Neutrophil-to-lymphocyte ratio in schizophrenia: A systematic review and meta-analysis

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A B S T R A C T

Background: The immune system appears to be dysregulated in schizophrenia (SZ). The potential prognostic or diagnostic value of neutrophil-to-lymphocyte ratio (NLR), an inexpensive proxy marker for a wide spectrum of conditions, has not been established in SZ. We seek to investigate a) whether NLR is increased in SZ patients, b) if this difference in more prominent in relapsed SZ or first-episode psychosis.
Methods: A structured algorithm was applied in MEDLINE (1946–2018), PsychInfo, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) (1999–2018), PSYNDEX (1984–2017) and Clinicaltrials.gov (2008–2018) databases.
Results: Through the database search, 1023 articles were screened. Ten studies (804 SZ patients, 671 controls) were included in the meta-analysis. In SZ patients, the NLR was increased by 0.65 (95% CI: 0.54, 0.86, p $< 10^{-5}$). This difference was significant in both acute relapse and first-episode psychosis subgroups. Studies of moderate and high quality also showed a significant NLR increase in SZ patients ($I^2 = 0\%$). Meta-regression analysis showed that the polymorphonuclear count and antipsychotic use may confound the result. In leave-one-out meta-analysis, no study altered the significance of the result when omitted.
Conclusions: NLR in SZ patients is increased, both in chronic disease and in first-episode psychosis. Baseline characteristics, such as polymorphonuclear count and antipsychotic use, may affect its accuracy. The application of this marker in clinical practice requires the description of its normal values in the general population, its potential change after antipsychotic administration and its correlation with disease activity. A large-scale, prospective study design would resolve these issues.

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1. Introduction

Schizophrenia is a chronic mental disorder with distortions in thought, perception and behavior. It is a major cause of disability, associated with a chronic course, relapses and a decrease in disability-adjusted life years (Murray et al., 2012). The underlying pathophysiology remains unclear and most likely multifactorial, attributable to both genetic and environmental factors. Recently identified genetic loci predisposing to schizophrenia include areas coding for immune-related functions (Ripke et al., 2014). A recent study found that some of the SZ risk genes formed 4 densely interconnected modules, one of which contained 7 genes, among which interleukin and interferon genes, and related to immune response (Liu et al., 2018). This finding may be related with the multitude of studies describing a characteristic immunological imprint on schizophrenia patients, as well as the efficacy of adjunct treatment modalities such as celecoxib (Zheng et al., 2017) in the management of the disorder. A recent meta-analysis (2014) found a

moderately increased CRP ($+0.45$ mg/L, 95% CI: 0.34, 0.55, p $< 10^{-3}$, $I^2 = 95.6\%$) in schizophrenia patients vs. healthy controls (Miller et al., 2014). Peripheral (Miller et al., 2011) and CSF (Gallego et al., 2018) cytokine levels are also exhibiting a characteristic pattern in schizophrenia patients. However, a recent study (Kalmady et al., 2018) that took into account the points raised by the authors considering the confounding by smoking and BMI (Miller et al., 2011) found that antipsychotic naïve SZ patients only have elevated serum IL-6 after correcting for confounding demographic differences.

A variety of mechanisms involving the immune system in pathogenesis of schizophrenia is suggested (Drexhage et al., 2011). One mechanism involves the chronic activation of macrophages, T lymphocytes and microglia which secrete inflammatory cytokines such as Interleukin-2 (IL-2), IL-6, IL-10, interferon gamma (IFN-γ) and IL-4 (Upthegrove et al., 2014). This proposed mechanism is consistent with the cytokine profile described in first episode psychosis (FEP) patients with the only differences being an increase in serum Interleukin-2 receptor (sIL-2R) (30 patients), a non-significant difference in IL-2 (140 patients) and a decrease, not an increase in IL-4 (193 patients) (Goldsmith et al., 2016). Another promising field of research is the

study of autoantibodies in schizophrenia (Khandaker et al., 2015). Various autoantibodies, such as anti-NMDA receptor autoantibodies, have been found to cause a psychotic symptomatology in the context of encephalitis (Barry et al., 2015). Novel autoantibodies, based on the genetic profile of SZ patients as this was described by GWAS studies, have also been found increased in the plasma of SZ patients. Specifically, high anti-TRANK1 IgG titers were specific for SZ (n = 356 participants) irrespectively of risperidone treatment (Whelan et al., 2018). Another mechanism describes a Th1 arm precipitation and Th2 attenuation in patients with schizophrenia. This leads to a decrease in IL-2 and IFN-γ (Upthegrove et al., 2014). In FEP patients, a decrease in IL-2 levels has been described but IFN-γ levels are increased (Goldsmith et al., 2016). In contrast with this evidence, another meta-analysis found that both IL-2 and IFN-γ levels are decreased, suggesting that there is indeed an imbalance between the Th1-Th2 arms (Guo et al., 2015). A different mechanism involves an activation of microglia which causes neuronal destruction (Upthegrove et al., 2014). Activated microglia cells secrete anti-inflammatory and pro-inflammatory cytokines. This neurotoxic state can lead to cell death if it is sustained (Lurie, 2018). The activation of microglia signals an increase in 18 k-Da translocator protein (TSPO) that can be measured with PET (Marques et al., 2018). This protein was found increased in a meta-analysis based on PET tracer binding evidence (Marques et al., 2018). The exact role of microglia in predicting disease course or acting as a potential therapeutic target is not yet determined (Laskaris et al., 2016). Animal models have also shown that increased inflammatory cytokines act as a trigger for the activation of microglia (Khandaker et al., 2015).

