Interleukin-6 and ischemic stroke: From mechanisms to clinical prospects (Review)

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Abstract. Neuroinflammation is a central component of the pathophysiology of ischemic stroke (IS). Suppressing excessive inflammatory responses after stroke can markedly improve patient outcomes. Interleukin-6 (IL-6), a key mediator of the inflammatory cascade, serves a notable role in the pathological process of acute IS through multiple mechanisms. Elevated serum IL-6 levels serve as an important biomarker for predicting the onset and recurrence of IS and are closely associated with disease severity and prognosis. Anti-inflammatory interventions are notably important during the acute phase and secondary prevention of stroke. Currently, therapeutic strategies targeting the IL-6/IL-6R signaling axis are under investigation and have shown promising clinical potential. The present review summarizes the important role of IL-6 in neuroinflammation associated with IS, its association with disease severity and prognosis and previous advances in anti-inflammatory therapeutic strategies targeting the IL-6/IL-6R pathway during both the acute phase and secondary prevention of IS.

Contents

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1. Introduction

A 2024 study in 'The Lancet' reported that, in 2021, stroke accounted for almost 50% of cardiovascular disease-related mortalities in the Western Pacific region, making it a leading cause of mortality. As populations age, stroke-related mortalities and disabilities are projected to rise, imposing an increasing burden on healthcare systems (1,2). Ischemic stroke (IS) represents 70-80% of all strokes. Mounting evidence suggests that persistent systemic inflammation after IS promotes infarct expansion, worsens neurological deficits and aggravates brain injury (3-5). Studies on post-stroke inflammation indicate that attenuating acute inflammatory responses can limit cerebral damage, while anti-inflammatory therapies may reduce recurrence in patients with residual inflammation (6,7). Interleukin (IL)-6, a key mediator of the inflammatory cascade following IS, serves a central role in its pathophysiological progression (8). Advances in neuroimmunology in the field of IS mean that elucidating the mechanism of action of IL-6, investigating its association with IS and developing IL-6-targeted interventions could lead to new methods for improving the outcomes for patients with IS.

2. Pathological mechanism of acute IS (AIS)

Following IS, the brain rapidly initiates the ischemic cascade, in which disrupted energy metabolism triggers excitotoxicity and oxidative stress, leading to neuronal injury and the release of damage-associated molecular patterns (DAMPs) (9,10). DAMPs activate downstream signaling through pattern recognition receptors (PRRs), inducing microglial M1 polarization and the production of pro-inflammatory cytokines, including TNF-α and IL-6 (11,12). Concurrently, activated neutrophils release reactive oxygen species (ROS), amplifying inflammation and tissue damage (13,14). These processes collectively disrupt the blood-brain barrier (BBB), cause microcirculatory failure and promote vasogenic cerebral edema. Neuroinflammation is not confined to the infarcted region but propagates throughout the brain, persistently impairing neurological recovery (15). In the acute phase of IS, widespread pathological alterations, such as excitotoxicity, oxidative stress and neuronal apoptosis, as well as systemic responses, including autonomic dysfunction, hypothalamic/pituitary/adrenal (HPA) axis overactivation and immune dysregulation, further aggravate IS-induced injury (9,16) (Fig. 1).

Notably, inflammation exerts a dual role in regulating IS-induced neuronal injury: Excessive early responses exacerbate ischemic damage, whereas moderate inflammation during later phases facilitates debris clearance, glial scar formation and neuroregeneration (17,18). Hence, timely modulation of acute inflammation may slow infarct core expansion and alleviate ischemic brain injury (19).

3. IL-6

IL-6 is a globular glycoprotein composed of 184 amino acids, with a molecular weight of 21-30 kDa. IL-6 contains two N-glycosylation sites and four conserved cysteine residues that form a stable antiparallel α-helical structure, maintained by hydrophobic interactions and disulfide bonds, which are important for receptor binding and signal transduction. IL-6 has three receptor-binding sites, one for IL-6 receptor (IL-6R) and two for glycoprotein 130 (gp130), and is primarily secreted by macrophages and activated T cells, although endothelial cells and hepatocytes also contribute to its production (20,21).

IL-6 mediates three distinct signaling modes via two types of receptors. The membrane-bound IL-6R (mIL-6R) activates the classical pathway, which exerts regenerative and anti-inflammatory effects, whereas the soluble IL-6R (sIL-6R) triggers trans-signaling, which is predominantly pro-inflammatory (22,23). Both pathways require gp130 for downstream activation (24,25). Because gp130 is ubiquitously expressed, trans-signaling can occur in nearly all cell types, amplifying inflammation (26). Additionally, in trans-presentation, IL-6 bound to dendritic cells is presented to naïve $CD4^+$ T cells, inducing their differentiation into pro-inflammatory T helper 17 cells (27). Notably, neurons respond to IL-6 only in the presence of sIL-6R (26).

