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Neutrophil to lymphocyte ratio and early seizures after ischemic stroke: A case-control study

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ABSTRACT

Background: Early post-stroke seizures (EPSS) are associated with an increased risk of mortality and post-stroke epilepsy. This study aimed to identify potential risk factors for EPSS, focusing on blood parameters, such as the neutrophil-to-lymphocyte ratio (NLR), which is a biomarker for inflammation.
Methods: Patients treated for ischemic stroke between 2017 and 2019 were retrospectively identified. 44 of them had a first epileptic seizure within 7 days after the stroke. They were matched 1:2 for age and sex with controls who had a stroke but no EPSS. Information on demographics, stroke characteristics, and blood parameters were collected on admission. Logistic regression was used to identify variables associated with EPSS and the area under the receiver operating characteristic curve (AUROC) to estimate their predictive accuracy.
Results: The NLR value ($p = 0.035$), National Institutes of Health Stroke Scale (NIHSS) ($p = 0.016$) and cortical localization of stroke ($p = 0.03$) were significantly correlated with the occurrence of EPSS in univariate logistic regression. In multivariable logistic regression, after adjusting for age, sex, baseline NIHSS, and stroke localization, the NLR values [adjusted odds ratio 1.097, 95% confidence interval (CI): 1.005–1.197; $p = 0.038$] were independently associated with the occurrence of EPSS. The AUROC for NLR was 0.639 (95% CI: 0.517–0.761) with 2.98 as the best predictive cut-off value. There was a significant positive relationship between NLR and NIHSS, $r_S(87) = 0.383$, $p = <0.001$.
Conclusion: Higher NLR values were associated with increased risk of EPSS. This biomarker appears useful to assess the risk of developing EPSS.

1. Introduction

Ischemic stroke represents one of the most common causes of mortality and permanent disability [1], and its global incidence is expected to increase in the next decades [2]. Possible complications of ischemic stroke are early post-stroke seizures (EPSS), which occur in approximately 3.3% of ischemic stroke patients [3]. According to the International League Against Epilepsy (ILAE), EPSS are acute symptomatic seizures that occur within the first seven days after the acute event [4].

The impact of EPSS on morbidity and mortality after acute ischemic stroke is controverse [5–8]. Recent evidence has shown an increased risk of mortality associated with EPSS [5]. Furthermore, EPSS, and particularly acute post-stroke status epilepticus, are associated with an increased risk of subsequent epilepsy [6–9]. This emphasizes the need to identify risk factors for EPSS, as their primary prevention, prompt identification and treatment could improve outcome after stroke.

Stroke is associated with both local and systemic inflammatory response [10]. Inflammation is also relevant in the development of epilepsy and epileptic seizures [11]. The pathophysiology of EPSS involves temporary inflammatory and other biochemical changes in ischemic tissue [12–16].

A parameter that has recently become of increasing interest is the neutrophil-to-lymphocyte ratio (NLR), which is a valuable prognostic parameter in several diseases, a reliable marker of inflammation and can be easily obtained from a blood sample [17]. An increased NLR is associated with higher severity of ischemic stroke, worse functional

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outcome [18,19] and higher 3-month mortality [20,21]. Similarly, an increased NLR increases the risk of secondary hemorrhage and 3-month mortality rate after stroke due to large vessel occlusion [22,23].

The aim of this study was to evaluate the association between NLR on admission and the risk of EPSS in patients with ischemic stroke.

