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Review Article

The Correlation of Blood Immune Cells with the Pathogenesis of Schizophrenia: A Meta-Analysis

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Abstract

Background: We have included literature on changes in immune cells in patients with schizophrenia and have systematically and quantitatively reviewed these studies through meta-analysis, with a view to understanding the potential effects of immune system dysfunction on the pathophysiology of schizophrenia.

Methods: We conducted a systematic search in PubMed, Embase, Web of Science, and the Cochrane Library, covering publications from inception to Sep 25, 2023. The systematic review followed the PRISMA guidelines, and a random-effects meta-analysis was performed. Heterogeneity was evaluated using the I^2 index, and sensitivity analyses were conducted to assess the stability of the findings.

Results: The systematic review includes 42 studies on schizophrenia. Meta-analysis revealed that compared to the control group, schizophrenia patients had significantly higher white blood cell counts (WBC, $P<0.01$), CD4 absolute values ($P=0.02$), CD4 percentage (CD4%, $P=0.05$), CD4/CD8 ratio ($P<0.01$), monocyte-to-lymphocyte ratio (MLR, $P<0.01$), neutrophil-to-lymphocyte ratio (NLR, $P<0.01$), and platelet-to-lymphocyte ratio (PLR, $P<0.01$). No significant differences were observed for other immune markers in the meta-analysis.

Conclusion: The number of immune cells in the blood of patients with schizophrenia increased. Therefore, more research on immune system abnormalities in schizophrenia patients is needed to better understand the underlying mechanisms between schizophrenia and immune cell parameters.

Keywords: Schizophrenia; White blood cells; Meta-analysis; Immune cells; Systematic review

Introduction

Schizophrenia (SCZ) is a severe mental disorder with a relatively low incidence; however, it imposes a substantial social and economic burden. Although the global prevalence is only 1% and the incidence rate is about 1.5/10000, the disease burden is huge, and WHO ranks it as a top 10 disease contributing to the global disease burden (1-3). The disease can easily lead to disability and impose a huge economic burden. The excess direct medical costs of schizophrenia were $37.7 billion, direct non-medical costs were $9.3 billion, and indirect costs were $117.3 billion, for a total

economic burden expenditure of $155.7 billion (4). The clinical symptoms of schizophrenia are complex and varied between individuals, and may have positive symptoms such as delusions, hallucinations, and thought disorders, or negative symptoms such as pleasure deficits, depression, social withdrawal, poor thinking, or cognitive dysfunction (5). The main risk age range is 20-35 yr old, and the disease rarely occurs in early childhood and old age (after 45 yr old); On average, the onset of women is 3 to 4 yr later than that of men, therefore, late-onset schizophrenia of women is more frequent and more serious than that of men. There is no difference in the types and core symptoms between genders (6).

The exact etiology and pathogenesis of schizophrenia are not clear, but it is generally understood that it is the result of the comprehensive action of genetic, neurological, chemical and environmental factors. In recent years, an increasing number of studies have focused on the immunopathological mechanisms of schizophrenia, suggesting that immune dysfunction may play a crucial role in its pathogenesis. Although the research on the immune system abnormalities of schizophrenic patients has a history of several decades, it has recently become a hot spot. At least part of this interest is due to our growing understanding of how the immune system and other chronic diseases interact in the brain (7). Advances in genetics lead to greater confirmation of association between immune system-regulating genes and increased risk of schizophrenia (8). Furthermore, epidemiological studies have indicated that factors such as viral infections, autoimmune diseases, and chronic inflammation may be associated with the onset of schizophrenia (9-11). There are immune abnormalities in the blood, cerebrospinal fluid (CSF) and central nervous system (CNS) of schizophrenic patients, including the number of immune cell, inflammatory markers, oxidative stress and antibody titers (12).

Although numerous studies support the presence of immune dysfunction in patients with schizophrenia, the findings are not entirely consistent and exhibit considerable heterogeneity. This heterogeneity may arise from various factors, including study methodologies, sample selection, disease stages, comorbidities, and different experimental techniques. For example, some studies have reported elevated white blood cell counts in patients with schizophrenia, while others have found no significant differences (13, 14). Moreover, immune indicators such as T-cell subsets, neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR) have shown considerable variability across different studies. The inconsistency in these findings makes it challenging to draw definitive conclusions. Therefore, further integration of existing research data is needed to achieve a more systematic understanding of immune dysfunction in schizophrenia. To gain a more comprehensive understanding of the role of the immune system in the pathogenesis of schizophrenia, this study conducted a systematic and quantitative review to summarize and evaluate existing evidence on immune cell alterations in patients with schizophrenia. Building on this, we further performed a meta-analysis to quantify the association between immune cell abnormalities and schizophrenia and to assess their potential pathophysiological significance.

