Review Article

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Neutrophil Lymphocyte Ratio as a Prognostic Marker in Acute Ischemic Stroke: a Systematic Review and Meta-analysis

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ABSTRACT

Background: Acute ischemic stroke leads to an inflammatory response and the neutrophil-to-lymphocyte ratio is an inflammatory indicator for determining prognosis in acute ischemic stroke. This meta-analysis aims to show evidence that neutrophil-to-lymphocyte can act as an independent and early prognostic marker in cases of acute ischemic stroke.

Methods: Databases of PubMed, and Embase were searched for literature. Relevant data were extracted by SSP and BT from eligible literature. Odds ratios with 95% confidence intervals were pooled and a Forest plot was used to evaluate the prognostic value of neutrophil-to-lymphocyte in acute ischemic stroke. Modified Rankin Scale ≥ 3 was defined as a poor functional outcome. A funnel plot is used to show the symmetric distribution and no publication bias.

Results: According to Joanna Briggs Institute assessment for analytical observational studies, the studies included are of fair to good quality. Eight relevant studies with 3011 patients were included, one with no data on OR. The pooled OR of 6 studies with the poor functional outcome at 3 months was 1.47(P<0.02 95%CI: 1.40-2.31) while one study with the poor functional outcome at discharge was OR=2.49.

Conclusions: In patients with acute ischemic stroke, elevated neutrophil-to-lymphocyte correlates with poorer functional outcome and increased chances of developing symptomatic Intracranial Hemorrhage. Baseline neutrophil-to-lymphocyte can be an inexpensive and easily available biomarker, especially in resource-poor settings, for predicting clinical outcomes in patients with ischemic stroke.

Keywords: Ischemic stroke; lymphocyte; neutrophil; prognosis

INTRODUCTION

Stroke is the second most common cause of mortality and morbidity in terms of disability-adjusted life years (DALY).[1] In the United States, annual burden of stroke is around 800,000 with mortality of around 140,000.[2] Similarly, it has a significant impact on health care economics and overall economy.[2,3] Ischemic strokes account for around 87% of all strokes.[4] The common treatment in Acute ischemic stroke (AIS) are thrombolysis and mechanical thrombectomy.[5, 6] Inflammation plays a major role in development and progression of ischemic stroke.[7, 8] Neutrophils tend to exacerbate ischemic brain injury. Research showed that neutrophilia increases infarct size and volume.[9-13] Decreased lymphocyte count is associated with lesser improvement within the first week and poorer prognosis within next three months.[14] Increased Neutrophil Lymphocyte ratio (NLR) is associated with poorer prognosis and vice-versa.[15,16]

This study aims to show the NLR is an independent and early prognostic marker in AIS.

Methods

International guidelines that were laid down for the study of meta-analysis and systematic review were used.[17,18] Pubmed and Embase, database were searched for relevant studies and literature (Last searched on April 2020). Searches included "Neutrophil" and "Lymphocyte"; with the addition of a "prognostic marker in stroke" and "prognostic marker in acute ischemic stroke". The search strategy can be found in the supplementary file Table 1. We also performed a

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manual search of the reference list of relevant articles and included them in our study. Free full-text articles in the English language were included in our study. Google Scholar was used as a source to find out research article which was added from reference.

The selection of studies was done independently by SSP and BT and overall study data was prepared. Any disagreements were discussed with RL and rectified on consensus. The following inclusion criteria were laid down:

1) The patients were diagnosed as a case of ischemic stroke 2) Hemogram panel was sent after admission. 3) NLR was calculated. 4) Patients were followed-up for inquiry of their functional status. 5) A significant number of patients diagnosed with ischemic stroke were present. All other studies including case series and case reports, review articles, commentaries, letters to the editor, and conference papers were excluded.

SSP and BT were involved in retrieving the data from the eligible studies. The primary data retrieved were odds ratio (OR) with 95% Confidence interval (CI). First author, year of publication, a country in which study was conducted, the total number of patients (male and female), age of patients, hemogram sample time, cut off value of NLR, outcome measures were derived from eligible studies.

