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Personalized Psychiatry and Neurology

Review

Neutrophil-to-Lymphocyte Ratio Any Association with Metabolic Syndrome in Schizophrenia

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Abstract: To date, hematologic inflammation coefficients (HICs) have been considered as biological markers linking the functions of the immune, endocrine, and autonomous nervous systems. HICs are markers of immune abnormalities that accompany various pathologic conditions and, to a large extent, determine disease prognosis, survival time, and function. According to the results of a meta-analysis covering the results of examination of more than 168 thousand patients, it was found that the ratio of neutrophils to lymphocytes (NLR) is associated with higher levels in patients with metabolic syndrome and can potentially be used for early detection of this pathology. Given these facts, it seems reasonable to test the assumption of the role of HICs in the pathogenesis of psychiatric disorders, their participation in the mechanisms of development of comorbid conditions, or predicting the outcome and effects of therapy. In 2024, the team of the Bekhterev Center began to perform work under the state assignment of the Ministry of Health of the Russian Federation, the purpose of which was to develop and validate a model for predicting individual risks of metabolic disorders in patients with psychiatric disorders, on the basis of which interpretive software will be presented. The team of authors of this article focused on conducting a systematic review of publications to test this hypothesis.

Keywords: *neutrophil-to-lymphocyte ratio (NLR); schizophrenia; metabolic syndrome; hematologic inflammation coefficients (HICs); systemic inflammation; psychiatric disorders; immune dysregulation; biomarkers; antipsychotic therapy; psychoneuroimmunology.*

1. INTRODUCTION

The first mention of the significance of the index of absolute or percentage neutrophil-lymphocyte ratio (neutrophil-lymphocyte ratio, NLR) refers to the publication of a surgical intensive care unit physician who found that as the severity and multiorgan nature of surgical pathology increased, the gap between neutrophilia and lymphocytopenia indices according to the results of routine peripheral blood analysis increased [1]. The author designated this ratio as neutrophil-lymphocyte stress factor [1], and some of the followers - after his name - index Zahorec [2], emphasizing the deep biological meaning of NLR, which links the functions of the immune, endocrine and autonomous nervous system and determines the prognosis of diseases [3].

To date, hematologic inflammation coefficients (HIC) (Neutrophil to lymphocyte ratio/NLR, Monocyte lymphocyte ratio/MLR, Systemic immune-inflammation index/SII) are considered as biological markers of immune disorders accompanying various pathological conditions, largely determining survival and functioning time [4].

Interest in HICs is related to their ability to characterize both innate and acquired immunity [5]. Studies have shown a significant correlation of HICs on the basis of routine clinical blood analysis with other established markers of inflammation (C-reactive protein, oxidative stress indicators and some proinflammatory cytokines) in studies of somatic pathology [6,7]. It is important to note that the studies proved the absence of influence of modifying factors on HICs, which shows their advantage in comparison with other widely used inflammatory markers [5,8].

The homeostasis of the organism is ensured by the coherent functioning of the immune system and metabolic processes [9]; imbalance of this coherence triggers dysfunctional cascades of reactions leading to the development of endocrine, cardiovascular and psychiatric diseases [10,11]. Moreover, a meta-analysis covering the results of more than 168,000 patients found that neutrophil to lymphocyte ratios are associated with higher levels in patients with metabolic syndrome and thus can potentially be used for early detection of metabolic syndrome [12]

Bearing in mind that the NLR links the functions of the nervous, immune and endocrine systems [2,13], it is reasonable to test the assumption of its role, as a link of immune processes, in the pathogenesis of psychiatric disorders or in the mechanisms of development of comorbid conditions, or predicting the outcome and effects of therapy [14,15].

Inflammatory imbalance can affect mental functioning from the earliest stages of nervous system development [16] and, under certain conditions, lead to the formation of mental disorders and/or correlate with the severity of psychopathological manifestations, such as schizophrenia [17].

Chronic neuroinflammation in schizophrenia along with oxidative stress reactions may be the factors that allow us to label schizophrenia as a syndrome of accelerated aging [18-21]. Life expectancy of schizophrenia patients is reduced by 10-15 years compared to the general population due to early cell degradation, decreased brain and bone tissue mass, humoral and, importantly, endocrine disorders [19,22,23]. The results of HICs screening in patients with various manifestations of psychiatric disorders can be very informative in terms of prognosis [26,27].

Many modern studies consider inflammation as a pathogenetic basis of metabolic disorders in schizophrenia and affective disorders [28]. At the same time, metabolic syndrome as a proinflammatory process [29] may lead to aggravation of the effects of oxidative stress, worsening the prognosis of schizophrenia [30].

In 2024, the team of the Bekhterev Center started to perform work under the state assignment of the Ministry of Health of the Russian Federation, the purpose of which was to develop and validate a model for predicting individual risks of metabolic disorders formation in patients with psychiatric disorders, based on which interpretive software will be presented.

These tasks seem feasible as we verify the hypothesis formulated before the beginning of all works: systemic inflammation factors are the link between psychiatric disorders and metabolic disorders (MD). Accordingly, the use of hematologic inflammation coefficients (HICs) in combination with the analysis of clinical and psychosocial factors allows to identify the risks of MD formation in a group of patients with psychiatric disorders.

Working groups of researchers have already prepared narrative reviews on the role of hematologic indices in the development of psychiatric disorders in adolescents [31] and affective pathology in adults [32].

The team of authors of the present article focused on conducting a systematic review of publications to test the above hypothesis.

To conduct a systematic review of scientific publications suitable for testing the working hypothesis.

