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Evaluation of Acute Phase Reactants in Patients with Ankylosing Spondylitis

Ankilozan Spondilitli Hastalarda Akut Faz Reaktanlarının Değerlendirilmesi

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Abstract

Objective: The aim of this study is to determine the high levels of acute phase reactants (APR) of ankylosing spondylitis (AS) patients at diagnosis and follow-up, and to investigate the relationship between patients' high levels of APR and patients' disease activity levels and clinical characteristics.

Material and Method: 948 patients who were diagnosed with AS according to the modified 1984 New York criteria and followed-up at the university rheumatology clinic were included in this study. The patients' erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels across all visits were retrospectively reviewed through the hospital's database.

Results: At first visit, high levels of CRP and ESR were observed in 626 (68.5%) and 578 (64.6%) patients respectively. During follow-up 84.6% of patients had high CRP and 69.5% patients had high ESR, however in 10% of patients APRs did not increase at all. There was good correlation between ESR and CRP (r=0.666, p=0.000). A better correlation was observed at first visit between CRP and BASDAI (r=0.81, p=0.23) or ASDAS (r=0.468, p=0.000) compared to ESR and BASDAI (r=0.111, p=0.02) or ASDAS (r=0.334, p=0.000). Compared to BASDAI, ASDAS with either ESR (p=0.00) or CRP (very high disease activity-p=0.000, inactive disease-p=0.001) had better performance in evaluating the activity of the patient in inactive and very high levels of severe disease.

Conclusion: Our results showed, high levels of acute phase reactants is not rare in AS patients. APR should be considered the most significant laboratory diagnostics in the evaluation of AS and/or response to the treatment.

Keywords: Ankylosing spondylitis, acute phase reactant, erythrocyte sedimentation rate, C-reactive protein, disease activity index.

Öz

Amaç: Ankilozan spondilit (AS) hastalarının tanı ve takipteki yüksek akut faz reaktanları (AFR) düzeylerini belirlemek ve hastaların yüksek AFR düzeyleri ile hastalık aktivite düzeyleri ve klinik özellikleri arasındaki ilişkiyi araştırmak.

Gereç ve Yöntem: Modifiye 1984 New York kriterlerine göre AS tanısı alan ve üniversite romatoloji kliniğinde takip edilen 948 hasta bu çalışmaya dahil edildi. Tüm ziyaretlerdeki hastaların eritrosit sedimantasyon hızı (ESH) ve C-reaktif protein (CRP) seviyeleri kayıt defteri ve hastanenin veri tabanı aracılığıyla geriye dönük olarak incelendi.

Bulgular: İlk ziyarette, sırasıyla 626 (%68,5) ve 578 (%64,6) hastada yüksek CRP ve ESH seviyeleri gözlendi. Takip sırasında hastaların %84,6'sında yüksek CRP ve %69,5'inde yüksek ESH vardı, ancak hastaların %10'unda AFR hiç yükselmedi. ESH ile CRP arasında iyi bir korelasyon vardı (r=0,666 , p=0,000). İlk ziyarette CRP ile BASDAI (r=0,81, p=0,23) veya ASDAS (r=0,468 , p=0,000) arasında ESH ve BASDAI (r=0,111 , p=0,02) veya ASDAS ile karşılaştırıldığında daha iyi bir korelasyon gözlendi r=0,334, p=0,000). BASDAI ile karşılaştırıldığında, ESH (p=0,00) veya CRP (çok yüksek hastalık aktivitesi-p=0,000, inaktif hastalık-p=0,001) olan ASDAS, hastanın aktivitesini inaktif ve çok yüksek düzeyde şiddetli hastalık olarak değerlendirmede daha iyi performans gösterdi.

Sonuç: Sonuçlarımız, AS hastalarında yüksek düzeyde akut faz reaktanlarının nadir olmadığını gösterdi. AFR, AS'nin değerlendirilmesinde ve/veya tedaviye yanıtta en önemli laboratuvar diagnostiği olarak düşünülmelidir.

