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ORIGINAL RESEARCH

Application Value of Novel Inflammatory Indicators in Response to Ursodeoxycholic Acid Therapy in Patients with Primary Biliary Cholangitis

Siqi Liu[1], Yongli Pang[2], Xiaoxi Wang[3], Ruihang Lin[4], Siqing Tunala[5]

[1]Inner Mongolia Medical University, Hohhot, Inner Mongoli, People's Republic of China; [2]Ordos second People's Hospital, Ordos, Inner Mongoli, People's Republic of China; [3]People's Hospital of Ordos Dongsheng District, Ordos, Inner Mongoli, People's Republic of China; [4]Ordos Central Hospital, Ordos, Inner Mongoli, People's Republic of China; [5]Ordos Mongolian Medicine Hospital, Ordos, Inner Mongoli, People's Republic of China

Correspondence: Siqing Tunala, Ordos Mongolian Medicine Hospital, Ordos, Inner Mongoli, People's Republic of China, Email tutu88600@126.com

Objective: To analyze the application value of novel inflammation indicators such as the lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) in patients with primary biliary cholangitis (PBC) undergoing ursodeoxycholic acid (UDCA) treatment. We plan to further seek simple and convenient methods to assess the response of patients to UDCA treatment.

Methods: We recorded routine blood tests, liver function, and vitamin D (VD) levels of PBC patients and healthy controls visiting the hospital between October 2022 and October 2023. LMR, NLR, and PLR were calculated, and differences between the two groups were analyzed. PBC patients were divided into good response and poor response groups according to the Paris I criteria, and differences in laboratory tests between the two groups were analyzed. The predictive value of novel inflammation indicators in UDCA treatment response was further analyzed using ROC analysis.

Results: LMR and VD levels were significantly lower in the PBC group compared to the control group (P=0.000, P=0.000). In PBC patients, the good response group had higher LMR than the poor response group (P=0.001) and lower NLR than the poor response group (P=0.015). The areas under the ROC curve for LMR and NLR were 0.682±0.049 and 0.630±0.052, respectively. There was a significant negative correlation between PLR and VD in PBC patients (r=−0.252, P=0.005).

Conclusion: Low LMR and high NLR may indicate poor treatment response. And PLR also have certain predictive values for treatment response.

Keywords: primary biliary cholangitis, lymphocyte/monocyte ratio, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, vitamin D

Introduction

Primary biliary cholangitis (PBC) is a chronic progressive non-suppurative inflammatory disease of the small intrahepatic bile ducts, leading to cholestasis. It is a type of autoimmune liver disease most common in women and people over 50 years old. The cause is not clear but is considered to be related mainly to genetic and environmental factors. The treatment is lifelong.[1,2] In recent years, the incidence of PBC has gradually increased, and mortality has decreased after treatment,[3] although there are currently few drug options. Undergoing ursodeoxycholic acid (UDCA) is the only approved first-line treatment for PBC. Patients with poor response to UDCA treatment have poor long-term prognosis and should consider second-line drug therapy. At present, commonly used models are based on a one-year period of UDCA treatment, and early use of simple methods to assess patient response is necessary in clinical treatment.

Lymphocyte/monocyte ratio (LMR), neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) are novel inflammation indicators that are inexpensive, simple, and can reflect the body's inflammatory and immune status. In studies related to liver diseases, elevated NLR is associated with the progression and prognosis of viral hepatitis and non-alcoholic fatty liver disease. It is an independent prognostic risk factor for mortality in cirrhosis and acute-on-chronic liver failure. NLR is also associated with the prognosis of PBC patients.[4–7] LMR can predict the prognosis of various

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liver diseases, including survival after radiofrequency ablation for hepatocellular carcinoma and mortality rates for hepatitis B-related cirrhosis, among others. Patients with low LMR generally have a poorer prognosis,[8,9] and a low LMR can increase the risk of acute-on-chronic liver failure, reflecting the patient's prognosis.[10] Vitamin D (VD) is an essential fat-soluble vitamin that, besides regulating calcium and phosphorus metabolism through classical pathways, is also related to inflammation and autoimmune diseases.[11] Its levels are correlated with novel inflammation indicators. Studies have indicated that new inflammatory markers such as NLR and PLR are negatively correlated with vitamin D levels, while LMR is positively correlated with vitamin D levels.[10,12,13]

