IMMUNOPSYCHIATRY IN SUICIDE AND MOOD DISORDERS – EXPLORING NOVEL BIOMARKERS

Doctoral (PhD) thesis

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1. INTRODUCTION

Suicide risk assessment remains on of the greatest unsolved issues in psychiatric care – although the global health burden is significant, as suicide takes 700 000 lives every year (Lovero et al., 2023). Different theories have aimed to explain the emergence of suicidal ideations, plans and attempts (Joiner, 2005; O'connor, 2011; Klonsky et al., 2018) and certain frameworks have been developed to evaluate predisposing and precipitating risk factors (Galynker et al., 2025) – among others, the latter include psychiatric illnesses, such as major depressive disorder (MDD) or bipolar affective disorder, with affected individuals facing a significantly elevated risk of suicide (Too et al., 2019).

Apart from genetic and environmental factors, novel studies have found inflammatory mechanisms to contribute to not only the pathogenesis of mood disorders (Barbosa et al., 2014; E. Leonard, 2010), but the emergence of suicidal behavior, as well (Costanza et al., 2024). Cytokines have been identified as important mediators of these immunological processes (Schwarz, 2003). The latter are low-molecular-weight regulatory glycoproteins that play a crucial role in the initiation and maintenance of acute and chronic inflammatory responses (Kany et al., 2019). Subgroups of cytokines include interleukins (IL's), interferons (IFN's) and tumor necrosis factors (TNF's). Interactions between pro-inflammatory cytokines – such as IL-1β, IL-6, IL-8 or TNF-α – may lead to synergistic effects enhancing immunological activity, while cytokines with anti-inflammatory properties – such as IL-4, IL-10 or transforming growth factor-β1 (TGF-β1) – may counterbalance these effects by modulating pro-inflammatory cytokine signaling (Myint & Kim, 2003).

Cytokines possess the ability to regulate neurotransmitter systems, therefore influencing behavior (Felger et al., 2013). A clear example of the effect of immunological activation on the central nervous system (CNS) is the phenomenon known as sickness behavior: the host response to infection, mediated by cytokines, results in behavioral changes associated with illness: anorexia, lethargy, decreased interest in social interaction, reduced activity, as well as affective and cognitive components such as anhedonia, anxiety, impaired concentration and loss of memory function (Maes et al., 2012). Notably, similar behavioral disturbances may be observed in the symptomatology of MDD. It is therefore understandable that inflammatory mechanisms may be responsible for the development of psychiatric symptoms – although an acute activation of inflammatory cytokines may result in adaptive behavioral responses,

facilitating host defense against infection, chronic exposure to elevated levels of these mediators, along with the dysregulation of neurotransmitter systems may in contrast contribute to the development of psychiatric symptoms (Felger & Lotrich, 2013).

Furthermore, inflammatory cytokines may influence the hypothalamic-pituitary-adrenal (HPA) axis – the dysregulation of the latter is a well-known pathophysiological finding in MDD. Individuals with this illness exhibit elevated cortisol levels, accompanied by increased corticotropin-releasing hormone (CRH) levels (Pariante & Miller, 2001). Although the underlying mechanisms of the increased CRH activity in MDD remain incompletely understood, the latter may be the result of an impaired negative feedback by endogenous glucocorticoids. Inflammatory cytokines alter glucocorticoid receptor function through specific intracellular signaling pathways, including molecular cascades modulated by mitogen-activated protein kinase (MAPK) and nuclear factor κB (NF-κB). The disruption in the negative feedback mechanism leads to further release of both CRH and pro-inflammatory agents. This phenomenon is referred to as glucocorticoid resistance, the impaired negative feedback resulting from reduced glucocorticoid receptor expression, which is a consequence of chronic cytokine exposure. Therefore, the immunosuppressive effects of glucocorticoids – which are present under physiological conditions – become attenuated, leading to inflammatory dysregulation that is thought to contribute to the development of MDD (Pace et al., 2007).

Furthermore, cytokines have been proved to influence CNS functioning through regulating the generation of new neurons. Neurogenesis plays a critical role in cognitive processes, which are often compromised in mood disorders (Spalding et al., 2013). According to the neurogenic hypothesis of MDD, the continuous generation of new neurons in the brain contributes to mood regulation and is essential for the therapeutic action of antidepressant treatment (Eisch & Petrik, 2012). Serotonin has been found to exert a significant effect on neurogenesis: in clinical studies, systemic treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants resulted in an increase in the number of newly generated cells in the hippocampus (Malberg et al., 2000). The inhibition of neurogenesis has been associated with the emergence of depressive symptomatology in clinical populations: patients undergoing chemotherapy, in whom neurogenesis was secondarily suppressed, frequently exhibited memory deficits and further depressive symptoms (Jacobs et al., 2000).

Moreover, cytokines influence the synthesis, release and metabolism of neurotransmitters. As implied by the monoamine hypothesis, the reduced availability of serotonin, dopamine and

noradrenaline observed in MDD is believed to be responsible for functional alterations in brain regions regulated by these neurotransmitters, resulting in depressive symptomatology (Jiang et al., 2022). The implication that the cytokine-mediated modulation of monoaminergic signaling may contribute to the pathogenesis of MDD is supported by clinical observations indicating that certain depressive symptoms may be attenuated by anti-inflammatory therapeutic interventions (Gong et al., 2025).