Through the Janus kinase (JAK)/STAT pathway and other related pathways, IL-6 regulates cell proliferation, differentiation and immune homeostasis, serving as an important bridge between innate and adaptive immunity (8). Under physiological conditions, IL-6 levels in the central nervous system are minimal but rise sharply during AIS (28). Notable cellular sources of IL-6 include neurons within the ischemic core, endothelial cells, microglia and astrocytes (29). Endothelial cell-derived IL-6 and chemokines recruit neutrophils, which cleave mIL-6R to generate sIL-6R, thereby amplifying endothelial trans-signaling and inflammatory responses (22). Consequently, serum IL-6 levels are markedly elevated in patients with AIS (30), and clinical studies have demonstrated a strong association between IL-6 concentration and stroke risk (31). The present review provides a detailed overview of the pathological mechanisms by which IL-6 contributes to AIS progression.

4. IL-6 participates in the pathological mechanism of AIS

IL-6 in oxidative stress. Oxidative stress refers to a disruption of redox homeostasis, characterized by excessive oxidant activity leading to cellular injury. Cerebral ischemia and reperfusion provoke cellular responses that generate excessive ROS (32). When ROS production surpasses cellular antioxidant capacity, it triggers lipid peroxidation and protein and DNA oxidation, also activating redox-sensitive kinases such as IKKβ, thereby initiating inflammatory and cell death signaling pathways (33).

Under ischemic conditions, ROS have been shown to promote neuroinflammation and activate the NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome, while also inducing IL-6 expression through NF-κB activation in vascular smooth muscle cells (34). In turn, IL-6 upregulates NADPH oxidase 4 via the JAK/STAT3 pathway, sustaining ROS production (35). This ROS/IL-6 positive feedback loop amplifies oxidative stress and aggravates ischemic brain injury.

IL-6 in inflammatory responses. Following cerebral ischemia, DAMPs released from injured neurons activate inflammatory cascades through PRRs (6). PRR-mediated activation of Toll-like receptor (TLR) 2 and TLR4 initiates myeloid differentiation primary response protein MYD88 (MYD88)- and TIR domain-containing adapter molecule 1 (TRIF)-dependent signaling pathways, leading to NF-κB activation and the subsequent secretion of pro-inflammatory cytokines, such as IL-1β and IL-6 (6,11,15). Activated microglia and astrocytes further amplify the inflammatory response by releasing IL-6, which stimulates the JAK/STAT3 pathway (11). This results in STAT3 phosphorylation and nuclear translocation, driving the transcription of pro-inflammatory genes and aggravating neuronal injury and repair impairment (Fig. 2).

In AIS, endothelial injury and BBB disruption promote sustained NF-κB activation, which enhances IL-6 production. Elevated IL-6 in turn further amplifies NF-κB-mediated inflammatory signaling, forming a positive feedback loop that exacerbates neuroinflammation and tissue damage (36). Peripheral immune cells infiltrate through the disrupted BBB, propagating local inflammation into a widespread cerebral response (15). IL-6 promotes microglial M1 polarization via the JAK1/2/STAT1/3 pathway and upregulates endothelial adhesion molecules, enhancing neutrophil recruitment and amplifying local inflammation. Furthermore, IL-6 induces endothelial cadherin disassembly and complement C5a receptor expression, further compromising BBB integrity (37). It also activates platelets, facilitating aggregation and contributing to thrombosis by impairing endothelial function (38,39). Activated M1-type microglia secrete pro-inflammatory cytokines, including IL-1β, IL-6 and TNF-α, during the acute phase of IS. These cytokines have a combined destructive effect, promoting neuronal death, disrupting the BBB and causing overall brain tissue damage (40). Clinically, serum IL-6 levels are independently associated with infarct volume (41).

Over the long term, as a key pro-inflammatory mediator, IL-6 accelerates atherosclerotic plaque progression by activating vascular endothelial cells, forming a notable pathological basis for large-artery atherosclerotic stroke (42,43). Through its classical signaling pathway, IL-6 also stimulates hepatic synthesis of C-reactive protein (CRP); both IL-6 and CRP serve as established biomarkers for systemic inflammation and atherosclerotic cardiovascular disease (ASCVD) risk assessments.

IL-6 in neuronal death. In a hypoxia-ischemia (HI) rat model, small interfering RNA-mediated silencing of the IL-6 gene