Modified Rankin Scale (mRs) ≥ 3 was considered to be a poor functional outcome. Pooled odds ratio and variance (I^2 variance to measure consistency) were calculated from the odds ratio and 95% Confidence Interval. A Forest plot was used to access the prognostic value of NLR in AIS. Pooled OR was considered significant if $P<0.05$. As the studies included in our study were conducted in different years, populations, and countries, significant heterogeneity is present. Thus, the fixed-effects model became implausible. So, a random-effects model with between-study variance was considered to incorporate heterogeneity. Joanna Bricks Institute (JBI) analytical cross-sectional study checklist was used to assess bias in studies included for meta-analysis. A funnel plot was used to study the publication bias. If an inverted funnel-shaped plot from the data set is found, it will make the publication bias less likely. All necessary statistical evaluation and plots (funnel and forest plot) were done with Medcalc Statistical software (Free version) and Comprehensive meta-analysis toolkit- Version 3.

RESULTS

Literature search

In our study, a four-stage study selection process was done, namely, Identification, Eligibility, Screening, and Inclusion. Altogether 518 studies were identified. Manual screening of studies and literature was performed to look for duplicate studies. After the removal of duplicate studies, the remaining 321 research studies were screened. These studies were screened based on contents in the English language, availability of full free text, and exclusion of review studies. Only one of the studies with a language other than English was included as the full text was available and was converted to English language using Google translator. Following the screening, 15 studies were selected for further review, out of which 10 were excluded due to lack of complete data or being non-related. References for the final 5 studies were studied thoroughly. Additional 3 new relevant research studies were included in our study based on our inclusion criteria. Thus, 8 studies were included in our meta-analysis. The study selection process is shown in figure 1.

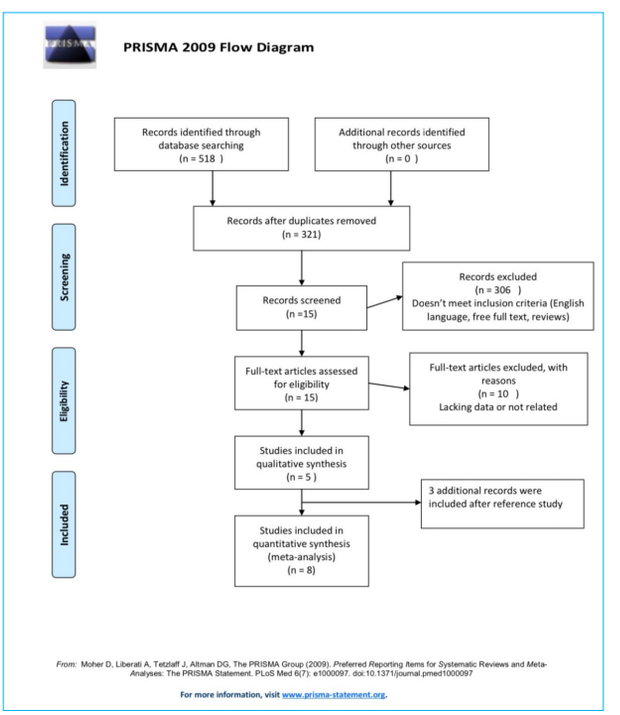

Figure 1. Flowchart of systematic literature search and selection.

FINDINGS OF THE STUDY

Table 1. Key characteristics of the included studies.

Author	Year (AD)	Country	Number (M/F)	Age (yrs)	Sample time	Optimal cut-off NLR	Outcome measure (mRs)	Adjusted odds ratio
Park et al[19]	2010	Korea	371(220/151)	68	At adm	N/R	mRs at 3months	Yes(2.28)
Brooks et al[20]	2013	USA	116(53/63)	67	At adm	>5.9	mRs at 3months and death at 3 month	Yes (6.70)
Celikbilek et al[21]	2013	Turkey	120	66	Within 24 hrs	4.1	mRs at >3 months	N/R
Gokhan et al[22]	2013	Turkey	868(448/420)	68	At adm	3.97 9.92	mRs at discharge death at discharge	Yes(2.49)
Maestrini et al[23]	2015	Lille (France) and Helsinki (Finland)	846(430/416)	71	At adm	N/R N/R 4.80	mRs at discharge mRs at 3months sICH	Yes(3.71)
Lattanzi et al[24]	2016	Italy	177(63/114)	67	At adm	4.58	mRS at 3months	Yes(1.16)
Xue et al [25]	2017	China	280(173/107)	61.8	Within 24 hours	2.39	mRs at 3months	Yes(1.45)
Goyal et al[26]	2018	USA	293(147/122) sICH-21	62	At adm	4.4 3.7 5.4 8.5	mRs≥4 at 3 months mRs(0-3) at 3 month death at 3 months sICH	Yes 1.08 for 3months 1.11 for sICH

