e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 514-520

Original Research Article

A Retrospective Study to Investigate the Association between NPAR and Outcomes of Stroke

Rajeev Kumar[1], S.K. Astik[2], Subham Bhaskar[3], Narendra Kumar[4], Ajay Kumar Sinha[5]

[1]Assistant Professor, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India

[2]Associate Professor, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India

[3]Senior Resident, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India

[4]Assistant Professor, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India

[5]Associate Professor and HOD, Department of Medicine, Nalanda Medical College and Hospital, Patna, Bihar, India

Received: 25-12-2022 / Revised: 20-01-2023 / Accepted: 08-02-2023

Corresponding author: Dr. Ajay Kumar Sinha

Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to investigate the association between NPAR and outcomes of stroke.

Methods: The present study was conducted at Department of General Medicine Nalanda Medical College and Hospital, Patna, Bihar, India from two years and total 1000 participants were included in the study. The vital signs, medications, demographic information and other essential data of the patients admitted to intensive care unit were collected.

Results: The subjects were categorized into 3 groups based on NPAR values: group A: NPAR < 20.5 (330); group B: NPAR 20.5–25.0 (330); and group C: NPAR >25.0 (340). Compared with group A, participants in groups with higher NPAR (>25.0) showed lower SBP, bicarbonate, MBP, hematocrit, hemoglobin, and DBP, and had higher levels of creatinine, BUN, potassium, chloride, heart rate, respiratory rate, PT, APTT, INR, and increased the proportion of CHF, renal disease, pneumonia, respiratory failure, and mortality. In addition, tertiles were not significantly related to age and gender in our study population. For 30- day all-cause mortality, in an unadjusted model, the HR (95% CIs) in group B and C were 1.17 (0.85, 1.63) and 1.55 (1.13, 2.11), respectively, in comparison with group A. This association was significant after adjusting for age, gender, ethnicity, sodium, chloride, CHF, CAD, AF, renal disease, liver disease, COPD (HR= 1.45, 95% CI: 1.05, 2.00). The trend was also statistically significant (P = 0.0196). For 90-day all-cause mortality and 365- day all-cause mortality, a similar relationship was also observed.

Conclusion: A strong correlation was present between increased levels of the novel biomarker NPAR and increased risk of mortality in stroke patients.

Keywords: Neutrophil-Albumin Ratio, Mortality, Stroke, Biomarker.

Introduction

Stroke is reported to be the leading lethal disease in People's Republic of China, which is also the principal cause of disability among adults. [1,2] Ischemic stroke accounts for 80% of all kinds of stroke. [3] Stroke may affect the first stroke patients again at a specific time point after rehabilitation in hospital. [4] Among patients in intensive care unit, critical stroke is very common. [5] However, the treatment outcomes are not satisfied for stroke patients, which brings their family and society great burden and economic loss. [3] Therefore, it is urgent to find a predicting biomarker of the prognosis of patients who are in an early stage of stroke. The pathogenesis of stroke is closely related to inflammation, and the pathological processes involved in the development of acute ischemic stroke include endothelial activation, blood-brain barrier impairment, secretion of multiple inflammatory mediators, oxidants, and cytokines, and infiltration of platelet and leukocytes. [6,7]

NPAR (neutrophil percentage-to-albumin ratio) was a newly reported inflammatory biomarker. [8] The prognostic and predictive functions of NPAR were found in various diseases, such as cardiovascular disease. [9] It was reported that reduced Albumin levels were closely correlated with worse outcomes of patients who had stroke. [10] Neutrophils play crucial roles in the innate cellular immune system. [11] Previous studies suggested that early higher neutrophil counts were correlated with increased stroke severity. [12]

The neutrophil percentage-to-albumin ratio (NPAR) is an emerging marker of inflammation and oxidative stress. The NPAR has been reported to have prognostic significance in patients with cancer, spinal cord injury, acute kidney injury, acute myocardial infarction, and cardiogenic shock. [13,14 Neutrophils play crucial roles in the innate cellular immune system. Previous studies suggested that early higher neutrophil counts correlated with increased sepsis severity [15,16], and neutrophil percentage was predictive of bloodstream infection. [17] Albumin is a mediumsized molecule that is the most abundant protein in human plasma. For a variety of physiological mechanisms, albumin is indispensable. It has a variety of functions, including serving as a major buffer, extracellular antioxidant, immunomodulator, antidote and transporter in plasma. [18] According to the previous studies, admission neutrophil percentage-to-albumin ratio (NPAR) was an independent predictor of in-hospital mortality in patients with acute ST-segment elevation myocardial infarction (STEMI). [19] In the another study, in critically ill patients with coronary artery disease (CAD), the higher NPAR level was closely correlated with the higher rate of 30-day, 90-day, and 365-day all-cause death. [9]

The aim of the present study was to investigate the association between NPAR and outcomes of stroke.

