Admission neutrophil-to-lymphocyte ratio predicts length of hospitalization and need for ICU admission in adults with Status Epilepticus

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ARTICLE INFO

Keywords:
Status epilepticus
Inflammation
Systemic inflammatory response syndrome
Biomarkers

ABSTRACT

Background and objectives: Status epilepticus (SE) is a time-dependent neurological emergency. The current study evaluated the prognostic value of admission neutrophil-to-lymphocyte ratio (NLR) in patients with status epilepticus.
Methods: In this retrospective observational cohort study we included all consecutive patients discharged from our neurology unit with the clinical or EEG diagnosis of SE from 2012 to 2022. Stepwise multivariate analysis was conducted to test the association of NLR with length of hospitalization, need for Intensive Care Unit (ICU) admission and 30 days mortality. Receiver operating characteristic (ROC) analysis was performed to identify the best cutoff for NLR to identify patients who will need ICU admission.
Results: A total of 116 patients were enrolled in our study. NLR was correlated with length of hospitalization ($p = 0.020$) and need for ICU admission ($p = 0.046$). In addition, the risk of ICU admission increased in patients with intracranial hemorrhage and length of hospitalization was correlated with C-reactive protein-to-albumin ratio (CRP/ALB). ROC analysis identified a NLR of 3.6 as best cutoff value to discriminate need of ICU admission (area under the curve [AUC]=0.678; $p = 0.011$; Youden's index=0.358; sensitivity, 90.5%, specificity, 45.3%).
Discussion: In patients with SE admission NLR could be a predictor of length of hospitalization and need for ICU admission.

1. Introduction

Status epilepticus (SE) is a neurological emergency characterized by a high mortality and morbidity rate, and high healthcare costs associated [1]. Early seizure interruption, to prevent time-dependent neuronal damage, must be considered the primary goal of the treatment. The speed of intervention and the risk of long-term consequences depends mainly on the type of clinical presentation, roughly divided into convulsive status epilepticus and non-convulsive status epilepticus (NCSE) according to the presence or absence of prominent motor symptoms [2]. The introduction of reliable prognostic markers into clinical practice could be useful in rapidly identify critically ill patients, discriminating patients who may need admission in the Intensive Care Unit (ICU) from those with a favorable prognosis. Currently, two different prognostic scores are used: the Status Epilepticus Severity Score (STESS) [3] and the Epidemiology-based Mortality score in Status Epilepticus (EMSE) [4]. STESS considers at the time of presentation the level of consciousness, the seizure type, the patient's age and history of seizures while EMSE rating depends on etiology, comorbidities and EEG findings. However, both scores lack the evaluation of biomarkers reflecting the response of the immune system, which has been shown to be associated with SE severity by several studies on animal models, but also through clinical evidence [5,6]. The onset of SE activates an inflammatory cascade that leads to the synthesis and release of a large amount of inflammatory mediators, which can induce blood-brain barrier (BBB) disruption and edema, with the result of increasing the risk of epileptogenesis [7]. Over the past 20 years, several studies have reported that neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (MRL), and C reactive protein-to-albumin ratio (CRP/ALB) can be considered as potential novel biomarkers of systemic inflammation. Recently, investigators have examined the role of NLR and inflammation

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in human disorders, such as sepsis [8], spontaneous bacterial peritonitis [9], nonalcoholic fatty liver disease [10], Guillain Barré syndrome [11], infectious diseases, cardiovascular diseases, and different forms of cancer [12–15]. Numerous evidences have also been collected in the neurological field, demonstrating the possible usefulness of NLR in stroke, spontaneous intracerebral hemorrhage, and traumatic brain injury [16–18]. Accordingly, a recent manuscript had systematically reviewed the role of NLR in epilepsy [19]. However, there was not any study on the predictive role of NLR in length of hospitalization and need for ICU admission in Status Epilepticus. Regarding the availability and low cost that requires a blood test necessary for the evaluation of these parameters, an association with the prognosis of SE could facilitate early risk stratification and thus clinical management. The aim of our study was to explore the correlation between admission NLR and the hospitalization time, need for ICU admission and 30 days mortality. Therefore, we assessed if PLR, MLR and CRP/ALB correlates with the same outcome measures.

