RESEARCH ARTICLE

The association between albumin-dNLR score and disease activity in patients with rheumatoid arthritis

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Background: Recently, clinical studies have described an association between albumin and the derived neutrophil to lymphocyte ratio (dNLR) with several diseases. This study was aimed to investigate the albumin-dNLR (ALB-dNLR) score in rheumatoid arthritis (RA) patients and assess its relationship with clinical and laboratory parameters of RA.

Methods: We retrospectively enrolled 127 RA patients, 155 osteoarthritis (OA) patients, and 155 healthy controls. The ALB-dNLR score was based on serum albumin level, neutrophil count, and white cell count. The Spearman's rank test was used to measure the correlations between ALB-dNLR score and disease activity as well as laboratory indexes.

Results: The ALB-dNLR score was significantly higher in RA patients than in OA patients ($P < 0.001$) and in healthy controls ($P < 0.001$). The proportion of higher ALB-dNLR score has been raised along with increased disease activity ($P < 0.001$). The Spearman's rank test showed that ALB-dNLR score was positively associated with DAS28 score, CRP, ESR, IgA, and platelet count. Moreover, the receiver operating characteristic (ROC) curve showed that the area under the curve (AUC) of ALB-dNLR was 0.693 (95% CI: 0.631-0.755), which was higher than that of albumin (AUC: 0.625, 95% CI: 0.559-0.692) and dNLR (AUC: 0.680, 95% CI: 0.617-0.743) alone.

Conclusions: The results demonstrate that the ALB-dNLR score increased in RA patients. The ALB-dNLR score may be a useful marker to estimate the disease activity of RA patients.

KEYWORDS

albumin-dNLR score, DAS28 score, disease activity, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a common inflammatory autoimmune disease characterized by disordered immunity and dysregulated cytokine.¹ The main clinical symptoms are symmetric joint involvement, synovial inflammation, and progressive articular damage, typically leading to physical disability, destruction of cartilage, and decreased quality of life.² Increasing evidences show that systemic inflammation and nutritional status are associated with RA patients.

Derived neutrophil to lymphocyte ratio (dNLR) was defined as the neutrophil count to (leukocyte-neutrophil count).³ Several evidences have demonstrated that systemic inflammation and malnutrition might be associated with disease activity of RA patients and might contribute to the pathogenesis and progression of RA.^{4,5} Circulating immune cells such as lymphocytes, neutrophils, and monocytes can reflect the severity of systematic inflammation.⁶ Albumin is a routine marker reflecting both nutritional status and systemic inflammation, while the synthesis of albumin

can be suppressed by systematic inflammation and malnutrition. Recent studies have demonstrated that serum albumin functions as an antioxidant in the host defense mechanism.^{7,8} The ALB-dNLR (albumin-dNLR) score consists of the serum albumin and derived neutrophil to lymphocyte ratio, indicating nutritional status and inflammatory conditions that are associated with the disease activity of RA patients, while there is no investigation about the associations between ALB-dNLR score and disease activity in RA patients.

Accordingly, we retrospectively collected clinical and laboratory data of RA patients, then investigate the correlation of the ALB-dNLR score with the laboratory characteristics and disease activities of RA patients.

2 | MATERIALS AND METHODS

2.1 | Patients identification

We retrospectively collected data on 286 RA patients in our hospital between January 2012 and August 2018. RA patients were diagnosed according to the rheumatoid arthritis classification criteria published in 2010 (American College of Rheumatology/European League Against Rheumatism).⁹ We collected the laboratory data and clinical characteristics, including age, sex, smoking and alcohol habits, disease duration, presence of morning stiffness, rheumatoid factor (RF), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, leukocyte and neutrophils counts. As multiple diseases could affect serum albumin, leukocyte, and neutrophils, one hundred and fifty-nine patients were excluded for having other autoimmune diseases, malignancies, infections, hypertension, diabetes mellitus, or cardiovascular diseases. Finally, we included 127 RA patients with complete information in the study and categorized them into three groups according the DAS28 score criteria: a score of DAS28 $\leq$ 3.2 was defined as low disease activity, $3.2 < \text{DAS28} \leq 5.1$ as moderate disease activity, and $\text{DAS28} > 5.1$ as high disease activity.¹⁰ In addition, 155 healthy subjects and 155 OA patients were included in this study. The present study was approved by the institutional ethics committee of Taizhou hospital of Zhejiang Province.

