Received: 25 October 2018 | Revised: 20 January 2019 | Accepted: 22 January 2019

DOI: 10.1002/jcla.22862

RESEARCH ARTICLE

WILEY

The clinical value of hematological markers in rheumatoid arthritis patients treated with tocilizumab

Li Zhou[1] | Dong-Mei Xiao[1] | Wen Qin[1] | Bin-Hua Xie[1] | Ting-Hui Wang[1] | Hua Huang[1] | Bao-Jing Zhao[1] | Xi Han[1] | Qing-Qing Sun[2,3] | Xiu-Di Wu[1] | Han Cen[2,3]

[1]Department of Rheumatology, Ningbo First Hospital, Ningbo Hospital of Zhejiang University, Ningbo, China

[2]Department of Preventive Medicine, Medical School of Ningbo University, Ningbo, China

[3]Zhejiang Provincial Key Laboratory of Pathophysiology, School of Medicine, Ningbo University, Ningbo, China

Correspondence
Han Cen, Department of Preventive Medicine, Medical School of Ningbo University, Ningbo, China.
Email: cenhan@nbu.edu.cn

Funding information
Medical and Health Planned Science and Technology Project of Zhejiang Province, Grant/Award Number: 2017KY582; Nature Science Foundation of Ningbo city, Grant/Award Number: 2016A610159; K.C. Wong Magna Fund in Ningbo University; National Natural Science Foundation of China, Grant/Award Number: 81602921; Scientific Research Foundation of Graduate School of Ningbo University; Ningbo Scientific Innovation Team for Environmental Hazardous Factor Control and Prevention, Grant/Award Number: 2016C51001

Background: Emerging evidence indicates that some hematological markers have critical value in evaluating treatment response. This study was performed to determine the clinical value of hemoglobin (Hb), platelet (Plt), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) in rheumatoid arthritis (RA) patients treated with tocilizumab (TCZ).

Methods: Fifty-two RA patients receiving TCZ were recruited and followed for 6 months. The values of abovementioned hematological markers were collected. Clinical disease activity index (CDAI) and disease activity score based on 28 joints (DAS28)-ESR were calculated. Correlation analysis was conducted by calculating Pearson's correlation coefficient. The change in disease activity between groups according to the baseline level of hematological markers was compared by *t* test.

Results: Significant correlation between change in NLR (△NLR), change in PLR (△PLR), and change in CDAI (△CDAI) was found (△NLR: $r = 0.30$, $P = 0.03$; △PLR: $r = 0.31$, $P = 0.03$). The change in Plt (△Plt) was correlated with change in DAS28-ESR (△DAS28-ESR) ($r = 0.36$, $P = 8.24 \times 10^{-3}$). Greater improvement in CDAI was seen in patients categorized into Plt high group ($t = 2.06$, $P = 0.04$), NLR high group ($t = 2.15$, $P = 0.04$), and PLR high group ($t = 2.41$, $P = 0.02$) compared with the contrast group.

Conclusion: Our study demonstrated that △Plt, △NLR, and △PLR could be used to monitor the clinical response to TCZ. RA patients with high baseline levels of Plt, NLR, and PLR achieved more improvement, indicating these hematological markers might be utilized to guide TCZ treatment.

KEYWORDS
hemoglobin, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, rheumatoid arthritis, tocilizumab

Abbreviations: bDMARD, biological disease-modifying anti-rheumatic drugs; CCP, cyclic citrullinated peptide; CDAI, Clinical disease activity index; DMARDs, disease-modifying anti-rheumatic drugs; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; HAQ, Health Assessment Questionnaire; IQR, interquartile range; LOCF, last observation carried forward; NLR, neutrophil-to-lymphocyte ratio; PGA, patient global assessment; PLR, platelet-to-lymphocyte ratio; PLS, prednisolone; SJC, swollen joint count; TCZ, tocilizumab; TJC, tender joint count; TNF, tumor necrosis factor; TPO, thrombopoietin; VAS, visual analogue scale.