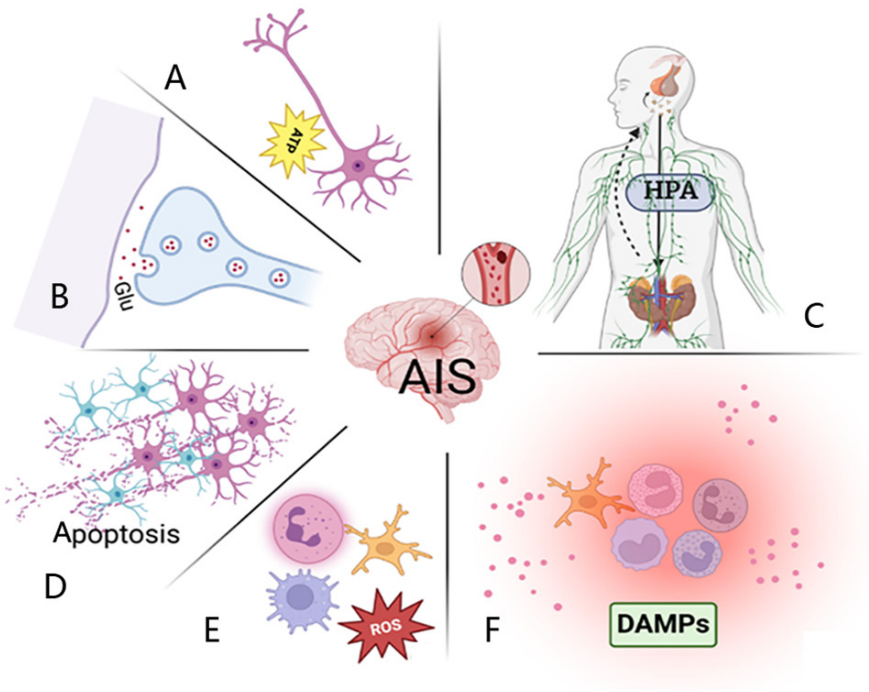

Figure 1. AIS-related pathological alterations within and beyond the brain. (A) Impaired cerebral energy metabolism. (B) Excitotoxic effects of Glu at synaptic sites. (C) Extracerebral pathological alterations, including autonomic dysfunction, hyperactivation of the HPA axis and systemic immune dysregulation. (D) Increased neuronal apoptosis. (E) Oxidative stress-induced neuronal injury. (F) Excessive neuroinflammation. Created with BioRender.com and used with permission under BioRender's Academic License. ATP, adenosine triphosphate; Glu, glutamate; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; HPA, hypothalamic/pituitary/adrenal axis; AIS, acute ischemic stroke; HPA, hypothalamic/pituitary/adrenal.

markedly inhibited the activation of the pro-apoptotic protein Bax and the apoptotic executor protein caspase-3, thereby reducing brain injury and neuronal apoptosis (44). In both middle cerebral artery occlusion (MCAO) and oxygen-glucose deprivation/reoxygenation models, targeting IL-6R was found to block IL-6 signaling, resulting in reduced expression of the pro-apoptotic proteins Bax and caspase-3 and upregulation of the anti-apoptotic protein Bcl-2. This was shown to ultimately lead to the inhibition of neuronal apoptosis (45). Following IS, inflammatory factors induce neuronal and glial cell apoptosis by regulating apoptosis-related genes and signaling pathways, and this apoptosis is one of the key mechanisms underlying brain injury (44,45).

IL-6 in extracerebral pathophysiology. Following AIS, activation of the HPA axis promotes the release of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone, markedly increasing cortisol (CORT) levels, which disrupt BBB integrity, facilitate inflammatory cytokine entry into brain tissue and exacerbate neuroinflammation (46). Stroke also induces sympathetic dominance and systemic immune dysregulation, characterized by increased gut permeability, translocation of bacterial components into the bloodstream and dysfunction of peripheral immune organs, such as the bone marrow and thymus (16).

Under physiological conditions, CORT exerts anti-inflammatory effects; however, chronic HPA axis hyperactivation leads to excessive CORT release, resulting in sustained activation of microglia and astrocytes. Elevated IL-6 suppresses HPA axis negative feedback, maintaining its hyperactive state (46). IL-6 also promotes CORT secretion either by directly stimulating hypothalamic CRH release or by enhancing pituitary sensitivity to CRH (47). Prolonged CORT upregulation may also induce glucocorticoid receptor resistance, leading to increased secretion of pro-inflammatory cytokines such as IL-6 (48).

Patients with diabetes frequently exhibit HPA axis dysregulation and elevated CORT levels (49). A study performed by Kim *et al* (50) reported that in diabetic mice subjected to MCAO, the HPA axis was markedly overactivated, with mice displaying elevated IL-6, IL-1β and TNF-α expression. Treatment with metyrapone, a glucocorticoid synthesis inhibitor, subsequently reduced IL-6 expression and infarct volume. These findings suggest that under diabetic conditions, IL-6 may exacerbate stroke-related inflammation by modulating the HPA axis, providing an extracerebral mechanism linking metabolic and neuroinflammatory pathways and offering theoretical support for IL-6-targeted strategies to improve stroke outcomes in diabetic patients.

