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Neutrophil to lymphocyte ratio and early clinical outcomes in patients with acute ischemic stroke

Sungwook Yu[a,b,c], Hisatomi Arima[b], Carin Bertmar[c], Stephen Clarke[c], Geoffrey Herkes[c], Martin Krause[c,*]

[a] Department of Neurology, Korea University College of Medicine, Seoul, Republic of Korea
[b] The George Institute for Global Health, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia
[c] Department of Neurology, Royal North Shore Hospital, St Leonards and University of Sydney, Sydney, Australia

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ABSTRACT

Background: The neutrophil to lymphocyte ratio (NLR) is closely linked to mortality in patients with cardiovascular disease. We investigated whether NLR is associated with early clinical outcomes in patients with acute ischemic stroke.

Methods: We collated data from a tertiary hospital's stroke registry including admitted patients with a first-ever acute ischemic stroke within 72 h of onset. White blood cell counts and peripheral differential counts were measured on admission. Early clinical outcomes were in-hospital mortality and disability at discharge assessed by the modified Rankin scale (mRS).

Results: Among 1131 stroke patients, 454 patients were included and classified into tertile groups based on NLR on admission. Patients in higher tertiles of NLR were likely to have severe neurologic deficit at discharge. Higher NLR tertiles were associated with an unfavourable shift of mRS score ($p < .0001$). This association remained significant after adjustment for clinical and laboratory variables including age, sex, hypertension, hypercholesterolemia, atrial fibrillation, stroke severity, and glucose level ($p = .032$ for trend). However, risk of death or major disability (score of 3–6 on mRS) and in-hospital mortality were not significantly different across NLR tertile groups.

Conclusions: In patients with acute ischemic stroke, NLR was predictive of short-term functional outcome.

1. Introduction

Inflammation after stroke contributes to brain injury [1–3] and a number of inflammatory biomarkers have been investigated in stroke patients [4]. Elevated peripheral leukocyte count has been shown to be associated with mortality or poor clinical outcome in patients with acute ischemic stroke [5–8] or with higher risks of stroke in patients with symptomatic intracranial atherosclerotic disease [9]. However, post-stroke immunologic response is a complex process inducing activation of diverse inflammatory cells and immunodepression [2,3]. Neutrophils and lymphocytes among subtypes of leukocytes might have different effects on clinical outcomes since a prior study suggested an inverse association between lymphocyte counts within three days of stroke onset and functional outcome at three months [10].

Recently, neutrophil to lymphocyte ratio (NLR) has emerged as a strong predictor of mortality in patients with cardiovascular disease [11,12] or peripheral arterial occlusive disease [13]. Previous studies in stroke patients also proposed the prognostic value of NLR for prediction of mortality [12,14–17]. Furthermore, higher NLR has been shown to be independently associated with worse outcome at 3 months in ischemic stroke patients treated with thrombolytic therapy [18,19]. However, this relationship has been investigated in a relatively narrow range of stroke patients and the literature on the association between NLR and functional outcomes is limited.

We undertook this study to evaluate whether NLR was associated with short-term clinical outcome in patients with acute ischemic stroke.

2. Materials and methods

2.1. Study design

We included consecutive patients with stroke or transient ischemic attack who were admitted to Royal North Shore Hospital (RNSH), a tertiary hospital in Sydney, Australia, and registered in the hospital's

* Corresponding author at: Department of Neurology, Royal North Shore Hospital, University of Sydney, Sydney, New South Wales, Australia.
E-mail address: martin.krause@sydney.edu.au (M. Krause).

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stroke registry database from January 2009 to March 2013. Patients who were older than 18 years and were admitted to the hospital within 72 h of onset due to a first-ever acute ischemic stroke were selected. Patients were excluded if they had a transient ischemic attack, thrombolysis therapy, an in-hospital stroke, a history of steroids or immunosuppressive agents, an infection history within one week before admission, and the occurrence of infection during hospitalization. Infection including pneumonia and urinary tract infection was defined by typical symptoms with supported evidence from physical examination, blood or urinary tests, imaging etc. This study was approved by the Institutional Review Board with a waiver of patients' informed consent due to the retrospective study design.

Ischemic stroke was diagnosed by the World Health Organization's definition [20] and confirmed by computerized tomography or magnetic resonance imaging. Baseline demographics were collated from the stroke registry database including vascular risk factors, e.g. hypertension, diabetes, hypercholesterolemia, atrial fibrillation, ischemic heart diseases, smoking status and alcohol consumption. Information on previous medication was obtained including antiplatelet agents, anticoagulants, and lipid lowering agents.

Stroke severity was assessed by the Scandinavian Stroke Scale (SSS) on admission and categorised into four groups with very severe (score of 0 to 14 points), severe (15 to 29 points), moderate (30 to 44 points), and mild (45 to 58 points) deficit [21]. We assessed disability at discharge by the modified Rankin scale (mRS) and in-hospital mortality as clinical outcomes.