2. Methods

2.1. Study design and population.

We conducted a retrospective case-control study at a single stroke

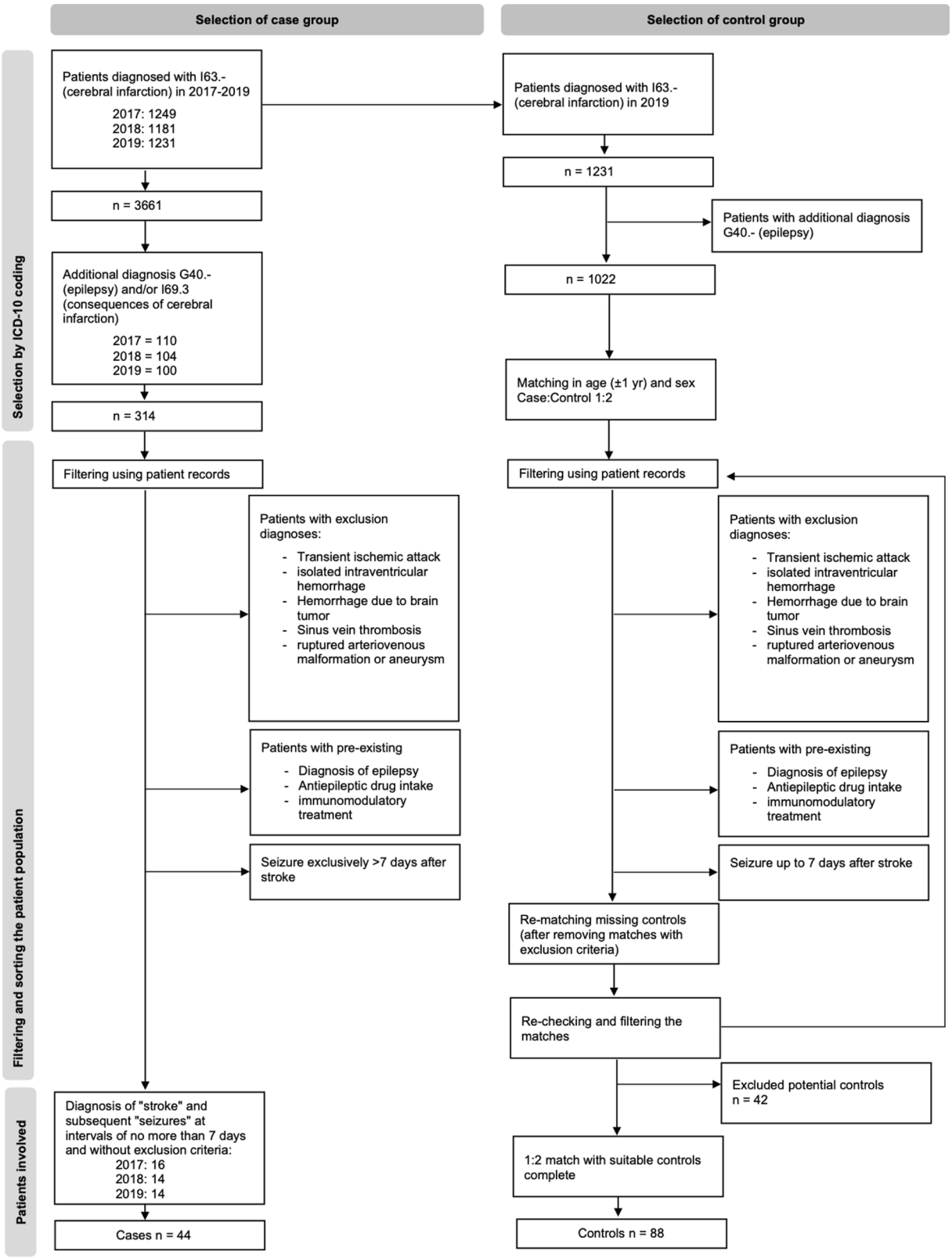

Fig. 1. Patient selection process.

Table 1
Demographic data of participants.

	Cases (n = 44)	Controls (n = 88)	p value
Female sex	24 (54.5%)	48 (54.5%)	1.00[b]
Median age, yr	76 [66.25–85.75]	76.14 [66.55–85.81]	0.99 [a]
Medications			
Antiplatelet agents	20 (45.5%)	35 (39.8%)	0.53[b]
Anticoagulation	10 (22.7%)	21 (23.9%)	0.89[b]
Statins	16 (36.4%)	30 (34.1%)	0.8[b]
Clinical history			
Prior ischemic stroke	16 (36.4%)	27 (30.7%)	0.51[b]
Chronic alcohol abuse	3 (6.8%)	4 (4.5%)	0.69[c]
Diabetes mellitus	12 (27.3%)	18 (20.5%)	0.38[b]
Arterial hypertension	34 (77.3%)	73 (83%)	0.43[b]

Data are presented as median [interquartile range] for continuous variables, and n (%) for categorical variables.
[a]Mann-Whitney *U* test [b]Chi-squared test [c]Fisher's exact test.

