Neutrophil-to-lymphocyte ratio exhibits the different correlation with psychiatric symptoms in the different status of antipsychotic therapy in schizophrenia: a large-scale retrospective cross-sectional study.

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Research article

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Abstract

Background There are some conflicting results regarding the neutrophil-to-lymphocyte ratio (NLR) and the severity of disease in patients with schizophrenia. Inconsistent findings among the studies might be caused by several limitations, such as, heterogeneous patient populations lacking stratification by antipsychotic therapy, small sample sizes lacking statistical power, ignoring multicollinearity between NLR and other related factors, and lack of controlling for potential confounding factors. In this study, we evaluated the possible correlation between NLR and disease severity as manifested in clinical scores in patients with schizophrenia. In particular, NLR is correlated with discrepant psychiatric symptoms in the different status of antipsychotic medication administration.

Methods This was a cross-sectional study conducted in our hospital. We identified inpatients with schizophrenia between July 12, 2018 and March 27, 2019 and who had NLR, Clinical Global Impression Severity scale (CGIS) and Brief Psychiatric Rating Scale (BPRS) scores.

Results The records of 1144 identified patients (32.4% male, 76.6% with NLR $\leq$ 1.98, and 10.8% drug-free patients) were analyzed. Multivariate logistic regression showed that NLR was positively associated with worse psychiatric symptoms, both the CGIS score (moderately ill: OR: 63.578, p = 0.011; severely ill: OR: 53.617, p = 0.015) and the BPRS total score (moderately ill: OR: 4.049, p = 0.055; severely ill: OR: 4.312, p = 0.045). In the drug-therapy subgroup, there was a negative correlation between NLR and severe negative symptoms (severely ill: OR: 0.850, p = 0.018) after controlling for potential confounding factors.

Conclusions The study is the first to confirm the hypothesis that NLR is independently associated with severe psychopathology in schizophrenia. There is the different correlation between NLR and psychiatric symptoms in the different status of antipsychotic therapy. Therefore, NLR is not appropriate to be an inflammatory biomarker for assessment of disease severity, but provide potential mechanistic insights on specific pathological cellular processes, as well be a potential target to improve the course of the psychotic disorder.

Background

Schizophrenia is a complex and multifactorial mental disorder mainly characterized by a wide scope of psychotic symptomatology, such as anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behavior, motor retardation, unusual thought content, blunted affect, and excitement[1].Though established biological mechanisms, immune system abnormalities in schizophrenia have been one of the more enduring findings in the field. A growing body of evidence supports that the existence of central and peripheral immune and inflammatory biomarker alterations in numerous neuropsychiatric conditions[2]. Nevertheless, not many researches have been conducted on which alterations of immunological biomarker, such as immune cells may affect schizophrenic symptoms.

Abnormality of immune cells in circulation may be involved in schizophrenia [3, 4]. For example, the white blood cells (WBCs, leucocytes) that form the peripheral immune system and are crucial in inflammatory processes were initially found to have abnormal changes in patients with schizophrenic over half of a century ago [5, 6]. Significant correlation were found between WBCs (log transformed) and the BPRS (the Brief Psychiatric Rating Scale) total score ($r = 0.18$, $p = 0.014$), negative symptoms score ($r = 0.15$, $p = 0.039$) as well as anxious depression factor score ($r = 0.21$, $p = 0.004$) in antipsychotic- naïve patients with non-affective psychosis after potential confounding variables were taken into consideration [7]. Thus far, it was observed that there were possible differences between normal and schizophrenic subjects in the levels of subtypes of leukocytes, such as neutrophils and lymphocytes. Neutrophil count was described to be increased in schizophrenia [8, 9]. A study reported that neutrophil count was associated with the total PANSS (the Positive and Negative Syndrome Scale) score ($\beta = 0.173$, $p = 0.038$) in first-episode psychosis[10]. These results were not replicated in the study of Garcia-Rizo et al [11]. Concerning lymphocytes, a meta-analysis noted that absolute levels of total lymphocytes were significantly increased in drug-naïve first-episode psychosis [12], but there was no report of the association of peripheral lymphocytes with psychiatric symptoms. Thus, despite both of these factors may aggravate the severity of disease; the two factors have few pronounced results about their association with psychiatric symptoms.

The neutrophil-to-lymphocyte ratio (NLR) has received more attention, as it is an easily measured, reproducible, and inexpensive marker of systemic inflammation. NLR may reflect the combined prognostic information of neutrophils and lymphocytes. A meta-analysis of eight studies (including 683 patients and 551 healthy controls) showed that subjects with non-affective psychosis had a significantly higher NLR and monocyte-to-lymphocyte ratio (MLR) compared with healthy controls [respectively, standardized mean difference (SMD) = 0.715; $p < 0.001$; $I^2 = 57.565\%$ and SMD = 0.417; $p = 0.001$; $I^2 = 65.754\%$][13]. Another meta-analysis of 10 studies (804 schizophrenia patients, 671 controls) found that NLR in patients with schizophrenia was increased, both in chronic disease and in first-episode psychosis[14]. However, several studies have reported controversial results about the association of NLR with psychotic symptomatology. Kulaksizoglu et al. documented the significantly positive relationship of the Positive and Negative Syndrome Scale (PANSS) total subscale and leukocytes and NLR[15]. In contrast, data from two studies provided some evidence that there was no significant relation between NLR values and disease severity as manifested in clinical scores [e.g., BPRS, PANSS, and the Clinical Global Impression Severity scale (CGI-S)] in patients with schizophrenia[16, 17]. Bustan et al. found consistent results in non-affective psychotic adolescent inpatients[18].

