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Serum level of macrophage migration inhibitory factor predicts severity and prognosis in patients with ischemic stroke

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ABSTRACT

Objective: To evaluate whether the macrophage migration inhibitory factor (MIF) level in serum of ischemic stroke patients was associated with their clinical severity and early outcome.

Methods: During February 2017–March 2018, consecutive patients admitted to our hospital because of first-ever ischemic stroke were identified. The prognostic value of MIF was set for predicting the outcome of these patients at discharge. The results were compared with existing methods, including National Institutes of Health Stroke Scale (NIHSS) score and validated indicators.

Results: 289 patients were enrolled. The serum level of all patients was determined (median: 20.6 ng/ml). At admission, 131 patients (45.3%) were evaluated as minor stroke (NIHSS < 5). When serum level of MIF was increased by each 1 ng/ml, the unadjusted and adjusted risk of moderate-to-high clinical severity was elevated by 5% (OR = 1.05 [95% CI: 1.01–1.09], P = 0.006) and 3% (1.03 [1.00–1.08], P = 0.02), respectively. At discharge, 82 patients (28.4%) had poor functional outcomes. The median serum level of MIF was lower in group with good outcomes than that observed in poor outcomes (19.4[15.8–24.2] vs. 24.0[19.9–29.4] ng/ml; P < 0.001). When serum level of MIF was increased by each 1 ng/ml, the unadjusted and adjusted risk of poor outcomes was elevated by 9% (1.09 [1.05–1.13], P < 0.001) and 6% (1.06 [1.02–1.10], P < 0.01), respectively.

Conclusions: High MIF levels are independently related to the moderate to high clinical severity in ischemic stroke patients, as well as the poor outcome at discharge.

1. Introduction

Inflammatory processes played essential roles in ischemic stroke [1]. Furthermore, during the onset of cerebral ischemia, multiple molecular and cellular responses would be triggered [2]. The severity of acute inflammatory response was reported to greatly affect cerebral injury degree, early and late clinical outcomes, as well as clinical worsening [3–6]. Inflammatory factors were applied for predicting adverse stroke outcome, such as C-reactive protein (CRP) [7], interleukin-6 [8] and intercellular adhesion molecule-1 [9].

Macrophage migration inhibitory factor (MIF) has been a critical regulator for innate immunity, functioned in the pathophysiological process of inflammation [10]. Previous studies had reported that high MIF levels were in relation with rising risk of cardiovascular diseases [11], such as myocardial infarction [12], atherosclerosis [13–16] and coronary artery disease [17].

Interestingly, a previous study proposed that serum level of MIF could be a predictor for inflammation, clinical severity and prognosis of intracerebral hemorrhage [18]. Another study suggested that serum MIF levels of patients at admission were positively related to infarct volume and long-term outcome of ischemic stroke [19]. High MIF level in plasma was reported as a risk factor for post-stroke depression [10], and Zis et al. [20] reported that the hypoxia signaling-induced abnormal expression of MIF functioned in neuronal death during stroke. However, in this study, we aimed to explore whether MIF levels were associated with clinical severity or functional outcome in ischemic stroke patients.

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2. Patients and methods

2.1. Ethics

The design of study was reviewed and approved by investigational review board of the Affiliated Hospital of Xinxiang Medical University. The study was carried out per the relevant rules. Informed consents were obtained from patients or their relatives (patients unable to communicate) prior to their inclusion in this study.

2.2. Patients

During February 2017–March 2018, consecutive patients admitted to our hospital because of first-ever ischemic stroke were identified. Symptoms onset was < 24 h. Stroke was diagnosed and identified per World Health Organization recommendations [21]. The exclusion criteria were as follows: (1) malignant tumor; (2) liver and kidney function insufficiency; (3) acute and chronic inflammation; (4) Other neurological diseases (such as intracerebral hemorrhage, cerebral hemorrhage, Parkinson's disease and Alzheimer's disease).

