



## Neutrophil-to-lymphocyte ratio as a predictive biomarker for early diagnosis of depression: A narrative review

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### ABSTRACT

Depression is a mood disorder that causes persistent feelings of sadness, hopelessness, loss of interest, and decreased energy. Early diagnosis of depression can improve its negative impacts and be effective in its treatment. Previous studies have indicated that inflammation plays an important role in the initiation and development of depression, hence, various inflammatory biomarkers have been investigated for early diagnosis of depression, the most popular of which are blood biomarkers. The Neutrophil to lymphocyte ratio (NLR) may be more informative in the early diagnosis of depression than other widely used markers, such as other leukocyte characteristics or interleukins. Considering the importance of early diagnosis of depression and the role of NLR in early diagnosis of depression, our paper reviews the literature on NLR as a diagnostic biomarker of depression, which may be effective in its treatment. Various studies have shown that elevated NLR is associated with depression, suggesting that NLR may be a valuable, reproducible, easily accessible, and cost-effective method for the evaluation of depression and it may be used in outpatient clinic settings. Closer follow-up can be performed for these patients who have higher NLR levels. However, it seems that further studies on larger samples, taking into account important confounding factors, and assessing them together with other inflammatory markers are necessary to draw some conclusive statements.

### 1. Introduction

Depressed mood, lack of interest or pleasure, decreased energy, feelings of guilt or low self-worth, interrupted sleep or food, and impaired concentration are all signs of depression, a potentially fatal condition. It can occur at any age from childhood to late life and is a tremendous cost to society as this disorder causes severe distress and disruption of life and, if left untreated, it can cause suicidal thoughts and the death of 800,000 people annually around the world, according to confirmed statistics (Mehdi et al., 2023; Brigitta, 2022; Amini et al., 2022). Depression is currently thought to impact 350 million people worldwide, and by 2030, it is anticipated to be the major cause of disease burden in high-income nations (Thati et al., 2023; Seid et al., 2020). Depression is not a homogeneous disorder, but a complex phenomenon, which has many subtypes and more than one etiology (Fig. 1). Historically, there has been a lengthy discussion about the types and causes of depression (Brigitta, 2022; Benazzi, 2022). In summary, the types of

depression include: major depression (or clinical depression), dysthymia (or chronic depression), seasonal affective disorder (SAD), postpartum disorder, bipolar disorder (or manic depression), and atypical depression (Xiang, 2010; Balch et al., 2012). Although the exact causes of depression are still unknown, it is thought that a variety of factors, such as physical changes in the brain, as well as psychological factors contribute to depression (Xiang, 2010; Dean and Keshavan, 2017). Other factors that contribute to depression include genetics, stress, trauma, pessimism, sleep disturbances, physical problems (such as illnesses, malnutrition, and hormonal imbalances), and other psychiatric disorders (Xiang, 2010; Talei et al., 2021). Another element that could contribute to depression is gender. According to reports, depression affects women more frequently than males, nearly two to one (Association AP, 1990). The majority of depressed individuals, particularly men, are unaware of their condition and never seek treatment. Due to the possibility that symptoms may not be qualitatively different from those of everyday experience. We must assume that only about one-third of

