# Prognostic significance of neutrophil-to-lymphocyte ratio in the development of post-stroke cognitive impairment

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***Abstract.*** *The inflammatory process is involved in the development of cognitive impairment after hemorrhagic stroke. The neutrophil-lymphocyte ratio (NLR) is an indicator reflecting systemic inflammation and a reliable marker of the severity and adverse outcomes of stroke. The aim of the study was to evaluate the predictive value of NLR for the first time 24 hours of stroke in the development of post-stroke cognitive impairment after intracerebral hemorrhage.*

***Materials and methods:*** *115 patients with previous supratentorial intracerebral hemorrhage were included in this case-control study. 58 patients were included in the main group with a total of ≤17 MoCA points, ≤19 MMSE points, and GDR stages 2-7; 57 patients in the control group - with ≥ 26 MoCA points, with ≥ 27 MMSE points and stage 1 GDR. The NLR was analyzed as a continuous variable with a cut-off level> 3.53.*

***Results:*** *In the main group, the NLR range was 1.2378-19.2, the median value was 4.3583. In the control group, the NLR was within 0.2881-21, the median was 2.6667. Patients with PSCI were more likely to have an elevated NLR than patients without PSCI (p=0.002). An increase in NLR of more than 3.53 was determined in 62.07% of patients with PSCI (95% CI: 49.33-74.81), in patients without PSCI - in 33.33% (95% CI: 20.85-45.82). An increase in NLR> 3.53 increased the incidence of PSCI by 1.78 times (RR - 1.785, 95% CI: 1.216-2.621). An increase in NLR> 3.53 is associated with a high chance of developing post-stroke cognitive dysfunction at 6 months after ICH (OR - 3.273, 95% CI: 1.524-7.030).*

***Conclusion:*** *An increase in NLR> 3.53 for the first time 24 hours of intracerebral hemorrhage is associated with the development of post-stroke cognitive impairment. NLR can be used as a prognostic marker in the development of post-stroke cognitive impairment.*

***Keywords:*** *neutrophil-lymphocyte ratio, inflammatory marker, inflammation, post-stroke cognitive impairment, stroke.*

## Introduction

Post-stroke cognitive impairment (PSCI) is a serious disabling disorder due to stroke. Cognitive impairment develops in more than 30% of stroke patients, reaching the degree of dementia and leads to disability [1, 2] Currently, about 50 million people suffer from dementia, in 2030 the number of patients with dementia will reach 82 million [3].

According to experimental and clinical studies, the inflammatory process has an important role in the development of PSCI [4-7]. Several previous studies have examined the association of markers of inflammation with PSCI, but the results for certain biomarkers have been mixed. In a study by K. Narasimhalu et al. in patients after ischemic stroke, C-reactive protein (CRP), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-10 (IL-10) did not confirm the relationship with PSCI [8]. However, the results were different for CRP in the L.S. Rothenburg et al. The results showed that a high level of CRP is associated with a deterioration in cognitive functions 1 month after stroke, with respect to IL-6, no relationship was found [9]. In other studies, an association between CRP and PSCI has also been found [10, 11]. Regarding IL-1β, IL-6, IL-10, according to the results of the study by V.G. Cherkasova et al., Patients with PSCI had a high concentration of IL-1β and IL-10 in the cerebrospinal fluid and IL-6 in the blood serum, in comparison with patients with normal cognitive ability [12].

One of the inflammatory markers reflecting systemic inflammation is the neutrophil-lymphocyte ratio (NLR). Compared to the above markers, NLR is readily available with a complete blood count, which is usually done for all inpatients, without additional financial costs. Several meta-analyzes have shown that an increase in NLR is a predictor of acute ischemic and hemorrhagic strokes [13-15]. In addition, NLR is a reliable marker for predicting the severity [16] and adverse outcomes of stroke [17-19], such as infectious complications, increased hematoma volume after intracerebral hemorrhage (ICH) [20,21] and post-stroke disability [16,22,23, 24].

Based on the results of previous studies and the role of inflammation in the development of post-stroke cognitive impairment, NLR may be a prognostic marker of the occurrence of post-stroke cognitive impairment in intracerebral hemorrhage.

