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Original

The Platelet-Lymphocyte Count Ratio as a Biomarker in Autism Spectrum Disorder

El índice de recuento de plaquetas-linfocitos como biomarcador en el trastorno del espectro autista

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Abstract

Introduction: Autism spectrum disorder is a neurodevelopmental disorder with multiple causes. Research on biomarkers, such as the systemic inflammation index may improve early intervention.

Objective: Analyze the platelet-lymphocyte count ratio as a biomarker in autism spectrum disorder.

Methods: A case-control analytical study was conducted at the Pediatric Hospital of Sancti Spíritus to measure the systemic inflammation index in patients with autism spectrum disorder, from January to July, 2024. The universe and sample consisted of 30 children diagnosed with autism spectrum disorder, and 29 neurotypical children, matched by age and sex. Samples were taken to assess inflammatory indices derived from blood cell counts.

Results: The most significant index was the platelet-lymphocyte ratio. The area under the curve for the platelet-lymphocyte ratio was 0.717, and the cut-off value was 70. It was found to provide a sensitivity of 65.5%, a specificity of 67%, a positive predictive value of 70.3%, a negative predictive value of 67.7%, and an accuracy of 66.6%.

Conclusions: In males, the platelet-lymphocyte count ratio was higher than in females. The predominant risk factors were maternal infections and chronic diseases. The platelet-lymphocyte ratio is a key parameter in neuroinflammation, and its study in a larger population could be relevant as a biomarker of inflammation and a predictor of autism severity.

Keywords: autism spectrum disorder; systemic inflammation index; neuroinflammatory markers

Resumen

Introducción: el trastorno del espectro autista es una afección del neurodesarrollo con múltiples causas. Investigar sobre los biomarcadores, como el índice de inflamación sistémica, puede mejorar la intervención temprana.

Objetivo: analizar el índice de recuento de plaquetas-linfocitos como biomarcador en el trastorno del espectro autista.

Métodos: se llevó a cabo un estudio analítico de casos y controles en el Hospital Pediátrico de Sancti Spíritus, para medir el índice de inflamación sistémica en pacientes con trastorno del espectro autista, en el periodo de enero a julio de 2024. El universo y la muestra estuvieron constituidos por 30 niños diagnosticados con trastorno del espectro autista y 29 niños neurotípicos, emparejados por edad y sexo. Se tomaron muestras para evaluar los índices inflamatorios derivados de los recuentos de células sanguíneas.

Resultados: el índice más significativo fue el relacionado con las plaquetas-linfocitos. El área bajo la curva para la relación plaqueta-linfocito fue de 0,717 y el valor de corte de 70. Se encontró que proporcionaba una sensibilidad del 65,5 %, una especificidad del 67 %, un

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valor predictivo positivo del 70,3 %, un valor predictivo negativo del 67,7 %, así como un valor de precisión del 66,6 %.
Conclusiones: en el sexo masculino el índice de recuento plaqueta-linfocito fue más alto que en el femenino. Los factores de riesgo predominantes fueron las infecciones maternas y las enfermedades crónicas. El índice plaqueta-linfocito es clave en la neuroinflamación y su estudio en mayores poblaciones podría ser relevante como biomarcador de inflamación y predictor de la gravedad del autismo.
Palabras clave: trastorno del espectro autista; índice de inflamación sistémica; marcadores neuroinflamatorios

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with a multifactorial etiology. It is characterized by altered brain development due to the influence of multiple environmental and genetic factors. Synaptic connections are affected from an early age, leading to poor communication and behavioral disorders in children with genetic susceptibility.[1,2]

Immune system dysfunction contributes to the development of ASD and is linked to the neuroinflammation present in neuropsychiatric disorders. Therefore, in recent years, the scientific community has addressed these connections to establish parameters that contribute to improving diagnosis, as well as predicting severity and complications.[3]

Until recently, ASD diagnoses were lower than the figures reported today in statistical sources. It is believed that since its inclusion in classification systems, numerous cases have been definitively diagnosed; however, the age at which this definition is made exceeds four years. The prevalence of ASD worldwide reached 15 to 20 cases per 1,000 births. In 2018, the World Health Organization reported a continued increase estimated at more than one per 160 children.[4]

In Latin America, high figures are reported. Epidemiological data show an ASD prevalence between 1 and 1.5 %. In Mexico, values reach 0.87%, and in Brazil, it is estimated that 25 out of every 10,000 people suffer from ASD.[5]

