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Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review

Velasco A^{a,b,c,d}, Lengvenyte A^{e,f,g}, Rodriguez-Revuelta J^{a,d,h}, Jimenez-Treviño L^{a,d,h}, Courtet P^{e,f}, Garcia-Portilla MP^{a,b,c,d,h}, Bobes J^{a,b,c,d}, Sáiz PA^{a,b,c,d,h}

a. Department of Psychiatry, University of Oviedo, Oviedo, Spain

b. Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Spain

c. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Spain

d. Instituto de Neurociencias del Principado de Asturias (INEUROPA), Spain

e. Department of Emergency Psychiatry and Acute Care, CHU Montpellier, France

f. IGF, University of Montpellier, CNRS, INSERM, Montpellier, France

g. Psychiatric Clinic, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

h. Mental Health Services of the Principality of Asturias (SESPA), Oviedo, Spain

Corresponding author:

María Paz García-Portilla

Department of Psychiatry, School of Medicine, University of Oviedo

Av. Julian Claveria, 6, 33006, Oviedo, Asturias – Spain

albert@uniovi.es

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Short title:

NLR, PLR, and MLR in depression and suicidal behavior

Abstract

Background: Inflammatory biomarkers are reportedly increased in depressed patients. Several studies have been conducted using neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR). The objective of this systematic review was to study the relationship between these peripheral biomarkers and suicidality in depressed patients with/without suicidal behavior, including suicide attempts and ideation, and healthy controls.

Methods: We searched the following relevant terms in the PubMed, Web of Science, and Scopus databases published in the last five years. We assessed the methodological quality of included studies using the Oxford criteria and reviewed the evidence following PRISMA guidelines.

Results: Eleven studies were retained for the data synthesis, with a total sample of 1,701 participants, of which the majority (819) were patients with depression and suicidal behavior, 494 were depressed patients without suicidal behavior, and only 388 were healthy participants. Our results reinforce the idea that NLR could be an attractive, convenient, and cost-effective trait marker of suicidal vulnerability in patients with major depressive disorder (MDD).

Conclusion: Future large-scale replication studies are needed to examine the apparently understudied role of PLR and MLR in depressed patients in greater depth.

Keywords: Neutrophil/lymphocyte ratio; Platelet/lymphocyte ratio; Monocyte/lymphocyte ratio; Suicidal behavior; Depression

1. Introduction

Suicidal behavior (SB) is a serious public health concern. More than 700,000 people die by suicide every year, representing one death every 40 seconds on average (1). Factors contributing to increased risk of suicidal behaviors are diverse and complex, but epidemiological studies indicate that the vast majority of attempted and completed suicides occur in people with mental disorders with mood disorders being the most frequently associated with SB (2,3).

Understanding the pathophysiology of suicide is still a long-term goal. The evidence increasingly indicates a possible role of the immune-inflammatory response in the development and maintenance of depression and SB (4). Inflammation has been associated with increased risk of suicidal behaviors above and beyond the risk associated with depression (5). Neuroinflammatory processes are a pathophysiological mechanism that is essential for understanding SB in depressed patients. To explain the role of the immune system in the pathophysiology of suicide, a comprehensive model has been proposed. In this model, sleep disturbances, stress, childhood abuse, and infections induce dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that is associated with a chronic low-grade inflammatory state and increased risk of suicidal behaviors (6). It has therefore been suggested that inflammatory biomarkers are potentially useful in predicting and monitoring suicide risk in patients with depression (7).

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) indexes are convenient and cost-effective blood indicators of inflammatory status (8).

NLR is the most studied hematological parameter (9). Neutrophils are the first defense cells of the innate immune system, representing an active nonspecific inflammatory mediator of

phagocytosis and apoptosis functions (10), and lymphocytes represent the regulatory or protective component of the immune system (11,12,13). NLR is the ratio between two different immune pathways reflecting the intensity of chronic stress. It may be more informative and perhaps less changed by unknown factors. PLR index is related to stress. The presence of stress activates the sympathetic nervous system, increases platelets, and induces endothelial permeability. When this permeability occurs, neutrophils and macrophages appear, generating peripheral inflammation (14). Some studies suggest that PLR could be a better predictor than NLR for determining the severity of inflammation (15,16). An elevated level of MLR is associated with an overexpression of immunological genes that increases the production of cytokines related to monocytes and, as a consequence, activates microglia in the brain, causing neuroinflammation (14).

