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Original Research Article

ASSOCIATION BETWEEN INFLAMMATORY BIOMARKERS AND FUNCTIONAL RECOVERY IN ACUTE ISCHEMIC STROKE PATIENTS

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ABSTRACT

Background: Inflammation is a critical pathway in the pathophysiology of acute ischemic stroke (AIS), impacting neuronal injury, progressive infarction, and functional recovery. There are several circulating inflammatory biomarkers (e.g. C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor–alpha (TNF-α)) associated with stroke severity and prognosis; understanding how these are related to functional outcomes in stroke may allow for early risk stratification and intervention. **Aim and Objectives:** This study aimed to investigate the relationship between serum inflammatory biomarkers and functional recovery in patients with acute ischemic stroke, and their predictive value on neurological outcomes.

Materials and Methods s: A prospective observational study was conducted over 18 months at a tertiary care hospital. A total of 120 patients presenting with first-ever AIS within 24 hours of symptom onset were enrolled. Serum levels of CRP, IL-6, and TNF-α were measured on admission. Functional recovery was assessed using the modified Rankin Scale (mRS) and National Institutes of Health Stroke Scale (NIHSS) at baseline, 7 days, and 90 days post-stroke. Patients were categorized into favorable (mRS ≤2) and unfavorable (mRS >2) outcome groups at 90 days. Statistical analysis included correlation, regression, and ROC curve analysis to determine predictive value of biomarkers.

Results: Higher baseline serum levels of CRP, IL-6, and TNF-α were observed in patients with unfavorable outcomes compared to those with favorable recovery (CRP: 18.4 ± 6.2 mg/L vs. 8.7 ± 3.5 mg/L, $p < 0.001$; IL-6: 42.6 ± 12.1 pg/mL vs. 22.3 ± 8.4 pg/mL, $p < 0.001$; TNF-α: 21.8 ± 7.5 pg/mL vs. 12.9 ± 5.3 pg/mL, $p < 0.001$). Significant positive correlations were observed between biomarker levels and baseline NIHSS scores, while negative correlations were noted with 90-day functional recovery. Multivariate regression demonstrated that elevated IL-6 and CRP were independent predictors of poor functional outcome. ROC analysis showed IL-6 had the highest predictive accuracy for unfavorable recovery (AUC = 0.87).

Conclusions: Elevated inflammatory biomarkers, particularly IL-6 and CRP, are associated with poorer functional recovery in AIS patients. Early measurement of these biomarkers may provide valuable prognostic information and facilitate targeted interventions to improve neurological outcomes.

Keywords: acute ischemic stroke, inflammatory biomarkers, C-reactive protein, interleukin-6, TNF-alpha, functional recovery, modified Rankin Scale, NIHSS.

INTRODUCTION

Acute ischemic stroke (AIS) is one of the leading causes of death and long-term disability globally and it is caused by a sudden blockage of cerebral arteries ultimately resulting in ischemia (restricted blood flow) to the brain. Beyond the duration and anatomic location of ischemia, the degree of neuronal injury and recovery from AIS is influenced by complex and time course-dependent molecular mechanisms including inflammation.[1] These post-ischemic inflammatory mechanisms can contribute to secondary brain injury mediated by blood brain barrier dysfunction, neuronal apoptosis, and recruitment of immune system cells, mediating both infarct expansion and neurologic outcomes.[2]

There has been increased interest in the role of circulating inflammatory markers or biomarkers in AIS including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). CRP is an acute phase reactant that is synthesized by the liver after inflammatory cytokines are released and has been associated with infarct volume, stroke severity, and poor functional outcomes.[3] IL-6 is a pleiotropic cytokine responsible for activating the immune system, initiating vascular inflammation and stimulating apoptosis, while TNF-α mediates neurotoxicity and endothelial dysfunction. The elevations of these inflammatory biomarkers in the acute phase of stroke may reflect the degree/intensity of the inflammatory response and have been suggested as prognostic markers of recovery.[4]

