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Expression and significance of HMOX1, STAT3, ferritin, GPX4, and hs-CRP in patients with ischemic stroke

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Abstract

Background & Objective: Ischemic stroke (IS) is a leading cause of global mortality and disability, and as such, reliable biomarkers for its early diagnosis and prognosis are needed. This study explored the expression and clinical relevance of HMOX1, STAT3, ferritin, GPX4, and hs-CRP in patients with IS. *Methods:* The serum levels of these biomarkers in 159 patients with IS and 150 healthy controls were compared and analyzed across subgroups stratified by neurological severity, infarct size, and clinical outcomes. *Results:* IS patients showed higher levels of HMOX1, STAT3, ferritin, and hs-CRP, as well as lower GPX4 levels, than healthy controls (all $p < 0.05$). Biomarker levels differed significantly among mild-, moderate-, and severe-stroke groups, as well as across different infarct sizes. Diabetes history increased the infarction deterioration risk by 2.86-fold. Among the biomarkers, hs-CRP, ferritin, and GPX4 demonstrated predictive value for disease progression, with AUC values of 0.608, 0.611, and 0.729, respectively, while HMOX1 and STAT3 did not distinguish progression status.
Conclusion: Serum levels of HMOX1, STAT3, ferritin, GPX4, and hs-CRP are potential biomarkers for assessing IS severity and prognosis.

Keywords: Ischemic stroke, HMOX1, STAT3, hs-CRP, GPX4, ferritin, prognosis.

INTRODUCTION

Ischemic stroke (IS) is caused by transient or irreversible blockage of cerebral blood vessels and the ensuing disruption of the oxygen and glucose supply to neural tissue as well as accumulation of toxic metabolic byproducts. Severe ischemia in the core of the vessel perfusion field usually leads to rapid necrosis and irreversible neurological impairment, while less severe ischemia in the surrounding region (penumbra) results in sporadic and slower neurodegeneration due to pathogenic processes that trigger programmed cell death (PCD), such as glutamate excitotoxity, calcium dysregulation, oxidative stress, and neuroinflammation.[1-3] While this slower neurodegeneration in the penumbra provides a therapeutic window for intervention, successful treatment requires a more complete understanding of the mechanisms and pathways mediating PCD. Evidence accrued over the past decade indicates that there are multiple distinct forms of PCD contributing to IS-associated neurodegeneration, including classical apoptosis, pyroptosis, and ferroptosis.[4] Among these, ferroptosis is now strongly implicated in neurodegeneration following IS and an emerging candidate target for treatment.[5,6]

Heme oxygenase 1 (HMOX1) is an antioxidant, anti-inflammatory, and cytoprotective enzyme demonstrated to alleviate intestinal, renal, and cardiac ischemia-reperfusion injury through regulation of ferroptosis.[7-10] Liu *et al*.[11] identified 4 candidate therapeutic targets for acute IS related to ferroptosis, including HMOX1, and reported that elevated HMOX1 demonstrated good diagnostic performance as a biomarker. The transcription factor signal transducer and activator of transcription 3 (STAT3) also regulates ferroptosis[12,13] and similarly was identified as a candidate therapeutic target.[11]

In addition to pathogenic mechanisms and therapeutic targets, it is essential to identify minimally invasive biomarkers for diagnosis, prognosis, and treatment response. For this

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purpose, blood biomarkers are highly valued as samples can be collected conveniently and safely at multiple time points during the disease course. The current study examined the changes in peripheral blood HMOX1, STAT3,C-reactive protein (CRP), and other ferroptosis-related factors after IS and the utility of these markers for severity evaluation and prognosis.