Materials and Methods

Research Subjects

PBC patients and physical examinees visiting secondary or higher public hospitals in Ordos from October 2022 to October 2023 were selected. PBC patients met the diagnostic criteria of the "Guidelines for the Diagnosis and Treatment of Primary Biliary Cholangitis (2021)" by the Chinese Medical Association Liver Disease Committee and had been receiving standard oral UDCA treatment for at least 12 months. Exclusion criteria included the presence of other types of hepatitis, liver cirrhosis, malignant liver tumors, acute/chronic liver failure, renal failure, severe cardiovascular diseases, acute respiratory, gastrointestinal, or urinary tract infections, and a history of hormone, immunosuppressant, or VD treatment within the past three months. This study was approved by the hospital's ethics committee (2022–027), and all enrolled patients voluntarily signed informed consent forms.

Methodology

All enrolled patients had fasting venous blood collected in the morning for routine blood tests (including platelet, neutrophil, lymphocyte, monocyte counts), liver function tests [including alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ- glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TB), albumin (ALB)], and 25-hydroxyvitamin D [25(OH)D] levels. Novel inflammation indicators (including LMR, NLR, and PLR) were calculated based on routine blood test results.

All enrolled PBC patients are early-stage patients. So they were divided into good response and poor response groups according to the Paris I criteria: good response was defined as ALP ≤ 3×ULN, AST ≤ 2×ULN, and bilirubin ≤ 17.1μmol/L after 12 months of UDCA treatment.

PBC patients were also divided into VD sufficient, insufficient, deficient, and severely deficient groups based on serum 25(OH)D levels. VD sufficiency was defined as 25(OH)D >30μg/L, insufficiency as 20–30μg/L, deficiency as <20 μg/L, and severe deficiency as <10μg/L.

Statistical Analysis

Data were analyzed using SPSS27.0 software. Normally distributed data were expressed as mean ± standard deviation ($\bar{x}$±s) and compared between groups using independent sample *t*-tests or analysis of variance. Non-normally distributed data were expressed as median and interquartile range [M(P_{25}, P_{75})] and compared between groups using independent rank-sum tests. Categorical data were expressed as n (%) and compared using chi-square tests or Fisher's exact tests. Correlation analyses were performed using Pearson or Spearman correlation analysis. Binary logistic regression was used to analyze factors affecting treatment response, and ROC curves were drawn to analyze their predictive value. $P<0.05$ was considered statistically significant.

Results

General Information and Laboratory Results of PBC and Control Patients

A total of 123 PBC patients met the inclusion criteria, with an average age of 55.62±10.57 years; 10.57% were male, and 89.43% were female. Based on the age range and gender ratio of the PBC group, 123 control patients were selected for comparative analysis.

When age and gender showed no statistical differences, 25(OH)D levels in the PBC group (17.07 [12.20, 24.08] μg/L) were lower than those in the control group (20.23 [16.44, 27.30] μg/L). (Figure 1) The LMR in the PBC group (5.44 [3.76, 7.05]) was significantly lower than in the control group (6.91±2.10), with both differences being statistically