5. Role of IL-6 in IS

IL-6 and the risk of IS. IL-6 serves a notable role in atherosclerotic development and progression, as well as in the pathogenesis of associated complications. Persistent elevation of IL-6 is a notable risk factor for atherosclerotic and thrombotic vascular events (42). Clinical and imaging studies have demonstrated the potential of IL-6 in predicting carotid plaque severity, instability and progression (51,52). As a key pro-inflammatory cytokine, circulating IL-6 reflects chronic low-grade inflammation that promotes atherothrombosis. Elevated IL-6 concentrations are consistently associated with

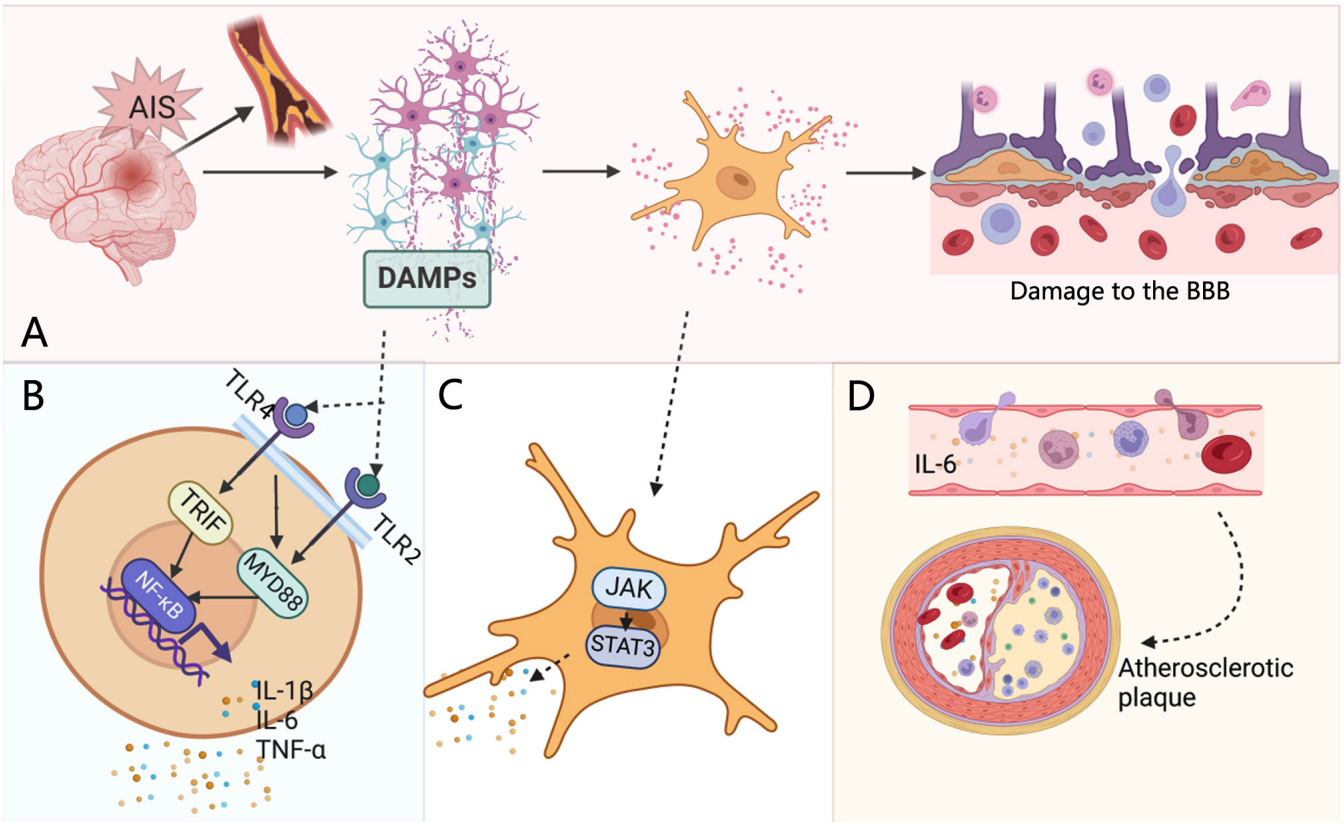

Figure 2. Inflammatory response in AIS. (A) Following cerebral blood flow interruption, ischemic neurons release DAMPs, which activate resident glial cells and induce the secretion of numerous inflammatory mediators. This cascade upregulates chemokines and adhesion molecules, leading to BBB disruption. (B) DAMPs activate TLR2 and TLR4, triggering MYD88- and TRIF-dependent signaling pathways that converge on NF-κB activation, thereby promoting the expression of inflammatory cytokines such as IL-1β, IL-6 and TNF-α. (C) Pro-inflammatory cytokines activate the JAK/STAT3 pathway, amplifying the inflammatory response and driving microglial polarization toward the M1 phenotype. (D) IL-6 further acts on vascular endothelial cells to promote atherosclerotic processes. Created with BioRender.com and used with permission under BioRender's Academic License. AIS, acute ischemic stroke; DAMPs, damage-associated molecular patterns; BBB, blood-brain barrier; TLR, Toll-like receptor; TRIF, TIR domain-containing adapter molecule 1; JAK, Janus kinase.

increased risks of coronary artery disease, stroke and myocardial infarction (52-54). However, the standardization of IL-6 measurement remains a core bottleneck in clinical practice, constraining its application (8). Unified testing standards must be established; otherwise, the adoption of IL-6 measurements in routine clinical practice will remain limited.

