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Neutrophil to Lymphocyte Ratio in Patients With a First Episode of Psychosis: A Two-Year Longitudinal Follow-up Study

Miquel Bioque[*,1,2,3,4], Ana Catarina Matias-Martins[3], Vicent Llorca-Bofí[3], Gisela Mezquida[1,2,3,5], Manuel J. Cuesta[6,7], Eduard Vieta[2,3,4,8], Sílvia Amoretti[2,3,8,9], Antonio Lobo[3,10], Ana González-Pinto[3,11], Carmen Moreno[3,12,13], Alexandra Roldán[3,14,15], Anabel Martinez-Aran[2,3,4,8], Immaculada Baeza[2,3,4,16], Daniel Bergé[3,17,18], Clemente García-Rizo[1,2,3,4], Sergi Mas Herrero[5,3], Miquel Bernardo[1,2,3,4], and 2EPs GROUP[19]

[1]Barcelona Clínic Schizophrenia Unit (BCSU), Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain; [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Centro de Investigación Biomédica en red en salud Mental, Instituto de Salud Carlos III, Barcelona, Spain; [4]Department of Medicine, University of Barcelona, Barcelona, Spain; [5]Department of Basic Clinical Practice, Pharmacology Unit, University of Barcelona, Barcelona, Spain; [6]Department of Psychiatry, Hospital Universitario de Navarra, Pamplona (Navarra), Spain; [7]Navarra Institute of Health Research (IdiSNA), Pamplona, Spain; [8]Bipolar and Depressive Disorders Unit, Institute of Neuroscience, Hospital Clinic Barcelona, Barcelona, Spain; [9]Group of Psychiatry, Mental Health and Addictions, Vall d'Hebron Research Institute (VHIR), Psychiatric Genetics Unit, Vall d'Hebron Research Institute (VHIR), Catalonia, Barcelona, Spain; [10]Department of Medicine and Psychiatry, Universidad de Zaragoza, Zaragoza, Spain; [11]Hospital Universitario Araba, Servicio de Psiquiatria, UPV/EHU, Bioaraba, Spain; [12]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain; [13]School of Medicine, Universidad Complutense, Madrid, Spain; [14]Psychiatry Department, Institut d'Investigació Biomèdica-Sant Pau, (IIB-SANT PAU), Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [15]Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [16]Child and Adolescent Psychiatry and Psychology Department, SGR-881, Hospital Clínic de Barcelona, Barcelona, Spain; [17]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [18]Pompeu Fabra University (UPF), Barcelona, Spain

[*]To whom correspondence should be addressed; Barcelona Clínic Schizophrenia Unit, Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Spain; tel: 34932275400 (X 4568), fax: 34932275548, e-mail: mbioque@clinic.cat

[19]*2EPs GROUP:* Santiago Madero, Jairo González, Álvaro Andreu-Bernabeu, Sandra Recio, Judit Selma,Maria Tonda, Edurne García-Corres, Jéssica Fernández-Sevillano, Concepción De-la-Cámara, Pedro Modrego-Pardo, Mª José Escartí, Marta Pérez-Rando, Guillermo Vázquez, Silvia Cristeto, Jose Sanchez-Moreno, Anna Gimenez-Palomo, Josefina Castro-Fornieles, Elena de la Serna, Fernando Contreras, Leticia González-Blanco, Pilar A Sáiz, Miguel Gutiérrez-Fraile, Arantzazu Zabala, Luis Sanchez-Pastor, Roberto Rodriguez-Jimenez, Judith Usall, Anna Butjosa, Edith Pomarol-Clotet, Salvador Sarró, Ángela Ibáñez, Ana M. Sánchez-Torres and Vicent Balanzá.