Moreover, an increasing number of investigations support the hypothesis that antidepressant treatment – exerting its effect by inhibiting the neuronal reuptake of monoamines – may attenuate the inflammatory state observed in MDD. Although the precise mechanisms remain incompletely understood, some studies imply that these agents may reduce the release of pro-inflammatory cytokines and other immunological mediators (Lanquillon, 2000).

Furthermore, apart from antidepressants, antipsychotic medication has been suggested to have an inhibitory effect on inflammatory processes: studies have found first, second and third generation agents to reduce the levels of pro-inflammatory cytokines, while causing elevations in the levels of anti-inflammatory mediators (Šafářová et al., 2025). As for mood stabilizers, literature remains inconsistent, with studies indicating both pro-inflammatory and anti-inflammatory mechanisms (Nassar & Azab, 2014).

All in all, inflammatory processes have been associated with the development of mood disorders and the emergence of suicidal behavior, although the background is complex and not completely understood. Immunological alterations may be signaled not only by cytokines, but also by blood cells responsible for the production of these mediators and therefore the development of the immune response (Chaplin, 2010). An increasing number of studies have focused on investigating alterations in blood cell numbers and specific cell ratios as a more accessible way of ascertaining the extent of inflammation associated with psychiatric symptomatologies.

2. OBJECTIVES

In psychiatric care, the assessment of an individual's risk of suicide remains a major challenge for clinicians. Currently, risk stratification relies mainly on self report-based methods (Andreotti et al., 2020) – the effectiveness of which may be compromised by the lack of trust and cooperation by patients possibly affected by the acute symptomatology of a psychiatric illness, resulting in attempted or completed suicide in many cases.

At present, there is no biomarker available which could objectively indicate suicidal vulnerability in patients with MDD, bipolar affective disorder or any other psychiatric illness. However, there is a substantial need for an easily accessible, cost-effective, reproducible parameter, which could complete assessment methods currently in use to help identify increased risk for suicide in individuals.

The aim of our research was to investigate alterations in blood cell counts among psychiatric patients diagnosed with MDD and bipolar I disorder (BD), with regard to short-term and long-term risk of suicide. Furthermore, we hoped to contribute to a more comprehensive understanding of the immunological changes associated with MDD, BD and suicidal behavior. We anticipated that, in the future, the parameters examined in this investigation may serve as potential biomarkers, which may allow more punctual identification of patients at increased risk for suicide. In such cases, closer monitoring, adjustments in the duration of hospitalization or the implementation of further psychotherapeutic and pharmacological interventions may help prevent an imminent attempt (Consolata Uzzi et al., 2024).

3. MATERIALS AND METHODS

In both of our retrospective investigations, we collected data from psychiatric inpatients diagnosed with MDD (n = 101) and with BD (n = 116). We registered data regarding the number of neutrophil granulocytes, monocytes, lymphocytes, platelets and white blood cells (WBC's), along with mean platelet volume (MPV), erythrocyte sedimentation rate (ESR), red blood cell distribution width (RDW) and C-reactive protein (CRP). We calculated neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR) and platelet-to-lymphocyte ratio (PLR). Three patient groups were created based on the presence of a suicide attempt (SA): recent (≤ 48 hours prior) (n_{MDD} = 19, n_{BD} = 21), past (> 48 hours prior) attempters (n_{MDD} = 22, n_{BD} = 16) and patients with no history of SA (n_{MDD} = 60, n_{BD} = 79). Further dividing individuals according to SR, participants with recent or past SA represented the high SR group (n_{MDD} = 41, n_{BD} = 37) and patients with no history of SA were considered as individuals with intermediate SR (n_{MDD} = 60, n_{BD} = 79). Recent SA was carried out by self-poisoning with benzodiazepines. The exclusion criteria of both investigations included acute or chronic inflammatory illnesses, autoimmune diseases, hematological or oncological disorders and current treatment with anti-inflammatory or immunosuppressive medication. Due to the confounding effects of trauma-related inflammation, individuals having attempted suicide by causing physical injury were excluded from the recent SA group.

In our investigation on MDD patients, all of the participants were undergoing antidepressant treatment and a subset of them received antipsychotic therapy. Antidepressant treatment consisted of SSRI, serotonin antagonist and reuptake inhibitor (SARI), serotonin-noradrenaline reuptake inhibitor (SNRI), noradrenaline and selective serotonergic antidepressant (NaSSA) and noradrenaline-dopamine reuptake inhibitor (NDRI) medication. Antipsychotic treatment included first, second and third generation agents. In the past SA group, significantly more patients were treated with antipsychotic medication compared to the recent SA and no history of SA groups, therefore we paid close attention to the alterations of the investigated values related to antipsychotic treatment. In our study on BD patients, all of the participants had been undergoing pharmacological treatment. Subsets of them received antipsychotic, antidepressant therapy and mood stabilizers. Antipsychotic treatment included first, second and third generation agents. Antidepressant therapy consisted of SSRI, SNRI, NaSSA, SARI, selective

serotonin reuptake enhancer (SSRE), multimodal and tricyclic antidepressant (TCA) medication. Mood stabilizers incorporated lithium, carbamazepine, valproate and lamotrigine.