**Purpose of the study –** to evaluate the predictive value of NLR for the first time 24 hours of stroke in the development of post-stroke cognitive impairment after ICH.

## Materials and methods

This retrospective case-control study included 115 patients with previous supratentorial intracerebral hemorrhage. Inclusion criteria were: age from 18 years, established diagnosis of supratentorial intracerebral hemorrhage, a complete blood count was performed on the analyzer for the first time 24 hours ICH, early recovery period. Patients with aphasia, pathology of the organs of

vision and/or hearing, with acute infectious, mental illnesses and taking sedatives, glucocorticosteroid, immunosuppressive drugs or other therapy affecting the immune and cognitive status were excluded.

In order to identify pre-stroke cognitive impairments in the subjects of the study, close relatives were questioned using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). According to the results of IQCODE, 32 patients were excluded, the results of which were more than 78 points. Cognitive status was assessed 6 months after stroke according to the American Psychiatric Association's Diagnostic and Statistical Manual using the Montreal Cognitive Assessment Scale (MoCA), Mental Status Assessment Summary (MMSE), and General Deterioration Scale (GDR). In order to exclude false results and taking into account the sensitivity of the scales, patients with mild cognitive impairment according to the results of MoCA and with mild dementia according to the MMSE were not included [25, 26]. In the categorical table of the General Impairment Scale (GDR), patients were classified into 7 stages of cognitive impairment [27]. Based on the test results, the main group included patients with a total of ≤17 MoCA points, ≤19 MMSE points, and GDR stages 2-7; in the control group - with ≥ 26 MoCA points, with ≥ 27 MMSE points and stage 1 GDR.

Absolute Neutrophil Count (NEUT #), Absolute Lymphocyte Count (LYM #) were recorded through the Integrated Medical Information System case history data. The NLR analysis was performed as a continuous variable with a range within the normal range from 0.78 to 3.53 [28].

According to the results of computed tomography (CT) of the brain, the affected hemisphere, localization and volume of the hematoma were recorded. The volume of hematoma was measured using the ABC/2 method by means of non-contrast CT of the brain [29], the indicator of which was entered as a continuous variable. Localization of ICH was classified as lobar, medial, lateral and mixed intracerebral hematomas [30]. The degree of neurological deficit on admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Statistical processing of the results was carried out using Microsoft Excel 14.0.4760.1000 and Statistica 6.0 software. The distribution of features was assessed using the Shapiro-Wilk test. Quantitative characteristics were compared using the nonparametric Kruskal-Wallis test (H-test). Comparison of the proportions between groups was carried out using the Z-test. Correlation was assessed using Spearman's correlation coefficient. To assess the risk, the relative risk (RR) was determined. The strength of association between NLR and PSCI was assessed using odds ratio (OR). The significance level of the data was $\alpha=0.05$.

The scientific research was approved by the Bioethics Committee of the NJSC "Medical University of Karaganda" (protocol №8 of 10.11.20). The study was conducted with the voluntary consent of the participants and the legal representative with the receipt of written informed consent.

**Results and discussion**

The groups were matched by sex and age (p> 0.05). In the main and control groups, the average age was 55.1897 and 55.193 years, the proportion of men was 46.55% (95% CI: 33.45-59.65) and 45.61% (95% CI: 32.42-58.81), respectively (Table 1).

