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Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio as predictors of 12-week treatment response and drug persistence of anti-tumor necrosis factor-α agents in patients with rheumatoid arthritis: a retrospective chart review analysis

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Abstract

Data are scarce regarding the association of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) with treatment response and persistence of anti-TNF-α agents in patients with rheumatoid arthritis (RA). Thus, we investigated whether baseline NLR and PLR could predict 12-week treatment response and long-term persistence of anti-TNF-α agents in RA patients. This is a retrospective chart review analysis of 82 women with RA who started anti-TNF-α agents as the first-line biologic therapy and 328 healthy age-matched women. RA patients were divided into high and low baseline NLR or PLR subgroups using the median split. European League against Rheumatism (EULAR) treatment response was evaluated at 12 weeks. RA patients had significantly higher NLR and PLR than controls. High baseline NLR and PLR groups showed higher 12-week EULAR non-response rate than low NLR (30% vs 7.1%, $p=0.01$) and PLR groups (27.5% vs 9.5%, $p=0.047$), respectively. After adjusting for confounding factors, high baseline NLR (OR 5.57, $p=0.014$) and PLR (OR 4.24, $p=0.04$) were significantly associated with a higher risk of EULAR non-response at 12 weeks. During the study period, 47 (57.3%) RA patients (lack of efficacy: $n=31$; adverse events: $n=16$) discontinued anti-TNF-α agents. High baseline NLR was associated with an increased risk of anti-TNF-α agent withdrawal due to lack of efficacy (HR 2.12, $p=0.045$). Our data suggest that baseline NLR and PLR are useful markers for predicting the treatment outcome of anti-TNF-α agents in RA patients.

Keywords Rheumatoid arthritis · Tumor necrosis factor-alpha · Blood cells · Treatment outcome · Biomarkers

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory arthritis leading to joint destruction and disability; it has no cure and generally requires lifelong therapy with disease-modifying anti-rheumatic drugs (DMARDs) [1, 2]. The current goal of RA treatment focuses on the abrogation of inflammation (i.e., disease activity) to control symptoms and prevent structural damage [1]. Because of their well-established efficacy in controlling disease activity, anti-tumor necrosis factor-α (anti-TNF-α) agents have become a mainstay of treatment and initiating these agents is recommended for patients with RA who have an inadequate response to methotrexate

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(MTX) and/or other conventional DMARDs [3]. Although anti-TNF-α agents have revolutionized the management of RA, a substantial proportion (20–40%) of patients with RA do not respond or lose response over time and some RA patients do not tolerate these agents owing to adverse events [4, 5]. Actually, previous studies reported that the persistence rate of anti-TNF-α agents ranged from 60 to 80% for 1 year and from 40 to 70% for 2 years in RA patients [2]. Hence, there is need to identify potential predictors of treatment response and persistence regarding anti-TNF-α agents to optimize the management of RA.

Recently, accumulating evidence suggests that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used as markers of systemic inflammation in various diseases including malignancy and cardiac and inflammatory-mediated disorders [6–15]. Increased NLR and PLR have also been reported to be associated with a poor prognosis in patients with cancer and cardiovascular diseases [6, 8]. In a recent meta-analysis, NLR and PLR were significantly higher in patients with RA than in healthy subjects [12]. In addition, NLR and PLR were positively correlated with disease activity and the levels of acute-phase reactants and were predictive of sustained remission in RA patients in previous studies [16–21]. These findings suggest that NLR and PLR can serve as less expensive and useful markers with prognostic significance in RA. However, there are few data regarding the association of NLR and PLR with treatment response and persistence of anti-TNF-α agents in RA patients. Thus, the primary objective of the present study was to investigate whether baseline NLR and PLR could predict treatment response at 12 weeks and long-term persistence of anti-TNF-α agents in patients with RA in clinical practice.