Functional recovery following acute ischemic stroke (AIS) is typically measured with standardized neurological scales like the National Institutes of Health Stroke Scale (NIHSS) to assess the initial magnitude of the stroke, and the modified Rankin Scale (mRS) used to assess long-term disability.[5] Previous studies have observed that higher inflammatory markers levels are associated with more significant neurological deficits and poor functional outcomes at three months but there has been limited consistency across studies related to this construct, and variability in study design, sample size, and timing of biomarker assessment.[6]

Gaining an understanding of the relationship between inflammatory markers and functional recovery may help with risk stratification at an early stage, assist with individualizing the rehabilitation approach, and most importantly, find a group of patients who might benefit from targeted anti-inflammatory treatment. This study was designed to examine the association between serum levels of C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α) and functional recovery in people with AIS. This study also looked at whether these inflammatory markers could identify participants who were likely to have an unfavorable outcome, thus clarifying a clinical role for them can be useful as prognostic indicators in daily practice.

MATERIALS AND METHODS

Study design and duration

This prospective observational study was conducted over 18 months, from January 2023 to June 2024, at the Department of Neurology of a tertiary care hospital. The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants or their legal representatives.

Study population

A total of 120 patients with first-ever acute ischemic stroke (AIS) presenting within 24 hours of symptom onset were enrolled consecutively.

Inclusion criteria:

- Age ≥18 years.
- Clinical diagnosis of AIS confirmed by neuroimaging (CT or MRI).
- Onset of stroke symptoms within 24 hours prior to admission.

Exclusion criteria:

- Hemorrhagic stroke or stroke mimics.
- History of previous stroke or transient ischemic attack.
- Severe infection, autoimmune disease, or malignancy at presentation.
- Patients receiving immunomodulatory therapy.

Clinical assessment

Neurological severity was assessed at admission using the National Institutes of Health Stroke Scale (NIHSS). Functional outcomes were evaluated using the modified Rankin Scale (mRS) at baseline, day 7, and 90 days post-stroke. Patients were categorized into favorable (mRS ≤2) and unfavorable (mRS >2) outcome groups at 90 days.

Blood sample collection and biomarker measurement

Peripheral venous blood samples (5 mL) were collected on admission prior to any therapeutic intervention. Serum was separated by centrifugation at 3000 rpm for 10 minutes and stored at –80°C until analysis.

Biomarker analysis:

- **C-reactive protein (CRP):** measured using high-sensitivity immunoturbidimetric assay.
- **Interleukin-6 (IL-6):** quantified using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions.
- **Tumor necrosis factor-alpha (TNF-α):** measured using commercially available ELISA kits.

All assays were performed in duplicate to ensure reliability, and laboratory personnel were blinded to clinical outcomes.

Statistical analysis

Data analysis was performed using SPSS version 26.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) as appropriate, while categorical variables were expressed as frequencies and percentages.

- Differences in biomarker levels between favorable and unfavorable outcome groups were analyzed using independent t-test or Mann–Whitney U test.
- Correlation between biomarker levels and NIHSS scores or mRS scores was assessed using Pearson or Spearman correlation coefficients.
- Multivariate logistic regression was conducted to identify independent predictors of unfavorable functional outcome at 90 days.
- Receiver operating characteristic (ROC) curves were generated to evaluate the predictive accuracy of individual biomarkers.

A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

The study included 120 patients with first-ever acute ischemic stroke (AIS). Mean age was 62.5 ± 11.2 years, 56.7% were male. At admission, median NIHSS was 12 (IQR 8–18). At 90 days, 54 patients (45%) had favorable functional recovery (mRS ≤2), 66 (55%) had unfavorable outcomes (mRS >2). Baseline serum inflammatory biomarkers (CRP, IL-6, TNF-α) were elevated in patients with poor outcomes and correlated with stroke severity and recovery.

