Relação Neutrófilo-Linfócito: Acrescentando um Biomarcador a uma Escala Preditiva de Pneumonia Pós-Acidente Vascular Cerebral

Neutrophil-to-Lymphocyte Ratio: The Role of Adding a Biomarker to a Predictive Post-Stroke Pneumonia Score

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Resumo:

Introdução: Avaliar a associação da relação neutrófilo-linfócito (NLR) e a incidência de pneumonia pós-acidente vascular cerebral (PSP), subtipo de acidente vascular cerebral (AVC), gravidade e prognóstico.

Material e Métodos: Foi realizado um estudo prospetivo observacional durante um período de 42 meses numa Unidade de AVC de um hospital terciário. Todos os doentes com AVC isquémico agudo (AIS) foram sequencialmente incluídos. O valor de NLR foi calculado na admissão. As características dos doentes como subtipo de AVC, gravidade e diagnóstico de PSP foram obtidos. A escala A2DS2 foi utilizada como preditor clínico de PSP.

Resultados: Foram identificados 521 doentes com AIS. A idade média foi 76,17 ± 10,16 anos, 46,9% eram homens. Verificou-se uma associação entre NLR, tipo e gravidade de AVC (p <0,01), persistindo em análise estratificada após exclusão de infeção concomitante. Doentes com NLR mais elevado apresentavam défice neurológico mais grave na admissão, maior mortalidade e maior grau de dependência na alta (p < 0,01). Foi realizada uma regressão logística para caracterizar a capacidade preditiva da NLR (≥3) e do A2DS2 (≥6) na probabilidade de desenvolver PSP (p < 0,005). O modelo explicou 17,1% (Nagelkerke R^2) da variância nos diagnósticos de pneumonia, classificando corretamente 77,0% dos doentes com uma especificidade de 96,3%. Doentes com A2DS2 ≥6 (OR 8,36, p < 0,01) e doentes com NLR ≥3 (OR 2,35, p < 0,01) apresentaram um maior risco de desenvolver pneumonia.

Conclusão: NLR parece estar relacionando com a gravidade dos AIS, possivelmente como marcador de ativação neuroimune. Avanços na compreensão dos efeitos imunobiológicos da isquemia no cérebro poderão levar a desenvolvimentos terapêuticos futuros. Atualmente, sendo um biomarcador relativamente pouco dispendioso, talvez exista um papel da NLR na melhoria das escalas preditoras de PSP.

Palavras-chave: Acidente Vascular Cerebral/complicações; Linfócito; Neutrófilo; Pneumonia.

Abstract:

Introduction: *To assess the association of neutrophil-to-lymphocyte ratio (NLR) with post-stroke pneumonia (PSP) incidence, stroke subtype, severity, and prognosis.*

Material and Methods: *Prospective observational study over a 42-month period in a Stroke Unit of a tertiary University Hospital. All patients with acute ischaemic stroke (AIS) were sequentially included. NLR was obtained at admission. Patient characteristics such as stroke subtype, severity and PSP diagnosis were ascertained. Score A2DS2 was used as clinical predictor of PSP.*

Results: *521 patients with AIS were identified. The mean age was 76.17 ± 10.16 years years, 46.9% were men. Association was found between NLR and type and severity of stroke ($p < 0.01$), persisting in stratified analysis after excluding concomitant infection. Patients with higher ratio presented severer neurological deficits at admission, higher mortality, and dependency on discharge ($p < 0.01$). A logistic regression was performed to ascertain the predictive capacity of NLR (≥3) and A2DS2 (≥6) on the likelihood of developing PSP ($p < 0.005$). The model explained 17.1% (Nagelkerke R^2) of the variance in pneumonia diagnoses, correctly classifying 77.0% of patients with 96.3% specificity. Patients with A2DS2 ≥6 were likelier to develop pneumonia (OR 8.36, $p < 0.01$). Moreover, patients with NLR ≥3 had higher odds of developing pneumonia (OR 2.35, $p < 0.01$).*

Conclusion: *NLR appears to be related to severity in AIS, possibly as surrogate of neuroimmune mediation. Advances in the understanding of the immunobiological effects of ischemia in the brain may lead to future therapeutic developments. Presently, as a relatively inexpensive biomarker, there may be a potential role for NLR in improving PSP prediction scores.*