Methods

Study design and population

This was a retrospective cohort study performed in a university-affiliated tertiary hospital in South Korea. We evaluated 82 female biologics-naïve patients with RA who started anti-TNF-α agents as the first-line biologic therapy due to inadequate response to MTX and/or conventional DMARDs treatment between January 2007 and October 2017. We also evaluated 246 age-matched (±2 years) female healthy subjects. Because of the small numbers of male RA patients treated with anti-TNF-α agents as the first-line biologic therapy in our center, we only analyzed female patients with RA. The following anti-TNF-α agents available during the study period in our hospital were investigated: subcutaneous etanercept, subcutaneous adalimumab, and intravenous infliximab. The date of the first dispensation of anti-TNF-α agents was defined as the index date. Patients with RA who had were treated with anti-TNF-α agents for 12 weeks or more and followed for at least 24 weeks after the index date were included. All RA patients met the 1987 American College of Rheumatology (formerly American Rheumatism Association) revised classification criteria for RA [22]. The decision to initiate anti-TNF-α agents was made by experienced rheumatologists based on clinical need and national reimbursement criteria. In Korea, patients with RA can receive reimbursement for anti-TNF-α agents if the 28-joint count for swelling and tenderness (DAS28) > 5.1, despite, at least, 6 months of therapy with two or more conventional DMARDs, one of which should be MTX. The following RA patients were excluded: those (1) below 18 years at the time of the index date; (2) who started anti-TNF-α agents for the treatment of a disease other than RA; (3) with anti-TNF-α therapy lasting less than 12 weeks; (4) with exposure to biologic agents before the index date; and (5) with concomitant hematologic diseases or active infection. All RA patients who met the inclusion and exclusion criteria in our hospital were evaluated in this study. Healthy subjects having no history of rheumatic or autoimmune diseases were selected from individuals that underwent annual health check-ups in the same hospital. Eligible study subjects were identified by electronic medical record system in our hospital. Data were collected using a standardized data abstract form and a trained data collector (HN Lee) collected all data under the supervision of the principle investigator (SG Lee). This study protocol was approved by the Research and Ethical Review Board of Pusan National University Hospital, which waived written informed consent due to the study's retrospective design (IRB no. 1809-010-071).

Clinical assessments

For patients with RA, the following baseline data at time of the index date were obtained by a review of medical records: age, disease duration, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), counts of white blood cells, neutrophils, lymphocytes and platelets, titer of immunoglobulin M-rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP) antibody, and the previous and current medications, including DMARDs and glucocorticoids. Disease activity score assessed using the 28-joint count for swelling and tenderness (DAS28)-ESR was calculated as $= [0.56 \times \sqrt{(\text{tender joint count 28})}] + [0.28 \times \sqrt{(\text{swolle joint count 28})}] + [0.70 \times \ln \text{ESR}] + [0.0014 \times \text{visual analog scale score}]$and DAS28-CRP was calculated as $[0.56\times \sqrt{(\text{tender joint count 28})}] + [0.28 \times \sqrt{(\text{swolle joint count 28})}] +[0.36 \times \ln(\text{CRP} + 1)] + [0.0014 \times \text{visual analog scale score}] +0.96$ [23, 24]. NLR and PLR were calculated as dividing the absolute neutrophil count by the absolute lymphocyte count and the absolute platelet count by the absolute

lymphocyte count, respectively. NLR, PLR, ESR, CRP, DAS28-ESR, and DAS28-CRP were also evaluated 12 and 24 weeks after the index date. RF titer was assessed using a particle-enhanced immunoturbidimetric assay (range 0–14 IU/mL) and anti-CCP antibody titer was determined using a chemiluminescent microparticle immunoassay (range 0–5 U/mL). For healthy controls, the following data at baseline were collected: age, CRP, counts of white blood cells, neutrophils, lymphocytes, and platelets, and NLR and PLR.

Assessment of treatment response and remission rate in patients with RA was conducted at 12 and 24 weeks. The European League against Rheumatism (EULAR) response criteria was used to measure treatment response to anti-TNF-α agents. Good response was defined as a decrease in DAS28-ESR > 1.2 and DAS28-ESR ≤ 3.2, and non-response was defined as a decrease in DAS28-ESR ≤ 0.6 or a decrease of 0.6 12 with DAS28-ESR > 5.1 [25]. Any scores between good response and non-response were defined as moderate response [25]. Remission was defined as DAS28-ESR < 2.6. The primary outcome of interest was whether baseline NLR or PLR could predict EULAR non-response to anti-TNF-α agents at 12 weeks in patients with RA.