Anahtar Kelimeler: Ankilozan spondilit, akut faz reaktanı, eritrosit sedimantasyon hızı, C-reaktif protein, hastalık aktivite indeksi.

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INTRODUCTION

The term spondyloarthritis (SpA) is currently used for a group of chronic inflammatory diseases associated with interdependent clinical manifestations, such as sacroiliitis, uveitis, enthesitis, dactylitis, and arthritis with common clinical, radiological and genetic characteristics.[1] Ankylosing spondylitis (AS) is the prototype disease of this group. An increase may occur in acute phase reactants (APR) because of inflammation in the disease process. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most commonly used acute phase reactants during the follow-up period.[2] While APRs may be a quantitative follow-up parameter that can be used to monitor the AS treatment response, some of the patients with AS do not have an increase in AFRs even in the inflammation periods during the diagnosis and follow-up.[3] In the literature, rates of patients with increased CRP levels have been reported in a wide range of 39% -75%.[4-7] The present study aims to determine the rate of high APR values at the time of diagnosis and during the follow-up in AS patients, and to demonstrate the relationship between these high APR values and the clinical characteristics and disease activities of the patients.

MATERIAL AND METHOD

Patients

This study includes all 948 patients followed up with the diagnosis of Ankylosing Spondylitis according to the 1984 modified New York criteria[8] in the Rheumatology Outpatient Clinic of Dokuz Eylul University Faculty of Medicine Department of Internal Medicine. The data of the patients were retrospectively reviewed from October 2011 through Dokuz Eylül University Hospital's database. Patients with chronic disorders and patients who applied to the infectious diseases outpatient clinic were excluded from the study.

Data Collection

All ESR and CRP values of the patients at the time of diagnosis and during the follow-up period, demographic information such as age and gender, clinical findings such as peripheral arthritis and enthesitis, laboratory values such as HLA B27, drug use information, and the score of the disease assessment scales such as visual analog scale (VAS), ankylosing spondylitis disease activity score (ASDAS), bath ankylosing spondylitis metrology index (BASMI), bath ankylosing spondylitis functional index (BASFI) and bath ankylosing spondylitis disease activity index (BASDAI) were recorded by retrospective screening via the same database.[9-12]

Ethical Approval

The study was approved by Dokuz Eylül School of Medicine Local Ethic Committee. (Date: 07/09/2017 Decision No: 2017/21-44). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statistical Analysis

The statistical analysis of the data was made using the (Statistical Package for the Social Sciences) SPSS® version 22.0 package program. Continuous variables were expressed as mean±standard deviation (SD.) and categorical variables as the percentage. Pearson's chi-square test was used to compare the categorical values between the groups and the correlation between the disease monitoring parameters was investigated with Spearman's correlation analysis. Student's t-test was applied in the presence of normal distribution to compare the means of independent groups. The following points are the accepted guidelines for interpreting the correlation coefficient: a)Values between 0 and 0.3 (0 and −0.3) indicate a weak correlation; b)Values between 0.3 and 0.7 (0.3 and −0.7) indicate a moderate correlation; Values between 0.7 and 1.0 (−0.7 and −1.0) indicate a strong correlation.13

The mean, minimum (Min.), and maximum (Max.) values were given for continuous variables and the number (n) and percentage (%) values were given for categorical variables as descriptive values, while $p<0.05$ was considered statistically significant.

RESULTS

A total of 948 AS patients ranging from 21-86 years of age were included in the study, including 293 females (30.9%) and 655 (69.1%) males. The mean age of the patients was 46.6±12.1. HLA B27 was positive in 25% and negative in 10.5% of the patients, while it could not be analyzed in 64.5% of the patients due to reasons arising from the social security system. There was a family history of the disease in 13.2% of patients. The demographic data of the patients included in the study are given in **Table 1**.