2.2 | dNLR and ALB-dNLR score

The derived neutrophil to lymphocyte ratio (dNLR) was calculated as neutrophils to (leukocyte-neutrophil count). The cutoff values of serum albumin concentrations and dNLR were set at 37.6 g/L and 1.37, respectively, based on the ROC curve. The ALB-dNLR score was classified into three groups based on each cutoff value of serum albumin and dNLR as follows: an ALB-dNLR score of 2 for patients with both hypoproteinemia (≤ 37.6 g/L) and high dNLR (> 1.37), an ALB-dNLR score of 1 for those with either of the two abnormalities, and an ALB-dNLR score of 0 for those with neither hypoproteinemia nor high dNLR.

2.3 | Statistical analysis

Mann-Whitney *U* test and Kruskal-Wallis *H* nonparametric test were used to compare the clinical and laboratory parameters between groups for continuous variables, and the results were shown as median (interquartile range [IQR]); Categorical data were analyzed by chi-square test and presented as frequencies and percentages.

TABLE 1 Clinical and laboratory characteristics of rheumatoid arthritis (RA) patients (n = 127)

	RA (n = 127)
Age (y)	56.0 (48.0-64.0)
Female, n (%)	95 (74.8)
Smoking history, n (%)	20 (15.7)
Alcohol intake, n (%)	19 (15.0)
ESR (mm/h)	46.0 (24.0-76.0)
CRP (mg/L)	7.1 (1.7-29.3)
Total protein (g/L)	69.5 (66.1-75.3)
Albumin (g/L)	39.8 (35.6-43.3)
Leukocyte ($\times 10^9$ /L)	5.8 (4.7-7.4)
Neutrophils ($\times 10^9$ /L)	3.7 (2.7-4.9)
Platelet ($\times 10^9$ /L)	258.0 (200.0-313.0)
dNLR	1.71 (1.38-2.23)
ALB-dNLR score	
0	22 (17.3)
1	66 (52.0)
2	39 (30.7)
Disease duration (y)	7.0 (3.0-10.0)
DAS28 score	4.2 (3.4-5.1)
Morning stiffness (n, %)	70 (55.1)
RF positive	92 (72.4)
Anti-CCP positive	99 (78.0)
Medications (n, %)	
NSAIDs	44 (34.6)
DMARDs	70 (55.1)
Methotrexate	52 (40.9)
Leflunomide	38 (29.9)
Sulfasalazine	19 (15.0)
Glucocorticoids	27 (21.3)
Chinese Medicine	20 (15.7)
No medication	12 (9.4)
Unknown	17 (13.4)

ALB-dNLR score, Albumin-dNLR score; Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS28 score, 28-joint count Disease Activity Score; DMARDs, disease-modifying anti-rheumatic drugs; dNLR (Derived neutrophil to lymphocyte ratio), Neutrophil count to (Leukocyte-Neutrophil count) ratio; ESR, Erythrocyte Sedimentation Rate; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor. Quantitative data are presented as median (IQR) or n (%), depending on the distribution.

TABLE 2 Clinical and laboratory characteristics of RA, OA patients and healthy controls

	RA (n = 127)	OA (n = 155)	P value	Healthy control (n = 155)	P value
Age (y)	56.0 (48.0-64.0)	63.0 (59.0-71.0)	<0.001	58.0 (49.0-64.0)	0.324
Female, n (%)	95 (74.8)	108 (69.7)	0.341	106 (68.4)	0.237
ESR (mm/h)	46.0 (24.0-76.0)	17.0 (9.0-26.0)	<0.001	10.0 (5.0-16.8)	<0.001
CRP (mg/L)	7.1 (1.7-29.3)	3.0 (2.2-4.7)	0.001	—	—
Leukocyte ($\times 10^9$ /L)	5.8 (4.7-7.4)	5.7 (4.9-6.7)	0.630	5.9 (5.1-6.8)	0.988
Neutrophils ($\times 10^9$ /L)	3.7 (2.7-4.9)	3.4 (2.7-4.0)	0.013	3.4 (2.8-4.0)	0.032
Platelet ($\times 10^9$ /L)	258.0 (200.0-313.0)	226.0 (185.0-261.0)	<0.001	227.0 (200.0-262.0)	0.001
Albumin (g/L)	39.8 (35.6-43.3)	41.5 (39.0-44.3)	<0.001	45.9 (44.3-47.8)	<0.001
dNLR	1.71 (1.38-2.23)	1.35 (1.10-1.78)	<0.001	1.36 (1.14-1.71)	<0.001
ALB-dNLR score (0/1/2)	22/66/39	66/81/8	<0.001	83/72/0	<0.001

ALB-dNLR score, Albumin-dNLR score; Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS28 score, 28-joint count Disease Activity Score; DMARDs, disease-modifying anti-rheumatic drugs; dNLR (Derived neutrophil to lymphocyte ratio), Neutrophil count to (Leukocyte–Neutrophil count) ratio; ESR, Erythrocyte Sedimentation Rate; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; RA, rheumatoid arthritis; RF, rheumatoid factor.