2. MATERIAL AND METHODS

The work was conducted from April to July 2024 according to the principles of the PRISMA guidelines for systematic reviews [33] (Figure 1) by a team of five physicians - psychiatrists, clinical pharmacologists and one data analyst, a mathematician.

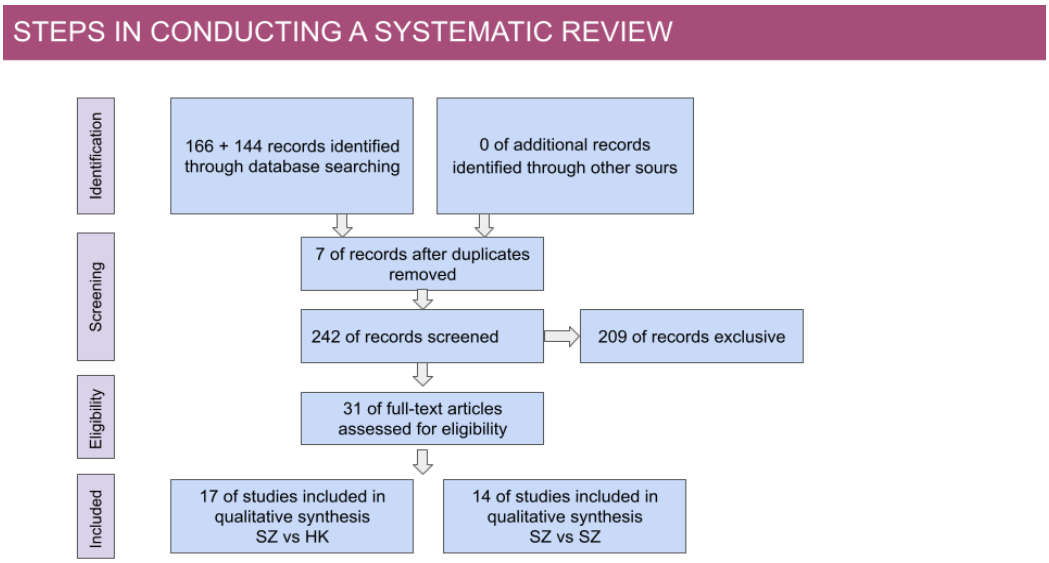

Figure 1. This a Block diagram of PRISMA 2020 [34]

Searches were performed on PubMed and ScienceDirect libraries.

Screening in databases

A systematic literature review aimed at answering the question "Is NLR a risk marker for metabolic syndrome in schizophrenia?" within the PECO framework:

P - patients with schizophrenia

E - hematologic parameters

C - comparison groups (healthy volunteers or patients with different forms or at different stages of schizophrenia)

O - risk of metabolic syndrome

Search terms:

Neutrophil to Lymphocyte Ratio/ NLR

Monocyte to Lymphocyte Ratio/ MLR

Systemic Immunoinflammation Index/SII

Metabolic Syndrome

Schizophrenia

Search parameters: by terms in article titles and abstracts, no restrictions on dates, article language, article format.

We performed a series of queries with null search results:

query 1. markers + metabolic syndrome + schizophrenia (0 articles)

(("Neutrophil to lymphocyte ratio" [Title/Abstract] OR "NLR" [Title/Abstract] OR ("monocyte lymphocyte ratio"[Title/Abstract] OR "MLR"[Title/Abstract])) OR ("Systemic immune-inflammation index"

[Title/Abstract] OR "SII" [Title/Abstract]) AND "metabolic syndrome" [Title/Abstract]) AND “schizophrenia” [Title/Abstract]

query 2: Markers + metabolic syndrome + antipsychotics/neuroleptics (0 articles)
(("Neutrophil to lymphocyte ratio"[Title/Abstract] OR "NLR" [Title/Abstract] OR "monocyte lymphocyte ratio" [Title/Abstract] OR "MLR"[Title/Abstract])) OR "Systemic immune-inflammation index" [Title/Abstract] OR "SII" [Title/Abstract]) AND "metabolic syndrome" [Title/Abstract]) AND “antipsychotics” [All Fields]

After which we tried to modify the search strategies by removing some term restrictions.

query 3: markers + metabolic syndrome (118 articles)
(("Neutrophil to lymphocyte ratio" [Title/Abstract] OR "NLR" [Title/Abstract]) OR ("monocyte lymphocyte ratio " [Title/Abstract] OR "MLR" [Title/Abstract]) OR ("Systemic immune-inflammation index" [Title/Abstract] OR "SII" [Title/Abstract])) AND "metabolic syndrome" [Title/Abstract]

No papers on schizophrenia appeared among these publications.

query 4. NLR + (metabolic syndrome OR schizophrenia) = 166 papers (("Neutrophil to lymphocyte ratio"[Title/Abstract] OR "NLR" [Title/Abstract]) AND ("metabolic syndrome" [Title/Abstract] OR "schizophrenia" [Title/Abstract])

The same query in the ScienceDirect library provided 144 publications.

Thus, an initial search of the two databases identified 310 publications. Each article was read independently by four experts. After removing duplicated articles, the following data were entered into the table: article title, authors, doi of publication, year of publication, sample size, number of patients with schizophrenia, number of comparison group patients, number of healthy controls, mean age of participants (with mean deviation), criteria for diagnosis verification, if there were indications in the text - features of the disease clinic, drug therapy at the time of the study, results of psychometric examination, NLR scores, metabolic syndrome scores.

After extraction of the above data, articles and publications that met the search criteria were included in the review.

Reviews and book chapters were not considered - there were 209 publications of this type of material.

3. RESULTS

Eligibility Assessment

After screening procedures, 31 articles remained (Table 1) with publications of results from observational cohort and case-control studies.