***Background and Hypothesis*: A pro-inflammatory phenotype has been related to psychotic disorders. The neutrophil-lymphocyte ratio (NLR) is an accessible biomarker that could be helpful to characterize this systemic inflammation state. *Study Design*: This study evaluated the NLR in a cohort of 310 subjects with a first episode of psychosis (FEP) and a matched group of 215 healthy controls, recruited in 16 Spanish centers participating in the PEPs Project. We investigated the NLR measures over 2 years in a prospective, naturalistic study. *Study Results*: At baseline, the FEP group showed a significant higher mean NLR compared to the control group (1.96 ± 1.11 vs 1.72 ± 0.74, $P = 0.03$). These ratio differences between groups grew at the 24 months follow-up visit (2.04 ± 0.86 vs 1.65 ± 0.65, $P < 0.001$). Within the FEP group, there were no significant differences in NLR across the follow-up visits, between genders or diagnosis groups (affective vs nonaffective). NLR values did not correlate with the Positive and Negative Symptoms Scale scores. The group of patients who did not reach remission criteria at the end of the study showed a significant higher NLR than those who remitted (2.1896 ± 0.85 vs 1.95 ± 0.87, $P = 0.042$). A significant correlation between antipsychotic doses and NLR was found at the two-years follow-up visit (r=0.461, $P < 0.001$). *Conclusions*: Our results highlight the existence of an underlying predisposition of FEP patients to present an increased mean NLR. The use of NLR in clinical practice could be helpful to identify this inflammatory imbalance.**

Key words: antipsychotics/first episode/inflammation/neutrophil to lymphocyte ratio/NLR/psychosis/schizophrenia

Introduction

Psychotic disorders are among the most disabling mental disorders.[1] A first episode of psychosis (FEP) is characterized by the presence of positive symptoms (delusions, hallucinations, and bizarre behavior), usually accompanied by negative (apathy and alogia), affective and cognitive symptoms. Around 3% of the general population suffers a psychotic episode during their life, generally appearing in adolescence or early adulthood.[2]

The underlying pathophysiology of the FEP remains unclear, being considered multifactorial and based on genetic and environmental interaction.[1,3] In the last decade, several processes involving inflammatory pathways and consequent oxidative/nitrosative stress have been linked to schizophrenia and related psychotic disorders, suggesting both peripheral and central pro-inflammatory state.[4,5] Scientific evidence supporting the hypothesis that inflammatory changes may play an important role in psychotic disorders has mostly been described in the chronic stage of the disorder.[4] New data are supporting that low-grade proinflammatory changes may already be present from early phases.[6–8] Thus, it has been reported that, compared to healthy controls, patients with a FEP have a pro-inflammatory imbalance (ie, higher levels of homocysteine, interleukin-6, and tumoral necrosis factor alpha), and a reduced antioxidant capacity (ie, lower levels of docosahexaenoic acid (DHA).[8]

Neutrophil to lymphocyte ratio (NLR) has been identified as a marker of systemic inflammation in a vast spectrum of diseases, especially in different cancers, since it is associated with an increase in cytokines and C-reactive protein (CRP).[9] The use of NLR is interesting at the clinical practice since it is an inexpensive, easy to use marker of disease, calculated from the complete blood count dividing the number of neutrophils by the number of lymphocytes. In mental disorders, a recent study has proposed that NLR could be a predictor for bipolar depression.[10] Another recent study has showed that high NLR upon admission is associated with a better response in psychotic depression.[11] A systematic review and metanalysis showed increased NLR both in FEP and in multi-episodic schizophrenia, but it is not entirely clear whether this is a characteristic of the disease itself or whether treatment or metabolic changes could influence this value.[12] Another metanalysis has reported that in FEP compared with controls, neutrophils and monocytes were significantly increased.[13]

In this vein, the study of the population with a FEP is of great interest since it mitigates the effect of confounding variables. Cohort studies are crucial to identify biomarkers and predictors of outcome in this population.[14,15] Our group has previously reported that isolated neutrophil count is associated with reduced gray matter and enlarged ventricles in FEP.[16] The aim of the present study is to analyze the NLR differences between a well-characterized group of patients with a FEP and a control group during a two-year follow-up.

