Am J Transl Res 2024;16(6):2369-2378
www.ajtr.org /ISSN:1943-8141/AJTR0155170

Original Article

Diagnostic efficacy of ACA, aβ2-GP1, hs-CRP, and Hcy for cerebral infarction and their relationship with the disease severity

Xuefeng Shang[1], Jinhong Li[2], Xiaohui Wang[2], Pengxuan Zhang[1]

[1]Department of Neurology, Yanan University Affiliated Hospital, Yan'an 716000, Shaanxi, China; [2]Department of Radiology, Yanan University Affiliated Hospital, Yan'an 716000, Shaanxi, China

Received December 29, 2023; Accepted February 28, 2024; Epub June 15, 2024; Published June 30, 2024

Abstract: Objective: To evaluate the diagnostic efficacy of anti-cardiolipin antibodies (ACA), anti-β2-glycoprotein I antibodies (aβ2-GP1), high-sensitivity C-reactive protein (hs-CRP), and homocysteine (Hcy) in cerebral infarction and to explore their relationship with disease severity. Methods: Medical records of 67 cerebral infarction patients admitted from May 2020 to January 2023 and 50 healthy individuals undergoing health checkups were retrospectively analyzed. The levels of ACA, aβ2-GP1, hs-CRP, and Hcy were compared, their correlation with National Institutes of Health Stroke Scale (NIHSS) scores was assessed, and their diagnostic efficacy across different disease severities were evaluated. A joint predictive score formula, defined as -6.054712173 + aβ2-GP1*1.906727231 + Hcy*0.576221974, which combines aβ2-GP1 and Hcy levels, was developed to assess the likelihood of cerebral infarction in our study population. Results: The levels of ACA, aβ2-GP1, hs-CRP and Hcy, and joint predictive score were significantly higher in the patient group (all $P < 0.001$). ROC analysis yielded AUCs of 0.887 for ACA, 0.894 for aβ2-GP1, 0.899 for hs-CRP, 0.880 for Hcy, and 0.954 for the joint predictive score. Delong's test showed no statistical difference in most indicators compared to the joint predictive score ($P > 0.05$), except aβ2-GP1 ($P < 0.05$). Pearson's correlation analysis indicated that aβ2-GP1, Hcy, and the joint predictive score were positively correlated of with NIHSS score (all $P < 0.05$), while ACA and hs-CRP were not ($P > 0.05$). Notable differences in aβ2-GP1 and the joint predictive score were observed among varying severity levels ($P < 0.01$), with the joint predictive score showing superior diagnostic efficacy in distinguishing between mild and moderate/severe cases ($P < 0.01$). Conclusion: ACA, aβ2-GP1, hs-CRP, and Hcy are effective biomarkers for diagnosing cerebral infarction, and are positively correlated with disease severity. The joint predictive score demonstrates enhanced accuracy in discerning degree of severity.

Keywords: Anti cardiolipin antibody, aβ2-GP1, hs-CRP, Hcy, cerebral infarction

Introduction

Stroke, increasingly prevalent in aged populations, is a leading cause of death and disability worldwide [1, 2]. In particular, ischemic stroke, the most common subtype, poses significant public health challenges, especially in regions such as China, where its incidence exceeds that of heart disease [3, 4]. The rapid progression of stroke, which can cause irreversible brain damage within minutes, underscores the critical need for advanced diagnostic tools [5].

Although traditional risk factors such as hyperlipidemia, atherosclerosis, hypertension, atrial thrombosis, smoking, and diabetes mellitus are well established [6-8], they do not fully account for all cases of stroke, suggesting unidentified risk factors and diagnostic gaps [9, 10]. Current research on various biomarkers for stroke diagnosis points to their limitations in sensitivity, specificity, or adaptability across diverse patient groups, underscoring the necessity for broader and adaptable diagnostic methods [11-13].

Recognizing the limitations of cranial CT in diagnosing acute cerebral infarction, our study suggests that a more comprehensive approach may improve diagnostic accuracy. While cranial CT remains a critical tool for confirming cerebral infarction, it fails to elucidate underlying pathophysiological processes and disease progression [14]. To bridge this gap, we turn to the combined role of specific biomarkers. Inflammation and oxidative stress have been recognized as significant contributors to stroke [15], paving

the way for biomarkers such as anti-cardiolipin antibody (ACA), anti-β2-glycoprotein I antibody (aβ2-GP1), high-sensitivity C-reactive protein (hs-CRP), and homocysteine (Hcy) to emerge as potential indicators of cerebral infarction risk [16]. Our study introduces a novel perspective by focusing on these biomarkers, not only as isolated metrics but as a collective panel that may reflect the complex interplay of factors contributing to stroke.

The utility of ACA, aβ2-GP1, hs-CRP, and Hcy goes beyond simple risk assessment; these biomarkers may provide deeper insights into inflammation, vascular integrity, and coagulation status, which are critical for stroke onset and progression. By analyzing these biomarkers, our research aims to provide a more subtle understanding of acute cerebral infarction, potentially facilitating early detection, precise risk assessment, prognostication, and tailored therapeutic strategies [17]. Thus, our investigation seeks to establish a more integrative diagnostic model that complements traditional imaging techniques and captures the complex biological narrative of stroke.