These indexes have been suggested as new indicators of low-grade inflammation and have been used as systemic inflammation prognostic scores in diseases such as cancer, coronary heart disease, and pancreatitis (17) and are also being investigated in neuropsychiatric disorders such as Alzheimer's disease, schizophrenia, bipolar disorder, and major depressive disorder (MDD) (11,18). Recently, a meta-analysis (18) reported that inflammatory activation occurs in mood disorders and that NLR and PLR may be useful to detect this activation. NLR has been found to increase in depressed patients compared with healthy controls (HC) (15,19) and in depressed patients with SB. Moreover, studies have suggested that NLR may be a significant predictor of SB in MDD (4,20) and could be more elevated in patients with recent Suicide Attempt (SA) (21). In parallel, increased PLR levels have also been associated with diagnosis and severity of depression (15,22). Finally, MLR was significantly higher in adolescents with SA than in HC (23).

However, potential mechanisms underlying inflammatory processes in depression and suicidal behavior have yet to be fully elucidated. Biomarkers would provide more

personalized methods for their assessment and treatment and would help to enhance our understanding of suicidal pathophysiology and improve prevention (24). No previous reviews have examined NLR, PLR, and MLR in depressed patients with/without SA and Suicidal Ideation (SI) and HC. Therefore, we aimed to explore if there are significant differences in NLR, PLR, and MLR in i) depressed patients with or without a lifetime history of SA; ii) depressed patients with a lifetime history of SA vs healthy controls; and iii) depressed patients with SI before and after treatment.

2. Materials and methods

A systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (25). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022361238).

2.1. Search criteria

We systematically searched PubMed, Web of Science, and Scopus databases in September 2022. A single search strategy has been used for each of the databases:

Studies of neutrophil-to-lymphocyte ratio were systematically searched using the terms “(NLR OR neutrophil-to-lymphocyte ratio OR neutrophil-to-lymphocyte index OR neutrophil-to-lymphocyte rate OR neutrophil to lymphocyte ratio OR neutrophil to lymphocyte index OR neutrophil to lymphocyte rate OR neutrophil lymphocyte ratio OR neutrophil lymphocyte index OR neutrophil lymphocyte rate OR neutrophil/lymphocyte ratio OR neutrophil/lymphocyte index OR neutrophil/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicide attempt OR suicidal thoughts OR self-mutilation).”

In the same way, studies of platelet-to-lymphocyte ratio were systematically searched using the terms “(PLR OR platelet-to-lymphocyte ratio OR platelet-to-lymphocyte index OR platelet-to-lymphocyte rate OR platelet to lymphocyte ratio OR platelet to lymphocyte index OR platelet to lymphocyte rate OR platelet lymphocyte ratio OR platelet lymphocyte index OR platelet lymphocyte rate OR platelet/lymphocyte ratio OR platelet/lymphocyte index OR platelet/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicidal attempt OR suicidal thoughts OR self-mutilation).”

Finally, studies of monocyte-to-lymphocyte ratio were systematically searched using the terms “(MLR OR monocyte-to-lymphocyte ratio OR monocyte-to-lymphocyte index OR monocyte-to-lymphocyte rate OR monocyte to lymphocyte ratio OR monocyte to lymphocyte index OR monocyte to lymphocyte rate OR monocyte lymphocyte ratio OR monocyte lymphocyte index OR monocyte lymphocyte rate OR monocyte/lymphocyte ratio OR monocyte/lymphocyte index OR monocyte/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicidal attempt OR suicidal thoughts OR self-mutilation).”

We reviewed titles and abstracts to select potentially relevant papers. After this screening process, we reviewed the full texts and checked the references in the included studies, meta-analyses, and systematic reviews to identify additional studies. Some data was extracted from previous meta-analyses and systematic reviews.

2.2. Eligibility criteria

Case-control studies and cross-sectional data from longitudinal studies that compared NLR, PLR, and/or MLR indexes among depressed patients with SB, depressed patients without SB,

and healthy controls were included, based on the following criteria: (i) patients with MDD according to standardized diagnostic criteria; (ii) measurement of NLR, PLR, and/or MLR in young people and adults; (iii) patients with current SI and history of SB. Only articles in English published in the last 5 years were included. Conference and meeting abstracts, meta-analyses, reviews, and pilot studies were excluded (see Supplementary Table).

