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Effective Factors on Sharp Score in Patients with Rheumatoid Arthritis: A Retrospective Study

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Effective factors on sharp score in patients with rheumatoid arthritis: a retrospective study

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Abstract

Background: This study aims to describe the association between Sharp Score and clincial indexes, bone metabolism indexes, Disease Activity Score (DAS28) and sociodemographic factors in rheumatoid arthritis (RA).

Methods: Data were were collected from the HIS (hospital information system), a national inpatient database in China, with information on the patients hospitalized during the period from 2012 to 2019. The association between Sharp Score and effective factors were identified using multinomial logistic regression and association rule mining (ARM).

Results: Three thousand eight hundred and forty patients were included: 82.66% males, 17.34% females, mean (SD) age 56.95 (12.68) years and symptom duration 3.45 (1.09) years. Spearman correlation analysis and Association rules analysis showed that there were significant positive correlations between Sharp Score and effective factors. Logistic regression analysis presented that erythrocyte sedimentation rate (ESR), high-sensitivity C-reactive protein (CRP), rheumatoid factor (RF) were

risk factors of Sharp Score. In the analysis of individual outcomes, sex, age, symptom duration, DSA28 score, RF, ever drinker, radiographic grading of hands were influencents of Sharp Score.

Conclusion: Sharp Score should be taken into consideration in formulating treatment strategies in RA.

Keywords: Sharp Score, Rheumatoid arthritis, Effective factors, Retrospective study

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial membrane inflammation[1,2]. Erosive joint damage and bone destruction are the most common manifestation of RA, which might induce ankylosis, malformation, even loss of normal joint function[3,4]. Current goals of treatment in RA include achieving disease remission, reducing functional disability as well as minimizing pain[5,6]. Erosions are the hallmark of bone destruction in RA[7,8]. Controlling joint destruction and bone destruction have become the major objective for treating RA, because radiographic joint damage correlates strongly with long-term functional decline in RA patients[9,10]. Radiographic grading of hands is the most commonly used method for the evaluation of different levels of bone erosion in clinical practice[11,12]. Bone erosion score (vdH Sharp Score) has also been used to measure morphological parameters that quantify the bone erosion and bone destruction, giving useful information for early detection and early treatment of RA[13,14]. Few studies to date have studied the overall impact of RA on Sharp Score and its effective factors. In addition, there has been no study that looks for effective factors associated with Sharp Score of RA on the basis of large data by doing the mining and analysis of this data.

This study retrospectively analyzed the clinical data of enrolled patients to investigate the value of Sharp Score and its effective factors in RA. The Spearman correlation analysis, Association rules analysis and Logistic regression analysis are methods of analysis that allows for the identification of risk factors associated with Sharp Score. Using these three methods, this study aims to: (a) Sharp Score exhibits diagnostic value for RA; and (b) analyze the role of effective factors as determinants

of Sharp Score in RA.

Methods

Patients and study design

A total of 3840 RA patients were included in this retrospective study, which were obtained from the First Affiliated hospital of Anhui University of Traditional Chinese Medicine since January 2012. All the subjects fulfilled the 2010 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) criteria for the classification of RA[15]. Sharp Score, demographic data, lifestyle factors, clinical parameters and laboratory data were determined by clinical examination or review of electronic medical records. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients and ethics approval was obtained from the Ethics Committee of the First Affiliated hospital of Anhui University of Traditional Chinese Medicine.

Data collection and measures

All RA patients data were recorded soon after hospitalization, which including the details regarding patients' past medical, personal, and family histories. Besides this, RA-related data (age, sex, marital status, health insurance status, education level, employment status, and housing status, hypertension, hyperlipidaemia, smoking history, alcohol consumption history, treatment-condition) was collected from medical records. On the second day of hospitalization, patients general condition was monitored via vital signs, X-ray radiography of both hands, Sharp Score, blood biochemistry tests, bone metabolism indicators, DAS28 score.

