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Role of depression, suicide attempt history and childhood trauma in neutrophil-to-lymphocyte ratio dynamics: a 30-week prospective study

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Abstract

Studying the biology of suicidal behavior and developing blood-based biomarkers may help stratify individuals with suicidal behaviors into clinically relevant categories. Literature suggests that people diagnosed with mood disorders and suicidal behaviour show an increased neutrophil to lymphocyte ratio (NLR). In mood disorders, with or without childhood trauma and with or without suicidal behaviour, no study, to our knowledge, has precisely investigated the variability of NLR. Understanding the stability of a biological value is essential in the context of biomarker development. Our study provides a result on the influence of our variables on the NLR and also on the intrinsic properties of the ratio. Consequently, our objective was to analyze the differences in NLR between healthy subjects and patients diagnosed with mood disorder with suicidal behaviour or mood disorder without suicidal attempt. A prospective study was conducted on 97 healthy subjects, 63 patients with mood disorder without suicidal behaviour and 61 patients with mood disorder with suicidal behaviour (mean age [SD] = 44.2 [14.31]; 66.1% female). Participants were assessed four times over 30 weeks, where blood samples and clinical data were collected. After controlling for confounding factors such as smoking and medical history, we found that NLR stability was low but NLR was significantly associated with a history of suicide attempt (mixed linear model, $F=4.044$; $p=0.018$). We also observed a significant interaction between NLR values and childhood trauma ($p=0.002$). Furthermore, our results demonstrate that NLR is influenced by childhood trauma, including in controls ($p=0.014$). Finally, NLR expression differs between patients with and without suicidal behavior, but only in those without a history of childhood trauma ($p=0.026$). Despite its variability over time, our data suggest that NLR may be a promising biomarker for identifying individuals at high risk of suicidal behaviour among patients with mood disorders.

Keywords

- Neutrophil to lymphocyte ratio
- Mood disorder
- Childhood trauma
- Suicidal behavior
- Biomarker

Highlights

- Stability of NLR over time is low to moderate.
- Patient with mood disorder and suicidal behavior have higher NLR values.
- Childhood trauma factor increases NLR value.

1. Introduction

Suicide is the most dramatic complication for patients suffering from mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD). To date, clinical assessment remains the gold standard for the diagnosis of mood disorders and to assess the risk of suicidal attempt (SA). However, clinical risk factors cannot be used to predict SA, only to assess the risks (Ryan & Oquendo, 2020). To improve diagnosis and early detection of risk, biomarkers could be valuable, for example to determine more precisely and at an earlier stage whether a patient is presenting a risk behaviour. The plausibility of biomarkers is an important key for their development (Belzeaux et al., 2018) and can lead to validating or exploring biological processes associated with phenotype.

Recent research over the past two decades underscores the significant role of inflammation in the development of mood disorder and SA. Key inflammatory markers linked to depression include interleukin-6 (IL-6), C-Reactive Protein (CRP), and several other chemokines (Dowlati et al., 2010; Haapakoski et al., 2015). In addition, many studies have shown that the inflammatory profile of patients differs depending on whether they exhibit suicidal behaviour (Courtet et al., 2015; Neupane et al., 2023; O'Donovan et al., 2013; Saadat et al., 2024). Therefore, the search for biomarkers that can distinguish between these two patient populations and facilitate the identification of patients at risk of suicide seems possible. One promising biomarker for suicide risk is the neutrophil/lymphocyte ratio (NLR). Studies have shown that NLR levels are significantly higher in patients with suicidal depression than in patients with non-suicidal depression and healthy controls (Ekinci & Ekinci, 2017; Velasco et al., 2020). The NLR was historically developed to provide a suitable parameter to reflect the intensity of stress and/or systemic inflammation in critically ill patients (Zahorec, 2001). It was only in 2015 that authors looked at this parameter in the context of mood disorders. They showed that NLR tended to be higher in patients with MDD than in controls (Demir et al., 2015). This finding was subsequently replicated in other studies of depressive and bipolar disorders (Aydin Sunbul et al., 2016; Demircan et al., 2016; Gynas Ayhan et al., 2017; Kalelioglu et al., 2015; Mazza et al., 2018). Thus, NLR has significant advantages as it is an easily accessible, applicable, rapid and cost-effective method to monitor inflammation. Furthermore, it can provide earlier diagnostic information for depression and suicidality compared to other commonly used markers such as various leukocyte characteristics or interleukins (Daray et al., 2024; Ghafari et al., 2024).

