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Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Associated with Disease Activity in Patients with Takayasu's Arteritis

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Running title: PLR and NLR are associated with TAK

Abstract

Background Platelet-to-lymphocyte ratio (PLR) and Neutrophil-to-lymphocyte ratio (NLR) has been reported to reflect inflammatory response and disease activity in a variety of autoimmune diseases. **Objectives** This study aimed to evaluate the predictive value of PLR and NLR in disease activity in Takayasu's arteritis (TAK). **Methods** A retrospective study involving 88 TAK patients and 78 healthy controls was performed. We compared the PLR and NLR between patients and healthy controls, and also analyzed the correlations between PLR or NLR and indexes of TAK disease activity. **Results** Increased PLR and NLR were observed in TAK patients. PLR was positively correlated with hs-CRP ($r=0.239$, $P=0.010$) and ESR ($r = 0.270$, $P=0.010$), NLR also exhibited a positive relationship with Kerr's score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$). In addition, a PLR level of 183.39 was determined as predictive cut-off value of TAK (sensitivity 37.8%, specificity 93.0%, AUC=0.691); An NLR level of 2.417 was determined as predictive cut-off value of TAK (sensitivity 75.6%, specificity 55.8%, AUC=0.697). **Conclusions** PLR and NLR could be as useful marker to reflect inflammation and disease activity in TAK patients.

Keywords Takayasu's arteritis; platelet-to-lymphocyte ratio; neutrophil-to-lymphocyte ratio

Strengths and limitations of this study

- This study is the first to assess the PLR and NLR could be as useful marker to reflect inflammation and disease activity in TAK patients.
- This study provides the accurate cutoff value of PLR and NLR to evaluated disease activity of TAK.
- This study provides a simple and convenient method for the clinical evaluation of TAK disease activity.
- This is a retrospective cross-sectional study, prospective cohort study to be further carried out in the future.

Introduction

Takayasu's arteritis (TAK) is a systemic autoimmune large vessel vasculitis, mainly involving the aorta and its branches. TAK causes aortic injury such as stenosis, occlusion, hemangioma or dissection and other serious complications, which result in tissue and organ ischemia, dysfunction and even vascular rupture leading to sudden death in severe cases[1]. The pathology of TAK is characterized by inflammatory cell infiltration along with granulomatous inflammation as well as by excessive pro-inflammatory cytokines production[2]. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to monitor disease progression. Although CRP and ESR are often useful to follow patients with TAK, some patients suffer from worsening of vasculitis without increasing CRP or ESR. These systemic inflammatory markers do not always show a positive correlation with inflammatory activity in the vessel wall[3].

Recent studies have shown that an abnormal NLR level is also associated with autoimmune disease, such as psoriasis[4], ulcerative colitis[5], rheumatoid arthritis (RA)[6], systemic lupus erythematosus (SLE), Sjögren's syndrome (pSS)[7] and Behçet's disease[8]. Likewise, platelets also play an active role in inflammation, and play regulatory roles in the immune system, and platelet-to-lymphocyte ratio (PLR) is also suggested as a potential marker to determine inflammation in recent years.

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3 Similar to NLR, PLR is also used as an index for differential diagnosis or prognostic
4 prediction of diverse diseases such as cancer[9], metabolic syndrome[10] and in-
5 flammatory diseases, especially for evaluating the cardiovascular risk and events[11].
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7 However, research about the association of PLR and NLR with TAK is limited. There-
8 fore, in this retrospective study, we analyzed the medical records of 88 TAK patients
9 and 78 healthy individuals, to evaluate the PLR or NLR in patients with TAK and com-
10 pared it with controls. We aim to define the possible association of PLR and NLR with
11 inflammatory response and disease activity in TAK. Furthermore, we also evaluated
12 the relationship with PLR or NLR on TAK disease activity.
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20 **Methods**

21 **Patients**

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24 A total of 88 patients with TAK were enrolled in this study according to the criteria
25 for classification of TAK developed by American College of Rheumatology (ACR) in
26 1990, all of the patients had glucocorticoid withdrawal for at least 6 months or were
27 newly diagnosed without treatment. Patients who had chronic or current infections,
28 tumors, hematologic diseases, other autoimmune diseases, lymphoproliferative dis-
29 orders, hepatosplenic diseases or a history of allergic diseases were excluded. Dis-
30 ease activity was assessed in TAK patients by using a modified version of Kerr's crite-
31 ria. Kerr's criteria is used to define "active disease" if two of the following criteria are
32 positive: (1) systemic features with no other cause; (2) elevated ESR; (3) indications
33 of vascular ischemia or inflammation (e.g., claudication, diminished or absent pulses,
34 bruit, vascular pain, asymmetric blood pressure); or (4) typical angiographic features
35 (including any imaging method in addition to conventional angiography). All the pa-
36 tients were recruited from the Department of Rheumatology and Immunology, Bei-
37 jing Anzhen Hospital during the period of January 2013 to December 2015. 78 age-
38 and sex-matched healthy donors were recruited from the Health Care Center of An-
39 zhen Hospital. This study was approved by the Ethics Committee of Beijing Anzhen
40 Hospital.
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55 **Blood sample collection**

56 For each subject, 4 ml of venous blood was drawn in the morning after a 12-hour
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3 fasting. The blood was then placed in a tube without anticoagulation, and the serum
4 was collected after the blood was coagulated and centrifuged 3000 r/m for 5
5 minutes. The total and differential leukocyte counts were determined by the Beck-
6 man Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). A Hitachi
7 7600-120 automatic biochemical analyzer was used to test the serum parameters.
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10 11 12 13 14 15 16 **Statistical analysis**

17 Values are expressed as means \pm standard error (means \pm SEM). Differences be-
18 tween measured parameters in patients and controls were assessed by unpaired T
19 test. If the data were not normally distributed, the Mann-Whitney test was applied;
20 the assessment of qualitative parameters was performed by χ^2 test. Pearson's ap-
21 proach was used to quantitate the correlation between variables. A receiver-
22 operating characteristic (ROC) curve was constructed to determine the predictive
23 value of PLR and NLR in patients group. A P value <0.05 was considered statistically
24 significant. All statistical studies were carried out with the SPSS program (version
25 16.0, SPSS, Chicago, Illinois).
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35 **Results**

36 **Basic characteristics of the study sample**

37 Clinical characteristics and laboratory findings of the 88 TAK patients and 78 healthy
38 controls are given in Table 1. Patients with TAK had a median age of 39.35 years
39 (range: 17-63), with a gender distribution of 78 women (88.63%) and 10 men
40 (11.36%). In the control group, the median age was 36.46 years (range: 18-57) with a
41 gender distribution of 68 women (87.18%) and 10 men (12.82%). There was no dif-
42 ference in age or gender between the TAK and control groups. The total WBC count
43 and neutrophil count were significantly higher in the patient group ($p=0.000$)
44 ($p=0.000$). PLR and NLR were markedly elevated in TAK patients than that of the con-
45 trols ($p=0.023$) ($p=0.001$). ESR and serum hs-CRP levels were higher in the patient
46 group than that in the controls ($p=0.000$) ($p=0.000$). No differences of other blood
47 parameters such as lymphocyte (LY) count, PLT count, serum levels of alanine ami-
48 notransferase (ALT), urea nitrogen (BUN) and creatinine (Cr) were observed between
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3 the groups (Table 1).
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6 **PLR and NLR were increased in TAK patients with disease activity**

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8 In our study the total WBC count, neutrophil count and platelet count were all in-
9 creased in the active TAK group ($p=0.001$) ($p=0.001$) ($p=0.004$). Serum immunoglobu-
10 lin (Ig)A, IgG and complement 3 were significantly higher in the active TAK group
11 than those in the inactive patients ($p=0.007$) ($p=0.011$) ($p=0.000$). ESR and serum hs-
12 CRP levels were higher in the active patients group than those in the inactive group
13 ($p=0.000$) ($p=0.000$) (Table 2). As shown in figure 1, both PLR and NLR were signifi-
14 cantly elevated in the active TAK patients compared to the inactive group ($p=0.012$)
15 ($p=0.010$).
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24 **PLR and NLR had positive correlations to disease activity in TAK patients.**

25 As shown in Table3, PLR was positively correlated with hs-CRP ($r =0.239$, $P=0.010$)
26 and ESR ($r = 0.270$, $P=0.010$). NLR also exhibited a positive relationship with Kerr's
27 score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$) (Fig-
28 ure 3).
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35 **Receiver-operating characteristic (ROC) curves of PLR and NLR for the TAK disease** 36 **activity (Kerr's score)**

37 We performed an ROC analysis to determine whether the best cutoff value of PLR
38 and NLR predicts TAK disease activity (Kerr's score). For PLR, the area under the
39 curve was 0.691 (95% confidence interval [CI] 0.580-0.802, $P =0.002$), and the best
40 cutoff value was 183.390, with sensitivity and specificity of 37.8% and 93.0%. For
41 NLR, the area under the curve was 0.697 (95% confidence interval [CI] 0.588-0.806, P
42 $=0.001$), and the best cutoff value was 2.417, with sensitivity and specificity of 75.6%
43 and 55.8% (Figure 2), respectively (Figure 3).
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52 **Discussion**

