypoperfusion; VILIP-1: visinin-like protein-1; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin; Lp-PLA2: lipoprotein-associated phospholipase A2.

Table 3. Association between serum marker levels and CBF in the ischemic regions

Serum marker	Correlation coefficient	*p*-value
BDNF level (ng/mL)	-0.058	0.672
IMA level (U/mL)	-0.078	0.573

CBF: cerebral blood flow; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin.

mL for IMA achieved a sensitivity of 83.6%, specificity of 62.1%, and AUC of 0.738 (95% confidence interval [CI], 0.627-0.848). Correspondingly, a cut-off value of 6.714 ng/L for BDNF yielded a sensitivity of 41.8%, specificity of 93.1%, and AUC of 0.631 (95% CI, 0.512-0.751), as presented in **Figure 2**. Additionally, the combined AUC was 0.803 (95% CI, 0.708-0.898; **Figure 3**), with no significant diagnostic difference between IMA and BDNF (Z = 1.166; P > 0.05; **Figure 4**).

Predictive efficacy analysis of IMA and BDNF and their combined model for diagnosing CCH

CCH status served as state variable (CCH group = 1, non-CCH group = 0), while IMA and BDNF were designated as test variables for ROC curve analysis. As detailed in **Table 5** and **Figure 5**, the combined "IMA+BDNF" prediction model had an AUC of 0.803 (95% CI, 0.708-0.898; P < 0.001), specificity of 0.655, sensitivity of 0.855, and a Youden's index of 0.510 for diagnosing CCH. Additionally, IMA exhibited an AUC of 0.738 (95% CI, 0.627-0.848; P < 0.001), specificity of 0.621, sensitivity of 0.836, and a Youden's index of 0.457, along with an optimal cut-off value of 24.292 U/mL for detecting CCH. Finally, BDNF displayed an AUC of 0.631 (95% CI, 0.512-0.751; P = 0.049), specificity of 0.931, sensitivity of 0.418, and a Youden's index of 0.349, using an optimal cut-off value of 6.714 ng/L for predicting CCH occurrence.

Table 4. Comparison of abnormally expressed serum marker levels between the lowest (< 15.76 mL/100 g/min) and highest CBF (> 32.28 mL/100 g/min) groups

Serum marker	CBF < 15.76 mL/100 g/min (*n* = 13)	CBF > 32.28 mL/100 g/min (*n* = 12)	*p*-value
BDNF level (ng/mL)	7.467 ± 1.729	7.011 ± 1.452	0.982
IMA level (U/mL)	27.922 ± 4.308	28.324 ± 4.939	0.112

CBF: cerebral blood flow; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin.

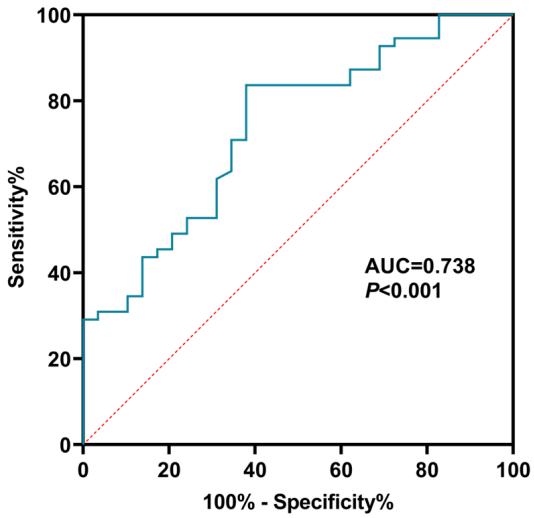

Figure 1. ROC curve of serum IMA for diagnosing CCH. ROC: receiver operating characteristic; IMA: ischemia-modified albumin; CCH: chronic cerebral hypoperfusion.

