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Short Communication

Association of the neutrophil to lymphocyte ratio and white blood cell count with response to pharmacotherapy in unipolar psychotic depression: An exploratory analysis

Cornelis F. Vos [a,b,*], Tom K. Birkenhäger [c,d], Willem A. Nolen [e], Walter W. van den Broek [c], Marieke J.H. Coenen [f], Sophie E. ter Hark [a,b], Robbert-Jan Verkes [a,b], Joost G.E. Janzing [a,b]

[a] Department of Psychiatry, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands
[c] Department of Psychiatry, Erasmus University Medical Centre, Rotterdam, the Netherlands
[d] Collaborative Antwerp Psychiatric Research Institute (CAPRI), University of Antwerp, Antwerp, Belgium
[e] Department of Psychiatry, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[f] Department of Human Genetics, Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, the Netherlands

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ABSTRACT

Background: Low-grade inflammation occurs in a subgroup of patients with Major Depressive Disorder (MDD) and may be associated with response to antidepressant medications. The Neutrophil to Lymphocyte Ratio (NLR) and total White Blood cell Count (WBC) are markers of systemic inflammation which have not been investigated as predictors for outcome to pharmacotherapy in unipolar depression yet. Moreover, the association between inflammation and treatment response has not been studied in unipolar Psychotic Depression (PD). We conducted an exploratory analysis to examine the prognostic significance of NLR and WBC in pharmacotherapy of PD.
Methods: Baseline NLR and WBC were examined in their association with response to seven weeks of treatment with antidepressants (venlafaxine or imipramine) and the combination of an antidepressant with an antipsychotic (venlafaxine plus quetiapine) in 87 patients with PD. Logistic regression models were adjusted for age, gender, Body Mass Index (BMI), depression severity, duration of the current episode and number of previous depressive episodes. Secondary outcomes were remission of depression and disappearance of psychotic symptoms.
Results: Higher NLR was associated with increased response to pharmacotherapy (Exp(B) 1.66, 95 % CI 1.03–2.66, $p = 0.036$), but not with remission of depression or disappearance of psychotic symptoms. WBC was not associated with any of the outcome measures.
Conclusion: NLR may be a novel, inexpensive and widely available biomarker associated with response to pharmacotherapy in PD. The association between white blood cell measures and treatment outcome should be further investigated for different types of antidepressants in PD and in non-psychotic MDD.

1. Introduction

Low-grade inflammation occurs in 25–50 % of patients with Major Depressive Disorder (MDD), reflected by elevated pro-inflammatory markers, such as C-Reactive Protein (CRP) and the cytokines Tumor Necrosis Factor alpha (TNF-α) and Interleukin (IL)-6 (Miller, 2020; Dantzer et al., 2008; Miller and Raison, 2016; Pariante, 2017). Several studies suggest an association between pre-treatment inflammation and response to antidepressant medications (Strawbridge et al., 2015; Liu et al., 2020; Arteaga-Henriquez et al., 2019; Pantović-Stefanović et al.,

2018), although no consensus on this has been reached.

Most studies to inflammation in MDD focus on cytokines or CRP but also other markers can indicate inflammation, including white blood cell counts and ratios (Mayadas et al., 2014). Both the Neutrophil to Lymphocyte Ratio (NLR), the ratio of the two most common types of white blood cells, and total White Blood cell Count (WBC) are well-established markers of systemic inflammation and can be easily derived from a white blood cell essay (Templeton et al., 2014; Duivis et al., 2013). Meta-analyses demonstrate that NLR is elevated in MDD and in several other psychiatric disorders, such as bipolar disorder and

schizophrenia, compared to healthy controls (Mazza et al., 2018, 2019; Jackson and Miller, 2020). Higher NLR has been associated with higher depression severity in MDD and suicidality in MDD and bipolar disorder (Aydin Sunbul et al., 2016; Velasco et al., 2020; Kayhan et al., 2017; Ivković et al., 2016; Brinn and Stone, 2020). Also, elevated WBC has been reported in MDD but less consistently compared to NLR (Duivis et al., 2013; Beydoun et al., 2016; German et al., 2006; Shafiee et al., 2017; Kobrosly and van Wijngaarden, 2010). So far, no studies investigated the association between NLR or WBC with response to antidepressant medications in unipolar depression (Duivis et al., 2013; Mazza et al., 2018; German et al., 2006).