X-ray radiography of both hands were performed to assess the extent of joint destruction, bone erosion and joint space narrowing. The Sharp Score of each patients was calculated by 2 independent blinded radiologists. Each joint bone erosion was scored as follows: 0 = normal; 1 = cell infiltration with no signs of joint erosion; 2 = inflammation with the presence or erosions limited to discrete foci; and 3 = severe and extensive joint erosion with loss of architecture. Each joint stenosis was scored as follows: 0=normal; 1=focal or doubtful narrowing; 2=generalized narrowing <50%;

3=generalized narrowing >50% or subluxation; 4=complete luxation or bony ankylosis.

Clinical indexes: ESR, CRP, RF, anti-cyclic citrullinated peptide antibody (CCP), immunoglobulins A (IGA), immunoglobulin G (IGG), immunoglobulin M (IGM), complement 3 (C3), and complement 4 (C4), DAS28, bone alkaline phosphatase (BALP), osteocalcin (OC), Osteoprotegerin (OPG), receptor activator for nuclear factor- κ B ligand (RANKL).

Statistical analysis

Normally distributed variables were presented as the mean values (standard deviation), nonnormally distributed variables were presented as median values (*p*50, *p*75), and count data were presented as the number of cases (%). We conducted univariate analyses on important covariates, including age, gender, CCP or RF positivity, ESR, CRP, IGA, IGG, IGM, C3 and C4. Continuous variables with a normal distribution were compared using Student's t-test, while non-normally distributed variables were compared using the Wilcoxon rank sum test. Categorical variables were evaluated using Fisher's exact test. The correlations between Sharp Score and clinical indexes were analyzed by Spearman's correlation coefficients. In addition, we constructed a binary linear regression model to determine the association of important covariates with Sharp Score. Statistical tests were performed in Excel or in GraphPad Prism version 8.0.

The indicators rise was set to "T", while the indicators decline was set to "F". The Aprior module of SPSS Clementine 11.1 software was used to analyze the correlation between observation indicators.The most famous association rule is the Apriori algorithm, which aims to find out the relationship between items in a data set, also known as shopping blue analysis[16]. In our data, each drug was treated as a variable. The formulae were as follows:

$$\text{support}(X \rightarrow Y) = \sigma \frac{(X \cup Y)}{N},$$

$$\text{counfidence}(X \rightarrow Y) = \sigma \frac{(X \cup Y)}{\sigma(X)},$$

$$\text{lift}\ (X \rightarrow Y) = \text{counfidence}\ \frac{(X \rightarrow Y)}{\sigma(Y)},$$

where $X \rightarrow Y$ is an association rule, X (left-hand side [LHS]) and Y (right-hand side [RHS]) represent the set of herb items, $\sigma(X)$ is the frequency of itemset X, $X \cup Y$ is the union of itemset X and Y, $\sigma(X \cup Y)$ is the frequency with which itemset X and itemset Y appear together, support($X \rightarrow Y$) is the frequency with which X and Y appear together, and confifidence($X \rightarrow Y$) is the probability that itemset Y appears in the presence of X. The lift is the ratio of the probability of itemset Y appearing in the presence of X to the frequency of Y. Support and confifidence are often used to eliminate meaningless combinations; lift is the validity of the rules.

Results

Characteristics of the study population

The study sample was composed of 3840 RA patients, with a mean age of 56.95 years (standard deviation 12.68, range 18 – 95) and of whom 82.66% were female. The median number of Sharp Score was 20.00 (IQR: 7.00, 56.00). 3003 (78.15%) were seropositive for either RF and 3636 (94.68%) were seropositive for CCP. The mean (SD) symptom duration was 3.45 (1.09) years and the mean (SD) disease duration was 6.92 (1.20) years. The main characteristics of the study population are detailed in Table 1.

Table 1. Characteristics of study population (n = 3840).

