JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
2023 August, XIV (02)

ORIGINAL ARTICLE

The Effectiveness of Meloxicam Adjuvant Therapy against Negative Symptoms and Neutrophil Lymphocyte Ratio (NLR) in Schizophrenic Patients

Katarina Bernadet Dinda Sekar Melati[1], Adriesti Herdaetha[2*], Wijaya Kusuma[3]

[1]Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
[2]Department of Psychiatry, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.
[3]Dr. Arif Zainuddin Regional Mental Hospital Surakarta/Universitas Sebelas Maret, Surakarta, Indonesia.

ABSTRACT

Introduction: Neutrophil-lymphocyte ratio is a simple and affordable marker of inflammation that has recently been widely used to assess systemic inflammation in psychiatric patients. This study aimed to determine and analyze the effectiveness of meloxicam as adjuvant therapy to improve negative symptoms and changes in the neutrophil-lymphocyte ratio (NLR) in schizophrenic patients.

Methods: This was a quasi-experimental study using a single-blind, pretest–post-test design. Subjects were determined using a purposive sampling technique based on inclusion criteria. This study examined 34 samples and divided them into two groups. The treatment group consisted of 17 subjects who received adjuvant therapy with meloxicam 15 mg/day for 4 weeks and 17 subjects in the control group. Data collection was obtained from medical records, interviews, field notes, positive scale, negative scale, and general psychopathology scale (PANSS) assessment sheets, and blood NLR examinations. Data analysis used SPSS 25.0.

Results: The negative subscale PANSS score in the treatment group decreased lower than in the control group, with p-value = 0.640. However, the decrease in NLR values was more significant in the treatment group than in the control group, with p-value = 0.094. There was a decrease in the negative subscale PANSS scores and clinical NLR scores, but it was not statistically significant.

Conclusion: Adjuvant therapy with Meloxicam, given once a day for four weeks, had an effect on decreasing the negative subscale PANSS score and NLR scores for schizophrenic patients at Dr. Arif Zainudin Regional Mental Hospital (RSJD), Surakarta, clinically, but it was not statistically significant.

Highlights:
1. The NLR value can show the role of neuroinflammation in schizophrenic patients.
2. Meloxicam as adjuvant therapy can improve negative symptoms and changes in the NLR in schizophrenic patients.

ARTICLE INFO

Article history:

Received 09-07-2022

Received in revised form 12-07-2023

Accepted 28-07-2023

Available online 10-08-2023

Keywords:
Meloxicam,
Mental illness,
Negative symptoms,
Neutrophil-lymphocyte ratio,
Schizophrenia.

Cite this as:
Melati KBDS, Herdaetha A, Kusuma W. The Effectiveness of Meloxicam Adjuvant Therapy against Negative Symptoms and Neutrophil Lymphocyte Ratio (NLR) in Schizophrenic Patients. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2023; 14: 57–62.

* Correspondence: aherdaetha@gmail.com

JUXTA: Jurnal Ilmiah Mahasiswa Kedokteran Universitas Airlangga
p-ISSN: 1907-3623; e-ISSN: 2684-9453
DOI: 10.20473/juxta.V14I22023.57-62

Introduction

Schizophrenia is a psychotic disorder signed by psychotic symptoms accompanied by impaired cognitive and social functioning. The symptoms are divided into positive and negative symptoms. Although the use of antipsychotics is effective for positive symptoms, there are still many limitations to the response and resistance to the treatment of negative symptoms.[1] Some works suggest that the pathophysiology of schizophrenia is related to the abnormality of cytokines and immune systems. Those take an important role in schizophrenia management. The etiology of schizophrenia remains unclear, but a shred of evidence has been found to support the hypothesis.

