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Inflammatory Markers for Predicting Ischemic Stroke Outcome: Review Article

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ABSTRACT

Background: In developed countries, stroke is the third leading cause of mortality and the leading cause of lifelong disability. Chronic inflammation, oxidative and nitrosative damage to the immune, metabolic and cellular systems and, neurotoxicity therefore has a role in acute ischemic stroke (IS). It may be possible to employ various biomarkers simultaneously to forecast the occurrence and prognosis of IS. When inflammation subsides after a stroke, it accelerates tissue repair and neurodegenerative processes, which are known to expand the ischemic lesion. Post-stroke inflammation has a substantial impact on a patient's capacity to recover from the disease, and novel diagnostic, prognostic, and therapeutic treatments are urgently needed.

Objective: An overview of the role of inflammation in stroke pathology is provided in the following review. Stroke patients' prognosis can be better predicted by using biomarkers of inflammation.

Material and methods: These databases were searched for articles published in English in 3 data bases [PubMed – Google scholar - Science direct] and Boolean operators (AND, OR, NOT) had been used such as [Ischemic stroke OR Neuroinflammation AND Stroke outcome] and in peer-reviewed articles between Jun 2001 and November 2021; a 20-year date range was selected. Documents in a language apart from English have been excluded as sources for interpretation

Conclusion: Clearly, inflammation is a major contributor to stroke pathogenesis. Inflammation plays a dual role during an ischemic stroke, showing both positive and detrimental effects depending on the stage of the disease. Stroke prognostication is hampered by the absence of sensitive and speedy blood tests for diagnosis.

Keywords: Ischemic stroke, Neuroinflammation, Stroke outcome.

INTRODUCTION

One in three adults in the United States suffers from a stroke each year, with an estimated 795,000 happening annually. Stroke incidence is expected to climb by 3.4 million people between 2012 and 2030, owing to an ageing population and a drop in the number of stroke deaths. It was thought that the fatality rate from stroke has been declining steadily for the past two decades, but current patterns in mortality show that this decline may have stopped or even increased. However, it's possible that the obesity global epidemic and its accompanying diabetes are to blame for this. Stroke-related mortality is still high, and the annual healthcare, medication, and lost productivity expenses are estimated at 34 billion $ **(1).**

Hemorrhagic and ischemic strokes are both types of stroke. Hemorrhagic strokes account for a smaller percentage of all strokes (about 20%), whereas ischemic strokes account for the vast majority (around 80%). Transient ischemic attacks can be intraparenchymal or subarachnoid hemorrhagic strokes. Subtypes of ischemic stroke, or classifications that indicate the origins of the stroke, include cardioembolic, atherosclerosis, lacunar and other particular causes (dissections, vasculitis and specific genetic abnormalities, among others) **(2).**

Ischemic stroke has distinct risk factors, some of which are shared by hemorrhagic stroke and others that are distinct among the many etiologies of ischemic stroke. Blood clots in the brain can be caused by hypertension, but it also adds to atherosclerosis, which can cause ischemic stroke. When it comes to strokes caused by atherosclerosis of the extracranial and intracranial blood vessels as well as coronary artery disease, hyperlipidemia is an especially relevant risk factor. Cardioembolic stroke is a possibility for people with atrial fibrillation **(3).**

Objective: An overview of the role of inflammation in stroke pathology is provided in the following review. Stroke patients' prognosis can be better predicted by using biomarkers of inflammation.

METHODS

These databases were searched for articles published in English in 3 data bases [PubMed – Google scholar - Science direct] and Boolean operators (AND, OR, NOT) had been used such as [Ischemic stroke OR Neuroinflammation AND Stroke outcome] and in peer-reviewed articles between Jun 2001 and November 2021; a 20-year date range was selected, and no language limitations, and filtered in selected data basis for the last 20 years, however, the range of time interval for researches is wide as there's scarcity of data on the particular reviewed, accurate and depth in the retrieved literature. Documents in a language apart from English have been excluded as sources for interpretation was not found. Papers apart from main scientific studies had been excluded: documents unavailable as total written text, conversation, conference abstract papers and dissertations.