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Patients older than 18 years and treated for ischemic stroke between January 1, 2017, and December 31, 2019, were included. As cases, we included patients with an ischemic stroke and in whom a first epileptic seizure occurred within the first 7 days after stroke.

Controls had an ischemic stroke and were admitted to the same stroke center in 2019, but had no EPSS. Each case was matched to two controls for age (±1 year) and sex (assigned at birth).

ICD-10-GM (International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification) coding [24] was used for the primary selection of patients from the internal database. The patients admitted with "Cerebral infarction" I63.- in the previously described timeframes were divided into two groups, based on additional diagnostic codes:

The combination of I63.- with "Sequelae of cerebral infarction" I69.3 and/or "Epilepsy" G40.- was used to identify patients with possible seizures after stroke (314 patients). Potential control patients were excluded if they had received the diagnosis "Epilepsy" G40.- in addition to I63.-, with 1022 potential controls remaining.

The selected patient records of the first group were then individually reviewed for possible inclusion in this study as cases. We excluded patients with transient ischemic attack (TIA), a previous diagnosis of epilepsy, any type of cerebral hemorrhage, and patients who had received antiseizure medications or immunomodulatory treatment prior to admission. As a result, we identified 44 patients with EPSS.

These 44 patients with EPSS were then matched with the potential controls for age (±1 year) and sex. Afterwards, the matched control patients' records were also individually reviewed for the above-mentioned exclusion criteria. 42 controls were excluded in the process and the corresponding case was re-matched to a new potential control.

Thus, 44 cases and 88 controls remained.

For further details on the patient selection process also see Fig. 1.

2.2. Data collection

The available data were obtained from the electronic patient records. In addition to data concerning stroke and seizure type, information about the patient's demographic, their medical history, and laboratory parameters were collected. The full list of extracted variables is reported in Tables 1-3.

Only laboratory parameters obtained within the first 24 h after admission were analyzed.

The NLR, lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte-ratio (PLR) on admission were determined as follows: NLR = absolute neutrophil count/absolute lymphocyte count; LMR = absolute lymphocyte count/absolute monocyte count; PLR = platelet count/absolute lymphocyte count.

The localization of the acute stroke was assessed using computed tomography (CT) scan and, if available, magnetic resonance imaging (MRI); it was dichotomized into "cortical involvement" versus "other localization".

Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) [25], Glasgow Coma Scale [26] and modified Rankin Scale (mRS) [27] on admission.

Information on intravenous thrombolysis and/or mechanical thrombectomy was also recorded; both procedures were conducted according to the European [28,29] and German [30,31] guidelines that were valid at the time of the admission of the patients. For each patient we calculated the time interval between the onset of ischemic stroke and the occurrence of first epileptic seizure.

The study was approved by the local ethics committee (40/20).

Table 2
Stroke characteristics and treatment.

	Cases	n [d]	Controls ES	n [e]	p value
GCS	13 [11–15]		15 [12–15]		**0.01*** [a]
NIHSS	13 [4–18]		5.5 [2–12]		**0.004**** [a]
mRS	4 [2–5]		3 [2–5]		**0.047*** [a]
Cause of stroke					0.59[b]
Cardioembolism	13 (29.5%)		31 (35.2%)		
Large artery atherosclerosis	7 (15.9%)		9 (10.2%)		
Other	24 (54.5%)		48 (54.5%)		
Localization		42		77	**0.03*** [b]
Cortical involvement	31 (70.5%)		41 (46.6%)		
Other	11 (25%)		36 (40.9%)		
Treatment					0.64[b]
Mechanical thrombectomy	11 (25%)		14 (15.9%)		
Intravenous thrombolysis	4 (9.1%)		11 (12.5%)		
Combined	4 (9.1%)		9 (10.2%)		
No revascularization treatment	25 (56.8%)		54 (61.4%)		
Complications					
Hemorrhagic transformation	9 (20.5%)	42	8 (9.1%)	72	0.14[b]
Days between stroke and early seizure	0 [0–1]				