Materials and Methods

This meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(15).

Search Method

We systematically reviewed the literature research on blood immune cells of schizophrenia patients in PubMed, Embase, Web of Science and Cochrane Library. Search time range from inception through Sep 25, 2023. For a comprehensive and systematic literature search, we used controlled vocabulary and free text terms. In order to conduct a comprehensive and systematic literature search, we used controlled vocabulary and free-text terminology. The search uses the Boolean operators "AND" and "OR" to combine the following terms: “white blood

cell"OR"WBC"OR"Neutrophil"OR"Lymphocyte "OR"Eosinophil"OR"Basophil"OR "PMN"AND"Schizophrenic"OR"Schizophrenias "OR"Schizophrenic Disorders"OR "Disorder,Schizophrenic"OR"Disorders,Schizophrenic" OR"Schizophrenic Disorder"OR "Schizophrenia". In addition to checking the titles of the articles, we also checked conference proceedings, abstracts, full texts, and reference lists of articles, etc., hoping to find as many articles as possible that met the inclusion and exclusion criteria. We had all articles reviewed by two collaborators, and data disagreements were resolved by discussion.

Selection criteria

Studies that met all the following inclusion criteria are considered as eligible for inclusion: 1) Subjects were schizophrenia or non-affective psychotic patients (including schizophrenia, schizoaffective disorder, delusional disorder, schizophrenia-like disorder, transient psychotic disorder, and psychotic disorders not otherwise specified) and healthy people; 2) The clinical status of the patients was clearly defined as: acute relapse inpatient (AR), first-episode psychosis (FEP), and inpatient; 3) The literature reports data on immune cell counts in patients with schizophrenia and healthy controls; 4) The mean and standard deviation (SD) in the literature can be extracted directly or indirectly. The following papers were excluded: 1) Studies without a control group (except for studies in which immune cells were measured serially in patients with acute exacerbations) ; 2) Studies that did not provide the mean and standard deviation of immune cells after trying to contact the authors; 3) Studies with significantly overlapping populations, with the same patients or control groups in multiple publications, are considered overlapping studies; 4) Genetic study of peripheral blood immune cells; 5) Studies in which more than 20% of patients in the study were taking clozapine; 6) More than 20% of the patients in the study were on drug treatment studies; 7) Some special types of literature such as literature reviews, conference abstracts, animal experiments and case reports.

Data extraction and processing

A data extraction table was designed in advance before data extraction, and two researchers independently extracted data that met the inclusion and exclusion criteria. For the lack of information in the literature, try to supplement it by contacting the author by email.

The research included in this meta-analysis is case-control study and cross-sectional study, so the Newcastle-Ottawa Quality Assessment Scale (NOS) and Agency for Healthcare Research and Quality (AHRQ) were used for quality assessment (13). The quality of the literature was independently assessed by 2 researchers based on the NOS and AHRQ, and consensus was reached through deliberation when disagreements were reached. In order to ensure the high quality of the analysis of this study, we choose that the NOS score of all case-control studies should be greater than or equal to 6, and the AHRQ score of all cross-sectional studies should be greater than or equal to 8 (Table 1).

Statistical analysis

The purpose of this study was to evaluate the difference in blood immune cell counts between schizophrenia patients and healthy controls. Meanwhile, the standardized mean difference (SMD) and SD were selected as the effect sizes of continuous variables (16). We used the Cochrane Q test and the I^2(defined as significant when $P<0.05$ or $I^2> 75\%$) test to assess the heterogeneity included in the studies(17, 18). Analyze heterogeneity by sensitivity analysis and subgroups. For studies that met the inclusion and exclusion criteria, subgroup analyses were performed according to patients' clinical status (FEP and inpatient) and type of study (case-control study and cross-sectional study). Publication bias was assessed by visual inspection of Begg's funnel plot and Egger's test, and corrected by trim and filling method (19, 20). All statistical analyses in this meta-analysis were performed using R 4.1.2, and $P<0.05$ was considered statistically significant.

Results

Literature search and basic characteristics of included studies

We initially retrieved 3135 articles. After multiple rounds of screening, 42 articles finally met the inclusion and exclusion criteria. The literature screening process is shown in Fig. 1. Table 1 shows the basic characteristics of the 42 included studies. The 42 studies included 23224 patients with schizophrenia and 14998 controls. The included studies involved both male and female subjects, with different male-female ratios. The average age of the subjects in each study ranged from 10 to 65 yr. All studies were observational studies, including 33 case-control studies and 9 cross-sectional studies.