Persistence was defined as the time interval between the index date (the first prescription) and the first discontinuation of anti-TNF-α agents or the end of the study period (31 October 2018). Switching to another biologic agents including anti-TNF-α agents, tocilizumab, abatacept, or rituximab was considered as discontinuation [26]. A patient was considered to exhibit non-persistence to anti-TNF-α agent when a prolonged interruption of therapy (permissible gap) had lasted for 90 days or more. The permissible gap most frequently used in previous studies investigating the persistence of anti-TNF-α agents in RA patients was 90 days [27–29] while other studies employed 30 days [26], 45 days [30] or 6 months [31]. The reasons for the discontinuation of anti-TNF-α agents were categorized as lack of efficacy (LOE) and adverse events [2].

Statistical methods

All statistical analyses were performed using STATA 15.0 (StataCorp, LP, College Station, Texas) and statistical significance was set at a p value of less than 0.05. Descriptive statistics are reported as mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables as appropriate, and as number of cases with percentages for categorical variables. The Kolmogorov–Smirnov test was used to determine the normality of the data. Group comparisons were conducted with the Student's t test, paired t test, Mann–Whitney U test, and Wilcoxon signed-rank test for continuous variables as appropriate, and with the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Pearson's or Spearman's correlation analyses were used to assess the correlations among clinical and laboratory variables. The independent association between baseline NLR or PLR values and the likelihood of EULAR non-response at 12 weeks was assessed using backward multivariable logistic regression models, including variables with clinical relevance and significant results from univariable analyses. Because baseline NLR and PLR showed a high correlation ($\rho = 0.788$), these variables were included in separate logistic regression models to avoid multicollinearity. Persistence of anti-TNF-α agents was computed using Kaplan–Meier methods, and whether baseline NLR or PLR values were predictive of anti-TNF-α agent discontinuation was evaluated with Cox-proportional hazard regression models with backward selection.

Results

Baseline clinical characteristics in 82 patients with RA and 246 healthy controls are summarized in Table 1. Compared with healthy controls, patients with RA had significantly higher median NLR [3.43 (2.35–5.32) vs 1.37 (1.02–1.75), $p < 0.001$], PLR [168.67 (131.03–236.75) vs 125 (102.8–151.1), $p < 0.001$], and CRP [1.8 (0.58–3.15) mg/dL vs 0.03 (0.02–0.07) mg/dL, $p < 0.001$]. The mean DAS28-ESR and DAS28-CRP in RA patients were 6.61 ± 0.9 and 5.84 ± 0.92, respectively. Sixty-three (76.8%), 15 (19.3%), and 4 (4.9%) RA patients started treatment with adalimumab, etanercept, and infliximab, respectively (Table 1). The flow diagram of the current study is depicted in Fig. 1. All patients with RA were taking MTX at the index date. Changes in NLR, PLR, DAS28-ESR, DAS28-CRP, and treatment response over 24 weeks are described in Supplementary Table 1. The frequencies of RA patients achieving good response, moderate response, non-response, and remission were 20.7%, 61%, 18.3%, and 9.8%, respectively, at 12 weeks and 48%, 43.8%, 8.2%, and 21.9%, respectively, at 24 weeks, and NLR, PLR, DAS28-ESR, and DAS28-CRP significantly decreased over time (Supplementary Table 1).

