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Article

Peripheral Blood Cell Ratios, Promising Predictive Biomarkers for the Diagnosis of Pediatric Autoimmune Encephalitis

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Abstract

Background: Autoimmune encephalitis (AE) is an increasingly well recognized disorder in the past decade both in adults and in children, yet pediatric data are still limited. A full peripheral blood cell count is a routine examination that provides valuable information regarding the immune system. Thus, there are peripheral blood cell count (PBCC)- derived ratios that reflect systemic inflammatory activity and have been associated with disease severity in adults: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratios (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI). **Methods:** This study is a retrospective chart review of children under 18 years diagnosed with definite or probable AE and treated in our institution from January 1, 2018 until December 1, 2025. Only patients with available PBCC results prior to any immunomodulatory therapy were included. An age-matched control group was created by selecting results of PBCC of patients presenting for routine pediatric follow-ups with normal inflammatory and hematologic parameters. Group means were compared using independent samples t-test or the Mann Whitney U test for non-normally distributed data. Analysis of the receiver operating characteristics curve (ROC curve) was conducted followed by the area under the curve ROC curve (AUC). **Results:** 45 children with AE and 150 controls were included in the study. NLR, PLR, SII, SIRI and AISI values were significantly higher in AE patients compared with controls, suggesting an overall pro-inflammatory profile at presentation. Concerning the platelet indices, a trend toward higher medium platelet volume and platecrit was observed in the AE group. These findings point to distinct peripheral immune alterations in pediatric AE, consistent with reports in adult patients. **Conclusions:** Our results suggest that at the time of the initial hospitalization, children with AE already show altered peripheral immune cell profiles compared to their age-matched peers. The high specificity and the low sensitivity of the inflammatory indices make them more suitable for supporting the AE diagnosis in suggestive clinical circumstances, but not for screening. These results represent a foundation for further investigating the roles that these indices have both as diagnostic and prognostic factors for these children.

Keywords: pediatric autoimmune encephalitis; neuroinflammation; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratios; monocyte-to-lymphocyte ratio; systemic immune-inflammation index; systemic inflammation response index; aggregate index of systemic inflammation

Introduction

Autoimmune encephalitis (AE) is an increasingly well recognized disorder in the past decade. Whereas clinical and pathophysiological studies mostly report on adult patient, pediatric autoimmune encephalitis (PAE) remains less well studied, presumably due to its lower incidence [1].

Patients with an initial PAE presentation require thorough clinical and laboratory examinations to establish diagnosis and treatment [2,3]. A full peripheral blood cell count is a routine investigation providing important information regarding the immune system.

The concept of calculating ratios of various components of the peripheral blood cell count (PBCC) as a measure of the immune and inflammatory status of patients was initially described in a paper investigating the neutrophil-to-lymphocyte ratio (NLR) in critically ill cancer patients [4]. Since then, peripheral blood cell ratios have expanded. Considerable data exists from both adult and pediatric studies involving the NLR, platelet-to-lymphocyte ratios (PLR), monocyte-to-lymphocyte ratio (MLR, sometimes calculated as the inverse of the MLR, the “lymphocyte to monocyte ratio” or LMR) in various conditions such as cancer, infection and a variety of autoimmune or inflammatory conditions [5–10]. Several indices have also been developed, based solely on the readily available peripheral blood cell counts: systemic immune-inflammation index (SII) [11], systemic inflammation response index (SIRI) [12], aggregate index of systemic inflammation (AISI) [13].

The *platelet* count is an important factor in many of the ratios and indices summarized above. There is evidence that platelet-specific parameters such as the mean platelet volume (MPV), the platelet distribution width (PDW), plateletcrit (PCT) are also correlated with immune or inflammatory disease states in adults [14,15] but data from children is more ambiguous [16–18].

There has been comparatively little evidence published regarding peripheral blood cell ratios and indices in patients with autoimmune encephalitis.

Most data come from adult studies. Recent work shows that peripheral immune cell ratios are associated with worse prognosis of AE in adults with higher ratios [19,20]. Other studies indicated that higher NLR is correlated with treatment failure of first line treatment options such as intravenous corticosteroids, plasma exchange or intravenous immunoglobulins [21,22]. Very limited data exists regarding the additional indices peripheral blood cell indices in patients with AE. Data from a single study shows that higher values of the SII correlates with worse outcome after 30 days after treatment initiation [23].