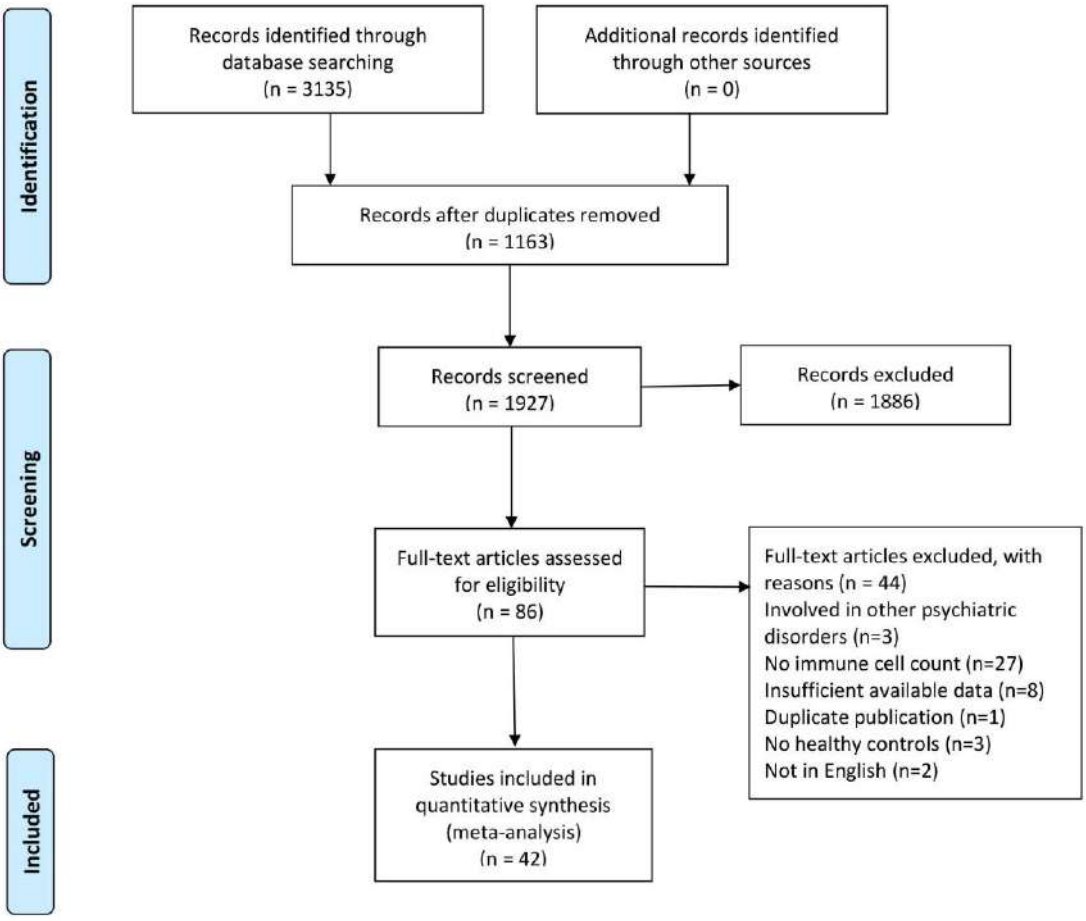

Fig. 1: Flow diagram of literature search and study selection

Table 1: The characteristics of included studies

Author, Year	Country	SCZ/CTL	Cell Subsets	Clinical Status	Psychotropics(Y/N)	Scoring Result (NOS/AHRQ)
Özdin S(21),2017	Turkey	163/157	NLR;MLR;NEU;LYM;MONO;PLR	inpatient	Y	7
Steiner J(22),2010	Germany	26/32	CD3;CD4;CD19;	inpatient	N	8
Achiron A(23),1994	Israel	16/16	LYM;CD4;CD8	inpatient	N	8
Baskak SC(24),2008	Turkey	14/14	CD3;CD4;CD8;CD4/CD8	inpatient	N	9
Carlton E(25),2021	America	86/86	MONO;LYM	inpatient	Y	6
Ganguli R(26),1993	America	116/166	CD19;CD5;CD5%	inpatient	Y	8
Henneberg A(27),1990	Germany	18/18	CD4%;CD8%CD4/CD8	inpatient	N	7
Maino K(28),2007	Germany	40/20	CD3%;CD19%	inpatient	N	7
Masserini C(29),1990	Italy	9/37	LYM;CD3;CD3%;CD4;CD4%;CD19;CD19%	FEP	N	7
Müller N(30),1911	Germany	51/38	CD3;CD3%;CD4;CD4%;CD8;CD8%;CD4/CD8	inpatient	N	6
Nyland H(31),1980	Norway	27/30	LYM;CD19;CD19%	inpatient	Y	6
Rudolf S(32),2004	Germany	31/31	LYM;CD3;CD3%;CD4;CD4%;CD8;CD8%; CD4/CD8; CD19;CD19%;	inpatient	Y	6
Sasaki T(33),1994	Japan	14/20	WBC;LYM%;CD3%;CD4%;CD8%; CD4/CD8	inpatient	Y	7
Sperner-Unterweger B(34),1999	Austria	21/16	LYM;CD3;CD4;CD8; CD4/CD8	FEP	N	6
Theodoropoulou S(35),2001	Greece	53/60	CD3%	FEP	N	7
Orhan F(36),2018	Sweden	42/21	MONO;LYM;NEU;EOS	FEP	N	8
Kulaksizoglu B(37),2016	Turkey	64/61	NLR	inpatient	Y	7
Bustan Y(13),2018	Israel	20/20	WBC;NLR	inpatient	Y	8
Chang SH(14),2011	China	46/22	WBC;LYM	inpatient	Y	7
Núñez C(38),2019	Spain	137/81	NEU;EOS;BASO;LYM;MONO	FEP	Y	9
Printz DJ(39),1999	America	29/30	CD5;CD5%;LYM; CD19;CD19%;CD3;CD3%;CD4%;CD8%;CD4/CD8	inpatient	Y	9
Schleifer SJ(40),1985	America	15/15	LYM;CD19;CD19%CD3;CD3%	inpatient	Y	6
Kelly DL(41),2018	America	26/17	WBC;NEU;LYM;MONO;EOS;BASO	inpatient	Y	7
