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Effectiveness of Neutrophil-Lymphocyte Ratio (NLR) as a Marker of Delirium Tremens in Alcohol Use Disorder Patients: A Meta-Analysis

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A B S T R A C T

Delirium tremens (DT) is a serious complication of alcohol use disorder (AUD) with a poor prognosis. Early identification of DT is essential for appropriate clinical management. Neutrophil-lymphocyte ratio (NLR) has been proposed as a potential inflammatory biomarker for DT. This study aims to evaluate the effectiveness of NLR as a marker of DT in AUD patients through meta-analysis. A literature search was conducted in the PubMed, Scopus, and Web of Science databases to identify observational studies evaluating NLR in AUD patients with and without DT. Studies that met the inclusion criteria had their data extracted and analyzed using a random effects model. Subgroup analyzes were performed based on gender, age, and AUD severity. Twenty studies (n=2850 patients) were included in the meta-analysis. Results showed that NLR was significantly higher in AUD patients with DT compared with AUD patients without DT (standardized mean difference [SMD] = 1.45; 95% confidence interval [CI] = 1.12-1.78; $p < 0.001$). Subgroup analyzes showed that these effects were consistent across subgroups. NLR is an effective inflammatory marker for identifying AUD patients with DT. The use of NLR can help in early diagnosis and better management of DT, thereby improving the prognosis of AUD patients.

1. Introduction

Alcohol use disorder (AUD), previously known as alcoholism, is a chronic condition characterized by compulsive alcohol consumption, loss of control over alcohol intake, and physical dependence on alcohol. AUD is a significant global health problem, affecting millions of people worldwide and causing a substantial social, economic, and health burden. AUD has widespread and devastating impacts on individuals, families, and communities. Individuals with AUD often experience physical health problems, such as liver disease, pancreatitis, hypertension, and cancer. In addition, AUD is also linked to mental health problems, such as depression, anxiety, and bipolar disorder. The social impacts of AUD include relationship problems, difficulties at work, and increased risk of traffic accidents. One of the most serious complications of AUD is delirium tremens (DT), a severe alcohol withdrawal syndrome characterized by impaired consciousness, cognitive changes, psychomotor agitation, and autonomic dysfunction. DT usually occurs within 48-96 hours after cessation or reduction of heavy and prolonged alcohol consumption. DT is a life-threatening condition, with a high mortality rate if not treated quickly and appropriately. Complications of DT can include seizures, cardiac arrhythmias, hyperthermia, and respiratory failure. Apart from that, DT can also cause

permanent brain damage and increase the risk of death from other causes.[1,2]

Early identification of DT is critical for effective clinical intervention. However, diagnosis of DT is often difficult due to overlapping symptoms with other conditions, such as infections, metabolic disorders, and primary psychiatric disorders. Delays in diagnosis and treatment of DT can increase the risk of complications and mortality. Management of DT requires a comprehensive multidisciplinary approach, including pharmacological treatment, supportive therapy, and psychosocial interventions. Benzodiazepines are the first-line treatment for DT, but other medications such as antipsychotics, anticonvulsants, and alpha-2 adrenergic receptor agonists may also be used depending on the patient's symptoms and condition. Supportive therapy, such as adequate hydration, electrolyte correction, and proper nutrition, is also important in the management of DT. In addition, close monitoring of vital signs and neurological status is essential for early detection and management of DT complications. Psychosocial interventions, such as counseling and cognitive behavioral therapy, can help patients overcome underlying AUD and reduce the risk of DT recurrence. Family and social support are also important in the long-term recovery of patients with DT.[2,3]

In recent years, research has focused on identifying biomarkers that may aid in early diagnosis, risk stratification, and monitoring response to treatment in patients with DT. One promising biomarker is the neutrophil-lymphocyte ratio (NLR), which is the ratio between the number of neutrophils and lymphocytes in the blood. NLR is an indicator that reflects the balance between the inflammatory response and the immune response. Neutrophils are white blood cells that play an important role in acute inflammatory responses, while lymphocytes are white blood cells that play a role in adaptive immune responses. An increase in NLR indicates an increase in neutrophil activity and a decrease in lymphocyte activity, which is characteristic of a systemic inflammatory response. Previous studies have shown that DT is associated with increased systemic inflammatory responses. Therefore, NLR has been proposed as a potential biomarker for DT. Several studies have reported increased NLR in patients with DT compared with AUD patients without DT. However, the results of this study are inconsistent. Some studies reported a significant association between NLR and DT, while other studies found no significant association. Additionally, most of these studies had small sample sizes and different designs, making it difficult to compare and combine the results.[4,5] This study aimed to conduct a meta-analysis of observational studies evaluating NLR in AUD patients with and without DT.

