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RAPID COMMUNICATION

Transcriptomic analysis identifies the S100 calcium-binding protein β subunit (S100B) and intercellular adhesion molecule-1 (ICAM-1) as potential diagnostic biomarkers for acute cerebral infarction

Due to its high mortality, disability, and recurrence rates, cerebral infarction has a serious impact on the economy and is a physical and psychological burden on patients.[1] There is a huge unmet medical need for biomarkers to predict acute cerebral infarction.

Studies have shown that the ischemic damage to neurons, myelin, and glia caused by a stroke leads to the release of the S100 calcium-binding protein beta subunit (S100B) through the blood–brain barrier into the systemic circulation, resulting in an increase in the level of S100B in the peripheral blood.[2] The overexpression of ICAM-1 was associated with the activation of endothelial cells, disruption of the blood–brain barrier, and the transendothelial migration of leukocytes into the brain tissues in a model of cerebral ischemia-reperfusion injury, leading to increased stroke severity.[3] Although these previous experiments provided new information, they only generally explored the changes in the level of the two biomarkers. The clinical predictive value, sensitivity, specificity, and the impact of the combination of the two factors, need to be further explored.

"Ischemic stroke" was searched as a keyword in National Center for Biotechnology Information (NCBI) GEO database. The results were filtered by *Homo sapiens* as the organism and "tissue" as the attribute name. The results were then examined to compare healthy human tissue with tissue from patients who had experienced a stroke. This led to the selection of the GSE16561 dataset. This dataset comprises the mRNA expression profiles of 63 tissue samples (39 stroke cases and 24 normal subjects) examined by the GPL6883 Illumina HumanRef-8 v3.0 expression beadchip platform. We refer to this dataset as "GSE". According to the GSE analysis, the expression levels of ICAM-1 and S100B were up-regulated in stroke cases compared to control samples (Fig. 1A). Acute cerebral infarction was further explored in this study.

A total of 135 patients with acute cerebral infarction were recruited from the 960th Hospital of the Chinese People's Liberation Army as the experimental group. All the patients had a time of onset within 72 h and met the diagnostic criteria for stroke based on the 1989 WHO guidelines. All patients had typical positive signs of the nervous system and imaging evidence of stroke. During the same period, 135 patients undergoing outpatient health examinations were enrolled in the control group. There were no statistically significant differences in age or sex between the two groups. Both groups excluded patients with neurodamaging or degenerative diseases other than acute cerebral infarction, as well as those with systemic inflammation, vascular inflammatory diseases, hematological diseases, cancer, and those taking drugs that affected the S100B and ICAM-1 levels. The serum concentrations of S100B and ICAM-1 in the two groups of people were analyzed by an enzyme-linked immunosorbent method and statistically compared.

The blood levels of S100B and ICAM-1 in the experimental group were higher than those in the control group ($P < 0.001$; Fig. 1B, C). A logistic regression analysis showed that the levels of both S100B and ICAM-1 were significantly different between the cerebral infarction and control subjects, as indicated by $P < 0.05$ and OR ≥ 1. A subsequent receiver operator characteristic curve analysis of the levels of S100B, ICAM-1, and their combination showed that the area under the curve of S100B, ICAM-1, and S100B & ICAM-1 were 0.837, 0.753, and 0.885 (Fig. 1D–F), respectively, indicating that S100B and ICAM-1 had diagnostic value for acute cerebral infarction, and the diagnostic value of their

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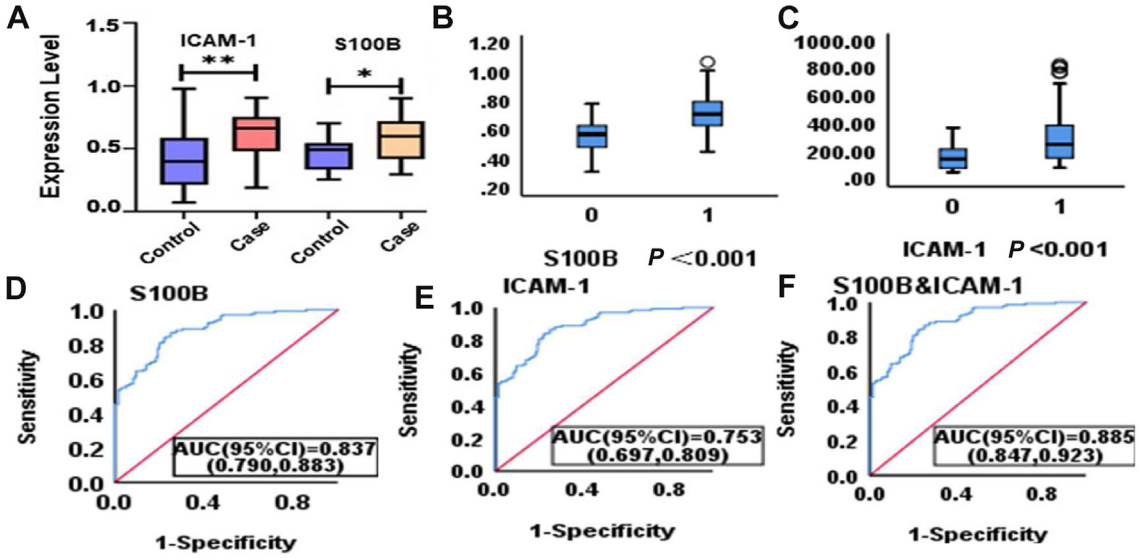

