The serum C-reactive protein to prealbumin ratio and fibrinogen to prealbumin ratio are two relevant indicators for evaluating the disease activity of ankylosing spondylitis

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Abstract
The C-reactive protein to prealbumin ratio (CPR) and fibrinogen to prealbumin ratio (FPR) in serum are two emerging biomarkers. The purpose of this study is to explore the relationship between these two markers and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Scores (ASDAS). A total of 163 patients with AS and 120 healthy examinees were included in this study. The t-test and Mann-Whitney U ranking test were used to analyze the differences between groups. The spearman-test was used to analyze the correlation between erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), fibrinogen (Fib), prealbumin (PAlb), CPR, FPR, and AS disease activity in the test group. We generated the receiver operating characteristic curves (ROC) of CPR and FPR and determined the discriminating ability by calculating the area under the curve (AUC). Compared with the healthy group, ESR (p < 0.001), CRP (p < 0.001), Fib (p < 0.001), CPR (p < 0.001), and FPR (p < 0.001) of AS patients were significantly increased, while PAlb was significantly reduced. CPR and FPR were more correlated to ASDAS-CRP. CPR was positively correlated with CRP, ESR, BASDAI, and ASDAS-CRP in AS patients (r = 0.959, p < 0.001, r = 0.717, p < 0.001, r = 0.704, p < 0.001, r = 0.763, p < 0.001). FPR was positively correlated with CRP, ESR, BASDAI, and ASDAS-CRP in AS patients (r = 0.779, p < 0.001, r = 0.709, p < 0.001, r = 0.551, p < 0.001, r = 0.763, p < 0.001). ROC showed that the AUC levels of CPR and FPR were high (AUC = 0.952 and AUC = 0.893). CPR and FPR are two promising new biological indicators for assessing disease activity in AS patients.

Keywords
ankylosing spondylitis, C-reactive protein to prealbumin ratio, disease activity, fibrinogen to prealbumin ratio

Introduction
AS is a common chronic systemic inflammatory autoimmune disease that occurs mainly in young men. The main symptom of AS is inflammation of the sacroiliac joint and spine attachment point. This condition involves the sacroiliac joints, causing spinal rigidity and fibrosis, causing different degrees of eye, lung, muscle, and bone lesions, so the social and economic burden caused by it cannot be ignored.\(^1\,\,^2\) It is well known that it is difficult to assess the clinical disease status of AS. Currently, there is no gold standard for disease activity in AS.

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The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is one of the most commonly used and widely validated tools. In recent years, the ankylosing spondylitis disease activity score (ASDAS) has been proposed by ASAS (Assessment Ankylosing Spondylitis Working Group) as a new indicator. Its scores include the evaluation of low back pain, morning stiffness duration, patients with generalized pain, swelling, and CRP or ESR. ASDAS has proved to be effective in the evaluation of ankylosing spondylitis disease activity and has a high degree of specificity. Analysis shows that ASDAS has better discrimination ability in the subgroup of high inflammation markers. ASDAS and BASDAI showed the same good performance in a cross-sectional study in a local Chinese cohort. ASDAS performed better even in the subgroup with elevated inflammation markers.

Many recent studies have shown that various blood parameters are related to systemic disease activity, including fibrinogen to albumin ratio (FAR), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR) and monocyte to lymphocyte ratio (MLR), and other indicators. Chronic inflammation throughout the body may lead to abnormal levels of prealbumin, fibrinogen, and peripheral blood immune cell counts. Systemic inflammatory response leads to nutritional damage. Previous studies have shown that albumin can be used as both a marker of inflammation and a parameter for nutritional status assessment. Fibrinogen plays an important role in coagulation and regulating inflammation. Some studies report that fibrinogen levels can independently predict the prognosis of certain cancers. Based on new inflammatory markers, CPR and FPR have a significant relationship with inflammatory diseases and cancer prognosis. However, it is unclear whether CPR and FPR are related to disease activity in AS.

Therefore, in this study, we retrospectively studied the correlation between CPR and FPR and AS disease activity and their diagnostic value. Our results indicate that CPR and FPR are positively correlated with CRP, ESR, and ASDAS, indicating that CPR and FPR may be potential indicators for monitoring disease activity in AS patients.

