The Link between Social Anxiety and Peripheral Inflammatory Markers in Patients with Schizophrenia Diagnoses

By Amelia Dias Teixeira, Victor Hugo Schaly Cordova
& Paulo Belmonte-de-Abreu

Universidade Federal do Rio Grande do Sul (UFRGS)

Abstract- Background: It exist increasing studies on the inflammatory process in psychiatric disorders, in which inflammation in schizophrenia (SZ) isquestioned.

Objective: assess the association between social anxiety (SA) and inflammation in patients with SZ, measuring primarily the neutrophil-to-lymphocyte ratio (NLR) and secondarily the systemic immune-inflammation index (SII), monocyte-to-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR).

Methods: A cross-sectional study.

Results: Of the 82 patients who met the inclusion criteria, 59 patients had SA and observed a significant alteration in inflammation markers in patients with SZ, especially NLR.

Keywords: social anxiety, schizophrenia, peripheral markers of inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index.

GJMR-A Classification: LCC: RC516

THELINKBETWEENSOCIALANXIETYANDPERIPHERALINFLAMMATORYMARKERSINPATIENTSWITHSCHIZOPHRENIADIAGNOSES

Strictly as per the compliance and regulations of:

The Link between Social Anxiety and Peripheral Inflammatory Markers in Patients with Schizophrenia Diagnoses

Amelia Dias Teixeira [α], Victor Hugo Schaly Cordova [σ] & Paulo Belmonte-de-Abreu [ρ]

Abstract- Background: It exist increasing studies on the inflammatory process in psychiatric disorders, in which inflammation in schizophrenia (SZ) isquestioned.

Objective: assess the association between social anxiety (SA) and inflammation in patients with SZ, measuring primarily the neutrophil-to-lymphocyte ratio (NLR) and secondarily the systemic immune-inflammation index (SII), monocyte-to-lymphocyte ratio (MLR) and platelet-lymphocyte ratio (PLR).

Methods: A cross-sectional study.

Results: Of the 82 patients who met the inclusion criteria, 59 patients had SA and observed a significant alteration in inflammation markers in patients with SZ, especially NLR.

Conclusion: NLR was significantly higher when compared to the cut-off point in the general sample. The greater the severity of SZ symptoms, the higher the SA in these patients and patients with SA showed higher scores on Brief Psychiatric Rating Scale(BPRS)and Generalized Anxiety Disorder Scale(GAD-7), and the higher the SA scores, the higher the NLR, SII, and PLR. Our findings indicate that inflammation appears to be a characteristic of patients diagnosed with SZ, agreeing with the conclusions of the literature and that SA may cause an additional increase in inflammatory indices in these patients. In addition, inflammation was seen to interfere with SA, independent of the other variables.

Keywords: social anxiety, schizophrenia, peripheral markers of inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index.

I. Introduction

Schizophrenia (SZ) is a serious and complex mental disorder that affects around 1% of the world's population, causing damage to the patient and family, of multifactorial origin [1].Its diagnosis involves a set of signs and symptoms and impaired professional or social functioning [2]. Its symptoms affect perception, thought, affect, and behavior [3] without any pathognomonic symptoms [2] and involve distortions of perception about oneself and with external reality [1]. Two or more of the following symptoms are required for diagnosis: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms such as diminished emotional expression or avolition, with at least one of the symptoms being the first three [3]. Social anxiety (SA) or social phobia is not included among the necessary symptoms, but is frequent before the onset of the disorder [1] and can represent both a residual and a complication of the illness, contributing to great personal suffering and functional impairment after the acute phase of SZ.

SA can be defined by intense or heightened fear or anxiety of one or more social events in which the person is exposed to the likely evaluation of other individuals [2], as a result of negative assessment [2,4], the possibility of judgment or rejection [4]. It is an interpersonal, intrapersonal, and social system disorder, with impaired reciprocal interaction and communication, such as failure of social cohesion and rejection, emotional and physical feelings such as nervousness and sweating, avoidance attitude of feared situations, and dysfunctional beliefs in social situations or imagining these events [5]. Fear, anxiety or avoidance in people with SA, or social phobia imply clinically significant distress or impairment in social, occupational, or other essential spheres of functioning [2].

Several peripheral markers derived from blood count have been increasingly used as an indirect measure of inflammatory activity in the brain in psychiatric disorders [6-10], calculated under simple laboratory exams [10], from a complete blood count [6,11-13].

The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR)and platelet-to-lymphocyte ratio (PLR) have been investigated as clinical circulating markers of chronic inflammation in many diseases [9,10,14-17], especially NLR [7,8,18]which constitutes baselines of the innate (neutrophil) and adaptive (lymphocyte) immune systems [6,19,20]and may be less affected by confounding variables, being an effective biomarker to identify patients who may benefit from pharmacological

Author α σ ρ: Graduate Program in Psychiatry and Behavioral Sciences, Schoolof Medicine, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.

Author ρ: Department of Psychiatry and Forensic Medicine, Schoolof Medicine. Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil.

Corresponding Author α: Amelia Dias Teixeira, Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Campus Saúde. Rua Ramiro Barcelos, 2400, 2º andar. 90035003 - Porto Alegre, RS – Brasil. e-mail: amelia_psico@hotmail.com

treatment adjuvant anti-inflammatory [6] and therefore more reliable in severe mental disorders [10,19].