In IS, IL-6 demonstrates notable prognostic potential. Large-scale prospective studies, including the Reasons for Geographic and Racial Differences in Stroke cohort, have shown a dose-dependent relationship between baseline IL-6 levels and future IS risk, independent of conventional vascular risk factors (55,56). In AIS, higher IL-6 levels are associated with multiple acute infarctions (43), greater recurrence risk (57) and worse functional outcomes (58,59). Kaplan-Meier analyses further reveal that IL-6 levels above specific thresholds at AIS onset predict higher rates of stroke recurrence (30). Individual-participant data meta-analyses have corroborated these findings, showing that IL-6 independently predicts post-stroke vascular events regardless of underlying atherosclerosis (60).

Genetic evidence indicates that reduced IL-6 pathway activity markedly lowers the risk of IS, particularly large artery atherosclerosis (LAA) and small artery occlusion (SAO) subtypes, as well as coronary and peripheral artery disease, and this protective association, consistently observed in both European and East Asian populations, is also linked to a lower incidence of type 2 diabetes (61). Furthermore, clinical findings of IL-6 inhibition with ziltivekimab align with these genetic observations, providing mechanistic support for ongoing phase III trials and highlighting IL-6 as a promising therapeutic target for cardiovascular-metabolic disease prevention and treatment (62). Table I (43,51,54-61) lists the relevant studies.

IL-6 and the severity and prognosis of AIS. The intensity of the inflammatory response in AIS is closely associated with disease severity. Numerous studies have provided evidence that higher serum or cerebrospinal fluid levels of pro-inflammatory cytokines, particularly IL-6, associate with greater neurological deficits, larger infarct volumes and worse functional outcomes (63-77). Compared with healthy individuals, patients with AIS show markedly elevated serum IL-6 levels, and IL-6-based prediction models for AIS demonstrate strong diagnostic and prognostic performance (63). Experimental evidence also indicates that IL-6 measurements can help estimate stroke onset time (64). Ischemia, hypoxia, oxidative stress, vascular occlusion and inflammation itself can all induce IL-6 upregulation, which in turn promotes hepatic acute-phase response protein synthesis, leukocyte

Table I. Association between IL-6 and IS risk.

First author, year	Study type (study ID)	Population/n	Follow-up duration, years	Findings	(Refs.)
Jenny *et al*, 2019	Case-cohort study (REGARDS)	IS/557; CohS/951	N/A	Higher baseline IL-6 levels are notably associated with future IS risk.	(55)
Georgakis *et al*, 2020	Mendelian randomization (MEGASTROKE)	IS/34,217; GP/404,630	N/A	Genetic downregulation of IL-6 signaling reduces the risk of IS, particularly in the LAA and SAO subtypes, but is not associated with the CE subtype.	(61)
Xu *et al*, 2022	Observational (CNSR-III)	AIS + TIA/9,733	1.00	For patients with LAA and SAO-type IS, elevated IL-6 levels are closely associated with residual recurrence risk after secondary prevention.	(58)
Li *et al*, 2022	Observational (CNSR-III)	AIS + TIA/10,472	1.00	Acute-phase IL-6 levels have been demonstrated to be associated with an elevated risk of recurrence and unfavorable functional outcomes.	(59)
Papadopoulos *et al*, 2022	Prospective cohort and meta-analysis	GP/27,411	12.40	IL-6 levels are linearly associated with IS risk.	(56)
Kamtchum-Tatuene *et al*, 2022	Prospective cohort (CHS)	GP/4,334	5.00	IL-6 is an independent predictor of carotid plaque severity, fragility and progression.	(51)
Mo *et al*, 2024	Prospective cohort (CNSR-III)	sICAD/1,919	N/A	Higher IL-6 levels are markedly associated with the incidence of MAIs.	(43)
Jiang and Fan, 2024	Prospective cohort	AIS/305	0.25	IL-6 levels are closely related to recurrence and have good predictive value.	(57)
Kitagawa *et al*, 2025	post-hoc analysis (TWMU-CVD)	CVD/471	4.60	Serum IL-6 levels can predict IS and cardiovascular events in patients with vascular risk factors.	(54)
McCabe *et al*, 2025	Individual-participant data meta-analysis	IS + TIA/10,148	N/A	IL-6 was associated with post-stroke recurrence irrespective of atherosclerosis.	(60)

REGARDS, Reasons for Geographic and Racial Differences in Stroke; CHS, cardiovascular health study; TWMU-CVD, Tokyo Women's Medical University Cardiovascular Disease Study; CNSR-III, China National Stroke Registry-III; sICAD, symptomatic intracranial atherosclerotic disease; AIS, acute ischemic stroke; IS, ischemic stroke; CohS, cohort sample; GP, general population; CVD, cardiovascular disease; NA, not available; LAA, large artery atherosclerosis; SAO, small artery occlusion; CE, cardioembolic stroke; MAIs, multiple acute infarctions; TIA, transient ischemic attack.

recruitment and thrombogenesis, thereby exacerbating ischemic injury (65). Prospective studies have further validated the clinical relevance of IL-6. Elevated IL-6 levels reflect acute disease severity and independently predict short-term functional outcomes (66-70). In patients undergoing endovascular therapy (EVT) for large-vessel occlusion, both circulating and intrathrombus IL-6 concentrations are notably associated with poor prognosis (71). Longitudinal studies have demonstrated that dynamic IL-6 changes mirror the intensity and extent of post-stroke inflammation: Patients with lower IL-6 levels before thrombolysis achieve improved 90-day outcomes compared with patients with high IL-6 levels, suggesting that IL-6 may serve as a potential marker of neurorecovery (72). After reperfusion, a decline in patient IL-6 levels indicates successful recanalization and neurological stabilization, whereas persistent elevation of IL-6 reflects failed or incomplete reperfusion (73).

