Inflammatory Hematological Ratios in Adolescents with Mental Disorders: A Scoping Review

Гематологические коэффициенты воспаления при психических расстройствах в подростковом возрасте: обзор предметного поля

doi: 10.17816/CP15514

Review

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ABSTRACT

BACKGOUND: Inflammatory hematological ratios (IHRs), such as neutrophil to lymphocyte, monocyte to lymphocyte, and platelet to lymphocyte ratios, are associated with mental disorders, symptoms severity, and the disease phase. Evidence from the studies in adult patients has been summarized in systematic reviews and meta-analyses. The results of the studies in adolescents remain poorly systematized.

AIM: To summarize the findings from the studies that investigated the relationship of IHRs with mental disorders in adolescent patients.

METHODS: This scoping review included studies of IHRs in patients aged 10–19 years with mental disorders (other than anorexia nervosa), published in English by December 31, 2023. The search for relevant papers was performed in MEDLINE. The studies were categorized into two groups: studies with external controls (healthy adolescents) and studies with internal controls (patients in different phases of mental disorder, with or without self-harm/suicidal behaviors).

RESULTS: A total of 11 studies were included in the review (all cross-sectional ones). The results of these studies demonstrate that 1) adolescents with mental disorders (major depressive disorder, psychotic disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder, substance use disorders) have higher IHR values than individuals of the same age without corresponding disorders (5 studies); 2) IHR values are positively correlated with the severity of psychopathological symptoms (1 study); 3) higher IHR values are associated with the phase of the mental disorder — manic episode in bipolar disorder (1 study) and exacerbation of psychosis in psychotic disorders (1 study); and 4) higher IHR values are associated with self-harm/suicidal behaviors — suicide attempts (1 study) and non-suicidal self-injury (1 study).

CONCLUSION: IHRs are associated with mental disorders in adolescents, and higher IHR values are associated with a more severe/acute clinical presentation (severity of symptoms, mania, acute psychosis, self-harm/suicidal behaviors). Further studies of higher methodological quality are needed to evaluate the diagnostic and prognostic value of IHRs as biomarkers of mental disorders in adolescence.

АННОТАЦИЯ

ВВЕДЕНИЕ: Гематологические коэффициенты воспаления (ГКВ), такие как нейтрофильно-лимфоцитарное, моноцитарно-лимфоцитарное, тромбоцитарно-лимфоцитарное отношение, ассоциированы с психическими расстройствами, их тяжестью, фазой заболевания. Данные, полученные у взрослых пациентов, обобщены в систематических обзорах и метаанализах. Результаты подобных исследований у подростков не систематизированы.

ЦЕЛЬ: Обобщить результаты исследований, в которых изучали связь ГКВ с психическими расстройствами у пациентов подросткового возраста.

МЕТОДЫ: В обзор предметного поля включали исследования ГКВ у пациентов в возрасте 10–19 лет с психическими расстройствами (кроме нервной анорексии), результаты которых опубликованы на английском языке до 31 декабря 2023 года. Поиск потенциально релевантных работ проводили в базе данных MEDLINE. Отобранные работы анализировали, разделив их на 2 группы: исследования с внешним контролем (здоровые подростки) и исследования с внутренним контролем (пациенты с разной фазой психического расстройства, наличием/отсутствием аутоагрессивного поведения).

РЕЗУЛЬТАТЫ: В обзор включены результаты 11 кросс-секционных исследований. Анализ их результатов показал: 1) у подростков с психическими расстройствами (депрессия, психотические расстройства, обсессивно-компульсивное расстройство, синдром дефицита внимания и гиперактивности, расстройства, связанные с употреблением психоактивных веществ) значения ГКВ выше, чем у их сверстников без соответствующих расстройств (5 исследований); 2) значения ГКВ положительно коррелируют с выраженностью психопатологических симптомов (1 исследование); 3) высокие значения ГКВ связаны с фазой психического расстройства — манией при биполярном аффективном расстройстве (1 исследование) и обострением психоза при психотических расстройствах (1 исследование); 4) высокие значения ГКВ связаны с аутоагрессивным поведением — суицидными попытками (1 исследование) и несуицидальными самоповреждениями (1 исследование).

ЗАКЛЮЧЕНИЕ: ГКВ связаны с психическими расстройствами у подростков, их тяжестью/остротой (выраженностью симптомов, фазой заболевания, наличием аутоагрессии). Для оценки диагностической и прогностической ценности ГКВ в качестве биомаркеров психических расстройств в подростковом возрасте необходимы дальнейшие исследования более высокого методологического качества.

Keywords: *inflammatory hematological ratios; systemic inflammation; mental disorders; adolescents; biomarkers*
Ключевые слова: *гематологические коэффициенты воспаления; системное воспаление; психические расстройства; подростки; биомаркеры*

INTRODUCTION

Low-grade systemic inflammation is a persistent condition characterized by subclinical activation of systemic immunoinflammatory processes [1, 2]. It is known that systemic inflammation is involved in the pathophysiology of cardiovascular [3], endocrine [4], dermatological [5], oncological [6], and neurological diseases [7]. There is also evidence of activation of immune and inflammatory mechanisms in mental disorders such as depression [8–10], schizophrenia [8, 11, 12], and anxiety disorders [13]. Genetic predisposition, early life adversity, acute or chronic stress, unhealthy diet, and changes in the microbiome all contribute to this activation [1, 9, 14]. Systemic inflammation might influence the course of mental disorders, their clinical features, and severity of psychopathological symptoms [15–17]. An association between systemic inflammation and treatment therapeutic resistance has been established [18, 19]. In addition, systemic inflammation may be one of the common pathogenetic links between mental disorders and the metabolic syndrome, contributing to their frequent comorbidity [20, 21].

Peripheral blood levels of pro- and anti-inflammatory cytokines are usually considered as biomarkers of systemic inflammation in various mental disorders [22, 23].

Inflammatory hematological ratios (IHRs), such as the neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratio (PLR) can serve as inexpensive and readily available biomarkers [24, 25]. The above listed ratios, which characterize both innate and acquired immunity [26], have been studied as risk factors and/or predictors of the severity of COVID-19 [27], oncological [28], endocrine [29], and cardiovascular disorders [30, 31].

The rationale for studying IHRs in the context of mental disorders stems from the involvement of certain immune cells in the pathological processes associated with inflammation. One of the reasons for a decrease in the number of lymphocytes relative to other cells, in particular neutrophils, may be an increase in catecholamines, as well as in the blood prolactin and cortisol levels, which is observed, for example, under stress. There is evidence that monocytes can enter the central nervous system (CNS) and increase neuroinflammation, which, combined with a potential decrease in the lymphocyte count, justifies interest in the ratio of these cells. Platelets contain pro-inflammatory factors (metalloproteinases, chemokines, cytokines, etc.) and can be involved in an increase in the permeability of the blood-brain barrier and the regulation of inflammation in the CNS, which suggests that it is important to study their number relative to other cells; in particular, lymphocytes [32]. Elevated IHRs have been observed in patients with schizophrenia [33–35] and affective disorders [36, 37]. Research into the relationship between IHRs and schizophrenia is summarized in the scoping review that includes the results of 13 studies, predominantly in adult patients [38]. Given that many chronic and recurring mental disorders manifest themselves in adolescence [39, 40], systematizing IHRs studies in this age group is important. Moreover, many mental disorders in adolescence are "transdiagnostic" [41], posing challenges for their diagnosis and prognosis [42–44].

The aim of this scoping review was to summarize the findings from the studies that investigated the relationship of IHRs with mental disorders in adolescent patients. The following study questions were addressed in this review: 1) In what mental disorders in adolescents is there a difference in IHRs compared with healthy individuals of the same age? Have IHRs been examined as diagnostic biomarkers of mental disorders in adolescence (with cut-off values, sensitivity, and specificity calculations)? 2) Is there an association between IHRs and clinical features reflecting more severe/acute manifestations of mental disorders (severity of symptoms, acute phase of the disorder, presence of self-harm/suicidal behaviors), as well as the treatment response and the components of the metabolic syndrome? Have IHRs been examined as prognostic biomarkers for these variables (with cut-off values, sensitivity, and specificity calculations)?

METHODS

Protocol and registration

The aim of this scoping review, eligibility criteria, and methods for this review were defined in a protocol which is available upon request addressed to the corresponding author. The protocol was not registered in a public database. No changes were made to the protocol during the study (search, data extraction, and analysis). No deviations from the protocol were identified.

Eligibility criteria

The review included original studies that:

1. Were conducted in adolescents (aged 10 to 19 years inclusive) with mental disorders;
2. Assessed ihrs as a studied parameter (study factor);
3. Were published in english; and
4. Were published before December 31, 2023.

The following studies were not included:

1. Those with mixed-age samples (younger children and adolescents, adolescents and adults); and
2. Those that assessed IHRs in anorexia nervosa (criterion is justified by the likely influence of undernutrition on the activity of immune inflammation [45]).

