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Original Article

Role of systemic immune-inflammation index (SII) in assessing clinical efficacy of TNF-α inhibitors for rheumatoid arthritis

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Abstract: Objective: To find out if systemic immune-inflammation index (SII) has the potential to determine the clinical efficacy of TNF-α inhibitors in treating rheumatoid arthritis (RA). Methods: A retrospective analysis was conducted in 154 RA patients who were treated from January 2021 to January 2023. The patients were grouped, based on their treatment response, into ineffective (32 cases) and effective (122 cases) groups. Univariate analysis was conducted to evaluate the clinical data, test indicators, and functional scores. Lasso regression was employed to identify factors impacting patient outcomes. Predictive utility of these factors was assessed via receiver operating characteristic curves, and differences were evaluated using the DeLong test. Results: No significant difference was identified in age, gender, disease duration, and other clinical parameters between the two groups (P>0.05). The effective group exhibited lower pre-treatment counts of neutrophils, lymphocytes, as well as SII, C-reactive protein (CRP), rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR), but higher platelet count (P<0.01). Lasso regression found that neutrophil count, lymphocyte count, SII, CRP, RF, and ESR were associated with the treatment efficacy (P<0.05). Among these, SII and lymphocytes demonstrated the highest predictive value in the DeLong test. Conclusion: SII along with multiple other pre-treatment parameters are significantly associated with the efficacy of TNF-α inhibitors in the treatment of RA. Notably, SII emerges as a crucial tool in evaluating the efficacy of this treatment.

Keywords: Systemic immune-inflammation index, rheumatoid arthritis, clinical efficacy, C-reactive protein, rheumatoid factor, erythrocyte sedimentation rate

Introduction

Rheumatoid arthritis (RA) is an immune-mediated chronic inflammatory disease, primarily characterized by inflammation of multiple small joints, resulting in cartilage damage, joint deformity, functional loss, and a consequent decline in quality of life [1, 2]. The prevalence of RA in China stands between 0.31% and 0.37%, with the female incidence rate being approximately three times that of males. The exact pathogenesis of RA is still unclear, but it is predominantly attributed to genetic, environmental, and immune factors [3].

Traditional disease modifying antirheumatic drugs (DMARDs) have long been the clinical cornerstone for RA treatment [4]. While numerous studies have validated the efficacy of DMARDs as both monotherapy and combined treatments [5], a substantial portion of RA patients still do not respond favorably to these treatments. Moreover, adverse reactions associated with these drugs are another reason that restrict their clinical applications. In recent years, TNF-α inhibitors, functioning as targeted drugs, offer a more precise intervention by directly addressing the inflammatory factors associated with RA, which hold promising therapeutic outcomes and broaden the treatment options for RA patients [6, 7].

Currently, RA diagnosis and progression assessments predominantly hinge on clinical

manifestations, imaging diagnostics, and laboratory indicators [8]. Imaging techniques like CT, X-ray, and MRI primarily pinpoint alterations in joint spaces, such as narrowing and osteoporosis [9]. While a number of clinical testing indicators are available for RA patients, the chronic nature of RA necessitates prolonged treatments and tests, inadvertently escalating patients' financial burdens [10]. Furthermore, some of these established prediction tools do not consistently exhibit precision or broad applicability across diverse patient groups. The systemic immune-inflammation index (SII), derived from neutrophil, platelet, and lymphocyte counts, has emerged as a promising prognostic marker in non-small cell lung cancer, pancreatic cancer, and gastric cancer, functioning as an inflammatory index that mirrors the body's inflammatory state in patients with tumors and chronic inflammations [11, 12]. Notwithstanding its potential, there is a lack of extensive literature correlating SII with prognostics in RA.

This study aims to investigate if the pre-treatment SII levels in patients could serve as potential indicators of the clinical efficacy following TNF-α inhibitors treatment. The objective is to determine whether a correlation exists between initial SII values and subsequent treatment outcomes, so as to provide insights for refining clinical assessments and treatment strategies.