In Cuba, there are few studies on the prevalence of ASD, but the incidence rate is known to be 0.4 per 10,000 inhabitants. In the province of Villa Clara, the rate is 0.335 per 10,000 children, while in Sancti Spíritus, the rate is 0.5 per 10,000 children. This study is consistent with findings of a similar rate of patients with ASD in other provinces in the country.[6,7,8]

Neuroinflammation has been shown to be responsible for brain tissue damage through several mechanisms, such as a marked increase in the release of proinflammatory cytokines, which

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could modulate brain function aberrantly. In fact, increased levels of proinflammatory cytokines (TNF-α and IL-6) have been found in both the blood and brain of autistic patients, triggering chronic neuroinflammation in autism.[9,10,11]

Other studies show different levels of proinflammatory cytokines in serum, plasma, brain tissue, and cerebrospinal fluid of autistic subjects compared to normal subjects. This could affect the immune capacity of the central nervous system (CNS) in children with primary autism.[10]

Blood mononuclear cell derivatives in the peripheral compartment have been relevant, including tumor necrosis factor (TNF-α) and IL-1β 3 in neurodevelopmental disruption, as well as IL-6 and TNF-α. These proinflammatory cytokines are found at high levels in the brain of autistic patients.[12]

Increased inflammatory activity in children with ASD is demonstrated by an imbalance of Th1 and Th2 plasma cytokines. Other groups have reported significant differences in IL-1β, IL-6, IL-17, IL-12p40, and IL-12p70 levels compared to typically developing children, with specific changes related to comorbidities.[13,14]

Neutrophils, monocytes, and lymphocytes play an important role in the inflammatory process. In this regard, we propose analyzing the platelet-lymphocyte count ratio as a biomarker in autism spectrum disorder.

Methods

A case-control analytical study was conducted at the Pediatric Hospital of Sancti Spíritus to measure the systemic inflammation index in patients with autism spectrum disorder from January to July, 2024. The selection process began with a group of 50 patients diagnosed in the province of Sancti Spíritus who did not have any type of infection or were taking medication at the time of the study.

The sample was selected by simple random sampling from a defined population and according to exclusion criteria. A numbered list of eligible patients was created using Excel's random number function, resulting in a group of 30 patients.

The control group consisted of 29 patients, matched by age and sex, who presented neurotypical development, without immunological, neurological, or psychiatric diseases, infections, or the use of antibiotics or other medications. A clinical characterization of the study group was performed beforehand, which included prenatal and perinatal risk factors, as well as the severity of the disorder, for example: maternal infections, chronic non-

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communicable diseases (NCDs), medication use, cesarean section and high obstetric risk (HOR).

Eligibility criteria included:

Inclusion criteria

• Patients diagnosed with ASD from the province of Sancti Spíritus.

• Patients who did not have any type of infection, medication use, or decompensation at the time of the study.

• Patients between the ages of 3 years and 18 years, 11 months, and 29 days.

Exclusion criteria

• Patients who meet the above criteria and whose parents did not provide consent to participate in the study.

For the selection of controls

• Patients whose age and sex were consistent with those established for the study group.

• Patients without significant personal medical history, such as neurological, endocrine, immunological, or hematological diseases, infections, or medication use.

• Patients with neurotypical development.

The age groups were established taking into account the aforementioned ages and the sociodemographic characteristics of the child population in which the disorder occurs. They were not organized into homogeneous groups because blood values were determined by age group. Blood cell counts are known to vary by age.

The project was approved by the Scientific Council and the Ethics Committee of the Pediatric Hospital of Sancti Spíritus (Agreement #: 234/2023). The ethical criteria contained in the Declaration of Helsinki were met. Parents gave their approval by signing informed consent. Data confidentiality was guaranteed, and the children received no additional medical intervention resulting from the study.

Hematological Assessments

Common blood parameters were studied using an automated hematology analyzer (Cobas c311, Roche). Blood cell counts, including neutrophils, lymphocytes, monocytes, erythrocytes, and platelets, were measured using standard laboratory methods. The presence

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of inflammation was assessed by analyzing indices derived from blood cell counts, such as: neutrophil-lymphocyte ratio (NLR; neutrophils/lymphocytes), systemic inflammation index (SII; platelets x neutrophils/lymphocytes), and platelet-lymphocyte ratio (PLR; platelets/lymphocytes).