Therefore, this study aims to fill this gap by analyzing the collective and individual performance of these biomarkers in diagnosing acute cerebral infarction. We seek to improve the diagnostic process for stroke by addressing the limitations of current studies and potentially leading to improved strategies for prediction, prevention, and treatment.

Materials and methods

Patient source

We conducted a retrospective analysis of medical records from patients with cerebral infarction admitted to Yanan University Affiliated Hospital between May 2020 and January 2023. Data collected from individuals undergoing routine medical checkups during this period, served as the normal controls. This study was approved by the Yanan University Affiliated Hospital Ethics Committee with approval number of L2020184.

Inclusion-exclusion criteria for patient cohort

Inclusion criteria: (1) Diagnosis of acute cerebral infarction for the first time, confirmed by CT or MRI, adhering to the 2018 diagnostic criteria for acute ischemic cerebral infarction established by the Neurology Section of the Chinese Medical Association [18]. (2) Age above 18. (3) Onset within 72 hours before admission. (4) Availability of complete clinical data for analysis.

Exclusion criteria: (1) Conditions of hyperthyroidism, hypothyroidism, severe malnutrition, or hepatic or renal insufficiency. (2) Presence of various systemic malignancies, acute or chronic infections, hematologic disorders, connective tissue disorders, or autoimmune disorders. (3) A history of cerebral hemorrhage. (4) A recent history of surgical procedures or trauma. (5) A previous episode of cerebral infarction.

Inclusion-exclusion criteria for healthy population

Inclusion criteria: (1) Normal results in all clinical, biochemical, microbiological, and immunological indices. (2) Availability of complete clinical information and laboratory test data. (3) Age above 18.

Exclusion criteria: (1) Recent surgery or radiotherapy. (2) Presence of malignant tumors or congenital defective diseases.

Sample screening and grouping

Out of 284 patients, 117 eligible individuals were selected as the patient group based on inclusion and exclusion criteria. From 184 samples in the normal population, 50 eligible individuals were chosen as the normal group. Patients were categorized into mild (the National Institutes of Health Stroke Scale (NIHSS) score 2-7), moderate (8-14), and severe (≥ 15) groups based on their NIHSS scores.

Clinical data collection

Clinical and laboratory data, including age, gender, BMI, smoking history, hypertension, diabetes, ACA, aβ2-GP1, hs-CRP, Hcy, and NIHSS, were collected from both groups. Laboratory indices represent pre-treatment results obtained upon hospital admission. The aβ2-GP1 and Hcy levels were calculated as diagnostic parameters by logistic regression, whereas ACA and hs-CRP resulted in the presence of 0 or 1 values in the model prediction values, therefore exclusion occured. The predictive score formula = -6.054712173 + aβ2-GP1*1.906727231 + Hcy*0.576221974. Specific values for each case were calculated by the formula.

