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Review Article

A review of the relationship between stroke and neutrophil-lymphocyte ratio

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ABSTRACT

Neutrophil-lymphocyte ratio (NLR) has been a novel biomarker in the literature over decades to assess systemic inflammation. This easily available and cost-effective marker has shown clinical significance in various disease conditions such as infections, sepsis, malignancies, cardiovascular events and even in SARS-COVID-19 pneumonia. NLR has a major association in ischemic stroke patients. Inflammation is a crucial step in the development of ischemic stroke, with neutrophils and lymphocytes comprising the first line defence mechanism. It has a role in stroke initiation, progression of injury, and recovery. This article showed significant correlation between NLR and stroke patients in terms of days of hospital stay, severity and prognosis. High NLR values were found to be associated with higher risk of stroke, prolonged hospital stay and a worse 3 month mortality rate. NLR can thus be integrated into any clinical practice, having an impact on early diagnosis in many clinical scenarios.

Keywords: Stroke, Ischemic stroke, NLR, Inflammation, Stroke prognosis

INTRODUCTION

Stroke is the leading cause of disability and the third-leading cause of death.[1] Ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage are the three main types of strokes. Acute ischemic stroke (AIS) occurs when a blood artery is blocked, limiting blood flow to the brain, whereas hemorrhagic stroke happens when a blood vessel ruptures, spilling blood into the cerebral cavity.[2] Hemorrhagic strokes can be classed as intracerebral hemorrhage or subarachnoid hemorrhages, depending on where the blood spills. Ischemic strokes account for 60-80% of all strokes.

In India, the prevalence of stroke ranges from 84-262 per 100,000 in the rural setting and from 334-424 per 100,000 in the urban areas. The incidence is about 119-145 per 100,000 based on recent population-based studies.[3] Ischemic strokes account for 68% of all strokes, while hemorrhagic strokes account for 32%.[4] Although there is not much data on the prevalence of stroke in India, data from the West can be extrapolated.[5] According to previous research, the overall prevalence of stroke varies between 147 and 922/100,000.[6] We can fairly predict that India has a very high stroke incidence based on the aforementioned data and the fact that stroke and ACS share common risk factors which are smoking (40%), high blood pressure (38%), and diabetes (30%) are the three most common risk factors for acute coronary syndrome (ACS) in India.[7]

Ischemic stroke is the most frequent type of stroke, and it is caused by obstruction of the intracranial artery in the most cases.[8] Although much effort has been put into establishing therapeutic methods for stroke, the condition still carries a high chance of having a poor outcome. Another study found that the global number of patients with stroke experienced stroke-related death and disability-adjusted life-years lost based on a prior study's findings.[9] Finding potential prognostic indicators for ischemic stroke may help to increase the accuracy with which outcomes can be predicted and implementing early therapies may help to improve the prognosis as well.[10]

Etiology of ischemic stroke involves a complicated process of inflammation. Both pro-and anti-inflammatory mediators contribute to the aetiology of ischemic stroke, with an imbalance resulting in inflammation. Inflammatory cells from both the innate and acquired immune systems are implicated in the inflammation associated with ischemic stroke. Among such markers the NLR is identified as a critical indicator of systemic inflammation.[11] Once activated, inflammatory cells can produce a range of lethal chemicals, including increased levels of cytokines, matrix metalloproteinases, nitric oxide, and reactive oxygen species.[12] Neutrophils are typically the first leukocyte subtype recruited to ischemic brain lesions; lymphocytes were recruited following neutrophils. Numerous studies have demonstrated that decreasing leukocyte adherence via the targeting of multiple adhesion molecules prevents leukocytes from entering ischemic brain, resulting in decreased neurologic damage.[13]

The NLR in complete hemogram has been extensively explored as a predictive factor because it is inexpensive and generally available.[14,15] Numerous previous studies have shown an association between increased NLR levels and adverse outcomes including stroke outcomes.[16-18] Numerous meta-analyses have established that an elevated NLR level is a poor prognostic predictor in patients with AIS and spontaneous intracerebral haemorrhage.[19-22]

REVIEW OF LITERATURE

The most common cause of mortality worldwide after cardiovascular events is stroke. Ischemic stroke is also one of the most frequent cause of chronic adult disability. The lifetime risk of stroke after 55 years of age is 1 in 5 for women and 1 in 6 for men.[23] This review aims to provide an overview of stroke disorder and its correlation with NLR in India as derived through previous studies.