Figure 1 Analysis of the diagnostic value of S100B and ICAM-1 for acute cerebral infarction. **(A)** Relative expression of two candidate biomarkers in stroke patients and normal patients (*$P < 0.05$, **$P < 0.01$). **(B)** Comparison of the levels of S100B in the two groups (1 = stroke group, 0 = normal group; **$P < 0.001$). **(C)** Comparison of the levels of ICAM-1 in the two groups (**$P < 0.001$). **(D)** The receiver operator characteristic (ROC) curve of S100B ($n = 270$). AUC, the area under the curve; CI, confidence interval. **(E)** The ROC curve of ICAM-1 ($n = 270$). **(F)** The ROC curve of the combination of S100B and ICAM-1 ($n = 270$).

combination was higher than the diagnostic value of either index alone. When 0.605 was used as the cut-off point for S100B, the sensitivity for the diagnosis of cerebral infarction was 0.859 and the specificity was 0.659. When 278.615 was used as the cut-off point for ICAM-1, the sensitivity was 0.459 and the specificity was 0.904. When 0.449 was used as the cut-off point for the predictive value of their combination, the sensitivity was 0.807 and the specificity was 0.800.

This study demonstrates that both indicators have a high diagnostic value for acute cerebral infarction, and the diagnostic value of the combination of the two indicators is higher than that of either alone. In terms of sensitivity and specificity, S100B has high sensitivity and low specificity, while ICAM-1 has high specificity and low sensitivity. However, the sensitivity and specificity of the combination of the two factors are higher, suggesting that the combination would be better for the clinical diagnosis of acute cerebral infarction. It should be noted that S100B is elevated by various diseases (acute brain injury, neurodegenerative diseases, psychiatric disorders, *etc.*), reducing its specificity.[4] However, the level of S100B can still be used as an important adjunct for the detection of acute cerebral infarction when combined with ICAM-1 because of the higher diagnostic value, sensitivity, and specificity of the combination. Our data, therefore, suggest that S100B and ICAM-1 can be used as potential biomarkers for acute cerebral infarction. Of interest, S100B and ICAM-1 can also be regarded as potential drug treatment targets for acute cerebral infarction, resulting in comprehensive anti-inflammatory and anti-adhesion effects, potentially opening a new field of treatment for acute ischemic stroke. Importantly, such treatments may extend the application time frame for reperfusion thrombolytic therapy and provide a better outcome for patients with acute cerebral infarction.

Previous research has shown that S100B can induce the release of ICAM-1 by activating nuclear transcription factors through RAGE.[5] However, the experimental results show that there was no obvious correlation between S100B and ICAM-1, which may be related to the lack of stability of ICAM-1 expression and the relatively small sample size. Future studies should involve a larger sample size and a more diverse patient population. Moreover, acute cerebral infarction is complex, and the indicators will likely change during the progression of the condition and treatment. This study did not dynamically monitor the expression of the markers, and the differences over time should be addressed in future studies.

Author contributions

Dan Cheng and Yushuo Wang carried out the data collection and analysis and drafted the manuscript. Jingnan Li and Dan Cheng designed the experiment. Yulan Yao and Simiao Zhang provided resources and performed the data analysis. Yunliang Wang revised/edited the manuscript. All authors read and approved the submitted manuscript.

Conflict of interests

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.03.006.

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Dan Cheng [a,1], Yushuo Wang [b,1], Jingna Li [a], Yulan Yao [a], Simiao Zhang [a], Yunliang Wang [a,c,*]

[a] *Department of Neurology, Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450014, China*
[b] *School of Medicine, Medical Sciences and Nutrition University of Aberdeen, Aberdeen AB25 2ZD, UK*
[c] *Department of Neurology, The 960th Hospital of PLA, Zibo, Shandong 255300, China*

*Corresponding author. Department of Neurology, Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450014, China.
E-mail address: wangyunliang81@163.com (Y. Wang)

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[1] These authors share co-first authorship.