Keywords: *Lymphocytes; Neutrophils; Pneumonia; Stroke/complications.*

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Introduction

Neutrophil-to-lymphocyte ratio (NLR) at hospital admission, defined as the quotient between both absolute values in a complete blood count, has been suggested to be a promising marker in cardiovascular ischaemic events, such as coronary artery occlusion.[1,2] A higher NLR was independently associated with arterial stiffness and coronary calcium score in a large Korean study,[3] proposing that NLR might be a useful additional measure of assessing cardiovascular (CV) risk. In fact, a high NLR despite a normal white blood cell (WBC) count is proposed to be predictive of atherosclerosis,[4] and a more powerful predictor of CV disease than any leukocyte subtype,[5] presumably due to the role of inflammation in the atherogenic process.[6] It has also been associated with a poor short-term clinical outcome in patients with acute ischaemic stroke[7,8] and hemorrhagic stroke,[9,10] on par with other inflammatory biomarkers.[11-13]

Post-stroke pneumonia (PSP) is defined as a lower respiratory tract infection complicating the first week after stroke onset,[14] the period where pneumonia most frequently occurs in stroke patients.[15] This fact probably reflects the period of highest risk in terms of dysphagia, immobility, impaired consciousness, and immunosuppression.[16,17] It has an estimated incidence of 7% to 38%[15,18-27] and has been consistently associated with a high attributable risk of early mortality, increased length of stay and medical cost.[18,22,28-30] As such, prompt identification of patients at high risk for PSP is clinically relevant by promoting an increased monitoring and potential tailored prophylactic or therapeutic measures.[31-33]

The A^2DS^2 score – a ten-point score (age ≥75 years=1, atrial fibrillation=1, dysphagia=2, male sex=1, stroke severity, National Institutes of Health Stroke Scale NIHSS 0–4=0, 5–15=3, ≥16=5) developed from the Berlin Stroke Registry, is currently the most used tool. It was validated in the independent Northwest Germany Stroke Registry 34, and with external validation 35. A prospective multicentre comparison between A^2DS^2, ISAN and AIS-APS scores (also commonly used to predict the risk of PSP), suggest that A^2DS^2 might be the best score in the identification of patients at high risk of PSP, though none with a good positive predictive value. In fact, a A^2DS^2 score of ≥4 yields a sensitivity of 91% and specificity of 57% for the occurrence of PSP, while a A^2DS^2 score ≥5 has a sensitivity of 83% and specificity of 72%.[34]

The authors aim to assess the relationship between NLR and stroke severity, subtype, how it relates to mortality, and post-stroke pneumonia incidence.

Material and Methods

A prospective observational study over a 42-month period in a Stroke Unit of a tertiary University Hospital was conducted. All patients presenting with acute ischemic stroke during this period were included. Patients that underwent thrombolysis or mechanical thrombectomy were not included. Population and event characteristics were collected, namely: time of onset, type of event, Oxfordshire Community Stroke Project – OCSP, National Institute of Health Stroke Scale – NIHSS, mortality, mRankin at discharge and length of stay in days), risk factors such as chronic obstructive pulmonary disease, heart failure or active smoking, presence of respiratory tract infections, A^2DS^2 and NLR at admission to the emergency department. NLR cut-off was selected based on previous published methodology.[36]

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS® statistical software version 24. Relevant variables were stratified in categories (A^2DS^2 < 6, >= 6; NIHSS at admission <6, 6-13, >13; NLR <3, ≥3). When comparing two categorical variables the Pearson's Chi-square test was used. A binomial logistic regression multivariate analysis was also performed. Applicability conditions were verified. The significance level was set at $p < 0.05$.

Results

A total of 606 patients were admitted to the Stroke Unit during the study's period. Of these, 521 patients with acute ischemic stroke (AIS) were identified (Table 1). The remaining 85 patients were excluded due to being hospitalized with either a haemorrhagic event or a stroke mimic. Of the included 521 patients classified as AIS, 66 had a transient ischaemic attack (TIA).

Table 1: Diagnosis at admission

Type of Event	Frequency
Ischaemic stroke	455
Transient ischaemic attack	66
Haemorrhagic stroke	21
Stroke mimic	64
Total	606

Concerning the included patients, the mean age was 76.17 ± 10.16 years (min. 47; max. 96 years old). Population demographics are summarized on Table 2. Missing data was characterized as unknown.

Association was found between NLR and type and severity of stroke according to OSCP classification – lower NLR in lacunar stroke and higher in total anterior circulation infarct (Table 3, $p < 0.001$).