Patients with RA were divided into high and low baseline NLR or PLR subgroups using the median split and comparisons of clinical and laboratory data according to these subgroups are shown in Table 2. Baseline DAS28-ESR and DAS28-CRP were significantly higher in the high baseline NLR groups than in the low baseline NLR groups. RA patients with high baseline NLR showed a significantly higher frequency of non-response at 12 weeks than those with low NLR (30% vs 7.1%, $p = 0.01$), but the proportion of RA patients showing non-response at 24 weeks did not significantly differ between high and low baseline NLR groups. In addition, the frequency of non-response at 12 weeks was significantly higher in RA patients with high

Table 1 Baseline clinical characteristics in patients with rheumatoid arthritis and healthy controls

	Patients with RA ($n=82$)	Healthy controls ($n=246$)	p value
Age, years, mean ± SD	45.3 ± 11.1	46.6 ± 9	0.312
NLR, median (IQR)	3.43 (2.35–5.32)	1.37 (1.02–1.75)	< 0.001
PLR, median (IQR)	168.67 (131.03–236.75)	125 (102.8–151.1)	< 0.001
CRP, mg/dL, median (IQR)	1.8 (0.58–3.15)	0.03 (0.02–0.07)	< 0.001
Female, *n* (%)	82 (100)	328 (100)	–
Disease duration, months, median (IQR)	17.1 (4.3–54)		
RF positivity, *n* (%)	75 (91.5)		
Anti-CCP antibody positivity, *n* (%)	63/69 (91.3)		
ESR, mm/hr, median (IQR)	46.5 (32.8–65)		
DAS28-ESR, mean ± SD	6.61 ± 0.9		
DAS28-CRP, mean ± SD	5.84 ± 0.92		
Anti-TNF-α agents			
Adalimumab, *n* (%)	63 (76.8)		
Etanercept, *n* (%)	15 (19.3)		
Infliximab, *n* (%)	4 (4.9)		
Previous DMARDs			
MTX, *n* (%)	81 (98.8)		
SSZ, *n* (%)	20 (24.4)		
HCQ, *n* (%)	30 (36.6)		
LEF, *n* (%)	41 (50)		
TAC, *n* (%)	14 (17.1)		
Number of previous DMARDs			
1, *n* (%)	10 (12.2)		
2, *n* (%)	57 (69.5)		
≥ 3, *n* (%)	15 (18.3)		
GCs, *n* (%)	79 (96.3)		
GCs dose, mg, median (IQR)	5 (5–7.5)		

RA rheumatoid arthritis, *SD* standard deviation, *NLR* neutrophil-to-lymphocyte ratio, *IQR* interquartile range, *PLR* platelet-to-lymphocyte ratio, *CRP* C-reactive protein, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *ESR* erythrocyte sedimentation rate, *DAS28* disease activity score using the 28-joint count for swelling and tenderness, *TNF-α* tumor necrosis factor-alpha, *MTX*, methotrexate, *SSZ* sulfasalazine, *HCQ* hydroxychloroquine, *LEF* leflunomide, *TAC* tacrolimus, *DMARDs* disease modifying anti-rheumatic drugs, *GCs* glucocorticoids

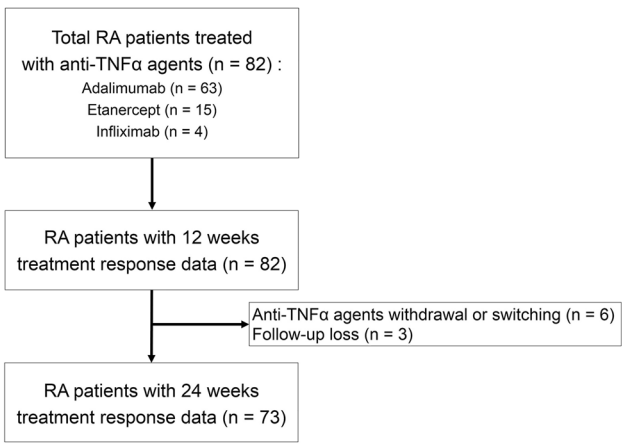

Fig. 1 Flow diagram of the current study

baseline PLR than in those with low baseline PLR (27.5% vs 9.5%, $p=0.047$), while the difference in the frequency of non-response at 24 weeks was not significant between these two groups. The rate of remission at 12 weeks and 24 weeks did not significantly differ according to the level of baseline NLR or PLR values.

