

Original Research Paper

Assessment of Serum Interleukin-23 as a Biomarker for Diagnosis and Disease Activity Evaluation in Ankylosing Spondylitis Patients

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Abstract: Ankylosing spondylitis (AS) is an inflammatory arthritis mediated by the immune system. The axial skeleton is the main portion affected by AS. Interleukin-23 is a pro-inflammatory mediator that plays a complex role in the pathophysiology of AS, particularly in bone remodeling and new bone formation. The objective of this study is to determine whether IL-23 plays an effective role in the diagnosis and evaluation of AS activity. A case-control study, involving 30 patients with Ankylosing Spondylitis (AS), 30 patients with chronic back pain (CBP), and 28 healthy individuals. Also, IL-23 and CRP levels were measured for all three groups using an ELISA technique. The study also evaluated the CBC and ESR levels. The IL-23 level in AS, CBP, and healthy control groups were 37.45 ± 4.59 pg/ml, 50.60 ± 7.83 pg/ml, and 63.36 ± 8.04 pg/ml, respectively, with no significant difference between AS group and CBP group ($P=0.153$), but with a significant difference between AS group and healthy control group ($P=0.008$). In patients with AS, based on ASDAS-ESR, there was a significant difference in the IL-23 level among the disease activity groups ($P=0.017$). This study evaluates IL-23 as a diagnostic tool for AS, with the healthy group, which showed an AUC of 0.234, 72.4% sensitivity, and 69% specificity. Furthermore, IL-23 was assessed as a diagnostic tool between AS and CBP groups, with an AUC of 0.348, 60% sensitivity, and 57.1% specificity. The findings showed that IL-23 has a significant difference between the AS group and the healthy group, also, it plays a significant role in evaluating disease activity in patients with AS by the ASDAS-ESR index; however, it does not have a diagnostic value and is not involved in the initial diagnosis of AS.

Keywords: Ankylosing spondylitis, chronic back pain, IL-23, ASDAS-ESR

1.Introduction

Ankylosing spondylitis is an inflammatory arthritis mediated by the immune system. The axial skeleton is the main portion affected by AS, especially the spinal and sacroiliac joints, which cause disability and severe chronic pain [1]. Ankylosing spondylitis can result in significant disability and joint deformity over time, with symptoms often including back stiffness, eye inflammation, and fatigue [2,3]. Prevalence of AS is commonly assumed to be in the range of 0.1% to 1.4% worldwide [4]. Diagnosing patients with AS is

challenging for several reasons. First, back pain is not uncommon in populations. Second, the disease is slowly progressive with no specific symptoms or biomarkers. While inflammatory reactants such as ESR and CRP may be normal in AS patients, they are often used for the diagnosis and follow-up of patients with AS. Third, the strong association of HLA-B27 with AS, in combination with the high population frequency of HLA-B27 positivity, is useful if combined with other criteria in clinical, radiographic, and laboratory investigations. On the other hand, no specific laboratory finding can accurately diagnose patients with AS [5,6,7]. Moreover,

it is important to find new biomarkers for the diagnosis and evaluation of disease activity in patients with AS. Attention has increasingly been drawn to cytokines' participation in the inflammation of autoimmune diseases and the connection between cytokines and clinical disease activity. Interleukin-23 is a heterodimeric pro-inflammatory cytokine and plays a significant part in impacting the pathophysiology of AS, including bone remodeling and new bone formation. Furthermore, IL-23 is known to modulate osteoclast function, indirectly promoting osteoblast differentiation, which suggests a mechanism for new bone formation in AS [8,9]. The aim of this study is to evaluate the role of IL-23 in the diagnosis and assessment of disease activity in patients with AS.