Subjects and Methods

Subjects

From April 2009 to April 2012, 16 Spanish centers participated in PEPs project ("Phenotype-genotype and environmental interaction. Application of a predictive model in first psychotic episodes").[15,17] 335 patients with a FEP and 253 healthy controls were recruited. The local ethics committee of each center approved the study, and it was obtained an informed consent from all participants or from parents/legal keeper in under 18-year-old subjects. The rationale and the complete clinical protocol used in the PEPs project were previously published.[17]

All patients included in this study were aged 7–35 years old, presented their first psychotic symptoms (positive symptoms or disorganization) for at least 1 week in the previous 12 months and spoke Spanish correctly. Patients with mental retardation according to the Diagnostic and Statistical Manual of mental disorders, 4th edition Text Revised (DSM-IV-TR) criteria,[18] history of head injury with loss of consciousness, and presence of an organic disease with mental repercussions were excluded. Those who met the inclusion criteria to this study were invited to participate, on either an inpatient or outpatient basis.

Healthy controls were matched by age, gender, and socio-economic status (measured by Hollingshead-Redlich scale [±1 level])[19] and they also had to speak Spanish correctly. The exclusion criteria of control subjects were the same as for patients plus having a personal antecedent of psychotic and/or major affective disorder and/or having a first-degree relative with history of psychotic disorders.

Diagnostic, Demographic, and Clinical Data Collection

In order to confirm each patient diagnosis, the Spanish translation of the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL) was used to evaluate current and past psychopathology according to DSM-IV-TR criteria for children and adolescents,[20] and the Spanish translation of Structured Clinical Interview for DSM Disorders (SCID) parts I and II (SCID-I & II) for adults.[21]

A dichotomous categorization of affective vs nonaffective psychosis was used for some analyses. Affective psychosis includes DSM-IV-TR diagnosis of unipolar depression or bipolar disorder with psychotic features and schizoaffective disorder.[18] Psychotic symptoms were assessed using the validated Spanish version of the Positive and Negative Symptom Scale (PANSS).[22,23] To determine the rate of patients who achieve symptomatic remission during the last 6 months of the 2-year follow-up, we implemented the Remission in Schizophrenia Working Group (RSWG) criteria by Andreasen et al.[24]

As the PEPs Project was an observational naturalistic study, there were no specific guidelines for treatments, so the antipsychotic treatment was based on clinician's choice.[25] Thus, dosing, comedications, duration, or treatment changes were based on clinical need and registered in the common data base. To compare the different antipsychotics between them, the prescribed daily doses of antipsychotics were converted to an estimated equivalent amount of chlorpromazine (CPZ) following the international consensus.[26] Baseline polypharmacy was registered considering simultaneous treatment in the same patient with one antipsychotic together with an antidepressant, an anticholinergic drug, a mood stabilizer, a benzodiazepine, or another antipsychotic. A previous report gave a full description of the psychopharmacological treatment used in the PEPs project.[25]

Study Assessments

At baseline, a complete medical history was taken. Laboratory data of lymphocytes and neutrophils were assessed at baseline and at 2-, 6-, 12-, and 24-months follow-up visits in patients, and at baseline and at 24 months visit in controls. K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey) were used to collect blood samples which were stored at −20°C and sent to each site laboratory for analysis. The reference values at each site were recorded in a common database called GRIDSAM, where individual values were homogenized and included.[17,27]

Statistical Analysis

Continuous data are expressed as a mean ± standard deviation and categorical data are expressed as absolute values and percentages. A two-tailed Chi-square test was used to assess differences in categorical variables and a two-tailed *t*-test was used to assess differences on continuous variables with approximately normal distributions. The normality of continuous variables was tested using the Kolmogorov–Smirnov and Shapiro–Wilk tests, and the equality of the variance between groups was assessed using Levene's test. The Mann–Whitney U was used to assess nonparametric variables. Within the FEP group, a one-way repeated measures ANOVA was conducted to compare changes in patients' NLR measures between visits.