Table 1: Demographic and clinical profile of AIS patients

Variable	Frequency	Percentage (%)
Age <60	48	40.0
Age 60–70	42	35.0
Age >70	30	25.0
Male	68	56.7
Female	52	43.3
Hypertension	78	65.0
Diabetes	50	41.7
Hyperlipidemia	32	26.7
Smoking	40	33.3
Baseline NIHSS (median, IQR)	12 (8–18)	—

Table 2: Serum inflammatory biomarkers in favorable vs. unfavorable outcome groups

Biomarker	Favorable (n=54)	Unfavorable (n=66)	p-value
CRP (mg/L)	8.7 ± 3.5	18.4 ± 6.2	<0.001
IL-6 (pg/mL)	22.3 ± 8.4	42.6 ± 12.1	<0.001
TNF-α (pg/mL)	12.9 ± 5.3	21.8 ± 7.5	<0.001

Table 3: Correlation of biomarkers with baseline NIHSS

Biomarker	r	p-value
CRP	0.62	<0.001
IL-6	0.68	<0.001
TNF-α	0.54	<0.001

Table 4: Correlation of biomarkers with 90-day mRS

Biomarker	r	p-value
CRP	–0.59	<0.001
IL-6	–0.65	<0.001
TNF-α	–0.51	<0.001

Table 5: Multivariate logistic regression for predictors of unfavorable outcome

Variable	AOR	95% CI	p-value
CRP (per 5 mg/L)	2.1	1.4–3.2	0.001
IL-6 (per 10 pg/mL)	2.5	1.6–3.9	<0.001
TNF-α (per 5 pg/mL)	1.4	0.9–2.1	0.08
Age >70	1.5	0.8–2.9	0.22
Baseline NIHSS (per 5-point increase)	2.0	1.3–3.0	0.002

Table 6: ROC analysis for prediction of unfavorable 90-day outcome

Biomarker	AUC	Sensitivity (%)	Specificity (%)	Optimal cutoff
CRP	0.81	78	75	12 mg/L
IL-6	0.87	82	80	30 pg/mL
TNF-α	0.76	72	70	17 pg/mL

Table 7: Biomarker levels by age groups

Age group	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)
<60	11.2 ± 5.1	27.5 ± 9.8	15.8 ± 6.2
60–70	13.8 ± 6.3	33.2 ± 11.2	18.4 ± 7.1
>70	16.5 ± 7.0	38.7 ± 12.5	20.9 ± 7.8

Table 8: Biomarker levels by gender

Gender	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)
Male	13.6 ± 6.7	33.9 ± 12.1	18.6 ± 7.3
Female	14.1 ± 6.9	34.8 ± 12.8	19.2 ± 7.4

Table 9: Biomarker levels by stroke subtype (TOAST classification)

Subtype	CRP	IL-6	TNF-α
Large artery	15.8 ± 6.8	37.5 ± 11.9	20.5 ± 7.5
Small vessel	12.7 ± 5.9	29.6 ± 10.4	16.9 ± 6.7
Cardioembolic	14.9 ± 6.5	35.2 ± 12.0	19.8 ± 7.2

Table 10: Early neurological improvement (NIHSS reduction ≥4 at day 7) and biomarker levels

Early improvement	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)	p-value
Yes (n=48)	9.5 ± 4.2	24.8 ± 8.7	13.6 ± 5.4	<0.001
No (n=72)	16.2 ± 6.8	39.7 ± 12.3	21.5 ± 7.6	

Table 1 details demographic and clinical characteristics. Table 2 demonstrates significantly higher biomarker levels in patients with unfavorable outcomes. Tables 3 and 4 show correlations with baseline NIHSS and 90-day mRS. Table 5 identifies CRP and IL-6 as independent predictors of poor recovery. Table 6 presents ROC analysis for predictive accuracy. Tables 7–10 highlight the influence of age, gender, stroke subtype, and early neurological improvement on biomarker levels, reinforcing the relationship between systemic inflammation and functional outcomes.

DISCUSSION

This study investigated the relationship between circulating inflammatory biomarkers CRP, IL-6, and TNF-α and functional recovery in patients with acute ischemic stroke (AIS). The results demonstrate that elevated baseline levels of these biomarkers are strongly associated with poorer functional outcomes at 90 days, and that CRP and IL-6 serve as independent predictors of unfavorable recovery.[7] Higher biomarker levels were observed in patients with greater baseline stroke severity, as evidenced by positive correlations with NIHSS scores (Tables 3 and 4). This suggests that the magnitude of the inflammatory response is proportional to the initial ischemic insult and may contribute to secondary brain injury through mechanisms such as blood brain barrier disruption, neuronal apoptosis, and oxidative stress. The negative correlation of biomarkers with 90-day mRS scores further emphasizes their prognostic significance for long-term functional outcomes.[8,9]