Laboratory tests were performed at the Department of Laboratory Medicine, Medical School, Clinical Center, University of Pécs. For the statistical analysis, GraphPad Prism version 9.5.0 Windows program (GraphPad Software, San Diego, CA, USA, www.graphpad.com, accessed in 2022), GraphPad Prism version 10.0 Windows program (GraphPad Software, San Diego, CA, USA, www.graphpad.com, accessed in 2024) and MedCalc 16.8 Windows program (MedCalc Software Ltd., Ostend, Belgium, www.medcalc.org, accessed in 2023) were used. Statistical operations were carried out first by performing a descriptive analysis and then by determining the distribution of samples. Outliers were identified using the robust regression and outlier removal method and excluded from further statistical analyses. For comparisons between groups, the unpaired t-test, Mann-Whitney U test, Brown-Forsythe and ordinary one-way ANOVA test, Kruskal-Wallis test and Tukey's, Dunn's or Dunnett's multiple comparison analyses were used. To compare two normally distributed groups with different homogeneity of variance, Welch's correction was applied. For testing the categorical variables, the chi-squared analysis with Fisher's exact test was performed. The receiver operating characteristic (ROC) curve analysis was used to assess the overall diagnostic performance and to determine the cut-off value, specificity and sensitivity of laboratory parameters. In all cases, $p \leq 0.05$ was considered statistically significant.

4. RESULTS

4.1. Results I.

4.1.1. Inflammatory markers in patients with recent suicide attempt and no history of suicide attempt

Neutrophil granulocyte count and NLR were significantly elevated in patients with recent SA ($n_{neutrophil\ granulocyte}$ = 19, $mean_{neutrophil\ granulocyte}$: 5.42 ± 1.49; n_{NLR} = 19, $mean_{NLR}$: 3.26 ± 2.24) compared to patients with no history of SA ($n_{neutrophil\ granulocyte}$ = 60, $mean_{neutrophil\ granulocyte}$: 4.44 ± 1.76; n_{NLR} = 60, $mean_{NLR}$: 2.10 ± 1.01) ($p_{neutrophil\ granuloctyte}$ = 0.016, p_{NLR} = 0.031).

Furthermore, we found a significant increase in monocyte count and MLR in patients with recent SA ($n_{monocyte}$ = 19, $mean_{monocyte}$: 0.53 ± 0.14; n_{MLR} = 16, $mean_{MLR}$: 0.23 ± 0.07) compared to patients with no history of SA ($n_{monocyte}$ = 57, $mean_{monocyte}$: 0.40 ± 0.12; n_{MLR} = 56, $mean_{MLR}$: 0.18 ± 0.06) ($p_{monocyte} \leq$ 0.0001, p_{MLR} = 0.005).

Considering further inflammatory parameters, ESR and WBC were significantly elevated in patients with recent SA (n_{ESR} = 12, n_{WBC} = 19) compared to patients with no history of SA (n_{ESR} = 43, n_{WBC} = 60) (p_{ESR} = 0.037, p_{WBC} = 0.048).

4.1.2. Inflammatory markers in relation to suicide risk

We detected a significant increase in monocyte count and MLR in patients with high SR ($n_{monocyte}$ = 40, $mean_{monocyte}$: 0.52 ± 0.16; n_{MLR} = 36, $mean_{MLR}$: 0.21 ± 0.08) compared to patients with intermediate SR ($n_{monocyte}$ = 57, $mean_{monocyte}$: 0.40 ± 0.12; n_{MLR} = 56, $mean_{MLR}$: 0.18 ± 0.06) ($p_{monocyte} \leq$ 0.0001, p_{MLR} = 0.020).

As for further inflammatory parameters, ESR and RDW were significantly elevated in patients with high SR (n_{ESR} = 29, n_{RDW} = 39) compared to patients with intermediate SR (n_{ESR} = 43, n_{RDW} = 56) (p_{ESR} = 0.041, p_{RDW} = 0.037).

4.1.3. Effects of antidepressant and antipsychotic therapy

All of the participants were undergoing antidepressant treatment, therefore we aimed to observe the effect of pharmacotherapy on the investigated parameters. We divided data into four groups according to the received dose of antidepressant medication: under or 100% (n_{NLR} = 40, mean$_{NLR}$: 1.98 ± 0.80; n_{MLR} = 40, mean$_{MLR}$: 0.19 ± 0.06), 200% (n_{NLR} = 25, mean$_{NLR}$: 2.44 ± 1.33; n_{MLR}= 23, mean$_{MLR}$: 0.20 ± 0.08), 300% (n_{NLR} = 22, mean$_{NLR}$: 1.97 ± 0.90; n_{MLR} = 20, mean$_{MLR}$: 0.17 ± 0.06), 400% or above (n_{NLR} = 8, mean$_{NLR}$: 1.47 ± 0.37; n_{MLR} = 8, mean$_{MLR}$: 0.16 ± 0.03) the minimal effective daily dose (Posternak, 2017).

NLR was affected by antidepressant therapy. We detected a significantly lower value in the group „400 or above" compared to the group „200" (p_{NLR} = 0.016). However, MLR remained unaffected by antidepressant medication, with no significant differences between the groups (p_{MLR} = 0.321).

As for further parameters, neutrophil granulocyte count was significantly decreased in the group „400 or above" (n = 7, mean: 2.91 ± 0.69) compared to the group „under or 100" (n = 43, mean: 4.81 ± 1.71) (p = 0.0163). The groups did not differ significantly regarding the rest of the values (p > 0.05).