Neuroinflammation-induced glutamate and N-methyl-D-aspartate receptor dysfunction (NMDARs) may contribute to the etiology of schizophrenia.[2] The role of neuroinflammation in schizophrenia has been elaborated, and it is postulated that microglia activation responds to small pathological changes in the brain by releasing pro-inflammatory cytokines. Persistent microglial hyperactivity causes neuronal apoptosis, neuronal degeneration, and brain damage. If anti-inflammatory regulators cannot balance the pro-inflammatory reaction, the inflammation persists and coexists with neuropsychiatric symptoms.[3]

Neutrophil-lymphocyte ratio (NLR) is a simple and affordable inflammation marker obtained from complete blood counts. Its etiology role has been studied in a variety of diseases. NLR is the value obtained by dividing the absolute number of neutrophils by the absolute number of lymphocytes within normal in healthy adults between 0.78 to 3.53. NLR is an inexpensive disease marker calculated from complete blood counts, and its pathogenetic role has been investigated in a broad spectrum of diseases. Increased NLR has been associated with increased cytokines and C-reactive protein (CRP) and is widely used in the literature as a process in systemic inflammation.[3] The elevated NLR has been associated with cytokines and CRP elevation. NLR testing is commonly used and is considered a marker of the occurrence of a systemic inflammatory process. High NLR positively correlates with elevated IL8 and IL-6 in patients with liver cirrhosis,[4] laryngeal cancer,[5] and ovarian cancer.[6]

A meta-analysis that evaluated the effectiveness and tolerability of non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvant therapy in treating schizophrenia showed that adjuvant NSAID therapy outperformed placebo concerning positive symptoms, negative symptoms, total psychopathology, and general psychopathology scores.[2] Another meta-analysis that aimed to explore the effects of anti-inflammatory agents in schizophrenic patients comprehensively demonstrated a significant reduction in negative symptoms with anti-inflammatory augmentation therapy. The overall anti-inflammatory agent significantly improves general function.

Total PANSS score and disease duration were identified as moderate factors in evaluating anti-inflammatory augmentation's effect on improving psychiatric symptoms.[1] Non-pharmacological therapies such as cognitive behavioral therapy (CBT) and motivation and engagement training (MOVE) could optimize the treatment efficacy.[7] Other therapies, such as cognitive enhancement therapy (CET), could improve the quality of life of schizophrenic patients which can also be achieved with pharmacotherapy combinations.[8] Family models could also be applied in schizophrenia management. The concept aids families in managing their stress by reducing burden and stigma. Hence, the patients can survive, rise, become stronger, and provide better care for schizophrenic patients.[9] There needs to be a long-term cure for schizophrenia. High treatment adherence may reduce the symptoms of schizophrenia and guard against relapse. Family support is essential to ensure that the patients continue to take their medication regularly.[10]

This study aimed to determine and analyze meloxicam as an adjuvant therapy to improve negative symptoms and changes in the NLR in schizophrenic patients.

Methods

This was a quasi-experimental study using a single-blind, pretest–post-test design conducted to determine the effect of additional therapy with meloxicam on NLR levels and negative subscale PANSS scores in schizophrenic patients receiving risperidone-chlorpromazine therapy in the Inpatient Unit of the Psychiatric Department Dr. Arif Zainuddin Regional Mental Hospital (RSJD), Surakarta, from May to July 2020.

The sample size in this study was 34 subjects, randomly divided into two groups, namely the treatment group, which consisted of 17 subjects, and the control group, which consisted of 17 subjects who had met the inclusion and exclusion criteria. Inclusion criteria include a) schizophrenic patients who were hospitalized at RSJD from May to July 2020, b) patients who received treatment with a combination antipsychotic risperidone-chlorpromazine, and/or intramuscular haloperidol injection, c) patients aged 18-40 years old, and d) patients who got caregiver approval. Exclusion criteria include a) schizophrenic patients with organic disorders such as epilepsy, stroke, and mental retardation or head injury with a history of decreased consciousness, b) substance and alcohol abuse, c) taken anti-inflammatory drugs or steroids or taken anti-inflammatory drugs or steroids for less than one month, and d) gotten electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

Subjects in the treatment group received additional therapy of meloxicam 15 mg per day for 4 weeks, in addition to antipsychotic therapy with risperidone-chlorpromazine combination, while subjects in the control group received antipsychotic therapy with the combination of risperidone-chlorpromazine. The research subject data was obtained by examining NLR levels and the negative subscale PANSS score assessment results. After all research data had been collected, data analysis was performed using the Statistical Package for the Social Sciences (SPSS) 25.0 program. From the study, data were obtained about the demographic characteristics of the research subjects and the results of the NLR examination

and the PANSS negative subscale pre- and post-test assessment.

