Association of Monocytes and the Monocyte/high-density Lipoprotein Ratio With Intracranial and Extracranial Atherosclerotic Stenosis

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Research

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Abstract

Background and aims: Although the monocyte/high-density lipoprotein ratio (MHR) has been shown to be a potential inflammatory marker of cardiovascular and cerebrovascular diseases, there are few studies on the relationship between intracranial and extracranial atherosclerotic stenosis degree and its distribution.

Methods: A total of 271 patients were admitted for digital subtraction angiography (DSA) examination. (1) The non-stenosis group and the stenosis group were compared, and the artery was grouped according to the degree of intracranial and extracranial atherosclerotic stenosis (if ≥2 branches were stenotic, the artery with the most severe stenosis was used). (2) According to the locations of the intracranial and extracranial artery stenosis groups, clinical baseline data and laboratory indexes of each group of patients were collected.

Results: (1) MHR (odds ratio (OR)=1.119, \( P<0.001 \)), age (OR=1.057, \( P=0.007 \)), and lymphocyte (OR=0.273, \( P=0.002 \)) could significantly affect cerebral atherosclerotic stenosis, the AUC (area under the ROC curve) of MHR was 0.82, and the optimal diagnostic value was 0.486. Further analysis of the mild, moderate, and severe stenosis groups showed that MHR (OR=1.07, \( P<0.001 \)) significantly affected the severity of stenosis in patients. (2) According to the analysis of stenosis at different sites, the rate of extracranial artery stenosis in patients who smoked (OR=3.86, \( P=0.023 \)) and had a reduced lymphocyte level (OR=0.202, \( P=0.001 \)) was significantly higher than that in patients who smoked (OR=3.86, \( P=0.023 \)). With increasing age, the rate of extracranial and extracranial artery stenosis increased significantly. With the increase in MHR level, the stenosis rate of each group was significantly higher than that of the non-stenosis group.

Conclusion: MHR has predictive value for the diagnosis of intracranial and extracranial atherosclerotic stenosis and is correlated with the degree and distribution of stenosis.

Introduction

Atherosclerosis is a clinically common chronic disease characterized by endovascular atheroma or fibrous plaque. The pathophysiological changes of arterial wall hardening, decreased elasticity and lumen stenosis or even occlusion are important risk factors for the occurrence and development of ischaemic cerebrovascular diseases and even the difference in mortality\(^{[1-2]}\). In addition to traditional lipid metabolic disorders, the important role of inflammatory mechanisms in thrombosis, plaque rupture and stenosis of atherosclerosis has been increasingly mentioned\(^{[3]}\). Studies on the correlation of the MHR with coronary stenosis and myocardial infarction have shown that MHR is a potential inflammatory marker of cardiovascular and cerebrovascular diseases\(^{[4-5]}\). Currently, there are few reports on cerebrovascular diseases, and most of them are related to the occurrence and prognosis of ischaemic stroke\(^{[6-7]}\). Digital subtraction angiography (DSA) is the gold standard for judging intracranial and extracranial arterial stenosis. However, studies on the relationship between intracranial and extracranial arterial stenosis and MHR are rarely reported by using DSA technology. This study investigated the relationship between MHR and intracranial and extracranial arterial stenosis and related risk factors, aiming to provide a more reliable theoretical basis and guide the prevention and treatment of intracranial and extracranial arterial stenosis.

Data And Methods

Study population

From May 2017 to May 2020, 216 inpatients with intracranial and extracranial atherosclerotic stenosis confirmed by cerebrovascular DSA examination in Qinghai People's Hospital were consecutively enrolled. There were 55 hospitalized patients without intracranial and extracranial atherosclerotic stenosis. The exclusion criteria were as follows: signs of acute infection; acute cardiovascular disease; immunosuppressive therapy; patients with tumours, haematological system disorders, connective tissue disease, severe liver and kidney function impairment, moyamoya disease, and arteriovenous malformation. The study was approved by the ethics committee of Qinghai Provincial People's Hospital.