2.3. Clinical variables and laboratory testing

The general information of all the patients was collected at admission, including age, gender and vascular risk factors (hypertension, type 2 diabetes mellitus, hypercholesterolemia, atrial fibrillation, coronary heart disease, previous myocardial infarction and transient ischemic attack). Therapy received before stroke and acute treatment was also recorded. National Institutes of Health Stroke Scale (NIHSS) was referred to evaluate clinical severity at admission. Trial of Org 10,172 in Acute Stroke Treatment (TOAST) criteria were applied to classify the stroke causes, including large-artery arteriosclerosis, cardioembolism, small-artery occlusion, the other causative factor, and undetermined causative factor [22]. Functional outcome at discharge was applied as the endpoint, which was assessed by the modified Rankin Scale (mRS) [23]. The mRS of 0–2 points was identified as a good functional outcome, and 3–6 points indicated poor outcome [24].

The blood samples were collected for MIF determination. The serum of all patients was collected under fasting at 8:00 on the first morning of admission. Furthermore, for some patients (n = 46), serum was collected at 12, 24, 48 and 72 h after admission. Serum level of MIF was determined with Quantikine Human MIF ELISA kit (Catalog Number DMF00B; R&D, Inc. Minneapolis, USA). The determined MIF level was ranged from 2 to 100 ng/ml (a 10-fold dilution). The coefficients of variation (CV) of the intra-assay was 4.5–6.5% and the CV of inter-assay was 6.0–9.0%. Other indicators were also determined with standard assays, such as serum levels of C-reactive protein (CRP), glucose, and interleukin-6 (IL-6) (Quantikine Human IL-6 ELISA Kit, R&D, Inc., Minneapolis, MN, USA). The serum level of tumor necrosis factor alpha (TNF-α) was tested per manufacturer's instructions (OPTEIA ELISA kit, BD, San Jose, CA).

2.4. Statistical analyses

The results of categorical variable and continuous variable were described as percentage and median value (interquartile ranges, IQRs). Chi-square and Mann-Whitney *U* test were applied for comparing the proportions and medians values of baseline characteristics between groups. Logistic regression was utilized for exploring the relationship between serum MIF level and clinical severity (dichotomized as NIHSS < 6 and NIHSS ≥ 6) [25] or functional outcomes (defined as mRS of 3–6 and 0–2). The results were described as odds ratios (OR) with 95% confidence intervals (CI).

The accuracy of serum MIF level for predicting outcome of stroke was evaluated with Receiver operating characteristic (ROC) curves and results were calculated with Area under the curve (AUC). The ROC R package (version 1.0–2) and GraphPad Prism 5.0 were applied for plotting. Furthermore, logistic regression was applied to analyze the risk of poor outcomes when MIF serum levels ≥ cut-off. All statistics was analyzed with SPSS software. P < 0.05 was defined as statistical significance.

Table 1
Characteristics of stroke patients.

	N = 289
Age (years), median (IQR)	61(53–68)
Sex-male, n (%)	155(53.6)
Prior vascular risk factors, n (%)	
Hypertension	211(73.0)
Diabetes	85(29.4)
Hypercholesterolemia	73(25.3)
Coronary heart disease	68(23.5)
Prior TIA	33(11.4)
Atrial fibrillation	48(16.7)
Pre-stroke treatment, n (%)	
Antihypertensive	157(54.3)
Anticoagulant	25(8.7)
Antiplatelet agents	77(26.6)
Statins	69(23.9)
Acute treatment, n (%)	
IV thrombolysis	39(13.5)
Mechanical thrombectomy	12(4.2)
IV thrombolysis and/or mechanical thrombectomy	46(15.9)
Stroke causative factors, n (%)	
Small-vessel occlusive	55(19.0)
Large-vessel occlusive	58(20.1)
Cardioembolic	95(32.9)
Other	11(3.8)
Unknown	70(24.2)
Laboratory findings, median (IQR)	
Glucose level, mmol/L	5.5(4.8–6.9)
C-reactive protein, mmol/L	4.6(2.3–11.0)
White blood cell count	8.4(6.8–9.6)
IL-6, pg/ml	7.7(6.5–9.1)
MIF, ng/ml	20.6(16.9–26.0)
TNF-α, pg/ml	16.8(10.3–23.5)
NIHSS at admission, median (IQR)	6(3–10)
NIHSS at admission, n (%)	
≥5	158(54.7)
< 5	131(45.3)
Rankin at discharge, median (IQR)	
Rankin at discharge, n (%)	1(0–3)
0–2	207(71.6)
3–6	82(28.4)

MIF, macrophage migration inhibitory factor; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; IL-6, interleukin-6; IQR, interquartile ranges; TNF-α, tumor necrosis factor alpha.