Methods and materials

Sample source

This retrospective analysis included 214 RA patients treated at the 215 Hospital of Shaanxi Nuclear Industry from January 2021 to January 2023. The study was approved by the Medical Ethics Committee of the 215 Hospital of Shaanxi Nuclear Industry. The study flow chart is presented in **Figure 1**.

Inclusion and exclusion criteria

Inclusion criteria: 1. Patients met the diagnostic criteria set forth in the *Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis* [13]. 2. Patients received treatment for the first time. 3. The disease duration did not exceed one year. 4. Patients tested negative in T-cell spot test for tuberculosis infection. 5. Patients received treatment with tumor necrosis factor antagonists. 6. Patients had complete case records. 7. Patients were treated with a drug and received an outcome evaluation after the treatment.

Exclusion criteria: 1. Patients had other infections during the treatment. 2. Patients had severe cardiovascular issues or liver and kidney diseases. 3. Patients diagnosed with malignant tumors. 4. Individuals suffered from mental disorders. 5. Patients used drugs that might affect tumor necrosis factor antagonists prior to the study. 6. Lactating or pregnant patients.

Sample screening

According to the inclusion and exclusion criteria, we selected a total of 154 eligible patients, who were grouped based on the clinical efficacy after treatment. There were 32 ineffective cases (ineffective group) and 122 effective cases (effective group). The efficacy evaluation criteria were referring to the standards set by the American College of Rheumatology (ACR) [14]. Namely, a response of ACR20 (improvement of 20% or more) or greater, based on blood test results, disease activity score 28 (DAS28), visual analog scale (VAS) score, and morning stiffness duration, was considered effective. A response of less than ACR20 was considered ineffective.

Treatment protocol

All patients received routine treatment, including oral celecoxib capsules (trade name: Xilebao, approval number J20140072, Pfizer Pharmaceutical Co., Ltd.), 0.2 g per dose, once daily; oral methotrexate tablets (approval number H31020644, Shanghai Shangyao Xinyi Pharmaceutical Factory Co., Ltd.), 10 mg per dose, once weekly; oral leflunomide tablets (trade name: Tuosu, approval number H2005-0175, Fujian Huitian Bio-pharmaceutical Co., Ltd.), 20 mg per dose, once daily. In addition, recombinant human tumor necrosis factor receptor-antibody fusion protein (trade name: Etanercept, approval number S20050059, Livzon MABPharm Biopharmaceuticals Co., Ltd.) was injected into joints with obvious swelling and pain. The dosage was 25 mg per injection for large joints and 12.5 mg per injection for small joints, administered once weekly. The treatment cycle was three months.

