

Neuroinflammation After Stroke: Considering the Role of IL-6 on a Broader Canvas

Zahra Sadat Mousavi Bafrouei¹, Mahdiah Rahmani², Nazanin Nasiri¹, Seyed Mehrad Razavi¹, Zahra Najafi Arab¹, Zahra Nikbakht¹, Nematollah Jaafari³, Farshad Hashemian^{1*}

¹Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran.

²Department of Pharmaceutics and Food Technology, School of Pharmacy, Universidad Complutense de Madrid, Ciudad Universitaria, Madrid, Spain.

³Université de Poitiers, Unité de recherche clinique intersectorielle Pierre Deniker du Centre Hospitalier Henri Laborit F-86022 France, Groupement De Recherche CNRS 3557, Poitiers, France.

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Abstract

Cerebrovascular diseases, including ischemic and hemorrhagic strokes, rank among the leading causes of worldwide mortality and long-term morbidity. An acute systemic inflammatory reaction is one of the primary acute-phase responses that occur following the onset of a stroke. Elevated expression of inflammatory markers such as cytokines can be observed early after a stroke's onset and may negatively influence the outcome. Interleukin-6 (IL-6) is considered a pleiotropic cytokine with both pro-inflammatory and anti-inflammatory effects and plays a crucial role in the inflammatory cascade following a stroke. IL-6 is essential for regulating the immune response. However, during the acute phase of a stroke, its overproduction can promote inflammation by acting as a proinflammatory cytokine, potentially exacerbating both the disease progression and the inflammatory response. Despite numerous investigations, the exact role and mechanism of action of IL-6 after a stroke remain complex and have yet to be fully explained. The present narrative review aims to assess serum and cerebrospinal fluid changes in IL-6 during different phases of the disease in both ischemic and hemorrhagic strokes and their possible correlation with short-term and long-term functional and neurological outcomes. We explore the potential application of IL-6 as a prognostic factor for diagnosis, recognition of subtypes, assessment of stroke severity, and prediction of outcomes. In this narrative review, peer-reviewed journal articles from 1990 to 2022 were searched on PubMed, MEDLINE, ScienceDirect, and Google Scholar to identify original studies. Several relevant articles were then selected based on their comprehensiveness and informativeness. Results suggest that IL-6 levels peak during the acute phase of both ischemic and hemorrhagic strokes, with elevated concentrations correlating with worse clinical outcomes, including poorer functional recovery and an increased risk of complications. The findings underscore the potential value of IL-6 as a biomarker for early prognostication and guiding clinical decision-making. In conclusion, IL-6 shows potential as a prognostic tool and therapeutic target in stroke management. However, its exact role remains unclear, and further research is needed to better understand its mechanisms and determine the optimal timing for measurement to ensure accurate predictions.

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Introduction

Stroke stands as a prominent contributor to both mortality and enduring disability on a global scale. In 2019 alone, there were 12.2 million newly reported cases, 101 million existing cases, and a staggering 6.55 million fatalities attributed to stroke. Stroke remains the fifth leading cause of mortality and one of the primary contributors to long-term disability in the United States, according to the American Stroke Association. Despite its significant

burden on public health, research indicates that up to 80% of strokes may be preventable through appropriate risk factor management, including lifestyle modifications and medical interventions. This underscores the importance of early detection and comprehensive stroke prevention strategies to mitigate its impact on individuals and healthcare systems (1, 2).

This condition manifests as a sudden and irreversible demise of neuronal cells brought about by either ischemia

* **Corresponding Author:** Farshad Hashemian
Address: No. 99 Yakhchal Street, Shariati Avenue, Tehran, 1941933111, Iran.
Email: hashemian.f@iaups.ac.ir, fhashemian@yahoo.com

or hemorrhage. Survivors of stroke are confronted with an array of aftermaths, including sensory impairment, functional incapacities, and aphasia, as well as additional neurological complexities such as post-stroke depression, dementia, and fatigue. Regrettably, many stroke survivors must grapple with these functional and neurological repercussions indefinitely, often impeding their ability to lead independent lives (3).

During an ischemic stroke, the abrupt halt of blood supply to a specific cerebrovascular region gives rise to an ischemic core, where neurons undergo rapid cellular necrosis. Encircling this ischemic core is an area known as the penumbra, in which neurons are functionally compromised due to reduced blood flow. Nevertheless, they remain viable and can potentially be rescued if blood flow is reinstated (4).

Conversely, in a hemorrhagic stroke, the sudden rupture of a cerebral vessel leads to the extravasation of blood directly into the brain, resulting in the formation of a hematoma. This hematoma has the potential to exert pressure on cerebral tissue and vessels, giving rise to additional complications such as vasospasm and delayed ischemia (5, 6).

As substantiated by a multitude of reports, subsequent to the initial brain injury upon stroke onset, an acute-phase immune response coordinated by neuronal demise sets in motion distinct biochemical cascades, including excitotoxicity, oxidative stress, and inflammation. This inflammation, occurring locally and globally, precipitates the release of an array of inflammatory mediators, such as cytokines and chemokines. These mediators can potentially impact both short-term and long-term functional and neurological outcomes. Despite the heterogeneous origins of ischemic and hemorrhagic stroke, this inflammatory response appears to be activated through a shared pathway, exerting a substantial influence on the ensuing pathophysiological repercussions (7, 8).

During the initial acute phase of the disease, the deprivation of blood and oxygen supply induces damage to neuronal cells and triggers the release of danger-associated molecular patterns. This, in turn, instigates the activation and mobilization of immune cells, particularly macrophages. These infiltrating macrophages subsequently initiate the secretion of inflammatory mediators, including cytokines and chemokines, which further propagate inflammation, disrupt the integrity of the blood-brain barrier, and contribute to neuronal impairment (9). Interleukins are pivotal cytokines that serve vital functions in activating, regulating, and mediating immune cells, as well as in

promoting the proliferation and differentiation of T and B cells. They also facilitate the transmission of critical information during inflammatory responses (10).

Among the interleukin family, IL-6, a pleiotropic cytokine, is widely considered a central player in the cytokine network (11) and the primary inflammatory marker associated with stroke (12, 13). Given the numerous recent investigations that have shed light on the role of IL-6 in stroke, this narrative review aims to elucidate the beneficial and detrimental effects of IL-6 in the context of the inflammatory response following stroke onset.

Interleukin-6 and its related pathways

The interleukin-6 (IL-6) superfamily consists of several cytokines, including IL-6, IL-11, IL-27, IL-31, ciliary neurotrophic factor, leukemia inhibitory factor, oncostatin M, novel neurotrophin-1/B-cell-stimulating factor-3, neuropoietin, cardiotrophin-1, and cardiotrophin-like cytokine (14, 15). This cytokine group is classified as a family due to the shared core structure among all its members and the presence of a common signal-transducing subunit (gp130) in their receptor complexes (16).

IL-6 is a pleiotropic cytokine and a leading member of the IL-6 superfamily. This glycoprotein comprises 212 amino acids, which are cleaved at the NH₂-terminal site to produce a 184-amino acid peptide with a molecular weight of 20 to 30 kDa (10, 17).

IL-6 is synthesized by various cell types, encompassing both lymphoid and non-lymphoid cells, thereby exerting its influence on diverse target cells (18).

Being a pleiotropic cytokine, IL-6 is predominantly recognized as a proinflammatory marker, yet it also possesses the capacity to elicit anti-inflammatory and regenerative effects (19, 20). For instance, it has been proposed that during cerebral ischemia, overexpression of IL-6 in the acute stage of the disease serves as a mediator of the inflammatory response, contributing to neurodegeneration. However, IL-6 can exert neurotrophic and advantageous effects during the late and chronic stages of the disease (13, 21).