In fact, there are several limitations of the mentioned above studies, such as, heterogeneous patient populations lacking stratification by antipsychotics therapy, small sample sizes lacking statistical power, ignoring multicollinearity between NLR and other related factors, and lack of controlling for potential confounding factors. This study is therefore to perform a large-scale cross-sectional study to evaluate the possible correlation between NLR and disease severity in patients with schizophrenia when potential

confounding factors and their interactions are taken into consideration. In particular, NLR is correlated with discrepant psychiatric symptoms in the different status of antipsychotic medication administration.

Methods

Aim

Here, we verify first, whether higher NLR indeed aggravates the severity of disease as manifested in clinical scores (i.e. BPRS and CGIS); second, whether there is an association between NLR and psychiatric symptoms and their subscale including affect, positive symptoms, negative symptoms, resistance and activation; and third, whether NLR is correlated with discrepant psychiatric symptoms in the different status of antipsychotic medication administration, ultimately clarify and lead the hypotheses that NLR is independently associated with severe psychiatric symptoms in patients with schizophrenia.

Patients and Study design

We used data from patients with schizophrenia who had undergone a physical examination in Nanjing Medical University Affiliated Brain Hospital between July 12, 2018 and March 27, 2019. The inclusion criteria in the study were as follows: (1) inpatients with the diagnosis of schizophrenia, any subtype, as evaluated by two independent experienced psychiatrists according to the International Classification of Diseases (ICD10); and (2) patients with schizophrenia who had taken no antipsychotics or were off psychiatric medication for at least 1 month before blood sampling (the drug-free patients), as well as received antipsychotic therapy (the drug-therapy patients). All participants were Han Chinese. The exclusion criteria were as follows: (1) aged less than 18 or greater than 60 years; (2) has an ongoing hematologic, cardiovascular, hepatic, or renal disease; diabetes mellitus; hypertension; hyperlipidemia; systemic disorders known to be associated with immunological abnormalities; thyroid disease; acute infection; history of severe head injury and surgery; or malignancy; (3) currently pregnant or breastfeeding; (4) no data available for outcomes.

For all participants, the data of demographics and laboratory measurements including neutrophil and lymphocyte counts were noted retrospectively, and NLR was calculated from these. For inpatients with schizophrenia, we used the electronic medical record system of Nanjing Medical University Affiliated Brain Hospital to collect patients' clinical data including sex, age, medical diagnoses, age of illness onset, and illness duration. The BPRS was assessed by two independent experienced psychiatrists. For all laboratory measurements, laboratory personnel were blinded to clinical information. All data were collected by two independent observers, without any knowledge of this study. The study was based on data with routine clinical care and administration. All inpatients were nonsmokers and consumed no alcohol during hospitalization.

Brief Psychiatric Rating Scale (BPRS)

The symptoms of schizophrenia were assessed using the BPRS. The present version of the instrument contains 18 items that assess the following symptoms: somatic concern, anxiety, emotional withdrawal, conceptual disorganization, guilt feelings, tension, mannerisms and posturing, grandiosity, depressive mood, hostility, suspiciousness, hallucinatory behavior, motor retardation, uncooperativeness, unusual thought content, blunted affect, excitement, and disorientation. The items are administered by a clinician based on an 8-point scale ranging from 1 (not present) to 7 (extremely severe) with total scores ranging from 0 to 126, with the higher scores representing greater severity of symptoms [19]. The 18 items are composed of five subscale scores: affect (anxiety, guilt, depression, somatic), positive symptoms (unusual thought content, conceptual disorganization, hallucinatory behavior, grandiosity), negative symptoms (blunted affect, emotional withdrawal, motor retardation), resistance (hostility, uncooperativeness, suspiciousness), and activation (excitement, tension, mannerisms and posturing) [20]. The categories of the BPRS total score were classified as follows: 1-31 = not or mildly ill; 32-53 = moderately ill; and 54-126 = severely ill [21].

Clinical Global Impression Severity scale (CGIS)

The CGIS was also available for the evaluation of the severity of disease with the clinician's impression of the patient's current illness state, and ranged from 0 to 7, with the higher scores representing greater severity of disease [22].

Statistical analyses

The demographic and clinical characteristics of patients with schizophrenia were checked for data normality using the Shapiro-Wilk test. Descriptive analyses included the calculations of mean [standard deviation (SD)] or median [interquartile range (IQR)] for continuous variables, as appropriate, and frequencies and percentages for categorical variables. The demographic characteristics, blood count parameters, CGI-S and BPRS scores between patients with NLR $\leq$1.98 and >1.98 were compared with the chi-square test or the Fisher exact test for categorical variables, as appropriate, and the Kruskal-Wallis test for continuous variables. The cut-off point of 1.98 was referred to recommendation by Kulaksizoglu et al [23].

Using spearmen correlation coefficients, we assessed potential associations between NLR in a continuous fashion and BPRS scores, as well as other variables, such as age, sex, age of illness onset, illness duration, and antipsychotic administration. Sex [male (0) and female (1)] and antipsychotic administration [drug-free (0) and drug-therapy (1)] were denoted nominally; other variables were denoted in a continuous fashion. These analyses were undertaken for the total group, as well as across categories of antipsychotic administration subgroups.