Table 1. The demographic data of the patients included in the study

Parameter	N (%), Mean±SD. (Min./Max.)
Age (year)	46.6±12.1 (21/86)
Age of onset (year)	27.3±10.5 (6/67)
Age of diagnosis (year)	34.5±12.0 (9/76)
Gender (Female/Male)	293 (%30.9)/655 (%69.1)
HLA B27 (Positive/negative/unknown)	237 (%25)/100 (%10.5)/611 (%64.5)
Family history for spondyloarthritis (present/absent)	123 (%13.2)/806 (%86.8)
Incidence of peripheral arthritis	330 (%34.8)
Incidence of enthesitis	319 (%36.6)
Incidence of uveitis	161 (%18.5)
Incidence of dactylitis	69 (%8)
Incidence of inflammatory bowel disease	36 (%4.1)
Incidence of psoriasis	23 (%2.7)

Data were presented as mean±SD. (min.: max.) and n (%); Min.: Minimum; Max.: Maximum; HLA: Human leucocyte antigen; SD.: Standard deviation.

While the ESR level was high in 578 (60.9%) patients, CRP level was high in 626 (66%) patients at the first visit. The ESR and CRP levels were higher in males at the first visit (p=0.000) (**Figure 1**).

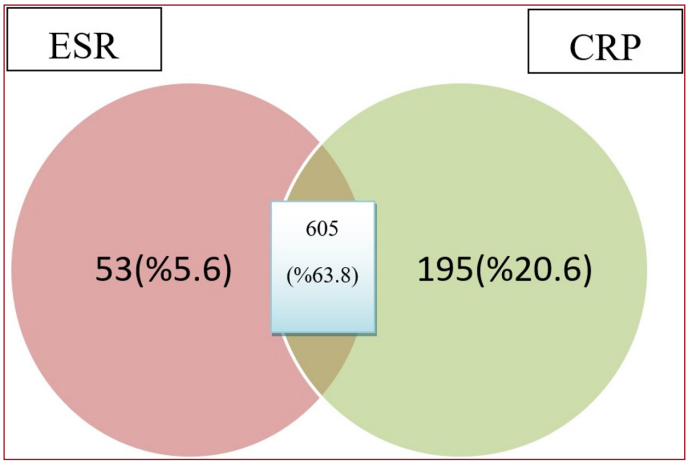

Figure 1. Vein diagram of patients ascending only ESR/CRP or both at any time

When the data of the patients with high levels of both ESR and CRP were analyzed, it was seen that there was a significant difference in terms of gender, and the ESR and CRP levels were higher in male patients (p=0.019).

There was no significant difference between the positive or negative HLA-B27 and the CRP elevation in AS patients. A similar situation was seen between the HLA-B27 positivity and the ESR elevation (**Table 1**).

The CRP and ESH levels of the patients were checked at the time of diagnosis, and they were monitored third month, sixth month and at last visit. The mean CRP value of the patients at the first visit was 19.92±29.67 mg/L, and the mean ESR value measured at the first visit was 32.33±22.82 mm/hour. The mean value of CRP measured at the 3rd month visit was 13.51±21.66 mg/L, and the mean value of ESR measured at the first visit was 10.40±18.97 mm/hour. The mean value of CRP measured at the 6th month visit was 14.70±22.47 mg/L, and the mean value of ESR was 21.21±21.35 mm/hour. The mean ESR value measured at the last visit was 22.95±19.55 mm/hour, and the mean CRP value measured at the last visit of the patients was 14.03±24.71 mg/L (**Table 2**).

Table 2: Mean ESR and CRP at first visit, third month, sixth month and at last visit.

		Mean±SD.	Min./Max.
First visit	CRP (mg/L)	19.92±29.67	0/296
	ESH (mm/h)	32.33±22.82	0/161
Third month	CRP (mg/L)	13.51±21.66	1/105
	ESH (mm/h)	10.40±18.97	0/90
Sixth month	CRP (mg/L)	14.70±22.47	1/112
	ESH (mm/h)	21.21±21.35	1/105
Last visit	CRP (mg/L)	14.03±24.71	0/359
	ESH (mm/h)	22.95±19.55	0/110

We have checked mean values of disease rating scales at the 3rd month, 6th month and last visit of the patients. It was observed that the patients' disease activity scales, BASDAI, BASFI, VAS Global, and ASDAS scales, showed a decreasing trend at the 3rd and 6th months compared to the first visit (**Table 3**).

