Title: Inflammatory blood cells and ratios at remission for psychosis relapse prediction: A three-year follow-up of a cohort of first episodes of schizophrenia.

Abstract:

Background: The clinical course following a first episode of schizophrenia (FES) is often characterized by recurrent relapses, resulting in unfavorable clinical and functional outcomes. Inflammatory dysregulation has been implicated in relapse risk; however, the predictive value of inflammatory blood cells in clinically remitted patients after a FES has not been previously explored.

Methods: In this study, we closely monitored 111 patients in remission after a FES until relapse or a three-year follow-up endpoint. The participants were recruited from the multicenter 2EPS Project. Data on inflammatory blood cells and ratios were collected at baseline and at the time of relapse or after three years of follow-up.

Results: Monocyte counts (OR=1.91; 95% CI=1.07-3.18; p=0.009) and basophil counts (OR=1.09; 95% CI=1.01-1.12; p=0.005) at baseline were associated with an increased risk of relapse, while the platelet-lymphocyte ratio (OR=0.98; 95% CI=0.97-0.99; p=0.019) was identified as a protective factor. However, after adjusting for cannabis and tobacco use during the follow-up, only monocyte counts (OR=1.73; 95% CI=1.03-2.29; p=0.027) and basophil counts (OR=1.08; 95% CI=1.01-1.14; p=0.008) remained statistically significant. ROC curve analysis indicated that the optimal cut-off values for discriminating relapsers were 0.52 x 10^9/L (AUC: 0.66) for monocytes and 0.025 x 10^9/L (AUC: 0.75) for basophils. When considering baseline inflammatory levels, no significant differences were observed in the inflammatory biomarkers at the endpoint between relapsers and non-relapsers.

Conclusion: This study provides evidence that higher monocyte and basophil counts measured at remission after a FES are associated with an increased risk of relapse during a three-year follow-up period.

Keywords: First episode schizophrenia, second episode, relapse, monocyte, basophil

1. Introduction

Clinical course in schizophrenia (SCZ) is often characterized by recurrent relapses (Emsley, 2013), which are associated with adverse outcomes such as treatment-resistant symptoms, cognitive decline, and functional disability (Keepers, 2020; Takeuchi, 2018). Relapse occurs within 1 year for approximately 30% (Brown, 2020) of individuals with SCZ and up to 50% over 3 years (Bioque, 2022b). Several factors have been identified to increase the risk of relapse, including non-adherence to medication, persistent substance use and poorer premorbid adjustment (Alvarez-Jimenez, 2012; García, 2016; González-Pinto, 2011; Lauriello, 2020). Recent evidence has shown the positive impact of specific relapse prevention interventions on relapse rates (Abu Sabra and Hamdan-Mansour, 2022; Bighelli, 2021; Højlund, 2021; Rodolico, 2022). However, due to the limited real-life implementation and the modest effect of the interventions, relapse rates in SCZ remain high, increasing the personal, social, and financial burden of the disease (Pennington and McCrone, 2017; Pilon, 2021). Therefore, there is an urgent need to better understand the pathophysiology of relapse and identify endophenotypes with higher risk of relapse to develop and target efficient relapse-prevention interventions (Kapur, 2012; Rubio, 2021).

Inflammatory hypothesis in SCZ has gained increasing support (Benros, 2014; Steen, 2023). Total white blood cells (WBC) and differentials, including monocytes, lymphocytes, and neutrophils, are classified as immune blood cells due to their role in promoting systemic inflammation by releasing pro-inflammatory molecules. Elevated levels of total WBC, neutrophils, and monocytes have been observed in individuals with SCZ (Jackson and Miller, 2020; Mazza, 2020a) and have been linked to severity and treatment response (Steiner, 2020). By utilizing differential WBC counts, we can calculate inflammatory ratios that reflect the balance between innate immunity (indicated by neutrophil, monocyte, or platelet counts) and adaptive immunity (lymphocyte count) (Bhikram and Sandor, 2022). These ratios have been found to be increased in SCZ (Karageorgiou, 2019; Mazza, 2020b) and may offer enhanced predictive value when identifying imbalances between the innate and adaptive immune pathways (Llorca-Bofí, 2023). Higher inflammatory measures during the first episode of psychosis have been shown to predict worse treatment response at follow-up (Bioque, 2022a; Nettis, 2019; Osimo, 2023, 2021; Schwarz, 2012). However, the predictive value of immune blood cell counts for relapse in stable SCZ patients at early stages of the disease has not been previously studied. This raises the question: regardless of the underlying etiology, are inflammatory blood counts at remission predictive of relapse in SCZ? In our group, we have published longitudinal studies designed from the acute first episode of psychosis to clinical remission and assessing inflammatory factors (Bernardo, 2017; Bernardo and Bioque, 2014). Instead, in the 2EPs study we explore the opposite direction