To date, there is a single study concerning pediatric AE, indicating that in 36 children with AE associated with N-methyl-D-aspartate receptor antibodies (NMDA AE), a higher NLR predicted the need for intubation in the ICU of these patients.

Our research studies the value of the peripheral blood cell ratios for AE diagnosis prediction in children with suggestive AE symptoms. To our knowledge, we provide the first measurement of AISI in AE.

2. Methods

This is a retrospective study (January 1, 2018, to December 1, 2025) of the medical records of a group of patients with AE and an age matched control group, admitted in a single Reference Center for Rare Pediatric Neurology disorders. All data were anonymized prior to analysis to ensure patient confidentiality. This study was approved by the Ethics Committee of the “Prof. Dr. Alexandru Obregia” Clinical Hospital of Psychiatry, according to the Declaration of Helsinki (Ethics approval number: 142/May 17, 2024).

2.1. The Study Group

We searched the patients in the electronic archive of the hospital using the diagnostic keywords “Autoimmune Encephalitis”.

The diagnosis of possible, probable or definite Autoimmune Encephalitis was established at the moment of this research, using De Bruijn et al. (2020) criteria [1].

The inclusion criteria for the study group were: 1. Diagnosis of definite or probable AE [1]; 2. < 18 years old at the time of disease onset; 3. PBCC available at the time of disease onset; 4. Immunomodulatory treatment not used before PBCC prelevation.

Exclusion criteria were: 1. Lack of PBCC at first admission; 2. Immunomodulatory treatment prior to first available PBCC; 3. Clinical or paraclinical evidence suggesting a structural, metabolic or infectious etiology as a more reasonable explanation for seizures or encephalopathy.

2.2. The Control Group

A group of hospital-based control participants was created by selecting anonymized normal results of PBCC of patients presenting for routine pediatric follow-ups and children presenting for physical therapy and rehabilitation procedures in our institution. Exclusion criteria were: 1. Any elevated inflammatory biomarkers at the time of PBCC; 2. Abnormal absolute values of white blood count, neutrophils, lymphocytes, monocytes, red blood cells, hemoglobin and platelets.

Extracted data included: sex, age at onset, type of AE (probable or definite AE, specific antibody –defined categories when available), PBCC at diagnosis (absolute values of white blood count, neutrophils, lymphocytes, monocytes, red blood cells, hemoglobin and platelets, MPV, PDW, PCT). We calculated the peripheral blood cell ratios (NLR, MLR, PLR, SII, SIRI, AISI).

2.3. Statistical Analysis

All data were analyzed using the JASP software, version 0.95.4, which is based on the R language for statistical programming [24,25]. Normality was assessed using the Shapiro-Wilk test and homogeneity of variance was evaluated using the Brown-Forsythe test. The groups were compared using the independent samples t-test or the Mann Whitney U test for non-normally distributed variables. Effect sizes were reported using Cohen's d.

Receiver operating characteristics ROC (analysis) and the area under the ROC curve (AUROC) were computed to evaluate the discriminative ability of each PBCC derived inflammatory ratio in distinguishing AE patients from controls. For ROC, AUROC and Youden's index we used Jamovi software, version 2.7.16.

Within the study group, subgroups based on etiology (NMDA, GAD, VGCK, Rasmussen, Seronegative) and type of AE (probable/definite) were created to compare the PBCC ratios.

3. Results

A total of 55 children and adolescents diagnosed with AE during the study period (January 2018-December 2025) were initially screened. After applying the predefined inclusion and exclusion criteria, 45 patients were included in the final analysis. The primary reasons for exclusion were absence of a PBCC at initial presentation or before the initiation of immunomodulatory therapy and the diagnosis of possible AE. Among them, 27 (60%) were female and 18 (40%) male (female-to-male ratio 1.5:1). Based on previously published pediatric AE criteria [1,2], 22 patients (49%) had probable AE, and 23 patients (51%) - definite AE.

The control group included 150 individuals that fulfilled the inclusion and exclusion criteria.