2. Methods

In this retrospective observational cohort study, we reviewed all the consecutive patients discharged from a university hospital neurological ward and neurological sub-intensive care unit from 2012 to 2022 with the clinical diagnosis of SE. All the data were obtained from institutional digital registry. We collected the demographic data, clinical characteristics, comorbidities, length of hospitalization, necessity for Intensive Care Unit (ICU) admission, number of antiseizure medications (ASMs) used to treat the patient during the hospitalization, and previous history of seizures. Laboratory data were collected only if comprehensive of complete cell blood count (CBC) and performed within 24 h from the admission. Patients with missing clinical or laboratory data, hematological disease (such as leukemia affecting neutrophils and lymphocytes), and those using medication affecting the neutrophils and lymphocytes counts were excluded from the study. For a better interpretation of clinical records participants were grouped into two categories of state of consciousness based on Leitinger [20] (Unaltered Consciousness (UC) = fully awake + awake with altered cognition, Altered Consciousness (AC) = Somnolence + Stupor + Coma). All EEG of patients diagnosed with non-convulsive status epilepticus (NCSE) were reviewed by an expert neurophysiologist and the diagnosis was confirmed according to Salzburg's Criteria [21].

Statistical analysis was performed using SPSS statistics version 24 (IBM, Armonk/NY, USA). Kolmogorov–Smirnov test was used to evaluate the normal distribution of variables. Continuous variables with a normal distribution are presented as mean and standard deviations (SDs), those with a skewed distribution as median and interquartile ranges (IQRs) indicating the first and third quartiles, and categorical variables as counts and percentages (%). To determine factors associated with length of hospitalization, need for ICU and 30 days mortality, stepwise linear and binary regressions were performed. In particular, variables associated with p values < 0.10 at univariate analysis were selected as candidate factors linear model. Results are presented as B or OR and 95% confidence intervals (95% CI). Significance is set for $p<0.05$. A receiver operating characteristic (ROC) curve and Youden's J statistic were used to determine the cutoff value for NLR [22]. Then, patients were dichotomized according to the identified cutoff value.

This retrospective study has been approved by the local IRB. For this type of study, formal consent is not required. The study conforms with the World Medical Association Declaration of Helsinki.

3. Results

3.1. Baseline characteristics

A total of 140 patients were identified; 8 patients were excluded from the analysis for erroneous diagnosis, 15 were excluded for lack of complete blood count (CBC), and one for severe pancytopenia (Fig. 1). 116 patients fulfilled the inclusion criteria. The median age of included patients was 73 (63 – 81) years. Of 116 patients 98 (84.5%) were woman and 18 (15.5%) males. Ninety patients were diagnosed with NCSE (77.6%) while convulsive status epilepticus affected 26 patients (22.4%). We found UC in 77 patients (66.4%) while 39 had AC (33.6%). Fifty-three (44.2%) patients had a previous diagnosis of epilepsy at ward admission. Other information about SE etiology and comorbidities conditions are reported in Table 1.

3.2. Laboratory tests and clinical course

At the time of admission, the median plasma level of C-reactive protein (CRP) was 11.7 (2.6 – 25.6) and the median white blood cell (WBC) count was 8.00 (6.38 – 10.7) of which 5.66 neutrophils (4.175 – 8.36) and 1.30 lymphocytes (0.86 – 1.80). Median NLR, PLR and MLR were 4.53 (2.59 – 9.00), 164.92 (113.99 – 230.32) and 0.47 (0.33 – 0.76) respectively. Median albumin to CRP ratio was 3.68 (0.69 – 10.81). Median length of hospital stay was 17 days (8 – 33) and the number of patients admitted to the ICU was 21 (17.5%). For other information on laboratory findings see Table 2.