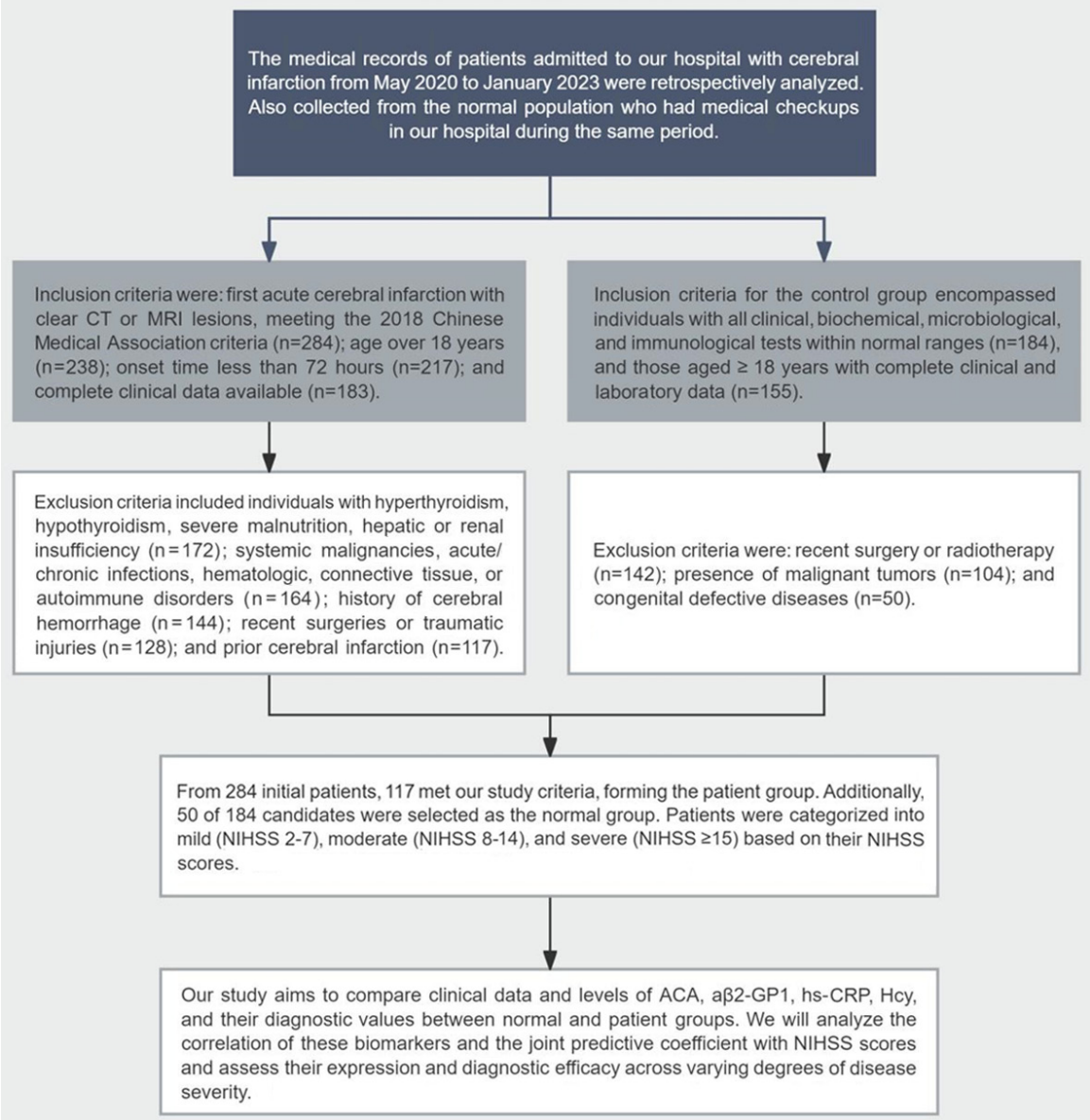

Figure 1. Sample inclusion exclusion flowchart.

Indicator testing

The serum was separated by centrifugation at 3000 rpm for 10 minutes. Hcy levels were detected using an AU5800 automatic biochemistry analyzer (Beckman), hs-CRP levels with a BNII particular protein analyzer (Siemens), and aβ2-GP1 (mI057833, Shanghai mibio) and ACA (mI063368, Shanghai mibio) titers were measured using enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions. (All the above are detection methods. We only collected the data of patients and did not conduct direct serum test for patients).

Outcome measurement

Main indicators: The levels of ACA, aβ2-GP1, hs-CRP and Hcy were compared between the normal group and the patient group, and the diagnostic value of these biomarkers for cerebral infarction was analyzed. The expression and diagnostic efficacy of aβ2-GP1, Hcy, and joint prediction coefficients were compared across patients with different disease severity.

Secondary indicators: The differences in baseline data were compared between the two groups of patients (**Figure 1**).

Table 1. Comparison of clinical baseline data

Variant	Normal group (n = 50)	Patient group (n = 67)	χ^2-value	*P*-value
Age				
≥ 65 years	28	40	0.161	0.688
< 65 years	22	27		
Gender				
Male	27	30	0.975	0.323
Female	23	37		
BMI				
≥ 25 kg/m^2	12	12	0.651	0.420
< 25 kg/m^2	38	55		
Smoking history				
Yes	20	25	0.087	0.768
No	30	42		
History of hypertension				
Yes	13	22	0.638	0.424
No	37	45		
History of diabetes				
Yes	8	12	0.074	0.786
No	42	55		

Note: BMI, body mass index.

Statistical analysis

Data were analyzed using SPSS 26.0 and GraphPad 9 for graphical representations. Measurement data were expressed as mean ± standard deviation (Mean ± SD). Group comparisons utilized independent samples t-tests, while count data were represented as percentages (%) using the chi-square test. The diagnostic value of each marker was assessed using Receiver Operating Characteristic (ROC) curves, with the area under the curve (AUC) indicating clinical significance. AUC differences among markers were analyzed using the Delong test. P < 0.05 indicated statistical significance.

Results

Comparison of baseline information

Upon comparing the clinical data of the normal population with that of the patients, we observed no statistical differences in age, gender, BMI, smoking history, and histories of hypertension and diabetes mellitus between the two groups (all P > 0.05, **Table 1**).

Diagnostic value of ACA, aβ2-GP1, hs-CRP, and Hcy for cerebral infarction

We further compared the serum levels of ACA, aβ2-GP1, hs-CRP, and Hcy between the normal and patient groups. Our findings indicated that these levels, along with the predictive score, were significantly higher in the patient group compared to the normal group (all P < 0.001, **Table 2**). ROC curve analysis revealed that the AUCs for ACA, aβ2-GP1, hs-CRP, Hcy, and the predictive score (predictive score formula = -6.054712173 + aβ2-GP1*1.906727231 + Hcy* 0.576221974) were 0.887, 0.894, 0.899, 0.880, and 0.954, respectively, suggesting a high diagnostic value of the prediction coefficient in cerebral infarction (**Figure 2**; **Table 3**). However, Delong's test showed that, except for the AUC of aβ2-GP1, which was smaller than the predictive score, there were no significant differences between the other indicators and the predictive score (P > 0.05, **Table 4**), indicating that the predictive score does not significantly improve its diagnostic accuracy for cerebral infarction.

Correlation analysis of ACA, aβ2-GP1, hs-CRP, Hcy, and predictive score with disease severity

Patients were categorized into mild (n = 26), moderate (n = 21), and severe (n = 20) groups based on NIHSS scores. We analyzed the relationships between ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score with NIHSS scores using Pearson's test. The results indicated that aβ2-GP1, Hcy, and predictive score were positively correlated with NIHSS scores (all P < 0.05, **Figure 3**), whereas ACA and hs-CRP were not (P > 0.05, **Figure 3**).

