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ORIGINAL ARTICLE

Role of some Hematological and Immunological Parameters in Ankylosing Spondylitis Disease in a Sample of Iraqi Male Patients

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ABSTRACT

Ankylosing spondylitis (AS) is an autoimmune disease that is chronic, systemic seronegative inflammatory spondyloartropathy. The magnetic resonance imaging (MRI) were used in diagnosis of AS patients also other clinical and laboratory criteria like symptoms, elevated levels of ESR and C-reactive protein. The current study intends to establish the role of certain hematological and immunological factors in the development of AS and to analyze the connections between these indicators. The methods of work included blood sample collection from 100 participant (50 AS male patients and 50 healthy control). The age of both groups were between 20-60 years. Two milliliters of blood used for CBC (Hb and WBC) and ESR analysis, while three milliliters of the blood were put in a gel tube to measure serum levels of CRP, IL-17, IL-22 using ELISA technique. It shows that the AS was most prevalent in the age between 20-35 years ($p=0.013$). There was a highly significant increase ($p<0.001$) in, ESR, CRP, IL17 and IL22 in AS patients as a result of inflammation compared to controls while the Hb is significantly raised in the control group as compared with patients and except for WBC level that was Non-significant. The WBC was non-specific parameter associated with AS development, while AS patients have lower Hb, and increased levels of CRP, ESR, IL17 and IL22 that were an excellent biomarkers for the diagnosis of AS they were all greater in AS patients than in healthy controls, and they might be recommended as a predictive measure for AS patients.

Keywords: Ankylosing spondylitis (AS), C-reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Magnetic Resonance Imaging (MRI), Receiver Operating Characteristics (ROC)

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INTRODUCTION

AS is a chronic, inflammatory immunological disease of the axial spine which affects male joints gradually. It is predominant pathotype of spondylo-arthropathy. About 0.1–1.4% of the men in the population are affected with the illness, and the prevalence varies greatly depending on ethnicity and geography [1, 2]. Since the condition of the AS develops slowly it's difficult to diagnose. The diagnosis of AS patients involve the clinical examination and the use of bone scan or magnetic resonance imaging (MRI) for the early detection of the axial skeleton inflammation that shows bone marrow edema (the fluid that builds up in the soft tissue inside the bone marrow causing a swelling) and structural lesions for AS patients [3].The current study aimed to determine the correlation between theimmunological markers, including WBC, Hb, ESR, interleukin-17 (IL-17), C-reactive protein (CRP), and interleukin-22 (IL-22) with AS disease. generate a soluble factor which is cytokines Th17/Treg and Th1/Th2.[4]

The main causes of AS's persistent inflammation are the Pro-inflammatory cytokines. Recently, there has been speculation regarding the role of IL-17F in spondyloarthritis inflammation and new bone development. In AS, IL-17 is generated through several pathways. The stimulation of T cells (CD8+), NK cells, and $\delta\gamma$T cells by IL-23 pathway all of which lead to the secretion of IL-17. However CD4+ Th17 cells are the major secretors of IL-17 in AS [5]. The recruitment of neutrophils through IL-6 is mostly mediated by IL-17. The IL-17 also responsible for activation of osteoclasts and direct stimulation of B cells, which in AS are assumed to produce germinal centers [6]. On the other hand, the pro- and anti-inflammatory effect of IL-22, a newly identified cytokines of IL-10 family, have been linked to a receptor complex consist of two subunits, IL-22Rα1 and IL-10Rβ2. A subset of CD4 + T cells are the Th22 cells that have an exclusive phenotypic and biological effects that are mostly driven by IL-22[7]. T-cells can produce IL-17A and other cytokines with a similar effect like, IL-22. These cells include innate lymphoid cells and mucosal-associated invariant T (MAIT) cells, which were recently found in AS. Recent studies have shown that via producing IL-17A, the MAIT cells may play a part in AS [8]. This research aims to describe the contribution of the hematological tests including Hb, WBC and ESR and the immunological markers including CRP, IL-22 and IL-17 to the development and diagnosis of AS disease.