METHODS

Patient and control groups

In this study, 159 inpatients admitted to Nanchong Central Hospital in Sichuan Province between August 2023 and July 2024, as well as 150 healthy individuals who underwent routine physical examinations at the same hospital during this period, were recruited as research participants. All relevant clinicodemographic information was collected and recorded from both groups. Inclusion criteria were as follows: (1) diagnosis according to Chinese Stroke Association guidelines for clinical management of ischaemic cerebrovascular diseases: executive summary and 2023 update[14], (2) 40–80 years of age, (3) first disease onset or past stroke without sequelae, (4) anterior circulation cerebral infarction confirmed by cranial computed tomography (CT) or magnetic resonance imaging (MRI), (5) treated within 24 h of symptom onset, (6) paralyzed limb muscle strength grade 0–4 and National Institutes of Health Stroke Scale (NIHSS) score 1–25 at presentation, and (7) providing informed consent. Exclusion criteria were (1) cerebral hemorrhage, subarachnoid hemorrhage, or intracranial aneurysm during the study period, (2) comorbid severe cardiovascular disease, liver disease, kidney disease, or tumors at presentation, (3) coma with unstable vital signs, (4) history of psychiatric disorders, (5) unwilling to participate or with incomplete clinical data, and (6) receiving intravenous thrombolysis or arterial thrombectomy during the study period. All patients provided a 5-mL peripheral blood sample at admission. The study was approved by the institutional ethics committee (ethics approval no.: 2023 (064)) and conducted in compliance with the Declaration of Helsinki (1964 and all subsequent amendments).

The following demographic and clinical variables were collected for analysis: age, sex, height, weight, time of onset, past medical history (such as hypertension, hyperlipidemia, diabetes mellitus, and atrial fibrillation), cranial MRI/CT examination results, NIHSS score (on admission and 72 h post-onset).

All patients were treated according to Chinese Stroke Association guidelines for clinical management of ischaemic cerebrovascular diseases: executive summary and 2023 update.[14] Antiplatelet aggregation, anticoagulant, and anti-arteriosclerosis drugs were administered, such as aspirin, clopidogrel, rivaroxaban, dabigatran, warfarin, and statins. Blood pressure and blood glucose level were controlled, and cerebral edema alleviation, brain cell protection, and symptomatic and supportive treatments were administered as required.

Stroke severity was evaluated according to the NIHSS, and patients subgrouped as mild (1–4 points), moderate (5–15 points), and severe (>15 points) according to established classification guidelines.

Based on the focal volume of cerebral infarction, patients were divided into three groups: a small-size infarction group (<5 cm^3), medium-size infarction group (5–10 cm^3), and large-size infarction group (>10 cm^3).

Control group participants were physically healthy adults receiving physical examinations and providing a 5-mL peripheral venous blood sample during the study period. All provided informed consent before participation.

Experimental materials

Blood samples were centrifuged at 3000 × g for 15 min while avoiding intense shaking and heat. The supernatant was collected, labeled, and stored at −80°C until analysis, which was conducted within a week of sample collection. Briefly, samples were rewarmed to room temperature and aliquoted for testing. Serum concentrations of HMOX1, STAT3, GPX4, and ferritin were measured by enzyme-linked immunosorbent assay (ELISA) kits (Human HMOX1 ELISA Kit and STAT3 ELISA Kit, Thermo Fisher Scientific, USA; GPX4 ELISA Kit, Shanghai Shuangying Biotechnology Co., Ltd.; Ferritin ELISA Kit, DRG, Germany). The hs-CRP was measured using an immunoturbidimetric assay kit (Shanghai Huzhen Biotechnology Co., Ltd.).

Observational indices for statistical analysis

The following inter-group and intra-group comparisons were included in the statistical analyses: 1) baseline characteristics between patient and control groups; 2) concentrations of peripheral blood HMOX1 and other ferroptosis-related markers between patient and control groups, among patients stratified by neurological

impairment severity (NIHSS score), and between patients stratified by clinical outcome (worsening vs. non-worsening).

Statistical methods

All statistical analyses and data graphing were conducted using GraphPad Prism 8.2.1. Quantitative data are expressed as mean ± standard deviation (x ± SD). Continuous variables were compared using one-way analysis of variance followed by Tukey's post-hoc test for multi-group comparisons, or the Mann-Whitney U test for non-normally distributed data (as assessed by the Shapiro-Wilk test). Categorical data were analyzed using the χ^2 test with Yates' correction. $P < 0.05$ (two-tail) was considered statistically significant for all tests.

RESULTS

Patients and controls were well-matched for baseline demographic and clinical characteristics

The baseline clinicodemographic characteristics of the IS and control groups are shown in Table 1. Groups were well-matched in terms of age and sex ratio. Additionally, the frequencies of stroke-related risk factors did not differ significantly between the two groups.