Results

Demographical Characteristics of Research Subjects

Table 1. Demographic characteristics of research subjects

Characteristic	Group		p-value
	Treatment (n = 17)	Control (n = 17)	
Gender			
Male	11 (32.4%)	15 (44.1%)	0.225*
Female	6 (17.6%)	2 (5.9%)	
Age			0.097**
Mean ± SD	34.76±5.4	32.29±4.91	
Education			
≤ JHS	14 (41.2%)	12 (35.3%)	0.668***
≥ SHS	3 (8.8%)	5 (14.7%)	
Score of PANSS Pretest Negative Subscale			
Mean ± SD	26.58±4.56	32.35±4.59	0.002****
Score of NLR Pretest			
Mean ± SD	3.43±1.08	2.75 ±1.19	0.091**

*Fisher's Exact test; **T-independent test; ***Chi-Square test; ****Mann-Whitney test; JHS : junior high school; SHS: senior high school

Table 2. The effect of Meloxicam on changes in the PANSS score on the negative subscale of the treatment and control groups pre- and post-therapy

Parameter	Mean		p-value
	Treatment (n = 17)	Control (n = 17)	
PANSS pretest	26.58	32.35	0.002
PANSS post-test	15.58	20.47	0.000
Decrease in PANSS	11.00	11.88	0.640

Source: Research data, processed

Table 3. The effect of Meloxicam on NLR changes in the treatment and control groups pre- and post-therapy

Parameter	Mean		p-value
	Treatment (n = 17)	Control (n = 17)	
NLR pretest	3.43	2.75	0.091
NLR post-test	0.35	3.30	0.628
Decrease in NLR	0.35	0.54	0.094

Source: Research data, processed

The demographic assessment of the research group consisting of age, gender, and education level showed equality, as shown in Table 3. Overall, based on the results of statistical tests, it can be said that the research subjects came from a homogeneous sample of gender (p = 0.225), age (p = 0.097), education (p = 0.668), and pre-test NLR scores (p = 0.091). Still, the negative subscale PANSS pre-test score (p = 0.002) was not homogeneous. Gender is also one of the risk factors for other mental illnesses, such as anxiety.[11]

Based on the normality test, it was found that the distribution of PANSS scores on the negative subscale of the treatment group and the control group of this study had abnormal initial data. Thus, the sample of this study was not homogeneous. However, homogeneous results were obtained for the distribution of the initial NLR values in the treatment and control groups based on the normality test.

This study found that both the treatment and control groups experienced a decrease in the negative subscale PANNS score in both groups. In the treatment group, there was a decrease in the negative subscale PANNS score which was lower than in the control group. After analyzing with statistical calculations, there was an insignificant difference in the decrease in the negative subscale PANSS score. Therefore, it can be said that administering additional therapy with Meloxicam 15 mg/day in reducing the negative subscale PANSS score in schizophrenic patients undergoing hospitalization at RSJD was not statistically significant but clinically significant.

The results of this study are contradictory to a previous study conducted by Purwono (2018), which stated that the addition of Meloxicam therapy was effective in reducing Hs-CRP levels and improving PANSS scores.[12] A similar study by Müller, *et al.* (2008) also suggested that administering NSAID adjuvant therapy improved negative symptoms in schizophrenic patients.[13]

Discussion

Schizophrenia is a complicated and severe brain disorder, with a reported median incidence of 15.2 per 100,000 persons. Its prevalence in China ranged from 0.39% (0.37% – 0.41%) in 1990, 0.57% (0.55% – 0.59%) in 2000, and 0.83% (0.75% – 0.91%) in 2010.[14] Meanwhile in Southeast Asia, the number of schizophrenic patients has increased from about 2 million people in 1990, to almost 4 million people in 2016. This figure has almost two times the fold.[15]

NLR is currently known as a marker, which is calculated from complete blood counts. NLR takes a pathogenetic role and has been investigated in a broad spectrum of diseases. The increased of NLR has been associated with increased cytokines and CRP. It is widely used as a process in the presence of systemic inflammation.[3] The adjunctive anti-inflammatory therapy may be beneficial for schizophrenic patients, specifically for those in the early stages of the disease.[16]