Multivariate logistic regression analyses were used to evaluate the associations between NLR as a continuous independent variable and categorical dependent variables, including the CGIS score, the BPRS total score and the five subscale scores when other categorical and/or continuous independent variables such as sex, age, age of illness onset, illness duration, neutrophil count, lymphocyte count, antipsychotic

administration, and their interactions were taken into consideration. The categorical dependent variables were divided into trisections, with the first trisection serving as the referent category. The categories of the CGIS score and the five subscale scores were discriminated by ROC curve analysis. The sex and antipsychotic administration were categorical variables, with male sex and drug-therapy serving as the referent categories. After the logistic regression analysis of the whole study population, we conducted the logistic regression stratified by antipsychotic administration to further examine the possible association of NLR and the clinical manifestion. The model in the entire study population was constructed using forced entry of all co-variables, and other models in the subgroups were used entry stepwise elimination, including variables with $p < 0.10$. We used ORs [95% confidence intervals (CIs)] to report the results of logistic regression.

Before running the logistic regression analyses, the collinearity was checked by the variance inflation factor (VIF). The VIF values of greater than 2.5 were considered as high collinearity [24]. ROC curves were created by plotting the range of sensitivity and specificity pairs for the CGIS and BPRS subscale scores, with BPRS total score categories (the BPRS total: ≤ 31 vs. > 32 or ≤ 53 vs. > 54) as the classifier variable. To determine the threshold of the subscale scores, the Youden index was used to discriminate between patients (the BPRS total: > 32 or > 54) and controls (the BPRS total: ≤ 31 or ≤ 53). When the Youden index reached the maximum value, the corresponding CGIS and BPRS subscale scores were considered the optimum cut-off threshold. Then, the cut-off thresholds of the subscale scores were defined.

All *p* values were two-tailed. The significance level was set at 0.05. The statistical analyses were performed with the Statistical Package for Social Sciences (SPSS, version 19; IBM, Armonk, NY, USA).

Results

The data of the retrospective study were from Nanjing Medical University Affiliated Brain Hospital between July 12, 2018 and March 27, 2019. A total of 7164 patients were identified from the initial search. The study inclusion and exclusion processes are shown in Figure 1. Finally, 1144 eligible patients with schizophrenia had available data for analysis (Table 1). The characteristics for those patients with NLR ≤1.98 and >1.98 are provided in Table 2. As depicted, patients with NLR >1.98 were significantly younger, older onset age, shorter during of illness, more likely to have a higher neutrophil count (4.72 vs. 3.28, p <0.001), a lower lymphocyte count (1.62 vs. 4.57, p <0.001), and more drug-free patients (20.1% vs. 7.9%, p <0.001). Psychopathologically, patients with NLR >1.98 have higher BPRS total score (40 vs. 37, $p = 0.019$) and BPRS subscale scores, including affect (6 vs. 5, $p = 0.013$), resistance (8 vs. 7, $p = 0.014$), and activation (5 vs. 4, $p = 0.003$).

Spearman correlation coefficients were used to assess the association between NLR and potential confounding factors in schizophrenia preferences as shown in Table 3. Overall, NLR was significantly associated with the CGIS score ($r = 0.099$, $p = 0.001$), the BPRS negative symptoms score ($r = -0.062$, $p = 0.036$) and the BPRS resistance score ($r = 0.063$, $p = 0.033$). In the drug-free subgroup, NLR was

significantly associated with the CGIS score (r = 0.296, p = 0.001) and the BPRS activation score (r = 0.272, p = 0.002); whereas, in the drug-therapy subgroup, NLR was negatively related to the BPRS negative symptoms score (r = -0.111, p <0.001). In addition, there was a negative relation between NLR and antipsychotic medication in total (r = -0.193; p <0.001).

To interpret the regression analyses, we had to (i) ascertain that there was no sign of multicollinearity and (ii) define the cut-off thresholds of the CGIS and BPRS subscale scores. First, with regard to checking for collinearity, the VIF value of other variables ranged from 1.077 to 1.492 and only that of age was more than 2.5. Thus, there was multicollinearity between NLR and age. Second, based on the results of ROC curve analyses, the cut-off values and the categories of CGIS and BPRS subscale scores were determined. The categories of CGIS and BPRS subscale scores were as follows: CGIS score [(1) 0-3 = not or mildly ill, (2) 4-4 = moderately ill, and (3) 5-7 = severely ill], affect [(1) 0-5 = not or mildly ill, (2) 6-6 = moderately ill, and (3) 7-28 = severely ill], positive symptoms [(1) 0-6 = not or mildly ill, (2) 7-10 = moderately ill, and (3) 11-28= severely ill], negative symptoms [(1) 0-5 = not or mildly ill, (2) 6-6 = moderately ill, and (3) 7-21 = severely ill], resistance [(1) 0-6 = not or mildly ill, (2) 7-9 = moderately ill, and (3) 10-21 = severely ill], and activation [(1) 0-4 = not or mildly ill, (2) 5-6 = moderately ill, (3) 7-21 = severely ill].