Many authors cite the hypothesis of frequent inflammation in SZ [6,7,9,10,17,18], both in pathogenesis [7,9] and pathophysiology [18], where the lymphocyte count was lower and that of neutrophils considered higher in schizophrenics patients [7,9,17].

Moreover, a new index, defined as the systemic immune-inflammation index (SII), based on the count of lymphocytes, neutrophils and platelets [13,16,21,22], has been considered a good index [22], and even a better index to reflect local immune response and systemic inflammation, as its high predictive value has been confirmed in a variety of tumors [13,22], brain infarction, cardiovascular disease, and acute pancreatitis [13].

In addition, there may be a connection between anxiety disorders and inflammation, in which the immune system and inflammation play a role. It is suggested the values of NLR [6,23], MLR and PLR are significantly higher in this disorder, even with a limited number of studies [22]. Despite these two independent observations of increased inflammatory markers in SZ and SA, there are no studies, as long we identified, addressing comorbid SZ-SA and checking if the simultaneous SZ-SA diagnosis may reveal increased inflammation.

II. Objective

Assess the association between social anxiety (SA) and inflammation in patients diagnosed with schizophrenia (SZ), measuring primarily the NLR, and secondarily the SII, MLR and PLR.

III. Methods

It´s about a cross-sectional study of the association between comorbid AS in SZ and levels of peripheral markers of inflammation, especially NLR.

The first hypothesis is the increased inflammation (revealed by increased NLR) in patients with comorbid SZ-SA compared to patients with SZ without SA. The second hypothesis is that the other markers (SII, MLR and PLR) are also altered in schizophrenics patients with SA than without SA.

The sample comprised 82 patients attending the schizophrenia outpatient clinic of a major teaching hospital in southern Brazil (Hospital de Clínicas de Porto Alegre- HCPA) under the Public Health System, diagnosed with schizophrenia of both genders and aged between 18-70 years. Patients with other psychiatric diagnoses, active or chronic inflammatory or autoimmune diseases, and under treatment with anti-inflammatory or immunosuppressive medication were excluded.

All participants were aware of the research objectives and received an invitation to participate.

Those who agreed to contribute to the study signed the Informed Consent Form (ICF) approved by the Ethics Committee of the HCPA. Patient´s medical records were also accessed and consulted to ascertain the information needed for the study.

a) Instruments

Liebowitz Social Anxiety Scale (LSAS): developed in 1987 by Michel Liebowitz and translated, adapted and validated in four languages [23]. It is a 24-item questionnaire that assesses fear/anxiety and avoidance in specific social situations [24] with 11 items related to social interaction and 13 items related to public performance [25]. Four-point scale ranging from 0 = none to 3 = severe, and the total score is obtained by adding the fear and avoidance columns [24,26]. As for the classifications of the scores, there is no consensus in the literature. We based ourselves on the Brazilian study by Dos Santos et al. [23]mentions 32 as a good value for the cut-off point, so we followed the following classification: mild social phobia (32-43 points), moderate (44-81) and severe (from 82 points).

Brief Psychiatric Rating Scale (BPRS): developed by Overall and Gorham, is one of the most widely used scales in psychiatric research; where it originally consisted of 16 items, but in 1966 had two additional things (arousal and disorientation), the BPRS-18 [27]. It is a 7-point Likert scale score, where 0 = absent, 1 = normal, 2 = borderline illness, 3 = mild illness, 4 = moderately ill, 5 = markedly ill, 6 = severely ill and 7 = extremely ill. The cut-off score for the remission of schizophrenia on the BPRS-6 was less than 5, while the ranges for mild, moderate, and severe severity were 5-9, 10-19, and greater than 20, respectively [28]. Some studies address the domains/dimensions of this scale [29-31], we based ourselves on that of Van Dorn et al. [31]for the following classification: positive domain (items ideas of grandeur, distrust, hallucinatory behavior, and altered thought content), negative (affective withdrawal, psychomotor retardation, and blunted affect), affective (somatic worry, anxiety, feelings of guilt, depressed mood, and hostility), and cognitive disorganization (conceptual disorganization, tension, mannerisms and posture, lack of cooperation, excitement, and disorientation).

Generalized Anxiety Disorder Scale (GAD-7): is a 4-point Likert scale (0-3) ranging from "never" to "every "day", asking how often the patient was bothered. The index is obtained by summing the scores, with cut-off points 5, 10, and 15 allowing the classification of anxiety into none/normal (0-4), mild (5-9), moderate (10-14), and severe (15-21) [32].

Blood count: through a blood test of the patient, to measure biomarkers of inflammation. The complete blood count is routinely collected at the outpatient clinic and included in patients' charts. Some patients have

their CBC performed elsewhere, and the patient or family member is asked to access it (we had eight cases in these conditions).

b) Statistical Analysis

Data analysis was performed using the Statistical Package of Social Science (SSP) software version 27.0, where 82 individuals were analyzed. A descriptive analysis was made of the clinical and sociodemographic characteristics of the total sample and both groups, shown as mean and standard deviation or frequency and percentage. Quantitative variables (inflammation markers, age, time of diagnosis of schizophrenia, number of psychiatric hospitalizations) were described using the mean and standard deviation or median and interquartile range. Categorical variables (gender, family income, education, scales, medications, comorbidities) were described by absolute frequencies and percentages.