Semiz M(42),2014	Turkey	156/89	WBC;NLR	inpatient	Y	9
Garcia-Rizo	Spain	75/80	WBC;NEU;LYM;NLR;BASO;EOS;BASO	FEP	N	8

Table 1: Continued...

C(43),2019						
Moody G(44),2017	America	25/44	WBC;NEU;LYM;MONO;NLR;MLR	FEP	N	9
Yüksel RN(45),2018	Turkey	52/53	NEU;LYM;MONO;EOS;NLR	inpa-tient	Y	8
Miller BJ(46),2015	108/44	case-control study	WBC;NEU;LYM;MONO	inpatient	Y	8
Pavlović M(47),2016	100/100	cross-sectional study	NEU;EOS;BASO;LYM;MONO;NLR	inpatient	Y	9
Yu Q(48),2020	82/120	case-control study	NLR;MLR;PLR	FEP	N	8
Rabin BS(49),1988	48/36	case-control study	LYM;CD8%;CD4/CD8;CD4%	inpatient	Y	6
Wilke I(50),1996	51/39	case-control study	MONO;NEU;CD4%;CD8%	inpatient	Y	8
Balcioglu YH(51),2020	439/445	cross-sectional study	NLR;MLR	inpatient	Y	9
Kronfol Z(52),1988	22/37	case-control study	WBC;NLR	FEP	N	9
Necati(53),2021	91/95	cross-sectional study	NLR	inpatient	Y	
Ali İNAL-TEKİN(54),2023	88/66	case-control study	WBC;LYM;MEU;MONO;NLR;MLR;PLR	inpatient	Y	8
Nülüfer(55),2023	85/50	case-control study	WBC;NEU;LYM;MONO;EOS;BASO	inpatient	Y	8
Cigdem(56),2020	40/40	cross-sectional study	MONO	inpatient	Y	10
Musa(57),2022	37/43	case-control study	WBC;LYM;NEU;NLR	FEP	N	8
Yan-yan(58),2022	13329/5810	cross-sectional study	NEU;LYM;MONO	inpatient	Y	8
Haiting(59),2022	6937/6404	cross-sectional study	WBC;LYM:NEU;MONO;NLR;MLR;PLR	inpatient	Y	9
Xiaoyu(60),2021	395/395	cross-sectional study	LYM;NEU;MONO;NLR;MLR;PLR	inpatient	Y	7

Abbreviations: SCZ, schizophrenia; CTL, control; FEP, first-episode psychosis; WBC, white blood cell; NEU, neutrophils; LYM, lymphocytes; MONO, monocytes; BASO, basophils; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

White Blood Cell

Compared with the control group, the WBC (SMD = 0.27, 95% CI: 0.15–0.39, $P < 0.01$, I^2=50%) of schizophrenic patients in 14 studies was significantly higher (Fig. 2 and Table 2).