2.3. Data extraction and assessment of methodological quality

Data were extracted by two independent authors (A.V. and P.A.S.) and verified by the other two (J.R. and L.J.). Extracted data included author, year of publication, country, diagnosis, study population, sample size, age, ratios of females, depression and suicide scales, type of outcome (SI/SA), and type and quality of the study. Results were ordered according to indexes (Table 1). The methodological quality of the included studies was assessed using the Oxford criteria (26). Only medium- and high-quality papers were included in the final review. Any disagreements between reviewers were resolved by discussion and consensus.

3. Results

3.1. Study selection and characteristics

A total of 86 studies were identified from electronic databases and, after removing duplicates, there were 37 single records to be screened. After reading titles and abstracts, we identified 21 full-text articles to be assessed for eligibility but excluded 10 studies after the full text was read (the inclusion and exclusion process is depicted in Figure 1). Of those, 11 studies met the inclusion and quality criteria and were selected for this review.

A total of 10 papers were rejected for the following reasons: (i) type of article (review, letter, meeting abstract): 2 articles were meeting abstracts and 2 articles were letters to the editor; (ii) 2 articles did not include a study of suicidal behavior, 2 articles did not specify depressed

patients, and 1 study included parameters of peripheral inflammation other than NLR, PLR, and MLR; and (iii) 1 article was published in the Turkish language (see Supplementary Table).

All included studies were published between August 2017 and September 2022. Five studies were conducted in Turkey (8,20,27–29), one in India (30), two in Spain (4,31), one in Sweden (32), one in Israel (33), and one in Thailand (9).

The 11 records included in the review yielded a total sample of 1,701 participants, of which 819 were patients with MDD and suicidal behavior (including current SI and lifetime SA), 494 were control patients (MDD without SB), and 388 were healthy controls.

We included data from (i) six studies of NLR, PLR, and/or MLR in depressed patients with or without SB (4,20,27,31–33); (ii) six studies of NLR, PLR, and/or MLR in depressed patients with SB vs HC (9,20,28,29,31,32); (iii) two studies of NLR in depressed patients with SI before (with or without monotherapy 4 weeks prior) and after pharmacotherapy (2 to 12 weeks after treatment), one of which also explored PLR (8,30), respectively (Table 1).

3.2. Patients with major depressive disorder with or without suicidal behavior

In three studies with patients with moderate to severe depression, NLR was reported to be higher in suicide attempters compared with depressed patients without a history of SA (4,20,33). NLR could be potentially used as a biomarker to predict recent and past SA (4). However, these results were not confirmed in other studies. First, in two studies there was a (non-significant) tendency towards an increase in NLR in patients with a history of SA vs without any (27,31). One study examining the association between current SI and NLR in patients with MDD found no differences between patients with and without current SI in NLR (32) (Table 2).

Regarding the PLR index in patients with MDD, two studies reported PLR to be higher in patients with a history of SA vs those without any (4,33). Conversely, this difference was not observed in three other studies (20,27,31) (Table 2).

Finally, only two studies explored the MLR index in relation to SB in MDD, with no reported statistically significant differences between depressed patients with and without SB (4,31) (Table 2)..

3.3. Patients with major depressive disorder and suicidal behavior vs healthy controls

In three studies, NLR was reported to be higher in depressed patients with a history of SA vs HC (9,20,28). However, three other studies reported no statistically significant differences (29,31,32) (Table 3).

Regarding the PLR index, two studies reported that PLR was higher in depressed patients (including SA, SI and nSI) vs HC (28,23). Conversely, in two studies, this difference was not observed (20,31) (Table 3).

MLR was investigated in only two out of six studies, with inconsistent results. MLR was reported to be higher in depressed patients with SA vs HC (9). However, MLR was reported to be decreased in depressed patients with SB vs HC (31) (Table 3).

3.4. Depressed patients with suicidal ideation before and after treatment for depression

There were two studies that evaluated NLR before and after antidepressant treatment. First, Demirkol et al. (2019) studied depressed patients ($n = 74$) with monotherapy four weeks before treatment and found a decrease in NLR during and after treatment with antidepressant therapy (AD) and bright light therapy (BLT), with a greater decrease compared with AD monotherapy [NLR mean (SD) = 2.31(1.05) pretreatment vs 2.25 (0.96) after treatment vs 1.9 (0.9) 2 weeks after treatment; $p < 0.001$]. In addition, HDRS scores and SI were also

significantly decreased after treatment [HDRS mean (SD) = 20.69 (4.21) pretreatment vs 16.69 (5.96) after treatment vs 15.14 (5.33) 2 weeks after treatment; $p < 0.001$; and SI median (Q1-Q3): 5 (3-10) pretreatment vs 5 (1-9) after treatment vs 3.5 (0-7) 2 weeks after treatment; $p < 0.001$] (8). However, in a sample of 50 depressed patients without antidepressant treatment the previous month, Adhikari et al. (2018) found a significant increase in NLR after 12 weeks of antidepressant treatment only in females [NLR mean in females (SD) = 2.55 (0.87) pretreatment vs 2.85 (0.89) 12 weeks after treatment; $p < 0.001$] (30).