METHODS

Subject and Collection of Blood Samples

This study included blood sample collection from 100 participant (50 AS male patients and 50 healthy control). The age of both groups were between 20-60 years, all the patients were from Baghdad Teaching Hospital / Consultant of Arthritis / in Baghdad in period from September to November / 2023. A written informed consent forms were submitted by all subjects, in addition this study method was centrally authorized by the Ethical Reviewany

additional illness was documentedas well asand diagnosis, also the CBC, Eresonance imaging (MRI) or bone scan for the AS patients

Hematological analysis

Five milliliters of blood were collected from both patients and controls. Two milliliters of the blood were divided and placed in an EDTA tube for the hematological analytical measurement (CBC) using Automated CBC analyzer for the WBC and Hb and the ESR using the Westergren's methodwere allowed to besedimentedthe blood in a long vertical tube after that the ESR expressed after an hour in millimeter per hour.

Serum CRP, Cytokines Determination

The serum was separated from the gel tube that was filled with three milliliters of the collected blood using a centrifuge set to run at 3000 rpm for ten minutes. After that, the serum was moved into 0.5 milliliter Eppendorf tubes, which were immediately frozen at -20˚C.

The C-reactive protein and the cytokines IL-17 and IL-22 were determined by utilizing the Enzyme-linked Immunosorbent Assay ELISA, Sandwich Human ELISA Kit (Cloud Clone-USA) the three kites were adapted from Bio-connect, Houston (USA). ELISA was carried out in compliance with the manufacturer's guidelines. The micro-plate reader (HumaReader HS, Germany) was used to measure the absorbance at a wavelength of 450 nm. An EXCEL sheet was used to plot a standard curve (measured absorbance against the concentration of serially diluted standards). The C-reactive protein and cytokine levels were determined according to the curve-fitting equation.

Analysis of the Receiver Operating Characteristics Curve (ROC

ROC has been used to assess the classifier model's prediction accuracy for each of the parameters that have been analyzed.

STATISTICAL ANALYSIS

The differences in the study parameters have been elucidated by the IBM SPSS (Statistical Package for Social Science) version 26 program (Armonk, NY: IBM Corp). The continuous variables' mean and standard deviation (SD) were given. Numbers and percentages were used to express the category variables and the Chi-squared test was employed to see whether there were any significant differences. A significance level of $P < 0.05$ was set for probability values. ROC analysis was used to measure the area under the curve (AUC) of the research parameters for both AS patients and normal controls. The correlation between the parameters was examined using the Pearson Correlation Coefficient Test.

RESULTS

Age

The distribution of AS patients' age groups and that of the seemingly healthy control group. The first age group comprised those in the 20–35 age range, the second, people in the 36–50 age range, and the third, people over 50. In the first age group, 20–35 years old, the AS was substantially more prevalent (23,46%, p=0.013). as shown in Table 1.

Table 1. Distribution of Ankylosing spondylitis and control groups according to age

Age group	Patient (No. = 50)		Control (No. = 50)	
	No.	**%**	**No.**	**%**
20-35	**23**	**46**	**24**	**48**
36-50	**20**	**40**	**22**	**44**
Over 50	**7**	**14**	**4**	**8**
χ^2	**8.68**		**14.56**	
P – value	**0.013 ***		**0.001 ****	

Where: (*) significant increase P<0.05, (**) significant increase P<0.01, No: number, χ^2: chi-square, P: probability.

Hematological and Serological Analysis

Certain hematological markers were measured in both AS patients and controls were like WBC (8.15+2.19 in patient and 8.035+1.69 in control group), Hb (13.87+1.87 in patient and 15.86+1.59 in control) and ESR (11.60+12.6 in patient and 3.92+3.45 in control). While the immunological parameters, CRP (4.97+1.33 in patient and 1.74+0.35 in control), IL-17 (168.15+24.38 in patient and 87.45+12.54 in control), and IL-22 (215.21+34.59 in patient and 81.87+19.79 in control) and studying these parameters association with AS as shown in Table2.