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patients are receiving treatment (Brigitta, 2022). To deal with various forms of depression, people need to adopt healthy lifestyles and have a clear understanding of the factors that contribute to depression. Prevention, early detection, and Intervention are essential. Even though it's not always possible to stop depression from happening, preventive measures like self-education, a healthy lifestyle (including enough sleep, a balanced diet, exercise, and a good work-life balance, etc.), emotion control, social support, and spiritual wellness may help to lessen the risk factors that cause depression (Muñoz, 1993; Gillman, 2006). Antidepressants are frequently prescribed to alleviate the symptoms of depression. In order to improve the effectiveness of the therapy, Antidepressants are occasionally taken with augment medications. There are a variety of herbal and alternative therapies besides anti-depressants that can be used either alone or in conjunction with anti-depressant therapy (Xiang, 2010; Lam et al., 2002). Rapid intervention, which may prevent the condition from escalating, depends on early discovery. According to the Institute of Medicine Committee on the Prevention of Mental Disorders, depression is the condition that is most treatable and whose harmful effects can be reduced by early diagnosis and treatment (Cacheda et al., 2019; Munoz et al., 1996). Depression treatment can lessen the disorder's harmful effects (Picardi et al., 2016). Therefore, it is essential to identify those who are depressed as soon as possible in order to respond quickly and reduce the burden on public health by possibly slowing the progression of the illness (Cacheda et al., 2019). There are numerous clinical interview-based tools and laboratory techniques for diagnosing depression, and several fresh ideas—such as structured diagnostic interview, genomics, proteomics, metabolomics, and biological pathway biomarker panel—are now being developed. It's vital to assess their technique and clinical efficacy in order to comprehend the function of these quite distinct diagnostic methods for depression in the clinic (Smith et al., 2013). Currently, poor patient reporting and patient symptoms that can overlap with other illnesses can impair the use of clinical tests and conventional interviews to assess depression (Cameron et al., 2011; Smarr and Keefer, 2011). Structured clinical examinations are not frequently used in basic care, which leads to extremely varied and frequently incorrect depression diagnoses. Any attempt to standardize or otherwise enhance these methods will only result in minor advancements because these instruments are inherently subjective. The identification of biomarkers for the diagnosis of depression using genomic, proteomic, and metabolic profiling is still in its infancy. The multiparameter biomarker panel and algorithm, for which there is a

biological justification, show better improvement, and outcomes can be produced using conventional laboratory procedures and a routine blood sample. Its clinical effectiveness and dependability are highly encouraging and superior to other newly developed multiparameter approaches (Smith et al., 2013). The advantages of having an objective and aetiologically sound panel of biomarkers for depression are substantial: (Mehdi et al., 2023) their existence can be used to predict the likelihood of onset or presence of the disorder; (Brigitta, 2022) they can be used to stratify the disorder according to severity and symptomatology; (Amini et al., 2022) they can be used as an indicator of disease prognosis; and (Thati et al., 2023) they can be used to predict response and track progress after a therapeutic intervention (Bohner, 2021). Previous studies have indicated that inflammation is crucial for the emergence of depression. Several inflammatory biomarkers have been investigated for the early identification of depression, including interleukins, C-reactive protein (CRP), cortisol, tumor necrosis factor-alpha (TNF- $\alpha$ ), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) (Adhikari et al., 2018; Dionisie et al., 2021). The most popular way to examine inflammatory processes in psychiatry is through blood biomarkers, however many of these are expensive or challenging to routinely collect (Brinn and Stone, 2020a, 2020b). Recently, it has been discovered that the NLR is a biomarker of inflammatory status in people with schizophrenia, multiple sclerosis, Alzheimer's dementia, and bipolar disorder, as well as in people with depression (Adhikari et al., 2018; Çakır et al., 2015). White blood cell count can be used to calculate NLR, which is a ratio of absolute neutrophil count to absolute lymphocyte count. It is readily available, reproducible, simple to measure, and affordable compared to many other things (Arabska et al., 2018; Ivković et al., 2016). This is owing to the prevalence of these parameters in routine blood tests and the assessment's lack of a need for additional kits or modern technology (Azab et al., 2010). Here, we will review the literature on NLR as a diagnostic biomarker of depression, which may be useful in its treatment, taking into account the significance of early detection of depression and the role of NLR as a diagnostic biomarker of depression.