Regarding PLR, only one study examined PLR levels in depressed patients with SI before and after treatment and concluded there was no significant change in PLR during AD treatment [PLR mean (SD) = 118.61 (39.01) pretreatment vs 118.16 (40.57) after treatment vs 117.96 (40.82) 2 weeks after treatment; $p = 0.985$] (8).

None of the studies included MLR.

4. Discussion

SB is a leading cause of death and disability worldwide (34). Detecting and identifying potential biomarkers of peripheral inflammation in suicidal behavior has the potential to provide the knowledge needed to understand the pathophysiology of SB, develop personalized therapies, and improve prevention. To date, this is the first review that has examined NLR, PLR, and MLR in depressed patients with and without SA and current SI versus healthy controls.

NLR, PLR, and MLR indexes emerge as relatively stable biomarkers of systemic inflammation (35), which, in turn, is cost-effective and easily accessible. Perhaps, for this reason, most of the studies included in this systematic review were conducted in low-income countries, which seem to be interested in this option given the potential value for clinical application.

According to our review, in depressed patients, NLR was higher in patients with a history of SA, suggesting that, if confirmed in larger studies, it could be a biomarker of suicidal vulnerability in these patients. Although this result was not observed in all studies, in the majority there was a tendency for increased NLR. To the best of our knowledge, only one study that examined the differences in patients with and without SI did not find this association (32). However, it has been previously suggested that SA and SI are different phenomena with different explanations and predictors (36), and it seems that the relationship between the increase in NLR and suicidality occurs only in SA and not in SI (32). In addition, NLR was higher in depressed patients with SA vs HC. However, these differences were not observed in depressed patients with SI vs HC. Mounting evidence indicates that activation of the immune-inflammatory response is linked to the development and maintenance of depression and SB (4,7,18).

Some studies suggest that PLR could be a better predictor than NLR for determining the severity of inflammation (15,16). Our review shows inconsistent results regarding PLR in MDD patients (including SB). However, when compared with HC, the difference in the PLR index is observed more clearly in depressed patients. This phenomenon might be explained by the fact that platelets are one of the first cells to start an inflammatory cascade (cytokines, chemokines, the serotonin pathway), and patients with depression had a loss of equilibrium in hematopoietic production, resulting in an imbalance or distress in modulation (31).

The present review found no evidence for the link between MLR and SB in depressed patients, in contrast to some studies that showed MLR was higher in the manic episodes of bipolar disorder compared with euthymic states (37). However, despite not being related to suicidal behavior, high MLR in young people appears to be associated with self-harm when compared with young people without this behavior (14).

Finally, discrepant, and limited results were found regarding SI changes and inflammatory indexes following antidepressant treatment. These results may indicate that: (i) not all depressed patients show changes in inflammatory response (30); (ii) the mechanisms underlying the relationship between inflammation and suicide are still unclear (38); and (iii) it has not been determined whether inflammation is a causative factor or a consequence of depression (11). However, we also need to keep in mind that inflammatory response is influenced by multiple factors, such as body mass index, use of tobacco and other psychoactive substances, duration and severity of illness, resistance to antidepressant treatment, other psychiatric comorbidities, unbalanced diet, lack of exercise, and stress or traumatic life events in childhood or adulthood (30,31,39).

5. Limitations

First, our results are mostly based on cross-sectional studies, and a causal relationship between NLR and SI and SB in patients with MDD cannot be inferred. Second, other inflammatory parameters were not assessed in the review, precluding us from concluding whether increased NLR is an independent biomarker or is related to other immune and inflammatory changes in depressed patients. Third, the studies included in the systematic review are very heterogeneous (i.e., sample characteristics, small sample sizes, recruitment, and assessment of depression and suicidality), and therefore results remain preliminary and cannot be generalized to any specific population. Finally, due to the small number and small scale of studies included, we cannot exclude publication and reporting bias in those studies, possibly biasing the results of the systematic review.