Under normal circumstances, a small amount of IL-6 is detected in human serum samples; however, these serum concentrations may rise a thousandfold during infection, autoimmune disease, and inflammatory states. The IL-6 serum levels in healthy individuals are documented to range from 1 to 5 pg/mL. In contrast, these levels can dramatically increase following inflammatory states and might even reach several milligrams per milliliter in cases of life-threatening septic shock (22).

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IL-6 synthesis is dependent on Tumor Necrosis Factor- α (TNF α) and IL-1, which stimulate their target cells to increase the expression of IL-6 (23). Moreover, not only does IL-6 inhibit the reciprocal release of IL-1 and TNF α and can also act as a stimulus for synthesizing their antagonists (13, 24).

IL-6 primarily exerts its effects by interacting with a receptor system consisting of a binding site (IL-6Ra) and a signal transducer (IL-6R β). IL-6Ra represents a receptor subunit with a molecular weight of 80 kDa (also known as gp80 or CD126). This subunit is present in two distinct forms: a membrane-bound receptor (mIL-6Ra) and a soluble variant (sIL-6Ra) (25, 26). The transmembrane IL-6Ra can be cleaved and removed from the cell membrane by ADAM17, a membrane-bound metalloprotease, to form a soluble receptor subunit with a similar affinity for the IL-6 ligand (27).

IL-6R β is a signal-transducing receptor and a transmembrane protein with a molecular mass of 130 kDa (gp130 or CD130) (26). IL-6 signal transduction can mainly occur in two different forms: classic signaling and trans-signaling, which can remarkably provoke different cellular responses (Fig. 1a) (28).

Forming a hexamer consisting of two IL-6 ligands and two mIL-6Ra with dimerized gp130 transduces a signal called classic signaling. Conversely, the signal transduction produced by the interaction between IL-6, sIL-6Ra, and gp130 is called trans-signaling (11). IL-6 implements its proinflammatory activities by trans-signaling via the soluble IL-6 receptor (sIL-6R). On the contrary, the anti-inflammatory effects of this cytokine are mainly mediated

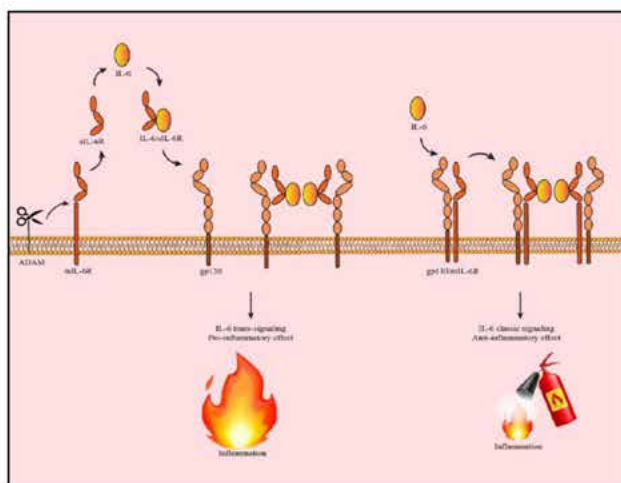
by the membrane-bound IL-6 receptor (mIL-6R) through classic signaling (11, 15, 19, 29).

IL-6 can transduce signals through three pathways: JAK/STAT, RAS/MAPK, and PI3K/AKT (22).

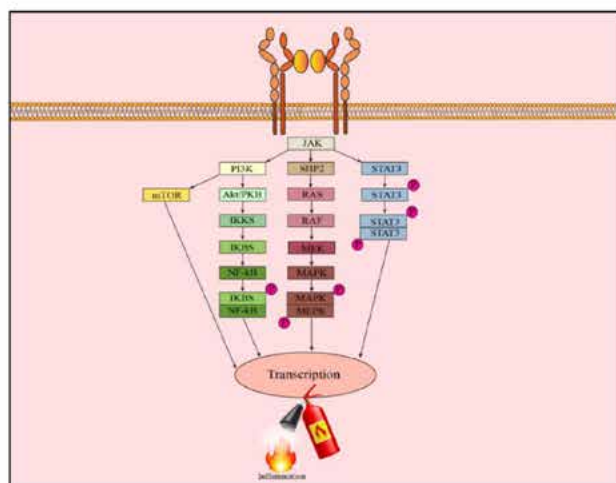
First, activation of Janus-associated kinase, a member of the tyrosine kinase family, can, in turn, lead to tyrosine phosphorylation and activation of the signal transducer and activator of transcription (STAT). STAT3 then dimerizes to transmit signals to the nucleus, consequently regulating gene expression and leading to cellular proliferation, differentiation, growth, and survival (24, 30).

Following the second downstream pathway of IL-6 signaling, the Src homology 2 domain-containing protein tyrosine phosphatase binds to phosphorylated gp130 at the tyrosine 759 site. This can activate the cascade of RAS, RAF, and MEK that subsequently triggers mitogen-activated protein kinase, bringing about diverse effects such as immunoglobulin and antibody production, acute-phase protein synthesis, and cell growth (31).

In another signaling pathway, phosphatidylinositol 3-kinase (PI3K) is activated by IL-6-induced signaling, and this PI3K activation can lead to phosphorylation of phosphatidylinositol-4,5-bisphosphate, resulting in the production of phosphatidylinositol-3,4,5-trisphosphate (PIP3). This PIP3 can phosphorylate and activate protein kinase B (AKT-PKB), leading to DNA transcription and the expression of several genes involved in cell survival (26). Hence, Figure 1 has been illustrated to better understand the various signaling pathways in which IL-6 plays a pivotal role (Fig. 1b).



(a)



(b)

Figure 1. (a) Dual Role of IL-6 in Stroke; (b) IL-6 classic signaling pathways.

Method

This narrative review conducted a comprehensive literature search to identify peer-reviewed journal articles published between 1990 and 2022. The databases searched included PubMed, MEDLINE, ScienceDirect, and Google Scholar. The search focused on studies examining the role of IL-6 in stroke, using the keywords: “interleukin-6,” “stroke,” “hemorrhagic stroke,” “ischemic stroke,” and “transient ischemic attack.”

An initial screening based on titles identified 230 relevant articles. After reviewing the abstracts, 120 articles were selected for further evaluation. Ultimately, 60 articles were included in the final review based on their relevance, novelty, and clinical significance. Only human studies were considered, while animal studies were excluded to maintain a focus on clinical applicability.

Results

Cerebrovascular disease constitutes one of the principal health problems worldwide. There is a strong body of evidence that stroke is intimately linked to the inflammatory process. Proinflammatory cytokines appear to be involved in the pathogenesis and progression of brain damage, among which IL-6 is one of the most influential cytokines, playing a prominent role in regulating the inflammatory response following the acute phase reaction after stroke (32).

IL-6 in ischemic stroke

Numerous studies have aimed to unravel the potential relationship between IL-6 levels and functional or neurological outcomes in stroke. A comprehensive review of these studies necessitates consideration of factors such as short-term and long-term outcomes, acute neurological status, lesion volume, and the timing of blood/cerebrospinal fluid (CSF) collection. Most of these investigations have focused on patients during the acute phase, predominantly exploring short-term prognoses. In the subsequent section, a selection of pertinent clinical studies will be reviewed.