Correlations between laboratory and clinical parameters including NLR, PLR, DAS28-ESR, and DAS28-CRP are presented in Table 3. Baseline NLR and PLR showed significantly positive correlations with baseline DAS28-ESR, DAS28-CRP, ESR, and CRP. Twelve-week changes in NLR and PLR were significantly and positively correlated with 12-week changes in DAS28-ESR, DAS28-CRP, ESR, and CRP. These findings suggest that NLR and PLR were highly correlated with the levels of acute-phase reactants and disease activity in RA patients. Significant positive correlations

Table 2 Comparisons of clinical features and treatment response of anti-tumor necrosis factor-α agents in patients with rheumatoid arthritis according to the levels of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

	Low baseline NLR ($n=42$)	High baseline NLR ($n=40$)	p value	Low baseline PLR ($n=42$)	High baseline PLR ($n=40$)	p value
Age, years, mean ± SD	43.5 ± 11.8	47.3 ± 10.1	0.122	43.5 ± 12	47.3 ± 9.9	0.115
Female, *n* (%)	37 (88.1)	39 (95)	0.433	36 (85.7)	39 (97.5)	0.11
Disease duration, months, median (IQR)	26.9 (9.4–61.7)	9.4 (1.6–44.2)	0.031	21 (6.9–63.1)	2.5 (11.8–44.2)	0.122
RF positivity, *n* (%)	37 (88.1)	38 (95)	0.433	36 (85.7)	39 (97.5)	0.11
Anti-CCP antibody positivity, *n* (%)	33/35 (94.3)	30/34 (80.2)	0.428	32/35 (91.4)	31/34 (91.2)	0.97
Baseline DAS28-ESR, mean ± SD	6.42 ± 0.88	6.81 ± 0.9	0.049	6.55 ± 0.88	6.68 ± 0.94	0.52
Baseline DAS28-CRP, mean ± SD	5.62 ± 0.88	6.08 ± 0.92	0.023	5.79 ± 0.83	5.9 ± 1.02	0.583
DAS28-ESR at 12 weeks, mean ± SD	4.07 ± 1.1	4.41 ± 1.22	0.193	4.03 ± 1.1	4.43 ± 1.21	0.11
DAS28-CRP at 12 weeks, mean ± SD	3.22 ± 0.98	3.7 ± 1.14	0.042	3.25 ± 0.9	3.67 ± 1.22	0.077
EULAR response at 12 weeks						
Moderate to good response, *n* (%)	39 (92.9)	30 (70)	0.01	38 (90.5)	29 (72.5)	0.047
Non-response, *n* (%)	3 (7.1)	12 (30)		4 (9.5)	11 (27.5)	
Remission[a] at 12 weeks, *n* (%)	6 (14.3)	2 (5)	0.265	6 (14.3)	2 (5)	0.265
DAS28-ESR at 24 weeks, mean ± SD	3.66 ± 1.24	3.58 ± 1.44	0.804	3.61 ± 1.2	3.63 ± 1.47	0.951
DAS28-CRP at 24 weeks, mean ± SD	2.93 ± 1.16	2.85 ± 1.33	0.773	2.91 ± 1.11	2.88 ± 1.38	0.916
EULAR response at 24 weeks						
Moderate to good response, *n* (%)	36/40 (90)	31/33 (93.9)	0.683	36/39 (92.3)	31/34 (91.2)	0.861
Non-response, *n* (%)	4/40 (10)	2/33 (6.1)		3/39 (7.7)	3/34 (8.8)	
Remission[a] at 24 weeks, *n* (%)	7/40 (17.5)	9/33 (23.3)	0.398	7/39 (17.9)	9/34 (26.5)	0.41

NLR neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *SD* standard deviation, *IQR* interquartile range, *RF* rheumatoid factor, *CCP* cyclic citrullinated peptide, *DAS28* disease activity score using the 28-joint count for swelling and tenderness, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *EULAR* the European League against Rheumatism

[a]Defined as DAS28-ESR less than 2.6

between baseline NLR and PLR and 12-week changes in NLR and PLR were also observed.