Information sources

The search for information sources was carried out in the electronic database MEDLINE (access via PubMed[1]). The final search was conducted on January 16, 2024.

Search

To identify potentially relevant sources, a search query was used, which was generated through the following steps:

1. Identifying 3 primary concepts consistent with the aim of the review: IHRs, adolescence, mental disorders;

[1] Available from: https://pubmed.ncbi.nlm.nih.gov

2. Expanding these concepts with relevant synonyms;
3. Combining keywords using boolean operators;
4. Finalizing the search query based on the result of a discussion and consensus amongst all authors after a pilot search in the MEDLINE electronic database: (blood count parameters) OR (inflammatory ratios) OR (lymphocyte monocyte ratio) OR (platelet lymphocyte ratio) OR (systemic immune inflammation index) OR (monocyte-to-high-density lipoprotein ratio) AND (adolescents) AND (mental disorders) OR (depression) OR (suicide) OR (schizophrenia) OR (bipolar disorder).

The search was conducted by one of the authors (OL).

Selection of sources of evidence

The selection of publications from the identified sources was carried out in 3 stages:

1. Screening by titles and abstracts to exclude obviously irrelevant sources of information (e.g. *In vitro* studies, studies on laboratory animals, studies that included only adults);
2. Full texts retrieval; and
3. Analysis of the retrieved full-text sources using the eligibility criteria indicated above.

If the inclusion criteria were met and no exclusion criteria were met, studies were selected for inclusion in the review regardless of their design. Sources were selected independently by two authors (MP and OL). Discrepancies identified during comparison were corrected through discussion and consensus-building amongst all authors.

Data charting process

Data were extracted from the selected publications according to a pre-designed data collection form. Data were charted by one of the authors (OL) and subsequently cross-checked by another author (MP). Inconsistencies were discussed by all authors. All identified discrepancies were of a technical nature. There were no major discrepancies.

Data items

The following data were extracted: authors, country, year of publication, study design, diagnoses and diagnostic criteria, age, sample size, sex distribution of participants, presence/absence of treatment, study setting (inpatient or outpatient), IHR values (any parameters were extracted – all ratios calculated by the authors of the original papers based on hematology data), and the statistical significance of the differences compared with the control group. If there were healthy controls in the study, data from both the patients and the healthy participants were extracted.

Additionally, we extracted the findings regarding relationship between IHRs and the severity of symptoms, the disease phase, the presence of self-harm/suicidal behaviors, the treatment response, the components of the metabolic syndrome (body mass index, waist circumference, blood pressure, plasma glucose and glycated hemoglobin levels, lipid profile), as well as the results of the Receiver Operator Characteristic (ROC) curve analysis with IHRs cut-off values, sensitivity, and specificity (if the source contained these data).

Critical appraisal of individual sources of evidence

Not performed.

Synthesis of results

All relevant publications were analyzed after being assigned to one of the two groups. The first group included studies that compared IHR values between adolescents with a mental disorder and healthy individuals of the same age (healthy controls). The second group included studies that examined the relationship between IHRs and clinical variables (such as the phase of the disease, the presence of self-harm/suicidal behaviors). Data extracted from publications within each group were tabulated. Statistical methods were not used to analyze the data.

RESULTS

Selection of sources of evidence

The search query identified 490 publications. After reviewing the titles of the articles and their abstracts, 465 publications were excluded as not relevant to the scope of the review (the reasons for the exclusion of each source were not recorded at this stage). Of the remaining publications, 1 was excluded from the review due to the unavailability of the full text. After reviewing the full texts of 24 articles, we included 11 publications in the review [46–56]. The main reason for exclusion from analysis was that the studies were ineligible due to the age of the participants (Figure 1).

Characteristics of sources of evidence

The articles selected for the review were published between 2018 and 2023. All the publications included original studies. Geographically, 6 studies were conducted in Turkey

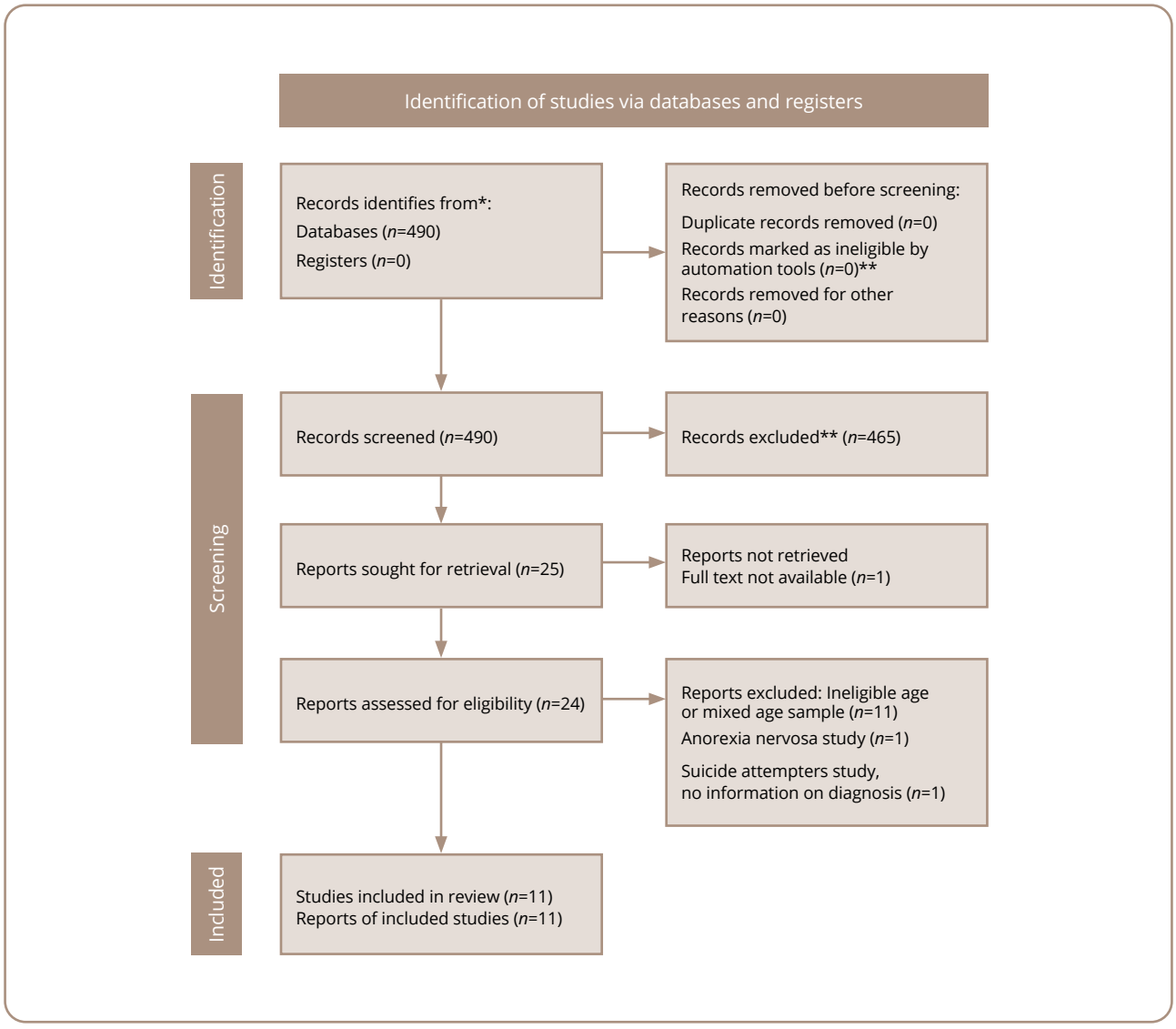

Figure 1. PRISMA flow diagram [57] of the literature search and the selection process.

Note: *All records were identified from MEDLINE database search (accessed via PubMed). **Automation tools were not used in this study. Records were excluded by a human.

[47–52], 2 in China [53, 54], 2 in Israel [55, 56], and 1 in Slovakia [46]. Six studies examined data from adolescents with affective disorders: 2 studies included patients with bipolar disorder (BD) [50, 52], 2 studies included patients with major depressive disorder (MDD) [51, 53], 1 study included patients with affective episodes of BD/MDD [55], and 1 study included patients with various types of affective disorders [54]. One study included adolescents with psychotic disorders [56]; 1 — obsessive-compulsive disorder (OCD) [49]; 1 — attention-deficit hyperactivity disorder (ADHD) [47]; and 1 — substance use disorders (SUD) [48]. Another study examined 2 groups of adolescents with autism spectrum disorders (ASD) and with ADHD [46]. All included studies were cross-sectional. The characteristics of the studies included in the review, as well as their main results, are presented in Tables 1 and 2. The description of the study designs in the Tables is indicated as per original sources.