by analyzing the natural course of the disease: a longitudinal study to identify factors associated with a relapse within the years immediately following clinical remission of a first episode of schizophrenia (FES) (Bernardo, 2021). Using this design, we attempt to identify biomarkers for risk of relapse after FES and to move towards precision psychiatry (Vieta, 2015).

In this three-year follow-up study, we aimed to investigate (1) the potential value of inflammatory cells and ratios at baseline as biomarkers of relapse in a cohort of remitted FES patients with less than five years of evolution and (2) the itinerary of the inflammatory biomarkers over the course of the disease. We hypothesized that higher inflammation at baseline would be associated with higher risk of relapse during the follow-up.

2. Methods

2.1. Study setting, inclusion and exclusion criteria

The participants of this study came from the 2EPs Project. The background, rationale and study design have been previously presented elsewhere (Bernardo, 2021; Bioque, 2022b). The main aim of this project was to closely monitor the clinical course of clinical remitted FES patients and compare the subgroup of patients with a second episode to that which remains in remission. The sample was recruited from 15 clinical tertiary centers in Spain with experience of the preceding PEPs Study project (Bernardo, 2017) and affiliated with the Spanish Network of Translational Research in Mental Disorders (CIBERSAM) (Salagre, 2019).

The inclusion criteria for the 2EPs Project were: (1) age between 16 and 40 years; (2) met diagnostic criteria according to DSM-IV-TR for SCZ or schizophreniform disorder (American Psychiatric Association, 1994); (3) in remission from the first psychotic episode (which should have occurred within the last 5 years) according to the criteria set forth by the Remission in Schizophrenia Working Group (RSWG) (Andreasen, 2005). The exclusion criteria were: (1) intellectual disability defined by an estimated Intelligent Quotient (IQ) < 70, together with malfunctioning and difficulties with adaptive process, (2) history of head trauma with loss of consciousness and/or (3) presence of an organic disease with mental repercussions.

Out of the 223 patients initially included in the 2EPS cohort, only those who had completed the 3-year follow-up or had experienced a relapse during that period were considered in the present analysis. A total of 95 patients dropped out of the study, primarily due to their reluctance to attend demanding-time follow-up visits, and changes in their geographical locations affecting access to healthcare services (Bioque, 2022b). Additionally, we excluded nine patients whose

diagnosis had changed during the follow-up period (seven to bipolar disorder, one to major depressive disorder with psychotic features, and another to substance-induced psychosis), as well as eight patients with incomplete biological data. Ultimately, the final analysis comprised 111 patients.

2.2. Clinical assessment and biological measures

Demographic data were collected for all patients through semi-structured interviews. Diagnoses were determined according to the DSM-IV-TR criteria (American Psychiatric Association, 1994). Clinical symptomatology was assessed using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS) (Kay, 1987; Peralta Martín and Cuesta Zorita, 1994). Anthropometrical measures, pharmacological treatment and substance abuse at baseline and follow-up were recorded. See Bernardo et al. (2021) for a complete description of the methodology used.

Laboratory data of white blood cells (WBC), neutrophils, monocytes, lymphocytes, basophils, eosinophils and platelet counts were assessed at baseline and, at relapse or 3-years follow-up. Inflammatory ratios where selected based on recent literature in SCZ (Bhikram and Sandor, 2022; Mazza, 2020b). The following ratios were calculated: neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR) and basophil-lymphocyte ratio (BLR). K2EDTA BD Vacutainer EDTA tubes (Becton Dickinson, Franklin Lakes, New Jersey, USA) were used to collect blood samples which were stored at −20°C and sent to each site laboratory for analysis.