All the parameters including ESR (11.60+12.6 3), the levels of the serum in CRP was (4.97+1.33), IL17 (168.15+24.38) and IL22 (215.21+34.59) all of which were found to be much higher in AS patient as compared to the normal (ESR, 3.92+3.45), (CRP, 1.74+0.35), (IL17 ,87.45+12.54) and (IL22, 81.87+19.79) respectively, while The AS patients have lower Hb (13.87+1.87) compared to controls (Hb, 15.86+1.59) and that shows the association with AS development. Except for WBC that was non-significant in patient group (8.15+2.19) compared to the control group (8.035+1.69). Table 2 shows these results.

Table 2. Hematological and serological Parameters in ankylosing Spondylitis Patients and Control Groups.

		N	Mean	Std.Deviation	Std.Error	P-value
WBC	**Patients**	**50**	**8.15**	**2.19**	**0.31**	**0.765**
	Control	**50**	**8.035**	**1.69**	**0.23**	**NS**
HB	**Patients**	**50**	**13.87**	**1.87**	**0.26**	**< 0.001**
	Control	**50**	**15.86**	**1.59**	**0.22**	
ESR	**Patients**	**50**	**11.60**	**12.63**	**1.78703**	**< 0.001**
	Control	**50**	**3.92**	**3.45**	**0.48893**	
CRP	**Patients**	**48**	**4.97**	**1.33**	**0.19301**	**< 0.001**
	Control	**42**	**1.74**	**0.35**	**0.05479**	
IL17	**Patients**	**48**	**168.15**	**24.38**	**3.51938**	**< 0.001**
	Control	**42**	**87.45**	**12.54**	**1.93567**	
IL22	**Patients**	**48**	**215.21**	**34.59**	**4.99297**	**< 0.001**
	Control	**42**	**81.87**	**19.79**	**3.05461**	

Where: S.E: standard error, P: probability, No: Number, *: significant at < 0.05, **: significant at < 0.01, S.D: Standard Deviation.

Examining and determining ROC value

The finding of the ROC showed that the immunological parameter IL22 (AUC- **1.000**, cut- off: **132.29** pg/ml, had 100%sensitivity, 100%specificity, p-value < 0.001) are the most discriminating factors connected to AS development. followed by IL17 (AUC: **0.998**, cut-off: **112.28** pg/ml, had 100% sensitivity, 97%specificity, p-value< 0.001), CRP (AUC: **0.995**, cut- off: **7.50 mm/hr**, had 60%sensitivity, 88%specificity, p-value< 0.001) and ESR (AUC: **0.808**, cut-off: **132.29** pg/ml, had 100% sensitivity, 100% specificity, p-value< 0.001) respectively. Table 3 and figure 1 illustrate these results.

Table 3. Area under the Curve of the Research Parameters for Patients with Ankylosing Spondylitis.

Parameters	AUC	sensitivity	specificity	cut-off value	P - value
ESR	**0.808**	**60%**	**88%**	**7.50 mm/hr**	**<0.001****
CRP	**0.995**	**95%**	**100%**	**2.48 mg/dL**	**<0.001****
IL17	**0.998**	**100%**	**97%**	**112.28** pg/ml	**<0.001****
IL22	**1.000**	**100%**	**100%**	**132.29** pg/ml	**<0.001****

The age, WBC and HB of AS patients and control were calculated, and the receiver operating characteristic curve (ROC) assessed the classifier model's prediction accuracy. The three parameters are age, HB and WBC. The age (AUC : **0.540**, cut- off: **46.5 Year**, **26 %**sensitivity, **90 %**specificity, p-value **0.491 NS**) and WBC (AUC: **0.486**, cut-off: **9.59** $10^3/\mu$L, had **28 %**, **82 %** specificity, p-value **0.812 NS**) while HB (AUC : **0.130**, cut-off: **18.50** g/dL, **0%**, **100 %**specificity, p **< 0.001****) that show lower threshold than the reference line in identifying AS patients from the control group. Table 4 and Figure 2 illustrate these results.