Study method
Basic clinical data, such as age, sex, ethnicity, smoking, drinking, hypertension, diabetes mellitus, and cerebral infarction, were collected from patients meeting the inclusion criteria; additionally, laboratory measures of monocytes, high-density lipoprotein (HDL), and MHR of patients were obtained within 24 hours after admission. (1) First, the stenosis group and the non-stenosis group were compared and analysed. Then, DSA examination results were based on relevant diagnostic criteria for The Warfarin-Aspirin Symptomatic Intracranial Disease Study to evaluate the degree of intracranial and extracranial atherosclerotic stenosis: Degree of stenosis (%) = (1-diameter at the narrowest point of a narrow segment/the diameter of the proximal normal vessel)×100%. Outside the intracranial and extracranial atherosclerotic stenosis according to the degree of artery stenosis (if there are two or more people who will be subject to a narrow degree is the highest), the patients can be divided into the mild stenosis group (stenosis degree of 29% or less), moderate stenosis group (stenosis degree of 30% - 69%) and severe stenosis group (stenosis degree of 70% - 99%). To study the factors related to the degree of atherosclerotic stenosis and their influence on the degree of stenosis and to analyse the predictive value of MHR for cerebral atherosclerotic stenosis. (2) According to the location of intracranial and extracranial atherosclerotic stenosis, they were divided into four groups: one with non-stenosis group, one with intracranial atherosclerosis only (the ICAS group), one with extracranial atherosclerosis only (the ECAS group), and one with intracranial and extracranial atherosclerosis (the I-ECAS group). In addition, the non-stenosis group was used as the control group and compared with the other 3 groups to analyse the relevant influencing factors of the corresponding groups.

Statistical analysis

SPSS 26.0 (Chicago, IL, USA) was used to statistically analyse all data. The chi-square test was used for count data. The measurement data were tested by the S-W normality test, the normal distribution was expressed as the mean± standard deviation (MEAN±SD), and one-way analysis of variance (ANOVA) was used. In contrast, the expression of the median (lower quartile:upper quartile) was adopted, and a nonparametric test was used. The predictive power of MHR on the occurrence of cerebral atherosclerotic stenosis was analysed using the subject working characteristic curve, and the optimal threshold was determined. Finally, variables with statistical significance (P<0.05) in univariate screening were included in the logistic regression model.

Results

2.1 Analysis of logistics regression and ROC curve for cerebral artery stenosis Compared with no stenosis group (n=55), stenosis group (n=216) of age, white blood cells, neutrophils, c-reactive protein and MHR level and proportion of males, smoking, drinking, hypertension, diabetes mellitus were higher, and the lymphocyte is no stenosis group is low, the comparative differences are statistically significant (P<0.05), and the single factor whether Logistic regression notable index together into a narrow multivariable Logistic regression analysis for the dependent variable, age, the greater the probability of a narrow (P=0.007<0.05, OR=1.057>1); The higher the MHR level, the greater the probability of stenosis (P<0.001, OR=1.119>1). The higher the lymphocyte level was, the smaller the probability of stenosis was (P=0.002<0.05, OR=0.273<1), as shown in Table 1. The ROC curve analysis of MHR on cerebral atherosclerotic stenosis showed an AUC of 0.82, and the optimal diagnostic value was 0.486, which is plotted in Figure 1.

Table 1 Comparison of related factors between the non-stenosis group and the atherosclerotic stenosis group
### Variable