NSAID therapy gives promising results and shows a more beneficial treatment effect when standard antipsychotic therapy is given together with anti-inflammatory drugs compared to treatment using a single antipsychotic to improve negative symptoms in schizophrenic patients. This finding may reflect a complex interaction between anti-inflammatory effects and modulation of glutamatergic and dopaminergic systems by a COX-2 inhibitor.[17] Various other reasons were also

considered to explain the negative study in this study, such as sample size and subgroup heterogeneity. A review by Kantrowitz, *et al*. (2017) suggested a significant effect of anti-inflammatory agents on the improvement of PANSS values of negative symptoms (13% reduction, p = 0.001) along with the effect of trend level on total symptoms (16% reduction, p = 0.054) after 8 weeks of anti-inflammatory use.[18] Also, adjunctive anti-inflammatory and anti-oxidant therapy may increase the benefits in schizophrenic patients, who are still in the early stages of the disease.[19]

There was a change in the mean value for the NLR values in the two research groups. In the treatment group, there was a decrease in the NLR value, while in the control group, there was an increase in the post-test NLR value. After analyzing with statistical calculations, there were no significant differences in the decrease in NLR values. Thus, it can be said that the addition of Meloxicam 15 mg/day in reducing the NLR value in schizophrenic patients who were hospitalized at RSJD was not statistically significant but clinically significant. This is in accordance with several previous studies. However, a study revealed the association between NLR and the positive symptoms of schizophrenia. It can be shown that the NLR will be elevated in schizophrenic patients.[20] Elevated NLR can reflect the immunology process, which can be found in psychiatric patients.[21] The NLR level also determined the severity level of schizophrenic patients. In other words, the NLR level could be used as a biomarker.[22] The other parameter that also increased in schizophrenic patients was the monocyte-lymphocyte ratio (MLR) level.[23]

In an RCT study conducted by Jaehne, *et al*. (2015), there was a decrease in the inflammatory response in schizophrenic patients, especially in periods of remission who received antipsychotic treatment.[24] On the other hand, the chronic inflammatory process in schizophrenia is related to the fact that inflammatory markers such as NLR do not return to normal in the remission phase, and the inflammatory process will continue, even during periods of remission.[25] The increase in serum cortisol levels in chronic schizophrenic patients causes a decrease in the number of lymphocytes compared to periods of relapse and remission.[26] In addition, theoretically, NLR will not be a reliable marker in patients who have a history of treatment with clozapine associated with agranulocytosis. This finding may be due to the generalized inflammatory response reported in antipsychotic-treated patients resulting in granulocytosis.

The patients in this study were not evaluated for confounding factors, such as previous history of antipsychotic medication, inflammatory disease that may have occurred between periods of relapse or remission, or how long and how often the patients had relapses. A meta-analysis conducted by Karageorgiou, *et al*. (2019) examined the association between NLR and schizophrenia in ten studies (804 schizophrenic patients and 671 controls).[3] In schizophrenic patients, the NLR increased by 0.65. Several studies on schizophrenia and its relationship with NLR, both moderate and high quality, showed a significant increase in NLR in schizophrenic patients (heterogeneity = 0%).

A multicenter cross-sectional study in 156 schizophrenic patients and 89 healthy control subjects and complete blood counts assessed its clinical pathological severity using Psychiatric Brief Rating Scales.[27] The results of this study showed that the NLR of schizophrenic patients was significantly higher than healthy controls (2.6 ± 1.1 vs 1.9 ± 0.6, respectively, p < 0.001). NLR did not significantly correlate with the severity and duration of schizophrenia (r = 0.065. p > 0.05). The occurrence of aggressive behavior in schizophrenic patients could be a sign of its severity. In this case, NLR can be used as a biomarker to evaluate the risk of aggression quickly.[28] The elevated mean of NLR was also observed in a patient with the first episode of psychosis (FEP). This can be helpful in order to identify inflammatory imbalance through NLR as a biomarker.[29]

A study that involved 52 schizophrenic patients and 53 healthy subject groups revealed that the number of neutrophils, leukocytes, NLR values, and monocytes was higher in schizophrenic patients than in the control group. However, the NLR values did not show a significant relationship with the illness duration, the disease severity, or number of hospitalizations.[30] A literature review also revealed the potential of NLR means in other psychological disorders, such as suicidal willingness. After controlling some variables, such as sex, age, and the severity of depression in 393 patients, the NLR was significantly associated with suicidal behavior. NLR might be cost-effective, accessible, and easily reproducible for daily practice.[31] Suicidal thoughts were more prevalent in those who were younger in age, had illnesses that lasted longer, scored lower on the Global Assessment of Functioning (GAF) scale, were largely female, were unemployed, made less money, and had less education.[32]