53 Our present study analyzed the correlations of PLR and NLR with the disease activity
54 in patients with TAK. The findings first showed that both PLR and NLR were increased
55 in TAK, especially in the patients with disease activity. There were positive correla-
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3 tions in TAK patients between PLR and disease activity and between NLR and disease
4 activity. Furthermore, our results suggest that PLR and NLR may be potential indica-
5 tors of assessment of the disease activity in TAK.
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10 Platelets play an active role in inflammation. In many studies of chronic inflammato-
11 ry arthritis, evidence has been found for an increase in platelet activation[11, 12].
12 Platelet inhibition was found to counterbalance the rises in IL-6 and the C-reactive
13 protein in patients with acute cardiovascular diseases. Platelets extensively interact
14 with leukocytes in vascular diseases such as atherosclerosis and are regarded as cen-
15 tral players in the pathophysiology of vascular inflammation. Increased mass of cir-
16 culating platelets is likely a consequence of chronic inflammation. Activated platelets
17 not only produce growth factors such as platelet-derived growth factor (PDGF) and
18 transforming growth factor- β (TGF- β), but also release chemokines, which have im-
19 portant effects in vascular inflammation, leading to thrombosis[13]. Similar to other
20 inflammatory diseases, even in inactive TAK patients, atherosclerosis risk is also in-
21 creased[14]. Study has suggested the scores of delayed contrast-enhanced magnetic
22 resonance imaging were moderately correlated to CRP, platelet count and fibrinogen
23 levels ($p < 0.05$) [15]. There are some basic studies about use of antiplatelet agents in
24 TAK [16, 17]. Antiplatelet treatment may also lower the frequency of ischaemic
25 events in TA[18]. In the affected limb by arterial stenosis, more platelet aggregation
26 and higher levels of thromboxane were reported in TAK patients, and these findings
27 were shown to improve after 80mg/day aspirin treatment[14]. It is believed that en-
28 dothelial injury and dysfunction caused by increased platelet activity and vascular
29 inflammation are important factors for thrombosis development in TAK. A recent
30 retrospective observational study suggested that antiplatelet therapy was associated
31 with a lower frequency of ischemic events in patients with TAK[19]. Prednisone at a
32 dosage of 1 mg/kg twice a day decreased the platelet count within 45 days of its ini-
33 tiation. Takayasu's arteritis should be considered in the differential diagnosis of un-
34 explained thrombocytosis, particularly in young women[20]. In our current study,
35 there was no difference in PLT counts between TAK patients and controls, while the
36 PLT counts of active patients were significantly higher than those of inactive pa-
37 tients, and that correlated with disease activity indexes such as hs-CRP and ESR. ROC
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3 analysis has suggested that PLR predicts TAK disease activity (Kerr's score). Our re-
4 sults indicated that the platelet is activated in TAK, and parallel to disease activity.
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8 Neutrophils, also essential mediators of host defense, can produce many inflam-
9 matory mediators and cytokines and bridge the innate and adaptive immune re-
10 sponses in autoimmune diseases[21]. Research evidence has demonstrated that
11 neutrophils persist beyond acute inflammation to initiate and perpetuate chronic
12 inflammation. Recent studies have indicated that changes in neutrophil are involved
13 in the development of a variety of autoimmune diseases. There was a higher NLR in
14 psoriasis vulgaris patients than the control group[4], and the abnormal NLR level was
15 associated with RA[6], systemic lupus erythematosus (SLE), Sjögren's syndrome
16 (pSS)[10] and Behçet's disease[8]. Another study investigated the neutrophil-platelet
17 interaction in patients with granulomatosis with polyangiitis and suggested that
18 platelet-neutrophil aggregates correlating positively with the disease activity
19 score[22]. Pro-inflammatory cytokines IL-17, IL-8, IFN- γ and TNF- α also play promi-
20 nent roles in the recruitment, activation and survival of neutrophils at inflammatory
21 sites[23], and expression of these cytokines was significantly increased in TAK [24]. In
22 RA, anti-TNF- α therapies reduce IL-33 receptor expression on neutrophils and subse-
23 quently decrease neutrophil migration and impaired chemotaxis of neutrophils may
24 lead to a decrease in inflammation and disease severity in RA[25]. Our data showed
25 that neutrophils in TAK patients were increased in the patient group, and positively
26 correlated with disease activity. This is similar to previous results in other autoim-
27 mune diseases. Similarly, our study found that both total WBC and neutrophil counts
28 were significantly higher in TAK patients than those in the controls, and NLR was sig-
29 nificantly higher in active patients. In order to clarify the correlations between NLR
30 and TAK disease activity, we evaluated the level of the NLR and Kerr's score, hs-CRP
31 and ESR in patients with TAK and found that NLR is positively correlated with TAK
32 disease activity. All these findings suggest that PLR and NLR could be used to reflect
33 inflammatory response and disease activity in TAK.
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56 This study was a retrospective study of a sample of patients undergoing immuno-
57 suppressive agents, which may influence of peripheral cell counts. A prospective co-
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hort study with larger numbers of TAK cases is desired to clarify the mechanism of PLR and NLN in TAK disease activity.

Conclusion

In conclusion, the present study is the first to assess PLR and NLR in TAK patients and evaluates their relations with disease activity. We found a higher level of PLR and NPLR in the patient group compared with the control group and in patients with active disease compared with patients in remission. We evaluated their correlation with Kerr's Score, hs-CRP and ESR in the patient group. In light of results of our study, a high PLR or NLR may prove to be indicators of increased inflammatory response associated with the disease activity in TAK patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Contributorship Statement

LP conceived of the study, performed the statistical analysis and drafted the manuscript. JD, HL and TL participated in the design of the study, helped to revise the manuscript. All authors read and approved the final manuscript

Data sharing statement

No additional data are available

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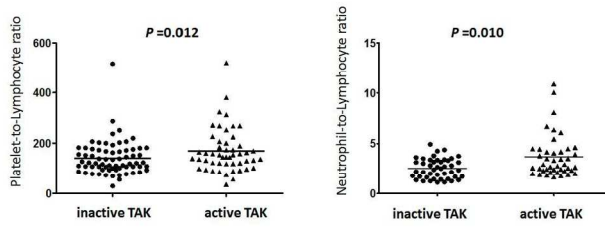


Figure 1. Comparison of Platelet-to-Lymphocyte ratio (PLR) and Neutrophil-to-Lymphocyte ratio (NLR) between inactive and active TAK patients.

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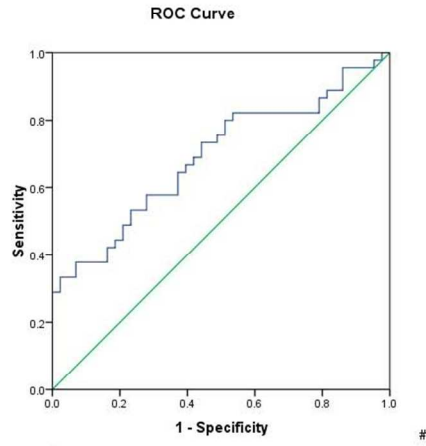


Figure 2. Receiver-operating characteristic curve for the platelet-to-lymphocyte ratio (PLR). The area under the curve was 0.691, with 37.8% sensitivity and 93.0% specificity.

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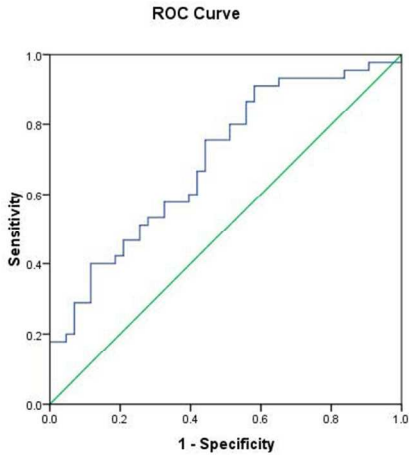


Figure 3. Receiver-operating characteristic curve for the neutrophil-to-lymphocyte Ratio (NLR). The area under the curve was 0.697, with sensitivity and specificity of 75.6% and 55.8%. #

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Table1. Laboratory parameters of TAK patients and health controls