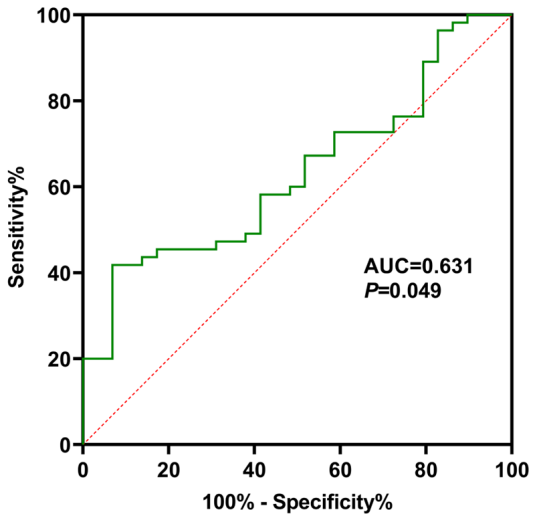

Figure 2. ROC curve of serum BDNF for diagnosing CCH. ROC: receiver operating characteristic; BDNF: brain-derived neurotrophic factor; CCH: chronic cerebral hypoperfusion.

Discussion

Chronic cerebral hypoperfusion (CCH) is a pathologic condition in which oxygen supply to the intracranial brain parenchyma falls below the requisite level for maintaining normal physiological function, potentially due to changes in the intracranial and extracranial vascular walls, blood flow components, or blood flow mechanics. However, further clarification is required on the pathogenesis of CCH, which possibly arises from various diseases and manifests as an early alteration in neurological conditions like acute ischemic stroke, vascular dementia, Alzheimer's disease, transient ischemic attack, and cerebrovascular disease [9, 10]. In this study, we revealed that the hypoperfusion regions in patients with CCH were predominantly located in the cerebral cortex areas such as the frontal, parietal, and occipital lobes, consistent with previous study findings [11]. The aging population is gradually increasing, with the population of older adults aged ≥ 65 years reaching 16.7 billion in 2018 and accounting for 11.9% of the total population in China. CCH, as a reversible disease, commonly occurs in middle-aged and older people, exhibiting a hidden onset, nonspecific clinical symptoms, and no obvious neurological signs during physical examination. However, detecting lesions using conventional head CT or MRI can be challenging, thereby hindering timely screening and administration of clinical treatment. Therefore, identifying accurate and effective indicators to aid in the early screening of CCH in middle-aged and older populations and provide intervention during the early stage is critical to improving patient prognosis. CCH is primarily caused by insufficient CBF in the whole brain or local regions for maintaining normal physiological requirements [12].

CCH diagnosis typically relies on confirmation by imaging techniques. However, these clinical imaging tests are limited by high cost and risks associated with contrast-enhanced imaging [13]. Moreover, patients may have already reached the stage of decompensated cerebral ischemia at the time of imaging-based CCH diagnosis, rendering this approach unsuitable for the initial screening of suspected CCH cases. Hence, cost-effective and convenient

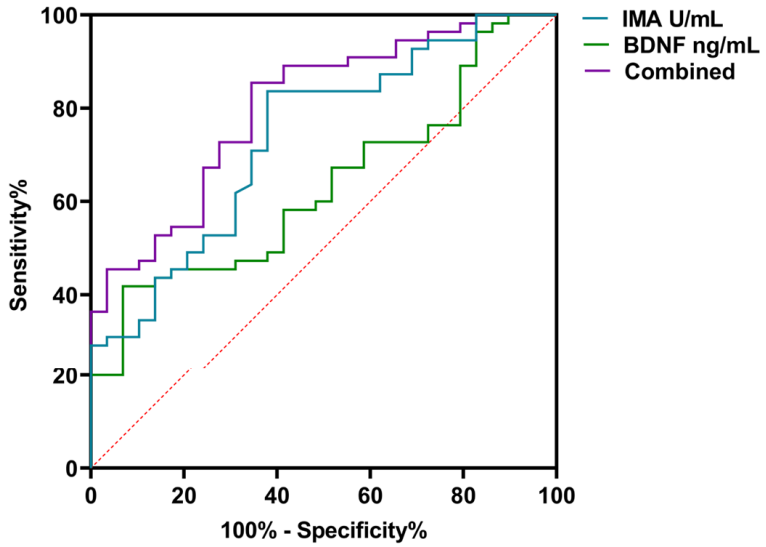

Figure 3. ROC curves of serum IMA and BDNF and their combination for diagnosing CCH. ROC: receiver operating characteristic; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin; CCH: chronic cerebral hypoperfusion.