A NLR ≥3 was related to more severe neurological deficit as ascertained by the NIHSS scale ≥6 ($p < 0.001$) and was associated with a higher mortality – from 26 patients that died,

Table 2: Demographic characteristics of the studied population

Age (years)*	76.17 ± 10,16; [min. 47, max. 96]
Inpatient days (days)**	7; [min. 1, max. 67]
mRankin before the event**	0; [min. 0, max. 5]
mRankin on discharge**	2; [min. 0, max. 6]
Gender	
• Male	250 (48%)
• Female	271 (52%)
Type of Stroke (OCSP)	
• LACi	109 (21%)
• TACi	100 (19%)
• PACi	207 (40%)
• POCi	96 (18%)
• Unknown	9 (2%)
NIHSS at admission	
• < 6	238 (45%)
• 6-13	92 (18%)
• > 13	56 (11%)
• Unknown	135 (26%)
Admitted < 24 hours after onset	
• Yes	335 (64%)
• No	68 (13%)
• Unknown	118 (23%)
Previous anti-thrombotic therapy	
• Oral anticoagulation therapy	40 (8%)
• Direct oral anticoagulation therapy	4 (1%)
• Anti-platelet therapy	190 (36%)
• Anti-platelet + anticoagulation therapy	4 (1%)
• Dual anti-platelet therapy	16 (3%)
• None	251 (48%)
• Unknown	16 (3%)
Lower respiratory tract infection	
• yes, pre-stroke	30 (6%)
• yes, post-stroke	111 (21%)
• No	371 (71%)
• Unknown	9 (2%)
Chronic pulmonary obstructive disease	
• Yes	41 (8%)
• No	475 (91%)
• Unknown	5 (1%)
Heart failure	
• Yes	133 (26%)
• No	383 (73%)
• Unknown	5 (1%)
Active smoking	
• Yes	56 (11%)
• No	460 (88%)
• Unknown	5 (1%)
Outcome	
• Death	29 (6%)
• Survival	488 (93%)
• Unknown	4 (1%)
A^2DS^2	
• < 6	472 (91%)
• ≥ 6	49 (9%)
Age	
• Age ≥ 75 years	321 (62%)
• Age < 75 years	200 (38%)
Atrial fibrillation	
• Atrial fibrillation	106 (20%)
• No atrial fibrillation	415 (80%)
Dysphagia	
• Dysphagia	95 (18%)
• No dysphagia	426 (82%)
Gender	
• Male	250 (48%)
• Female	271 (52%)
NIHSS on admission	
• NIHSS on admission 0-4	209 (40%)
• NIHSS on admission 5-15	132 (25%)
• NIHSS on admission > 15	45 (9%)
• NIHSS on admission unknown	135 (26%)
Neutrophil to lymphocyte ratio	
• < 3	228 (44%)
• ≥ 3	267 (51%)
• Unknown	26 (5%)

*average ± std deviation; [min, max]. **median; [min, max]. OCSP: Oxfordshire Community Stroke Project. LACi: lacunar infarct; TACi: total anterior circulation infarct; PACi: partial anterior circulation infarct; POCi: posterior circulation infarct.

77% had a NLR ≥ 3, *vs* 52% of those in the survival group (Table 3, $p = 0.016$). NLR ≥ 3 was also associated with higher disability as ascertained by mRankin score at discharge (Table 3, $p < 0.0001$). This association persisted after stratified analysis excluding infection (PSP).

The relationship between NLR at admission and the development of pneumonia is shown in Fig. 1. Patients with NLR ≥ 3 had higher odds of developing pneumonia (OR 2.531, 95%CI 1.654, 3.873).

Since a statistically significant relationship between NLR and post-stroke pneumonia was found, a logistic regression was performed to assess the predictive capacity of NLR (≥3) and A^2DS^2 (≥6) on the likelihood of developing post-stroke pneumonia. The model including both variables explained 17.1% (Nagelkerke R^2) of the variance in pneumonia diagnoses, correctly classifying 77.0% of patients and showing a 96.3% specificity and a 25.6% sensibility ($p < 0.005$), with a better *fitness* than a model using A2DS2 alone (13.2%, Nagelkerke R2). The specificity and sensibility found in our

Table 3: Comparison between low and high NLR and stroke according to OSCP, death and mRankin at discharge.

	Neutrophil to Lymphocyte ratio		
Type of Stroke	**< 3**	**≥ 3**	
LACi	60 (57%)	45 (43%)	
TACi	27 (29%)	67 (71%)	χ^2 = 18.147,
PACi	91 (47%)	104 (53%)	*p*-value <0.001
POCi	49 (53%)	44 (47%)	
Outcome			
Death	6 (23%)	20 (77%)	χ^2 = 5.822,
Survival	220 (47%)	245 (53%)	*p*-value =0.016
mRankin at discharge			
0	47 (58%)	34 (42%)	
1	59 (56%)	47 (44%)	
2	28 (67%)	14 (33%)	χ^2 = 32.576,
3	21 (45%)	26 (55%)	*p*-value <0.0001
4	30 (38%)	49 (62%)	
5	11 (21%)	41 (79%)	
6	6 (30%)	14 (70%)	
NIHSS			
< 6	49 (53%)	44 (47%)	χ^2 = 13.996,
6-13			*p*-value <0.001
> 13			
Post-stroke pneumonia	3 (9.7%)	1 (9.1%)	χ^2 = 18.902, *p*-value <0.0001

