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Review

Highlighting the Role of Universally Available and Innate Immune Cell Counts in Acute Ischemic Stroke: A Scoping Review

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Abstract: Stroke is one of the leading causes of adult disability and the second leading cause of death worldwide. The immune system actively participates in the pathobiological process of acute ischemic stroke (AIS), during the index event and the repair process. Research on neurovascular inflammation has created a renewed interest in the use of easily available biomarkers reflective of innate and adaptive immunological changes with potential diagnostic, prognostic, and therapeutic implications particularly in AIS. The current scoping review aimed to assess the significance the neutrophil to lymphocyte (NLR) in AIS and its related complications and explore their association with post-stroke recovery trajectory. The Arksey and O'Malley methodological framework was employed to review the published papers on the neutrophil–lymphocyte ratio (NLR) and AIS in late November 2020. Only studies published in English from 2000–2020 were included in this scoping review. Fifty-three published papers were reviewed. This review's key finding is that a canonical inflammatory response occurs in the hyperacute, acute, subacute, and chronic stages of stroke. An excessive circulating innate immune cells (neutrophils) and reduced circulating adaptive immune cells (lymphocytes) are associated with poorer outcomes during the acute interventions as well as the recovery trajectory. This scoping review's findings highlights the utility of a systems biology-based approach in stroke care.

Keywords: acute ischemic stroke; neuroinflammation; neutrophil-lymphocyte ratio; NLR

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1. Introduction

On 12 November 2020, the World Health Assembly (WHA), the global decision-making body of the World Health Organization (WHO), went on to pass the landmark resolution WHA73.10 for "global actions on epilepsy and other neurological disorders" with 13 new paragraphs on key aspects of global brain health as a matter of high priority [1]. The resolution confirmed the enormous impact of stroke-related death and disability [2] This was noted to be the main reason behind the 80% death and disability in low to middle-income countries worldwide [3–6]. Furthermore, these long term underlying trends among the Emerging BRICS (Brazil, Russia, India, China, and South Africa) and EM7 (Brazil, China, India, Indonesia, Russia, and Turkey) Markets play particularly sensitive role shaping the global landscape in epidemiology of stroke and consecutive challenge of financial sustainability [7,8].

Approximately 85% of strokes are of ischemic origin, and the rest is accounted for by intracerebral and subarachnoid hemorrhage and other types [9]. Prognostic assessments are crucial for treatment selection in stroke and remains a challenging aspect for clinicians. Numerous prognostic factors validated by previous studies are not without limitations, including too much emphasis on motor systems, observer-dependent variability and cost [10]. Inflammation plays a key role in acute ischemic stroke (AIS) from pathobiology, index, and recovery [11–14]. Neutrophils and lymphocytes are common markers of inflammation and representatives of innate and adaptive immunity, respectively [15]. The neutrophil–lymphocyte ratio (NLR) and systemic immune-inflammatory response (SII) provide an excellent biomarker of the innate and adaptive immune response in AIS [16,17]. As a cost-effective and easy to perform test in routine practice, NLR has been previously validated as a prognostic indicator in other conditions such as cancer, cardiac disease, sepsis, coronary artery disease, and metabolic syndrome [17,18]. It is obtained from the differential white blood cell count and is calculated by absolute neutrophil count divided by total lymphocyte count.

2. Methodology

This review included published articles, abstracts, letters, and commentaries of neutrophil studies to lymphocyte ratio and its relationship to AIS. In particular, studies were included if they looked into the relation of NLR and ischemic stroke and related complications. There were no limitations on the sample size, duration and follow-up. Only studies in English and those that were published from the year 2000 onwards were included.

The following computerized databases were acceded: PUBMED, EMBASE, British Library, Library of Congress, and National Lib of Medicine. Each article's bibliography was also manually searched for additional publications. The following search terms were used: neutrophil to lymphocyte ratio; (NLR); inflammation; stroke and post-stroke complications. Two reviewers extracted the data (TW, CS), and a third reviewer (LK) resolved any conflicts for inclusion. The quality of the studies was also independently assessed.

3. Results

A total of 263 articles were generated from the electronic search. There were 50 duplicates, and the rest were screened on the title level. Further screening of the abstracts yielded 180 articles, of which 47 articles were deemed relevant and included in the study. Additional six studies were included from manual search of bibliographies. Figure 1 shows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart for the search. Table 1 summarizes the utility of elevated NLR among patients with AIS. (Main papers in this reviews are listed in the Supplementary Material Table S1).