Vila et al. conducted a study that unveiled a positive correlation between circulating levels of IL-6 during the acute phase of stroke and neurologic deficits, infarct size, and serum levels of acute-phase reactants like erythrocyte sedimentation rate (ESR) and C4BP. Their findings also indicated a negative correlation between IL-6 levels and free Protein S levels, affecting the modulation of the natural anticoagulant system (33).

In their study, Szczudlik et al. made significant findings

regarding the changes in serum levels of IL-6 and cortisol following an acute ischemic stroke (AIS) and their potential associations with neurological status and infarct size. Szczudlik and colleagues uncovered that serum levels of IL-6 and cortisol increase following AIS. Additionally, they observed that morning serum IL-6 levels have predictive value for evening/night serum cortisol levels. These cortisol levels were correlated with the neurological status assessed upon admission using the Scandinavian Stroke Scale and with the infarct size (34). Szczudlik et al.'s study highlights the dynamic changes in IL-6 and cortisol levels in response to AIS. Moreover, it suggests potential connections between these biomarkers and clinical parameters, such as neurological status and infarct size. These findings contribute to our understanding of the physiological responses to stroke and may have implications for developing biomarkers or therapeutic interventions to improve stroke outcomes. However, further research is needed to confirm and expand upon these findings.

Following a series of blood IL-6 level measurements and their subsequent correlation with stroke outcomes, Andreassen and colleagues undertook a small-scale case study involving 11 patients. Their investigation unveiled a noteworthy pattern wherein IL-6 serum levels increased during the acute phase of ischemic stroke. Moreover, these elevated IL-6 levels demonstrated significant associations with two key factors: lesion volume and one-year clinical outcomes, as assessed through the European Stroke Scale and the Barthel Index (BI). The findings from this modest-scale case study shed light on the potential utility of IL-6 as a prognostic and diagnostic biomarker in ischemic stroke. These compelling observations warrant further investigation on a larger scale to substantiate their clinical significance and explore potential interventions to modulate IL-6 levels, ultimately enhancing stroke outcomes. Moreover, comprehending the role of inflammation in the pathophysiology of stroke is pivotal for developing targeted therapeutic strategies in this domain (35).

Domac et al. have demonstrated that serum IL-6 levels increase following AIS and are even higher among patients with a larger infarct volume and a 2-month modified Rankin Scale (mRS) score greater than 2. They concluded that there is an association between IL-6 levels, lesion volume, and clinical prognosis. Elevated IL-6 levels correspond to a greater extent of brain damage (36).

Orion et al. demonstrated that high plasma levels of IL-6

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in patients with AIS are strongly associated with stroke severity, as measured by the National Institutes of Health Stroke Scale (NIHSS), and with poor functional outcomes after 3 months (mRS > 2, SIS < 85) (37).

A study conducted by Tuttolomondo et al. unveiled that blood levels of IL-6 rise during the acute phase of ischemic stroke, with the most significant elevation observed in cardioembolic stroke subtypes and the lowest increase noted in lacunar stroke subtypes. In addition, IL-6, IL-1 β , and TNF- α were significantly elevated in stroke patients compared to controls, with the highest increase in cardioembolic stroke. Conversely, IL-6, IL-1 β , and TNF- α levels were significantly decreased in lacunar stroke. Furthermore, markers of endothelial activation, such as E-selectin, P-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1), were also elevated in stroke patients. The median Scandinavian Stroke Scale score was lower in cardioembolic stroke patients, while it was higher in lacunar stroke patients, further reflecting differences in inflammatory responses between stroke subtypes (38).

Bharosay et al. have also demonstrated that IL-6 levels increase following the onset of ischemic stroke. Furthermore, the acute IL-6 plasma level correlates with stroke severity (measured by NIHSS at admission) and early neurological deterioration (END) (Δ NIHSS 0–7th day >2) (39).

A study by Shaafi et al. has shown that circulating levels of IL-6 positively correlate with NIHSS, mRS, lesion volume, and mortality following AIS (40).

El-Shazly et al. also demonstrated in a case-control clinical study that peak serum concentration of IL-6 is correlated with infarct size, 1-month functional outcome based on BI, and first- and 7th-day neurological status/stroke severity based on NIHSS (41).

Fahmi et al. proved that IL-6 serum levels increase after AIS, with IL-6 serum levels and infarct volume as predictors of short-term outcomes based on NIHSS. Additionally, IL-6 and C-reactive protein (CRP) serum levels were elevated in stroke patients compared to controls. The synergistic interaction between IL-6 and infarct size (measured by CT) was also identified as a key predictor of short-term outcomes based on NIHSS (42).

A study conducted by Choudhary et al. showed that following AIS, serum IL-6 levels increase, having a positive correlation with stroke severity (NIHSS) and lesion volume. It also showed that IL-6 serum levels could be an independent predictor of short-term (7th-day

NIHSS) and long-term outcomes (1- and 3-month mRS) (43).

Another study conducted by Lasek-Bal et al. revealed that the serum level of IL-6 in the acute stage of ischemic stroke has a significant positive correlation not only with neurological status and stroke severity based on NIHSS but also with 30th-day functional status based on mRS (44).

The PREDICT trial, a prospective multicenter clinical trial conducted by Mengel et al., showed that the increase in IL-6 on day 1 is associated with poor functional outcome (mRS>3) and shorter survival time after 3 months of stroke onset (45).

Li et al. showed that levels of proinflammatory cytokines such as IL-6 have a negative correlation with stroke severity based on NIHSS. Moreover, IL-6 serum levels were significantly higher in patients with poor outcomes based on mRS. The authors also indicated that IL-6 serum concentration is an independent risk predictor of AIS. This study shows that IL-6, along with other proinflammatory cytokines like IL-1 β , IL-4, IL-5, IL-7, IL-9, IL-10, IL-15, and Granulocyte-Colony Stimulating Factor, was significantly reduced in severe stroke patients based on NIHSS. Specifically, IL-6 was notably higher in patients with poor outcomes (mRS >2), whereas IL-1 β , IL-4, IL-5, IL-7, IL-9, IL-10, IL-15, Granulocyte-Colony Stimulating Factor, and Granulocyte-Macrophage Colony-Stimulating Factor were significantly decreased. Serum levels of IL-6, neutrophils, IL-4, IL-5, and MIP-1 α were significantly associated with functional outcomes, further emphasizing the role of inflammation in stroke prognosis. Only IL-9 levels decreased in patients with large infarct volumes, indicating a potential link between cytokine profiles and infarct size. These findings reinforce the idea that inflammatory responses, particularly IL-6, play a significant role in both stroke severity and patient outcomes (46).

Aref et al. observed that serum IL-6 levels would be higher in ischemic stroke patients with small vessel occlusion and those with recurrence. They also showed that IL-6 levels have a positive correlation with 3-month NIHSS and mRS. They concluded that IL-6 can predict clinical outcomes and the rate of recurrence following AIS (47).

A study performed by Huang et al. concluded that serum IL-6 levels following AIS were correlated with baseline NIHSS, lesion volume, and 6-month functional outcome based on mRS (48).

Reiche et al. demonstrated that acute elevation of IL-6, glucose, ferritin, and lipid hydroperoxides (CL-LOOH)

levels and a reduction in 25(OH)D levels could be a reliable predictor of short-term mortality after ischemic stroke. The authors found that elevated IL-6 was significantly associated with increased levels of high-sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate, and WBC, suggesting that IL-6-associated immune-inflammatory responses play a crucial role in death following AIS. Furthermore, they concluded that targeting the blockade of IL-6 trans-signaling pathways and addressing redox imbalances might provide potential therapeutic strategies for preventing short-term mortality after AIS (49).