Stroke etio-pathogenesis

WHO defines stroke as an event caused by the interruption of the blood supply to the brain, usually because a blood vessel bursts or is blocked by a clot. This cuts off the supply of oxygen and nutrients, causing damage to the brain tissue.[24] The most common symptom of a stroke is sudden weakness or numbness of the face, arm, or leg, most often on one side of the body, occurring in 90% of the strokes. Other clinical manifestations include confusion, speech or vision disturbances, dizziness, loss of balance or coordination, severe headache with no known cause, syncope or loss of consciousness. The effects of a stroke depend on which part of the brain is affected and the degree of severity. A severe stroke can cause sudden death. Globally, stroke is the third commonest cause of mortality[25] and the fourth leading cause of disease burden.[26] It makes an important contribution to morbidity, mortality, and disability in developed as well as developing countries. In recent years, there has been increasing economic and demographic development in developing countries resulting in a shift from diseases caused by poverty toward chronic, noncommunicable, lifestyle-related diseases.[27]

It is of utmost importance to know the neurovascular anatomy in order to understand the clinical profile of the stroke. The blood supply of the brain includes two internal carotids anteriorly and two vertebral arteries posteriorly (the circle of Willis). Ischemic stroke is caused by hypoperfusion and decreased oxygen supply to the brain; hemorrhagic stroke is caused by rupture of blood vessels. In India, the pooled data incorporating all the studies reveal that ischemic stroke occurs in 68-80% and hemorrhagic stroke in 20-32%. Ischemic stroke comprises large vessel (41%), lacunar (18%), cardioembolic (10%), other determined (10%) and undetermined (20%) subtypes. The extracranial carotid disease is the etiological factor in 25-26% and intracranial carotid disease in 30% of ischemic stroke cases.[28]

Ischemic stroke

The Kolkata study demonstrated that the subcortical region was the most common site of infarction (75.6%).[29] In other Asian races as well, high incidence of subcortical infarcts were noticed. A study based on noninvasive tests to determine subtypes of ischemic stroke from a hospital-based registry of Southern India has attributed 41% of strokes to large artery atherosclerosis, 18% to lacunar causes, 10% to cardioembolic causes, and 4% to causes such as Takayasu syndrome, Moya Moya disease, carotid dissection, hyper-homocysteinemia, anticardiolipin antibody, and protein S deficiency and the rest 27% of the cases of ischemic stroke were of undetermined origin.[30]

Among cardioembolic stroke, rheumatic heart disease (29%) and ischemic heart disease (27%) are predominant causes.[31] In a clinic radiological study among young strokes, the common site of arterial occlusion was the supraglenoid internal carotid artery, whereas, narrowing or occlusion of major neck vessels occurred in only 10.8% cases.[32] But studies conducted in the last decade in large academic centers from northern and southern India both have documented a high frequency of intracranial vessels affected based on noninvasive vascular studies.[30,32] This is consistent with findings in other oriental countries.

Ischemic occlusions contribute to around 85% of casualties in stroke patients, with the remaining being due to intracerebral bleeding. Ischemic occlusion generates thrombotic and embolic conditions in the brain.[33] In thrombosis, the blood flow is affected by narrowing of vessels due to atherosclerosis. The formation of plaque will constrict the vasculature and lead to the development of clots, thereby causing thrombotic stroke. In an embolic stroke, there is dislodgment of the thrombus causing reduced blood flow to the brain leading to severe stress and necrosis. Necrosis is followed by disruption of the plasma membrane, organelle swelling and leaking of cellular contents into extracellular space, and loss of neuronal

function.[34] Inflammation, loss of homeostasis, increased intracellular calcium activation, free-radical and cytokine-mediated toxicity, oxidative stress are some of the other key events contributing to pathology of stroke.[35]