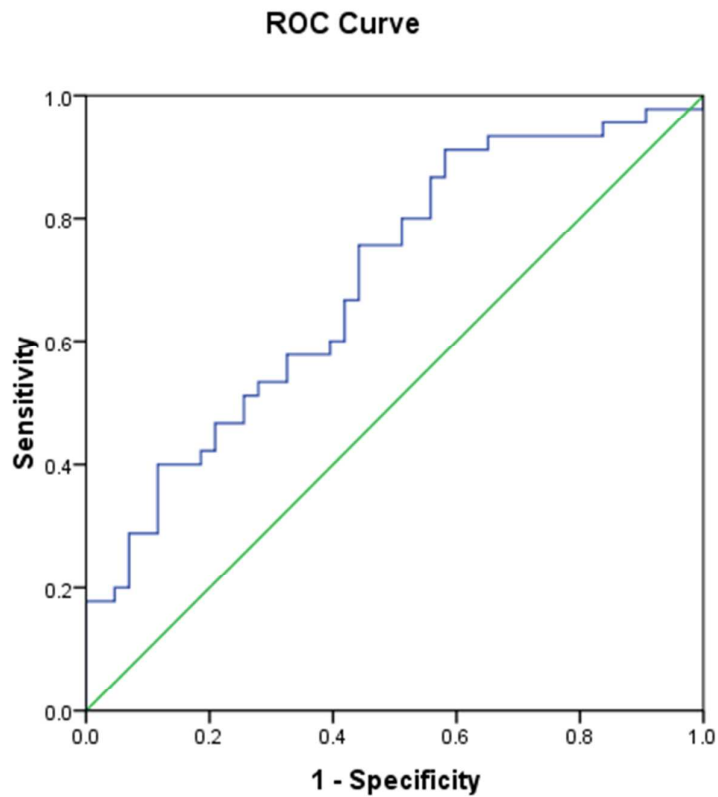
Parameter	Control (n=78)	TAK (n=88)	P-value
Age (year)	36.46±7.23	39.35±15.03	0.235
Gender (female/male)	68/10	78/10	0.774
WBC (10 ⁹ /L)	5.53±1.60	7.43±2.88	0.000
LY (10 ⁹ /L)	1.72±0.46	1.81±0.73	0.342
NE (10 ⁹ /L)	3.37±1.29	4.97±2.44	0.000
PLT (10 ⁹ /L)	247.21±45.49	241.82±79.69	0.387
MPV (fL)	10.21±0.98	10.37±0.97	0.269
PDW %	12.43±1.73	11.98±1.95	0.052
ALT (U/L)	15.40±8.94	17.00±12.48	0.152
BUN (mmol/L)	5.31±2.01	5.52±3.29	0.177
Cr (μmol/L)	63.87±10.47	75.57±14.37	0.422
ESR (mm/1hr)	4.39(2.00-12.00)	19.62(1.00-92.00)	0.000
hs-CRP(mg/L)	0.63(0.08-2.30)	9.50(0.08-38.62)	0.000
NLR	2.01±0.89	3.86±3.28	0.001
PLR	149.58±39.65	167.44±76.58	0.023

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ;MPV, mean platelet volume; PDW, Platelet distribution width; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; NRL, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2. Comparison of the parameters in active and inactive TAK patients

Parameter	inactive TAK (n=45)	Active TAK (n=43)	P-value
Age (year)	39.54±14.75	37.90±15.68	0.227
Gender (female/male)	41/4	37/6	0.454
Disease duration (month)	15.59±6.86	13.94±7.43	0.853
WBC($10^9/L$)	6.61±2.04	8.74±3.65	0.001
LY($10^9/L$)	1.77±0.62	1.87±0.81	0.526
NE ($10^9/L$)	4.33±1.81	5.86±2.34	0.001
PLT($10^9/L$)	224.16±64.14	266.34±91.68	0.004
ALT (U/L)	19.49±16.06	17.62±9.46	0.622
BUN(mmol/L)	5.69±3.96	5.26±2.21	0.498
Cr($\mu\text{mol/L}$)	71.10±21.12	81.60±14.75	0.563
IgA (g/L)	1.82±0.95	2.57±1.30	0.007
IgG (g/L)	9.50±2.27	11.58±4.57	0.011
IgM (g/L)	1.33±0.76	1.38±0.85	0.812
C3 (g/L)	0.97±0.15	1.21±0.20	0.000
C4 (g/L)	0.59±0.29	0.71±0.32	0.079
ESR (mm/1hr)	8.39(1.00-19.00)	33.81(4.00-92.00)	0.000
hs-CRP(mg/L)	1.85(0.08-32.83)	20.04(0.49-38.62)	0.000

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.



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Figure 3. Receiver-operating characteristic curve for the neutrophil -to-lymphocyte Ratio (NLR). The area under the curve was 0.697, with sensitivity and specificity of 75.6% and 55.8%.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT		Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio were Associated to Disease Activity in Patients with Takayasu's Arteritis	
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	3
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
<i>Participants</i>	6	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	4
	10b	Reference standard, in sufficient detail to allow replication	4
	11	Rationale for choosing the reference standard (if alternatives exist)	4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	4
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	4
	15	How indeterminate index test or reference standard results were handled	4
	16	How missing data on the index test and reference standard were handled	4
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	4
	18	Intended sample size and how it was determined	4
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	4
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	5
	25	Any adverse events from performing the index test or the reference standard	5
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	7
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	8

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



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Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Associated with Disease Activity in Patients with Takayasu's Arteritis

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Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Associated with Disease Activity in Patients with Takayasu's Arteritis

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Running title: PLR and NLR are associated with TAK

Abstract

Background Platelet-to-lymphocyte ratio (PLR) and Neutrophil-to-lymphocyte ratio (NLR) has been reported to reflect inflammatory response and disease activity in a variety of autoimmune diseases. **Objectives** This study aimed to evaluate the predictive value of PLR and NLR in disease activity in Takayasu's arteritis (TAK). **Methods** A retrospective study involving 88 TAK patients and 78 healthy controls was performed. We compared the PLR and NLR between patients and healthy controls, and also analyzed the correlations between PLR or NLR and indexes of TAK disease activity. **Results** Increased PLR and NLR were observed in TAK patients. PLR was positively correlated with hs-CRP ($r=0.239$, $P=0.010$) and ESR ($r = 0.270$, $P=0.010$), NLR also exhibited a positive relationship with Kerr's score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$). In addition, a PLR level of 183.39 was determined as predictive cut-off value of TAK (sensitivity 37.8%, specificity 93.0%, AUC=0.691); An NLR level of 2.417 was determined as predictive cut-off value of TAK (sensitivity 75.6%, specificity 55.8%, AUC=0.697). **Conclusions** PLR and NLR could be as useful marker to reflect inflammation and disease activity in TAK patients.

Keywords Takayasu's arteritis; platelet-to-lymphocyte ratio; neutrophil-to-lymphocyte ratio

Strengths and limitations of this study

- This study is the first to assess the PLR and NLR could be as useful marker to reflect inflammation and disease activity in TAK patients.
- This study provides the accurate cutoff value of PLR and NLR to evaluated disease activity of TAK.
- This study provides a simple and convenient method for the clinical evaluation of TAK disease activity.
- This is a retrospective cross-sectional study, prospective cohort study to be further carried out in the future.

Introduction

Takayasu's arteritis (TAK) is a systemic autoimmune large vessel vasculitis, mainly involving the aorta and its branches. TAK causes aortic injury such as stenosis, occlusion, hemangioma or dissection and other serious complications, which result in tissue and organ ischemia, dysfunction and even vascular rupture leading to sudden death in severe cases[1]. The pathology of TAK is characterized by inflammatory cell infiltration along with granulomatous inflammation as well as by excessive pro-inflammatory cytokines production[2]. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to monitor disease progression. Although CRP and ESR are often useful to follow patients with TAK, some patients suffer from worsening of vasculitis without increasing CRP or ESR. These systemic inflammatory markers do not always show a positive correlation with inflammatory activity in the vessel wall[3].

Recent studies have shown that an abnormal NLR level is also associated with autoimmune disease, such as psoriasis[4], ulcerative colitis[5], rheumatoid arthritis (RA)[6], systemic lupus erythematosus (SLE) ,Sjögren's syndrome (pSS)[7] and Behçet's disease[8]. Likewise, platelets also play an active role in inflammation, and play regulatory roles in the immune system, and platelet-to-lymphocyte ratio (PLR) is also suggested as a potential marker to determine inflammation in recent years.

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3 Similar to NLR, PLR is also used as an index for differential diagnosis or prognostic
4 prediction of diverse diseases such as cancer[9], metabolic syndrome[10] and in-
5 flammatory diseases, especially for evaluating the cardiovascular risk and events[11].
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7 However, research about the association of PLR and NLR with TAK is limited. There-
8 fore, in this retrospective study, we analyzed the medical records of 88 TAK patients
9 and 78 healthy individuals, to evaluate the PLR or NLR in patients with TAK and com-
10 pared it with controls. We aim to define the possible association of PLR and NLR with
11 inflammatory response and disease activity in TAK. Furthermore, we also evaluated
12 the relationship with PLR or NLR on TAK disease activity.
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21 **Methods**

22 **Patients**

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24 A total of 88 patients with TAK were enrolled in this study according to the criteria
25 for classification of TAK developed by American College of Rheumatology (ACR) in
26 1990, all of the patients had glucocorticoid withdrawal for at least 6 months or were
27 newly diagnosed without treatment. Patients who had chronic or current infections,
28 tumors, hematologic diseases, other autoimmune diseases, lymphoproliferative dis-
29 orders, hepatosplenic diseases or a history of allergic diseases were excluded. Dis-
30 ease activity was assessed in TAK patients by using a modified version of Kerr's crite-
31 ria. Kerr's criteria is used to define "active disease" if two of the following criteria are
32 positive: (1) systemic features with no other cause; (2) elevated ESR; (3) indications
33 of vascular ischemia or inflammation (e.g., claudication, diminished or absent pulses,
34 bruit, vascular pain, asymmetric blood pressure); or (4) typical angiographic features
35 (including any imaging method in addition to conventional angiography). All the pa-
36 tients were recruited from the Department of Rheumatology and Immunology, Bei-
37 jing Anzhen Hospital during the period of January 2013 to December 2015. 78 age-
38 and sex-matched healthy donors were recruited from the Health Care Center of An-
39 zhen Hospital. This study was approved by the Ethics Committee of Beijing Anzhen
40 Hospital.
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56 **Blood sample collection**