2.3. Relapse definition

Relapse was defined as when participants scored 4 or more on any of the following eight items of the PANSS Scale for at least one week during the follow-up: delusions, unusual thought content, hallucinatory behavior, mannerisms/posturing, blunted affect, social withdrawal, lack of spontaneity. Hospitalizations were also recorded during every follow-up visit and considered a relapse only when they were related to symptoms of schizophrenia (SCZ) and not due to other causes. Follow-up visits to detect relapses were scheduled every three months, where information was collected from the entire period between visits and both patients, family members or caregivers and clinical teams in charge of the clinical follow-up could notify the research team of the possible relapse of a participant.

2.4. Statistics

Data were analyzed using SPSS 23.0 (IBM-SPSS Statistics for Windows, Armonk, NY: IBM Corp., USA). Two-tailed p-values <0.05 were considered statistically significant. Continuous data were

expressed as mean and standard deviation (SD), while categorical data were expressed as absolute values and percentages (%). The normality of continuous variables was tested using the Kolmogorov–Smirnov tests, and the equality of the variance between groups was assessed using Levene's test. Chi-square and t-student tests were used to compare those who did (relapsers) and those who did not experience a relapse (non-relapsers) after the three-year follow-up. As non-parametric alternatives, Fisher's exact and Mann-Whitney U tests were used when appropriate. Univariate logistic regressions analysis was used to explore whether inflammatory biomarkers at baseline were associated with relapse. We used two adjusted models: first, by including sex, age, duration of untreated psychosis (DUP), PANSS total score, body mass index (BMI) and antipsychotic treatment; and second, by adding cannabis and tobacco use during the follow-up to the first model. Fisher's exact test provided the significance, and the odds ratios (OR) and their 95% confidence intervals (CI) provided the effect size. The relapse predictive properties of inflammatory biomarkers at baseline were tested using non-parametric ROC curve analysis. ANCOVA analysis using endpoint inflammatory levels as a dependent variable and baseline levels as covariates were used to compare inflammatory differences at endpoint between relapsers and non-relapsers. In order to account for multiple testing in our analysis, we applied the Benjamini & Hochberg method to the p-values.

3. Results

3.1. Demographic and baseline clinical characteristics

Demographic and baseline clinical characteristics of the cohort are shown in **Table 1**, differentiating relapsers and non-relapsers during the 3-years follow-up. In the univariate analyses, significant lower age and higher duration of untreated psychosis were found in relapsers ($p=0.039$ and $p=0.046$ respectively). During the follow-up, we found higher use of cannabis and lower use of tobacco in relapsers ($p<0.001$ and $p<0.001$ respectively). No statistically significant differences were found in the other variable.

3.2. Predictive value of inflammatory cells and ratios

At baseline, relapsers showed higher monocyte (1.93 ±2.70 vs 0.53 ±0.40; $p=0.003$), lymphocyte (7.65 ±11.25 vs 2.40 ±2.11; $p<0.001$), basophil (0.252 ±0.619 vs 0.025 ±0.046; $p<0.001$) and eosinophil (0.84 ±1.42 vs 0.17 ±0.11; $p=0.004$) counts. Furthermore, they showed lower PLR (80.29 ±45.51 vs 111.3 ±46.88; $p=0.001$) and higher BLR (0.058 ±0.155 vs 0.010 ±0.020; $p<0.001$) (**Table 2**).

In the univariate logistic regression for relapse monocyte (OR= 1.91; 95% CI= 1.07 to 3.18, $p=0.009$) and basophil (OR= 1.09; 95% CI= 1.01 to 1.12; $p=0.005$) counts increased the risk to

relapse. In contrast, PLR (OR=0.98; 95% CI =0.97 to 0.99; p=0.019) was a protective factor for relapse (**Table 2**). When adjusting for cannabis and tobacco use during the follow-up monocyte counts maintained the association (OR= 1.73; 95% CI = 1.03 to 2.29; p=0.027) but this was not significant after correcting the *P*-value for multiple testing. Basophil counts maintained the statistically significant increased risk of relapse (OR= 1.08; 95% CI = 1.01 to 1.14; p=0.008) (**Table 2**).

By using ROC curve analysis, we determined cut-off values of monocyte and basophil counts at baseline to predict relapse. ROC curve analysis suggested that the optimum cut-off values to discriminate patient's relapse were 0.52 $x10^9$/L (sensitivity: 59.3%; specificity: 73.7%; AUC: 0.66; 95% CI: 0.56-0.77; p=0.002) for monocyte count, 0.025 $x10^9$/L (sensitivity: 66.7%; specificity: 77.2%; AUC: 0.75; 95% CI: 0.65-0.84; p<0.001) for basophil count.