3.3. Regression analysis

Univariate regression analysis suggested a potential association between length of hospitalization and sex ($p = 0.089$), NLR ($p = 0.017$), PLR ($p = 0.033$), infection at the time of admission ($p = 0.010$), and CRP/ALB ($p<0.001$). When these variables were included in the multivariate analysis, only NLR and CRP/ALB remained significant predictors of length of hospitalization. In the univariate analysis the need for ICU admission resulted significantly associated with intracerebral hemorrhage (ICH), age, NLR and AC. In the stepwise multivariate analysis the association between AC and risk for ICU admission lost significance while NLR and the other items retained their significance. Data of stepwise regression are reported in Table 3. In univariate analysis age ($p = 0.028$) and CRP/ALB ($p = 0.068$) were potential predictors of 30 days mortality from admission, but neither showed significance in multivariate analysis.

ROC analysis identified a NLR of 3.6 as the best cutoff threshold to predict the need for ICU admission (Fig. 2) (area under the curve [AUC]=0.678; $p = 0.011$; Youden's index=0.358; sensitivity, 90.5%, specificity, 45.3%; ICU admission: NLR$\geq$3.6 (19/21, 90.5%) vs non ICU admission NLR$\geq$3.6 (52/95, 54.7%) $p = 0.02$).

4. Discussion

In the current study, admission NLR was strongly associated with length of hospitalization and need for ICU admission. The NLR is the number of neutrophils divided by the number of lymphocytes. Under physiologic stress, the number of neutrophils increases, while the number of lymphocytes decreases. The NLR combines both changes, making the score more sensitive. Endogenous cortisol and catecholamines may be major drivers of the NLR variations. Increased levels of cortisol are known to increase the neutrophil count while simultaneously decreasing the lymphocyte count [23]. Likewise, endogenous catecholamines may cause leukocytosis and lymphopenia [24]. Neutrophils are the most abundant leukocytes in the circulation and act as our immune system's first line of defense. Epileptic seizure triggers a systemic inflammatory reaction that leads to increased levels of neutrophils. As demonstrated by several studies, neutrophils can cause neuronal hyperexcitability both directly and indirectly, by stimulating the release of inflammatory cytokines and chemokines [25]. On the other hand the role of lymphocytes in epilepsy has been less studied. However, it seems that lymphocyte levels are significantly lower in patients with epilepsy compared to controls, particularly in the acute phase [25,26]. So the NLR combines both changes, making the score