6. Conclusion

In conclusion, the present review found preliminary evidence for an association between NLR and SB in patients with MDD. Our results reinforce the idea that neuroinflammatory

processes may be important in the pathophysiology of suicidal behavior in depressed patients. NLR could be an attractive, convenient, and cost-effective trait marker of suicidal vulnerability in patients with MDD. Future large-scale replication studies are needed to confirm the observed associations and to examine the apparently understudied role of PLR and MLR in depressed patients in greater depth.

7. Acknowledgment

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8. Conflict of interest

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

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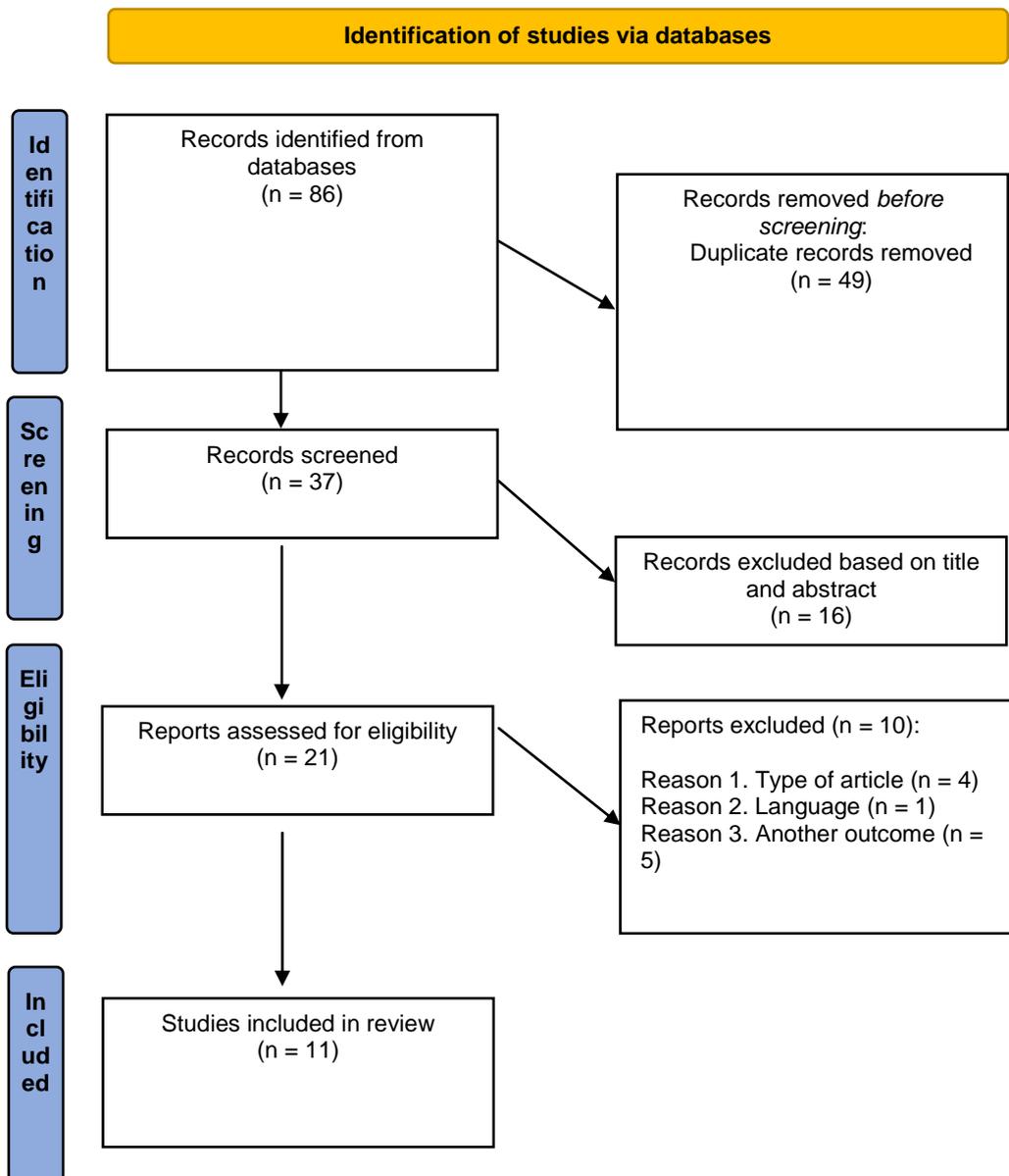