Among etiological subtypes, anti-NMDA receptor encephalitis was the most frequent form, 12 of 45 cases (26.7%), consistent with current epidemiologic data describing its predominance among pediatric AE presentations [35]. Four patients (8.9%) were diagnosed with AE associated with antibodies against voltage-gated potassium channel complex (VGCK). One patient had dual anti-NMDA and anti-GAD antibodies; one patient had isolated anti-GAD antibody-associated encephalitis. Five patients (11.1%) were diagnosed with Rasmussen encephalitis.

Due to the small number of cases within each etiological subgroup, no subgroup-specific comparisons of inflammatory indices were performed. Consequently, analyses were limited to

comparisons between control group and study group (Table 1), and between definite and probable AE (Table 5).

Before performing the group comparisons, data distribution and homogeneity of variance were assessed. The Shapiro-Wilk test showed that most parameters displayed non-normal distributions in both groups ($p<0.05$). The Brown- Forsythe test further indicated unequal variances between patients and controls for most variables, supporting the use of non-parametric testing for the majority of comparisons.

Table 1 provides descriptive statistics of the study and control groups. There is no statistically significant difference in age between the 2 groups ($p=0.959$). Patients with AE displayed significantly higher leukocyte counts than controls and elevated neutrophil counts. In contrast, lymphocyte levels are lower in the AE group. Platelet characteristics showed a heterogeneous pattern. Platelet count and PDW did not differ significantly. MPV was modestly but significantly higher in AE patients, while PCT demonstrated a more robust elevation. Inflammatory composite indices derived from PBCC demonstrated the most discriminative power. Compared with controls, AE patients exhibited significantly increased NLR, PLR, MLR, SII, AISI, SIRI. NLR and SII had the highest effect size.

Table 1. Study and control group PBCC indices analysis.

Mann Whitney U (T-Test*)						
	C/P	N	Median (Mean*)	IQR (SD*)	p	Effect size
Age (months)#	P	45	94.500	72.750	0.920	-0.010
	C	150	92.000	91.000		
WBC	P	45	7.365	6.697	0.017	0.210
	C	150	8.450	3.430		
Ne	P	45	3.155	0.737	0.002	0.292
	C	150	4.209	0.590		
Ly [†]	P	45	2.810	2.800	0.003	-0.276
	C	150	2.370	2.000		
Mon	P	45	0.565	91.000	0.204	0.081
	C	150	0.590	110.000		
Hgb	P	45	12.800	147.150	0.005	-0.124
	C	150	41.000	50.800		
PLT*	P	45	291.200	5.582	0.120	-0.129
	C	150	309.900	98.520		
MPV	P	45	9.900	1.100	0.045	0.172
	C	150	10.350	1.975		
PDW	P	45	12.550	5.650	0.827	-0.096
	C	150	12.200	3.200		
PCT	P	45	0.285	0.090	0.007	0.251
	C	150	0.320	0.122		
NLR	P	45	1.105	0.735	<.001	0.310
	C	150	1.609	2.983		
MLR	P	45	0.183	0.106	0.050	0.162
	C	150	0.220	0.199		
PLR	P	45	104.613	45.198	0.008	0.238
	C	150	110.550	108.244		
SII	P	45	330.735	253.917	<.001	0.308
	C	150	403.930	794.003		
SIRI	P	45	0.580	0.545	0.004	0.259
	C	150	0.968	1.829		

AISI	P	45	170.017	205.956	0.004	0.262
	C	150	248.698	448.443		

AISI, aggregate index of systemic inflammation; C, control group; Effect size reflects the magnitude of group differences; Hgb, hemoglobin; IQR, interquartile range; Ly, lymphocytes; Median, median value for the whole group; MLR, monocyte-to-lymphocyte ratio; Mon, monocytes; MPV, mean platelet volume; N, number; Ne, neutrophils; NLR, neutrophil-to-lymphocyte ratio; *p*, measure of statistical significance (significant < 0.05); PBCC, peripheral blood cell count; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PLT, platelet count; P, study group (AE patients); SII, systemic immune–inflammation index; SIRI, systemic inflammation response index; WBC, white blood cell count.*Normally distributed variables analyzed using the *t*-test. # Two-sided hypothesis (*P* ≠ *C*). † One-sided hypothesis (*P* < *C*). All the other values are compared using a one-sided hypothesis (*P* > *C*).

