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Proinflammatory Cytokines and insight into mediators of pathophysiology of Ischemic stroke

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ABSTRACT

Abstract

Stroke is the fifth leading cause of death and the most frequent cause of disability worldwide. Currently, stroke diagnosis is based on neuroimaging; therefore, the lack of a rapid tool to diagnose stroke is still a major concern. In addition, therapeutic approaches to combat ischemic stroke are still scarce, since the only approved therapies are directed toward restoring blood flow to the affected brain area. However, due to the reduced time window during which these therapies are effective, few patients benefit from them; therefore, alternative treatments are urgently needed to reduce stroke brain damage in order to improve patients' outcome. The inflammatory response triggered after the ischemic event plays an important role in the progression of stroke; consequently, the study of inflammatory molecules in the acute phase of stroke has attracted increasing interest in recent decades. Here, we provide an overview of the inflammatory processes occurring during ischemic stroke, as well as the potential for these inflammatory molecules to become stroke biomarkers and the possibility that these candidates will become interesting neuroprotective therapeutic targets to be blocked or stimulated in order to modulate inflammation after stroke.

Keywords: Inflammation, Ischemic Stroke, Interleukins, tumor necrosis factor.

INTRODUCTION

Primary care providers frequently encounter cerebrovascular diseases, with stroke being the most serious and prevalent manifestation. Stroke ranks as the fifth-leading cause of death in the United States and is a major contributor to severe disability, as well as the primary reason for hospital admissions related to neurological conditions.

Age remains the most significant demographic risk factor, and although stroke incidence has declined in recent years, the overall lifetime risk has risen due to the aging population.

Stroke is growing more common at younger ages and is the leading cause of death and severe disability worldwide [1]. The high death and disability rates place a significant burden on society. Stroke has severe negative social and economic repercussions and ranks third in terms of cause of death, behind cancer and heart attacks. Strokes are further sub-categorized as ischemic and hemorrhagic strokes. Hemorrhagic strokes can again be divided as intracerebral and subarachnoid hemorrhage. The blood flow is restored for a while following cerebral ischemia. Nevertheless, cerebral ischemia results in severe neurological impairment and cannot be reversed. Moreover, the process of cerebral ischemia-reperfusion nerve function degradation is largely dependent on secondary injury, and a significant component of secondary injury is the inflammatory response following a stroke [2].

The management of acute ischemic stroke (AIS) involves a collaborative, multidisciplinary approach, with critical care specialists playing a more significant role than ever. Prior to the 1990s, treatment options were limited, primarily focusing on symptom management, secondary prevention, and rehabilitation. However, the field underwent a major transformation with two key advancements. The first was the groundbreaking approval of intravenous tissue plasminogen activator (IV-tPA) by the U.S. Food and Drug Administration (FDA) in 1995, following a landmark study by the National Institutes of Neurological Disorders and Stroke (NINDS), which revolutionized acute stroke care.

Etiology of Ischemic Stroke- Ischemic stroke results from either a thrombotic or embolic event that restricts blood flow to a particular region of the brain. A thrombotic stroke occurs when a blood clot forms within a cerebral artery,

obstructing blood flow. This typically arises from underlying conditions such as atherosclerosis, arterial dissection, fibromuscular dysplasia, or inflammatory vascular diseases. In contrast, an embolic stroke happens when debris or a clot formed elsewhere in the body travels through the bloodstream and lodges in a cerebral artery, cutting off circulation. The embolic source may be a proximal artery, such as the internal carotid artery, where an atherosclerotic plaque dislodges and causes artery-to-artery embolization. Alternatively, emboli may originate from the heart, particularly in individuals with atrial fibrillation, cardiac thrombi, or valvular disease. In some instances, emboli may travel from the venous system through a right-to-left cardiac shunt, such as a patent foramen ovale, reaching the cerebral circulation. Identifying the cause of stroke is crucial, as it directly influences prognosis, treatment strategies, and long-term outcomes [3, 4].

Classification of Ischemic Stroke

1. Cardioembolic Stroke

Cardioembolic strokes result from emboli originating in the heart that travel to the brain, obstructing blood flow. Cardiac conditions that increase the risk of embolism are categorized into high-risk and medium-risk groups, based on their likelihood of generating emboli. To diagnose cardioembolic stroke, at least one cardiac source of embolism must be identified. Imaging findings in these cases often resemble those seen in large artery atherosclerosis. The presence of previous transient ischemic attacks (TIAs) or strokes affecting multiple vascular territories, as well as evidence of systemic embolization, strengthens the clinical suspicion of a cardioembolic stroke. Before confirming the diagnosis, physicians must rule out alternative causes, such as large artery atherosclerosis. If a patient has a medium-risk cardiac source but no other clear cause of stroke, it may be classified as a possible cardioembolic stroke [5].

2. Large Artery Atherosclerosis

This type of ischemic stroke occurs due to significant narrowing or complete blockage (≥50% stenosis) of a major brain artery or a branch cortical artery. The primary underlying mechanism is atherosclerosis, where plaque buildup leads to vascular occlusion or artery-to-artery embolism. Patients with large artery atherosclerosis often present with neurological deficits indicative of cerebral cortical impairment, such as aphasia, neglect, or motor function deficits, or symptoms related to brainstem and cerebellar dysfunction [6].

Certain clinical indicators can support this diagnosis, including:

- A history of TIAs in the same vascular territory
- Symptoms of intermittent claudication
- Presence of a carotid bruit or reduced peripheral pulses

On imaging studies such as CT or MRI, infarcts larger than 1.5 cm in the cortex, brainstem, cerebellum, or subcortical hemispheres suggest a large artery atherosclerotic stroke. Additional tests such as duplex ultrasound or arteriography can confirm the presence of ≥50% stenosis in an intracranial or extracranial artery. Importantly, before establishing a definitive diagnosis, potential cardiac embolic sources must be ruled out. If vascular imaging does not reveal significant arterial narrowing or only minimal changes, a diagnosis of large artery atherosclerosis cannot be confirmed.

3. Small Vessel Occlusion (Lacunar Stroke)

Strokes caused by small vessel disease are commonly referred to as lacunar infarcts. These occur due to the occlusion of small penetrating arteries, typically in the subcortical regions, brainstem, or basal ganglia. The primary risk factors for small vessel strokes include chronic hypertension and diabetes mellitus, which contribute to lipohyalinosis and microatheroma formation in small arteries [7].