Serum ferroptosis-related marker concentrations increased in parallel with clinical severity score among IS patients

Serum HMOX1, STAT3, ferritin, and hs-CRP concentrations were significantly higher in the IS group than the control group upon admission (all $p < 0.05$, Table 2), while the GPX4 concentration was significantly lower ($p < 0.05$, Table 2). These factors also differed among the mild-, moderate-, and severe-stroke groups stratified by NIHSS score (all $p < 0.05$). Furthermore, post-hoc pairwise comparisons revealed that the HMOX1, STAT3, ferritin, and hs-CRP concentrations were significantly higher in both the severe-stroke group and large-size infarction group than their respective mild-stroke or small-size counterparts (all $p < 0.05$). Additionally, the ferritin concentrations were higher in the moderate-stroke and medium-size infarction groups (both $p < 0.05$; Tables 3 and 4), and GPX4 concentrations were lower in the moderate-stroke group ($p < 0.001$; Table 3).

Serum ferroptosis-related marker concentrations were higher in IS patients exhibiting short-term deterioration

The patient subgroup characterized by deterioration was defined as consisting of those patients exhibiting an increase of ≥ 2 points in the NIHSS score within 72 hours of onset. Compared to the non-deteriorating group, the proportion of patients with diabetes in the deteriorating group was significantly higher ($p < 0.05$, Table 5). Furthermore, multivariate logistic regression analysis, adjusted for age, sex, hypertension, hyperlipidemia, and atrial fibrillation, revealed that patients with a history of diabetes had a 2.86-fold increased risk of deterioration compared to those without a history of diabetes (95% CI: 1.166–7.016) (Table 6).

The levels of hs-CRP and ferritin were significantly higher in the deteriorating group than those in the non-deteriorating group (hs-CRP, $p < 0.05$; ferritin, $p < 0.001$). Conversely, GPX4 levels were lower in the deteriorating group than those in the non-deteriorating group ($p < 0.05$). There were no significant differences in the protein levels of HMOX1 or STAT3 between the two groups (both $p > 0.05$, Table 7). The AUC values for

Table 1: Comparison of baseline data between the ischemic stroke group and control group

Indicator	Ischemic stroke group (n=159)	Control group (n=150)	$\chi^{2/t}$	P-value
Age (years)	63.26±9.45	62.14±11.69	0.932	0.352
Gender (Male, N(%))	96(48)	104(52)	0.067	0.796
Hypertension (Yes, N(%))	99(48.3)	106(51.7)	0.015	0.901
Diabetes (Yes, N(%))	51(49.5)	52(50.5)	0.058	0.809
Hyperlipidemia (Yes, N(%))	58(47.9)	63(52.1)	0.03	0.863
Smoking History (Yes, N(%))	71(47.7)	78(52.3)	0.127	0.721
Alcohol History (Yes, N(%))	69(48.9)	72(51.1)	0.016	0.899
Atrial Fibrillation (Yes, N(%))	12(44.4)	15(55.6)	0.199	0.656

Table 2: Comparison of ferroptosis-related marker levels in peripheral blood between the cerebral infarction group and control group

Item	Ischemic stroke group (n=159)	Control group (n=150)	t	P-value
HMOX1 (ng/mL)	5.18±4.27	3.62±2.89	3.995	<0.001
STAT3 (ng/mL)	13.34±8.55	10.67±5.27	10.69	<0.001
GPX4 (pmol/L)	17.96±6.94	20.62±8.85	2.156	0.036
Ferritin (μg/L)	147.85±53.18	94.93±26.14	3.235	0.001
hs-CRP (mg/L)	2.64±1.13	1.42±0.91	3.235	0.001

predicting cerebral infarction progression were 0.608 ($p < 0.05$) for hs-CRP, 0.611 ($p < 0.05$) for GPX4, and 0.729 ($p < 0.001$) for ferratin, (Table 8).