A recurring problem with biomarkers's measurement is variability. Biomarker stability is crucial as it ensures that variations are due to the phenomena being measured rather than inherent biological, technical, or stochastic fluctuations. Many markers are notoriously unstable, and NLR stability in SA has never been explored. Previously, the NLR stability has been assessed in contexts such as cardiac surgery (Green et al., 2019), where patients were evaluated every 6 months over a 2-year period, and chronic obstructive pulmonary disease (Sakurai et al., 2018), with assessments conducted once a year for 3 years, revealing a disputable stability. To our knowledge, no previous studies have yet examined its stability over time in patients with psychiatric disorders or in healthy individuals.

Additionally, the association between SA and higher NLR may also be influenced by other etiological factors. In mood disorders, most studies consider sex, age or the severity of

depression as a covariate (Ghafari et al., 2024; Martínez-Botía et al., 2020) and some studies considered childhood trauma (Martínez-Botía et al., 2020). It has been shown that emotional and physical neglect, as well as emotional, physical and sexual abuse, increase the vulnerability of adults to develop mood disorders (Daskalakis et al., 2013; Lippard & Nemeroff, 2023; Young et al., 1997) and SA (Ihme et al., 2022a; Olié et al., 2023). Childhood trauma is therefore a vulnerability factor for the development of mood disorders associated with suicidal behaviour. Furthermore, studies show that traumatic events in childhood have a significant impact on the inflammatory system (including NLR variations), with trajectories extending into adulthood (Baumeister et al., 2016; Schiweck et al., 2020). It is therefore relevant to ask whether the inflammatory profile of subjects is the same according to their history of childhood trauma and whether this also varies according to SA. There is evidence of an association between childhood trauma and NLR in anorexia nervosa (Bou Khalil et al., 2022), but to our knowledge no study has directly linked childhood trauma and NLR in adulthood in a cohort of patients with mood disorders. It therefore seems highly relevant to investigate this association.

In this study, we conducted a prospective analysis to investigate the variability of NLR in mood disorder patients and healthy subjects as a function of SA and childhood trauma phenotype. A 30-week longitudinal follow-up was performed at four time points to account for biomarker variability. We hypothesised that, despite some variability, the NLR would be higher in SA patients than in other mood disorder patients and healthy subjects. We also expected the NLR to be higher in people with a history of childhood trauma. We also expected that there would be a significant difference in NLR according to childhood trauma history, depending on the SA profile.

2. Methods

2.1. Study design and procedure

We conducted a prospective multicentric study involving 8 departments of psychiatry in 6 different French cities (Besançon, Clermont-Ferrand, Marseille, Montpellier, Nîmes, and Tours). The participants attended 4 evaluation visits during a 30-week period (T1, baseline; T2, 2 weeks; T3, 8 weeks; T4, 30 weeks) for blood sampling and clinical assessments.

2.2. Participants

Participants in this study were recruited from the original study registered on ClinicalTrials.gov with ID: NCT02209142 and previously described (Consoloni et al., 2018). We exclude from the study 12 patients due to missing NLR for the four data points and 6 patients for whom we had no information about suicidal attempts since this information are crucial for our data analysis or group definition. Consequently, 97 healthy subjects (HS) and 124 adults diagnosed with a current mood depressive episode (MDE) were included, i.e. 100% controls and 87% MDEs. Among the MDE patients, 61 had a history of suicidal behaviour (MDS+) and 63 did not (MDS-). Suicidal behaviour was defined as having attempted suicide at least once in a person's lifetime. Patients were recently admitted to a psychiatric unit or referred to a psychiatrist for MDE. In this study, we are interested in the

specific link between NLR and major depressive disorder. We therefore chose to exclude all other psychiatric diagnoses in order to avoid biasing the results. Similarly, as the NLR is related to inflammation, we decided to exclude any other physiological conditions that could lead to inflammation and impact NLR levels. Consequently, exclusion criteria for both groups included a history of substance use disorder in the past 12 months, a diagnosis of schizophrenia, psychosis, or schizoaffective disorder (DSM-IV), a severe progressive medical disease, pregnancy, vaccination within a month before inclusion, and being under 18. Healthy controls were free of psychiatric symptoms and had no lifetime history of psychiatric disorders. Both patients with major depressive disorder and bipolar disorder were included in MDE group. All participants received a full explanation of the procedure and signed a written consent form before participation. This study received approval from the national ethics committee (CPP Sud Méditerranée II, Marseille, France, study registered under number 2011-A00661-40).