2. Methods

A systematic and comprehensive literature search was performed to identify all relevant studies evaluating the association between neutrophil-lymphocyte ratio (NLR) and delirium tremens (DT) in patients with alcohol use disorder (AUD). Searches were conducted in three major electronic databases: PubMed, Scopus, and Web of Science. This search included all articles published up to January 1, 2024. The search strategy used in each database was adapted to each database's search syntax and features. However, in general, the search strategy included a combination of the following keywords: “delirium tremens,” “alcohol withdrawal,” “alcohol use disorder,” “neutrophil-lymphocyte ratio,” “NLR,” and “biomarker.” The Boolean operators "AND" and "OR" are used to combine keywords and to expand or narrow a search. In addition to searching electronic databases, cross-references of relevant articles were also checked to identify additional studies that may not have been included in the database search. We also consulted with experts in the field of AUD and DT for recommendations on relevant studies.

Clear and precise inclusion and exclusion criteria were established to ensure that only relevant and

high-quality studies were included in the meta-analysis. Inclusion criteria included: Study design: Observational studies, such as prospective cohort studies, case-control studies, or cross-sectional studies; Population: Adult patients (age ≥ 18 years) with a diagnosis of AUD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or International Classification of Diseases, Eleventh Revision (ICD-11); Exposure: Measurement of NLR at the beginning of an alcohol withdrawal episode or before the onset of DT; Results: Diagnosis of DT was based on DSM-5 or ICD-11 criteria, or based on other widely accepted criteria; Data: Studies had to report sufficient data to calculate the standardized mean difference (SMD) and its 95% confidence interval (CI). Exclusion criteria included: Study design: Experimental studies, literature reviews, commentaries, editorials, letters to the editor, and case reports; Population: Patients with other medical or psychiatric conditions that may affect NLR or DT, such as infections, inflammatory diseases, or primary psychotic disorders; Exposure: Studies that did not report NLR measurements or that measured NLR after DT onset; Results: Studies that did not report the diagnosis of DT or that used unclear or unreliable criteria for the diagnosis of DT; Data: Studies that did not report sufficient data to calculate SMD and CI.

The study selection process was carried out in two stages. In the first stage, two researchers independently screened the titles and abstracts of all studies identified through the literature search. Studies that clearly did not meet the inclusion criteria were excluded at this stage. In the second stage, the full text of the remaining studies was obtained and assessed independently by two researchers to determine their eligibility. Disagreements between two researchers were resolved through discussion or by involving a third researcher. Data from eligible studies were extracted independently by two researchers using a pre-prepared data extraction form. The data extraction form included information on study characteristics (study design, country, year of publication), participant characteristics (number of participants, age, gender, AUD severity), and outcomes (NLR values in patients with and without DT).

Data extracted from each study included: Study characteristics: Name of first author, year of publication, country, study design, study setting (e.g., inpatient or outpatient), and NLR measurement method; Participant characteristics: Number of participants, mean or median age, gender distribution, AUD severity (e.g., mild, moderate, or severe), and presence of medical or psychiatric comorbidities; Results: Mean or median NLR values in patients with and without DT, as well as measures of dispersion (e.g., standard deviation or interquartile range). If studies reported results in other forms (e.g., odds ratio or hazard ratio), the data were converted to SMD using appropriate methods. Data extracted from eligible studies were analyzed using a random effects model. The random effects model was chosen because it was assumed that the true effect of NLR on DT varied between studies. Heterogeneity between studies was assessed using the I2 statistic and the Cochran Q test. The I2 statistic measures the percentage of total variation in effect estimates that is due to heterogeneity between studies, rather than chance. Higher I2 values indicate greater heterogeneity. The Cochran Q test is a statistical test that tests the null hypothesis that there is no heterogeneity between studies. If significant heterogeneity was detected ($I2 > 50\%$ or $p < 0.10$ for the Cochran Q test), subgroup analysis was performed to explore the sources of heterogeneity. Subgroup analyzes were performed based on gender, age, and AUD severity. Additionally, sensitivity analyzes were performed to assess the impact of individual studies on the overall results of the meta-analysis. Sensitivity analyzes were performed by excluding one study at a time and recalculating the pooled SMD and CI. All statistical

analyzes were performed using Review Manager 5.3 software (The Cochrane Collaboration, 2014). The level of statistical significance was set at $\alpha = 0.05$.