Table 1. The utility of elevated Neutrophil to Lymphocyte Ratio (NLR) and. Acute Ischemic Stroke.

• Predicts length of hospitalization, cost, disability, and death among patients with AIS
• Correlated with the volume of infarct in anterior circulation
• Associated with more severe and disabling ischemic strokes
• Increased risk of hemorrhagic complications among patients receiving reperfusion therapy
• Higher risk of recurrent strokes
• Increases risk of stroke among patients with or without traditional cardiovascular risk factors
• Increased odds for post-stroke complications such as stroke-associated pneumonia, delirium, and post-stroke depression

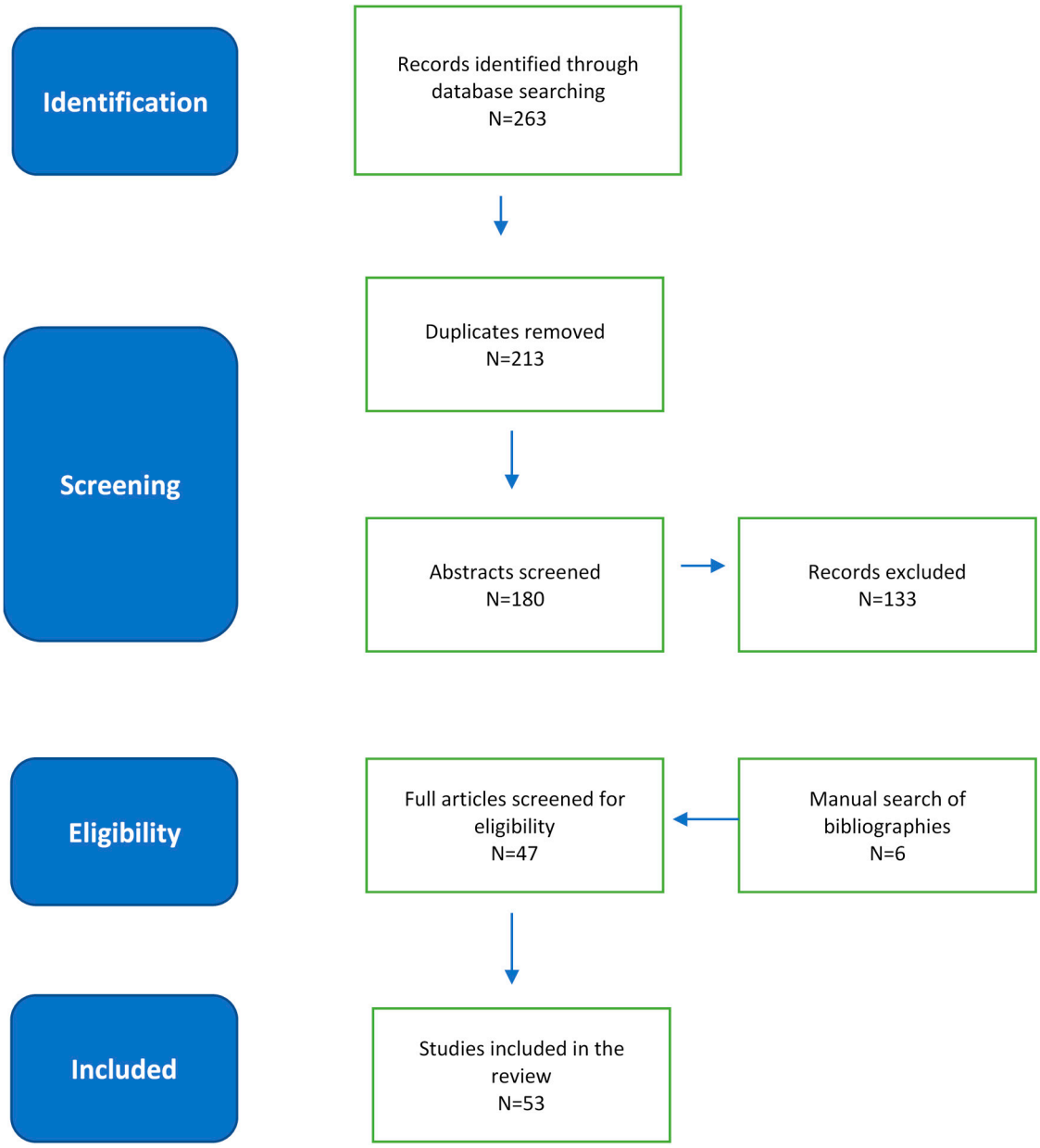

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) chart.