We then investigated the association of NLR with psychiatric symptoms and examined whether there was an association between NLR and severe psychiatric symptoms in schizophrenia on multivariate analysis controlling for other variables and the interactions of NLR and age (Table 3). Unfortunately, we did not find that NLR was significantly associated with the CGIS score, the BPRS total score and any of BPRS subscale scores in the whole study population.

To assess associations of NLR with psychiatric symptoms in the different subgroups, the results of logistic regression stratified by antipsychotic administration are shown in Table 4. In the drug-free subgroup, NLR was significantly associated with worse psychiatric symptoms, both the CGIS score (moderately ill: OR: 63.578, p = 0.011; severely ill: OR: 53.617, p = 0.015) and the BPRS total score (moderately ill: OR:4.049, p = 0.055; severely ill: OR: 4.312, p = 0.045) and there was a marginal correlation between NLR and worse BPRS resistance (moderately ill: OR:3.412, p = 0.089; severely ill: OR: 3.526, p = 0.080). In the drug-therapy subgroup, there was a significant correlation between lower NLR (as a continuous variable) and severer negative symptoms (severely ill: OR: 0.850, p = 0.018).

Discussion

The present large-scale study demonstrates the independent association of NLR with severe psychiatric symptoms in schizophrenia. We found that NLR exhibited the different associations with the severity of disease following the different status of antipsychotics therapy. NLR is positively associated with the severity of disease (i.e. the BPRS total score and the CGIS score) in drug-free patients with schizophrenia, whereas NLR is negatively associated with severe negative symptoms (i.e. the BPRS negative symptoms score) in drug-therapy patients. These findings remained significant after controlling for potential

confounding factors including sex, age, age of illness onset, illness duration, neutrophil count, lymphocyte count, and the interaction of NLR and age.

There are conflicting results about evaluation of the possible correlation of NLR and disease severity between previous literatures and our present study, because of heterogeneous patient populations and methodological discrepancies, additionally small sample sizes. First, our findings presented that the decreased NLR in the drug-therapy patients when compared to the drug-free patients. Further, it was observed that there was a negative relation between NLR and antipsychotic medication in total patients either with Spearman correlation analysis or with logistic regression analysis. It is indicated that there was a significant effect of antipsychotics on NLR in patients with schizophrenia, which lead to heterogeneous patient populations. Thus, it is necessary to stratify the patients into drug-free and drug-therapy. Second, the collinearity between the explanatory variables in the regression models may cause indeterminate parameters, infinitely large standard errors of the estimates, and then statistically insignificant coefficients. To control for the presence of multicollinearity, we computed the VIF, which shows how much the variance of the coefficient estimate is inflated by multicollinearity. Our results appeared that there was the collinearity between NLR and age. The result was consistent with the results of Li et al. that NLR was positive correlation with age (Pearson's $r = 0.161$, $p < 0.001$) in 3262 healthy subjects [25]. Then, the interaction between NLR and age was taken into consideration as a potential confounding factor in the regression models. Third, these results of previous literatures were gained by Spearman or Pearson correlation analyses. Spearman or Pearson correlation tests can be used to assess whether two variables have a linear relationship with each other, but variables should be not necessarily independent. To avoid the interference of the potential confounding such as sex, age, age of illness onset, illness duration, neutrophil count, lymphocyte count, and antipsychotic administration, we conducted logistic regression analyses to assess the associations of NLR and psychiatric symptoms when other variables been considered. Then, it is observed that with logistic regression analyses stratified by drug administration, NLR is independently and significantly associated with severe psychiatric symptoms in drug-free patients with schizophrenia, while lower NLR is independently and significantly related to severer negative symptoms in drug-therapy patients.

Of note, the present study shows that in drug-free patients with schizophrenia, there is a trend that higher NLR is associated with severe resistance subscale symptoms. The BPRS was initially designed to produce a total score, indicating an overall level of psychiatric symptoms[26]. Because contrasted groups with similar total scores may have different patterns of item endorsement, support for these subscales' structural validity is encouragingly given their widespread use in clinical practice and research. Moreover, the subscales are more reliable than single items, as they may document specific areas of treatment change and groups with different diagnoses may have different score patterns [27]. The 18-item BPRS subscales of the five factor model are clearly identified and strongly supported [20]. The five components, affect, positive symptoms, negative symptoms, resistance, and activation, are defined and available in the patients with schizophrenia. Based on the five-factor structure of the BPRS, we found that higher NLR was prone to more severe resistance subscale in drug-free patients. A resistance subscale is defined by the three items: hostility, uncooperativeness, and suspiciousness symptoms and was first proposed in the

18-item BPRS subscales of the five factor model [28]. A resistance component is a well-supported subscale and should probably be considered one of the cores of the BPRS structure, although it has slightly less support than do the three dimensions (affect, negative symptoms, and positive symptoms). Our findings first suggest that in drug-free patients with schizophrenia, there is a trend that higher NLR is associated with severer resistance subscale symptoms not positive or negative symptoms. Generally, negative symptoms refer to poor emotional reactions or thought processes, including emotion impoverishment, speech barrier, thought inflexibility, and decreased activity. In our study, we found that the drug-therapy patients exhibited the lower NLR level than the drug-free patients; NLR was negatively related to negative symptoms ($r = -0.111$, $p < 0.001$); and lower NLR remained significantly associated with severer negative symptoms (severely ill: OR: 0.850, $p = 0.018$) in drug-therapy patients after controlling for potential confounding factors. That is, for every 1-unit decrease in NLR, there was a 17.6% increased risk of severe negative symptoms. According to a series of results, it is speculated that antipsychotic treatment could reduce NLR, consequently induce severe negative symptoms.