Hemorrhagic stroke

The Kolkata study demonstrated that the basal ganglia-thalamic region was, by far, the commonest site (75%) of hemorrhage.[29] Hemorrhagic stroke accounts for approximately 10-15% of all strokes and has a high mortality rate. Elevated stress in brain tissues and internal injury causes rupture of blood vessels which produces toxic effects in the vascular system, resulting in infarction.[35] It is classified into intracerebral and subarachnoid hemorrhage. In ICH, rupture of these cause accumulation of blood within the brain parenchyma. The main causes for ICH are accelerated hypertension, excessive use of anticoagulants and thrombolytic agents, and disrupted cerebral vasculature. In subarachnoid hemorrhage, blood accumulates in the subarachnoid space of the brain due to a head trauma or cerebral aneurysm.[36]

NLR

Neutrophils and lymphocytes comprise first line of defence mechanisms in our body against foreign organisms. They are the preliminary inflammatory and regulatory markers, respectively, found in injured areas. They activate the inflammatory cascade by releasing major cell types which result in acute and chronic inflammation.[37]

The NLR is an emerging novel inflammatory marker to assess the ongoing systemic inflammation in any patient. It has been proven useful in various medical conditions. It is a component of routine blood count analyses performed in hospitals. It is calculated by dividing the neutrophil count by the lymphocyte count-on the basis of absolute peripheral granulocyte (N;$\times 10^9$/Liter) and lymphocyte (L; $\times 10^9$ /liter) using the formula NLR=N/L.[38] Normal NLR values in an adult, non-geriatric population are between 0.78 and 3.53.[39] NLR is derived from leucocyte differentials which is a well-standardized, in-expensive measurement and readily accessible biomarker that reflects systemic inflammation.[38] It can be easily integrated into the clinical practice.

Neutrophils and lymphocytes have their respective roles in the process of inflammation. Neutrophils are the key cellular component of the host defence in innate immunity to combat against any infectious agents, whereas lymphocytes are considered as a major cellular component of the adaptive immune system. Lymphocytes regulate inflammatory response. Sepsis-induced apoptosis causes depletion of lymphocytes and further leads to immune system suppression and non-resolution of inflammation.[40]

Endothelial dysfunction triggers cellular response of the blood components. Inability of the endothelium to produce nitric oxide and prostacyclin can result in the depletion of antithrombotic, vasodilatory and anti-atherogenic properties of the vascular endothelium. The leucocytes that are thus stimulated cause increased adherence to the vascular endothelium resulting in capillary leucocytosis and subsequent increased vascular resistance.[41] In another mechanism, the incomplete eradication of nidus of infection along with the viability of the infection is the cause for increased leucocyte production by the medulla and decrease lymphocyte counts by apoptosis. This is, thus resulting in rise of NLR in patients with non-resolution of inflammation along with poor prognostic indices.[40]

Conventional inflammatory markers such as erythrocyte sedimentation rate (ESR), c-reactive protein (CRP) and plasma viscosity (PV) are commonly used in the clinical setup for diagnosis and monitoring of inflammatory conditions, including malignancies, infections and autoimmune conditions. In a study, it was shown that CRP has a statistically significant value in diagnosing infections as compared to other markers such as ESR and PV.[42] CRP is recommended over ESR to detect acute phase inflammation as it has more sensitivity and specificity over ESR. It falls quickly once the cause of inflammation is resolved, hence labelled as a useful marker.[43] Procalcitonin is a new marker useful in bacterial infections. It has a high predictive value in sepsis.[44] Other new inflammatory markers such as hypersensitive CRP to albumin and fibrinogen to albumin ratio are being used for disease severity in community-acquired pneumonia.[45]

