

The stromal cell-derived factor-1 α (SDF-1 α)/cysteine-X-cysteine chemokine receptor 4 (CXCR4) axis: a possible prognostic indicator of acute ischemic stroke

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Abstract

Objective: The stromal cell-derived factor-1 α /cysteine-X-cysteine chemokine receptor 4 (SDF-1 α /CXCR4) axis promotes neuroprotection and angiogenesis in animal studies. Few studies have investigated the potential clinical implications of the SDF-1 α /CXCR4 axis in patients with acute ischemic stroke (AIS). We evaluated the prognostic values of the SDF-1 α /CXCR4 axis in patients with proximal middle cerebral artery occlusion.

Methods: Fifty-five patients and 18 age- and sex-matched volunteers were enrolled. Baseline clinical characteristics and risk factors of stroke were recorded. Peripheral whole blood cells were double stained with anti-CD34 and anti-CXCR4 (CD184). CD34⁺CXCR4⁺ cells were analyzed by flow cytometry. Plasma SDF-1 α levels were measured by enzyme-linked immunosorbent assay.

Results: In the AIS group, plasma SDF-1 α levels and the number of circulating CD34⁺CXCR4⁺ cells were significantly higher than those in controls. Day 1 SDF-1 α levels were negatively correlated with infarct volume ($r = -0.521$) and the initial National Institutes of Health Stroke Scale score ($r = -0.489$). SDF-1 α levels (day 1: $r = -0.514$; day 3: $r = -0.275$; day 7: $r = -0.375$) and circulating CD34⁺CXCR4⁺ cells (day 7: $r = -0.282$) were inversely associated with the 90-day modified Rankin Scale score.

Conclusion: The SDF-1 α /CXCR4 axis has potential applications for predicting the clinical outcome of AIS.

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Keywords

Stromal cell-derived factor-1 α , acute ischemic stroke, collateral circulation, middle cerebral artery occlusion, cysteine-X-cysteine chemokine receptor 4, collateral circulation

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Introduction

Acute ischemic stroke (AIS) is characterized by the sudden loss of blood circulation to the brain, resulting in a corresponding loss of neurological function.¹ Arteriogenesis, angiogenesis, and neurogenesis play an important role in promoting functional recovery of stroke.^{2,3} Previous studies have shown that circulating progenitor cells promote repair of the endothelium and maintain vascular homeostasis.⁴ Moreover, animal research has shown that intracerebral peripheral blood stem (CD34+) cell transplantation might induce neuroprotection.⁵ However, among these repair mechanisms, stromal cell-derived factor-1 α (SDF-1 α) and its cellular receptor cysteine-X-cysteine chemokine receptor 4 (CXCR4) are key regulators.⁶⁻⁸

SDF-1 α , also known as cysteine-X-cysteine chemokine ligand 12 (CXCL12), is a type of inflammatory chemokine that is derived from bone marrow mesenchymal stem cells (BMSCs), and affiliated to the CXC chemokine family. CXCR4, a seven transmembrane-spanning G protein-coupled receptor, mediates transmembrane signaling of SDF-1 α . SDF-1 α is upregulated in the penumbra following stroke, and promotes neuroprotection, mobilization/homing of BMSCs, and angiogenesis in animal models.⁶⁻⁸ Moreover, a CXCR4 antagonist can disrupt migration of stem cells and leads to failure of newborn neurons to migrate to the ischemic area.² Therefore, the SDF-1 α /CXCR4 axis might play a critical role in reducing cerebral