4. Discussion

4.1. The Role of NLR in Acute Ischemic Stroke

The role of NLR has been most widely investigated in ischemic strokes. Current interventions of acute ischemic stroke (AIS) include intravenous thrombolysis and mechanical thrombectomy, which aim for recanalization of the cerebral arteries blocked by a clot or an embolus, thus resulting in reperfusion of the hypoxic brain tissue.

NLR has been identified to be a useful clinical predictor of outcome in AIS patients being considered for mechanical thrombectomy, as NLR can predict functional dependence and mortality after adjustment for potential confounders including vascular risk factors. Multiple analyses reveal that NLR correlates with a greater functional disability at admission and at three months (increased mRS (modified Rankin Score) and NIHSS (National Institutes of Health Stroke Scale) scores, increased 90-day mortality and associated with prolonged hospital stay and greater cost of hospitalization [19–25]. Patients with NLR > 3.3 were two times more likely to be at risk of death [24]. This elucidates the role of NLR as a potential biomarker of prognosis, thereby providing an additional level of risk

stratification in AIS. Interestingly, high NLR was also significantly correlated with the volume of infarct in anterior circulation strokes but not in those of posterior circulation origin [24]. In addition, Switonska identified that elevated NLR was significantly higher in patients treated with both thrombolysis and thrombectomy than those who either received thrombolysis alone or were not treated suggesting that elevated NLR levels is suggestive or more severe strokes warranting aggressive treatment [21].

Current literature describes the role of NLR in predicting AIS complications particularly in those receiving reperfusion therapy. NLR obtained at 12–18 h after treatment with intravenous recombinant tissue plasminogen activator (rtPA) was positively associated with hemorrhagic transformation, characterized by symptomatic intracerebral hemorrhage or parenchymal hematomas [26]. Various studies identified that high NLR values translated to increased hemorrhagic complications especially among patients receiving systemic thrombolysis and mechanical thrombectomy [27–29].

Other complications with a potential link to high NLR include recurrent ischemic strokes [30]. Promisingly, elevated NLR was also an independent risk factor for the incidence of AIS in generally healthy adults in a study compared with other traditional cardiovascular risk factors, demonstrating the potential utility of this biomarker in primary prevention of stroke [31]. The role of INR in AIS and its co-morbid conditions have also been explored. Studies suggest that NLR may reflect the severity of carotid artery stenosis [32–34] and aortic arch calcification [35], both of which are important risk factors of AIS. Nam et al. showed that high NLR could predict early neurological deterioration in cryptogenic stroke patients with active malignancy [36].

Ischemic injury to the brain triggers a systemic inflammatory response involving brain cells' activation in the ischemic area, inducing leucocytes' migration from this area. Neutrophils are described as the first leucocytes to act on the infarcted cells contributing to the ongoing innate immune response while lymphocytes accumulate later during the stroke recovery as part of the adaptive immune response [37]. High NLR reflects both an amplified innate immune response characterized by higher neutrophils (polymorphonuclear cells) and an attenuated adaptive immune response as demonstrated by decreased lymphocytes [21,22,38–40]. The same responses were demonstrated among patients with neonatal ischemic injury suggestive of the potential role of anti-inflammatory therapy in ischemic brain injury [41].