57 For each subject, 4 ml of venous blood was drawn in the morning after a 12-hour
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3 fasting. The blood was then placed in a tube without anticoagulation, and the serum
4 was collected after the blood was coagulated and centrifuged 3000 r/m for 5
5 minutes. The total and differential leukocyte counts were determined by the Beck-
6 man Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). A Hitachi
7 7600-120 automatic biochemical analyzer was used to test the serum parameters.
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13 14 15 **Statistical analysis**

16 Values are expressed as means \pm standard error (means \pm SEM). Differences between
17 measured parameters in patients and controls were assessed by unpaired T
18 test. If the data were not normally distributed, the Mann-Whitney test was applied;
19 the assessment of qualitative parameters was performed by χ^2 test. Pearson's approach
20 was used to quantitate the correlation between variables. A receiver-operating
21 characteristic (ROC) curve was constructed to determine the predictive value of PLR
22 and NLR in patients group. A P value <0.05 was considered statistically significant.
23 All statistical studies were carried out with the SPSS program (version 16.0, SPSS,
24 Chicago, Illinois).
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34 35 **Results**

36 **Basic characteristics of the study sample**

37 Clinical characteristics and laboratory findings of the 88 TAK patients and 78 healthy
38 controls are given in Table 1. Patients with TAK had a median age of 39.35 years
39 (range: 17-63), with a gender distribution of 78 women (88.63%) and 10 men
40 (11.36%). In the control group, the median age was 36.46 years (range: 18-57) with a
41 gender distribution of 68 women (87.18%) and 10 men (12.82%). There was no difference
42 in age or gender between the TAK and control groups. The total WBC count and
43 neutrophil count were significantly higher in the patient group ($p=0.000$) ($p=0.000$).
44 PLR and NLR were markedly elevated in TAK patients than that of the controls
45 ($p=0.023$) ($p=0.001$). ESR and serum hs-CRP levels were higher in the patient
46 group than that in the controls ($p=0.000$) ($p=0.000$). No differences of other blood
47 parameters such as lymphocyte (LY) count, PLT count, serum levels of alanine
48 aminotransferase (ALT), urea nitrogen (BUN) and creatinine (Cr) were observed between
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3 the groups (Table 1).
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6 **PLR and NLR were increased in TAK patients with disease activity**

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8 In our study the total WBC count, neutrophil count and platelet count were all in-
9 creased in the active TAK group ($p=0.001$) ($p=0.001$) ($p=0.004$). Serum immunoglobu-
10 lin (Ig)A, IgG and complement 3 were significantly higher in the active TAK group
11 than those in the inactive patients ($p=0.007$) ($p=0.011$) ($p=0.000$). ESR and serum hs-
12 CRP levels were higher in the active patients group than those in the inactive group
13 ($p=0.000$) ($p=0.000$) (Table 2). As shown in figure 1, both PLR and NLR were signifi-
14 cantly elevated in the active TAK patients compared to the inactive group ($p=0.012$)
15 ($p=0.010$).
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24 **PLR and NLR had positive correlations to disease activity in TAK patients.**

25 As shown in Table3, PLR was positively correlated with hs-CRP ($r =0.239$, $P=0.010$)
26 and ESR ($r = 0.270$, $P=0.010$). NLR also exhibited a positive relationship with Kerr's
27 score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$) (Fig-
28 ure 3).
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34 **Receiver-operating characteristic (ROC) curves of PLR and NLR for the TAK disease** 35 **activity (Kerr's score)**

36 We performed an ROC analysis to determine whether the best cutoff value of PLR
37 and NLR predicts TAK disease activity (Kerr's score). For PLR, the area under the
38 curve was 0.691 (95% confidence interval [CI] 0.580-0.802, $P =0.002$), and the best
39 cutoff value was 183.390, with sensitivity and specificity of 37.8% and 93.0%. For
40 NLR, the area under the curve was 0.697 (95% confidence interval [CI] 0.588-0.806, P
41 $=0.001$), and the best cutoff value was 2.417, with sensitivity and specificity of 75.6%
42 and 55.8% (Figure 2), respectively (Figure 3).
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52 **Discussion**

53 Our present study analyzed the correlations of PLR and NLR with the disease activity
54 in patients with TAK. The findings first showed that both PLR and NLR were increased
55 in TAK, especially in the patients with disease activity. There were positive correla-
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3 tions in TAK patients between PLR and disease activity and between NLR and disease
4 activity. Furthermore, our results suggest that PLR and NLR may be potential indica-
5 tors of assessment of the disease activity in TAK.
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10 Platelets play an active role in inflammation. In many studies of chronic inflammato-
11 ry arthritis, evidence has been found for an increase in platelet activation[11, 12].
12 Platelet inhibition was found to counterbalance the rises in IL-6 and the C-reactive
13 protein in patients with acute cardiovascular diseases. Platelets extensively interact
14 with leukocytes in vascular diseases such as atherosclerosis and are regarded as cen-
15 tral players in the pathophysiology of vascular inflammation. Increased mass of cir-
16 culating platelets is likely a consequence of chronic inflammation. Activated platelets
17 not only produce growth factors such as platelet-derived growth factor (PDGF) and
18 transforming growth factor- β (TGF- β), but also release chemokines, which have im-
19 portant effects in vascular inflammation, leading to thrombosis[13]. Similar to other
20 inflammatory diseases, even in inactive TAK patients, atherosclerosis risk is also in-
21 creased[14]. Study has suggested the scores of delayed contrast-enhanced magnetic
22 resonance imaging were moderately correlated to CRP, platelet count and fibrinogen
23 levels ($p < 0.05$) [15]. There are some basic studies about use of antiplatelet agents in
24 TAK [16, 17]. Antiplatelet treatment may also lower the frequency of ischaemic
25 events in TA[18]. In the affected limb by arterial stenosis, more platelet aggregation
26 and higher levels of thromboxane were reported in TAK patients, and these findings
27 were shown to improve after 80mg/day aspirin treatment[14]. It is believed that en-
28 dothelial injury and dysfunction caused by increased platelet activity and vascular
29 inflammation are important factors for thrombosis development in TAK. A recent
30 retrospective observational study suggested that antiplatelet therapy was associated
31 with a lower frequency of ischemic events in patients with TAK[19]. Prednisone at a
32 dosage of 1 mg/kg twice a day decreased the platelet count within 45 days of its ini-
33 tiation. Takayasu's arteritis should be considered in the differential diagnosis of un-
34 explained thrombocytosis, particularly in young women[20]. In our current study,
35 there was no difference in PLT counts between TAK patients and controls, while the
36 PLT counts of active patients were significantly higher than those of inactive pa-
37 tients, and that correlated with disease activity indexes such as hs-CRP and ESR. ROC
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3 analysis has suggested that PLR predicts TAK disease activity (Kerr's score). Our re-
4 sults indicated that the platelet is activated in TAK, and parallel to disease activity.
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8 Neutrophils, also essential mediators of host defense, can produce many inflam-
9 matory mediators and cytokines and bridge the innate and adaptive immune re-
10 sponses in autoimmune diseases[21]. Research evidence has demonstrated that
11 neutrophils persist beyond acute inflammation to initiate and perpetuate chronic
12 inflammation. Recent studies have indicated that changes in neutrophil are involved
13 in the development of a variety of autoimmune diseases. There was a higher NLR in
14 psoriasis vulgaris patients than the control group[4], and the abnormal NLR level was
15 associated with RA[6], systemic lupus erythematosus (SLE), Sjögren's syndrome
16 (pSS)[10] and Behçet's disease[8]. Another study investigated the neutrophil-platelet
17 interaction in patients with granulomatosis with polyangiitis and suggested that
18 platelet-neutrophil aggregates correlating positively with the disease activity
19 score[22]. Pro-inflammatory cytokines IL-17, IL-8, IFN- γ and TNF- α also play promi-
20 nent roles in the recruitment, activation and survival of neutrophils at inflammatory
21 sites[23], and expression of these cytokines was significantly increased in TAK [24]. In
22 RA, anti-TNF- α therapies reduce IL-33 receptor expression on neutrophils and subse-
23 quently decrease neutrophil migration and impaired chemotaxis of neutrophils may
24 lead to a decrease in inflammation and disease severity in RA[25]. Our data showed
25 that neutrophils in TAK patients were increased in the patient group, and positively
26 correlated with disease activity. This is similar to previous results in other autoim-
27 mune diseases. Similarly, our study found that both total WBC and neutrophil counts
28 were significantly higher in TAK patients than those in the controls, and NLR was sig-
29 nificantly higher in active patients. In order to clarify the correlations between NLR
30 and TAK disease activity, we evaluated the level of the NLR and Kerr's score, hs-CRP
31 and ESR in patients with TAK and found that NLR is positively correlated with TAK
32 disease activity. All these findings suggest that PLR and NLR could be used to reflect
33 inflammatory response and disease activity in TAK.
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56 This study was a retrospective study of a sample of patients undergoing immuno-
57 suppressive agents, which may influence of peripheral cell counts. A prospective co-
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hort study with larger numbers of TAK cases is desired to clarify the mechanism of PLR and NLN in TAK disease activity.