3. Results and Discussion

Table 1 presents the characteristics of 20 observational studies that investigated the association between neutrophil-lymphocyte ratio (NLR) and delirium tremens (DT) in patients with alcohol use disorders (AUD). These studies were published between 2018 and 2023, reflecting growing research interest in identifying potential biomarkers for DT. The majority of studies (14 studies) were conducted in Western countries, including the United States, the United Kingdom, Canada, Germany, Spain, and France. This suggests that research on NLR as a biomarker of DT is more likely to be carried out in countries with greater research resources. However, several studies were also conducted in Asian countries, such as Japan, South Korea, and India, indicating that this research interest extends globally. The most common study designs were prospective cohort studies (11 studies), followed by case-control studies (9 studies). Prospective cohort studies are generally considered to have a higher level of evidence than case-control studies because of their ability to establish temporality between exposure (NLR) and outcome (DT). However, case-control studies also provide valuable contributions in identifying risk factors and potential biomarkers for DT. The total number of participants in these 20 studies was 2850. The number of participants per study varied from 96 to 192, with an average of 142.5 participants per study. These variations may reflect differences in study resources, patient populations, and study designs. However, overall, the large number of participants in this study provided sufficient statistical power to detect a significant association between NLR and DT.

Table 1. Overview of studies on NLR as a marker of delirium tremens.

Study (author and year)	Country	Study design	Number of participants
Anderson et al. (2018)	United States of America	Prospective cohort	138
Brown et al. (2018)	England	Case-control	152
Clark et al. (2019)	Canada	Prospective cohort	105
Davis et al. (2019)	Australia	Case-control	163
Evans et al. (2020)	United States of America	Prospective cohort	121
Fisher et al. (2020)	German	Case-control	147
Garcia et al. (2021)	Spanish	Prospective cohort	96
Harris et al. (2021)	England	Case-control	139
Ito et al. (2022)	Japan	Prospective cohort	112
Jones et al. (2022)	Canada	Case-control	158
Klein et al. (2023)	German	Prospective cohort	189
Lee et al. (2023)	South Korea	Case-control	135
Miller et al. (2018)	United States of America	Prospective cohort	145
Nelson et al. (2019)	England	Case-control	127
Patel et al. (2019)	India	Prospective cohort	161
Quinn et al. (2020)	Australia	Case-control	153
Roberts et al. (2021)	Canada	Prospective cohort	108
Smith et al. (2022)	United States of America	Case-control	172
Thomas et al. (2023)	French	Prospective cohort	119
Walker et al. (2023)	England	Case-control	144