Quantitative Variables	Mean	Standard Deviation
Age (years)	56.95	12.68
Symptom duration (years)	3.45	1.09
Disease duration (years)	6.92	1.20
BMI (Kg/m2)	22.80	4.51

Tender joint count, 0-28	10.73	5.63
	Subjects	**Percentage**
Sharp Score		
⩽ 0 score	111	2.89
＞ 0 score, ⩽ 50 score	2674	69.64
＞ 50 score	1055	27.47
Gender		
Male	666	17.34
Female	3174	82.66
Ever smoker	458	11.93
Ever drinker	582	15.16
RF positivity	3001	78.15
CCP positivity	3636	94.68
Presence of radiographic erosions	2162	56.32
Prenisolone use	2150	55.98
DMARD treatment (at baseline)		
DMARD-naive	3017	78.56
MTX monotherapy	1368	35.62
Non-MTX csDMARD	888	23.13
Combination csDMARD	905	23.56
Education status		
None or primary	1545	40.23
Secondary or vocational	1740	45.31
Tertiary	555	14.45
Housing status		
Private housing	2397	62.42
Government housing	1443	37.58
Employment status		
Currently employed	1735	45.18
Unemployment, retired or homemaker	2105	54.82
Marital status		
Currently married	3657	95.23
Single, divorced or widowed	183	4.77
	Interquartile range (IQR)	
Sharp Score	20.00 (7.00, 56.00)	
DAS28 score	5.50 (4.00, 7.28)	
ESR (mm/h)	42.00 (22.00, 68.00)	
CRP (mg/L)	15.82 (3.61, 41.49)	
RF (U/ml)	79.15 (19.90, 195.05)	
CCP (U/ml)	132.98 (25.00, 402.67)	
IGA (g/L)	2.47 (1.87, 3.27)	
IGG (g/L)	13.45 (11.00, 16.40)	
IGM (g/L)	1.35 (0.91, 1.68)	

C3 (g/L)	112.45 (96.50, 129.30)
C4 (g/L)	24.7 (19.20, 30.80)
BALP (ng/ml)	660.13 (431.37, 851.60)
BGP (ng/ml)	3479.49 (2871.84, 4825.99)
OPG (ng/ml)	117.20 (948.12, 1338.62)
RANKL (ng/ml)	1085.40 (955.51, 1322.46)

Spearman correlation analysis of Sharp Score and clincial indexes

To determine whether correlations existed between Sharp Score and clincial indexes, a Spearman correlation test was performed. Age, ESR, CRP, RF, IGA, IGG, IGM, C3, C4, BALP, BGP, OPG, RANKL, DAS28 were all positively correlated with Sharp Score, as seen in Figure 1.