The associations of clinical and laboratory parameters with the risk of EULAR non-response at 12 weeks, assessed using logistic regression models, are shown in Table 4. After adjusting for confounding factors, high baseline NLR (OR 5.57, 95% CI 1.45–26.99, $p=0.014$) and PLR (OR 4.24, 95% CI 1.07–16.81, $p=0.04$) were independently associated with a higher risk of non-response at 12 weeks. Longer disease duration was also significantly related with a higher risk of non-response at 12 weeks. Otherwise, neither baseline NLR nor PLR showed significant associations with EULAR non-response at 24 weeks and remission at 12 weeks and 24 weeks (data not shown).

During the study period, discontinuation of anti-TNF-α agents occurred in 47 (57.3%) patients with RA (adalimumab, $n=36$; etanercept, $n=9$; and infliximab, $n=2$). The median follow-up duration was 23.1 (8.5–52.8) months. The 12, 24, and 60-week persistence rates were 68.9%, 57.8%, and 38.9%, respectively, and 50% of RA patients discontinued TNF-α agents 33.4 months after the index date (Supplementary Figure 1). Thirty-one (66%) and 16 (34%) patients discontinued anti-TNF-α agents due to LOE and adverse events, respectively. High baseline NLR or PLR did not show any significant relationship with a higher risk of discontinuation of anti-TNF-α agents (data not shown). Otherwise, high baseline NLR was associated with an increased risk of anti-TNF-α agent withdrawal due to LOE after adjustment for confounding factors (HR 2.12, 95% CI 1.02–4.44, $p=0.045$); however, this relationship was not observed in high baseline PLR groups (Supplementary Table 2). No significant factors for the discontinuation of anti-TNF-α agents due to adverse events were found in our data (data not shown).

Table 3 Correlations between laboratory and clinical parameters in patients with rheumatoid arthritis

	1	2	3	4	5	6	7	8	9	10	11
1. Baseline NLR	–	–	–	–	–	–	–	–	–	–	–
2. Baseline PLR	0.788**	–	–	–	–	–	–	–	–	–	–
3. Baseline DAS28-ESR	0.304*	0.248*	–	–	–	–	–	–	–	–	–
4. Baseline DAS28-CRP	0.342*	0.262*	0.938**	–	–	–	–	–	–	–	–
5. Baseline ESR	0.224*	0.352*	0.509**	0.383**	–	–	–	–	–	–	–
6. Baseline CRP	0.368*	0.375*	0.347**	0.503**	0.611**	–	–	–	–	–	–
7. 12-Week changes in NLR	0.626**	0.536**	0.245*	0.215	0.228*	0.197	–	–	–	–	–
8. 12-Week changes in PLR	0.56**	0.71**	0.263*	0.222*	0.24*	0.161	0.785**	–	–	–	–
9. 12-Week changes in DAS28-ESR	0.05	0.077	0.473**	0.452**	0.131	0.109	0.229*	0.324*	–	–	–
10. 12-Week changes in DAS28-CRP	0.05	0.067	0.471**	0.497**	0.113	0.182	0.242*	0.292*	0.956**	–	–
11. 12-Week changes in ESR	0.21	0.307*	0.351*	0.315*	0.588**	0.494**	0.266*	0.35*	0.499**	0.419**	–
12. 12-Week changes in CRP	0.213	0.235*	0.292*	0.413**	0.404**	0.692**	0.29*	0.273*	0.401**	0.485**	0.703**

NLR neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *DAS28* disease activity score using the 28-joint count for swelling and tenderness, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein

*$p < 0.05$, **$p < 0.001$

Discussion

In the present study, we found that elevated baseline NLR and PLR were associated with a higher risk of non-response to anti-TNF-α agents at 12 weeks, and high baseline NLR, but not high baseline PLR, showed a significant association with a greater risk of discontinuation of anti-TNF-α agents due to LOE in patients with RA. These findings propose that baseline NLR and PLR can be surrogate markers for predicting the clinical outcome of anti-TNF-α agent treatment in RA patients. NLR and PLR levels were positively correlated with disease activity measures (DAS28) and the levels of ESR and CRP both cross-sectionally and longitudinally in our data, which suggests that NLR and PLR are useful indicators for the assessment and monitoring of inflammatory status in patients with RA receiving anti-TNF-α agents.