Table 3: Mean values of disease rating scales at the 3rd month, 6th month and last visit of the patients

	First visit	Third month	Sixth month	Last visit
BASDAI	3.88±2.31	2.93±2.16	2.55±2.02	2.89±2.17
BASFI	3.28±2.60	2.56±2.28	2.36±2.24	2.67±2.41
ASDAS	2.88±1.18	0.44±1.05	0.11±0.56	2.25±1.07
VAS Global	4.83±2.84	4.07±2.63	4.06±2.57	3.76±2.40

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

Similarly, there was a decrease in BASDAI, BASFI, VAS Global, and ASDAS scores at the 3rd and 6th month visits when compared with the first visit in patients using Anti-TNF (**Table 4**).

Table 4: Mean values of disease rating scales at the first, 3rd and 6th month visits of patients using anti-TNF

	First visit	Third month	Sixth month
BASDAI	4.78±2.43	3.35±2.34	2.84±2.09
BASFI	4.14±2.69	3.76±2.46	3.45±2.42
ASDAS	3.45±1.24	4.04±2.48	3.43±2.43
VAS Global	5.62±2.81	0.14±0.62	0.11±0.54

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

The relationship between ESR (baseline) levels and disease activity parameters (first visit) was evaluated. A weak positive correlation was found between ESR levels and BASDAI and BASFI and BASMI scores (r=0.111, p=0.020, r=0.219, p=0.000, and r=0.123, p=0.003 respectively). A moderate positive correlation was found between ESR levels and ASDAS score (r=0.334, p=0.000). However, CRP had a high correlation with BASDAI (r=0.810, p=0.023), a mild correlation with BASFI (r=0.224, p=0.000), and a moderate correlation with ASDAS (r=0.468, p=0.000) (**Table 5**).

Table 5: Relationship between ESR and CRP at first visit and disease activity parameters

	ESR (mm/h)		CRP (mg/L)	
	r	p	r	p
BASDAI	0.111	0.020	0.810	0,023
BASMI	0.123	0.003	0.205	0.000
BASFI	0.219	0.000	0.224	0.000
ASDAS	0.334	0.000	0.468	0.000

Spearman correlation test; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ESR: Erytrocyte sedimentation rate (mm/h); CRP: C-Reactive protein; r: correlation coefficient.

DISCUSSION

It is difficult to define the disease activity, progression, prognosis and complete disease status of AS. APR measurements are used as part of routine clinical care in determining the clinical activity of AS, although they are not as indicative as in rheumatoid arthritis during the disease follow-up.[3] Different rates have been reported in the literature for the ESR and CRP values measured in the baseline in ankylosing spondylitis. The CRP levels were found as %39, %47.3, %62, and %75 in various studies.[4-6,14] The mean ESR and mean CRP were determined as 33.1±24.8/ 22.3±21.4 in the study by Lin et al.[15], as 31±23.3/ 8.3 in the study by Bodur et al.[16], as 24.9/1.5 in the study by Çağlar et al.[17], and as 23.9± 21.9/ 15±13.9 in the study by Başkan et al.[18]

Considering the early axial SpA cohorts, it is seen the rate of patients with high levels of ESR and CRP is not high. In a literature review by Ruof et al.[3] 13 studies were evaluated. The researchers analyzed the relationship between the ESR and/or CRP and the disease activation and saw that the correlation coefficient ranged between 0.55 and 0.69 and there was a strong relationship between the ESR and CRP. In the same review, it was reported that the CRP was more closely associated with the disease activity. However, in the literature, there are studies reporting that the high levels of CRP and ESR are not encountered frequently in the AS, and they were not in good correlation with clinical activity and radiological progression.[2,3] In the present study, the mean CRP value of the patients measured at the first visit was 19.92±29.67 mg/L, and the mean ESR value was 32.33±22.82 mm/h. There was a high level of ESR in 60.9%, and a high level of CRP in 66% of the patients at the first visit. This shows similarities with studies where higher ESR and CRP rates were reported.