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by chronic synovitis.[1] During the past decade, several novel discoveries pertaining to the pathogenesis of RA have led to the development and application of biological disease-modifying anti-rheumatic drugs (bDMARDs), including tumor necrosis factor-α (TNF-α) inhibitor, T-cell co-stimulation inhibitor, B-cell depletion, and interleukin-6 (IL-6) receptor inhibitor.[2]

IL-6 is a pleiotropic pro-inflammatory cytokine and could exert a wide range of biological effects on different target cells implicated in the pathogenesis of RA, making IL-6 as a therapeutic target for RA.[3] Tocilizumab (TCZ) is a recombinant humanized anti–IL-6 receptor monoclonal antibody that blocks IL-6–mediated biological functions by binding to its soluble and membrane-expressed IL-6 receptor, and the efficacy and safety of TCZ monotherapy or combination therapy of TCZ with other conventional DMARDs (cDMARDs) has been well demonstrated; thus, TCZ has been approved and recommended as a first-line bDMARDs for RA patients.[4,5] However, a considerable proportion of RA patients do not respond well to TCZ. Uncontrolled disease activity and inflammation due to unsuccessful treatment would result in disease progression and joint damage. Additionally, the cost of TCZ is relatively high, and some other bDMARDs are available. Thus, it is imperative to identify those patients who will clinically respond well to TCZ before treatment initiation.

Recently, emerging evidence indicates that some readily obtained hematological markers have critical value in evaluating treatment response. Of note, multiple studies suggest that the baseline levels of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) might be used to guide treatment in the field of oncology.[7,8] However, the clinical value of NLR and PLR for treatment response in RA patients has been rarely investigated. A recent study was conducted to analyze the relationship between NLR and treatment response to bDAMRDs (including infliximab, etanercept, adalimumab, TCZ, and abatacept) in RA patients, and the results indicated that the change in NLR (△NLR) could reflect the efficacy of bDMARDs.[11] Another study found that the levels of NLR but not PLR significantly increased at flare compared with their levels at pre-flare time point, suggesting that NLR is a reliable marker to assess disease activity in RA patients receiving TCZ treatment.[12] Furthermore, it has been demonstrated that the baseline levels of another two common blood-routine parameters, hemoglobin (Hb)[13,14] and platelet (Plt),[14,15] could predict the clinical response to TCZ in RA patients. Nevertheless, no other replication studies have been reported. Thus, the current study was undertaken to comprehensively assess the clinical value of hematological markers of interest (Hb, Plt, NLR, and PLR) in RA patients treated with TCZ, especially to test whether these simple, convenient biomarkers could provide information for personalized TCZ treatment in RA patients.

2 | STUDY SUBJECTS AND METHODS

2.1 | Study subjects

In this prospective study, fifty-two RA patients receiving intravenous TCZ treatment were consecutively enrolled and followed for 6 months from the Department of Rheumatology, Ningbo First Hospital, between November 2013 and February 2017. All these RA patients fulfilled American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis[16] or the 2010 American College of Rheumatology/European League Against Rheumatism (EULAR) criteria for RA.[17] TCZ was given intravenously every 4 weeks at a usual dose of 8 mg/kg, following related recommendations.[18] The doses of prednisone (PLS) and cDMARDs were allowed to adjust at the discretion of the physician. This study was reviewed and approved by the ethics committee of Ningbo First Hospital, and informed consent was obtained from all participants.

2.2 | Data collection

The information of the following variables was collected before the initiation of TCZ treatment: age, gender, disease duration, anti-cyclic citrullinated peptide (CCP) antibody and rheumatoid factor (RF) status, Health Assessment Questionnaire (HAQ) score, details of prior and concomitant use of cDMARDs and bDMARDs, and concomitant use of PLS and corresponding doses. The baseline values of hematological markers (Hb level, Plt count, white blood cell count, the percentage of neutrophil count, and the percentage of lymphocyte count) were extracted from blood-routine test performed in the central laboratory of our hospital. The NLR was calculated as the ratio of the percentage of neutrophil count to the percentage of lymphocyte count, and the PLR was obtained as the ratio of the Plt count to the lymphocyte count. In addition, the values of the following variables were collected at baseline, month 3, and month 6: tender joint count (TJC) and swollen joint count (SJC) in 28 joints, patient global assessment (PGA) and physician global assessment (PhGA) on visual analogue scale (VAS) (0-100 mm), and erythrocyte sedimentation rate (ESR). Since TCZ could significantly inhibit acute-phase reactants,[19] the disease activity of RA patients was mainly evaluated based on clinical disease activity index (CDAI),[20] and the disease activity score based on 28 joints (DAS28)-ESR was also calculated.[21]