2.Methodology

A case-control study was carried out in Najaf City-Iraq, between September 2024 and December 2024 and included 30 patients with AS, who were enrolled in the Biological Therapy Unit in Al-Najaf Al-Ashraf Hospital. There were 19 males and 11 females, ranging in age from 20 to 66 years. The control groups are two, the first control group included 30 patients with chronic back pain (CBP) who attended the Rheumatological Center in Al-Sader Medical City, they were 14 males and 16 females, ranging in age from 25 to 68 years, and the second control group included 28 healthy persons, they were 18 males and 10 females, there aged from 19 to 65 years. Any patients with other autoimmune diseases, malignant disease, central nervous system disease, cardiovascular disease, and/or thyroid disease, as well as pregnant or lactating women, were excluded. The AS and CBP groups were selected randomly. The patients with AS were divided into four subgroups (inactive, low, high, and very high) according to the disease activity determined by BASDAI, ASDAS-CRP, and ASDAS-ESR indices. Each participant was asked to complete a questionnaire designed to collect demographic and clinical characteristics (age, sex, BMI, hypertension, etc.) and history of the disease with clinical data. Furthermore, IL-23 and CRP were assessed for the three groups by using an ELISA kit from Sunlong, China. The study also assessed the CBC by hematology analyzer and ESR by using the Westergren method.

3.Results and discussion

A case-control study was conducted on 30 patients with AS, 30 patients with CBP, and 28 healthy individuals. The mean age and SD were 42.07 ± 12.55 years, 46.07 ± 12.36 years, and 40.32 ± 10.34 years in the AS, CBP, and healthy control groups, respectively, with non-significant differences between AS patients and CBP patients ($P=0.219$), and between AS patients and the healthy control group ($P=0.565$). Regarding sex, there was a highly significant difference between the AS patients and the CBP patients ($P=0.003$), but the AS group showed a non-significant difference from the healthy control group ($P=0.883$). Ankylosing spondylitis patients had a BMI mean and SD of 29.97 ± 5.65 kg/m², which was slightly equal to that of the CBP group (29.50 ± 5.69 kg/m²), and it was higher than that of the healthy control group (26.11 ± 5.22 kg/m²). Regarding hypertension and diabetes, there were non-significant differences between AS patients and CBP patients ($P=1,000$), but with highly significant differences between the AS patients and the healthy control group ($P < 0.001$). Also, there was a significant difference between the AS patients and the CBP patients in smoking ($P=0.022$), while there was no significant difference between the AS patients and the healthy control group ($P=0.500$). Regarding the smoking index, the AS group showed no difference from the CBP group ($P=0.341$) but had a significant difference with the healthy control group ($P=0.029$). According to the contraceptive pill use, there was no significant difference between the AS group and the CBP group ($P=0.113$), whereas a highly significant difference was observed between the AS group and the healthy control group ($P=0.001$), as shown in Table 1.

Table 1: Demographic and Clinical Characteristics of the Ankylosing Spondylitis Patients, Chronic Back Pain Patients, and Healthy Controls

Characteristics	AS patients n=30	CBP patients n=30	Healthy controls n=28	P-value (AS&CBP)	P-value (AS&HC)
Age, years	42.07± 12.55	46.07± 12.36	40.32± 10.34	0.219	0.565
Sex, male, n (%)	19 (63.3%)	13 (43.3%)	18 (64.3%)	0.003**	0.883
BMI, kg/m ²	29.97± 5.65	29.50± 5.69	26.11± 5.22	0.748	0.009**
Hypertension, n (%)	10 (33.3%)	10 (33.3%)	0 (0.0%)	1.000	<0.001*
Diabetes, n (%)	3 (10%)	3 (10%)	0 (0.0%)	1.000	<0.001*
Smoking, n (%)	9 (30%)	5 (16.7%)	8 (28.6%)	0.022*	0.500
Smoking index, pack per year	30.54± 29.17	14.68± 17.55	8.94± 6.73	0.341	0.029**
Contraceptive pill use, n (%)	1 (11.11%)	3 (18.75%)	0 (0.0%)	0.113	0.001**

BMI body mass index *: significant difference, **: highly significant difference.