Neutrophil to lymphocyte ratio (NLR) is an inexpensive marker of disease, calculated from the complete blood count, and its pathogenetic role has been investigated in a wide spectrum of diseases. Elevated NLR has been associated with an increase in cytokines and CRP and is increasingly used in the literature as a proxy of systemic inflammation. High NLR has been found to positively correlate with both IL-6 and IL-8 in patients with liver cirrhosis (Lin et al., 2018), laryngeal cancer patients (Du et al., 2017) and ovarian cancer patients (Sanguinete et al., 2017). In addition, Ackland et al. (2018) showed that, in a large patient cohort (n = 1624) of patients scheduled to undergo a major surgery, both NLR and CRP were associated with lower heart rate recovery, an index test studied as a proxy for systemic inflammation.

An increased NLR is associated with poor prognosis in various neoplasms, such as lung cancer (Akinci Ozyurek et al., 2017), colorectal cancer (Dong et al., 2016), breast cancer (Chen et al., 2015), gastric cancer (Hu et al., 2015), and in acute pulmonary embolism (Wang et al., 2018). In mental disorders, the role of NLR remains unclear. A recent meta-analysis investigated its merit in mood disorders, indicating a significant increase in both bipolar disorder and major depressive disorder patients versus controls (Mazza et al., 2018). However, the authors reported that the available evidence did not allow for an investigation of the potential correlation of NLR with disease severity. Based on the aforementioned disrupted immunological status of SZ patients and the value of NLR in a spectrum of immune-mediated diseases as well as its association with cytokines (IL-6, TNF-α) whose concentration has been established to be increased in SZ, NLR could be a marker of immune dysregulation in SZ. A few studies have reported increased NLR in schizophrenia (Chow et al., 2015; Kulaksizoglu and Kulaksizoglu, 2016; Semiz et al., 2014). However, the role of NLR has not been studied through a systematic review. Therefore, the present meta-analysis aims to investigate the difference in NLR between patients with schizophrenia and control subjects and its potential utility in clinical practice.

2. Materials and methods

2.1. Study design

The present systematic review is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). The PRISMA checklist is presented in Suppl. Table 1. All studies comparing the NLR in schizophrenia patients and controls were deemed eligible. The study selection was performed in three consecutive stages. The titles and abstracts of all electronic articles were screened and subsequently articles presumed to meet the criteria were retrieved as full texts. Finally, all studies reporting the outcome of interest were included in the present systematic review. Review articles, animal studies, in silico simulations, safety studies and non-comparative studies (case reports, case series) were excluded. Any discrepancies regarding the methodology, retrieval of articles and statistical analysis were resolved through the consensus of all authors.

2.2. Literature search and data collection

The literature search was conducted based on the algorithm: (neutrophil OR lymphocyte OR "neutrophil to lymphocyte ratio" OR NLR) AND (schizophrenia OR psychosis OR "psychotic syndrome"), which was applied in the MEDLINE (1946–2018), PsychInfo, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) (1999–2018), PSYNDEX (1984–2017) and Clinicaltrials.gov (2008–2018) databases. To retrieve any additional relevant articles, the citations within articles were also manually screened (snow-ball method). No language or date restrictions were applied. The date of the last search was set at 2 August 2018. The flowchart of the literature search is presented in Fig. 1. The extracted data from each study included the following: name of the first author, date of publication, outcome of interest (NLR) and demographic parameters [patient age, sample size, study location, duration of illness, gender, smoking status, polymorphonuclear (PMN) count, platelet count, antipsychotic use, positive and negative syndrome scale (PANSS)].

2.3. Quality assessment

Two researchers (V.K., G.M.) independently evaluated the studies with the use of Newcastle-Ottawa Assessment Scale (NOS) (Stang, 2010). This scale applies to nonrandomized studies and assigns stars (maximum score: 9) according to the selection of the study groups, comparability of the groups and the ascertainment of exposure (case-control or) or outcome of interest (cohort studies). Any potential disagreements were resolved through the consensus of all authors.