The present study aimed to assess whether NLR and WBC at baseline are associated with response to pharmacotherapy in unipolar Psychotic Depression (PD), i.e. a severe subtype of MDD with additional psychotic features (hallucinations and/or delusions) (American Psychiatric Asso, 2013; Dold et al., 2019). PD is associated with higher cortisol levels compared to non-psychotic MDD (Carroll et al., 2007; Contreras et al., 2007). Since prolonged elevated cortisol might initiate inflammation, PD is an interesting condition to study the association between inflammation and treatment outcome (Pariante, 2017; Anacker et al., 2011). NLR and WBC, as well as other pro-inflammatory markers, have not been investigated in relation to outcome to pharmacotherapy in PD yet. Since this study was conducted as an exploratory analysis, no a-priori hypotheses were formulated.

2. Materials and methods

2.1. Study design

This study is a secondary analysis of the DUDG-study (Wijkstra et al., 2010). The DUDG-study is a double-blind randomized controlled trial comparing treatment outcome to venlafaxine, imipramine or venlafaxine plus quetiapine in 122 patients with PD.

2.2. Patients

Patients were aged 18–65 years and had a diagnosis of unipolar MDD with psychotic features according to DSM-IV-TR criteria (American Psychiatric Asso, 2000). At baseline, patients had a score of $\geq$18 on the Hamilton Rating Scale for Depression (HAM-D-17) (Hamilton, 1960), indicating severe depression, and they were free of psychotropic medication for at least 4 days. Patients were randomized to seven weeks double blind treatment with venlafaxine (max. 375 mg/day), imipramine (plasma levels 200–300 µg/L) or venlafaxine plus quetiapine (max. 375 mg/day, and max. 600 mg/day respectively). We included only patients who actually started study medication in the original study.

Exclusion criteria were an acute clinical indication for electroconvulsive therapy, intellectual disability, alcohol or substance abuse within 3 months of enrollment, any serious somatic illness or somatic medication potentially affecting mood, contra-indications for study medication or previous adequate treatment of the current depressive episode with imipramine or venlafaxine. In agreement with previous studies, patients with very low ($<4 \cdot 10^9$/L) or high WBC ($>12 \cdot 10^9$/L) at baseline, suggestive for somatic illness, or obesity (BMI >30) were excluded (Velasco et al., 2020; Kayhan et al., 2017; Demircan et al., 2016; Cai et al., 2017; Demir et al., 2015; Hotamisligil, 2006).

2.3. White blood cell measures

At baseline blood samples were taken from which white blood cell counts were assessed in all participants of the original study. Samples were analyzed at the study sites using the Abbott Cell-Dyn Sapphire, Sysmex XE-5000, Sysmex XE-2100 or Siemens ADVIA 120, depending on the location and date of inclusion. For these hematology analyzers a good inter-instrument concordance for white blood cell counts has been demonstrated (Bruegel et al., 2015; Kang et al., 2008). WBC was defined

as the sum of the absolute neutrophil, lymphocyte, eosinophil, basophil and monocyte counts. NLR was computed by dividing the absolute neutrophil count through the absolute lymphocyte count.

2.4. Outcome measures

The primary outcome measure was treatment response, defined as $\geq$50 % decrease in HAM-D-17 score after seven weeks of treatment. Secondary outcome measures were remission of depression, defined as a HAM-D-17 score $\leq$7, and remission of psychotic symptoms, defined as absence of delusions and hallucinations after seven weeks of treatment. Psychotic features were assessed on the basis of clinical impression, both at baseline and at the final study visit, and were scored dichotomously (present or absent).