The levels of routine inflammatory biomarkers of the three groups were determined. The ESR level in the AS group (21.47±4.16 mm/h) was higher than that in the CBP group (16.57±3.24 mm/h) but remained with a non-significant difference (P=0.357), while in the AS group it was more than that in the healthy control group (8.11±1.09 mm/h) and showed a highly significant difference (P=0.004). Furthermore, there was no significant difference (P=0.134) between the CRP level in the AS group (59.42±16.63 mm/h) and that in the CBP group (92.99±14.33 mm/h). Also, a non-significant difference (P=0.085) between the CRP level of the healthy control group (140.03±42.06 mm/h) and that in the AS group, as shown in Table 2. Additionally, IL-23 levels in the AS and CBP groups were 37.45±4.59 pg/ml and 50.60±7.83 pg/ml, respectively, and reflecting no significant difference between them (P=0.153), while IL-23 level in the healthy control group was 63.36±8.04 pg/ml and reflecting a highly significant difference compared to that of the AS group (P=0.008), as shown in Table 2.

Table 2: Levels of ESR, CRP, and IL-23 of the Ankylosing Spondylitis Patients, Chronic Back Pain Patients, and Healthy Controls

Characteristics	AS patients n=30	CBP patients n=30	Healthy controls n=28	P-value (AS&CBP)	P-value (AS&HC)
ESR, mm/h	21.47± 4.16	16.57± 3.24	8.11± 1.09	0.357	0.004**
CRP, pg/ml	59.42± 16.63	92.99± 14.33	140.03± 42.06	0.134	0.085
IL-23, pg/ml	37.45± 4.59	50.60± 7.83	63.36± 8.04	0.153	0.008**

IL-23 interleukin-23, ESR erythrocyte sedimentation rate, CRP C-reactive protein, **: highly significant difference.

According to the AS activity, there was no significant difference observed in the levels of IL-23 among the disease activity groups according to BASDAI and ASDAS-CRP indices (P=0.632 and P=0.456, respectively). While based on the ASDAS-ESR index, there is a significant difference in the levels of IL-23 among the disease activity groups (P=0.017), as shown in Table 3.

Table 3: Levels of IL-23 in Patients with AS among Different Disease Activity Groups Using the BASDAI, ASDAS-CRP, and ASAS-ESR indices

Characteristic	AS activity index				
IL-23, pg/ml	BASDAI index of AS patients (n=30)				
	Inactive n=1	Low activity n=6	High activity n=6	Very high activity n=17	P- value
	21.69± 0.0	33.76± 3.68	48.79± 20.81	35.67± 3.74	0.632
	ASDAS-CRP index of AS patients (n=30)				
	Inactive n=11	Low activity n=15	High activity n=4	Very high activity	P- value
	42.99± 11.17	31.58± 3.35	44.22± 10.24	-	0.456
	ASDAS-ESR index of AS patients (n=30)				
	Inactive n=2	Low activity n=18	High activity n=17	Very high activity n=3	P- value
	89.86± 61.093	33.07± 3.83	34.16± 3.74	32.86± 8.07	0.017*

IL-23 interleukin-23, BASDAI bath ankylosing spondylitis disease activity index, ASDAS ankylosing spondylitis disease activity score, CRP C-reactive protein, ESR erythrocyte sedimentation rate *: significant difference.

According to the BASDAI, ASDAS-CRP, and ASDAS-ESR indices, there was no significant correlation [(r= -0.001, P=0.498), (r= -0.132, P=0.244), and (r= -0.286, P-value=0.063), respectively] between IL-23 level and AS activity, as shown in Figure 1, Figure 2, and Figure 3.