2.3 | Statistical analysis

Quantitative variable was expressed as mean (standard deviation, SD) or median (interquartile range, IQR) according to the distribution whether conformed to normal distribution. Categorical variable was expressed as absolute number and percentage (%). The normality of the distribution was evaluated by the Kolmogorov-Smirnov test. Student's *t* test was employed for quantitative variables. Paired-sample *t* test was used to compare the change in the levels of hematological markers of interest from baseline to month 6. Correlation

analysis was conducted by calculating Pearson's or Spearman's correlation coefficient. Regarding patients who withdrew before month 6 and in cases of missing data, the last observation carried forward (LOCF) method was applied. All above analysis was performed with PASW Statistics 18.0 software (SPSS, Inc, Somers, NY, USA), and a two-tailed *P* value <0.05 was considered statistically significant.

3 | RESULTS

The baseline characteristics of RA patients included in the present study are summarized in Table 1, and 42 of them were female (80.77%). The mean age of these RA patients was 50.60 ± 12.16 years, and the median of disease duration was 90.00 (24.00-174.00) months. The proportion of CCP-positive and RF-positive RA patients was 84.62% and 92.31%, respectively. The mean of CDAI and DAS28-ESR was 28.38 ± 9.71 and 5.69 ± 0.95, respectively. Of the 52 patients, 38 were bDMARD-naive (73.08%). Fifty-one (98.08%) patients received concomitant cDMARDs, and 45 (86.54%) patients received concomitant prednisolone. At the end of the 6-month follow-up period, six patients discontinued the treatment (4 due to lack of efficacy, 1 due to adverse events, and 1 due to economic reason), and their related information was collected on the last visit point.

TABLE 1 The baseline characteristics of RA patients receiving intravenous TCZ

Characteristics	All patients (n = 52)
Female, n (%)	42.00 (80.77)
Age, years, mean (SD)	50.60 (12.16)
Disease duration, months, median (IQR)	90.00 (24.00-174.00)
RF-positive, n (%)	44.00 (84.62)
CCP-positive, n (%)	48.00 (92.31)
TJC (per 28 joints), mean (SD)	8.77 (4.04)
SJC (per 28 joints), mean (SD)	8.48 (4.20)
ESR, mm/h, mean (SD)	56.63 (26.04)
DAS28-ESR, mean (SD)	5.69 (0.95)
CDAI, mean (SD)	28.38 (9.71)
HAQ (0-3), mean (SD)[a]	1.09 (0.58)
No. of prior cDMARDs, median (IQR)	2.00 (1.00-2.00)
DMARD-naive, n (%)[b]	38.00 (73.08)
No. of prior bDMARDs, median (IQR)	0 (0-1.00)
Concomitant cDMARDs use, n (%)	51.00 (98.08)
Concomitant PLS use, n (%)	45.00 (86.54)
PLS dose, mg/d, mean (SD)[b]	6.11 (3.72)
Hemoglobin (g/dL)	11.74 (1.78)
Platelet ($\times 10^9$/L)	292.12 (85.39)
White blood cell ($\times 10^9$/L)	7.91 (2.18)
Neutrophil %	68.76 (10.20)
Lymphocyte %[c]	22.96 (9.30)
Neutrophil-to-lymphocyte ratio[c]	3.75 (2.19)
Platelet-to-lymphocyte ratio[c]	192.03 (90.96)

bDMARDs, biological disease-modifying anti-rheumatic drugs; CCP anti-cyclic citrullinated peptide; CDAI, clinical disease activity index; cDMARDs, conventional disease-modifying anti-rheumatic drugs; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate, HAQ, Health Assessment Questionnaire; IQR, interquartile range; PLS, prednisolone; RF, rheumatoid factor; SD, standard deviation; SJC, swollen joint count; TJC, tender joint count.
[a]One patient with outlier was discarded.
[b]Prednisolone equivalent.
[c]One patient with lymphocyte data missing.

3.1 | The correlation between disease activity and hematological markers of interest at baseline

As shown in Table 2, Plt and PLR were found to be positively correlated with CDAI (Plt: $r = 0.44$, $P = 1.15 \times 10^{-3}$; PLR: $r = 0.34$, $P = 0.01$) and DAS28-ESR (Plt: $r = 0.46$, $P = 6.86 \times 10^{-4}$; PLR: $r = 0.30$, $P = 0.03$), while Hb was detected to be inversely correlated with CDAI ($r = -0.32$, $P = 0.02$) and DAS28-ESR ($r = -0.37$, $P = 7.16 \times 10^{-3}$). However, non-significant evidence was found for correlation between NLR and disease activity.