Materials and methods

Research object

This study is a retrospective analysis of patients with AS diagnosed and admitted to the First Affiliated Hospital of Zhengzhou University from January 2018 to December 2019. Inclusion criteria for the AS group: all patients met the diagnostic criteria of the Assessment of SpondyloArthritis International Society (ASAS) 2014. Exclusion criteria: patients suffering from other systemic diseases (such as cardiovascular diseases, blood diseases, endocrine diseases, respiratory diseases, kidney diseases, infections, malignant tumors) and chronic autoimmune diseases using corticosteroids in the past 3 months. A total of 163 patients were selected into the control group. We randomly selected 120 healthy examinees who were examined in the First Affiliated Hospital of Zhengzhou University at the same period as the control group. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (No. 2019-KY-285) and is in accordance with the Declaration of Helsinki. Written informed consents were obtained from participants. The results of the study do not affect on the further management of these patients.

Research methods

We obtained the clinical characteristics of AS patients and healthy examinees from the hospital medical record system, including age, gender, CRP, ESR, PAlb, Fib, etc., and calculated BASDAI and ASDAS. We conducted a comparative analysis of the clinical characteristics and differences in ASDAS between the blank group and the control group. The correlation between CRP, ESR, PAlb, Fib, CPR, FPR, BASDAI, and ASDAS in the control group was analyzed, and finally, the diagnostic value of CPR and FPR to assess AS disease activity was analyzed.

Statistical methods

SPSS 22 statistical software (SPSS, Inc., Chicago, Illinois, USA) was used to evaluate the normality of the data distribution using the Kolmogorov-Smirnov test. The data that conforms to the normal distribution are represented by mean ± SD, and the data that do not conform to the normal distribution are represented by median (interquartile range). The categorical variables were expressed as percentages. Comparisons of the differences of continuous variables were performed by the Student’s t-test or Mann–Whitney U test. Categorical variables were compared with the χ²-test. Spearman’s correlation analysis was used to examine the
association between variables. Graphpad Grism 8 (Graphpad, Inc., San Diego, California, USA) was used for linear regression analysis to compare the goodness of fit of CRP, ESR, PAIb, Fib, CPR, FPR, BASDAI, and ASDAS, and to determine the correlation. The ROC was generated by MedCalc 19.0 (Maryak, Belgium) and analyzed to determine the AUC, cutoff value, sensitivity, specificity, positive predictive value, and negative predictive value of these biological indicators. A value of $p < 0.05$ is considered a statistically significant difference.

**Result**

**Clinical characteristics of the enrolled participants**

Table 1 summarizes the clinical characteristics of 163 AS patients and 120 healthy controls. There was no significant difference in age ($p = 0.683$) or gender ($p = 0.425$) between AS patients and healthy controls. Compared with the healthy group, Fib, CRP, and ESR counts of AS patients increased significantly ($p < 0.001$), while PAIb counts of AS patients decreased significantly ($p < 0.001$). In AS patients, CPR and FPR increased significantly ($p < 0.001$, all patients).

**Correlation of CRP, ESR, Fib, PAIb, CPR, and FPR with clinical disease activity in patients with AS**

In patients with AS, ESR, CRP, Fib, CPR, and FPR are positively correlated with ASDAS-CRP and ASDAS-ESR, while PAIb is negatively correlated with ASDAS-CRP and ASDAS-ESR. The goodness of fit of CRP, ESR, Fib, PAIb, CPR, and FPR to ASDAS-CRP are $r = 0.763, r = 0.689, r = 0.549, r = -0.561, r = 0.863$, and $r = 0.701$ (Figure 1). The goodness of fit of CRP, ESR, Fib, PAIb, CPR, and FPR to ASDAS-ESR are $r = 0.658, r = 0.685, r = 0.626, r = -0.571, r = 0.671$, and $r = 0.701$ (Figure 2). The goodness of fit of CRP, ESR, Fib, PAIb, CPR, and FPR to BASDAI are $r = 0.763, r = 0.689, r = 0.549, r = -0.561, r = 0.863$, and $r = 0.701$ (Figure 3). Analysis of the correlation between CPR and FPR and AS disease activity showed that CPR was positively correlated with BASDAI ($r = 0.704, p < 0.001$), ASDAS-CRP ($r = 0.863, p < 0.001$), and ASDAS-ESR ($r = 0.671, p < 0.001$). Similarly, FPR was positively correlated with BASDAI ($r = 0.551, p < 0.001$), ASDAS-CRP ($r = 0.763, p < 0.001$), and ASDAS-ESR ($r = 0.625, p < 0.001$) (Figure 4).