3.3. Differences in inflammatory cells and ratios at relapse or no relapse

By using ANCOVA analysis adjusted for baseline inflammatory levels and confounding factors (sex, age, DUP, PANSS total score, BMI and antipsychotic treatment), we found no significant differences in the inflammatory biomarkers at endpoint between those who relapse and those who did not (**Figure 1**).

4. Discussion

Using routine blood counts form the 2EPs study cohort, we longitudinally examined the association of blood cell counts and ratios at remission after a FES and the risk of relapse. In this three-year follow-up study, we found: 1) At baseline, relapsers showed higher monocyte, lymphocyte, basophil and eosinophil counts, lower PLR and higher BLR; 2) Monocyte and basophil counts at baseline increased the risk to relapse; 3) when adjusting for established risk factors for relapse, such as cannabis or tobacco use, basophil count maintained its association, but monocyte counts lost significance after correcting for multiple testing probably due to the limited sample size; 4) ROC curve analysis suggested that the optimum cut-off values to discriminate relapsers were 0.52 $x10^9$/L (AUC: 0.66) for monocytes and 0.025 $x10^9$/L (AUC: 0.75) for basophils; 5) Considering baseline inflammatory levels, no significant differences were found in the inflammatory biomarkers at endpoint between relapsers and non-relapsers.

To our knowledge, this is the first study measuring longitudinal associations between blood cell counts and ratios at remission after a FES and long-term relapse in a cohort of patients with a close follow-up. Our results suggest that monocyte and basophil cells may have a prognostic potential for patients at remission after a FES. Previous cross-sectional literature demonstrates

immune blood cell alterations in first-episode psychosis (Jackson and Miller, 2020; Karageorgiou, 2019; Mazza, 2020a). Furthermore, higher inflammatory measures during the first episode of psychosis predict worse symptoms severity and treatment response at follow-up in longitudinal studies (Bioque, 2022a; Nettis, 2019; Osimo, 2021; Schwarz, 2012). However, studies analyzing the predictive value to relapse of peripheral inflammation in stable SCZ patients at early stages of the disease are scarce (Gonzalez-Blanco, 2018; Schwarz, 2012). In this study we were able to examine blood cell counts at remission after a FES to study associations with relapse in a cohort of 111 patients with a close 3-years follow-up.

Our findings of an association between inflammatory blood cells and longitudinal prognosis are in line with some studies but not with others. Using electronic health records of a naturalistic cohort of 749 patients with first-episode of psychosis, Osimo et al. (2021) showed that baseline monocyte, lymphocyte and platelet counts were associated with an unfavorable outcome (continued involvement of secondary mental health services) while baseline basophil and BLR ratios were associated with a favorable outcome (discharged to primary care with no onward referrals to community mental health teams) in a 3-yers follow-up study. In contrast, Horsdal (2017) found no association between C-Reactive Protein and WBC levels and psychiatric readmission in a longitudinal population-based study in 690 patients with inflammatory biomarkers collected ±30 days from first diagnosis SCZ. In our study we found that monocyte and basophil count at baseline but not the other inflammatory blood cells increased the risk to relapse. Although we included a smaller sample than in the above-mentioned studies, it is important to note that in our study all patients were in remission after the first episode of SCZ and a close follow-up was scheduled every three months to detect relapse. This could explain some differences with the Osimo's study, which included patients in a first psychotic episode and unfavorable outcome was defined as involvement in secondary mental health services and not relapsing specifically. It highlights the importance of choosing the most relevant time to collect prognostic biomarkers in early stages of SCZ. Despite the differences in study design, the opposing results on basophil predictivity are surprising. Basophil has been associated with autoimmune diseases (Yang, 2017) and appear to be involved with insulin resistance (Lee, 2014). However, apart from the study by Osimo et al. (2021), research on basophils in SCZ is practically non-existent. We also found evidence of a protective association between PLR and relapse albeit with no significance after adjusting for substance use. This finding is new and need replication.