2.4. Statistical analysis

Statistical meta-analysis was performed with the RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) and the confidence intervals were set at 95%. Due to the significant heterogeneity in the methodological characteristics of the included studies, the Der Simonian-Laird random effect model (DerSimonian and Laird, 1986) was applied to calculate standardized mean differences (SMD) and 95% confidence intervals (CI). Each individual study effect on mean difference was explored by performing leave-one-out analyses; one study was sequentially omitted at a time in order to find out its effect in the overall outcome. Subgroup analysis for a) acute relapse (AR) vs. first-episode psychosis (FEP) and b) low quality vs. moderate and high quality studies was planned post-hoc. Low quality was defined as 0–3 stars, moderate quality as 4–6 stars and high quality as 7–9 stars of the NOS scale. For the meta-regression analysis, the parameters chosen were reported by at least 3 studies. The software used to conduct the meta-regression analysis was Open Meta-Analyst. For the evaluation of publication bias, trim-and-fill method and Egger's test were performed using the metafor package in R-3.5.1 software (Viechtbauer, 2010).
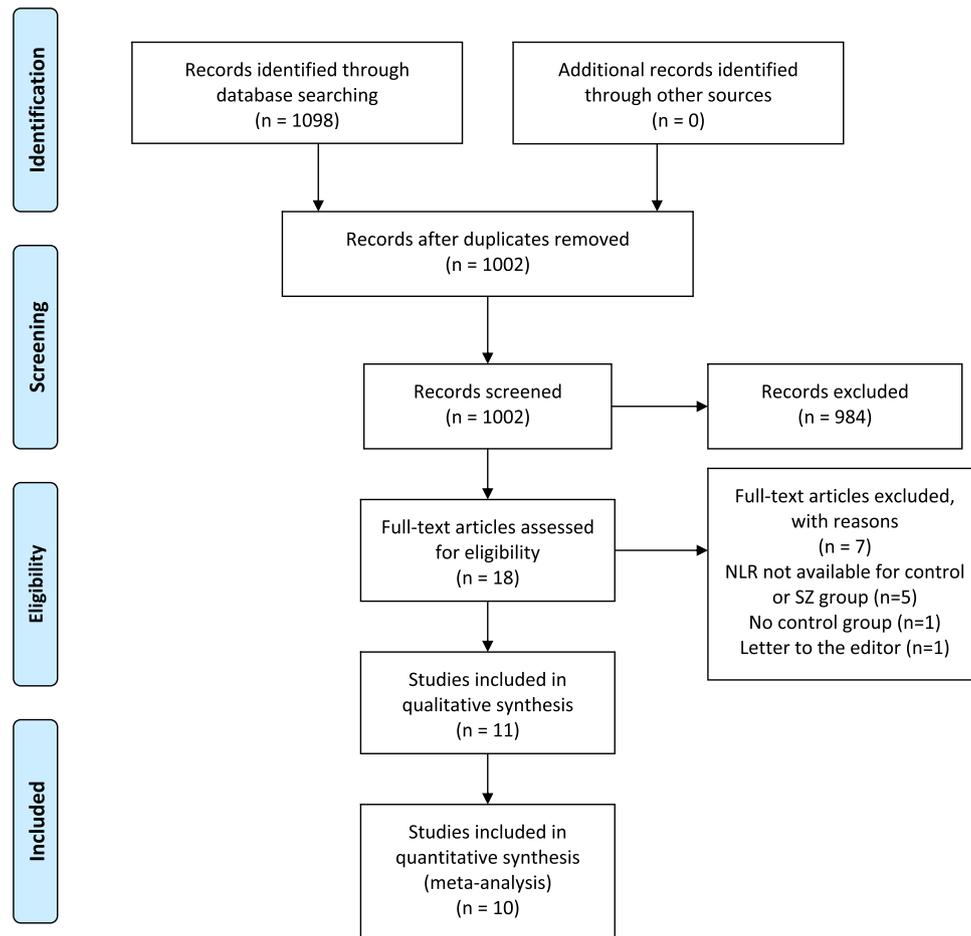
PRISMA 2009 Flow Diagram

Fig. 1. Flow diagram of the literature search.

3. Results

3.1. Included studies

Through the database search, 1023 articles were screened (title and abstract) and evaluated for eligibility. In the present meta-analysis, 10 studies (Bustan et al., 2018; Chow et al., 2015; Garcia-Rizo et al., 2017; Kulaksizoglu and Kulaksizoglu, 2016; Moody and Miller, 2018; Özdin et al., 2017; Pavlović et al., 2016; Semiz et al., 2014; Varsak et al., n.d.; Yuksel et al., 2018), recruiting a total of 804 schizophrenia patients and 671 controls, were included. The methodological characteristics of the included studies are presented in Table 1 (study design, country, inclusion and exclusion criteria, NOS). Patient characteristics (age, gender, BMI, smoking, antipsychotic use) are summarized in Tables 2, 3, 4. Quantitative synthesis consisted of 10 studies. One study (Barzilay et al., 2016) was included only in the qualitative synthesis.

3.2. Excluded studies

Seven studies were excluded after reading the full text. Five studies (Cosentino et al., 1996; Karakas Ugurlu et al., 2016; Kloukina-Pantazidou et al., 2010; Miller et al., 2015; Wilke et al., 1996) did not explicitly provide the NLR either for the case or for the control group. One study (Fang et al., 2016) correlated NLR with sleep quality but did not

calculate the NLR in the control group. One article was a letter to the editor (Bolu et al., 2015).

3.3. Quality assessment

The outcomes of the NOS score are presented in Table 1. Four studies (40%) scored 3 stars, 2 studies (20%) scored 4 stars, 1 study (10%) scored 5 stars, 1 study (10%) scored 6 stars and 2 studies (20%) scored 8 stars.

3.4. Qualitative synthesis

Ten studies with a median of 70 schizophrenia patients (Interquartile range (IQR) = 44, range = 20–163) and 57 controls (IQR = 48, range = 20–157) were included. The median NLR for the schizophrenia patients was 2.625 (IQR = 0.463, range = 2.03–3.24) and 1.78 (IQR = 0.233, range = 1.6–2) for the controls. One study (Barzilay et al., 2016) positively correlated the NLR with C-reactive protein, which in turn was associated with aggressive behavior in schizophrenia patients.

3.5. Quantitative synthesis

In Fig. 2, the SMD of the NLR between the schizophrenia and the control group is illustrated. For the overall effect, in a total of 803

Table 1

Study characteristics of the included studies. NOS: Newcastle-Ottawa Scale score; WBC: white blood cell count; VTE: venous thromboembolism; NSAID: non-steroid anti-inflammatory drugs; ECT: electroconvulsive therapy. The asterisks in the NOS column signify the total score received by each study.

