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Predictive value of inflammatory markers for functional outcomes in patients with ischemic stroke

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Keywords
Brain Infarction; Inflammation; Cytokines; Tumor Necrosis Factor-Alpha; Outcome Assessment; Health Care

Abstract

Background: Inflammatory processes have been proposed in the pathophysiology of ischemic stroke. The present study was designed to evaluate the relationship between tumor necrosis factor-alpha (TNF-α), interleukin 6 (IL-6), IL 1 beta (IL-1β), and high sensitivity C-reactive protein (hsCRP) with the prognosis and functional outcome in patients with less severe ischemic stroke.

Methods: We measured the level of IL-1β, IL-6, hsCRP, and TNF-α on days 1 and 5 after stroke onset by enzyme-linked immunosorbent assay (ELISA). The infarct volume was assessed using Alberta Stroke Program Early CT Score (ASPECTS) and posterior circulation ASPECTS (pcASPECTS) score in brain computed tomography (CT) scan and magnetic resonance imaging (MRI). The severity of stroke was assessed by applying the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS) in 24 hours on day 5 and after 3 months from stroke onset. Good outcome was defined as the third month MRS ≤ 2. The association of inflammatory markers and the course of stroke symptoms over time was examined.

Results: Forty-four first-ever stroke patients without concurrent inflammatory diseases with a mean age of 65 years were included. The mean NIHSS and MRS in admission time were 6.5 ± 3.5 and 3.07, respectively. The day 1 and the day 5 levels of IL-1β, IL-6, hsCRP, and TNF-α were not significantly different in good and poor outcome groups (all P-values > 0.05). In

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addition, they were not significantly associated with the ASPECTS, pcASPECTS, and changes of NIHSS and MRS over time.

Conclusion: The levels of hsCRP, IL-1β, IL-6, and TNF-α are not reliable predictors of functional outcomes in patients with less severe acute ischemic stroke (AIS).

Introduction

Stroke poses a huge burden on the health care services worldwide, due to its high morbidity and disability rate.[1] There is evidence indicating inflammatory reactions in the pathophysiology of acute ischemic stroke (AIS). Increased plasma and cerebrospinal fluid (CSF) levels of various inflammatory markers, in particular, cytokines, have been shown in stroke patients.[2]

In light of these findings, inflammatory processes seem as promising potential targets for assessment of AIS, as well as its prognosis and management. A better understanding of the interplay between inflammatory markers and stroke has been proposed to achieve more effective preventive, prognostic, and therapeutic measures.

Conflicting results have been reported by the previous studies investigating the association of inflammatory cytokines with the outcome of stroke patients.[3] Arguably, demographic factors, such as ethnicity, may influence the level of inflammatory cytokines and their effect on stroke outcomes.[4] To the best of our knowledge, this association has not yet been studied in an Iranian population which has a higher incidence of stroke at younger ages.[5] Also, little is known about the effect of these cytokines on different types and severity of stroke.

In this study, we aimed to characterize the influence of the levels of interleukin 1 beta (IL-1β), IL-6, high sensitivity C-reactive protein (hsCRP), and tumor necrosis factor-alpha (TNF-α) in predicting functional outcome in patients with first-time less severe AIS.

Materials and Methods

Participants: We consecutively included patients with a diagnosis of first-ever AIS admitted to the Ghaem Hospital, Mashhad, Iran, from March 2018 to March 2019.

The diagnosis of ischemic stroke was made based on clinical exam and brain computed tomography (CT) on the first day. A confirmative magnetic resonance imaging (MRI) was also performed in the third to fifth day. The participants had to meet the inclusion criteria including (1) having their first episode of AIS, (2) age between 45 to 80 years, (3) having the National Institutes of Health Stroke Scale (NIHSS) < 20 (mild to moderate severity), and (4) being conscious and cooperative.

The exclusion criteria were: (1) hemorrhagic strokes, (2) lacunar strokes (diameter < 1.5 mm), (3) history of recent transient ischemic attack (TIA) or heart attack, (4) infectious diseases or fever on admission, (5) severe abnormalities in the screening laboratory tests on admission, (6) history of chronic rheumatologic, lung, liver, or kidney diseases, poorly controlled diabetes [hemoglobin A1c (HbA1c) > 7%], or cancer, (7) history of valvular heart diseases, prosthetic valve heart, cardiomyopathy, and heart rhythm disorders [with the exception of chronic atrial fibrillation (AF)], (8) pregnancy, (9) indication for taking intra-arterial and intra-venous thrombolytic agents and neuro-interventional procedures, (10) history of immunosuppressive, anti-inflammatory, anticoagulant, and antibiotic medications, (11) history of seizure and epilepsy, (12) and death and myocardial infarction (MI) within the first week of study.

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad (no. IR.MUMS.sm.REC.1396.316) and informed consent was received from each participant.