Schizophrenic patients can be classified into two groups, FEP and chronic disease. Even though NLR mean can be used as a biomarker, it might be difficult to analyze its accuracy due to the antipsychotic use. Therefore, using NLR in clinical practices requires the standard of its normal values in the general population.[3] A scoping review revealed an interesting fact. Albeit an individual uses antipsychotic therapy, the NLR value seems to be increased and significantly correlates with schizophrenia-positive symptoms.[33] The classification of biomarkers of schizophrenia are central and peripheral biomarkers. However, some biomarkers collected from post-mortem brains are changed to be found in blood-based biomarkers, which may lead to the useful and important value of blood-biomarkers to deciphered the process in the brain.[34]

As a serious mental disorder or mental illness, that hit as many as 20 million worldwide, many factors supported or contributed to this disease. Untreated patients can lead to frequent hospital admissions, decreased life quality, decreased social function, and decreased life expectancy. A psychiatrist will treat the patient who reported their behavioral abnormalities and can be improved. However, many patients are still untreated due to being underreported. Thus, a potential biomarker that will be applicated may be important to reduce the possibility of untreated patients.[34]

Any biomarker that already exists should be evaluated regularly to increase its accuracy. Hence, biomarkers may still have various error levels. The heterogeneity of schizophrenia can increase the potential of applying multiple biomarkers as diagnosis tools.[35] Combining different markers or complex multimarker panels can differentiate patients with different underlying diseases and better classify more homogeneous groups.[36] Schizophrenia is a chronic and severe disabling neuro-disorder with various genetic and neurobiological histories. Symptoms of schizophrenia can differentiate into two groups, negative and positive symptoms. Clinical manifestations of positive symptoms include a) delusions, b) hallucinations, and c) disorganized behaviors. Meanwhile, positive symptoms can be shown with various symptoms, including a) lack of language, b) decreased effect, and c) loss of interest and motivation, but cognitive symptoms are present.[37]

This study has some limitations, including a) the number of samples was relatively small, which similar study requires a larger sample size; b) the duration of history and the number of relapses of schizophrenic patients were not mentioned in this study, which can lead to the unknown effectivity of the adjuvant meloxicam on the degree or stage of the severity of schizophrenia. This is associated with the negative subscale PANSS scores and NLR scores; c) the assessment or the evaluation of the negative subscale PANSS score was only performed at the beginning and end of treatment. Of these, it is not known exactly when the negative subscale of the PANSS score began to decline; and d) between the evaluation process, there was no special monitoring regarding the occurrence of secondary infectious processes that may occur during hospitalization that can affect the effectivity of meloxicam and influence the NLR value.

Strength and Limitations

The strength of this study was that the sample selection was performed randomly, and interrater assessors performed the PANSS assessment. The limitation of this study was that the length of history of schizophrenia was not included. Hence, it was not known about the effectiveness of the adjuvant meloxicam on the degree or severity of schizophrenia.

Conclusion

There was a difference in the decrease in the negative subscale PANSS score in the treatment and control groups, whereas the control group showed a greater mean decrease in the negative subscale PANSS score. There were differences in changes in NLR values in the treatment group and the control group, where the treatment group showed an average decrease in the post-test NLR value, while the control group experienced an increase in post-test NLR. It was concluded that adjuvant therapy meloxicam 15 mg/day effectively improved negative symptoms and NLR values of hospitalized schizophrenic patients at RSJD clinically, but not statistically effective.

Acknowledgments

The authors would like to thank the Head of the Department of Psychiatry, Universitas Sebelas Maret, the lecturers of the Department of Psychiatry, Universitas Sebelas Maret, and the Psychiatric Unit in RSJD for their assistance in this study.

Conflict of Interest

The authors declared there is no conflict of interest.

Funding

This study did not receive any funding.

Ethical Clearance

This study had received ethical clearance from the Committee for Health Research, Dr. Moewardi General Academic Hospital, Surakarta (no. 1.410/XI/HERC/2020) on 8 April 2020.

Authors' Contributions

Designing and implementing the research, analyzing the results, writing of the manuscript: KBDSM, AH, WK.

