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Opinion

Neutrophil-to-lymphocyte ratio as a biomarker of neurological deterioration in acute ischemic stroke: Argumentative Scientific Essay

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Abstract

Ischemic stroke is a public health issue due to its high morbidity and mortality. Some patients experience early neurological deterioration, potentially leading to coma or death within the first week of illness despite initially normal brain imaging. This is attributed to cerebral edema caused by the inflammatory reaction within the ischemic lesion. Despite our understanding of the proinflammatory cytokines involved in this neurotoxic reaction, studies over the past two decades have not demonstrated their utility as inflammatory biomarkers due to contradictory results. Recently, promising studies have been published on certain leukocyte indices from the complete blood count as inflammatory biomarkers for progression in acute ischemic stroke. The aim of this scientific essay is to discuss the most recent literature on the use of the neutrophil-to-lymphocyte ratio as a biomarker for neurological deterioration in acute ischemic stroke.

Keywords: Hemogram, biomarker, coma, stroke.

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Abbreviations:
FNT-α; Tumor Necrosis Factor alpha.
ICAM-1; Intercellular Adhesion Molecule 1.
IL-6; Interleukin 6.
MMP-9; Matrix Metalloproteinase-9.
NLR; Neutrophil-to-Lymphocyte Ratio.
RNL; relación neutrófilo-linfocito.

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During my clinical practice as an emergency neurologist, I have noticed that most hospital admissions to the neurology service are due to acute ischemic strokes. Some patients experience early neurological deterioration, potentially progressing to coma or death within the first week, despite initially normal brain imaging. This contributes to increased mortality or greater future disability in these patients.

The prevalence of stroke was 3.7% in the United States in 2018, with an annual incidence of approximately 795,000 new cases. 87% of these cases were ischemic strokes. In Peru, 12,835 cases of stroke were reported for the same year, with an annual incidence of ischemic stroke of 18.4 cases per 100,000 inhabitants. At the National Institute of Neurological Sciences in Lima, a mortality rate of 7.6% [2] was estimated for ischemic stroke.

The unfavorable outcomes observed in some patients are due to cerebral edema, which begins to increase from the second day and reaches its maximum around the fifth day, potentially leading to the patient's death.[3f]The inflammatory response in the brain plays a crucial role in the early neurological deterioration of these patients. Therefore, it is evident that we need inflammation markers from hospital admission to predict the clinical evolution of ischemic stroke patients, enabling us to take diagnostic and therapeutic measures and make appropriate use of resources.[4]

This study aims to analyze the most recent scientific literature on the use of the neutrophil-to-lymphocyte ratio (NLR) as an inflammatory biomarker for the early neurological deterioration of acute ischemic stroke.

Stroke is currently considered a significant public health problem due to its high morbidity and mortality worldwide. In the United States, there was a mortality rate of 15.4 deaths per 100,000 inhabitants in 2018. It was also the fifth leading cause of death, with one person dying from stroke every 3.5 minutes, accounting for 1 in 19 deaths. The total annual cost of caring for these patients was estimated at $49.8 billion.[5]

In Peru, a mortality rate of 11.4 deaths per 100,000 inhabitants was reported for the year 2015, with some cities experiencing increased mortality compared to the previous 10 years. In La Libertad, the mortality rate was recorded at 22.7 deaths per 100,000 inhabitants in 2005 and 25.8 deaths per 100,000 inhabitants in 2015, making it one of the regions with the highest mortality rates from this disease.[6]

Patients with acute ischemic stroke are treated in emergency rooms where an initial brain computed tomography (CT) scan is performed to confirm the diagnosis and rule out other potential causes. However, this neuroimaging, conducted within the first 24 hours of symptom onset, often appears normal regardless of the severity of the clinical presentation.[7]

Early and subtle tomographic signs of cerebral ischemia can be detected in a few cases, particularly when the occlusion is in the carotid circulation, as early signs of ischemia in the vertebrobasilar circulation are extremely rare to visualize.[7] Nonetheless, the latter are more frequently associated with worse clinical outcomes.

Some patients with moderate ischemic stroke may experience early neurological deterioration within a few days, with worsening typically starting between 48 and 72 hours after symptom onset, potentially progressing to coma or death before the end of the first week.

This acute-phase mortality in ischemic stroke is primarily due to neurological causes: focal reduction in cerebral blood flow from arterial occlusion triggers an inflammatory cascade of neurotoxicity within the ischemic lesion. This cascade leads to progressive perilesional edema, initially cytotoxic and then vasogenic, resulting in increased intracranial pressure. Ultimately, this intracranial hypertension causes brain herniations that can be fatal for the patient.[8]

Molecularly, neuronal death occurs through necrosis accompanied by the release of pro-inflammatory cytokines such as interleukins (IL-6), tumor necrosis factor-alpha (TNF-α), and intercellular adhesion molecules (ICAM-1). This process involves the recruitment and migration of neutrophils that release matrix metalloproteinases type 9 (MMP-9) enzymes.[9]

These inflammatory reactions in acute cerebral ischemic lesions are most pronounced between days 2 and 3 of the illness, explaining the early neurological deterioration in some patients and the subsequent high mortality or increased disability, despite initially normal brain CT scans. All of this underscores the need for inflammation markers that can predict the course of these patients from the moment of admission.