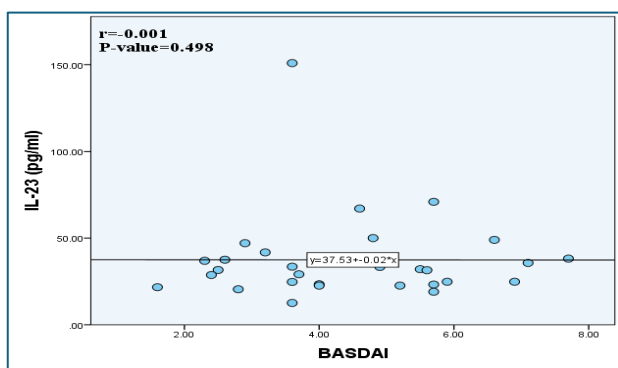


Fig 1: Correlation of IL-23 Level with AS Activity Based on BASDAI

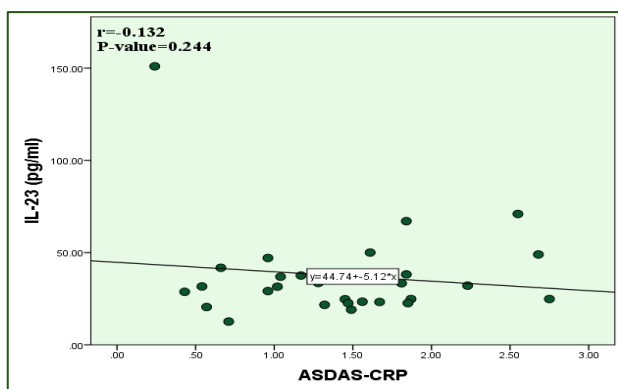


Fig 2: Correlation of IL-23 Level with AS Activity Based on ASDAS-CRP

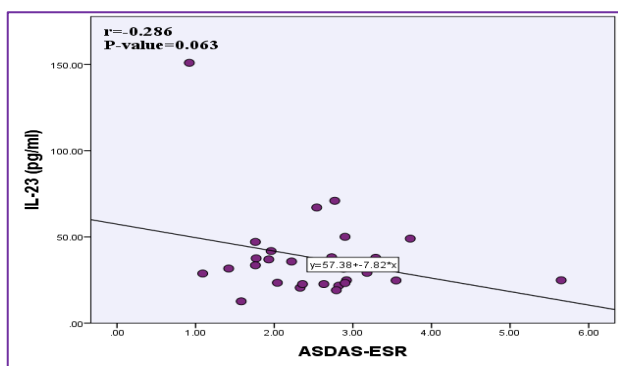


Fig 3: Correlation of IL-23 Level with AS Activity Based on ASDAS-ESR

Furthermore, IL-23 had a significant positive correlation with BMI ($P=0.027$), while it had a significant negative correlation with the response to treatment ($P=0.009$). As well, IL-23 had a non-significant correlation with age, sex, hypertension, diabetes mellitus, smoking index, family history, age of the AS onset, duration of

biological treatment, and contraceptive pill use ($P=0.205$, $P=0.343$, $P=0.103$, $P=0.922$, $P=0.318$, $P=0.983$, $P=0.205$, $P=0.896$, and $P=0.999$, respectively), as shown in Table 4.

Table 4: Correlations of IL-23 Levels with Demographic Characteristics, BMI, and Features of Treatment History in the AS Patients

Characteristics	AS patients n=30	
		IL-23
Age, years	r	0.156
	P	0.205
Sex	r	-0.023
	P	0.343
Hypertension	r	-0.091
	P	0.103
Diabetes mellitus	r	-0.006
	P	0.922
BMI, kg/m ²	r	0.355
	P	0.027*
Smoking index, pack per year	r	-0.183
	P	0.318
Family history	r	0.001
	P	0.983
Age of AS onset, years	r	0.156
	P	0.205
Duration of biological treatment, years	r	0.031
	P	0.896
Response to treatment	r	-3.140
	P	0.009**
Contraceptive pill use	r	-0.883
	P	0.999

IL-23 interleukin-23, BMI body mass index, *r* correlation coefficient, *P* P-value
*: Significant **: Highly Significant difference

Interleukin-23 had no significant correlation with the hematological parameters (hemoglobin level, WBC count, RBC count, and platelet count) ($P=0.449$, $P=0.340$, $P=0.063$, and $P=0.383$, respectively), as shown in Table 5.