Observing the effect of antipsychotic treatment, we found a significant decrease in ESR in patients undergoing antipsychotic medication (n_{ESR} = 48, mean$_{ESR}$: 7.23 ± 4.96) compared to untreated individuals (n_{ESR} = 25, mean$_{ESR}$: 17.56 ± 13.28) (p_{ESR} = 0.0002). There were no significant differences between the recent SA and no history of SA groups regarding the number of patients receiving antipsychotic medication. Although there were more treated patients in the high SR group compared to the intermediate SR group, we detected significantly higher ESR values in the high SR group.

The rest of the investigated parameters were not significantly affected by antipsychotic medication (p > 0.05).

4.1.4. Investigation of the diagnostic value of inflammatory parameters

We examined the diagnostic value of NLR and MLR in differentiating patients with recent SA (n_{NLR} = 19, n_{MLR} = 16) from individuals with no history of SA (n_{NLR} = 60, n_{MLR} = 56). According to the AUC value (AUC_{NLR}: 0.669, 95% CI_{NLR} = 0.529 – 0.809, p_{NLR} = 0.031; AUC_{MLR}: 0.728, 95% CI_{MLR} = 0.60 – 0.857, p_{MLR} = 0.006), the diagnostic performance of NLR was limited. The diagnostic value of MLR was acceptable. Calculated according to the Youden-index, the optimal cut-off value was 1.54 for NLR (sensitivity = 88.2%, specificity = 40.7%) and 0.14 for MLR (sensitivity = 87.5%, specificity = 46.4%) in predicting SA.

As for further inflammatory parameters, monocyte count had an acceptable diagnostic performance. Neutrophil granulocyte count, WBC and ESR had a limited diagnostic value.

4.2. Results II.

4.2.1. Inflammatory parameters in bipolar I patients with recent suicide attempt and no history of suicide attempt

We found a significant increase in MLR (p = 0.0021, n = 21, mean: 0.29 ± 0.13, median: 0,28), monocyte count ($p \leq$ 0.0045, n = 21, mean: 0.56 ± 0.20 G/l, median: 0,54), CRP (p = 0.0036, n = 18, mean: 3.62 ± 2.05 mg/l, median: 3,00) and ESR ($p \leq$ 0.0001, n = 6, mean: 18.50 ± 11.78 mm/h, median: 15,50) in patients with recent SA compared to individuals with no history of SA (n_{MLR} = 78, $mean_{MLR}$: 0.21 ± 0.07, $median_{MLR}$: 0,19 ; $n_{monocyte}$ = 78, $mean_{monocyte}$: 0.42 ± 0.13 G/l, $median_{monocyte}$: 0,41; n_{CRP} = 68, $mean_{CRP}$: 2.44 ± 2.33 mg/l, $median_{CRP}$: 1,45; n_{ESR} = 41, $mean_{ESR}$: 4.76 ± 3.09 mm/h, $median_{ESR}$: 4,00).

There were no significant differences between the two groups regarding neutrophil granulocyte, lymphocyte and platelet count, WBC, NLR, PLR, RDW and MPV.

4.2.2. Inflammatory parameters in bipolar I patients with high suicide risk and intermediate suicide risk

We found a significant increase in MLR ($p = 0.0120$, $n = 37$, mean: 0.26 ± 0.12, median: 0,25), monocyte count ($p = 0.0293$, $n = 37$, mean: 0.51 ± 0.19 G/l, median: 0,46), CRP ($p = 0.049$, $n = 32$, mean: 2.80 ± 1.67 mg/l, median: 2,55) and ESR ($p = 0.0009$, $n = 13$, mean: 14.54 ± 13.49 mm/h, median: 9,00) in patients with high SR compared to participants with intermediate SR ($n_{MLR} = 78$, $mean_{MLR}$: 0.21 ± 0.07, $median_{MLR}$: 0,19; $n_{monocyte} = 78$, $mean_{monocyte}$: 0.42 ± 0.13 G/l, $median_{monocyte}$: 0,41; $n_{CRP} = 68$, $mean_{CRP}$: 2.44 ± 2.33 mg/l, $median_{CRP}$: 1,45; $n_{ESR} = 41$, $mean_{ESR}$: 4.76 ± 3.09 mm/h, $median_{ESR}$: 4,00).

We found no significant differences between the two groups regarding neutrophil granulocyte, lymphocyte and platelet count, WBC, NLR, PLR, RDW and MPV.

4.2.3 Effects of pharmacological treatment

We investigated alterations of the parameters related to antidepressant and antipsychotic medication. Comparing treated and untreated patients, we found no significant differences regarding antidepressant treatment ($p > 0.05$). We found no significant differences between individuals receiving antipsychotic pharmacotherapy and untreated participants ($p > 0.05$).