Conclusion

In conclusion, the present study is the first to assess PLR and NLR in TAK patients and evaluates their relations with disease activity. We found a higher level of PLR and NPLR in the patient group compared with the control group and in patients with active disease compared with patients in remission. We evaluated their correlation with Kerr's Score, hs-CRP and ESR in the patient group. In light of results of our study, a high PLR or NLR may prove to be indicators of increased inflammatory response associated with the disease activity in TAK patients.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Contributorship Statement

LP conceived of the study, performed the statistical analysis and drafted the manuscript. JD, HL and TL participated in the design of the study, helped to revise the manuscript. All authors read and approved the final manuscript

Data sharing statement

No additional data are available

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For peer review only

Table1. Laboratory parameters of TAK patients and health controls

Parameter	Control (n=78)	TAK (n=88)	P-value
Age (year)	36.46±7.23	39.35±15.03	0.235
Gender (female/male)	68/10	78/10	0.774
WBC (10 ⁹ /L)	5.53±1.60	7.43±2.88	0.000
LY (10 ⁹ /L)	1.72±0.46	1.81±0.73	0.342
NE (10 ⁹ /L)	3.37±1.29	4.97±2.44	0.000
PLT (10 ⁹ /L)	247.21±45.49	241.82±79.69	0.387
MPV(fL)	10.21±0.98	10.37±0.97	0.269
PDW %	12.43±1.73	11.98±1.95	0.052
ALT (U/L)	15.40±8.94	17.00±12.48	0.152
BUN (mmol/L)	5.31±2.01	5.52±3.29	0.177
Cr (μmol/L)	63.87±10.47	75.57±14.37	0.422
ESR (mm/1hr)	4.39(2.00-12.00)	19.62(1.00-92.00)	0.000
hs-CRP(mg/L)	0.63(0.08-2.30)	9.50(0.08-38.62)	0.000
NLR	2.01±0.89	3.86±3.28	0.001
PLR	149.58±39.65	167.44±76.58	0.023

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ;MPV, mean platelet volume; PDW, Platelet distribution width; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; NRL, neutrophil -to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2. Comparison of the parameters in active and inactive TAK patients

Parameter	inactive TAK (n=45)	Active TAK (n=43)	P-value
Age (year)	39.54±14.75	37.90±15.68	0.227
Gender (female/male)	41/4	37/6	0.454
Disease duration (month)	15.59±6.86	13.94±7.43	0.853
WBC(10 ⁹ /L)	6.61±2.04	8.74±3.65	0.001
LY(10 ⁹ /L)	1.77±0.62	1.87±0.81	0.526
NE (10 ⁹ /L)	4.33±1.81	5.86±2.34	0.001
PLT(10 ⁹ /L)	224.16±64.14	266.34±91.68	0.004
ALT (U/L)	19.49±16.06	17.62±9.46	0.622
BUN(mmol/L)	5.69±3.96	5.26±2.21	0.498
Cr(μmol/L)	71.10±21.12	81.60±14.75	0.563
IgA (g/L)	1.82±0.95	2.57±1.30	0.007
IgG (g/L)	9.50±2.27	11.58±4.57	0.011
IgM (g/L)	1.33±0.76	1.38±0.85	0.812
C3 (g/L)	0.97±0.15	1.21±0.20	0.000
C4 (g/L)	0.59±0.29	0.71±0.32	0.079
ESR (mm/1hr)	8.39(1.00-19.00)	33.81(4.00-92.00)	0.000
hs-CRP(mg/L)	1.85(0.08-32.83)	20.04(0.49-38.62)	0.000

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Correlations of laboratory findings with disease activity in TAK Patients

	Kerr's Score		hs-CRP		ESR	
	<i>r</i>	<i>p-value</i>	<i>r</i>	<i>p-value</i>	<i>r</i>	<i>p-value</i>
WBC	0.336	0.000	0.458	0.000	0.388	0.000
LY	0.054	0.602	0.119	0.205	0.276	0.023
NE	0.311	0.001	0.466	0.000	0.327	0.356
PLT	0.353	0.000	0.345	0.000	0.490	0.000
PLR	0.185	0.052	0.239	0.010	0.270	0.010
NLR	0.284	0.002	0.313	0.006	0.249	0.019

Abbreviations: ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C - reactive protein; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ; PLR, platelet-to-lymphocyte ratio; NRL, neutrophil -to-lymphocyte ratio;.

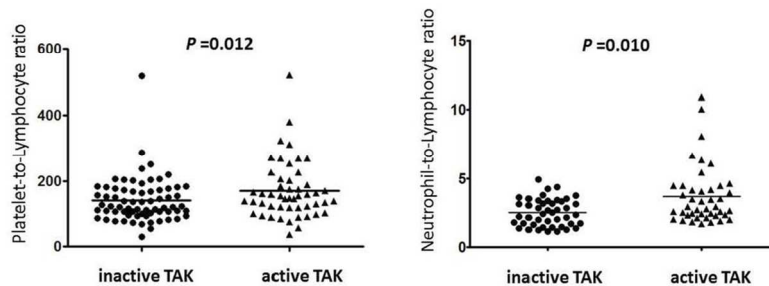


Figure 1. Comparison of Platelet-to-Lymphocyte ratio (PLR) and Neutrophil-to-Lymphocyte ratio (NLR) between inactive and active TAK patients.

105x74mm (300 x 300 DPI)

Review only

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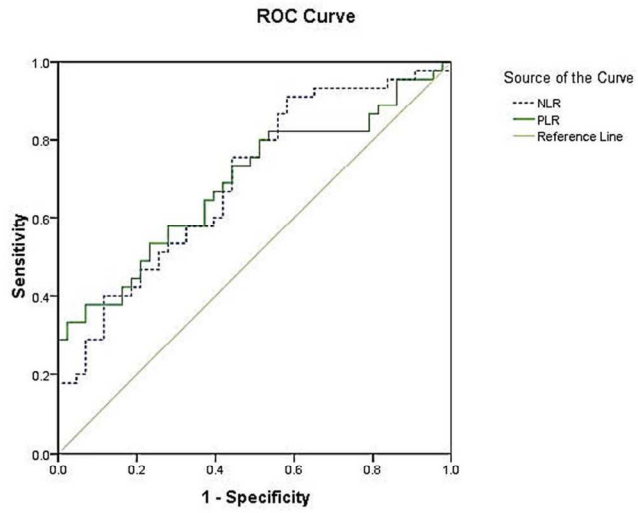


Figure 2. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (Kerr: Criteria as the standard). For PLR, the area under the curve was 0.691, with 37.8% sensitivity and 93.0% specificity. for NLR, the area under the curve was 0.697, with sensitivity and specificity of 75.6% and 55.8%.

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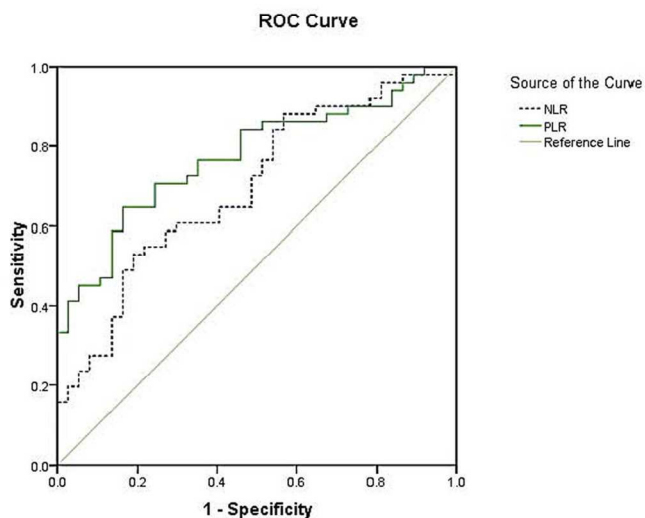


Figure 3. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (CRP as the standard). For PLR, the area under the curve was 0.775, with 64.7% sensitivity and 83.8% specificity, for NLR, the area under the curve was 0.698, with sensitivity and specificity of 52.9% and 81.1%.

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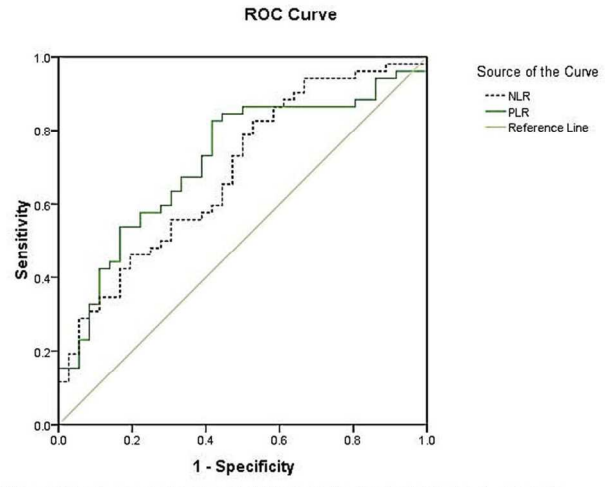


Figure 4. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (ESR as the standard). For PLR, the area under the curve was 0.718, with 53.8% sensitivity and 83.3% specificity, for NLR, the area under the curve was 0.688, with sensitivity and specificity of 82.7% and 47.2%.