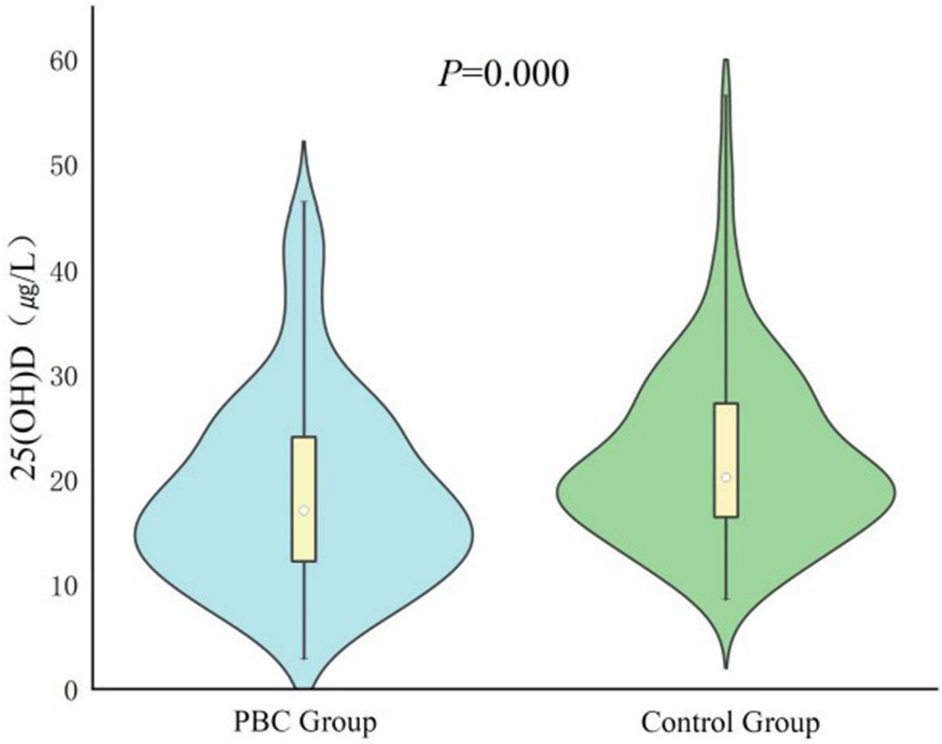

Figure 1 Comparison of 25(OH)D levels between PBC patients and controls.
Abbreviation: PBC, primary biliary cholangitis.

significant ($P<0.01$). There were no significant differences in other novel inflammation indicators ($P>0.05$). Liver function indicators between the two groups showed significant statistical differences ($P<0.01$) (Table 1).

Vitamin D Levels and Laboratory Tests in PBC Patients

There were significant differences in PLR among different VD level groups, with statistical significance ($P<0.05$). No significant differences were observed in other laboratory tests ($P>0.05$). The response rates to UDCA treatment did not show significant differences between the different VD level groups ($P>0.05$) (Table 2).

Table 1 Comparison of Relevant Data Between the PBC Group and the Control Group

	PBC Group (n=123)	Control Group (n=123)	*P* value
Age (years)	55.62±10.57	52.00 (48.00, 58.00)	0.051
Gender (M/F)	14/109	14/109	1.000
LMR	5.44 (3.76, 7.05)	6.91±2.10	0.000
NLR	1.62 (1.27, 2.49)	1.57 (1.26, 2.11)	0.481
PLR	112.50 (83.20, 155.81)	121.46 (98.01, 157.85)	0.130
ALT (U/L)	32.00 (20.00, 65.00)	20.00 (15.00, 29.00)	0.000
AST (U/L)	37.20 (24.00, 52.60)	21.00 (18.00, 28.00)	0.000
ALB (g/L)	44.30 (39.90, 46.70)	46.27±2.56	0.000
TB (μmol/L)	14.20 (10.00, 19.66)	11.61±4.37	0.000
ALP (U/L)	137.00 (100.00, 198.00)	77.39±20.77	0.000
GGT (U/L)	79.00 (30.00, 205.00)	18.00 (13.00, 33.00)	0.000
25(OH)D (μg/L)	17.07 (12.20, 24.08)	20.23 (16.44, 27.30)	0.000

Abbreviations: PBC, primary biliary cholangitis; M, male; F, female; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; ALP, alkaline phosphatase; GGT, γ- glutamyl transpeptidase; 25(OH)D, 25-hydroxyvitamin D.

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Table 2 Comparison Between VD Level and Laboratory Examination

