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ORIGINAL ARTICLE

The association between the lymphocyte-monocyte ratio and disease activity in rheumatoid arthritis

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Abstract The lymphocyte-monocyte ratio (LMR) is a systemic inflammatory marker for prediction of disease development, progress, and survival. Recently, a genome-wide association study identified genetic variations in ITGA4 and HLA-DRB1 that affect the LMR levels and were widely believed to be susceptibility genes for autoimmune diseases, including rheumatoid arthritis (RA). However, the role of LMR in RA patients remains unclear. The LMR level and other laboratory data of 66 RA patients, 163 osteoarthritis (OA) patients, and 131 healthy controls (HC) were compared using binary logistic regression. The correlations between LMR and disease activity and other inflammatory markers were measured using the Spearman rank test. ROC curve analyses assessed the diagnostic accuracy of LMR in RA. The LMR and lymphocyte count were significantly lower in RA patients, whereas the monocyte count was significantly higher relative to the HC group/OA patients ($p < 0.01$). A decreased LMR has been associated with increased disease activity ($p = 0.012$). In addition, the DAS28 and traditional inflammatory markers, including ESR, CRP, RDW, PLR, and NLR, and immune-related factors, such as C4, IgA, and IgM, were inversely correlated with LMR, while hemoglobin and albumin were positively correlated with LMR. The ROC curve showed that the area under the curve of LMR was 0.705 (95%CI = 0.630–0.781). The corresponding specificity and sensitivity were 82.82 and 45.45%, respectively. The present study shows that the LMR is an important inflammatory marker which could be used to identify disease activity in RA patients and to distinguish RA from OA patients.

Keywords Disease activity · Inflammatory marker · Lymphocyte-monocyte ratio (LMR) · Rheumatoid arthritis (RA) · Disease Activity Score of 28 joints (DAS28)

Introduction

The lymphocyte-monocyte ratio (LMR), in addition to the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), is a simple biomarker of systemic inflammation [1] and has been examined as a prognostic predictor in various cancers, such as esophageal cancer [2], colorectal cancer [3], non-small-cell lung cancer [4], and pancreatic adenocarcinoma [5, 6]. Recently, a genome-wide association study determined that variants of ITGA4 and HLA-DRB1 were associated with LMR levels and monocyte counts [7]. Interestingly, these genetic variants have been considered as autoimmune disease susceptibility loci, especially for rheumatoid arthritis (RA) [8–10]. RA is a chronic systemic inflammatory disease with unknown etiology and is characterized by consistent synovial inflammation and joint deformity. Impaired immune system function contributes to the activation and progress of the disease. Higher levels of inflammatory markers are observed and correlate with high disease activities [11–13]. However, to our knowledge, the relationship between LMR and RA has not been established.

The aim of the present study was to determine LMR levels in RA patients and to explore their relation to clinical disease activities and other inflammatory markers, e.g., NLR, PLR,

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erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).

Patients and methods

Patients and study design

One hundred seventy-four consecutive patients diagnosed with RA at Taizhou Hospital of Zhejiang Province from January 2012 to December 2016 were enrolled in this retrospective cohort. All the patients fulfilled the 2010 ACR/EULAR for RA. Since LMR was an inflammatory marker and could be affected by various diseases, patients who had a history of other autoimmune diseases, cancers, or other persistent inflammatory diseases (e.g., hypertension, cardiovascular disease, infection, diabetes, and so on) were excluded. Therefore, 66 patients were remained in this study for further analysis. The disease activities of RA patients were measured by the Disease Activity Score of 28 joints (DAS28) system and divided into three groups: severe activity group (DAS28 ≥ 5.1), moderate activity group (3.2 ≤ DAS28 < 5.1), and low activity group (DAS28 < 3.2). Moreover, 163 consecutive hospitalized osteoarthritis (OA) patients and 131 healthy controls (HC) were randomly recruited to this study. The two control groups were confirmed to have no history of autoimmune diseases, hypertension, cardiovascular disease, cancers, diabetes, infection, or other inflammatory diseases. The study received approval from the institutional review board of the Ethics Committee of the Taizhou hospital of Zhejiang province.