3.2 | The effect of TCZ treatment on hematological markers of interest

Paired-sample *t* test was applied to analyze the change in hematological markers of interest from baseline to month 6, and the results indicated that Plt ($t = 8.57$, $P < 0.01$), NLR ($t = 4.45$, $P < 0.01$), and PLR ($t = 6.80$, $P < 0.01$) decreased significantly, while Hb increased significantly ($t = 9.21$, $P < 0.01$) (Table 3).

3.3 | The correlation between change in hematological markers of interest and change in disease activity from baseline to month 6

To determine whether the change in hematological markers of interest was in parallel with the change in disease activity, the correlation analysis was performed. As shown in Table 4, significant correlation between △NLR, △PLR, and △CDAI was found (△NLR: $r = 0.30$, $P = 0.03$; △PLR: $r = 0.31$, $P = 0.03$). In addition, the change in Plt (△Plt) was found to be correlated with change in DAS28-ESR (△DAS28-ESR) ($r = 0.36$, $P = 8.24 \times 10^{-3}$). Nevertheless, we did not find significant correlation between change in Hb (△Hb), △CDAI, and △DAS28-ESR.

3.4 | The change in disease activity from baseline to month 6 in RA patients categorized according to the baseline level of hematological markers of interest

To determine whether there was significant difference in clinical response between RA patients with different baseline levels of hematological markers of interest, the change in disease activity from baseline to month 6, which was used to assess the clinical response to TCZ, was compared between the two groups of RA patients

TABLE 2 The correlation between disease activity and interested hematological markers at baseline

Hematological indices	CDAI	DAS28-ESR
Hemoglobin	−0.32*	−0.37**
Platelet	0.44**	0.46**
Neutrophil-to-lymphocyte ratio	0.11	0.08
Platelet-to-lymphocyte ratio	0.34*	0.30*

*$P < 0.05$.
**$P < 0.01$

categorized according to the levels of hematological markers of interest.

In our laboratory, the reference range of Hb is 13.0-17.5 g/dL in men and 11.5-15.0 g/dL in women, respectively. The reference range of Plt count is 125-350 × 10^9/L. RA patients with Hb and Plt within the reference range were classified into normal group. The patients with Hb levels lower than the reference range were categorized into low group, and patients with Plt counts higher than the reference range were categorized into high group. With regard to NLR and PLR, there is no validated consensus on the reference values, so the median value of all RA patients was adopted as the cutoff value. The values higher than the cutoff value were categorized into high group, and the rest were sorted into low group.

As shown in Table 5, greater improvement in CDAI was seen in RA patients categorized into Plt high group ($t = 2.06$, $P = 0.04$), NLR high group ($t = 2.15$, $P = 0.04$), and PLR high group ($t = 2.41$, $P = 0.02$) compared with the contrast group, whereas non-significant difference was found in △CDAI between RA patients sorted into Hb normal group and low group ($t = 0.26$, $P = 0.79$). In addition, when the △DAS28-ESR was used to evaluate the clinical response to TCZ, no significant signal was detected between the groups of RA patients categorized according to the baseline level of hematological markers of interest.

4 | DISCUSSION

Recently, a growing body of evidence indicates that some simple, convenient, and cost-effective hematological markers (Hb, Plt, NLR, and PLR) have significant clinical value in evaluating treatment response.[7-10] In the present study, the clinical significance of Hb, Plt, NLR, and PLR in RA patients treated with TCZ was investigated, and the results of our study indicated that Hb, Plt, and PLR might serve as tools to reflect disease activity, and △Plt, △NLR, and △PLR could be used to monitor the clinical response to TCZ. Moreover, patients with high levels of Plt, NLR, and PLR at baseline achieved more improvement, indicating that these hematological markers might be utilized to guide TCZ treatment in RA patients.