Figure 1. PRISMA 2020 flow diagram for new systematic reviews that included database searches

Table 2. Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, and Monocyte-to-lymphocyte ratio in Major Depressive Disorder with Suicidal Behavior versus non-Suicidal Behavior patients

<i>Author, date</i>	<i>Type of SB</i>	<i>MDD with SB</i>	<i>MDD without SB</i>	
NLR		Mean (SD)	Mean (SD)	<i>p-value</i>
Velasco et al., 2020	Recent SA	2.37 (2.36)	1.68 (0.80)	0.001
	Past SA	2.22 (2.17)		
Amitai et al., 2022	SA	2.16 (0.78)	1.64 (0.96)	0.019
Ekinci and Ekinci, 2017	Recent SA	2.840 (0.162)	1.858 (0.98)	0.001
Meydaneri and Meydaneri, 2018	SA	2.04 (0.89)	1.85 (0.81)	0.054
Martínez-Botía, Velasco and Rolle et al., 2020	SA	2.17 (1.66)	1.68 (0.57)	0.291
Grudet et al., 2020	SI	2.3 (1.0)	2.2 (0.8)	0.81
PLR		Mean (SD)	Mean (SD)	<i>p-value</i>
Velasco et al., 2020	Recent SA	128.20 (61.65)	109.97 (38.75)	0.024
	Past SA	127.76 (58.91)		
Amitai et al., 2022	SA	159.31 (53.98)	133.56 (58.18)	0.044
Ekinci and Ekinci, 2017	Recent SA	141.4 (83.25)	128.11 (48.76)	0.248
Meydaneri and Meydaneri, 2018	SA	120.81 (39.34)	118.55 (42.39)	0.73
Martínez-Botía, Velasco and Rolle et al., 2020	SA	122.39 (64.51)	109.30 (28.50)	0.416
MLR		Mean (SD)	Mean (SD)	<i>p-value</i>

Velasco et al., 2020	Recent SA	0.28 (0.16)	0.25 (0.10)	0.573
	Past SA	0.27 (0.15)		
Martínez-Botía, Velasco and Rolle et al., 2020	SA	0.26 (0.12)	0.25 (0.08)	0.851

MDD: Major Depressive Disorder; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SA: Suicide Attempt; SB: Suicidal Behavior; SI: Suicidal Ideation; SD: Standard Deviation.

Table 3. Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, and Monocyte-to-lymphocyte ratio in Major Depressive Disorder with Suicidal Behavior versus Healthy Controls

<i>Author, date</i>	<i>MDD with SB</i>	<i>Healthy Controls</i>	
NLR	Mean (SD)	Mean (SD)	<i>p-value</i>
Ekinici and Ekinici, 2017	2.840 (0.162)	1.81 (0.33)	0.001
Puang Sri and Ninla-Aesong, 2021	2.01 (0.07)	1.49 (0.04)	0.001
Yagci and Avci, 2021	2.77 (1.6)	2.05 (0.59)	0.009
Martínez-Botía, Velasco and Rolle et al., 2020	1.97 (1.35)	1.87 (0.80)	0.510
Grudet et al., 2020	2.3 (1.0)	2.3 (1.2)	0.81
Önen et al., 2021	1.94 (1.11)	1.65 (0.66)	0.780
PLR	Mean (SD)	Mean (SD)	<i>p-value</i>
Puang Sri and Ninla-Aesong, 2021	123.18 (3.35)	105.80 (3.11)	0.024
Önen et al., 2021	133.95 (41.65)	114.44 (40.53)	0.005
Ekinici and Ekinici, 2017	141.4 (83.25)	134.3 (61.4)	0.248
Martínez-Botía, Velasco and Rolle et al., 2020	117.26 (53.49)	117.99 (54.77)	0.952
MLR	Mean (SD)	Mean (SD)	<i>p-value</i>
Puang Sri and Ninla-Aesong, 2021	0.21 (0.02)	0.15 (0.01)	0.027
Martínez-Botía, Velasco and Rolle et al., 2020	0.26 (0.11)	0.30 (0.13)	0.017

MDD: Major Depressive Disorder; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SA: Suicide Attempt; SB: Suicidal Behavior; SI: Suicidal Ideation; SD: Standard Deviation.