5. DISCUSSION

An increasing amount of research suggests the potential role of inflammatory processes in the background of psychiatric disorders such as MDD or bipolar affective disorder and furthermore, the emergence of suicidal behavior. The implication that the pathomechanism of mood disorders and the development of inflammatory response are intertwined, with the processes mutually reinforcing one another, may be supported by previous studies reporting that, in a subset of patients, immune system activation contributes significantly to the pathogenesis of MDD, whereas the presence of an ongoing depressive episode increases inflammatory cytokine responses to stressors and pathogens (Kiecolt-Glaser et al., 2015). It remains unclear whether different levels of the same immunological mechanism or several distinct inflammatory processes are responsible for the pathogenesis of mood disorders and the emergence of suicidal behavior, however, significantly higher concentrations of immunological mediators have been consistently observed in patients with MDD (Dowlati et al., 2010) and bipolar disorder (Vega-Núñez et al., 2022). Furthermore, pro-inflammatory cytokines are assumed to play a vital role in the emergence of stress response (Johnson et al., 2019), the latter being an important potentiating factor for suicidal behavior (Miller & Eisenlohr-Moul, n.d.) – many findings support the hypothesis that an upregulated immune response may underlie the increased risk of suicide (Janelidze et al., 2011; Keaton et al., 2019; Pandey et al., 2012).
Alterations in cytokine concentrations may reflect the severity of immunological processes – however, as mentioned before, a more accessible way of assessing the extent of inflammatory activity may involve the measurement of laboratory parameters such as immune cell counts and their ratios (Chaplin, 2010). WBC count has been proposed as a general indicator of inflammatory status and considering the immunological background of MDD, this parameter may possibly be associated with symptom severity and potential SR. Several studies aimed to evaluate alterations of WBC values observed in patients with MDD, however, findings have been inconsistent (Köhler-Forsberg et al., 2017; Shafiee et al., 2017). Results on WBC count in association with SR remain scarce – however, an inflammatory profile with increased leukocyte count has been linked to SR in previous research (Keaton et al., 2019). Our investigation on individuals with MDD showed singificantly higher WBC values in patients with recent SA compared to individuals with no history of SA. Furthermore, we found WBC count to have a limited diagnostic value in differentiating patients with a recent SA from

individuals with no history of SA (Pethő et al., 2024). Normalization of elevated leukocyte counts following SSRI treatment has been described in patients with MDD, suggesting that, as mentioned previously, antidepressant therapy may indeed exert anti-inflammatory effects (Jaykaran et al., 2011). In our investigation, antidepressant and antipsychotic treatment did not influence WBC values (Pethő et al., 2024).

Several studies have examined alterations in the inflammatory markers RDW and ESR in relation to MDD, observing significant elevations (Chang et al., 2017; Shafiee et al., 2017) – however, the latter were normalized following SSRI therapy (Demircan et al., 2016; Jaykaran et al., 2011). In our research, we did not find antidepressant medication to significantly influence ESR and RDW values, however, we detected a significant decrease in ESR in patients undergoing antipsychotic medication compared to untreated individuals. Although there were more treated patients in the high SR group compared to the intermediate SR group, we still detected significantly higher ESR values in the high SR group (Pethő et al., 2024). Not only ESR, but RDW values were also significantly elevated in patients with high SR compared to individuals with intermediate SR. Furthermore, ESR values were significantly elevated in patients with recent SA compared to individuals with no history of SA, indicating the efficiency of ESR in signaling both acute and long-term SR (Pethő et al., 2024).

Platelets are anucleate cells derived from megakaryocytes in the bone marrow. Their dense granules contain, among other substances, serotonin, and on their surface, they express noradrenergic and serotonergic receptors. Beyond their fundamental role in hemostasis, platelets contribute to inflammatory processes through the production and release of cytokines (Parkin & Cohen, 2001). Several studies have found an association between elevated MPV values and MDD (Cai et al., 2017; Canan et al., 2012). In another investigation, individuals with MDD exhibited increased MPV in comparison with the control group. After SSRI treatment, patients with MDD showed a significant reduction in MPV values (Ataoglu & Canan, 2009). As for suicidal behavior, not many investigations have found MPV values to differ in individuals with higher SR. Our results are in accord with this finding, as we detected no significant differences in MPV in association with either acute or long-term SR (Pethő et al., 2024).

Platelet abnormalities have been observed in MDD – as platelets share several functional and biochemical characteristics with the brain's neuronal monoamin system, the alterations observed in MDD are closely related to the dysregulation of the serotonergic and noradrenergic

systems. In addition, elevated platelet count (Seidel et al., 1996) and increased platelet reactivity has been described in depressive states (Strike & Steptoe, 2004) – with several studies reporting a reduction in platelet activity following antidepressant treatment, particularly with SSRI's (Serebruany et al., 2001). In our investigation, we detected no significant differences in platelet count regarding SR (Pethő et al., 2024).

Lymphocytes are a class of white blood cells that are morphologically uniform yet functionally diverse, encompassing T cells, B cells, and natural killer cells. They play central roles in immune defense through antibody production, direct cell-mediated cytotoxicity against virus-infected and malignant cells, and the regulation of the immune response (LaRosa & Orange, 2008). Early investigations demonstrated a reduction in lymphocyte count in patients with MDD, while further studies found MDD patients to have significantly higher lymphocyte counts compared to healthy controls (Cai et al., 2017). Results regarding lymphocyte count alterations associated with SR are also conflicting (Aguglia et al., 2021; Ucuz & Kayhan Tetik, 2020) – however, all of these findings suggest that, beyond inflammation associated with MDD, additional independent immunological processes may contribute to suicidal behavior. As for our results, we found no significant alterations in lymphocyte count in association with acute or long-term SR (Pethő et al., 2024).