Results of individual sources of evidence

Comparison of adolescents with mental disorders with healthy controls

IHR values in adolescents with mental disorders and healthy adolescents were compared in 7 [46–52] out of the 11 studies (see Table 1). In these studies, higher NLR and PLR values were found in adolescents with ADHD [47],

Table 1. Comparison of inflammatory hematological ratios in adolescents with psychiatric disorders vs healthy controls

Reference	Country	Type of study	Diagnosis/ diagnostic criteria	Eligible age, range	Patients					Healthy controls				*p*-value
					n	Average age*	Gender (M/F)	Treatment/ setting	IHR*	*n*	Average age*	Gender (M/F)	IHR*	
Ferencova, et al., 2023 [46]	Slovakia	Cross-sectional	ASD/ DSM-5	10–19	20	12.4 (1.9)	15/5	Naive/ inpatient	NLR 1.15 (1.02–1.43) MLR 0.20 (0.15, 0.28) PLR 113.0 (99.7–119.0) LMR 4.92 (3.64–6.52) PMR 409 (370–590)	20	13.2 (1.9)	15/5	NLR 0.97 (0.80-1.37) MLR0.19 (0.16-0.22) PLR 103.0 (85.4-113.0) LMR 5.23 (4.56-6.45) PMR 531 (466-688)	>0.05 (all variables)
			ADHD/ DSM-5	10–19	20	13.4 (1.8)	15/5	Naive/ inpatient	NLR 1.21 (0.91-1.73) MLR 0.19 (0.14–0.24) PLR 102.0 (72.1–125.0) LMR 5.22 (4.17–7.05) PMR 583 (415–700)					
Önder, et al., 2021 [47]	Turkey	Retrospective cross-sectional	ADHD/ DSM-5	12–17	24	NR	NR	Mixed (both naive and treated)/ outpatient	NLR 1.95 (0.81) PLR 132.50 (42.35)	29	NR	NR	NLR 1.16 (0.38) PLR 97.57 (18.37)	<0.001 (NLR) 0.001 (PLR)
Karatoprak, et al., 2021 [48]	Turkey	Retrospective cross-sectional	SUD/ DSM-5	12–18	55	17 (16–17)	55/0	Naive/ outpatient	NLR 1.65 (1.17–2.18) PLR 111.05 (86.11–130.62)	61	17 (16–17)	61/0	NLR 1.44 (1.10–1.68) PLR 92.39 (83.75–107.28)	0.006 (NLR) 0.007 (PLR)
Özyurt, et al., 2019 [49]	Turkey	Cross-sectional	OCD/ DSM-5	12–18	60	14.61 (1.81)	17/43	Naive/ outpatient	NLR 190.91 (148.00) PLR 118.02 (49.96)	128	14.37 (1.80)	27/101	NLR 148.81 (0.73) PLR 104.61 (44.66)	0.003 (NLR) 0.004 (PLR)
Ceylan, et al., 2019 [50]	Turkey	Cross-sectional	BD-type I (remission)/ DSM-5	14–17	38	16.3 (0.9)	10/28	NR/ outpatient	LMR 4.71 (1.7) NLR 1.84 (0.8)	37	16.8 (0.6)	10/27	LMR 5.57 (1.5) NLR 1.80 (0.6)	0.54 (LMR) 0.75 (PLR)
Özyurt, et al., 2018 [51]	Turkey	Cross-sectional	MDD/ DSM-5	12–18	67	14.47 (1.85)	20/47	Naive/ outpatient	NLR 2.1 (1.1) PLR 127.14 (35.26)	121	14.46 (1.77)	26/95	NLR 1.59 (0.57) PLR 113.3 (36.86)	<0.001 (NLR) 0.005 (PLR)
Binici, et al., 2018 [52]	Turkey	Cross-sectional	BD-type I (remission)/ DSM-IV-TR	NR	36	16.42 (1.29)	15/21	Treated/ outpatient	NLR 1.9 (0.78) PLR 107.03 (32.04)	30	16.3 (1.19)	16/14	NLR 1.72 (0.77) PLR 122.35 (32.04)	0.38 (NLR) 0.05 (PLR)

Note: ADHD — attention deficit/hyperactivity disorder; ASD — autism spectrum disorders; BD-type I — bipolar disorder, type I; DSM-IV-TR — Diagnostic and Statistical Manual of mental disorders, fourth edition, text revision; DSM-5 — Diagnostic and Statistical Manual of mental disorders, fifth edition; IHR — inflammatory hematological ratios; LMR — lymphocyte to monocyte ratio; MDD — major depressive disorder; MLR — monocyte to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio; NR — not reported; OCD — obsessive-compulsive disorder; PLR — platelet to lymphocyte ratio; PMR— platelet to monocyte ratio; SUD — substance use disorders. *Data is presented in the following way: mean (standard deviation), if one value in parentheses; median (interquartile range), if two values in parentheses separated by a dash.

Table 2. Comparison of inflammatory hematological ratios in adolescents with psychiatric disorders with regard to clinical features

Reference	Country	Type of study	Diagnosis/ diagnostic criteria	Eligible age, range	Treatment/ setting	Patients					Controls (comparison group of patients)					*p*-value
						Clinical feature under study	*n*	Average age*	Gender (M/F)	IHR*	Clinical feature under study	*n*	Average age*	Gender (M/F)	IHR*	
Cui, et al, 2023 [53]	China	Retrospective cross-sectional	MDD/ ICD-10	10–18	Naive/ inpatient	Suicide attempt	38	14.87 (1.89)	9/29	SII index 537.49 (261.62)	No suicide attempt	225	14.75 (1.78)	76/149	SII index 396,92 (200.68)	0.002
Zheng, et al., 2022 [54]	China	Cross-sectional	Mood or emotional disorders/ ICD-10	13–18	Treated/ inpatient	NSSI, DSM-5	106	15 (median)	17/89	NLR 1.46 (0.33) MLR 0.19 (0.01) PLR 115.66 (3.4)	No NSSI, DSM-5	95	15 (median)	21/74	NLR 1.34 (0.53) MLR 0.16 (0.04) PLR 107.85 (17.52)	0.091 (NLR) 0.001 (MLR) 0.007 (PLR)
Drapisz, et al., 2022 [55]	Israel	Retrospective cross-sectional	Major affective episodes/ DSM-5	10–19	Treated/ inpatient	Manic episode	63	15.9 (1.6)	38/25	NLR 2.36 (1.7)	Depressive episode	242	15.1 (1.8)	147/95	NLR 1.87 (1.00)	0.001
						Manic episode	13	14.9 (mean)	6/7	NLR 2.00 (0.8)	Remission	13 **	15.6 (mean)	6/7	NLR 1.50 (0.5)	0.001
Bustan, et al., 2018 [56]	Israel	Retrospective cross-sectional	Patients hospitalized in the acute ward without evidence of affective episodes (depressive, manic, hypomanic or mixed episodes)/ DSM-5	10–19	Treated/ inpatient	Psychotic	81	15.9 (1.6)	47/34	NLR 2.51 (1.8)	Non psychotic	285	14.7 (1.8)	147/138	NLR 1.91 (1.0)	0.001
						Acute psychosis	20	15.9 (mean)	NR	NLR 2.65 (2.0)	Remission	20 **	16.3 (mean)	NR	NLR 1.74 (0.8)	0.048

Note: DSM-5 — Diagnostic and Statistical Manual of mental disorders, fifth edition; ICD-10 — International Classification of Diseases, 10th revision; IHR — inflammatory hematological ratios; MDD — major depressive disorder; MLR — monocyte to lymphocyte ratio; NLR — neutrophil to lymphocyte ratio; NR — not reported; NSSI — non-suicidal self-injury; PLR — platelet to lymphocyte ratio; SII — systemic immune-inflammation.
*Data is presented in the following way, unless otherwise stated: mean (standard deviation). ** Same patients as in the Patients group.

substance use disorders [48], MDD [51], and OCD [49]. In the latter study, the NLR values were many times higher (approximately 100 times) than in other studies, which may be the result of a technical error on the part of the authors of the original article (for more details, see below, section "Limitations"). No statistically significant differences in IHRs between patients and healthy individuals were found in the studies of adolescents with BD [50, 52], as well as in the study that included 2 samples — adolescents with ASD and ADHD [46].

Diagnostic value of IHRs

None of the 7 studies listed above assessed the diagnostic value of IHRs (cut-off values, sensitivity, and specificity were not reported).

Association between IHRs and the severity of symptoms of mental disorders

The association between IHRs and the severity of psychopathological symptoms was examined in 2 studies [47, 51]. In adolescents with ADHD, no association was found between IHRs and the symptoms severity [47]. In adolescents with MDD, NLR values were positively correlated with the Beck's Depression Inventory score and the disease duration [51]. It is worth noting that in adolescents with BD, neither NLR nor PLR were correlated with the duration of the disorder or age of its onset [52]. Adolescents with OCD and comorbid anxiety disorders (which indirectly suggests a greater severity of the disorder) had higher NLR compared with OCD without comorbidity [49].