Table 2 presents ROC results and AUC values; the ROC curve analysis confirmed modest but statistically significant discriminatory performance across all markers. The NLR, PLR, SII, SIRI and AISI have AUC values between 0.6 and 0.7, while MLR has a lower AUC value.

Table 2. ROC Curve Summary.

95% Confidence Interval				
	AUC	Lower	Upper	p
NLR	0.655	0.550	0.760	.004
MLR	0.581	0.473	0.689	.141
PLR	0.619	0.514	0.724	.026
SII	0.654	0.551	0.757	.003
SIRI	0.629	0.522	0.737	.018
AISI	0.631	0.525	0.737	.015

AISI, aggregate index of systemic inflammation; AUC, area under the curve; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; *p*, measure of statistical significance (significant < 0.05); PLR, platelet-to-lymphocyte ratio; ROC, receiver operating characteristic; SII, systemic immune–inflammation index; SIRI, systemic inflammation response index.

Optimal cut-off values identified by Youden’s index are listed in Table 3. Across the analyzed inflammatory indices, sensitivities ranged from 37.8% to 51.1%, while specificities varied between 78.0% and 91.3%, resulting in overall accuracies between 71.8% and 89.0%. Among the evaluated markers, SII demonstrated the highest diagnostic performance, with the greatest specificity, positive likelihood ratio and overall accuracy. In contrast, negative likelihood ratios remained relatively high across all indices (0.63-0.73), indicating limited ability to rule out AE.

Table 3. Diagnostic performance of inflammatory indices (Based on ROC Youden’s Index).

Marker	Optimal Cut-off	Sensitivity (%)	Specificity (%)	LR+	LR–	Accuracy (%)
NLR	≥ 1.95	44.44	87.33	3.51	0.64	77.44
MLR	≥ 0.299	37.78	86.67	2.83	0.72	75.38
PLR	≥ 147.38	40.00	89.33	3.75	0.67	77.95
SII	≥ 669.79	42.22	91.33	4.87	0.63	80.00
SIRI	≥ 0.959	51.11	78.00	2.32	0.63	71.79
AISI	≥ 325.54	48.89	80.67	2.53	0.63	73.33

AISI, aggregate index of systemic inflammation; LR+, positive likelihood ratio; LR–, negative likelihood ratio; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR,

platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; SIRI, systemic inflammation response index.

Pairwise AUC comparisons using DeLong’s test for NLR, SII, SIRI, AISI revealed no statistically significant differences between inflammatory markers (Table 4).

Table 4. Pairwise AUC Comparisons (DeLong’s Test).

		95% Confidence Interval			
	AUC Difference	Lower	Upper	z	p
NLR vs. MLR	0.07407	-0.0294	0.1776	1.4026	.161
NLR vs. PLR	0.03593	-0.0621	0.1340	0.7181	.473
NLR vs. SII	9.63e-4	-0.0351	0.0370	0.0524	.958
NLR vs. SIRI	0.02556	-0.0404	0.0915	0.7599	.447
NLR vs. AISI	0.02393	-0.0476	0.0955	0.6552	.512
MLR vs. PLR	-0.03815	-0.1533	0.0770	-0.6494	.516
MLR vs. SII	-0.07311	-0.1790	0.0328	-1.3528	.176
MLR vs. SIRI	-0.04852	-0.1124	0.0154	-1.4881	.137
MLR vs. AISI	-0.05015	-0.1205	0.0202	-1.3967	.162
PLR vs. SII	-0.03496	-0.1156	0.0457	-0.8493	.396
PLR vs. SIRI	-0.01037	-0.1276	0.1069	-0.1733	.862
PLR vs. AISI	-0.01200	-0.1205	0.0965	-0.2167	.828
SII vs. SIRI	0.02459	-0.0465	0.0957	0.6778	.498
SII vs. AISI	0.02296	-0.0408	0.0868	0.7054	.481
SIRI vs. AISI	-0.00163	-0.0290	0.0257	-0.1169	.907

AISI, aggregate index of systemic inflammation; AUC, area under the curve; CI, confidence interval; DeLong’s test, nonparametric test for comparison of correlated ROC curves; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; p, measure of the statistical significance (significant <0,05); PLR, platelet-to-lymphocyte ratio; SII, systemic immune–inflammation index; SIRI, systemic inflammation response index; vs., versus; z, z-statistic.