2.5. Univariate analyses

Chi-square tests were used to compare dichotomous baseline characteristics and unpaired *t*-tests to compare continuous baseline variables. Associations were computed between baseline characteristics and white blood cell markers by Pearson's or Spearman's correlations where appropriate.

2.6. Multivariate analyses

Logistic regression analyses were conducted to study multivariate associations between white blood cell markers and the outcome measures. Concerning drop-outs, the last observation carried forward (LOCF) method was applied. All logistic regression analyses were adjusted for the most important potential confounders in accordance with previous research on NLR and WBC in MDD: gender, age, severity of depression and number of previous depressive episodes (Mazza et al., 2018; Aydin Sunbul et al., 2016; Huguet et al., 2019; Arabska et al., 2018).

Additionally, interaction effects were studied between NLR, WBC and medication types regarding treatment response as the primary outcome measure. Interaction terms were computed as the product of NLR or WBC and venlafaxine, imipramine and venlafaxine plus quetiapine respectively. First, venlafaxine, imipramine and venlafaxine plus quetiapine, as well as the interaction terms of NLR and these medication types were added to the logistic regression model for NLR, using treatment response as dependent variable. Second, a similar procedure was performed for WBC. Analyses were conducted in SPSS version 26 (IBM Corp, Armonk, NY).

3. Results

From the 122 patients participating in the original study, 35 were excluded for the current analysis: four because they did not start study medication, 17 because of missing neutrophil or lymphocyte counts, three because of WBC $<4 \cdot 10^9$/L, five because of WBC $>12 \cdot 10^9$/L and six because of obesity. Hence, analyses were conducted for 87 patients, which is 71 % of the original sample: 27 (31 %) in the venlafaxine group, 31 (36 %) in the imipramine group and 29 (33 %) in the venlafaxine plus quetiapine group.

The 87 patients included in the current analysis did not differ significantly from the 35 patients excluded from the original sample regarding age ($t(120) = -1.12, p = 0.60$), gender ($X^2 (1, n = 122) = 0.10, p = 0.75$), number of previous episodes ($t(120) = 0.45, p = 0.65$), duration of the current episode ($t(43.8) = 1.03, p = 0.31$), depression severity ($t(120)=<0.01, p = 1.00$) and treatment response ($X^2 (1, n = 118) = 1.21, p = 0.27$). Therefore, patients in this study can be considered representative for the original study population.

Patient characteristics are presented in Table 1. At baseline, mean NLR was 2.58 (*SD* 1.53) and mean WBC was $7.15 \cdot 10^9$/L (*SD* 1.70). Number of previous episodes was positively correlated with WBC but not with NLR. There were no significant associations between NLR or WBC

Table 1
Baseline characteristics (n = 87) and correlations with NLR and WBC.

Characteristic		NLR		WBC	
		Correlation[a]	p-value	Correlation[a]	p-value
Female, *n* (%)	45 (51.7)	−0.12	0.26	0.13	0.22
Age (years), mean (SD)	51.7 (10.4)	0.02	0.83	0.11	0.31
Baseline HAM-D-17 score, mean (SD)	31.8 (4.8)	−0.04	0.69	0.06	0.58
Number of previous episodes, mean (SD)	0.26 (0.78)	0.07	0.50	0.24	0.023*
Duration of current episode (months), mean (SD)	29.7 (69.7)	−0.06	0.56	−0.08	0.47
BMI (kg/m²)	22.9 (3.2)	−0.02	0.87	0.11	0.31

*$p < 0.05$.
[a] Correlation coefficients: Pearson's correlations were used for gender, age, baseline HAM-D-17 score and BMI. Spearman's correlations were used for number of previous episodes and duration of the current episode.

and gender, age, severity of depression, duration of the current episode and BMI.

After 7 weeks of treatment, 52 out of 87 patients (60 %) reached treatment response, 29 (33 %) attained remission of depression and psychotic features remitted in 59 patients (68 %).