Table 5: Correlations of IL-23 Levels with the Hematological Parameters in the AS Patients

Characteristics	AS patients n=30	
		IL-23
Hemoglobin level, g/dl	r	0.024
	P	0.449
WBC count, x 10 ⁹ /liter	r	0.079
	P	0.340
RBC count, x 10 ¹² /liter	r	0.285
	P	0.063
Platelet count, x10 ⁹ /liter	r	-0.057
	P	0.383

IL-23 interleukin-23, WBC white blood cell, RBC red blood cell, *r* correlation coefficient, *P* P-value.

Furthermore, IL-23 had a significant negative correlation with ESR ($P=0.043$), whereas it had no significant correlation with CRP ($P=0.153$), as shown in Table 6.

Table 6: Correlations between Biomarkers in the AS Patients

Characteristics	AS patients n=30			
		IL-23	CRP	ESR
IL-23, pg/ml	r	1		
	P	-		
CRP, pg/ml	r	0.194	1	
	P	0.153	-	
ESR, mm/h	r	-0.318	-0.200	1
	P	0.043*	0.145	-

IL-23 interleukin 23, CRP C-reactive protein, ESR erythrocyte sedimentation rate, *r* correlation coefficient, *P* P-value *: Significant

The diagnostic performance of IL-23 and CRP in distinguishing the AS patients from the healthy individuals was evaluated using the receiver operating characteristic (ROC) curve, as shown in Table 7. At the cut-off value of 37.7 pg/ml, IL-23 showed a highly significant p-value (<0.001), with AUC 0.234, 72.4% sensitivity, and 69% specificity. Additionally, at the cut-off value 46.5 pg/ml, CRP has AUC of 0.244 with 84.5% sensitivity and 72.2% specificity, as shown in Figure 4 and Figure 5.

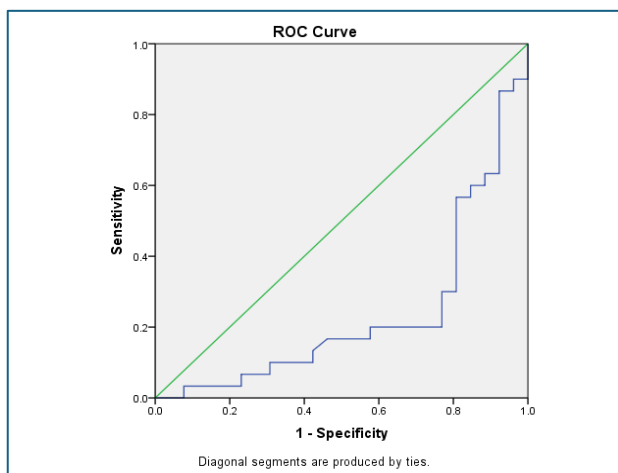


Fig 4: Receiver Operator Characteristic (ROC) Curve of IL-23 in Distinguishing the AS Patients from the Healthy Individuals

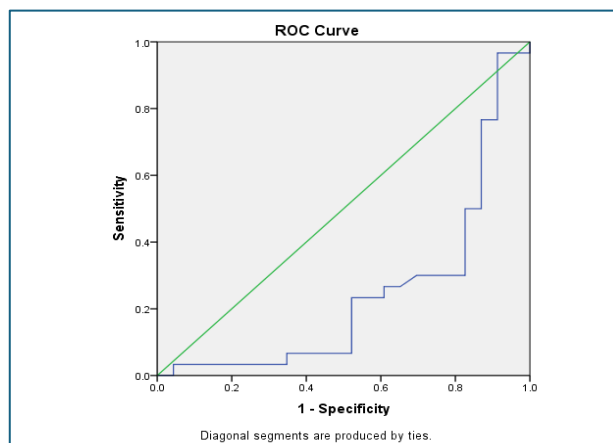


Fig 5: Receiver Operator Characteristic (ROC) Curve of CRP in Distinguishing the AS Patients from the Healthy Individuals

Table 7: The Diagnostic Performance of IL-23 and CRP in Distinguishing the AS Patients from the Healthy Individuals