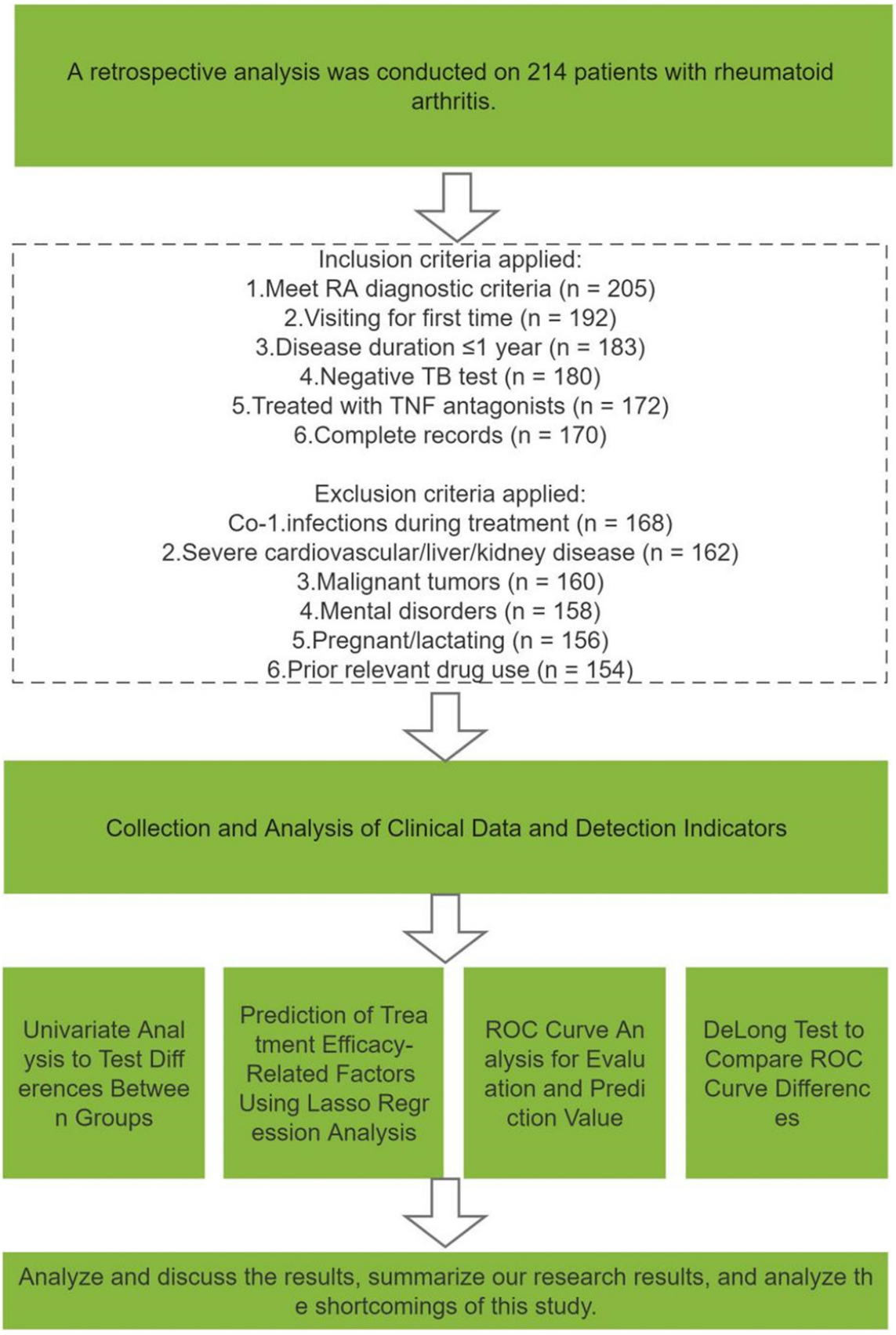
A retrospective analysis was conducted on 214 patients with rheumatoid arthritis.
Inclusion criteria applied:
1.Meet RA diagnostic criteria (n = 205)
2.Visiting for first time (n = 192)
3.Disease duration ≤1 year (n = 183)
4.Negative TB test (n = 180)
5.Treated with TNF antagonists (n = 172)
6.Complete records (n = 170)
Exclusion criteria applied:
Co-1.infections during treatment (n = 168)
2.Severe cardiovascular/liver/kidney disease (n = 162)
3.Malignant tumors (n = 160)
4.Mental disorders (n = 158)
5.Pregnant/lactating (n = 156)
6.Prior relevant drug use (n = 154)
Collection and Analysis of Clinical Data and Detection Indicators
Univariate Analysis to Test Differences Between Groups
Prediction of Treatment Efficacy-Related Factors Using Lasso Regression Analysis
ROC Curve Analysis for Evaluation and Prediction Value
DeLong Test to Compare ROC Curve Differences
Analyze and discuss the results, summarize our research results, and analyze the shortcomings of this study.

Figure 1. Flow chart of screening and outcome analysis of patients with rheumatoid arthritis.

Clinical data collection

Clinical data were collected through electronic medical records and outpatient review records. The baseline data included age, gender, disease duration, history of diabetes, history of hypertension, morning stiffness duration, adverse reactions, etc. Detection indicators included neutrophil count, lymphocyte count, platelet count, C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and SII calculated as platelet count × neutrophil count)/lymphocyte count. Functional scores included DAS28 and VAS. All test indicators and scores were evaluated before the first treatment after admission.