Materials and Methods

The present study was conducted at Department of General medicine, Nalanda Medical College and Hospital, Patna, Bihar, India from two years and total 1000 participants were included in the study. The vital signs, medications, demographic information and other essential data of the patients admitted to intensive care unit were collected. All data accessed complies with relevant data protection and privacy regulations.

Population Selection Criteria

We enrolled stroke patients (over 16 years) first admitted to the hospital with hospital stay over one day. And the patients were excluded if they stayed in ICU less than 48 hours, or had no data on the NPAR within the first 24 hours of admission.

Study Variables and Outcomes

The data upon admission were recorded, including vital signs, laboratory parameters, demographics, and comorbidities, etc. Comorbidities included malignancy, AF (atrial fibrillation), liver disease, pneumonia, renal disease, respiratory failure, CAD (coronary artery disease), and CHF (congestive heart failure). Laboratory parameters were WBC (white blood cells), BUN (blood urea nitrogen), APTT (activated partial thromboplastin time), PT (prothrombin time), potassium, anion gap, hemoglobin, creatinine, glucose, lactate, chloride, carbonate, sodium, platelet, hematocrit, albumin, bilirubin, INR (international normalized ratio), and the percentage of neutrophil were taken. SAPSII (simplified acute physiology scores II) and APSIII (acute physiology score III) scores were also calculated. Furthermore, MBP (mean blood pressure), heart rate, DBP (diastolic blood pressure),

tory rate, SBP (systolic blood pressure), SPO2, temperature, ethnicity, gender, and age were also recorded.

The primary outcome was 30-day mortality rate in our study, and the secondary outcomes included 90-day and 1-year mortality rates. The patients were followed up for at least one year since admission. The date of death was based on Social Security Death Index records.

Statistical Analysis

R (Version 3.6.1) was used in all the analyses. P values were two-sided. P values <0.05 was considered statistically significant.

Results

Table 1: Characteristics of the Study Patients According to Neutrophil Percentage-to-Albumin Ratios

Characteristics	Neutrophil Percentage-to-Albumin Ratios			P Value
	<20.5 (n = 330)	≥20.5, <25.0 (n = 330)	≥25.0 (n = 340)	
Age, years	66.5 ± 14.8	67.2 ± 15.0	67.0 ± 14.2	0.840
Gender				
Male	155	150	173	0.850
Female	175	180	157	
NPAR	16.7 ± 4.2	22.6 ± 1.3	31.3 ± 7.1	<0.001
SBP, mmHg	130.5 ± 17.8	129.4 ± 17.5	121.4 ± 17.7	<0.001
DBP, mmHg	64.5 ± 11.1	64.8 ± 11.7	61.5 ± 11.0	<0.001
MBP, mmHg	83.5 ± 11.4	83.7 ± 12.0	79.3 ± 11.3	<0.001
Heart rate, beats/minute	80.4 ± 16.2	81.8 ± 14.5	87.6 ± 17.4	<0.001
Respiratory rate, beats/minute	18.4 ± 3.5	18.4 ± 3.4	20.3 ± 4.7	<0.001
Temperature, °C	36.9 ± 0.6	37.0 ± 0.6	36.9 ± 0.8	0.840
SPO2, %	97.5 ± 1.9	97.8 ± 2.1	97.5 ± 2.6	0.307
Co-morbidities				
Congestive heart failure	28	25	50	0.001
Atrial fibrillation	80	90	100	0.100
Renal disease	28	35	60	<0.001
Pneumonia	75	85	125	<0.001
Respiratory failure	80	100	180	<0.001
Laboratory parameters	66.9 ± 18.9	83.3 ± 7.5	85.4 ± 7.2	<0.001
Neutrophil percentage, %				
Albumin, g/dl	4.0 ± 0.6	3.7 ± 0.4	2.8 ± 0.5	<0.001