### 1.1. The role of inflammation in depression

Inflammation is a complex and necessary component of the response to biological, chemical, or physical stimuli, and the cellular and molecular events that initiate and regulate the interactions between the



Fig. 1. Symptoms, types, causes, and diagnosis of depression.

various players in the inflammatory process remain a source of ongoing investigation. Many studies have recently concentrated on the relationship between depression and inflammation, considering the co-occurrence of these two conditions (Arabska et al., 2018; Amidfar et al., 2017). Inflammation and depression serve as fuel for one another. Depression increases inflammatory responses in this vicious cycle, which in turn increases depression. The key players in inflammatory processes are neutrophils (ÖZTÜRK et al., 2019). Through the production of numerous inflammatory mediators, they operate as an active nonspecific inflammatory mediator, starting the first line of defense and demonstrating phagocytic and apoptotic effects. In contrast, lymphocytes are the immune system's regulating or defense mechanism (Azab et al., 2010; Özyurt and Binici, 2018). While lymphocyte counts are related to physiological stress and serve as a crucial immune system regulator, neutrophil numbers suggest an unspecific inflammatory process (Avanzas et al., 2004). NLR may be more informative than other leukocyte characteristics or other commonly used markers, such as interleukin-6 (IL-6), TNF- $\alpha$ , or CRP, because it reflects both immunological pathways and is likely less impacted by confounding factors (Ivković et al., 2016; Gibson et al., 2007).

### 1.2. NLR as a diagnostic biomarker of depression

Over the past few decades, there has been a substantial increase in the prevalence of depression in the general population, which has now become a significant global health issue. There is mounting evidence that inflammation is crucial to the etiology of depression. NLR, a straightforward and useful marker of inflammation and immunology, can help us better understand the role of inflammation in the pathophysiology of depression (Amidfar et al., 2017; Meng et al., 2019). Most studies have indicated that NLR levels may be associated with the degree of depression in people who don't have any other conditions that could trigger an inflammatory response (Su et al., 2022; Mazza et al., 2018). However, in a few studies, the NLR between the depressed patients and controls did not differ significantly from each other (Su et al., 2022; Kayhan et al., 2017). The relatively small sample sizes used in all of these research were a limitation. Additionally, several significant confounding variables, including lifestyle, and body mass index (BMI), were not taken into consideration in these investigations (Meng et al., 2019; Su et al., 2022). Additionally, it has been demonstrated that NLR, can be altered by gender (Meng et al., 2019). According to Wu et al. study, the NLR was higher in women than in men between the ages of 30–49 years, and it was higher in men than in women between the ages of 60 and 69 years. The estrogen level may be responsible for the discrepancy, even if the processes behind sex-related changes in the NLR are still unknown (Zhang et al., 2005; Chen et al., 2016; Wu et al., 2019). Generally, NLR appears to be a straightforward, affordable approach for assessing depression that can be employed in an outpatient therapy environment. These patients who have greater NLR levels can receive closer follow-up.

### 1.3. NLR as a diagnostic biomarker of major depressive disorder (MDD) and psychotic depression (PD)

A frequent psychiatric condition, major depressive disorder affects 3%–10% of the general population (Munoz et al., 2010). Some neurobiological theories have suggested that major depression has a psychoneuroimmunological foundation (Jaremka et al., 2013). Recent hypotheses on the causes of depression have suggested that neuroinflammation contributes to the onset and maintenance of the disorder and that the condition itself may change inflammatory and immunological biomarkers (Hurley and Tizabi, 2013). Increased leukocyte counts and their subtypes in total blood count tests can serve as a sign of inflammation. The NLR has been studied in a variety of medical conditions and neuropsychiatric disorders and is acknowledged as a straightforward clinical biomarker of inflammation (Özyurt and Binici, 2018). Studies that examine the connection between NLR and major

depression are available (Table 1). It appears that major depressive patients had higher levels of NLR than the control group (Demircan et al., 2016; Vos et al., 2021). However, meta-analyses on depression and inflammation suggest a large heterogeneity across studies (Dowlati et al., 2010; Chai et al., 1999). This variation may be caused in part by

**Table 1**

Summary table of studies included in the present review study. MDD, major depressive disorder; PD, psychiatric depression; BD, bipolar disorder; SB, suicidal behavior; PSD, post-stroke depression; GD, geriatric depression; LCD, lung cancer depression; DD, diabetic depression; ICH, intracranial hemorrhage.