Characteristics	IL-23	CRP
AUC	0.234	0.244
SE	0.066	0.072
Sig.	<0.001**	2.22
95% confidence interval	0.105- 0.363	0.104- 0.384
Optimal cut-point value (pg/ml)	37.7	46.5
Sensitivity (%)	72.4%	84.5%
Specificity (%)	69%	72.2%
PPV (%)	70%	70%
NPV (%)	71.4%	85.71%
Diagnostic effectiveness (accuracy)	70.68%	77.58%
Youden's index	0.41	0.57

IL-23 interleukin-23, CRP C-reactive protein, AUC area under the curve, SE standard error, Sig significant, PPV positive predictive value, NPV negative predictive value.

In addition, the diagnostic performance of IL-23 and CRP in distinguishing the AS patients from the CBP patients was demonstrated in Table 8. The cut-off value of 32 pg/ml, IL-23 showed AUC of 0.348 with 60% sensitivity and 57.1% specificity. While the CRP cut-off was 54.2 pg/ml, and showed a highly significant p-value (<0.001), its AUC was 0.235 with 61.8% sensitivity and 65.4% specificity, as shown in Figure 6 and Figure 7.

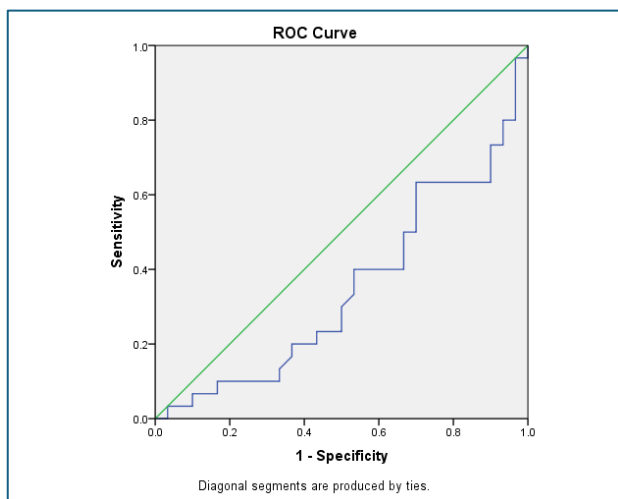


Fig 6: Receiver Operator Characteristic (ROC) Curve of IL-23 in Distinguishing the AS Patients from the CBP Patients

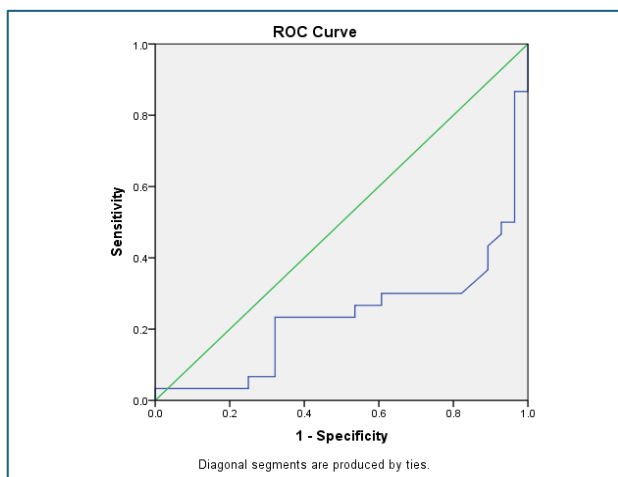


Fig 7: Receiver Operator Characteristic (ROC) Curve of CRP in Distinguishing the AS Patients from the CBP Patients

Table 8: Receiver Operator Characteristic (ROC) Curve of IL-23 and CRP in Distinguishing the AS Patients from the CBP Patients

Characteristics	IL-23	CRP
AUC	0.348	0.235
SE	0.071	0.065
Sig.	0.051	<0.001**
95% confidence interval	0.209-0.487	0.108-0.362
Optimal cut-point value (pg/ml)	32	54.2
Sensitivity (%)	60%	61.8%
Specificity (%)	57.1%	65.4%
PPV (%)	50%	70%
NPV (%)	66.6%	56.6%
Diagnostic effectiveness (accuracy)	58.33%	63.3%
Youden's index	0.17	0.27

IL-23 interleukin-23, CRP C-reactive protein, AUC area under the curve, SE standard error, Sig significant, PPV positive predictive value, NPV negative predictive value **: highly significant difference.