Data are presented as median [interquartile range] for continuous variables, and n (%) for categorical variables. Abbreviations: GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale.
* $p < 0.05$ ** $p < 0.01$.
[a]Mann-Whitney *U* test [b]Chi-squared test.
[d] n = 44 unless otherwise stated. [e] n = 88 unless otherwise stated.

Table 3
Laboratory parameters on admission.

	Cases	n [d]	Controls	n [e]	p value
MAP, mmHg	110 [99–117]		106.67 [97–120]		0.82 [a]
Leukocyte count, 10^9/l	9.05 [7.33–12.43]		8.7 [6.825–10.4]		0.44 [a]
Neutrophil count, 10^9/l	6.15 [4.7–11.1]	29	6.1 [4.35–8.08]	60	0.31 [a]
Lymphocyte count, 10^9/l	1.14 [0.87–1.69]	29	1.454 [1.15–1.76]	60	0.12 [a]
Monocyte count, 10^9/l	0.67 [0.55–0.8]	28	0.67 [0.55–0.84]	60	0.78 [a]
Platelet count, 10^9/l	212 [173–289]		216 [187–254]	87	0.9 [a]
Neutrophil to lymphocyte ratio	5.6 [3.5–9.5]	29	4.4 [2.6–7.1]	60	**0.03*** [a]
Lymphocyte to monocyte ratio	1.8 [1.3–2.5]	28	2 [1.6–3]	60	0.12 [a]
Platelet to lymphocyte ratio	157.4 [122.2–262.9]	29	148.6 [109.1–198.6]	60	0.22 [a]
INR	1.06 [1.0–1.2]		1.0 [0.9–1.1]		**0.03*** [a]
PTT, s	23 [21–27]		23.5 [22–25]		0.9 [a]
Blood glucose, mmol/l	6.58 [6.66–7.8]		6.5 [5.55–8.15]		0.83 [a]
CRP, mg/l	33 [13–310]		39 [16–135]	86	0.74 [a]
Sodium, mmol/l	140 [136–142]		140 [138–142]		0.22 [a]

* $p < 0.05$.
Data are presented as median [interquartile range]. Abbreviations: MAP = Mean arterial pressure; INR = International normalized ratio; PTT = Partial thromboplastin time; CRP = C-reactive protein.
[a]Mann-Whitney *U* test.
[d] n = 44 unless otherwise stated. [e] n = 88 unless otherwise stated.

Table 4
Association between baseline characteristics and the occurrence of early seizure.