Association between IHRs and other clinical features of mental disorders

Four studies [53–56] investigated the association between IHRs and certain clinical features of a mental disorder (see Table 2). One study demonstrated a statistically significant increase in the systemic immune-inflammation index (SII, the product of platelet and neutrophil counts divided by the lymphocyte count) in adolescents with MDD who had attempted suicide compared with patients with MDD without a history of suicide attempts [53]. Another study found a significant increase in MLR and PLR in adolescents with non-suicidal self-injuries in affective disorders compared with similar patients without self-injuries [54]. In the third study, higher NLR values were observed in adolescents in a manic episode of BD than in a depressive episode [55]. Additionally, a significant decrease in NLR in remission was observed compared with a manic episode (mean interval between blood tests was 264 days) [55]. Finally, the fourth study demonstrated that the mean value of NLR in adolescents with psychotic disorders (mainly schizophrenia spectrum) was higher than in non-psychotic patients (with conduct disorders, adjustment disorder, ADHD) [56]. The same study showed a decrease in NLR after patients had achieved clinical remission compared with an acute psychotic state (mean interval between blood tests was 157 days) [56].

Prognostic value of IHRs

Although a ROC analysis was conducted in two studies that included adolescents with self-harm/suicidal behaviors to determine the IHR cut-off values, their sensitivity and specificity [53, 54], the results did not allow us to assess the prognostic value of IHRs. In the study that included adolescents with MDD — with or without a history of suicide attempts [53] — the area under the curve for the SII index was 0.661 (95% confidence interval, CI, 0.550–0.772; p=0.002), the optimal cut-off value for the SII index (based on the maximum value of Youden's index) was 548.15, with a sensitivity of 63% and specificity of 83%. Based on this cut-off value, patients were divided into high and low SII groups and a binary logistic regression analysis was performed. After adjusting for sex, age, body mass index, illness duration, and Hamilton Depression Rating Scale score, the odds of a suicide attempt within the last 7 days in the group of adolescents with high SII index were almost 14 times higher compared with the group of patients with SII index below the cut-off (odds ratio, OR=13.92; 95% CI 5.60–34.69; p <0.001). At the same time, a high SII index was not associated with a suicide attempt more than 7 days prior (OR=0.55; 95% CI 0.06–4.84; p=0.587) [53]. For non-suicidal self-injury in patients with affective disorders [54], the area under the curve was 0.638 (95% CI 0.561–0.715; p <0.001) for MLR and 0.611 (95% CI 0.533–0.689; p <0.001) for PLR. The cut-off values calculated by the authors of the original study were 0.135 for MLR (sensitivity 91%, specificity 34%) and 127.5 for PLR (sensitivity 40%, specificity 81%) [54]. It should be emphasized that although the authors of these studies indicate the association between increased "risk" of self-harm/suicidal behaviors and higher IHR values, this conclusion is based on data from retrospective cross-sectional studies, which completely excludes the possibility of assessing the prognostic value of IHRs (for more details, see below, section "Limitations").

Association between IHRs and metabolic disturbances

The relationship between IHRs and the metabolic syndrome was not examined in the studies included in this review. In one study, which included adolescents with BD, no correlations between NLR or PLR and body mass index were found [52].

Association between IHRs and the treatment response

None of the studies included in this review examined the association between IHRs and the treatment response in mental disorders. One study revealed no differences in NLR or PLR in adolescents with ADHD who did and did not receive pharmacological treatment for their disorder, as well as no correlation of either NLR or PLR with the duration of atomoxetine and/or methylphenidate use [47].

DISCUSSION

Summary of evidence

Our search strategy did not identify any narrative reviews, scoping reviews, systematic reviews, or meta-analyses that systematized studies on the relationship between IHRs and mental disorders in adolescents. Having summarized the findings from 11 original studies selected for this scoping review, we can state the following. First, adolescents with mental disorders (depression, psychotic disorders, OCD, ADHD, substance use disorders) have higher IHRs compared with adolescents without these disorders. Second, IHRs are higher in adolescents with more severe/acute manifestations of the mental disorder (severity of symptoms, mania, exacerbation of psychosis, self-harm/suicidal behaviors). Third, the study results do not allow for the assessment of the diagnostic or prognostic value of IHRs in adolescents with mental disorders.

Limitations

The studies included in our review demonstrated heterogeneity (demographic and clinical characteristics of participants, different diagnoses, study settings, presence/absence of treatment, sample sizes). Although we did not assess the quality of the selected studies, several evident shortcomings are notable. In particular, most of the studies lack information on the procedures of blood collection and hematological analysis. In one study [49], the NLR values in both the patient and control groups were approximately 100 times higher than in other studies. The authors of the original article do not explain this in any way. Additionally, the existing discrepancy between the mean NLR value and its standard deviation in the control group (a difference of approximately two decimal orders, see Table 1) indicates a possible technical error (typo). However, such errors, combined with the above-mentioned heterogeneity of the studies, limit the comparability and generalizability of the results.

All the studies included in the review, according to their authors, were cross-sectional, which makes it impossible to establish causal relationships. Only 2 of these studies included a longitudinal (retrospective) part [55, 56], allowing to track the changes in the variables under study across time in some patients. About half of the studies were retrospective, raising concerns about the quality of the data that the study authors extracted from medical records not initially intended for study purposes. Both of the studies that performed an ROC analysis to calculate IHR cut-off values, sensitivity, and specificity were retrospective cross-sectional [53, 54]. Although the authors of these studies related high IHR values to the "risks" of self-harm/suicidal behaviors (suicide attempts and non-suicidal self-injury), those "risks" corresponds solely to past behaviors, precluding an assessment of the prognostic value of the suggested statistical models.

This review did not consider any other markers of inflammation, which prevents one from drawing conclusions about whether IHRs are independent indicators of systemic inflammation or are related to other immune inflammatory changes associated with mental disorders. This limitation precludes the possibility of assessing the influence of age on the associations of IHRs with other immune inflammatory markers.

Finally, some relevant studies may have been missed for the following reasons. First, the search for sources was limited to one database. Second, the search query used may not have been sensitive enough. Third, auxiliary search methods were not used, in particular, in searching through reference lists in the relevant sources and other work published on the topic that used a systematic literature search methodology. For example, a published retrospective study of IHRs in 32 adolescents with early-onset schizophrenia was identified after the completion of the selection of information sources [58]. The reason for the omission was that the publication was not indexed in the MEDLINE database in which the search was conducted. The omitted study showed higher NLR in adolescents with

schizophrenia compared with healthy controls of the same age, which is consistent with the results of the study included in our review demonstrating elevated NLR in adolescents with psychotic disorders (including schizophrenia) compared with non-psychotic adolescents [56].

Discussion of the main results in comparison with the results of IHR studies in adults and younger children

Association between IHRs and mental disorders

Several systematic reviews and meta-analyses have been published summarizing data on IHRs in mental disorders across various age groups, including children [25, 59], adults [33, 36, 37, 60, 61], and mixed-age samples [38]. The majority of these studies focus on affective disorders in adult patients.

A meta-analysis of the results of 7 studies on IHRs in BD in adults (1,334 participants) demonstrated that patients had higher NLR and PLR than healthy individuals: standardized mean difference, SMD=0.672; 95% CI 0.516–0.828; p <0.001 and SMD=0.425; 95% CI 0.004–0.846; and p=0.048, respectively [36], reflecting a moderate effect size. The results of 2 studies of BD in adolescents included in our review did not show differences in IHRs compared with the healthy controls [50, 52]. However, both adolescent studies included patients in remission, and, given this, their results are entirely consistent with the adult studies on BD which also included patients in remission and similarly revealed no differences from healthy controls [36].

A meta-analysis of the results of 4 studies on IHRs in MDD (553 participants) demonstrated higher NLR in adult patients compared with healthy controls (SMD=0.670; 95% CI 0.072–1.268; p=0.028) [36]. A meta-analysis of the results of studies examining any relationship between IHRs and depression (2,580 adult patients with depression and 2,664 healthy participants) allowed us to draw similar conclusions: higher NLR in depressive patients than in healthy controls (SMD=0.33; 95% CI 0.15–0.45; p <0.001) and no differences in PLR or MLR [60]. Another meta-analysis (18 studies, 2,264 adults with depression and 2,415 healthy participants) confirmed the increase in NLR (SMD=0.33; 95% CI 0.15–0.52; p <0.001) and PLR (SMD=0.24; 95% CI 0.02–0.46; p <0.05) in depression compared with healthy individuals [37]. All these results are consistent with the results of the study included in our review [51], which found higher NLR and PLR in adolescents with MDD compared with healthy individuals of the same age.

A meta-analysis of studies on IHRs in psychotic disorders in adults (8 studies, 3 of which included patients with the first psychosis episode and 5 with schizophrenia; a total of 683 patients and 551 healthy participants) demonstrated that patients with non-affective psychosis had higher NLR and MLR than healthy controls (SMD=0.715; 95% CI 0.525–0.905; p <0.001 and SMD=0.417; 95% CI 0.147–0.686; p=0.002, respectively) [33]. A study in adolescents with acute psychotic disorders included in our review also found an increase in NLR compared with healthy adolescents (MLR was not assessed in that study) [56]. The increase in NLR in adolescents with psychotic disorders compared with non-psychotic adolescents is also confirmed by a meta-analysis of the results of 3 studies in this age group including 557 participants [25].