This study indicates that the mean level of IL-23 in AS patients was lower than that of the healthy controls, with a statistically significant difference between them. Immune dysregulation would result from chronic inflammatory disease that impairs the production of IL-23 by immune exhaustion and negative feedback. This finding corresponds to the findings of a study by Devenci and colleagues [10], who found AS patients to have lower concentrations of both IL-17 and IL-23 compared to healthy controls, indicating that uncontrolled IL-23/IL-17 expression is implicated in the pathogenesis of AS [10]. Similarly, Yeo [11] reported that former patients with spondyloarthritis, including AS, had a markedly decreased serum IL-23 level compared with that in healthy controls, indicating that patients with AS presented with lower expression of IL-23 [11]. Moreover, these results agree with the concept that the IL-23/IL-17 axis is critical to the immunopathogenesis of AS. Nevertheless, the exact processes and consequences of the deregulated levels of these cytokines were not fully understood. It was, however, poignant to further explore the role of IL-23 in the progression of AS due to existing literature that has analyzed the IL-23 genetic association and molecular characteristics in the scenario of AS. Therefore, additional research may cover the IL-23 receptor polymorphisms and the role of IL-23 in regulating osteoblast function and bone formation [12,13]. The

CBP group had a higher, yet non-significant mean value of IL-23 compared to the AS group, as per the CBP group. In the non-specific chronic back pain, represented by lumbar disc herniation, a factor that contributes to back pain, IL-23 expression is upregulated, indicating that IL-23 is capable of involvement in pro-inflammatory mechanisms of intervertebral disc degeneration by participation in the IL-23/IL-17 axis [14]. Other biological treatments, such as tumour necrosis factor- α (TNF- α) inhibitors (e.g., infliximab, etanercept and adalimumab), which are well-documented for the treatment of AS and can lead to substantial symptoms relief and improved patient outcomes by inhibiting inflammation to prevent structural damage, might explain the finding of lower levels of IL-23 in patients with AS compared to those in the CBP group [15]. The current study shows a non-significant difference in IL-23 levels among disease activity groups based on BASDAI and ASDAS-CRP indices. This finding is consistent with previous studies conducted by [10,16,17] which found a non-significant difference in IL-23 levels among disease activity based on the BASDAI index [10,16,17]. However, there is a significant difference in IL-23 levels among disease activity groups based on the ASDAS-ESR index. The highest level was found in the inactive group, which may not be relied upon due to the small size of this activity group (only two patients), whereas low, high, and very high activity groups had similar levels. However, IL-23 is a cytokine implicated in the pathogenesis of AS, primarily through its role in the IL-23/IL-17 axis, which is crucial for the differentiation and function of Th17 cells, a subset of T-helper cells involved in inflammatory responses [18,19]. Studies have shown that IL-23 levels are elevated in AS patients, suggesting its involvement in disease activity and progression [20]. There was a significant positive correlation between IL-23 with BMI. Obesity is known to be associated with systemic inflammation and can exacerbate inflammatory conditions. However, systemic inflammatory conditions, such as those that may be impacted by obesity, may have an impact in IL-23 dynamics in AS given the presence of IL-23 in multiple tissues, including the gut and bone marrow, and its function in regulating immune responses [21,22]. Also, there is a significant negative correlation of IL-23 with response to treatment. Elevated levels of IL-23 have been observed in AS patients, and these levels correlate with increased production of pro-