Clinical evaluation: We interviewed patients and recorded the demographic characteristics and history of comorbid diseases. The severity of stroke was determined by applying the NIHSS and Modified Rankin Scale (MRS).[6] During hospitalization, all patients received standard ischemic stroke treatment by neurologists. We followed the patients for three months and evaluated NIHSS and MRS scores on three visits: on the first day, on the fifth day, and at the end of the third month. Good outcome was defined as an MRS score ≤ 2 at the end of the third month. Additionally, other events including death, recurrent stroke, seizure, and pneumonia were recorded throughout the study.

Imaging and laboratory tests: We measured the serum levels of IL-1β, IL-6, hsCRP, and TNF-α on admission and fifth day of hospitalization. Blood samples were obtained in citrate tubes and were centrifuged for 15 minutes at 3000x g within 30 minutes after sampling. The separated plasma was stored in -80 °C. Specimens were then

analyzed by an enzyme-linked immunosorbent assay (ELISA) method. IL-1β, IL-6, and TNF-α were measured using laboratory kits (Diaclone, France), and hsCRP was measured using a turbidimetric technique. Brain CT scan was performed on admission and within 6 to 24 hours after the onset of symptoms. Alberta Stroke Program Early CT Score (ASPECTS) and posterior circulation ASPECTS (pcASPECTS) were recruited with MRI on days 3 to 5 of stroke onset to calculate the extent of stroke volume more accurately.[7]

Statistical analyses were performed using SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (range) and categorical variables were reported as frequencies. We compared the study variables between good and poor outcome groups using Mann-Whitney test or independent samples t-test for continuous variables and chi-squared or Fischer's exact test for categorical variables. Furthermore, we evaluated the changes of NIHSS and MRS over time (in three times including baseline, day 5, day 90) using repeated measures analysis of variance (ANOVA) test. The effect of IL-1β, IL-6, hsCRP, and TNF-α levels, as well as ASPECTS or pcASPECTS on the course of NIHSS over time, was evaluated by entering them in the model as covariates. The level of significance was $P < 0.05$ for all tests.

Results

Outcomes and baseline characteristics: Forty-four patients, including 23 men and 21 women, participated in this study. During the study, three patients experienced a recurrence of ischemic stroke, two patients had seizures, nine patients developed pneumonia, and one patient passed away.

The mean NIHSS and MRS score showed a decreasing trend over three months, so at the end of the study, 74.4% of the survivors had a good outcome, i.e., MRS ≤ 2.

The age and sex distributions as well as the rate of cardiovascular risk factors and comorbidities were not significantly different between the good and poor outcome groups (Table 1).

Brain MRI showed that 75.0% of patients had a stroke in the territory of middle cerebral artery (MCA), 20.5% in basilar artery (BA), 4.5% in posterior cerebral artery (PCA), and 4.5% in anterior cerebral artery (ACA) territory. No significant difference in the location of infarcts was observed between the good and poor outcome groups. The median of ASPECTS/pcASPECTS score was 9 in the good outcome group, which was significantly higher than a median of 7 in the poor outcome group.

Inflammatory markers: The serum levels of IL-1β and IL-6 significantly increased from admission to day five of stroke onset. However, TNF-α and hsCRP levels showed no significant change in this period. IL-1β, IL-6, hsCRP, and TNF-α baseline and day 5 levels were not significantly different between good and poor outcome groups based on MRS (Table 2). MRS significantly decreased in patients with increasing or decreasing/unchanged IL level changes (Figure 1, Table 3). Similarly, the increasing or decreasing/unchanged serum levels of IL-1β, IL-6, hsCRP, and TNF-α were not significantly associated with the changes of NIHSS over time (Table 4). Moreover, no significant correlation was observed between the ASPECTS/pcASPECTS score with the baseline and follow-up levels of inflammatory markers.

Table 1. Baseline characteristics of patients with good and poor outcomes

Variable	Total	MRS ≤ 2 (n = 32)	MRS > 2 (n = 11)	P
Age (year) [median (Q1-Q3)]	65 (55.50-74.75)	64 (53.25-74.75)	64 (63.00-74.00)	0.389[m]
Sex (female) [n (%)]	21 (50.0)	16 (50.0)	5 (45.5)	0.795[c]
HTN [n (%)]	28 (65.1)	19 (59.4)	9 (81.8)	0.178[c]
DM [n (%)]	11 (25.6)	7 (21.9)	4 (36.4)	0.430[f]
Hyperlipidemia [n (%)]	12 (27.9)	7 (21.9)	5 (45.5)	0.133[c]
IHD [n (%)]	7 (16.3)	4 (12.5)	3 (27.3)	0.347[f]
AF [n (%)]	5 (11.6)	4 (12.5)	1 (9.1)	> 0.999[f]
Smoking [n (%)]	15 (34.8)	10 (31.2)	5 (45.5)	0.394[c]
NIHSS on admission (mean ± SD)	6.6 ± 3.6	5.7 ± 2.7	9.0 ± 4.6	0.007[t]
ASPECTS or pcASPECTS [median (Q1-Q3)]	8.00 (7.00-9.00)	9.00 (8.00-9.00)	7.00 (6.00-8.00)	< 0.001[m]

NIHSS on admission was significantly higher in the poor outcome group. ASPECTS/pcASPECTS was significantly higher in the good outcome group. No significant difference was observed in other variables.