2.2. Neutrophil to lymphocyte ratio

Blood samples were collected on admission and white blood cell counts and peripheral differential counts were measured. NLR was calculated by neutrophil count divided by lymphocyte count. All patients were grouped into tertiles according to their NLR on admission.

2.3. Statistical analysis

Data were presented as number (%), mean (standard deviation) or median (interquartile range [IQR]) as appropriate. Baseline demographic and laboratory data were compared across NLR tertile groups using Fisher's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Correlation between two variables was assessed by Pearson or Spearman correlation test. Clinical Outcomes were mRS distribution at discharge, in-hospital mortality and death or major disability (mRS 3–6) at discharge. We used binomial and multinomial logistic regression to investigate the association between NLR and clinical outcomes. To adjust for other potential confounding variables, multivariable analyses including age, sex, and other variables, that were significant in univariable analyses with $P < .05$, were performed. P value $< .05$ for two-sided hypothesis testing was considered as statistically significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics

Among 1131 consecutive stroke patients, 626 had the first ever ischemic stroke. Of 626 patients, 172 were excluded due to age under 18 years (n = 3), thrombolysis treatment (n = 38), onset to admission time over 72 h (n = 49), unknown onset time (n = 16), and occurrence of infection during hospitalization (n = 66). Finally, 454 patients were included in this study. Number of patients who were admitted within 24 h after stroke onset was 376 (82.8%).

Baseline clinical characteristics are presented in Table 1. Median (IQR) age of included patients was 72.4 years (62.1–82.6) and 201 (44.3%) were male. Median (IQR) score of SSS on admission was 54 (44–56). Median duration of hospitalization was 5.5 days (3.3–9.0). Dyslipidemia was more frequently observed in patients with the highest NLR tertile. Other stroke risk factors were not different across NLR tertile groups. Patients in higher tertiles of NLR were more likely to have severe neurologic deficit. (Table 1) Median SSS scores from the lowest to the highest tertiles of NLR were 56 (50–58), 55 (46–56), and 50 (32–56), respectively. Moreover, patients in higher NLR tertiles stayed longer at hospital. Duration of hospitalization was significantly correlated to the severity of neurologic deficit assessed by SSS ($r = -0.40$, $p < .0001$). Time intervals from stroke onset to admission or to blood sampling were not different among the tertile groups. WBC and neutrophils counts increased in higher NLR tertile groups. However, lymphocytes and eosinophils counts decreased as the NLR increased. Elevated levels of glucose were found in the higher tertile groups.

3.2. Clinical outcomes

During hospitalization, 98 (21.6%) patients had unfavourable outcomes: 78 patients with major disability (mRs 3–5) and 20 patients who died in hospital (4.4%). Higher tertiles of NLR were significantly associated with unfavourable shift of mRS scores in multinomial logistic regression analysis ($p < .0001$) (Table 2). The highest tertile group had 2.68 fold-increased risks of unfavourable shift of mRS compared to the lowest tertile group of NLR. [95% confidence interval (CI) 1.77–4.06]. In univariable analysis, age, sex, hypertension, smoking, hypercholesterolemia, atrial fibrillation, glucose level, and SSS score were confounding variables significantly associated with unfavourable shift of mRS. After adjustments for clinical and laboratory variables that had significant association with outcomes, the association between tertiles of NLR and unfavourable shift of mRS remained significant ($p < .032$).

Risk of death or major disability (mRS 3–6) significantly increased in higher tertiles of NLR ($p = .0002$ for trend). However, the association was no longer significant after adjustment of confounding variables as outlined above. There was a trend towards increased in-hospital mortality in the higher NLR, but this association did not reach statistical significance.

4. Discussion

In patients with acute first-ever ischemic stroke, higher NLR within 3 days after the stroke onset was an independent predictor for unfavourable functional outcomes at discharge. NLR on admission, however, was not significantly associated with increased in-hospital mortality after adjustment for other potential predictors. These results suggest that NLR on admission after acute ischemic stroke is a simple and useful hematologic biomarker to estimate short-term functional outcomes.

Post-stroke inflammation causes a deleterious effect on brain injury while it might play a different role in tissue repair and regeneration in a time-dependent way [2]. Neutrophils are a major subtype of leukocytes to respond early after stroke and represent active inflammatory reaction [2,22]. Subsets of lymphocyte, specific T cell lymphocytes, might have a regulatory function in inflammation inducing neuroprotection [1–3]. It has been well known that stroke-induced systemic immunosuppression, e.g. lymphopenia, could increase susceptibility to infection including pneumonia and urinary tract infections [3,23], which cause a harmful effect on clinical outcomes. In acute ischemic stroke patients, total WBC and neutrophil counts within three days after symptom onset had a positive correlation with stroke severity and infarct volume, while higher lymphocyte counts was associated with early improvement during the first week after admission and good functional outcome at three months [10,24]. Therefore, higher NLR could be a more sensitive marker indicating higher level of post-stroke inflammation [25].