A mixed between-within subjects' analysis of variance was conducted to assess the impact of gender and diagnosis (affective vs nonaffective psychosis) on NLR measures. Wilks' Lambda was used to explore the relationship between gender and diagnostic and NLR measures at the 24 months of follow-up. Correlation of NLR with clinical scales scores was assessed by Spearman rank tests.

The relationship between the NLR outcomes and antipsychotic mean daily doses (in chlorpromazine equivalents) was investigated using Pearson correlation coefficient. A simple linear regression was used to evaluate the relationship between the antipsychotic doses and the NLR values.

Two-tailed *P*-values < .05 were considered to be of statistical significance. Statistical analyses were performed using IBM-SPSS v.25.[28]

Results

Baseline Characteristics and Study Drop-outs

From the 335 patients with a FEP and 253 healthy controls participants of the PEPs project, 25 patients, and 38 control subjects were excluded from the present study as NLR data were not available. Demographic, anthropometric, and diagnosis characteristics are presented in table 1. There were no differences between cases and controls in the matching variables, so the differences found do not result from an inadequate case-control group matching, or weight at baseline.

Of the total number of participants who started the study, it was possible to obtain the NLR data from 184 cases and 143 controls at two years. There were no baseline differences in gender, age, weight, or ethnicity among patients and controls who dropped out of follow-up, with the exception that a significant higher proportion of patients diagnosed with non-affective psychosis dropped out of the study early (43.2% vs 27.5%, χ^2=4.41, P = .036).

NLR Comparison Between FEP and Control Groups

At baseline, the FEP group showed a higher mean NLR compared to the control subjects (1.96 ± 1.11 vs 1.72 ± 0.74, P = .03). Mean NLR differences between cases and controls were even higher at the 24 months of follow-up (2.04 ± 0.86 vs 1.65 ± 0.65, P < .001). See table 2 for details.

There were no differences in the mean NLR values at baseline and 24 months within the control group (1.72 ± 0.84 vs 1.64 ± 0.65, F = 1.54, P = .28).

NLR Measures in the Follow-up Visits in Between FEP Group

Mean NLR values at baseline, 2, 6, 12, and 24 months within the FEP group are described in table 3. The one-way repeated measures ANOVA analyses did not detect statically significant increases in the NLR within the FEP group across the follow-up visits.

Within the FEP group, there were no differences at baseline NLR between women and men (2.07 ± 1.31 vs 1.91 ± 0.99; U = 10 348; P = .67). After 24 months of follow-up, there were still no differences (2.16 ± 0.96 vs 1.98 ± 0.81; P = .2). There were significant lower baseline NLR values in the underage (<18 years, n = 51)

Table 1. Demographic, Anthropometric, and Baseline Characteristics

	FEP (n = 310)	Control (n = 215)	Statistic	P-value
Age – years [mean (SD)]	23.6 ± 6	24.2 ± 6.4	$t = -1.07$	.29
Gender (male) – no. (%)	207 (66.8%)	140 (65.1%)	$X^2 = 0.16$	.69
Ethnic group – no. (%)			$X^2 = 8.59$	.28
Caucasian	266 (85.8%)	193 (89.8%)		
Gipsy	5 (1.6%)	0 (0)		
Maghrebian	7 (2.3%)	2 (0.9%)		
Sub-saharan	2 (0.6%)	0 (0)		
Asian	4 (1.3%)	1 (0.5%)		
Caribbean	7 (2.2%)	3 (1.4%)		
Hispanic	16 (5.2%)	12 (5.6%)		
Other	3 (1%)	4 (1.8%)		
Weight – (kg)	69.26 ± 14.06	69.23 ± 12.75	t = 0.023	.98
Tobacco use				
Active smoker (yes) – no. (%)	188 (60.6%)	70 (32.6%)	$\chi 2 = 43.77$	$P < .001$
Number of cigarettes per month	239.63 ± 263.65	68.45 ± 144.55		
Diagnosis				
Affective psychosis	51 (16.4%)	–		
Bipolar disorder	37 (11.9%)	–		
Major depressive disorder	7 (2.3%)	–		
Schizoaffective disorder	7 (2.3%)	–		
Non-affective psychosis	259 (83.6%)	–		
Psychotic disorder NOS	99 (31.9%)	–		
Schizophreniform disorder	62 (20%)	–		
Schizophrenia	48 (15.5%)	–		
Brief psychotic disorder	48 (15.5%)	–		
Delusional disorder	2 (0.6%)	–		
hospitalization				
Patients with hospitalization (%)	231 (74.5%)	–		
Duration (days) – mean (SD)	21.02 ± 22.48			
PANSS				
Positive subscale score – mean (SD)	18.69 (8.01)	–		
Negative subscale score – mean (SD)	18.6 (8.15)	–		
General subscale score – mean (SD)	37.8 (12.96)	–		
Total score – mean (SD)	75.1 (24.7)	–		