Recently, the role of hematological parameters such as NLR and PLR in the diagnosis of disease and evaluation of disease activity and severity in patients with RA has been extensively studied [16–21, 32, 33]. Not only can the inflammatory process induce changes in the number, size, and shape of peripheral blood cells [33], these cells are also known to be involved in the pathophysiology of RA [34, 35]. Neutrophils can produce TNF-α in the inflamed RA joint and recruit and stimulate B and T lymphocytes by releasing CCL18 and B lymphocyte stimulators leading to the perpetuation of inflammation [34]. Platelets can also stimulate synovitis by releasing inflammatory prostaglandins and promoting vascular permeability [35]. In addition, activated platelets can interact with other cells such as endothelial cells and leukocytes and induce thrombus formation in synovial microcirculation contributing to joint damage of RA [36]. Neutrophilia and thrombocytosis are frequently observed in active RA patients. Otherwise, lymphopenia has been noted in the progression of RA [19] although its mechanism remains unclear. Accordingly, NLR and PLR could be a good reflection of inflammation in patients with RA. Our data, which showed that both NLR and PLR were positively correlated with DAS28 and acute-phase reactants levels such as ESR and CRP, also support this notion.

The principal finding in this study was that increased baseline NLR and PLR were predictive of non-response to anti-TNF-α agents at 12 weeks in patients with RA after adjusting for confounding factors. Similar to our findings, higher NLR showed a significant association with RA flare in patients during tocilizumab therapy [37]. Otherwise, Koiwa et al. reported that pretreatment NLR did not predict treatment response to biological agents in patients with RA despite a significant correlation between NRL and DAS28 [38]. We assumed that this discrepancy might be due to differences in study design or population. First, Koiwa et al. investigated the relationship between

Table 4 Associated factors for no response to anti-tumor necrosis factor-α agents in patients with rheumatoid arthritis analyzed by logistic regression models

Variables	Univariable model		Multivariable model 1[a]		Multivariable model 2[b]	
	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value	Adjusted OR (95%CI)	*p* value
High baseline NLR (ref: low baseline NLR)	5.57 (1.44–21.6)	0.013	6.26 (1.45–26.99)	0.014		
High baseline PLR (ref: low baseline PLR)	3.6 (1.04–12.48)	0.043			4.24 (1.07–16.81)	0.04
Age, years	1.06 (1.01–1.13)	0.033	1.06 (0.99–1.14)	0.085	1.06 (1–1.14)	0.066
Disease duration, per 12 month	1.16 (1.01–1.33)	0.041	1.19 (1.01–1.42)	0.036	1.19 (1.02–1.4)	0.028
Baseline DAS28-ESR	0.82 (0.44–1.53)	0.527	–	–	–	–
Anti-TNF-α agents						
Adalimumab (ref.)	–	–				
Etanercept	0.28 (0.03–2.29)	0.232				
Infliximab	1.28 (0.12–13.36)	0.835				

OR odds ratio, *CI* confidence interval, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *DAS28* disease activity score using the 28-joint count for swelling and tenderness, *ESR* erythrocyte sedimentation rate, *TNF-α* tumor necrosis factor-alpha

[a]Multivariable logistic regression model with backward selection including high baseline NLR, age, disease duration and baseline DAS28-ESR

[b]Multivariable logistic regression model with backward selection including high baseline PLR, age, disease duration and baseline DAS28-ESR

baseline NLR and EULAR response to biological agents at 6 months [38]. As mentioned above, our data also showed that baseline NLR or PLR was not significantly associated with EULAR response to anti-TNF-α agents at 24 weeks, contrary to their significant association with treatment response at 12 weeks. This notion suggests that NLR and PLR could represent sensitive and rapid response to changes in inflammatory status and the ability of these markers to predict treatment response may be only limited to the short-term (i.e. 12 weeks). Second, Koiwa et al. analyzed RA patients treated not only with anti-TNF-α agents but also with tocilizumab and abatacept and did not adjust for potential confounding factors of the relationship between baseline NLR and EULAR response, which may also have resulted in this inconsistency. Besides NLR and PLR, changes in mean platelet volume was also reported to be associated with response to anti-TNF-α agents in RA patients [39], suggesting that hematologic parameters may be used as biomarkers for monitoring response to anti-inflammatory therapy of RA.