Remarkable, we found higher levels of innate (monocyte, basophil and eosinophil) and adaptative (lymphocyte) cell counts at baseline in relapsers; however, only innate cell counts at baseline (monocyte and basophil counts) increased the risk to relapse. These results are in line

with previous literature showing activation of both innate and adaptative immunity in SCZ (Ermakov, 2022) and support the evidence that innate but not adaptative immunity may have a prognosis value in SCZ (Steiner, 2020). Furthermore, our results of monocyte implication in relapse supports the hypothesis of the role of mononuclear phagocyte system in the pathophysiology of psychotic disorders and their shared genetics with cortical structure (Drexhage, 2010; Parker, 2024). Microglia is a monocyte-derived cell in the central nervous system and circulating monocyte count has been considered an accessible peripheral marker of microglia activation (Mazza, 2020a). As propose by Miller & Buckley (2012), abnormal homeostasis during remission after a FEP results in cellular activation and proinflammatory cytokine production, which in turn stimulates an inflammatory response. In the setting of increased blood brain barrier permeability, cytokine abnormalities and mononuclear phagocyte system may modulate microglial activation and dopaminergic neurotransmission resulting in acute psychosis relapse. In this line, despite being at remission after the FES, higher monocyte counts may have higher microglial activation (Bisht, 2016; Casquero-Veiga, 2019) resulting in an increased risk of relapse, as shown in our sample.

Substance use after the FEP has been linked to higher relapse rates (Weibell, 2017). More specifically, cannabis use is a well stablished independent risk factors for relapse (González-Pinto, 2011; Schoeler, 2016), and tobacco use has been associated with worse clinical and functional outcomes in SCZ (Quigley and MacCabe, 2019). In the entire 2EPs cohort, we were able to objectively monitor substance use during the follow-up after the FES and found that relapsers exhibited higher rates of cannabis use (93.2% vs. 56.7%, $p<0.001$) during the follow-up (Bioque, 2022b). In the present study, to gain a deeper understanding of the influence of substance use on the relationship between inflammatory blood cells and the risk of relapse, we employed a second predictive model that included cannabis and tobacco use during the follow-up in addition to the first predictive model. Our findings support the association between certain inflammatory cells (monocyte and basophils) even when adjusting for established risk factor for relapse like cannabis or tobacco use. It's worth noting that while monocyte counts maintained their association, they lost significance after correcting for multiple testing, possibly due to the limited sample size.

Finally, ROC curve analysis was employed to assess the predictive effectiveness of baseline monocyte and basophil counts for relapse. The monocyte count exhibited an AUC of 0.66, indicating low discrimination, while the basophil count showed an AUC of 0.75, suggesting acceptable discrimination but likely of limited clinical relevance. Despite their association with an increased risk of relapse, both monocyte and basophil counts displayed low sensitivity and

specificity, with AUC values falling below the 0.8 threshold proposed as minimally useful (Abi-Dargham, 2023). Therefore, inflammatory cell counts at remission after a FES may be involved in the pathophysiology of relapse but possess limited predictive power for relapse in clinical practice. Future studies with larger sample sizes and similar designs should seek to replicate these findings.

4.1. Strengths and limitations

The major strength of our study is that the sample included is much closer to the "real life" population with a FES, as the diagnostic evaluation was performed with a very comprehensive protocol, with strict inclusion-exclusion criteria (Bernardo, 2021). Being SCZ a heterogeneous clinical entity, the first episode subgroup is of great interest because it avoids the effect of confounding variables, such as prolonged antipsychotic treatment, medical comorbidities or chronicity (Bernardo and Bioque, 2014). In terms of biological measures, blood samples were collected following a strict and unified protocol, which is especially relevant since white blood cells levels fluctuate throughout the day (Sandberg, 2021; Villar, 2023). Other advantages of the study are the long period of follow-up and the deep characterization of the sample included allowing the detection of key variables closely related to the risk of presenting a relapse after having remitted from a FES.