To be classified under this category, patients must exhibit one of the typical lacunar syndromes, such as:

- Pure motor stroke
- Pure sensory stroke
- Ataxic hemiparesis
- Dysarthria-clumsy hand syndrome

Unlike strokes involving larger arteries, cortical dysfunction symptoms (e.g., aphasia, neglect) are absent in small vessel strokes. Imaging findings often show small infarcts [<1.5 cm] in the deep brain structures, such as the internal capsule, thalamus, or pons. There should be no evidence of a major artery stenosis [>50%] or cardiac embolic sources in these patients [8].

4. Stroke of Undetermined Etiology

In many cases, determining the precise cause of a stroke remains challenging. Some patients undergo extensive diagnostic evaluations without identifying a specific etiology, while others may receive only a limited workup, leaving the cause uncertain. This category also includes cases where multiple potential causes are identified, making it difficult to pinpoint a primary source. Examples of stroke of undetermined etiology include:

- A patient with atrial fibrillation and moderate carotid stenosis (50%), where both conditions could potentially be responsible for the stroke.
- A patient with a lacunar syndrome but also moderate ipsilateral carotid stenosis, leading to diagnostic uncertainty.

5. Stroke of Other Determined Etiology

This category includes strokes caused by rare or less common conditions, such as:

- Nonatherosclerotic vasculopathies (e.g., vasculitis, Moyamoya disease)
- Hypercoagulable states (e.g., antiphospholipid syndrome, malignancy-related thrombosis)
- Hematologic disorders (e.g., sickle cell disease, polycythemia vera)

Patients with strokes of unusual etiology should exhibit clinical symptoms and imaging findings consistent with acute ischemic stroke, regardless of the infarct's size or location. Diagnostic workup, including blood tests, genetic studies, and advanced vascular imaging, should reveal an identifiable cause. In addition, other potential stroke mechanisms, such as cardioembolism and large artery atherosclerosis, should be excluded through appropriate testing [9].

Risk factors responsible for stroke:

There are several factors responsible for causing the risk of stroke which include modifiable and non-modifiable factors. Modifiable factors include:

1. Hypertension: One of the main risk factors for stroke is hypertension, also referred to as high blood pressure. It harms arteries all across the body, causing circumstances that may increase their vulnerability to rupture or occlusion. The risk of stroke is greatly increased by brain arteries that are weak or blocked. Mechanisms Connecting Stroke and Hypertension: Blocked or weak brain arteries significantly raise the possibility of stroke. Mechanistic links between hypertension and stroke: Over time, chronically high blood pressure could produce artery blockages and blood clots, limiting blood flow to vital organs. Tissue damage caused by too little oxygen and nutrients increases the chance of stroke. Hypertension speeds up atherosclerosis, which is a condition in which arteries harden, constrict, and become blocked with fatty plaque. This method raises the probability of a clot developing, which might block brain blood delivery and result in an ischemic incident. Higher blood pressure, which weakens artery walls and hence leads to aneurysms—bulges in blood vessels that might burst and produce hemorrhagic strokes—increases their chances [10].
2. Diabetes mellitus (DM): DM causes vascular damage by increasing the stroke risk of both ischemic and hemorrhagic stroke, hence stroke is a significant risk factor. Diabetics experience strokes twice to four times as often as non-diabetic people do. Over time, high blood sugar levels damage blood vessels, leading to atherosclerosis, vitamin deficiency helps to harden the arteries or restrict pushing.

Metabolic Syndrome and Insulin Resistance: Obesity, elevated cholesterol, and insulin resistance are frequently linked to diabetes. These elements raise the chance of cardiovascular illnesses, such as stroke. Third most common cause of death for diabetes is stroke. The Framingham Study reported that the incidence of non-hemorrhagic stroke is 2.5 to 3.5 times higher in individuals with type 2 diabetes compared to non-diabetic subjects [11]. The InterStroke study, encompassing data from 22 countries, found that diabetes increases the risk of stroke by 36% [12].

3. Dyslipidemia: Stroke is also defined by abnormal blood lipid levels helps to define dyslipidemia, which is a significant stroke risk factor. A threatening disease in which plaque accumulation narrows arteries is atherosclerosis; hence, low high-density lipoprotein cholesterol [HDL-C] and high low-density lipoprotein cholesterol (LDL-C) and triglycerides raise the risk of ischemic stroke. Atherosclerosis is a condition whereby high LDL-C levels promote plaque formation in the brain arteries, which could result in blockage or narrowing and hence an ischemic stroke [13]. If accumulated plaques rupture, blood clots will obstruct cerebral blood supply and result in stroke. Epidemiological studies have shown a relationship between high cholesterol and ischemic stroke. Dyslipidemia is related to small-vessel disease, which affects the brain's microvasculature and raises stroke risk [15]. Lowering LDL-C has been linked to atherothrombotic ischemic stroke occurrence and recurrence.
4. Smoking and obesity: By means of several mechanisms, smoking introduces the body to many harmful chemicals that degrade the cardiovascular system and raise stroke risk. Arterial Damage: Plaque building in the arteries can result in damage that might impede the heart's ability to pump blood and increase the risk of stroke. Thousands of dangerous chemicals released from the lungs, where they cause inflammation and blood vessel damage, are spread out throughout the circulation from smoke. Smoking alters blood properties, raising the risk of clot formation; these clots obstruct brain arteries and cause ischemic strokes. With reduced oxygen supply from carbon monoxide in cigarette smoke, blood oxygen levels drop and the brain is deprived of essential oxygen and nutrients that may kick off a stroke. Statistics show that people who smoke 20 cigarettes a day have six times the stroke risk as non-smokers. Secondhand smoke exposure can also increase the possibility of stroke from 20% to 30%. Stroke risk is increased by obesity both directly and indirectly. The main source of stroke—high blood pressure, often connected with extra weight and is closely related to obesity. Being overweight raises the chances of type 2 diabetes, which destroys blood vessels and sharply increases the stroke risk. Obesity is a major cause of bad lipid profiles, including high triglyceride and low-density lipoprotein (LDL) cholesterol levels that worsen atherosclerosis and increase the possibility of stroke.
5. Excessive alcohol use: Both substance addiction and excessive alcohol use are important modifiable risk factors for stroke, and they each contribute to cerebrovascular events in different ways. Drinking too much alcohol damages the cardiovascular system and raises the risk of stroke in a number of ways: Hypertension: One of the main causes of stroke