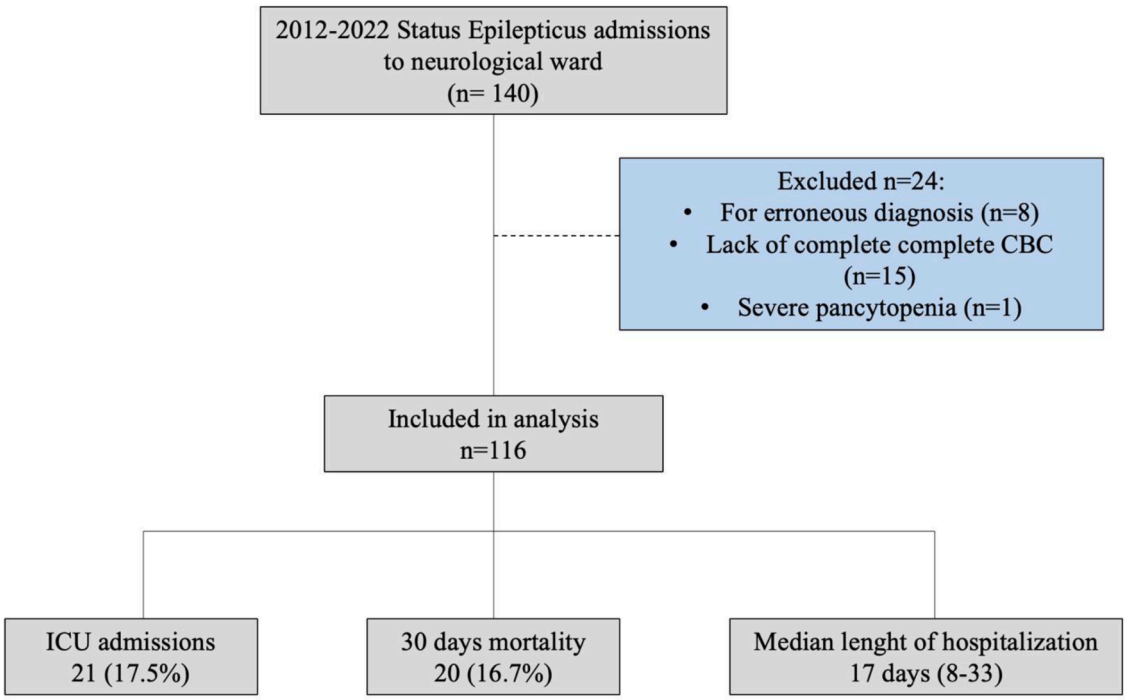

Fig. 1. Flowchart of included patients. A total of 140 Status Epilepticus patients were identified. Twenty-four of them did not meet the inclusion criteria; 116 were included in the final analysis. CBC = Complete Blood Cell count, ICU = intensive care unit.

Table 1
Demographic characteristics of the included sample (n = 116). Medians (IQRs) and proportions as appropriate.

Sex n (%)	
M	18 (15.5%)
F	98 (84.5%)
Age (y)	73 (63 – 81)
Clinical presentation n (%)	
CSE	26 (22.4%)
NCSE	90 (77.6%)
State of consciousness	
Unaltered Consciousness	77 (66.4%)
Altered Consciousness	39 (33.6%)
SE etiology n (%)	
Ischemic stroke	9 (7.5%)
Intracerebral hemorrage	7 (5.8%)
Brain metastases	3 (2.5%)
Primary CNS neoplasia	4 (3.3%)
Acute coronary syndrome	4 (3.3%)
Bacterial infection	20 (17.2%)
Viral encephalitis	3 (2.5%)
Comorbidities n (%)	
Arterial hypertension	46 (38.3%)
Diabetes mellitus	19 (15.8%)
Chronic heart disease	13 (10.8%)
Atrial fibrillation	17 (14.2%)
Chronic kidney failure	10 (8.3%)
Previous stroke	20 (16.7%)
Epilepsy history	53 (44.2%)

Notes: CSE = Convulsive Status Epilepticus, NCSE = Non-Convulsive Status Epilepticus, CNS = Central Nervous System, IQRs = Interquartile Range (25th −75th percentile).

Table 2
Laboratory tests and outcomes; data represented as median (IQR) or number (%) as appropriate.

Laboratory findings	Median	IQR
RBC ($x10^6/\mu L$)	3.90	3.42 – 4.40
Plts($x10^3/\mu L$)	200.00	166.25 – 258.00
WBC ($x10^3/\mu L$)	8.00	6.38 – 10.7
Neutrophils ($x10^3/\mu L$)	5.66	4.175 – 8.36
Lymphocytes ($x10^3/\mu L$)	1.30	0.86 – 1.80
Monocytes ($x10^3/\mu L$)	0.64	0.44 – 0.81
Eosinophils ($x10^3/\mu L$)	0.06	0.01 – 0.15
CRP (mg/L)	11.7	2.6 – 25.6
ESR (mm/h)	30.5	16.0 – 45.5
Ferritin (μg/L)	97.8	42.75 – 261.65
Albumin (g/dL)	3.40	3.12 – 3.73
NLR	4.53	2.59 – 9.00
PLR	164.92	113.99 – 230.32
MLR	0.47	0.33 – 0.76
CRP/ALB	3.68	0.69 – 10.81
Clinical course and outcome		
Lenght of hospitalization (days)	17.00	8.00 – 33.00
Patients admitted to ICU (%)	21 (17.5%)	
30 days mortality	20 (16.7%)	