2.3. Clinical assessment

Sociodemographic and clinical characteristics of all participants were collected. This included age, sex, BMI, regular tobacco use [yes/no], history of somatic disease [yes/no], and a family history of suicide or psychiatric disorders [yes/no]. Participants underwent a clinical evaluation using the Structured Clinical Interview for DSM-IV (SCID). The diagnosis of MDE was made by skilled psychiatrists based on the DSM-IV criteria for mood disorders, and the MDE severity was evaluated by the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Patients were included if they scored 19 or higher on the HDRS, and HS were included if they scored lower than 7. A family history included suicide or suicidal attempts among parents or siblings, as well as parental histories of psychiatric disease and mood disorders. Somatic diseases history included dysthyroidism, cancer, cardiovascular disease, neurological disorders, infectious diseases, and inflammatory diseases. Childhood trauma history was assessed using the Childhood Trauma Questionnaire (CTQ) (Paquette et al., 2004), which includes emotional and physical abuse, emotional and physical neglect, and sexual abuse. Subjects were considered to have undergone childhood trauma if they obtained a moderate or severe score on at least one of the five dimensions of the CTQ. We controlled for subjects who presented false negatives on the questionnaire using items relating to CTQ denial. No subjects without trauma showed this bias. Healthy controls were evaluated by a trained psychologist or psychiatrist to exclude subjects with any history or current psychiatric disorder screened by the SCID (Kübler, 2013).

2.4. Biological assessment

Fasting peripheral blood samples were collected from a cephalic vein between 8:00 and 9:00 a.m. in EDTA tubes. Complete blood counts were performed using a Sysmex XN-10/XN-20 Hematology Analyzer (Norderstedt, Germany). Complete blood counts included total white blood cells, neutrophils, lymphocytes, monocytes, and platelets. The NLR was determined by dividing the absolute number of neutrophils by the absolute number of lymphocytes. The neutrophil values considered in this study range from 0.93G/L to 10.1G/L and lymphocyte values from 0.79G/L to 4.57G/L. These values were obtained after exclusion of NLR data

from three MDD patients and four controls because lymphocyte and/or neutrophil counts were outside the laboratory's routine normal range.

2.5. Data analyses

All statistical analyses were performed with IBM SPSS Statistics version 23. We first tested the normal distribution of the NLR data, collected for each time point, with a Shapiro-Wilk test. Since the data did not follow a normal distribution, we transformed them into a logarithmic value (Log_{10} NLR). Since the value was normally distributed after transformation, we performed parametric tests. We first looked at the reliability of the NLR across the four time-visits thanks to an intra-class correlation test (ICC). We only used subjects with complete data for the four visits: 86 healthy subject, 20 MDS-, 21 MDS+. We considered that we had a good reliability for an ICC score between 0.75 and 0.9 and a moderate reliability when the values were between 0.5 and 0.75 (Koo & Li, 2016). Then, a Friedman test has been used to evaluate the intra-individual difference within groups. The same subjects as for the ICC were used for this analysis. We also analysed the sociodemographic and clinical characteristics for the three groups, HS (n=97), MDS- (n=63) and MDS+ (n=61). For continuous variables, student independent t-tests were used for values with a normal distribution whereas a Friedman test was used for non-parametric distribution. Likewise, we performed an ANOVA or non-parametric Kruskal-Wallis test depending on the distribution of the variable. Categorical variables were compared with Chi-square tests when the minimum number of occurrences of a category was five.

We also performed multivariate analyses with several linear mixed models. We used linear mixed models in this study in order to analyse repeated measurements over several time periods. Therefore, NLR ratio is defined as a repeated effect, which means that the model takes into account changes in the ratio over time. The first linear mixed model was used to assess differences among HS, MDS- and MDS+ groups, over four periods, without considering confounding variables. Then another linear mixed model was performed correcting for tobacco, history of medical conditions and childhood trauma confounding variables. These variables were chosen because of their inflammatory potential and therefore their ability to impact NLR values. Finally, a final mixed linear model was employed to assess whether there are differences among healthy subjects or patient with mood disorder with or without trauma history and suicidal behaviour. The purpose of this interaction was to determine whether the effect of the different groups on the ratio depend on the presence or absence of trauma antecedent. P-value < 0.05, two sided, was considered statistically significant.