117x166mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT		Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio were Associated to Disease Activity in Patients with Takayasu's Arteritis	
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	3
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
<i>Participants</i>	6	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	4
	10b	Reference standard, in sufficient detail to allow replication	4
	11	Rationale for choosing the reference standard (if alternatives exist)	4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	4
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	4
	15	How indeterminate index test or reference standard results were handled	4
	16	How missing data on the index test and reference standard were handled	4
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	4
	18	Intended sample size and how it was determined	4
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	4
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	5
	25	Any adverse events from performing the index test or the reference standard	5
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	7
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	8

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



BMJ Open

Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Associated with Disease Activity in Patients with Takayasu's Arteritis: A case-control study

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Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	IMMUNOLOGY, Rheumatology < INTERNAL MEDICINE, Vascular medicine < INTERNAL MEDICINE

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Manuscripts

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Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio Associated with Disease Activity in Patients with Takayasu's Arteritis

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Running title: PLR and NLR are associated with TAK

Abstract

Background Platelet-to-lymphocyte ratio (PLR) and Neutrophil-to-lymphocyte ratio (NLR) has been reported to reflect inflammatory response and disease activity in a variety of autoimmune diseases. **Objectives** This study aimed to evaluate the predictive value of PLR and NLR in disease activity in Takayasu's arteritis (TAK). **Methods** A retrospective study involving 88 TAK patients and 78 healthy controls was performed. We compared the PLR and NLR between patients and healthy controls, and also analyzed the correlations between PLR or NLR and indexes of TAK disease activity. **Results** Increased PLR and NLR were observed in TAK patients. PLR was positively correlated with hs-CRP ($r=0.239$, $P=0.010$) and ESR ($r = 0.270$, $P=0.010$), NLR also exhibited a positive relationship with Kerr's score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$). In addition, a PLR level of 183.39 was determined as predictive cut-off value of TAK (sensitivity 37.8%, specificity 93.0%, AUC=0.691); An NLR level of 2.417 was determined as predictive cut-off value of TAK (sensitivity 75.6%, specificity 55.8%, AUC=0.697). **Conclusions** PLR and NLR could be as useful markers to reflect inflammation and disease activity in TAK patients.

Keywords Takayasu's arteritis; platelet-to-lymphocyte ratio; neutrophil-to-lymphocyte ratio

Strengths and limitations of this study

- This study is the first to assess the PLR and NLR could be as useful marker to reflect inflammation and disease activity in TAK patients.
- This study provides the accurate cutoff value of PLR and NLR to evaluate disease activity of TAK.
- This study provides a simple and convenient method for the clinical evaluation of TAK disease activity.
- This is a retrospective cross-sectional study, prospective cohort study to be further carried out in the future.

Introduction

Takayasu's arteritis (TAK) is a systemic autoimmune large vessel vasculitis, mainly involving the aorta and its branches. TAK causes aortic injury such as stenosis, occlusion, hemangioma or dissection and other serious complications, which result in tissue and organ ischemia, dysfunction and even vascular rupture leading to sudden death in severe cases[1]. The pathology of TAK is characterized by inflammatory cell infiltration along with granulomatous inflammation as well as by excessive pro-inflammatory cytokine production[2]. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are commonly used to monitor disease progression. Although CRP and ESR are often useful to follow patients with TAK, some patients suffer from worsening of vasculitis without increasing CRP or ESR. These systemic inflammatory markers do not always show a positive correlation with inflammatory activity in the vessel wall[3].

Recent studies have shown that an abnormal NLR level is also associated with autoimmune disease, such as psoriasis[4], ulcerative colitis[5], rheumatoid arthritis (RA)[6], systemic lupus erythematosus (SLE), Sjögren's syndrome (pSS)[7] and Behçet's disease[8]. Likewise, platelets also play an active role in inflammation, and play regulatory roles in the immune system, and platelet-to-lymphocyte ratio (PLR) is also suggested as a potential marker to determine inflammation in recent years.

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3 Similar to NLR, PLR is also used as an index for differential diagnosis or prognostic
4 prediction of diverse diseases such as cancer[9], metabolic syndrome[10] and in-
5 flammatory diseases, especially for evaluating the cardiovascular risk and events[11].
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7 However, research about the association of PLR and NLR with TAK is limited. There-
8 fore, in this retrospective study, we analyzed the medical records of 88 TAK patients
9 and 78 healthy individuals, to evaluate the PLR or NLR in patients with TAK and com-
10 pared it with controls. We aim to define the possible association of PLR and NLR with
11 inflammatory response and disease activity in TAK. Furthermore, we also evaluated
12 the relationship with PLR or NLR on TAK disease activity.
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21 **Methods**

22 **Patients**

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24 A total of 88 patients with TAK were enrolled in this study according to the criteria
25 for classification of TAK developed by American College of Rheumatology (ACR) in
26 1990, all of the patients had glucocorticoid withdrawal for at least 6 months or were
27 newly diagnosed without treatment. Patients who had chronic or current infections,
28 tumors, hematologic diseases, other autoimmune diseases, lymphoproliferative dis-
29 orders, hepatosplenic diseases or a history of allergic diseases were excluded. Dis-
30 ease activity was assessed in TAK patients by using a modified version of Kerr's crite-
31 ria. Kerr's criteria is used to define "active disease" if two of the following criteria are
32 positive: (1) systemic features with no other cause; (2) elevated ESR; (3) indications
33 of vascular ischemia or inflammation (e.g., claudication, diminished or absent pulses,
34 bruit, vascular pain, asymmetric blood pressure); or (4) typical angiographic features
35 (including any imaging method in addition to conventional angiography). All the pa-
36 tients were recruited from the Department of Rheumatology and Immunology, Bei-
37 jing Anzhen Hospital during the period of January 2013 to December 2015. 78 age-
38 and sex-matched healthy donors were recruited from the Health Care Center of An-
39 zhen Hospital. This study was approved by the Ethics Committee of Beijing Anzhen
40 Hospital.
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56 **Blood sample collection**

57 For each subject, 4 ml of venous blood was drawn in the morning after a 12-hour
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3 fasting. The blood was then placed in a tube without anticoagulation, and the serum
4 was collected after the blood was coagulated and centrifuged 3000 r/m for 5
5 minutes. The total and differential leukocyte counts were determined by the Beck-
6 man Coulter LH 780 (Beckman Coulter Ireland Inc., Mervue, Galway, Ireland). A Hitachi
7 7600-120 automatic biochemical analyzer was used to test the serum parameters.
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13 14 15 **Statistical analysis**

16 Values are expressed as means \pm standard error (means \pm SEM). Differences be-
17 tween measured parameters in patients and controls were assessed by unpaired T
18 test. If the data were not normally distributed, the Mann-Whitney test was applied;
19 the assessment of qualitative parameters was performed by χ^2 test. Pearson's ap-
20 proach was used to quantitate the correlation between variables. A receiver-
21 operating characteristic (ROC) curve was constructed to determine the predictive
22 value of PLR and NLR in patients group. A P value <0.05 was considered statistically
23 significant. All statistical studies were carried out with the SPSS program (version
24 16.0, SPSS, Chicago, Illinois).
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35 **Results**

36 **Basic characteristics of the study sample**

37 Clinical characteristics and laboratory findings of the 88 TAK patients and 78 healthy
38 controls are given in Table 1. Patients with TAK had a median age of 39.35 years
39 (range: 17-63), with a gender distribution of 78 women (88.63%) and 10 men
40 (11.36%). In the control group, the median age was 36.46 years (range: 18-57) with a
41 gender distribution of 68 women (87.18%) and 10 men (12.82%). There was no dif-
42 ference in age or gender between the TAK and control groups. The total WBC count
43 and neutrophil count were significantly higher in the patient group ($p=0.000$)
44 ($p=0.000$). PLR and NLR were markedly elevated in TAK patients than that of the con-
45 trols ($p=0.023$) ($p=0.001$). ESR and serum hs-CRP levels were higher in the patient
46 group than that in the controls ($p=0.000$) ($p=0.000$). No differences of other blood
47 parameters such as lymphocyte (LY) count, PLT count, serum levels of alanine ami-
48 notransferase (ALT), urea nitrogen (BUN) and creatinine (Cr) were observed between
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3 the groups (Table 1).
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6 **PLR and NLR were increased in TAK patients with disease activity**

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8 In our study the total WBC count, neutrophil count and platelet count were all in-
9 creased in the active TAK group ($p=0.001$) ($p=0.001$) ($p=0.004$). Serum immunoglobu-
10 lin (Ig)A, IgG and complement 3 were significantly higher in the active TAK group
11 than those in the inactive patients ($p=0.007$) ($p=0.011$) ($p=0.000$). ESR and serum hs-
12 CRP levels were higher in the active patients group than those in the inactive group
13 ($p=0.000$) ($p=0.000$) (Table 2). As shown in figure 1, both PLR and NLR were signifi-
14 cantly elevated in the active TAK patients compared to the inactive group ($p=0.012$)
15 ($p=0.010$).
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24 **PLR and NLR had positive correlations to disease activity in TAK patients.**