| Variable              | Univariate difference | Multifactor Logistic |
|-----------------------|-----------------------|----------------------|
|                       | Non-stenosis group (n=55) | Stenosis group (n=216) | $Z/c^2$ | $P$   | OR | 95% CI | $P$ |
| Age                   | 53(42|61) | 62|52|69 | -4.715 | <0.001 | 1.057 | 1.016|1.1 | 0.007 |
| Sex, Male             | 19(11.2%) | 150(88.8%) | 22.747 | <0.001 | 0.733 | 0.286|1.879 | 0.518 |
| Smoking               | 12(12.1%) | 87(87.9%) | 6.443 | 0.011 | 1.129 | 0.425|2.998 | 0.807 |
| Drinking              | 2(4.3%) | 45(95.7%) | 9.044 | 0.003 | 2.353 | 0.43|13.835 | 0.344 |
| Hypertension          | 25(14.3%) | 150(85.7%) | 11.029 | 0.001 | 0.994 | 0.397|2.487 | 0.989 |
| Diabetes mellitus     | 4(6%) | 63(94%) | 11.291 | <0.001 | 2.702 | 0.734|9.945 | 0.135 |
| WBC                   | 5.21(4.43|6.62) | 6.4(5.47|7.63) | -3.949 | <0.001 | 1.057 | 0.921|1.086 | 0.997 |
| Neutrophil            | 3.22(2.24|3.83) | 4.16(3.24|5.28) | -4.916 | <0.001 | 1.313 | 0.966|1.785 | 0.083 |
| Lymphocyte            | 1.83(1.39|2.23) | 1.62(1.23|1.96) | -2.563 | 0.01 | 0.273 | 0.119 | 0.624 | 0.002 |
| PLT                   | 195(160|253) | 186.5(144|227.5) | -1.92 | 0.055 | 0.998 | 0.99|1.005 | 0.551 |
| CRP                   | 1.27(0.56|2.45) | 2.28(1.07|5.63) | -3.872 | <0.001 | 1.119 | 1.07|1.17 | <0.001 |
| TC                    | 4.27(3.43|5.14) | 4.21(3.64|4.86) | -0.053 | 0.958 |
| TG                    | 1.38(1.08|1.92) | 1.55(1.09|2.24) | -1.095 | 0.274 |
| LDL                   | 2.54(1.95|3.3) | 2.49(2.03|3.08) | -0.233 | 0.816 |
| Apolipoprotein A      | 1.19(1.1|1.47) | 1.16(1.05|1.31) | -1.741 | 0.082 | 2.302 | 0.362|14.636 | 0.377 |
| Apolipoprotein B      | 0.85(0.66|1.05) | 0.91(0.75|1.04) | -1.215 | 0.224 |
| MHR                   | 0.31(0.25|0.43) | 0.5(0.39|0.58) | -7.366 | <0.001 | 1.119 | 1.07|1.17 | <0.001 |

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2.2 Only patients with mild (N =72), moderate (n=35) and severe (n=60) stenosis were selected, and the differences in WBC, neutrophil, C-reactive protein, apolipoprotein A and MHR were statistically significant ($P<0.05$). The significant indexes of univariate ordered logistic regression analysis were included in the multivariate ordered logistic regression analysis with the severity of stenosis as the dependent variable, and it was concluded that MHR alone could significantly influence the trend of stenosis aggravation ($P<0.001$, OR=1.07>1); that is, the greater the MHR value, the greater the trend of stenosis aggravation, as shown in Table 2.

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Table 2 Comparison of correlation factors of severity of intracranial atherosclerotic stenosis
2.3 Analysis of correlation factors of distribution of atherosclerotic stenosis in intracranial and extracranial arteries

There were statistically significant differences in sex, smoking, drinking, hypertension, diabetes mellitus, WBC, neutrophil, lymphocyte, CRP, LDL, apolipoprotein A and MHR between the atherosclerosis-free, ICAS, ECAS, and I-ECAS groups (P<0.05), as shown in Table 3.

Table 3 Comparison of related factors in the distribution of intracranial atherosclerotic stenosis
### Table 4 Multivariate logistic regression analysis of the distribution of intracranial atherosclerotic stenosis