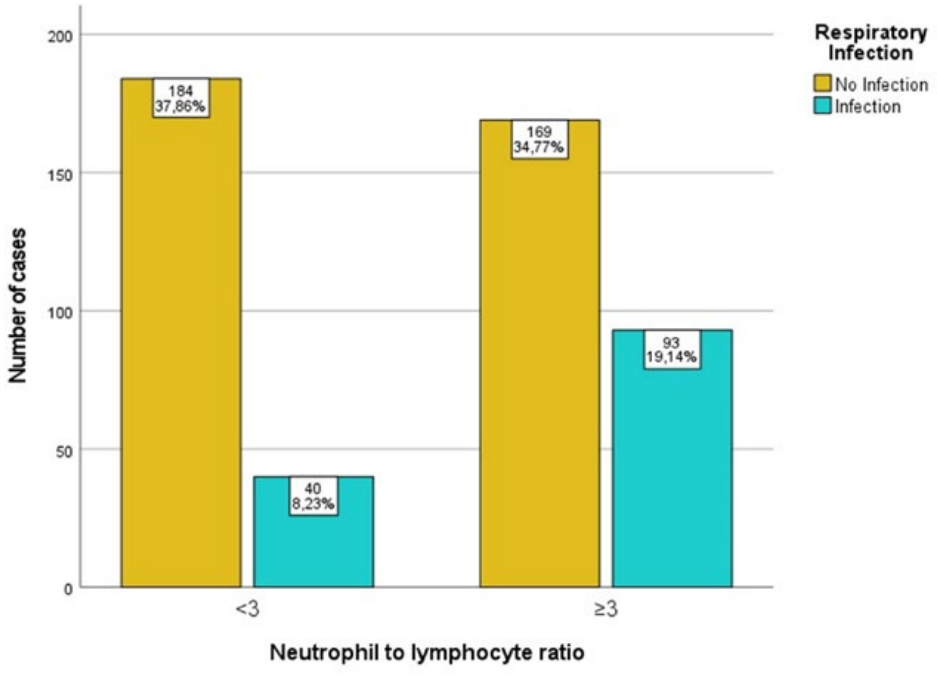

Figure 1: Relationship between NLR at admission and post-stroke pneumonia. Missing.35. *p*-value < 0.0001. X2 = 18.902. OR 2.531, 95%CI (1.654, 3.873), unadjusted.

sample with A^2DS^2 alone was similar. The positive predictive value was 72.3% and the negative predictive value was 77.4%.

$A^2DS^2 \geq 6$ was 8.36 times more likely to exhibit post-stroke pneumonia than $A^2DS^2 < 6$ ($p < 0.001$), while NLR ≥ 3 had 2.349 higher odds (Table 4).

Discussion

There is little doubt that post-stroke inflammation is an important factor in brain injury.[17,37-39] In fact, leucocytosis has

Table 4: Variable analysis for the logistic regression for post-stroke pneumonia on NLR and A^2DS^2.

	Odds ratio	*p - value*	95% C.I.	
			Inferior	Superior
A^2DS^2 (≥6; <6)	8.358	< 0.001	4.197	16.643
NLR (≥3; <3))	2.349	< 0.001	1.504	3.671

been associated to a poorer clinical outcome in patients with AIS.[40-43] Nevertheless, this inflammatory response is complex and involves several protagonists and immune pathways.[17,38] NLR has been suggested as an interesting marker in patients with cardiovascular disease.[44,45] It has been associated with a poor short-term clinical outcome in patients with acute ischaemic stroke[7,8] and is also a marker of poor prognosis 3 months after AIS.[46] In fact, the immune system might arise as a potential therapeutic target in patients with ischaemic brain lesion.[47-49]

In our study, there was an association between higher NLR, higher NIHSS and poorer outcome, with increased risk of mortality and a higher mRankin score at discharge. These results persisted after stratified analysis excluding infection.

Post-stroke pneumonia is a frequent but potentially preventable stroke complication, often associated with a significant increase in morbidity and mortality. It has been associated with a 4 times higher fatality rate in the first 30 days, 3 times higher length of stay and a significant increase in medical expenses.[16,30] Our incidence of 21% falls within what has been reported in the literature.[15,18-27] NLR is an established marker for inflammation and infection, having been studied as a predictor in pneumonia and bacterial infections[50-53] However, its role in PSP is not as well supported. In a cohort of 1317 patients in a 2-center retrospective study, Nam K-W, *et al* report an association between NLR and an increased risk and severity of PSP.[54] We also report an association between higher NLR and an increased risk of developing PSP.