A meta-analysis of the results of 8 studies on IHRs in younger children with ADHD (mean age of participants of these studies varied from 8.3±1.7 to 10.33±3.15 years) demonstrated that they had higher NLR and PLR than healthy children (939 patients and 652 healthy children; SMD=0.49; 95% CI 0.15–0.82; p=0.004 and SMD=0.31; 95% CI 0.03–0.59, respectively), while no difference in MLR was observed [59]. The results of the studies in adolescents included in our review were inconsistent: one study demonstrated increased NLR and PLR in adolescents aged 12–17 years with ADHD [47], while another found no differences compared with healthy controls [46].

As for other mental disorders (which have been studied in adolescents), elevated IHRs compared with healthy controls were demonstrated in adult patients with OCD [62, 63] and SUD [64, 65], and in children with ASD [66–68]. It should be noted that the number of such studies is limited and their results are somewhat contradictory, which makes comparisons extremely difficult, especially regarding the age-specificity.

Overall, a comparison of studies on IHRs in mental disorders between adolescents and adults indicates that the most reproducible abnormalities compared with healthy individuals in both age groups are NLR and (to a lesser extent) PLR increase in affective disorders [36, 37, 51, 60], as well as NLR increase in schizophrenia spectrum disorders (first psychotic episode and schizophrenia) [25, 33, 56]. Comparison of studies of IHRs in ADHD between adolescents [46, 47] and younger children [59] demonstrates an increase in NLR compared with healthy controls (although not in all studies) in both age groups. Thus, for those indications which were studied across various age groups

(younger children, adolescents, adults), we did not find any age-related differences in the association between IHRs and mental disorder.

Association between IHRs and the clinical features of mental disorders

Relationships between IHRs and the severity of psychopathological symptoms have been investigated in a few studies. One of the studies included in our review demonstrated a correlation between NLR and the severity of depressive symptoms in adolescents with MDD [51]. In adults, the severity of depression correlated for stronger with PLR than NLR [69, 70], which may indicate age-related differences in the relationship between IHRs and the severity of depressive symptoms. A correlation between NLR and symptom severity has been observed in adult patients with schizophrenia [71]. In ADHD, no correlations between IHRs and symptom severity have been found in either adolescents [47] or younger children [72]. Given the limited number of studies, it is difficult to determine the age-specific differences in the relationship between IHRs and the severity of psychopathological symptoms. Therefore, further studies are needed to confirm the reproducibility of the relevant findings.

In the studies investigating the relationship between IHRs and the illness phase, higher NLR values were observed in adolescents in a manic episode of BD than in a depressive episode or remission [55], as well as in adolescents with an acute psychosis compared with remission [56], which is fully consistent with the results of the studies in adults with BD [36, 73, 74] and psychotic disorders, including schizophrenia [33, 75]. These data confirm that higher IHR values are associated with more acute manifestations (mania, exacerbation of psychosis). However, no conclusions about the age-specificity in the relationship between IHRs and the disease phase can be drawn.

One of the important "indicators" of the acuity/severity in psychiatry is self-harm/suicidal behaviors. A study included in our review demonstrated an increase in the SII index in adolescents with MDD who attempted suicide compared with adolescents with MDD without suicide attempts [53]. Another study (193 adolescents aged 11–18 years with a history of suicide attempts and 109 non-suicidal participants of the same age), excluded from our review due to the lack of information regarding psychiatric diagnoses of study participants, demonstrated the association between suicidality and higher NLR, MLR, and PLR values [76]. In a sample of young adults (137 patients with MDD aged 18 to 24 years and 56 healthy controls of the same age), suicidality was associated with higher MLR values [77]. In adults, a systematic review of 11 studies (819 patients with MDD and suicidal behavior, 494 patients with MDD without suicidal behavior, and 388 healthy participants) revealed that suicidal behavior was associated with increased NLR, but not MLR or PLR [61]. This finding was supported by the results of the study of adult patients with depression who had survived a suicide attempt, and in whom NLR was also higher compared with controls [78]. The association between suicidal behavior in adults and high NLR values has been demonstrated not only in depression, but also in BD [26]. All these findings suggest age-related differences in the associations between IHRs and suicidal behavior in adolescents (increased NLR, MLR, and PLR [76]), young adults (only MLR increased [77]), and adult patients (only NLR increased [26, 61, 78]). It is noteworthy that non-suicidal self-injury in adolescents was associated with elevated MLR and PLR, but not NLR [54]. The differences between age groups in the correlation between certain IHRs with self-harm/suicidal behaviors may reflect age-related differences (to date unproven) in the biological mechanisms of such behaviors.

In our opinion, the associations between IHRs and certain clinical features of mental disorders (severity of symptoms, phase of the disease, presence of self-harm/suicidal behaviors) might hypothetically indicate a higher degree of activation of systemic inflammation in more severe/acute cases. One can assume that patients with higher IHR values (i.e. with more pronounced systemic inflammation) may represent a specific subtype of psychiatric disorders, likely differing in course and prognosis [16, 17]. However, the studies included in our review do not allow one to speculate on a causal relationship between IHRs and the severity of mental disorders. Elevated IHRs in various mental disorders may indicate common etiopathogenetic pathways, specifically common predisposing genetic factors [79–81]. Conversely, an increase in IHRs may be a consequence of a mental disorder, reflecting concomitant nonspecific physiological stress [17, 82]. It is quite likely that there is a bidirectional relationship between systemic inflammation and mental disorders, with each exerting a negative influence on the other [83]. Additionally, high intra- and inter-individual variability of inflammatory biomarkers is obvious, depending on a large number of factors (hereditary and environmental), which

largely accounts for the low reproducibility and frequent inconsistency of study results [84].

Association between IHRs and the treatment response

The hypothetical influence of systemic inflammation on the development of treatment resistance [18, 19, 85] provides a rationale to study the relationship between IHRs and the response to treatment. We were unable to find studies that examined this relationship in adolescents with mental disorders. Studies in other age groups (young adults, adults) demonstrate conflicting results. On the one hand, higher values of the SII index and SIRI (systemic inflammatory response index) have been demonstrated in non-responders compared with responders in bipolar depression [86, 87]. On the other hand, elevated IHRs have been shown to be associated with higher treatment efficacy in psychotic depression [88, 89] and schizophrenia [90, 91].

Association between IHRs and metabolic disturbances

Our search strategy did not identify studies specifically aimed at assessing the relationship between IHRs and the metabolic syndrome or its components in adolescents with mental disorders. In most of the selected studies, excess weight or obesity was an exclusion criterium, which likely explains the lack of association between the body mass index and IHRs in the only study that assessed their relationship [52]. This assumption is supported by the results of the study in a sample of young adults (18–24 years) demonstrating higher NLR in MDD comorbid with obesity than in MDD without obesity, as well as a weak positive correlation between NLR and the body mass index [92].

Diagnostic and prognostic value of IHRs in adolescents with mental disorders

The findings from the studies showing higher IHRs in adolescents with mental disorders compared with controls [47–49, 51, 56] are promising in regards of using IHRs as diagnostic biomarkers. However, there is no consistent data on differences in IHRs in various diseases, which could have objectified and significantly facilitated the differential diagnosis, which poses particular difficulties in adolescents due to the transdiagnostic clinical presentations [42–44]. The results of IHR comparisons between various mental disorders in adults have low reproducibility. As an example, one study demonstrated that adults with exacerbation of schizophrenia had higher NLR than patients with BD in a manic episode [93], while the other study showed the opposite results [94]. In another study differences in IHRs between adult patients with bipolar and unipolar depression were observed [95], however in the large-scale cross-sectional study (13,888 participants) no significant differences in IHRs either between BD and MDD, or between BD and schizophrenia, were found [82].

Although the results of 2 studies included in our review indicate an association between IHRs and self-harm/suicidal behaviors [53, 54], the retrospective cross-sectional design of both studies excludes the possibility of using calculated cut-off values to predict the risk of future suicide attempts or non-suicidal self-injury. In the absence of studies linking IHRs to treatment response and metabolic syndrome, one can speculate on a possible use of IHRs for predicting the treatment response or assessing metabolic risks in adolescents solely on the grounds of the studies conducted in young adults and adults [88–92].

Perspectives for future research

One of the potential directions for future research would appear to be clarifying the role of systemic inflammation in the etiopathogenesis of mental disorders at different stages of their development, which requires a comprehensive assessment of not only IHRs, but also other immune inflammatory markers in conjunction with neurobiological, genetic, socio-demographic, and clinical variables across various age groups (younger children, adolescents, young adults, adults) at different stages of development/manifestation of a mental disorder.