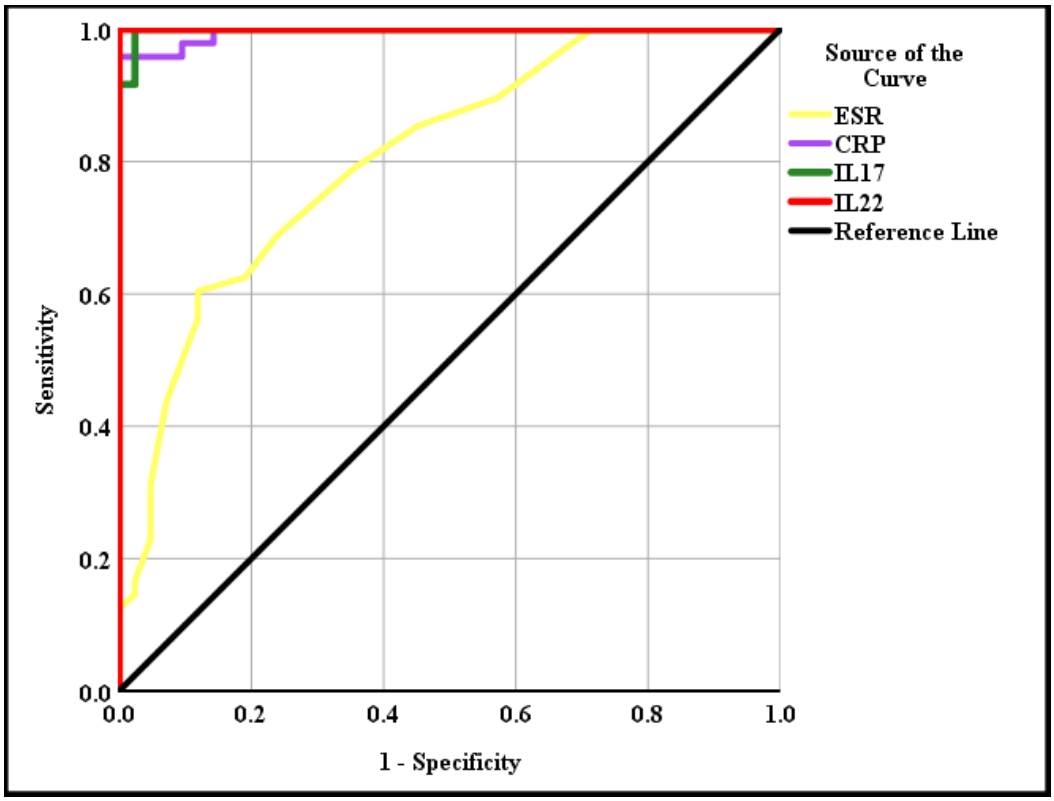

Figure1 The Immunological parameters Receiver operating characteristic (ROC) of AS patients

Table 4. Area under the Curve of Studies Parameters of Ankylosing Spondylitis Patients.

parameters	AUC	sensitivity	specificity	cut- off value	P -Value
Age	**0.540**	**26%**	**90%**	**46.5 year**	**0.491NS**
WBC	**0.486**	**28 %**	**82 %**	**9.59** $10^3/\mu$L	**0.812 NS**
HB	**0.130**	**0 %**	**100 %**	**18.50** g/dL	**< 0.001****

According to the Pearson Correlation of AS parameters the age of the AS patients was shown to be adversely connected with WBC (P=0.8), HB (p=0.6), CRP (P=0.42), IL-17 (p=0.36), IL-22 (p=0.952) but, not with ESR (p=0.004) in the AS patients. Table5 shows these results.

However, the blood parameters indicate a negative correlation between Hband ESR (p=0.022), CRP (p=< 0.001), IL-17 (p=<0.001), IL-22 (p-value=<0.001) in the AS patients' blood as well as the CRP shows a positive correlation with the interleukins IL-17 (p=), IL-22 (p-value=positivecorrelation with CRP (p-value=) and also a positive correlation with the interleukins IL-17 (p-value=IL-22 (p-value=with all the blood parameters Hb (p-value=0.8), ESR (p-value=0.2), CRP (p-value=0.8), IL-17 (p-value=0.3), IL-22 (p-value=0.85) in the blood of patients with AS.Table6illustrate these results.