Note: FEP, First Episode of Psychosis; NOS, Not otherwise specified; PANSS, Positive and Negative Symptom Scale.

Table 2. NLR Comparison Between the Patients and Healthy Control Group at the Two-year Follow-up Visit

	FEP	Control	Statistic	P-value
NLR baseline – mean (SD)	1.96 ± 1.11 (n = 310)	1.72 ± 0.74 (n=215)	$U = 29.637.50$	**.03***
NLR 24 months – mean (SD)	2.04 ± 0.86 (n = 184)	1.65 ± 0.65 (n=143)	$U = 19.883.00$	**<.001***

Note: FEP, First Episode of Psychosis.
*$P < .05$ marked in bold.

Table 3. NLR Mean Measures for Patients Along All the Visits of the PEPs Study

	Baseline (n = 310)	2 Months (n = 140)	6 Months (n = 140)	12 Months (n = 140)	24 Months (n = 184)	Statistics	P-value	Partial Eta Squared[a]
NLR	1.96 ± 1.11	2.08 ± 1.11	1.99 ± 1.09	1.93 ± 0.91	2.04 ± 0.86	WL = 0.974 F = 0.895	.47	0.03

Note: WL, Wilk's Lambda.
[a]Partial Eta Squared value of effect size (0.01–0.05 = small, 0.06–0.13 = moderate, >0.14 = large).

cases: 1.62 ± 0.68 vs 2.03 ± 1.17, $U = 8048.5$, $P = .014$), but not at the end of the follow-up.

As expected, a greater proportion of patients smoked tobacco compared to controls at baseline (60.6% vs 32.6%, $\chi 2=43.77$, $P < .001$). However, both in the group patients and in controls, there were no differences in baseline NLR between smokers or non-smokers. NLR values also did not correlate with the number of cigarettes smoked daily ($r = 0.05$, $P = .21$).

There were no significant differences between diagnostic categories (nonaffective vs affective psychosis) neither at baseline (1.96 vs 2.00; $t = -0.251$, $P = .802$) nor at 24 months of follow-up (1.94 vs 2.06; WL = 0.94, $F = 2.14$, $P = .08$). No differences in NLR values were found between patients who had required hospital admission at baseline and those who did not, and the ratio was not correlated with the number of days hospitalized, both at baseline and at the end of the study. Nor was there a statistically significant correlation between NLR values and PANSS scores (positive, negative, general, and total) at both baseline and 24-month follow-up visits.

Of the 190 patients evaluated at the two-year follow-up visit, 123 (64.7%) met the RSWG remission criteria. The percentage of patients with affective psychosis who achieved remission at two years of follow-up was higher than the nonaffective psychosis group (80% vs 61.3%, $\chi^2=4.38$, $P = .036$). The group of patients who did not reach remission criteria at the end of the two-year follow-up showed a significantly higher NLR than the group in remission (2.19 ± 0.85 vs 1.95 ± 0.87, $U = 3896.5$, $P = .042$).