Another direction is examining the diagnostic utility of IHRs, taking into account the transdiagnostic nature of clinical presentation in adolescence and complicated differential diagnosis. This area requires large-scale comparative studies, including samples of adolescents with various psychiatric diagnoses.

Evaluating IHRs as prognostic biomarkers also seems to be a promising direction. Models predicting the risks of suicide attempts and non-suicidal self-injury could assist in identifying adolescents at increased risk of self-harm/suicide and developing personalized preventive programs. Research on the prognostic value of IHRs in predicting treatment response and the risk of treatment resistance is essential for the development of adolescent-specific interventions aimed at the management of treatment resistance. Finally, there is an obvious research gap in the

study of the relationship between IHRs and the metabolic syndrome, which are more prevalent in individuals with mental disorders than in the general population [96, 97]. The metabolic syndrome increases the risk of cardiovascular diseases [98, 99], leading to excessive early mortality and significant reduction in life expectancy for patients with mental disorders [100, 101]. That is why identifying adolescents with a high metabolic risk is, in our opinion, of great importance due to the potential reversibility of metabolic disturbances in the early stages. For the development of prognostic models predicting treatment response, the risk of self-harm/suicidal behaviors, and the risk of developing the metabolic syndrome, prospective studies are required.

CONCLUSION

The results of this scoping review support the hypothesis of systemic inflammatory mechanisms activation in mental disorders and demonstrate that IHRs can be used as indicators of immune inflammation in adolescent patients. Elevated IHRs have been observed across a wide range of mental disorders in adolescents (depression, psychotic disorders, OCD, ADHD, substance use disorders); however, the cut-off values for any of these disorders have not been calculated, which makes it impossible to assess IHRs diagnostic value. Also, there is no evidence to suggest that the association between IHRs and these disorders depend on age: similar patterns are observed in adolescents and adults. In both adolescents and adults, higher IHRs correspond to more severe/acute manifestations of mental disorders. Additionally, there is some evidence of age-specificity in the relationship of IHRs with both the severity of psychopathological symptoms and self-harm/suicidal behavior. At the same time, the limitations of the studies included in our review do not allow neither the assessment of the utility of IHRs as prognostic biomarkers for self-harm/suicidal behaviors in adolescents nor age-related comparisons. Assessment of the clinical value of IHRs as diagnostic and prognostic biomarkers requires confirmation of the reproducibility and specificity of their changes in various mental disorders in studies of higher methodological quality.

Article history

Submitted: 12.02.2024
Accepted: 11.06.2024
Published Online: 24.06.2024

Authors' contribution: Mikhail Popov — study idea and purpose, searching and reviewing publications, data extraction, writing the draft; Yuri Popov — reviewing and approval of the final draft; Dmitry Kosterin — writing the draft; Olga Lepik — searching and reviewing publications, data extraction, writing the draft.

Funding: The research was conducted as a part of the government assignment for V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology of the Ministry of Health of the Russian Federation for 2024–2026 (XSOZ 2024 0012).

Conflict of interest: The authors declare no conflicts of interest.

For citation:

Popov MYu, Popov YuV, Kosterin DN, Lepik OV. Inflammatory hematological ratios in adolescents with mental disorders: a scoping review. *Consortium Psychiatricum*. 2024;5(2): CP15514. doi: 10.17816/CP15514

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References

1. Minihane AM, Vinoy S, Russell WR, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. Br J Nutr. 2015;114(7):999–1012. doi: 10.1017/S0007114515002093

2. Nogueira Silva Lima MT, Howsam M, Anton PM, et al. Effect of advanced glycation end-products and excessive calorie intake on diet-induced chronic low-grade inflammation biomarkers in murine models. Nutrients. 2021;13(9):3091. doi: 10.3390/nu13093091
3. Gupta L, Thomas J, Ravichandran R, et al. Inflammation in cardiovascular disease: A comprehensive review of biomarkers and therapeutic targets. Cureus. 2023;15(9):e45483. doi: 10.7759/cureus.45483
4. Nie Y, Zhou H, Wang J, Kan H. Association between systemic immune-inflammation index and diabetes: a population-based study from the NHANES. Front Endocrinol (Lausanne). 2023;14:1245199. doi: 10.3389/fendo.2023.1245199
5. Zhao X, Li J, Li X. Association between systemic immune-inflammation index and psoriasis: a population-based study. Front Immunol. 2024;15:1305701. doi: 10.3389/fimmu.2024.1305701
6. Wellenstein MD, Coffelt SB, Duits DEM, et al. Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature. 2019;572(7770):538–542. doi: 10.1038/s41586-019-1450-6
7. Yacoubian TA, Fang YD, Gerstenecker A, et al. Brain and systemic inflammation in de novo Parkinson's disease. Mov Disord. 2023;38(5):743–754. doi: 10.1002/mds.29363
8. Butoma BG, Petrova NN, Mayorova MA. On the status of autoimmunity in the disorders of schizophrenic and depressive spectra. Vestnik of Saint Petersburg University. Medicine. 2019;14(4):284–287. doi: 10.21638/spbu11.2019.406
9. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: Double trouble. Neuron. 2020;107(2):234–256. doi: 10.1016/j.neuron.2020.06.002
10. Suhee FI, Shahriar M, Islam SMA, et al. Elevated serum IL-2 levels are associated with major depressive disorder: A case-control study. Clin Pathol. 2023;16:2632010X231180797. doi: 10.1177/2632010X231180797
11. Müller N. Inflammation in schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull. 2018;44(5):973–982. doi: 10.1093/schbul/sby024
12. Wang C, Zhu D, Zhang D, et al. Causal role of immune cells in schizophrenia: Mendelian randomization (MR) study. BMC Psychiatry. 2023;23(1):590. doi: 10.1186/s12888-023-05081-4
13. Michopoulos V, Powers A, Gillespie CF, et al. Inflammation in fear- and anxiety-based disorders: PTSD, GAD, and beyond. Neuropsychopharmacology. 2017;42(1):254–270. doi: 10.1038/npp.2016.146
14. Quidé Y, Bortolasci CC, Spolding B, et al. Systemic inflammation and grey matter volume in schizophrenia and bipolar disorder: Moderation by childhood trauma severity. Prog Neuropsychopharmacol Biol Psychiatry. 2021;105:110013. doi: 10.1016/j.pnpbp.2020.110013
15. Klyushnik TP, Zozulya SA, Oleichik IV, et al. The status of leukocyte-inhibitory system of inflammation in different age groups of patients with endogenous depression. Zh Nevrol Psikhiatr Im S S Korsakova. 2021;121(5. Vyp. 2):67–74. doi: 10.17116/jnevro202112105267
16. Zozulya SA, Golubev SA, Tikhonov DV, et al. Immunological and clinical aspects of the long-term stages of youth schizophrenia. Zh Nevrol Psikhiatr Im S S Korsakova. 2022;122(1. Vyp. 2):5–12. doi: 10.17116/jnevro20221220125
17. Thylur DS, Goldsmith DR. Brick by brick: Building a transdiagnostic understanding of inflammation in psychiatry. Harv Rev Psychiatry. 2022;30(1):40–53. doi: 10.1097/HRP.0000000000000326
18. Mondelli V, Ciufolini S, Belvederi Murri M, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophr Bull. 2015;41(5):1162–1170. doi: 10.1093/schbul/sbv028
19. Choi W, Stewart R, Kang HJ, et al. Interactive effects of systemic inflammation and life stressors on treatment response of depressive disorders. Brain Behav Immun. 2021;95:61–67. doi: 10.1016/j.bbi.2021.01.029
20. Leonard BE, Schwarz M, Myint AM. The metabolic syndrome in schizophrenia: is inflammation a contributing cause? J Psychopharmacol. 2012;26(5 Suppl):33–41. doi: 10.1177/0269881111431622
21. Rethorst CD, Bernstein I, Trivedi MH. Inflammation, obesity, and metabolic syndrome in depression: analysis of the 2009-2010 National Health and Nutrition Examination Survey (NHANES). J Clin Psychiatry. 2014;75(12):e1428–1432. doi: 10.4088/JCP.14m09009
22. Yuan N, Chen Y, Xia Y, et al. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl Psychiatry. 2019;9(1):233. doi: 10.1038/s41398-019-0570-y
23. Wautier JL, Wautier MP. Pro- and anti-inflammatory prostaglandins and cytokines in humans: A Mini Review. Int J Mol Sci. 2023;24(11):9647. doi: 10.3390/ijms24119647
24. Moosmann J, Krusemark A, Dittrich S, et al. Age- and sex-specific pediatric reference intervals for neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and platelet-to-lymphocyte ratio. Int J Lab Hematol. 2022;44(2):296–301. doi: 10.1111/ijlh.13768
25. Taylor JH, Bermudez-Gomez J, Zhou M, et al. Immune and oxidative stress biomarkers in pediatric psychosis and psychosis-risk: Meta-analyses and systematic review. Brain Behav Immun. 2024;117:1–11. doi: 10.1016/j.bbi.2023.12.019
26. Ivković M, Pantović-Stefanović M, Dunjić-Kostić B, et al. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: Moderatory effect of family history. Compr Psychiatry. 2016;66:87–95. doi: 10.1016/j.comppsych.2016.01.005
27. Nalbant A, Kaya T, Varim C, et al. Can the neutrophil/lymphocyte ratio (NLR) have a role in the diagnosis of coronavirus 2019 disease (COVID-19)? Rev Assoc Med Bras (1992). 2020;66(6):746–751. doi: 10.1590/1806-9282.66.6.746
28. Liu D, Czigany Z, Heij LR, et al. The value of platelet-to-lymphocyte ratio as a prognostic marker in cholangiocarcinoma: A systematic review and meta-analysis. Cancers (Basel). 2022;14(2):438. doi: 10.3390/cancers14020438
29. Adane T, Melku M, Worku YB, et al. The association between neutrophil-to-lymphocyte ratio and glycemic control in type 2 diabetes mellitus: A systematic review and meta-analysis. J Diabetes Res. 2023;2023:3117396. doi: 10.1155/2023/3117396
30. Angkananard T, Anothaisintawee T, McEvoy M, et al. Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. Biomed Res Int. 2018;2018:2703518. doi: 10.1155/2018/2703518
31. Wang P, Guo X, Zhou Y, et al. Monocyte-to-high-density lipoprotein ratio and systemic inflammation response index are associated with the risk of metabolic disorders and cardiovascular diseases in general rural population. Front Endocrinol (Lausanne). 2022;13:944991. doi: 10.3389/fendo.2022.944991