These variables related to inflammation indices were determined using established indices. First, the absolute neutrophil and lymphocyte counts were determined based on the blood cell count by multiplying their values by the leukocyte count. The procedures established for each to calculate the indices were applied, as described in the previous paragraph.

Statistical Analysis

Data analysis was performed using a commercially available software package (Statistical Version 8). The normality of distribution of each variable in the study groups (autistic and control subjects) and within the disorder severity groups (mild, moderate, and severe) was assessed using the Kolmogorov-Smirnov test. Homogeneity of variance was determined using the Levene test.

For variables that followed a normal distribution, data are presented as mean ± standard deviation. Comparisons between the autistic and control groups were performed using the Student t test for independent samples. In cases where homogeneity of variances was not met (according to the Levene test), the Welch correction was applied to the t test.

Receiver operating characteristic (ROC) curves were used to test the ability of systemic inflammation indices to differentiate autistic patients with poor or good prognosis for the development of the disease in question. 95 % confidence intervals (CIs) were calculated for the areas under the curves. Standard measures of test validity, including sensitivity and specificity, were also estimated.

Results

The research data were taken from the medical records of patients diagnosed with autism spectrum disorder (ASD). The patients in this study were 59 individuals, comprised of 29 developing/non-ASD patients and 30 patients diagnosed with ASD.

Table 1 shows the demographic and clinical characteristics and warning signs of subjects with ASD. In this study, there was a higher prevalence of male subjects in the ASD group (22/73.3 %) compared to the control group (17/58.6 %). The majority of patients were aged 5 to <10 years, representing 46.6 %, followed by those aged 10 years and older. High obstetric risk was present in 22 of the mothers, with cesarean delivery being observed frequently (in 17 mothers of children with ASD).

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Table 1. Demographic and clinical characteristics and risk factors in subjects with ASD

Variables						
Demographic			Clinical signs			
Age	ASD	Control	Severity	1	2	3
3- < 5 ages	6 (20)	8 (27.6)		14	8	8
5- < 10 ages	14 (46.6)	12 (41.4)	Risk factors and severity			
10- < 19 ages	10 (33.3)	9 (31.0)	HOR (n= 22)	10	7	5
Sex						
Male	22(73.3)	17 (58.6)	Infections (n= 7)	5	1	1
Female	8 (26.7)	22 (41.4)	CNCD (n= 16)	9	3	4
			Caesarean (n= 17)	7	5	5

Source: own elaboration
Note: ARO: high obstetric risk; NCDs: chronic non-communicable diseases

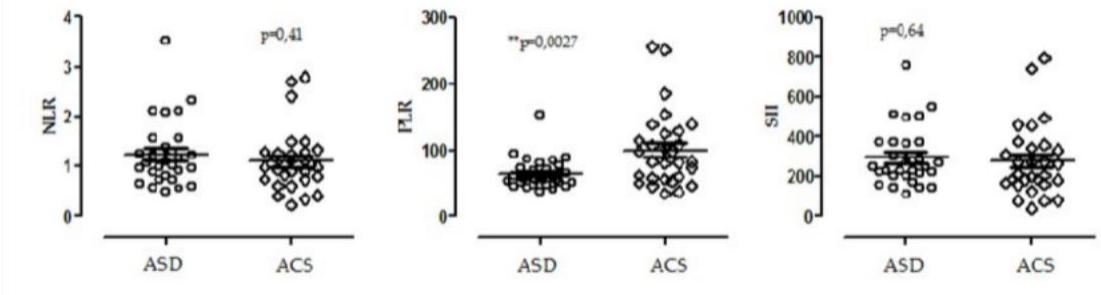
Regarding the average neutrophil, lymphocyte, and platelet counts, NLR, PLR, and IIS are shown in table 2. Analysis of hematological and ratio tests showed that the ASD cohort showed a significant reduction in platelet counts. Similar levels of all blood cell counts were observed compared to controls (Table 2). The mean absolute neutrophil, lymphocyte, and platelet counts of 30 ASD subjects are shown below. The average NLR was 1.24 ± 0.6 x 10 /µL (Fig. 1).

Table 2. Average neutrophil, lymphocyte and platelet counts

Blood cell count	**ASD (n=30)**	**Controls (n=29)**	**p**
Neutrophils	4.66 ± 1.2	2.81 ± 0.9	∈ 0.01
Lymphocytes	4.12 ± 1.1	3.03 ± 1.0	> 0.05
Platelets	243.6 ± 30.4	264.4 ± 98.9	> 0.05

Source: own elaboration
Note: Values are given as absolute cell counts (100/µL). Significant differences in neutrophil counts were p= 0.01.