References

1. Cho M, Lee TY, Kwak Y Bin, *et al*. Adjunctive Use of Anti-Inflammatory Drugs for Schizophrenia: A Meta-Analytic Investigation of Randomized Controlled Trials. *Aust N Z J Psychiatry* 2019; 53: 742–759. [PubMed]
2. Zheng W, Cai D-B, Yang X-H, *et al*. Adjunctive Celecoxib for Schizophrenia: A Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. *J Psychiatr Res* 2017; 92: 139–146. [PubMed]
3. Karageorgiou V, Milas GP, Michopoulos I. Neutrophil-to-Lymphocyte Ratio in Schizophrenia: A Systematic Review and Meta-Analysis. *Schizophr Res* 2019; 206: 4–12. [PubMed]
4. Lin T, Liu GA, Perez E, *et al*. Systemic Inflammation Mediates Age-Related Cognitive Deficits. *Front Aging Neurosci* 2018; 10: 236. [NCBI]
5. Du C, Cai F, Zidan MA, *et al*. Reservoir Computing Using Dynamic Memristors for Temporal Information Processing. *Nat Commun* 2017; 8: 2204. [Journal]
6. Sanguinetti A, Kurani K, Davies J. The Many Reasons Your Mileage May Vary: Toward a Unifying Typology of Eco-Driving Behaviors. *Transp Res Part D Transp Environ* 2017; 52: 73–84. [ScienceDirect]
7. Lolobua MFIP, Khairina K, Wardani IAK, *et al*. Negative Symptoms Management in Schizophrenia. *J Psikiatri Surabaya* 2021; 10: 6–12. [Journal]
8. Syulthoni ZB, Gunadi IGN. Cognitive Enhancement Therapy in Schizophrenia. *J Psikiatri Surabaya* 2020; 9: 7–13. [Journal]
9. Fitryasari R, Nursalam N, Yusuf A, *et al.* Development of a Family Resiliency Model to Care of Patients with Schizophrenia. *Scand J Caring Sci* 2021; 35: 642–649. [PubMed]
10. Jessica L, Fithriyah I, Ardani IGAI. The Importance of Family Support in Successful Treatment Adherence of Schizophrenic Patient. *J Psikiatri Surabaya* 2021; 10: 83–91. [Journal]
11. Arisyna A, Sustini F, Muhdi N. Anxiety Level and Risk Factors in Medical Students. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2020; 11: 79–82. [Journal]