	Adequate Group (n=11)	Insufficient Group (n=32)	Deficient Group (n=60)	Severely Deficient Group (n=20)	*P* value
Age (years)	55.09±9.63	55.81±8.33	55.68±10.10	55.40±15.44	0.997
Gender (M/F)	2/9	3/29	7/53	1/19	0.693
LMR	5.50±3.60	5.66 (4.36, 8.31)	5.30±1.95	5.23±2.38	0.550
NLR	1.90±0.98	1.57 (1.15, 2.46)	1.63 (1.32, 2.30)	1.60 (1.27, 2.61)	0.978
PLR	82.56 (72.13, 90.82)	113.19±52.69	163.20 (116.43, 203.11)	138.82±64.03	0.035
ALT (U/L)	24.00 (19.00, 74.00)	32.45 (17.03, 64.00)	33.10 (21.40, 63.98)	30.85 (14.10, 63.75)	0.938
AST (U/L)	31.00 (26.00, 92.40)	37.50 (21.70, 48.20)	40.10 (25.33, 52.90)	29.65 (24.70, 53.78)	0.869
ALB (g/L)	42.96±6.40	43.50±5.44	43.63±4.66	43.45 (37.55, 46.45)	0.719
TB (μmol/L)	17.80 (6.90, 26.00)	13.60 (10.98, 20.18)	14.75 (10.48, 19.52)	13.40 (8.28, 16.40)	0.903
ALP (U/L)	159.55±43.32	117.15 (81.25, 153.20)	149.50 (97.00, 215.50)	152.50 (109.40, 368.99)	0.072
GGT (U/L)	158.00 (18.00, 181.00)	65.00 (24.00, 149.00)	76.55 (32.50, 217.75)	139.00 (57.75, 387.50)	0.211
Response rate (%)	45.46	65.63	60.00	60.00	0.707

Abbreviations: M, male; F, female; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; ALP, alkaline phosphatase; GGT, γ- glutamyl transpeptidase.

Correlation Between 25(OH)D and Novel Inflammation Indicators in PBC Patients

Correlation analysis between 25(OH)D and novel inflammation indicators in PBC patients revealed a significant negative correlation between 25(OH)D and PLR (r=−0.252, P<0.01) (Figure 2). No significant correlation was found between 25 (OH)D and LMR or NLR (P>0.05) (Table 3).

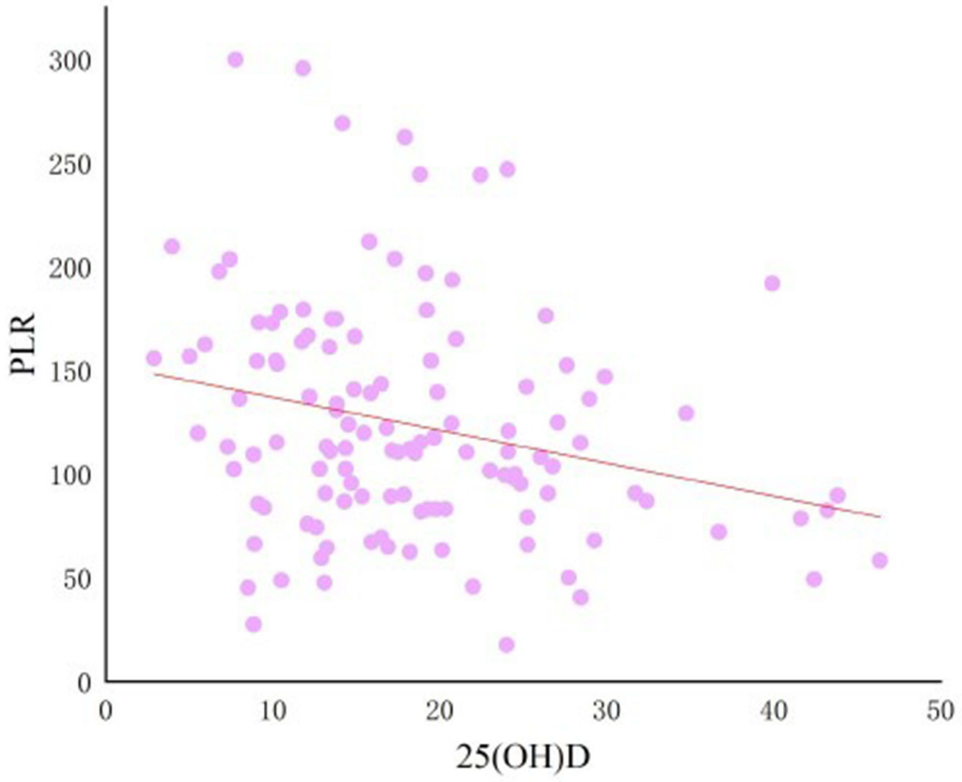

Figure 2 Correlation between 25 (OH) D and PLR.
Abbreviations: PLR, platelet/lymphocyte ratio; 25(OH)D, 25-hydroxyvitamin D.