DISCUSSION

Biomarkers indicative of disease onset and progression are invaluable for diagnosis and prognosis, especially blood biomarkers as analytic samples can be collected conveniently at multiple times with minimal patient discomfort. We report that peripheral blood HMOX1 and STAT3 concentrations are elevated in patients with IS, consistent with the bioinformatics analysis by Liu *et al.*[11] Moreover, the serum concentration of HMOX1 increased progressively with neurological impairment severity, and short-term deterioration, strongly suggesting a direct contribution to post-stroke pathogenesis. In addition, plasma HMOX1 concentration distinguished patients from controls with relatively high sensitivity and specificity, indicating good diagnostic utility. These results provide a rationale for further studies on the pathogenic functions of HMOX1 signaling in stroke and the association with ferroptosis.

Ferroptosis is a type of PCD associated with aberrant free ferrous iron accumulation and oxidative stress. As a key enzyme in heme catabolism, excessive activation of HMOX1 can lead to the accumulation of free Fe^{2+}, which generates excessive reactive oxygen species (ROS) via the Fenton reaction, thereby inducing lipid peroxidation.[20] This study found that peripheral blood HMOX1 levels in patients with IS were positively correlated with infarct volume and NIHSS scores, which is consistent with previous reports highlighting the pro-oxidant role of HMOX1 in cerebral ischemia-reperfusion injury.[21] Notably, HMOX1 can translocate to the nucleus and interact with STAT3[22], while STAT3 phosphorylation is a central event in JAK/STAT signaling pathway activation. We observed that STAT3 levels in patients with IS positively correlated with HMOX1, and both showed a negative correlation with GPX4. These findings align with the proposed mechanism that HMOX1 enhances STAT3 phosphorylation via the IL-6/JAK2/STAT pathway[23], suggesting

Table 3: Expression levels of ferroptosis-related proteins in ischemic Fstroke group with different neurological deficits

Item	Severe ischemic stroke group (n=32)	Moderate ischemic stroke group (n=68)	Mild ischemic stroke group (n=59)	F	P-value
HMOX1 (ng/mL)	6.43±5.02[a]	5.55±3.14	4.08±2.75	5.439	0.005
STAT3 (ng/mL)	18.08±10.73[ab]	13.17±7.41	11.25±7.38	7.333	0.001
Ferritin (μg/L)	190.52±61.26[ab]	164.82±40.01[c]	110.56±26.70	46.881	< 0.001
GPX4 (pmol/L)	11.83±4.67[ef]	16.54±6.28[d]	22.91±5.26	44.169	< 0.001
hs-CRP(mg/L)	4.43±2.06[a]	3.39±1.06	1.54±1.19	4.936	0.008

[a]$P < 0.05$, compared with severe ischemic and mild ischemic groups.
[b]$P < 0.05$, compared with moderate ischemic and severe ischemic groups.
[c]$P < 0.01$, compared with moderate ischemic and mild ischemic groups.
[d]$P < 0.05$, compared with moderate ischemic and mild ischemic groups.
[e]$P < 0.001$, compared with severe ischemic and mild ischemic groups.
[f]$P < 0.001$, compared with severe ischemic and moderate ischemic groups.

Table 4: Expression levels of ferroptosis-related proteins in ischemic stroke group with different infarct size

Item	Large size infarction group (n=39)	Medium size infarction group (n=66)	Small size infarction group (n=54)	F	P-value
HMOX1(ng/ml)	5.78±4.78[a]	5.79± 3.10[b]	4.00± 2.76	4.67	0.011
STAT3(ng/ml)	16.90± 10.48[c]	13.51± 7.57	10.55± 7.20	6.71	0.002
Ferritin (μg/L)	192.42±61.68[de]	156.00± 33.75[f]	105.70±20.89	57.36	<0.001
GPX4(pmol/L)	15.78±8.05[d]	17.90±5.96	19.62±6.86	3.59	0.030
hs-CRP(mg/L)	4.34±3.54[c]	2.66± 1.20	1.40± 0.69	6.19	0.003

[a]P < 0.05, compared with large size infarction and small size infarction groups.
[b]P < 0.05, compared with medium size infarction and small size infarction groups.
[c]P < 0.01, compared with large size infarction and medium size infarction groups.
[d]P < 0.001, compared with large size infarction and small size infarction groups.
[e]P < 0.001, compared with large size infarction and medium size infarction groups.
[f]P < 0.001, compared with medium size infarction and small size infarction groups.