**Table 1. Characteristics of patients in the test groups**

| Indicator | Main group n=58 | Control group n=57 | p- value |
|---|---|---|---|
| Age, Me, (Q25; Q75) | 56.5 (49; 63) | 57 (48; 62) | 0.984 |
| Male, % | 46.55 | 45.61 | 0.920 |
| Left hemisphere,% | 48.28 | 57.89 | 0.301 |
| ICH localization: | | | |
| Lobar,% | 1.72 | 12.28 | **0.026** |
| Medial,% | 1.72 | 3.51 | 0.548 |
| Lateral,% | 37.93 | 45.61 | 0.404 |
| Mixed,% | 58.62 | 38.60 | **0.032** |
| Hematoma volume ($ml^3$), Me,(Q25; Q75) | 16.4 (9.5; 30) | 5 (3.5; 8) | **<0.001** |
| NIHSS score (points), Me, (Q25; Q75) | 14.5 (13; 16) | 8 (5; 11) | **<0.001** |
| Laboratory indicators: | | | |
| The absolute number of neutrophils ($x10^9$/l), Me, (Q25; Q75) | 6.6 (4.3; 9.5) | 4.85 (3.4; 7) | **0.014** |
| Absolute lymphocyte count ($x10^9$/l), Me, (Q25; Q75) | 1.4 (1.1;1.9) | 1.7 (1.38; 2.4) | **0.009** |
| NLR, Me, (Q25; Q75) | 4.35 (2.59; 7.15) | 2.67 (1.76; 3.73) | 1 |
| NLR>3,53, % | 62.07 | 33.33 | **0.002** |
| Cognitive status assessment: | | | |
| MoCA (points), Me, (Q25; Q75) | 15 (14; 16) | 26 (26; 27) | **<0.001** |
| MMSE (points), Me,(Q25; Q75) | 16 (15; 17) | 28 (28; 28) | **<0.001** |
| GDR: | | | |
| Stage 1, % | - | 100 | **<0.001** |
| Stages 2-3, % | 32.76 | - | **<0.001** |
| Stages 4-7, % | 67.24 | - | **<0.001** |

According to Spearman's correlation analysis, the level of cognitive impairment on the MoCA, MMSE, and GDR scales strongly positively correlated with the NIHSS score, moderately positively correlated with the volume of the hematoma, and a weak direct relationship with the localization of the hematoma was found. Consequently, cognitive dysfunction is associated with stroke severity and damage to the critical site of stroke [31,32]. In addition, MMSE and GDR had a weak positive association with ICH treatment. No correlation was found between MoCA, MMSE, GDR and age, gender, affected hemisphere (p> 0.05, Table 1).

In the main group, the NLR ranged from 1.2378-19.2, in 62.07% (95% CI: 49.33-74.81) the NLR was more than 3.53. In the control group, NLR was in the range of 0.2881-21, NLR over 3.53 was found in 33.33% (95% CI: 20.85-45.82). When comparing the proportions using the Z-

test, it was revealed that in the acute period of ICH, more patients had cognitive dysfunction with an NLR level> 3.53, in comparison with the control (p = 0.002) (Table 1).

Spearman's correlation analysis revealed that NLR had a weak direct relationship with the NIHSS score at admission, localization, hematoma volume (p <0.05, Table 2). There was no statistically significant correlation between NLR and the affected hemisphere (p> 0.05, Table 2). According to Jie Qin et al. NLR was moderately positively correlated with hematoma volume assessed by NIHSS, but was not associated with ICH localization [33]. These results indicate that neutrophils and lymphocytes associated with stroke severity are involved in brain tissue damage in ICH.

**Table 2. Spearman's correlation analysis between NLR and stroke severity**

| **Indicator** | **Spearman** | **t(N-2)** | **p-level** |
|---|---|---|---|
| Affected hemisphere | -0.16638 | -1.7937 | 0.075537 |
| Localization of hematoma | 0.26214 | 2.8875 | **0.004654** |
| Hematoma volume | 0.28928 | 3.2125 | **0.001715** |
| NIHSS score | 0.25251 | 2.7741 | **0.006478** |

As a result of the risk assessment, an increase in NLR> 3.53 increases the incidence of PSCI by 1.78 times (RR-1.785, 95% CI: 1.216-2.621). An increase in NLR> 3.53 for the first time 24 hours of stroke is associated with a high chance of developing post-stroke cognitive dysfunction at 6 months after ICH (OR - 3.273, 95% CI: 1.524-7.030). This is due to the fact that in acute ICH, intraparenchymal blood and local aseptic necrosis trigger inflammation [34]. Through the highly permeable blood-brain barrier, neutrophils infiltrate the hematoma area from 30 minutes to several hours, reaching a peak of 1–3 days [35]. Unlike neutrophils, T-lymphocytes are recruited later, approximately 3-4 days after hemorrhagic stroke [36]. Despite the fact that neutrophils are involved in recovery, they also have a damaging effect [37,38]. Localized brain damage leads to neuronal death and loss of synapses, contributing to the development of cognitive dysfunction [39].