At adm: at admission, sICH: symptomatic Intracranial Hemorrhage, mRs: modified Rankin scale, NLR: Neutrophil Lymphocyte ratio, N/R: Not reported.

Our research included studies from 3 continents and 7 different countries. Two studies were from Turkey[21,22] and the United States of America (USA)[20,26] and one from each of Italy,[24] France and Finland,[23] Korea[19] and China.[25] The publication date ranges from 2010[19] to 2018.[26] In the included studies, venous blood was the source for hemogram analysis. Table 1 lists the details of the study characteristics.[19-26] The following legends are tabulated here: the last name of the first author, year of first publication of the study, country or region of publication, number of patients included in their study (with male and female), age of the patient (either mean or median age), time at which hemogram was done, an optimal cut-off measure of NLR, a measure of functional outcome or disability (modified Rankin Scale-mRs) and the adjusted odds ratio. In one of the studies, the odds ratio was derived after the study of the research paper and in two of them, the odds ratio was not reported.

Similarly, values of 95% Confidence Interval used to calculate pooled OR are tabulated in Table 2.

Table 2. Confidence Interval of studies.

Author	Lower limit of 95% CI	Upper limit of 95% CI	Adjusted OR
Park et al,2010	1.13	4.60	2.28
Brooks et al,2013	1.27	35.73	6.73
Maestrini et al,2015	1.01	1.11	1.06
Lattarnzi et al,2016	1.02	1.33	1.16
Xue et al,2017	1.10	1.69	1.36
Goyal et al, 2018	1.01	1.16	1.08

META-ANALYSIS

In our study, we have considered the presence of significant heterogeneity. So, we applied a random-effects model to estimate the pooled odds ratio (OR) and 95% Confidence Intervals (CIs). Five studies used the outcome measure of poor functional outcome at 3 months. The pooled OR of the 6 studies was 1.47(P<0.02, 95%CI: 1.40-2.31). Meta-analysis established a significant

association between NLR and ischemic stroke. Between study heterogeneity was observed with I^2=78.3%, P<0.002. Forest plot of the studies with the functional outcome as mRs at 3 months is demonstrated in figure 2. Similarly, one study used functional outcome as mRs at discharge[21] with OR=2.49, 95% CI, and another used mRs at 3-6 months.[22]

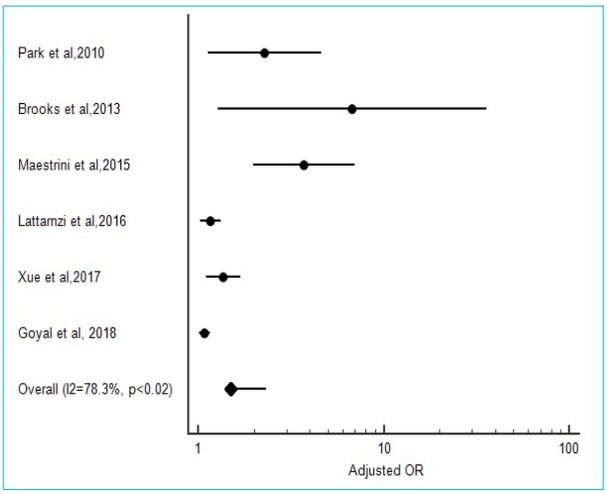

Figure 2. Forest plot of studies with pooled odds ratio with high NLR in patients with poor functional outcome diagnosed as a case of ischemic stroke.

Sensitivity analysis was done by exclusion of one of the studies[24] included in determining pooled odds ratio. After the exclusion, pooled OR was found to be 1.31. Despite the exclusion of one of the studies, we found that increased NLR has a poorer prognosis in stroke patients as compared to patients with normal NLR.