Notes: RBC = Red Blood Cells, Plts = Platlets, WBC = Wite Blood Cells, CRP = C-Reactive Protein, ESR = Erythrocytes Sedimentation Rate, NLR = Neutrophil to Lymphocyte Ratio, PLR = Platlet to Lymphocyte Ratio, MLR = Monocyte to Lymphocyte Ratio, CRP/ALB = C-Reactive Protein to Albumin ratio, ICU = Intensive Care Unit.

more sensitive. In previous studies NLR was a strong predictor of good clinical outcome in patients with neurological acute conditions such as traumatic brain injury [18], ischemic stroke [22] and subarachnoid hemorrhage [27]. Regarding epilepsy, previous studies have shown that NLR levels increase in the acute phase of SE, and then decrease, remaining higher than healthy controls in the following days [28]. However, to our knowledge, this study is the first that evaluated the prognostic value of NLR in SE. Our results suggest how NLR is an independent predictor of length of hospitalization and need for ICU admission in patients with status epilepticus. This phenomenon could be explained by the predominant role of inflammation in generating neuronal and astroglial damage. Animal studies support that induction of SE can cause a rapid and intense brain inflammatory cascade, causing the activation of microglia and astrocytes. The direct consequence is the release by the microglia of large amounts of pro-inflammatory mediators, including IL-1β, cyclooxygenase-2 (COX-2), HMGB1 and tumor necrosis factor α (TNF-α), which can induce neuroinflammation through

Table 3
Regression analysis. Results are represented as OR and B as appropriate.

ICU admission			
	OR	CI 95%	*p*
ICH	10.013	1.811 – 58.899	0.009
NLR	1.065	1.001 – 1.134	0.046
Age	0.941	0.906 – 0.977	0.002
Length of hospitalization			
	B	CI 95%	*p*
CRP/ALB	0.604	0.315 – 0.892	<0.001
NLR	0.759	0.112 – 1.395	0.020

ICU = Intensive Care Unit, ICH = Intracerebral Hemorrhage, NLR = neutrophil-to-lymphocyte ratio, CRP/ALB = C-Reactive Protein to Albumin ratio.

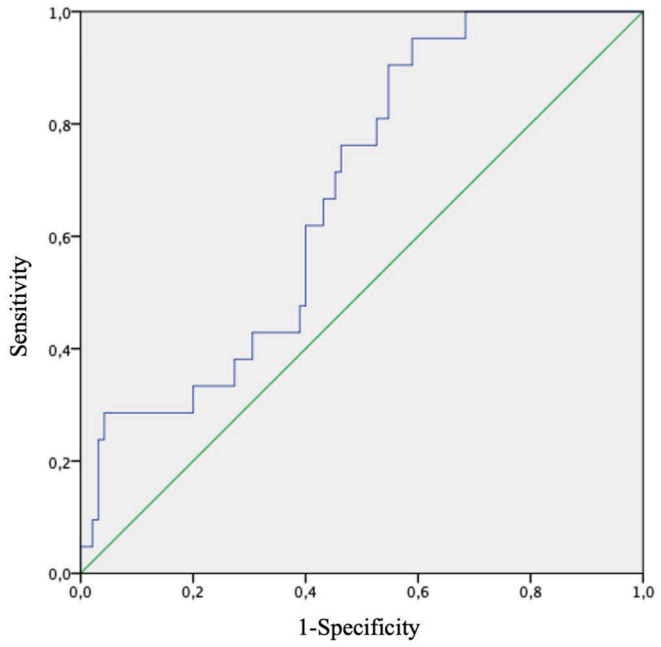

Fig. 2. Association of neutrophil-to-lymphocyte ratio with intensive care unit (ICU) admission. Receiver operating characteristic plot demonstrated the area under the curve (AUC) for ICU admission (AUC=0.678; $p = 0.011$; Youden's index=0.358; sensitivity, 90.5%, specificity, 45.3%). The cutoff value was detected at 3.6.