There are several limitations to this study. First, the study was retrospective with a limited number of samples, which led to hematomas varying in volume and location. Second, due to the complex nature of ICH, it was not possible to exclude possible factors influencing the patient's baseline cognitive level. Nevertheless, our results will serve to improve the prediction of post-stroke cognitive impairment in patients with intracerebral hemorrhage for early cognitive rehabilitation.

**Conclusion.** Based on the results obtained, an increase in NLR> 3.53 for the first time 24 hours ICH is associated with the development of post-stroke cognitive impairment at 6 months after stroke. Thus, NLR can be used as a marker for the first time 24 hours of spontaneous intracerebral hemorrhage for early prediction of the development of post-stroke cognitive impairment.

## References

1. Rist P. M., Chalmers J., Arima H., Anderson C., Macmahon S., Woodward M., Kurth T., Tzourio C. Baseline cognitive function, recurrent stroke, and risk of dementia in patients with stroke. Stroke. 2013; 44(7), 1790–1795. https://doi.org/10.1161/STROKEAHA.111.680728

2. Park JH, Kim BJ, Bae HJ, Lee J, Lee J, Han MK, et al. Impact of post-stroke cognitive impairment with no dementia on health-related quality of life. J Stroke 2013;15:49-56.

3. World Health Organization, 2020 https://www.who.int/ru/news-room/fact-sheets/detail/dementia

4. Gorelick P.B. Role of inflammation in cognitive impairment: results of observational epidemiological studies and clinical trials. Annals of the New York Academy of Sciences. 2010; 1207: 155-162. https://doi.org/10.1111/j.1749-6632.2010.05726.x

5. Gary A. R. Extracellular matrix inflammation in vascular cognitive impairment and dementia. Clin Sci (Lond) 1 March 2017; 131 (6): 425–437. https://doi.org/10.1042/cs20160604

6. Alam A, Hana Z, Jin Z, Suen K.C. Surgery, neuroinflammation and cognitive impairment. EBioMedicine. 2018;37:547–556. https://doi.org/10.1016/j.ebiom.2018.10.021

7. Van Harten, A. E., Scheeren, T. W., Absalom A. R. A review of postoperative cognitive dysfunction and neuroinflammation associated with cardiac surgery and anaesthesia. Anaesthesia. 2012; 67: 280-293. https://doi.org/10.1111/j.1365-2044.2011.07008.x

8. Narasimhalu K, Lee J, Leong YL, Ma L, De Silva DA, Wong MC, Chang HM, Chen C. Inflammatory markers and their association with post stroke cognitive decline. Int J Stroke. 2015 Jun;10(4):513-8.https://doi.org/10.1111/ijs.12001

9. Rothenburg LS, Herrmann N, Swardfager W, Black SE, Tennen G, Kiss A, Gladstone DJ, Ween J, Snaiderman A, Lanctôt KL. The relationship between inflammatory markers and post stroke cognitive impairment. J Geriatr Psychiatry Neurol. 2010;23(3):199-205.https://doi.org/10.1177/0891988710373598

10. Kliper E, Bashat DB, Bornstein NM, Shenhar-Tsarfaty S, Hallevi H, Auriel E, Shopin L, Bloch S, Berliner S, Giladi N, Goldbourt U, Shapira I, Korczyn AD, Assayag EB. Cognitive decline after stroke: relation to inflammatory biomarkers and hippocampal volume. *Stroke.* 2013 May;44(5):1433-5. https://doi.org/10.1161/strokeaha.111.000536

11. Alexandrova ML, Danovska MP. Cognitive impairment one year after ischemic stroke: predictorsand dynamics of significant determinants. *Turk J Med Sci.* 2016 Nov 17;46(5):1366-1373. https://doi.org/10.3906/sag-1403-29