that in IS, HMOX1 may suppress GPX4 expression by activating the JAK2/STAT3 pathway, thereby impairing cellular antioxidant capacity and promoting ferroptosis. While our data show correlated changes in serum markers, it should be noted that peripheral levels may reflect systemic inflammation rather than brain-specific mechanisms. Previous animal studies suggest HMOX1-STAT3 interactions in cerebral ischemia[23], but the cellular origins of these serum proteins require further validation. GPX4 is a critical negative regulator of ferroptosis, and its dysfunction impairs the clearance of lipid peroxides.[24] In this study, GPX4 levels decreased with infarct severity in patients with IS, exhibiting an inverse trend compared to HMOX1/STAT3, implying their potential co-regulation of GPX4 through a shared pathway. Previous studies have demonstrated that STAT3 activation can directly bind to the GPX4 promoter region and suppress its transcription.[25] For instance, curcumin has been shown to upregulate GPX4 expression and alleviate neuronal ferroptosis by inhibiting the JAK2/STAT3 pathway.[26,27] Integrating these findings with our results, we hypothesize that the HMOX1–STAT3 axis may transcriptionally repress GPX4, thereby forming a vicious cycle of "oxidative stress–inflammation–ferroptosis."

In the current cohort of IS patients, STAT3 concentration in serum increased progressively with neurological severity, and with the degree of neurological deterioration post-onset. As expected, ferritin concentration was significantly elevated following IS, with its concentration increasing with greater neurological dysfunction at presentation and further deterioration in the patient's condition occurring over subsequent days. In contrast, GPX4 concentrations decreased after IS, with their levels declining with worsening neurological dysfunction at presentation and

Table 5: Comparison of baseline data between the deteriorating and non-deteriorating groups of ischemic stroke

Item	Deteriorating group (n=26)	Non-Deteriorating group (n=133)	$\chi^{2/t}$	P-value
Age (years)	65.543±8.04	62.82±9.67	1.345	0.181
Gender (Male, N(%))	18(69.23)	86(64.66)	0.201	0.654
Hypertension (Yes, N(%))	16(61,54)	90(67.67)	0.368	0.544
Diabetes (Yes, N(%))	13(50.00)	39(29.32)	4.225	0.04
Hyperlipidemia (Yes, N(%))	10(38.46)	53(39.85)	0.018	0.895
Smoking History (Yes, N(%))	10(38.46)	62(46.62)	0.584	0.445
Alcohol History (Yes, N(%))	14(53.85)	64(48.12)	0.25	0.617
Atrial Fibrillation (Yes, N(%))	2(7.7)	13(9.77)	0.11	0.74

Table 6: Multivariate logistic regression analysis of ischemic stroke deterioration

	B	S.E.	Wald	Sig.	Exp(B)	95% C.I	
						Lower limit	Upper limit
Gender (Female Reference)	-0.178	0.492	0.131	0.718	0.837	0.319	2.196
Age	0.043	0.027	2.609	0.106	1.044	0.991	1.1
Hypertension History (No Reference)	-0.228	0.465	0.241	0.624	0.796	0.32	1.98
Diabetes History (No Reference)	1.051	0.458	5.271	0.022	2.86	1.166	7.016
Hyperlipidemia (No Reference)	0.082	0.476	0.03	0.863	1.085	0.427	2.757
Smoking History (No Reference)	0.244	0.464	0.277	0.599	1.276	0.514	3.169
Alcohol History (No Reference)	-0.28	0.458	0.372	0.542	0.756	0.308	1.857
Atrial Fibrillation (No Reference)	-0.327	0.818	0.16	0.69	0.721	0.145	3.582

Table 7: Comparison of ferroptosis-related marker levels in peripheral blood between the deteriorating and non-deteriorating groups

Item	Deteriorating group (n=26)	Non-deteriorating group (n=133)	t	P-value
HMOX1 (ng/mL)	5.87±2.12	5.18±2.51	0.754	0.452
STAT3 (ng/mL)	14.06±4.37	13.20±3.78	0.468	0.640
GPX4 (pmol/L)	15.47±6.13	18.45±4.75	-2.026	0.044
Ferritin (μg/L)	182.19±63.17	142.14±46.31	3.88	<0.001
hs-CRP (mg/L)	4.76±1.99	2.23±1.01	2.084	0.046