4.2. NLR and Its Role in Predisposition to Acute Ischemic Stroke

Low-grade systemic inflammation is a common denominator for metabolic syndrome and cardiovascular diseases such as AIS and aging [41]. In a retrospective literature published by Suh et al., it has been demonstrated that among almost 25,000 normal subjects, elevated NLR is a risk factor for ischemic stroke [31]. This study further concluded that the addition of NLR improved the Framingham risk for reclassification of ischemic stroke [35]. Elevated values, especially among normal subjects, highlight the importance of subtle and ongoing chronic inflammation and its predisposition to pathologies such as diabetes and stroke [31,40,42]

On the other hand, patients with preexisting cardiovascular risk factors are also prone to stroke if NLR is elevated [42]. A study of more than 32,000 atrial fibrillation subjects without prior anticoagulation were prospectively followed up for the first-ever stroke and has been shown that independent of patients' CHADS-Vasc scores; there is a dose-dependent increase in the incidence of stroke with increasing NLR quartiles which were estimated to be 2.27, 2.72, 3.26, and 4.54 per 100 person-years, respectively [43]. This is further corroborated in another study that compared patients with AF with and without stroke suggesting that patients belonging to the former had a higher NLR than their non-stoke counterparts [44]. The same study concluded that aside from AF, NLR was also positively correlated to NIHSS and diabetes among ischemic stroke patients [44]. It is clear that both AF and stroke are related to a state of chronic inflammation which may be manifested serologically by the dissociation of neutrophils and lymphocytes [42–45].

The occurrence of stroke among patients with AF is linked to the formation of a cardiac thrombus, which is also linked to a higher NLR state [46]. In animal models, there has been a success in using corticosteroids in minimizing atrial-tissue related inflammation which contributes to a pro-arrhythmic state, but this has yet to be fully evaluated in humans [47]. There is also limited information on anti-inflammatory agents in stroke prevention, particularly in AF patients.

4.3. NLR and Its Role in Post-Stroke Complications

4.3.1. Stroke Associated Pneumonia

Stroke Associated Pneumonia (SAP) is one of the most common post-stroke complication occurring in 2.3–44% of patients [48]. It is an important risk factor for mortality at one and six months, with death rates at 19% and 44%, respectively [48]. The neutrophil to lymphocyte ratio on admission has also been explored as a prognostic indicator for pneumonia among stroke patients. Nam et al. observed that a high NLR on admission was associated with severe pneumonia and higher frequency of mortality at one month, and worse mRS at three months [49]. Similar observations were noted in another study and concluded that compared to other hematologic parameters such as WBC, lymphocyte, and neutrophil counts, NLR was a better predictor of 90-day mortality [50].

While impairment in swallowing mechanisms largely contributes to pneumonia among post-stroke patients, there is increasing evidence that stroke itself induces an immunocompromised state predisposing patients to infection [51]. This is supported by observations of decreased lymphocyte number and an increase in neutrophil count in acute stroke patients [52]. While targeted neutrophil therapy may have the theoretical advantage, Ruhnau recommends that therapy's potential benefits may be countered by its opposing effects in the brain and systemically [52]. This is made true in a clinical trial of an anti-inflammatory drug Enlimomab on patients with ischemic stroke (Enlimomab) [53]. Comparing the former with placebo, it has been shown that among Enlimomab-treated patients, there were more serious adverse events, particularly fever and infection, and higher mortality rates [53].

4.3.2. Post-Stroke Delirium

Delirium is another complication known to occur in 13% to 48% of patients with acute stroke [54]. There is clinical data to suggest that risk of death, institutionalization and hospital stay is significantly higher among stroke patients with delirium [54,55]. The use of the neutrophil to lymphocyte ratio as a prognostic factor in patients with delirium was first explored by Egberts et al. in acutely ill patients [56]. This study's results, which involves 86 patients, prove that patients who are clinically unwell and subsequently develop delirium have higher NLR [56].

A prospective observational study of 1001 patients with acute ischemic stroke diagnosed with delirium using the CAM-ICU (Confusion Assessment Method for Intensive Care Unit) corroborated this condition's increased incidence as previously observed in other studies [56]. In the same study, along with NLR, clinical (hemianopia, aphasia, and NIHSS) and laboratory variables (leukocytes and CRP) which comprise the Delirium in Acute Ischemic Stroke (DELIAS) score, this has been shown to have good predictive value for detecting early-onset delirium and of moderate predictive value for delirium up to the fifth day from the stroke [57]. On the other hand, a follow-up study of patients with first-ever acute ischemic stroke has shown that instead of NLR, platelet to white cell count ratio was associated with early delirium occurrence [57]. These studies support previous evidence that acute brain injury may result in the loss of adaption of the immune cells as manifested by the disproportionate changes of these hematologic parameters [56,57].