Detection of indicators

Peripheral blood samples were collected before treatment. Blood cell counts were measured using a BC-6800 automated hematology analyzer (Mindray Medical International Limited). Serum RF (reagents from Jinrui Technology Bio Co., Ltd. Cat: 0541) and CRP (reagents from Jinrui Technology Bio Co., Ltd.) levels were measured by turbidimetric inhibition immunoassay using a PA200 automated specific protein analyzer (Jinrui Technology Bio Co., Ltd. Cat: 0504). ESR was assessed by the Westergren method.

Functional scoring

DAS28 is the most common method used in clinical practice to evaluate RA disease activity. It incorporates tender and swollen joint counts, patient self-reported 100-mm VSA, and ESR to calculate the DAS28 score [15]. The VAS is a psychological measurement tool used to assess subjective attributes like pain that cannot be directly measured. For pain, it consists of a rating scale with two endpoints representing the extremes of pain experience. Scores range from 0 to 10 [16]. Patients were asked to mark their pain level on the line between the two endpoints. Marks closer to the maximum pain endpoint indicate higher perceived pain intensity.

Statistical analysis

SPSS 20.0 software was used for data processing and analysis. The normally distributed measurement data were expressed as mean ± standard deviation (mean ± SD), and single factor analysis between groups was performed using a t-test. Count data were represented as rate (%). Lasso regression analysis was used to predict the factors affecting clinical efficacy and select key variables related to treatment outcomes. Regression coefficient estimates were shrunk to zero via penalized maximum likelihood estimation to reduce model complexity and multicollinearity. The optimal lambda regularization hyperparameter was determined through 10-fold cross-validation to avoid overfitting. We chose the lambda.1se criterion, which ensures stable and accurate variable selection. Only factors with non-zero coefficients after Lasso regularization were selected as key variables associated with clinical efficacy. The Lasso regression model coefficient estimates for the selected variables were then used to calculate a risk score for each patient to classify effectiveness. The risk score was calculated using the following formula: Risk score = $\sum_i^n Xi \times Yi$ (X: coefficient of each clinical factor, Y: expression of each clinical factor). The value of the factors in predicting patient efficacy was analyzed using receiver operating characteristic (ROC) curves. The Hosmer-Lemeshow test was used to adjust the ROC curve to assess the model's discriminative ability and fitness. Differences between the ROC curves were analyzed using Delong-test. A *p*-value <0.05 was considered statistically significant.

Results

Comparison of clinical data

There were no statistically significant differences in age, gender, disease duration, history of diabetes, history of hypertension, and morning stiffness duration before treatment between patients in the effective and ineffective groups (P>0.05, **Table 1**).

Comparison of laboratory indicators

The neutrophil count, lymphocyte count, SII, CRP, RF, and ESR were lower in the effective group than those in the ineffective group before treatment. In contrast, the platelet count was higher in the effective group than that in the

Table 1. Clinical efficacy evaluation

Factors	Effective group (n=122)	Ineffective group (n=32)	Chi-square value	*P*-value
Age			0.592	0.441
≥50 years	67	20		
<50 years	55	12		
Gender			0.477	0.489
Male	31	10		
Female	92	22		
Duration of illness			0.609	0.435
≥6 months	59	13		
<6 months	63	19		
History of diabetes			0.784	0.375
Present	22	8		
Absent	100	24		
History of hypertension			0.437	0.508
Present	24	8		
Absent	98	24		
Morning stiffness before treatment			0.786	0.375
≥90 min	43	14		
<90 min	79	18		

Table 2. Comparison of laboratory indicators

Factors	Effective group (n=122)	Ineffective group (n=32)	t-value	*P*-value
Neutrophil count (10^9/L)	4.56±1.62	5.65±1.69	3.350	0.001
Lymphocyte count (10^9/L)	245.43±95.15	392.06±86.03	7.908	<0.001
Platelet Count (10^9/L)	2.31±0.76	1.73±0.58	3.971	0.001
SII	734.68±651.66	1404.86±649.16	7.884	<0.001
CRP (mg/L)	25.38±5.83	30.94±7.47	4.516	<0.001
RF (U/mL)	191.66±42.13	231.81±71.17	4.087	<0.001
ESR (mm/H)	30.27±9.62	39.03±11.84	4.361	<0.001

Note: C-reactive protein (CRP), Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR), Systemic Immune-Inflammation Index (SII) = (Platelet Count × Neutrophil Count)/Lymphocyte Count.