Statistical analysis

Statistical analyses were conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA), and all the graphics were plotted with GraphPad Prism 5.0 (GraphPad Prism Software Inc., San Diego, CA, USA). All continuous variables were shown as medians (interquartile range, IQR). The LMR was defined as the lymphocyte count divided by the monocyte count. Binary logistic regression was performed to compare the medians of clinical and laboratory data between RA patients and OA/HC groups with adjustment for age and gender. Spearman correlation was conducted to evaluate the linear relationship between LMR and other laboratory data. The differences between three groups were determined by the Kruskal-Wallis H nonparametric test. The receiver operating characteristics (ROC) curve was used to assess the prediction accuracy of RA by LMR. The area under the curve (AUC), specificity, and sensitivity were also determined. A two-sided p value of < 0.05 was regarded as statistically significant.

Results

Lower LMR level in RA patients compared to OA patients and healthy controls

Table 1 gave detailed characteristics of RA patients, including disease duration, stiffness, RF positive rate, medication history, and so on. The median duration of RA was 5.5 (IQR = 2.8–10.0) years. Of the 66 RA patients, 52 (78.8%) were treated with medicine in recent 2 months. As shown in Table 2, there was a higher number of female RA patients (78.8%) than OA patients (69.3%) and healthy controls (64.1%). The median age of RA patients was higher than healthy controls but lower than the OA group (56, 43, and 63, respectively).

As age and gender might be confounding factors, logistic regression adjusted by gender and age was performed to compare the median of groups. In the RA group, the median of the lymphocyte count was 1.60×10^9/L. This was significantly lower than that of the HC group (1.94×10^9/L) and the OA group (1.90×10^9/L) ($p < 0.01$). In contrast, the monocyte count was remarkably higher compared to that of OA patients and the HC group ($p < 0.001$). Moreover, LMR levels of RA patients were significant lower than those of OA patients

Table 1 Demographic and clinical characteristics of RA patients ($n = 66$)

Variable	RA patients
Female *n* (%)	52 (78.8)
Age (years)	56 (47–66)
Disease duration	5.5 (2.8–10)
Stiffness	45 (68.2)
DAS28-ESR	4.47 (3.43–5.23)
RF positive[a]	44 (72.1)
Medicine use	
DMARDs	23 (34.8)
Methotrexate	15 (22.7)
Sulfasalazine	11 (16.7)
Leflunomide	9 (13.6)
NSAIDs	37 (56.1)
Meloxicam	7 (10.6)
Celecoxib	12 (18.2)
Prednisolone	15 (22.7)
Chinese medicine	14 (21.2)
No treatment	7 (10.6)
Unknown	7 (10.6)

Data were expressed as *n* (%) and median (interquartile range, 25th–75th)

DAS28-ESR 28-joint count Disease Activity Score using ESR, *RF* rheumatoid factor, *DMARDs* disease-modifying antirheumatic drugs, *NSAIDs* non-steroidal anti-inflammatory drugs

[a] 44 RF positive found in 61 RA patients due to lack of RF data in five patients