The t-student test was used to compare means between the groups with social anxiety and without social anxiety. In the case of asymmetry, the Mann-Whitney test was applied. Pearson's chi-square or Fisher's exact tests were used to compare proportions. Spearman's correlation coefficient was applied to evaluate the correlations between the inflammation markers and the scales under study. Wilcoxon's test was used to compare Liebowitz Scale items about fear and avoidance and between performance and social anxieties. The significance level adopted was 5% ($p<0.05$).

To control for possible confounding variables, multivariate Poisson Regression analysis was used to assess factors independently associated with social anxiety. The criterion for entering the variable in the model was that it had a p-value <0.20 in the bivariate analysis. The standard for remaining in the final model was that it had a p-value <0.10. The effect measure used was the Prevalence Ratio (PR) and the 95% confidence interval.

c) NLR, SII, PLR, and MLR values

There are several studies of typical values for NLR, such as that of Forget [15], in the Belgian adult, non-geriatric population with good health status (between 0.78 and 3.53); Iranian population (NLR 1.70±0.70, MLR 11.15±3.14 and PLR 117.05±47.73, respectively[12]); Chinese (NLR 18-65 years old female =0.85-3.06 and male = 0.90-2.94, PLR 61-179, MLR female (0.10-0.32) and male (0.12-0.35) and IIS (161-761)[16]; IIS had a cut-off value of 679.96 (Adali etal. [36]) in research in Turkey.

Cut-off points for patients with squamous cell carcinoma of the external auditory canal with and without preoperative recurrence and those considered ideal were 3.75 × 109/L for neutrophil count, 1.77 × 109/L for lymphocyte count, 2.325 for NLR, 157.9 for PLR, and 3.065 for LMR[34]. Szor[35] studied the

Brazilian population, with the cut-off value for NLR was 2.44; Eyff et al.[36] also studied Brazilian adults, with cut-off points for NLR and PLR of 2.80 and 362, respectively.

For the present study, we used the following cut-off points: 2.80 for NLR, 761 for SII, 0.35 for MLR, and 362 for PLR.

IV. Results

a) Sample Specifics

As shown in the flowchart in Figure 1, 140 patients were screened and 45 patients were excluded, 15 of these because the electronic medical records did not show a diagnosis of schizophrenia, 06 because they were in the telemedicine care modality, and 24 because they did not accept to participate in the research.

We interviewed 95 patients and excluded 13 patients, 10 of them because they presented other diagnoses (schizoaffective disorder, bipolar disorder, autism, acute psychotic disorder, psychosis due to cognitive disease, organic personality disorder) and 03 patients because of missing information and did not answer all the scales.

As a result, the sample ended up comprising 82 patients, 61 of whom (74.4%) were men and 21 (25.6%) women. The mean age was 47.3 years, and the most frequent schooling was complete high school (47.6%), followed by entire elementary school (32.9%).

As for the clinical characteristics, the mean ages of onset and duration of schizophrenia were 21.9 years and 25.4 years, respectively. The median number of psychiatric hospitalizations was two. The frequency of patients with comorbidities was 79.3%, and the main comorbidities found in these patients were obesity (28%), dyslipidemia (17.1%), smoking (15.9%), and diabetes (14.6%). Most patients were being treated with Clozapine (96.3%) and 31.7% were using other antipsychotics. The other most used drugs were Clonazepam (37.8%) and Amitriptyline (12.2%).

There were no significant differences in all variables between the groups with SA and without SA ($p>0.050$).

b) Social anxiety in schizophrenia

In the present investigation, of the 82 patients meeting the inclusion criteria, 59 patients (72%) had AS comorbidity, with scores higher from 32 in the LSAS, 12.2% being at a mild level of AS, 29.3% moderate, and 30.5% severe.

To complement the study, generalized anxiety was calculated in these patients using the GAD-7 scale, in which 32.9% of patients were at a mild level, 26.8% moderate and 7.3% severe. On the BPRS scale, the classification of the groups was 8.5%, 31.7% and 54.9% in mild, moderate and severe scores, respectively.

c) Social anxiety and inflammation in schizophrenia

The descriptive statistical analysis with the prevalence of the scores of the scales and markers of inflammation (CBC) in the total sample can be seen in Table 1. There was a significant difference in NLR, with 42.7% above the estimated cut-off point. There were also changes in the MLR (30.5%) and SII (25.6%), with no changes in the PLR (0.0%). It is also noted that in addition to 72% of patients showing SAD, 67.1% also had generalized anxiety.

The correlations between the LSAS, GAD-7, and BPRS scales with the inflammation markers NLR, SII, MLR, and PLR are shown in Table 2. There was a statistically significant positive correlation between the LSAS and the NLR, SII, and PLR markers, and the higher the SA scores, the higher the values of these markers; there was no correlation with MLR ($p > 0.50$), as can also be seen in Figures 2 to 4. No correlation was also obtained between the GAD-7 and BPRS scales with inflammation markers.

It was It was observed an association of increased GAD-7 and BPRS with increased NLR only in patients with comorbid SA (LSAS score $\geq$ 32 points) (Table 3), and a trend of MLR and IIS failing to reach statistical significance. There were no PLR altered levels.