Table 3. Comparison of the functional scores

Factors	Effective group (n=122)	Ineffective group (n=32)	t-value	*P*-value
DAS28 score	4.75±1.10	4.91±1.03	0.768	0.443
VAS score	7.43±0.91	7.66±1.14	1.033	0.303

Note: Disease Activity (DAS28) and Visual Analogue Scale (VAS).

ineffective group before treatment (P<0.01, **Table 2**).

Comparison of functional scores

No statistically significant difference was identified in DAS28 and VAS scores before treatment between the effective and ineffective groups (P>0.05, **Table 3**).

Lasso regression analysis of factors associated with efficacy

We identified six factors strongly associated with patient efficacy (P<0.05, **Figure 2A**, **2B**). To validate the predictive value of these factors, we used ROC curve to evaluate their performance. The areas under the curve (AUCs) for neutrophil count, lymphocyte count, SII, CRP, RF, and ESR were 0.668, 0.869, 0.891, 0.708, 0.678, and 0.725, respectively (**Figure 3** and **Table 4**). Furthermore, DeLong testing was performed to validate the differences in AUC, and SII was found to have a significantly larger AUC than the other indicators in predicting patient efficacy (P<0.05, **Table 5**).

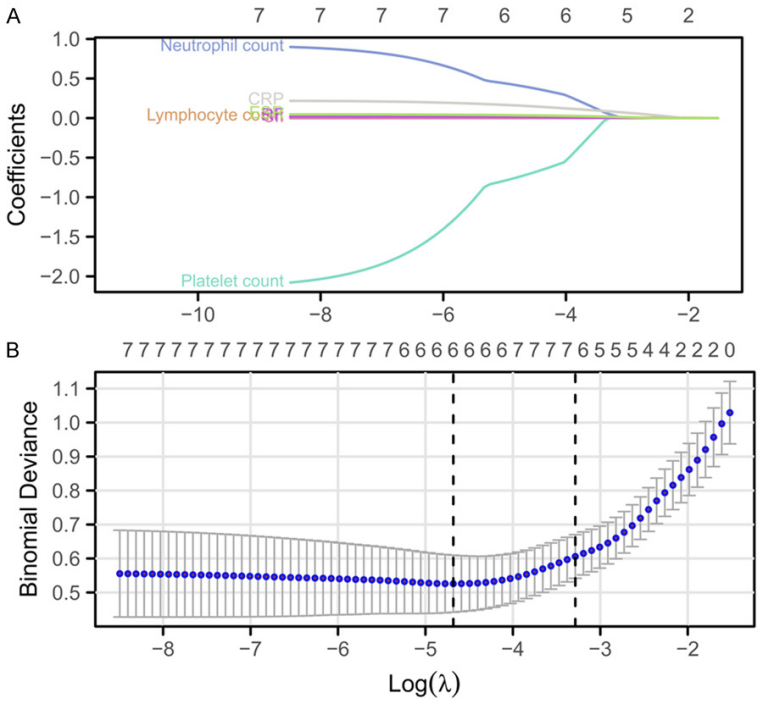

Figure 2. Risk model for predicting patient efficacy using Lasso regression model. A, B. Coefficient distribution in LASSO regression analysis, along with the calculation of tuning parameters (lambda) based on 10-fold cross-validation partial likelihood deviation.