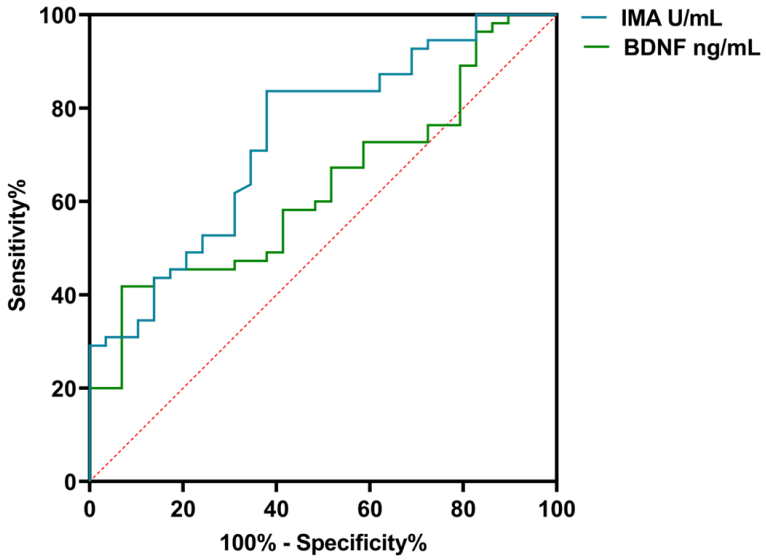

Figure 4. ROC comparative analysis of serum BDNF and IMA by the DeLong test (Z = 1.166; P > 0.05). ROC: receiver operating characteristic; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin.

serum biomarkers with high sensitivity are warranted for early detection of CCH.

IMA can serve as a screening biomarker for CCH. It is a protein generated due to changes induced in the amino acid sequence of albumin by substances such as free radicals, leading to altered albumin-binding capacity and decreased transition metal binding during the ischemia-reperfusion process [14]. Thus, IMA is sensitive to ischemic events. IMA has been proposed as an early nonspecific biomarker associated with ischemia and oxidative stress in various diseases, including myocardial infarction, acute ischemic stroke, diabetes, renal failure, and hyperthyroidism [15, 16]. IMA has also demonstrated prognostic value in patients with acute ischemic stroke [17]. Given the possibility of oxidative stress in patients with decreased cerebral tissue perfusion and CCH [18], we further analyzed the diagnostic ability of IMA for detecting CCH. The intergroup comparison revealed significantly elevated serum IMA levels in the CCH group. Furthermore, the ROC curve analysis showed that serum IMA had a sensitivity of 83.6%, specificity of 62.1%, and AUC of 0.738 for independently diagnosing CCH. These findings suggest that IMA can not only serve as a marker for acute ischemic events but also have a high sensitivity for early screening of CCH.

While IMA proves beneficial in identifying CCH, it does not allow quantitative correlation with the degree and duration of chronic ischemia. Additionally, a poor correlation exists between IMA levels and ASL-estimated CBF in ischemic areas, with no differences found in the IMA levels of patients with different disease durations. Similar results were reported in myocardial ischemia studies, wherein IMA was found to be sensitive to myocardial ischemia but could not reflect the extent of ischemia [19]. This observation may be attributed to the high sensitivity of IMA to ischemia, the dynamic changes in serum IMA levels following acute ischemia, and IMA susceptibility to interference from concur-

Table 5. Analysis of the efficacy of IMA and BDNF and their combination for diagnosing CCH

Serum marker	Cut-off value	AUC	95% CI		*p*-value	Specificity	Sensitivity	Youden's index
			Lower limit	Upper limit				
IMA+BDNF	-	0.803	0.708	0.898	< 0.001	0.655	0.855	0.510
IMA	24.292	0.738	0.627	0.848	< 0.001	0.621	0.836	0.457
BDNF	6.714	0.631	0.512	0.751	0.049	0.931	0.418	0.349

CCH: chronic cerebral hypoperfusion; BDNF: brain-derived neurotrophic factor; IMA: ischemia-modified albumin.