is high blood pressure, which can be brought on by prolonged heavy drinking. Overindulgence in alcohol can cause atrial fibrillation (AF), an irregular heartbeat that increases the risk of embolic stroke.
Liver Damage: Chronic excessive drinking can harm the liver, raising the risk of hemorrhagic stroke and blood clotting problems.
6 Drug Abuse and the Risk of Strokes: The use of illegal drugs is linked to a higher risk of hemorrhagic and ischemic strokes [16]: Amphetamines and cocaine are stimulants that can cause vasospasm and sharply raise blood pressure, which might result in hemorrhage or cerebral infarction [17]. Cannabis: Regular use may significantly raise the risk of stroke, although further study is required to completely comprehend this relationship [18]. Heroin: This opioid can raise the risk of stroke and induce hypoxia. According to a study done in the Baltimore-Washington area, 12.1% of stroke cases had recent reports of illicit drug use, and 4.7% of these instances had drug use as a plausible cause [19].

Methods for identification of Stroke: Good patient outcomes and effective therapy depend on timely and precisely stroke detection. Mostly depending on imaging tests, the stroke diagnosis rests upon certain assessm ent standards for which some techniques serve as the best available reference.
1. Non-contrast computed tomography or NCCT: Because NCCT is readily available and rapidly gathers data, it is typically the first imaging technique employed in cases of suspected stroke. A very important instrument for distinguishing between ischemic and hemorrhagic strokes is its remarkable capacity to detect cerebral hemorrhage. Notwithstanding, its sensitivity in early hours detection of acute ischemia changed is limited. Studies have shown that the sensitivity of NCCT for early identification of ischemic stroke varies depending on factors such as the imaging features of the infarction as well as the time between start and examination.
2. Magnetic Resonance Imaging [MRI]: Diffusion-Weighted Imaging [DWI], in particular, is a very sensitive and specific test for early detection of ischemic stroke. Early diagnosis is one of the biggest advantages of DWI given that it can pick up changes in ischemia minutes after their onset. Studies show MRI can overall accuracy of 84% diagnose acute stroke, but CT can just manage 54%. Still, MRI might be rather limited in acute situations due to its restricted availability, longer acquisition times, and contraindications in some patients [such those with metallic implants] [21].
3. With Magnetic Resonance Angiography [MRA] and Computed Tomography Angiography [CTA]: Magnetic resonance angiography provides similar vascular imaging without ionizing radiation by using magnetic fields and radio waves, while CTA, which involves injecting contrast material to create detailed images of blood arteries, is vital for spotting vascular disruptions or anomalies.
4. Angiography through digital subtraction [DSA] remains the best available technique for a complete analysis of the cerebral vasculature. Because digital subtraction angiography is invasive and carries hazards like stroke and artery damage, it is not often employed in favor of noninvasive methods even though it an accurate diagnostic tool; it shows hig h-resolution blood vessel pictures and is especially helpful when treatment planning requires exact anatomical information or when non-invasive imaging results are unclear. Different methods to identify stroke and their comparison is illustrated in the table 1.

Table 1: Comparison of different methods to identify stroke

Imaging Modality	**Sensitivity**	**Specificity**	**Key Advantages**	**Limitations**
Non-Contrast CT [NCCT]	12–92%*	~100%	Rapid, widely available, and good for detecting hemorrhage	Poor sensitivity for early ischemic stroke
MRI-Diffusion Weighted Imaging [DWI]	88–100%	95–100%	Best for early ischemic stroke detection	Limited availability, longer scan time, contraindications
CT Angiography [CTA]	80–95%	95–99%	Excellent for detecting large vessel occlusions	Requires contrast, radiation exposure
Magnetic Resonance Angiography [MRA]	75–98%	90–99%	Non-invasive vascular imaging	Less sensitive for smaller vessel occlusions

Digital Subtraction Angiography [DSA]	~100%	~100%	Gold standard for vascular assessment	Invasive, risk of complications

Pathophysiology of ischemic stroke - The pathophysiological causes of progressive stroke include cellular apoptosis, inflammation, oxidative stress, and damage to the blood-brain barrier. Due to the complex nature of cross-communication between neuronal and glial cells, pro-inflammatory cytokines act as early inflammatory factors, which are possible stroke biomarkers. Cytokines potentially act in different phases as inflammatory markers. TNF-α and IL-6 are proinflammatory cytokines and inflammatory mediators respectively. hs-CRP is also another inflammatory marker whose raised levels are seen in ischemic stroke.

Furthermore, inflammatory interactions at the blood-endothelial interface that are crucial to the pathogenesis of tissue destruction in cerebral infarction involve adhesion molecules, cytokines, chemokines, and white blood cells [22]. Neuronal death may result from pathophysiological changes following an ischemic stroke, such as ion imbalance, neuroinflammation, and aberrant immune cell activation. But even with a great deal of research, the precise pathophysiology of stroke damage is still unclear. Cytokines such as IL, TNF, IFN, and human serum complement protein [HsCRP] function as important mediators in this cascade of inflammatory alterations and are regarded as a therapeutic target and predictive indicator.

The efficacy of existing stroke treatments in reversing neurodegeneration and returning pre-morbid function is limited. While it is commonly accepted that strokes cause disruptions to the blood-brain barrier, it is less well-known that these changes also have an impact on the course of strokes and neuroregeneration [23].

The term "IL" describes a lymphocyte medium that facilitates communication between immune or white blood cells. It belongs to the same class of cytokines as growth factor for blood cells. Hemocyte growth factor and interleukin [IL] are both classified as cytokines, and they work together to complete the processes of hematopoiesis and immune control. Information transmission, immune cell activation and control, mediating T and B cell activation, multiplication, and differentiation, and the inflammatory response are all significantly impacted by IL [24]. The pathophysiology of ischemic stroke, the interactions between various IL-mediated pathways, the effects of various mediators on different cell types, and how various ILs govern intricate inflammatory cascades are all closely related to one another.