	Design	Country	Exclusion criteria	NOS	Schizophrenia diagnosis
Bustan et al., 2018	Cross-sectional	Israel	Leukocytosis (WBC > 14,000/mm³), lithium use, fever (>37.9 °C) at admission	*****	DSM-5
Chow et al., 2015	Cross-sectional	Australia	Antipsychotic prescription for <1 year, noncompliance (psychiatric review, blood clozapine levels), history of VTE, ischemic heart disease, long-term anticoagulation	****	DSM-IV
Garcia-Rizo et al., 2017	Case control	Spain	Antipsychotic prescription	***	DSM-IV
Kulaksizoglu and Kulaksizoglu, 2016	Case control	Turkey	≥1 of: alcohol or substance abuse or dependence, hypertension, heart disease, diabetes, liver or renal failure, autoimmune disorders, active infection, active or chronic inflammatory disease, smoking >15 cig/d, BMI > 30, treatment with anti-inflammatory, antioxidant, immunosuppressive medications	***	DSM-IV
Moody 2017	Case control	USA	Alcohol abuse or intellectual disability, exposure to one of the following drug categories: Anti-hypertensive agents, corticosteroids, NSAID or immunomodulatory agents, current UTI's, pregnancy, diabetes, history of antibiotic treatment the prior 2 weeks, history of malignancy-immune disorder-thyroid disease-liver or renal dysfunction, illicit drug use in the past 30 days, extremely outlying WBC counts (>11 × 103 cells/μL) and NLR (>4.0).	******	DSM-IV
Özdin et al., 2017	Case control	Turkey	For schizophrenia group, contact not possible, no consent, anti-inflammatory medications (NSAIDs, corticosteroids, other), systemic disease (COPD, heart disease, hematological disease, other). For control group, not a blood donor to the hospital, chronic disease, long-term drug use	***	NA
Pavlović et al., 2016	Cross-sectional	Bosnia and Herzegovina	Age <18 or >70 years old, autoimmune, degenerative, rheumatic, acute or chronic infectious disease, malignancy, pregnancy, alcoholism, drug addiction	***	ICD-10
Semiz et al., 2014	Cross-sectional	Turkey	≥1 of: alcohol or substance abuse or dependence, hypertension, heart disease, diabetes, liver or renal failure, autoimmune disorders, active infection, active or chronic inflammatory disease, smoking >15 cig/d, BMI > 30, treatment with anti-inflammatory, immunosuppressive medications	*******	DSM-IV
Varsak 2017	Case control	Turkey	Alcohol, substance abuse, hypertension, diabetes, heart disease, liver, renal failure, active infection, active or chronic inflammatory or autoimmune diseases, treatment with anti-inflammatory or immunosuppressive medication.	****	NA
Yuksel et al., 2018	Cross-sectional	Turkey	Refusal to participate, ECT, fever, epilepsy, substance use, mental retardation, anoxia or hypoxia during birth, major medical disorder, neuropsychiatric symptoms secondary to a metabolic disorder or structural lesion, psychiatric comorbidities	*******	DSM-5

schizophrenia patients and 671 controls (10 studies), the SMD is 0.65 [95% CI: 0.47, 0.84, p < 10⁻⁵, I² = 62%].

3.5.1. Subgroup analysis

Subgroup analysis for AR vs. FEP groups also revealed a significantly larger NLR for the schizophrenia group in both subgroups. Specifically, in the AR subgroup analysis, the MD was 0.71 [95% CI: 0.50, 0.91, p < 10⁻⁵, I² = 60%] in a total of 645 schizophrenia patients and 510 controls (7 comparisons). In the FEP subgroup analysis, the MD was 0.52 [95% CI: 0.14, 0.90, p = 0.008, I² = 62%] in a total of 158 schizophrenia patients and 161 controls (3 studies). The test for subgroup differences did not reveal a significant difference (p = 0.39, I² = 0%).

In the low vs. moderate-high quality subgroup analysis, the significant difference in NLR among both subgroups persisted (low: SMD = 0.61, 95% CI: 0.46, 0.75, p < 10⁻⁵, moderate-high: SMD = 0.70, 95% CI: 0.54, 0.86, p < 10⁻⁵). It is noteworthy that, in the moderate-high quality subgroup, the heterogeneity is I² = 0% whereas, in the low quality subgroup, it is I² = 86%.

3.5.2. Meta-regression analysis

The results of the meta-regression analysis are depicted in Table 5. The SMD remains unaffected by the differing patient age, sample size,

duration of illness, gender as expressed by percentage of male participants, smoking status as expressed by percentage of smokers, patient platelet, monocyte count (Suppl. Fig. 1) or PANSS+. On the other hand, the patient PMN count and the antipsychotic use as expressed by percentage of participants on antipsychotics significantly affect the SMD (coefficient = 0.502, SE = 0.130, p < 0.001, coefficient = 0.006, SE = 0.002, p = 0.007 respectively).

3.5.3. Sensitivity analysis and publication bias

The sensitivity analysis, as illustrated in Fig. 3, shows that no single study renders the SMD non-significant when omitted. However, the omission of one study (Kulaksizoglu and Kulaksizoglu, 2016) displaces, albeit non-significantly, the SMD to 0.599 (95% CI: 0.426, 0.773).Visual inspection of the funnel plot (Fig. 4) diverges from the expected shape and reveals asymmetry. The rank correlation test for funnel plot asymmetry (Begg's test) was not significant for publication bias (Kendall's tau = −0.11, p = 0.7275). This implication was further encouraged by the regression test for funnel plot asymmetry (Egger's test) which was also non-significant (z = 0.3622, p = 0.7172). Trim-and-fill method estimated 2 missing studies on the left side of the plot (SE = 2.1967) and calculated an adjusted estimate of 0.5751 (SE = 0.0963, I² = 68.6%, p < 10⁻⁴).