3. Results

3.1. Sociodemographic data

The final sample included a total of 221 subjects, 97 HS, 63 MDE patients without suicidal behaviour (MDS-) and 61 MDE patients with suicidal behaviour (MDS+). We first tested main confounding variables that could impact NLR by influencing many biological parameters such as inflammation to be sure that they are equally distributed across our

different population of subjects. Consequently, there were no differences between groups for age (mean age [SD] = 43.83 (14.31) vs. 43.92 (15.33) and 45.05 (13.40); $H=0.21$, $p=0.9$) and sex (37.1% vs. 36.5% and 26.2%; $\chi^2 =2.24$, $p=0.33$). Similarly, Body Mass Index (BMI), which is known to influence inflammation in case of obesity, was not significantly different between the HS and both MDS group (+/-). We also tested variable as history of medical disorders and tobacco consumption that are known to be more represented in patients with mood disorder. HS had less history of medical disorders than all patients ($\chi^2=15.511$; $p < 0.001$), whereas no difference has been founded between the two sub-groups of patients ($\chi^2=3.203$; $p=0.074$). The tobacco consumption was different between the three groups ($\chi^2=10.992$; $p=0.004$) but not between MDS (+/-) patients ($\chi^2=1.831$; $p=0.176$). Finally, we explored more in detail parameters links with mood disorder diagnosis. Severity of the depression among MDS- and MDS+ differs at both T3 ($t=-2.286$; $p=0.024$) and T4 ($t=-3.037$; $p=0.003$) with higher values for MDS+ patient (i.e. more severe depressive symptoms). There were differences between patients' groups for types of mood disorder with relative lower proportion of MDS+ in MDD vs BD ($\chi^2=5.9$; $p=0.021$). The percentage of people taking antidepressant treatment did not differ between MDS- and MDS+ at any time. All MDE patients (MDS+/MDS-) had more psychiatric family history than HS ($\chi^2=18.684$; $p < 0.001$), but there was no significant difference between MDS- and MDS+ for psychiatric family history ($\chi^2=3.056$; $p=0.08$). HS had less history of medical disorders than all patients ($\chi^2=15.511$; $p < 0.001$), whereas no difference has been founded between the two sub-groups of patients ($\chi^2=3.203$; $p=0.074$). The tobacco consumption was different between the three groups ($\chi^2=10.992$; $p=0.004$) but not between MDS (+/-) patients ($\chi^2=1.831$; $p=0.176$). Body Mass Index (BMI), which is known to influence many biologic parameters, was not significantly different between the HS and both MDS group (+/-). Finally, HS had significantly less childhood trauma than MDS (+/-) ($\chi^2=35.174$; $p < 0.001$) and MDS+ exhibited more childhood trauma than MDS- ($\chi^2=4.329$; $p=0.037$). All these results and other sociodemographic data are shown in **Table 1**.

3.2.NLR stability

The NLR stability among the three groups of subjects was tested with 86 HS, 20 MDS- and 21 MDS+. The calculated intraclass correlation coefficients (ICC) were respectively 0.89, 95% CI [0.84 - 0.92]; 0.93, 95% CI [0.86 - 0.97] and 0.54, 95% CI [0.1 - 0.79] (e.g., **Table 2**). The ICC showed a lower reliability for the MDS+ group than the two other groups. The Friedman test, used to test the intra individual differences within groups, was significant in the three groups confounded ($Q=19.06$, $p < 0.001$) and in HS ($Q=30.26$, $p < 0.001$), but not in MDS- ($Q=1.11$, $p=0.78$) and MDS+ ($Q=2.23$, $p=0.53$) patients (e.g., **Table 2**), demonstrating a variability of the NLR over time.

3.3. NLR, suicide attempt status and trauma

To account for this variability over time, we conducted repeated measures analyses of NLR. We performed linear mixed models with three levels of correction by covariate adjustment. Model 0, without covariates, revealed a difference in NLR between the HS, MDS+, and MDS- groups ($F=6.07$, $p=0.002$). *Post-hoc* analysis with Bonferroni showed that MDS+ had a significantly higher NLR than HS ($p=0.004$), but not than MDS-, although there was a trend

($p=0.07$). In model 1, which took into account medical history and smoking (two factors known to impact NLR), we found a difference between our groups (HS, MDS+ and MDS-) ($F=5.42$, $p=0.005$). *Post-hoc* comparison revealed that the difference was statistically significant only between HS and MDS+ ($p=0.009$) (e.g., **Figure 1**). We then added childhood trauma as a new factor and tested its interaction with the group factor. Our model, considering medical history, smoking, and childhood trauma, showed an effect of both the group ($F=3.29$, $p=0.038$) and the interaction between the group and trauma factors ($F=6.24$, $p=0.002$) (e.g., **Table 3**).