IL-6 demonstrated the highest predictive accuracy among the biomarkers (AUC = 0.87, Table 6), consistent with prior studies reporting IL-6 as a potent mediator of post-stroke inflammation and poor prognosis. CRP, an acute-phase reactant induced by IL-6, also independently predicted unfavorable outcomes, whereas TNF-α, although elevated, was not independently predictive after adjusting for confounders (Table 5). These findings align with the pathophysiological role of IL-6 as a central driver of systemic inflammation in AIS and highlight its potential as a clinical biomarker.[10,11]

Age and comorbidities such as hypertension and diabetes influenced biomarker levels (Tables 7–9), suggesting that systemic inflammatory burden may be compounded by vascular risk factors. Stratification by stroke subtype revealed higher biomarker levels in large artery and cardioembolic strokes compared with small vessel disease (Table 9), consistent with greater infarct volumes and more extensive tissue injury in these subtypes. Early neurological improvement, defined as a reduction of NIHSS ≥4 at day 7, was associated with lower biomarker levels (Table 10), reinforcing the link between reduced systemic inflammation and better early recovery.[12]

These findings have important clinical implications. First, measurement of CRP and IL-6 upon hospital admission may provide early prognostic information, allowing clinicians to identify patients at risk for poor functional recovery and tailor rehabilitation strategies accordingly. Second, serial assessment of inflammatory biomarkers could facilitate monitoring of disease progression or therapeutic response. Third, the study supports the rationale for exploring targeted anti-inflammatory interventions as adjunct therapy in AIS, particularly for patients with elevated IL-6 and CRP levels.[13,14,15]

Strengths of this study include its prospective design, inclusion of multiple inflammatory biomarkers, standardized functional outcome assessment, and comprehensive stratified analyses. Limitations include single-center enrollment, which may limit generalizability, and lack of longitudinal biomarker measurements beyond the acute phase, precluding assessment of dynamic changes over time. Additionally, the sample size, while adequate for primary analyses, may limit subgroup comparisons, particularly by stroke subtype or comorbidity profile.

In conclusion, this study provides robust evidence that elevated systemic inflammatory biomarkers, particularly IL-6 and CRP, are associated with poorer functional recovery in AIS patients. Integration of these biomarkers into early clinical assessment may improve risk stratification and guide individualized management to optimize neurological outcomes.

CONCLUSION

This study highlights that increased baseline inflammatory biomarkers (e.g., IL-6 and CRP) are abounding predictors of poor functional recovery in acute ischemic stroke (AIS) patients. Both IL-6 and CRP both positively correlated with initial stroke severity and had negative correlations with 90-day functional measures, which lends utility to their prognostic capacity. Of all three biomarkers, IL-6 was the most predictive of unfavorable recovery and CRP was also independently predictive. While TNF-α elevated in patients with poorer recovery, it did not serve as an independent predictor of functional recovery after adjusting for confounders.

The findings here illustrate the relevance of systemic inflammation in the pathophysiology of AIS and neurological recovery, and the role IL-6 and CRP may play as markers of inflammation in early assessments. Timing of IL-6 and CRP levels may be able to help serve not only as baseline levels as a basis to recognize early prognosis, but also as reasons to stratify risk in rehabilitation approaches and identify those at risk and potential candidates for intervention with directed anti-inflammatory measures.

Recommendations

1. Clinical integration: Serum IL-6 and CRP should be considered in the early evaluation of AIS at the time of hospital admission to identify patients with a high risk of poor functional recovery.
2. Risk stratification: Incorporation of inflammatory biomarker levels and baseline NIHSS scores together can improve prognostic performance for longer term outcomes.
3. Targeted therapies: Patients with high IL-6 and CRP may benefit from anti-inflammatory treatment or more intensive rehabilitation specific to their initial inflammatory status.
4. Serial monitoring: Repeated biomarker measurements done during hospitalization or early recovery could be beneficial to monitor disease process and response to treatment.
5. Future studies: Multi-centre studies with larger cohorts are required to legitimize the information presented in this review, provide a basis for optimum biomarker cut-offs, and explore potential inclusion in a patient-specific AIS treatment approach.

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