Recently, NLR and PLR, two simple hematological markers of subclinical systemic inflammation, have been extensively explored in malignancies and cardiovascular diseases, and it has been demonstrated that these two indices have the potential as prognostic factors for these diseases.[25,26] Besides, some studies also found that these two indices might be applied to guide personalized treatment in some types of tumor.[7,8] During the past few years, NLR and PLR have also received widespread attention in the field of rheumatology. A recent meta-analysis showed that NLR and PLR were significantly up-regulated in some types of rheumatic diseases including RA.[31] Moreover, NLR and PLR were also found to be positively correlated with disease activity of RA patients,[32,33] and we also found that PLR was positively correlated with CDAI and DAS28-ESR at baseline in the present study, suggesting PLR might be used to reflect disease activity for RA patients. However, there was no significant correlation between NLR and disease activity scores, and this discrepancy might be partially owing to the different clinical and treatment background, and most of the patients included in our study had been treated with at least two cDMARDs.

Apart from the value of assessing disease activity, a few studies were performed to determine the clinical value of NLR and PLR in treatment response in the field of rheumatology.[11,12,22,23] In a study involving 358 RA patients treated with bDMARDs (infliximab, etanercept, adalimumab, TCZ, and abatacept), NLR decreased significantly after treatment with each bDMARDs except for abatacept, and △NLR was positively correlated with △DAS28-ESR, indicating that △NLR might be applied to reflect the efficacy of bDMARDs.[11] In another study involving 52 RA patients treated with TCZ, 16 patients experienced flares, and NLR was found to be significantly upregulated in all but one patient at flares compared with pre-flare time point, suggesting that NLR is a reliable marker to evaluate clinical response to TCZ.[12] In other words, this study also implies that △NLR could be used to monitor clinical response to TCZ in RA patients. Furthermore, in a study consisting of 186 patients with plaque-type psoriasis (PsV) and 50 patients with psoriatic arthritis (PsA) treated with biologics, NLR and PLR decreased sharply in parallel with a decrease in CRP after treatment for up to 12 months, irrespective of the type of biologics used, indicating that NLR and PLR might serve as biomarkers to monitor the disease course after systemic therapy.[24] Similar to the results of abovementioned studies, NLR and PLR decreased significantly after TCZ treatment in our study, and

TABLE 3 The levels of hematological markers before and after 6 months of TCZ treatment

Hematological indices	Baseline	Month 6	*t*	*P*
Hemoglobin	11.74 ± 1.78	13.15 ± 1.74	9.21	<0.01
Platelets	292.12 ± 85.39	216.35 ± 57.60	8.57	<0.01
Neutrophil-to-lymphocyte ratio	3.75 ± 2.19	2.37 ± 1.69	4.45	<0.01
Platelet-to-lymphocyte ratio	192.03 ± 90.96	128.81 ± 63.65	6.80	<0.01

TABLE 4 The correlation between the change in interested hematological markers and the change in disease activity from baseline to month 6

Change in hematological markers	△CDAI	△DAS28-ESR
△Hemoglobin	−0.05	−0.23
△Platelets	0.16	0.36**
△Neutrophil-to-lymphocyte ratio	0.30*	0.14
△Platelet-to-lymphocyte ratio	0.31*	0.12

Data in the table were the Pearson correlation coefficient.
*$P < 0.05$.
**$P < 0.01$.

the decrease could be attributed to the inhibition of systemic inflammation by TCZ. Additionally, △NLR and △PLR were positively correlated with △CDAI, indicating that △NLR and △PLR could be used to monitor the treatment response to TCZ in RA patients.

Besides monitoring treatment response, NLR was found to have the capacity to predict the clinical response to one bDMARD, infliximab, in patients with Crohn's disease (CD)[22] and ulcerative colitis (UC).[23] In a retrospective study, a total of 30 CD patients who underwent full 52-week infliximab therapy were included, and the results revealed that the NLR levels at baseline and at week 14 were significantly lower in CD patients who responded to induction treatment at week 14 and maintained the response compared with those who lost response to maintenance infliximab treatment.[22] Subsequently, the predictive value of NLR for clinical response to infliximab in UC patients was also examined in one study involving 59 patients with moderate-to-severe active UC treated with infliximab, and 37 patients experienced clinical response after induction therapy. During the observational period, 14 of 37 patients on maintenance therapy lost the response, and the NLR baseline levels of patients who lost to response were significantly higher than those in patients with sustained response.[23] Taken together, these two studies indicated that the pre-treatment levels of NLR could serve as predictor of sustained response to a 52-week course of infliximab therapy among patients with CD and UC, and taking NLR into account in patients with CD and UC may lead to more appropriate clinical management of those patients treated with infliximab. Of note, adopting the method of categorizing patients using the median level of NLR and PLR, significantly greater improvement was seen in patients with high baseline levels of NLR and PLR, and this indicates that TCZ might be preferred for patients with relatively high NLR and PLR.