High baseline NLR was associated with poor persistence of anti-TNF-α agents due to LOE in RA patients in this study. High baseline disease activity was reported to increase the risk of discontinuation of anti-TNF-α agents [40, 41] and conventional DMARDs [2] due to LOE in previous studies, because RA patients with greater inflammatory burden had more chances to switch to another treatment, as noted by Park et al. [2]. NLR is positively correlated with disease activity in RA patients, which could explain the relationship between high baseline NLR and the greater risk of anti-TNF-α agent withdrawal due to LOE in our data. However, this association was not observed in high PLR groups, although PLR also showed a significant correlation with DAS28 in patients with RA. Therefore, beyond inflammatory indexes, NLR might have prognostic value to predict long-term treatment persistence of anti-TNF-α agents, although the exact mechanism is uncertain, which warrants further investigations.

We obtained follow-up data of NLR and PLR and analyzed the association of their changes with other clinical parameters. Twelve-week changes in NLR and PLR were significantly and positively correlated with 12-week changes in DAS28, ESR, and CRP, implying that NLR and PLR gradually decreased in proportion to the reduction of disease activity and acute-phase reactants levels in patients with RA treated with anti-TNF-α agents. Similar to our findings, Koiwa et al. reported that 6-month changes in NLR were significantly correlated with 6-month changes in DAS28 in patients with RA treated with biological agents [38]. Thus, we suggest that NLR and PLR may be reliable markers for the follow-up of disease activity in RA patients receiving biological agents including anti-TNF-α agents.

The present study has several limitations. First, it was a retrospective study with a small sample size. In addition, there were few RA patients on infliximab treatment. Thus, comparisons of changes in NLR and PLR according to the type of anti-TNF-α agents were not possible. Second, due to the small number of male RA patients receiving anti-TNF-α agents in our center, only female subjects were investigated, as mentioned above. Although the exact reason remains unclear, NLR levels were reported to be higher in male patients with rheumatic diseases than in their female

counterparts in a previous study [32]. Thus, we considered that the inclusion of a small number of male RA patients would hamper the analysis of our data. Finally, although it is important to ascertain standardization of the laboratory procedure, our study could not fully adjust potential confounding factors for the results for NLR and PLR due to its retrospective design. As mentioned above, study subjects with active infection were excluded in this study, but cases with mild upper respiratory tract infection such as common cold may not be fully excluded because this study was a retrospective chart review analysis, which may affect NLR and PLR values. In addition, it was not possible to collect the blood samples of all study subjects at the exact same time of the day and we did not fully adjust for the effect of conventional DMARDs including MTX or glucocorticoids on the levels of NLR and PLR in RA patients, because this study was observational, not a randomized-trial.

In conclusion, the present study demonstrated that baseline NLR and PLR values could predict treatment response of anti-TNF-α agents and baseline high NLR showed a significant association with worse drug persistence. Both NLR and PLR were increased in RA patients and were correlated with disease activity and acute-phase reactant levels, indicating that they are good indicators of the inflammatory status in these populations. Because NLR and PLR are not only objective and inexpensive markers but can also be easily measured and calculated, we believe they may be useful and valuable in clinical practice for monitoring disease status and for predicting treatment outcome in patients with RA receiving anti-TNF-α agents. However, larger prospective researches are needed to validate our results.

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Author contributions HNL: study design, data collection and analysis and writing manuscript, YKK: data interpretation, GTK: data interpretation and revision of manuscript, MWS: data interpretation and revision of manuscript, EA: data interpretation, DHS: data interpretation and revision of manuscript, SGL: study design, data analysis and interpretation, writing manuscript and coordination of entire study.

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Ethical standards This study protocol was approved by the by the Research and Ethical Review Board of the Pusan National University Hospital, which waived written informed consent due to retrospective study design (IRB no. 1809-010-071).

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