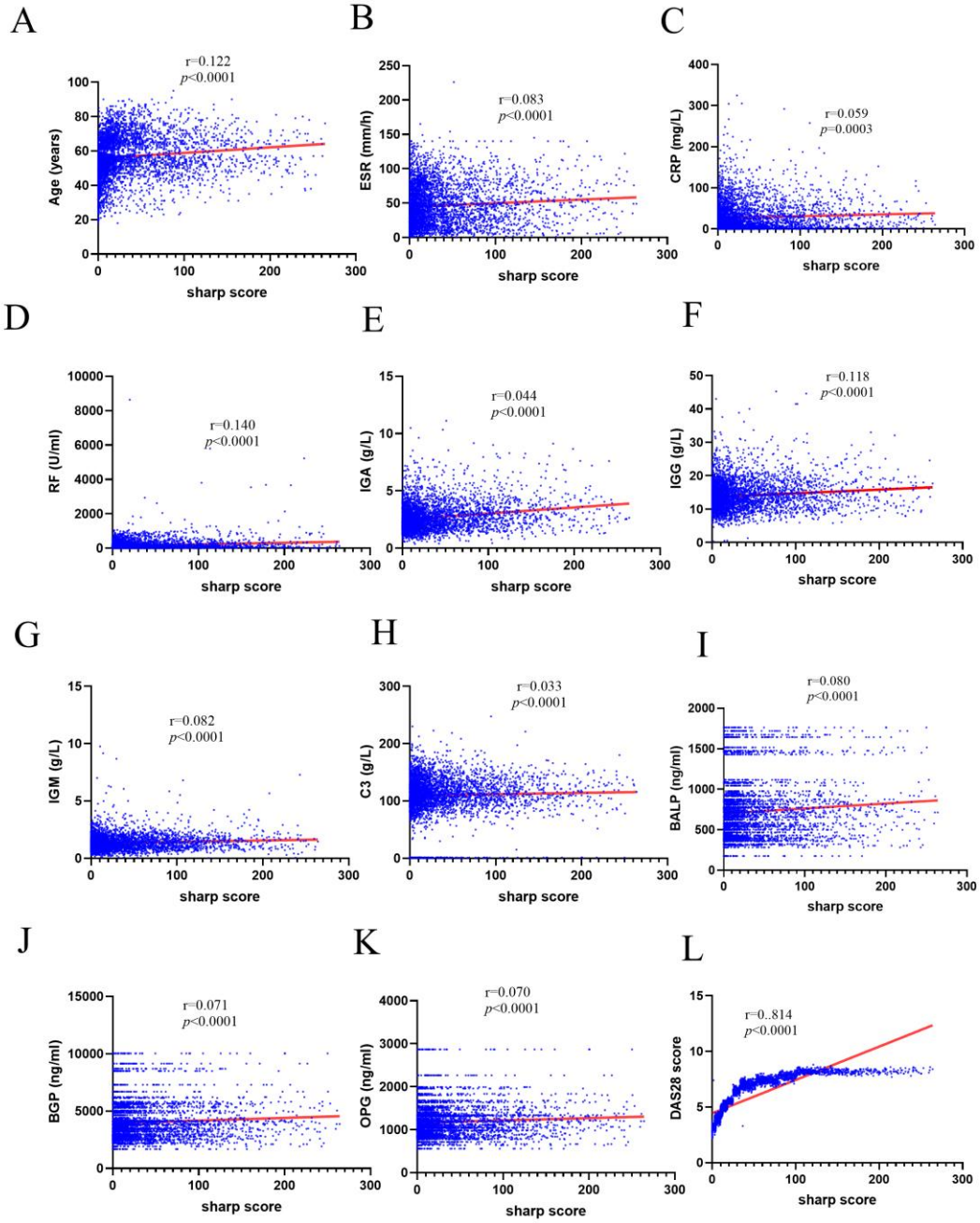

Figure 1. Spearman correlation analysis of Sharp Score and clincial indexes.

Association rules analysis of Sharp Score and clincial indexes

Association rules analysis of Sharp Score and clincial indexes can be found in Table 2. Set the minimum support to 80% and the minimum confidence to 80%. Through Aprior module analysis, the correlation between Sharp Score and clincial indexes was obtained, and the degree of lift was more than 1 and $P<0.05$.

Table 2. Association rules analysis of Sharp Score and clincial indexes.

Items(LHS ⇒ RHS)	Support	Confidence	Lift	P value

{ Sharp Score ↑ } ⇒ { ESR ↑ }	83.68%	91.72%	1.05	<0.01
{ Sharp Score ↑ } ⇒ { CRP ↑ }	83.05%	91.03%	1.04	<0.01
{ Sharp Score ↑ } ⇒ { RF ↑ }	81.25%	91.03%	1.04	<0.01
{ Sharp Score ↑ } ⇒ { IGA ↑ }	83.05%	87.71%	1.05	<0.01
{ Sharp Score ↑ } ⇒ { IGG ↑ }	87.67%	87.55%	1.05	<0.01
{ Sharp Score ↑ } ⇒ { C3 ↑ }	81.25%	87.55%	1.05	<0.01
{ Sharp Score ↑ } ⇒ { BGP ↑ }	83.68%	87.04%	1.05	<0.01
{ Sharp Score } ⇒ { RANKL ↑ }	81.25%	86.79%	1.05	<0.01
{ Sharp Score } ⇒ { DAS28 ↑ }	81.25%	86.34%	1.05	<0.01

Logistic regression analysis of Sharp Score and clincial indexes

Logistic regression analysis of risk factors of Sharp Score was carried out. Significant differences in Sharp Score was found between RA patients with ESR (p = 0.000), CRP (p = 0.023), RF (p = 0.000) , indicating that ESR, CRP, RF were risk factors for Sharp Score, the higher expression of ESR, CRP, RF, the high score of sharp (Figure 2).