Methodological quality assessment was conducted using the Newcastle-Ottawa Scale (NOS) for observational studies by three physicians. The results were disparate due to imperfections in the evaluation methodology. For example, the NOS scale does not specify how many points a study should score to determine its methodological quality as high, medium, or low. This scale does not assess to what extent the influence of confounding factors was taken into account, etc. It is also important to note that the assessment of the methodological quality of studies is seriously hindered by the poor

quality of information presentation about their methods and results in publications from our search query in the PubMed and ScienceDirect knowledge bases.

Table 1. Results of a systematic review of publications with neutrophil to lymphocyte ratio research results in patients with schizophrenia

Study Group	Total Group Size, people	NLR	Conclusions	Bibliography
Schizophrenia without additional data	9148	2.27±1.43	The general conclusion for all articles is that an increase in NLR is a sign of systemic inflammation and immune imbalance, which confirms the inflammatory hypothesis of schizophrenia and also opens up prospects for new treatment strategies targeting the immune system.	[38-53]
First Episode Schizophrenia	648	1.94±1.09	The existence of a hidden predisposition of FEP patients to an increase in average NLR.	[27,54-56]
Schizophrenia in remission	3019	2.03-±1.17	The results show that psychosis is associated with peripheral markers of inflammation in the early stages of mental pathology,and that inflammation may represent a condition that accompanies psychosis and decreases during clinical remission.	[26,57-61]
Schizophrenia without remission	1256	2.43±1.23	Persistence of elevated NLR values in the acute period	[27,55,56,62-64]
Healthy controls	1150	1.62±0.78	Lower indicators relative to patients suffering from schizophrenia.	[27,38–40,42–47,49–53,56–58,63,65–67]

Overall effect size:0.5976 Note:NLR-neutrophil to lymphocyte ratio;FEP-first episode psychosis schizophrenia.

For further analysis of the extracted data, we defined criteria for the pathological conditions of interest:

Schizophrenia criteria: Diagnosis based on the current international classification systems at the time of the study (DSM-IV, DSM-5, ICD-10, or ICD-11) - found 17 articles.

Metabolic syndrome criteria [35-37] at least three of the following metabolic risks: increased waist circumference (men >102 cm; women >88 cm); elevated triglyceride levels (≥150 mg/dL); reduced high-density lipoprotein (HDL) cholesterol levels (men <40 mg/dL; women <50 mg/dL); elevated fasting glucose (fasting glucose ≥100 mg/dL or taking medication for hyperglycemia); and elevated blood pressure (≥130/85 mm Hg or taking medication for hypertension). This item (indication of diagnostic criteria for metabolic syndrome) was not fulfilled in any of the studies.

Consequently, a consensus decision was made to focus on the role of NLR in the pathogenesis of schizophrenia, taking into account its stages.

All 31 identified articles contained information about the number of participants in different comparison groups, their mean age - 37.245 in the group of patients with schizophrenia and -36.02 in the group of healthy volunteers.

We calculated the difference in mean NLR values for all schizophrenia groups and healthy controls. A positive value indicates that patients with schizophrenia have higher NLR than healthy people in the control group.

95% Confidence Interval

This is a range of values within which we can be 95% confident that the true effect value in the population lies. If the confidence interval (CI) does not include zero, it indicates a statistically significant difference between patients with schizophrenia and healthy individuals from the control group.

Forest plot

Graphically shows individual effect sizes for each schizophrenia subgroup with their confidence intervals and the overall effect size across all subgroups.

Calculation Formula

The weighted average for all schizophrenia subgroups is calculated as:

Weighted average = Σ(n_i * Mean_i) / Σ(n_i),

where n_i is the sample size and Mean_i is the mean of each subgroup. This gives us the average NLR value across all schizophrenia subgroups, weighted by sample size. The result is 2.22.

The pooled standard deviation (SD) for schizophrenia groups is calculated as:

Pooled SD = √[Σ(n_i * (SD_i^2 + (Mean_i - Weighted average)^2)) / Σ(n_i)],

where SD_i is the standard deviation of each subgroup. This gives us the overall standard deviation for schizophrenia groups, accounting for different sample sizes and deviations from the overall mean. The result is 1.35.

The difference in means (effect size) is calculated as:

Difference in means = Weighted average (Schizophrenia) - Mean (Control) = 2.22 - 1.62 = 0.5976.

This is the difference in NLR between the combined schizophrenia group and the control group.

The standard error of this difference is calculated as:

SE = √[(Pooled SD^2 / N_schizophrenia) + (SD_control^2 / N_control)] = √[(1.35^2 / 14071) + (0.78^2 / 1150)] = 0.0257.

This gives us the precision of our estimate of the difference in means.

The 95% confidence interval is calculated as:

95% CI = Difference in means ± (1.96 * SE) = 0.5976 ± (1.96 * 0.0257) = [0.5472, 0.6480].

Finally, the Z-score and p-value are calculated as:

Z = Difference in means / SE = 0.5976 / 0.0257 = 23.2773,

p-value = 2 * (1 - Φ(|Z|)),

where Φ is the cumulative distribution function of the standard normal distribution. This Z-score is extremely high, resulting in a p-value that is effectively zero (< 0.0001). This indicates a statistically significant difference in NLR between patients with schizophrenia and the control group.

Python 3.11 and libraries numpy 1.25.2 and matplotlib 3.7.1 were used for calculation of indicators and visualization.