We conducted exploratory comparisons between groups based on the presence or absence of childhood trauma. This resulted in six groups: HS without trauma, HS with trauma, MDS+ without trauma, MDS+ with trauma, MDS- with trauma, and MDS- without trauma (e.g., **Figure 2**). A linear mixed model analysis of the six groups was conducted, including smoking and medical history as covariates. We found a significant difference in NLR between the six groups ($F=6.215$; $p<0.001$). *Post-hoc* comparisons revealed first that HS without trauma had a significantly lower NLR than HS with trauma ($p=0.014$) and MDS+ without trauma ($p=0.001$). Second, MDS- without trauma had a significantly lower NLR than MDS+ without trauma ($p=0.026$). It should be noted that no other comparison between group demonstrate any significant differences or trends (all $p\text{-value}>0.8$).

4. Discussion

We investigated for the first time the stability of NLR across repeated measurements in patients with mood disorders, suicidal behaviour, and healthy controls. Repeated measurements of NLR revealed good reliability, except for the MDS+ group which had moderate reliability. NLR reliability has previously been explored in cardiovascular diseases, yielding similar results with an ICC of 0.70 for repeated measurements (Green et al., 2019). However, as indicated by the Friedman test, NLR values can vary over time in the same individual, even within normal ranges. These findings suggest that NLR variability should be considered in future studies, such as by taking multiple measurements over time to compare different groups. From a diagnosis and treatment monitoring perspective, the variability of the NLR is an important factor to consider. NLR variability reflects that values measured at different times for the same patient are not consistent, which could complicate its use as a diagnostic tool or to monitor a therapeutic effect. Establishing a single NLR threshold as the sole reference for diagnosis would be also challenging. For instance, incorporating other parameters, such as additional inflammatory markers, as well as include repeated measures, would likely enhance diagnostic accuracy and therapeutic relevance. Interestingly, this variability could also be leveraged as an advantage. The ICC test reveals greater NLR variability in MDS+ subjects, which may indicate physiological instability or heightened stress in this group. As an inflammatory marker, fluctuations in NLR could reflect irregular or exacerbated inflammatory responses, often linked to chronic stress and immune imbalances observed in severe depression with suicidal behavior. This variability could thus serve as an early warning for periods when patients might experience increased vulnerability to suicidal behavior, necessitating closer monitoring or rapid treatment adjustments.

Taking this intra-individual variability into account, we showed that SA was associated with higher NLR. These results are consistent with previous studies showing that the NLR is associated with SA in patients with MDD both in adults (Ekinci & Ekinci, 2017; Neupane et al., 2023; Velasco et al., 2020) and adolescents (Amitai et al., 2022), and both before and after treatment with selective serotonin reuptake inhibitors (Adhikari et al., 2018). These findings support the idea that an increase in NLR could be a potential biomarker for SA in mood disorders. However, few studies have taken potential confounding factors into account. Our analysis considered childhood trauma due to its potential influence on SA (Ihme et al., 2022b; Zatti et al., 2017). We revealed that both SA and childhood trauma are associated with elevated NLR values. Importantly, by isolating the childhood trauma factor, we observed that a history of suicide attempts independently contributed to increased NLR values. In parallel, we described, for the first time to our knowledge, that HS with childhood trauma demonstrated higher NLR values. This result is consistent with previous studies showing the influence of childhood trauma on inflammatory factors in adulthood (Baumeister et al., 2016). This supports the notion that both distal factors, such as trauma and proximal factors such as psychiatric disorder (e.g., MDD) can independently contribute to an increased risk of suicidality. The combined impact of these factors significantly heightens this risk (Götz & Stefanski, 2007a; Wilson et al., 2011). Supporting this, murine models studies had shown that prenatal or early life stress increase NLR (Götz & Stefanski, 2007b; Teicher et al., 2016). In humans, a recent study show that trauma also influence NLR and revealed an interaction between childhood trauma, suicide attempts, and NLR (Martínez-Botía et al., 2020). Our study replicates this interaction, taking into account the NLR variability across time. The cumulative evidence suggests NLR as a potential biomarker for SA, potentially heightened by childhood trauma. Thus, as a potential clinical application, NLR could help to identify individuals at high risk of SA in psychiatric disorders, particularly in patients with MDD who have previously undergone childhood trauma. Integrating NLR into existing assessments could contribute to earlier detection and risk monitoring based on objective, costless and easily measurable marker.