32. Gorbunova AP, Rukavishnikov GV, Kasyanov ED, Mazo GE. 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;58(1):47–55. doi: 10.31363/2313-7053-2024-794
33. Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: A meta-analysis and systematic review. World J Biol Psychiatry. 2020;21(5):326–338. doi: 10.1080/15622975.2019.1583371
34. Zhu X, Zhou J, Zhu Y, et al. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in schizophrenia. Australas Psychiatry. 2022;30(1):95–99. doi: 10.1177/10398562211022753
35. Sugita S, Tomioka H, Mera K, et al. Neutrophil-lymphocyte ratio in patients with acute schizophrenia. Cureus. 2024;16(1):e52181. doi: 10.7759/cureus.52181
36. Mazza MG, Lucchi S, Tringali AGM, et al. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):229–236. doi: 10.1016/j.pnpbp.2018.03.012
37. Cheng Y, Wang Y, Wang X, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depression: An updated systematic review and meta-analysis. Front Psychiatry. 2022;13:893097. doi: 10.3389/fpsyt.2022.893097
38. Sandberg AA, Steen VM, Torsvik A. Is elevated neutrophil count and neutrophil-to-lymphocyte ratio a cause or consequence of schizophrenia? – A scoping review. Front Psychiatry. 2021;12:728990. doi: 10.3389/fpsyt.2021.728990
39. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):593–602. doi: 10.1001/archpsyc.62.6.593
40. Solmi M, Radua J, Olivola M, et al. Age at onset of mental disorders worldwide: large-scale meta-analysis of 192 epidemiological studies. Mol Psychiatry. 2022;27(1):281–295. doi: 10.1038/s41380-021-01161-7
41. Shah JL, Scott J, McGorry PD, et al. Transdiagnostic clinical staging in youth mental health: a first international consensus statement. World Psychiatry. 2020;19(2):233–242. doi: 10.1002/wps.20745
42. Reimherr JP, McClellan JM. Diagnostic challenges in children and adolescents with psychotic disorders. J Clin Psychiatry. 2004;65 Suppl 6:5–11.
43. Zechowski C. Diagnostic difficulties in adolescent patients – subjective psychiatrist-side factors. Psychiatr Pol. 2012;46(2):241–247.
44. Copeland WE, Adair CE, Smetanin P, et al. Diagnostic transitions from childhood to adolescence to early adulthood. J Child Psychol Psychiatry. 2013;54(7):791–799. doi: 10.1111/jcpp.12062
45. Lawson EA, Miller KK, Mathur VA, et al. Hormonal and nutritional effects on cardiovascular risk markers in young women. J Clin Endocrinol Metab. 200;92(8):3089–3094. doi: 10.1210/jc.2007-0364
46. Ferencova N, Visnovcova Z, Ondrejka I, et al. Peripheral inflammatory markers in autism spectrum disorder and attention deficit/hyperactivity disorder at adolescent age. Int J Mol Sci. 2023;24(14):11710. doi: 10.3390/ijms241411710
47. Önder A, Gizli Çoban Ö, Sürer Adanır A. Elevated neutrophil-to-lymphocyte ratio in children and adolescents with attention-deficit/hyperactivity disorder. Int J Psychiatry Clin Pract. 2021;25(1):43–48. doi: 10.1080/13651501.2020.1804940
48. Karatoprak S, Uzun N, Akıncı MA, Dönmez YE. Neutrophil-lymphocyte and platelet-lymphocyte ratios among adolescents with substance use disorder: A preliminary study. Clin Psychopharmacol Neurosci. 2021;19(4):669–676. doi: 10.9758/cpn.2021.19.4.669
49. Özyurt G, Binici NC. The neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in adolescent obsessive-compulsive disorder: Does comorbid anxiety disorder affect inflammatory response? Psychiatry Res. 2019;272:311–315. doi: 10.1016/j.psychres.2018.12.131
50. Ceylan MF, Tural Hesapcioglu S, Kasak M, et al. Increased prolidase activity and high blood monocyte counts in pediatric bipolar disorder. Psychiatry Res. 2019;271:360–364. doi: 10.1016/j.psychres.2018.11.066
51. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. Psychiatry Res. 2018;268:426–431. doi: 10.1016/j.psychres.2018.08.007
52. Binici NC, Alşen Güney S, İnal Emiroğlu FN. Neutrophil-lymphocyte and platelet-lymphocyte ratios among adolescents with bipolar disorder: A preliminary study. Psychiatry Res. 2018;269:178–182. doi: 10.1016/j.psychres.2018.08.065
53. Cui S, Liu Z, Liu Y, et al. Correlation between systemic immune-inflammation index and suicide attempts in children and adolescents with first-episode, drug-naïve major depressive disorder during the COVID-19 pandemic. J Inflamm Res. 2023;16:4451–4460. doi: 10.2147/JIR.S433397
54. Zheng Q, Liu J, Ji Y, et al. Elevated levels of monocyte-lymphocyte ratio and platelet-lymphocyte ratio in adolescents with non-suicidal self-injury. BMC Psychiatry. 2022;22(1):618. doi: 10.1186/s12888-022-04260-z
55. Drapisz A, Avrahami M, Ben Dor DH, et al. Association between neutrophil to lymphocyte ratio and mood polarity in adolescents admitted to an inpatient psychiatric ward. Int Clin Psychopharmacol. 2022;37(6):242–246. doi: 10.1097/YIC.0000000000000412
56. Bustan Y, Drapisz A, Ben Dor DH, et al. Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for early association between inflammation and psychosis. Psychiatry Res. 2018;262:149–153. doi: 10.1016/j.psychres.2018.02.002
57. Tricco AC, Lillie E, Zarin W, et al. PRISMA extension for scoping reviews (PRISMA-ScR): Checklist and explanation. Ann Intern Med. 2018;169(7):467–473. doi: 10.7326/M18-0850
58. Önder A, Adanir AS, Çoban ÖG, et al. Elevated neutrophil/lymphocyte ratio in adolescents with early-onset schizophrenia. Neurochem J. 2020;14(4):444–448. doi: 10.1134/s1819712420330016
59. Gędek A, Modrzejewski S, Gędek M, et al. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio in ADHD: a systematic review and meta-analysis. Front Psychiatry. 2023;14:1258868. doi: 10.3389/fpsyt.2023.1258868
60. Su M, Ouyang X, Song Y. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and monocyte to lymphocyte ratio in depression: A meta-analysis. J Affect Disord. 2022;308:375–383. doi: 10.1016/j.jad.2022.04.038
61. Velasco A, Lengvenyte A, Rodriguez-Revuelta J, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review. Eur Psychiatry. 2023:1–25. doi: 10.1192/j.eurpsy.2023.18