#	Type	Findings	References
1	MDD	NLR tends to be higher in patients with MDD, and a high NLR value supports the view that inflammation is a critical factor in the etiology of MDD.	Demir et al. (2015)
2	MDD	NLR as a subclinical inflammatory marker is related to a later onset of depression.	Euteneuer et al. (2017)
3	MDD	NLR is closely correlated with depression and may be a parameter for predicting depression.	Su et al. (2022)
4	MDD	Findings of this study supported the inflammation hypothesis for MDD in adolescents.	Özyurt and Binici (2018)
5	PD	NLR is an accessible biomarker in clinical practice, and in PD patients it could guide the therapeutic strategy and be a predictor of response.	Llorca-Boff et al. (2021)
6	PD	NLR may be a novel, inexpensive and widely available biomarker associated with response to pharmacotherapy in PD.	Vos et al. (2021)
7	PD	Elevated NLR may reflect a transdiagnostic pathological process occurring in a subpopulation of psychiatric patients.	Brinn and Stone (2020a)
8	BD	Higher neutrophil-lymphocyte ratios in bipolar manic episodes was found, suggesting that inflammatory changes occur especially during acute episodes of mania.	Mazza et al. (2019)
9	BD	NLR is an independent predictor of the bipolar type of depression in depressive patients.	Dionisie et al. (2021)
10	BD	The neutrophil lymphocyte ratio between the patient and control groups did not differ significantly.	Sağlam Aykut et al. (2018)
11	SB	In children and adolescents who are depressed and nervous, a high NLR value may be linked to suicide behavior.	Amitai et al. (2022)
12	SB	NLR may be a useful, repeatable, accessible, and economical method to assess the risk of suicide in MDD.	Velasco et al. (2020)
13	SB	an enhancing effect of a family history of successful suicide attempts on the NLR's ability to predict suicide risk	Ivković et al. (2016)
14	SB	NLR may be a trait marker for suicidal vulnerability via a relationship between NLR and a recent suicide attempt in depressed inpatients.	Ekinci and Ekinci (2017)
15	PSD	Six months after a stroke, depression was found to be associated with higher NLRs.	Hu et al. (2020)
16	PSD	Increased NLRs at admission are found to be correlated with PSD and may add prognostic information for the early discovery of PSD.	Chen et al. (2018)
17	PSD	NLR combined with CRP has higher sensitivity and specificity in predicting PSD, which means it has a higher prediction value.	Yingshi et al. (2021)
18	GD	Increased NLR was significantly associated with geriatric depression in women, but not men.	Liang et al. (2020)
19	LCD	NLR provides a reasonable assessment of lung cancer related inflammation with survival implications that may indicate the presence of depression.	McFarland (2020)
20	DD	Elevated levels of NLR are independently associated with increased odds of clinically relevant depressive symptoms in people with diabetes.	Wang et al. (2020)
21	ICH	At three months following an ICH, elevated NLR is linked to depression, indicating that NLR may be a useful biomarker to predict depression	Gong et al. (2020)