Expression across different disease levels

Our correlation analysis revealed positive associations of aβ2-GP1, Hcy, and joint predictive score with NIHSS scores. We further compared their expressions in patients with different disease severities. It was found that aβ2-GP1 and the joint predictive score varied among different disease groups (P < 0.01, **Figure 4**). However, no significant difference in Hcy levels was observed between the moderate and severe groups (P > 0.05, **Figure 4**).

Table 2. Expression levels of ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score in two groups

Variables	Normal group (n = 50)	Patient group (n = 67)	t/Z value	*P*-value
ACA (RU/mL)	4.42±1.11	13.98±8.07	9.586	< 0.001
aβ2-GP1 (RU/mL)	0.85 [0.60, 1.28]	3.30 [2.10, 4.50]	7.281	< 0.001
hs-CRP (mg/L)	7.92±2.32	18.00±7.26	10.663	< 0.001
Hcy (μmol/L)	3.42±1.51	9.00±4.06	10.341	< 0.001
Predictive score	-2.24±1.27	5.30±3.74	15.355	< 0.001

Note: ACA, anti-cardiolipin antibody; aβ2-GP1, anti-β2-glycoprotein I antibodies; hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine.

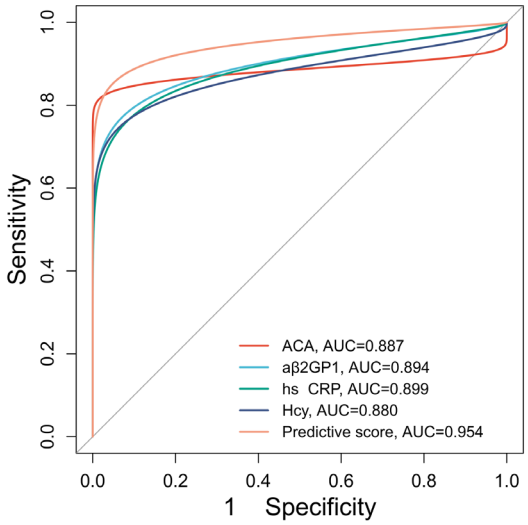

Figure 2. ROC curves of ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score in the diagnosis of cerebral infarction. Note: ACA, anti-cardiolipin antibody; aβ2-GP1, anti-β2-glycoprotein I antibodies; hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine.

Efficacy in differentiating disease severity

Finally, we assessed the efficacy of aβ2-GP1 and the joint predictive score in differentiating patients with varying disease severities through ROC curves. The analysis showed that the diagnostic efficacy of the joint predictive score was comparable to that of aβ2-GP1 in differentiating moderate and severe disease. However, it outperformed aβ2-GP1 in distinguishing between mild and moderate groups and mild and severe groups (all P < 0.01, **Figure 5**; **Tables 5**, **6**).

Discussion

In our research, we observed that ACA, aβ2-GP1, hs-CRP, Hcy, and the predictive score were notably higher in the patient group compared to the normal group. ROC analysis revealed that the AUCs for ACA, aβ2-GP1, hs-CRP, Hcy and predictive score were 0.887, 0.894, 0.899, 0.880, and 0.954, respectively. These findings align with previous research by Hua et al. [19], which reported an AUC of 0.896 for diagnosing large atherosclerotic cerebral infarcts using serum lipoprotein-associated phospholipase A2 combined with myeloperoxidase. Furthermore, Cao et al. [20] noted an elevation in miR-497 expression in patients with atherosclerotic cerebral infarction, with its AUC for predicting recurrence and poor prognosis being 0.924 and 0.937, respectively. Such findings underscore the potential of serum markers in diagnosing and prognosticating large-artery diseases, particularly atherosclerotic cerebral infarction. Our study reinforces the role of serum biochemical markers as invaluable tools for risk assessment and prognostic prediction in atherosclerotic cerebral infarction. However, it is noteworthy that in the Delong test, no significant difference was observed, and the AUC of aβ2-GP1 was slightly lower than the AUC of predictive score. This discrepancy could be attributed to the complex interplay of these biomarkers, the combined effect of the predictive score, and individual physiological variances.

The critical role of these biomarkers in cardiovascular disease progression and prognosis has been emphasized in prior studies. Wang et al. [21] identified a correlation between elevated hs-CRP levels and poor clinical outcomes in patients with acute ischemic stroke undergoing endovascular therapy. Su et al. [22] highlighted that a transient increase in ACA might signify or serve as a biomarker for thrombotic cardiac events in young atherosclerotic patients. Xu et al. [23] observed a significant rise in coronary artery disease risk among current smokers, particularly in aβ2-GP1 IgM-positive patients. The risk of subsequent cardiovascular events,

Table 3. ROC parameters of ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score in the diagnosis of cerebral infarction

Markers	AUC	95% CI	Cut off	Specificity	Sensitivity	Youden index
ACA	0.887	0.815-0.887	6.25	98.00%	82.09%	80.09%
aβ2-GP1	0.894	0.833-0.894	1.75	98.00%	82.09%	80.09%
hs-CRP	0.899	0.839-0.899	12.15	98.00%	79.10%	77.10%
Hcy	0.880	0.814-0.880	6.05	100.00%	77.61%	77.61%
Predictive score	0.954	0.913-0.954	0.486	100.00%	91.04%	91.04%

Note: ACA, anti-cardiolipin antibody; aβ2-GP1, anti-β2-glycoprotein I antibodies; hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine.