In comparison to all these markers, NLR was found to be a more easily available, faster to calculate, efficient and a more economic indicator of systemic inflammation.[46] NLR is used as a critical biomarker in a realm of diseases in clinical medicine. It plays a role in the prediction of survival rates in various malignancies such as lung, breast and colon.[47] It is also used as a prognostic marker in cardiovascular medicine, predicting the survival rates after coronary artery bypass surgeries and in chronic heart failure.[47] Interestingly, in a recent study, it was reported to predict bacteremia in patients admitted with suspected community-acquired infections. In a study, NLR was significantly a better marker than conventional inflammatory markers like C-reactive protein (CRP).[47] In another study, NLR's association with early mortality in the general population has been studied for the first time. Inflammation and mortality were found to have an independent relationship.[48] Apart from malignancies, cardiovascular events and infectious pathologies, it was reported to have a poor prognostic value in ischemic stroke patients.[49]

In a study, NLR was independently associated with unfavourable outcomes in patients with sepsis when taking into account the APACHE II scoring system.[40] With the ongoing pandemic of SARS-COVID 19 infection, NLR and its association with the disease severity was studied. It was found that NLR had a significantly higher value as compared with other inflammatory makers like ESR and

CRP in determining the severity of pneumonia. Higher the NLR value, the more severe the disease.[50] Similarly, in another study, NLR was associated with an increased risk of all-cause mortality during hospitalization.[51] As NLR can be quickly calculated, it has helped clinicians in determining early diagnosis of severe infection.

Clinical significance of NLR in stroke

Central role of inflammation is the key underlying mechanism in all types of strokes from its initiation, progression and recovery. Thus, NLR has a clinical significance on stroke.[52] The inflammation cascade is initiated by reduced blood flow resulting from either ischemic or hemorrhagic lesions.[53] Proinflammatory mediators such as TNF-α, IL-1, IL-6, and matrix metalloproteinase-9 (MMP-9) are released from endothelium and brain parenchyma which further aggravate tissue injury. This also causes the release of damage-associated molecular patterns (DAMP) from injured neurons. The main target of inflammation is the brain–blood barrier (BBB).

However, recent human studies indicate that BBB permeability remains elevated especially in the acute phase (6–48 h after stroke onset) due to the inflammatory cascade.[54] Disrupted BBB or the cerebrospinal fluid drainage system are the main paths for these DAMPs and proinflammatory markers to gain access. Once these mediators are in circulation, they activate the systematic inflammatory response. In the inflammation cascade, neutrophils first infiltrate the lesion within 30 mins to few hours, peak by 24-72 h and then decrease rapidly with time.[55] Locally, neutrophils participate in brain injury by exacerbating oxidative stress and BBB damage.[56] The consequence of BBB breakdown is related to the many complications of stroke.

Most commonly, pathologic cerebral edema results from increased BBB permeability and tends to develop within the first 24 to 48 h in AIS or within the first 24 h in ICH.[57,58] Breakdown of BBB is also associated with an elevated risk of hemorrhagic transformation in AIS. Inflammation restores the function of BBB. Neutrophil levels start to decrease once there is a peak of proinflammatory factor production and neutrophils in acute/subacute phase (from onset to more than 48 h). This decrease during stroke recovery may help BBB integrity and be associated with good prognosis.[59] Therefore, the post-stroke inflammatory response has become a therapeutic target, as an adjacent treatment to reperfusion therapy using thrombolysis or intravascular clot removal.[60]

Several drugs have been tested in randomized trials such as Fingolimod, Natalizumab, interleukin-1 receptor antagonist (IL-1ra) and Minocycline (ACTRN12611001053910).[61-63] The findings are anticipated to improve treatment options and clinical outcomes in of patients with acute stroke.[64] Moreover, suppression of inflammation is also beneficial in models of cerebral hemorrhage.[65]

Some major pathways to reduce lymphocyte counts (T and NK cells) are the increased release of glucocorticoids from the hypothalamic-pituitary axis and the circulating epinephrine by adrenal medulla. Accordingly, infection is the most prevalent complication after stroke and contributes to the main cause of in-hospital death.[66] This is consistent with our results that higher NLR levels were especially related to in-hospital mortality in ischemic stroke. In post stroke phase, there is an increased neutrophil count and decreased lymphocyte count, thereby elevating the overall NLR levels.