In this study, the explanations about the association between NLR and psychiatric symptoms are complex. Two phenomena should be explained: one is NLR is positively associated with significantly severe psychiatric symptom in drug-free patients, and another is NLR is negatively associated with severe negative symptoms in drug-therapy patients.

Because the BBB may be disrupted and allow peripheral blood cells to enter the brain, as has been observed in schizophrenia [29], peripheral immune system can mirror the brain's immune response. NLR reflects neutrophil-dependent and/or lymphocyte mediated immune responses. Immune responses of both immune cells are likely relative to the manifestation of schizophrenia symptoms. Moreover, immune responses involved in the interaction between neutrophils and lymphocytes play an important role on the clinical manifestion.

Currently, despite "the microglia hypothesis of schizophrenia", scarce studies have the direct evidence of the effects of immune cells in the brain tissue on clinical symptomatology of schizophrenia, either microglia or other immune cells including neutrophils and lymphocyte. A few previous studies reported that the increased number of lymphocytes in the brain parenchyma or hippocampus of patients with schizophrenia [30, 31], but merely Busse et al.[32] distinguished between residual (prevailing negative symptoms) and paranoid schizophrenia (prominent positive symptoms), and reported that in the posterior hippocampus, higher densities of CD3 + T-lymphocytes and CD20 + B-lymphocytes were observed in residual versus healthy controls (CD3: left: $p = 0.057$, right: $p = 0.069$; CD20: left: $p = 0.008$, right: $p = 0.006$). It was indicated that blood-brain barrier (BBB) impairment and infiltration of T cells and B cells may contribute to the pathophysiology of residual schizophrenia (prevailing negative symptoms). In contrast, HLA-DR+ (human leukocyte antigen, dopamine-receptor) microglia tended to be increased in paranoid schizophrenia (prominent positive symptoms) when compared to healthy controls (left: $p = 0.090$, right: $p = 0.090$). Regarding the other factor of NLR, neutrophils, there is no data on the association between infiltrating neutrophils in brain and psychiatric symptom. However, neutrophils appear to exert destructive actions in the cerebral tissue after they infiltrate the brain, as has been reported in the autopsy

material of patients that have suffered neurodegenerative diseases, including Alzheimer's disease (AD) and multiple sclerosis (MS) [33]. Neutrophil infiltration has been investigated in mice with experimental autoimmune encephalomyelitis (EAE) that is the most widely used experimental model of MS. Immunohistochemistry and flow cytometry revealed that neutrophils were the most abundant population immediately before and at the onset of disease, whereas their number and percentage dropped at the disease peak, when they were found also in the CNS parenchyma, and during the phase of recovery [33]. Moreover, neutrophils may boost leukocyte recruitment during EAE, facilitating cell migration from the perivascular space to the brain parenchyma [34]. In AD, a combination of experimental and clinical evidence suggested that T cells and neutrophils migrate into the brain[34]. Although schizophrenia is not a neurodegenerative disease, just like AD and MS, it may involve some neurodegenerative processes; not only dementia but also schizophrenic patients have a significant volume reduction of some specific regions in the brain [35]. Thus, it is speculated that in schizophrenia patients without antipsychotic treatment, neutrophils, as the first recruited innate immune defense against bacteria and antigens, are increased in the bloodstream, they subsequently enter into the brain and secrete a wide range of chemokines and cytokines either constitutively or in response to different local stimuli, aversely affect the integrity of the BBB, which trigger alterations in vascular permeability and infiltration of other innate and adaptive immune cells, such as macrophages (microglia) and subsets of T cells, into the inflammation areas in the CNS, consequently, aggravation of schizophrenia severity.

The marketed antipsychotics mainly act as dopamine (DA) antagonists. These antagonists, like clozapine, chlorpromazine and pimozide, reduced the neutrophil count owing to drug-induced apoptosis [36]. In 1977, eight fatal cases of clozapine-induced agranulocytosis were observed in Finland. [37] Clozapine-induced neutropenia occurs in ~1% of patients. In recent decades, it was found that patients with schizophrenia who take other antipsychotics had an equal risk of developing neutropenia as those taking clozapine [38]. Notable, neutrophils are mainly known for their pro-inflammatory role in anti-bacteria. Recent data show the existence of multiple functional phenotypes of neutrophils and neutrophils described novel immunosuppressive functions. For example, neutrophils are involved in T cell-mediated responses through contact-dependent inhibition [39]. One important sub-population of circulating neutrophils is the granulocytic myeloid derived suppressor cells (G-MDSC) that has been shown to directly suppress T cell functions in murine models of cancer, infectious diseases, and bone marrow [40]. The in vitro study reported that the $CD62L^{dim}$ hypersegmented neutrophils potently suppressed T cell proliferation in dose-dependent manner within range of 1:10 – 2:1 NLR both upon phytohaemagglutinin (PHA) and upon CD3/CD28 stimulation [39]. In our study, drug-therapy patients presented decreased neutrophils and increased lymphocytes, secondarily lower NRL in comparison with drug-free patients. It is speculated that antipsychotics could induce neutrophil apoptosis leading to decreased neutrophil count, alleviation of suppression of T cell proliferation, consequently, production of low NRL.