In addition to NLR and PLR, several recent studies also found that the levels of another two common hematological markers before initiation of TCZ treatment, Hb[13,14] and Plt,[14,15] might hold the potential as predictors of clinical response to TCZ in RA patients. In a multicenter ambispective observational study, 126 RA patients treated with TCZ were enrolled, and the results suggested that patients with higher concentrations of Hb were less likely to achieve remission at month 3.[13] Another study comprising 87 RA patients treated with TCZ compared the improvement in terms of DAS28-ESR and CDAI between two groups of RA patients classified according to Hb level or Plt count (low and normal Hb group, and high and normal Plt group), and their results were consistent with our results, greater improvement being seen in high Plt group in comparison with normal Plt group. Nevertheless, non-significant difference in improvement was found between low Hb and normal Hb groups.[15]

Intriguingly, a recent study was performed to develop scoring system based on common laboratory indices to discriminate between individuals more likely to respond to TCZ or TNF-α inhibitor, and the results indicated that the values of Hb and Plt were significantly correlated with the efficacy of TCZ. Thus, the final scoring system was constructed based on several items including Hb and Plt.[14] As the author explained, this may reflect the predominant role of IL-6 in RA pathogenesis. It has been revealed that IL-6 could act on maturational stages in megakaryocytopoiesis and promotes Plt production in vivo in mice, suggesting that IL-6 could function as thrombopoietin.[37] In inflammatory thrombocytosis, IL-6 could induce thrombocytosis through thrombopoietin (TPO).[38] In addition, it has been reported that administration of IL-6 to humans leads to an increase in circulating Plt counts.[39,40] As a pro-inflammatory cytokine, available evidence indicates that IL-6 is involved in anemia of inflammation, since IL-6 could strongly induce the production of hepcidin, which is a peptide hormone synthesized mainly by hepatocytes, and could function as a negative iron regulator through inhibiting iron absorption from the duodenum and iron release from macrophages.[41] Given the critical role of IL-6 in Plt production and anemia of inflammation, it could be anticipated that TCZ treatment could result in decrease in Plt and increase in Hb, and our results confirmed this point. Furthermore, IL-6 might be the dominant cytokine in RA patients with high Plt counts and low Hb levels; thus, superior efficacy should be seen in patients falling into high Plt group and low Hb group. In the current study, greater improvement in terms of disease activity scores was found in patients with high Plt counts than those with normal Plt counts, whereas non-significant difference in disease activity improvement between patients with low Hb and normal Hb was detected, and this is in accordance with the results of previous study.[15] Although other studies found the predictive value of Hb in the efficacy of TCZ,[13,14] it should be noted that the analytical means, response criteria, and sample size might account for the discrepancy. In addition, we also found significant positive correlation between Plt and disease activity scores, and inverse correlation between Hb and disease activity scores was also detected, indicating that these two markers could also be utilized to reflect disease activity for RA patients. To test whether these two markers could be applied to monitor clinical response to TCZ, △Plt was found to be positively correlated with △DAS28-ESR, indicating that △Plt could be used to monitor the clinical response to TCZ in RA patients.

Our results should be interpreted with caution due to the limitations. First, since the majority of RA patients included in the present study were female and bDMARD-naive, the generalizability of our

TABLE 5 Change in disease activity from baseline to month 6 in RA patients categorized according to the level of interested hematological markers

△DAS	Hemoglobin			Platelet			Neutrophil-to-lymphocyte ratio			Platelet-to-lymphocyte ratio		
	Normal	Low	*P*	Normal	High	*P*	Low	High	*P*	Low	High	*P*
△CDAI	20.71 ± 8.70	20.00 ± 10.78	0.79	19.16 ± 9.21	26.22 ± 9.93	0.04	17.62 ± 9.98	23.15 ± 8.57	0.04	17.31 ± 8.93	23.46 ± 9.46	0.02
△DAS28-ESR	2.92 ± 1.15	2.58 ± 1.29	0.32	2.74 ± 1.22	2.87 ± 1.28	0.78	2.68 ± 1.20	2.85 ± 1.25	0.63	2.63 ± 1.14	2.89 ± 1.30	0.45

study might be limited. In addition, the sample size of this study is relatively small, and some statistically significant results might be caused by sampling error, so the results of our study need further confirmation in studies with larger sample sizes.