[m]Mann-Whitney test; [t]Independent samples t-test; [c]Chi-squared test; [f]Fischer's exact test

HTN: Hypertension; DM: Diabetes mellitus; IHD: Ischemic heart disease; AF: Atrial fibrillation**;** MRS: Modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; ASPECTS: Alberta Stroke Program Early CT Score; pcASPECTS: Posterior circulation ASPECTS; SD: Standard deviation

Table 2. Admission and follow-up levels of inflammatory markers in good and poor outcome groups

Variable	Total	MRS ≤ 2 (n = 32)	MRS > 2 (n = 11)
hsCRP (mg/l)			
Admission	7.30 (0.00-47.00)	6.60 (0.00-47.00)	6.80 (0.20-45.30)
5th day	10.10 (0.00-51.00)	10.20 (0.00-51.00)	8.00 (0.60-45.80)
IL-1β (pg/ml)			
Admission	0.51 (0.33-1.14)	0.50 (0.33-1.04)	0.53 (0.33-0.80)
5th day	0.60 (0.37-1.81)	0.60 (0.37-1.81)	0.59 (0.43-1.09)
IL-6 (pg/ml)			
Admission	49.80 (22.00-825.00)	49.80 (22.00-825.00)	46.00 (25.00-162.80)
5th day	63.90 (23.80-340.00)	63.90 (23.80-340.00)	63.20 (27.70-280.00)
TNF-α (pg/ml)			
Admission	7.30 (2.80-43.60)	7.30 (4.10-20.50)	7.00 (2.80-43.60)
5th day	7.60 (3.70-22.00)	7.60 (4.10-22.00)	7.00 (3.70-18.20)

The admission and follow-up levels of high sensitivity C-reactive protein (hsCRP), interleukin 1 beta (IL-1β), IL-6, and tumor necrosis factor-alpha (TNF-α) were not significantly different between good and poor outcome groups. The values are reported as median (range) and Mann-Whitney test was used to compare them between the two groups.

MRS: Modified Rankin Scale; hsCRP: High sensitivity C-reactive protein; IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; TNF-α: Tumor necrosis factor-alpha

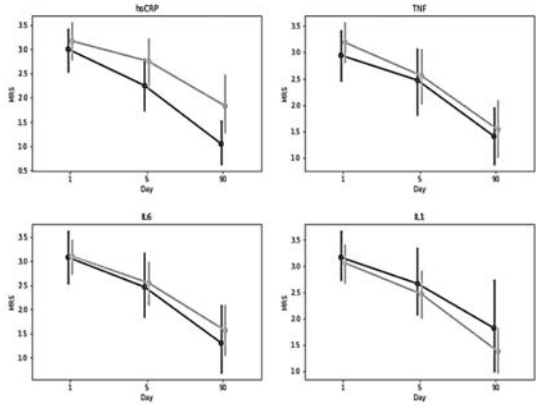

Figure 1. The relationship between changes in Modified Rankin Scale **(**MRS) and the inflammatory factor changes

MRS significantly decreased in patients with increasing (light gray) or decreasing/unchanged (dark gray) interleukin (IL) level changes ($P < 0.001$).

Discussion

Inflammatory cells and cytokines play a crucial role in the AIS predisposing conditions, the progression to brain infarction, and probably in regeneration in the later stages.[8] AIS is accompanied by increased serum concentration of hsCRP,[6] TNF-α,[9] IL-1β, and IL-6.[10] As demonstrated in our study, the levels of IL-1β and IL-6 increased within five days of onset. However, we failed to show an association between the absolute values or changes in the levels of these inflammatory markers with functional outcomes of less severe stroke in an Iranian population.