Increased PLR values have been positively correlated with the incidence of MDD (Zhu & Li, 2025) and the emergence of suicidal behavior (Ucuz & Kayhan Tetik, 2020) in previous studies. Regarding PLR, we found no significant differences between patients with recent SA and those with no history of SA, and there were no significant differences between individuals with high and intermediate SR (Pethő et al., 2024). As for effects of medication, antidepressant treatment did not significantly affect the values of MPV, platelet and lymphocyte count or PLR in our study. We detected no significant differences between patients treated with antipsychotics and untreated individuals regarding these values (Pethő et al., 2024).

Neutrophil granulocytes are bone marrow-derived cells, which play a central role in inflammation through phagocytic activity and cytokine production. Elevation of neutrophil granulocyte count in association with MDD has been reported in several studies (Cai et al., 2017; Seidel et al., 1996). Moreover, investigations proved NLR to be increased in patients with MDD compared to healthy individuals (Atli et al., 2015; Mazza et al., 2018). In further studies on patients diagnosed with MDD, higher NLR was found in suicidal individuals compared to non-suicidal participants (Ucuz & Kayhan Tetik, 2020; Velasco et al., 2020).

These results indicate that elevated NLR values may represent not only a trait marker of suicidal behavior – reflecting the presence of MDD as a risk factor – but also a state-related characteristic of MDD patients with increased vulnerability for suicide. Therefore, NLR emerges as a reliable biomarker of SR according to an increasing amount of research in the field of immunopsychiatry (Ekinci & Ekinci, 2017).

We observed significantly higher neutrophil granulocyte count and NLR values in MDD patients with recent SA compared to individuals with no histoy of SA. Furthermore, we found the diagnostic performance of NLR to be limited in differentiating individuals with a recent SA from those with no history of SA (Pethő et al., 2024). Neutrophil granulocyte count also had a limited diagnostic value in this regard. However, the significant differences in neutrophil count and NLR values were no longer present when comparing all high SR patients – recent and past attempters – to individuals with no history of SA (Pethő et al., 2024). A possible explanation may be that all patients were undergoing antidepressant treatment, which has been found to cause a singificant decrease in both neutrophil granulocyte count and NLR values, therefore masking the potential alterations of these inflammatory parameters associated with high SR.

Monocytes are produced in the bone marrow and are present in nearly all tissues of the body. Their primary functions include antigen presentation, as well as the phagocytosis of pathogens and apoptotic cells (Parkin & Cohen, 2001). Restrospective studies have found that MDD patients exhibit higher monocyte counts (Uyar & Budak, 2022) – further investigations revealed the association of monocyte count with clinical status and treatment response (Seidel et al., 1996). These findings suggest that the changes in monocyte count may represent the acute affective state in MDD – an aspect particularly important regarding suicidal behavior – and therefore its levels may reflect clinical improvement (Pedraz-Petrozzi et al., 2024). Further findings suggest the presence of neuroinflammatory processes underlying MDD and suicidal behavior, manifested by enhanced monocyte recruitment to the brain (Torres-Platas et al., 2014). Studies have described a singificant elevation in MLR values in patients with suicidal behavior (Ni Made Citra Riesti Wulan & Wayan Wiradana, 2025). We found a significant increase in monocyte count and MLR in MDD patients with recent SA compared to those with no history of SA. The diagnostic performance of MLR was acceptable in differentiating between the aforementioned patient groups. Furthermore, high SR patients – recent and past attempters – exhibited significantly higher monocyte count and MLR values relative to patients with intermediate SR (Pethő et al., 2024).

As previously mentioned, numerous studies have examined the anti-inflammatory potential of antidepressant (Hannestad et al., 2011) and antipsychotic therapy in MDD (MacDowell et al., 2013). Prolonged administration of such pharmacological treatments may therefore conceal alterations in immune cell counts, possibly attenuating inflammatory processes assumed to play a role in the development of MDD or suicidal behavior. In our investigation, antipsychotic treatment did not significantly influence either neutrophil count and NLR or monocyte count and MLR. However, as stated earlier, antidepressant medication caused a significant decrease in neutrophil granulocyte count and NLR values in a dose-dependent manner – while monocyte count and MLR remained unaffected by antidepressant treatment (Pethő et al., 2024).
Our results underscore the prognostic relevance of monocyte count and MLR, as both parameters remained significantly elevated not only in patients with a recent SA but also in all individuals with high SR – recent and past attempters – undergoing pharmacological treatment, the latter causing no significant alterations in the values of monocyte count and MLR. These findings support the potential utility of these parameters as biomarkers of both acute and long-term SR in MDD patients. Considering that an increased risk of suicidality is a well-known adverse effect during the initial weeks of antidepressant therapy, it is of critical importance that an indicator of high SR does not solely correlate with the level of inflammation potentially reversed by pharmacotherapy in the long term, but one that reliably signals the probability of an upcoming attempt independently (Bielefeldt et al., 2016).