The study conducted by Deng *et al.* demonstrated that ischemic stroke patients with END (Δ NIHSS 0-24 h >4) had higher IL-6 serum levels. They also concluded that serum IL-6 levels were associated with 3-month mRS after endovascular therapy. In this study, IL-6, IL-4, and IL-10 expressions showed significant changes over 7 days in patients with END (50).

Purroy *et al.* observed that IL-6 and Human S100 Calcium-Binding Protein B (S100B) could independently predict infarct volume after AIS (51).

When evaluating long-term mortality in the context of ischemic stroke, studies such as the one conducted by Ramiro *et al.* provide valuable insights. In their research, which encompassed a 4.8-year follow-up of 941 ischemic stroke patients, they aimed to assess a panel of 14 biomarkers, including IL-6, within the first 6 hours of symptom onset. The study revealed that the acute elevation of endostatin, IL-6, and TNF-R1 following an ischemic stroke independently predicts long-term mortality (52).

In the same way, Conway *et al.* showed that a high plasma concentration of IL-6 could be a predictor of stroke incidence and a high mortality rate in the long term among atrial fibrillation patients (53).

Shenhar-Tsarfaty *et al.* conducted a study that demonstrated a significant correlation between the acute plasma concentration of IL-6 and 1-year mortality, as well as the severity of stroke as determined by the NIHSS and mRS scales after AIS and transient ischemic attack. These findings suggest that IL-6 levels may be an early predictive indicator for stroke survival (54).

Beridze *et al.* reported that, in the context of AIS, there is an increase in CSF levels of IL-6, with a more substantial elevation observed in severe stroke cases. Their study demonstrated a positive correlation between acute IL-6 CSF levels, lesion volume, and NIHSS scores on the seventh day post-stroke and a negative correlation with functional outcomes at 1 month based on BI. The authors

suggested that CSF levels of IL-6, in conjunction with CSF Nitric Oxide levels, could serve as the most reliable prognostic indicators during the acute phase of ischemic stroke (55).

Spalletta *et al.* conducted a study to examine the connection between circulating IL-6 levels and various aspects of neurological, psychological, and functional characteristics during the acute phase of ischemic stroke. Their findings revealed that IL-6 levels positively correlate with the Hamilton Rating Scale for Depression (HAMD/Ham-D) and NIHSS. Additionally, they observed a negative correlation between IL-6 levels and word recognition scores and functional status, as assessed using BI. The study suggested that elevated levels of IL-6 in the serum might play a significant role in the severity of stroke and the development of post-stroke depression. This, in turn, could lead to increased disability and poorer outcomes during the acute stage of ischemic stroke (56). Another study by Kang *et al.* showed a similar phenomenon; they found that higher levels of IL-6 and IL-18 were associated with the presence of depressive disorders during both the early phase (within 2 weeks) and the chronic phase (within 1 year) following an ischemic stroke (57).

In the same way, Mu *et al.* observed that serum levels of inflammatory markers, including IL-6, TNF α , and CRP, were elevated in patients who experienced post-stroke depression, whether due to ischemic or hemorrhagic stroke. Furthermore, they noted that the levels of these three factors were positively correlated with the severity of depression following a stroke (58).

Kowalska *et al.* conducted a study focusing on post-stroke psychiatric complications and their relationship with inflammatory cytokines. Their research demonstrated that elevated IL-6 serum levels correlated with post-stroke delirium (59).

A study conducted by Gyawali *et al.* suggests a positive correlation between circulating IL-6 levels and post-stroke fatigue, indicating that individuals with higher IL-6 levels are more likely to experience fatigue after a stroke. Additionally, the fatigue assessment score was significantly correlated with IL-6 and hsCRP levels in stroke patients. Notably, stroke survivors exhibited increased levels of IL-6, hsCRP, and the fatigue assessment score compared to controls, further highlighting the potential role of inflammation in post-stroke fatigue (60). A study by Choi *et al.* claimed that among patients with AIS, individuals who had underlying dementia exhibited higher levels of serum IL-6 and CRP (61). Loga *et al.*

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demonstrated that AIS patients with cognitive impairment had higher serum IL-6 and TNF α levels. Notably, female patients had higher baseline IL-6 levels. The authors concluded that proinflammatory cytokines are likely linked to the pathophysiology of cognitive decline in AIS (62).

Similarly, a clinical study on 1,003 patients conducted by Wang et al. demonstrated that the acute elevation of circulating IL-6 was positively correlated with the risk of cognitive decline (MoCA) within 1 year after ischemic stroke and TIA (63).

Srivastava et al. conducted research that demonstrated an increase in IL-6 blood levels following ischemic stroke and a positive correlation between IL-6 levels and NIHSS. The authors concluded that IL-6 levels are associated with stroke severity and suggested a possible correlation between IL-6 levels and acute or chronic *C. pneumoniae* infection in stroke patients. In other words, the percentage of stroke patients with serologic evidence of *C. pneumoniae* infection (IgG and IgA) was significantly higher than controls (64).

Other results from Kumar et al. show that plasma IL-6 and 24-hour urinary cortisol levels measured on the third day after stroke onset could serve as predictive factors for the development of post-stroke infection. Specifically, 24-hour urinary cortisol levels were significantly higher in stroke patients with infection. IL-6 and IL-10 plasma levels were elevated on day 3 and day 45 in stroke patients. Notably, IL-6 plasma levels exhibited a 15-fold decrease on day 45 compared to day 3 in stroke patients with infection, although they remained higher than in patients without infection. In contrast, IL-6 plasma levels had an 8-fold decrease on day 45 compared to day 3 in stroke patients without infection. These findings suggest that IL-6 plasma and 24-hour urinary cortisol levels on day 3 could be reliable predictors for post-stroke infections (65).

A study by Pusch et al. found that serum IL-6 levels increased significantly at 6 and 72 hours following an ischemic stroke. These elevated IL-6 levels were associated with the size of the damaged tissue, as indicated by S100B levels, and were also positively correlated with baseline stroke severity assessed using NIHSS. Additionally, the study revealed that higher IL-6 levels were predictive of neurological worsening within 48 hours after the stroke. Furthermore, an elevation in IL-6 serum levels by 72 hours post-stroke was linked to an increased likelihood of post-stroke infection and death. The research suggested that these early dynamic changes in IL-6 levels could serve as valuable predictors of short-

term outcomes in individuals who have experienced an ischemic stroke (66). These findings highlight the potential importance of monitoring IL-6 levels in stroke patients to assess stroke severity, predict outcomes, and identify those at a higher risk of complications such as infection and death.

Hervella et al. conducted a retrospective study involving 4,295 cases of ischemic stroke, revealing somewhat conflicting results. They found that increased serum IL-6 levels 24 hours after stroke onset were associated with a modest improvement during the hospital stay (Δ NIHSS admission to discharge >1). However, it was more significantly correlated with greater improvement beyond the hospitalization period (Δ NIHSS discharge to 3 months after onset >1). This suggested that certain excitatory and inflammatory mechanisms might be linked to delayed brain recovery, possibly indicating that administering anti-inflammatory medications in extended therapeutic windows could have adverse effects. Furthermore, inflammatory markers like IL-6 might serve as a diagnostic tool and potentially as neuroprotectors in managing ischemic stroke (67).