3. Results

292 stroke patients were finally included. The serum level of MIF was obtained in 289 patients (99.0%) and the median value was 20.6 ng/ml (IQR, 16.9–26.0 ng/ml). The general information of all included stroke patients was summarized (Table 1). For a subgroup of 46 patients, blood samples were collected each day at 5 time-points. As shown in Fig. 1, the serum level of MIF was significantly varied with time (P < 0.001). The peak was observed at hour 12 (P < 0.001, compared to hours 0, 24, 48 and 72, respectively) and getting stable from hours 48 to 72.

At admission, there were 131 cases of minor stroke (45.3%, NIHSS < 5). The median MIF levels of the patients with minor stroke were lower compared to those of patients with moderate-to-high stroke (19.4 ng/ml [IQR, 14.9–24.5] vs. 22.2 ng/ml [18.4–26.2], P < 0.001). As a continuous variable, modest correlation was obtained between NIHSS score and serum MIF level (r = 0.252; P < 0.001). In univariate model, when serum level of MIF was elevated by each 1 ng/ml, the unadjusted risk of moderate-to-high stroke was increased by 5%

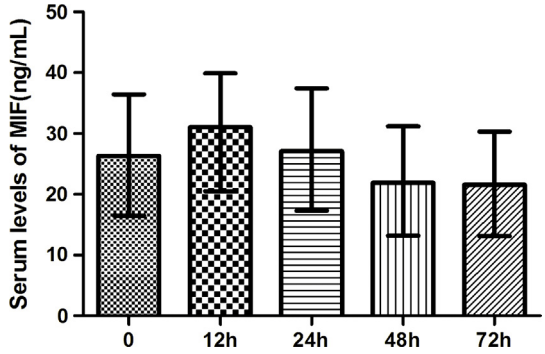

Fig. 1. Box plots (median, interquartile ranges) of serum levles of MIF in the first 3 days after stroke (N = 46). MIF = Macrophage migration inhibitory factor.

(OR = 1.05 [1.01–1.09], P = 0.006). In multivariable models adjusted for age, gender, and other risk factors, the adjusted risk of moderate-to-high clinical severity was increased by 3% for each 1 ng/ml elevated MIF level (1.03 [1.00–1.08], P = 0.02).

At discharge, there were 82 cases of poor functional outcome (28.4%) and 207 cases of good outcomes (71.6%). *The median serum level of MIF was lower in the cases of good outcomes than that observed in cases with poor outcomes (19.4[15.8–24.2]* vs. *24.0[19.9–29.4] ng/ml; Z = 5.190, P < 0.001)* (Fig. 2). In logistic regression analysis of univariate model, OR of MIF level against NIHSS score was calculated, as well as MIF level against other risk factors (Table 2). When serum level of MIF was elevated by each 1 ng/ml, the unadjusted risk of poor outcomes was increased by 9% (OR = 1.09 [1.05–1.13], P < 0.001), while the adjusted risk was increased by 6% (1.06 [1.02–1.10], P < 0.001) (Table 3).

The cutoff of serum MIF level as a predictor for poor outcome was calculated according to the ROC curve, with an optimized value of 19.5 ng/ml. The obtained sensitivity and specificity were 80.5% and 50.5%, yielding an AUC of 0.70 (95%CI, 0.63–0.76; P < 0.001). With an optimal cutoff, MIF exhibited a significantly higher discriminatory ability than CRP (0.60; 0.53–0.68; P < 0.001), age (0.60; 0.52–0.67;

Table 2
Univariate analysis of functional outcome.