Table 2 Clinical characteristic of RA patients, OA patients and healthy control

	RA patients (66 cases) median (IQR)	Healthy control (131 cases) median (IQR)	P_{ad}	OR_{ad}(95%CI)	OA patients (163 cases) median (IQR)	P_{ad}	OR_{ad}(95%CI)
Age (y)	56 (47–66)	43 (36–52)	0.000	1.084 (1.052–1.118)	63 (59–71)	0.000	0.909 (0.877–0.942)
Female	52 (78.8)	84 (64.1)	0.006	0.341 (0.158–0.736)	113 (69.3)	0.430	0.746 (0.360–1.546)
Hemoglobin, g/L	112 (102–128)	141 (133–154)	0.000	0.896 (0.866–0.928)	134 (127–142)	0.000	0.894 (0.864–0.925)
Leukocytes, $\times10^9$/L	6.0 (5.0–7.8)	5.8 (5.0–6.6)	0.129	1.166 (0.956–1.423)	5.8 (5.1–6.8)	0.114	1.158 (0.966–1.389)
Neutrophils, $\times10^9$/L	3.70 (2.89–5.29)	3.18 (2.75–4.10)	0.009	1.404 (1.089–1.811)	3.50 (2.80–4.10)	0.009	1.304 (1.068–1.591)
Lymphocytes, $\times10^9$/L	1.60 (1.20–2.10)	1.94 (1.63–2.37)	0.003	0.340 (0.168–0.688)	1.90 (1.60–2.20)	0.002	0.384 (0.208–0.710)
Monocytes, $\times10^9$/L	0.40 (0.30–0.52)	0.32 (0.28–0.40)	0.000	245.591 (15.791–3819.507)	0.30 (0.30–0.40)	0.000	188.111 (14.432–2451.948)
Platelet, $\times10^9$/L	270 (223–331)	231 (193–262)	0.000	1.012 (1.006–1.017)	233 (185–270)	0.000	1.007 (1.003–1.011)
LMR	4.04 (3.08–5.50)	6.10 (4.69–7.20)	0.000	0.569 (0.451–0.717)	5.59 (4.20–6.97)	0.000	0.608 (0.491–0.752)
RDW	13.9 (13.2–15.1)	12.6 (12.3–13.1)	0.000	3.174 (2.113–4.768)	12.9 (12.5–13.3)	0.000	3.349 (2.161–5.190)
NLR	2.20 (1.78–3.21)	1.74 (1.34–2.16)	0.000	2.477 (1.581–3.882)	1.76 (1.40–2.33)	0.020	1.237 (1.033–1.480)
PLR	151(127–236)	116 (94–140)	0.000	1.023 (1.014–1.033)	121 (99–157)	0.001	1.007 (1.003–1.011)
CRP, mg/L	10.10 (2.75–32.45)	-	–	–	2.90 (2.15–4.40)	0.000	1.071 (1.034–1.109)
ESR, mm/h	35 (25–88)	10 (5–16)	0.000	1.140 (1.086–1.196)	16 (9–25)	0.000	1.069 (1.048–1.090)

Binary logistic regression analysis with adjustment age and gender was used to control confounding factors

LMR lymphocyte-monocyte ratio, *RDW* red distribution width, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate

($p < 0.001$, OR = 0.569, 95%CI = 0.451–0.717) and healthy controls ($p < 0.001$, OR = 0.608, 95%CI = 0.491–0.752). All the other inflammatory markers, such as ESR, NLR, PLR, and RDW, were significantly higher in RA patients than in OA patients or healthy controls ($p < 0.001$). The CRP level was also higher in the RA group than in the OA group (median: 10.10 vs. 2.90 mg/L).

Correlation of LMR levels with RA disease activity and laboratory data

According to the DAS28 scoring system, we divided the RA patients into three groups. There were no statistically significant differences in age and gender among the three groups ($p > 0.05$) (Table 3). A decreasing trend of LMR levels was observed along with increased disease activity (median, 5.33 vs. 4.68 vs. 3.13, $p < 0.05$, Table 3 and Fig. 1), while increasing trend observed in rheumatoid factor (RF) levels (median, 48.8 vs. 73.7 vs. 382.0 KU/L, $p = 0.037$, Table 3). Additionally, we measured detailed medication used in the three RA groups. The data showed that there was no difference in the proportion of medication (including DMARDs, NSAIDs, prednisolone, and Chinese medicine) used in different disease activity in RA patients ($p > 0.05$).

Analysis of correlations of LMR with DAS28, ESR, and CRP, the three most extensively used parameters for RA disease activity assessment, showed that all these indices were inversely correlated with LMR ($r = -0.299$, $p = 0.015$; $r = -0.350$, $p = 0.004$; $r = -0.250$, $p = 0.050$, respectively; Table 4 and Fig. 2). Moreover, we also found that LMR was negatively correlated with other inflammatory markers (NLR, $r = -0.628$, $p < 0.001$; PLR, $r = -0.684$, $p < 0.001$; RDW, $r = -0.326$, $p = 0.008$, respectively) and immune-related indices (IgM, $r = -0.259$, $p = 0.042$; IgA, $r = -0.280$, $p = 0.023$; C4, $r = -0.254$, $p = 0.047$, respectively). On the other hand, the levels of hemoglobin and albumin were positively correlated with LMR ($p < 0.05$).

ROC curve evaluation of LMR for RA diagnosis

As the LMR was lower in RA patients than in OA patients, we defined the OA patients as the "state variable." The area under the curve of LMR was 0.705 (0.630–0.781), with moderate diagnostic value (Fig. 3). The specificity of distinguishing RA from OA patients was 82.82% and the sensitivity was 45.45%. The diagnostic accuracy of LMR was similar to NLR (AUC = 0.668, 95%CI = 0.592–0.745) and PLR (AUC = 0.717, 95%CI = 0.644–0.789).