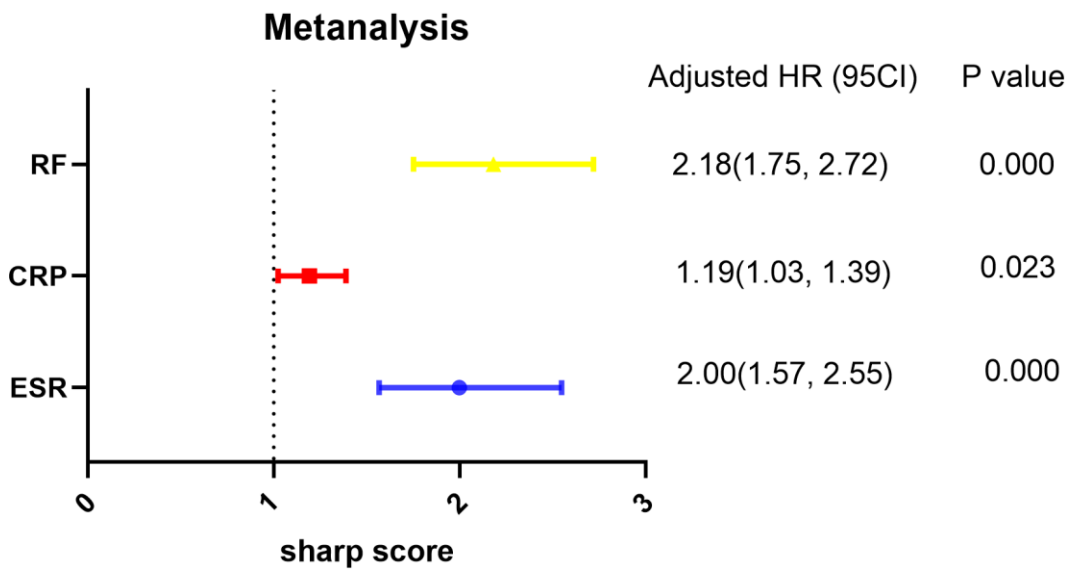

Figure 2. Logistic regression analysis of Sharp Score and clincial indexes.

Comparison of Sharp Scores among different variables

As shown in Table 3, there was a higher Sharp Score of female patients compared to male (21.00, IQR (7.00, 60.13) vs 17.00 (IQR (7.00, 42.13)) and a high Sharp Score of over 50 years old compared to under 50 years old (24.00, IQR (10.00, 60.13) vs

10.00 (IQR (3.00, 45.00)). There was a higher Sharp Score of RF‐positive compared to RF-negative (23.00, IQR (8.00, 64.63) vs 13.00 (IQR (4.38, 35.63)). There was a higher Sharp Score of ever-smoker compared to never-smoker (20.00, IQR (7.50, 56.50) vs 19.50 (IQR (4.50, 55.00)).

Table 3. Comparison of Sharp Scores among different variables

Quantitative Variables	Group	Sharp Score	Z	P value
Sex	Female	21.00 (7.00, 60.13)	9.482	0.002
	Male	17.00 (7.00, 42.13)		
Age	＜50 years	10.00 (3.00, 45.00)	154.33	0.000
	≥50 years	24.00 (10.00, 60.13)		
Symptom duration	＜5 years	5.5 (0.00, 1.50)	443.97	0.000
	≥5 years	25 (10.50, 64.00)		
DSA28 score	＜3.2	0.50 (0.00, 1,50)	2813.43	0.000
	≥3.2＜5.1	6.50 (3.50, 10.00)		
	≥5.1	47.00 (25.50, 89.00)		
RF	Positivity	23.00 (8.00, 64.63)	94.01	0.000
	Negativity	13.00 (4.38, 35.63)		
CCP	Positivity	20.00 (7.00, 57.38)	3.027	0.082
	Negativity	17.50 (5.50, 47.00)		
Ever smoker	Yes	20.75 (4.50, 55.50)	0.996	0.318
	No	19.50 (7.00, 56.50)		
Ever drinker	Yes	20.00 (7.50, 56.50)	3.827	0.050
	No	19.50 (4.50, 55.00)		
Radiographic grading of hands	I	1.50 (0.50, 2.50)	3546.75	0.000
	II	10 (6.50, 14.00)		
	III	28.50 (23.00, 37.00)		
	IV	87.00 (61.50, 122.50)		

Discussion

This study was a large-sample retrospective study, which has characterized Sharp Score and its effective factors in RA. The role of clincial indexes, bone metabolism indexes, DAS28 and sociodemographic factors as determinants of Sharp Score was examined. Age, ESR, CRP, RF, IGA, IGG, IGM, C3, C4, BALP, BGP, OPG, RANKL, DAS28 were associated with Sharp Score. ESR, CRP, RF were also risk factors of Sharp Score.