Table 2

Patient characteristics. Sex: percentage of male participants; BMI: body mass index.

	Psychotic patients							Controls					
	N	Age	Sex	BMI	Smoking	Clozapine	Antipsychotic use	N	Age	Sex	BMI	Smoking	Antipsychotic use
Bustan et al., 2018	81	15.9 (1.6)	58%	22.9 (4.9)	14.8%	NA	33.3%	285	14.7 (1.8)	51.6%	23.2 (5.8)	27.7%	33.7%
Chow et al., 2015	90	40 (13)	68%	29.1 (6.5)	39%	76%	100%	30	43 (12)	57%	27.6 (4.4)	7%	NA
Garcia-Rizo et al., 2017	75	27.95 (6.2)	68%	22.3 (3.5)	50.7%	NA	0%	80	27.79 (5.6)	59%	23.06 (2.5)	61.25%	0%
Kulaksizoglu and Kulaksizoglu, 2016	64	40.17 (11.13)	56.2%	NA	39%	NA	100%	61	40.9 (14.19)	54%	NA	45.9%	NA
Moody 2017	25	26.1 (8.4)	52%	25.4 (8.1)	28%	0%	0%	44	29.9 (8.2)	45%	28.4 (5.8)	11%	0%
Özdin et al., 2017	163	34.51 (9.23)	63.2%	NA	NA	NA	NA	157	33.92 (9.56)	54,14%	NA	NA	NA
Pavlović et al., 2016	100	NA	NA	NA	NA	NA	NA	100	NA	NA	NA	NA	NA
Semiz et al., 2014	156	34.7 (7.9)	56.4%	25.4 (2.8)	NA	NA	58.3%	89	33.4 (9.7)	53.9%	24.9 (2.1)	NA	0%
Varsak 2017	58	29.08 (9.24)	50%	NA	NA	0%	0%	37	28.40 (6.82)	37.8%	NA	NA	0%
Yuksel et al., 2018	52	35.69 (10.32)	57.7%	NA	NA	NA	NA	53	37.06(12.29)	37.7%	NA	NA	NA

Table 3

Hematological parameters of SZ patients and controls. N: sample size; Plt: platelet count; WBC: white blood cell count; HbA1c: glycated hemoglobin A1c.

	SZ patients						Controls					
	Plt	WBC	Monocytes	HbA1c	PMN	CRP	Plt	WBC	Monocytes	HbA1c	PMN	CRP
Bustan et al., 2018	223 (44)	7.42 (2)	NA	58%	Suppl data	NA	224 (40)	7.12 (1.4)	NA	51.6%	NA	NA
Chow et al., 2015	261 (75)	7.8 (2.5)	NA	5.9 (1.1)	4.9 (2.1)	3.7 (5.3)	249 (53)	6.5 (1.5)	NA	5.6 (0.9)	3.6 (1)	0.9 (0.8)
Garcia-Rizo et al., 2017	NA	7.02 (2.2)	0.43 (0.2)	NA	4.25 (1.8)	NA	NA	6.5 (1.7)	0.36 (0.1)	NA	3.84 (1.3)	NA
Kulaksizoglu and Kulaksizoglu, 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Moody 2017	NA	7.3 (1.7)	0.60 (0.24)	NA	4.5 (1.5)	NA	NA	6 (1.8)	0.45 (0.19)	NA	3.2 (1.3)	NA
Özdin et al., 2017	254 (70.9)	7.84 (2.27)	0.4 (0.1)	NA	5.2 (1.7)	NA	235.3 (58.6)	7.43 (1.55)	0.4 (0.1)	NA	4.5 (1.2)	NA
Pavlović et al., 2016	NA	7.17 (2.03)	0.62 (0.54)	NA	4.38 (1.75)	NA	NA	6.25 (1.88)	0.42 (0.26)	NA	3.62 (1.24)	NA
Semiz et al., 2014	240.7 (55.6)	7.1 (1.4)	NA	NA	NA	NA	252.1 (43.6)	6.9 (1.3)	NA	NA	NA	NA
Varsak 2017	255.53 (65.06)	7.02 (3.75–29.0)	NA	NA	4.20 (1.48)	NA	254.72 (49.35)	7.24 (5.34–9.71)	NA	NA	4.03 (0.70)	NA
Yuksel et al., 2018	255.9 (62.36)	9.03 (2.10)	0.62 (0.24)	NA	5.94 (1.94)	NA	267.09 (71.79)	7.18 (1.56)	0.48 (0.14)	NA	4.28 (1.22)	NA

4. Discussion

This study made a systematic review and meta-analysis of the neutrophil to lymphocyte ratio (NLR) in patients with schizophrenia compared to controls. Ten studies with 804 patients and 671 controls were included. Our results show a significant increase of NLR in patients with schizophrenia, both in chronic disease and in first episode.