Table 3 The Correlation Between 25 (OH) D and Novel Inflammatory Indicators in PBC Patients

	r	*P* value
LMR	0.116	0.203
NLR	−0.073	0.421
PLR	−0.252	0.005

Abbreviations: LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio.

UDCA Treatment Response in PBC Patients

The good response group had an LMR of 6.09±2.34, higher than the poor response group (4.48 [3.00, 5.98]). The NLR was 1.56 (1.11, 1.97) in the good response group, lower than the poor response group (1.92 (1.55, 3.08)). Both differences were statistically significant ($P<0.01$). There was no significant difference in PLR between the two groups ($P>0.05$) (Table 4).

Through single factor binary logistic regression preliminary screening, it was found that besides the factors influencing response specified in the Paris I criteria, LMR, NLR, ALT, ALB, and GGT also significantly affect the treatment response in PBC patients (Table 5).

Consequently, ROC curves were drawn to analyze the predictive value of LMR, NLR, ALT, ALB, and GGT for UDCA treatment response (Table 6 and Figure 3).

LMR: The area under the curve (AUC) was 0.682±0.049, with an optimal cutoff value of 6.0167. At this cutoff, the sensitivity was 0.486, and the specificity was 0.796.

NLR: The AUC was 0.630±0.052, with an optimal cutoff value of 2.1376. At this cutoff, the sensitivity was 0.811, and the specificity was 0.49.

Perform multiple logistic regression analysis on the statistically significant factors in the single factor regression analysis, and the specific results are shown in Table 7.

Table 4 Comparison of UDCA Treatment Response

	Good Response Group (n=74)	Poor Response Group (n=49)	*P* value
Age (years)	55.54±10.54	55.74±10.72	0.921
Gender (M/F)	4/70	9/40	0.034
LMR	6.09±2.34	4.48 (3.00, 5.98)	0.001
NLR	1.56 (1.11, 1.97)	1.85 (1.33, 2.80)	0.015
PLR	111.64 (82.94, 152.65)	130.55±1.05	0.238
ALT (U/L)	25.75 (17.50, 41.50)	56.40 (25.56, 89.40)	0.000
AST (U/L)	30.00 (22.75, 43.35)	48.90 (33.25, 84.60)	0.000
ALB (g/L)	44.60 (41.75, 47.53)	42.40 (38.45, 45.50)	0.011
TB (μmol/L)	12.08 (8.53, 14.45)	20.70 (18.22, 28.40)	0.000
ALP (U/L)	114.00 (87.00, 162.48)	167.10 (127.00, 232.00)	0.001
GGT (U/L)	62.50 (26.75, 158.00)	148.00 (40.00, 303.50)	0.015
25(OH)D (μg/L)	16.19 (11.78, 24.03)	17.15 (13.18, 24.10)	0.565

Abbreviations: M, male; F, female; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; ALP, alkaline phosphatase; GGT, γ- glutamyl transpeptidase; 25(OH)D, 25-hydroxyvitamin D.

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Table 5 Single Factor Logistic Regression Results

	OR	95% CI	*P* value
Gender	3.105	0.973~9.910	0.056
LMR	0.775	0.649~0.924	0.005
NLR	1.793	1.183~2.718	0.006
ALT (U/L)	1.025	1.011~1.039	0.000
AST (U/L)	1.044	1.023~1.056	0.000
ALB (g/L)	0.906	0.824~~0.976	0.009
TB (μmol/L)	1.295	1.172~1.432	0.000
ALP (U/L)	1.008	1.003~1.013	0.001
GGT (U/L)	1.003	1.001~1.006	0.010

Abbreviations: LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; ALP, alkaline phosphatase; GGT, γ- glutamyl transpeptidase.

Table 6 ROC Curve Related Results

	AUC	95% CI	*P* value
LMR	0.682±0.049	0.586~0.777	0.001
NLR	0.630±0.052	0.527~0.732	0.015
ALT (U/L)	0.689±0.052	0.586~0.792	0.000
ALB (g/L)	0.635±0.051	0.536~0.735	0.011
GGT (U/L)	0.630±0.053	0.526~0.735	0.015

Abbreviations: LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; ALT, alanine aminotransferase; ALB, albumin; GGT, γ- glutamyl transpeptidase.