12. Purwono H. *Pengaruh Pemberian Terapi Tambahan Meloxicam terhadap Kadar Hs-CRP dan Skor PANSS pada Pasien Skizofrenia di RSJD Arif Zainudin Surakarta*. Universitas Sebelas Maret, https://digilib.uns.ac.id/dokumen/detail/58379/Pengaruh-Pemberian-Terapi-Tambahan-Meloxicam-terhadap-Kadar-Hs-Crp-dan-Skor-Panss-pada-Pasien-Skizofrenia-di-Rsjd-Arif-Zainudin-Surakarta (2018).
13. Müller N, Schwarz MJ. A Psychoneuroimmunological Perspective to Emil Kraepelins Dichotomy: Schizophrenia and Major Depression as Inflammatory CNS Disorders. *Eur Arch Psychiatry Clin Neurosci* 2008; 258 Suppl: 97–106. [PubMed]
14. Xie P, Wu K, Zheng Y, *et al*. Prevalence of Childhood Trauma and Correlations between Childhood Trauma, Suicidal Ideation, and Social Support in Patients with Depression, Bipolar Disorder, and Schizophrenia in Southern China. *J Affect Disord* 2018; 228: 41–48. [PubMed]
15. Charlson FJ, Ferrari AJ, Santomauro DF, *et al*. Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophr Bull* 2018; 44: 1195–1203. [PubMed]
16. Buchanan RW, Weiner E, Kelly DL, *et al*. Anti-Inflammatory Combination Therapy for the Treatment of Schizophrenia. *J Clin Psychopharmacol* 2020; 40: 444–450. [PubMed]
17. Akhondzadeh S, Tabatabaee M, Amini H, *et al*. Celecoxib as Adjunctive Therapy in Schizophrenia: A Double-Blind, Randomized and Placebo-Controlled Trial. *Schizophr Res* 2007; 90: 179–185. [PubMed]
18. Kantrowitz JT. Managing Negative Symptoms of Schizophrenia: How Far Have We Come? *CNS Drugs* 2017; 31: 373–388. [PubMed]
19. Wolters FJ, Chibnik LB, Waziry R, *et al*. Twenty-Seven-Year Time Trends in Dementia Incidence in Europe and the United States: The Alzheimer Cohorts Consortium. *Neurology* 2020; 95: e519–e531. [PubMed]
20. Sandberg AA, Steen VM, Torsvik A. Is Elevated Neutrophil Count and Neutrophil-to-Lymphocyte Ratio a Cause or Consequence of Schizophrenia? - A Scoping Review. *Frontiers in Psychiatry* 2021; 12: 728990. [PubMed]
21. Brinn A, Stone J. Neutrophil-Lymphocyte Ratio across Psychiatric Diagnoses: A Cross-Sectional Study Using Electronic Health Records. *BMJ Open* 2020; 10: e036859. [PubMed]
22. Zhou X, Wang X, Li R, *et al*. 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; 11: 581061. [PubMed]
23. 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; 71: 509–512. [PubMed]
24. Jaehne A, Unbehaun T, Feige B, *et al*. Sleep Changes in Smokers before, during and 3 Months after Nicotine Withdrawal. *Addict Biol* 2015; 20: 747–755. [PubMed]
25. Fond G, D'Albis M-A, Jamain S, *et al*. The Promise of Biological Markers for Treatment Response in First-Episode Psychosis: A Systematic Review. *Schizophr Bull* 2015; 41: 559–573. [PubMed]
26. Girshkin L, Matheson SL, Shepherd AM, *et al*. Morning Cortisol Levels in Schizophrenia and Bipolar Disorder: A Meta-Analysis. *Psychoneuroendocrinology* 2014; 49: 187–206. [PubMed]
27. Semiz M, Yildirim O, Canan F, *et al*. Elevated Neutrophil/Lymphocyte Ratio in Patients with Schizophrenia. *Psychiatr Danub* 2014; 26: 220–225. [PubMed]
28. Tong Z, Zhu J, Wang J-J, *et al*. The Neutrophil-Lymphocyte Ratio is Positively Correlated with Aggression in Schizophrenia. *Biomed Res Int* 2022; 2022: 4040974. [PubMed]
29. Bioque M, Catarina MMA, Llorca-Bofí V, *et al*. Neutrophil to Lymphocyte Ratio in Patients with a First Episode of Psychosis: A Two-Year Longitudinal Follow-Up Study. *Schizophr Bull* 2022; 48: 1327–1335. [PubMed]
30. Yüksel RN, Ertek IE, Dikmen AU, *et al*. High Neutrophil-Lymphocyte Ratio in Schizophrenia Independent of Infectious and Metabolic Parameters. *Nord J Psychiatry* 2018; 72: 336–340. [PubMed]
31. Velasco Á, Rodríguez-Revuelta J, Olié E, *et al*. Neutrophil-to-Lymphocyte Ratio: A Potential New Peripheral Biomarker of Suicidal Behavior. *Eur Psychiatry* 2020; 63: e14. [PubMed]
32. Salsabila KN, Khairina K, Djuari L. Profile of Chronic Mental Disorder Patients with or without Suicide Ideation in the Psychiatric Ward of Dr. Soetomo General Hospital, Surabaya. *JUXTA J Ilm Mhs Kedokt Univ Airlangga* 2021; 12: 48–53. [Journal]
33. Savitz SI, Chopp M, Deans R, *et al*. Stem Cell Therapy as an Emerging Paradigm for Stroke (STEPS) II. *Stroke* 2011; 42: 825–829. [PubMed]
34. Lin P, Sun J, Lou X, *et al*. Consensus on Potential Biomarkers Developed for Use in Clinical Tests for Schizophrenia. *Gen Psychiatry* 2022; 35: e100685. [PubMed]
35. Weickert CS, Weickert TW, Pillai A, *et al*. Biomarkers in Schizophrenia: A Brief Conceptual Consideration. *Dis Markers* 2013; 35: 3–9. [PubMed]
36. Perkovic MN, Erjavec GN, Strac DS, *et al*. Theranostic Biomarkers for Schizophrenia. *Int J Mol Sci*; 18. Epub ahead of print March 2017. [PubMed]
37. Halldorsdottir T, Binder EB. Gene × Environment Interactions: From Molecular Mechanisms to Behavior. *Annu Rev Psychol* 2017; 68: 215–241. [PubMed]