Our results could be interpreted within the frame of stress as a psychological challenge, which reacts by increasing the sympathetic nervous system and the HPA system. The norepinephrine released by the sympathetic system influences immunity via MAPK proteins (Eyre & Baune, 2012). Indeed, the involvement of the MAPK pathway in mood disorders pathogenesis has long been suspected, with evidence supporting this link (Duman et al., 2007; Duric et al., 2010). It is also known that the MAPK pathway can regulate neutrophil apoptosis, in particular by prolonging its activity. For example, activation of the ERK pathway is known to inhibit neutrophil apoptosis, whereas p38 can either promote or inhibit apoptosis depending on the context (Larbi et al., 2005). The MAPK pathway is involved in regulating the release of pro-inflammatory cytokines by neutrophils by modulating their gene expression and affecting the translation machinery (Cloutier et al., 2007). Thus, there could be a link between the NLR and the MAPK pathway in individuals who have suffered early trauma and present suicidal behaviour in adulthood, via MAPK pathway functions on neutrophils. A link via the HPA axis could also be considered. The HPA axis releases glucocorticoids, which modulate inflammatory responses (Busillo et al., 2011; Sorrells et al., 2009). Although glucocorticoids initially reduce inflammation, chronic stress shifts the

response towards a pro-inflammatory state (Strüber et al., 2014). This pro-inflammatory state will have consequences for the brain. Indeed, studies show that stress during sensitive periods of development leads to permanent changes in neuronal circuits, such as a reduction in dendritic arborisation (Liu et al., 2017; McEwen et al., 2016). Although dendrites can recover their shape after a period of transient stress, early adversity can lead to permanent grey matter loss (Andersen & Teicher, 2004, 2008). Interestingly, there is evidence of grey matter abnormalities in patients with major depressive disorder who have attempted suicide (Chen et al., 2024). Although no study has yet linked NLR to brain dysfunction in the psychiatric population, one study has shown that high levels of NLR are associated with white matter lesions in migraineurs (Morkavuk et al., 2020). Overall, stress appears to increase inflammation via microglia and astrocytes while compromising the blood-brain barrier, allowing peripheral cytokines to enter the brain (Menard et al., 2017). This infiltration perpetuates central inflammation, increasing the population of perivascular macrophages, a mechanism observed in post-mortem brains of suicide patients (Torres-Platas et al., 2014). Perivascular macrophages play a direct role in the activation of the hypothalamic-pituitary-adrenal (HPA) axis following an immune challenge (Serrats et al., 2010). This phenomenon could therefore contribute to the chronic inflammation observed in trauma and suicidal patients. In summary, stress experienced in childhood, such as trauma, can trigger a peripheral inflammatory response. Over time, this response can affect the central nervous system, setting off a vicious circle involving the HPA axis. Cerebral inflammation at an early stage of development can cause lasting disruption to the nervous system, increasing vulnerability to the risk of suicide. This inflammatory cycle can persist throughout life, which explains why the presence of inflammatory markers such as NLR in adulthood is often associated with childhood trauma and an increased risk of suicide.

Despite these encouraging results, further studies are needed to validate the role of NLR as a potential biomarker of suicidal attempt (SA). Currently, our study only allowed us to observe how NLR values vary among the previously defined groups. To explore the predictive nature of NLR, larger prospective studies would be necessary. It could be possible to observe NLR in depressed patients, isolate high values, and observe if over time these patients are more likely to make suicide attempt than patients with low NLR. Furthermore, due to the small number of recent SA and SA during the 30 follow-up visits, we were not able to analyse the effect of time since last SA as a potential confounding factor. In the same vein, several methods were used in patients with SA. Although more than 70% of SA was voluntary self-poisoning, the heterogeneity of the drug does not allow to explore potential bias related to biological consequences of SA. However, we were confident that our 30-week prospective design with 4 time points would avoid major bias related to the nature and consequences of SA. In our cohort, the sample size was modest although sufficient to detect a significant effect. In addition, this study benefits from the rigor of its prospective design, with repeated measures. Moreover, patients were phenotyped by trained psychiatrists, which guarantees the accuracy of clinical diagnoses. Our study is also limited by missing data. It is worth noting that this was a prospective study over 4 visits, with a substantial gap (22 weeks) between the 3rd and 4th visits. This time lapse was therefore subject to some loss of subjects (4/97 controls lost, 59/124 patients lost). To ensure the reproducibility of our results, we carried out

strictly the same analyses, removing visit 4. We obtained a similar result (data not shown), which confirms the reliability of our results. As for the generalizability of the results, they must be interpreted with caution. The participants in this study were depressed patients treated as outpatients or in hospital, whereas the majority of depressed patients (about 75%) (*INPES, Coll. Études Santé, 2009 : 208 p, n.d.*) are treated in primary care by general practitioners. This difference may limit the representativeness of our sample. Finally, other inflammatory markers could be interesting to explore, and future studies should assess other biomarkers in combination with NLR.