ischemic damage and promoting repair of neurological function.^{2,3,7}

Recently, Kim et al.⁹ evaluated the association between serum SDF-1 α levels and stroke outcomes. They showed that SDF-1 α levels were significantly increased in AIS compared with healthy controls, and are inversely correlated with infarct volume. However, Wurster et al.¹⁰ did not find different SDF-1 α levels between patients with ischemic stroke and healthy patients. Accordingly, these conflicting results indicate that the prognostic value of SDF-1 α in AIS is still unclear. Additionally, research regarding the relation between the SDF-1 α /CXCR4 axis and stroke outcomes in humans is rare. Therefore, to determine the potential clinical implications of the SDF-1 α /CXCR4 axis in patients with ischemic stroke, we dynamically observed plasma SDF-1 α levels and circulating CD34 and CXCR4 double-positive (CD34+CXCR4+) cells on the 1st, 3rd, and 7th days after admission. We also investigated the predictive roles of the SDF-1 α /CXCR4 axis on neurological impairment (admission National Institutes of Health Stroke Scale [NIHSS] score) and prognostic values (90-day modified Rankin Scale [mRS] score) for stroke.

Materials and methods

Subjects

The Institutional Review Board in our hospital approved the study protocol.

All subjects provided informed consent. A total of 73 individuals, including patients with first AIS (AIS group) in the territory of the middle cerebral artery (MCA), and age- and sex-matched volunteers (control group) with cardiovascular risk factors and without a history of stroke, were enrolled in this study in Yijishan Hospital between March 2014 and August 2016.

The inclusion criteria were as follows: acute neurological deficit within 24 hours of admission; computed tomographic excluded brain hemorrhage; and infarction located in the MCA region and M1 segment of MCA occlusion (MCAO) as determined by magnetic resonance angiography, computed tomography angiography, or digital subtraction angiography. Patients were excluded by the following criteria: undergoing thrombolysis therapy or decompressive craniectomy; having been infected or had signs of infection during the past 3 months (white blood cell count $> 10 \times 10^9$); having surgery or trauma within 3 months; acute myocardial infarction or other acute ischemic events occurring within the past 3 months; and having cancer or related immune diseases.

All information, including general information (sex, age), medical history (hypertension and diabetes), and imaging data, were retrospectively analyzed.

Blood sampling

Peripheral venous blood samples (3 mL) with EDTA anticoagulation were obtained from the AIS group ($n = 55$) on the 1st, 3rd, and 7th days after hospitalization and from the control group ($n = 18$). Peripheral whole blood samples (100 μ L) were used for flow cytometric analysis, and plasma samples were collected and stored at -80°C .

Flow cytometric analysis

Samples of whole blood (50 μ L) were stained with fluorescein isothiocyanate-

conjugated anti-CD34 (eBioscience, San Diego, CA, USA) and phycoerythrin (PE)-conjugated anti-CXCR4 (CD184) (eBioscience) monoclonal antibodies for 30 minutes at 4°C . The cells in each sample were double-labeled for CD34+CXCR4+ stain. Red blood cells and platelets were subsequently lysed for 30 minutes by an erythrocyte lysing solution (Beckman Coulter, Brea, CA, USA) in the dark, and the samples were centrifuged, washed twice, and resuspended in phosphate-buffered saline. This suspension was then analyzed by using a FC500 MPL model flow cytometer (Beckman Coulter). Isotype-matched fluorescein isothiocyanate-conjugated immunoglobulin G 1 and PE-conjugated immunoglobulin G 2 antibodies (eBioscience) were used as controls. The level of CD34+CXCR4+ cells in peripheral blood was calculated on the basis of the percentage (%) of peripheral blood mononuclear cell (PBMCs).

Enzyme-linked immunosorbent assay analysis

Plasma SDF-1 α levels were measured by an enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions.

Classification of infarction size

Infarct volume was measured by 1.5 T or 3.0 T magnetic resonance imaging-diffusion-weighted imaging sequences within 24 hours after admission. Volumetric analyses depended on the different sizes of the MCA territory (Figure 1). Infarction volume accounted for the size of the MCA territory, and was divided into a small size of cerebral infarction (ischemic changes $<$ one third of the MCA territory), a middle size of cerebral infarction (ischemic changes between \geq one third and $<$ two