	Univariable results			**Multivariable results** [g]	
Variable	Odds ratio [CI 95%]	p value	n[f]	Adj. Odds Ratio [CI 95%] [h]	p value
Female sex	1.000 [0.483–2.068]	1.0			0.158
Age	1.000 [0.970–1.032]	0.99			0.184
Continuous medication					
Antiplatelet agents	1.262 [0.608–2.621]	0.533			
Anticoagulation	0.938 [0.398–2.215]	0.885			
Statins	1.105 [0.519–2.353]	0.796			
Pre-diagnoses					
Prior ischemic stroke	1.291 [0.602–2.769]	0.512			
Chronic alcohol abuse	1.537 [0.328–7.188]	0.585			
Diabetes mellitus	1.458 [0.629–3.348]	0.38			
Arterial hypertension	0.699 [0.285–1.714]	0.434			
Laboratory parameters					
MAP, mmHg	0.992 [0.969–1.015]	0.470			
Leukocyte count, 10^9/l	1.034 [0.947–1.130]	0.453			
Neutrophil count, 10^9/l	1.092 [0.971–1.228]	0.142	89		
Lymphocyte count, 10^9/l	0.420 [0.176–1.001]	0.05	89		
Monocyte count, 10^9/l	1.270 [0.236–6.846]	0.78	88		
Platelet count, 10^9/l	1.003 [0.999–1.008]	0.170	131		
Neutrophil to lymphocyte ratio	1.097 [1.007–1.195]	**0.035***	89	1.097 [1.005–1.197]	**0.038***
Lymphocyte to monocyte ratio	0.676 [0.411–1.111]	0.122	88		
Platelet to lymphocyte ratio	1.003 [0.999–1.007]	0.187	89		
INR	2.205 [0.795–6.897]	0.174			
PTT, s	1.064 [0.994–1.140]	0.073			
Blood glucose, mmol/l	1.000 [0.991–1.009]	0.999			
CRP, mg/l	1.008 [0.998–1.018]	0.126	130		
Sodium, mmol/l	0.952 [0.872–1.040]	0.280			
GCS	0.887 [0.785–1.002]	0.054			
NIHSS	1.051 [1.009–1.095]	**0.016***			0.187
mRS	1.240 [0.977–1.573]	0.077			
Cause of stroke		0.591			
Cardioembolism	Ref.	Ref.			
Large artery atherosclerosis	1.855 [0.569–6.043]	0.305			
Other	1.192 [0.529–2.686]	0.671			
Localization			119		
Cortical involvement	2.475 [1.089–5.622]	**0.03***			0.785
Other	Ref.	Ref.			
Treatment					
Mechanical thrombectomy	1.768 [0.701–4.456]	0.227			
Intravenous thrombolysis	0.818 [0.236–2.831]	0.751			
Combined	1.250 [0.379–4.127]	0.714			
No specific treatment	Ref.	Ref.			
Complications					
Hemorrhagic transformation	2.182 [0.770–6.178]	0.142	114		

* $p < 0.05$.
Abbreviations: CI = Confidence interval; MAP = Mean arterial pressure; INR = International normalized ratio; PTT = Partial thromboplastin time; CRP = C-reactive protein; GCS = Glasgow Coma Scale; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; ORs for every 1-point increase in age, GCS, NIHSS, mRS and laboratory parameters.
[f] n = 132 unless otherwise stated.
[g] n = 81 Patients were included in the multivariable logistic regression analysis. There were 28 cases and 53 controls.
[h] Adjustment for age, sex, neutrophil-to-lymphocyte ratio, NIHSS, stroke localization.

2.3. Statistical analysis

Normal distribution of data was examined using the Shapiro-Wilk-test. All included variables were not normally distributed. They were presented as median and interquartile range (IQR) and compared using Mann-Whitney U-tests.

Categorical variables were presented as absolute frequencies and percentages (%) and compared using the chi-squared test or Fisher's exact test.

We identified risk factors for the occurrence of EPSS using univariate binary logistic regression. Results were presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Age, sex, and variables statistically significant in the univariate regression analysis were entered into multivariable binary logistic regression (method: forward Wald, p-value cut off 0.05 for inclusion).

Patients with relevant missing values were excluded from multivariable logistic regression.

Results of multivariable logistic regression were presented as adjusted ORs with 95% CIs.

A receiver operating characteristic (ROC) analysis [32] was performed to evaluate the ability of the NLR to predict the occurrence of EPSS. The cut-off point that better predicted the presence versus absence of the study outcome (occurrence of EPSS) was determined as the value with the highest Youden's index.

To evaluate the relationship between age, NIHSS and NLR, Spearman's correlation analysis and visual assessment using scatter plots were employed.

We considered p-values < 0.05 as statistically significant. All reported p-values are two-sided.

We used IBM SPSS Statistics for Macintosh (Version 28.0.1.1) for matching and statistical analysis.

3. Results

Cases (patients with EPSS) included were 44 and controls (patients without EPSS) were 88. No differences were found in the demographic data and prior medical histories of participants (Table 1).