After adjustment by the multivariate model (table 4), the following variables remained significantly and independently associated with SA: GAD7 $\geq$ 5 points ($p = 0.029$), positive, cognitive disorganization, and total domains of the BPRS ($p = 0.003$, $p = 0.004$ and $p = 0.001$, respectively) and NLR $\geq$ 2.80 ($p < 0.001$).

Patients who score five points or more on the GAD-7 scale, i.e. who show generalized anxiety at some level, have a 53% higher prevalence of AS compared to those who score less than five points (no generalized anxiety), regardless of BPRS and NLR.

Patients with one point more in the Positive and Cognitive Disorganization domains of the BPRS have a 4%growth in the prevalence of SA. As for the total score of this same scale, the increase is 2%, regardless of GAD-7 and NLR scores.

Finally, patients with an NLR equal to or greater than 2.80, which is the cut-off point, show a 55% increase in the prevalence of AS when compared to those with scores below 2.80 (no change in NLR), regardless of the GAD-7 and BPRS scales.

V. Conclusion

Social anxiety in schizophrenia arises from the difficulty of understanding social situations, where the person does not distinguish the intentions of others. Although it is not primary but secondary to the disease, it promotes excellent harm and disability in these patients, even with stabilized psychosis.

As shown above, we found the prevalence of 72% of SA in patients diagnosed with schizophrenia attending HCPA outpatient clinic. NLR was significantly higher in patients with comorbid SA compared to schizophrenic patients without this condition.

It was observed the severity of schizophrenia symptoms was associated with increased frequency of SA, with patients with SA with increased BPRS and GAD-7 scores. There also appeared to be a greater degree of inflammation in schizophrenia patients with SA, specially NLR, with increased SA scores associated with increased NLR, SII, and PLR (and no association with MLR).

Our findings support previous studies of increased inflammation in schizophrenia and provide new evidence that comorbid SA in people with schizophrenia is linked to increased inflammatory indices. However the design cannot tell us about causality.

In addition to the link between markers of inflammation and social anxiety in patients with schizophrenia, we saw that NLR interferes with SA and this is independent of schizophrenia.

Finally, since the analyzed factors were independence, we concluded that SA depends on the degree of schizophrenia and generalized anxiety, and inflammation caused by increased NLR and that these factors predict SA.

These findings become critical in thinking about new forms of treatment, addressing disability and impairment by social anxiety, with complementary therapies addressing inflammation that may modify the course and prognosis of the disease.

The results of these analyses may be limited by the modest sample size, but even so the results seem to have been significant. Not to mention the patients were interviewed by trained professionals and are being monitored by a team of residents and professors at the outpatient clinic where they have already been diagnosed.

References Références Referencias

1. Silva AM, Dos Santos CA, Miron FM, Miguel NP, Furtado CC, Bellemo AIS. Schizophrenia: a literature review. UNILUS Journal Teaching and Research, 2016;13,30. ISSN 2318-2083.
2. American Psychiatric Association. DSM-5-TR: Diagnostic and statistical manual of mental disorders. Porto Alegre: Artmed; 2022.
3. Ruiz-Iriondo M, Salaberría K, Echeburúa E, Iruín Á, Gabaldón O, Fernández-Marañón I. Global

functioning among middle-aged patients with chronic schizophrenia: the role of medication, working memory and verbal comprehension. Anal. Psicol, Murcia, 2019; 35, 2, 204-213. ISSN 1695-2294. Doi: https://dx.doi.org/10.6018/analesps.35.2.336251.

4. Barzeva SA, Richards JS, Meeus WHJ, Oldehinkel AJ. The social withdrawal and social anxiety feedback loop and the role of peer victimization and acceptance in the pathways. DevPsychopathol. 2020; 32(4): 1402-1417. PMID: 31668152.

5. Hunger C, Hilzinger R, Klewinghaus L, Deusser L, Sander A, Mander J, Bents H, et. al. Comparing cognitive behavioral therapy and systemic therapy for social anxiety disorder: randomized controlled pilot trial (sopho-cbt/st). Family Process, 2020; 59(4): 1389-1406. Doi: doi: 10.1111/famp.12492. Epub 2019 Oct 27.

6. Brinn A, Stone J. Neutrophiltolymphocyte ratio in psychiatric diagnoses: a cross-sectional study using electronic health records. BMJ Open, 2020; 10: e036859. Doi: http://dx.doi.org/10.1136/bmjopen-2020-036859

7. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. Neuropsychiatric Disease and Treatment. 2016: 12,1999–2005. PMCID: PMC4991539. Doi: 10.2147/NDT.S110484

8. Binici NC, Özyurt G. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescent obsessive-compulsive disorder: Does comorbid anxiety disorder affect inflammatory response? Psychiatry Research, 2019; 272: 311-315. PMID: 30597382.
   Doi: 10.1016/j.psychres.2018.12.131

9. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. PsychiatryResearch. Elsevier. 271(2019)131–135. PMID: 30472508.
   Doi: 10.1016/j.psychres.2018.11.043

10. Sahin SK, Yasamali C, Özyürek MB, Elboga G, Altindag A, Sahin AZ. Neutrophil-lymphocyteratio in catatonia. Archive. ClinicalPsychiatry São Paulo, 2020; 47(2). Doi: https://doi.org/10.1590/0101-60830000000232

11. Balcioglu YH, Kirlioglu SS. C-Reactive Protein/Albumin and Neutrophil/Albumin Ratios as Novel Inflammatory Markers in Patients with Schizophrenia. Psychiatry Investig. 2020; 17(9): 902-910. PMID: 32894927; PMCID: PMC7538240.