IL-6:

Depending on the cellular source and preparation, IL-6 is a glycoprotein with a molecular mass ranging from 20 to 30 kDa. It is a pleiotropic cytokine that contributes to central host defense [25]. gp130 is recruited by the cytokine family IL-6 for signaling. In particular, for IL-6, a hexamer consisting of two gp130, two IL-6, and two IL-6R can activate intracellular tyrosin-kinases like JAK and, to a lesser extent, TYK. This, in turn, activates multiple proteins such as the RAS-RAF-MAPK pathway, PI3K, IRS [insulin receptor substrate], or the STAT family of transcription factors [26]. Multi-effector cytokines such as IL-6 are primarily produced by lymphoid cells, T cells, B cells, granulocytes, mast cells, and endothelial cells. IL-6, mostly through autocrine or paracrine mechanisms, plays a crucial role in immunological responses, acute phase response, and hematopoiesis regulation. IL-6 functions as a differentiation and growth factor for hematopoietic cells, B cells, T cells, osteoclasts, and endothelial cells and promotes the growth, differentiation, regeneration, and destruction of nerve cells in the peripheral and central nervous systems through target gene activation. IL-6 promotes the release of adhesion molecules and other inflammatory transmitters by vascular endothelial cells, activates and attracts neutrophils and monocytes, and intensifies the local inflammatory response [27]. Pre-thrombosis is caused by both local and circulating IL-6 production, which can stimulate the growth of smooth muscle cells and cause the creation of TNF, fibroblast growth factor, platelet-derived growth factor, and macrophage colony-stimulating factor [28].

2. Dual Function of IL-6 in Ischemic Stroke

Numerous clinical disorders, such as ischemic stroke, leukemia, hypertension, and coronary heart disease, are intimately associated with dysregulation of IL-6 [29]. Su et al. found that increased IL-6 brought on by inflammation, ischemia and hypoxia, oxidative stress, vascular occlusion, and leukocyte recruitment causes the liver to produce more acute phase protein, which in turn promotes leukocyte recruitment and thrombosis, which in turn causes a variety of cardio-cerebrovascular diseases, including ischemic stroke [30]. Racial disparities in stroke are mediated by elevated serum IL-6 levels, which are linked to an increased risk of incident stroke and the inflammatory effects of risk factors [31]. According to reports, one indicator of post-stroke delirium is elevated plasma IL-6 [32]. Furthermore, in patients treated with mechanical thrombectomy for acute ischemic stroke and major artery blockage, elevated levels of IL-6 at 24 hours are linked to ineffective reperfusion [33]. Furthermore, the first-pass effect—defined as complete or almost complete reperfusion after a single thrombectomy pass—is positively connected with lower admission levels of IL-6 and is indicative of a better prognosis for patients with acute ischemic stroke [34]. These results suggest that IL-6 might be a predictor of an ischemic stroke patient's prognosis. Increased IL-6 is thought to be an adverse prognostic factor and is mostly secreted by endothelial cells, microglia, astrocytes, and neurons in the ischemic hemisphere [35]. Inflammation after a stroke is indicated by IL-6. The primary location of IL-6 protein in the ischemic brain is in the cerebral cortex's

neurons. After 3.5 hours of ischemia, IL-6 neuronal expression peaks 24 hours after reperfusion and lasts for 7 days. In ischemic penumbra, the immunological reactivity of IL-6 was highest elevated. Following a stroke, IL-6 released into the CSF fluid may cause increased histopathology and poorer cerebrovascular autoregulation. Furthermore, IL-6 is associated with inflammation, which plays a role in the process of damage and healing following an ischemic stroke [36]. Elevations in serum IL-6 have been linked to fever, infarct volume, early neurologic impairment, and unfavorable long-term prognosis. It has been determined that the brain is the primary source of IL-6 following a stroke [37]. Furthermore, raised in tandem with IL-6 are inflammatory biomarkers such as fibrinogen, TNF-α, IL-1 receptor antagonist, and C-reactive protein [38]. IL-6's reciprocal function in ischemic stroke. Following an ischemic stroke, IL-6 can be produced by microglia, neurons, endothelial cells, and astrocytes. The following are caused by elevated IL-6: temperature rise; inflammatory cascades; Treg-induced TGF-β production; microglia polarization and angiogenesis; Th1 polarization to Th2; NPC proliferation; neuronal differentiation; and neuroblast migration. Nevertheless, leukemia inhibitory factor [LIF] and ciliary neurotrophic factor [39] are two more neurotrophic cytokines that share the receptor subunit gp130 with IL-6. The ischemic penumbra region's neural cells are the primary source of IL-6 expression, and LIF expression follows a similar pattern. Cerebral ischemia damage can be lessened by injecting these cytokines directly into the brain tissue following an ischemic stroke. JAK-STAT is the primary downstream signaling pathway of IL-6, and following ischemia-reperfusion, neuronal cells are the primary site of STAT3 activation. More research is required to determine the precise function of STAT3 signaling in the neuroprotective effect because the involvement of STAT3 in stroke is likewise varied and debatable [40]. To mediate the immunosuppressive milieu, IL-6 released by astrocytes encourages Th1 polarization into Th2, which in turn contributes to neurogenesis, angiogenesis, and neuronal differentiation [41]. In the delayed phase following an ischemic stroke, IL-6 promotes the phosphorylation of STAT3 and the early transcriptional activation of genes linked to angiogenesis. This results in increased cerebral blood flow and angiogenesis. The JAK-STAT and PI3K/AKT pathways, which are essential for angiogenesis following ischemic stroke, are simultaneously activated by IL-6R [41]. Furthermore, IL-6 has been shown to promote endothelial cell repair during post-traumatic recovery in the central nervous system [42]. This suggests that IL-6 may also promote angiogenesis or revascularization following an ischemic stroke. In response to NMDA-mediated injury, IL-6 promotes CNS neuronal survival, reduces excitotoxic neuronal damage, and shields neurons from apoptosis [42]. Injecting recombinant IL-6 continuously into the lateral ventricle of gerbils undergoing acute cerebral ischemia for seven days has been shown to prevent learning impairments and delayed neuronal death [43]. In summary, IL-6 has two distinct roles in ischemic stroke: it functions as a neurotrophic mediator throughout the subacute and protracted phases of the disease and as an inflammatory agent during the acute stage. Because of its many and sometimes conflicting signaling pathways, IL-6 is a cytokine with a wide range of effects. However, upon connecting to its receptor—which exists in both the membrane-bound and soluble forms IL-6 can activate many downstream pathways that regulate cell growth, differentiation, survival, inflammation, and oxidative stress [44]. This chemical is linked to both successful aging and acute inflammation in the brain, as well as potential negative effects [45]. There is ongoing scientific discussion over the function of IL-6 during ischemic stroke. Although some research suggests that this molecule may not directly affect ischemic stroke, newer data indicates that IL-6 can have neuroprotective effects during a stroke, particularly in the later stages, by promoting neurogenesis and functional recovery [45, 46]. Clinically, after a stroke, there is an increase in circulating IL-6, particularly in patients whose infarct sizes exceed 3 cm. In addition, this substance has demonstrated prognostic qualities. Indeed, IL-6 plasma levels are associated with stroke size, functional outcome, and recurrence. [47]

There are other interleukins also that play direct and indirect role in ischemic stroke. The table 2 represents the different interleukins and their role in progression of ischemic stroke.