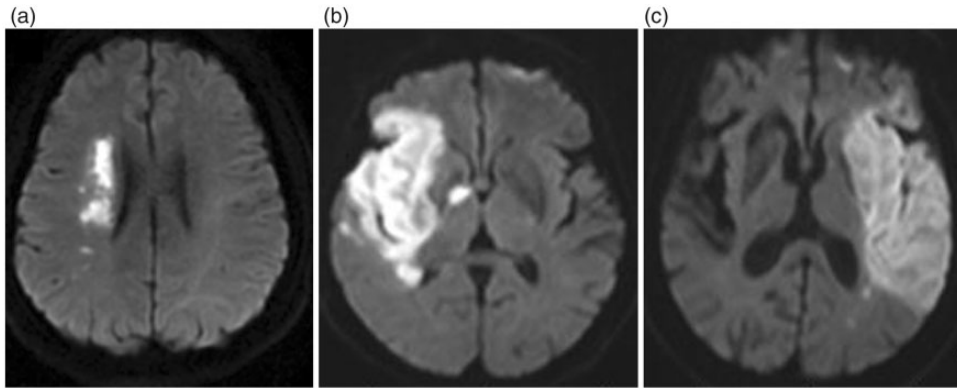


Figure 1. Classification of infarction volume according to the size of the MCA territory. (a) Small volume, ischemic changes of $<$ one third of the MCA territory. (b) Middle volume, ischemic changes between \geq one third and $<$ two thirds of the MCA territory. (c) Large volume, ischemic changes of \geq two thirds of the MCA territory. MCA, middle cerebral artery.

thirds of the MCA territory), and a large size of cerebral infarction (ischemic changes \geq two thirds of the MCA territory).¹¹

The NIHSS score

Neurological impairment was assessed by the NIHSS¹² score after onset of AIS. The NIHSS score is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment.

The mRS score

The clinical prognosis was assessed with the 90-day follow-up mRS score. The mRS score is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke.^{13,14}

Statistical methods

Because of the small sample size, measurement data are expressed as the mean \pm standard deviation (standard error).

Comparisons were performed using the Mann–Whitney U test for two groups. Quantitative data are expressed as percentages, and the chi-square test or Fisher's exact probability test was used for data comparisons between groups. Correlations between nonparametric variables were analyzed using Spearman's rank correlation test. The Pearson correlation test was used for analyzing the relationship between SDF-1 α levels and circulating CD34+ CXCR4+ cells. *P* values $<$ 0.05 were considered to be statistically significant. All analyses were performed using the SPSS 19.0 system (SPSS software, IBM, Armonk, NY, USA).

Results

Patients' characteristics

Fifty-five patients with AIS (mean age, 67.0 ± 10.1 years; male sex, 56%) and 18 age- and sex-matched controls (mean age, 62.5 ± 13.6 years; male sex, 38.9%) were enrolled in this study. Except for fasting blood glucose levels (AIS group vs. control group; *P* $<$ 0.001), there were no significant

Table 1. Summary of the subjects' characteristics.

	AIS group (n = 55)	Control group (n = 18)	Statistical test	P value
Sex (male, %)	31 (56.4)	7 (38.9)	1.659	0.198 [#]
Age (years)	67.0 ± 10.1 (1.3)	62.5 ± 13.6 (3.2)	-1.255	0.209*
Hypertension (%)	38 (69.1)	8 (44.4)	3.535	0.060 [#]
Diabetes mellitus (%)	14 (25.5)	1 (5.6)	3.289	0.070 [#]
FBG (mM)	6.50 ± 2.84 (0.38)	5.07 ± 0.97 (0.23)	-3.597	<0.001*
Chol (mM)	4.28 ± 1.25 (0.17)	4.01 ± 0.74 (0.17)	-0.531	0.595*
TG (mM)	1.45 ± 0.70 (0.09)	1.38 ± 0.93 (0.21)	-0.883	0.377*
HDL (mM)	1.24 ± 0.26 (0.04)	1.22 ± 0.18 (0.04)	-0.506	0.613*
LDL (mM)	2.60 ± 1.02 (0.14)	2.33 ± 0.64 (0.15)	-1.018	0.309*
Plasma SDF-1 α (pg/mL)				
Day 1	1218.96 ± 297.27 (400.83)	1016.40 ± 149.48 (35.23)	-2.739	0.006*
Day 3	1289.81 ± 411.22 (554.48)	-	-	-
Day 7	1628.08 ± 433.94 (585.12)	-	-	-
CD34+ CXCR4+ cells (% PBMCs)				
Day 1	0.462 ± 0.525 (0.071)	0.117 ± 0.052 (0.038)	-2.637	0.008*
Day 3	0.562 ± 0.734 (0.099)	-	-	-
Day 7	0.919 ± 0.735 (0.099)	-	-	-
Initial NIHSS score	11.42 ± 5.85 (0.79)	-	-	-