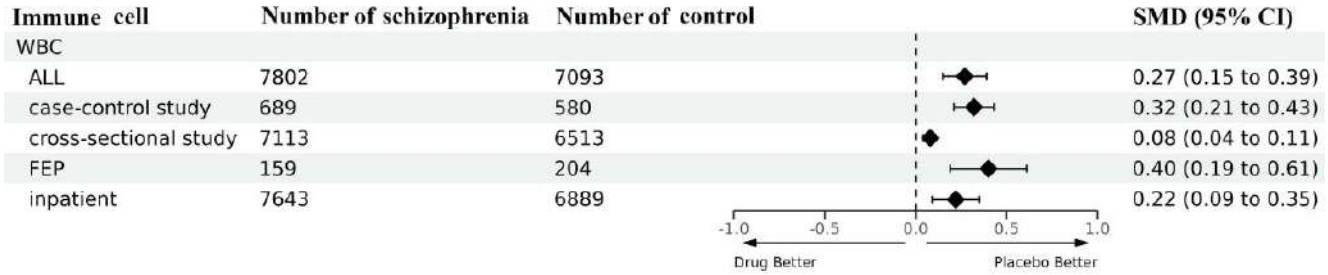

Fig. 2: Results of meta-analysis of white blood cells between schizophrenia and control group

Table 2: A meta-analysis of blood immune cell counts in patients with schizophrenia

Variables	Number of Study	All Subjects	Control	Association test			Heterogeneity test		Publication bias
				SMD	95%CI	*P*-value	I^2 (%)	*P*-value	*P*-value
Lymphocyte	28	21976	13751	0.22	-0.44-0.87	0.52	100	0	0.34
Basophils	6	454	359	0.02	-0.28-0.32	0.91	76	<0.01	0.55
Eosinophils	9	548	433	0.04	-0.09-0.17	0.55	0	0.47	0.19
Monocytes	18	21770	13518	2.26	-0.24-4.76	0.08	100	0	0.34
Neutrophils	17	21735	13454	1.58	-0.85-4.01	0.21	100	0	0.39
WBC	14	7802	7093	0.27	0.15-0.39	<0.01	50	0.01	<0.01
MLR	7	8129	7631	0.88	0.47-1.28	<0.01	98	<0.01	0.22
NLR	15	8788	8233	0.96	0.67-1.25	<0.01	97	<0.01	<0.01
PLR	5	7665	7142	1.20	0.47-1.92	<0.01	99	<0.01	0.10
CD3	8	196	213	0.35	-0.06-0.76	0.09	74	<0.01	0.45
CD3%	8	242	251	-0.01	-0.42-0.40	0.95	78	<0.01	0.62
CD4	7	160	170	0.27	0.04-0.50	0.02	49	0.07	0.98
CD4%	9	273	286	0.17	0 -0.34	0.05	28	0.20	0.86
CD4/CD8	9	248	240	0.38	0.19-0.56	<0.01	34	0.15	0.87
CD5	2	145	196	0.22	-0.41-0.85	0.49	79	0.03	
CD5%	2	145	196	0.10	-0.73-0.92	0.82	88	<0.01	
CD8	6	142	152	0.17	-0.26-0.60	0.44	67	0.01	0.46
CD8%	9	273	286	-0.08	-0.25-0.09	0.62	44	0.08	0.19
CD19	7	253	341	0.06	-0.61-0.73	0.87	92	<0.01	0.98
CD19%	6	253	341	0.06	-0.61-0.73	0.87	92	<0.01	0.98

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SMD, standardized mean difference; 95% CI, 95% confidence interval.

Diamonds represent the size of the aggregation effect, each diamond represents the standard mean difference, and the horizontal line running through each diamond illustrates the width of the 95% CI. WBC, white blood cell; FEP, first-episode psychosis; SMD, standardized mean difference.

Granulocyte

The neutrophil level in schizophrenia patients in the 17 studies showed an increased trend compared with the control group (SMD = 1.58, 95% CI: -0.85-4.01, *P*=0.21, I^2 =100%). Compared with the control group, the eosinophils of schizophrenia patients in the 9 studies did not change (SMD=0.04, 95% CI: -0.09–0.17, *P*=0.55, I^2=0). For basophils in 6 studies, no differences between schizophrenia patients and controls were observed (SMD = 0.02, 95% CI: -0.28–0.32, *P*=0.91, I^2=76%) (Fig. 3 and Table 2).