There are no significant differences regarding PBCC indices in patients with definite versus probable AE (Table 5).

Table 5. Comparison between probable and definite AE patients (Mann-Whitney test).

	U	p	Rank-Biserial Correlation	SE Rank-Biserial Correlation
NLR	230.0	.613	0.091	0.172
MLR	234.0	.677	0.075	0.172
PLR	248.0	.919	0.020	0.172
SII	245.0	.866	0.032	0.172
SIRI	252.0	.991	0.004	0.172
AISI	265.0	.796	-0.047	0.172

AISI, aggregate index of systemic inflammation; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; p, p-value; PLR, platelet-to-lymphocyte ratio; Rank-biserial correlation, effect size measure for the Mann-Whitney test; SE, standard error; SII, systemic immune–inflammation index; SIRI, systemic inflammation response index; U, Mann-Whitney U statistic.

4. Discussion

AE is a group of conditions that have been better categorized and scientifically described in the past decade [26]. Both innate and adaptative immunity play a role in the pathogenesis of AE. Different subtypes of AE are influenced by different effectors both in the innate and the adaptative immune system [27]. The innate immune response plays an important role in the pathogenesis of

AE. Current evidence suggests that innate immune cells are involved in the disruption of the blood-brain barrier (BBB) [28,29]. After disruption of the BBB, microglial activation occurs leading to recruitment of the adaptive side of the immune system, explaining the pathogenesis of AE.

There is also evidence of the role that platelets play in neuroinflammation [30]. Platelets activate and modulate macrophages and subgroups of T cells leading to activation and progression of the neuroinflammatory effects [30,31].

To our knowledge, our results are the first report of peripheral immune cell ratios comparing children with AE and hospital-based controls. Our study is also the first one to publish data regarding the AISI ratio in patients with AE and to compare with those of a control group of children attending the pediatric neurology service for non-acute evaluations and treatments. Our results suggest that at the time of the initial hospitalization, children with AE already show altered peripheral immune cell profiles compared to their age-matched peers. This may be helpful when first considering the differential diagnosis at presentation. Neurologic examination is time consuming and often difficult in children, more so in children with prominent behavioral symptoms. Furthermore, establishing a positive diagnosis of AE requires additional neurophysiological testing, imaging and specialized blood and cerebrospinal fluid (CSF) testing for antibodies and other advanced parameters that require a long time until ready [2]. By comparison, a PBCC is readily available, often within minutes to hours of the initial presentation of a patient. Knowing that patients with AE present with high immune cell ratios could be of significant help to the clinician considering various differential diagnoses at the time of initial presentation, in favor of AE and leading to early specific treatment.

The NLR is the most studied ratio both in organic (including neurologic) and psychiatric illnesses [32–34]. Studies of NLR in adult populations with AE have indicated that larger NLR values at admission or at the time of treatment initiation are correlated with worse long-term outcomes and less satisfactory response to treatment respectively. Recent literature showed that values of 4 or higher of NLR ratio are associated with higher morbidity and mortality in AE patients [20,22]. The only study that estimated NLR values in children with anti-NMDAR antibody AE also found that an NLR above 6 predicted the need for intubation and mechanical ventilation [35].

In our study, patients with AE have higher NLR ratios than their hospital-based control age-peers. Although NLR and SII yielded the highest effect sizes among the analyzed indices, the magnitude of these effects was small. In our group, we could not differentiate among patients with better rather poorer prognoses using the NLR value. This is due to the relatively low number of patients with definite or probable AE with sufficiently complete records that we were able to recover.

Other PBCC-derived ratios also showed statistically significant differences between patients with AE and controls, with higher values observed in the AE group; however, their effect sizes were even smaller. This finding is not unexpected, as SII, SIRI, and AISI all incorporate the neutrophil count, which is also the numerator of the NLR.