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Stroke-Induced Neuroinflammation:

As a result of the lack of cerebral blood flow in the ischemic core, brain neurons and other supporting cells get much less oxygen and glucose. Depletion of these critical fuels results in cell death through a variety of metabolic and physiological changes [(4)]. Brain tissue that is still alive surrounds and feeds off the dying core, this is known as the ischemia penumbra. Because the cells in this region are both functionally damaged and structurally intact, therapeutic techniques can be used here. If oxygen and glucose supplies in the surrounding area are not restored, apoptosis of neurons is induced, resulting in less salvageable tissue and an increase in ischemic lesion. In the ischemia zone, dying cells emit alarmins, which are detected by microglia. Once triggered by immunological cues, they and peripheral leukocytes quickly enter the brain and play an essential part in the immune system's response [(5)]. When a high concentration of pro-inflammatory mediators surrounds an ischemic area, it allows leukocytes to enter and remove the massive amount of debris left behind by the death of brain cells. Leukocyte adhesion molecules and chemokines, which guide leukocytes to the site of injury, are increased by proinflammatory cytokines that target endothelial cells. Inflammation has been linked to the complement system component leukotaxis [(6)]. An increasing number of studies, however, indicates that immune cells invading the ischemic brain are equally harmful. Because of the protracted inflammatory response, increased brain injury, and the development of edema and hemorrhagic transformation caused by infiltrated leukocytes, these secondary consequences often have a significant impact on whether or not a stroke will be fatal [(7)]. To put neurons at danger in the early stages of a stroke, it is possible that these inflammatory mediators exist.

The degree of brain damage caused by a major stroke is directly related to the severity of the neuroinflammatory response. Secondary pathogenic stimuli are often ineffective because of an overwhelming surge of pro-inflammatory mediators in extreme conditions [(8)]. Because mature leukocytes are depleted by over-stimulated peripheral immune systems, immature leukocytes must be recruited. Due to their inability to respond effectively following brain injury, this subpopulation causes the immune system to be deregulated. Lymphocytopenia, which is associated with post-stroke immunosuppression, is caused when monocytes' immature subpopulation is recruited and expanded [(4)]. Furthermore, the immune system seeks to alleviate this post-ischemic inflammation later on, even if it has negative repercussions and side effects. Anti-inflammatories are made and inflammatory chemicals are removed as part of the process of reducing inflammation following the first flare-up.

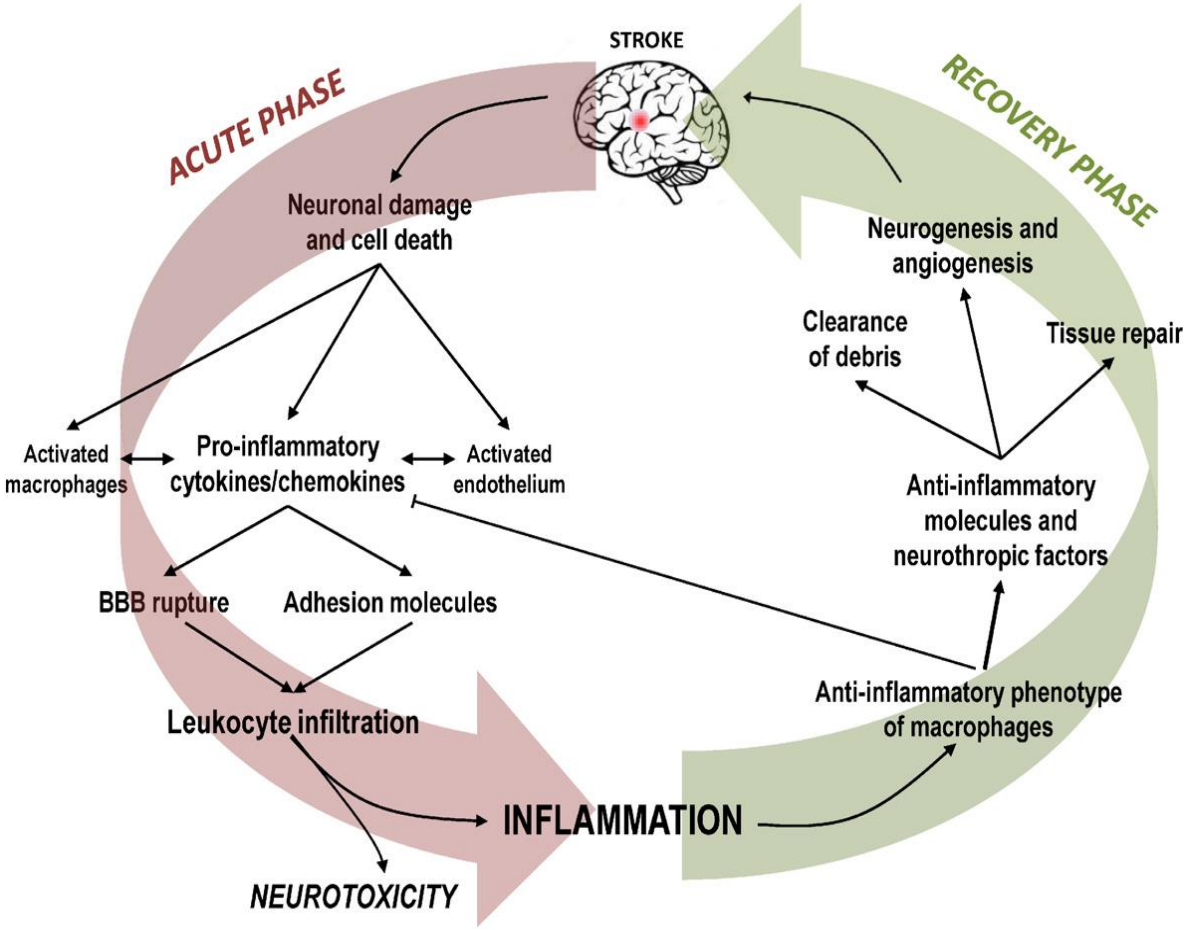

Figure (1): Post-ischemic inflammatory response mechanisms.