IL-6 also exhibits early warning value for early neurological deterioration (END). Serial monitoring shows that increased IL-6 levels associate with worsening National Institutes of Health Stroke Scale scores and adverse neurological evolution (74-77). In EVT-treated patients, elevated postoperative IL-6 independently predicts END, underscoring its role as a quantitative biomarker for early IS risk stratification and treatment optimization (77). Collectively, serum IL-6 represents a reliable indicator of AIS severity and prognosis, and early dynamic monitoring of IL-6 levels may facilitate the identification of high-risk patients and guide individualized therapeutic strategies. Table II (41,66-77) lists the relevant studies.

6. Therapeutic studies targeting the IL-6/IL-6R axis

Biologic agents targeting the IL-6/IL-6R axis are generally divided into three classes: Anti-IL-6R antibodies, anti-IL-6 antibodies and soluble gp130 (sgp130)-Fc fusion proteins. Representative IL-6R inhibitors include tocilizumab, sarilumab and satralizumab, while siltuximab, ziltivekimab and pacibekitug selectively target IL-6 itself (78).

Basic research. Animal studies have shown that targeting the IL-6/IL-6R axis is therapeutically beneficial. In MCAO mouse models, sgp130-Fc administration improved long-term survival outcomes by blocking IL-6 trans-signaling (79). Tocilizumab administered during the acute phase of IS was shown to reduce infarct volume, with female mice requiring higher doses compared with males due to elevated sIL-6R levels (80). Inhibition of IL-6 trans-signaling also slows or reverses atherosclerotic plaque formation (81). Table III (79-82) lists the relevant studies.

Clinical studies. Phase II clinical evidence further supports the therapeutic potential of IL-6 pathway inhibition. The IL-6R Inhibition in Stroke (IRIS) trial demonstrated that in patients with anterior circulation large-vessel occlusion-induced AIS, EVT combined with tocilizumab within 24 h of onset markedly reduced infarct core volume and may have improved functional outcomes (83). The Assessing the Effect of Anti-IL-6 Treatment in Myocardial Infarction trial showed that a single dose of tocilizumab attenuated myocardial injury in patients with acute ST-segment elevation myocardial infarction without serious adverse events (84). In the RESCUE trial, treatment with the fully human monoclonal antibody ziltivekimab markedly reduced the levels of atherosclerosis-related inflammatory and thrombotic biomarkers in patients with moderate-to-severe chronic kidney disease, likely through inhibition of collagen-induced platelet activation (82,85). Furthermore, the TRANQUILITY trial demonstrated that quarterly administration of the IL-6 inhibitor pacibekitug effectively lowered high-sensitivity (hs)-CRP levels, prompting a phase III trial for ASCVD (86). The ongoing ZEUS trial, with an expected completion date during 2026, aims to determine whether ziltivekimab can reduce the incidence of cardiovascular events in the high-risk population that is patients with ASCVD (87,88). Table IV (83-86) lists the relevant studies.

7. Conclusions and future perspectives

IL-6 exerts a prototypical dual effect in neuroinflammation, with its biological outcomes determined by the dynamic balance between the anti-inflammatory classical signaling pathway, mediated by mIL-6R/gp130 signaling and the pro-inflammatory trans-signaling pathway comprising sIL-6R/gp130 signaling. Notably, sgp130-Fc selectively binds the IL-6/-sIL-6R binary complex, resulting in blockage of trans-signaling without interfering with classical IL-6 signaling (89,90). This property makes sgp130-Fc a promising precision therapeutic target. IL-6 antagonists have been shown to protect BBB integrity, reduce cerebral edema and inflammatory injury and attenuate systemic inflammation by downregulating CRP expression and inhibiting the JAK/STAT3 pathway (91). Clinically, serum IL-6 levels rise sharply within the first week after AIS, whereas sgp130 levels decrease markedly, with sIL-6R levels showing no notable change (92). This imbalance increases the ratio of pro-inflammatory IL-6/sIL-6R binary (B) complexes to inactive IL-6/sIL-6R/sgp130-Fc ternary (T) complexes (B/T ratio). A biomarker study has shown that elevated B/T ratios are independently associated with higher future stroke risks in non-atrial fibrillation populations, suggesting the potential of this ratio as a biomarker for individualized anti-IL-6 therapy (93).