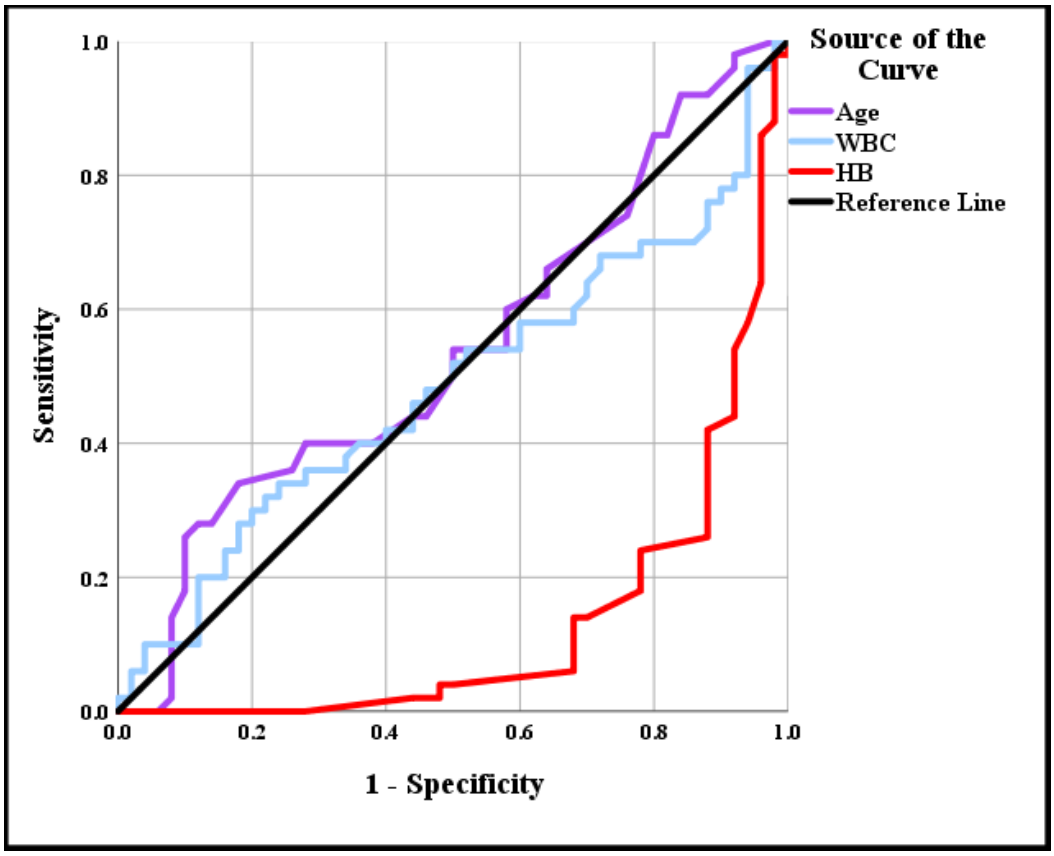

Figure 2 **Age and the hematological parameters (HB and WBC) Receiver operating characteristic (ROC) of AS patients.**

Table 5. Age according to Pearson Correlation

parameters	R - value	P - value
Age vs. WBC	**0.015**	**0.8 NS**
Age vs. HB	**- 0.044**	**0.6 NS**
Age vs. ESR	**0.289**	**0.004****
Age vs. CRP	**- 0.084**	**0.42 NS**
Age vs. IL-17	**0.097**	**0.36 NS**
Age vs. IL-22	**- 0.007**	**0.952 NS**

DISCUSSION:

According to the study results the young males show a considerable occurrence of AS. Since AS can strike at any age, almost all of the male patients are identified and treated before the age of forty and the symptoms mostly first appear in adolescence or early adulthood[9 10]. The diagnosis of AS patients involve the clinical examination and the use of MRI many hematological parameters could be used as a helpful tools in the diagnosisblood issues that have beenidentified in this study in AS patientswasHb level that was considerably lower in

Table 6. Pearson

parameters	R - value	P -value
WBC vs. HB	**0.015**	**0.8 NS**
WBC vs. ESR	**0.128**	**0.2 NS**
WBC vs. CRP	**0.024**	**0.8 NS**
WBC vs. IL-17	**0.097**	**0.3 Ns**
WBC vs. IL-22	**- 0.02**	**0.85 NS**
HB vs. ESR	**- 0.228**	**0.022***
HB vs. CRP	**- 0.46**	**< 0.001****
HB vs. IL-17	**- 0.475**	**< 0.001****
HB vs. IL-22	**- 0.517**	**< 0.001****
ESR vs. CRP	**0.259**	**0.014***
ESR vs. IL-17	**0.435**	**< 0.001****
ESR vs. IL-22	**- 0.517**	**< 0.001****
CRP vs. IL-17	**0.681**	**< 0.001****
CRP vs. IL-22	**0.738**	**< 0.001****

AS patient as compared with normal[11 12].