Bicarbonate, mg/dl	25.8 ± 3.7	25.3 ± 3.5	24.3 ± 4.8	<0.001
Creatinine, mEq/l	1.4 ± 2.5	1.5 ± 1.8	2.0 ± 1.7	<0.001
Chloride, mmol/l	106.6 ± 6.1	107.2 ± 6.7	108.8 ± 7.4	<0.001
Hemoglobin, g/dl	13.0 ± 2.1	13.0 ± 1.9	11.7 ± 2.2	<0.001
Platelet, 109 /l	246.3 ± 112.6	258.6 ± 105.3	250.6 ± 144.0	0.446
WBC, 109 /l	13.9 ± 21.5	14.0 ± 6.1	15.9 ± 8.9	0.109
INR	1.5 ± 1.2	1.5 ± 1.4	2.0 ± 1.9	<0.001
BUN, mg/dl	24.1 ± 19.1	24.4 ± 16.7	38.5 ± 29.3	<0.001
APTT, second	35.4 ± 21.2	37.1 ± 26.4	50.2 ± 36.5	<0.001
PT, second	15.9 ± 9.2	15.8 ± 9.1	20.0 ± 14.4	<0.001
30-day mortality, n (%)	70	75	100	0.008
90-day mortality, n (%)	78	90	125	<0.001
365-day mortality, n (%)	95	105	150	<0.001

The subjects were categorized into 3 groups based on NPAR values: group A: NPAR < 20.5 (330); group B: NPAR 20.5–25.0 (330); and group C: NPAR >25.0 (340). Compared with group A, participants in groups with higher NPAR (>25.0) showed lower SBP, bicarbonate, MBP, hematocrit, hemoglobin, and DBP, and had higher levels of creatinine, BUN, potassium, chloride, heart rate, respiratory rate, PT, APTT, INR, and increased the proportion of CHF, renal disease, pneumonia, respiratory failure, and mortality. In addition, tertiles were not significantly related to age and gender in our study population.

Table 2: HRs (95% CIs) for All-Cause Mortality Across Groups of Neutrophil Percentage-to-Albumin Ratios

NAR	Non-Adjusted		Model I		Model II	
	HR (95% CIs)	P value	HR (95% CIs)	P value	HR (95% CIs)	P value
30-day all-cause mortality						
<20.5	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥20.5, <25.0	1.17 (0.85, 1.63)	0.3389	1.11 (0.80, 1.55)	0.5175	1.10 (0.79, 1.54)	0.5670
≥25.0	1.55 (1.13, 2.11)	0.0058	1.52 (1.11, 2.07)	0.0083	1.45 (1.05, 2.00)	0.0254
P trend	0.0044		0.0054		0.0196	
90-day all-cause mortality						
<20.5	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥20.5, <25.0	1.21 (0.90, 1.64)	0.2102	1.16 (0.86, 1.57)	0.3421	1.15 (0.85, 1.56)	0.3719
≥25.0	1.71 (1.29, 2.26)	0.0002	1.67 (1.26, 2.22)	0.0004	1.60 (1.19, 2.15)	0.0020
P trend	0.0001		0.0002		0.0013	
365-day all-cause mortality						
<20.5	1.0 (ref)		1.0 (ref)		1.0 (ref)	
≥20.5, <25.0	1.14 (0.87, 1.50)	0.3539	1.08 (0.82, 1.42)	0.5774	1.08 (0.81, 1.42)	0.6105
≥25.0	1.63 (1.26, 2.11)	0.0002	1.60 (1.24, 2.07)	0.0003	1.50 (1.15, 1.97)	0.0030
P trend	<0.0001		0.0001		0.0017	

For 30- day all-cause mortality, in an unadjusted model, the HR (95% CIs) in group B and C were 1.17 (0.85, 1.63) and 1.55 (1.13, 2.11), respectively, in comparison with group A. This association was significant after adjusting for age, gender, ethnicity, sodium, chloride, CHF, CAD, AF, renal disease, liver disease, COPD (HR= 1.45, 95% CI: 1.05, 2.00). The trend was also statistically significant (P = 0.0196). For 90-day all-cause mortality and 365- day all-cause mortality, a similar relationship was also observed.

Discussion

We found that higher NPAR was closely associated with increased all-cause mortality of stroke patients in the short or long term. Compared with the complex scoring systems, NPAR is easy to access and can help clinicians quickly make clinical strategies in time.