Youden's index based cut-off values were associated with high specificity and modest sensitivity. Accordingly, these indices appear to have limited screening value but may contribute to diagnostic confirmation in the appropriate clinical context.

A study conducted in Australia on adults with antibody-positive AE proved that SII has a good predictive value concerning the acute treatment outcomes, i.e., 30 days after immune modulation was initiated [21]. The same study found that the NLR and PLR also share this predictive capacity, albeit with the smaller AUC values.

Our study also provides the first description of the aggregate index of systemic inflammation (AIS) in patients with AE. Similarly, to the other ratios, AIS is higher in children with AE but with a small effect size.

Platelets are another class of cellular elements in peripheral blood. Production of platelets from megakaryocytes is driven by thrombopoietin, a liver-produced protein that acts like an acute-phase reactant [36,37]. Platelets play an important role in the immune system. They interact both with the innate and adaptive branches of the immune system. Platelets activate neutrophils and monocytes; they have complex feedback interactions with the complement system and they interact with and

influence differentiation of T lymphocytes [38]. Platelets are known to contribute significantly to neuroinflammation, interacting with different T lymphocyte subtypes and altering the blood-brain barrier (BBB) [30,31].

Thus, it stands to reason that platelets might also be important contributors to the pathogenesis of inflammatory diseases. In adults, a single study has evaluated the PLR (together with NLR and SII) in association with disease severity after treatment. Those patients with higher values of these ratios had worse outcomes after treatment [23]. In our study, the PLR is higher in patients with AE compared to their aged-matched controls. The PCT is also significantly higher, but due to the high variability it was considered not useful in identifying AE patients. Exploring this finding in larger patient cohorts and in other immune-inflammatory diseases might lead to relevant results associated to disease pathogenesis and platelet physiology and their role in pathogenic processes.

Our study provides the first formal evaluation of the PBCC ratios in children with probable and definite autoimmune encephalitis. The results represent a foundation for further research of the diagnostic and prognostic roles of the studied indices in children with AE. A complete PBCC is easily available in many clinical settings. Thus, during the acute presentation of the patient with clinical suspicion of AE, higher values of these indices provide support to the physician and spare time and resources avoiding further electroencephalographic, serologic, CSF or imaging testing.

One limitation is the retrospective nature of the study. This led to exclusion of the patients having incomplete records. Another limitation was the considerable practical and financial challenge of testing for specific antibodies in the past (unconfirmed seropositivity placed these patients in the "probable AE" group and excluded from this study).

We could not compare the indices between AE subtypes due to low number of patients within each subgroup (e.g., anti NMDAR antibody AE compared to other seropositive patients).

There are no significant differences of the PBCC indices in patients with definite versus probable AE.

Patients' stratification regarding treatment outcomes was not possible, due to inhomogeneous evaluation of the functional results (no annual modified Rankin scale score was performed in all cases). This retrospective study highlighted the importance of standardized approach of assessing and monitoring these patients, both for research and clinical utility purposes.

Great opportunity for future research in this area exists. The parameters we investigated are affordable and easily available in any medical setting. Analyzing larger cohorts of patients with clearly defined sub-groups should be a priority. Whether or not those patients with AE with positive antibody testing differ significantly from seronegative AE patients is a topic that should receive more scrutiny. Additionally, there would be immense practical value in demonstrating whether the immune cell ratios can function as monitors or predictors of therapy success or, respectively, of the chances of relapse.

5. Conclusion

Children with AE have significantly higher PBCC immune cell ratios at the time of first admission compared to age-matched hospital-based controls. The high specificity and the low sensitivity of the inflammatory indices make them more suitable for supporting the AE diagnosis in suggestive clinical circumstances, but not for screening. These inflammatory indices provide quick, easily available information to guide the differential diagnosis and additional testing. These indices have a high practical value, do not imply supplementary costs, only simple ratios calculation. They may reduce the expensive and time consuming imaging, electrophysiological or neuropsychological testing with great benefit to patients, care-givers, medical staff and healthcare systems as a whole. Additional research to prove that these parameters are useful for establishing the appropriate treatment and for predicting prognosis is necessary. Future research should focus on larger cohorts of patients with clearly defined serological diagnoses and standardized clinical approaches to monitoring outcomes.

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