Table 2: Different Interleukins and their role in Ischemic stroke

Interleukin	**Role in Ischemic Stroke**	**General Function**
IL-1β	Pro-inflammatory, aggravates BBB dysfunction, mediates inflammatory response, promotes apoptosis	IL-1β is a powerful pro-inflammatory cytokine that plays a crucial role in ischemic stroke progression.
IL-6	Pro-inflammatory, predicts poor functional outcome, associated with increased risk of recurrent stroke	Elevated IL-6 levels are associated with poor functional outcomes and increased risk of recurrent stroke.
IL-10	Anti-inflammatory, may be involved in the inflammatory process of ischemic stroke	IL-10 is a multifunctional cytokine with anti-inflammatory properties that is involved in the inflammatory process of ischemic stroke.

IL-17A	Mediates neuronal injury, neutrophil chemotaxis, and neuronal apoptosis	IL-17A is elevated after ischemic stroke and mediates neuronal injury through neutrophil chemotaxis and neuronal apoptosis.
IL-33	Protective role in cardiovascular diseases, role in acute ischemic stroke unclear	IL-33 is a newly recognized IL-1 family member, and its role in acute ischemic stroke remains unclear.
IL-1Ra	Endogenous regulator, therapeutic prospect in ischemic stroke	IL-1Ra is an endogenous regulator of IL-1 signaling and has therapeutic potential in ischemic stroke.

TNF alpha

The processes governing the cytokine tumor necrosis factor-a [TNF alpha] transit across the blood-brain barrier [BBB] and how they impact stroke recovery are the particular subject of attention. It is possible to ascertain how TNFa interacts with the BBB in both cultured cells and the whole organism. Finding new cellular targets for cytoprotection, developing novel therapeutic approaches for stroke victims, and determining the connections between TNF alpha permeation and ischemia tolerance are among the objectives of transport studies. TNF-α is a newly discovered pleiotropic cytokine that functions as the immune system's main regulating component. It can be generated by different cell types and is implicated in numerous disease processes [49]. In the central nervous system, it has a pathological and homeostatic function. Microglia emit a significant amount of TNF-α when they are in a diseased state. This neuroinflammatory response is linked to several neurological illnesses [50]. Adjustments in TNF-α were linked to stroke damage and recovery based on multiple strong pieces of evidence [51]. Tuttolo mondo et al., for instance, found that increased TNF-α expression following a stroke-induced the expression of tissue factors and leukocyte adhesion molecules while suppressing the fibrinolytic system [52]. The potential of TNF-α as a stroke marker is still present, despite the contradictory findings of multiple investigations. Researchers are paying more and more attention to anti-TNF-α-based antistroke treatments in addition to the role of TNF-α in stroke. TNF-α receptor inhibitors lessen brain damage in a preclinical investigation by lowering inflammatory responses in a rat model of ischemic stroke [53]. Thus, this paper addresses the potential use of TNF-α and its antagonists in stroke treatment and analyzes the progress of research in this area.

The Receptor of TNF-α and Its Molecule

While many different cells can create TNF-α, immune system cells such as mast cells, lymphoid cells, and macrophages are the primary producers of this cytokine [54]. The matrix metalloproteinase TNF-α-converting enzyme [TACE] first produces TNF-α as transmembrane protein [tmTNF-α]. This cleaves TNF-α to release soluble TNF-α [sTNF-α] homotrimer, which can attach to TNF receptor [TNFR] type 1 [TNFR1] and type 1 [TNFR2] [55]. Both of these receptors serve diverse purposes and show varied patterns of expression in various cell types. TNFR2 is expressed by certain immune cells and more selectively by specific endothelium, brain tissue, and regulatory cells than TNFR1, which is expressed by all cell types [56]. Because of the nature of the TNF-signaling complex, TNF-α can either enhance tolerance to ischemia after stroke or trigger inflammation and cell death. The major job of TNFR1 is to initiate apoptosis and activate cell survival mechanisms via its death domain. Inflammation and the immune response are associated with TNF-α-induced activation of the TNFR2 pathway [57]. It may also affect the activation of many intracellular signaling pathways that may lead to cell migration, necrosis, apoptosis, and survival [58]. Neurotoxicity is a result of both glutamate and TNF alpha. There are typically very few cytokines in an undamaged brain. They are only generated in reaction to inflammation caused by damage to the brain's architecture. The widely recognized cytokine TNF alpha is a pro-inflammatory signal that regulates caspase and apoptotic processes in addition to causing necrosis. The majority of TNF-α's biological actions are triggered by TNFR1, despite TNF-α's stronger affinity for TNFR2 than for TNFR1. The death domain [DD] found in the structure of TNFR1 is constitutively expressed in most cell types and is triggered by TNF-α either as soluble [sTNF-α] or membrane-bound [mTNF-α] [59]. When TNFR1 is activated, trimer formation occurs, which facilitates the recruitment of TNFR1-associated death domains [TRADD] via DD. Additionally, TRADD recruits TNFR-associated factor [TRAF] 2 and serine/threonine-protein kinase [RIPK] [60]. The precise mechanism is that the death domain silencer [SODD] protein is released when TNFR1 binds to trimer TNF-α. Following binding to the TNFR1 death domain [DD], the TNFR-associated death domain [TRADD] recruits the Fas-associated death domain [FADD], TNFR-associated factor 2 [TRAF2], and adapter protein receptor-interacting protein [RIP]. When TNFR1 signals apoptosis, Procaspase-8 is bound by FADD and activated, ultimately initiating the protease cascade reaction. The activation of endonucleases, including EndoG, which mediate DNA breakage, causes apoptosis. When TNFR1 indicates survival, TRAF2 enters the complex, and cytoplasmic apoptotic protein inhibitor [IAP] stops apoptosis. Through cJun N-terminal kinase [JNK] and mitogen-activated protein kinase [MAPK], TRAF2 activation initiates the activation of cFos/cJun transcription factors [61]. As a result, the TNFR1 core signaling complex is formed and stabilized by RIPK1