Strokes occur due to cerebral vascular occlusion or hemorrhage resulting in deprivation of oxygen and nutrients, causing a local inflammatory immune response. [20] This results in alteration of the systemic inflammatory response via the sympathetic pathway and the hypothalamus-pituitary-adrenal axis (poststroke immunosuppression) resulting in neutrophil demargina tion and stimulation of growth factors. [21,22] A positive correlation was observed within acute ischemic stroke patients, between total WBC-neutrophil counts increasing 3 days of symptom onset severity and infarct volume. [23,24]

It has been suggested by prior studies, that the relationship between hypoproteinemia and stroke-related mortality, heart attack and fractures of the hip illustrate poorer disease prognosis with lower albumin values. [25,26] According to previous studies, albumin may exert neuroprotective function via its anti- inflammatory activity, antioxidant characteristics, inhibiting endothelial apoptosis, and regulating microvascular permeability. [27-29] Another theory is that low albumin in time of acute stroke could illustrate the role albumin's concentration plays during inflammation states as a negative acute phase reactant. [30] Negative regulation of the albumin synthesis may be controlled via interleukin (IL-6 and tumor necrosis factor, which are seen in increased concentrations during states of acute inflammation, such as acute stroke. [31] In this serum albumin repression a possible detrimental effect may interfere with albumin's antioxidative and endothelial effects. [32] Based on our results, the novel biomarker that is NPAR can be used to significantly predict stroke prognosis via neutrophil percentage and albumin levels. [33]

Our study had some limitations. First, selection bias existed since this was a single-center retrospective study. Second, NPAR was only recorded when patients were admitted into the ICU and subsequent changes were not assessed. Third, other known and unknown factors still remain although we have made the best effort to control bias.

Conclusion

We demonstrated that higher NPAR was closely associated with increased all-cause mortality in stroke patients. Nevertheless, these findings need to be confirmed by large prospective multicenter studies.

References

1. Liu L, Wang D, Wong KS, Wang Y. Stroke and stroke care in China: huge burden, significant workload, and a national priority. Stroke. 2011;42(12): 3651–3654.
2. Zhou M, Wang H, Zeng X, et al. Mortality, morbidity, and risk factors in China and its provinces, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2019;394 (10204):1145–1158.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute

ischemic stroke: 2019 update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: a Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12): e344 –e418.
4. Wang Y, Zhao X, Jiang Y, et al. Prevalence, knowledge, and treatment of transient ischemic attacks in China. Neurology. 2015;84 (23):2354–2361.
5. McDermott M, Jacobs T, Morgenstern L. Critical care in acute ischemic stroke. Handb Clin Neurol. 2017;140: 153–176.
6. Anrather J, Iadecola C. Inflammation and stroke: an overview. Neurotherap - eutics. 2016;13(4):661–670.
7. Chamorro Á, Dirnagl U, Urra X, Planas AM. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol. 2016;15 (8):869–881.
8. Gong Y, Li D, Cheng B, Ying B, Wang B. Increased neutrophil percentage-to-albumin ratio is associated with all-cause mortality in patients with severe sepsis or septic shock. Epidemiol Infect. 2020;148: e8 7 .
9. Sun T, Shen H, Guo Q, Yang J, Zhai G, Zhang J, Zhang B, Ding Y, Cai C, Zhou Y. Association between neutrophil percentage-to-albumin ratio and all-cause mortality in critically ill patients with coronary artery disease. BioMed Research International. 2020 Aug 31;2020.
10. Famakin B, Weiss P, Hertzberg V, et al. Hypoalbuminemia predicts acute stroke mortality: Paul Coverdell Georgia Stroke Registry. J Stroke Cerebrovasc Dis. 2010;19(1):17–22.
11. Liew PX, Kubes P. The Neutrophil's Role during health and disease. Physiol Rev. 2019;99(2):1223–1248.
12. Kang L, Yu H, Yang X, et al. Neutrophil extracellular traps released by neutrophils impair revascularization and vascular remodeling after stroke. Nat Commun. 2020;11(1):2488.
13. He HM, Zhang SC, He C, You ZB, Luo MQ, Lin MQ, Lin XQ, Zhang LW, Lin KY, Guo YS. Association between neutrophil percentage-to-albumin ratio and contrast-associated acute kidney injury in patients without chronic kidney disease undergoing percutaneous coronary intervention. Journal of Cardiology. 2022 Feb 1;79(2):257-64.
14. Wang C, Yu X, Wang T, Ding M, Ran L, Wang L, Sun X, Wei Q, He C. Association between neutrophil percentage-to-albumin ratio and pneumonia in patients with traumatic spinal cord injury. Spinal Cord. 2022 Aug 9:1-5.
15. Shen XF, Cao K, Jiang JP, Guan WX, Du JF. Neutrophil dysregulation during sepsis: an overview and update. Journal of cellular and molecular medicine. 2017 Sep;21(9):1687-97.
16. Park I, Kim M, Choe K, Song E, Seo H, Hwang Y, Ahn J, Lee SH, Lee JH, Jo YH, Kim K. Neutrophils disturb pulmonary microcirculation in sepsis-induced acute lung injury. European Respiratory Journal. 2019 Mar 1;53(3).
17. Pan YP, Fang YP, Xu YH, Wang ZX, Shen JL. The Diagnostic Value of Procalcitonin Versus Other Biomarkers in Prediction of Bloodstream Infection. Clinical laboratory. 2017 Feb 1;63(2): 277-85.
18. Artigas A, Wernerman J, Arroyo V, Vincent JL, Levy M. Role of albumin in diseases associated with severe systemic inflammation: pathophysiologic and clinical evidence in sepsis and in decompensated cirrhosis. Journal of Critical Care. 2016 Jun 1; 33:62-70.
19. Cui H, Ding X, Li W, Chen H, Li H. The neutrophil percentage to albumin ratio as a new predictor of in-hospital mortality in patients with ST-segment elevation myocardial infarction.

Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2019; 25:7845.
20. Shim R, Wong CH. Ischemia, immunosuppression and infection–tackling the predicaments of post-stroke complications. Int J Mol Sci. 2016;17(1):64.
21. Hannawi Y, Hannawi B, Rao CP, Suarez JI, Bershad EM. Stroke-associated pneumonia: major advances and obstacles. Cerebrovasc Dis. 2013;35(5):430–443.
22. Prass K, Meisel C, Höflich C, et al. Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulant. J Exp Med. 2003; 198(5):725–736.
23. Westendorp WF, Vermeij JD, Zock E, et al. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomized open-label masked endpoint clinical trial. Lancet. 2015; 385 (9977):1519–1526.
24. Nam KW, Kwon HM, Jeong HY, et al. High neutrophil to lymphocyte ratio is associated with white matter hyperintensity in a healthy population. J Neurol Sci. 2017; 380:128–131.
25. Plakht Y, Gilutz H, Shiyovich A. Decreased admission serum albumin level is an independent predictor of long-term mortality in hospital survivors of acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II) project. Int J Cardiol. 2016; 219:20–24.
26. Pioli G, Barone A, Giusti A, et al. Predictors of mortality after hip fracture: results from 1-year follow-up. Aging Clin Exp Res. 2006;18 (5):381–387.
27. Yildirim T, Okutan O, Akpinar E, Yilmaz A, Isik HS. Neuroprotective effects of high-dose human albumin against traumatic spinal cord injury in rats. Bratisl Lek Listy. 2018;119(2): 86–91.
28. Belayev L, Pinard E, Nallet H, et al. Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. Stroke. 2002;33(4):1077–1084.
29. Belayev L, Liu Y, Zhao W, Busto R, Ginsberg MD. Human albumin therapy of acute ischemic stroke: marked neuroprotective efficacy at moderate doses and with a broad therapeutic window. Stroke. 2001;32(2):553–560.
30. Ebersole JL, Cappelli D. Acute-phase reactants in infections and inflammatory diseases. Periodontol 2000.
31. Ramadori G, Van Damme J, Rieder H, Meyer Zum Büschenfelde KH. Interleukin 6, the third mediator of acute-phase reaction, modulates hepatic protein synthesis in human and mouse. Comparison with interleukin 1 beta and tumor necrosis factor-alpha. Eur J Immunol. 1988;18(8):1259–12 64.
32. Halliwell B. Albumin–an important extracellular antioxidant? Biochem Pharmacol. 1988;37(4):569–571.
33. Tripathy, D. T., Tripathy, A., Dwivedi, D. R., Gautam, D. M., Prusty, D. U., & Nayak, D. C. Prelacteal feeding of neonants & amp; discardation of first breast milk Among recently delivered women of Uttar Pradesh, India. Journal of Medical Research and Health Sciences, 2020;3(5).