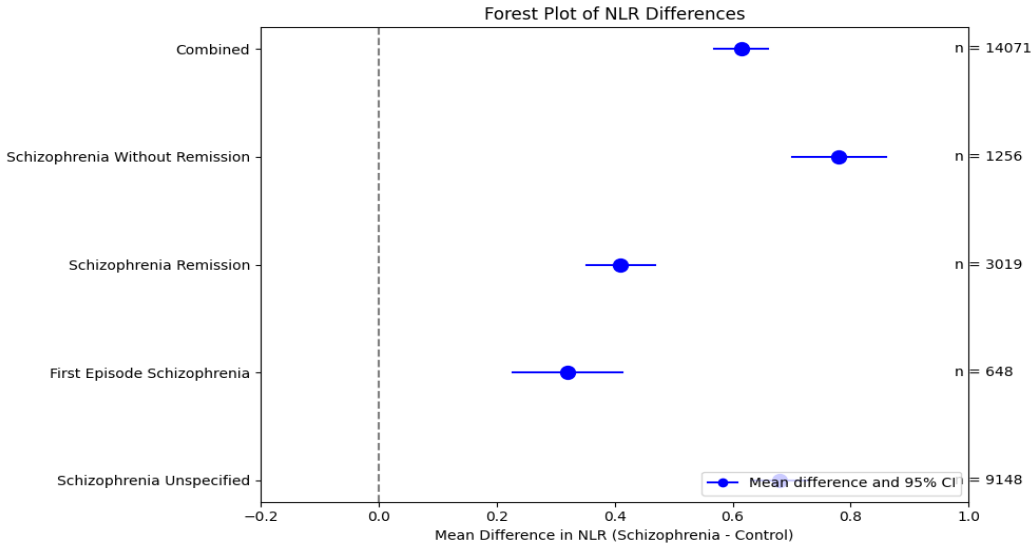

Figure 2. Graphical representation of neutrophil to lymphocyte ratio differences in schizophrenia

Each row represents a subgroup of schizophrenia or a combined group. Blue dots indicate the mean difference in NLR between each schizophrenia group and the control group, with horizontal blue lines showing the 95% confidence interval for this difference. The vertical dashed line at 0 represents no difference between the schizophrenia and control groups. The size of each blue dot is proportional to the sample size (n) of each group, which is also indicated on the right side of the graph.

4.DISCUSSION

Unfortunately, we must acknowledge a null result for the initially planned query. We were unable to answer the question "Is NLR a marker of metabolic syndrome risk in schizophrenia?" This may be due to imperfections in the methodology of the systematic review conducted. First of all, the null result may be a consequence of the fact that we

only accounted for publications from two knowledge bases, without including articles from other scientific repositories in the search.

However, it can be assumed that the formulated research hypothesis has not yet been tested regarding the risk of metabolic syndrome development depending on systemic inflammation indicators in patients with schizophrenia. Whereas for other mental disorders, in particular bipolar disorder, clinical and biological associations have already been found [68]. Thus, the hypothesis is a posteriori and requires verification in both cohort and case-control design studies, as evidenced by publications of individual cases predicting hematological abnormalities in the process of metabolic syndrome development during schizophrenia treatment [69]. In this article about a clinical case of a 48-year-old female patient with schizophrenia, an increase in hematological inflammation coefficients was recorded against the background of treatment for symptom exacerbation after clozapine prescription, which preceded the development of metabolic syndrome. The authors suggest causal relationships of these processes and propose widespread implementation of hematological predictors of metabolic syndrome in real clinical practice to improve the safety of antipsychotic therapy [69].

Our mathematical analysis of NLR indicators (Fig. 2) clearly illustrates that in schizophrenia, the NLR level is significantly higher than among healthy individuals (control group) $Z = 23.2773$ and $p < 0.00001$. It can be seen that the maximum NLR level is observed in the group of patients with schizophrenia in the acute stage, and the minimum level is in the group of patients with first-episode schizophrenia. Patients in remission have intermediate values. As expected, the groups of schizophrenia without additional specifications and combining all patients with schizophrenia, regardless of stage (combined), have similar NLR indicators and are average in the patient group. This once again confirms the correlation between the NLR level and the stage of schizophrenia.

5. CONCLUSIONS

Our review demonstrates that the hypothesis about the role of hematologic inflammation ratio in the pathogenesis of psychiatric disorders, their participation in the mechanisms of comorbid conditions development regarding the risk of metabolic syndrome development depending on the indicators of systemic inflammation in patients with schizophrenia has been insufficiently studied to date, with only a few publications available. It is necessary to continue studying the relationship between the ratio of neutrophils and lymphocytes and metabolic syndrome in schizophrenia.

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Sample Availability: Samples of the compounds ... are available from the authors.