Determination of Bias in included studies

We assessed bias in our study by using the Joanna Briggs Institute (JBI) checklist for observational studies.[27] The checklist used and the assessment performed in our study can be found in supplementary file section Table 2 and Table 3 respectively. The assessment showed that the included studies are of fair to good quality.

Publication bias

The study distribution of funnel plot in figure 3 with Eggers test value of 0.48 shows that the six studies (which accounts for mRs ≥3 as a predictor of the poor functional outcome by three months) included in our study are symmetrically distributed and no significant publication bias exists in our study.

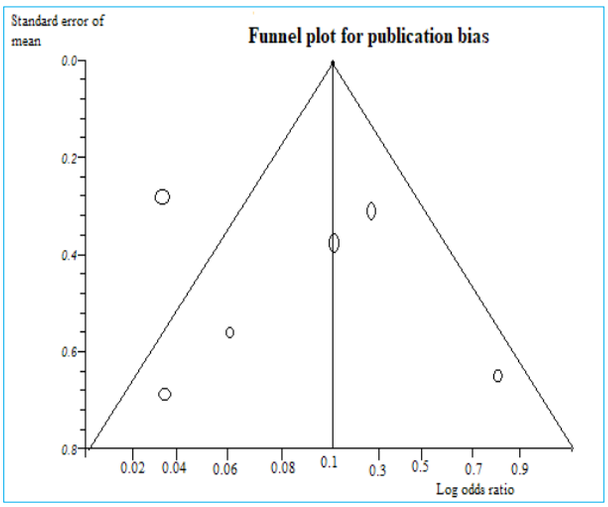

Figure 3. Funnel plot for the detection of publication bias in included studies.

DISCUSSION

There is growing evidence that blood cells, especially neutrophils and lymphocytes, play a vital role in estimating short-term prognosis and functional outcome in patients of acute ischemic stroke. This random effect meta-analysis study was performed to assess the role of NLR in estimating the short-term prognosis of patients suffering from AIS. Our study indicates that NLR can be used to predict the early prognosis of patients suffering from AIS. It has been found that in patients with poor functional outcomes and a higher risk of developing sICH, increased NLR is present. These cells play a pivotal role in developing ischemic stroke and its progression. Several studies have shown an independent association between increased NLR and number of other diseases such as hypertension,[28-31] atherosclerosis,[32] obstructive sleep apnea,[33,34] obesity,[35-37] heart failure,[38-41] renal failure,[42,43] diabetes,[44] pulmonary arterial hypertension,[45,46] treatment variations,[47,48] functional recovery,[49] and immunosuppression.[50,51] Therefore, increased NLR can be considered as one of the significant risk factors of cerebrovascular and cardiovascular diseases. Our meta-analysis study shows that increased NLR is associated with poor functional outcome at 3 months in a patient with acute ischemic stroke. The finding of our study is consistent with most of the included studies and some meta-analyses conducted.

In our study, we used a pooled odds ratio to examine this relationship between prognosis and functional outcome in patients of AIS and NLR. The pooled odds ratio is 1.47. This is consistent with the odds ratio of the included studies. The cutoff limit of NLR being based on mRs>4

at 3 months ranges from 2.39-5.9. These cut-off limits were found to be even higher when we take into account symptomatic intracranial hemorrhage (sICH) and the death of patients. Despite the population included were from different places around the globe, no or little variation was present. As the study was conducted is based on the random effect model, significant between-study heterogeneity was considered to be present. Between study heterogeneity was found to be 78.3%. This heterogeneity might be due to variation in the study population, variation in study methods and variables, time of blood withdrawal, and laboratory analysis of them, variation between NLR cut-offs, publication bias. However, significant publication bias is not present in our study as evidenced by the funnel plot and Eggers test. But, the complete exclusion of this bias can't be done. After assessing the included studies according to the JBI checklist, we found the majority of studies included were of good quality.