4.3.3. Post-Stroke Depression

Depression is one of the leading causes of morbidity among stroke patients and significantly impacts all aspects of rehabilitation [58]. A meta-analysis including seven

studies involving more than 17,000 patients has shown that post-stroke depression (PSD) is associated with increased risk of mortality with a relative risk of 1.50 (95%CI: 1.28 to 1.75; $p < 0.001$) [59]. One of the key implicated mechanisms is neurobiological systems' involvement, emphasizing post-stroke inflammation, which is the expectation rather than the exception [60–62]. Grundy and colleagues have demonstrated that inflammatory mediators produced after acute stroke may have damaging effects on rat models [63]. It has been further proposed that the production of IL-1 and other chemokines by mononuclear phagocytes attracts neutrophils, monocytes and T-lymphocytes which further play a role in the dysregulation of humoral and inflammatory systems and maybe indirectly correlated to its pathogenesis [61].

The NLR as a predictor for depression among stroke patients has been well documented in the literature [64–66]. In a prospective study involving 299 ischemic stroke patients, increased NLR during admission was correlated to PSD after one month, with diagnosis based on the 17-Hamilton rating scale [64]. Using the Quick Inventory for Depression Symptomology (QIDS), Wolde et al. showed the positive correlation between high NLR on acute stroke presentation and the occurrence of depression after 30 days [65]. A retrospective study of more than 300 patients also demonstrated that in conjunction with platelet to lymphocyte ratio, high admission NLR is associated with depression at six months after stroke [66]. On the other hand, a correlation of depression severity has also been demonstrated with increasing NLR among patients without stroke but with significant vascular risk factors [67].

5. Future Potential Therapeutic Opportunities

The unmet needs in stroke prevention and post stroke rehabilitation continue to remain an immense challenge to the world. It is clear that the human immune system is quite complex with synergistic (innate immune cells and mechanisms) as well as antagonistic (adaptive immune cells and mechanisms) roles with different cells playing different roles at different time points of AIS with likely shared pathobiology with other vascular diseases such as ischemic heart disease, acute myocardial infarction in particular [68–70]. Innate and adaptive immune cells and pathways should complement each other for an effective and optimum recovery process after the index event of AIS. Patients with an already compromised vascular system with AIS appear to show elevated NLR, suggesting an undue prominence of circulating neutrophils (innate immune cells) over lymphocytes (adaptive immune cells). This means the potential therapeutic targets such as reducing the innate immune system's hyperactivity while minimizing the depression of the adaptive immune system during the index event of AIS. There may be a role for safe, low cost, psycho-neuro-immuno-modulatory chemicals such as melatonin and curcumin with potential therapeutic benefits in disabling post-stroke complications post-stroke depression, post-stroke fatigue, post-stroke anxiety, etc. [71]. To date, the use of anti-inflammatory agents in post-stroke depression is minimally explored. Studies have shown that SSRI (selective serotonin reuptake inhibitors), one of the mainstays for PSD treatment, exhibits an anti-inflammatory activity by upregulating neurotrophins and enhancing neurogenesis [72–74]. A meta-analysis involving 14 publications with more than 6000 patients, has shown that nonsteroidal inflammatory drugs, most notably Celecoxib, alleviate depressive symptoms compared to placebo [75]. There is also evidence that Celecoxib and Infliximab's intake in patients with major depression has resulted in a concomitant decrease of the inflammatory markers, IL-6 and CRP, respectively [76,77]. While anti-inflammatory agents' role in depression seems to be promising, further studies are needed, especially among post-stroke patients, given the former's association with vascular events [78].

6. Conclusions

The neutrophil to lymphocyte ratio is a cheap, effective, yet an underutilized biological marker in AIS. It provides information on prognosis and risk stratification among stroke patients and individuals who are at risk of developing neurovascular events. While animal studies have proven the theoretical role of anti-inflammatory drugs in controlling the damaging the degree of systemic and neuro-inflammation, this has not translated significantly in human clinical trials. It should also be highlighted that a systems biology-based approach in AIS management should provide the best synergy to bring the best care for AIS throughout the recovery trajectory.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/su13074069/s1, Table S1: Summary of Studies on Neutrophil to Lymphocyte Ratio and Acute Ischemic Stroke. References [20–36,43,44,49,50,57,65,67] are cited in the Supplementary Materials.

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