Based on the conjectured immunological contribution to schizophrenia pathophysiology (see Introduction section), a number of recent studies calculated the NLR in schizophrenia patients and controls, investigating this straightforward and inexpensive blood count marker's utility in disease management. To our knowledge, this is the first time that the findings of these studies are treated in a systematic review and meta-analysis. We demonstrate a significant increase of NLR by 0.65 (95% CI: 0.54, 0.86, $p < 10^{-5}$). This finding is robust but should be interpreted with caution in patients with high PMN count, given the confounding effect that the meta-regression analysis showed (coefficient: 0.502, SE: 0.130, $p < 0.001$). Two other parameters that exhibited marginal statistical significance is the patient age (coefficient: 0.032, SE: 0.16, $p = 0.055$) and the study location (coefficient: 0.374, SE: 0.193, $p = 0.053$). In a study of 3262 healthy subjects (Li et al., 2015), NLR showed a positive correlation with age (Pearson's $r = 0.161$, $p < 10^{-3}$).

The monocyte count did not affect the NLR mean difference. Still, in our included studies that reported monocyte count (Table 3, n = 5 studies), SZ patients' monocyte count was 9.91/μL higher than in the control group (95% CI: 2.77, 17.05, $p = 0.0065$) (Suppl. Fig. 1). In a retrospective study of 80 SZ patients and 80 controls, it was shown that, in the blood sample preceding the onset of SZ, monocyte activation was impaired regardless of generalized inflammation status (Weber et al., 2018). Monocyte count was also a predictor of PANSS total score ($\beta = 0.22$, $p = 0.02$) in non-obese subjects aged <40 years old with a negative urine drug screen (Miller et al., 2018).

Subgroup analysis showed that the NLR mean difference in AR patients was larger than in the FEP group, although this did not reach statistical significance. This finding may be attributable to the generalized

inflammatory response reported in antipsychotic-treated patients that results in granulocytosis (Ng et al., 2014). In addition, theoretically the NLR would not be a reliable marker in clozapine-treated patients with agranulocytosis (Drew, 2013). Even in patients with infection, clozapine can mask its manifestation. A recent systematic review of case reports (Clark et al., 2018) showed that 25% of its clozapine-administered population that had a diagnosed infection did not present with elevated WBC count, even in the absence of agranulocytosis. In our study, one included comparison (Chow et al., 2015) featured clozapine-treated patients (n = 68) and it also showed a significant difference in NLR.

In the meta-regression analysis, a modest but significant effect of antipsychotics (as expressed by percentage of patients having been administered an antipsychotic) was noted (coefficient (SE) = 0.006 (0.002), $p = 0.007$). This finding may imply that antipsychotic-medicated subjects may exhibit a higher NLR irrespectively of SZ diagnosis. The disruption of lymphocyte subpopulations in antipsychotic-treated SZ patients has been studied (Miller and Goldsmith, 2017). In a 2014 meta-analysis, seven included studies reported the lymphocyte count and other blood count parameters in patients treated with antipsychotic medication after an acute relapse (Miller et al., 2013). The authors noted a marginal ($p = 0.09$) association of antipsychotic treatment with a decrease in total WBC count. The lymphocyte subpopulations CD8 and CD56 were also increased. An animal study of the effect of olanzapine and clozapine on neutrophil kinetics reported a decrease of neutrophils only in the clozapine-treated group, irrespectively of the dosage (Ng et al., 2014). These documented alterations (trend for decrease in total WBC count, increase in specific lymphocyte subpopulations with a non-significant decrease in total lymphocyte count, varying effect on neutrophils with granulocytosis being the most common) can be held accountable for the small yet significant increase in NLR in studies that included more antipsychotic-treated patients. However, future studies should further investigate the diagnostic value of NLR for each specific antipsychotic medication as a differential response is to be expected given the unique mechanism of action of each drug group.

Table 4

Clinical characteristics of the SZ patients. PANSS: Positive And Negative Syndrome Scale; CGI: Clinical Global Impression; BPRS: Brief Psychiatric Rating Scale.