Joint damage is very common in an early stage of RA, even within two years after

disease onset in the vast majority (70 – 93%) of patients[17,18]. Therefore, the probability of occurrence of erosions is adequately high in the early years of RA[8,19]. Therefore, joint damage may lead to the generation and maintenance of pain, which is a major cause of disability and functional decline[20]. In a study by Corbett et al the onset of erosions in hands during the first two years of RA was the strongest predictive feature of a poor functional outcome after 15 years[21]. Early quantitative assessment of joint destruction and bone erosion are the first step to prevent or decrease its damage[22,23].

Although there has not been a similar study to date describing Sharp Score and its effective factors in RA. A few studies have described Sharp Score as an important observation index and effective factor of RA[24]. LMAJansen followed early RA patients for one year, concluded that progression of these lesions was predicted by the number of radiographic lesions and Sharp/van der Heijde score[12]. Similar findings were also observed in a cross-sectional study of RA patients with secondary SS (sSS) by Lindsay E. Brown et al, which found that RA subjects with sSS had worse joint damage was associated with higher Sharp Score[13]. As a part of our ongoing research on the joint destruction and bone erosion, in the present study we focused on Sharp Score, which might have significant diagnostic value for RA.

Spearman correlation analysis and Association rules analysis showed that there were significant positive correlations between age, ESR, CRP, RF, IGA, IGG, IGM, C3, C4, BALP, BGP, OPG, RANKL, DAS28 and Sharp Score in our study. In addition, Logistic regression analysis presented that ESR, CRP, RF were risk factors of Sharp Score. Clincial indexes, bone metabolism indexes, DAS28 and sociodemographic factors differences in Sharp Score outcomes have not been well studied in the China and there has been no similar study on the impact of Sharp Score. There are differences in sharp score of different genders, which showed that a higher Sharp Score of female patients compared to male[25]. There are different explanations of these gender-based differences, which may be the both the biological progression of disease as well as self - perception and reporting of symptoms[26]. Higher DAS28, RF^+ and radiographic grading were also associated with Sharp score and this can be due

to its association with higher levels of inflammation and comorbidities[27,28]. Symptom duration and smoking history could affect Sharp Score progression through differences in health literacy, self - care and medication compliance[29,30].

There are several strengths in our study. First, this is the first retrospective study of Sharp Score in RA patients in China, and is uniquely placed to study the effective factors of Sharp Score in China. Furthermore, to the best of our knowledge, this is the only study to date that has used three methods to identify a significant correlation between Sharp Score and different variables. One of the limitations of our study was the lack of multi-center and inclusion of diverse ethnic/racial groups. Furthermore, our research size is small, and this may limit finding significant differences between Sharp Score and different variables. Additionally, we also need to study the diagnostic accuracy and importance of magnetic resonance imaging and take it into the next research.

In conclusion, the study has characterized the association between Sharp Score and clincial indexes, bone metabolism indexes, DAS28 and sociodemographic factors, and demonstrated that a significant correlation between Sharp Score and these variables. The demonstrated differences in joint damage and bone erosion in the early course of RA may have an impact on subsequent long - term outcomes. Disparities in Sharp Score should be taken into consideration in formulating treatment strategies in the early course of the disease, when intervention is most likely to benefit the patient. This is essential in improving disease control and functional outcomes.

Conclusions

In conclusion, the Sharp Score in patients with RA was significantly increased and closely related to disease activity. In addition to that, ESR, CRP and RF were risk factors of Sharp Score. So, Sharp Score should be taken into consideration in formulating treatment strategies in RA.

Abbreviations

RA: rheumatoid arthritis; DAS28: Disease Activity Score; CRP: C-reactive protein;

RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; CCP: anti-cyclic citrullinated peptide antibody; IGA: immunoglobulins A; IGG: immunoglobulin G; IGM: immunoglobulin M; C3: complement 3; C4: complement 4; BALP: bone alkaline phosphatase; OC: osteocalcin; OPG: Osteoprotegerin; RANKL: receptor activator for nuclear factor- κ B ligand; ARM: association rule mining.