Table 4. Comparison of AUCs for ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score in diagnosing cerebral infarction

Marker1	Marker2	Z value	*P* value	AUC difference	95% CI
ACA	aβ2-GP1	-0.150	0.881	-0.007	-0.105-0.090
ACA	hs-CRP	-0.269	0.788	-0.011	-0.095-0.072
ACA	Hcy	0.126	0.900	0.007	-0.098-0.111
ACA	Predictive score	-1.527	0.127	-0.067	-0.154-0.019
aβ2-GP1	hs-CRP	-0.095	0.924	-0.004	-0.087-0.079
aβ2-GP1	Hcy	0.326	0.745	0.014	-0.071-0.099
aβ2-GP1	Predictive score	-2.244	0.025	-0.06	-0.112--0.008
hs-CRP	Hcy	0.38	0.704	0.018	-0.076-0.112
hs-CRP	Predictive score	-1.49	0.136	-0.056	-0.129-0.018
Hcy	Predictive score	-2.534	0.011	-0.074	-0.131--0.017

Note: ACA, anti-cardiolipin antibody; aβ2-GP1, anti-β2-glycoprotein I antibodies; hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine.

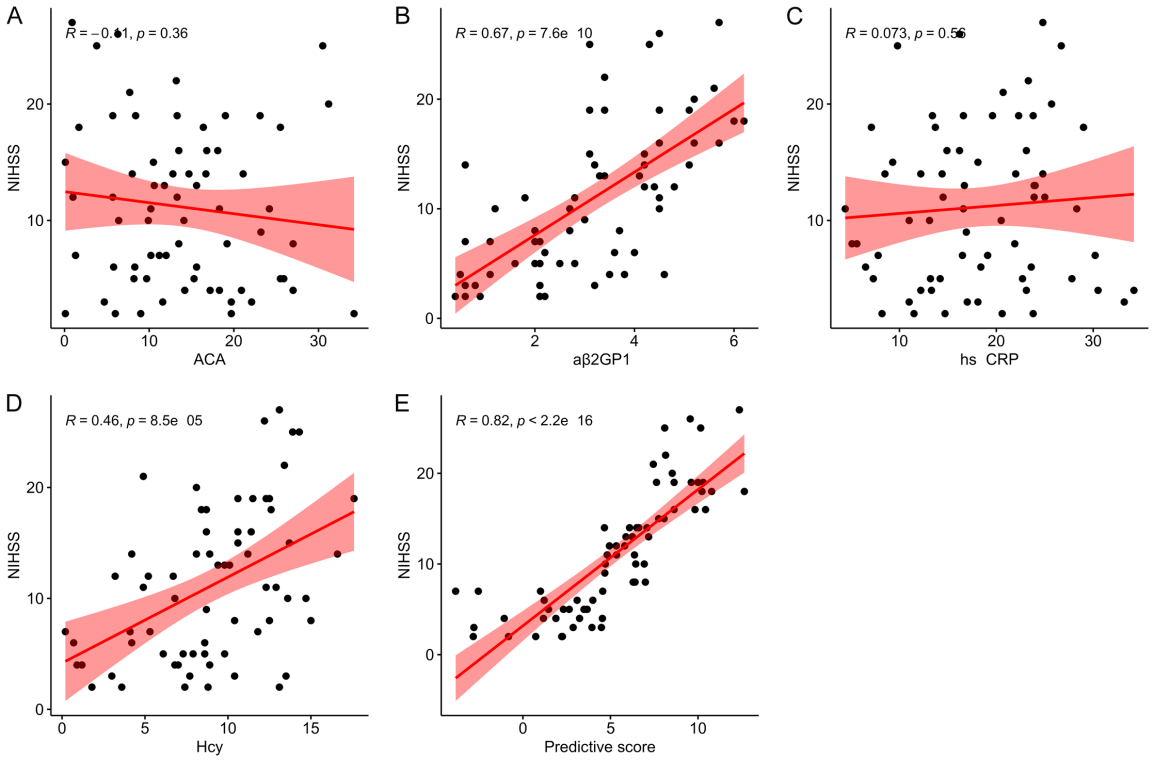

Figure 3. Correlation analysis of ACA, aβ2-GP1, hs-CRP, Hcy, and joint predictive score with NIHSS. A. Correlation analysis between ACA and NIHSS scores. B. Correlation analysis between aβ2-GP1 and NIHSS score. C. Correlation analysis between hs-CRP and NIHSS score. D. Correlation analysis between Hcy and NIHSS score. E. Correlation analysis between predictive score and NIHSS scores. Note: ACA, anti-cardiolipin antibody; aβ2-GP1, anti-β2-glycoprotein I antibodies; hs-CRP, high-sensitivity C-reactive protein; Hcy, homocysteine; NIHSS, the National Institutes of Health Stroke Scale.