	PANSS+	PANSS−	PANSS	CGI	Duration	Family history	BPRS
Bustan et al., 2018	NA	NA	NA	5.5 (0.9)	NA	30.4%	NA
Chow et al., 2015	NA	NA	NA	NA	15.9 (9.7)	20%	NA
Garcia-Rizo et al., 2017	24.88 (6.5)	NA	NA		NA	NA	NA
Kulaksizoglu and Kulaksizoglu, 2016	17.6 (5.1)	17 (4.1)	71.6 (17.7)	NA	12 (7.32)	NA	NA
Moody 2017	NA	NA	NA	NA	NA	NA	NA
Özdin et al., 2017	NA	NA	NA	NA	9.89 (7.28)	NA	NA
Pavlović et al., 2016	NA	NA	NA	NA	NA	NA	NA
Semiz et al., 2014	NA	NA	NA	NA	9.02 (7.18)	NA	41.27 (6.71)
Varsak 2017	NA	NA	NA	NA	0	NA	36.65 (8.15)
Yuksel et al., 2018	26.63 (8.4)	21.06 (6.11)	42.75 (7.39)	5.27 (1.01)	48.08% >6 years	51.92%	NA
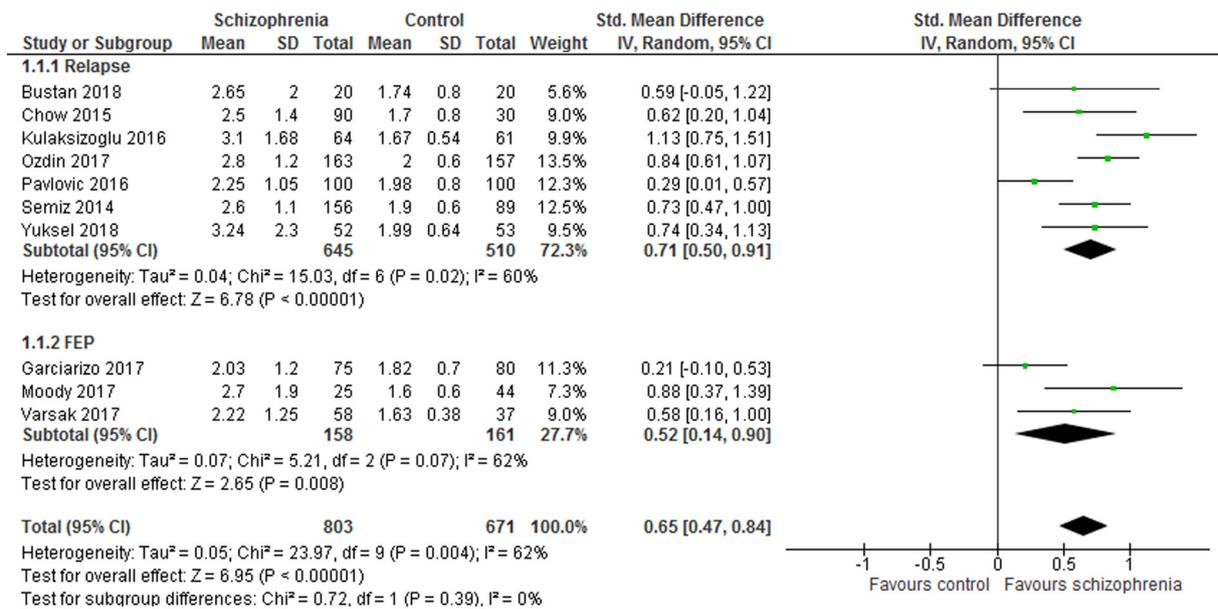
Fig. 2. Forest plot of NLR mean difference between SZ patients and controls. Subgroup analysis for acute relapse vs. first-episode psychosis indicates that the mean difference is significant in both groups. Random: random-effects model; std. mean difference: standardized mean difference; 95% CI: 95% confidence intervals.

A possible correlation of NLR with disease severity as manifested in clinical scores, e.g. BPRS, PANSS, is another major issue that would be of interest in the clinical follow-up of patients. Our analysis identified 3 studies (Garcia-Rizo et al., 2017; Kulaksizoglu and Kulaksizoglu, 2016; Yuksel et al., 2018) that reported the PANSS+, the positive symptomatology arm of the PANSS scale (Kay et al., 1987). As shown in Table 5, a differing PANSS+ score does not appear to alter the NLR mean difference. However, the possibility of NLR correlating with disease severity cannot be excluded from our analysis as sufficient data from other clinical scales was not available. In a cross-sectional study recruiting 199 SZ patients, the WBC count correlated with a more severe SZ symptomatology as manifested in BPRS ($r = 0.18$, $p = 0.014$) and especially the BPRS-anxious depression arm ($r = 0.21$, $p = 0.004$) (Fan et al., 2010).

4.1. Strengths and limitations of the study

In the present systematic review and meta-analysis, the difference of NLR in schizophrenia vs. controls is summarized for the first time. The literature search was extensive, encompassing a significant volume of the literature and applying strict exclusion criteria. A large number of patient data was included in the quantitative synthesis ($n = 804$ patients, $n = 671$ controls). In addition, various methodological and demographic parameters were examined as possible confounders, supporting the hypotheses that a) PMN count is a factor that alters the potential diagnostic value of NLR, b) antipsychotic use also influences the result. On the contrary, our results imply that smoking (as expressed by percentage of smokers) may not mask the NLR difference between schizophrenia patients and controls.

Post-hoc subgroup analysis of low vs. moderate-high quality studies allowed us to reach a homogeneous conclusion by omitting low-quality studies. Moderate-high quality studies show a uniform increase of the NLR in schizophrenia patients (SMD = 0.70, $p < 10^{-5}$, $I^2 = 0\%$). This strategy was further supported by the Baujat plot (Suppl. Fig. 3), which depicts the influence of each study on the overall Q statistic (Baujat et al., 2002). In the plot (Suppl. Fig. 3), 3 out of 4 studies omitted are depicted in the top right quartile. Finally, the tests for publication bias (Begg's test, Egger's test, trim-and-fill method) may imply that the calculated SMD is not distorted by publication bias. However, these results should be interpreted with caution as these tests perform suboptimally in a high between-study heterogeneity context (Ioannidis and Trikalinos, 2007), which is the case in the present meta-analysis ($I^2 = 62\%$).