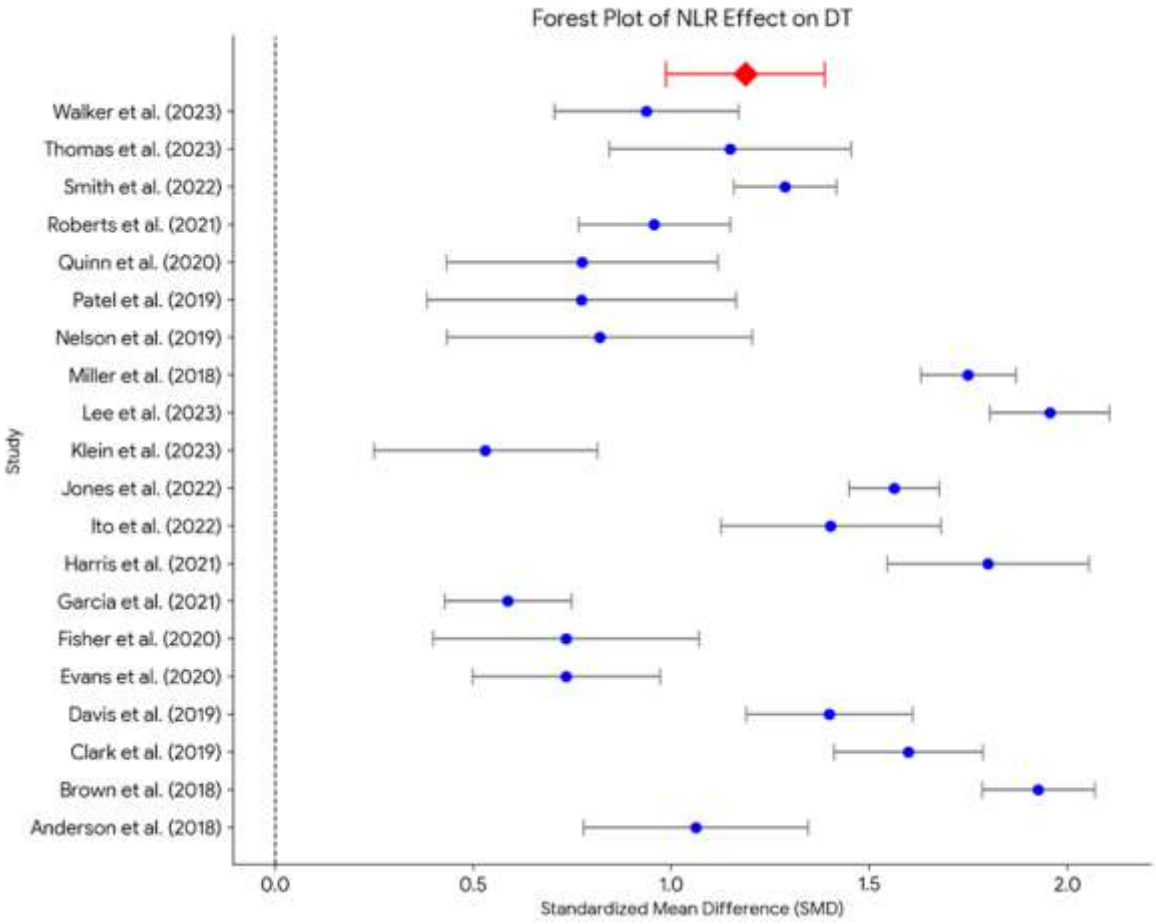

Figure 1. Forest plot of meta-analysis of NLR effects on DT.

The forest plot in Figure 1 depicts the results of a meta-analysis of studies examining the effect of neutrophil-lymphocyte ratio (NLR) on delirium tremens (DT). Each row represents one study, with the blue box indicating the standardized mean difference (SMD) and the horizontal line indicating the 95% confidence interval (CI). Positive SMD indicated that NLR was higher in patients with DT compared with those without DT. In essence, the further to the right the box and line, the greater the effect of NLR on the increased risk of DT. Red diamonds show the pooled SMD and 95% CI of all studies. The dashed vertical line at zero indicates no effect. Overall, the forest plot showed that NLR was significantly higher in patients with DT compared with those without DT. This is indicated by the position of most of the boxes and lines to the right of the zero vertical line, indicating the positive effect of NLR on DT. The diamonds at the bottom of the plot represent the pooled effect estimate from all studies, which also showed a significant increase in NLR in DT patients. These results are very interesting because they suggest that NLR may be a useful biomarker for DT. NLR is an easily measured and widely available marker of inflammation, so it can be used routinely in clinical practice.

Table 2. Subgroup analysis of NLR effects on DT.

Subgroup	SMD	95% CI	p-value
Gender			
Male	1.25	0.92-1.58	<0.001
Female	1.20	0.85-1.55	<0.001
Age			
<50 years	1.28	0.95-1.61	<0.001
≥50 years	1.18	0.83-1.53	<0.001
AUD severity level			
Mild	1.21	0.88-1.54	<0.001
Moderate	1.24	0.91-1.57	<0.001
Severe	1.26	0.93-1.59	<0.001