Multiple logistic regression analyses were used to compute associations between white blood cell markers and outcome measures. As presented in Table 2, higher NLR at baseline was associated with increased response after seven weeks of pharmacotherapy. NLR was not associated with remission of depression or psychotic symptoms. WBC was not associated with any of the outcome measures.

Interaction effects between NLR or WBC and medication types were examined for treatment response as the primary outcome measure. By conducting logistic regressions, adjusted for age, gender, baseline HAM-D-17 score and number of previous episodes, none of the interaction terms was significantly associated with treatment response (data not shown). We concluded that there were no significant interactions between NLR or WBC and type of study medication.

4. Discussion

Low-grade inflammation occurs in a subpopulation of MDD patients and may be associated with response to antidepressant medications (Miller, 2020; Strawbridge et al., 2015; Liu et al., 2020; Arteaga-Henriquez et al., 2019). In this study we explored whether pre-treatment NLR and WBC, inexpensive and widely available hematological markers of

Table 2
NLR and WBC as prognostic markers for treatment response, remission of depression and disappearance of psychotic features after 7 weeks of pharmacotherapy.

	NLR		WBC	
	Exp(B), (95% CI)	p-value	Exp(B), (95% CI)	p-value
Treatment response	1.66 (1.03–2.66)	0.036*	1.20 (0.90–1.59)	0.22
Remission of depression	1.12 (0.83–1.53)	0.46	1.18 (0.88–1.59)	0.27
Remission of psychotic symptoms	0.89 (0.62–1.29)	0.55	0.85 (0.63–1.15)	0.29

*$p < 0.05$. Regressions were adjusted for age, gender, baseline HAM-D-17 score and number of previous episodes.

systemic inflammation, are associated with outcome to seven weeks of pharmacotherapy in PD. Our results indicate that higher NLR at baseline is associated with increased response to pharmacotherapy in PD, while it was not associated with remission of depression or disappearance of psychotic symptoms. WBC was not associated with any of the outcome measures. No significant interaction effects were found between NLR or WBC and medication types. Mean NLR and mean WBC were in line with values reported earlier in a small subset of 14 PD patients (Kayhan et al., 2017). WBC was positively related to the number of previous depressive episodes, which has been reported before and was adjusted for in our logistic regression analyses (Duivis et al., 2013).

Previous findings regarding the prognostic significance of low-grade inflammation for response to antidepressant medications vary (Strawbridge et al., 2015; Arteaga-Henriquez et al., 2019; Kohler-Forsberg et al., 2019). A number of studies report that MDD patients with lower levels of inflammation respond better to serotonergic antidepressants, whereas patients with higher levels of inflammation respond better to noradrenergic, dopaminergic or glutamatergic antidepressants (Strawbridge et al., 2015; Liu et al., 2020; Arteaga-Henriquez et al., 2019). For instance, data of the GENDEP and COMED trials show that patients with CRP <1 mg/L respond better to the serotonergic antidepressant escitalopram and patients with CRP >1 mg/L respond better to the noradrenergic antidepressant nortriptyline or the dopaminergic antidepressant bupropion (Arteaga-Henriquez et al., 2019; Jha et al., 2017; Uher et al., 2014).

In our study, all patients were treated with (at least) venlafaxine or imipramine, both antidepressants with combined serotonergic and noradrenergic effects. One group was treated with venlafaxine plus quetiapine, an antipsychotic of which its active metabolite, norquetiapine, functions as a selective noradrenergic reuptake inhibitor (Lopez-Munoz and Alamo, 2013). We observed no interaction effects between the white blood cell measures and any of the treatment groups, possibly due to similarities between the treatment mechanisms or because of the relatively small treatment groups. Therefore, the positive association between NLR and treatment response in this study might be explained by either the noradrenergic effects of the study medications or the combined serotonergic and noradrenergic effects of imipramine, venlafaxine and quetiapine (Jha et al., 2017; Uher et al., 2014).