Psychopharmacological Treatment

Psychopharmacological treatment of the FEP cohort at baseline and at the 24-months follow-up is presented in table 4. At baseline, 285 patients were taking antipsychotics and 25 were antipsychotic naïve. When comparing the baseline NLR of these two groups there were no statistically significant differences (1.97 vs 1.85; $t = 0.548$, $P = .584$). There were not differences in baseline NRL between the groups who received mono and polytherapy (1.97 vs 1.99; $t = 0.117$, $P = .907$).

At baseline, we found a tendency of positive correlation between equivalent amount of CPZ doses and basal NLR ($r = 0.11$, $P = .056$). At 24 months of follow-up, this tendency was achieved, finding a statistically significant correlation between equivalent daily doses of CPZ and NLR ($r = 0.461$, $P < .001$) at 24 months of follow-up. A simple linear regression identified that CPZ equivalent doses explained the 21% of the variance in NLR values ($F = 25.13$, $P < .001$) at the end of the follow-up.

The group of patients who did not reach remission criteria at the end of the two-year follow-up showed a significantly higher mean antipsychotic doses than the group that reached remission (507 72 ± 310 84 vs 269 85 ± 243 73; $t = -4.17$; $P = .001$).

Table 4. Psychopharmacological Treatment in the Baseline and in the Two-year Follow-up Visit

	Baseline ($n = 310$)	24 Months ($n = 105$)
Antipsychotic treatment		
No antipsychotic therapy – no. (%)	25 (8.1%)	17 (5.5%)
Monotherapy – no. (%)	217 (70.0%)	77 (24.8%)
Polytherapy – no. (%)	68 (21.9%)	11 (3.5%)
2 antipsychotics – no. (%)	62 (20%)	10 (3.2)
3 antipsychotics – no. (%)	5 (1.6%)	1 (0.3%)
4 antipsychotics – no. (%)	1 (0.3%)	0
Chlorpromazine equivalent mean dose – mg/day (SD)	611.10 ± 449.91	346.30 ± 289.06
Subjects with other treatment		
Anticholinergics	39 (12.6%)	4 (1.3%)
Antidepressants	41 (13.2)	18 (5.8%)
Mood stabilizers	40 (12.9%)	27 (8.7%)
Benzodiazepines	123 (39.7%)	17 (5.5%)

The use of other psychopharmacological treatments (antidepressants, anticholinergics, mood stabilizers, or benzodiazepines) did not correlate with the NLR, neither at baseline nor in the two-year follow-up visit.

Discussion

A variety of mechanisms involving the immune system and an inflammatory activation has been related to the pathophysiology of schizophrenia and related psychosis.[4] Inflammatory ratios, especially NLR and monocyte/lymphocyte ratio (MLR), may be useful to detect this activation.[12,13,29] In this largest, longitudinal, case-control study analyzing NLR in FEP, we found: (1) Higher mean NLR values in a cohort of subjects with a FEP compared to a matched control group at baseline. These differences grew at the 24 months of follow-up; (2) Within the FEP group, there were no statistically significant differences in NLR across the study follow-up visits; (3) There was no significant correlation between NLR values and PANSS scores or hospitalization, but patients who reached remission criteria at the end of the two-year follow-up showed significantly lower mean NLR values than the non-remitted group; (4) significant lower NLR values at baseline in underage patients, compared to adults; (v) No significant differences in NLR values between genders, tobacco users/nonusers or affective vs non-affective psychosis; and (6) a significant positive correlation between antipsychotic equivalent daily doses of CPZ and NLR at the end of the study.

A major part of these findings are in line with previous studies.[12,30–32] Recent systematic reviews and metanalyses have concluded that NLR in schizophrenia patients is

increased, both in chronic disease and in first-episode psychosis.[12,13,29]