inflammatory cytokines, indicating that IL-23 contributes to the inflammatory milieu characteristic of AS [13,23]. Moreover, IL-23 affects the activity of osteoblasts, which may also play a role in the bone remodeling and ankylosis that occurs in AS, and reducing IL-23 levels may help prevent these processes, making it a viable therapeutic option [12]. Additionally [24] demonstrated that IL-23 blockers, along with other agents that inhibit the IL-23/IL-17 axis, could be beneficial in AS treatment, especially for patients who show no response to standard treatments or TNF- α blockers in combination with NSAIDs [24]. However, the results presented above show a close correlation of IL-23 with the response to treatment in AS, which suggests that in the pathophysiology of the disease, the role of IL-23 is critical and, at the same time, IL-23 is a prospective target for therapeutic intervention [10]. There was no significant relationship between IL-23 and other factors, including age, duration of the disease. Regarding the duration of the disease, our research agrees with the results initially presented by [10,25]. There was no significant relationship with sex, marital status, residency, hypertension, diabetes mellitus, smoking index, family history, age at AS onset, duration of biological treatment, regularity of the treatment intake, and contraceptive pill use. To the best of our knowledge, the above-presented various factors have never been researched before. In the present study also, IL-23 shows a significant negative correlation with ESR, an index of inflammation. This also emphasized the complexity of cytokine cross talk for AS pathogenesis and the importance of characterizing such associations in future investigations. In addition, no significant correlation between IL-23 and CRP; this result is consistent with a previous study conducted by [26]. In the current study, the receiver operating characteristic (ROC) curve analysis was constructed to quantify the utility of IL-23 and CRP in the diagnosis of AS and distinguish them from healthy individuals. The IL-23 demonstrated a moderate diagnostic performance with an accuracy, sensitivity, and specificity of more than 68%, and a Youden index of 0.41. Despite its low AUC value (0.234), it has a highly significant P-value. Interleukin-23 may still serve as a potential immunological biomarker. Regarding the CRP, it showed higher diagnostic performance than IL-23, with an accuracy, sensitivity, and specificity of more than 72%. These findings suggest that CRP remains a

valuable marker in identifying inflammatory activity in AS, even though its AUC was low (0.244). In a study conducted by Zhong [27], the sensitivity of CRP was 63.1%, and the specificity was 71.6%. In addition, Sieper & Poddubnyy [28] found that up to 50% of patients with active disease can have normal CRP levels, which may explain the mismatch between the low AUC and the observed high sensitivity [27,28]. As well, the ROC curve analysis was carried out to quantify the utility of IL-23 and CRP in distinguishing AS from other causes of CBP. Interleukin-23 achieved a sensitivity of 60% and a specificity of 57.1%, coupled with Youden's index of 0.17. Although the AUC was notably low (0.348), the p-value (0.051) approached statistical significance, suggesting that IL-23 may hold some potential value, albeit limited, in the diagnostic setting. Regarding the results of CRP, it exhibited the favorable diagnostic characteristics than IL-23. Despite a low AUC value of 0.235, CRP achieved the highest sensitivity of 61.8%, specificity of 65.4%, and PPV of 70%. Furthermore, it recorded the highest Youden's index of 0.27 and a highly significant difference p-value (<0.001). These results suggest that CRP, while limited in its discriminative capacity, remains a relatively reliable supportive biomarker in differentiating AS from CBP when interpreted alongside clinical findings. The limitations of this study, include the small sample size, were carried out in a single center and the exclusion of other forms of spondyloarthropathies, for example, psoriatic arthritis, reactive arthritis, and non-radiological axial spondyloarthritis, which restricted the broader applicability of the results to related disease entities.

Conclusion

The findings showed that IL-23 has a significant difference between the AS and the healthy group, also, it plays a significant role in evaluating disease activity in patients with AS by the ASDAS-ESR index; however, it does not have a diagnostic value and is not involved in the initial diagnosis of AS.

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Author's Contributions

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Ethics

Before this study began, ethical approval was obtained from the Ethics Committee of the College of Medicine at the University of Kufa. Additionally, permission was granted by the Biological Therapy Unit at Al-Najaf Al-Ashraf Hospital and the Rheumatology Department at Al-Sader Medical City. Informed consent was also obtained from each patient for participating in the questionnaire and blood sample collection.

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