Furthermore, essentially clinically effective antipsychotics target DRs. DRs are not only expressed in the CNS, but also expressed on the surface of peripheral immune system cells. Over-expression of D2

dopamine receptor mRNA in drug-naive schizophrenic peripheral blood lymphocytes (PBL) [41] and elevated D3 (D2-like) dopamine receptor mRNA levels among drug-free patients have been reported in schizophrenia [42]. An increase in proportion of D2/D3 DRs that is in the high-affinity state in the brain is a common basis for the dopamine supersensitivity leading to psychotic reactions in schizophrenia. The changes of dopamine receptor density in the brain are reflected in peripheral lymphocytes. Kwak et al. [43] ascertained that the patients with the higher D3R expression of peripheral lymphocytes had statistically significant high BPRS in the drug-free and drug-naïve patients. However, the administration of DA antagonists for disease treatment potentially cause decrease the sensitivity of DRs. It was observed that, D3 dopamine receptor mRNA expression of peripheral lymphocytes in drug-medicated schizophrenics significantly reduced when compared to that of drug-free schizophrenics [43]. In fact, antipsychotic drugs as DA antagonists are more likely to over-occupancy D2 receptor, to diminish receptor expression and cause manifest as secondary negative symptoms, in particular, akinesia or bradykinesia[44, 45, 46]. This suggests that the characteristics of peripheral lymphocytes in schizophrenic might reflect the clinical manifestion. Collectively, (1) antipsychotics treatment product decreased neutrophils via drug-induced apoptosis and (2) increased lymphocytes with DRs desensitization induced by drugs might explain the phenomenon that is lower NLR is significantly associated with severe negative symptoms in drug-therapy patients with schizophrenia.

The limitations of this study are the retrospective, nonrandomized nature, and the relatively small sizes of male and drug-free patients. First, this study included 123 drug-free patients and 1021 drug-therapy patients. Because the relatively small sizes of drug-free patients may cause potential bias in analyses of the total group, we put more attention on the results of stratification by antipsychotic administration. Second, the different sample sizes between male and female patients were likely to another potential bias. Nevertheless, these results represented that there was no sex difference in NRL. So we ignored the different sample sizes between the two sexes. Third, we did not discriminate between patients with acute psychotic state and those in clinical remission because a meta-analysis of 10 studies revealed that the increased NLR was found in patients with both chronic-type schizophrenia and first-episode psychosis [14].

Conclusions

The present large-scale study is the first to demonstrate the independent association of NLR with the severity of disease in schizophrenia. There is the different correlation between NLR and psychiatric symptoms in the different status of antipsychotics therapy. NLR is positively associated with significantly severe psychiatric symptom in drug-free patients, whereas NLR is negatively associated with severe negative symptoms in drug-therapy patients. The findings confirm the hypothesis that NLR is independently associated with severe psychopathological symptoms in schizophrenia. It is speculated that not only neutrophil-dependent and/or lymphocyte mediated immune responses, but also immune responses involved in the interaction between neutrophils and lymphocytes in schizophrenia are more likely related to the manifestation of symptoms. NLR may reflect the combined prognostic information of these two processes and be a stronger predictor of the outcome than either alone. Nevertheless, NLR is

not appropriate to be an inflammatory biomarker for assessment of disease severity due to different correlation between NLR and the severity of disease in the different status of antipsychotics therapy, but provide potential mechanistic insights on specific pathological cellular processes, as well be a potential target to improve the course of the psychotic disorder.

List Of Abbreviations

NLR: Neutrophil-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; CGIS: Clinical Global Impression Severity scale; BPRS: Brief Psychiatric Rating Scale; PANSS: Positive and Negative Syndrome Scale

Declarations

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Ethics approval and consent to participate

The study protocol was reviewed and approved by the ethics committee of Nanjing Medical University Affiliated Brain Hospital. Informed consent was not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare no conflict of interest.

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Authors' contributions

HS designed the study development program; XZ and XLW collected the data from the Electronic Medical Record and Laboratory Information System for the analyses, wrote and revised the paper; RL and YX

performed the statistical analyses; HS and WGL critically reviewed and interpreted the data; the study was set up and conducted under the supervision of HS. All authors contributed to and have approved the final manuscript.

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Tables

Table 1 Demographic and clinical characteristics of the patients with schizophrenia