Several clinical risk factors have previously been established for PSP, such as age, admission NIHSS score and stroke severity, presence of nasogastric tube, mechanical ventilation, and atrial fibrillation.[55] However, the concomitant use of biomarkers in PSP assessment is, to the best of our knowledge, scarce.[27,55,56] The PANTHERIS score included the total leukocyte count, but the lack of NIHSS evaluation seems to be a limitation.[27] In our study, patients with NLR ≥ 3 were 2.35 times more likely to exhibit post-stroke pneumonia than NLR < 3 (p <0.001) and NLR did appear to increase the fitness of the predictability of A^2DS^2 in our logistical regression model, even though we did not find an increase in sensitivity or specificity in our sample.

The percentage of "unknown data", namely in NIHSS, is attributed to logistical constraints in our practice setting: a tertiary centre involving two hospitals. Study inclusion was done at stroke unit admission in a different hospital from the emergency department (ED). When the details from the stroke physician's evaluation were not charted at the ED, data was classified as unknown/missing.

Post-stroke inflammation is characterized by a rapid activation of resident cells (mainly microglial cells), followed by the infiltration of circulating inflammatory cells, including granulocytes (neutrophils), T cells, monocyte/macrophages, and other cells in the ischemic brain region.[57-59] Microglial cell proliferation and proinflammatory mediator production, including IL-1β and TNF-α, has been documented within minutes of ischemia[60] and appear to play a role in exacerbating tissue damage but may also protect the brain against ischemic and excitotoxic injury.[60,61] In contrast, blood-derived leukocytes are recruited to the brain tissue with a delay of hours to a few days. Therefore, the timing of blood collection could affect NLR. NLR evolution during hospitalization was not evaluated due to concern of higher risk of bias due to infection, catheterization, and drugs. The NLR response in a severe cardiovascular event appears to be a surrogate of an immune-mediated response, not necessarily caused by infection but perhaps related to it (higher immune-dysregulation in more severe events).[62]

This, in our view, supports the current hypothesis of immune-mediated cell injury in stroke. Further studies are needed in determining the immunological mechanism of lesion and the possibility of therapeutic intervention.

Conclusion

NLR ≥3 is associated with a more severe stroke subtype, neurologic deficit, increased morbidity and mortality and higher rates of post-stroke pneumonia, though the relationships described do not seem to be attributable do the infection. NLR appears to be a surrogate of immunological dysregulation. Advances in the knowledge of the immunobiological effects of ischemia in brain may lead to future therapeutic developments. As an inexpensive, fast and widely available tool, NLR may have a role in identifying a subset of patients that may benefit in future immunomodulatory therapy trial. ■