References

1. Zahorec, R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. *Bratisl Lek Listy* **2001**, 1:5–14.
2. Firment, J.; Hulin, I. Zahorec index or Neutrophil-to-lymphocyte ratio, valid biomarker of inflammation and immune response to infection, cancer and surgery. *Bratisl Lek. Listy* **2024**, 2:75–83. doi: 10.4149/BLL_2024_012
3. Tang, H.; Lu, W.; Li, B.; Li, C.; Xu, Y.; Dong, G. Prognostic significance of neutrophil-to-lymphocyte ratio in biliary tract cancers: a systematic review and meta-analysis. *Oncotarget* **2013**, 22:36857–36868. doi: 10.18632/oncotarget.16143
4. Adali, M.; Buber, I.; Oguz, K.; Turkoz, A.; Yilmaz, S. Ticagrelor improves systemic immune-inflammation index in acute coronary syndrome patients. *Acta Cardiol*. **2022**, 77(7):632–638. doi: 10.1080/00015385.2021.1973770
5. Ivković, M.; Pantović-Stefanović, M.; Dunjić-Kostić, B.; Jurišić, V.; Lačković, M.; Totić-Poznanović, S.; Jovanović, A.; Damjanovićl, A. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: Moderatory effect of family history. *Compr. Psychiatry* **2016**, 87–95. doi: 10.1016/j.comppsych.2016.01.005
6. Kasama, T.; Miwa, Y.; Isozaki, T.; Odai, T.; Adachi, M.; Kunkel, S. Neutrophil-derived cytokines: potential therapeutic targets in inflammatio. *Curr. Drug Targets Inflamm. Allergy* **2005**, 3: 273–279. doi: 10.2174/1568010054022114
7. Gao, S.Q.; Huang, L.D.; Dai, R.J.; Chen, D.D.; Hu, W.J.; Shan, Y.F. Neutrophil-lymphocyte ratio: a controversial marker in predicting Crohn's disease severity. *Int. J. Clin. Expp. Pathol*. **2015**, 11:14779–14785.
8. Gibson, P.; Croal, B.; Cuthbertson, B.; Small, G.; Ifezulike, A.; Gibson, G.; Jeffrey, R.; Buchan, K.; El-Shafei, H.; Hillis, G. Preoperative neutrophil-lymphocyte ratio and outcome from coronary artery bypass grafting, *Am. Heart J.* **2007**, 5:995–1002. doi: 10.1016/j.ahj.2007.06.043
9. Hotamisligil, G.S. Inflammation and metabolic disorders. *Nature* **2006**, 7121: 860–867. doi: 10.1038/nature05485
10. Wang, J.; Ruotsalainen, S.; Moilanen, L.; Lepistö, P.; Laakso, M.; Kuusisto, J. Metabolic syndrome and incident end-stage peripheral vascular disease: a 14-year follow-up study in elderly Finns. *Diabetes Care* **2007**, 12:3099–3104. doi: 10.2337/dc07-0985
11. Mottillo, S.; Filion, K.; Genest, J.; Joseph, L.; Pilote, L.; Poirier, P.; Rinfret, S.; Schiffrin, E.; Eisenberg, M. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J. Am. Coll. Cardiol*. **2010**, 14:1113–1132. doi: 10.1016/j.jacc.2010.05.034
12. Mahmood, A.; Haider, H.; Samad, S.; Kumar, D.; Perwaiz, A.; Mushtaq, R.; Ali, A.; Farooq, M.; Farhat, H. Association of white blood cell parameters with metabolic syndrome: A systematic review and meta-analysis of 168,000 patients. *Medicine* **2024**, 10:e37331. doi:10.1097/MD.0000000000037331
13. Bahadır, A.; Baltacı, D.; Türker, Y.; Türker, Y.; Iliev, D.; Öztürk, S.; Deler, M.H.; Sarıgüze, Y.C. Is the neutrophil-to-lymphocyte ratio indicative of inflammatory state in patients with obesity and metabolic syndrome? *Anatol J Cardiol*. **2015**, 10:816–822. doi: 10.5152/akd.2014.5787
14. Benedetti, F.; Aggio, V.; Pratesi, M.L.; Greco, G.; Furlan, R. Neuroinflammation in Bipolar Depression. *Front. Psychiatry* **2020**, 71. doi: 10.3389/fpsyt.2020.00071
15. Leboyer, M.; Sommer, I.E.; Berk, M. The Role of Immune Components in Psychiatric Disorders. *Frontiers Media SA* **2020**, 124. doi: 10.1016/j.mcn.2012.10.002