Our study should, however, be considered in the context of several limitations. Firstly, the 2EPs Project was a naturalistic study, not a randomized controlled trial, which means that patients could change treatments during the follow-up period based on the clinician's discretion. Secondly, while most sociodemographic and clinical variables did not differ significantly between relapsers and non-relapsers, it's important to note that relapsers were younger and had a longer duration of untreated psychosis, both of which are associated with a higher risk of relapse (Bogers, 2022; Marshall, 2005). As a result, both variables were included as covariates in all the analyses. It's worth mentioning that older age has been linked to higher inflammatory ratios, but this significant increase typically occurs around the age of fifty and beyond (Brinn and Stone, 2020). Since our patients were in their twenties and thirties (24.1 ±4.7 for relapsers vs. 26.2 ±5.9 for non-relapsers), age alone is unlikely to account for the observed differences. Thirdly, among all the patients enrolled in the 2EPs study, we encountered a dropout rate of 49.6% during the follow-up, as reported by Bioque et al. (2022b), which reduced the sample size to 111 patients. This sample size could potentially affect statistical significance when adjusting for multiple comparisons and might lead to lower AUC values for the variables. Lastly, including information on medication adherence could have been beneficial in assessing the influence of continued oral antipsychotic medication on the likelihood of relapse.

5. Conclusion

In this 3-year longitudinal study of patients in remission after a first episode of psychosis (FES), we have observed that higher monocyte and basophil counts at baseline were linked to an increased risk of relapse during the follow-up period, even after adjusting for confounding factors such as cannabis and tobacco use. Nevertheless, it is important to note that the predictive capacity of these cell counts for relapse is limited. These findings should be validated through replication in larger samples with similar study designs.

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Table 1. Demographic and Clinical Baseline Characteristics and Univariate Comparisons Between Relapse and Non-Relapse Patients.

Mean ±SD	Relapse (n=54)	No Relapse (n=57)	Statistics	p-value
Female, nº (%)	24 (44.4)	32 (56.1)	χ^2=1.51	0.218
Age at inclusion, years	24.1 ±4.7	26.2 ±5.9	t=-2.08	**0.039**
Duration of untreated psychosis, days	241.6 ±395.6	122.2 ±187.6	t=2.04	**0.046**
PANSS				
- Positive	9.5 ±3.1	9.3 ±2.8	t=0.42	0.670
- Negative	14.1 ±5.7	14.5 ±4.9	t=-0.43	0.666
- General	24.8 ±7.0	24.7 ±6.6	t=0.05	0.954
- Total	48.4 ±13.8	48.5 ±12.8	t=-0.04	0.962
Antipsychotic treatment				
- Any use, nº (%)	51 (94.4)	49 (86.0)	χ^2=2.33	0.239
- Clozapine use, nº (%)	3 (5.6)	8 (14.0)	χ^2=2.23	0.204
- Chlorpromazine equivalent dose, mg/day	345.4 ±337.8	246.1 ±211.8	t=1.67	0.096
BMI	24.8 ±5.4	25.7 ±4.9	t=-0.08	0.390
Substance use at baseline				
- Tobacco use (yes), nº (%)	31 (57.4)	28 (49.1)	χ^2=0.76	0.382
- Cannabis use (yes), nº (%)	8 (15.1)	5 (8.9)	χ^2=0.98	0.321
Substance use during follow-up				
- Tobacco use (yes), nº (%)	35 (64.5)	53 (93.0)	χ^2=13.393	**<0.001**
- Cannabis use (yes), nº (%)	51 (94.4)	33 (57.9)	χ^2=20.124	**<0.001**

Abbreviations: PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression – Severity Scale; BMI: Body Mass Index. Significant values are highlighted in bold.