Considering the limitations of our study, it should be noted that NLR as a potential biomarker does not have strictly established (large population) normal values. Forget et al. (2017) calculated a mean NLR of 1.65 [± 1.96 SD: 0.78–3.53] (95% CI [0.75–0.81], [3.40–3.66] respectively) in a healthy, adult, non-geriatric population, thus it may be applicable to our population (median age: 34.5 years old, range: 15.9–40.7 years old). Not enough data (sensitivity, specificity) was available to construct a ROC curve and investigate the potential value of NLR alone or as an adjunct in diagnosis and/or follow-up of patients. One included study (Kulaksizoglu and Kulaksizoglu, 2016) that constructed a ROC curve showed an AUC of 0.855 (cutoff NLR value: 1.98), also performing better than oxidative stress markers, e.g. oxidative stress index, total thiol. Furthermore, the possibility of selection bias cannot be excluded as 5 studies adopt a case-control design (Table 1). In addition, we could not evaluate the effect of negative symptomatology (e.g. PANSS-) or general mental condition (e.g. BPRS) on the NLR.
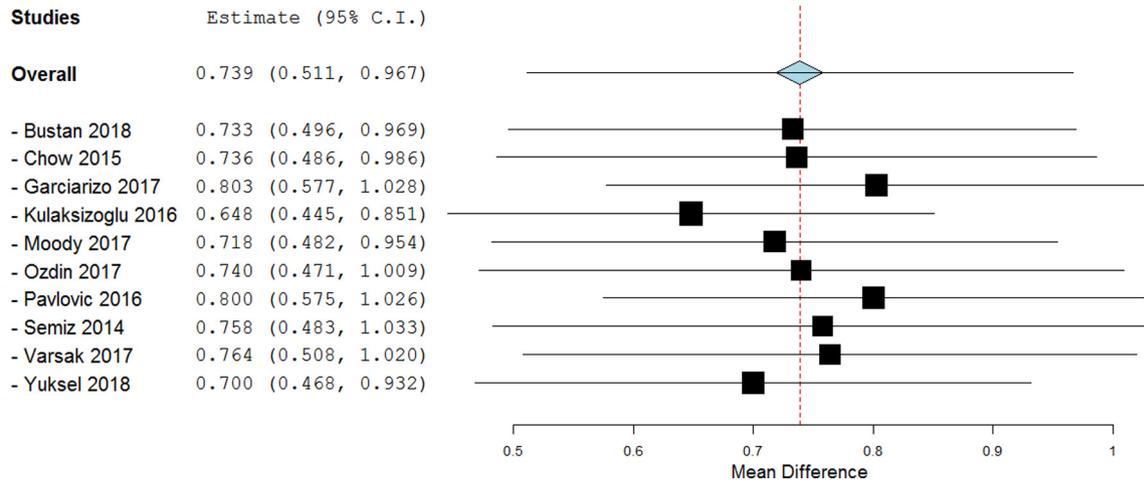
Table 5
Meta-regression analysis. Results that showed statistical significance (PMN count, antipsychotic use) are in bold. Patient age and study location (Turkey vs. other) both showed marginal significance ($p = 0.055$, $p = 0.053$ respectively). PMN: polymorphonuclear; PANSS+: positive arm of Positive And Negative Syndrome Scale.

Covariate	Level	Number of studies	Coefficient	Standard error	p-Value
Patient age	–	9	0.032	0.016	0.055
Sample size	Under 70	7		–	
	Over 70	3	−0.237	0.237	0.317
Study location	Turkey	5		–	
	Other	5	0.374	0.193	0.053
Duration of illness	Over 6 years	5		–	
		3	−0.093	0.210	0.659
Duration of illness	–	6	0.020	0.015	0.180
Family history	–	3	0.014	0.012	0.250
Gender	–	9	−0.021	0.018	0.242
Smoking status	–	5	−0.023	0.017	0.165
Patient PMN count	–	7	0.502	0.130	**<0.001**
Patient platelet count	–	6	0.003	0.008	0.691
Patient monocyte count	–	5	1.100	2.354	0.640
Antipsychotic use	–	7	0.006	0.002	**0.007**
PANSS+	–	3	−0.077	0.071	0.279

Fig. 3. Results of the leave-one-out meta-analysis. One study was omitted sequentially and the new effect size was estimated. No study altered the significance of the result.

4.2. Implications for current clinical practice and future research

The present systematic review and meta-analysis supports the significant increase of NLR in patients with schizophrenia, both in chronic type and in FEP. The application of this marker in clinical practice requires the description of its normal values in the general population, its potential change after intervention (e.g. antipsychotic administration) and its correlation with disorder activity. Thus, a large-scale, prospective study design would resolve these issues. A common repository for patient data (demographic parameters, disease status, treatment) would facilitate future overviews of NLR in schizophrenia.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2018.12.017.

Conflict of interest

All authors have no conflicts of interest to disclose.

Role of the funding source

No funding was secured for this study. All authors have no financial relationships relevant to this article to disclose.
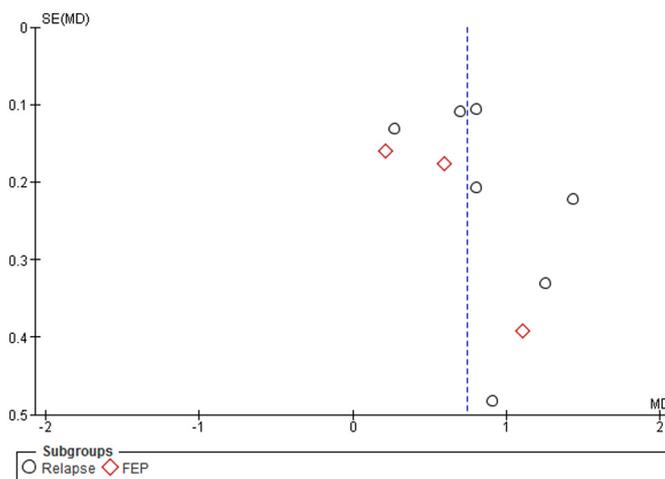

Fig. 4. Funnel plot. The visual assessment may indicate divergence from the expected funnel shape but publication bias tests did not support the existence of publication bias (see Section 3.5.3). FEP: first-episode psychosis; SE (MD): standard error of the mean difference; MD: mean difference.

CRediT authorship contribution statement

Vasilios Karageorgiou: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Gerasimos P. Milas:** Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ioannis Michopoulos:** Supervision, Validation, Writing - review & editing.

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