a variety of signaling pathways [29]. Neuroimaging-based studies support the evidence of a hypermetabolic state during SE. In fact, during epileptic activity in perfusional and metabolic we can detect studies an increased cerebral blood flow and metabolic activity, consistent with neuroinflammation [29–31]. Anyhow in status epilepticus, neuroinflammation seems to be a face of a systemic inflammatory process that contributes to the progression of brain damage. Indeed a recent study demonstrated how status epilepticus is frequently associated with systemic inflammation response syndrome (SIRS) which is an independent predictor of death in critically-ill patients [32–34]. Inflammatory response in SE could lead to a self-sustaining circle that can lead to direct brain damage through blood-brain barrier disruption and even indirect insult by conditions such as hyperglycemia, cardiovascular instability or immunodepression and consequent infection [35–37]. Those factors could lead to an increased risk of adverse events. A recent systematic review showed that even in people with epilepsy not suffering from SE the risk of cerebrovascular and cardiovascular events is increased [38]. We can speculate that risk could be even greater in SE and that inflammation could play a central role in developing structural multi-organ alterations [39]. Furthermore, the evidence that antagonizing peripheral inflammation through the use of systemic corticosteroids or targeted therapies could lead to interruption of SE supports this hypothesis [39–42].

Initial evaluation of status epilepticus should be based on two clinical scores: STESS and EMSE. STESS is a score that evaluates clinical features at the presentation such as age, history of seizures, worst type of seizure and consciousness [3]. EMSE tried to improve the prediction power including information about comorbidities, etiology and EEG features [4]. None takes in consideration serum or cerebrospinal fluid biomarkers. Our study supports the potential role of admission NLR in predicting the need of intensive care in patients with SE. In our opinion implementation of admission NLR in clinical scores could ameliorate the accuracy of the risk stratification.

We found a NLR value greater than 3.6 to be the best cutoff threshold to predict the need of ICU admission. However, in our sample we found a low specificity in the prediction: this finding could be explained by the high age of our population and consequently the lower chance to be admitted to ICU.

Our study has some limitations due to the observational nature and the consequent absence of randomization creating unbalances of population characteristics. Compared to other population-based studies the sample of this study was characterized by older people [20]. This could be due to the enrollment of patients that was performed from the records of our neurology unit admissions. Nevertheless, the region where the study was conducted is characterized by a high prevalence of elder people. Data from patients who were not admitted from the Emergency Department or were directly admitted in ICU were not available; therefore present results should be cautiously interpreted when translated to other populations. The advanced age of the population could influence negatively the prognosis of our patients and lower the chance of admission to ICU. Larger prospective studies are needed to validate the predicting value of NLR in SE.

5. Conclusion

In patients with SE, admission NLR is an independent predictor of length of hospitalization and need for ICU admission. NLR is no associated with 30 days mortality. Calculating admission NLR and implementing it to clinical scores could ameliorate prognosis prediction in SE.

CRediT authorship contribution statement

Sasha Olivo: Conceptualization, Writing – original draft, Data curation, Formal analysis, Writing – review & editing. **Alex Buoite Stella:** Conceptualization, Writing – original draft, Data curation, Formal analysis, Writing – review & editing. **Stefania Pavan:** Data curation, Writing – original draft, Formal analysis, Writing – review & editing. **Matteo Cegalin:** Writing – review & editing. **Giovanni Furlanis:** Writing – review & editing. **Marta Cheli:** Writing – review & editing. **Marinella Tomaselli:** Writing – review & editing. **David Stokelj:** Writing – review & editing. **Paolo Manganotti:** Conceptualization, Formal analysis, Writing – review & editing.

Declarations of Competing Interest

None.

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