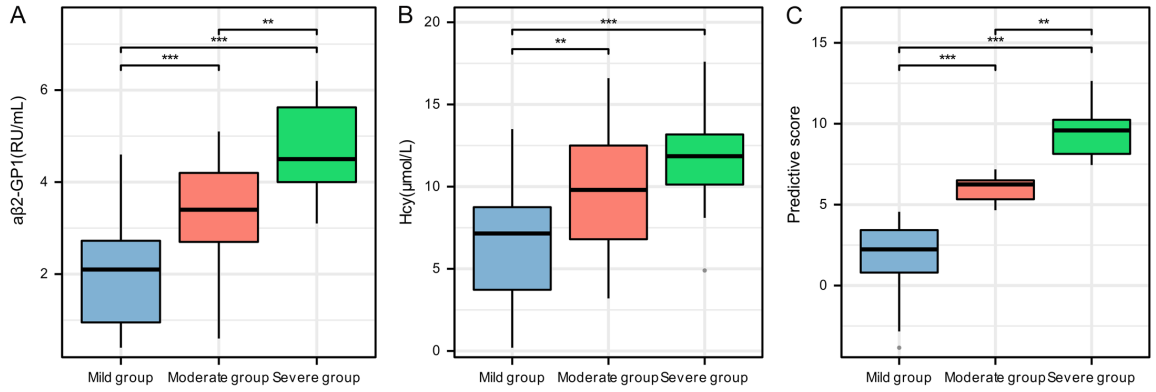

Figure 4. Expression levels of aβ2-GP1 and Hcy, and joint predictive score in patients with different disease severity. A. Expression of aβ2-GP1 in patients with different disease severity. B. Expression of Hcy in patients with different disease severity. C. Joint prediction score in patients with different disease severity. Note: aβ2-GP1, anti-β2-glycoprotein I antibodies; Hcy, homocysteine.

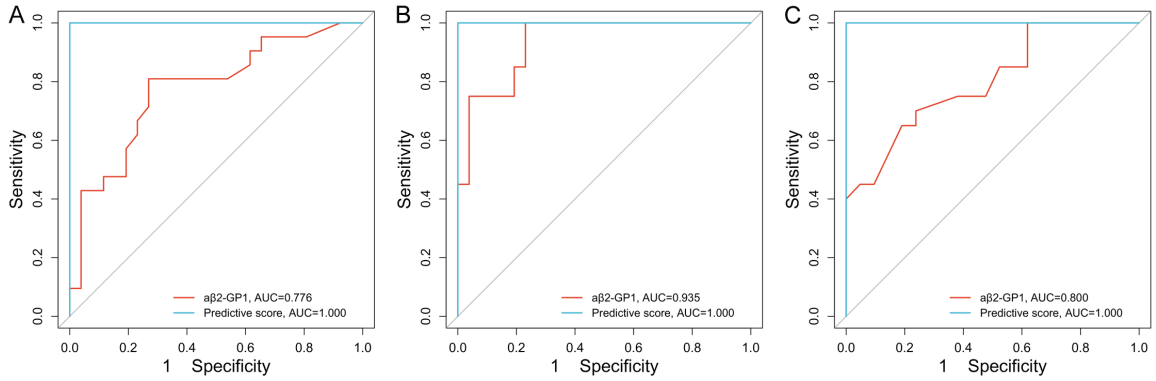

Figure 5. ROC curves of aβ2-GP1 and joint predictive score in distinguishing patients with different disease severity. A. Diagnostic efficacy of aβ2-GP1 and joint predictive score in the mild versus moderate group. B. Diagnostic efficacy of aβ2-GP1 and joint predictive score in the mild versus severe group. C. Diagnostic efficacy of aβ2-GP1 and joint predictive score in the moderate versus severe group. Note: aβ2-GP1, anti-β2-glycoprotein I antibodies.

including recurrent myocardial infarction and in-stent restenosis, was also found to be notably heightened in the smokers with IgM-type aPL positivity. Subsequent studies [24] have linked aβ2-GP1 with ischemic stroke, enhancing its diagnostic power for stroke risk. Ren et al. [25] reported an association between serum Hcy level, elevated lipid level, inflammation, infarct size, and major adverse cardiac events (MACE) risk in acute myocardial infarction patients. Collectively, these studies highlight the pivotal role of biomarkers like hs-CRP, ACA, aβ2-GP1, and Hcy in cardiovascular disease onset, progression, and prognosis, thereby contributing significantly to the diagnostic, preventive, and therapeutic strategies for these conditions.

The NIHSS, a comprehensive index for assessing neurological deficits in stroke patients, includes evaluations of consciousness, vision, motor function, sensation, speech, and language skills, each with a designated score [26]. Our study revealed that ACA, aβ2-GP1, hs-CRP,

Table 5. ROC parameters of aβ2-GP1 and joint predictive score in differentiating patients with different disease severity

Group	Marker	AUC	Cut off	95% CI	Specificity	Sensitivity	Youden index
Mild-moderate	aβ2-GP1	0.776	2.6	0.638-0.776	73.08%	80.95%	54.03%
Mild-moderate	Prediction score	1	4.606	1.000-1.000	100.00%	100.00%	100.00%
Moderate-Severe	aβ2-GP1	0.935	2.95	0.869-0.935	76.92%	100.00%	76.92%
Moderate-Severe	Prediction score	1	6.002	1.000-1.000	100.00%	100.00%	100.00%
Mild-Severe	aβ2-GP1	0.8	4.25	0.666-0.800	76.19%	70.00%	46.19%
Mild-Severe	Prediction score	1	7.313	1.000-1.000	100.00%	100.00%	100.00%

Table 6. Comparison of AUCs of aβ2-GP1 and joint prediction score in differentiating patients with different disease severity

Group	Marker1	Marker2	Z value	*P* value	AUC difference	95% CI
Mild-moderate	aβ2-GP1	Prediction score	-3.192	0.001	-0.224	-0.362–0.087
Moderate-Severe	aβ2-GP1	Prediction score	-1.948	0.051	-0.065	-0.131-0.000
Mild-Severe	aβ2-GP1	Prediction score	-2.931	0.003	-0.200	-0.334–0.066

Hcy and combined predictive score were associated with NIHSS score. Pearson's test revealed a positive correlation between aβ2-GP1, Hcy, the combined predictive score and NIHSS scores, indicating a direct relationship with the severity of cerebral infarction. The positive correlations for aβ2-GP1 and Hcy may be attributed to their direct effects on cerebrovascular obstruction.