[#]Chi-square test; *Mann-Whitney *U* test.

AIS, acute ischemic stroke; Chol, cholesterol; CXCR4, cysteine-X-cysteine chemokine receptor 4; FBG, fasting blood glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PBMCs, peripheral blood mononuclear cells; NIHSS, National Institutes of Health Stroke Scale; SDF-1 α , stromal cell-derived factor-1 α ; TG, triglycerides.

differences in baseline characteristics between the two groups (Table 1).

Changes in plasma SDF-1 α levels and the number of circulating CD34+CXCR4+ cells in patients with acute ischemic stroke

Plasma SDF-1 α levels were significantly higher on day 1 in the AIS group than in the control group ($P=0.006$). The number of peripheral blood CD34+CXCR4+ cells was significantly higher on day 1 in the AIS group than in the control group ($P=0.008$) (Table 1). During the first week of onset, SDF-1 α levels and the number of circulating CD34+CXCR4+ cells in the AIS group progressively increased (SDF-1 α : $r=0.411$, $P<0.001$; CD34+CXCR4+ cells: $r=0.418$, $P<0.001$; Figure 2a, b).

Assessment of neurological impairment by plasma SDF-1 α levels and circulating CD34+CXCR4+ cells on day 1

Day 1 SDF-1 α levels were negatively correlated with infarct volume ($r=-0.521$, $P<0.001$) and the initial NIHSS score ($r=-0.489$, $P<0.001$, Figure 2c, d). However, there was no correlation between day 1 circulating CD34+CXCR4+ cells and the severity of stroke as indicated by infarct volume ($r=-0.105$) and the NIHSS score ($r=-0.022$, data not shown).

Prognostic values of plasma SDF-1 α levels and circulating CD34+CXCR4+ cells

We also evaluated the prognostic value of plasma SDF-1 α levels and circulating CD34+CXCR4+ cells (Figure 3).