The inflammatory indices analyzed, except for the IPL, did not reach significant differences in the ASD group compared to the controls (fig. 1).



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Fig. 1. Inflammatory indices based on cell counts in autism spectrum disorder (ASD) and age-matched control subjects

Source: own elaboration
Note: LPI, platelet-to-lymphocyte ratio; *p significant with Welch's t correction

Following the significant differences observed in LPI in the autism group, inflammatory indices were analyzed in relation to disease severity using the unpaired t test with Welch's correction. Significant differences between the ASD-I and ASD-III patient groups are shown in fig. 2.

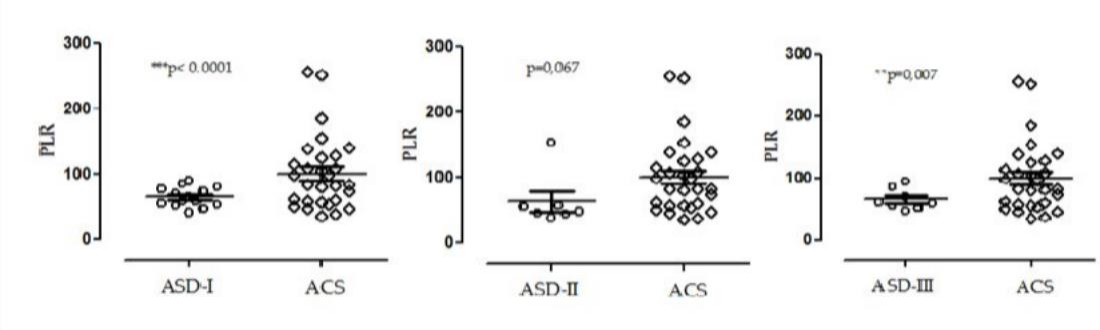


Fig. 2. Inflammatory indices based on cell counts in autism spectrum disorder (ASD) severity versus healthy controls

Source: own elaboration
Note: (B) Severity versus healthy controls. Welch-c, P value, Welch's critical value; LPR, platelet-lymphocyte ratio
Unpaired t test with Welch's correction. ASD-I: *Statistical significance after Welch's t correction

Diagnostic tests were performed to determine the accuracy of inflammatory ratios as a biomarker for stratifying ASD patients based on a history of prenatal and perinatal adverse events. First, the analysis was performed using the area under the curve (AUC) and the determination of the intercept. The cut-off value was then used to determine the LPR category. The results can be seen in the 2 x 2 table (table 3, fig. 3).

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Table 3. Platelet-Lymphocyte Ratio

PLR	GOLD STANDARD (HISTORY OF PERINATAL NOXAE)	
	Positive	**Negative**
Positive £ 70	19	8
Negative ³70	10	21

Source: own elaboration

The LPI cut-off was estimated using Welch's correction, yielding a cuto-ff of 0.68 (fig. 3). This showed good discriminatory ability to determine the positive and negative categories of the LPI test. The alternative hypothesis follows the criteria indicating that values below the cut-off are predictors of the development of autism in patients with a history of risk factors (table 2, fig. 2).

The AUC for the LPI was obtained at 0.717, and the cutoff of 0.68 was found to provide a sensitivity of 65.5%, a specificity of 67 %, a positive predictive value of 70.3 %, a negative predictive value of 67.7 %, and an accuracy of 66.6 %.

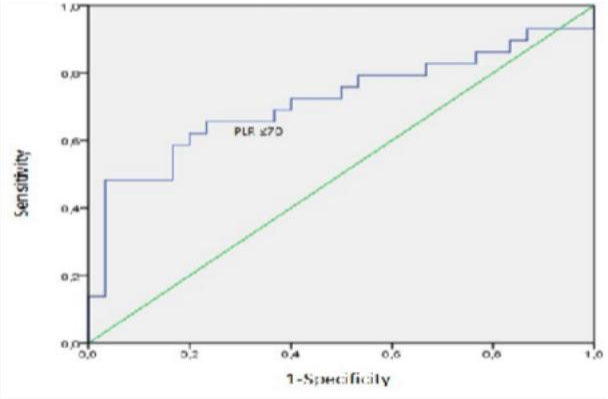


Fig. 3. ROC curve analysis using IPL to discriminate the risk of developing autism in children with a history of risk factors
Source: own elaboration
Note: the AUC obtained was 0.717 (p = 0.04). A cut-off value of 0.68 determined using Welch correction is indicated