Numerous clinical trials have demonstrated that reducing IL-6 levels can slow the progression of atherosclerosis, prevent recurrent strokes and reduce the severity of ischemia-reperfusion injury following stroke recanalization (51,58,61,85,94). The CANTOS trial further demonstrated that IL-1β inhibition indirectly suppresses IL-6 signaling, reducing cardiovascular event incidence independent of lipid lowering (94). Similarly, colchicine, by inhibiting NLRP3 inflammasome activation and subsequently reducing IL-6 levels, markedly decreases IS incidence and the occurrence of major adverse cardiovascular events in secondary prevention without increasing bleeding risk (95,96). Reperfusion therapies themselves can exacerbate inflammation. Tissue plasminogen activator, while restoring perfusion, may disrupt the BBB and increase hemorrhagic transformation risk through IL-6-driven inflammatory cascades (97). In mechanical

Table II. Association of IL-6 with the severity and prognosis of AIS.

First author, year	Population/n	IL-6 measurement time	Findings	(Refs.)
Li *et al*, 2019	AIS/180	Within 72 h after symptom onset	Acute-phase IL-6 level is an independent risk predictor, associated with stroke severity, short-term outcome and infarct volume.	(68)
Alfieri *et al*, 2020	AIS/176; GP/176;	Within 24 h after admission	Pre-stroke disability (baseline mRS ≥3) is associated with higher levels of ferritin, IL-6, hs-CRP, WBC, ESR and glucose.	(67)
Hervella *et al*, 2020	AIS 4295	At admission and 24 h later	At 24 h, IL-6 levels were markedly higher in PNR and PWER groups than in the PER group.	(73)
Mosarrezaii *et al*, 2020	AIS/60	Day 1 and 5 after onset	IL-6 level is associated with AIS severity and may serve as a prognostic indicator.	(66)
Purroy *et al*, 2021	AIS/332	Within 24 h after onset	Serum IL-6 level is independently associated with infarct volume.	(41)
Deng *et al*, 2021	LVO with EVT/210	Days 1, 2, 3 and 7 after EVT	IL-6 may be a potential marker for END after EVT.	(77)
Pawluk *et al*, 2022	AIS 125	Before thrombolysis, and at 24 h and 7 days	Serum IL-6 levels are notably lower in patients with promising outcomes.	(72)
Sabir Rashi *et al*, 2022	AIS 101	Within 24 h of admission	IL-6 levels are markedly higher in patients with poor functional outcomes.	(76)
Gu *et al*, 2023	AIS/7,053 (CNSR-III)	Within 24 h of admission	The association between acute-phase IL-6 and 90 day mRS is mainly driven by post-stroke inflammation leading to disability.	(70)
Jia *et al*, 2024	AIS/6931 (CNSR-III)	Within 24 h of admission	High IL-6 levels are notably associated with poor 3-month outcomes in patients with AIS.	(69)
Yi *et al*, 2024	AIS[a]/4031 (CNSR-III)	Within 24 h of admission	Elevated IL-6 is markedly associated with in-hospital neurological deterioration and improves risk prediction when added to traditional models.	(75)
Dargazanli *et al*, 2025	LVO with EVT/75	In intracranial blood samples before thrombectomy	Elevated intracranial IL-6 levels are linked to worse functional outcomes.	(71)
Băcilă *et al*, 2025	AIS/56	Days 1 and 7 after admission	IL-6 is an important biomarker for predicting AIS severity and functional. recovery	(74)

[a]Patients who arrive at the hospital within 24 h after the onset of illness and have a National Institutes of Health Stroke Scale score ≤5. CNSR-III, China National Stroke Registry-III; AIS, acute ischemic stroke; GP, general population; EVT, endovascular treatment; NA, not available; PNR, patients not receiving reperfusion therapy; PER, patients with effective reperfusion; PWER, patients without effective reperfusion; END, early neurological deterioration; LVO, large vessel occlusion; mRS, modified Rankin Scale; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cells; ESR, erythrocyte sedimentation rate.

Table III. Therapeutic studies targeting the IL-6/IL-6R axis.

First author, year	Ischemia model	Strain	Intervention	Results	(Refs.)
Hall *et al*, 2025	tMCAO (60 min, filament)	C57BL/6	sgp130	Inhibiting IL-6 trans-signaling via sgp130 markedly improves long-term functional outcomes after stroke in mice, with dosage differences observed between males and females.	(79)
Hudobenko *et al*, 2019	tMCAO (60 min, filament)	C57BL/6J	Tocilizumab	Blocking IL-6R may offer a new therapeutic approach for stroke, requiring higher doses in females.	(80)
Ministrini *et al*, 2025	pMCAO (photo-chemically)	C57BL/6J	Anti-mouse IL-6 mAb	Direct IL-6 inhibition slows arterial thrombosis by reducing collagen-induced platelet activation, especially under chronic low-grade inflammation.	(82)
Schuett *et al*, 2012	ApoE	C57BL/6J Ldlr$^{-/-}$	sgp130-Fc	As a selective inhibitor of IL-6 trans-signaling, sgp130-Fc markedly reduces the development and progression of atherosclerosis and can reverse established lesions.	(81)