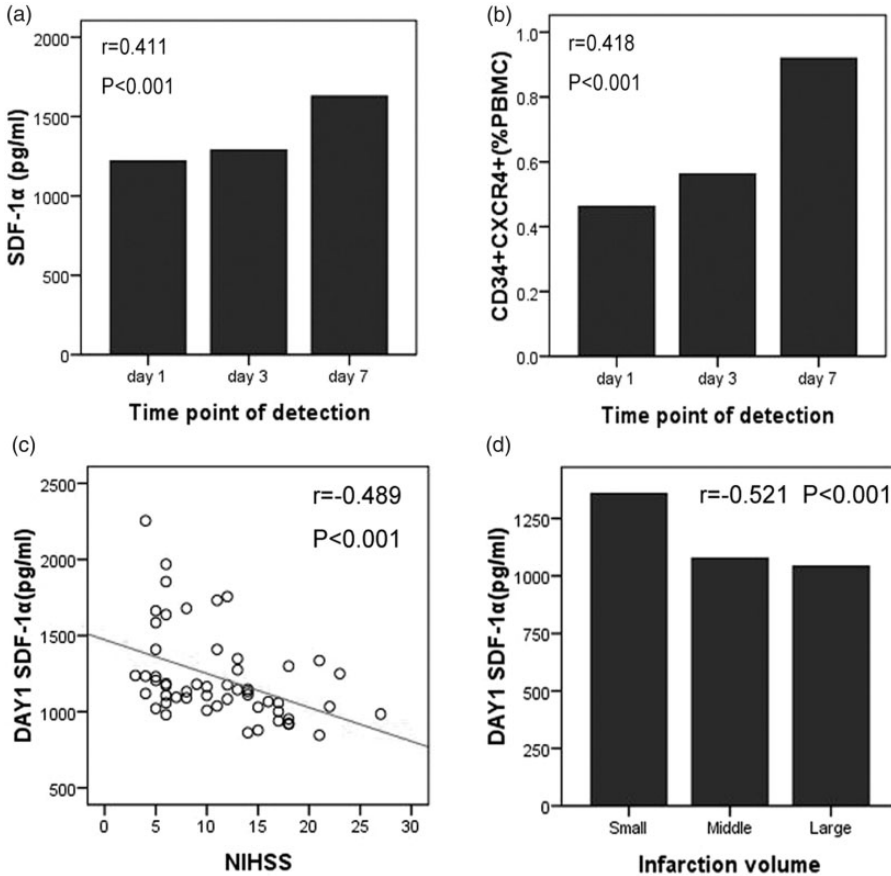


Figure 2. Plasma SDF-1 α levels and CD34+CXCR4+ cells on different days and the relations between plasma SDF-1 α levels on day 1 and clinical severity. (a) Positive correlation between SDF-1 α levels and different time points. (b) Positive correlation between circulating CD34+CXCR4+ cell numbers and different time points. (c) Inverse correlation between SDF-1 α levels (day 1) and the initial NIHSS score. (d) Inverse correlation between SDF-1 α levels (day 1) and infarct volume. SDF-1 α , stromal cell-derived factor-1 α ; CXCR4, cysteine-X-cysteine chemokine receptor 4; NIHSS, National Institutes of Health Stroke Scale.

We found significantly negative correlations between SDF-1 α levels and the 90-day mRS score (day 1: $r=-0.514$, $P<0.001$; day 3: $r=-0.275$, $P=0.042$; day 7: $r=-0.375$; $P=0.005$). However, only day 7 circulating CD34+CXCR4+ cells were inversely correlated with the 90-day mRS score ($r=-0.282$, $P=0.037$).

We then assessed the prognostic value of the incremental rates from days 1 to 7 for

plasma SDF-1 α levels and circulating CD34+CXCR4+ cells (Figure 4). A significantly negative correlation was found between the incremental rates of circulating CD34+CXCR4+ cells and the 90-day mRS score ($r=-0.356$, $P=0.008$). However, no correlation was found between the incremental rates of plasma SDF-1 α levels and the 90-day mRS score ($r=-0.163$).