16. Kowalczyk, M.; Szemraj, J.; Bliźniewska, K.; Maes, M.; Berk, M.; Su, K.-P.; Gałecki, P. An immune gate of depression - Early neuroimmune development in the formation of the underlying depressive disorder. *Pharmacol. Rep*. **2019**, 6:1299–1307. doi: 10.1016/j.pharep.2019.05.022
17. Zakharova, N.V.; Zozulya, S.A.; Sarmanova, Z.V.; Bravve, L.V.; Otman, I.N.; Klyushnik, T.P. Features of the immune profile of schizophrenic patients with catatonic syndrome. *Zh. Nevrol. Psikhiatr. Im. S S Korsakova* **2020**, 6:46–53. doi: 10.17116/jnevro202012006246
18. Kirkpatrick, B.; Messias, E.; Harvey, P.D.; Fernandez-Egea, E.; Bowie, C.R. Is schizophrenia a syndrome of accelerated aging? *Schizophr. Bull*. **2008**, 6:1024–1032. doi: 10.1093/schbul/sbm140
19. Shivakumar, V.; Kalmady, S.V.; Venkatasubramanian, G.; Ravi, V.; Gangadhar, B.N. Do schizophrenia patients age early? *Asian J. Psychiatr*. **2014**, 3–9. doi: 10.1016/j.ajp.2014.02.007
20. Okusaga, O.O. Accelerated aging in schizophrenia patients: the potential role of oxidative stress. *Aging Dis.* **2014**, 4:256–262. doi: 10.14336/AD.2014.0500256
21. Polho, G.B.; De-Paula, V.J.; Cardillo, G.; dos Santos, B.; Kerr, D.S. Leukocyte telomere length in patients with schizophrenia: A meta-analysis. *Schizophr. Res.* **2015**, 195–200. doi: 10.1016/j.schres.2015.04.025
22. Papanastasiou, E.; Gaughran, F.; Smith, S. Schizophrenia as segmental progeria. *J. R. Soc. Med*. **2011**, 11:475–484. doi: 10.1258/jrsm.2011.110051
23. Savolainen, K.; Räikkönen, K.; Kananen, L.; Kajantie, E.; Hovatta, I.; Lahti, M.; Lahti, J.; Pesonen, A.K.; Heinonen, K.; Eriksson, J.G. History of mental disorders and leukocyte telomere length in late adulthood: the Helsinki Birth Cohort Study (HBCS). *Psychiatr. Res*. **2012**, 10:1346–1353. doi: 10.1016/j.jpsychires.2012.07.005
24. de Leon, J.; Diaz, F.J. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr. Res.* **2005**, 2(3): 135–157. doi: 10.1016/j.schres.2005.02.010
25. Mittal, D.; Corrigan, P.; Sherman, M.D.; Chekuri, L.; Han, X.; Reaves, C.; Mukherjee, S.; Morris, S.; Sullivan, G. Healthcare providers' attitudes toward persons with schizophrenia. *Psychiatr. Rehabil. J.* **2014**, 4:297–303. doi: 10.1037/prj0000095
26. Bustan, Y.; Drapisz, A.; Ben Dor, D.H.; Avrahami, M.; Schwartz-Lifshitz, M.; Weizman, A.; Barzilay, R. Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for early association between inflammation and psychosis. *Psychiatry Res.* **2018,** 149–153. doi: 10.1016/j.psychres.2018.02.002
27. Jacomb, I.; Stanton, C.; Vasudevan, R.; Powell, H.; O'Donnell, M.; Lenroot, R.; Bruggemann, J.; Balzan, R.; Galletly, C.; Liu, D.; Weickert, C.S.; Weickert, T.W. C-Reactive Protein: Higher During Acute Psychotic Episodes and Related to Cortical Thickness in Schizophrenia and Healthy Controls. *Front. Immunol.* **2018**, 2230. doi: 10.3389/fimmu.2018.02230
28. Leonard, B.E.; Schwarz, M.; Myint, A.M. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? *J. Psychopharmacol.* **2012**, 5:33–41. doi: 10.1177/0269881111431622
29. Emanuela, F.; Grazia, M.; Marco de, R.; Maria Paola, L.; Giorgio, F.; Marco, B. Inflammation as a Link between Obesity and Metabolic Syndrome. *J. Nutr. Metab.* **2012**, 476380. doi: 10.1155/2012/476380
30. Robert, C.K.; Sindhu, K.K. Oxidative stress and metabolic syndrome. *Life Sci.* **2009**, 21(22):705–712. doi: 10.1016/j.lfs.2009.02.026
31. Popov, M.; Popov, Y.; Kosterin, D.; Lepik, O. Inflammatory hematological ratios in adolescents with mental disorders: A scoping review. Consortium Psychiatricum. *ECO-Vector LLC* **2024**, 2:45–61. doi:10.17816/CP15514
32. Gorbunova, A.P.; Rukavishnikov, G.; Kasyanov, E.D.; Mazo, G.E. The role of hematological coefficients of systemic inflammation in the diagnosis and risk assessment of affective disorders, *V.M.Bekhterev Review of Psychiatry and Medical Psychology* **2024**, doi:10.31363/2313-7053-2024-794
33. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* **2009**, b2535. doi: 10.1136/bmj.b2535
34. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; Chou, R.; Glanville, J.; Grimshaw, J.M.; Hróbjartsson, A.; Lalu, M.M.; Li, T.; Loder, E.W.; Mayo-Wilson, E.; McDonald, S., McGuinness, L.A.; Stewart, L.A.; Thomas, J.; Tricco, A.C.; Welch, V.A.; Whiting, P.; Moher, D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **2021**, n71. doi: 10.1136/bmj.n71
35. Grundy, S.M.; Brewer, H.B. Jr.; Cleeman, J.I.; Smith, S.C. Jr.; Lenfant, C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler. Thromb. Vasc. Biol.* **2004**, 2:e13–18. doi: 10.1161/01.CIR.0000111245.75752.C6
36. Oganov, R.G.; Simanenkov, V.I.; Bakulin, I.G.; Bakulina, N.V.; Barbarash, O.L.; Boytsov, S.A.; Boldueva, S.A.; Garganeeva, N.P.; Doshchitsin, V.L.; Karateev, A.E.; Kotovskaya, Yu.V.; Lila, A.M.; Lukyanov, M.M.; Morozova, T.E.; Pereverzev, A.P.; Petrova, M.M.; Pozdnyakov, Yu.M.; Syrov, A.V.; Tarasov, A.V.; Tkacheva, O.N.; Shalnova, S.A. Comorbidities in clinical practice. Algorithms for diagnostics and treatment. *Cardiovasc. Ther. Prev. Silicea - Poligraf, LLC* **2019**, 1: 5–66. doi:10.15829/1728-8800-2019-1-5-66