Discussion

The present study demonstrated that LMR was significantly decreased in RA patients compared to OA patients and healthy controls, especially RA patients with severe disease activity. Furthermore, the correlations between LMR and

Table 3 The association between LMR and RA disease activity

	DAS28 < 3.2 (n = 13)	3.2 ≤ DAS28 < 5.1 (n = 34)	DAS28 ≥ 5.1 (n = 19)	p value
Age (years)	51 (41–56)	58 (51–67)	55 (47–61)	0.110
Female, %	9 (69.2)	27 (79.4)	16 (84.2)	0.603
CRP (mg/L)	6.1 (2.5–11.4)	8.0 (2.3–28.9)	25.7 (6.7–63.4)	0.087
ESR (mm/h)	22.0 (12.5–27.5)	55.0 (39.0–82.5)	88.0 (70.0–104.0)	0.000
LMR	5.33 (3.50–5.71)	4.68 (3.56–5.53)	3.13 (2.50–3.80)	0.095
Medications	11 (84.6)	26 (76.5)	15 (78.9)	0.368
DMARDs	7 (53.8)	8 (23.5)	8 (42.1)	0.109
NSAIDs	4 (30.8)	20 (58.8)	13 (68.4)	0.097
Prednisolone	3 (23.1)	8 (23.5)	4 (21.1)	0.978
Chinese medicine	3 (23.1)	6 (17.6)	5 (26.3)	0.748
NLR	2.25 (1.76–3.32)	1.93 (1.74–2.86)	3.14 (1.84–4.12)	0.124
PLR	132 (115–202)	146 (119–221)	223 (155–253)	0.038
RF (KU/L)	48.8 (20.0–215.0)	73.7 (20.0–295.0)	382.0 (49.3–574.5)	0.037

LMR lymphocyte-monocyte ratio, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *DAS28* 28-joint count Disease Activity Score using ESR

disease activity and inflammatory markers were also revealed in this study.

Both monocytes and lymphocytes have been considered crucial for innate immunity and acquired immunity. LMR was first defined as a biomarker for infectious disease and a reflection of the balance between effector and host [14]. Iqbal and colleagues found that the LMR significantly increased after antituberculous therapy, and might be a systemic inflammatory marker to monitor the progress and treatment of tuberculosis [15]. Additionally, Cherfane et al. published a study in 2015 showing decreased LMR values in ulcerative colitis patients and a positive correlation with disease activities [16]. These findings support our results that lymphocytes and the LMR were remarkably decreased, and monocytes were significantly increased in RA patients compared to healthy controls, even in OA patients. In addition, decreased LMR values along with increased disease activity were observed, indicating a gradual impairment of lymphocyte/monocyte-mediated immunity. This is consistent with previous studies demonstrating that lymphopenia was a common complication that increased the risk of infection in autoimmune diseases [17, 18]. A decreased lymphocyte count and elevated $CD14^{bright}CD16^{+}$ monocyte levels [19], the major subset of monocytes in circulation, have been detected in RA patients. One reason might be due to that LMR level could be affected by gene variants in or near to the RA susceptibility loci, such as ITGA4, HLA-DRB1, and IRF8 [7, 20–22]. On the other hand, decreased lymphocyte count in peripheral blood is considered to be the result of persistent accumulation of lymphocytes at the sites of inflammatory joints and might be due to increased apoptotic markers such as heat shock protein 70 and caspase-3/7 in peripheral blood lymphocytes of RA patients [23]. Therefore, an aberrant lymphocyte-to-monocyte ratio might reflect systemic inflammation and the severity of immune injury.

However, it must be noted that lymphopenia is a common clinical manifestation induced by steroids and