**Diagnostic values of CPR and FPR**

We generated ROC to evaluate the diagnostic value of CPR and FPR under differentiated health controls. The AUC of CPR is 0.9521, the best cut-off value of CPR is 0.14 (sensitivity = 80.77%, specificity = 88.93%, positive predictive value = 90.38%, negative predictive value = 77.17%). In addition, the AUC of FPR is 0.8927, and the best cut-off value is 0.015 (sensitivity = 77.89%, specificity = 95.31%, positive predictive value = 95.02%, negative predictive value = 76.04%). (Table 2, Figure 5).

**Discussion**

The disease activity status of AS is an important indicator to evaluate the severity of AS, which directly affects the formulation of its clinical drug treatment plan. Currently, CRP, ESR, and ASDAS

| Characteristics | AS group N = 162 | Control group N = 120 | p-Value |
|-----------------|-----------------|-----------------------|---------|
| Age (years)     | 33.45 ± 12.71   | 34.06 ± 11.75         | 0.683   |
| Gender (F/M)    | 131/31          | 100/20                | 0.425   |
| ESR (mg/L)      | 28.00 (10.00–50.00) | 6.55 (4.85–9.00)     | <0.001  |
| CRP (mg/L)      | 24.50 (6.70–47.00) | 0.87 (0.39–1.74)     | <0.001  |
| Prealbumin (mg/L) | 201.16 ± 62.11  | 260.60 ± 48.87       | <0.001  |
| Fibrinogen (g/L) | 4.59 ± 3.33     | 2.815 ± 0.56         | <0.001  |
| CPR (%)         | 0.13 (0.34–0.26) | 0.02 (0.01–0.04)     | <0.001  |
| FPR (%)         | 0.0244 ± 0.0126 | 0.0112 ± 0.0029      | <0.001  |

F: female; M: male; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CPR: C-reactive protein to prealbumin ratio; FPR: fibrinogen to prealbumin ratio.

$p < 0.05$ was considered statistically significant.
are the most common non-specific indicators used to assess AS disease activity; however, the above indicators are susceptible to other physiological factors such as age, gender, infection, malignant tumor or smoking status, and other factors cannot accurately reflect the true disease activity status of AS, and its effectiveness in reflecting disease activity status is often questioned. Therefore, it is necessary to explore new and more effective biological indicators to assess the disease activity of AS. This study evaluated the correlation of CRP, ESR, PAlb, Fib, CPR, and FPR with disease activity in AS patients (BASDAI, ASDAS-CRP, and ASDAS-ESR). The results showed that CRP, ESR, PAlb, Fib, CPR, and FPR were significantly different between AS patients and healthy individuals. The goodness of fit of CPR and FPR with BASDAI, ASDAS-CRP, and ASDAS-ESR is significantly better than CRP, ESR, PAlb, Fib; that is, the correlation between CPR and FPR and AS patients’ disease activity is stronger than traditional biological indicators.
In the comparison, we found that the goodness of fit between CPR and FPR and ASDAS-CRP is better than that of BASDAI and ASDAS-ESR (Figure 4). Therefore, CPR and FPR may be effective indicators for predicting disease activity in patients with AS.

(Figures 1–3). In the comparison, we found that the goodness of fit between CPR and FPR and ASDAS-CRP is better than that of BASDAI and ASDAS-ESR (Figure 4). Therefore, CPR and FPR may be effective indicators for predicting disease activity in patients with AS.

Table 2. The diagnostic value of inflammatory biomarkers for ankylosing spondylitis severity.

| Biomarker | Cut-off value | AUC    | Sen (%) | Spe (%) | PPV (%) | NPV (%) |
|-----------|--------------|--------|---------|---------|---------|---------|
| CPR       | 0.142        | 0.9521 | 80.77   | 88.32   | 90.38   | 77.17   |
| FPR       | 0.015        | 0.8927 | 77.89   | 95.31   | 95.02   | 76.04   |