Steiner and collaborators found that positive symptoms correlated with neutrophil counts, describing a decreasing in NLR of FEP group after 6 weeks of follow-up of treatment, suggesting that these cells may act as a modulator of acute disease severity.[32] In our study, we didn't find a significant correlation between NLR and PANSS scores. These differences could be related, at least in part, to the fact the mean PANSS total score from our cohort was notably higher (more severe) at baseline than in the study from Steiner and collaborators (75.1 vs 31.0). In our study, we also did not find a correlation with another indirect marker of severity at baseline, such as the need for hospitalization and its duration. However, we found that the group of patients who did not reach remission criteria at the end of the two-year follow-up showed a significantly higher NLR than the group in remission. Similarly, Labonté et al. reported NLR decreases following treatment in the responsive group exclusively, but not in treatment resistant schizophrenia group.[33] Our results could be explained, at least in part, with the finding that nonremitted patients showed significantly higher mean antipsychotic doses than remitted at the two-year follow-up visit. These findings underscore the interest of studying NLR as a marker of severity in the evolution of psychotic disorders.

When analyzing by gender, there were no differences in both subgroups at baseline in the mean of NLR as it was observed in a similar study.[31] This observation was maintained during the 24-month follow-up. There was also no correlation between basal NLR values and smoking tobacco. On the other hand, we found significant lower NLR values at baseline in underage patients, compared to adults. This point could be related to a greater predisposition to present neutropenia in patients with an early onset of psychosis, which is especially relevant when starting certain antipsychotics, such as clozapine.[34] These differences, which were not maintained at 24 months, indicate the importance of considering age as a potential confounding factor to be considered when assessing the use of NLR in adolescent patients.

There is evidence of high neutrophil count and NLR in patients suffering from nonaffective psychosis and mood disorders compared to healthy controls.[29,35,36] Mazza and collaborators found in acute, multiepisodic patients that NLR was significantly more elevated in schizophrenia patients than in affective psychosis.[37] In our study, with patients in early phases, the affective psychosis subgroup showed comparable NLR values to the nonaffective psychosis subgroup, both at baseline and at 24 months of follow-up.

We did not find differences between the patients who were taking antipsychotics and antipsychotic naïve patients at the study entry. There is an interest in the field in clarifying the effects of antipsychotic treatment on NLR, having been proposed its increase after antipsychotic treatment.[12] However, there are studies that did not find significant differences in NLR between patients who had been receiving antipsychotic treatment and those who had not,[38–40] similarly to our results.

At baseline, we found a statistical trend for a positive correlation between equivalent amount of CPZ doses and NLR. This tendency was confirmed at the end of the 24 months of follow-up, when a statistically significant positive correlation between antipsychotic equivalent daily doses of CPZ and NLR was found. The previous study from Steiner and collaborators found that equivalent amount of CPZ doses was correlated negatively with the neutrophils count from baseline to follow-up.[32] The differences in antipsychotics patterns and psychotic symptoms severity between both studies could explain this contradictory results.

Another point we have focused on in our study was the effects of antipsychotic mono- and poly-therapy, which is a very common practice in everyday clinical practice.[25] At baseline, there were no differences in NLR between the patients who were in mono- and poly-therapy. The use of antidepressants and mood stabilizers did not affect the NLR value.

Some limitations should be considered at the moment of the analysis of these results. Firstly, patients could be included in the study being under antipsychotic treatment, which could be affecting the NLR in some cases. As the mean duration of the antipsychotic treatment at the study entry was of 54.08 days,[25] this effect could be mild. Correlation analyzes were performed to establish the relationship between antipsychotic doses and NLR results at both the baseline and final visit levels. Secondly, since the PEPs Project was a naturalistic study, treatments given during the follow-up were chosen by the clinicians according to clinical needs, so there was a certain level of heterogeneity of antipsychotic patterns.[25] In order to avoid these differences, a randomized controlled trial would be necessary. Thirdly, as most participating sites in this study are tertiary care centers linked to the Spanish network of translational research (CIBERSAM),[41] patient samples, and therapeutic strategies may differ from those used in other areas.[42] Besides, to better characterize the response to treatment and the clinical evolution during follow-up, we applied the RSWG remission criteria to the whole group of cases, despite the fact that a small percentage of patients had been diagnosed with an affective psychosis (16.4%), of which a greater proportion met these criteria (80% vs 61.3%, χ^2=4.38, P = .036). Finally, the relatively high number of drop-out during the follow-up period (40.6% of the cases and 33.5% of the controls) may have limited the capability to detect differences between groups in some analyses at the end of the study, although we did not find differences in demographic and baseline clinical variables between dropouts and completers.