In contrast, Rezaeitalab et al. reached different conclusions, noting that serum levels of IL-6 and IL-1 β increased from admission to day five following stroke onset. However, they found that acute serum levels of hsCRP, IL-1 β , IL-6, and TNF- α did not show significant correlations with infarct volume (ASPECTS, pcASPECTS), changes in NIHSS, or functional outcomes based on mRS in patients with non-severe AIS (68).

Furthermore, Sotgiu et al. presented findings indicating an inverse correlation between serum IL-6 levels in the acute stage of ischemic stroke, 3-month NIHSS scores, and infarct size. This observation suggests a potential neuroprotective role of IL-6 within a complex proinflammatory network following a stroke. Specifically, IL-6 serum levels were inversely correlated with 3-month NIHSS scores, with higher IL-6 levels observed in patients with mild stroke (NIHSS 0 and 1). Conversely, IL-6 levels were lower in patients with larger infarct sizes and poorer outcomes (3-month NIHSS score ≥ 2). Additionally, IL-6 and TNF- α levels showed a significant inverse correlation, further supporting the complex relationship between inflammatory cytokines and stroke severity and recovery (69).

Table 1 outlines key study features of studies examining the impact of inflammatory biomarkers, particularly IL-6, on disease severity, mental and functional outcomes, as well as mortality following ischemic stroke.

Table 1. Key characteristics of studies investigating the impact of il-6 and other inflammatory biomarkers on stroke severity, functional outcomes, and mortality in ischemic stroke

| Study Design | Stroke Model | Number of Patients | Time of blood/CSF collection | Time of outcome evaluation | Publication year | Ref |
|--|--|--------------------|---|--|------------------|------|
| Prospective sub-study | AIS/TIA | 1003 | On admission (Within 7 days of onset) | 3-month & 1-year MoCA | 2022 | (63) |
| Cohort study | AIS | 332 | Within 24 hours | DWI within a week of the onset | 2021 | (51) |
| Observational cohort study | AIS | 210 | Days:1,2,3,7 | Δ NIHSS 0-24h & 90th-day mRS | 2021 | (50) |
| Case-control study | AIS | 100 | Within the first three days of admission & 15 th day | Within the first three days of admission & 15 th day | 2021 | (62) |
| Prospective longitudinal study | AIS | 941 | On admission (<6 hours from onset) | 4.8-year follow up (mortality) | 2021 | (52) |
| Single-centre, prospective & observational study | AIS | 60 | On admission | Acute phase NIHSS & 6 th month BI | 2020 | (48) |
| Observational study | AIS | 44 | Days: 1,5 | Days 1, 5, and 3 months after onset | 2020 | (68) |
| Observational cohort study | AIS | 90 | Within 24 hours & 3 months after the onset | 24-hour & 3-month NIHSS and mRS | 2020 | (47) |
| Retrospective study | AIS | 4295 | Within 24 hours | On admission, 24 hours, 48 hours, at discharge, and at 3 \pm 1 months | 2020 | (67) |
| Case-control study | AIS in patients with underlying dementia | 35 (AIS) | Within 72 hours | – | 2020 | (61) |
| Observational cohort study | AIS | 138 | Within 24 hours | First-day NIHSS & 30th-day mRS | 2019 | (44) |
| Prospective multicenter study | AIS | 91 | Within the first 4 days of admission | NIHSS & lesion volume on admission & 3-month mRS | 2019 | (45) |
| Case-control study | AIS | 145 | Within 24 hours | mRS on admission & 3 months after onset | 2019 | (49) |
| Case-control study | AIS | 180 | Within 24 hours | NIHSS within 24 hours of admission and at discharge, and 3-month mRS | 2019 | (46) |
| Case-control study | AIS | 33 | Days: 1,7,30,90 | NIHSS on days: 1,7 1-month & 3-month mRS DWI volume within first 7 days | 2018 | (43) |
| Prospective cohort study | AIS | 144 | On day 3 | Delirium assessment during the first 7 days | 2018 | (59) |
| Longitudinal cohort study | IS | 286 | Within 2 weeks of onset | 2-week & 1-year assessment of depression | 2016 | (57) |
| Hospital-based study | AIS | 50 | Within 24 hours | Stroke severity (CANS) on the first day & short-term outcome (NIHSS) 15 days after the onset | 2016 | (42) |
| Case-control study | AIS | 76 | 6, 24, and 72 hours after onset | NIHSS daily for 7 days & 28 th day (BI) & tissue damage based on acute S100B levels | 2015 | (66) |

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Table 1. Continued

| | | | | | | |
|--|---------|-----|---|---|------|------|
| Case-control clinical study | AIS | 45 | 24 hours & 7 days after onset | NIHSS on days 1 & 7 1-month BI Infarct volume (CT) on day 7 | 2015 | (41) |
| Prospective observational case-control study | AIS | 80 | Within a week of stroke onset | NIHSS Within a week | 2014 | (64) |
| Cross-sectional descriptive study | AIS | 45 | Days: 1,5 | NIHSS on days: 1, 5, 90, 365 mRS on days: 5, 90, 365 DWI after 72 hours from onset | 2014 | (40) |
| Randomized case-control study | AIS | 19 | Days: 3,45 | Assessment of infection during 45 days | 2014 | (65) |
| Observational cohort study | AIS | 48 | 72 hours after the onset | 72 hours after the onset | 2013 | (56) |
| Case-control clinical study | AIS | 95 | 6 hours after the onset | Lesion volume within 24 hours NIHSS: day 1&7 BI: after 1 month | 2011 | (55) |
| Case-control study | AIS | 46 | Within 72 hours | NIHSS on admission & after 7 days | 2011 | (39) |
| Prospective cohort study | AIS/TIA | 250 | Within 24 hours | Acute NIHSS & mRS & 12-month mortality | 2010 | (54) |
| Case-control study | AIS | 107 | Within 12 hours | SSS on admission | 2009 | (38) |
| Observational cohort study | AIS | 113 | Within 36 hours | Serial NIHSS assessment & 3-month mRS & SIS | 2008 | (37) |
| Case-control study | AIS | 70 | Within 24 hours | CT & MRI within 3 weeks of onset 2-month mRS | 2007 | (36) |
| Case-control clinical study | AIS | 50 | Within 20 hours | NIHSS & GCS on admission CT on admission and at days 4-7 NIHSS & GOS after 3 months | 2006 | (69) |
| Case-control clinical study | AIS | 11 | 4, 8, 12, 24, 48 and 72 hours, 7 and 12 days, 3 months and 1 year after the onset | ESS & BI: on admission, during hospital stay & after 1 year Lesion volume between days 5-7 | 2005 | (35) |
| Case-control clinical study | AIS | 22 | Serial measurement on day 2 & after 3 months | SSS on admission CT on days 5-7 | 2004 | (34) |
| Observational cohort study | AIS | 44 | Within 48 hours | Severity & infarct size on admission 3-month mRS | 2000 | (33) |

AIS: Acute Ischemic Stroke, BI: Barthel Index, CANS: Canadian Neurological Scale, CSF: Cerebrospinal Fluid, CT: Computed Tomography, DWI: Diffusion-Weighted Imaging, ESS: European Stroke Scale, GCS: Glasgow Coma Scale, GOS: Glasgow Outcome Scale, MoCA: Montreal Cognitive Assessment, MRI: Magnetic Resonance Imaging, mRS: modified Rankin Scale, NIHSS: National Institute of Health Stroke Scale, S100B: Human S100 Calcium-Binding Protein B, SIS: Stroke Impact Scale, SSS: Scandinavian Stroke Scale, TIA: Transient Ischemic Attack

IL-6 in hemorrhagic stroke

Hemorrhagic strokes, including subarachnoid hemorrhage (SAH) and intraventricular hemorrhage (IVH), are debilitating conditions often associated with complex pathophysiological processes. The involvement of inflammation in the pathogenesis of complications, such as intracranial hypertension, cerebral vasospasm (CVS), and delayed cerebral ischemia (DCI) following aneurysmal SAH, is a subject of controversy. IL-6, a multifunctional cytokine, has emerged as a focal point of interest in understanding the inflammatory response and its implications in these neurological emergencies. Some studies emphasize IL-6 as an early indicator of clinical outcomes after a hemorrhagic stroke.