There is some strength to our paper. More than 3000 cases of ischemic stroke patients were taken as sample in our study. We performed a comprehensive search to include in our studies. During this process, we translated one Korean paper into English language using Google translator. Our study includes patients from across the globe of both Asian and Caucasian ethnicities. Between study heterogeneity was present which was due to a difference in the study population and methodological differences of included studies. Lastly, no significant publication bias was present. No studies are without limitations. Similarly, our study also has some limitations. Some studies are included in our study that has a smaller sample size and has lower statistical significance. Different possible variations among the included studies like time of sample collection and its laboratory analysis; and the cut-off values of NLR used in respective studies could not be taken into consideration. Being based on our limitations, we must analyze the results with caution. For increasing the statistical significance, studies containing multi-center larger sample studies should be performed.

CONCLUSIONS

This meta-analysis concludes that in patients with AIS, NLR helps to predict clinical outcomes. Elevated NLR correlates with poorer functional outcomes and increasing chances of developing sICH in patients in AIS. Especially, in resource-poor settings, this easily available biomarker may prove beneficial in evaluating risks and outcomes in AIS patients and thus help consider further treatment and framing accurate prognosis. Larger multi-center studies with cohorts of patients with diverse ethnicities should be performed to reproduce a more reliable conclusion.

REFERENCES

1. Johnson CO, Nguyen M, Roth GA, Nichols E, Alam T, Abate D, et al. Global, regional, and national burden of stroke, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Neurology. 2019;18(5):439-58. [Article] [Google Scholar] [Download PDF]
2. Stroke Facts | cdc.gov [Internet]. Cdc.gov. 2020 [cited 30 April 2020]. Available from: https://www.cdc.gov/stroke/facts.htm
3. Zhao L, Dai Q, Chen X, Li S, Shi R, Yu S, et al. Neutrophil-to-lymphocyte ratio predicts length of stay and acute hospital cost in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis. 2016;25(4):739-44. [Article] [Google Scholar] [PubMed]
4. Benjamin E, Blaha M, Chiuve S, Cushman M, Das S, Deo R et al. Heart Disease and Stroke Statistics—2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603. [Article] [PMC]
5. El Tawil S, Muir KW. Thrombolysis and thrombectomy for acute ischaemic stroke. Clinical Medicine. 2017;17(2):161. [Article] [Google Scholar] [PMC]
6. Bansal S, Sangha K, Khatri P. Drug Treatment of Acute Ischemic Stroke. Am J Cardiovasc Drugs. 2013;13(1):57-69. [Google Scholar] [PMC]
7. Jin R, Liu L, Zhang S, Nanda A, Li G. Role of Inflammation and Its Mediators in Acute Ischemic Stroke. Journal of Cardiovascular Translational Research. 2013; 6(5):834-851. Available from: [PMC]
8. Anrather J, Iadecola C. Inflammation, and Stroke: An Overview. Neurotherapeutics. 2016;13(4):661-670. [PMC]
9. Chamorro A, Hallenbeck J. The Harms and Benefits of Inflammatory and Immune Responses in Vascular Disease. Stroke. 2006;37(2):291-3. [PMC]
10. Ruhnau J, Schulze J, Dressel A, Vogelgesang A. Thrombosis, Neuroinflammation, and Post-stroke Infection: The Multifaceted Role of Neutrophils in Stroke. J Immunol Res. 2017; 2017:1-7. [PMC]
11. Buck B, Liebeskind D, Saver J, Bang O, Yun S, Starkman S et al. Early Neutrophilia Is Associated With Volume of Ischemic Tissue in Acute Stroke. Stroke. 2008; 39(2):355-60. [PubMed]
12. Kocaturk O, Besli F, Gungoren F, Kocaturk M, Tanriverdi Z. The relationship among neutrophil to lymphocyte

ratio, stroke territory, and 3-month mortality in patients with acute ischemic stroke. Neurological Sciences. 2018; 40(1):139-46. [PubMed]

13. Wu T, Chien K, Lin H, Hsu H, Su T, Chen M, et al. Total white blood cell count or neutrophil count predict ischemic stroke events among adult Taiwanese: a report from a community-based cohort study. BMC Neurology. 2013;13(1). [PMC]

14. Kim J, Song T, Park J, Lee H, Nam C, Nam H et al. Different prognostic value of white blood cell subtypes in patients with acute cerebral infarction. Atherosclerosis. 2012; 222(2):464-7. [PubMed]

15. 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;387:115-118.[PubMed]