25 As shown in Table 3, PLR was positively correlated with hs-CRP ($r = 0.239$, $P=0.010$)
26 and ESR ($r = 0.270$, $P=0.010$). NLR also exhibited a positive relationship with Kerr's
27 score ($r=0.284$, $P=0.002$), hs-CRP ($r=0.313$, $P=0.006$) and ESR ($r=0.249$, $P=0.019$) (Fig-
28 ure 3).
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34 **Receiver-operating characteristic (ROC) curves of PLR and NLR for the TAK disease** 35 **activity (Kerr's score)**

36 We performed an ROC analysis to determine whether the best cutoff value of PLR
37 and NLR predicts TAK disease activity (Kerr's score). For PLR, the area under the
38 curve was 0.691 (95% confidence interval [CI] 0.580-0.802, $P = 0.002$), and the best
39 cutoff value was 183.390, with sensitivity and specificity of 37.8% and 93.0%. For
40 NLR, the area under the curve was 0.697 (95% confidence interval [CI] 0.588-0.806, P
41 $=0.001$), and the best cutoff value was 2.417, with sensitivity and specificity of 75.6%
42 and 55.8% (Figure 2), respectively (Figure 3).
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52 **Discussion**

53 Our present study analyzed the correlations of PLR and NLR with the disease activity
54 in patients with TAK. The findings first showed that both PLR and NLR were increased
55 in TAK, especially in the patients with disease activity. There were positive correla-
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3 tions in TAK patients between PLR and disease activity and between NLR and disease
4 activity. Furthermore, our results suggest that PLR and NLR may be potential indica-
5 tors of assessment of the disease activity in TAK.
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10 Platelets play an active role in inflammation. In many studies of chronic inflammatory
11 arthritis, evidence has been found for an increase in platelet activation[11, 12].
12 Platelet inhibition was found to counterbalance the rises in IL-6 and the C-reactive
13 protein in patients with acute cardiovascular diseases. Platelets extensively interact
14 with leukocytes in vascular diseases such as atherosclerosis and are regarded as cen-
15 tral players in the pathophysiology of vascular inflammation. Increased mass of cir-
16 culating platelets is likely a consequence of chronic inflammation. Activated platelets
17 not only produce growth factors such as platelet-derived growth factor (PDGF) and
18 transforming growth factor- β (TGF- β), but also release chemokines, which have im-
19 portant effects in vascular inflammation, leading to thrombosis[13]. Similar to other
20 inflammatory diseases, even in inactive TAK patients, atherosclerosis risk is also in-
21 creased[14]. Study has suggested the scores of delayed contrast-enhanced magnetic
22 resonance imaging were moderately correlated to CRP, platelet count and fibrinogen
23 levels ($p < 0.05$) [15]. There are some basic studies about use of antiplatelet agents in
24 TAK [16, 17]. Antiplatelet treatment may also lower the frequency of ischaemic
25 events in TA[18]. In the affected limb by arterial stenosis, more platelet aggregation
26 and higher levels of thromboxane were reported in TAK patients, and these findings
27 were shown to improve after 80mg/day aspirin treatment[14]. It is believed that en-
28 dothelial injury and dysfunction caused by increased platelet activity and vascular
29 inflammation are important factors for thrombosis development in TAK. A recent
30 retrospective observational study suggested that antiplatelet therapy was associated
31 with a lower frequency of ischemic events in patients with TAK[19]. Prednisone at a
32 dosage of 1 mg/kg twice a day decreased the platelet count within 45 days of its ini-
33 tiation. Takayasu's arteritis should be considered in the differential diagnosis of un-
34 explained thrombocytosis, particularly in young women[20]. In our current study,
35 there was no difference in PLT counts between TAK patients and controls, while the
36 PLT counts of active patients were significantly higher than those of inactive pa-
37 tients, and that correlated with disease activity indexes such as hs-CRP and ESR. ROC
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3 analysis has suggested that PLR predicts TAK disease activity (Kerr's score). Our results
4 indicated that the platelet is activated in TAK, and parallel to disease activity.
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8 Neutrophils, also essential mediators of host defense, can produce many inflam-
9 matory mediators and cytokines and bridge the innate and adaptive immune re-
10 sponses in autoimmune diseases[21]. Research evidence has demonstrated that
11 neutrophils persist beyond acute inflammation to initiate and perpetuate chronic
12 inflammation. Recent studies have indicated that changes in neutrophil are involved
13 in the development of a variety of autoimmune diseases. There was a higher NLR in
14 psoriasis vulgaris patients than the control group[4], and the abnormal NLR level was
15 associated with RA[6], systemic lupus erythematosus (SLE), Sjögren's syndrome
16 (pSS)[10] and Behçet's disease[8]. Another study investigated the neutrophil-platelet
17 interaction in patients with granulomatosis with polyangiitis and suggested that
18 platelet-neutrophil aggregates correlating positively with the disease activity
19 score[22]. Pro-inflammatory cytokines IL-17, IL-8, IFN- γ and TNF- α also play promi-
20 nent roles in the recruitment, activation and survival of neutrophils at inflammatory
21 sites[23], and expression of these cytokines was significantly increased in TAK [24]. In
22 RA, anti-TNF- α therapies reduce IL-33 receptor expression on neutrophils and subse-
23 quently decrease neutrophil migration and impaired chemotaxis of neutrophils may
24 lead to a decrease in inflammation and disease severity in RA[25]. Our data showed
25 that neutrophils in TAK patients were increased in the patient group, and positively
26 correlated with disease activity. This is similar to previous results in other autoim-
27 mune diseases. Similarly, our study found that both total WBC and neutrophil counts
28 were significantly higher in TAK patients than those in the controls, and NLR was sig-
29 nificantly higher in active patients. In order to clarify the correlations between NLR
30 and TAK disease activity, we evaluated the level of the NLR and Kerr's score, hs-CRP
31 and ESR in patients with TAK and found that NLR is positively correlated with TAK
32 disease activity. All these findings suggest that PLR and NLR could be used to reflect
33 inflammatory response and disease activity in TAK.
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56 This study was a retrospective study of a sample of patients undergoing immunosup-
57 pressive agents, which may influence of peripheral cell counts. A prospective cohort
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3 study with larger numbers of TAK cases is desired to clarify the mechanism of PLR
4 and NLN in TAK disease activity.
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8 **Conclusion**

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10 In conclusion, the present study is the first to assess PLR and NLR in TAK patients and
11 evaluates their relations with disease activity. We found a higher level of PLR and
12 NPLR in the patient group compared with the control group and in patients with ac-
13 tive disease compared with patients in remission. We evaluated their correlation
14 with Kerr's Score, hs-CRP and ESR in the patient group. In light of results of our
15 study, a high PLR or NLR may prove to be indicators of increased inflammatory re-
16 sponse associated with the disease activity in TAK patients.
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23 **Declaration of Conflicting Interests**

24
25 The author(s) declared no potential conflicts of interest with respect to the research,
26 authorship, and/or publication of this article.
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31
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34 analysis, decision to publish, or preparation.
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40 **Contributorship Statement**

41 LP conceived of the study, performed the statistical analysis and drafted the manu-
42 script. JD, HL and TL participated in the design of the study, helped to revise the
43 manuscript. All authors read and approved the final manuscript
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47 **Data sharing statement**

48 No additional data are available
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Table1. Laboratory parameters of TAK patients and health controls

Parameter	Control (n=78)	TAK (n=88)	P-value
Age (year)	36.46±7.23	39.35±15.03	0.235
Gender (female/male)	68/10	78/10	0.774
WBC (10 ⁹ /L)	5.53±1.60	7.43±2.88	0.000
LY (10 ⁹ /L)	1.72±0.46	1.81±0.73	0.342
NE (10 ⁹ /L)	3.37±1.29	4.97±2.44	0.000
PLT (10 ⁹ /L)	247.21±45.49	241.82±79.69	0.387
MPV(fL)	10.21±0.98	10.37±0.97	0.269
PDW %	12.43±1.73	11.98±1.95	0.052
ALT (U/L)	15.40±8.94	17.00±12.48	0.152
BUN (mmol/L)	5.31±2.01	5.52±3.29	0.177
Cr (μmol/L)	63.87±10.47	75.57±14.37	0.422
ESR (mm/1hr)	4.39(2.00-12.00)	19.62(1.00-92.00)	0.000
hs-CRP(mg/L)	0.63(0.08-2.30)	9.50(0.08-38.62)	0.000
NLR	2.01±0.89	3.86±3.28	0.001
PLR	149.58±39.65	167.44±76.58	0.023

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ;MPV, mean platelet volume; PDW, Platelet distribution width; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; NRL, neutrophil -to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2. Comparison of the parameters in active and inactive TAK patients

Parameter	inactive TAK (n=45)	Active TAK (n=43)	P-value
Age (year)	39.54±14.75	37.90±15.68	0.227
Gender (female/male)	41/4	37/6	0.454
Disease duration (month)	15.59±6.86	13.94±7.43	0.853
WBC(10 ⁹ /L)	6.61±2.04	8.74±3.65	0.001
LY(10 ⁹ /L)	1.77±0.62	1.87±0.81	0.526
NE (10 ⁹ /L)	4.33±1.81	5.86±2.34	0.001
PLT(10 ⁹ /L)	224.16±64.14	266.34±91.68	0.004
ALT (U/L)	19.49±16.06	17.62±9.46	0.622
BUN(mmol/L)	5.69±3.96	5.26±2.21	0.498
Cr(μmol/L)	71.10±21.12	81.60±14.75	0.563
IgA (g/L)	1.82±0.95	2.57±1.30	0.007
IgG (g/L)	9.50±2.27	11.58±4.57	0.011
IgM (g/L)	1.33±0.76	1.38±0.85	0.812
C3 (g/L)	0.97±0.15	1.21±0.20	0.000
C4 (g/L)	0.59±0.29	0.71±0.32	0.079
ESR (mm/1hr)	8.39(1.00-19.00)	33.81(4.00-92.00)	0.000
hs-CRP(mg/L)	1.85(0.08-32.83)	20.04(0.49-38.62)	0.000