Predictors	OR (95%CI)	P
MIF (increase per unit)	1.09(1.05–1.13)	< 0.001
IL-6 (increase per unit)	1.26(1.05–1.39)	< 0.001
TNF-α (increase per unit)	1.17(1.06–1.37)	< 0.001
CRP (increase per unit)	1.07(1.02–1.15)	0.005
WBC (increase per unit)	1.13(1.02–1.39)	0.082
Glucose (increase per unit)	1.33(1.14–1.58)	0.001
Age (increase per unit)	1.08(1.04–1.15)	< 0.001
Male sex	1.38(0.92–2.76)	0.58
NIHSS (increase per unit)	1.18(1.10–1.25)	< 0.001
Hypertension	1.75(0.85–3.02)	0.19
Diabetes	1.19(0.93–1.77)	0.38
Hypercholesterolemia	0.80(0.50–1.33)	0.33
Coronary heart disease	1.34(0.85–2.08)	0.16
Prior TIA	1.22(0.79–2.04)	0.42
Atrial fibrillation	1.95(1.22–3.05)	0.02
Small-vessel occlusive	0.60(0.39–1.03)	0.06
Large-vessel occlusive	0.55(0.21–1.43)	0.24
Cardioembolic	1.45(0.85–2.84)	0.43
Other	0.75(0.50–1.33)	0.28
Unknown	1.53(0.95–2.44)	0.09
Anticoagulants	4.33(1.28–13.15)	0.02
IV thrombolysis and/or mechanical thrombectomy	0.20(0.15–0.31)	< 0.001

MIF, macrophage migration inhibitory factor; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; IL-6, interleukin-6; CRP, C-reactive protein; WBC, White blood cell count; TNF-α, tumor necrosis factor alpha.