Compared to controls, patients with EPSS had more severe stroke, lower GCS, and higher NIHSS and mRS values at baseline (Table 2). Similarly, EPSS patients had a higher prevalence of stroke with cortical involvement. There were no significant differences in the type of treatment and the frequency of hemorrhagic transformation across groups.

Regarding laboratory parameters (Table 3), EPSS patients had higher NLR values (5.6 [3.5–9.5] vs. 4.4 [2.6–7.1]; $p = 0.03$) and INR values (1.06 [1.0–1.2] vs. 1 [0.9–1.1]; $p = 0.03$) on admission.

The NLR value ($p = 0.035$), NIHSS ($p = 0.016$) and cortical localization of stroke ($p = 0.03$) were significantly associated with the occurrence of EPSS in univariate logistic regression (Table 4). The multivariable logistic regression confirmed the independent association between NLR and EPSS (adjusted OR 1.097, 95% CI 1.005–1.197; $p = 0.038$). The AUROC for NLR to predict EPSS was 0.639 (95% CI: 0.517–0.761) with 2.98 as the best predictive cut-off value (Fig. 2).

There was a significant positive relationship between NLR and NIHSS ($r_S(87) = 0.383$, $p = < 0.001$). The relationships between NIHSS and age, as well as NLR and age were not significant ($r_S(130) = 0.129$, $p = 0.14$ and $r_S(87) = 0.153$, $p = 0.153$, respectively).

Correlations between metric predictor variables included in the multivariable logistic regression were low (all calculated correlation coefficients were below 0.40), indicating that multicollinearity was not a confounding factor in the analysis.

4. Discussion

This study suggested that the NLR on admission was significantly higher in patients with acute ischemic stroke and EPSS compared to patients with ischemic stroke and no EPSS, and that higher NLR values could predict the occurrence of EPSS in this stroke population.

In the present study, the NIHSS score did not remain independently associated with EPSS, even though stroke severity has been shown to be a factor in the development of EPSS [33,34]. This likely is due to the selection of patients that were included in the multivariable analysis ($n = 81$). In this patient subgroup, NIHSS was not significantly associated with the occurrence of EPSS in univariate binary logistic regression (OR 1.036, 95% CI: 0.987–1.087, $p = 0.151$ and OR 1.380, 95% CI: 0.544–3.499, $p = 0.498$, respectively).

If NLR was excluded from multivariable logistic regression analysis in our study group, more patients could be included in the multivariable regression ($n = 119$) and the NIHSS solely remained statistically significant (adjusted OR 1.046, 95% CI: 1.004–1.09, $p = 0.03$, variables also included: age $p = 0.947$; female sex $p = 0.671$; cortical localization $p = 0.084$). Therefore, the results of the multivariable logistic regression in this study should be interpreted taking the difference in sample group into account.

Previous studies have shown that patients with epilepsy or seizures have an increased NLR in the acute phase of a seizure [35,36]. However, this association does not automatically mean that there is a causal relationship between increased NLR and occurrence of epileptic seizures.

In the current study, the EPSS group not only had an increased NLR but also higher stroke severity. Stroke can elicit an inflammatory response [10], as the lack of blood flow to brain tissue leads to uncontrolled release of neurotransmitters within the ischemic penumbra that can result in increased excitotoxicity. At the same time, inflammatory processes begin immediately after the cerebral ischemia. Thrombin acts as a chemotaxin for leukocytes [10] and activates the complement system, which further leads to a strong inflammatory response [37]. This favors the breakdown of the blood–brain barrier (BBB) and the invasion of brain tissue by inflammatory cells [10]. Neutrophils move into the brain tissue after cerebral ischemia and maintain the inflammatory response [38]. Such an increasing activity of neutrophils promotes the impairment of the BBB [39]; in turn, the disrupted BBB leads to the release of cytokines into the bloodstream [40], increasing neuronal excitability and promoting systemic inflammation [11].