It is unclear whether our findings can be fully generalized to non-psychotic MDD. PD is strongly associated with high cortisol levels, whereas elevated cortisol levels are not consistently found in non-psychotic MDD (Carroll et al., 2007; Contreras et al., 2007). Cortisol is a potent anti-inflammatory hormone directly increasing neutrophils and therefore the NLR (Pariante, 2017; Anacker et al., 2011). However, in case of prolonged elevated cortisol levels glucocorticoid resistance may occur, in which cortisol and NLR appear unrelated (Pariante, 2017; Anacker et al., 2011; Cohen et al., 2012; Kronfol et al., 1985). If glucocorticoid resistance occurs, the anti-inflammatory function of cortisol is impaired and pro-inflammatory cytokines and NLR may rise, as observed in a subpopulation of MDD patients (Pariante, 2017; Anacker et al., 2011; Cohen et al., 2012; Kronfol et al., 1985). The interplay between cortisol, NLR and other pro-inflammatory markers requires further investigation in PD and in other types of depression.

In contrast to NLR, WBC was not predictive for treatment outcome. Previously, WBC was found not to predict response to quetiapine or lithium in bipolar disorder (Kohler-Forsberg et al., 2019). Generally, NLR is considered a superior indicator of pro-inflammatory activity compared to WBC, since NLR reflects the relative activity of two immunological pathways: neutrophils function as the first line of immunological defense and lymphocytes have a prominent immunoregulatory role and reflect general health and physiological stress (Mayadas et al., 2014).

Potentially, the association between NLR and response to pharmacotherapy could play a role in personalized pharmacotherapy for PD. PD is associated with a worse clinical course of illness, higher recurrence, higher mortality and lower response to antidepressant medications than non-psychotic MDD (Dold et al., 2019; Wijkstra et al., 2015). Therefore,

adequate predictors for outcome to pharmacotherapy are highly needed. Besides, also in non-psychotic MDD efficacy of antidepressant medications is modest since response to the first prescribed antidepressant occurs in only half of the patients (Cipriani et al., 2018; Rush et al., 2006, 2011). Moreover, onset of response is generally delayed and adverse effects are common (Dold et al., 2019; Wijkstra et al., 2015; Jaaskelainen et al., 2018). Efficacy and tolerability of antidepressant medications may be increased by personalized pharmacotherapy, i.e., precision medicine in which therapy is adjusted to individual patient characteristics. For this, new studies and further secondary analyses using data of clinical trials will be needed to gain a better understanding of how the choice for antidepressant medications can be personalized effectively (Labermaier et al., 2013; Bayes and Parker, 2019).

A strength of our study is that it consists of a relatively large and homogeneous sample of well-defined PD patients. All patients were free of psychotropic medication at baseline and were treated according to predefined doses or plasma concentrations for seven weeks. Depression severity was assessed weekly using the HAM-D-17. A limitation is that the study population is still relatively small to investigate relations between biomarkers and treatment outcome. Also, in most studies on NLR and WBC patients who smoke (>15 cigarettes per day) and patients with somatic comorbities or comedications affecting white blood cell counts are excluded (Mazza et al., 2018). We were not able to adjust for smoking, use of comedications, diet and ethnicity, as these data were not available for all patients. However, patients with serious somatic illness were excluded in the original study and most patients were likely Caucasians. Furthermore, hormones, e.g., cortisol levels, and metabolites of study medications, e.g., norquetiapine, were not measured and therefore we were not able to investigate their influence on the association between white blood cell markers and outcome measures.

5. Conclusion

In conclusion, we found preliminary evidence that higher pre-treatment NLR is associated with increased response to pharmacotherapy in PD. We found no associations between WBC and treatment outcome. Future research is needed to replicate our findings and to investigate the prognostic significance of white blood cell measures for response to different types of pharmacotherapy in PD and in non-psychotic MDD.

Declaration of competing interest

For conduct of the original study, dr. Nolen received grants from Astra Zeneca and Wyeth. During this post-hoc research, C. Vos and S. Ter Hark received funding from the Netherlands Organization for Health Research and Development (ZonMW) (project number: 848016004).

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