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REFERENCES

1. Arbel Y, Finkelstein A, Halkin A, Birati Y E, Revico M, Zuzut M, et al. Neutrophil/lymphocyte ratio is related to the severity of coronary artery disease and clinical outcome in patients undergoing angiography. Atherosclerosis. 2012;225:456-60. doi:10.1016/j.atherosclerosis.2012.09.009
2. Kalay N, Dogdu O, Koc F, et al. Hematologic parameters and angiographic progression of coronary atherosclerosis. Angiology. 2012;63:213-7. doi:10.1177/0003319711412763
3. Park BJ, Shim JY, Lee HR, Lee JH, Jung DH, Kim HB, et al. Relationship of neutrophil-lymphocyte ratio with arterial stiffness and coronary calcium score. Clin Chim Acta. 2011;412:925-9. doi:10.1016/j.cca.2011.01.021
4. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al. Which white blood cell subtypes predict increased cardiovascular risk? J Am Coll Cardiol. 2005;45:1638-43. doi:10.1016/j.jacc.2005.02.054
5. Yu X, Li X, Li Y, Liu T, Wang R. Neutrophil-lymphocyte ratio is associated with arterial stiffness in postmenopausal women with osteoporosis. Arch Gerontol Geriatr. 2015;61:76-80. doi:10.1016/j.archger.2015.03.011
6. Mozos I, Malainer C, Horbanczuk J, Gug C, Stoian D, Luca CT, et al. Inflammatory Markers for Arterial Stiffness in Cardiovascular Diseases. Front Immunol. 2017;8:1058. doi:10.3389/fimmu.2017.01058
7. 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;387:115-8. doi:10.1016/j.jns.2018.02.002
8. Zhang J, Ren Q, Song Y, He M, Zeng Y, Liu Z, et al. Prognostic role of neutrophil-lymphocyte ratio in patients with acute ischemic stroke. Medicine. 2017;96:e8624. doi:10.1097/MD.0000000000008624
9. Switonska M, Piekus-Słomka N, Słomka A, Sokal P, Zekanowska E, Lattanzi S. Neutrophil-to-Lymphocyte Ratio and Symptomatic Hemorrhagic Transformation in Ischemic Stroke Patients Undergoing Revascularization. Brain Sci. 2020;10:771. doi:10.3390/brainsci10110771
10. Lattanzi S, Cagnetti C, Rinaldi C, Angelocola S, Provinciali L, Silvestrini M. Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage. J Neurol Sci. 2018;387:98-102. doi:10.1016/j.jns.2018.01.038
11. Wang L, Li Y, Wang C, Guo W, Liu M. C-reactive Protein, Infection, and Outcome After Acute Ischemic Stroke: A Registry and Systematic Review. Curr Neurovasc Res. 2020;16:405-15. doi:10.2174/1567202616666191026122011
12. Mengel A, Ulm L, Hotter B, Harms H, Piper SK, Grittner U, et al. Biomarkers of immune capacity, infection and inflammation are associated with poor outcome and mortality after stroke - the PREDICT study. BMC Neurol. 2019;19:148. doi:10.1186/s12883-019-1375-6
13. Lattanzi S, Di Napoli M, Ricci S, Divani AA. Matrix Metalloproteinases in Acute Intracerebral Hemorrhage. Neurotherapeutics. 2020;17:484-96. doi:10.1007/s13311-020-00839-0
14. Smith CJ, Kishore AK, Vail A, Chamorro A, Garau J, Hopkins SJ, et al. Diagnosis of Stroke-Associated Pneumonia: Recommendations From the Pneumonia in Stroke Consensus Group. Stroke. 2015;46:2335-40. doi:10.1161/STROKEAHA.115.009617
15. Westendorp WF, Nederkoorn PJ, Vermeij JD, Dijkgraaf MG, van de Beek D. Post-stroke infection: a systematic review and meta-analysis. BMC Neurol. 2011;11:110. doi:10.1186/1471-2377-11-110
16. Emsley HCA, Hopkins SJ. Acute ischaemic stroke and infection: recent and emerging concepts. Lancet Neurol. 2008;7:341-53. doi:10.1016/S1474-4422(08)70061-9
17. Chamorro Á, Meisel A, Planas AM, Urra X, van de Beek D, Veltkamp R. The immunology of acute stroke. Nat Rev Neurol. 2012;8:401-10. doi:10.1038/nrneurol.2012.98
18. Kammersgaard LP, Jørgensen HS, Reith J, Nakayama H, Houth JG, Weber UJ, et al. Early infection and prognosis after acute stroke: the Copenhagen Stroke Study. J stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2001;10:217-21. doi:10.1053/jscd.2001.30366
19. Meisel A, Smith CJ. Stroke: Preventive antibiotics for stroke-associated pneumonia. Nat Rev Neurol. 2015;11:672-3. doi:10.1038/nrneurol.2015.220
20. Vernino S, Brown RD, Sejvar JJ, Sicks JD, Petty GW, O'Fallon WM. Cause--specific mortality after first cerebral infarction: a population-based study. Stroke. 2003;34:1828-32. doi:10.1161/01.STR.0000080534.98416.A0
21. Wang PL, Zhao XQ, Yang ZH, Wang AX, Wang CX, Liu LP, et al. Effect of in-hospital medical complications on case fatality post-acute ischemic stroke: data from the China National Stroke Registry. Chin Med J. 2012;125:2449-54.
22. Kumar S, Selim MH, Caplan LR. Medical complications after stroke. Lancet Neurol. 2010;9:105-18. doi:10.1016/S1474-4422(09)70266-2
23. Vermeij FH, Scholte op Reimer WJ, de Man P, Oostenbrugge R J V, Franke C L, Jong G, et al. Stroke-associated infection is an independent risk factor for poor outcome after acute ischemic stroke: data from the Netherlands Stroke Survey. Cerebrovasc Dis. 2009;27:465-71. doi:10.1159/000210093
24. Smith CJ, Bray BD, Hoffman A, Meisel A, Heuschmann P U, Wolfe C D A, et al. Can a novel clinical risk score improve pneumonia prediction in acute stroke care? A UK multicenter cohort study. J Am Heart Assoc. 2015;4:e001307. doi:10.1161/JAHA.114.001307
25. Ji R, Shen H, Pan Y, Wang P, Liu G, Wang Y, et al. Novel risk score to predict pneumonia after acute ischemic stroke. Stroke. 2013;44:1303-09.