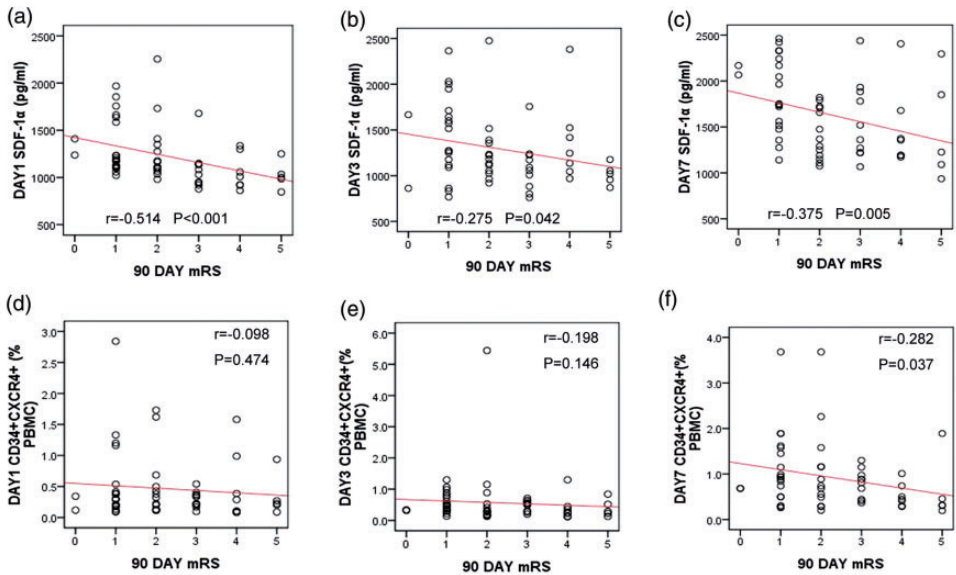


Figure 3. Prognostic values of the SDF-1 α /CXCR4 axis. (a, b, c) Negative correlations between SDF-1 α levels and the 90-day mRS score. (d, e, f) Negative correlations between circulating CD34+CXCR4+ cells and the 90-day mRS score. SDF-1 α , stromal cell-derived factor-1 α ; CXCR4, cysteine-X-cysteine chemokine receptor 4; mRS, modified Rankin Scale; PBMCs, peripheral blood mononuclear cells.

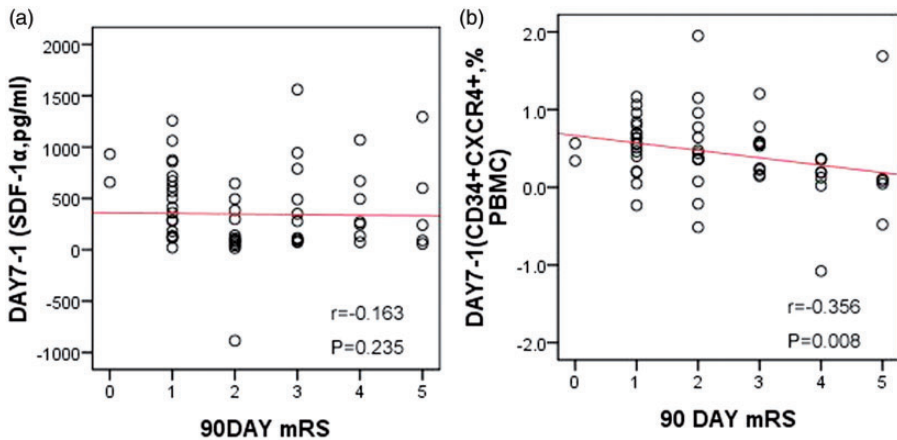


Figure 4. Prognostic value of the incremental rates of plasma SDF-1 α levels and circulating CD34+CXCR4+ cells. (a) There was no correlation between the incremental rates of plasma SDF-1 α levels and the 90-day mRS score. (b) Significantly negative correlation between the incremental rates of circulating CD34+CXCR4+ cells and the 90-day mRS score. SDF-1 α , stromal cell-derived factor-1 α ; CXCR4, cysteine-X-cysteine chemokine receptor 4; mRS, modified Rankin Scale; PBMCs, peripheral blood mononuclear cells.

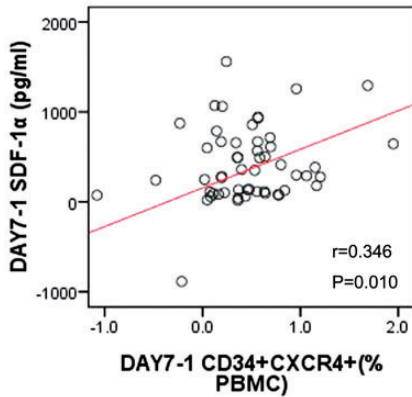


Figure 5. Correlation between the incremental rates of circulating CD34+ CXCR4+ cells and plasma SDF-1 α levels from days 1 to 7. A significantly positive correlation was observed between the change in circulating CD34+ CXCR4+ cells and plasma SDF-1 α levels. SDF-1 α , stromal cell-derived factor-1 α ; CXCR4, cysteine-X-cysteine chemokine receptor 4; PBMCs, peripheral blood mononuclear cells.