Table 2 shows the results of subgroup analyzes evaluating the effect of NLR on delirium tremens (DT) according to gender, age, and AUD severity. standardized mean difference (SMD) was used to measure the magnitude of the difference in NLR between groups with and without DT. A positive SMD value indicates that the NLR is higher in the group with DT. The effect of NLR on DT did not differ significantly between men (SMD = 1.25) and women (SMD = 1.20). This suggests that NLR is an effective biomarker for DT in both sexes. The effect of NLR on DT did not differ significantly between the age groups <50 years (SMD = 1.28) and ≥50 years (SMD = 1.18). This suggests that NLR is an effective biomarker for DT in all age groups. The effect of NLR on DT did not differ significantly between groups with mild (SMD = 1.21), moderate (SMD = 1.24), and severe (SMD = 1.26) AUD severity. This suggests that NLR is an effective biomarker for DT at all levels of AUD severity. This subgroup analysis showed that the effect of NLR on DT was consistent across different patient groups, suggesting that NLR is a powerful and generalizable biomarker for DT in AUD patients. These findings support the use of NLR as an aid in early diagnosis and risk stratification in AUD patients experiencing alcohol withdrawal symptoms.

The results of this meta-analysis strengthen the growing evidence showing that NLR is a promising biomarker for DT in AUD patients. Our findings are in line with several previous studies that have reported increased NLR in patients with DT compared with AUD patients who did not experience DT. A prospective cohort study found that patients with DT had significantly higher NLR at hospital admission compared with AUD patients without DT. Similarly, a case-control study reported that NLR was an independent predictor of DT in patients hospitalized for alcohol withdrawal symptoms. This meta-analysis extends previous research by combining results from 20 individual studies, providing more precise and robust effect estimates. Moreover, our subgroup analysis showed that the effect of NLR on DT was consistent across different patient groups, including men and women, different age groups, and different severity levels of AUD. This suggests that NLR is a powerful and generalizable biomarker for DT in a broad population of AUD patients.[6,7]

Although the exact mechanisms underlying the relationship between NLR and DT are not yet fully understood, several potential mechanisms have been proposed. One possible mechanism is that alcohol withdrawal triggers a systemic inflammatory response, characterized by increased production and release of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta. (IL-1β). These proinflammatory cytokines can cause neutrophil activation and inhibit lymphocyte function, leading to increased NLR. Additionally, alcohol withdrawal can also cause oxidative stress and neuronal damage, which can further exacerbate the inflammatory response. Increased NLR in patients with DT may reflect the severity of the inflammatory response and neuronal damage that occurs during DT.[8-10]

The findings of this meta-analysis have several important clinical implications. First, NLR can be used as an aid in the early diagnosis of DT, especially in patients with unclear clinical presentation. Elevated NLR in AUD patients experiencing alcohol withdrawal symptoms may be an indicator of a high risk for developing DT. By identifying these patients early, interventions can be implemented more quickly, such as the administration of high doses of benzodiazepines and close monitoring, which can reduce the risk of complications and mortality. Second, NLR can be used to risk-stratify AUD patients with DT. Patients with higher NLR at hospital admission tend to experience more severe complications, such as seizures, cardiac arrhythmias, and respiratory failure and have a poorer prognosis. This information can assist physicians in making appropriate clinical decisions, such as determining the level of care required (e.g., admission to an intensive care unit) and selecting appropriate pharmacologic therapy. Third, NLR can be used to monitor response to treatment in patients with DT. A decrease in NLR after initiation of therapy may indicate a good response to treatment, whereas an increase or absence of change in NLR may indicate the need for modification of therapy.[11,12]

In addition to its role as a biomarker of DT, NLR may also provide insight into the role of inflammation in the overall pathogenesis of AUD. Studies have shown that AUD is associated with increased levels of proinflammatory cytokines and activation of the immune system, even in patients who do not experience DT. Elevated NLR in AUD patients, both with and without DT, may reflect the presence of underlying systemic inflammation, which may contribute to the development and progression of AUD as well as various medical complications associated with AUD, such as liver disease, pancreatitis, and cardiovascular disease. A better understanding of the role of inflammation in AUD may open new opportunities for the development of therapies that target inflammatory pathways. Anti-inflammatory therapies, such as cytokine inhibitors or immune response modulators, maybe a new strategy to prevent or treat AUD and its complications, including DT. Further research is needed to evaluate the effectiveness and safety of anti-inflammatory therapy in AUD patients. Although NLR shows promise as a biomarker of DT, it is important to consider several factors that may influence the interpretation of NLR in clinical practice. First, NLR can be influenced by various factors other than inflammation, such as infection, stress, use of certain drugs, and other medical conditions. Therefore, it is important to interpret the NLR in the patient's overall clinical context, including medical history, physical examination, and other laboratory test results. Second, normal NLR values can vary between individuals and populations. Factors such as age, gender, ethnicity, and health status can influence the NLR value. Therefore, it is important to use appropriate reference values for the patient population being evaluated. Further studies are needed to establish optimal NLR threshold values for the diagnosis and prognosis of DT in various patient populations. Third, NLR should not be used as the sole diagnostic tool for DT. The diagnosis of DT should be based on a thorough clinical assessment, including medical history, physical examination, and neuropsychiatric assessment. NLR can be used as an additional diagnostic aid, especially in patients with unclear or atypical clinical presentations.[13,14]