ubiquitination, which triggers a physiological reaction. For example, cytokine signaling and cell survival are induced by activation of the NF-κB, JNK, and p38 pathways. Cell necrosis or apoptosis would ensue from the apoptotic pathway being activated if RIPK1 was not completely ubiquitinated [62]. TNFR2 is exclusively fully activated by mTNF-α and lacks a dead domain. TRAF2, TRAF1, or TRAF3 are directly recruited by TNFR2 when it forms a trimer. Then, to start their biological function, B cells' nuclear factor kappa-light chain enhancer [NF-κB], Akt [protein kinase B], and mitogen-activated protein kinase [MAPK] are activated. For instance, it influences the amplification and function of Treg, facilitates cell activation, migration, and proliferation, and, via its collaboration with TNFR1, induces apoptosis [63]. It also serves as a protective function in cells. The TNF receptor types are mentioned in the table 3.

Table 3: Characteristics of different TNF receptor types

Feature	**TNFR1 [TNF Receptor 1]**	**TNFR2 [TNF Receptor 2]**
Alternative Name	p55, TNFRSF1A	p75, TNFRSF1B
Molecular Weight	~55 kDa	~75 kDa
Expression Pattern	Ubiquitous [expressed on most cell types, including neurons, endothelial cells, and immune cells]	Restricted [mainly on immune cells, endothelial cells, and some neuronal populations]
Affinity for TNF-α	High affinity for soluble TNF-α	High affinity for membrane-bound TNF-α
Signaling Pathways	- Activates pro-inflammatory and apoptotic pathways via TRADD, FADD, and caspase-8 - Activates NF-κB, leading to inflammation - Induces cell death via caspase-dependent apoptosis and necroptosis	- Promotes cell survival through activation of NF-κB, PI3K/Akt, and MAPK pathways - Enhances tissue repair, neuroprotection, and angiogenesis
Pro-Inflammatory Role in Stroke	- Major contributor to neuroinflammation, apoptosis, and BBB disruption in early ischemic stroke - Promotes microglial activation and release of inflammatory cytokines [IL-1β, IL-6]	- Counteracts TNFR1-mediated damage by promoting anti-inflammatory and pro-survival mechanisms - Stimulates neurogenesis and vascular remodeling
Role in Blood-Brain Barrier [BBB]	Increases BBB permeability, leading to edema and immune cell infiltration	Helps in BBB stabilization and repair during later recovery stages
Apoptotic vs. Survival Role	Primarily pro-apoptotic [induces cell death]	Primarily pro-survival [prevents cell death]
Therapeutic Targeting	- Blocking TNFR1 has been proposed as a stroke treatment strategy to reduce inflammation and neuronal death - Anti-TNFR1 antibodies or small-molecule inhibitors are being studied	- Enhancing TNFR2 activation could support neuroprotection, angiogenesis, and stroke recovery - TNFR2 agonists or TNF-α variants that selectively activate TNFR2 are potential therapeutic options

3. Physiological Role of TNF-α Molecule in the Central Nervous System

Despite having modest levels in the adult brain, which is mostly derived from glia, astrocytes, and microglia, TNF has a complex and multidimensional role in the central nervous system [CNS] [64]. First, TNF-α regulates normal

neurotransmitter activities in a number of ways. For instance, in addition to causing a sharp rise in AMPA receptors, it can also raise tetrodotoxin-insensitive Na+ channel currents in the plasma membrane of dorsal root ganglion [DRG] neurons and decrease AMPAR levels in cortical surface and hippocampus neurons [a process accomplished in the striatum by removing Ca2+ permeability inhibition]. Additionally, it regulates glutamate release from astrocytes [65]. Second, TNF-α plays two roles in neurogenesis through different receptor subtypes and inductive settings. For instance, TNF-α can cease cell division suddenly, which results in progenitor cell death. When it interacts with TNFR2 receptors produced by human brain stem cells, it has neuroprotective benefits [66]. Third, TNF-α may have an impact on CNS endothelial cells. These pathways include altering endothelial cell morphology, which impacts BBB permeability; improving leukocyte-endothelial cell adhesion, which facilitates leukocyte migration to the central nervous system; and triggering angiogenic mediators, which impact the proliferation of vascular endothelial cells [67] [figure 1].