12. Kulesh A, Drobakha V, Kuklina E, Nekrasova I, Shestakov V. Cytokine Response, Tract-Specific Fractional Anisotropy, and Brain Morphometry in Post-Stroke Cognitive Impairment. J Stroke Cerebrovasc Dis. 2018 Jul;27(7):1752-1759. https://doi.org/10.18019/1028-4427-2019-25-3-413-423

13. Zhang J, Ren Q, Song Y, He M, Zeng Y, Liu Z, Xu J. Prognostic role of neutrophil-lymphocyte ratio in patients with acute ischemic stroke. Medicine (Baltimore). 2017 Nov;96(45):e8624. https://doi.org/10.1097/MD.0000000000008624

14. Zhang J, Cai L, Song Y, Shan B, He M, Ren Q, Chen C, Liu Z, Zeng Y, Xu J. Prognostic role of neutrophil lymphocyte ratio in patients with spontaneous intracerebral hemorrhage. Oncotarget. 2017 Sep 8;8(44):77752-77760. https://doi.org/10.18632/oncotarget.20776

15. Ye Z, Ai X, Fang F, Hu X, Faramand A, You C. The use of neutrophil to lymphocyte ratio as a predictor for clinical outcomes in spontaneous intracerebral hemorrhage. Oncotarget. 2017 Aug 10;8(52):90380-90389. https://doi.org/10.18632/oncotarget.20120

16. Brooks SD, Spears C, Cummings C, VanGilder RL, Stinehart KR, Gutmann L, Domico J, Culp S, Carpenter J, Rai A, Barr TL. Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. J Neurointerv Surg. 2014 Oct;6(8):578-83. https://doi.org/10.1136/neurintsurg-2013-010780

17. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M. Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review. Transl Stroke Res. 2019 Apr;10(2):137-145. https://doi.org/10.1007/s12975-018-0649-4

18. Tao C, Hu X, Wang J, Ma J, Li H, You C. Admission neutrophil count and neutrophil to lymphocyte ratio predict 90-day outcome in intracerebral hemorrhage. Biomark Med. 2017 Jan;11(1):33-42. https://doi.org/10.2217/bmm-2016-0187

19. Yu S, Arima H, Bertmar C, Clarke S, Herkes G, Krause M. Neutrophil to lymphocyte ratio and early clinical outcomes in patients with acute ischemic stroke. J Neurol Sci. 2018 Apr 15;387:115-118. https://doi.org/10.1016/j.jns.2018.02.002

20. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Neutrophil-to-Lymphocyte Ratio Predicts the Outcome of Acute Intracerebral Hemorrhage. Stroke. 2016 Jun;47(6):1654-7. https://doi.org/10.1161/STROKEAHA.116.013627

21. Wang F, Hu S, Ding Y, Ju X, Wang L, Lu Q, Wu X. Neutrophil-to-Lymphocyte Ratio and 30-Day Mortality in Patients with Acute Intracerebral Hemorrhage. J Stroke Cerebrovasc Dis. 2016 Jan;25(1):182-7. https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.09.013

22. Altun, I., F. Akın and M. Biteker. The Role of Epicardial Fat Thickness and Neutrophil-to-Lymphocyte Ratio Are Needed to Be Studied in Real-World Stroke Patients. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association 24 5 (2015): 1100. https://doi.org/10.1016/j.jstrokecerebrovasdis.2014.10.023

23. Nardi K, Milia P, Eusebi P, Paciaroni M, Caso V, Agnelli G. Admission leukocytosis in acute cerebral ischemia: influence on early outcome. J Stroke Cerebrovasc Dis. 2012 Nov;21(8):819-24. https://doi.org/10.1016/j.jstrokecerebrovasdis.2011.04.015

24. Wafeek M Elsheik, Ibrahim E Alahmar, Gelan M M. Ali, Eman S Matar Neutrophils-to-lymphocyte ratio in acute ischemic stroke patients Menoufia Medical Journal 2020 Volume : 33 Issue : 3: 1067-1071 https://doi.org/10.4103/mmj.mmj_371_18

25. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, Weintraub D. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009 Nov 24;73(21):1738-45. https://doi.org/10.1212/WNL.0b013e3181c34b47

26. Mitchell AJ. A meta-analysis of the accuracy of the mini-mental state examination in the detection of dementia and mild cognitive impairment. J Psychiatr Res. 2009 Jan;43(4):411-31. https://doi.org/10.1016/j.jpsychires.2008.04.014

27. Hardcastle, Cheshire & Taylor, Brad & Price, Catherine. (2019). Global Deterioration Scale. https://doi.org/10.1007/978-3-319-69892-2_697-1

28. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Res Notes. 2017 Jan 3;10(1):12. https://doi.org/10.1186/s13104-016-2335-5

29. Haley MD, Gregson BA, Mould WA, Hanley DF, Mendelow AD. Retrospective Methods Analysis of Semiautomated Intracerebral Hemorrhage Volume Quantification From a Selection of the STICH II Cohort (Early Surgery Versus Initial Conservative Treatment in Patients With Spontaneous Supratentorial Lobar Intracerebral Haematomas). Stroke. 2018 Feb;49(2):325-332. https://doi.org/10.1161/STROKEAHA.117.016677

30. Clinical protocol № 23 of the Ministry of Health of the Republic of Kazakhstan "Intracerebral hemorrhage" dated May 25, 2017

31. Kandiah N, Wiryasaputra L, Narasimhalu K, Karandikar A, Marmin M, Chua EV, Sitoh YY. Frontal subcortical ischemia is crucial for post stroke cognitive impairment. J Neurol Sci. 2011 Oct 15;309(1-2):92-5. https://doi.org/110.1016/j.jns.2011.07.013

32. Stephens S, Kenny RA, Rowan E, Allan L, Kalaria RN, Bradbury M, Ballard CG. Neuropsychological characteristics of mild vascular cognitive impairment and dementia after stroke. Int J Geriatr Psychiatry. 2004 Nov;19(11):1053-7. https://doi.org/10.1002/gps.1209

33. Qin J, Li Z, Gong G, Li H, Chen L, Song B, Liu X, Shi C, Yang J, Yang T, Xu Y. Early increased neutrophil-to-lymphocyte ratio is associated with poor 3-month outcomes in spontaneous intracerebral hemorrhage. PLoS One. 2019 Feb 7;14(2):e0211833. https://doi.org/10.1371/journal.pone.0211833

34. Zhou Y, Wang Y, Wang J, Anne Stetler R, Yang QW. Inflammation in intracerebral hemorrhage: from mechanisms to clinical translation. Prog Neurobiol. 2014 Apr;115:25-44. https://doi.org/10.1016/j.pneurobio.2013.11.003

35. Jickling GC, Liu D, Ander BP, Stamova B, Zhan X, Sharp FR. Targeting neutrophils in ischemic stroke: translational insights from experimental studies. J Cereb Blood Flow Metab. 2015 Jun;35(6):888-901. https://doi.org/10.1038/jcbfm.2015.45

36. Loftspring MC, McDole J, Lu A, Clark JF, Johnson AJ. Intracerebral hemorrhage leads to infiltration of several leukocyte populations with concomitant pathophysiological changes. J Cereb Blood Flow Metab. 2009 Jan;29(1):137-43. https://doi.org/10.1038/jcbfm.2008.114

37. Hermann DM, Gunzer M. Contribution of polymorphonuclear neutrophils in the blood periphery to ischemic brain injury. Neurol Neuroimmunol Neuroinflamm. 2019;6:e570. https://doi.org/10.1212/nxi.0000000000000570

38. Perez-de-Puig I, Miró-Mur F, Ferrer-Ferrer M, Gelpi E, Pedragosa J, Justicia C, Urra X, Chamorro A, Planas AM. Neutrophil recruitment to the brain in mouse and human ischemic stroke. Acta Neuropathol. 2015;129:239–57. https://doi.org/10.1007/s00401-014-1381-0

39. Stanimirovic DB, Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence? J Cereb Blood Flow Metab. 2012 Jul;32(7):1207-21. https://doi.org/10.1038/jcbfm.2012.25