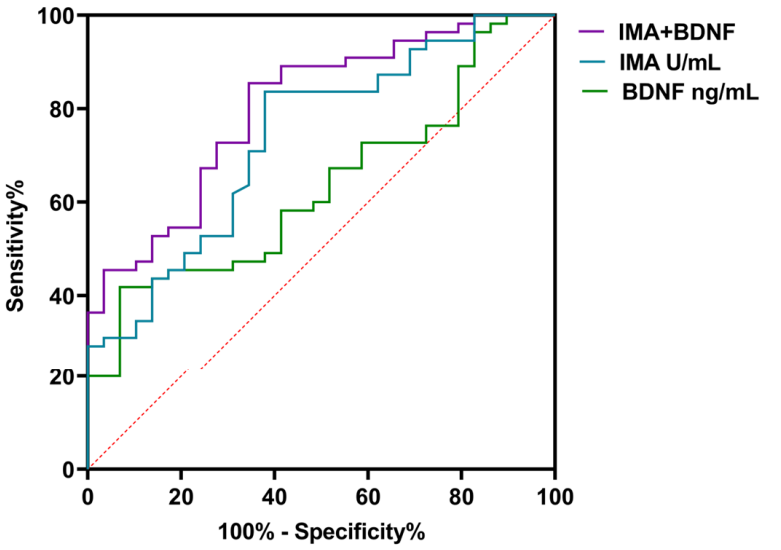

Figure 5. ROC curves of IMA and BDNF and their combination for diagnosing CCH, with sensitivity and specificity expressed as percentages. ROC: receiver operating characteristic; IMA: ischemia-modified albumin; BDNF: brain-derived neurotrophic factor; CCH: chronic cerebral hypoperfusion.

rent diseases, medications, and lifestyle habits [20, 21]. Another study suggested that continuous ischemia and hypoxia could lead to the accumulation of anaerobic metabolites and the increased production of free radicals in local brain tissue. These alterations result in a gradual increase in serum IMA levels within 12 h of acute CBF reduction, followed by a decline between 12 h and 24 h owing to the compensatory collateral circulation and the decreased release of free radicals [22]. Similar dynamic changes in serum IMA levels may also be present in CCH, which arises from comparable mechanisms.

BDNF is another CCH candidate biomarker displaying high specificity, with decreased BDNF concentration associated with CCH. Our data revealed diminished BDNF levels in the CCH group, with BDNF demonstrating a sensitivity of 41.8%, specificity of 93.1%, and AUC of 0.631 for independently diagnosing CCH. BDNF is a neurotrophic factor critical for the growth, development, differentiation, maintenance, and regeneration of various types of neurons in the central nervous system [23]. A previous study reported that blood BDNF concentrations could reflect brain-tissue BDNF levels across species [24]. Moreover, BDNF was recently suggested to induce the endothelium-dependent relaxation of precontracted peripheral isolated vessels and cerebral arteries by stimulating prostacyclin production [25, 26]. Other research suggested that BDNF may also exert a pro-angiogenic effect [27, 28]. Furthermore, low BDNF levels in healthy individuals are associated with an increased risk of future stroke/transient ischemic attack [29], and significantly reduced BDNF levels have been observed in patients with acute ischemic stroke [8]. Oxidative stress is one of the key factors causing ischemic brain injury. BDNF may prevent this oxidative stress reaction by multiple pathways, thereby reducing brain cell damage [30, 31]. However, the high specificity of BDNF for the diagnosis of CCH implies that its isolated application may lead to potential missed diagnosis. Finally, as noted for serum IMA concentration, BDNF level cannot reflect the extent of CBF reduction in the ischemic area.

To our knowledge, this study is the first to investigate the altered levels and diagnostic efficacy of multiple serum markers in patients with CCH, offering insights for their clinical applications. However, this research only included patients admitted to a single center and had a small sample size, leading to potential selec-

tion bias. Therefore, further large-scale, multicenter studies are warranted to validate these findings.

Conclusions

Patients with CCH exhibit increased IMA and decreased BDNF serum levels. While IMA demonstrates high sensitivity and BDNF has high specificity for CCH screening, both markers show promise for clinical diagnosis of CCH.

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Disclosure of conflict of interest

None.

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