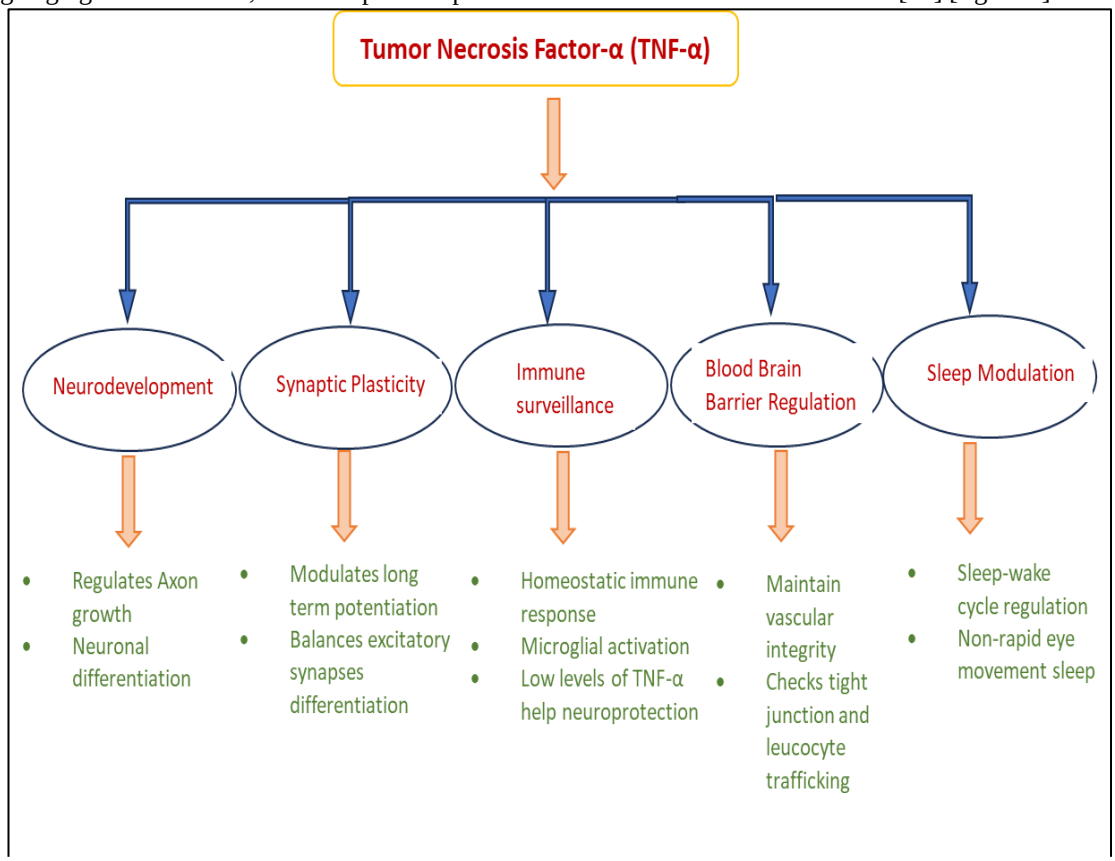

Fig 1 The figure represents the role of TNF-α in different functions involving central nervous system.

4. TNF-α in Stroke

The etiology of vascular lesions is based on stress and has a definite redox response. Neurovascular units in stroke patients may fail due to a lack of oxygen and nutrients. Ischemia causes changes in the brain, including the release of glutamate, the production of reactive oxygen species [ROS] that cause oxidative stress, and the activation of microglia, which may affect the release of proinflammatory mediators. Both the inflammatory response and oxidative stress have an effect on the stroke process as a whole. When blood vessels are obstructed or underperfused, the immune response begins at the ischemic parenchyma, travels to the ischemia zone, and then spreads throughout the body. Additionally, microglia are stimulated, which promotes TNF-α release [68]. According to studies, the amount of TNF-α in brain tissue may increase one day after ischemic damage and is correlated with the degree of the lesion. A key mediator in the immunological processes of autoimmunity, anticancer activity, allergy disorders, and infection control is TNF-α. TNF-α acts on vascular endothelium by inducing oxidative stress through xanthine oxidase, activating matrix metalloproteinases, and promoting the production of tissue factors and leukocyte adhesion molecules [69]. These actions cause localized thrombosis, bleeding, and inflammation by igniting specific blood vessel segments. TNF-α can damage the blood-brain barrier. Among these effects include twofold stimulation of astrocyte and microglia activation and proliferation, as well as regulation of apoptotic factors such as cysteine. Third, ischemia and penumbra inflammation induce the transcription of matrix metalloproteinase [MMP]. The latter caused cytokines including IL-1 and IL-6 to be transcribed [70].

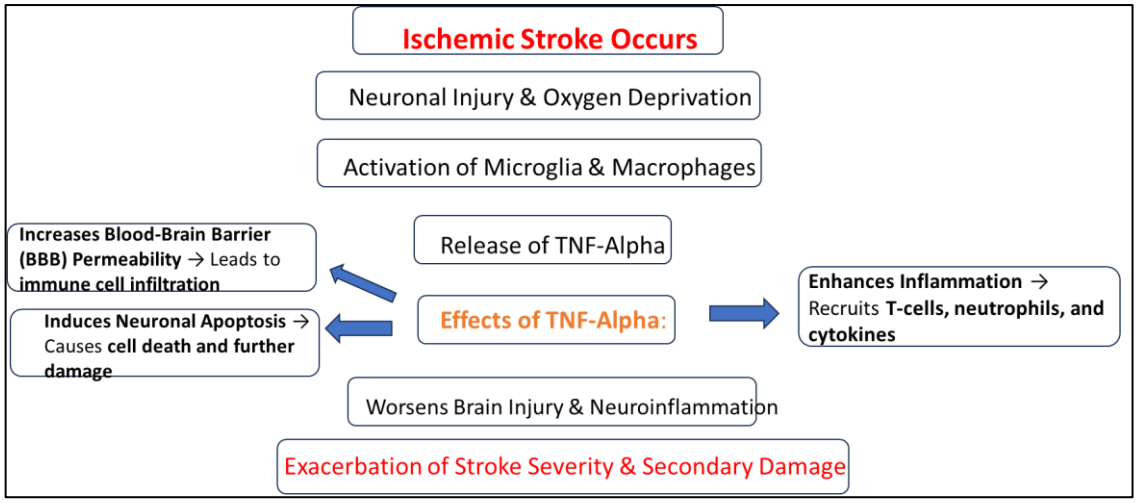

Fig 2 Figure represents the role of TNF alfa in ischemic stroke.