| Variable                | No stenosis (n=55) | Intracranial atherosclerosis alone (n=64) | Extracranial atherosclerosis alone (n=115) | Combined Intracranial and extracranial atherosclerosis (n=37) | F/c^2 | P |
|------------------------|--------------------|------------------------------------------|------------------------------------------|----------------------------------------------------------|-------|---|
| **Age**                | 50.91±12.56        | 56.17±11.6                               | 61.59±13.53                              | 65.16±8.5                                                | 13.752 | <0.001|
| **Sex, Male**          | 19(11.2%)          | 39(23.1%)                                | 83(49.1%)                                | 28(16.6%)                                                | 25.697 | <0.001|
| **Smoking**            | 8(8.1%)            | 29(19.2%)                                | 59(59.6%)                                | 13(13.1%)                                                | 23.615 | <0.001|
| **Drinking**           | 2(4.3%)            | 14(29.8%)                                | 22(46.8%)                                | 9(19.1%)                                                 | 9.639  | 0.022 |
| **Hypertension**       | 25(14.3%)          | 43(24.6%)                                | 77(44%)                                  | 30(17.1%)                                                | 13.673 | 0.003 |
| **Diabetes mellitus**  | 4(6%)              | 19(28.4%)                                | 30(44.8%)                                | 14(20.9%)                                                | 13.381 | 0.004 |
| **WBC**                | 5.21(4.43/6.62)    | 6.73(5.39/8.31)                          | 6.25(5.47/7.37)                          | 6.54(5.41/7.75)                                         | 17.34  | 0.001|
| **Neutrophil**         | 3.22(2.24/3.83)    | 4.24(3.17/5.38)                          | 4.13(3.23/5.03)                          | 4.09(3.29/5.6)                                          | 24.742 | <0.001|
| **Lymphocyte**         | 1.83(1.39/2.23)    | 1.71(1.28/2.11)                          | 1.57(1.19/1.88)                          | 1.65(1.29/2.19)                                         | 11.11  | 0.011 |
| **PLT**                | 195(160/253)       | 194.50(148/252)                          | 172(139/218)                             | 191(143.5/210.5)                                         | 7.503  | 0.057a |
| **CRP**                | 1.27(0.56/2.45)    | 2.33(1.27/6.54)                          | 2.20(0.99/5.63)                          | 2.25(1.23/5.24)                                         | 15.177 | 0.002b |
| **TC**                 | 4.27(3.43/5.14)    | 4.33(3.66/4.92)                          | 4.04(3.53/4.66)                          | 4.62(3.88/5.22)                                         | 5.166  | 0.16 |
| **TG**                 | 1.380(1.081/1.92)  | 1.55(1.06/2.15)                          | 1.51(1.16/2.25)                          | 1.60(1.11/2.31)                                         | 1.818  | 0.611 |
| **LDL**                | 2.54(1.95/3.3)     | 2.56(2.12/3.3)                           | 2.37(1.92/2.83)                          | 2.81(2.31/3.43)                                         | 8.604  | 0.035b |
| **Apolipoprotein A**   | 1.19(1.11/1.47)    | 1.22(1.11/1.43)                          | 1.16(1.04/1.28)                          | 1.11(1.11/1.3)                                          | 12.021 | 0.007 |
| **Apolipoprotein B**   | 0.85(0.66/1.05)    | 0.92(0.75/1.06)                          | 0.88(0.74/1.01)                          | 0.93(0.81/1.11)                                         | 3.898  | 0.273 |
| **MHR**                | 0.31(0.25/0.43)    | 0.46(0.38/0.55)                          | 0.50(0.38/0.58)                          | 0.55(0.43/0.7)                                          | 59.049 | <0.001 |

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2.4 Logistic regression analysis of atherosclerotic stenosis distribution in intracranial and extracranial arteries

In combination with single factor disorderly logistic results, excluding CRP and LDL, to join the platelets, further multifactor logistic regression analysis suggested that age, pure extracranial stenosis (P<0.003<0.05, OR=1.066>1) and combined intracranial and extracranial atherosclerosis stenosis (P<0.001, OR=1.102>1) were associated with a significantly higher probability than that without stenosis. Smoking (P=0.023<0.05, OR=3.86>1) significantly increased the incidence of simple extracranial atherosclerotic stenosis. The higher the lymphocyte value (P=0.001<0.05, OR=2.20>1), the lower the probability of developing simple extracranial atherosclerotic stenosis than that without stenosis. The higher the MHR, the higher the probability of developing simple intracranial atherosclerotic stenosis (P<0.001, OR=1.121>1), simple extracranial atherosclerotic stenosis (P<0.001, OR=1.121>1), and intracranial complicated extracranial atherosclerotic stenosis (P<0.001, OR=1.147>1) were significantly higher than those without stenosis, as shown in Table 4.