Studies conducted in the last two decades on pro-inflammatory cytokines that play a specific and significant role in the pathophysiology of ischemic stroke have shown contradictory results. A systematic review in 2008 demonstrated that elevated serum IL-6 does not play a specific causal role in increased mortality in patients with ischemic stroke.[10] However two recent studies found an association between elevated IL-6 levels and severe disability and/or increased mortality in ischemic stroke, but only when combined with other biomarkers.[11, 12]

On the other hand, two investigations found an association between ischemic stroke and elevated serum levels of ICAM-1 and TNF-α, respectively, but neither could demonstrate the practical utility of their results as predictors of unfavorable outcomes.[13, 14]

A systematic review from 2011 found that elevated serum levels of MMP-9, measured within the first 24 hours of ischemic stroke onset, were associated with larger parenchymal lesions, greater clinical severity, and worse functional outcomes.[15] However, another systematic review from 2012 concluded that no inflammatory biomarker could be recommended as a diagnostic or prognostic factor for ischemic stroke.[16]

Despite these molecules directly participating in the pathophysiological mechanism of cerebral infarction, they cannot yet be considered biomarkers for predicting early neurological deterioration. Additionally, they are expensive and not widely accessible to the general population. Nevertheless, there are other acute-phase inflammatory reactants that have some association with unfavorable outcomes in ischemic stroke. One such indicator is the hemogram, particularly some of its systemic inflammatory response indices, like the neutrophil-to-lymphocyte ratio (NLR).[17]

A meta-analysis in 2019 demonstrated that an NLR value greater than 7.5 could predict hemorrhagic transformation in ischemic stroke with an odds ratio (OR) of 7.93 (95% CI, 2.25–27.95; p=0.001) and predict higher mortality in these patients with an OR of 1.10 (95% CI, 1.05–1.15; p<0.0001).[18]

Another study in 2020 found that an NLR value greater than 2.94, measured early, was associated with unfavorable functional outcomes in patients with mild ischemic strokes and transient ischemic attacks, with an odds ratio (OR) of 4.50 (95% CI, 1.53–13.04; p=0.006).[19]

A systematic review in 2021 demonstrated that an NLR value greater than 7 was associated with higher mortality with an OR of 1.12 (95% CI, 1.07–1.16; p<0.00001) and worse functional outcomes with an OR of 1.29 (95% CI, 1.16–1.44; p<0.00001) in patients with ischemic stroke.[20]

An original study published in 2022 found that an NLR value greater than 3.86 is a risk factor for higher mortality and more severe disability in patients who suffered ischemic stroke, with ORs of 2.41 (95% CI, 1.37–4.26; p<0.002) and 2.24 (95% CI, 1.35–3.71; p<0.002), respectively.[21]

These results are based on the neurotoxic inflammatory reaction that occurs during ischemic stroke. Neutrophils rise early in the ischemic brain area, releasing proteolytic enzymes and oxygen free radicals that worsen cytotoxic edema. Additionally, they increase MMP-9 expression, leading to vasogenic cerebral edema secondary to disruption of the blood-brain barrier. Thus, high levels of neutrophils are associated with more severe initial ischemic strokes.

Lymphocytes rise after neutrophils and primarily function to regulate neuroprotection and neurorepair by increasing production of anti-inflammatory cytokines like IL-10, while decreasing production of pro-inflammatory cytokines such as IL-6 and TNF-α.[23] Therefore, low lymphocyte levels are associated with a worse prognosis.

Patients with acute ischemic stroke and elevated NLR values from hospital admission may experience unfavorable outcomes in the early days, warranting admission to a special care unit despite having a normal initial brain CT scan. NLR could also be used to monitor clinical progression. This is particularly useful in developing countries, as NLR is derived from a cheap, readily available hemogram in all hospitals.

However, it is essential to recognize the limitations of NLR as a biomarker in acute ischemic stroke. Optimal cutoff values for NLR vary between studies, leading to potential inconsistencies in its application. Additionally, NLR can be influenced by other factors such as comorbidities and medications, affecting its specificity and predictive power.

Future research should focus on standardizing NLR cutoff values and exploring its potential in combination with other biomarkers to improve predictive accuracy. Longitudinal studies with larger patient cohorts are needed to validate findings and better understand NLR dynamics in acute ischemic stroke.

In conclusion, elevated NLR values are associated with excessive inflammation and immunosuppression, making it a promising biomarker for neurological deterioration, disability, and mortality in acute ischemic stroke. However, further research and validation are necessary to address its limitations and refine its clinical utility.

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