12. Moosazadeh M, Maleki I, Alizadeh-Navaei R, Kheradmand M, Hedayatizadeh-Omran A, Shamshirian A, et. al. Normal values of neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio and platelet-to-lymphocyte ratio among Iranian population: Results of Tabari cohort. Caspian J Intern Med. 2019 Summer; 10(3): 320-325.

13. Wei Y, Wang T, Li G, Feng J, Deng L, Xu H, et. al. Investigation of systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. Front Psychiatry, 2022; 26; 13: 941728. PMID: 31558995; PMCID: PMC6729162.

14. Inanli I, Aydin M, Çaliskan AM, Eren I. Neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, and mean platelet volume as systemic inflammatory markers in different states of bipolar disorder. Nordic Journal of Psychiatry, 2019; 73 (6): 372-379. PMID: 31304832. Doi: 10.1080/08039488.2019.1640789

15. Forget P, Khalifa C, Defour JP, Latinne D, Van Pel MC, De Kock M. What is the normal value of the neutrophil-to-lymphocyte ratio? BMC Research Notes. 2017; 3; 10(1): 12. PMID: 28057051. PMCID; PMC5217256.

16. Meng X, Chang Q, Liu Y, Chen L, Wei G, Yang J, et. al. Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: A posteriori and big-data-based. J ClinLab Anal. 2018; 32(2): e22228. PMID: 28378887; PMCID: PMC6817185.

17. ÖzdinSelçuk, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients – a retrospective file review, Nordic Journal of Psychiatry, 2017; 71(7): 509-512. PMID: 28644753. Doi: 10.1080/08039488.2017.1340517

18. Semiz M, Yildirim O, Canan F, Demir S, Hasbek E, Tuman TC, et. al. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. Psychiatria Danubina, 2014; 26(3): 220-5. PMID: 25191768.

19. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. BratislLekListy. 2021; 122(7): 474-488. PMID: 34161115. Doi: 10.4149/BLL_2021_078.

20. Song M, Graubard BI, Rabkin CS, Engels EA. Neutrophil-to-lymphocyte ratio and mortality in the United States general population. Scientific Reports 11, 464(2021). Doi: https://doi.org/10.1038/s41598-020-79431-7

21. Demiryürek E, Çekiç D, Işsever K, Genç AC, Yaylaci S, Demiryürek BE. Depression and Anxiety Disorders in COVID-19 Survivors: Role of Inflammatory Predictors. NoroPsikiyatrArs. 2022; 14; 59(2): 105-109. PMCID: PMC9142020.

22. Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et. al. Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Patients with Cervical

Cancer. Sci Rep. 2019; 1; 9(1): 3284. PMID: 30824727; PMCID: PMC6397230.

23. Dos Santos LF. Validity and reliability study of Liebowitz Social Anxiety Scale - self-applied version. Dissertation (Master of Science, area Mental Health). Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (USP) 2012. Available at: https://teses.usp.br/teses/disponiveis/17/17148/tde-03112012-112449/pt-br.php. Accessedon: 10 February 2021.

24. Caballo VE, Salazar IC, Arias V, Hofmann SG, Curtiss J. Psychometric properties of the Liebowitz Social Anxiety Scale in a large cross-cultural Spanish and Portuguese speaking sample. Braz J Psychiatry. 2019; 41(2): 122-130. PMID: 30328964; PMCID: PMC6781681

25. Rytwinski NK, Fresco DM, Heimberg RG, Coles ME, Liebowitz MR, Cissell S, Stein MB, Hofmann SG. Screening for social anxiety disorder with the self-report version of the Liebowitz Social Anxiety Scale. Depress Anxiety. 2009; 26(1): 34-8. Doi: https://doi.org/10.1002/da.20503

26. Uzun N, Akinci MA. Hemogram parameters in childhood anxiety disorders: Could anxiety disorders be related with inflammation? Medical Hypotheses. Elsevier. 2020; 110440. PMID: 33317847. Doi: 10.1016/j.mehy.2020.110440

27. Crippa J.A.S., Sanches R.F., Hallak J.E.C., Loureiro S.R., Zuardi A.W. Factor structure of Bech's version of the Brief Psychiatric Rating Scale in Brazilianpatients. Neurosciences and behavior. Braz J MedBiol Res.2002; 35(10): 1209-13. Doi: https://doi.org/10.1590/S0100-879X2002001000014

28. Crippa J.A.S., Sanches R.F., Hallak J.E.C., Loureiro S.R., Zuardi A.W. Factor structure of Bech's version of the Brief Psychiatric Rating Scale in Brazilian patients. Neurosciences and behavior. Braz J MedBiol Res.2002; 35(10): 1209-13. Doi: https://doi.org/10.1590/S0100-879X2002001000014