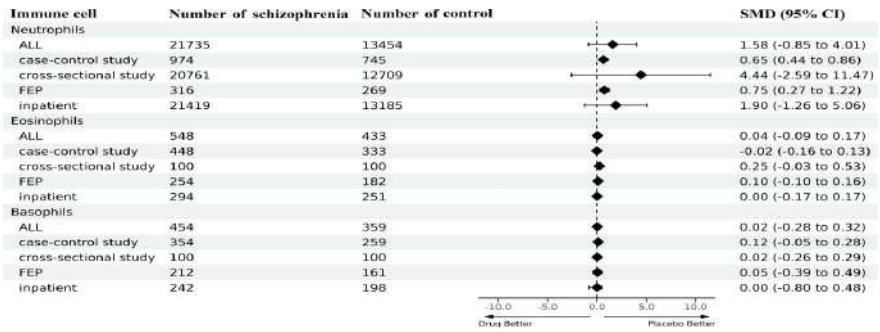

Fig. 3: Results of meta-analysis of granulocyte between schizophrenia and control group

Diamonds represent the size of the aggregation effect, each diamond represents the standard mean difference, and the horizontal line running through each diamond illustrates the width of the 95% CI. FEP, first-episode psychosis; SMD, standardized mean difference.

Lymphocyte

For lymphocytes in 28 studies, an increased level of schizophrenia was observed in this study (SMD=0.22, 95% CI: -0.44–0.87, *P*=0.52, I^2=100%). For the absolute values of CD3 in 8 studies, no differences were observed between schizophrenia patients and controls (SMD = 0.35, 95% CI: -0.06–0.76, *P*=0.09, I^2 = 74%). There was no significant change in the CD3 ratio (CD3%) level in schizophrenia patients in the 8 studies (SMD=-0.01, 95%CI:-0.42–0.40, *P*=0.95, I^2=78%). The absolute CD4 value of schizophrenia patients in 7 studies showed an upward trend compared with the control group (SMD=0.27, 95%CI:0.04-0.50, *P*=0.02, I^2 = 49%). In terms of CD4 percentage (CD4%) in 9 studies, there was a significant increase in schizophrenia patients compared with the control group (SMD=0.17, 95%CI: 0.00-0.34, *P*=0.05, I^2=28%). The CD4/CD8 ratio of schizophrenia patients in the 9 studies showed an increasing trend compared with the control group (SMD=0.38, 95%CI: 0.19-0.56, *P*<0.01, I^2=34%). There was no change in the absolute value of CD8 in schizophrenia patients in the 6 studies (SMD = 0.17, 95% CI: -0.26–0.60, *P* = 0.44, I^2=67%). As for the percentage of CD8 (CD8%) in the 9 studies, this study did not observe any difference between schizophrenia patients and controls (SMD = -0.08, 95% CI: -0.25–0.09, *P* = 0.62, I^2=44%). Compared with the control group, the absolute level of CD5 in schizophrenia group in 2 studies did not change (SMD = 0.22, 95% CI: -0.41–0.85, *P* = 0.49, I^2=79%). The level of CD5 percentage (CD5%) in schizophrenic patients in 2 studies did not change significantly (SMD = 0.10, 95% CI: -0.73–0.92, *P* = 0.82, I^2=88%). The absolute level of CD19 in schizophrenic patients in 7 studies did not change significantly (SMD = 0.06, 95% CI: -0.61–0.73, *P* =0.87, I^2=92%). Compared with the control group, the level of CD19 percentage (CD19%) in schizophrenia group in 6 studies has not changed (SMD = 0.06, 95% CI: -0.61–0.73, *P* =0.87, I^2=92%) (Fig. 4 and Table 2).