Discussion

TNF-α is a factor predominantly produced by activated macrophages, though it is also present in neutrophils, endothelial cells, NK cells, and activated lymphocytes. Its biological effects are mediated through the activation of TNF receptor 1 and TNF receptor 2 [17]. When traditional drug treatments lead to severe side effects or cannot yield the desired outcomes, TNF-α inhibitors can be considered as alternative treatments for rheumatic diseases. Infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol are widely utilized in this regard, all aiming to neutralize TNF-α in RA patients to alleviate symptoms. In recent times, these TNF-α inhibitors have demonstrated notable effects in disease control and mitigation of adverse reactions [18]. For instance, a randomized, double-blind, placebo-controlled phase II/III clinical trial showed the rapid efficacy of infliximab, particularly in moderate RA patients, which halted further disease progression. Nonetheless, it is essential to underscore that inhibiting TNF may suppress patients' immune system and weaken tumor surveillance, elevating the risk of other complications. As such, when using TNF antagonists, it is vital to make an informed decision by weighing potential therapeutic benefits against possible side effects [19].

Research has shown that the exosomes in the serum and synovial fluid of RA patients are abundant with citrullinated-specific proteins. These proteins have a significant correlation with the onset of RA [20]. Intriguingly, once the body identifies these proteins as self-antigens, they induce neutrophils to release leukotrienes, intensifying the inflammatory response [21]. Such inflammatory agents have the capability to activate platelets in RA patients. This activation triggers a sequence of reactions, leading to intensified synovitis, pannus formation, and a deterioration of overall disease condition [22]. Due to the persistent inflammatory stimuli, the functions and balance of neutrophils, platelets, and lymphocytes are disrupted. Notably, lymphocytes, crucial components of immune defense, exhibit an impaired T lymphocyte function and a hyperactive B lymphocyte function in RA patients. This results in an immune aberration [23]. This anomaly may be rooted in a disordered immune regulatory mechanism in RA patients. Overstimulation of the T lymphocyte population can lead to their exhaustion, sparking an overdrive in the proliferation of B lymphocytes, subsequently resulting in a surge of autoantibody production [24]. Various RA-focused studies have utilized the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as barometers for a patient's inflammatory state [25]. When compared to individual counts of each of these three indicators, the NLR and PLR provide a more precise and nuanced assessment of the shifts in balance between them. The SII, calculated by multiplying the counts of neutrophils and platelets and then dividing by the lymphocyte count, offers another layer of insight. Research has revealed a