29. Park S-C, Eun YJ, Kiwon K, Hoseon L, Joonho C, Amitava D, et al. Establishing the cut-off scores for the severity ranges of schizophrenia on the BPRS-6 scale: findings from the REAP-AP. Psychiatry and Clinical Psychopharmacology, 2019; 29:4, 895-898. Doi: 10.1080/24750573.2019.1695994

30. Medeiros HLV de, Rocha DM, Roudig RMEW, Silva AMP da. Validated schizophrenia assessment scales for use in brazil: a systematic review. Debates in Psychiatry 2017; 7(5): 22-8. Doi: https://doi.org/10.25118/2763-9037.2017.v7.78

31. Freitas RR De. Assessment of Psychopathological Dimensions of treatment-resistant and non-treatment-resistant Schizophrenia: an international multicentercross-sectional study. Dissertation (Psychiatry Program). Universityof São Paulo

Schoolof Medicine, 2018. Available at: https://www.teses.usp.br/teses/disponiveis/5/5142/tde-31102018-130536/publico/RosanaRamosdeFreitas.pdf. Accessedon: 17 February 2023.

32. Van Dorn RA, Desmarais SL, Grimm KJ, Tueller SJ, Johnson KL, Sellers BG, et. al. The latent structure of psychiatric symptoms across mental disorders as measured with the PANSS and BPRS-18. Psychiatry Res. 2016; 30; 245: 83-90. PMID: 27529666; PMCID: PMC5067208.

33. Sousa TV, Viveiros V, Chai MV, Vicente FL, Jesus G, Carnot MJ, et. al. Reliability and validity of the Portuguese version of the Generalized Anxiety Disorder (GAD-7) scale. Health Qual Life Outcomes 13,50(2015). Doi: https://doi.org/10.1590/0102-311X00212716

34. Adali MK, Buber I, Sen G, Yilmaz S. Relationship between Systemic Immune-Inflammation Index and Coronary Collateral Circulation in Patients with Chronic Total Occlusion. ArqBrasCardiol. 2022; 119(1): 69-75. PMID: 35703663; PMCID: PMC9352117. Doi: 10.36660/abc.20210414

35. Li F, Shi X, Dai C. Prognostic value of pre-operative peripheral inflammation markers in patients with squamous cell carcinoma of the external auditory canal. Brazilian Journal of Otorhinolaryngology. 2022; 88(2): 161-167. PMID: 32624372; PMCID: PMC9422596.
Doi: 10.1016/j.bjorl.2020.05.018

36. Szor DJ. Evaluation of the neutrophil-lymphocyteratio as a prognostic factor in gastric cancer patients undergoing potentially curative gastrectomy. Dissertation (Doctorate of Science in Gastroenterology). University of São Paulo Schoolof Medicine, 2019. Available at: https://www.teses.usp.br/teses/disponiveis/5/5168/tde-09032020-143134/pt-br.php. Accessedon: 05 January 2021.

37. Eyff TF, Bosi HR, Toni MS, Zilio MB, Corso CO, Bersch VP, et al. The role of immunoinflammatory markers in the prognosis and resectability of pancreaticadeno carcinoma. ABCD ArqBrasCirDig. 2018; 31(2): e1366. PMID: 29972394; PMCID: PMC6044203. Doi: 10.1590/0102-672020180001e1366

Table 1: Descriptive statistics and prevalences of altered instruments and inflammation markers (blood count = CBC)

Variables	Mean ± DP ou Median (P25 – P75)	n (%)
LSAS	54 (26,8 – 86,0)	
≥ 32 points		59 (72,0)
GAD-7	7 (3 – 11)	
≥ 5 points		55 (67,1)
BPRS	21,5 (13 – 30,3)	
≥ 5 points		78 (95,1)
BLOOD COUNT		
Neutrophils	4,98 ± 2,05	
Monocytes	0,59 ± 0,21	
Lymphocytes	2,05 ± 0,76	
Platelets	215,4 ± 65,5	
Neutrophil-lymphocyteratio	2,50 (1,50 – 3,49)	
≥ 2,80		35 (42,7)
Monocyte-lymphocyteratio	0,29 (0,22 – 0,37)	
≥ 0,35		25 (30,5)
Platelet-lymphocyteratio	108,1 (82,8 – 143,5)	
≥ 362		0 (0,0)
Systemicimmune-inflammatory index	535 (303,5 – 794,2)	
≥ 761		21 (25,6)

Table 2: Correlation between the LSAS, GAD-7 and BPRS scales with the inflammation markers NLR, SII, MLR and PLR, through Spearman's correlation coefficient.