As previously stated, inflammatory processes may play a role in the development of bipolar affective disorder (Barbosa et al., 2014). We have reason to assume that heightened inflammatory activity in association with not only MDD, but also bipolar disorder may contribute to the emergence of suicidal behavior in affected individuals (Bauer & Teixeira, 2021) – apart from changes in cytokine levels, alterations of previously mentioned cell counts, ratios and other inflammatory parameters have been described in suicidal psychiatric patients. Investigations have found significantly elevated levels of CRP, WBC and neutrophil count, along with decreased levels of lymphocytes in bipolar individuals in comparison to healthy controls (Bark & Sabet, n.d.; Munkholm et al., 2018). A further study reported significantly higher NLR values in patients with bipolar affective disorder relative to healthy individuals (Cakir et al., 2017). Novel findings suggest that not only the presence of an affective disorder, but also the type of affective episode may have an effect on inflammatory parameters (Koureta

et al., 2023). However, studies on the immunological parameters of suicidal bipolar patients are scarce – to the best of our knowledge, our investigation is novel in the way that it examined inflammatory markers in association with suicidal behavior in BD individuals specifically.

We found monocyte count, MLR, CRP and ESR to be significantly elevated in patients with recent SA. Furthermore, when comparing all high SR individuals – recent and past attempters –, all of these significant differences persisted in comparison to patients with no history of SA (Pethő et al., 2025). According to the AUC values, the majority of these parameters have an acceptable diagnostic performance and ESR has an outstanding diagnostic accuracy in differentiating patients with a recent SA from individuals with no history of SA (Pethő et al., 2025).

Our results suggest that the aforementioned inflammatory parameters are not solely associated with acute SR, but may also serve as indicators of long-term suicidal vulnerability. As a novel result, we found MLR and monocyte count to be potential biomarkers of SR in not only MDD, but also in BD patients – serving as reliable indicators of both acute and long-term suicidal vulnerability across multiple psychiatric diagnoses.

6. CONCLUSION

Mood disorders represent a significant risk factor with regard to suicidal behavior. Immunological mechanisms in the background of MDD, bipolar affective disorder and suicidal behavior have been investigated in an increasing amount of studies – novel findings suggest that the dysregulation of the immune system plays a significant role in the pathogenesis of these conditions.

SR stratification remains challenging for clinicans to this day. Currently in use are predominantly self report-based assessment methods, which are highly dependent on patient cooperation, the latter often being compromised due to an acute state of crisis or a psychiatric disorder. Consequently, elevated SR frequently remains undetected.

At present, there is no specific parameter available to reliably indicate SR in patients with mood disorders. However, beyond classical inflammatory markers, alterations in blood cell counts and their ratios appear promising, as several studies suggest their potential role as future biomarkers of SR – therefore we aimed to investigate these parameters in association with SR in patients with MDD and bipolar disorder.

To conclude our most important results, we observed a significant increase in monocyte count and MLR in patients with a recent SA and in all individuals with high SR (patients with recent or past SA) in comparison with participants with no history of SA – these results were applicable to patients with MDD and individuals with BD, as well.

The novelty of our research lies in the discovery that monocyte count and MLR may be reliable indicators of suicidal vulnerability, independent of the underlying affective illness, with their values – as observed in our first study – not significantly influenced by the anti-inflammatory effects of antidepressant and antipsychotic medication. Therefore these parameters may possess the ability to indicate both acute and long-term suicidal vulnerability.

Although the exact immunological mechanisms involved remain incompletely understood, with our investigations, we aimed to contribute to a better understanding of inflammatory processes in the background of mood disorders and suicidal behavior, with the expectation that the investigated inflammatory parameters, such as monocyte count or MLR may serve as potential biomarkers of SR in the future. Through incorporating these easily accessible, reproducible, cost-effective parameters, more accurate and efficient identification of patients with increased suicidal vulnerability may be possible – and ultimately, we may take one step forward to the solution of possibly the greatest challenge in psychiatric care.

7. PUBLICATIONS

7.1. Articles related to the thesis

Pethő B., Kovács M.Á., Simon D., Tóth T., Hajnal A.S., Csulak T., Hebling D., Albert N., Varga E., Herold M., Osváth P., Vörös V., Tényi T., Herold R./ 2024/: Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder. Frontiers in Psychiatry, Sec. Mood Disorders, Volume 15 - 2024 | doi: 10.3389/fpsyt.2024.1321354
Impact factor: 3,2

Pethő B., Herold R., Simon D., Kovács M.Á., Tóth T., Albert N., Hebling D., Hajnal A.S., Csulak T., Herold M., Tényi T. /2025/: Elevated monocyte-to-lymphocyte ratio, C-reactive protein and further inflammatory parameters as potential biomarkers of suicide risk in bipolar I disorder. Frontiers in Psychiatry, Sec Mood Disorders, Volume 16 - 2025 | doi: 10.3389/fpsyt.2025.1648202
Impact factor: 3,2

7.2. Oral and poster presentations related to the thesis

University of Pécs, Medical School Students' Research Conference (Pécs, 09-10. 03. 2022) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"* (1st place)

36th National Student Research Conference (Budapest, 19-21. 04. 2023) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"* (1st place)

III. Semmelweis University Students' Scientific Conference (online, 19. 02. 2022) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"*

University of Pécs, Ildikó Kriszbacher Scholarship Pogram Conference (Pécs, 20. 05. 2022) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"*

XXVI. Conference of the Hungarian Psychiatric Association (Szeged, 13-16. 09. 2023) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"*

32nd European Congress of Psychiatry (Budapest, 06-09. 04. 2024) – poster presentation in English: "*Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"*

New National Excellence Program Conference (Pécs, 26. 08. 2024) – oral presentation in Hungarian: *"Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depressive disorder"*