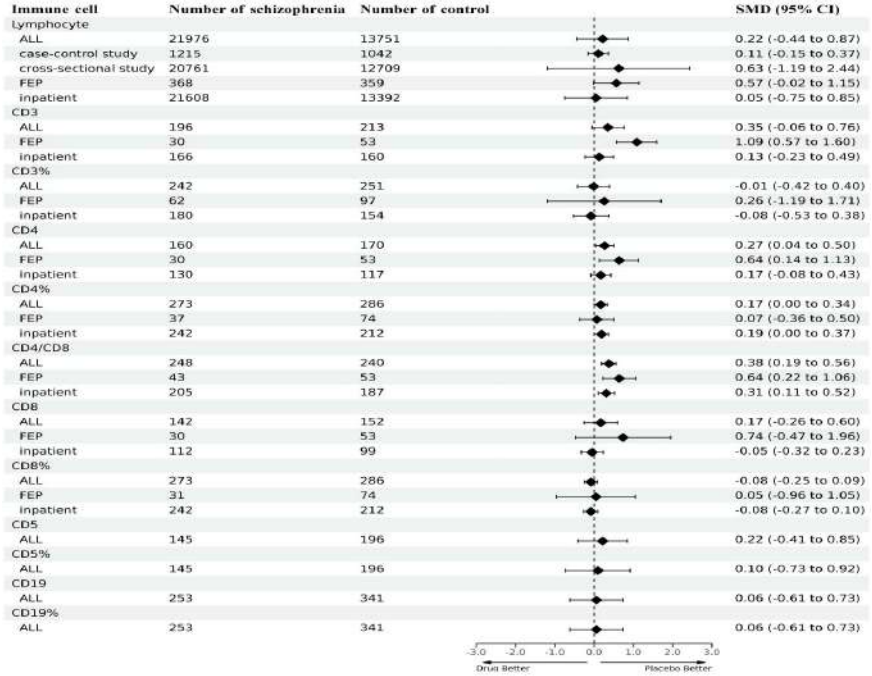

Fig. 4: Results of meta-analysis of lymphocyte between schizophrenia and control group

Diamonds represent the size of the aggregation effect, each diamond represents the standard mean difference, and the horizontal line running through each diamond illustrates the width of the 95% CI. FEP, first-episode psychosis; SMD, standardized mean difference.

Monocytes

This study observed no significant difference in monocyte levels between schizophrenia patients and controls in 18 studies (SMD = 2.26, 95% CI: -0.24–4.76, P=0.08, I^2=100%) (Fig. 5 and Table 1).

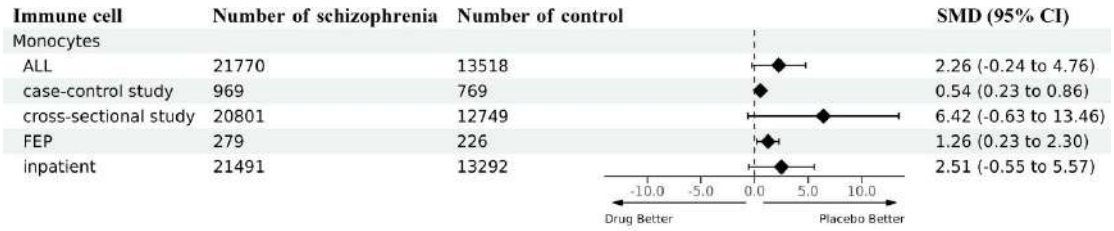

Fig. 5: Results of meta-analysis of monocytes between schizophrenia and control group

Diamonds represent the size of the aggregation effect, each diamond represents the standard mean difference, and the horizontal line running through each diamond illustrates the width of the 95% CI. FEP, first-episode psychosis; SMD, standardized mean difference.

NLR, MLR and PLR

The MLR of schizophrenia in 7 studies showed an increasing trend compared with the control group (SMD = 0.88, 95% CI: 0.47–1.28, P<0.01, I^2=98%). Compared with the control group, the NLR of schizophrenic patients in 15 studies was significantly higher (SMD = 0.96, 95% CI: 0.67–1.25, P<0.01, I^2=97%). Compared with the control group, the PLR of schizophrenic patients in 5 studies was significantly higher (SMD = 1.20, 95% CI: 0.47–1.92, P<0.01, I^2=99%) (Fig. 6 and Table 1).

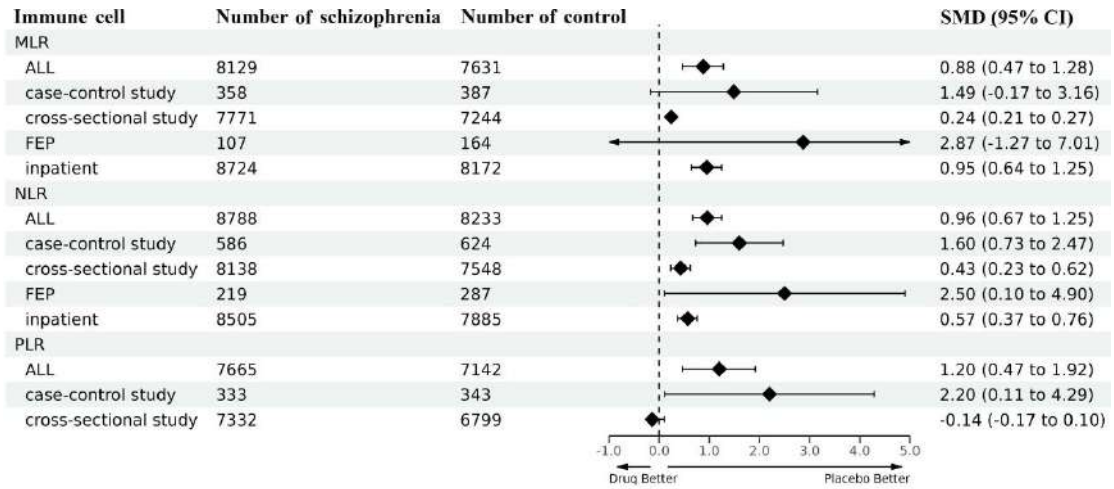

Fig. 6: Results of meta-analysis of NLR, MLR and PLR between schizophrenia and control group

Diamonds represent the size of the aggregation effect, each diamond represents the standard mean difference, and the horizontal line running through each diamond illustrates the width of the 95% CI. FEP, first-episode psychosis; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-

lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SMD, standardized mean difference.