LSAS = Liebowitz Social Anxiety Scale; BRPS = Brief Psychiatric Rating Scale; GAD-7 = Generalized Anxiety Disorder Scale; NLR = Neutrophil-to-Lymphocyte Ratio; SII = Systemic Immune-Inflammatory Index; MLR = Monocyte-to-Lymphocyte Ratio; PLR = Platelet-to-Lymphocyte Ratio; rs = Spearman's correlation coefficient.

| Markers of Inflammation	LSAS		GAD-7		BPRS	
	r_s	p	r_s	p	r_s	P
NLR	0,241	0,029	0,020	0,860	-0,058	0,606
SII	0,257	0,020	0,111	0,321	-0,054	0,630
MLR	0,110	0,326	-0,005	0,963	-0,043	0,702
PLR	0,236	0,032	0,112	0,318	-0,003	0,982

Table 3: Prevalence of alterations in the GAD-7 and BPRS scales and in the blood count according to the LSAS classification

Variables	No AS (n=23; 28%)	Yes AS (n=59; 72%)	P
GAD-7			
≥ 5 points	9 (39,1)	46 (78,0)	0,002
BPRS			
≥ 5 points	19 (82,6)	59 (100)	0,005
BLOOD COUNT			
Neutrophil-lymphocyteratio			
≥ 2,80	5 (21,7)	30 (50,8)	0,032
Monocyte-lymphocyteratio			
≥ 0,35	4 (17,4)	21 (35,6)	0,180
Systemicimmune-inflammatory index			
≥ 761	3 (13,0)	18 (30,5)	0,178

Table 4: Multivariate Poisson Regression Analysis to assess factors independently associated with social anxiety

Variables	Prevalence Ratio (95% CI)	P
GAD-7 ≥ 5 points	1.53 (1.04 – 2.25)	.029
BPRS		
Positive Domain	1.04 (1.01 – 1.06)	.003
Disorganized Cognitive Domain	1.04 (1.01 – 1.07)	.004
Total score	1.02 (1.01 – 1.03)	.001
Neutrophil-Lymphocyte Ratio ≥ 2,80	1.55 (1.21 – 1.98)	<.001
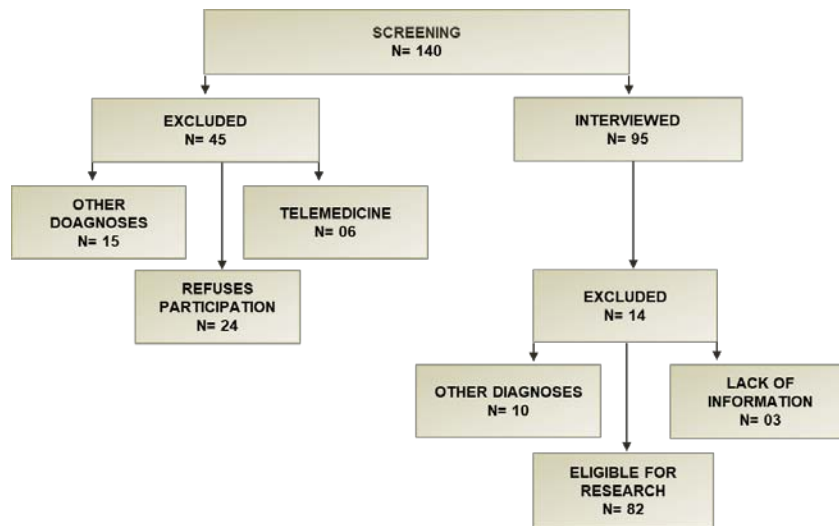
Source: Elaborated by the author.

Figure 1: PRISMA Flowchart: patients screened, interviewed, excluded, included, eligible.
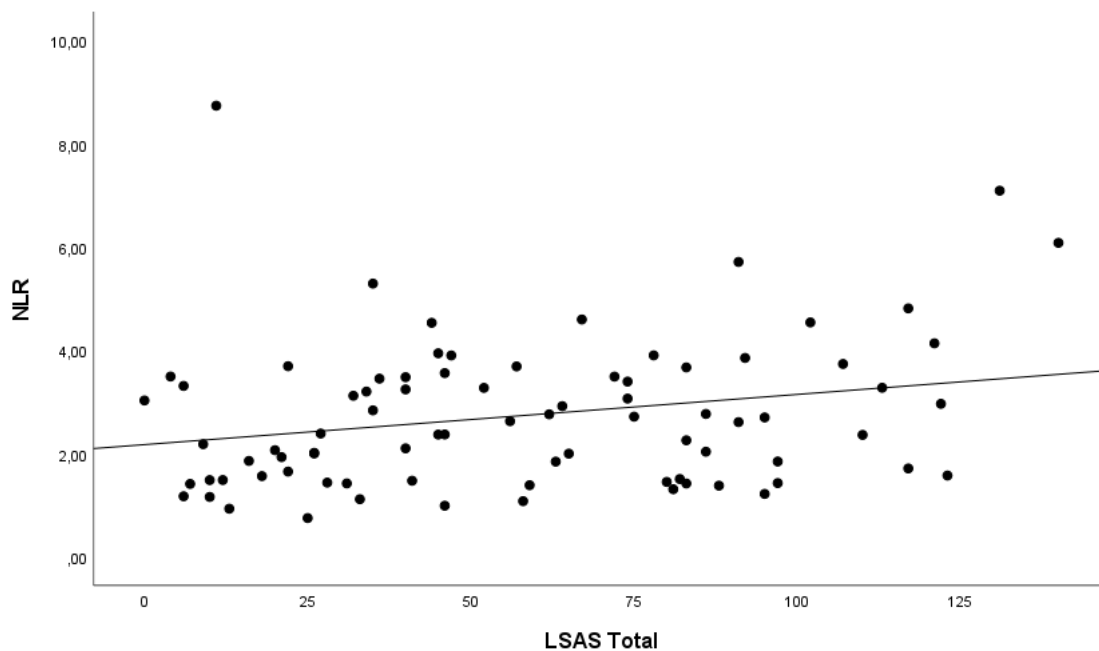