Conversely, the combined predictive score offer a more holistic assessment of cerebral infarction severity. No correlations were found between ACA, hs-CRP, and NIHSS scores, likely due to their lack of direct quantitative linkage with cerebral infarction severity. These findings suggest the necessity of an integrated approach combining multiple biomarkers and clinical indicators to assess and manage cerebral infarction effectively. Previous research supports this perspective. For instance, Wang et al. [27] demonstrated that plasma Hcy concentration, assessed via single-photon emission computed tomography, could serve as a diagnostic biomarker for postischemic hyperperfusion in patients with acute ischemic stroke. Furthermore, a recent study [28] underscored the crucial role of aβ2-GP1 antibody in antiphospholipid antibody syndrome, promoting platelet activation and thrombosis through the stimulation of the mTORC2/Akt signaling pathway. Our analysis indicated that aβ2-GP1 and the combined predictive score varied among patients with different disease severity. However, Hcy did not exhibit such variance between moderate and severe groups. ROC curve analysis demonstrated that the predictive score had comparable efficacy to aβ2-GP1 in differentiating patients of moderate and severe conditions. Moreover, the combined predictive score showed higher diagnostic efficiency in differentiating between mild, moderate, and severe groups than aβ2-GP1 alone. These observations underscore the importance of integrating multiple biomarkers in the decision-making process for diagnosing and treating cerebral infarction. Such an integrated approach is crucial for early detection of the severity of cerebral infarction and the development of effective treatment strategies.

Our study has some limitations, including a relatively small sample size and the absence of long-term follow-up data, which are crucial for substantiating the prognostic value of these indexes. Future studies should aim to collect more samples and conduct long-term follow-ups to solidify the validity of our conclusions.

Our study has demonstrated that ACA, aβ2-GP1, hs-CRP, and Hcy are valuable diagnostic markers for cerebral infarction. Additionally, these indicators positively correlate with the severity of the condition. However, the joint predictive score offers a more significant value in delineating the extent of the condition, highlighting the need for a comprehensive evaluation using multiple biomarkers in cerebral infarction management.

Disclosure of conflict of interest

None.

Address correspondence to: Pengxuan Zhang, Department of Neurology, Yanan University Affiliated Hospital, No. 94 Shuangyong Avenue, Baota District, Yan'an 716000, Shaanxi, China. E-mail: 263312584@qq.com

References

[1] Li L, Scott CA and Rothwell PM. Association of younger vs older ages with changes in incidence of stroke and other vascular events, 2002-2018. JAMA 2022; 328: 563-574.

[2] Yao H, Junna L, Hu Y, Sha X and Martikainen P. The relationship of income on stroke incidence in Finland and China. Eur J Public Health 2023; 33: 360-365.

[3] Zhou M, Wang H, Zeng X, Yin P, Zhu J, Chen W, Li X, Wang L, Wang L, Liu Y, Liu J, Zhang M, Qi J, Yu S, Afshin A, Gakidou E, Glenn S, Krish VS, Miller-Petrie MK, Mountjoy-Venning WC, Mullany EC, Redford SB, Liu H, Naghavi M, Hay SI, Wang L, Murray CJL and Liang X. Mortality, morbidity, and risk factors in China and its provinces, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019; 394: 1145-1158.

[4] Ouyang G, Liu Q, Wu Y, Liu Z, Lu W, Li S, Pan G and Chen X. The global, regional, and national burden of gallbladder and biliary tract cancer and its attributable risk factors in 195 countries and territories, 1990 to 2017: a systematic analysis for the Global Burden of Disease Study 2017. Cancer 2021; 127: 2238-2250.

[5] GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2023; 402: 203-234.

[6] Zheng D, Li X and Fu Y. Risk factors of acute cerebral infarction in patients with primary hypertension. Ir J Med Sci 2023; 192: 2441-2445.

[7] Yang Y, Huang Y, Yang H and Li X. Exploration of risk factors for acute myocardial infarction complicated with cerebral infarction. Panminerva Med 2020; 6: 1-10.

[8] Öcek L, Güner D, Uludağ İF, Tiftikçioğlu Bİ and Zorlu Y. Risk factors for hemorrhagic transformation in patients with acute middle cerebral artery infarction. Noro Psikiyatr Ars 2015; 52: 342-345.

[9] Duan J, Leng X, Han Z, Cai Y, Wang C, Rajah G, Song H, Ding Y and Ji X. Identifying biomarkers associated with venous infarction in acute/subacute cerebral venous thrombosis. Aging Dis 2021; 12: 93-101.

[10] Nakamori S, Matsuoka K, Kurita T, Kusagawa H and Katayama Y. Acute myocardial infarction and cardiogenic shock caused by a mobile thrombus in the ascending aorta unassociated with atherosclerosis. Eur Heart J 2009; 30: 2440.