The severity of anemia in AS patients correlates with the disease's inflammatory activity and can impact the quality of life, as reflected in lower quality of life indices in patients with anemia, especially ACD[13]. Treatment with anti-TNFα agents like infliximab and adalimumab has been shown to improve hemoglobin levels in AS patients, indicating a potential benefit in managing anemia associated with AS [14]. While the WBC was found to be non-significant in AS patients and this could be related to the usdrugs that used to keep WBC level normal such as the anti-TNF therapy[15]. [16].Another hematological parameter is ESR test that is usually used as a to assess inflammation in AS disease by physicians. [17]and as long as determining CRP is a routine task that can be easily accomplished in the hospital to determine the risk of AS, so the CRP testused as a follow up topatients [18 19 3].linked to the development of AS. Studies have shown that[20]An additional investigation revealed that AS patients' serum levels of IL-17 are greater than those of healthy people [21].it has been proposed that IL-17F plays a part in spondyloarthritis inflammation and the production of new bone. The primary IL-17 secretors in AS are CD4+ Th17 cells. [5].IL-22 which also was significantly highdiagnosis of AS disease.

In this study the tested parameters are correlated with each other. The age of the AS patients was shown to be adversely connected with WBC, Hb, CRP, IL-17, IL-22 but, not with ESR in the AS patients. A research found a significant positive correlation between age and ESR in AS patients, indicating that older age may be associated with higher ESR levels[22]. While Hb is negatively correlated with increased ESR, CRP, IL-17 and IL-22 of AS patients. Studies have shown that anemia is a common complication in individuals with AS. Also patients with AS who received infliximab treatment experienced improvements in hemoglobin levels, physical function, and fatigue, highlighting the importance of managing anemia in AS patients for overall well-being[23]. The patients' elevated CRP is correlated

with elevated IL-17 and IL-22 levels. While the ESR is connected with both CRP and IL-17 but not IL-22. Research has shown that at the initial visit, high levels of CRP and ESR were observed in a substantial percentage of AS patients, with a good correlation between the two markers [24]. Finally the WBC shows no correlation with all of the blood parameters in the AS patients, but other inflammatory markers like the platelet to lymphocyte ratio (PLR) have been identified as more effective indicators of disease activity in AS patients [25]. Relying solely on the correlation between some parameter may not provide a comprehensive assessment of disease severity in AS patients, and incorporating other inflammatory markers could offer a more accurate evaluation of disease activity. Therefor the diagnostic criteria for AS based on clinical sign that can be verified by the overall test parameter results [26].

CONCLUSIONS

In summary, AS most appear in young males. The WBC of the AS parameters was non-specific for AS development. The AS patients have lower Hb and high ESR and CRP levels. The immunological parameters IL-17, and IL-22 are associated with AS disease activity. IL22 is the most discriminating factor connected to AS development followed by IL17 which both were highly specific for AS.both these features and the entire clinical picture.

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DECLARATIONS

1. Authors' contributions

Contributor Role	Degree of Contribution		
	Lead	Equal	Supporting
Conceptualization	SHH		
Data curation	SHH		
Formal analysis		SHH	
Funding acquisition	SHH		
Investigation	SHH		
Methodology	SHH		
Project administration	SHH		
Resources	SHH		
Software			SHH
Supervision			SHH
Validation		SHH	
Visualization		SHH	
Writing-original draft	SHH		
Writing-review & editing	SHH		

2. Conflict of interest

The authors declares no conflict of interest.

3. Ethical Approval

(Institutional ethical approvals and informed consent)
This research does not conflict with our university's ethical standards, nor with any known ethical criteria.

4. Funding resources
This research is self-funded.

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