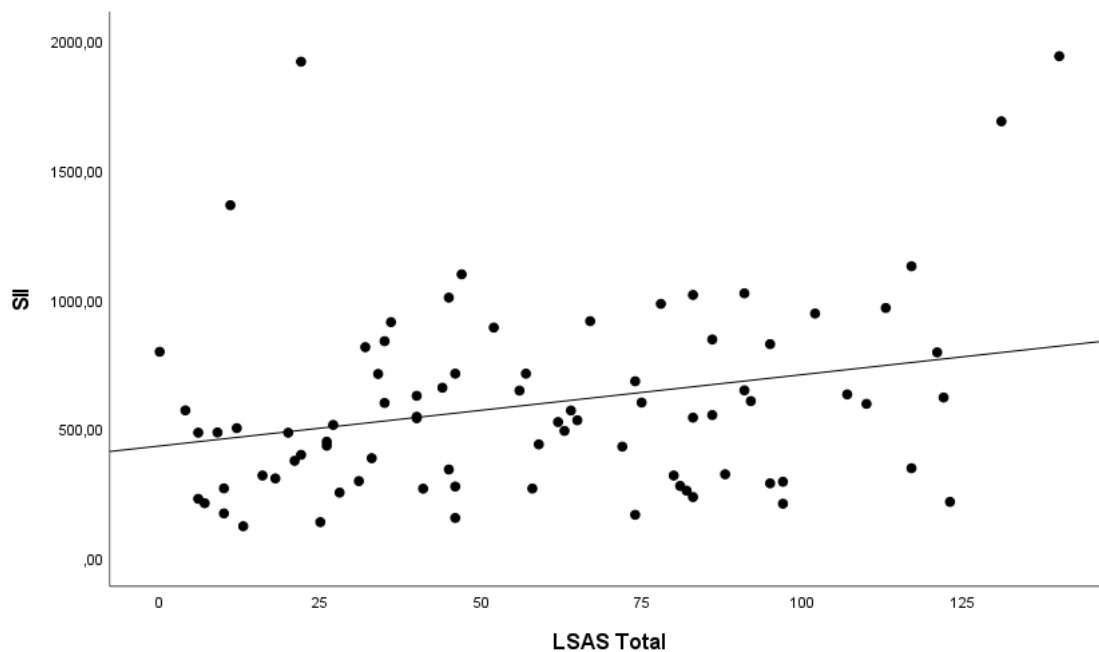*Figure 2:* Scatter diagram of LSAS's correlation with NLR.

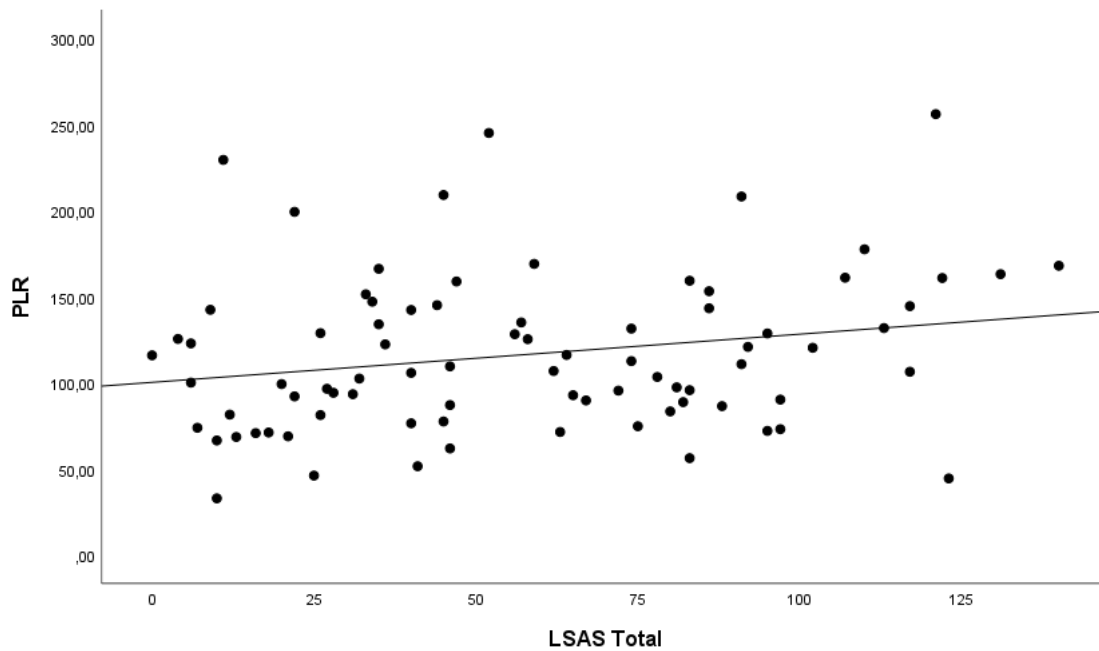*Figure 3:* Scatter diagram of the LSAS correlation with SII.

Figure 4: Scatter diagram of the correlation of LSAS with PLR.