methodological constraints and differences, such as the failure to account for significant confounders, poor data preparation, or various depression measurement techniques (Euteneuer et al., 2017). The high value of NLR is consistent with the idea that inflammation plays a significant role in the etiology of MDD and suggests that this parameter may be predictive for assessing the prognosis of major depression. Additionally, a recent study has reported that NLR in individuals with Psychotic Depression (PD) could direct the therapeutic approach and serve as a predictor of response (Llorca-Boff et al., 2021). About 0.4% of the general population suffers from unipolar major depression with psychotic characteristics (PD), a serious and incapacitating condition with a substantially greater frequency in individuals over 50 (Jääskeläinen et al., 2018). It has a more severe clinical course, more depressive symptoms, more cognitive dysfunction, and more psychomotor impairment than non-psychotic depression (da Costa et al., 2020). Additionally, it is linked to a higher risk of mortality and recurrence (Jääskeläinen et al., 2018). It has been suggested that non-psychotic major depression be treated as a distinct entity given the differences between the two, however, there are still disagreements on this topic (Keller et al., 2007). While it appears in certain classifications as a severe subtype of major depressive illness (ICD-10), it also appears in others (DSM-5) without regard to severity (Dubovsky et al., 2021). In comparison to MDD without psychosis, PD is linked to increased cortisol levels. Since persistently high cortisol may cause inflammation. High cortisol levels are closely related to PD, although elevated cortisol levels are not always present in non-psychotic MDD (Carroll et al., 2007). The NLR is directly increased by cortisol, a powerful anti-inflammatory hormone, which also increases neutrophils (Pariante, 2017). However, glucocorticoid resistance may happen in cases of persistently high cortisol levels, in which case cortisol and NLR seem unrelated. The anti-inflammatory function of cortisol is compromised by glucocorticoid resistance, and pro-inflammatory cytokines and NLR may increase. This has been seen in a subpopulation of MDD patients (Cohen et al., 2012). Further research is needed to understand how cortisol and NLR interact in PD and other forms of depression.

#### 1.4. The role of NLR as a diagnostic biomarker in bipolar disorder (BD)

Mood swings that range from mania or hypomania to depression and periods of euthymia are what is known as bipolar disorder (BD) (Grande et al., 2016). Around the world, BD affects 2–3% of the general population, and its beginning usually happens in adolescence or early adulthood (Silva Ribeiro et al., 2020). Because affective diseases involve several and complex pathophysiological routes, there is substantial uncertainty regarding their origin (Alonso et al., 2011). Hypothalamic-pituitary-adrenal axis dysregulation, imbalances in monoamine and glutaminergic neurotransmission, inflammation, and immunological dysfunctions have all been suggested as potential underlying mechanisms in mood disorders, including MDD and BD (Dean and Keshavan, 2017; Rosenblat and McIntyre, 2017). Growing attention has been given in recent years to the immune system's and inflammatory pathways' roles in the genesis of BD (Sigitova et al., 2017; Benedetti et al., 2020). Recently, the NLR has been suggested as an indicator of inflammation. Several studies have looked into the possible value of NLR as a BD biomarker up to this point (Çakır et al., 2015; Sağlam Aykut et al., 2018). The research on the subject was compiled in a meta-analysis, which found that subjects with BD had higher NLR than healthy controls. Particularly, subgroup analysis demonstrated significantly increased NLR in patients in manic and any bipolar phase than in controls (Mazza et al., 2018). Furthermore, it has been demonstrated that as compared to individuals with unipolar depression, bipolar manic patients exhibited a higher level of inflammation as measured by the NLR index. Additionally, it has been reported that the manic phase in BD was characterized by a higher inflammation activation, reflected by the NLR index, than the depression phase (Dionisie et al., 2021; Koureta et al., 2023). Since neutrophils are the first line of defense for the innate