Stroke biomarker research:

Indicators include pathogenic processes, pharmacological reactions to therapeutic treatments, and other biomarkers that can be measured objectively (Working Group on Biomarker at 2001). Indicators of illness progression that can be detected in bodily fluids such as blood, urine, or other bodily fluids (but also through imaging studies etc.) are known as clinical biomarkers. Thus, molecular biomarkers of stroke should represent current processes, such as brain specific markers released from damaged tissue or broader systemic signs, such as those generated by inflammation at either a local or peripheral level, in order to accurately identify stroke patients. There are a variety of clinical circumstances in which stroke biomarkers can be useful, from diagnosis to outcome. Many potential biomarkers for stroke diagnosis are linked to inflammation. In the acute phase of stroke, C-reactive protein (CRP) can help identify and predict the size of the ischemic lesion early on, and it is a crucial player in several inflammation systems, such as the complement system [(9)]. It has been found that CRP levels can increase by 6%, which is the first neurological severity's diagnostic value for ischemic stroke diagnosis [(10)], showing its potential, albeit limited, use in the early detection of stroke in individuals.

Predicting the fate of a stroke and the response to treatment, which can vary greatly from patient to patient, has also been studied using biomarkers. If a patient has a poor prognosis after a stroke, the doctor may decide to place them in a specialized facility or provide them with palliative care, rehabilitation, or decide when to discharge them. However, several clinical factors' predictive value has been investigated [(11)]. It's possible that inflammatory indicators might help predict things that can't be modified, such as age and neurological severity at diagnosis. But despite the fact that many of these inflammatory biomarkers are not specific to ischemic stroke, their levels are associated to the severity of the stroke and the outcome of the stroke. Multiple studies have associated poor functional outcome following cerebral ischaemia to CRP and a wide range of pro-inflammatory cytokines, including IL-6 [(12)]. TNF alpha and intercellular cell adhesion molecule 1 (ICAM-1) as well as MMP-13 have also been linked to the size of the infarct [(13, 14)].

There are various organizations attempting to pinpoint the exact elements that affect stroke outcome. Studies on biomarkers of stroke-related infections, for example, have received considerable attention. Some research suggests that the biomarker IL-6 may be an important one for predicting stroke infection and subsequent disabilities and mortality [(15)]. Circulating monocytes with high CD14 and low CD16 expression have recently emerged as an important biomarker for detecting infectious complications following stroke, and they have been linked to a poorer prognosis and death [(16)].

Table (1): Stroke biomarkers as valuable tools in clinics [(17)].

Clinical scenario	Biomarker use	Examples
Diagnosis	Facilitate the rapid identification of ischemic stroke	CRP D-dimer, BNP, MMP2, S100β D-dimer, caspase-3
	Speed stroke patient management and treatment	
Prognosis	Influence on medical decisions (discharge, rehabilitation, palliative care…)	CRP IL-6 TNF-α ICAM-1 MMP-13
	Prognosticate stroke-associated infections	$CD14^{high}CD16^{-}$ Th1/Th2 profile Cortisol and noradrenalin Copeptin Procalcitonin
Treatment response	Identify patients with unsuccessful tPA-induced recanalization	Soluble endothelial protein C Soluble thrombomodulin
	Predict the appearance of secondary intracranial hemorrhage	Fibronectin NURR1 MMP-9

Nuclear receptor related 1 protein (NURR1); MMP-2 (matrix metalloproteinase-2); MMP-13 (matrix metalloproteinase-13); CRP (C-reactive protein); ICAM-1 (intercellular adhesion molecule-1); IL-6 (interleukin-6); TNF-α (tumor necrosis factor-alpha); BNP (b-type natriuretic peptide); tPA (tissue-plasminogen activator).

Thrombolysis and mechanical reperfusion therapies each have varied effects on stroke patients in terms of therapy response. Hemorrhagic transformation is the most dreaded side effect of tPA therapy. As a result, biomarkers that assess tPA responsiveness that has grown in recent decades become a priority for methods that might predict the occurrence of recurrent intracranial hemorrhages and identify patients with tPA-induced recanalization failure. Biomarkers for the diagnosis of hemorrhagic transformation in the context of hemorrhages may include fibrinogen, endothelial cells and hepatocytes are the primary producers of fibronectin, which has a strong correlation with vascular injury [(18)].