	Total (n = 1144)	Total (n = 1144)		
		Drug-free (n=123)	Antipsychotic therapy (n=1021)	*p*
Age, year	35 (27-45)	34 (28-43)	35 (27-45)	0.549
Male sex, n (%)	371 (32.4)	32 (26.0)	343 (33.6)	0.036
Age of illness onset, year	23 (18-28)	24 (20-32)	23 (18-28)	**0.001**
During of illness, year	10 (5-17)	6 (3-12)	10 (5-17)	**<0.001**
Drug administration				
No，n (%)	123 (10.8)			
Yes, n (%)	1021 (89.2)			
Clozapine，n (%)	74 (6.5)			
Aripiprazole，n (%)	77 (6.7)			
Amisulpride，n (%)	117 (10.2)			
Olanzapine，n (%)	171 (14.9)			
Risperidone，n (%)	144 (12.6)			
Quetiapine，n (%)	17 (1.5)			
Chloropromazine，n (%)	2 (0.2)			
Ziprasidone，n (%)	5 (0.4)			
Perphenazine，n (%)	5 (0.4)			
Antipsychotic Combinations，n (%)	409 (35.8)			
Lymphocyte count, 10^9/L	2.73 (1.82-5.83)	2.06 (1.55-3.64)	2.86 (1.87-5.98)	**<0.001**
Neutrophil count, 10^9/L	3.60 (2.77-4.75)	4.27 (3.18-5.98)	3.55 (2.73-4.55)	**<0.001**
NLR (categorical), ≤1.98，n (%)	876 (76.6)	69 (56.1)	807 (79.0)	**<0.001**
NLR (continuous)	1.08 (0.60-1.90)	1.79 (0.85-2.98)	1.01 (0.60-1.80)	**<0.001**
CGIS score (continuous)	4 (3-5)	5 (5-6)	4 (3-5)	**<0.001**
BPRS total score (continuous)	38 (30-47)	49 (45-56)	37 (30-45)	**<0.001**
BPRS affect score (continuous)	5 (4-8)	7(4-9)	5 (4-7)	**<0.001**
BPRS positive symptoms score (continuous)	8 (6-11)	10 (8-13)	8 (6-10)	**<0.001**
BPRS negative symptoms score (continuous)	6 (4-8)	7 (5-10)	6 (4-8)	**<0.001**
BPRS resistance score (continuous)	7 (5-10)	12 (9-15)	7 (5-10)	**<0.001**
BPRS activation score (continuous)	5 (3-6)	6 (5-8)	4 (3-6)	**<0.001**

Table 2 Comparison of the clinical characteristics of the cohort

	Total (n=1144)			Drug-free (n=123)			Antipsychotic therapy (n=1021)		
	NLR ≤1.98 (n=876)	NLR >1.98 (n=268)	*p*	NLR ≤1.98 (n=69)	NLR >1.98 (n=54)	*p*	NLR ≤1.98 (n=807)	NLR >1.98 (n=214)	*p*
Age, year	36 (27-46)	32(25-41)	**<0.001**	33 (27-41)	34 (28-43)	0.345	36 (27-46)	31 (25-40)	**<0.001**
Male sex, n (%)	284 (32.4)	87 (32.4)	0.990	14 (20.3)	16 (29.6)	0.231	270 (33.5)	71 (33.2)	0.939
Age of illness onset, year	23 (17-27)	24 (19-30)	**0.001**	23 (19-32)	28 (22-35)	**0.020**	23 (17-27)	23 (18-30)	0.076
During of illness, year	11 (6-18)	5 (3-10)	**<0.001**	6 (2-11)	4 (2-8)	0.179	11 (6-18)	5 (3-10)	**<0.001**
Drug-free, n (%)	69 (7.9)	54 (20.1)	**<0.001**	□	□	□	□	□	□
Lymphocyte count, 10^9/L	4.57 (2.30-6.54)	1.62 (1.39-1.95)	**<0.001**	3.03 (2.06-4.90)	1.55 (1.20-1.92)	**<0.001**	4.70 (2.32-6.56)	1.63 (1.40-1.96)	**<0.001**
Neutrophil count, 10^9/L	3.28 (2.59-4.20)	4.72 (3.82-6.05)	**<0.001**	3.45 (2.78-5.41)	5.34 (4.48-6.63)	**<0.001**	3.24 (2.57-4.18)	4.49 (3.76-5.86)	**<0.001**
NLR	0.72 (0.57-1.36)	2.70 (2.27-3.65)	**<0.001**	0.99 (0.64-2.36)	3.18 (2.48-4.99)	**<0.001**	0.71 (0.57-1.33)	2.65 (2.24-3.41)	**<0.001**
CGIS score (continuous)	4 (3-5)	4 (4-5)	**<0.001**	5 (5-6)	5 (5-6)	**0.013**	4 (3-5)	4 (3-5)	0.454
BPRS total score (continuous)	37 (30-47)	40 (32-48)	**0.019**	48 (11)	51 (9)	0.109	37 (29-46)	36 (30-43)	0.901
BPRS affect score (continuous)	5 (4-7)	6 (4-8)	**0.013**	7 (4-9)	7 (5-9)	0.270	5 (4-7)	6 (4-7)	0.167
BPRS positive symptoms score (continuous)	8 (6-10)	8 (6-11)	0.155	10 (8-13)	10 (8-13)	0.462	8 (5-10)	8 (6-9)	0.496
BPRS negative symptoms score (continuous)	6 (4-8)	6 (4-8)	0.331	8 (6-10)	7 (6-10)	0.680	6 (4-8)	5 (4-7)	**0.039**
BPRS resistance score (continuous)	7 (5-10)	8 (6-11)	**0.014**	11 (4)	12 (3)	**0.050**	7 (5-10)	7 (5-10)	0.809
BPRS activation score (continuous)	4 (3-6)	5 (3-7)	**0.003**	6 (4-7)	7 (5-9)	**0.020**	4 (3-6)	4 (3-6)	0.327

Table 3 The spearman correlations analysis between NLR in a continuous fashion and CGIS and BPRS scores, and other variables including age, sex, age of illness onset, illness duration and antipsychotic administration