A study conducted by Ridwan et al. revealed notable findings regarding IL-6 in patients with SAH. They observed that IL-6 concentrations in CSF were much higher than in the bloodstream among SAH patients. Additionally, the study established a robust correlation between the peak level of IL-6 in CSF and the occurrence of DCI, particularly with IL-6 peak CSF levels between days 4–14, which were significantly correlated with DCI. The overall peak IL-6 levels in CSF and those observed between days 4–14 showed a strong correlation with DCI, suggesting that baseline CSF IL-6 levels could serve as a prognostic marker for DCI. High CSF IL-6 levels were also correlated with the development of vasospastic infarctions. In contrast, no significant correlation was found between peak serum IL-6 levels and DCI or vasospastic events. Furthermore, patients with peak CSF IL-6 levels greater than 35,000 pg/ml between days 4–14 had poor outcomes (mRS 0–2). The study also found that IL-6 levels had some associations with the initial severity of the hemorrhage, further highlighting the potential role of IL-6 in assessing the severity and prognosis of SAH (70).

Đuriš et al.'s study provided further insights into the dynamics of IL-6 in CSF following SAH. Their research revealed a substantial and rapid increase in CSF IL-6 levels within the first 72 hours after SAH, followed by an additional increase in later phases, although with high variability in IL-6 concentrations. Importantly, the study found a significant correlation between the Glasgow Outcome Scale (GOS) score and both overall IL-6 levels and their dynamic changes, suggesting that higher CSF IL-6 concentrations may serve as a predictor of patient outcomes. However, no associations were identified between CSF IL-6 levels and stroke severity, as determined by the Fisher grade, aneurysm treatment options, or the development of CVS. These findings underscore the role of CSF IL-6 as a prognostic indicator for patient recovery rather than a marker directly related to stroke severity or

treatment modalities (71).

In a study with comparable characteristics, Wu et al. reported that the concentrations of IL-6 and TNF- α in CSF increased following SAH. Moreover, they found that these elevated levels of IL-6 and TNF- α were correlated with the severity of the stroke, as assessed by the Hunt-Hess grade, and the occurrence of CVS in SAH patients. This suggests that IL-6 and TNF- α in CSF may serve as valuable markers for diagnosing SAH and monitoring the progression of the disease in SAH patients. These findings highlight the potential clinical utility of these markers in the management and assessment of SAH patients (72).

Gruber et al. conducted a study with a similar approach that provided valuable insights into the dynamics of IL-6 following SAH. They found that the level of IL-6 in CSF increased after SAH. Importantly, this increase in CSF IL-6 was correlated with the severity of the stroke, as assessed by the Hunt-Hess grade, and with the neurological outcome, as measured by the GOS. In other words, higher CSF IL-6 levels were associated with more severe strokes and worse neurological outcomes in SAH patients (73).

Oto et al. have highlighted the differences between hemorrhagic and ischemic strokes regarding IL-6 levels. Their research indicated that patients suffering from hemorrhagic stroke exhibited higher serum IL-6 levels compared to those experiencing ischemic strokes. Additionally, they noted a significant correlation between serum IL-6 levels and functional outcomes, as measured by the 1-month mRS, in hemorrhagic stroke patients. In other words, elevated serum IL-6 levels were associated with worse functional outcomes in individuals with hemorrhagic strokes.

Conversely, their study did not find any predictive value for clinical outcomes in ischemic stroke patients based on the levels of plasma cytokines and chemokines. This suggests that the relationship between IL-6 and clinical outcomes may be more pronounced in hemorrhagic strokes, while it may not hold the same significance in the context of ischemic strokes (74).

Yao et al. made a noteworthy discovery in their research, revealing that the concentration of IL-6 in small extracellular vesicles found in CSF, referred to as small extracellular vesicles (IL-6sEVs), exhibited a positive correlation with the severity of the stroke and the neurological outcome observed within the first year after SAH based on mRS. This finding underscores the potential significance of IL-6sEVs as a biomarker for predicting both the severity of the stroke and the long-term neurological prognosis following SAH (75).

A study conducted by Dziedzic et al. demonstrated that the levels of IL-6 and IL-10 in the serum increased

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following an intracerebral hemorrhage (ICH). Moreover, these concentrations were correlated with several clinical parameters, including the Glasgow Coma Scale score at admission, total blood volume, and mass effect. This suggests that both IL-6 and IL-10 in the serum may serve as valuable markers for assessing the severity and clinical characteristics of intracerebral hemorrhages (76).

Kamińska et al. conducted a study that revealed intriguing findings regarding unruptured intracranial aneurysms (UIA). They found that the ratio of IL-6 in CSF to serum IL-6 was significantly higher in patients with UIA compared to control subjects. Additionally, they established a positive correlation between CSF IL-6 concentration and the number of aneurysms, indicating that higher CSF IL-6 levels were associated with a greater number of aneurysms. Conversely, there was a negative correlation between CSF IL-6 concentration and aneurysm size, suggesting that smaller aneurysms were associated with higher CSF IL-6 levels. These findings may have implications for understanding the pathophysiology and potential markers of UIA (77).

Höllig et al. uncovered a significant association in their research, demonstrating that higher levels of IL-6 in the serum during the acute stage of SAH are linked to unfavorable functional outcomes, as determined by the mRS at discharge. This information can be crucial for clinicians in predicting and managing post-SAH care and rehabilitation for their patients (78).

In their study, Kao et al. discovered significant correlations regarding plasma IL-6 levels in the context of SAH. Elevated aneurysmal IL-6 levels were modestly to moderately correlated with the Glasgow Coma Scale scores on admission (day 0), vasospasm grade, and the extent of hemorrhage as determined by the Fisher grade. A strong correlation was also observed between aneurysmal IL-6 levels and the corresponding venous IL-6 levels, although the median aneurysmal IL-6 concentration was significantly lower than the venous IL-6 concentration. Notably, higher aneurysmal IL-6 levels were significantly associated with poor 30-day functional outcomes as assessed by the mRS, while venous IL-6 levels showed a marginal correlation with poor mRS scores. These findings suggest that plasma IL-6 levels, particularly those derived from the aneurysmal site, may be independent prognostic markers for predicting unfavorable neurological outcomes after SAH, providing valuable insights into disease severity and progression (79).

A study conducted by Ziai et al. demonstrated significant associations between increased levels of various CSF cytokines, including IL-6, and IVH volume upon admission, perihematomal edema (PHE) volume, and acute febrile

response during the early stages following IVH. Notably, CSF levels of IL-6, IL-8, IL-10, and CCL2 exhibited significant correlations with IVH volume at admission (T0). In contrast, PHE and/or relative PHE volume at T0 were significantly associated with the elevation of multiple cytokines, including IL-6. Furthermore, CSF levels of IL-1 β , IL-6, IL-8, and IL-10 measured on days 3-4 were positively correlated with the febrile response during the first week. These findings underscore the potential role of CSF cytokines, particularly IL-6, as valuable indicators of IVH severity and the inflammatory responses that occur during the acute phase of this condition (80).