Increased NLR levels had unfavorable prognosis due to neutrophil activation causing extensive brain injury and high risk of infection by lymphocyte suppression. NLR levels have shown to reduce after successful recanalization. Abdalla et al.[67] in his study with successful TICI 2b/3 recanalization has reported NLR fall 72 h post successful recanalization. Low NLR levels have correlated significantly with 90-day outcomes post stroke. In addition, an elevated neutrophil count was noted to be an independent predictor of poor outcome (>mRS3) at 90 days despite TICI 2b/3 recanalization by Bouisseau et al with higher infarct volumes.[68] Thus, NLR values post-stroke can serve as a marker for patients who may require hemicraniectomy for large infarcts despite recanalization. Recanalization of low-ASPECTS score, large-core strokes has been shown to decrease the rate of malignant transformation requiring hemicraniectomy, and reperfusion with decreasing NLR counts which may be one explanation/marker.[69] However, our meta-analysis was unable to evaluate the prognostic value of NLR in patients with different infarct sizes or a certain type of stroke treatment due to insufficient data. We highly recommend that future studies could highlight on these issues.

Although ischemic and hemorrhagic stroke shared similar inflammatory reaction, we found that prognosis of hemorrhagic stroke was weakly predicted by NLR level in contrast with that of ischemic stroke. Increased risk of ischemic stroke was associated with high levels of NLR. This could be due to the prothrombotic state that is induced by the inflammation cascade in ischemic stroke prodrome. During inflammation, leukocytes facilitate hemostasis by interacting with platelets, coagulation factors and endothelium, in various pathological conditions. For example, leukocytosis does not independently predict poor ICH prognosis when controlling for other outcome determinants including age, baseline hematoma volume, and admission Glasgow Coma Scale.[70]

Similarly, as hematoma expansion is related to poor outcome in hemorrhagic stroke, the inverse relationship between neutrophil counts and risk of hematoma expansion might relate to a better prognosis.[71,72] However, elevated baseline NLR levels correlated with high risk of

hemorrhagic transformation post-thrombolysis in ischemic stroke. Antithrombotic effect of thrombolysis or a poor BBB integrity can be a possible explanation for this. Thus, further clinical studies are required to evaluate the predicting role of NLR in patients post-thrombolysis.

The prognostic value of NLR in stroke was significant in subgroups of more than 65 years, male predominant, and patients from eastern countries, which was consistent with prior studies and our subgroup analysis.[73] Furthermore, as thromboembolism is the most common cause of ischemic stroke, we evaluated the vascular risk factors among the included studies. Cohorts with higher presence of hypertension (>65%), DM (>25%), and current smoking (>35%) tended to have more unfavorable functional outcomes in ischemic stroke. Cutoff values varied between studies due to different definitive methods, blood sampling time, and capacity of immune system.[73] Higher the cutoff value (>4) the worse the prognosis in patients with stroke. In addition, we observed that cutoff values that were defined by ROC curves were more likely to predict poor clinical outcomes. Thus, future studies are recommended to determine their specific cutoff values by ROC curves. Temporal dynamics of neutrophil and lymphocyte counts have been described in previous studies.[74] Therefore, we conducted subgroup analysis stratified by onset time and sample time. Shorter the time from onset of stroke to admission (within 24 h), and faster the procurement of the blood sample (within 72 h) was beneficial to record the NLR level at early stages of stroke-induced inflammation and guided in predicting the overall prognosis.

CONCLUSION

NLR level is an emerging biomarker of stroke prognosis. This study showed a significant correlation between raised NLR values with increased length of hospital stay, complications and 3-month outcome in acute ischemic stroke patients. Its use in various other medical conditions has helped clinicians stratify risk and initiate early treatment, thus preventing complications.

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