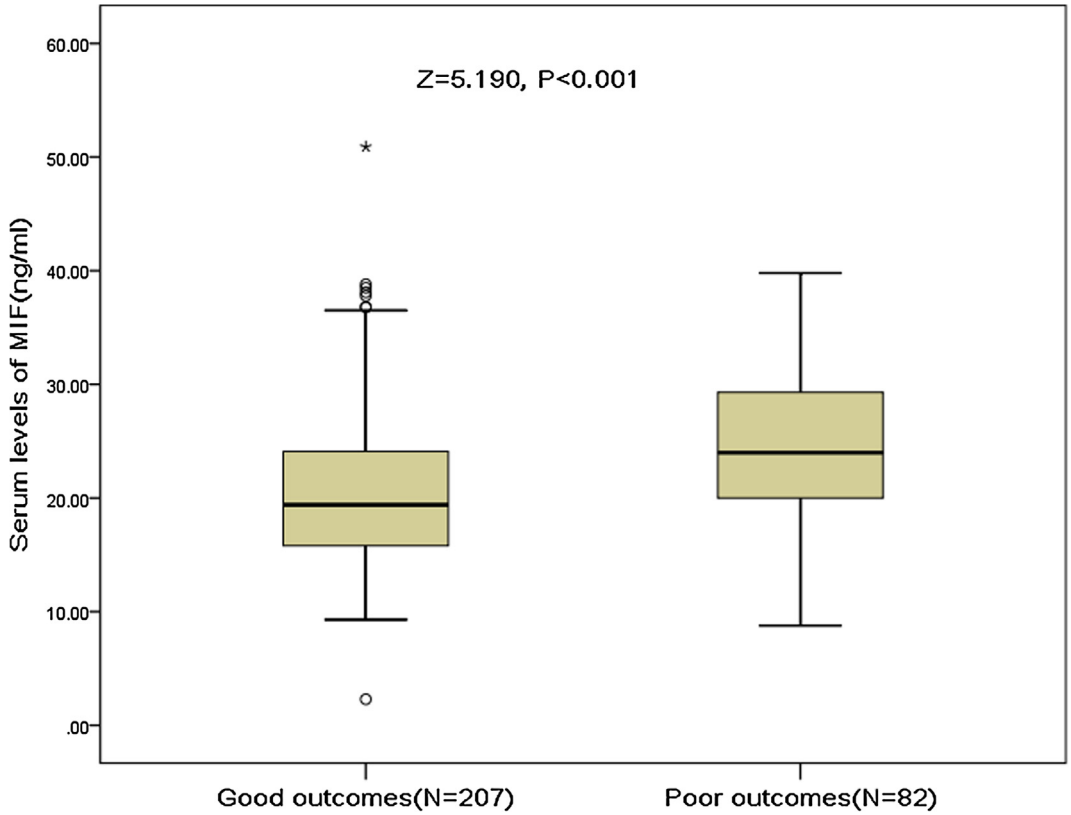

Fig. 2. Serum levels of MIF in patients with good outcomes and poor outcomes. A good functional outcome was defined as a mRS score of 0–2 points, while poor outcome was defined as 3–6 points. All data are medians and in-terquartile ranges (IQR). P values refer to Mann-Whitney *U* tests for differences between groups.

Table 3
Multivariate analysis of predictors of poor functional outcomes (Rankin 3–6)[a]

Predictors	OR (95%CI)	P
MIF (increase per unit)	1.06(1.02–1.10)	< 0.001
IL-6 (increase per unit)	1.15(1.03–1.30)	0.002
TNF-α (increase per unit)	1.11(1.04–1.27)	0.001
Glucose (increase per unit)	1.21(1.06–1.49)	0.02
Age (increase per unit)	1.06(1.03–1.13)	< 0.001
NIHSS (increase per unit)	1.14(1.09–1.20)	< 0.001
IV thrombolysis and/or mechanical thrombectomy	0.25(0.10–0.51)	< 0.001

MIF, macrophage migration inhibitory factor; NIHSS, National Institutes of Health Stroke Scale; IL-6, interleukin-6; CRP, C-reactive protein; WBC, White blood cell count; TNF-α, tumor necrosis factor alpha.

[a] Multivariable model included all of the following variables: age, gender, prior vascular risk factors, NIHSS at admission, stroke subtype, pre and acute stroke treatment, serum levels of MIF, IL-6, CRP, WBC and glucose.

P < 0.001), IL−6 (0.63; 0.58–0.70; P = 0.001), TNF-α (0.64; 0.60–0.71; P = 0.01) and NIHSS score (0.65; 0.59–0.72; P = 0.02). Interestingly, the combined inflammatory model (MIF/CRP/IL-6/TNF-α) improved the NIHSS score than the predictors alone to predict poor outcomes (AUC of the combined model: 0.77; 95% CI, 0.72–0.83). Classified by cut-off value, the high serum level of MIF could be a predictor for poor outcomes, with an adjusted OR of 3.12(95% CI, 2.03–4.84; P < 0.001).

4. Discussion

The outcome prediction of stroke may be improved by including inflammatory markers to existing clinical biomarkers. A meta-analysis suggested the correlation between elevated markers of the acute inflammatory response and poor outcomes after stroke [26]. This study found that high serum MIF level of stroke patients may be an independent predictor for the moderate to high clinical severity and poor early outcome. In addition, the prognosis prediction accuracy of NIHSS score could be significantly improved with MIF.

NIHSS and age have been validated predictors for clinical outcome after stroke [27]. However, the application of NIHSS required special training, with inevitable and notable variability between observers [28]. Thus, early and adequate risk assessment was significant for optimizing the management of stroke patients. In this study, serum MIF of stroke patients, as an easily determined biomarker, was added to existing biomarkers for predicting the clinical severity at admission and early outcome at discharge (see Table 4).

Several variables tested at admission were related to poor outcome of patients with stroke, such as age [24], glucose [29], CRP [30], white blood cell count [31] and IL-6 [26]. In this study, we also found that glucose, CRP and IL-6 were associated with poor early functional prognosis. Importantly, we found that the prognostic value of MIF was better than those factors.

Table 4
Prediction of poor functional outcomes according to ROC.