Discussion

PBC is an autoimmune disease involving both innate and adaptive immune cells in its pathogenesis. The primary pathological basis of PBC is the immune-mediated destruction of intrahepatic bile duct epithelial cells, predominantly

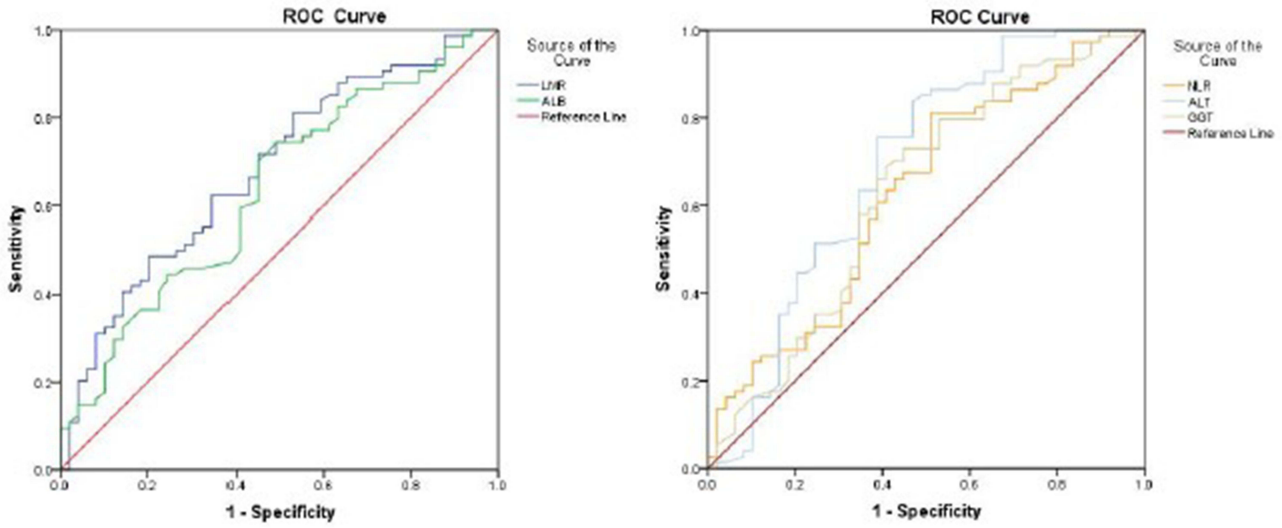

Figure 3 ROC curve for predicting UDCA treatment response.
Abbreviations: LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; ALT, alanine aminotransferase; ALB, albumin; GGT, γ- glutamyl transpeptidase.

Table 7 Multivariate Logistic Regression Results

	OR	95% CI	*P* value
LMR	0.878	0.540~1.428	0.600
NLR	1.628	0.561~4.721	0.370
ALT (U/L)	1.034	0.990~1.081	0.135
AST (U/L)	1.050	0.993~1.109	0.085
ALB (g/L)	0.977	0.821~1.162	0.788
TB (μmol/L)	1.547	1.267~1.889	0.000
ALP (U/L)	1.010	0.999~1.021	0.087
GGT (U/L)	0.995	0.989~1.001	0.134

Abbreviations: LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALB, albumin; TB, total bilirubin; ALP, alkaline phosphatase; GGT, γ- glutamyl transpeptidase.

characterized by T lymphocyte infiltration, with the participation of various other immune cells.[14] In the biliary system, different types of T cells, such as $CD4^+$ T cells and $CD8^+$ T cells, are present, and alterations in their levels can lead to an imbalance in intrahepatic immune responses, resulting in bile duct epithelial cell damage.[15] Among them, $CD8^+$ T cells can cause tissue damage through cytotoxic effects, making them the main effector cells in bile duct epithelial injury. In PBC patients, a significant increase in $CD14^{low}$and $CD16^+$ monocytes is observed in peripheral blood, which is associated with the extent of liver damage.[16] Changes in the levels of immune cells in the body are correlated with liver and bile duct injury.