XXVIII. Conference of the Hungarian Psychiatric Association (Siófok, 29.01.-01.02. 2025) – oral presentation in Hungarian: "*Monocyte-to-lymphocyte ratio and further inflammatory parameters as potential biomarkers of suicide risk in bipolar affective disorder"*

33rd European Congress of Psychiatry (Madrid, 05-08. 05. 2025) – poster presentation in English: "*Monocyte-to-lymphocyte ratio and further inflammatory parameters as potential biomarkers of suicide risk in bipolar affective disorder"*

University Research Scholarship Program Conference (online, 28. 08. 2025) – oral presentation in Hungarian: „*Monocyte-to-lymphocyte ratio and further inflammatory parameters as potential biomarkers of suicide risk in bipolar affective disorder"*

7.3. Abstracts published in scientific journals, related to the thesis

Pethő B., Tényi T., Simon D., Herold R., Kovács M. Á. /2023/: Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depression. Psychiatria Hungarica, 38, Suppl. 1., 83. (article in Hungarian)

Pethő B., Tényi T.,Herold R., Osváth P., Vörös V., Simon D., Molnar Cs., Kovács M. Á. /2024/: Investigation of peripheral inflammatory biomarkers in association with suicide risk in major depression. European Psychiatry, 67,S792-S793.
Impact factor: 6,7

Pethő B., Tényi T. Herold R., Kovács M.Á., Simon D. /2025/: Monocyte-to-lymphocyte ratio and further inflammatory parameters as potential biomarkers of suicide risk in bipolar affective disorder. Psychiatria Hungarica, 40, Suppl. 1, 71-72. (article in Hungarian)

Pethő B., Tényi T., Herold R., Simon D., Tóth T., Molnár Cs., Kovács M.Á. /2025/: Monocyte-to-lymphocyte ratio and further inflammatory parameters as potential biomarkers of suicide risk in bipolar affective disorder. European Psychiatry, 68,S340-S341.
Impact factor: 6,7

7.4. Articles unrelated to the thesis

Fekete J.D., Pótó Zs., Varga E., Hebling D., Herold M., Albert N., Pethő B., Tényi T., Herold R. /2023/: The effect of reading literary fiction on the theory of mind skills among persons with schizophrenia and normal controls. Frontiers in Psychiatry, Volume 14 - 2023 | doi: 10.3389/fpsyt.2023.1197677
Impact factor: 3,2

Herold M., Kovács. Gy., X., Herold R., Pótó Zs., Fekete J. D., Varga E., Hajnal A.,Csulak T., Pethő B., Hebling D., Albert N., Tényi T. /2024/: Patients with chronic bipolar disorder show

impairments in interpreting literary fiction – a preliminary explorative study with the short story task. Journal of Psychiatric Research, 171, 238-245.
Impact factor: 3,2

Tényi T., Lovig Cs., Pethő B. /2025/: Jean Marie Joseph Capgras (1873-1950) - the describer of the delusion of the double died 75 years ago. Hungarian Medical Weekly Journal, 166, 434-438. (article in Hungarian)
Impact factor: 0,9

Hajnal A.S., Varga E., Tényi T., Pethő B., Albert N., Herold M., Kovács M.Á., Csulak T., Hebling D., Herold R. /2025/: Irony comprehension in first-degree relatives of patients with bipolar disorder – a preliminary fMRI study. Frontiers in Psychiatry, Sec. Neuroimaging, Volume 16 - 2025 | doi: 10.3389/fpsyt.2025.1606988
Impact factor: 3,2

Hajnal A., Csulak T., Hebling D., Borbásné Farkas K., Herold M., Berke G., Sipos Z., Pethő B., Varga E., Tényi T., Mátrai P., Hegyi P., Albert N., Herold R. /2025/: Spontaneous mentalizing in patients with schizophrenia spectrum disorders: a meta-analysis. Psychological Medicine, 55, e195, 1-11. | doi: 10.1017/S0033291725100755
Impact factor: 5,5

Lovig Cs., Osváth P., Sághy E., Molnár Cs., Kovács M.Á., Pethő B., Simon D., Fekete S., Tényi T., Vörös V. /2026/: Low-grade inflammatory parameters may be associated with recent suicide attempts – a naturalistic study among psyciatric inpatients with depressive disorders. Frontiers in Psychiatry, Sec. Mood Disoders, https://www.frontiersin.org/journals/psychiatry/articles/10.3389/fpsyt.2026.1707768/abstract
Impact factor: 3,2

7.5. Abstracts published in scientific journals, unrelated to the thesis

Vörös V., Sághy E., Molnár Cs., Kovács M.Á., Pethő B., Kovács S., Zemplényi A., Fekete S., Tényi T., Osváth P. /2024/: Certain immune parameters may have a significant impact on suicidal behavior – a naturalistic study among psychiatric in-patients. European Psychiatry, 67,S349-S350
Impact factor: 6,7

Major F. N., Vörös V., Venczák Sz., Lovig Cs., Pethő B., Molnár Cs., Kovács M.Á., Fekete S., Tényi T., Osváth P. /2026/: The immunological background of suicide attempts. Psychiatria Hungarica, 41,Suppl. 1., 122. (article in Hungarian)

Impact factor of scientific articles related to the thesis: 6,4
Impact factor of all scientific articles (without abstracts): 25,6

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