	Total (n=1144)		Drug-free (n=123)		Antipsychotic therapy (n=1021)	
	R	*p*	R	*p*	R	*p*
Age	**-0.262**	**< 0.001**	0.023	0.797	**-0.290**	**< 0.001**
Sex	-0.012	0.693	-0.050	0.584	-0.019	0.551
Age of illness onset	**0.115**	**< 0.001**	**0.227**	**0.011**	**0.071**	**0.023**
During of illness	**-0.513**	**< 0.001**	-0.172	0.057	**-0.505**	**< 0.001**
CGIS score	**0.099**	**0.001**	**0.296**	**0.001**	0.005	0.882
BPRS total score	0.040	0.175	0.176	0.052	-0.045	0.154
BPRS affect score	0.037	0.206	0.099	0.277	-0.002	0.956
BPRS positive symptoms score	0.035	0.237	0.094	0.300	-0.011	0.727
BPRS negative symptoms score	**-0.062**	**0.036**	0.042	0.648	**-0.111**	**< 0.001**
BPRS resistance score	**0.063**	**0.033**	0.146	0.106	-0.012	0.699
BPRS activation score	0.047	0.109	**0.272**	**0.002**	-0.018	0.567
Drug administration	**-0.193**	**< 0.001**	□	□	□	□

Table 4 Logistic regression analyses of NRL associated with CGIS or BPRS scores after controlling for age, sex, age of illness onset, illness duration and antipsychotic administration.

	Total (n=1144)		Drug-free (n=123)		Antipsychotic therapy (n=1021)	
	OR（95%CI）	*p*	OR（95%CI）	*p*	OR（95%CI）	*p*
CGIS score						
Moderate (4-4) [a]	0.795 (0.508-1.244)	0.315	**63.578 (2.578-1567.894)**	**0.011**		
Severe (5-7) [a]	0.707 (0.447-1.117)	0.137	**53.617 (2.180-1318.767)**	**0.015**		
BPRS total score						
Moderate (32-53) [b]	1.295 (0.772-2.175)	0.327	4.049 (0.973-16.843)	0.055		
Severe (54-126) [b]	1.344 (0.701-2.577)	0.373	**4.312 (1.035-17.931)**	**0.045**		
BPRS affect score						
Moderate (6-6) [c]	0.966 (0.544-1.718)	0.907				
Severe (7-28) [c]	0.999 (0.657-1.520)	0.996				
BPRS positive symptoms score						
Moderate (7-10) [d]	1.245 (0.763-2.034)	0.380				
Severe (11-28) [d]	0.754 (0.430-1.324)	0.326				
BPRS negative symptoms score						
Moderate (6-6) [e]	0.596 (0.323-1.100)	0.098			1.058 (0.911-1.230)	0.459
Severe (7-21) [e]	0.886 (0.601-1.307)	0.542			**0.850 (0.742-0.973)**	**0.018**
BPRS resistance score						
Moderate (7-9) [f]	1.053 (0.639-1.737)	0.838	3.412 (0.829-14.049)	0.089		
Severe (10-21) [f]	0.911 (0.553-1.501)	0.714	3.526 (0.861-14.440)	0.080		
BPRS activation score						
Moderate (5-6) [g]	0.869 (0.517-1.462)	0.598				
Severe (7-21) [g]	1.337(0.797-2.242)	0.271				

a. CGIS score: not or mild (0-3) as the referent category; b. BPRS total score: not or mild (0-31) as the referent category; c. BPRS affect score: not or mild (0-5) as the referent category; d. BPRS positive symptom score: not or mild (0-6) as the referent category; e. BPRS negative symptom score: not or mild (0-5) as the referent category; f. BPRS resistance score: not or mild (0-6) as the referent category; g. BPRS activation score: not or mild (0-4) as the referent category.

Figures

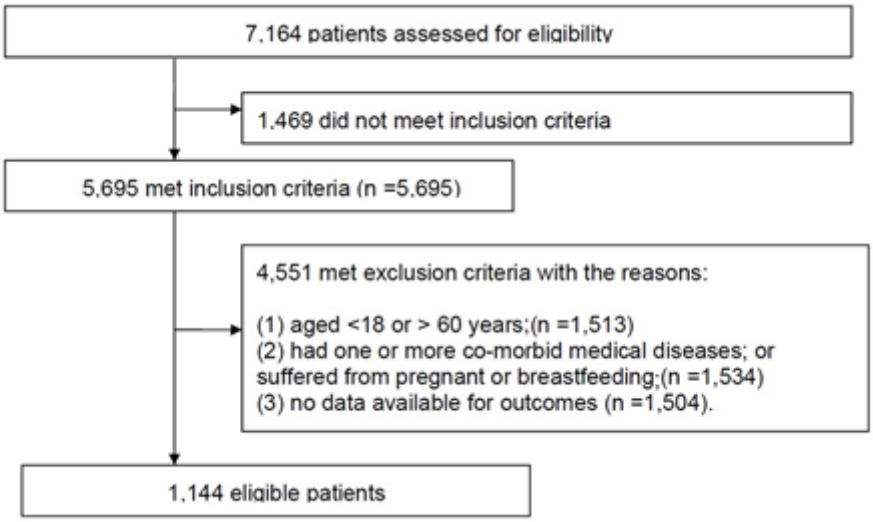

Figure 1

The study inclusion and exclusion process