Chou et al. presented findings indicating that serum IL-6 levels after SAH were not associated with clinical outcomes at 3 and 6 months, as assessed by the mRS, nor with the occurrence of vasospasm. Similarly, TNF- α levels showed no correlation with vasospasm; however, elevated TNF- α levels on post-SAH days 2 to 3 were associated with poor 3-month outcomes. These results suggest that while TNF- α may have prognostic value for long-term recovery, IL-6 levels in serum do not appear to predict functional outcomes or vasospasm in SAH patients (81).

Sharma et al. conducted a study revealing that the peak serum levels of IL-6 following SAH were correlated with various factors, including the severity of stroke based on the Hunt-Hess grade, functional outcome at 1 and 6 months using the mRS, the occurrence of cerebral infarction, and the development of systemic infection (82).

Kikuchi et al. conducted a study where they observed that the concentrations of IL-6 and IL-8 in CSF samples from patients with acute SAH were significantly higher than the concentrations of IL-6 and IL-8 in the serum. This suggests that the inflammatory response involving IL-6 and IL-8 is more pronounced within the central nervous system during acute SAH. Furthermore, the authors proposed that, in line with previous reports, IL-6 might have vasoconstrictive properties in vasospasm. They cited evidence suggesting that IL-6 can inhibit the production of prostaglandin I₂, a molecule with vasodilatory effects, and increase the mRNA levels of the c-sis gene, which implies a potential role for IL-6 in promoting vasoconstriction. These findings hint at the multifaceted role of IL-6 in SAH, which may contribute to both the inflammatory response within the central nervous system and the development of vasospasm, a significant complication associated with SAH (83).

Graetz et al. found that the concentration of IL-6 in CSF increased significantly following acute SAH. Interestingly, while serum and extracellular fluid (ECF) levels of IL-6 were higher in SAH patients with elevated intracranial pressure (ICP), patients with higher ICP had lower CSF levels of IL-6. Specifically, during the subacute phase (days

6-10), CSF concentrations of IL-6 were lower in the high ICP group compared to the low ICP group. In contrast, IL-6 concentrations in ECF and plasma were elevated in the high ICP group, with high plasma IL-6 levels observed between days 5-9 after SAH. The study also found that higher IL-6 plasma levels on days 5-9 and IL-6 ECF levels on days 4-5 were associated with worse outcomes, as assessed by the GOS, whereas no such correlation was observed for CSF IL-6 levels. Furthermore, no correlation was found between local tissue ischemia and IL-6 levels in ECF, CSF, or plasma. These findings highlight the complex relationship between IL-6, ICP, and patient outcomes following SAH, suggesting that IL-6 levels in ECF and plasma may predict outcomes more than CSF IL-6 (84). Based on these findings, the authors proposed that intracranial hypertension might act as a proinflammatory trigger, leading to elevated levels of inflammatory cytokines, such as IL-6. This proinflammatory response, in turn, may contribute to unfavorable outcomes following SAH. This study underscores the complex relationship between ICP, inflammation, and clinical outcomes in SAH patients.

Rasmussen et al., in their study, revealed specific associations related to plasma IL-6 levels following SAH. They found that plasma IL-6 concentration, measured three days after SAH, was higher in patients who developed systemic infection than those who did not experience infection. This suggests that IL-6 may be involved in the inflammatory response associated with systemic infections in SAH patients. This study showed that plasma IL-6 levels had no significant association with the occurrence of DCI. Similarly, there was no notable correlation between plasma IL-6 levels and angiographic vasospasm, or the 3-month clinical outcomes assessed by the GOS (85). According to this study, while plasma IL-6 levels appeared to be related to the development of systemic infection following SAH, they did not show significant associations with other SAH-related complications or the longer-term clinical outcome. These findings suggest that the role of IL-6 in SAH may be specific to certain aspects of the condition.

Vlachogiannis et al. conducted a study that provided important insights into the dynamics of IL-6 following SAH. They found that CSF IL-6 levels increased significantly from day 1 to day 4, followed by a decrease on day 10, although they remained significantly higher than day 1 values. This elevation in CSF IL-6 was identified as a potential prognostic factor for developing vasospasm and delayed neurological deficits, highlighting its role as an early predictor of these complications. In contrast, plasma IL-6 levels were above the reference interval from day 1, remained stable until day 4, and decreased on day 10. The study also revealed that SAH patients with systemic

infections had higher plasma IL-6 levels than those without infections, suggesting a role for IL-6 in the inflammatory response associated with infections. On the fourth day after SAH, IL-6 levels were identified as predictive markers for the intensity of the inflammatory response, which was found to be more pronounced within the central nervous system (intrathecal) compared to the systemic circulation (CSF IL-6 > plasma IL-6) (86).

Choudhary et al. conducted a study that revealed a significant increase in serum IL-6 levels during the acute stage following aneurysmal SAH (aSAH), with elevated levels compared to controls over the first two weeks post-hemorrhage. Elevated circulating IL-6 levels were positively correlated with several clinical factors, including higher Hunt-Hess grades, increasing age, and the presence of IVH and ICH. Additionally, serum IL-6 levels were significantly higher in aSAH patients who developed seizures, CVS, delayed ischemic neurological deficits, and chronic hydrocephalus. Notably, IL-6 levels were sensitive to the development of infections, showing a marked increase in patients with pneumonia. A delayed rise in serum IL-6 was observed in patients who developed cerebral infarction, with IL-6 levels being negatively associated with DCI on day 1 but positively associated on days 3, 7, and 9. Furthermore, IL-6 levels were significantly higher in patients with poor functional outcomes, as assessed by the mRS and GOS, than in those with better outcomes at discharge. These findings highlight the potential of serum IL-6 as a biomarker for stroke severity, complications, and long-term prognosis following aSAH (43). This study suggests that serum IL-6 levels in the acute stage of SAH may serve as a valuable prognostic marker, as they positively correlate with several factors related to disease severity, complications, and unfavorable functional outcomes.

Hopkins et al. demonstrated that CSF IL-6 levels surpass plasma IL-6 levels and that a CSF IL-6 concentration exceeding 10,000 pg/mL is linked to ventriculostomy-related infections. Their findings suggest that IL-6 may be an early indicator of infection in patients with external ventricular drains. Similarly, their study revealed that both IL-6 and IL-8 CSF levels were higher than their plasma counterparts, and concentrations of IL-6 in CSF greater than 10,000 pg/mL were significantly correlated with ventriculostomy-related infections. These results reinforce the potential of IL-6 as a valuable early biomarker for CSF infection in EVD patients (87).

Table 2 outlines key study features of studies examining the impact of inflammatory biomarkers, particularly IL-6, on disease severity, mental and functional outcomes, as well as mortality following hemorrhagic strokes.