62. Herdi O, Sayar-Akaslan D, İlhan RS, et al. Associations between subclinical inflammatory markers and OCD: A retrospective study. Psychiatry Res. 2020;290:113065. doi: 10.1016/j.psychres.2020.113065
63. Sekeryapan Gediz B, Ozturk M, Kilinc Hekimsoy H, et al. Choroidal vascularity index as a potential inflammatory biomarker for obsessive compulsive disorder. Ocul Immunol Inflamm. 2022;30(2):428–432. doi: 10.1080/09273948.2020.1800052
64. Guzel D, Yazici AB, Yazici E, Erol A. Evaluation of immunomodulatory and hematologic cell outcome in heroin/opioid addicts. J Addict. 2018;2018:2036145. doi: 10.1155/2018/2036145
65. Quraishi R, Kathiresan P, Verma K, et al. Effect of chronic opioid use on the hematological and inflammatory markers: A retrospective study from North India. Indian J Psychiatry. 2022;64(3):252–256. doi: 10.4103/indianjpsychiatry.indianjpsychiatry_751_21
66. Tural Hesapcioglu S, Kasak M, Cıtak Kurt AN, Ceylan MF. High monocyte level and low lymphocyte to monocyte ratio in autism spectrum disorders. Int J Dev Disabil. 2017;65(2):73–81. doi: 10.1080/20473869.2017.1371369
67. Esnafoglu E, Subaşı B. Association of low 25-OH-vitamin D levels and peripheral inflammatory markers in patients with autism spectrum disorder: Vitamin D and inflammation in autism. Psychiatry Res. 2022;316:114735. doi: 10.1016/j.psychres.2022.114735
68. Ellul P, Maruani A, Peyre H, et al. Abnormal neutrophil-to-lymphocyte ratio in children with autism spectrum disorder and history of maternal immune activation. Sci Rep. 2023;13(1):22424. doi: 10.1038/s41598-023-49789-5
69. Kayhan F, Gündüz Ş, Ersoy SA, et al. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res. 2017;247:332–335. doi: 10.1016/j.psychres.2016.11.016
70. Shan M, Yang Z, Sun Z, et al. Association between platelet to lymphocyte ratio and depression and symptom severity among adults in the United States: A cross-sectional study. Heliyon. 2023;9(9):e20127. doi: 10.1016/j.heliyon.2023.e20127
71. 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. doi: 10.3389/fpsyt.2020.581061
72. Abdel Samei AM, Mahmoud DAM, Salem Boshra B, Abd El Moneam MHE. The interplay between blood inflammatory markers, symptom domains, and severity of ADHD disorder in children. J Atten Disord. 2024;28(1):66–76. doi: 10.1177/10870547231197213
73. Mazza MG, Tringali AGM, Rossetti A, et al. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. Gen Hosp Psychiatry. 2019;58:7–12. doi: 10.1016/j.genhosppsych.2019.02.003
74. Fusar-Poli L, Natale A, Amerio A, et al. Neutrophil-to-lymphocyte, platelet-to-lymphocyte and monocyte-to-lymphocyte ratio in bipolar disorder. Brain Sci. 2021;11(1):58. doi: 10.3390/brainsci11010058
75. Özdin S, Böke Ö. Neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios in different stages of schizophrenia. Psychiatry Res. 2019;271:131–135. doi: 10.1016/j.psychres.2018.11.043
76. Ucuz İ, Kayhan Tetik B. Can suicide behavior and seasonality of suicide be predicted from inflammatory parameters in adolescents? Med Hypotheses. 2020;143:110061. doi: 10.1016/j.mehy.2020.110061
77. Puangsri P, Ninla-Aesong P. Potential usefulness of complete blood count parameters and inflammatory ratios as simple biomarkers of depression and suicide risk in drug-naive, adolescents with major depressive disorder. Psychiatry Res. 2021;305:114216. doi: 10.1016/j.psychres.2021.114216
78. Kumar K, Srivastava S, Sharma B, et al. Comparison between inflammatory biomarkers (high-sensitivity C-reactive protein and neutrophil-lymphocyte ratio) and psychological morbidity in suicide attempt survivors brought to medicine emergency. Cureus. 2021;13(8):e17459. doi: 10.7759/cureus.17459
79. Arango-Dávila CA, Rincón-Hoyos HG. Depressive disorder, anxiety disorder and chronic pain: Multiple manifestations of a common clinical and pathophysiological core. Rev Colomb Psiquiatr (Engl Ed). 2018;47(1):46–55. doi: 10.1016/j.rcp.2016.10.007
80. Perry BI, Upthegrove R, Kappelmann N, et al. Associations of immunological proteins/traits with schizophrenia, major depression and bipolar disorder: A bi-directional two-sample mendelian randomization study. Brain Behav Immun. 2021;97:176–185. doi: 10.1016/j.bbi.2021.07.009
81. Saccaro LF, Gasparini S, Rutigliano G. Applications of Mendelian randomization in psychiatry: a comprehensive systematic review. Psychiatr Genet. 2022;32(6):199–213. doi: 10.1097/YPG.0000000000000327
82. Brinn A, Stone J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. BMJ Open. 2020;10(7):e036859. doi: 10.1136/bmjopen-2020-036859
83. Bauer ME, Teixeira AL. Inflammation in psychiatric disorders: what comes first? Ann N Y Acad Sci. 2019;1437(1):57–67. doi: 10.1111/nyas.13712
84. Khalfallah O, Barbosa S, Martinuzzi E, et al. Monitoring inflammation in psychiatry: Caveats and advice. Eur Neuropsychopharmacol. 2022;54:126–135. doi: 10.1016/j.euroneuro.2021.09.003
85. Adzic M, Brkic Z, Mitic M, et al. Therapeutic strategies for treatment of inflammation-related depression. Curr Neuropharmacol. 2018;16(2):176–209. doi: 10.2174/1570159X15666170828163048
86. Decker K, Murata S, Baig N, et al. Utilizing the systemic immune-inflammation index and blood-based biomarkers in association with treatment responsiveness amongst patients with treatment-resistant bipolar depression. J Pers Med. 2023;13(8):1245. doi: 10.3390/jpm13081245
87. Murata S, Baig N, Decker K, Halaris A. Systemic inflammatory response index (SIRI) at baseline predicts clinical response for a subset of treatment-resistant bipolar depressed patients. J Pers Med. 2023;13(9):1408. doi: 10.3390/jpm13091408
88. Vos CF, Birkenhäger TK, Nolen WA, et al. Association of the neutrophil to lymphocyte ratio and white blood cell count with response to pharmacotherapy in unipolar psychotic depression: An exploratory analysis. Brain Behav Immun Health. 2021;16:100319. doi: 10.1016/j.bbih.2021.100319
89. Llorca-Bofí V, Palacios-Garrán R, Rey Routo D, et al. High neutrophil-lymphocyte ratio upon admission is associated with better response in psychotic depression. J Psychiatr Res. 2021;143:38–42. doi: 10.1016/j.jpsychires.2021.08.021

90. Labonté C, Zhand N, Park A, Harvey PD. Complete blood count inflammatory markers in treatment-resistant schizophrenia: Evidence of association between treatment responsiveness and levels of inflammation. Psychiatry Res. 2022;308:114382. doi: 10.1016/j.psychres.2021.114382
91. Llorca-Bofí V, Bioque M, Madero S, et al. Blood cell count ratios at baseline are associated with initial clinical response to clozapine in treatment-resistant, clozapine-naïve, schizophrenia-spectrum disorder. Pharmacopsychiatry. 2024. doi: 10.1055/a-2290-6386
92. Ninla-Aesong P, Puangsri P, Kietdumrongwong P, et al. Being overweight and obese increases suicide risk, the severity of depression, and the inflammatory response in adolescents with major depressive disorders. Front Immunol. 2023;14:1197775. doi: 10.3389/fimmu.2023.1197775
93. 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(7):509–512. doi: 10.1080/08039488.2017.1340517
94. Bulut NS, 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;75(8):624–632. doi: 10.1080/08039488.2021.1919201
95. Wei Y, Feng J, Ma J, et al. Characteristics of platelet-associated parameters and their predictive values in Chinese patients with affective disorders. BMC Psychiatry. 2022;22(1):150. doi: 10.1186/s12888-022-03775-9
96. Vancampfort D, Stubbs B, Mitchell AJ, et al. Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. World Psychiatry. 2015;14(3):339–347. doi: 10.1002/wps.20252
97. Penninx BWJH, Lange SMM. Metabolic syndrome in psychiatric patients: Overview, mechanisms, and implications. Dialogues Clin Neurosci. 2018;20(1):63–73. doi: 10.31887/DCNS.2018.20.1/bpenninx
98. Silveira Rossi JL, Barbalho SM, Reverete de Araujo R, et al. Metabolic syndrome and cardiovascular diseases: Going beyond traditional risk factors. Diabetes Metab Res Rev. 2022;38(3):e3502. doi: 10.1002/dmrr.3502
99. Chakraborty S, Verma A, Garg R, et al. Cardiometabolic risk factors associated with type 2 diabetes mellitus: A mechanistic insight. Clin Med Insights Endocrinol Diabetes. 2023;16:11795514231220780. doi: 10.1177/11795514231220780
100. Suggett J, Foster K, Lakra V, et al. Natural cause mortality of mental health consumers: A 10-year retrospective cohort study. Int J Ment Health Nurs. 2021;30(2):390–400. doi: 10.1111/inm.12797
101. Minhas S, Patel JR, Malik M, et al. Mind-body connection: Cardiovascular sequelae of psychiatric illness. Curr Probl Cardiol. 2022;47(10):100959. doi: 10.1016/j.cpcardiol.2021.100959