[11] Zuo L, Zhang L, Zu J, Wang Z, Han B, Chen B, Cheng M, Ju M, Li M, Shu G, Yuan M, Jiang W, Chen X, Yan F, Zhang Z and Yao H. Circulating circular RNAs as biomarkers for the diagnosis and prediction of outcomes in acute ischemic stroke. Stroke 2020; 51: 319-323.

[12] Lee EC, Ha TW, Lee DH, Hong DY, Park SW, Lee JY, Lee MR and Oh JS. Utility of exosomes in ischemic and hemorrhagic stroke diagnosis and treatment. Int J Mol Sci 2022; 23: 8367.

[13] Montellano FA, Ungethum K, Ramiro L, Nacu A, Hellwig S, Fluri F, Whiteley WN, Bustamante A, Montaner J and Heuschmann PU. Role of blood-based biomarkers in ischemic stroke prognosis: a systematic review. Stroke 2021; 52: 543-551.

[14] de Oliveira EP, Fiebach JB, Vagal A, Schaefer PW and Aviv RI. Controversies in imaging of patients with acute ischemic stroke: AJR expert panel narrative review. AJR Am J Roentgenol 2021; 217: 1027-1037.

[15] Li C, Zhao Z, Luo Y, Ning T, Liu P, Chen Q, Chu Y, Guo Q, Zhang Y, Zhou W, Chen H, Zhou Z, Wang Y, Su B, You H, Zhang T, Li X, Song H, Li C, Sun T and Jiang C. Macrophage-disguised manganese dioxide nanoparticles for neuroprotection by reducing oxidative stress and modulating inflammatory microenvironment in acute ischemic stroke. Adv Sci (Weinh) 2021; 8: e2101526.

[16] Wang L, Guo X, Xu X, Xu S, Han J, Wang R, Guo Z, Yi F and Qi X. No association of homocysteine, anticardiolipin antibody, and anti-β2 glycoprotein I antibody with portal venous system thrombosis in liver cirrhosis. Clin Appl Thromb Hemost 2021; 27: 10760296211010969.

[17] Lu W, Hou D, Chen X, Zhong P, Liu X and Wu D. Elevated SIRT2 of serum exosomes is positively correlated with diagnosis of acute ischemic stroke patients. BMC Neurol 2023; 23: 321.

[18] Peng B and Wu B. Chinese guidelines for diagnosis and treatment of acute ischemic stroke 2018. Chin J Neurol 2018; 51: 666-682.

[19] Hua M, Chen WY, Wang LH, Zou XH and Mao LL. The value of serum Lp-PLA2 combined with MPO in the diagnosis of cerebral infarction caused by large artery atherosclerosis. Clin Neurol Neurosurg 2023; 232: 107899.

[20] Cao Z, Wang H and Zhu X. The role of serum miR-497 on the predictive index of early diag-

nosis and poor prognosis of atherosclerosis cerebral infarction. Iran J Public Health 2021; 50: 927-937.

[21] Wang L, Wu L, Lang Y, Wu D, Chen J, Zhao W, Li C and Ji X. Association between high-sensitivity C-reactive protein levels and clinical outcomes in acute ischemic stroke patients treated with endovascular therapy. Ann Transl Med 2020; 8: 1379.

[22] Su X, Wang A, Zhu H, Su H, Duan Y, Wu S, Zhang M, Huang Y, Zhou X and Cao Y. Acute myocardial infarction and transient elevated anticardiolipin antibody in a young adult with possible familial hypercholesterolemia: a case report: anticardiolipin antibody and myocardial infarction. BMC Cardiovasc Disord 2019; 19: 156.

[23] Xu J, Fan Y, Zhou R, Shao J, Guo H, Chen Y, Wang Q, Dong Z, Li M, Chen Y, Wang S, Jiang T, Liu Y and Lin W. The interaction of persistent antiphospholipid antibodies positivity and cigarette smoking is associated with an increased risk of cardiovascular events: cross-sectional and longitudinal analysis. Int J Cardiol 2023; 374: 108-114.

[24] Dong S, Pei B, Xie W, Wang J and Zeng Q. Anticardiolipin antibody and anti-β2 glycoprotein I antibody are potential risk markers of ischaemic stroke in Chinese adults. Rheumatology (Oxford) 2020; 59: 1834-1841.

[25] Ren L, Guo J, Zhao W, Zuo R, Guo S, Jia C and Gao W. Serum homocysteine relates to elevated lipid level, inflammation and major adverse cardiac event risk in acute myocardial infarction patients. Biomark Med 2023; 17: 297-306.

[26] Kwah LK and Diong J. National institutes of health stroke scale (NIHSS). J Physiother 2014; 60: 61.

[27] Wang Y, Hou R and Liu Y. Plasma homocysteine (Hcy) concentration functions as a predictive biomarker of SPECT-evaluated post-ischemic hyperperfusion in acute ischemic stroke. Pharmgenomics Pers Med 2023; 16: 481-489.

[28] Tang Z, Shi H, Chen C, Teng J, Dai J, Ouyang X, Liu H, Hu Q, Cheng X, Ye J, Su Y, Sun Y, Pan H, Wang X, Liu J, Su B, Yang C, Xu Y and Liu T. Activation of platelet mTORC2/Akt pathway by anti-β2GP1 antibody promotes thrombosis in antiphospholipid syndrome. Arterioscler Thromb Vasc Biol 2023; 43: 1818-1832.