16. Xue J, Huang W, Chen X, Li Q, Cai Z, Yu T et al. Neutrophil-to-Lymphocyte Ratio Is a Prognostic Marker in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2017;26(3):650-7. [PubMed]

17. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews . 2015; 4(1). [PMC]

18. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;349:g7647-g7647. [Article]

19. Park JK, Oh HG, Park TH. Neutrophil to lymphocyte ratio at admission: a prognostic factor in patients with acute ischemic stroke. J Korean Neurol Assoc 2010; 28:172–8. [Article] [Download PDF]

20. Brooks SD, Spears C, Cummings C, VanGilder RL, Stinehart KR, Gutmann L, et al. Admission neutrophil–lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. J Neurointerv Surg. 2014;6(8):578-83. [PMC] [Google Scholar]

21. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to Lymphocyte Ratio Predicts Poor Prognosis in Ischemic Cerebrovascular Disease. J Clin Lab Anal. 2013; 28(1):27-31. [PMC]

22. Gökhan S, Özhasenekler A, Mansur Durgun H, Akil E, Üstündag M. et al. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. Eur Rev Med Pharmacol Sci. 2013;17(5):653-7. [PubMed]

23. Maestrini I, Strbian D, Gautier S, Haapaniemi E, Moulin S, Sairanen T et al. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. Neurology. 2015;85(16):1408-1416. [PMC]

24. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M. Neutrophil-to-Lymphocyte Ratio Predicts the Outcome of Acute Intracerebral Hemorrhage. Stroke. 2016;47(6):1654-1657. [PubMed]

25. Xue J, Huang W, Chen X, Li Q, Cai Z, Yu T et al. Neutrophil-to-Lymphocyte Ratio Is a Prognostic Marker in Acute Ischemic Stroke. J Stroke Cerebrovasc Dis. 2017;26(3):650-7. [PubMed]

26. Goyal N, Tsivgoulis G, Chang J, Malhotra K, Pandhi A, Ishfaq M et al. Admission Neutrophil-to-Lymphocyte Ratio as a Prognostic Biomarker of Outcomes in Large Vessel Occlusion Strokes. Stroke. 2018;49(8):1985-7. [Article]

27. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020.[cited 4th Dec 2020] Available from: https://synthesismanual.jbi.global

28. Derya M, Demir V, Ede H. Relationship between neutrophil/lymphocyte ratio and epicardial fat tissue thickness in patients with newly diagnosed hypertension. J Int Med Res. 2018;46(3):940-50. [PMC]

29. Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H et al. Blood Neutrophil to Lymphocyte Ratio as a Predictor of Hypertension. Am J Hypertens. 2015;28(11):1339-46. [Article]

30. Belen E, Sungur A, Sungur M, Erdoğan G. Increased Neutrophil to Lymphocyte Ratio in Patients with Resistant Hypertension. J Clin Hypertens (Greenwich). 2015;17(7):532-537. [Article]

31. Balta S, Ozturk C, Yildirim A, Aparci M, Demir M, Celik T. The Relation between Neutrophil–Lymphocyte Ratio, and Hypertension. Am J Hypertens. 2015; 28(11):1386-6. [Article]

32. Balta S, Celik T, Mikhailidis D, Ozturk C, Demirkol S, Aparci M, et al. The Relation between Atherosclerosis and the Neutrophil–Lymphocyte Ratio. Clin Appl Thromb Hemost. 2015; 22(5):405-411. [PubMed]

33. Altintas N, Çetinoğlu E, Yuceege M, Acet N, Ursavas A et al. Neutrophil-to-lymphocyte ratio in obstructive sleep apnea; a multi-center, retrospective study. Eur Rev Med Pharmacol Sci. 2015 Sep; 19(17):3234-40. [Article]

34. Oyama J, Nagatomo D, Yoshioka G, Yamasaki A, Kodama K, Sato M, et al. The relationship between neutrophil to lymphocyte ratio, endothelial function, and severity

in patients with obstructive sleep apnea. J Cardiol. 2016;67(3):295-302. [Article]

35. Karakaya S, Altay M, Kaplanefe F, Karadag İ, Ünsal O, Bulur O, et al. The Neutrophil-Lymphocyte Ratio and its Relationship with Insulin Resistance in Obesity. Turk J Med Sci. 2019;49(1):245-8. [Google Scholar] [Download PDF]