These hematological markers are easily available without additional cost, making them as preferred items in daily practice. Our study demonstrated that Hb, Plt, and PLR might serve as tools to reflect disease activity, and △Plt, △NLR, and △PLR could be used to monitor the clinical response to TCZ. Additionally, patients with high baseline levels of Plt, NLR, and PLR might achieve more clinical improvement, indicating that these hematological markers might be utilized to guide TCZ treatment in RA patients.

ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (Grant No. 81602921), Nature Science Foundation of Ningbo City (Grant No. 2016A610159), Medical and Health Planned Science and Technology Project of Zhejiang Province (Grant No. 2017KY582), Ningbo Scientific Innovation Team for Environmental Hazardous Factor Control and Prevention (Grant No. 2016C51001), Scientific Research Foundation of Graduate School of Ningbo University, and K.C. Wong Magna Fund in Ningbo University.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest associated with this study.

ORCID

Han Cen https://orcid.org/0000-0003-4616-2817

REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388:2023-2038.
2. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. *Nat Rev Rheumatol*. 2015;11:276-289.
3. Park JY, Pillinger MH. Interleukin-6 in the pathogenesis of rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007;65(Suppl 1):S4-10.
4. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76:960-977.
5. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol*. 2016;68:1-26.
6. Lau CS, Chia F, Harrison A, et al. APLAR rheumatoid arthritis treatment recommendations. *Int J Rheum Dis*. 2015;18:685-713.
7. McLaren PJ, Bronson NW, Hart KD, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can predict treatment response to neoadjuvant therapy in esophageal cancer. *J Gastrointest Surg*. 2017;21:607-613.
8. Kuzman JA, Stenehjem DD, Merriman J, et al. Neutrophil-lymphocyte ratio as a predictive biomarker for response to high dose