37. Verbovoy, A.F.; Verbovaya, N.I.; Dolgikh, Y.A. Obesity is the basis of metabolic syndrome. *Obe. Metab. Endocrinology Research Centre* **2021**, 2:142–149. doi:10.14341/omet12707
38. Yüksel, R.N.; Ertek, I.E.; Dikmen, A.U.; Göka, E. High neutrophil-lymphocyte ratio in schizophrenia independent of infectious and metabolic parameters. *Nord. J. Psychiatry* **2018**, 72(5): 336–340. doi: 10.1080/08039488.2018.1458899
39. Zhu, X.; Zhou, J.; Zhu, Y.; Yan, F.; Han, X.; Tan, Y.; Li, R. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas. Psychiatry. *SAGE Publications* **2022**, 1:95–99. doi: 10.1177/10398562211022753
40. Semiz, M.; Yildirim, O.; Canan, F.; Demir, S.; Hasbek, E.; Tuman, T.C.; Kayka, N.; Tosun, M. Elevated neutrophil/lymphocyte ratio in patients with schizophrenia. *Psychiatr. Danub.* **2014**, 3: 220–225.
41. Cabello-Rangel, H.; Basurto-Morales, M.; Botello-Aceves, E.; Pazarán-Galicia, O. Mean platelet volume, platelet count, and neutrophil/lymphocyte ratio in drug-naïve patients with schizophrenia: a cross-sectional study. *Front. Psychiatry* **2023**, 1150235. doi:10.3389/fpsyt.2023.1150235
42. Kulaksizoglu, B.; Kulaksizoglu, S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. *Neuropsychiatr. Dis. Treat.* **2016,** 1999–2005. doi: 10.2147/NDT.S110484
43. Wang, X.; Chen, X.; Guan, X.; Li, Z. The neutrophil-to-Lymphocyte ratio is associated with clinical symptoms in first-episode medication-naïve patients with schizophrenia. *Schizophrenia (Heidelb)* **2024**, 1:13. doi: 10.1038/s41537-024-00437-5
44. Inaltekin, A.; Yağci, İ. Evaluation of Simple Markers of Inflammation and Systemic Immune Inflammation Index in Schizophrenia, Bipolar Disorder Patients and Healthy Controls. *Turk Psikiyatri Derg.* **2023,** 1:11–15. doi: 10.5080/u26248
45. Zhu, X.; Li, R.; Zhu, Y.; Zhou, J.; Huang, J.; Zhou, Y.; Tong, J.; Zhang, P.; Luo, X.; Chen, S.; Li, Y.; Tian, B.; Tan, S.P.; Wang, Z.; Han, X.; Tian, L.; Li, C.R.; Tan, Y.L. Changes in Inflammatory Biomarkers in Patients with Schizophrenia: A 3-Year Retrospective Study. *Neuropsychiatr. Dis. Treat.* **2023**, 1597–1604. doi: 10.2147/NDT.S411028
46. Gokulakrishnan, K.; Nikhil, J.; Vs, S.; Holla, B.; Thirumoorthy, C.; Sandhya, N.; Nichenametla, S.; Pathak, H.; Shivakumar, V.; Debnath, M.; Venkatasubramanian, G.; Varambally, S. Altered Intestinal Permeability Biomarkers in Schizophrenia: A Possible Link with Subclinical Inflammation. *Ann Neurosci* **2022**, 2(3): 151–158. doi: 10.1177/09727531221108849
47. Paniagua, G.; González-Blanco, L.; Sáiz, P.A.; Moya-Lacasa, C.; Gutiérrez, L.; Martínez-Botía, P.; Dal Santo, F.; Jiménez-Treviño, L.; García-Portilla, M.P.; Bobes, J. Platelet and white blood-cell-based ratios: Differential inflammatory markers of severe mental disorders? *Span J Psychiatry Ment Health* **2023**, doi: 10.1016/j.sjpmh.2023.03.002
48. Özdin, S.; 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. *Nord. J. Psychiatry* **2017**, 7:509–512. doi: 10.1080/08039488.2017.1340517
49. Wang, Y.; Wang, G.; Gong, M.; Yang, Y.; Ling, Y.; Fang, X.; Zhu, T.; Wang, Z.; Zhang, X.; Zhang, C. Systemic inflammatory biomarkers in Schizophrenia are changed by ECT administration and related to the treatment efficacy. *BMC Psychiatry*. **2024**, 1:53. doi:10.1186/s12888-023-05469-2
50. İmre, O.; Caglayan, C.; Muştu, M. The Relationship of Cognitive Dysfunction with Inflammatory Markers and Carotid Intima Media Thickness in Schizophrenia, *J Pers Med*. **2023**, 9. doi: 10.17116/jnevro202012011170
51. Xu, H.; Wei, Y.; Zheng, L.; Zhang, H.; Luo, T.; Li, H.; Ma, J.; Chen, J. Relation Between Unconjugated Bilirubin and Peripheral Biomarkers of Inflammation Derived From Complete Blood Counts in Patients With Acute Stage of Schizophrenia. *Front. Psychiatry* **2022**, 843985. doi: 10.3389/fpsyt.2022.843985
52. Yang, C.; Tian, Y.; Yang, X.; Liu, L.; Ling, C.; Xia, L.; Liu, H. Hematological and inflammatory markers in Han Chinese patients with drug-free schizophrenia: relationship with symptom severity. *Front. Immunol.* **2024**, 1337103. doi: 10.3389/fimmu.2024.1337103
53. Zhou, L.; Ma, X.; Wang, W. Immune dysregulation is associated with symptom dimensions and cognitive deficits in schizophrenia: accessible evidence from complete blood count. *BMC Psychiatry* **2024**, 1:48. doi: 10.1186/s12888-023-05430-3
54. Ion, R.M.; Sibianu, M.; Hutanu, A.; Beresescu, F.G.; Sala, D.T.; Flavius, M.; Rosca, A.; Constantin, C.; Scurtu, A.; Moriczi, R.; Muresan, M.G.; Gabriel, P.; Niculescu, R.; Neagoe, R.M. A Comprehensive Summary of the Current Understanding of the Relationship between Severe Obesity, Metabolic Syndrome, and Inflammatory Status. *J. Clin. Med. Res.* **2023**, 11. doi:10.3390/jcm12113818
55. Llorca-Bofí, V.; Bioque, M.; Font, M.; Gich, I.; Mur, M. Correlation between C-reactive protein and the inflammatory ratios in acute schizophrenia inpatients: are they associated? *J. Psychiatr. Res.* **2023,** 191–196. doi:10.1016/j.jpsychires.2023.07.023
56. Steiner, J.; Frodl, T.; Schiltz, K.; Dobrowolny, H.; Jacobs, R.; Fernandes, B.S.; Guest, P.C.; Meyer-Lotz, G.; Borucki, K.; Bahn, S.; Bogerts, B.; Falkai, P.; Bernstein, H.G. Innate Immune Cells and C-Reactive Protein in Acute First-Episode Psychosis and Schizophrenia: Relationship to Psychopathology and Treatment. *Schizophr. Bull.* **2020,** 2:363–373. doi:10.1093/schbul/sbz068
57. Bioque, M.; Catarina Matias-Martins, A.; Llorca-Bofí, V.; Mezquida, G.; Cuesta, M.J.; Vieta, E.; Amoretti, S.; Lobo, A.; González-