doi:10.1161/STROKEAHA.111.000598
26. Finlayson O, Kapral M, Hall R, Asllani E, Selchen D, Saposnik G. Risk factors, inpatient care, and outcomes of pneumonia after ischemic stroke. Neurology. 2011;77:1338-45. doi:10.1212/WNL.0b013e31823152b1
27. Harms H, Grittner U, Dröge H, Meisel A. Predicting post-stroke pneumonia: the PANTHERIS score. Acta Neurol Scand. 2013;128:178-84. doi:10.1111/ane.12095
28. Koennecke H-C, Belz W, Berfelde D, Endres M, Fitzek S, Hamilton F, et al. Factors influencing in-hospital mortality and morbidity in patients treated on a stroke unit. Neurology. 2011;77:965-72. doi:10.1212/WNL.0b013e31822dc795
29. Ingeman A, Andersen G, Hundborg HH, Svendsen ML, Johnsen SP. In-hospital medical complications, length of stay, and mortality among stroke unit patients. Stroke. 2011;42:3214-8. doi:10.1161/STROKEAHA.110.610881
30. Katzan IL, Dawson N V, Thomas CL, Votruba ME, Cebul RD. The cost of pneumonia after acute stroke. Neurology. 2007;68:1938-43. doi:10.1212/01.wnl.0000263187.08969.45
31. Kwon HM, Jeong SW, Lee SH, Yoon BW. The pneumonia score: a simple grading scale for prediction of pneumonia after acute stroke. Am J Infect Control. 2006;34:64-8. doi:10.1016/j.ajic.2005.06.011
32. Sellars C, Bowie L, Bagg J, Sweeney M P, Miller H, Tilston J, et al. Risk factors for chest infection in acute stroke: a prospective cohort study. Stroke. 2007;38:2284-91. doi:10.1161/STROKEAHA.106.478156
33. Chumbler NR, Williams LS, Wells CK, Lo AC, Nadeau S, Peixoto AJ, et al. Derivation and validation of a clinical system for predicting pneumonia in acute stroke. Neuroepidemiology. 2010;34:193-9. doi:10.1159/000289350
34. Hoffmann S, Malzahn U, Harms H, Koennecke H C, Berger K, Kalic M, et al. Development of a clinical score (A2DS2) to predict pneumonia in acute ischemic stroke. Stroke. 2012;43:2617-23. doi:10.1161/STROKEAHA.112.653055
35. Zapata-Arriaza E, Moniche F, Blanca PG, Bustamante A, Martínez IE, Uclés O, et al. External Validation of the ISAN, A2DS2, and AIS-APS Scores for Predicting Stroke-Associated Pneumonia. J stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2018;27:673-6. doi:10.1016/j.jstrokecerebrovasdis.2017.09.059
36. Wang S, Zhang Z, Fang F, Gao X, Sun W, Liu H. The neutrophil/lymphocyte ratio is an independent prognostic indicator in patients with bone metastasis. Oncol Lett. 2011;2:735-40. doi:10.3892/ol.2011.304
37. Schwartz M, Moalem G. Beneficial immune activity after CNS injury: prospects for vaccination. J Neuroimmunol. 2001;113:185-92. doi:10.1016/s0165-5728(00)00447-1
38. Hou D, Wang C, Ye X, Zhong P, Wu D. Persistent inflammation worsens short-term outcomes in massive stroke patients. BMC Neurol. 2021;21:62. doi:10.1186/s12883-021-02097-9
39. Macrez R, Ali C, Toutirais O, Mauff BL, Defer G, Dirnagl H, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. Lancet Neurol. 2011;10:471-80. doi:10.1016/S1474-4422(11)70066-7
40. Peng Y, Wang D, Zhang J, Xue X, Wang Z, Tong W, et al. Relationship between white blood cell count at admission and short term outcome in patients with acute cerebral infarction. Clin Invest Med. 2011;34:E249. doi:10.25011/cim.v34i4.15368
41. Elkind MS V, Cheng J, Rundek T, Boden-Albala B, Sacco RL. Leukocyte count predicts outcome after ischemic stroke: the Northern Manhattan Stroke Study. J stroke Cerebrovasc Dis Off J Natl Stroke Assoc. 2004;13:220-7. doi:10.1016/j.jstrokecerebrovasdis.2004.07.004
42. Kazmierski R, Guzik P, Ambrosius W, Ciesielska A, Moskal J, Kozubski W. Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. Clin Neurol Neurosurg. 2004;107:38-43. doi:10.1016/j.clineuro.2004.03.003
43. 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 Off J Natl Stroke Assoc. 2012;21:819-24. doi:10.1016/j.jstrokecerebrovasdis.2011.04.015