Correlations between plasma SDF-1 α levels and circulating CD34+CXCR4+ cells

From days 1 to 7, the change in plasma SDF-1 α levels and circulating CD34+CXCR4+ cells showed a significantly positive correlation ($r=0.346$, $P=0.01$, Figure 5).

Discussion

In this study, we estimated the predictive role of the SDF-1 α /CXCR4 axis in AIS. First, in the AIS group, plasma SDF-1 α levels and the number of circulating CD34+CXCR4+ cells were significantly higher than those in control group. Second, SDF-1 α levels on day 1 were negatively correlated with infarct volume and the initial NIHSS score. Moreover, plasma SDF-1 α levels and circulating CD34+CXCR4+ cell numbers were inversely associated with the 90-day mRS score.

These data suggest that the SDF-1 α /CXCR4 axis may be an important prognostic predictor in AIS. Additionally, an unexpected finding was a hysteresis effect on the prognostic values of circulating CD34+CXCR4+ cells.

Circulating SDF-1 α levels in AIS have been evaluated in several studies.^{9,10,15,16} However, the conclusions of these studies are conflicting. An previous study reported that SDF-1 α levels were significantly increased approximately 7 days after stroke onset, but not within 24 hours.¹⁵ Kim et al. and Bogoslovsky et al.^{9,16} then showed a significant increase in circulating SDF-1 α levels in ischemic stroke within 24 hours. However, Wurster et al.¹⁰ recently found no difference in SDF-1 α levels between patients with stroke and controls. In contrast to these studies, we found significantly higher plasma SDF-1 α levels in patients with AIS compared with controls within 24 hours. Furthermore, SDF-1 α levels progressively increased during the first week of onset.

Several possible mechanisms may contribute to the discrepancies between studies. First, the enrolled subjects in previous studies were heterogeneous. In previous studies, patients with proximal and distal, as well as anterior and posterior circulation occlusions, were included.^{9,17} In our study, a unique characteristic of the patients was MCAO in the M1 segment. Second, the different time points of SDF-1 α detection may lead to the discrepancies. For this reason, we dynamically measured SDF-1 α levels on days 1, 3, and 7 in the present study. Additionally, animal studies have shown that SDF-1 α mainly mediates CXCR4 signaling in neurogenesis after cerebral ischemia.² Therefore, in our study, we also found that circulating CD34+CXCR4+ cell numbers were significantly higher in the AIS group compared with the control group, and progressively increased during the first week of onset. Furthermore, a striking

correlation was found between the incremental rates of CD34+CXCR4+ cells and plasma SDF-1 α levels. Taken together, these findings suggest that the SDF-1 α /CXCR4 axis participates in pathophysiological activity after stroke.

Animal models have shown that the SDF-1 α /CXCR4 axis promotes neuroprotection, angiogenesis, and mobilization/homing of bone marrow-derived cells in stroke, and can improve neurological function.²⁻³ Similarly, Kim et al.⁹ showed that serum SDF-1 α levels independently predicted a favorable outcome in patients with AIS. However, these authors did not examine the SDF-1 α /CXCR4 axis for predicting the outcome of AIS. Recently, a study reported that circulating CD133+CD34+ cells and plasma SDF-1 α levels can be used as predictive parameters for severity of AIS and short-term outcome (21 days).¹⁷ Consistent with these studies, we also showed a negative relation between SDF-1 α levels and the severity of stroke. Moreover, plasma SDF-1 α levels and circulating CD34+CXCR4+ cells were inversely associated with the 90-day mRS score. To the best of our knowledge, this is the first report on the prognostic value of the SDF-1 α /CXCR4 axis in AIS.