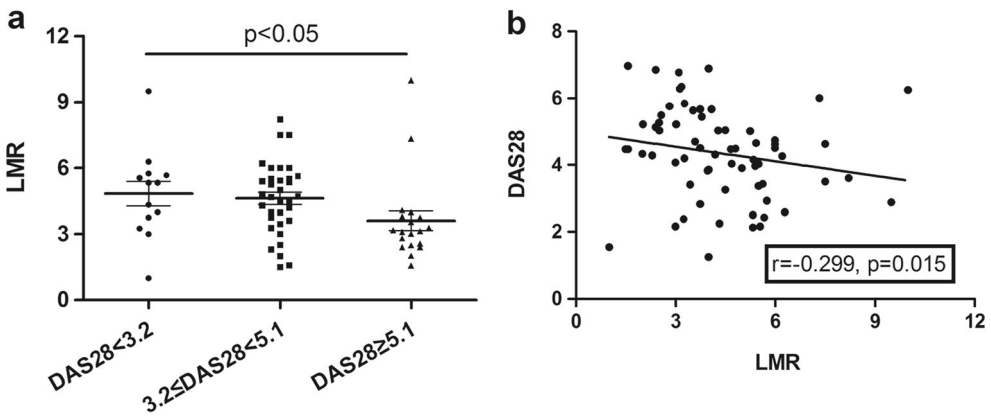

Fig. 1 Association between LMR and disease activity in RA patients. **a** Reduced LMR level along with increased disease activity. **b** The correlation between LMR and disease activity score (DAS28)

Table 4 Correlation between LMR and laboratory data

	LMR	
	r	*p*
ESR (mm/h)	− 0.349	0.004
DAS28	− 0.299	0.015
IgG (g/L)	− 0.235	0.057
IgA (g/L)	− 0.280	0.023
IgM (g/L)	− 0.259	0.042
C3 (g/L)	− 0.210	0.101
C4 (g/L)	− 0.254	0.047
Anti-CCP (U/ml)	− 0.050	0.763
CRP (mg/L)	− 0.250	0.050
NLR	− 0.628	0.000
PLR	− 0.684	0.000
Hemoglobin (g/L)	0.383	0.002
Platelet (10^9/L)	− 0.441	0.000
RDW	− 0.326	0.008
Albumin (g/L)	0.376	0.002
RF (KU/L)	− 0.154	0.271

The analysis was conducted by spearman correlation

LMR lymphocyte-monocyte ratio, *RDW* red distribution width, *NLR* neutrophil-lymphocyte ratio, *PLR* platelet-lymphocyte ratio, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RF* rheumatoid factor, *Anti-CCP* anti-cyclic citrullinated peptide antibody, *DAS28* 28-Joint Count Disease Activity Score using ESR

immunosuppressant in various autoimmune diseases as reported [17, 24, 25]. Thus, the reduced LMR level in our RA group might be caused by the influence of therapy, such as methotrexate, leflunomide, and glucocorticoids. However, we confused that why the LMR level was decreased along with increased disease activity, while no significant differences were found in medication usage among the three groups. A prospective longitudinal ESPOIR cohort of 813 recent-onset RA patients from Japan revealed that lymphopenia was often short-lived, even when DMARD or other therapy was prescribed [26], which indicated drugs were not the only factor contributed to the decreasing LMR level in RA, the disease itself or systemic inflammation might be another cause. The exact mechanism attributed to the reduction of LMR remains unclear and need further investigation.

The one certain thing was that LMR could be supported as a marker for disease activity reflection of degree of systemic inflammation. As we know, traditional inflammatory markers, such as ESR, CRP, RDW, NLR, and PLR, have been extensively explored and found to correlate well with disease activity in RA patients [27–30]. In our study, LMR exhibited negative correlation with DAS28 and these inflammatory markers, especially NLR and PLR. Moreover, ROC curves revealed that the AUC of LMR was similar to both NLR and PLR. This could be used to distinguish RA from OA patients, indicating a potential role for LMR in the diagnosis of RA. Interestingly, we also found that the LMR level was inversely correlated with platelet count and positively correlated with hemoglobin and albumin. This is consistent with previous findings that the risks of cardiovascular disease and anemia were relatively high in RA patients [31, 32]. Although relationships between LMR and C4, IgA and IgM were detected, no correlations showed for RF, anti-CCP, or IgG.