44. Tamhane UU, Aneja S, Montgomery D, Rogers E-K, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102:653-7. doi:10.1016/j.amjcard.2008.05.006
45. Giede-Jeppe A, Bobinger T, Gerner ST, Sembill JA, Sprügel MI, Beuscher VD, et al. Neutrophil-to-Lymphocyte Ratio Is an Independent Predictor for In-Hospital Mortality in Spontaneous Intracerebral Hemorrhage. Cerebrovasc Dis. 2017;44:26-34. doi:10.1159/000468996
46. Qun S, Tang Y, Sun J, Liu Z, Wu J, Zhang J, et al. Neutrophil-To-Lymphocyte Ratio Predicts 3-Month Outcome of Acute Ischemic Stroke. Neurotox Res. 2017;31:444-52. doi:10.1007/s12640-017-9707-z
47. 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 Off J Int Soc Cereb Blood Flow Metab. 2015;35:888-901. doi:10.1038/jcbfm.2015.45
48. Jian Z, Liu R, Zhu X, Smerin D, Zhong Y, Gu L, et al. The Involvement and Therapy Target of Immune Cells After Ischemic Stroke. Front Immunol. 2019;10:2167. doi:10.3389/fimmu.2019.02167
49. Malone K, Amu S, Moore AC, Waeber C. Immunomodulatory Therapeutic Strategies in Stroke. Front Pharmacol. 2019;10:630. doi:10.3389/fphar.2019.00630
50. Liu X, Shen Y, Wang H, Ge Q, Fei A, Pan S. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Patients with Sepsis: A Prospective Observational Study. Mediators Inflamm. 2016;2016:8191254. doi:10.1155/2016/8191254
51. Curbelo J, Luquero Bueno S, Galván-Román JM, Ortega-Gómez M, Rajas O, Fernández-Jiménez G, et al. Inflammation biomarkers in blood as mortality predictors in community-acquired pneumonia admitted patients: Importance of comparison with neutrophil count percentage or neutrophil-lymphocyte ratio. PLoS One. 2017;12:e0173947. doi:10.1371/journal.pone.0173947
52. de Jager CPC, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, et al. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. PLoS One. 2012;7:e46561. doi:10.1371/journal.pone.0046561
53. Holub M, Beran O, Kaspríková N, Chalupa P. Neutrophil to lymphocyte count ratio as a biomarker of bacterial infections. Cent Eur J Med. 2012;7:258-61. doi:10.2478/s11536-012-0002-3
54. Nam K-W, Kim TJ, Lee JS, Kwon HM, Lee YS, Ko SB, et al. High Neutrophil-to-Lymphocyte Ratio Predicts Stroke-Associated Pneumonia. Stroke. 2018;49:1886-92. doi:10.1161/STROKEAHA.118.021228
55. Huang GQ, Lin YT, Wu YM, Cheng QQ, Cheng HR, Wang Z. Individualized Prediction Of Stroke-Associated Pneumonia For Patients With Acute Ischemic Stroke. Clin Interv Aging. 2019;14:1951-62. doi:10.2147/CIA.S225039
56. Lan Y, Sun W, Chen Y, Miao J, Li G, Qiu X, et al. Nomogram Including Neutrophil-to-Lymphocyte Ratio for the Prediction of Stroke-Associated Infections. Front Neurol. 2020;11:574280. doi:10.3389/fneur.2020.574280
57. Jin R, Yang G, Li G. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J Leukoc Biol. 2010;87:779-89. doi:10.1189/jlb.1109766
58. Jin R, Liu L, Zhang S, Nanda A, Li G. Role of Inflammation and Its Mediators in Acute Ischemic Stroke. J Cardiovasc Transl Res. 2013;6:834-51. doi:10.1007/s12265-013-9508-6
59. Lindsberg PJ, Carpe´n O, Paetau A, Karjalainen-Lindsberg ML, Kaste M. Endothelial ICAM-1 Expression Associated With Inflammatory Cell Response in Human Ischemic Stroke. Circulation. 1996;94:939-45. doi:10.1161/01.CIR.94.5.939
60. Denes A, Vidyasagar R, Feng J, Narvainen J,McColl BW, Kauppinen RA, et al. Proliferating Resident Microglia after Focal Cerebral Ischaemia in Mice. J Cereb Blood Flow Metab. 2007;27:1941-53. doi:10.1038/sj.jcbfm.9600495
61. Hallenbeck JM. The many faces of tumor necrosis factor in stroke. Nat Med. 2002;8:1363-8. doi:10.1038/nm1202-1363
62. Döring Y, Drechsler M, Soehnlein O, Weber C. Neutrophils in atherosclerosis: from mice to man. Arterioscler Thromb Vasc Biol. 2015;35:288-95. doi:10.1161/ATVBAHA.114.303564