Quantitative data are presented as median (IQR) or n (%), depending on the distribution.

We also divided 127 RA patients into three groups according to the DAS28 score. The correlations between ALB-dNLR score and laboratory indexes were analyzed by the Spearman's correlation test. The receiver operating characteristic (ROC) curve was calculated to assess the prediction ability of RA by the ALB-dNLR. P value < 0.05 was considered as statistically significant. The analysis was performed using SPSS 22.0 statistical software (SPSS Inc., Chicago, IL, USA).

3 | RESULTS

3.1 | Comparison of ALB-dNLR score between RA patients, OA patients, and healthy controls

The main clinical and laboratory characteristics of 127 RA patients were summarized in Table 1. Ninety-five (74.8%) of the RA patients were female, and the median age was 56.0 (IQR, 48.0-64.0) years. The median disease duration and DAS28 score were 7.0 (IQR, 3.0-10.0) years and 4.2 (IQR, 3.4-5.1), respectively. Among the RA patients, 98 (77.2%) patients had taken medicine within the prior 2 months.

We compared the laboratory data among RA patients, OA patients and healthy group. As shown in Table 2, the median age of the RA patients was 56 years, which was lower than that of the healthy group (58 years) and the OA group (63 years). In the RA patients, the median albumin concentration was 39.8 g/L, significantly lower than that of the OA patients (41.5 g/L) ($P < 0.001$) and the healthy controls (45.9 g/L) ($P < 0.001$). In contrast, the level of dNLR was significantly higher in RA patients than in the OA patients ($P < 0.001$) or healthy controls ($P < 0.001$). According to the system of the ALB-dNLR score, 22 (17.3%), 66 (52.0%), and 39 (30.7%) RA patients had an ALB-dNLR score of 0, 1, and 2, respectively. In the OA patients, 66 (42.6%), 81 (52.3%), and 8 (5.1%) had an ALB-dNLR score of 0, 1, and 2, respectively. In the 155 healthy controls, 83 (53.5%) had an ALB-dNLR score of 0, and 72

(46.5%) had an ALB-dNLR score of 1 (Table 2). A high ALB-dNLR score was significantly more likely to be present in the RA patients, than in the OA patients and healthy controls ($P < 0.001$).

3.2 | Association of the ALB-dNLR score with disease activity of RA

The DAS28 score was used to classified RA patients into three groups (low, moderate, and high disease activity). 18.9% ($n = 24$) patients were classified as low disease activity ($\text{DAS28} \leq 3.2$), 55.9% ($n = 71$) as moderate disease activity ($3.2 < \text{DAS28} \leq 5.1$), and 25.2% ($n = 32$) as high disease activity ($\text{DAS28} > 5.1$). The gender, smoking habits, alcohol habits, and disease duration among three groups were not significantly different. The results showed that three (12.5%) patients had an ALB-dNLR score of 2 among the 24 patients in the $\text{DAS28} \leq 3.2$ group, 18 (25.4%) patients had an ALB-dNLR score of 2 among the 71 patients in the $3.2 < \text{DAS28} \leq 5.1$ group, and 18 (56.2%) patients had an ALB-dNLR score of 2 among the 32 patients in the $\text{DAS28} > 5.1$ group. The result demonstrated that patients with serious disease activity have higher proportion of high ALB-dNLR scores ($P < 0.001$) (Table 3). Additionally, we described in detail the usage of medication in the three groups of RA patients and found that the use of medication among different levels of disease activity of RA patients has no significant difference ($P > 0.05$), as shown in Table 3.