IL-6R, IL-6 receptor; tMCAO, transient middle cerebral artery occlusion; pMCAO, permanent middle cerebral artery occlusion; ApoE, apolipoprotein E; mAb, monoclonal antibody; sgp130, soluble glycoprotein 130; Ldlr$^{-/-}$, low-density lipoprotein receptor knockout.

thrombectomy (MT), postoperative systemic inflammation has been identified as a notable determinant of poor patient outcomes (98). Patients that develop systemic inflammatory response syndrome after MT exhibit higher mortality and worse neurological recovery compared with patients that do not (99). The IRIS trial demonstrated that adjunctive IL-6R blockade with tocilizumab during EVT markedly reduced infarct core size and improved neurological outcomes (83).

Genetic evidence also supports the notion that decreased IL-6 levels are associated with improved patient outcomes for a number of diseases: Attenuation of IL-6 signaling reduces the risk of poor IS outcomes among patients with rheumatoid arthritis (100). Genetic variability further influences IL-6 bioactivity. The 3' untranslated region polymorphism rs2228145 on the C allele of IL-6R markedly increases sIL-6R levels, enhancing the buffering capacity of patients against IL-6-mediated inflammation (61). As serum sgp130 concentrations generally exceed sIL-6R levels, the latter becomes the rate-limiting component of this neutralization system (101). Carriers of the rs2228145-C allele exhibit protective effects against cardiovascular and autoimmune diseases akin to treatment with tocilizumab (102). Mendelian randomization studies confirm that genetically-reduced IL-6 signaling lowers atherosclerotic and IS risk, particularly in LAA and SAO subtypes, although this potentially occurs at the cost of increased infection susceptibility (61,103).

Due to the low serum concentration, short half-life and multifactorial regulation of IL-6, including factors such as circadian rhythm, glucose level, age and comorbidities (104,105), precise monitoring and individualized assessment of IL-6 levels are necessary. Future studies should integrate differences in model sex, genetic polymorphisms, dynamic B/T ratio monitoring and hs-CRP trajectories to develop adaptive dosing algorithms, facilitating the transition of IL-6-related indicators from biomarkers to therapeutic targets. The present review also had certain limitations regarding the previous studies discussed, including small cohort sizes across individual studies, inconsistent timing of IL-6 testing and assay variability.

In summary, accumulating mechanistic and clinical evidence positions the IL-6/IL-6R axis as a notable link between neuroinflammation, atherosclerosis and ischemic injury. Targeted IL-6/IL-6R inhibition holds promise not only for neuroprotection in AIS but also for secondary cardiovascular prevention (83-86). Future clinical translation should establish unified standards for IL-6 detection, and focus on identifying appropriate patient subgroups for testing, optimizing treatment timing and dosage and balancing the anti-inflammatory efficacy of IL-6/IL-6R inhibition with immune safety to realize the full therapeutic potential of IL-6-targeted interventions in stroke management.

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Table IV. Therapeutic clinical phase II and III randomized controlled trials targeting the IL-6/IL-6 receptor axis.

First author, year	Phase	Anti-IL-6 mAb	Study population	Study (ID)	Results	(Refs.)
Ridker *et al*, 2021	II	Ziltivekimab	Moderate-to-severe CKD with high CV risk	RESCUE (NCT03926117)	This drug can notably reduce multiple inflammatory and thrombotic biomarkers associated with atherosclerosis and displays good safety.	(85)
Huse *et al*, 2022	II	Tocilizumab	Acute STEMI undergoing PCI within 6 h	ASSAIL-MI (NCT03004703)	By reducing the number of circulating neutrophils and weakening their function, it may help improve myocardial salvage in patients with STEMI.	(84)
Chu *et al*, 2024	II	Tocilizumab	AIS with anterior circulation LVO	IRIS (NCT06238024)	Combining tocilizumab with EVT can reduce infarct size in patients with anterior circulation LVO within 24 h of onset and may improve functional outcomes.	(83)
Tourmaline Bio, 2025	II	Pacibekitug	Moderate-to-severe CKD with hs-CRP ≥2 mg/l	TRANQUILITY (NCT06362759)	Marked reductions in hs-CRP can be achieved through quarterly dosing.	(86)
	III	Ziltivekimab	Moderate-to-severe CKD with hs-CRP ≥2 mg/l	ZEUS (NCT05021835)	Ongoing.	N/A

mAb, monoclonal antibody; ApoE, apolipoprotein E; CKD, chronic kidney disease; AIS, acute ischemic stroke; LVO, large vessel occlusion; CV, cardiovascular; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; hs-CRP, high-sensitivity C-reactive protein; EVT, endovascular thrombectomy.

Availability of data and materials

Not applicable.

Authors' contributions

XW was responsible for the conceptualization of the research project and drafting of the initial manuscript. XZ contributed to study conceptualization and reviewed the manuscript. JL contributed to the conclusion and provided critical insights. PL contributed towards conceptualization of the research project, as well as reviewing and revising the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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