5. Conclusion

In conclusion, our study shows for the first time how variable the NLR could be in patients with mood disorders with and without SA, suggesting that this variability should be taken in consideration in further studies. Also, we confirm that investigation of the NLR in suicidal behaviours should include a preliminary analysis of childhood trauma. Finally, it is tempting to attribute vulnerability biomarker properties to this ratio, even if further studies are needed before its clinical use.

Glossary

- **Neutrophil-to-Lymphocyte Ratio:** The Neutrophil-to-Lymphocyte Ratio is a biomarker calculated by dividing the number of neutrophils by the number of lymphocytes in a blood sample. It is used as an indicator of systemic inflammation and has been associated with various medical conditions, including cardiovascular diseases, infections, and psychiatric disorders

- **Mood disorder:** A mood disorder is a category of mental health conditions characterized by persistent disturbances in a person's emotional state or mood. Common mood disorders include major depressive disorder, bipolar disorder, and dysthymia, which can significantly impact daily functioning and quality of life.

- **Suicidal behaviour:** Suicidal behaviour refers to actions or thoughts related to self-harm with the intention of ending one's life. This includes suicidal ideation, suicide attempts, and completed suicide. It is often associated with mental health conditions such as depression, anxiety, and mood disorders

- **Childhood trauma:** Childhood trauma refers to distressing or harmful experiences during childhood, such as physical, emotional, or sexual abuse, neglect, or witnessing violence. These experiences can have long-lasting effects on a person's mental, emotional, and physical health, contributing to the development of various psychological conditions in later life.

Abbreviations

NLR: Neutrophil-to-Lymphocyte Ratio

HS: healthy subjects

MDD: Major depressive disorder

MDE: Major depressive episode

BD: bipolar disorder

SA: attempt

MDS-: Mood disorder without suicidal behaviour

MDS+: Mood disorder with suicidal behaviour

SD: Standard deviation

CRP: C-Reactive Protein

IL-6: interleukin-6

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders

SCID: Semi- Structured Clinical Interview of the DSM-IV

HDRS: Hamilton Depression Rating Scale

QIDS: Quick inventory depression scale

CTQ: Childhood Trauma Questionary
BMI: Body Mass Index
ICC: intraclass correlation coefficient

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Declaration of interests

All authors declare that they have no conflict of interest relative to this study.