This study had the advantage of having strict inclusion/exclusion criteria, a diagnostic evaluation done with a very comprehensive protocol, patients with a wide age of inclusion, trying to replicate the natural history of the diseases, which makes this sample as close as possible to the reality of the FEP population,[17] mitigating the effect of confounding variables. Besides, blood analyses were taken following a strict, unified protocol, which is especially relevant since leukocyte levels fluctuate throughout the day.[42]

Dysregulation of immunological and inflammatory processes has been repeatedly reported in peripheric samples from subjects with psychotic disorders,[4,43] and current research also suggests that schizophrenia patients may also present CSF abnormalities, including signs of blood-brain barrier impairment and inflammation.[44] However, despite numerous studies of the complex components of innate and adaptive immune processes, it still has not been clarified whether this imbalance occurs before psychosis (related to etiology), during its evolution (related to pathophysiology), or if it is an epiphenomenon accompanying it.[4,43] In this context, NLR values can be an accessible approach to know the inflammatory status in an individual, but the available evidence in FEP subjects does not rule out the possibility of alternative explanations to this association. Although NLR in peripheral blood can provide insights into the potential immunological contribution to psychosis, the central nervous system (CNS) is protected by the blood–brain-barrier. Thus, peripheral blood levels of NLR might not translate directly to changes within the central nervous system. In this line, Campana et al. have recently described no significant relationship between CSF alterations and peripheral inflammation measured with CRP, suggesting a FEP subgroup with an intrathecal inflammatory etiology of the disease.[45] NLR in blood and CSF at one time has been previously investigated in other fields like acute bacterial meningitis,[46] but studies in psychiatric patients are still scarce.[44,47] Future studies should focus on CSF measure to better understand the inflammatory process in the CNS in FEP.

Despite our attempt to control potential confounding factors (such as age, gender, tobacco use, or drug treatment), these variables and others (ie, primary and treatment-related metabolic differences, different health habits including nutrition and physical activity, gut dysbiosis, substance abuse, etc.) could be mediating in the differences we found between FEP and control groups.

It should also be noted that from other fields of medicine, for example in cancer, we have learned that the low diagnostic utility of unspecific inflammatory markers (such as C-reactive protein or erythrocyte sedimentation rate) is due to poor sensitivity.[48] In terms of NLR, oncological meta-analysis supported the relationship between elevated NLR and poor outcomes in cancer.[48] However, current evidence does not allow to determine whether the association is causal or due to confounding or reverse causation. Furthermore, the lack of a clinically relevant and accepted NLR cut-off hampers the applicability of the index in clinical practice. All these arguments are transferable to psychiatry, with fewer studies supporting causality and even less consensus on accurate cut-offs.[49] For all this, it is needed more evidence and clinical experience using NLR as a biomarker to determine neurobiological phenotypes or to be integrated in our treatment- decision algorithms (ie, choosing certain antipsychotic drug or adding co-adjuvant antiinflammatory drugs).

Overall, these findings support the existence of an underlying process in FEP patients to present an increased mean of NLR since the very beginning of the disorder, so its determination could be a useful tool to characterize this inflammatory imbalance, to define prognosis, and response to treatment in this population. As NLR is used in the scientific literature, once it starts to be used in the clinical practice, it would be interesting to describe its normal values in the general population. Future studies would also help to clarify the effects of antipsychotics over NLR and its correlation with clinical response, testing its utility as an accessible biomarker for treatment response.

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Author contribution

M.Bi. collected the clinical data, managed and analyzed the clinical data and wrote the first version of the paper; A.C.M.M. analyzed the clinical data and wrote the first version of the paper; G.M. collected the clinical data and managed the first version of the data base; M.Be. coordinated the PEPs study. All the authors contributed to the final version of the paper.

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