Discussion

ASD symptoms typically appear between the ages of 3 and 4. However, they can also emerge in children between 12 and 24 months (regressive autism). It has also been suggested that

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the ratio of males to females with ASD is close to 4:1, attributed to the male hormone testosterone, which plays a role in microglial genes and neurotransmitter production in the brain.[15]

Risk factors are associated with multiple disorders, and even events occurring during pregnancy are considered relevant for analyzing and understanding disruptive behaviors that may occur in children. A sociodemographic profile of 126 patients conducted in Ecuador describes multiple factors of interest in the prenatal stage, including hypertensive disorders, thyroid disorders, and infections.[16]

There is evidence that maternal infections put this behavior at risk. Once maternal immunity is activated, a series of inflammatory events occur that cause damage to glial cells and astrocytes, cells that are important in the nervous system for maintaining optimal functioning.[17]

Similarly, maternal illnesses, medication use, and other factors may contribute to the development of the disorder. An integrative review study on ASD describes other events of interest that occur during the prenatal and perinatal stages, including the use of antiepileptic medications and prematurity. The latter was not present in the study group.[18]

A high number of cases presented cesarean section as a risk factor, and a review of the literature shows this relationship. Some epidemiological studies suggest an association between cesarean delivery and an increased risk of ASD. In a cohort of Swedish children, a significant association was found between cesarean delivery and ASD, even after adjusting for confounding factors such as maternal age, socioeconomic status, and family history of ASD.[19]

Other studies focused on the search for this relationship between cesarean section and ASD have suggested increasing the number of investigations due to the contradictions reported in the literature.[20]

Different values in the absolute neutrophil count have been observed in autism compared to age-matched control subjects. One study reported a mean absolute neutrophil count of 3.88 ± 0.24 x 103/µL,[14] while other authors report in their studies that the mean absolute neutrophil count was 3,450 x 103/µL.[13]

In the present study, the mean absolute neutrophil count in autistic patients was 4.66 ± 1.2 x 103 /µL similar to that observed by Sibel and Cem,[21] while the mean absolute lymphocyte count (4.12 ± 1.1 x 103/µL) was similar to other previously reported values, although without a significant difference compared to controls.

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The mean NLR and IIS did not reach significant differences in any case. The LLR showed considerable ability to predict the risk of developing ASD in patients with a history of prenatal harmful effects (sensitivity, 65.5 %) and to predict a better prognosis, which means a negative risk for developing autism (specificity, 67 %).

The authors of this study believe that these results could be related to the small number of patients studied. Other studies demonstrate changes in these inflammatory indices and have even found different immune dysfunctions in different groups of patients depending on their developmental stage.[22,23]

Platelet activation, in response to vascular injury, induces the secretion of several cytokines and chemokines, which interact with the vascular endothelium to promote the expression of adhesion molecules and the secretion of cytokines, which in turn induces chemotaxis and adhesion of neutrophils and monocytes.[24,25] Furthermore, platelets contain serotonin in their granules, which is absorbed from the plasma through the serotonin transporter (SERT). Once secreted from their granules, it is capable of producing vasoconstriction and also preventing apoptosis.[26]

These inflammatory indices have been linked to the prognosis, progression, and severity of some diseases such as Alzheimer's. The severity of ASD symptoms could also underscore inflammatory events in the brain; unlike other peripheral indices, the platelet-lymphocyte ratio (PLR) could be a key parameter for detecting early signs of ASD.[27]

Although the study is based on the hypothesis of the value of the platelet/lymphocyte count as a biomarker in ASD, the results presented are not definitive, as they must be applied to broader population groups and related to other clinical characteristics of the disorder, this being one of the main limitations. The study of markers for this disorder should be expanded, and in addition to indices of systemic inflammation, the relationship between the immune and neurological systems should be taken into account, and the search for new neuroinflammatory markers for ASD should be pursued.

Conclusions

In males, the platelet-lymphocyte count ratio was higher than in females. The predominant risk factors were maternal infections and chronic diseases. The platelet- lymphocyte ratio is a key parameter in neuroinflammation, and its study in a larger population could be relevant as a biomarker of inflammation and a predictor of autism severity.

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Conflicts of interests

Authors declare no conflicts of interests.

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