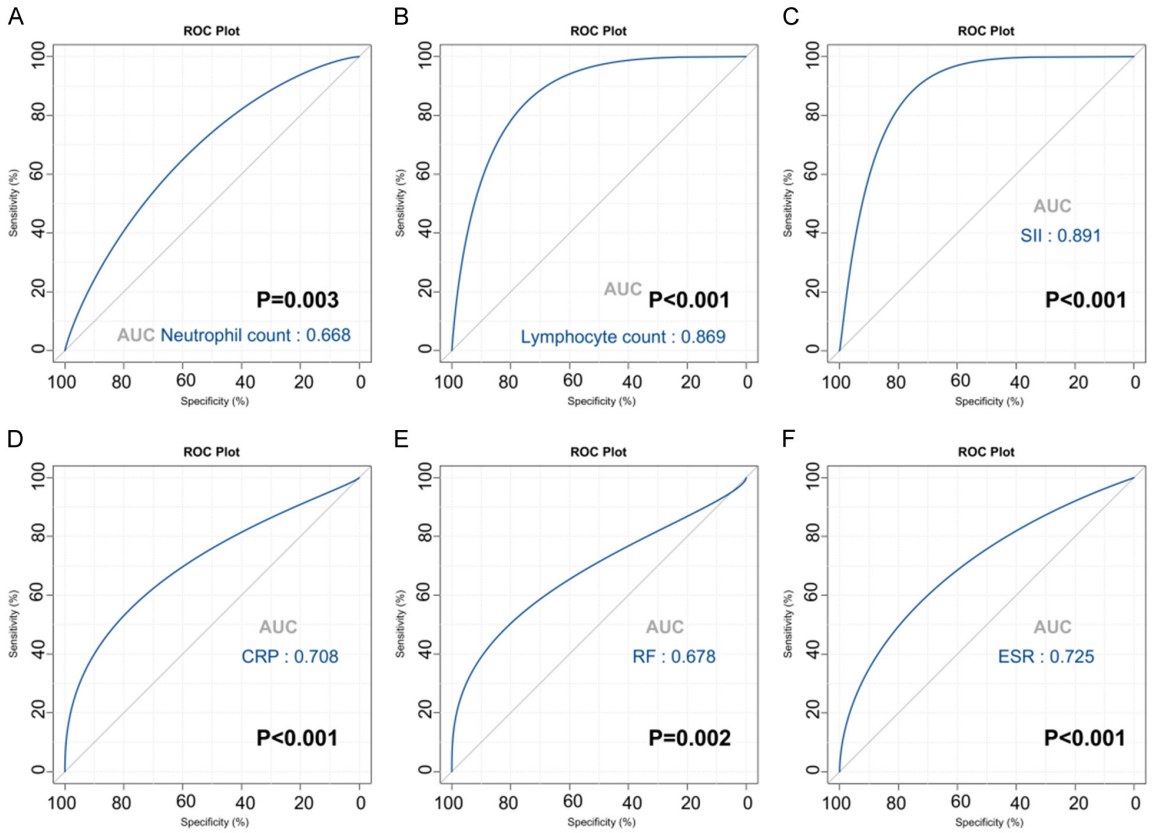

Figure 3. Area under the curve for predictive factors in predicting patient’s treatment effectiveness. A. Area under the curve for neutrophil count in predicting patient’s treatment effectiveness. B. Area under the curve for lymphocyte count in predicting patient’s treatment effectiveness. C. Area under the curve for SII in predicting patient’s treatment effectiveness. D. Area under the curve for CRP in predicting patient’s treatment effectiveness. E. Area under the curve for RF in predicting patient’s treatment effectiveness. F. Area under the curve for ESR in predicting patient’s treatment effectiveness. Note: C-reactive protein (CRP), Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR), SII = (Platelet Count × Neutrophil Count)/Lymphocyte Count.

positive correlation between SII and other key metrics such as DAS28 and ESR, underscoring its pivotal role in RA evaluation.

This study delved into the predictive potential of the SII and tumor necrosis factor antagonists concerning the treatment outcomes of RA. Notably, the findings indicated that patients who responded well to treatment exhibited significantly lower SII values, highlighting the potential of SII as a predictive marker for the therapeutic efficacy of tumor necrosis factor antagonists. Upon further examination using Lasso regression analysis, parameters such as the neutrophil count, lymphocyte count, SII, CRP, RF, and ESR showed a robust correlation with treatment outcomes [26]. All these markers are intricately intertwined with the body’s inflammatory processes and immune status. Their dynamic fluctuations offer insights into the activity, severity, and potential prognosis of RA, thereby providing a comprehensive assessment of clinical efficacy following treatment. Neutrophils, as the predominant white blood cells, typically surge in number during heightened inflammatory reactions [27]. Lymphocytes, on the other hand, are cornerstones of the immune system, and variations in their counts can mirror the overall state of the immune system [28]. The SII, as a holistic metric, is derived from the counts of neutrophils, lymphocytes, and platelets, and aptly encapsulates the body’s overall inflammatory and immune responses. Furthermore, CRP serves as an acute-phase reactant, RF is an RA-specific antibody, and ESR reflects the general state of systemic inflammation [29]. Consequently, monitoring shifts in these indicators during RA treat-

Table 4. ROC curve parameters

Predictive variable	Area under the curve	Confidence interval	Sensitivity	Specificity	Youden's index
Neutrophil count	0.668	0.564-0.771	87.71%	40.63%	28.33%
Lymphocyte count	0.869	0.811-0.928	77.87%	84.38%	62.24%
Platelet count	0.891	0.838-0.945	81.97%	87.50%	69.47%
SII	0.708	0.594-0.822	86.07%	56.25%	42.32%
CRP	0.678	0.555-0.800	95.08%	40.63%	35.71%
RF	0.725	0.619-0.831	89.34%	50.00%	39.34%

Note: Receiver Operating Characteristic (ROC), C-reactive protein (CRP), Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR), Systemic Immune-Inflammation Index (SII) = (Platelet Count × Neutrophil Count)/Lymphocyte Count.