interleukin-2 in patients with renal cell carcinoma. *BMC Urol*. 2017;17:1.
9. Hasegawa S, Eguchi H, Tomokuni A, et al. Pre-treatment neutrophil to lymphocyte ratio as a predictive marker for pathological response to preoperative chemoradiotherapy in pancreatic cancer. *Oncol Lett*. 2016;11:1560-1566.
10. Wang Y, Liu P, Xu Y, et al. Preoperative neutrophil-to-lymphocyte ratio predicts response to first-line platinum-based chemotherapy and prognosis in serous ovarian cancer. *Cancer Chemother Pharmacol*. 2015;75:255-262.
11. Koiwa M, Goto S, Takahashi K, Kamada T, Takai S, Nakamura H. Neutrophil/lymphocyte ratio in patients with rheumatoid arthritis treated with biological agents. *J Nippon Med Sch*. 2016;83:118-124.
12. Ghang B, Kwon O, Hong S, et al. Neutrophil-to-lymphocyte ratio is a reliable marker of treatment response in rheumatoid arthritis patients during tocilizumab therapy. *Mod Rheumatol*. 2017;27:405-410.
13. Narváez J, Magallares B, Díaz Torné C, et al. Predictive factors for induction of remission in patients with active rheumatoid arthritis treated with tocilizumab in clinical practice. *Semin Arthritis Rheum*. 2016;45:386-390.
14. Nakagawa J, Koyama Y, Kawakami A, et al. A novel scoring system based on common laboratory tests predicts the efficacy of TNF-inhibitor and IL-6 targeted therapy in patients with rheumatoid arthritis: a retrospective, multicenter observational study. *Arthritis Res Ther*. 2017;19:185.
15. Matsuno H. Remarkable efficacy of tocilizumab for treating rheumatoid arthritis in patients with high platelet counts. *Mod Rheumatol*. 2015;25:38-42.
16. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988;31:315-324.
17. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62:2569-2581.
18. Exper group of tocilizumab in treating rheumatoid arthritis. Expert recommendations on tocilizumab in treating rheumatoid arthritis. *Chin J Rheumatol*. 2013;17:436-438.
19. Kawashiri SY, Kawakami A, Iwamoto N, et al. Disease activity score 28 may overestimate the remission induction of rheumatoid arthritis patients treated with tocilizumab: comparison with the remission by the clinical disease activity index. *Mod Rheumatol*. 2011;21:365-369.
20. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther*. 2005;7:R796-806.
21. Prevoo ML, van 't Hof MA, Kuper HH, , et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum*. 1995;38:44-48.
22. Wlodarczyk MK, Sobolewska AE, Stec-Michalska K, et al. Neutrophil-lymphocyte ratio in Crohn's disease patients predicts sustained response to infliximab 52-week therapy. *J Gastrointestin Liver Dis*. 2015;24:127-128.
23. Nishida Y, Hosomi S, Yamagami H, et al. Neutrophil-to-lymphocyte ratio for predicting loss of response to infliximab in ulcerative colitis. *PLoS ONE*. 2017;12:e0169845.
24. Asahina A, Kubo N, Umezawa Y, et al. Neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume in Japanese patients with psoriasis and psoriatic arthritis: Response to therapy with biologics. *J Dermatol*. 2017;44:1112-1121.
25. Sun X, Liu X, Liu J, et al. Preoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio in predicting survival for patients with stage I-II gastric cancer. *Chin J Cancer*. 2016;35:57.
26. Salman T, Kazaz SN, Varol U, et al. Prognostic value of the pretreatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for patients with neuroendocrine tumors: an Izmir oncology group study. *Chemotherapy*. 2016;61:281-286.
27. Wu G, Yao Y, Bai C, et al. Combination of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio is a useful prognostic factor in advanced non-small cell lung cancer patients. *Thorac Cancer*. 2015;6:275-287.
28. Li C, Wen TF, Yan LN, et al. Postoperative neutrophil-to-lymphocyte ratio plus platelet-to-lymphocyte ratio predicts the outcomes of hepatocellular carcinoma. *J Surg Res*. 2015;198:73-79.
29. Akboga YE, Bektas H, Anlar O. Usefulness of platelet to lymphocyte and neutrophil to lymphocyte ratios in predicting the presence of cerebral venous sinus thrombosis and in-hospital major adverse cerebral events. *J Neurol Sci*. 2017;380:226-229.
30. Acet H, Ertaş F, Akıl MA, et al. Novel predictors of infarct-related artery patency for ST-segment elevation myocardial infarction: Platelet-to-lymphocyte ratio, uric acid, and neutrophil-to-lymphocyte ratio. *Anatol J Cardiol*. 2015;15:648-656.
31. Hao X, Li D, Wu D, et al. The relationship between hematological indices and autoimmune rheumatic diseases (ARDs), a meta-analysis. *Sci Rep*. 2017;7:10833.
32. Chandrashekara S, Mukhtar Ahmad M, Renuka P, et al. Characterization of neutrophil-to-lymphocyte ratio as a measure of inflammation in rheumatoid arthritis. *Int J Rheum Dis*. 2017;20:1457-1467.
33. Tekeoğlu İ, Gürol G, Harman H, et al. Overlooked hematological markers of disease activity in rheumatoid arthritis. *Int J Rheum Dis*. 2016;19:1078-1082.
34. Mercan R, Bitik B, Tufan A, et al. The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and Ankylosing spondylitis. *J Clin Lab Anal*. 2016;30:597-601.
35. Fu H, Qin B, Hu Z, et al. Neutrophil- and platelet-to-lymphocyte ratios are correlated with disease activity in rheumatoid arthritis. *Clin Lab*. 2015;61:269-273.
36. Uslu AU, Küçük A, Şahin A, et al. Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *Int J Rheum Dis*. 2015;18:731-735.
37. Ishibashi T, Kimura H, Shikama Y, et al. Interleukin-6 is a potent thrombopoietic factor in vivo in mice. *Blood*. 1989;74:1241-1244.
38. Kaser A, Brandacher G, Steurer W, et al. Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis. *Blood*. 2001;98:2720-2725.
39. Gordon MS, Nemunaitis J, Hoffman R, et al. A phase I trial of recombinant human interleukin-6 in patients with myelodysplastic syndromes and thrombocytopenia. *Blood*. 1995;85:3066-3076.
40. van Gameren MM, Willemse PH, Mulder NH, et al. Effects of recombinant human interleukin-6 in cancer patients: a phase I-II study. *Blood*. 1994;84:1434-1441.
41. Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. *Blood*. 2003;102:783-788.

How to cite this article: Zhou L, Xiao D-M, Qin W, et al. The clinical value of hematological markers in rheumatoid arthritis patients treated with tocilizumab. *J Clin Lab Anal*. 2019;33:e22862. https://doi.org/10.1002/jcla.22862