immune system and lymphocytes are predominantly involved in the adaptive immunological response, elevated NLR in BD (hypo) manic episodes may indicate an imbalance in favor of innate immunity. Notably, the cytokine cascade that follows systemic inflammation appears significantly associated with mood disorders. NLR was originally developed by intensivists to provide a suitable parameter that could reflect the intensity of stress and/or systemic inflammation in critically ill patients. It is conceivable to infer that cellular immunosuppression brought on by prolonged stress or inflammation would explain a higher neutrophil count and a significantly lower lymphocyte count (Anderson and Maes, 2015; Kim et al., 2016; Pfaffenseller et al., 2013). A clinical problem is still separating unipolar depression from bipolar depression. The fact that bipolar depression is frequently mistaken for MDD is a crucial factor (Grande et al., 2016; Hirschfeld, 2014). Additionally, there are significant treatment differences between these conditions, and prescribing antidepressants to people with bipolar disorder is debatable and may aggravate their clinical picture (Gitlin, 2018). These issues have compelled researchers to look for potential biomarkers that assist a more precise differential diagnosis between the depressive phase of bipolar disease and unipolar depression. According to studies, BD depressed patients exhibited higher levels of subclinical inflammation, as indicated by the NLR, than MDD patients. More specifically, there is a 5.31 percent greater likelihood of bipolar depression among depressive patients with higher NLR scores (Dionisie et al., 2021). As a result, NLR may serve as a biomarker for the inflammatory state that characterizes bipolar depression (Zeng et al., 2023). Future prospective research on bigger samples that replicate these findings and evaluate them with other inflammatory indicators will undoubtedly be required to make any firm conclusions.

#### 1.5. NLR as a diagnostic biomarker of suicidal behavior (SB)

Public health issues related to suicide are urgent. In the 15- to 29-year-old age group, suicide is the second greatest cause of mortality, with an average of 1 million suicides per year worldwide. Though it is estimated that there are at least 20 suicide attempts (SAs) for every suicide death, this rate may be greater (Organization, 2012). The etiology of suicidal conduct in depressive illnesses is still not fully understood. The role of the immune system and inflammation has gained particular attention in studies of putative biological indicators of SB (Lee and Kim, 2011), and a comprehensive model emphasizing the impact of the immune system on the pathophysiology of SB was proposed (Courtet et al., 2016). As a result, the feeling of threat that prompts suicidal thoughts may cause physiologic stress reactions, such as inflammatory reactions (Amitai et al., 2022). There is mounting evidence that the pathophysiology of suicidal behavior includes a vital function for neuroinflammation (Ivković et al., 2016). There are quick tests to evaluate inflammation, such as the NLR (Isaac et al., 2016). It's probable that an inflammatory or chronic stress-induced cellular immunosuppression in SB is the cause of a high neutrophil count and comparatively low lymphocyte count (Amitai et al., 2022; Velasco et al., 2020). In clinical practice, particularly in the emergency context, NLR may be a useful, repeatable, conveniently available, and affordable biomarker for identifying suicidal susceptibility in patients with mood disorders. This appears to be a viable new strategy for the acute setting because there are currently no biomarkers that can predict SB. However, it's crucial to keep in mind that, rather than using the conventional approach of discovering high-fold changes in one particular observation, biomarkers for complex phenomena like suicidality will likely be found by collectively assessing a panel of several differential observations. Therefore, from the standpoint of practical application, it is illogical to designate a single molecule as the exclusive and trustworthy biomarker of therapy response. However, NLR may be able to predict the risk of SB when combined with other biomarkers (Amitai et al., 2022; Isaac et al., 2016; Velasco et al., 2023). To pinpoint the precise effects of NLR as an inflammatory marker on suicidality in depression, further prospective