3.3 | Correlation between the ALB-dNLR score and laboratory data of RA patients

Table 4 presented the correlation between ALB-dNLR score and various laboratory variables in RA patients. The results indicated that ALB-dNLR score was positively correlated with DAS28 score

Variables	DAS28≤3.2 (n = 24)	3.2 < DAS28≤5.1 (n = 71)	DAS28>5.1 (n = 32)	P value
Age (y)	49.0 (44.0-58.8)	56.0 (49.0-64.0)	59.0 (50.5-65.0)	0.023
Female, n (%)	20 (83.3)	54 (76.1)	21 (65.6)	0.302
Smoking habit, n (%)	2 (8.3)	11 (15.5)	7 (21.9)	0.389
Alcohol habit, n (%)	4 (16.7)	12 (16.9)	3 (9.4)	0.595
Disease duration (y)	5.8 (1.0-10.0)	8.0 (3.5-16.0)	5.0 (3.0-10.0)	0.934
Morning stiffness, n (%)	10 (41.7)	32 (45.1)	28 (87.5)	<0.001
CRP (mg/L)	1.0 (0.0-1.0)	6.8 (1.9-20.7)	22.1 (5.8-58.2)	<0.001
ESR (mm/h)	14.0 (10.3-24.8)	51.0 (33.0-72.0)	76.5 (50.0-98.3)	<0.001
Leukocyte (×10 ⁹ /L)	5.4 (4.4-7.3)	5.8 (4.7-7.7)	6.0 (4.9-7.3)	0.750
Neutrophils (×10 ⁹ /L)	3.5 (2.4-4.9)	3.7 (2.5-4.8)	3.7 (3.2-5.2)	0.612
Albumin (g/L)	43.2 (40.8-46.8)	39.8 (36.6-42.6)	34.1 (30.1-41.1)	<0.001
dNLR	1.7 (1.2-2.3)	1.6 (1.3-2.1)	2.0 (1.4-2.7)	0.177
ALB-dNLR score (1/2/3)	6/15/3	12/41/18	4/10/18	0.004
RF(KU/L)	97.7 (26.1-181.6)	58.6 (20.0-264.0)	169.5 (48.9-426.0)	0.059
Medications, n (%)	21 (87.5)	52 (73.2)	25 (78.1)	0.246
NSAIDs	4 (16.7)	25 (35.2)	15 (46.9)	0.064
DMARDs	17 (70.8)	38 (53.5)	15 (46.9)	0.190
Methotrexate	14 (58.3)	28 (39.4)	10 (31.3)	0.118
Leflunomide	7 (29.2)	21 (29.6)	10 (31.3)	0.982
Sulfasalazine	7 (29.2)	10 (14.1)	2 (6.3)	0.057
Glucocorticoids	3 (12.5)	16 (22.5)	8 (25.0)	0.490
Chinese Medicine	2 (8.3)	11 (15.5)	7 (21.9)	0.389

ALB-dNLR score, Albumin-dNLR score; CRP, C-reactive protein; DAS28 score, 28-joint count Disease Activity Score; DMARDs, disease-modifying anti-rheumatic drugs; dNLR (Derived neutrophil to lymphocyte ratio), Neutrophil count to (Leukocyte-Neutrophil count) ratio; ESR, Erythrocyte sedimentation rate; NSAIDs, non-steroidal anti-inflammatory drugs; RF, rheumatoid factor.

Quantitative data are presented as median (IQR) or n (%), depending on the distribution.

TABLE 3 Comparison of Clinical and laboratory parameters among the three RA groups

($r = 0.323$, $P < 0.001$), CRP ($r = 0.463$, $P < 0.001$), and ESR ($r = 0.382$, $P < 0.001$). Moreover, we also found ALB-dNLR score was positively correlated with other laboratory data such as platelet count ($r = 0.195$, $P = 0.028$) and IgA ($r = 0.208$, $P = 0.034$) and negatively correlated with total protein ($r = -0.414$, $P < 0.001$).

To assess the diagnostic ability of the ALB-dNLR score in RA and OA patients and compare it with serum albumin and dNLR, we generated ROC curves and compared the area under the curve (AUC) values (Figure 1). The results showed that the ALB-dNLR had a higher AUC value (0.693, 95% CI = 0.631-0.755) than albumin (AUC: 0.625, 95% CI: 0.559-0.692) and dNLR (AUC: 0.680, 95% CI: 0.617-0.743) alone.

4 | DISCUSSION

The ALB-dNLR score, consisting of serum albumin and the derived neutrophil to lymphocyte ratio (dNLR), was established for measuring immune system and nutritional status. We therefore investigated

the relationship between the ALB-dNLR score and the disease activity of RA in our study. The results demonstrated that RA patients had higher ALB-dNLR scores than OA patients and healthy controls. A higher ALB-dNLR score was positively correlated with serious RA disease activity.