In line with our findings, several studies have shown no significant association between clinical outcomes and the levels of hsCRP,[11] IL-1β,[3] IL-6,[3] or TNF-α.[12] Conversely, an increased risk of adverse clinical outcomes with higher levels of CRP or hsCRP,[13] IL-1β,[12] IL-6,[14] and TNF-α[3] has been reported in other studies. As stated previously, demographic factors, such as ethnicity, can influence the relationship of inflammatory markers with stroke outcomes.[4] Therefore, a confounding variable that can explain this controversy is the genetic and environmental variability of study populations. Also, the heterogeneity of findings can also be due to a time-dependent association of inflammatory markers with stroke outcomes. For example, the follow-up but not the baseline level of hsCRP has been shown to influence the clinical outcomes of ischemic stroke.[15]

The association of inflammatory response with stroke outcomes is also a matter of controversy in its translation to the clinic. Anti-inflammatory treatments have shown promising results in animal studies.[16] However, they have not been successfully used in clinical settings.[17] For example, the Subcutaneous IL-1 Receptor Antagonist (SCIL-1RA) in Ischemic Stroke (SCIL-STROKE) trial has recently shown that the administration of SCIL-1RA is not associated with a better outcome in ischemic stroke.[18] The complex interaction of inflammatory responses with stroke outcomes could stem from their dual roles in the recovery of stroke damages at a cellular level.[19]

Table 3. The relationship between changes in Modified Rankin Scale (MRS) and the inflammatory factor changes

MRS	Changes in TNF-α (TNF-α after-TNF-α baseline)		Changes in CRP (CRP after-CRP baseline)		Changes in IL-6 (IL-6 after-IL-6 baseline)		Changes in IL-1β (IL-1β after-IL-1β baseline)	
	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend
Day 1	2.94 ± 1.09	3.15 ± 0.97	2.94 ± 1.02	3.16 ± 1.00	3.08 ± 1.04	3.06 ± 1.01	3.09 ± 0.83	3.06 ± 1.00
Day 5	2.47 ± 1.23	2.50 ± 1.30	2.15 ± 1.21	2.75 ± 1.26	2.46 ± 1.20	2.50 ± 1.31	2.54 ± 1.12	2.47 ± 1.31
Day 90	1.41 ± 1.22	1.54 ± 1.45	1.05 ± 1.02	1.83 ± 1.49	1.30 ± 1.25	1.56 ± 1.41	1.81 ± 1.66	1.37 ± 1.32
P*	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Data are presented as mean ± standard deviation (SD)

MRS significantly decreased in patients with increasing or decreasing/unchanged interleukin (IL) level trends.

*Repeated measures analysis of variance (ANOVA) test; the power analysis based on the result of table 3 indicated the power of > 95%

IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; MRS: Modified Rankin Scale

Table 4. The relationship between changes in the National Institutes of Health Stroke Scale (NIHSS) and the inflammatory factor changes

NIHSS	Changes in TNF-α (TNF-α after-TNF-α baseline)		Changes in CRP (CRP after-CRP baseline)		Changes in IL-6 (IL-6 after-IL-6 baseline)		Changes in IL-1β (IL-1β after-IL-1β baseline)	
	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend	Decreasing/unchanged trend	Increasing trend
Day 1	5.94 ± 3.45	6.96 ± 3.69	6.15 ± 4.50	6.87 ± 2.60	6.07 ± 3.50	6.76 ± 3.60	5.36 ± 2.30	6.96 ± 3.80
Day 5	4.94 ± 3.57	5.03 ± 3.84	4.68 ± 4.50	5.25 ± 2.92	4.38 ± 3.20	5.26 ± 3.80	4.09 ± 2.50	5.31 ± 4.01
Day 90	2.76 ± 2.60	3.07 ± 4.90	2.31 ± 3.36	3.45 ± 4.63	2.00 ± 2.30	3.36 ± 4.60	4.00 ± 6.40	2.50 ± 3.00
P*	< 0.001	0.007	< 0.001	0.001	< 0.001	0.001	0.585	< 0.001

Data are presented as mean ± standard deviation (SD)

*Repeated measures analysis of variance (ANOVA) test; the power analysis based on the result of table 4 indicated the power of > 95%

IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; NIHSS: National Institutes of Health Stroke Scale

The controversy of the literature regarding the association of inflammatory markers with outcomes of ischemic stroke highlights the importance of performing large multi-center studies or systematic reviews. Future studies should also focus on the investigation of inflammatory factors in patients with different degrees of severity of symptoms. Also, more research is needed for identifying novel inflammatory markers that are more specific to the central nervous system (CNS).

Limitations

Our study had several limitations. First, although our number of participants matched the required number estimated by our a priori power analysis, the small number of participants has undeniably limited our study. Second, we only included hospitalized patients, while some patients with minor deficits might have refused admission and were not investigated in our study. Furthermore, we excluded severe strokes (NIHSS > 20) and critically ill patients from our study, which might have posed more limitations on the generalizability of our results.

Conclusion

In summary, this study showed remarkably increased levels of IL-1β and IL-6 during the first few days after stroke. However, it failed to show a significant association between functional outcomes and stroke volume and the baseline or fifth day levels of hsCRP, IL-1β, IL-6, and TNF-α in conscious patients with less severe first-time AIS.

Conflict of Interests

The authors declare no conflict of interest in this study.

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