AUC: area under curve; Sen: sensitivity; Spe: specificity; PPV: positive predictive value; NPV: negative predictive value; CPR: C-reactive protein to prealbumin ratio; FPR: fibrinogen to prealbumin ratio.
AS is a chronic autoinflammatory disease. The long-term existence of disease-related inflammation may have a huge negative impact on the patient’s nutritional status. During AS, the patient’s autoimmune status and nutritional status have a considerable impact on the severity and prognosis of AS. CRP is a plasma protein of the pentosan family and is known for its rapid rise in serum during inflammation as part of the acute phase of inflammation. CRP is mainly produced by the liver, and it is an acute phase protein that reflects systemic inflammation. Its rapid increase in serum is related to the levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and other anti-inflammatory cytokines. During inflammation, the body reacts by producing large amounts of TNF-α, IL-6, and other cytokines, resulting in a low serum albumin concentration. Albumin is produced by the liver and can effectively reflect the nutritional status of the human body. However, because serum albumin is not sensitive to immediate nutritional changes, it has a long half-life. Additionally, many potential factors may cause hypoproteinemia. These factors include acute infection, burns, inflammatory diseases, malignant tumors, malnutrition, kidney disease, severe liver dysfunction, and trauma. In contrast, the half-life of PAIb (2–3 days) is much shorter than that of Alb (21 days), which makes PAIb as an indicator of nutritional status more accurate and timely. PAIb is closely related to the nutritional status of the body and is a good indicator of the nutritional and immune status of the body. When the body is in a state of malnutrition, its immune function is significantly reduced, thereby weakening the body’s anti-inflammatory ability. The stimulation of inflammation affects the synthesis of Alb and PAIb in the internal organs. Based on the above theory, a series of studies have shown that CRP and PAIb are related to the activities of various immune-related diseases. At the same time, PAIb is also an inflammation marker, which is a reverse proportional CRP. The predictive value of CRP for gastric cancer and other prognoses is better than other traditional inflammation indexes. Few studies have studied the relationship between CRP and autoimmune diseases. However, there is no more direct evidence to show the relationship between AS and malnutrition. Our results show that AS patients have a higher CP value, and the PAIb level in these patients is significantly lower than the reference value. ROC shows that CPR has a high AUC, which indicates that CPR may have great diagnostic value.

Both Fib and PAIb are produced by the liver, but studies have shown that these two have opposite expressions in the inflammatory state, so Fib is not only an important factor in the coagulation cascade but also a major acute-phase reactive protein in chronic inflammation. When the body is in systemic inflammation, the immune system interacts with all parts of the coagulation system and triggers the production of Fib through the liver and itself, resulting in high levels of Fib expression. Because Fib and serum PAIb are negatively correlated during the systemic inflammatory response, the integration of these two inflammatory indicators (FPR) can be used as a reliable indicator of systemic inflammatory status. Fib and PAIb are two key factors of the coagulation system, nutritional status and inflammation, and the current research in the field of cancer and cardiovascular disease has become a hot spot. There are few reports on the activity of rheumatoid diseases. Many reports indicate that the plasma level of Fib can be used as a new biomarker to independently predict the prognosis of malignant tumors such as colon cancer and liver cancer. Previous studies have shown that Fib can increase the expression of cytokines, such as interleukin-8 (IL-8) and intercellular adhesion fraction-1 (ICAM-1), and directly promote the development of systemic immune responses. These findings indicate that fibrinogen has great...
potential value in the assessment of AS disease activity. In this study, we combined the ratio of fibrinogen and prealbumin as a new indicator of inflammation. The disease activity of AS and FPR were significantly positively correlated, and ROC showed a high AUC. These findings further support the potential value of FPR as a biomarker for monitoring AS disease activity. It is reported that the common inflammatory cytokine IL-6 can inhibit the synthesis of Alb and PAlb, leading to hypoproteinemia in patients. Therefore, poor nutritional status and impaired patient immune monitoring directly affect the clinical outcome of the disease. These factors may be the reasons for the findings in this study.

However, our research also has some limitations. First of all, this was a retrospective study, conducted in a single-center, the sample size was relatively limited, and it cannot represent the overall situation of AS patients more effectively. Second, we did not study the correlation between CPR and FPR and TNF-α and other inflammatory factors, nor did we assess the impact of systemic drug therapy on CPR and FPR. Thirdly, we did not make statistics and analysis of the illness duration of all patients. Therefore, the correlation and diagnostic value of CPR and FPR with AS still need to be verified in multicenter and prospective cohort studies.

Conclusion

In summary, CPR and FPR are two promising biological indicators for judging the intensity of AS disease activity. Doctors can quickly judge the intensity of disease activity through these two laboratory indicators, to help doctors formulate the diagnosis and treatment plans suitable for patients. However, in the future, this field needs more in-depth research to reveal the relationship between these two indicators and the intensity of AS disease activity.

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