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Table 4 Multivariate logistic regression analysis of the distribution of intracranial atherosclerotic stenosis

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*a P<0.05 was expressed as a single factor logistics test, and multifactor analysis should be included. b P>0.05 by single-factor logistics test, and multifactor analysis does not need to be included. c There was a significant difference between the two groups (P<0.05).*
Discussion

Atherosclerosis is a clinically common chronic inflammatory disease. Inflammation is an important pathophysiological mechanism of atherosclerotic thrombosis, plaque rupture, stenosis or even occlusion. Monocytes are immune cells, and when the vascular endothelium is damaged, the expression of adhesion molecules on the cell surface increases, which is stimulated by cytokines and transformed into macrophages. Phagocytosis of lipids occurs, followed by the formation of foam cells under scavenger receptor mediation, thus forming the initial phase of atherosclerosis from a stable to an unstable state. In addition to lipid deposits, the lipid core of atherosclerotic lesions contains a variety of immune cells that evolve from monocytes and macrophages to form T cells, mast cells, and dendritic cells, which play a major role in the proliferation and progression of atherosclerosis\[9-10\]. In conclusion, it can aggravate inflammation and promote the development and instability of plaque, local thrombosis and a series of responses, thus causing the aggravation of vascular stenosis. Dyslipidaemia is also an important risk factor for atherosclerosis. The main function of HDL is reverse transport of total cholesterol in the tissues to the liver and out of the body. HDL can also reduce thrombosis risk via platelet stabilization and decrease leukocyte adhesion to stable plaques. It can prevent LDL oxidation and exhibit antithrombotic and anti-inflammatory properties, thereby playing a protective role\[11-12\]. Research on the treatment of atherosclerosis by HDL infusion has great prospects\[13-14\]. Monocytes are closely related to HDL. Abnormal blood lipids, especially elevated cholesterol, can stimulate the production of monocytes in the blood circulation, while conversely, reduced HDL can reduce the inflammatory inhibition of monocytes\[15\]. The ability of monocytes to phagocytose lipid particles in atherosclerotic stenosis is enhanced, making blood fat more likely to be deposited in the stenosis\[16\]. Therefore, it is speculated that MHR has more advantages than monocytes and HDL, and it has been proven to be a new inflammatory marker. This study found that MHR is an independent risk factor for the occurrence of cerebral atherosclerosis. The ROC curve analysis showed that the AUC of MHR was 0.82, and the optimal diagnostic value was 0.486, indicating that MHR can be used as a good indicator to predict the occurrence of intracranial and extracranial atherosclerotic stenosis. In addition, age has been proven to be one of the most important independent risk factors for the incidence of intracranial and extracranial atherosclerosis\[17-18\], which is consistent with the results of this study.

MHR is associated with cerebral atherosclerotic stenosis. However, there are few studies on the correlation between intracranial and extracranial atherosclerotic stenosis or even the degree of stenosis. This study concluded from the analysis of the mild stenosis group, moderate stenosis group and severe stenosis group that MHR level significantly affects the degree of stenosis. Chen Jiexia et al\[16\] found that monocytes are closely related to the degree of peripheral atherosclerosis stenosis. A population study of arterial
Atherosclerotic ischaemic stroke in southern China found severe high-density lipoprotein with carotid artery stenosis in the brain (cervico-cerebral atherosclerotic stenosis, CCAS)\textsuperscript{[19]}\textsuperscript{[20-21]}. The elevated level reflects the increased degree of inflammation and oxidative stress and is related to the severity of coronary artery stenosis\textsuperscript{[20-21]}

Studies at home and abroad have found ethnic differences in the distribution characteristics of intracranial and extracranial atherosclerotic stenosis. In Europe and the United States, extracranial artery stenosis is the dominant stenosis, while in Asia, intracranial arterial stenosis is more common\textsuperscript{[22-23]}. Nevertheless, the results of this study showed that the rate of extracranial artery stenosis was slightly higher than that of intracranial stenosis, which was consistent with the trend of increasing extracranial artery stenosis in Chinese people found by epidemiological surveys in recent years\textsuperscript{[25]}. It has to do with the following reasons: 1. due to regional, dietary, and lifestyle differences. In high-altitude areas, due to the cold climate, the temperature difference between day and night will lead to a relative lack of fruits and vegetables. In addition, the dietary structure of the population is more carnivorous, which can increase blood lipid levels and ATP (plasma arteriosclerosis index). The long-term hypoxic environment changes the blood microcirculation and even the anatomy and physiology\textsuperscript{[26]}. 2. With ageing, the proportion of intracranial artery stenosis decreases, while the proportion of extracranial artery stenosis increases\textsuperscript{[24]}. China's ageing society may also exacerbate this phenomenon.