LMR can predict the prognosis of various liver diseases, including survival after radiofrequency ablation of hepatocellular carcinoma and mortality in HBV-related cirrhosis. A lower LMR is associated with a poorer prognosis,[8,17] and it can also be associated with a higher chance of acute-on-chronic liver failure, reflecting the patient's prognosis.[10] Currently, there are no studies or reports on the relationship between LMR and the prognosis of patients with PBC, and previous research has not mentioned the difference in LMR between PBC patients and healthy individuals. This study found that the LMR in the PBC group was significantly lower than that in the physical examination group, and the LMR in the group with poor UDCA treatment response was lower than that in the good response group, suggesting that LMR may have predictive value for UDCA treatment response, with LMR < 6.0167 possibly indicating a poor response to UDCA treatment. Therefore, it is preliminarily considered that a low LMR is more likely to associated with an occurrence of a poor response to UDCA treatment, leading to relatively poor prognosis.

PBC pathological staging is divided into four stages: cholangitis stage (stage I), periportal inflammation stage (stage II) as early stages, and progressive fibrosis stage (stage III), cirrhosis stage (stage IV) as late stages. Studies have found that NLR (Neutrophil-to-Lymphocyte Ratio) is higher in late-stage PBC patients than in early-stage patients. NLR has certain clinical value in assessing the degree of liver damage in PBC patients, with NLR ≥ 1.8 being an independent risk factor for severe liver damage, and its elevation indicating disease progression.[4,5] ZHU[18] found that a high NLR is an independent risk factor for poor UDCA treatment response, but there is currently no specific consensus on the normal range of NLR. The study by Liu Tingting[9] showed that NLR in PBC patients is significantly higher than in healthy controls, and NLR levels can significantly decrease after treatment in PBC patients, with no statistically significant difference in PLR between PBC patients and healthy individuals. Our study results show no statistically significant differences in NLR and PLR between PBC patients after treatment and the physical examination group. However, among PBC patients, the NLR in the good UDCA response group was lower than in the poor response group, consistent with previous research results, supporting that a high NLR indicates a poor treatment response. After plotting the ROC curve, it was found that NLR>2.1376 indicates poor response to UDCA treatment, which is consistent with previous research results and also supports the idea that high NLR indicates poor treatment response.

VD deficiency is common in patients with chronic liver disease,[19] and VD deficiency is independently associated with advanced liver fibrosis.[20] PBC patients have significantly lower VD levels than the physical examination group, even lower than patients with other types of cirrhosis, possibly due to both synthetic and absorption disorders of VD in PBC patients. Additionally, studies suggest that low VD levels may be an independent pathogenic factor for PBC,[21] and a decrease in VD levels may indicate disease progression.[22] Serum VD levels are significantly associated with the risk of incomplete response to UDCA, with lower baseline VD levels more likely to result in a poor response.[23] In the study by GUO,[24] VD levels were negatively correlated with cholestasis markers and positively correlated with ALB (Albumin), with late-stage patients having higher rates of VD deficiency than early-stage patients. Patients with poor UDCA response had significantly lower pre-treatment VD levels than those with good response, and VD deficiency was independently associated with an increased risk of poor UDCA treatment response. In this study, there were no significant statistical differences in treatment response rates and liver function indicators between different VD level groups, which differs from previous research results. This discrepancy may be due to the relatively small sample size, and the significantly fewer patients in the VD sufficient group compared to the VD deficient group, which may have influenced the study results.

Scholars have found that increasing serum VD levels has a protective effect on PBC.[21] In the study by GUO et al[24] it was found that the VD deficiency rate in late stage PBC patients was higher than that in early stage patients. Studies have indicated that among novel inflammatory indicators, NLR and PLR are negatively correlated with VD levels,[13,25] while LMR is positively correlated with VD levels and serves as a protective factor against acute-on-chronic liver failure in cirrhosis.[10] Our study results show that VD levels in PBC patients are negatively correlated with PLR, suggesting that higher PLR is more likely to lead to an occurrence of a poor response to UDCA treatment, based on previous related research results.

Conclusion

In conclusion, low LMR and high NLR may indicate a poor treatment response in PBC patients, and PLR also has certain predictive values. But this conclusion still needs further confirmation through large-scale, multicenter studies in the future.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available because of further study in this area but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ordos Central Hospital, and all subjects provided written informed consent before participation in the study, which was performed in accordance with the relevant guidelines and regulations. Also this study complies with the Declaration of Helsinki.

Disclosure

The authors declare that they have no conflicts of interest in this work.

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