CONCLUSION

Clearly, inflammation is a major contributor to stroke pathogenesis. Inflammation plays a dual role during an ischemic stroke, showing both positive and detrimental effects depending on the stage of the disease. Stroke prognostication is hampered by the absence of sensitive and speedy blood tests for diagnosis. Finding reliable biomarkers for stroke will have various benefits, including improved methods for stroke diagnosis and prognosis as well as a better knowledge of stroke pathophysiology. We expect research to continue focusing on this in the future. In the acute phase of disease, stroke biomarkers have the potential to improve and assist in a better clinical assessment of patients, which is crucial in reducing stroke-related disability and mortality when paired with additional indicators of ischemic injury.

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REFERENCES

1. **Jackson S, Legvold B, Vahratian A *et al.* (2021):** Sociodemographic and Geographic Variation in Awareness of Stroke Signs and Symptoms among Adults—United States, 2017. Morbidity and Mortality Weekly Report, 69 (44): 1617-22.
2. **Boehme A, Esenwa C, Elkind M (2017):** Stroke risk factors, genetics, and prevention. Circulation Research, 120 (3): 472-495.
3. **Krishnamurthi R, Barker-Collo S, Parag V *et al.* (2018):** Stroke incidence by major pathological type and ischemic subtypes in the Auckland regional community stroke studies: changes between 2002 and 2011. Stroke, 49: 3–10.
4. **Mehta S, Manhas N, Raghubir R (2007):** Molecular targets in cerebral ischemia for developing novel therapeutics. Brain Res Rev., 54 (1): 34-66.
5. **Liesz A, Dalpke A, Mracsko E *et al.* (2015):** DAMP signaling is a key pathway inducing immune modulation after brain injury. J Neurosci., 35 (2): 583-98.
6. **D'Ambrosio A, Pinsky D, Connolly E (2001):** The role of the complement cascade in ischemia/reperfusion injury: implications for neuroprotection. Mol Med., 7 (6): 367-82.
7. **Lakhan S, Kirchgessner A, Hofer M (2009):** Inflammatory mechanisms in ischemic stroke: therapeutic approaches. J Transl Med., 7: 97-102.
8. **Liesz A, Hu X, Kleinschnitz C *et al.* (2015):** Functional role of regulatory lymphocytes in stroke: facts and controversies. Stroke, 46 (5): 1422-1430.
9. **Kara H, Akinci M, Degirmenci S *et al.* (2014):** High-sensitivity C-reactive protein, lipoprotein-related phospholipase A2, and acute ischemic stroke. Neuropsychiatr Dis Treat., 10: 1451-1457.
10. **Glickman S, Phillips S, Anstrom K *et al.* (2011):** Discriminative capacity of biomarkers for acute stroke in the emergency department. J Emerg Med., 41 (3): 333-9.
11. **Counsell C, Dennis M (2001):** Systematic review of prognostic models in patients with acute stroke. Cerebrovasc Dis., 12 (3): 159-70.
12. **Whiteley W, Jackson C, Lewis S *et al.* (2009):** Inflammatory markers and poor outcome after stroke: a prospective cohort study and systematic review of interleukin-6. doi: 10.1371/journal.pmed.1000145
13. **Sotgiu S, Zanda B, Marchetti B *et al.* (2006):** Inflammatory biomarkers in blood of patients with acute brain ischemia. Eur J Neurol., 13 (5): 505-13.
14. **Rosell A, Alvarez-Sabín J, Arenillas J *et al.* (2005):** A matrix metalloproteinase protein array reveals a strong relation between MMP-9 and MMP-13 with diffusion-weighted image lesion increase in human stroke, Stroke, 36 (7): 1415–1420.
15. **Bustamante A, Sobrino T, Giralt D *et al.* (2014):** Prognostic value of blood interleukin-6 in the prediction of functional outcome after stroke: A systematic review and meta-analysis. Journal of Neuroimmunology, 274 (1-2): 215-224.
16. **Urra X, Villamor N, Amaro S *et al.* (2009):** Monocyte subtypes predict clinical course and prognosis in human stroke. J Cereb Blood Flow Metab., 29 (5): 994-1002.
17. **Simatsa A, García-Berrocosoa T, Montanerab J (2016):** Neuroinflammatory biomarkers: From stroke diagnosis and prognosis to therapy. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1862(3): 411-424.
18. **Castellanos M, Leira R, Serena J *et al.* (2004):** Plasma cellular-fibronectin concentration predicts hemorrhagic transformation after thrombolytic therapy in acute ischemic stroke. Stroke, 35 (7): 1671-6.