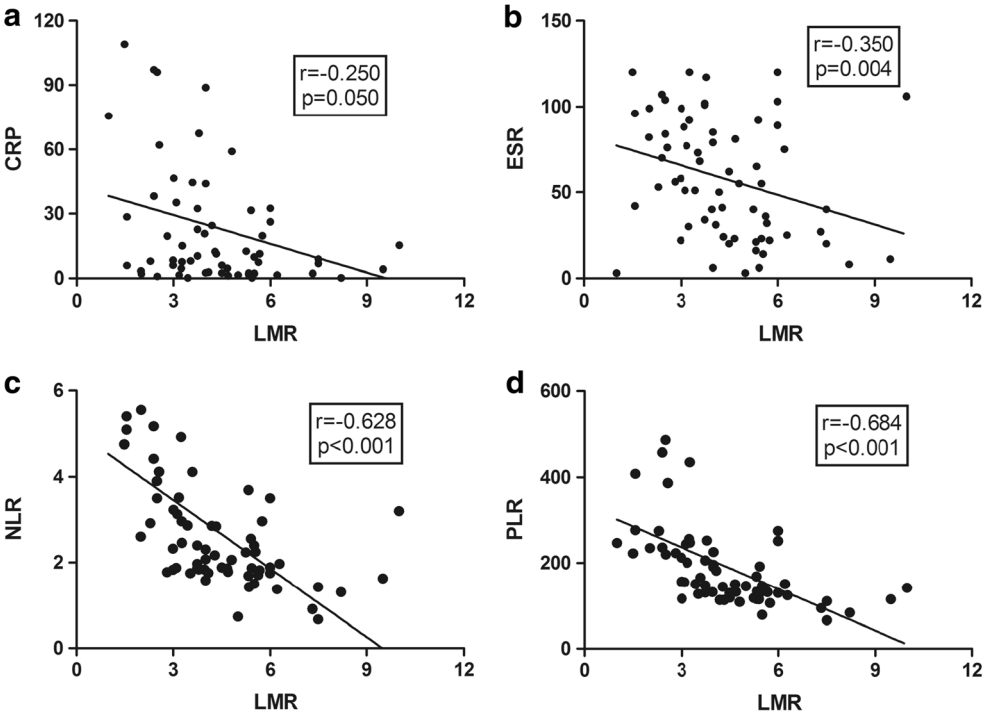

Fig. 2 The correlation between CRP (**a**), ESR (**b**), NLR (**c**), PLR (**d**), and LMR

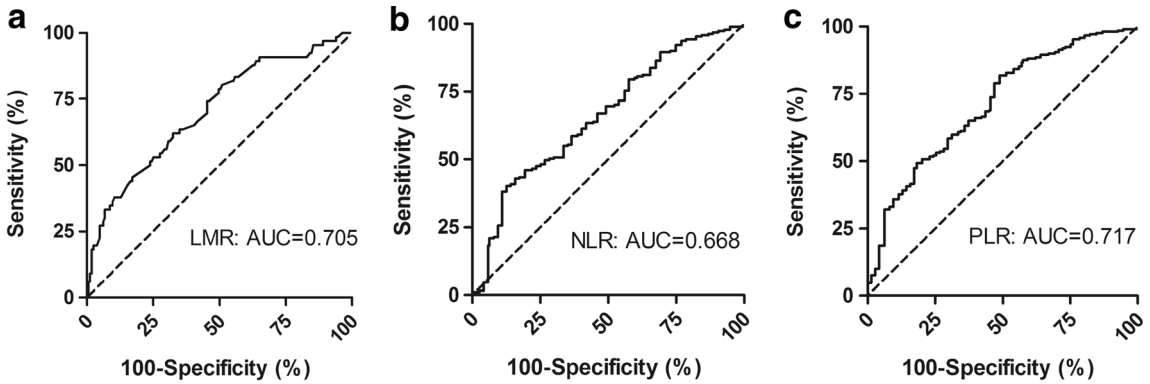

Fig. 3 Receiver operator curves of LMR (**a**), NLR (**b**), and PLR (**c**) in RA patients are compared to OA patients

The major limitations of our present study were the retrospective and single-center designs. Therefore, a multicenter prospective study is required in the future. The age and gender difference was another limitation in our study. Thus, we performed logistic regression with adjustment age and gender to eliminate these confounder factors. The sample size was relatively small because we excluded RA patients with the concomitant diseases that could affect LMR but, for this reason, the results of this study were relatively reliable. In addition, we did not take smoking and alcohol status into consideration due to a lack of detailed information. Finally, the relationship between LMR and RA progression did not demonstrate because of incomplete imaging data in RA patients.

In conclusion, we found a decreased LMR in RA patients relative to OA patients and healthy controls. Furthermore, LMR could be considered a new inflammatory marker to evaluate the disease activity of RA patients, since a relationship between LMR and DAS28 and other inflammatory markers have been detected. The present study also demonstrated a potential diagnostic value for LMR that should be confirmed in the future.

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Compliance with ethical standards

Disclosures None.

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