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Authors' contributions

JTW, JL, HJ, LW, LX, and YS contributed to the study design. JTW contributed to data analysis, wrote the first draft, and revised the manuscript. YQS, XW, and JW contributed to the questionnaire survey on patients, specimens, and data collection. JL supervised the project and helped revise the manuscript. All authors reviewed and accepted the content of the final manuscript.

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Availability of data and materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation to any qualified researcher.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine and carried out under the Helsinki Declaration. Before participating in the study, the patients filled in a written informed consent forms. A written informed consent was obtained from all the study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

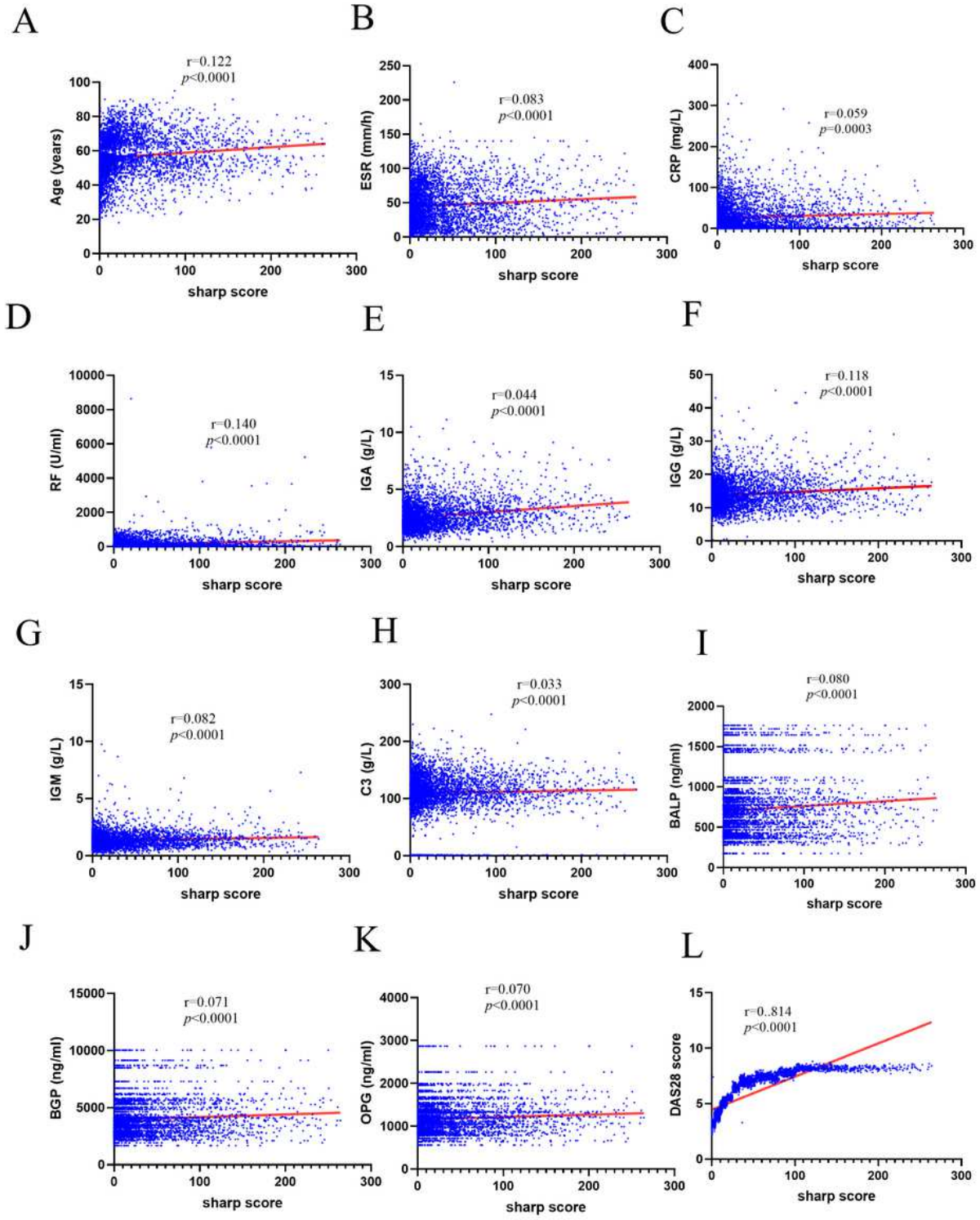

Figure 1

Spearman correlation analysis of Sharp Score and clincial indexes.