A possible mechanism of the prognostic value of the SDF-1 α /CXCR4 axis in AIS is that SDF-1 α promotes angiogenesis via its receptor CXCR4 during the acute phase of ischemia.^{3,8} SDF-1 α is secreted by BMSCs in several organs. Under a hypoxic condition, SDF-1 α levels are increased. SDF-1 α interacts with CXCR4 to move CD34+ cells from bone marrow to peripheral blood, and modulates angiogenesis.¹⁸ Furthermore, the SDF-1 α /CXCR4 axis may participate in regulating migration and proliferation of smooth muscle cell progenitors, which are involved in growth and maturation of capillaries and arterioles.¹⁹

The neuroregenerative and neuroprotective effect of the SDF-1 α /CXCR4 axis may

be another explanation for recovery after stroke. Circulating progenitor cells participate in tissue repair in response to ischemic injury. The SDF-1 α /CXCR4 axis promotes migration of progenitor cells to injured locations after stroke.⁷ Studies have shown that SDF-1 α can attract CD34+ cells to promote migration and this effect can be inhibited by CXCR4 antagonists.^{7,20} Additionally, Chiazza et al.²¹ found that the SDF-1 α /CXCR4 axis was involved in a gliptin-mediated neuroprotective mechanism via regulation of Ca²⁺ homeostasis and a reduction of calpain activity. Furthermore, SDF-1 α exerts its neuronal survival effect by increasing the synthesis or release of many neurotrophic factors to protect neurons.²

Notably, there was a hysteresis effect on the prognostic value of CD34+CXCR4+ cells in our study. We speculate that the delayed beneficial effect might be the result of SDF-1 α -mediated neuroregeneration. Neuroregeneration encompasses multiple processes, such as cell proliferation, and migration and differentiation of recruited cells. Additionally, we did not find a relationship between the incremental rates of plasma SDF-1 α levels and the 90-day mRS score. However, a higher incremental rate of CD34+CXCR4+ cells during the first week was associated with a lower 90-day mRS score. This finding could be explained by the fact that SDF-1 α acts not only through binding CXCR4, but also via binding a new receptor CXCR7 to have a biological effect. SDF-1 α may influence vascular, astroglial, and neuronal functions via CXCR7, and mediate cell recruitment to ischemic brain areas via CXCR4.¹⁸

This study has several limitations. First, this study was limited by the relatively small sample size. Selection biases may have occurred. Our results require independent confirmation with future large prospective studies. Additionally, the rate of a history of hypertension ($P=0.060$) and diabetes

($P=0.070$) tended to be higher in the AIS group than in the control group. Mismatch of cardiovascular risk factors between the groups may have resulted in bias. Second, we did not perform multivariate analysis between the outcome of stroke and the SDF-1 α /CXCR4 axis because of the small sample size. Another potential limitation is the fact that none of the biomarkers is disease specific and may be affected in the setting of medical comorbidities.

Conclusions

Our study shows that plasma SDF-1 α levels and the number of circulating CD34+CXCR4+ cells are significantly higher in patients with AIS than in controls. These findings suggest that the SDF-1 α /CXCR4 axis maybe an important biomarker for AIS. Furthermore, plasma SDF-1 α levels and circulating CD34+CXCR4+ cells are associated with the severity of stroke and the 90-day mRS score. This relationship can be explained by enhanced endogenous neurogenesis and angiogenesis via the SDF-1 α /CXCR4 axis. Therefore, we consider that the SDF-1 α /CXCR4 axis has potential clinical applications for predicting the clinical outcome in AIS. Although further studies are required, our results add to the literature regarding the SDF-1 α /CXCR4 axis and stroke in humans, and provide novel insight for subsequent studies.

Authors' contributions

XJ Huang and ZM Zhou designed the study. M Wan, Q Yang, and XH Ding collected the data. XJ Huang and M Wan wrote the manuscript. The manuscript was supervised and finally edited by ZM Zhou. All the authors read, edited, and approved the final version of the manuscript.

Declaration of conflicting interest

The authors declare that they have no conflict of interest.

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