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; ALT, alanine aminotransferase; BUN, urea nitrogen; Cr, creatinine; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Correlations of laboratory findings with disease activity in TAK Patients

	Kerr's Score		hs-CRP		ESR	
	<i>r</i>	<i>p-value</i>	<i>r</i>	<i>p-value</i>	<i>r</i>	<i>p-value</i>
WBC	0.336	0.000	0.458	0.000	0.388	0.000
LY	0.054	0.602	0.119	0.205	0.276	0.023
NE	0.311	0.001	0.466	0.000	0.327	0.356
PLT	0.353	0.000	0.345	0.000	0.490	0.000
PLR	0.185	0.052	0.239	0.010	0.270	0.010
NLR	0.284	0.002	0.313	0.006	0.249	0.019

Abbreviations: ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C - reactive protein; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ; PLR, platelet-to-lymphocyte ratio; NRL, neutrophil -to-lymphocyte ratio;

Figure legends

Table 1. Laboratory parameters of TAK patients and health controls

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ; MPV, mean platelet volume; PDW, platelet distribution width; ALT, alanine aminotransferase; BUN, brain urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein; NRL, neutrophil -to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

Table 2. Comparison of the parameters in active and inactive TAK patients

Abbreviations: n, number of patients; WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet; ALT, alanine aminotransferase; BUN, brain urea nitrogen; Cr, creatinine; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; C3, complement 3; C4, complement 4; ESR, erythrocyte sedimentation rate; hs-CRP, high-sensitivity C-reactive protein.

Table 3. Correlations of laboratory findings with disease activity in TAK Patients

Abbreviations: WBC, white blood cell; LY, lymphocyte; NE, neutrophil; PLT, platelet ; PLR, platelet-to-lymphocyte ratio; NRL, neutrophil -to-lymphocyte ratio.

Figure 1. Comparison of Platelet-to-Lymphocyte ratio (PLR) and Neutrophil -to-Lymphocyte ratio (NLR) between inactive and active TAK patients.

Figure 2. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR) (Kerr Criteria as the standard). For PLR, the area under the curve was 0.691, with 37.8% sensitivity and 93.0% specificity, for NLR, the area under the curve was 0.697, with sensitivity and specificity of 75.6% and 55.8%.

Figure 3. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR) (CRP as the standard). For PLR, the area under the curve was 0.775, with 64.7% sensitivity and 83.8% specificity, for NLR, the area under the curve was 0.698, with sensitivity and specificity of 52.9% and 81.1%.

Figure 4. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR) (ESR as the standard). For PLR, the area under the curve was 0.718, with 53.8% sensitivity and 83.3% specificity, for NLR, the area under the curve was 0.688, with sensitivity and specificity of 82.7% and 47.2%.

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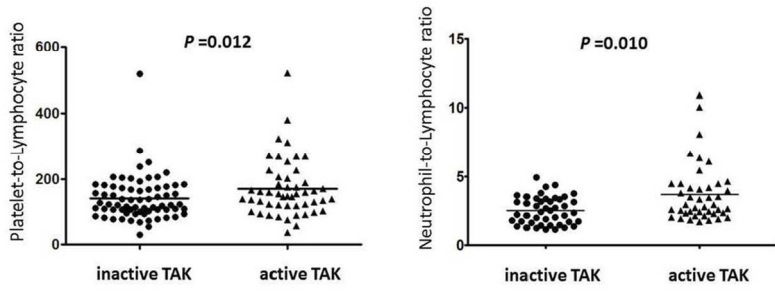


Figure 1. Comparison of Platelet-to-Lymphocyte ratio (PLR) and Neutrophil-to-Lymphocyte ratio (NLR) between inactive and active TAK patients.

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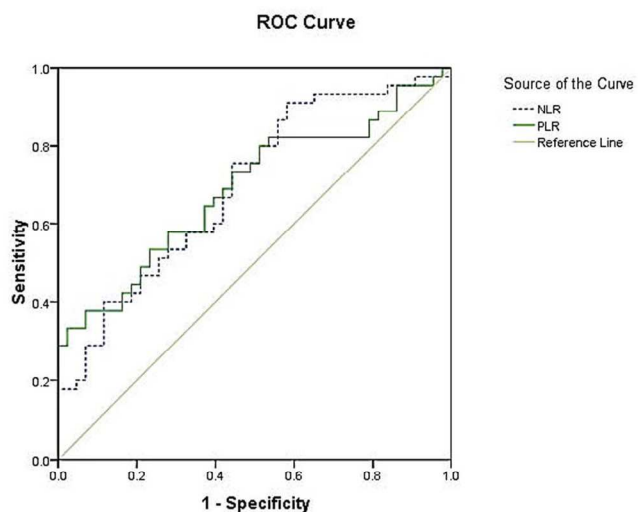


Figure 2. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (Kerr: Criteria as the standard). For PLR, the area under the curve was 0.691, with 37.8% sensitivity and 93.0% specificity. for NLR, the area under the curve was 0.697, with sensitivity and specificity of 75.6% and 55.8%.

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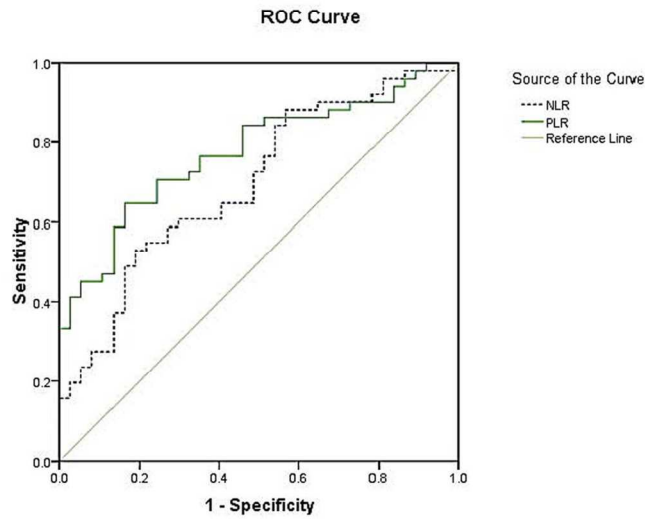


Figure 3. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (CRP as the standard). For PLR, the area under the curve was 0.775, with 64.7% sensitivity and 83.8% specificity, for NLR, the area under the curve was 0.698, with sensitivity and specificity of 52.9% and 81.1%.

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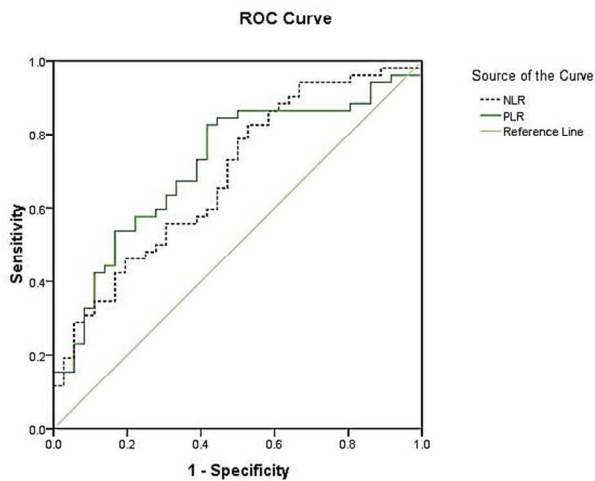


Figure 4. Receiver-operating characteristic curves for the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte Ratio (NLR). (ESR as the standard). For PLR, the area under the curve was 0.718, with 53.8% sensitivity and 83.3% specificity, for NLR, the area under the curve was 0.688, with sensitivity and specificity of 82.7% and 47.2%.

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Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT		Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio were Associated to Disease Activity in Patients with Takayasu's Arteritis	
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	1
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	2
	4	Study objectives and hypotheses	3
METHODS			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	3
<i>Participants</i>	6	Eligibility criteria	3
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	3
	8	Where and when potentially eligible participants were identified (setting, location and dates)	3
	9	Whether participants formed a consecutive, random or convenience series	
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	4
	10b	Reference standard, in sufficient detail to allow replication	4
	11	Rationale for choosing the reference standard (if alternatives exist)	4
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	4
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	4
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	4
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	4
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	4
	15	How indeterminate index test or reference standard results were handled	4
	16	How missing data on the index test and reference standard were handled	4
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	4
	18	Intended sample size and how it was determined	4
RESULTS			
<i>Participants</i>	19	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	4
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	5
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	5
	25	Any adverse events from performing the index test or the reference standard	5
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	7
	27	Implications for practice, including the intended use and clinical role of the index test	
OTHER INFORMATION			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	8

STARD 2015

AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