Table 5. Delong test compares the area under the curve of the predictors

Test results for	Z-value	*P*-value	AUC difference	Standard error difference	Confidence interval
Neutrophil Count - Lymphocyte Count	-2.675	0.007	-0.170	0.291	-0.294~-0.045
Neutrophil Count - SII	-3.21	0.001	-0.206	0.286	-0.331~-0.08
Neutrophil Count - CRP	-1.035	0.300	-0.07	0.307	-0.202~0.062
Neutrophil Count - RF	-0.693	0.488	-0.037	0.301	-0.141~0.067
Neutrophil Count - ESR	-0.701	0.483	-0.055	0.309	-0.209~0.099
Lymphocyte Count - SII	-0.735	0.462	-0.036	0.268	-0.132~0.06
Lymphocyte Count - CRP	1.761	0.078	0.100	0.291	-0.011~0.211
Lymphocyte Count - RF	2.108	0.035	0.133	0.289	0.009~0.256
Lymphocyte Count - ESR	2.112	0.035	0.114	0.290	0.008~0.221
SII - CRP	2.202	0.028	0.136	0.287	0.015~0.257
SII - RF	3.107	0.002	0.169	0.282	0.062~0.275
SII - ESR	2.809	0.005	0.151	0.285	0.046~0.256
CRP - RF	0.472	0.637	0.033	0.305	-0.104~0.17
CRP - ESR	0.254	0.800	0.015	0.305	-0.1~0.13
RF - ESR	-0.244	0.807	-0.018	0.306	-0.164~0.128

Note: C-reactive protein (CRP), Rheumatoid Factor (RF), Erythrocyte Sedimentation Rate (ESR), Systemic Immune-Inflammation Index (SII) = (Platelet Count × Neutrophil Count)/Lymphocyte Count, Area Under the Curve (AUC).

ment can provide invaluable feedback on therapeutic efficacy. Furthermore, this research revealed that the AUC for SII's predictive capacity concerning the efficacy of tumor necrosis factor antagonists stood impressively at 0.891, with a sensitivity of 81.97% and a specificity of 87.50%. The DeLong test further reinforced the superiority of SII as its AUC substantially surpassed other indicators, underscoring the premier potential of SII in predicting the efficacy of tumor necrosis factor antagonists.

This study did not use Lasso regression to create a more comprehensive predictive model, because our primary intent was to highlight the potential value of SII in assessing RA efficacy. While Lasso regression offers the potential to construct a predictive model through its β coefficients, our investigative lens was primarily aimed at discerning the relationship between SII and treatment outcomes. Constructing an encompassing predictive model through Lasso regression undeniably poses an intriguing research avenue. In upcoming studies, we will shift our approach towards this methodology, delving into its applicability for evaluating RA efficacy. Nevertheless, for the scope of this study, we considered it crucial to focus on the direct relationship between SII and treatment efficacy.

Although this study has determined the predictive value of SII in the efficacy of tumor necrosis factor antagonists for RA, there are still certain limitations in this study. First, as a retrospective study, the samples that met the require-

ments were limited, which prevented us from constructing a prediction model. Second, RA is a long-term disease, so whether SII can monitor and predict the long-term efficacy of patients requires further research. Therefore, we hope to conduct more subsequent experiments to improve our research conclusions.

In summary, this study preliminarily evaluated the correlation of factors such as SII, neutrophil count, lymphocyte count, CRP, RF, and ESR with the efficacy of TNF-α inhibitors on RA. Our results found that these factors played an important role in efficacy evaluation and were significantly correlated with the efficacy of RA. Among them, SII and lymphocytes exhibited the highest predictive value and could serve as an important index for evaluating the efficacy of TNF-α inhibitors.

Disclosure of conflict of interest

None.

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