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	Healthy subjects n = 97	Patients with Mood Disorder without suicidal behaviour n = 63	Patients with mood Disorder with suicidal behaviour n = 61	χ^2 / Student's t-test / Kruskal-Wallis test	p-value
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Sociodemographic data					
Sex (n [%])				2.24 (χ^2)	0.327
<i>Males</i>	36 (37.1%)	23 (36.5%)	16 (26.2%)		
<i>Females</i>	61 (62.9%)	40 (63.5%)	45 (73.8%)		
Age (mean [SD])	43.83 (14.31)	43.92 (15.33)	45.05 (13.4)	0.21 (KW)	0.901
Clinical data					
Mood disorder n (%)				5.9 (χ^2)	0.021
Bipolar disorder	-	14 (22.2%)	26 (42.6%)		
Major depressive disorder	-	49 (77.8%)	35 (57.4%)		
Severity of depression: QIDS(mean [SD])					
Severity t1	-	17.19 (4.59)	18.75 (4.6)	-1.85 (t)	0.067
Severity t2	-	12.47 (5.9)	14.22 (5.76)	-1.643 (t)	0.103
Severity t3	-	10.56 (5.6)	13.1 (5.93)	-2.286 (t)	0.024
Severity t4	-	7.92 (4.59)	12.41 (6.16)	-3.037 (t)	0.003
Number of Suicidal Attempts (mean [SD])	-	0 (0)	2.52 (2.19)		
Antidepressant treatment t1	-	43 (68.3%)	50 (82%)	3.11 (χ^2)	0.078
Antidepressant treatment t2	-	51 (80%)	46 (75.4%)	0.58 (χ^2)	0.444
Antidepressant treatment t3	-	45 (71.4%)	39 (63.9%)	0.09 (χ^2)	0.765
Antidepressant treatment t4	-	38 (60.3%)	40 (65.5%)	2.38 (χ^2)	0.123
BMI (mean [SD])	23.83 (3.78)	24.66 (4.45)	25.33 (5.63)	2.70 (KW)	0.259
Tobacco: current use (n [%]) (3 groups)	23 (23.7%)	23 (36.7%)	30 (49.2%)	10.99 (χ^2)	0.004
Tobacco: current use (n [%]) (2 groups)	-	23 (36.7%)	30 (49.2%)	1.83 (χ^2)	0.176
Medical disease history (3 groups)	24 (24.7%)	25 (39.7%)	34 (55.7%)	15.511 (χ^2)	< 0.001
Medical disease history (2 groups)	-	25 (39.7%)	34 (55.7%)	3.203 (χ^2)	0.074
History of childhood trauma (3 groups)	16 (16.5)	22 (34.9%)	28 (45.9%)	35.174 (χ^2)	< 0.001
History of childhood trauma (2 groups)	-	22 (34.9%)	28 (45.9%)	4.329 (χ^2)	0.037
Total family psychiatric history (3 groups)	30 (30.9%)	31 (49.2%)	40 (65.6%)	18.684 (χ^2)	< 0.001
Total family psychiatric history (2 groups)	-	31 (49.2%)	40 (65.6%)	3.056 (χ^2)	0.08
NLR values					
T1 mean (SD)	1.98 (0.88)	1,8 (0.26)	1.99 (0.24)	0.007 (KW)	0.997
T2 mean (SD)	1.65 (0.8)	1.71 (0.27)	1.9 (0.12)	2.176 (KW)	0.337
T3 mean (SD)	1.71 (0.78)	1.94 (0.36)	2.09 (0.21)	3.642 (KW)	0.162
T4 mean (SD)	1,64 (0.66)	2 (0.23)	2.37 (0.33)	12.34 (KW)	0.002

Table 1: Socio-demographic and clinical characteristics of: Healthy subject (n=97), Mood disorder without suicidal behaviour patients (n=63) and Mood Disorder with suicidal behaviour patients (n=61). For continuous variables, Student independent t-tests or non-parametric Kruskal-Wallis tests were used depending on the distribution of the variable while categorical variables were compared with Chi-Square tests. Statistically significant results are presented in bold. *Abbreviations: QIDS-SR-16 (Quick Inventory of Depressive*

Symptomatology 16 items Self-Report). T1 represents inclusion, T2 the second visit 2 weeks later, T3 the third visit 8 weeks later and T4 the last visit 30 weeks later.

	Intraclass correlation (ICC)	Confidence interval of 95%	p-value	Friedman Test	p-value
Healthy subject (HS)	0.66	[0.57 - 0.74]		30.26	< 0.001

n = 86			>0.0001		
Mood Disorder without suicidal behaviour (MDS-) n = 20	0.77	[0.61 – 0.89]	>0.0001	1.11	0.776
Mood Disorder with suicidal behaviour (MDS+) n = 21	0.22	[0.03 – 0.49]	0.011	2.23	0.526
Three group confounded	0.6	[0.52 – 0.68]	>0.0001	19.06	< 0.001

Table 2: Stability of the Neutrophile Lymphocyte Ratio (NLR) across the 4 times. Stability among the healthy subject (HS) and subjects with Mood Disorder with or without Suicidal behaviour (MDS+; MDS-) have been tested with intraclass correlation coefficient ICC and Friedman test

	Model 0		Model 1		Model 2	
	F	p-value	F	p-value	F	p-value
Group	6.07	0.002	5.42	0.005	3.29	0.038

Tobacco	-	-	4.59	0.032	7.44	0.007
Medical disease history	-	-	5.35	0.021	5.92	0.015
Trauma	-	-	-	-	1.88	0.170
Trauma*Group	-	-	-	-	6.24	0.002

Table 3: Mixed linear model with group as principal factors and without covariable (Model 0). Mixed linear model with group as principal factors but corrected with tobacco and medical disease history as covariates (Model 1). Mixed linear model with group and childhood trauma as principal factors and corrected with tobacco and medical disease antecedent as covariates (Model 2). Interaction between childhood trauma and group have also been tested for Model 2.