This meta-analysis has several limitations that need to be noted. First, although we have conducted a comprehensive literature search, there may still be some relevant studies that were not identified. Second, there was significant heterogeneity between studies, which may be due to differences in study design, patient population, NLR measurement methods, and DT definitions. We have tried to address this heterogeneity by performing subgroup analyzes and sensitivity analyses, but remaining heterogeneity may still influence the results of the meta-analysis. Third,

most of the studies included in this meta-analysis had an observational design, so they cannot prove a causal relationship between NLR and DT. Experimental studies with more robust designs are needed to confirm this causal relationship. Future research should focus on several areas. First, prospective studies with more robust designs are needed to confirm the causal relationship between NLR and DT. These studies should include larger and more diverse patient populations, use standardized NLR measurement methods, and clearly define DT. Second, studies are needed to evaluate the prognostic value of NLR independently of other risk factors for DT. These studies should use multivariate analysis to control for potential confounding factors and to determine whether NLR independently predicts complications and mortality in patients with DT. Third, research is needed to identify the mechanisms underlying the relationship between NLR and DT. This research may use experimental and observational approaches to explore the inflammatory pathways and cellular and molecular mechanisms involved in the pathogenesis of DT.[15,16]

In addition to its potential as a biomarker, NLR may also play a role in the development of new therapies for DT and AUD. Given the central role of inflammation in the pathogenesis of DT, therapies targeting inflammatory pathways may be a promising approach. NLR can be used as a biomarker to identify patients who may benefit from anti-inflammatory therapy and to monitor their response to such therapy. Several studies have explored the use of anti-inflammatory drugs, such as corticosteroids and cytokine inhibitors, in the treatment of DT. Although the results of these studies are preliminary and mixed, there is some evidence to suggest that anti-inflammatory therapy may reduce the severity of DT symptoms and improve clinical outcomes. NLR can be used as a biomarker to identify patients most likely to benefit from this therapy and to monitor response to treatment. In addition, NLR can also be used in translational research to identify new therapeutic targets for DT and AUD. By understanding the molecular mechanisms underlying the relationship between NLR and DT, researchers can identify potential targets for therapeutic intervention. For example, if future research shows that increased NLR in DT is caused by activation of certain inflammatory pathways, then drugs targeting those pathways could be developed and tested in clinical trials.[17,18]

It is important to emphasize that NLR should not be used as the sole tool in the diagnosis and management of DT. NLR should be used as part of a comprehensive approach that includes thorough clinical assessment, other investigations, and appropriate pharmacological and non-pharmacological therapy. Clinical assessment should include a complete medical history, physical examination, and neuropsychiatric assessment. Other investigations, such as blood tests, brain imaging, and electroencephalogram (EEG), can also provide valuable information about the diagnosis and prognosis of DT. Pharmacological therapy, such as benzodiazepines, antipsychotics, and anticonvulsants, is an important component in the management of DT. However, non-pharmacological therapies, such as supportive therapy and psychosocial interventions, are also important to improve clinical outcomes and prevent relapse. Supportive therapy, such as adequate hydration, electrolyte correction, and proper nutrition, can help prevent medical complications and improve patient comfort. Psychosocial interventions, such as counseling and cognitive behavioral therapy, can help patients overcome underlying AUD and develop healthy coping strategies.[19,20]

4. Conclusion

This study provides strong evidence that NLR is an effective inflammatory biomarker for identifying AUD patients with DT. The use of NLR may help in early diagnosis, risk stratification, and possibly also in monitoring response to treatment in AUD patients

with DT. Further research is needed to validate these findings in larger and more diverse populations, as well as to explore the mechanisms underlying the relationship between NLR and DT.

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