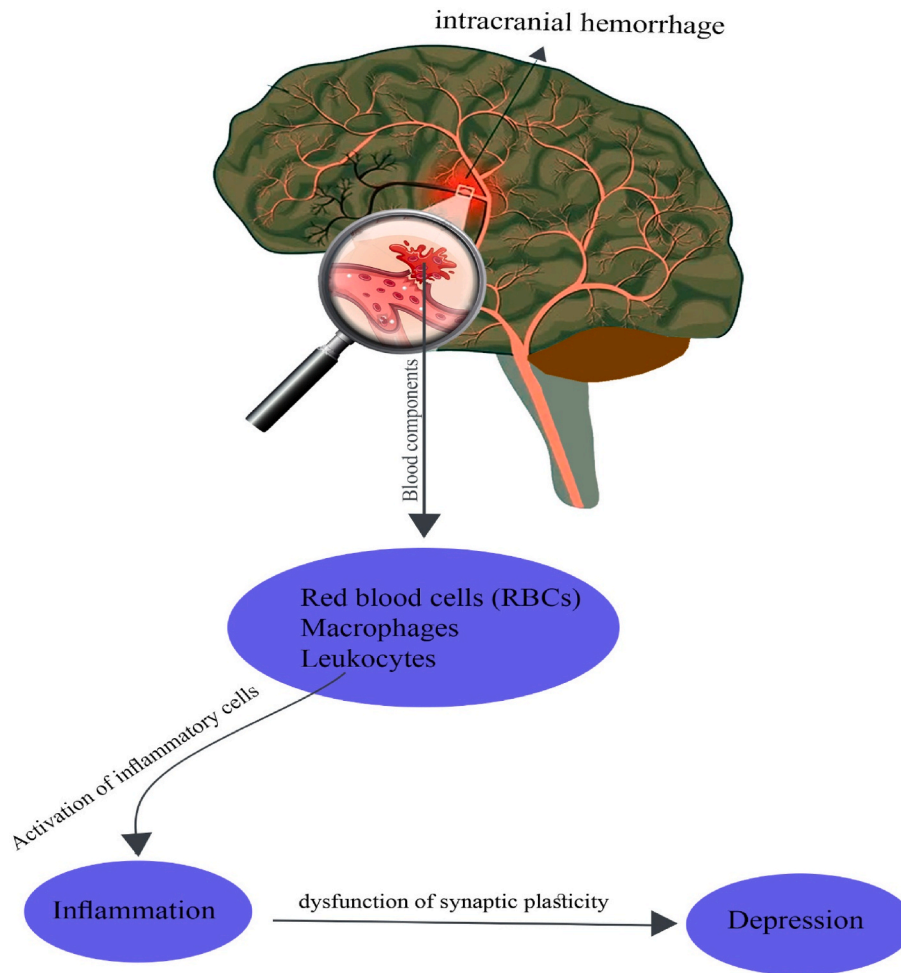
studies are required.

### 1.6. The role of NLR as a diagnostic biomarker in depression caused by various diseases

One of the most prevalent psychosomatic disorders, post-stroke depression (PSD) affects over 20% of those who have survived cerebral hemorrhage (ICH) (Stern-Nezer et al., 2017; Koivunen et al., 2015). Patients with PSD are more likely to experience mortality, cognitive decline, and stroke recurrence (Tu et al., 2018; Mutluer et al., 2020). Therefore, in clinical stroke rehabilitation, early detection, as well as effective management of PSD must be a priority (Hu et al., 2020). Therefore, it is essential to recognize and comprehend the etiology of PSD early on (Gong et al., 2020). Inflammation may be a key factor in PSD formation, according to earlier studies. The NLR has been a widely used biomarker for determining the overall level of inflammation in recent years (Hu et al., 2020). The following biochemical mechanism may account for the link between NLR and depression following ICH. NLR may be a key factor in the emergence of ICH and depression, according to several studies. Leukocytes, red blood cells (RBCs), and macrophages promptly enter into the surrounding brain tissues after the ICH occurs to activate the inflammatory cells. Notably, most investigations on ICH in animals show that neutrophils have infiltrated the

hematoma (Gong et al., 2000; Wang and Tsirka, 2005). The production of cytokines, free radicals, chemokines, and other harmful substances by neutrophils can then cause neurotoxicity through a variety of inflammatory signaling pathways, ultimately aggravating the brain injury caused by ICH (Chen et al., 2015). In contrast, it was discovered that lymphocytes reduced inflammation in ICH patients (Morotti et al., 2017). By altering neurotransmitters, particularly the synthesis and metabolism of 5-hydroxytryptamine and glutamine, inflammation causes the malfunction of synaptic plasticity and ultimately depression (Müller and Schwarz, 2007) (Fig. 2). As a result, an increased NLR may indicate severe inflammation, which likely encourages the development of depression after ICH. In conclusion, a higher NLR is independently linked to depression following ICH, which shows that NLR at admission can act as a substantial biomarker of systemic inflammation to foretell the development of depression following spontaneous ICH.