Parameter	AUC	95% CI		*p*
Prediction of outcomes				
MIF	0.70	0.63	0.76	–
Age	0.60	0.52	0.67	< 0.001
CRP	0.60	0.53	0.68	< 0.001
IL-6	0.63	0.58	0.70	0.001
TNF-α	0.64	0.60	0.71	0.01
NIHSS core	0.65	0.59	0.72	0.02
Combined score I[a]	0.77	0.72	0.83	< 0.001

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; MIF, macrophage migration inhibitory factor; NIHSS, National Institutes of Health Stroke Scale; IL-6, interleukin-6; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha.

[a] Including MIF, CRP, IL-6 and TNF-α. *P* value compared with NIHSS.

MIF was reported to function against glucocorticoid action if the immune system, and MIF acted as a direct proinflammatory factor in inflammatory diseases [32]. Previous studies had suggested the prognostic role in different patients, for example, traumatic brain injury [33], acute intracerebral hemorrhage [18], stable coronary artery disease [34] and severe sepsis [35]. Interestingly, Xu et al. [10] found that high MIF level at admission was correlated with the elevated risk of post-stroke depression. Furthermore, Wang et al. [36] reported that MIF was upregulated in patients with ischemic stroke, as well as rat stroke model. MIF was related to the pathological severity, which had been supported by our findings. In addition, previous studies had suggested that the expression of MIF could be altered during stroke [20,36]. However, we did not test MIF gene expression in this study.

The mechanism of MIF's roles on stroke outcomes pends further demonstration. First, as a pro-inflammatory cytokine, numerous pro-inflammatory factors could be induced by MIF [33]. MIF induced inflammatory responses could make effects on the pathophysiology of stroke outcomes. Second, the expression levels of toll-like receptor 4 (TLR4) and cyclooxygenase-2 could be elevated with MIF [37]. TLR4 was reported to participate in the inflammatory response after subacute stress, which worsened the effects on stroke. Third, MIF promoted neuronal death in the experimental stroke and neurologic deficits were also observed. These results suggested the effects of MIF on neuronal damage after stroke [38]. In addition, MIF regulated platelet survival and thrombotic potential both *in vitro* and *in vivo* by interacting with CXCR7, thus affecting thrombosis [39].

The limitations of our study were as follows: First, as a cross-sectional study, the obtained results could not prove any causal relationship. Second, for the lack of information, the association between MIF and many other factors was not discussed in this study. For example, vascular inflammation relevant inflammatory cytokines may induce the production of endothelial adhesion molecules, proteases and other molecules, which may lead to atherosclerosis [40]. Furthermore, roles of endothelial function, carotid intima-media thickness, lipoprotein(a), fibrinogen and homocysteine in pathogenesis and clinical manifestation of atherothrombotic disease had been proposed [41,42]. However, the association between these factors with MIF was not explored, as well as with stroke outcomes. Third, MIF was determined in serum instead of cerebral spinal fluid. Whether the variations in the central nervous system were consistent with peripheral levels of MIF, it could not be determined. It is uncertain MIF could cross the blood brain barrier [10]. In addition, independent value of MIF could not sufficiently reflect the inflammation status during stroke. Last, the sample size was relatively small and the early outcome was evaluated instead of long-term outcome.

5. Conclusion

To conclude, this study demonstrates that high MIF levels in patients with ischemic stroke are independently correlated with both the moderate to high clinical severity at admission and poor early functional outcome at discharge. MIF appears to be an innovative prognostic predictor with promising application in combined assay.

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Conflict of interest

The authors declare no other conflict of interests.

Author contribution

Zhao J.H. had full access to all of the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wang C.W., Ma P.J., Wang Y.Y., Yang M., Su L.L., Wang S., Liu Y.X., Yuan B., Zhao J.H.

Acquisition of data: Wang C.W., Ma P.J., Wang Y.Y., Yang M., Su L.L.

Analysis and interpretation of data: Wang S., Liu Y.X., Yuan B., Zhao J.H.

Drafting of the manuscript: Wang C.W., Ma P.J., Wang Y.Y.

Critical revision of the manuscript for important intellectual content: Yang M., Su L.L., Wang S.

Administrative, technical, or material support: Ma P.J., Wang Y.Y., Yang M., Su L.L., Wang S., Liu Y.X.

Obtain funding: Zhao J.H.

Study supervision: Zhao J.H.

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