The roles of malnutrition and inflammation in regulating autoimmune diseases have been reported. Derived NLR (dNLR) was initially defined by Proctor et al as the neutrophil count to (leukocyte-neutrophil count).³ The leukocyte-neutrophil value in the denominator is broadly mixing lymphocytes and monocytes, which have potentially inversed effects from each other. Several studies have regarded dNLR as an inflammation marker that can reflect the severity of systematic inflammation in several cancers, such as non-small cell lung cancer,¹¹ colorectal cancer,¹² and breast cancer.¹³ Serum albumin has been considered to have anti-inflammatory and possible immunomodulatory properties¹⁴; therefore, if albumin synthesis was restricted by systematic inflammation, damage to the immune defense system of the patient could occur.¹⁵ Moreover, previous

studies have shown that serum albumin can reflect nutritional status. Fukuda et al reported that the level of albumin was decreased in RA patients who were also suffering from malnutrition.¹⁶ Several studies have reported that malnutrition is a common symptom in RA patients, and impairment of nutrition may affect the immune system, physical functions, and pathologic condition of RA.¹⁷ It has been reported that the low concentration of albumin in RA patients may owing to excessive albumin consumption caused by inflammatory substances.^{16,18}

Rheumatoid arthritis is a chronic representative autoimmune disease associated with inflammation and nutritional status.^{19,20} In our study, we assessed the ALB-dNLR score, which was based on

albumin and dNLR in RA patients. The results found that RA patients tend to have higher ALB-dNLR scores than OA patients or healthy controls. To confirm the relationship between the ALB-dNLR score and the disease activity of RA patients, we investigated the ALB-dNLR score among different level of disease activity of RA patients: high disease activity patients had higher ALB-dNLR scores than those in states of moderate or low disease activity, indicating a gradual impairment of the immune system and nutritional status along with increased disease activity. In addition, we also found a significant positive correlation between ALB-dNLR score and DAS28 in RA patients. As serum albumin might be affected by drug therapy, such as NSAIDs, methotrexate, and leflunomide,²¹⁻²³ we included the medication usage over the past two months in our study. The results showed that the medication usage among the three different disease activity groups exhibited no significant differences.

As is well known, ESR and CRP are considered as traditional inflammatory markers closely related to disease activity in RA patients. Our data demonstrated that ALB-dNLR was positively associated with CRP and ESR, as well as the DAS28 score. Moreover, we also observed that the ALB-dNLR score was positively correlated with platelet count and IgA, while no correlations were detected for RF and anti-CCP. We also observed that the diagnostic AUC of ALB-dNLR was superior to albumin and dNLR in distinguishing RA from OA patients, indicating that a combination of albumin and dNLR can improve the diagnostic effectiveness of RA. This is consistent with a previous study performed by Liu et al demonstrating that the combination of albumin and dNLR can improve the diagnostic effectiveness of pancreatic cancer (PCC).⁶

However, there were several limitations in our study, as it was a retrospective and single center study. The number of RA patients was small as we excluded patients with any concomitant diseases that may become the potential confounding factors. Therefore, further prospective studies including a large sample are needed to validate the clinical value of ALB-dNLR in RA patients. In addition, as the follow-up was not evaluated, its correlation with prognosis of RA was not analyzed.

TABLE 4 Correlation between ALB-dNLR score and laboratory variables in RA patients

Variables	<i>r</i>	<i>P</i> value
Disease duration (y)	0.003	0.971
DAS28 score	0.323	<0.001
RF (KU/L)	0.169	0.064
Anti-CCP (U/ml)	0.057	0.548
CRP (mg/L)	0.463	<0.001
ESR (mm/h)	0.382	<0.001
Platelet ($\times 10^9$ /L)	0.195	0.028
IgG (g/L)	0.099	0.317
IgA (g/L)	0.208	0.034
IgM (g/L)	-0.071	0.474
C3 (g/L)	-0.185	0.062
C4 (g/L)	-0.108	0.279
Total protein (g/L)	-0.414	<0.001

The analysis was conducted by Spearman's correlation. ALB-dNLR score, Albumin-dNLR score; Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DAS28 score, 28-joint count Disease Activity Score; ESR, Erythrocyte Sedimentation Rate; RF, rheumatoid factor.

FIGURE 1 The areas under the curves (AUC) of ALB-dNLR (A), dNLR (B), and ALB (C) in RA patients compared to OA patients. ALB, albumin; dNLR, derived neutrophil to lymphocyte ratio; OA, osteoarthritis; RA, rheumatoid arthritis

In conclusion, the present study demonstrated that ALB-dNLR score was significantly increased in patients with RA and positively correlated with disease activity. Since ALB-dNLR was determined by serum albumin and dNLR, which can be calculated easily and are readily available as routine laboratory tests, it could be a simple and effective clinical indicator that may be associated with risk for RA incidence.

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