In addition, TNF can induce ischemia tolerance and regulate the signal transduction of cerebral hypoxia and ischemia tolerance. Aphasia, pain, sadness, aberrant movement, spasms, epileptic seizures, and cognitive impairment in stroke outcomes are all associated with TNF-α. Zaremba et al. discovered that stroke patients had considerably higher levels of TNF-α in their cerebrospinal fluid [CSF] [71]. The increase in CSF and serum TNF-α during the first 24 hours of a neurological stroke was also found to be substantially linked with the degree of dysfunction and the severity of the stroke. However, in a clinical study, the researchers found that the TNF-α level had no bearing on the functional outcomes after an acute stroke. We speculate that this is because TNF-α has a complex and multifaceted role in stroke prognosis; further study is needed to completely comprehend these specific mechanisms. Numerous preclinical and clinical studies suggesting that TNF-α may have either neuroprotective or neurotoxic effects on stroke patients were reviewed by Doll et al. There were conflicting findings once more when prognosis was predicted using TNF-α. These seem to indicate a complicated, bidirectional activity of TNF-α [72]. Given that TNF-α ligand-receptor interactions are implicated in almost every aspect of stroke-induced brain injury, using TNF-α as an inflammatory marker to predict stroke prognosis is one possible avenue. However, when TNF-α is used as a potential therapeutic target for stroke, it can reduce localized ischemia injury and improve clinical outcomes [73]. The liver produces human CRP [Pentraxin 1, Ptx1], an acute phase reactant, rapidly after tissue injury or infection [74]. CRP is a reliable indicator of inflammation [75]. Despite the fact that numerous other biomarkers have been demonstrated to aid in the prediction of clinical outcome after stroke, hs-CRP remains one of the most often used inflammatory biomarkers in clinical practice [76]. Elevated hs-CRP has been associated with atherosclerosis, ischemia events, hemorrhagic stroke, and disease outcomes [77]. According to research, inflammatory responses after a stroke may exacerbate tissue damage from the brain infarction and hinder recovery [78]. Elevated hs-CRP values have been found in recent research to be an independent predictor of the likelihood of developing ischemic cerebrovascular disorders and cardiovascular diseases in the future, including transient ischemic attacks in the elderly [79]. Approximately 75% of individuals have been observed to have a prolonged inflammatory response following an acute ischemic stroke [AIS], as shown by an elevated level of CRP. A more negative consequence is linked to a robust and enduring inflammatory response. Furthermore, it has been demonstrated that CRP at discharge is associated with a 1-year outcome [80]. Elevated baseline hsCRP levels have recently been linked, independently, to an increased risk of ischemic stroke, according to a meta-analysis. Nevertheless, the physiological function of CRP remains unclear; it may possess both pro- and anti-inflammatory characteristics [81]. Not only might inflammation be a result of a brain infarction, but it might also be a factor in ischemia damage. Furthermore, there is ongoing debate on the predictive power of inflammatory markers in the functional outcome of stroke [82]. The data on the predictive usefulness of hsCRP for ischemic stroke is compiled in this review, which also examines the possible impact of CRP on functional outcomes and highlights crucial difficulties that will need to be addressed in further research. Pneumococcal cell wall C-polysaccharide's phosphocholine moiety precipitates CRP [protein CRP], hence the name. On human chromosome 1, the CRP gene is situated between 159,712,289 and 159,714,589 bps. Five of its seven transcripts encode proteins. The protein with 224 aa produced by the CRP-001 transcript is widely referred to as the CRP protein, even though the precise activities of these protein variations are not entirely understood. The protein belongs to the family of proteins called pentraxins. An ancient family of proteins known as pentraxins, with a distinctive architecture, dates back as far back as the emergence of the horseshoe crab. Strong phylogenetic conservation and good proteolysis resistance characterize the structure of CRP [83]. It can therefore be measured with ease and is relatively steady.

Tumor necrosis factor, interleukin-6, interleukin-1, and other cytokines primarily control CRP expression at the transcriptional level; interleukin-6 is the predominant circulating physiologic mediator among them [84]. The modulation of CRP expression has been studied with IL-1β, the IL-1 receptor antagonist anakinra, and the IL-6 receptor blocker

tocilizumab [85]. According to an estimate, blood CRP level variance across individuals is 35–40% heritable [85]. and variabilities in genes have an impact on it. Environmental factors including injury and bacterial infection also affect the expression of CRP. In response to tissue injury or inflammation, plasma CRP values rise 100 times or more quickly. Therefore, significant infections or inflammatory conditions such as arthritis are linked to elevated CRP levels [10–1000 mg/L]. On the other hand, the low range of CRP, from 0.5 to 10 mg/L, is measured by the hsCRP. The hs-CRP test is used to detect low but persistent levels of inflammation at such a range. The hs-CRP is a more accurate measure of baseline concentrations than normal CRP. A hs-CRP can be quickly induced, and its blood half-life is long enough to allow for a stable temporal course. As a result, plasma hs-CRP is highly helpful in the diagnosis of viral and inflammatory illnesses.

Novel insights of blood-based biomarkers and stroke: Numerous blood biomarkers have been discovered as a result of attempts to get around the limits of multimodal neuroimaging and expert clinical judgment in stroke medicine. These biomarkers may help in stroke patient diagnosis and treatment. These proteins, RNA, lipids, and metabolites are the primary biomarkers that are implicated in many facets of stroke, such as brain damage and recovery. Combining markers in panels has been found to improve the diagnosis of stroke by separating stroke from mimics. One of the best candidates for differentiating between ischemic and hemorrhagic strokes is GFAP, which may work better when paired with certain brain-specific markers. Similarly, panels of markers may attain adequate sensitivity and specificity to address the variability in human stroke in order to identify the etiology of the stroke. Serum IL-10 and glutamate may be used to treat stroke in individuals with clinical-diffusion mismatch; however, more research is required to fully characterize the blood biomarkers of ischemic penumbra. Many blood indicators have been identified to predict HT; more study will clarify if they could direct the design of therapies to prevent HT or assist in the decision on whether to start anticoagulation after a stroke. In terms of stroke prognosis, plasma copeptin can be added to the ABCD2/ABCD3-I scores to predict stroke recurrence following TIA and to age and NHISS to predict functional outcome. YKL-40, RBP4, and neurofilament light are additional functional outcome markers that need to be validated [86]. Despite recent efforts to enhance research on prognostic factors,14 the identified literature's overall quality remains subpar, which is a common occurrence in prognostic studies. In the context of carefully designed, sufficiently powered prospective prognostic studies in cerebrovascular disease, efforts should be made to standardize the collection, storage, analysis, and reporting of data [highlighting the unique characteristics of potentially relevant types of prognostic factors, such as blood-based or imaging biomarkers]. This will enable accurate modeling and make it easier to perform individual participant data meta-analyses. Results from biomarker panels with etiology-stratified studies could be improved and more reliable [87].

CONCLUSION

It is now known that one of the main causes of parenchymal damage is the inflammatory milieu that stroke creates in the nervous system. Within this framework, inflammatory mediators including cytokines IL6, TNF alpha, and sharp may serve as potential targets for the creation of targeted therapies. perhaps though these methods showed promise in preclinical settings, they were ineffective or perhaps hazardous during the bench-to-bed shift. Two distinct roles post-stroke inflammation plays in the pathogenesis of ischemic stroke. In addition to contributing to the acute parenchymal damage following the ischemia insult, inflammatory chemicals, and cells are believed to play a significant role as long-term mediators of cerebral healing and neuronal plasticity. Furthermore, depending on factors associated with the disease [such as reperfusion, and type of stroke], as well as the subject [such as age, and comorbidities], each patient may experience the harmful effects of inflammation differently in the early stages following an ischemic stroke. A more targeted approach to patient-specific inflammation modulation may still be able to lessen the impact of this major killer. Such an ambitious objective necessitates a thorough understanding of the intricate interactions between inflammatory mediators in various disease stages and patient populations, which calls for additional research in this exciting area.

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