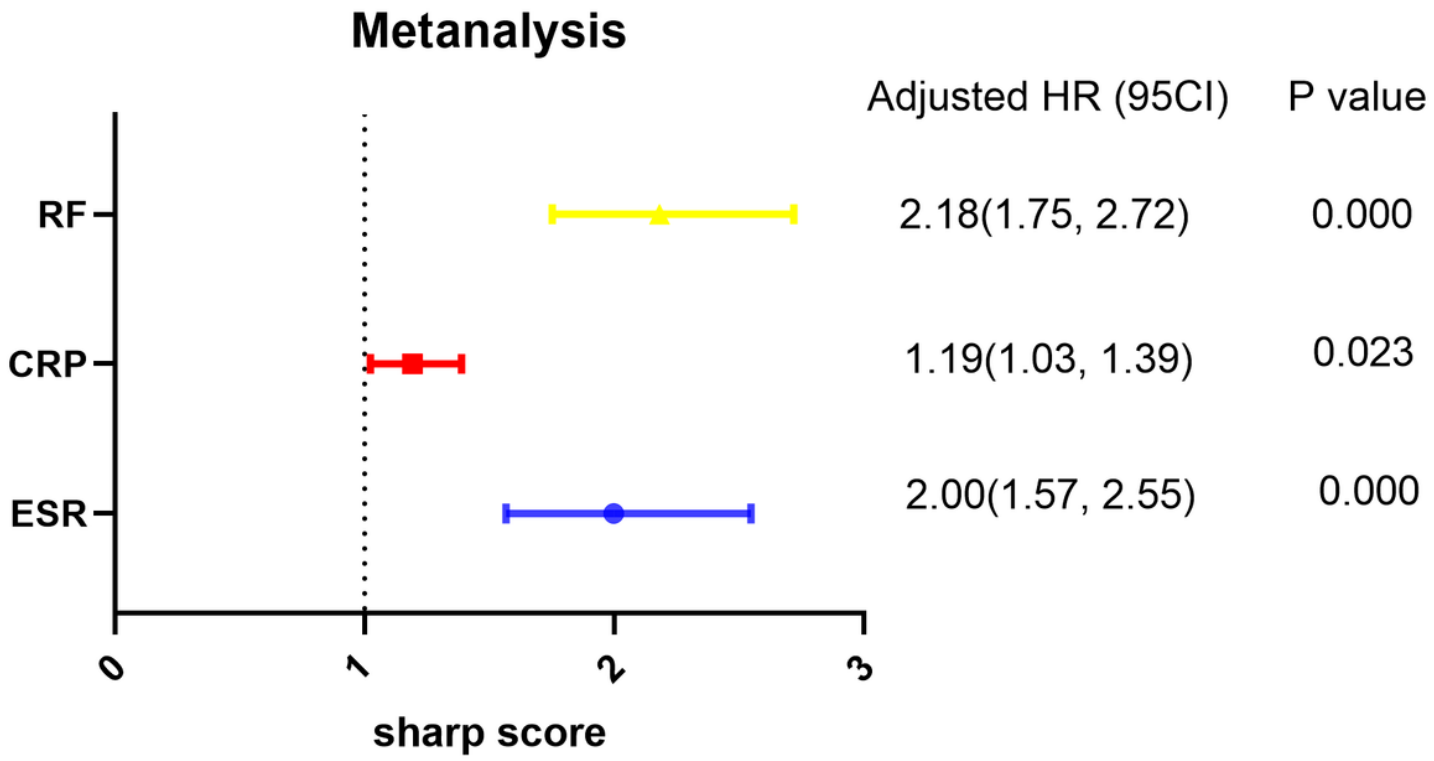

Figure 2

Logistic regression analysis of Sharp Score and clincial indexes.