Table 8: Predictive value of hs-CRP, GPX4, and Ferritin for ischemic stroke deterioration

Indicator	AUC	95% Confidence interval	Sensitivity	Specificity	Optimal cutoff	Youden index	P-value
GPX4	0.611	(0.509,0.713)	0.623	0.633	19.80	0.256	0.019
Ferritin	0.729	(0.590,0.852)	0.654	0.917	196.33	0.571	<0.001
hs-CRP	0.608	(0.52,0.696)	0.597	0.694	0.85	0.291	0.023

then further dropping as the patient's condition deteriorated over time. Collectively, these findings support ferroptosis as a significant contributor to neural injury and death during the early post-stroke period. Therefore, the suppression of ferroptosis through modulation of HMOX1, STAT3, or other regulators may be an effective strategy for reducing neurological damage and accelerating post-stroke recovery.

The pathogenesis of IS is complex, involving both acute necrosis and multiple forms of PCD activated by several mutually interacting mechanisms such as calcium dysregulation, oxidative stress, and neuroinflammation. High-sensitivity-CRP is an inflammatory marker reliably upregulated by cerebro-cardiovascular atherosclerosis and IS.[28] In the current study as well, peripheral blood hs-CRP concentration was markedly higher at IS presentation compared to healthy controls, in accord with Teng *et al.*[29] and further implicating neuroinflammation in early IS pathogenesis. Also, similar to the other markers, hs-CRP concentration increased with IS severity, indicating that hs-CRP concentration is indicative

of the severity of neuroinflammation, and that the strength of the neuroinflammatory response is directly associated with IS severity and risk of progression.

Moreover, peripheral blood HMOX1, STAT3, hs-CRP, GPX4, and ferritin concentrations can serve as indicators of stroke onset and severity, with hs-CRP, GPX4, and ferritin also predicting short-term outcomes. These findings strongly suggest that these biomarkers are involved in stroke pathogenesis and thus represent promising therapeutic targets.

Additionally, the association between diabetes and stroke progression may be mechanistically linked to ferroptosis. This study found that patients with a history of diabetes have a 2.86-fold higher risk of cerebral infarction progression than those without diabetes. This finding supports the potential role of diabetes in influencing cerebral infarction prognosis. Relevant research also suggests that diabetes may exacerbate ferroptosis by influencing iron metabolism or oxidative stress.[30] Therefore, patients with diabetes should receive intensified monitoring and management during both the acute phase and recovery phase of cerebral infarction to help slow disease progression.

This study has several limitations. Common to many investigations on the identification of blood biomarkers is the uncertain relationship with brain concentrations and related processes. In support of the notion that an elevation in blood concentration reflects enhanced brain production, many cell type-specific factors are found in serum following damage to the source cells, such as elevated glia-specific proteins following glial damage.[31] However, there are at least two mechanisms for the release of brain molecules into the circulation, damage to the blood-brain barrier and ensuing passive leakage, and active egress via the glymphatic system, which reflects a reparative mechanism rather than neural pathology per se. Moreover, the time to peak blood concentrations is highly variable and unpredictable[31], and we did not collect samples at multiple time points. Additional preclinical and clinical studies are required to confirm the relationship between neuronal production of these factors and corresponding elevations in peripheral blood. Also, the kinetics of these increases must be described with greater precision. Finally, we did not examine the diagnostic or prognostic efficacy of multiple factors, which may yield superior performance.

These results demonstrate the potential of serum HMOX1, STAT3, ferritin, GPX4, and hs-CRP as promising biomarkers for evaluating IS severity and short-term prognosis. However, this study only evaluated short-term outcomes (within 72 hours post-onset) using NIHSS score changes, and did not assess long-term functional prognosis (e.g., 90-day mRS score). Future studies should include extended follow-up periods to validate the prognostic value of these biomarkers for clinical recovery. However, larger-scale multicenter clinical studies are required to validate these findings for routine application in clinical practice.

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