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Table 2. Key characteristics of studies investigating the impact of il-6 and other inflammatory biomarkers on stroke severity, functional outcomes, and mortality in hemorrhagic stroke

| Study Design | Stroke Model | Time of blood/CSF collection | Time of blood/CSF collection | Time of outcome evaluation | Publication Year | Ref |
|--|-------------------------------|------------------------------|--|--|------------------|------|
| Case-control study | UIA | 67 | Before surgery | Assessment of size and number of aneurysms before surgery | 2021 | (77) |
| Prospective observational cohort study | SAH | 82 | Serial measurement between days 0 to 28 | DCI & vasospasm assessment for 14 days | 2021 | (70) |
| Pilot study | aSAH | 103 | Within 48 hours | mRS at discharge Day 1 and the first year after SAH onset | 2021 | (75) |
| prospective, observational study | aSAH | 69 | Days: 1 to 7 | Day 1 (H&H) and 30-day & 6-month after admission (mRS) | 2021 | (82) |
| Prospective three-centre study | IVH | 28 | From day1 and up to 10 days | First 10 days | 2021 | (80) |
| Cross-sectional study | stroke | 70 | In average, after 38.5 months | Fatigue assessment (chronic stage of stroke recovery) | 2020 | (60) |
| Prospective study | SAH | 44 | Days: 1,4,10 | Acute assessments and 1-year GOS | 2019 | (86) |
| Prospective observational study | SAH | 90 | Days: 3,8 | Day 8 And 3 months after SAH onset (GOS) | 2019 | (85) |
| Retrospective case-control study | Ischemic & hemorrhagic stroke | 120 | Within 24 hours of admission | Post-stroke depression by HAMD | 2018 | (58) |
| Prospective observational study | aSAH | 47 | Three times a day for 4 days | Daily for 2 weeks And 3 months after SAH onset | 2018 | (71) |
| Case-control study | aSAH | 80 | Days: 1,3,5,7,9,11,13 | mRS & GOS at discharge | 2018 | (43) |
| Case-control study | SAH | 57 | On the second day | – | 2016 | (72) |
| prospective cohort study | aSAH | 81 | On admission | mRS at discharge & 6 months after SAH | 2015 | (78) |
| Prospective cohort study | RIA | 53 | Within 24 hours of admission and three days of symptom onset | GCS on admission and 30-day mRS | 2015 | (79) |

Table 2. Continued

| | | | | | | |
|---------------------------------|-------------------------------|----|--|----------------------------------|------|------|
| Prospective cohort study | SAH | 52 | Days: 0 to1, 2 to 3, 4 to 5, 6 to 8, and 10 to14 | 3 and 6 months mRS | 2012 | (81) |
| prospective study | SAH | 21 | First 7 days after EVD insertion | 10 days | 2012 | (87) |
| Prospective cohort study | aSAH | 24 | First 10 days | 3 and 6 months (GOS) | 2010 | (84) |
| Prospective observational study | Ischemic & hemorrhagic stroke | 37 | Within 8 hours | NIHSS on admission & 1-month mRS | 2008 | (74) |
| Pilot clinical study | AF | 77 | During attendance | 2305 days follow-up | 2004 | (53) |
| Case-control study | ICH | 30 | 19-27 hours after the onset | Day 1 | 2002 | (76) |
| Prospective cohort study | aSAH | 44 | 5 serum and CSF sample collection between days: 0-2 & 3-5 & 6-8 & 9-11 & 12-14 | Day 1 (H&H) and 6-month GOS | 2000 | (73) |
| Prospective cohort study | SAH | 7 | CSF sample on days: 3 or 4 & 7 or 8 & 13 or 14 Serum sample on day 7 | – | 1995 | (83) |

AF: Atrial Fibrillation, aSAH: Aneurysmatic Subarachnoid Haemorrhage, CSF: Cerebrospinal Fluid, DCI: Delayed Cerebral Ischemia, EVD: External Ventricular Drain, GOS: Glasgow Outcome Scale, H&H: modified Hunt and Hess Scale, HAMD: Hamilton Depression Scale, ICH: Intracerebral Hemorrhage, IVH: Intraventricular Hemorrhage, mRS: modified Rankin Scale, NIHSS: National Institute of Health Stroke Scale, RIA: Ruptured Intracranial Aneurysms, SAH: Subarachnoid Hemorrhage, UIA: Unruptured Intracranial Aneurysm

The role of IL-6 in hemorrhagic stroke is complex, as it influences both local and systemic inflammatory responses. In SAH, elevated IL-6 levels in CSF have been consistently associated with greater disease severity, the development of DCI, and poorer neurological outcomes. However, its relationship with CVS remains a topic of debate, with studies reporting conflicting results. These discrepancies may stem from variations in study design, patient populations, or the timing of IL-6 measurement. Interestingly, while serum IL-6 has been explored as a prognostic marker, findings have been inconsistent. This suggests that IL-6 levels in CSF may provide a more accurate reflection of neuroinflammatory activity within the brain. Additionally, the emerging role of IL-6 in IL-6sEVs warrants further research, as it could serve as a more reliable biomarker for predicting long-term outcomes.

In ICH and UIA, IL-6 has been linked to stroke severity, hematoma volume, and aneurysm characteristics, highlighting its potential role in stratifying patients based on their inflammatory profiles. Differences in CSF-to-serum IL-6 ratios further illustrate the complexity of its dynamics across different hemorrhagic stroke subtypes. Despite these insights, IL-6's role in systemic complications,

such as post-stroke infections, remains an active area of investigation. While some studies have connected IL-6 to worse functional outcomes, the underlying mechanisms remain unclear. Given the variability in findings, future research should focus on longitudinal studies incorporating both CSF and serum IL-6 measurements and standardized protocols for evaluating its clinical impact. A deeper understanding of these mechanisms could open the door to targeted anti-inflammatory treatments aimed at improving recovery in hemorrhagic stroke patients.

Based on existing research, the most informative time window for measuring IL-6 in both hemorrhagic and ischemic stroke appears to be the acute phase within the first 24 to 72 hours. This period is marked by a strong inflammatory response, particularly in hemorrhagic stroke, where IL-6 levels rise sharply due to brain tissue damage. In ischemic stroke, IL-6 also peaks within this early window, reflecting inflammation triggered by ischemia and reperfusion injury. However, to gain a more complete picture of IL-6's role in recovery, additional measurements during the subacute phase (days 3 to 7) and chronic phase (weeks to months) may be necessary. Since IL-6 levels remain elevated during these later stages, monitoring its

trajectory over time could provide valuable insights into the ongoing inflammatory response and its influence on long-term outcomes.

Conclusion

The role of IL-6 in the context of stroke, whether ischemic or hemorrhagic, offers promising prospects for prognostication and therapeutic intervention. This multifaceted cytokine has emerged as a valuable biomarker for assessing stroke severity and predicting functional outcomes. The collective findings underscore the importance of monitoring IL-6 levels, particularly during the acute phase, typically within the first 24 to 72 hours, to help clinicians make informed decisions regarding treatment strategies and rehabilitation plans.

Moreover, the research highlights the critical need for timely intervention to manage the post-stroke inflammatory response. Modulating IL-6 levels or its downstream effects may provide a therapeutic approach to enhance outcomes by mitigating the adverse consequences of inflammation. IL-6's dynamic behavior, whether in CSF or plasma, accentuates its potential role in early predicting complications, including systemic infections, and offers valuable clinical insights.

Further studies are essential to better understand the precise mechanisms by which IL-6 influences stroke outcomes. These investigations should focus on developing and evaluating targeted interventions that harness the beneficial aspects of the inflammatory response while reducing its harmful effects.

In conclusion, the extensive research surrounding IL-6 and stroke sheds light on a pivotal aspect of stroke pathophysiology. These insights provide invaluable guidance for clinical practice and emphasize the need for continued research in stroke management and recovery. Ultimately, they offer new opportunities for risk assessment, treatment, and improved patient outcomes.

Conflicts of Interest

The authors declare no conflict of interest.

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