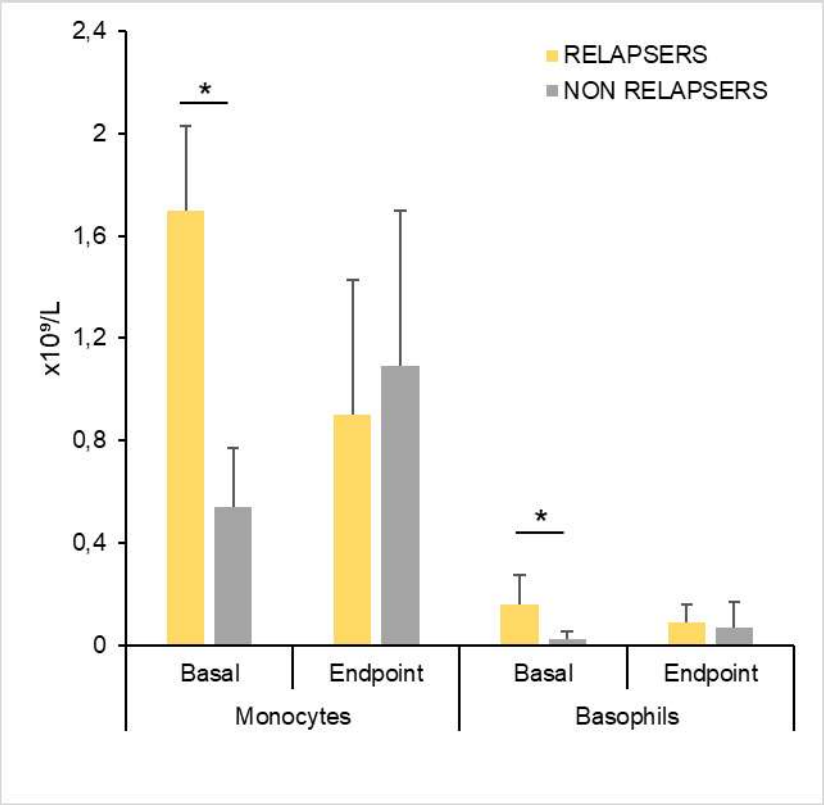
Table 2. Univariate Logistic Regression for Relapse Using Inflammatory Blood Cells and Ratios at Baseline.

	Relapse (n=54)	No Relapse (n=57)	Statistics	p-value	Adjustment 1 [a]	Adjustment 2 [b]
					OR univariate (CI 95%)	OR univariate (CI 95%)
WBC	7.25 ±2.01	6.68 ±1.96	U=1251.0	0.131		
Neutrophils	12.01 ±19.94	3.81 ±1.62	U=1276.1	0.121		
Monocytes	1.93 ±2.70	0.53 ±0.40	**U=1019.5**	**0.003***	**1.91 (1.07 to 3.18); p=0.009***	**1.73 (1.03 to 2.99); p=0.027**
Lymphocytes	7.65 ±11.25	2.40 ±2.11	**U=948.5**	**<0.001***	1.13 (0.99 to 1.30); p=0.055	1.09 (0.97 to 1.22); p=0.112
Basophils	0.252 ±0.619	0.025 ±0.046	**U=768.5**	**<0.001***	**1.09 (1.01 to 1.12); p=0.005***	**1.08 (1.01 to 1.14); p=0.008***
Eosinophils	0.84 ±1.42	0.17 ±0.11	**U=1033.0**	**0.004***	1.02 (0.975 to 1.04); p=0.110	1.01 (0.993 to 1.03); p=168
Platelets	226.7 ±62.2	216.9 ±50.9	U=1406.0	0.433		
NLR	1.62 ±0.63	1.90 ±1.04	U=1342.5	0.246		
MLR	0.46 ±0.95	0.23 ±0.07	U=1436.1	0.543		
PLR	80.29 ±45.51	111.3 ±46.88	**t=3.537**	**0.001***	**0.98 (0.97 to 0.99); p=0.019***	0.99 (0.98 to 1.01); p=280
BLR	0.058 ±0.155	0.010 ±0.020	**U=857.5**	**<0.001***	1.23 (0.99 to 1.53); p=0.061	1.29 (0.97 to 1.73); p= 0.076

Abbreviations: WBC: White Blood Cells, NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; PLR: platelet-lymphocyte ratio; BLR: basophil-lymphocyte ratio.

[a] Adjusted for Sex, Age, DUP, PANSS total score, BMI and AP treatment; [b] Adjustment 1 + Cannabis and Tobacco use during follow-up. Significant values are highlighted in bold, significant values adjusted for multiple comparisons using the Benjamini and Hochberg method are marked with an asterisk.

Figure 1: Differences in Monocyte and Basophil Counts Between Relapsers and Non-Relapsers at Baseline and Endpoint. *Significant Results (P < 0.05).



Title: Inflammatory blood cells and ratios at remission for psychosis relapse prediction: A three-year follow-up of a cohort of first episodes of schizophrenia.

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Conflict of interest

Dr. Bioque has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory board of has received honoraria from talks and/or consultancy of Adamed, Angelini, Casen-Recordati, Exeltis, Ferrer, Janssen, Lundbeck, Neuraxpharm, Otsuka, Pfizer and Sanofi, and grants from Spanish Ministry of Health, Instituto de Salud Carlos III (PI20/01066) and Fundació La Marató de TV3 (202206-30-31).

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