Publication bias

In terms of funnel plot visualization and Egger's test (Supplementary Figs. 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 40 and Table 2), there was no evidence of publication bias in lymphocytes, basophils, eosinophils, monocytes, neutrophils, MLR, PLR, CD3, CD3%, CD4, CD4%, CD4/CD8, CD5, CD5%, CD8, CD8%, CD19, CD19%. There was asymmetry in the WBC funnel plot, and the Egger's test tended to publish studies with larger effect sizes (Supplementary Fig. 2 and Table 2). There was asymmetry in the NLR funnel plot, and the Egger's test tended to publish studies with smaller effect sizes (Supplementary Fig. 38 and Table 2).

Discussion

This meta-analysis summarizes studies on peripheral blood immune cell abnormalities in patients with schizophrenia. The results indicate that compared to the control group, patients with schizophrenia exhibited significantly elevated levels of WBC, CD4, CD4%, CD4/CD8, MLR, NLR (P<0.01), and PLR. No significant differences were observed in other immune parameters. Subgroup analysis based on "type of study" revealed significant differences in neutrophils, monocytes, MLR, and PLR across different study designs, suggesting that variations in study design and experimental methods may influence immune cell count measurements. Additionally, subgroup analysis based on " patients' clinical status " indicated significant differences in CD4, CD4%, monocytes, and MLR at different disease stages, implying that immune cell counts may undergo dynamic changes as schizophrenia progresses.

The WBC count in patients with schizophrenia was significantly higher than that in healthy controls, a result consistent with the findings of Jackson AJ et al., suggesting that inflammation and the immune system may play a role in the pathophysiology of schizophrenia (61). Furthermore, the CD4, CD4%, and CD4/CD8 were significantly elevated in patients with schizophrenia, a finding supported by Miller BJ et al (62). The increased activation of $CD4^+$ T cells may reflect dysregulation of the immune system. This elevation in T cell counts may be associated with a state of chronic low-grade inflammation in schizophrenia, which in turn impacts neurotransmitter function and neuroinflammatory responses (63). Additionally, the observed increase in the CD4/CD8 may indicate immune system imbalance, characterized by a relative increase in $CD4^+$ T cells and a potential reduction or functional impairment of $CD8^+$ T cells (64). Similarly, this study found that MLR, NLR, and PLR were significantly elevated in patients with schizophrenia, suggesting that activation of the inflammatory response may play a crucial role in the onset and progression of the disease. Increased MLR may be associated with monocyte activation and an increased release of pro-inflammatory cytokines, reflecting abnormal immune regulation (65). Elevated NLR may indicate that patients are in a state of chronic low-grade inflammation, where increased neutrophils and decreased lymphocytes may affect neuroinflammation and neurotransmitter function (66). Increased PLR may suggest a potential role of platelets in immune imbalance in schizophrenia, given their ability to store and release neurotransmitters (such as serotonin and glutamate) and inflammatory mediators (such as IL-1 and TNF-α)(67).

This study has several limitations. First, some studies were excluded due to a lack of clinical status information or detailed immune parameter data, and the specific impact of these exclusions on the results remains unclear. Second, many studies did not control for potential confounding factors, such as age, sex, body mass index (BMI), and smoking status, which may contribute to variations in immune cell parameters across different populations. Additionally, the immune profiles of hospitalized patients may be influenced by antipsychotic medications. Although some studies reported that participants were drug-naïve, the

lack of stratified data prevented us from assessing the specific effects of medication use.

Conclusion

This study found that peripheral blood immune cell parameters were significantly elevated in patients with schizophrenia, suggesting that the immune system may play a crucial role in the onset and progression of the disease. Schizophrenia is characterized by recurrent episodes, cognitive decline, and persistent negative symptoms, future studies should further investigate the specificity of immune cell abnormalities and their potential as biomarkers for disease relapse. Moreover, it is essential to evaluate the relationship between immune cell parameters and clinical characteristics to gain a deeper understanding of the underlying mechanisms of schizophrenia and explore their potential applications in etiology, pathophysiology, and clinical diagnosis and treatment.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflicts of Interest

The authors declare no conflict of interest.

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