While the level of ESR was high at a rate of 60.9% and the level of CRP at a rate of 66% at the first visit, these rates rose up to 69.5% for the ESR and 84.6% for the CRP level during a 7-year follow-up period. In previous studies where the ESR and CRP levels were analyzed, the first visit measurements were evaluated in general but the APR levels and the rates of patient high APR levels were not reported. The results of the present study were similar to those of the studies reporting a high APR rate at the first visit, but an increase was observed in this rate during the follow-up visits.[15-18] In the present study, several APR measurements were detected during the follow-up period and, as a limitation, the factors that caused confounding conditions such as infection during these measurements could not be eliminated. Considering the patient-based distribution, the CRP was the group where the highest positivity was seen with a positivity value of 75-100% in 411 patients. This can be explained with the fact that it could be measured and a high value could be obtained only once in 122 patients.

The mean CRP values of patients before Anti-TNF ranged from 11.0 mg/L to 31.8 mg/L similar to our database of the patients in this study.[17] The percentages of patients with high CRP and ESR values were not given in these databases. These ESR and CRP values are those before all the patients started to use anti-TNF, and almost all of these records were obtained from patients receiving anti-TNF. One of the reasons for the high proportion of patients with high APR values in the present study is that our database is mainly focused on the patient group receiving anti-TNF. More than one-third of the patients used anti-TNF drugs.

As a result of the evaluation of 261 patients before the administration of anti-TNF, the mean value of CRP was 23.0 mg/L, which was close to the mean CRP in the present study[19] There are studies that show the relationship between the CRP and the disease scales like BASDAI and ASDAS, as well as studies that report the opposite results. In another study by Sheehan et al., there was a positive correlation between the acute phase reactants (ESR, CRP, orosomucoid, Alfa-1 antitrypsin), but no correlation was found between the disease activity and acute phase reactants.[20]

Similar to the observations that there was a positive correlation between acute phase reactants and disease activity parameters, in the present study, the ESR had a weak correlation with the BASDAI and a moderate correlation with the ASDAS score at the first visit. The correlation between the CRP and the BASDAI score was better than that of the ESR. Similarly, there was a moderate correlation with the ASDAS score.

The study by Cansu et al. showed that the ESR and CRP were associated with high BASFI scores.[21,22] However, while a correlation was determined between the acute phase responses and the BASMI and BASFI scores in the present study, it was not remarkably high.

Some studies in the literature argued that the symptoms were more severe in HLA-B27-positive AS patients than in HLA-B27-negative patients and demonstrated this by an increase in ESR and CRP values.[23-25] However, in a study by Chung et al., ESR and CRP were evaluated in spondyloarthropathy patients with positive and negative HLA-B27, and no significant relationship was found between patients with positive HLA-B27 and the ESR and CRP levels.[26]

In the present study, no significant difference was found between the positive or negative HLA B27 and BASDAI active/ inactive disease scores and ASDAS inactive disease, moderate disease activity, high disease activity, and very high disease activity. Furthermore, there was no significant relationship between the CRP and ESR levels and the HLA-B27.

In the present study, the fact that the ESR and CRP levels are high, measurement of APRs more or less frequent than 3 months, can be explained by the presence of cases in which the ESR and CRP levels were not measured concurrently. However, the high ESR and CRP levels measured may also be the cause of infection, especially in patients receiving anti-TNF. Our study has limitations. The study has a retrospective design, therefore has some limitations due to the nature of the study. We intend to replicate the other parameters with more patients in the future.

CONCLUSION

In the present study, long-term acute phase response measurements of the patients were evaluated differently from the general literature, and high CRP and ESR levels were found in the majority of patients during the follow-up period. ASDAS, as a disease activity score, show a performance better than BASDAI in general, even if not in all parameters. ESR and CRP are still the most significant markers in the daily practice for the evaluation of the disease activity in AS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dokuz Eylül School of Medicine Local Ethic Committee. (Date: 07/09/2017 Decision No: 2017/21-44).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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