Pinto, A.; Moreno, C.; Roldán, A.; Martinez-Aran, A.; Baeza, I.; Bergé, D.; García-Rizo, C.; Mas Herrero, S.; Bernardo, M. Neutrophil to Lymphocyte Ratio in Patients With a First Episode of Psychosis: A Two-Year Longitudinal Follow-up Study. *Schizophr. Bull.* **2022,** 6:1327–1335. doi: 10.1093/schbul/sbac089

58. Balcioglu, Y.H.; Kirlioglu, S.S. C-Reactive Protein/Albumin and Neutrophil/Albumin Ratios as Novel Inflammatory Markers in Patients with Schizophrenia. *Psychiatry Investig.* **2020**, 9:902–910. doi: 10.30773/pi.2020.0185
59. Messina, A.; Caraci, F.; Aguglia, E.; Signorelli, M.S. Catatonia-like behavior and immune activation: a crosstalk between psychopathology and pathology in schizophrenia. *Ann. Gen. Psychiatry* **2023,** 1:39. doi:10.1186/s12991-023-00471-0
60. Zhong, X.; Qiang, Y.; Wang, L.; Zhang, Y.; Li, J.; Feng, J.; Cheng, W.; Tan, L.; Yu, J. Peripheral immunity and risk of incident brain disorders: a prospective cohort study of 161,968 participants. *Transl. Psychiatry* **2023**, 1:382. doi: 10.1038/s41398-023-02683-0
61. Sugita, S.; Tomioka, H.; Mera, K.; Tazaki, T.; Nishiyama, H.; Yamada, H.; Sanada, K.; Inamoto, A.; Iwanami, A. Neutrophil-Lymphocyte Ratio in Patients With Acute Schizophrenia. *Cureus* **2024**, 1: e52181. doi: 10.7759/cureus.52181
62. Zhou, X.; Wang, X.; Li, R.; Yan, J.; Xiao, Y.; Li, W.; Shen, H. Neutrophil-to-Lymphocyte Ratio Is Independently Associated With Severe Psychopathology in Schizophrenia and Is Changed by Antipsychotic Administration: A Large-Scale Cross-Sectional Retrospective Study. *Front. Psychiatry* **2020**, 581061. doi:10.3389/fpsyt.2020.581061
63. Bulut, N.S.; Yorguner, N.; Çarkaxhiu Bulut, G. The severity of inflammation in major neuropsychiatric disorders: comparison of neutrophil-lymphocyte and platelet-lymphocyte ratios between schizophrenia, bipolar mania, bipolar depression, major depressive disorder, and obsessive compulsive disorder. *Nord. J. Psychiatry* **2021**, 8:624–632. doi: 10.1080/08039488.2021.1919201
64. Cordova, V.H.S.; Teixeira, A.D.; Anzolin, A.P.; Moschetta, R.; Belmonte-de-Abreu, P.S. Inflammatory markers in outpatients with schizophrenia diagnosis in regular use of clozapine: a cross-sectional study. *Front. Psychiatry* **2023**, 1269322. doi: 10.3389/fpsyt.2023.1269322
65. Mekori-Domachevsky, E.; Taler, M.; Weinberger, R.; Guri, Y.; Dar, S.; Shani, S.; Dekel, I.; Weizman, A.; Gothelf, D. Neutrophils to lymphocytes ratio and psychosis in 22q11.2 deletion syndrome - Clinical and scientific implication. *Schizophr. Res.* **2021**, 164–169. doi: 10.1016/j.schres.2021.03.023
66. Brinn, A.; Stone, J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. *BMJ Open* **2020**, 7:e036859. doi:10.1136/bmjopen-2020-036859
67. Šagud, M.; Madžarac, Z.; Nedic Erjavec, G.; Šimunović Filipčić, I.; Mikulić, F.L.; Rogić, D.; Bradaš, Z.; Bajs Janović, M.; Pivac, N. The Associations of Neutrophil-Lymphocyte, Platelet-Lymphocyte, Monocyte-Lymphocyte Ratios and Immune-Inflammation Index with Negative Symptoms in Patients with Schizophrenia. *Biomolecules* **2023**, 2. doi: 10.3390/biom13020297
68. Sanchez-Autet, M.; Arranz, B.; Sierra, P.; Safont, G.; Garcia-Blanco, A.; de la Fuente, L.; Garriga, M.; Marín, L.; García-Portilla, M.P. Association between neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and C-reactive protein levels and metabolic status in patients with a bipolar disorder. *World J. Biol. Psychiatry* **2022**, 6:464–474. doi: 10.1080/15622975.2021.2013089
69. Nasyrova, R.F.; Kidyaeva, A.V.; Shnayder, N.A. Hematological predictors of antipsychotic-induced metabolic syndrome in a female patient with schizophrenia: Case report. *V.M. Bekhterev National Research Medical Center for Psychiatry and Neurology* **2024**, 2: 39–46. doi:10.52667/2712-9179-2024-4-2-39-46