36. Bahadir A, Baltaci D, Turker Y, Turker Y, Iliev D, Ozturk S et al. Is the neutrophil-to-lymphocyte ratio indicative of an inflammatory state in patients with obesity and metabolic syndrome? Anatol J Cardiol. 2015; 15(10):816-822. [PMC]

37. Fang Q, Tong Y, Wang G, Zhang N, Chen W, Li Y et al. Neutrophil-to-lymphocyte ratio, obesity, and breast cancer risk in Chinese population. Medicine. 2018; 97(30):e11692. [PMC]

38. Wang X, Fan X, Ji S, Ma A, Wang T. Prognostic value of neutrophil to lymphocyte ratio in heart failure patients. Clinica Chimica Acta. 2018; 85:44-9. [Article]

39. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013;11(1):55-59. [Article]

40. Delcea C, Buzea C, Dan G. The neutrophil to lymphocyte ratio in heart failure: a comprehensive review. Rom J Intern Med. 2019;57(4):296-314. [Article]

41. Durmus E, Kivrak T, Gerin F, Sunbul M, Sari I, Erdogan O. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio are Predictors of Heart Failure. Arq Bras Cardiol. 2015;105(6):606–13. [PMC]

42. Tonyali S, Ceylan C, Yahsi S, Karakan M. Does neutrophil to lymphocyte ratio demonstrate deterioration in renal function?. Renal Failure. 2018;40(1):209-12. [PMC]

43. Yoshitomi R, Nakayama M, Sakoh T, Fukui A, Katafuchi E, Seki M, et al. High neutrophil/lymphocyte ratio is associated with poor renal outcomes in Japanese patients with chronic kidney disease. Renal Failure. 2019;41(1):238-43. [PMC Full Text]

44. Duman T, Aktas G, Atak B, Kocak M, Erkus E, Savli H. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. African Health Sciences. 2019;19(1):1602. [PMC]

45. Özpelit E, Akdeniz B, Özpelit M, Tas S, Bozkurt S, Tertemiz K et al. Prognostic value of neutrophil-to-lymphocyte ratio in pulmonary arterial hypertension. J Int Med Res. 2015;43(5):661-671. [Article]

46. Harbaum L, Baaske K, Simon M, Oqueka T, Sinning C, Glatzel A et al. Exploratory analysis of the neutrophil to lymphocyte ratio in patients with pulmonary arterial hypertension. BMC Pulmonary Medicine. 2017; 17(1):72. [PMC]

47. Świtońska M, Słomka A, Korbal P, Piekuś-Słomka N, Sinkiewicz W, Sokal P et al. Association of Neutrophil-to-Lymphocyte Ratio and Lymphocyte-to-Monocyte Ratio with Treatment Modalities of Acute Ischaemic Stroke: A Pilot Study. Medicina. 2019;55(7):342. [PMC]

48. Lux D, Alakbarzade V, Bridge L, Clark C, Clarke B, Zhang L, et al. The association of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with 3-month clinical outcome after mechanical thrombectomy following stroke. J Neuroinflammation. 2020;17(1). [Article]

49. Giede-Jeppe A, Reichl J, Sprügel M, Lücking H, Hoelter P, Eyüpoglu I et al. Neutrophil-to-lymphocyte ratio as an independent predictor for unfavorable functional outcome in aneurysmal subarachnoid hemorrhage. J Neurosurg. 2020;132(2):400-407. [Article]

50. Sacdalan D, Lucero J, Sacdalan D. Prognostic utility of baseline neutrophil-to-lymphocyte ratio in patients receiving immune checkpoint inhibitors: a review and meta-analysis. Onco Targets Ther. 2018;11:955–965. [PMC]

51. Gonda K, Shibata M, Sato Y, Washio M, Takeshita H, Shigeta H et al. Elevated neutrophiltolymphocyte ratio is associated with nutritional impairment, immune suppression, resistance to S1 plus cisplatin, and poor prognosis in patients with the stage? IV gastric cancer. Mol Clin Oncol. 2017(6):1073–8. [PMC]