There are still different conclusions regarding the factors influencing the distribution of intracranial and extracranial atherosclerotic stenosis. This study concluded that male sex and smoking are independent risk factors for extracranial atherosclerosis alone, which is consistent with the conclusions of previous large-sample data studies. However, diabetes mellitus was found to be not associated with extracranial and intracranial atherosclerotic stenosis, in contrast to previous results indicating that diabetes is mainly a risk factor for intracranial artery stenosis\textsuperscript{[23/26-28]}. The analysis may be related to the following reasons: 1. Chronic hypoxic acclimatization at high altitude increases the dependence of the body on and enhances glucose utilization. 2. With the improvement of residents' standards of living, the incidence of diabetes mellitus is rising rapidly. Diabetes mellitus has been shown to increase the incidence burden of vascular risk factors and is common in both intracranial and extracranial atherosclerotic stenosis\textsuperscript{[29-30]}. This study concluded that age is an independent risk factor for intracranial and extracranial atherosclerosis, and the incidence of cerebral artery stenosis increases significantly with age\textsuperscript{[23/28]}. Most people believe that extracranial artery stenosis is more correlated with age\textsuperscript{[23-28]}. However, a postmortem report\textsuperscript{[31]} showed that intracranial arterial stenosis developed with age. In addition, lymphocytes can be used as a protective factor for intracranial arterial stenosis in this study. Recent studies have found that the number of circulating lymphocytes is significantly reduced in the progression of atherosclerotic lesions, which may be related to weakened adaptive immunity and healing effects in the atherosclerotic process\textsuperscript{[3/32]}. Lymphocytes are significantly correlated with extracranial artery stenosis. The lack of elastic fibres in intracranial vessels, the dense internal elastic layer and the mechanism of increasing antioxidant enzyme activity with age all provide a good barrier effect. Intracranial atherosclerotic stenosis appeared later than extracranial stenosis, and lymphocyte values were further reduced\textsuperscript{[17]}. This study found that with the increase in MHR level, simple intracranial arterial stenosis, simple extracranial arterial stenosis and intracranial combined extracranial arterial stenosis were all significantly increased. As a common independent correlation factor in the above three groups, it was further confirmed that it was closely related to cerebral atherosclerotic stenosis.

Although the "gold standard" of cerebrovascular DSA examination was used in this study to diagnose intracranial and extracranial atherosclerotic stenosis, this method is traumatic, risky, and costly; thus, its use is mainly limited to the subset of cerebral infarction patients who need surgery. For the patients, DSA was found to be accurate for determining the stenosis rate and to have good precision and other advantages; however, patients with mild or no symptoms who did not opt for cerebrovascular DSA examination could not be included in the study. Thus, the total sample size should be increased to verify these results. Moreover, this study was limited to patients in plateau regions, so follow-up clinical control studies should be conducted at multiple centres and regions to further confirm the findings.

**Conclusions**

In conclusion, as a risk factor for intracranial and extracranial atherosclerotic stenosis, MHR has a certain predictive value and is closely related to the severity and location of stenosis. Our study also expounds the intracranial and extracranial atherosclerotic stenosis formed in the process of inflammation, provide theoretical basis for further targeted interventions, which to a certain extent, reduce the high altitude areas outside of cerebral atherosclerotic stenosis caused by ischemic cerebrovascular disease, and to provide better services to the health of the residents.
Declarations

Ethical Approval and Consent to participate

We further confirm that any aspect of the work covered in this manuscript that involved human patients was conducted with the ethical approval of all relevant bodies.

Consent for publication

All authors and participants have given their consent for publication of this article in Lipids in Health and Disease.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

In this study, ZL, SHZ, and QLF did the study design, statistical analyses and results interpretation. YCL and WFY participated as analyzing and resolving difficulties of analytic strategies and results discussion. Finally, QLF functioned as final reviewer and corresponding author. All authors read and approved the final manuscript.

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