Lymphocytes have a regulatory effect in the immune response [10] and the predominance of proinflammatory neutrophils as part of the innate immune system could lead to an imbalance and to a poorly controlled immune response in patients with seizures. It is also worth to notice that increased NLR values have been associated with worse outcome after ischemic strokes [18,23] and in people with epilepsy, the lymphocyte count has been shown to decrease and neutrophil count to increase [41].

There was a low correlation between NLR and NIHSS [42]. Therefore, the NLR seems to be a marker that is connected to stroke severity but also points to other factors at play. It may, hence, be speculated that the increased NLR acts as a surrogate marker of an exaggerated immune response and ischemic stroke patients with such an exaggerated immune response are more prone to develop EPSS. Of note, we found no differences across groups in any other inflammatory parameters on admission, such as CRP. This may suggest that NLR is a biomarker with higher and earlier predictive value than other parameters. Of note, one advantage of the NLR is that it can be easily and routinely measured. The NLR could, hence, be adopted by studies evaluating the role of short-term prophylaxis of post-stroke seizures, an area still surrounded by lack of robust evidence [13,43].

4.1. Strengths and limitations

The present study suffers some limitations due to its retrospective design, with lack of, or incomplete data in some patients, which needs to be considered when interpreting the results of the multiple regression analysis. However, since the study was conducted in an acute setting, the recall bias was likely negligible. An encephalogram was not recorded in

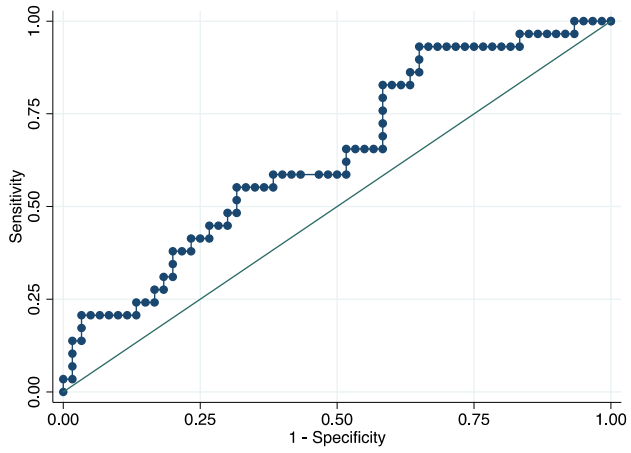

Fig. 2. Receiver operating characteristic curve for the prediction of acute symptomatic post-stroke seizures. Predictive values of the NLR for the occurrence of acute symptomatic post-stroke seizures. Area under the curve 0.639 (95% CI: 0.517–0.761). Abbreviations: CI = confidence interval; NLR = neutrophil-to-lymphocyte ratio.

most cases, with the potential risk of missing seizures with minor symptomatology. There is also the possibility of an unrecognized seizure occurring at stroke onset, prior to admission. This might lead to the missing of seizures or could alter the parameters recorded.

The patient sample included in the study was also rather small, and this carries the risk of imprecise estimates. However, the case-control design made it possible to efficiently study patients with a relatively rare disease [44] (the incidence of EPSS after an ischemic stroke is around 3.3% [3]) to pave the way for further studies in this field.

5. Conclusion

The NLR has gained increasing interest in recent years and is regarded as a reliable biomarker of inflammation. This study provided preliminary evidence supporting the role of the NLR in predicting the occurrence of EPSS following an ischemic stroke. Future prospective, multicenter studies are required to further investigate the potential of NLR in predicting the occurrence of EPSS as well as of subsequent post-stroke epilepsy.

CRediT authorship contribution statement

Lea Ebner: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing, Conceptualization. **Piergiorgio Lochner:** Conceptualization, Resources, Supervision, Writing – review & editing. **Simona Lattanzi:** Conceptualization, Formal analysis, Visualization, Writing – review & editing. **Francesco Brigo:** Conceptualization, Supervision, Writing – review & editing. **Gudrun Wagenpfeil:** Formal analysis, Supervision, Writing – review & editing. **Klaus Faßbender:** Resources, Supervision. **Frauke Röll:** Conceptualization, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: F. B. is a member of the editorial board of Epilepsy & Behavior. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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