Diabetes patients are more likely than the general population to experience depression, and those with DM are approximately twice as likely to experience a depressive illness (Roy and Lloyd, 2012; Eren et al., 2008). Those who have both conditions have a lower tendency to stick to diabetes therapy, spend more money, and have a higher risk of dying than those who only have diabetes without depression (Anderson et al., 2001). Due to these factors, it is critical to develop early detection and prevention strategies to lessen the burden on diabetic patients who



**Fig. 2.** NLR may play an important role in the development of ICH and depression. Once ICH occurs, blood components, such as leukocytes, red blood cells (RBCs), and macrophages, immediately infiltrate into the surrounding brain tissues to activate the inflammatory cells. Notably, numerous animal studies on ICH demonstrate the presence of neutrophil infiltration into the hematoma. Afterward, the neutrophils can induce neurotoxicity through a multitude of inflammatory signaling pathways, including the release of cytokines, free radicals, chemokines, and other toxic chemicals, ultimately exacerbating the ICH-induced brain injury. Inflammation induces the dysfunction of synaptic plasticity by mediating alterations in neurotransmitters, especially the synthesis and metabolism of 5-hydroxytryptamine and glutamine, and eventually leads to depression.

also suffer from depression. Depression's process includes a significant contribution from low-grade inflammation. NLR is a widely used biomarker for assessing the overall condition of inflammation. Increased probabilities of clinically significant depression symptoms are independently linked to elevated NLR levels in diabetics (Wang et al., 2020). In addition, patients with diffuse large B cell lymphoma and lung cancer may have high levels of NLR as a predictive and preventative biomarker for depression (Yi et al., 2021; McFarland, 2020; Yousefi et al., 2023; Yousefi and Eskandari, 2019; Andersen et al., 2023). To better understand how NLR contributes to depression in the aforementioned disorders, prospective studies are required.

## 2. Conclusion and perspective

In recent years, the neutrophil-to-lymphocyte ratio (NLR) has been reported to be a biomarker of inflammatory status in patients with depression. Since NLR reflects both immune pathways and is probably less affected by confounding conditions, it may be more informative than other leukocyte parameters or other widely used markers. NLR can be derived from white blood cell count and is a ratio between absolute neutrophil count to absolute lymphocyte count. It is widely available, reproducible, easy to measure, and unlike many others, inexpensive. This is owing to the prevalence of these parameters in routine blood tests and the assessment's lack of a need for additional kits or modern technology. Our review showed that, although the majority of studies have shown that NLR levels were significantly increased in patients with depression, however, in a few studies, the NLR between the depressed patients and controls did not differ significantly from each other. All of these studies were limited by relatively small sample sizes. In addition, several important confounding factors, such as body mass index (BMI), lifestyle, and gender, were not taken into account in these studies. It seems that further studies on larger samples, taking into account important confounding factors, and assessing them together with other inflammatory markers are necessary to draw some conclusive statements. Furthermore, since depression has different symptoms that vary from person to person. More studies are suggested in order to determine NLR in different symptoms of depression, such as impaired concentration, interrupted sleep or low self-worth. The results of such research can increase the accuracy of NLR in the diagnosis of depression.

## CRedit authorship contribution statement

**Sayed Soran Ghafari:** Writing – review & editing, Writing – original draft. **Zahra Yousefi:** Writing – review & editing, Validation, Conceptualization. **Elham Bakhtiari:** Writing – review & editing. **mohammad hossein mohammadi mahdiabadi hasani:** Writing – review & editing. **Gholamreza Hassanzadeh:** Writing – review & editing, Supervision, Project administration, Data curation, Conceptualization.

## Declaration of competing interest

The authors have no conflicts of interest to declare.

## Data availability

No data was used for the research described in the article.

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