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The Role of Matrix Metalloproteinase-3 as a Biomarker for Diagnosis and Disease Activity Assessment in Patients with Ankylosing Spondylitis

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ABSTRACT

Background: *Ankylosing spondylitis (AS) is a chronic, inflammatory, systemic disease, mainly affects the spine and sacroiliac joints, causing low back pain, stiffness, and spinal fusion. Matrix metalloproteinase-3 (MMP-3) is known to be an essential protease in cartilage and joint destruction due to it can cleave many ECM proteins.* ***purpose****: The purpose of this study is to assess whether MMP-3 plays an effective role in the diagnosis and evaluation of AS activity.* ***Methods, Subject, and Methods****: A case-control study included 30 patients with ankylosing spondylitis (AS), 30 patients with chronic back pain (CBP), and 28 apparently healthy persons. Furthermore, MMP-3 and CRP levels were assessed for the three groups using an ELISA technique. The study also measured the CBC and ESR levels.* ***Results****: The MMP-3 levels in AS, CBP, and healthy groups were 221.92 pg/ml±68.10, 193.29 pg/ml±25.02, and 279.17 pg/ml±80.44, respectively, with a non-significant difference between AS and CBP groups (P=0.699) and between AS and healthy groups (P=0.587). Based on ASDAS-ESR, there was a significant difference in the MMP-3 level (P=0.005). The diagnostic performance of MMP-3 for AS with the healthy group showed an AUC of 0.396, 61.8% sensitivity, and 62.5% specificity. While the diagnostic performance of MMP-3 for AS with CBP revealed an AUC of 0.400, 54.2% sensitivity, and 52.8% specificity.* ***Implications****: the findings support ASADAS-ESR as a tool for guiding treatment and highlight the need for further research on its long-term impact.* ***Additional materials****: this paper contains 18 references, 8 tables, and 7 figures.* ***Conclusion:*** *The findings showed that MMP-3 plays a significant role in evaluating disease activity in patients with AS based on the ASDAS-ESR index; however, it does not have a diagnostic value and is not involved in the initial diagnosis of the disease.*

Keywords: Ankylosing spondylitis, chronic back pain, MMP-3, ASDAS-ESR.

Article Information

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic condition recognized by persistent back pain, including the sacroiliac joints, enthesitis, and peripheral arthritis [(1)], with an estimated prevalence in the global population of 0.7% to 3.2%. Long-term back pain and progressive spinal stiffness are the most common manifestations of AS. Many patients with AS suffer from loss of mobility and lack their ability to work [(2)].

There is a challenge in the diagnosis of AS because it has numerous manifestations, and in certain conditions, it can be insidious. Therefore, it is important to find new biomarkers due to the absence of rheumatoid factor; AS was long thought to have a seronegative feature, and antibodies are therefore not considered a hallmark of the disease [(3)]. Biomarkers can also be useful for accurate measurement of AS activity, predicting response to the treatment, as well as predicting radiographic progression. Besides C-reactive protein (CRP) and human leukocyte antigen (HLA-B27), which are commonly used biomarkers for AS, most other biomarkers are still in the research phase and not yet widely used in clinical practice [(4)].

Matrix metalloproteinase-3, also known as Stromelysin-1, is a proteinase produced by synovial fibroblasts and chondrocytes in the joints. It is composed of proteins that are

involved in breaking down extracellular matrix proteins during tissue remodeling in normal physiological processes [5]. Matrix metalloproteinase-3 is considered a common inflammatory factor that can enhance inflammation in several parts of the body [6].

Therefore, the connection between serum levels of MMP-3 and the pathogenesis of AS brought attention [7][8]. MMP-3 is known to be an important protease in cartilage damage and joint destruction because it can cleave a diversity of ECM proteins [9].

The study is designed to assess the role of MMP-3 in the diagnosis and evaluation of disease activity in patients with AS.

METHODS

A case-control study was conducted in Najaf City, Iraq, between September and December 2024. The study included 30 patients diagnosed with AS, all of whom were receiving treatment at the Biological Therapy Unit in Al-Najaf Al-Ashraf Hospital. The AS group consisted of 19 males and 11 females, ranging in age from 20 to 66 years. Two control groups were included in the study. The first control group included 30 patients with chronic back pain (CBP) recruited from the Rheumatological Center in Al-Sader Medical City, there were 14 males and 16 females, ranging in age from 25 to 68 years. The second control group included 28 apparently healthy persons, they were 18 males and 10 females, ranging in age from 19 to 65 years. Participants with other autoimmune conditions, malignant diseases, central nervous system diseases, cardiovascular diseases, and thyroid diseases, as well as pregnant or lactating women, were excluded from this study [10]. The selection of patients in both the AS and CBP groups was done randomly. The patients with AS were categorized into four subgroups (inactive, low, high, and very high) according to the disease activity, that determined by BASDAI, ASDAS-CRP, and ASDAS-ESR indices [11]. Each participant completed a questionnaire designed to collect demographic and clinical information (age, sex, smoking, BMI, hypertension, etc.) and history of the disease with clinical data. In addition, levels of MMP-3 and CRP were measured 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.

Statistical Analysis

Data analysis was performed using the Statistical Package for Social Science (SPSS) software, Version 21 (San Diego, California, USA). Descriptive statistics included means ± standard deviations or standard error of the mean for continuous variables and frequencies with percentages for categorical variables.

Chi-square test was used for categorical data, while Pearson and Spearman correlations were applied for nominal and ordinal variables, respectively. An independent t-test compared serological markers between groups, and ANOVA assessed differences in clinical and laboratory parameters. Receiver Operating Characteristic (ROC) curves evaluated the diagnostic performance of MMP-3 and CRP, using the area under the curve (AUC). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for comparisons between AS, healthy controls, and CBP groups. A p-value < 0.05 was considered statistically significant, it is considered highly significant when it is < 0.001 and less.

RESULTS

A case-control study was conducted on 30 patients with AS, 30 patients with CBP, and 28 apparently healthy individuals. The mean and SD of age were 42.07±12.55 years, 46.07±12.36 years, and 40.32±10.34 years in the AS, CBP, and apparently healthy control groups, respectively, with non-significant differences between AS patients and CBP patients (P=0.219), and between AS patients and the apparently 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 no significant difference from the apparently healthy control group (P=0.883).

Ankylosing spondylitis patients had a BMI mean and SD of 29.97±5.65 kg/m^2, which was slightly equal to that of the CBP group (29.50±5.69 kg/m^2), and it was higher than that of the apparently healthy control group (26.11±5.22kg/m^2).

Regarding hypertension and diabetes, there were no significant differences between AS patients and CBP patients (P=1,000), but with highly significant differences between the AS patients and the apparently 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 a non-significant difference between the AS patients and the apparently 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 apparently health 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.

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 apparenlt healthy control group (8.11 ±1.09 mm/h) with a highly significant difference (P=0.004).

Additionally, there was no significant difference (P=0.134) between the CRP level in the AS group (59.42±16.63 pg/ml) and that in the CBP group (92.99±14.33 pg/ml). Also, a non-significant difference (P=0.085) between the CRP level of the apparently healthy control group (140.03±42.06 mm/h) and that in the AS group, as shown in Table 2.

Also, the mean and Std. Error mean of MMP-3 level between AS and CBP groups (221.92±68.10 pg/ml and 193.29±25.02 pg/ml, respectively), and between AS and apparently healthy control groups (279.17±80.44 pg/ml) revealed non-significant differences (P=0.699 and P=0.587, respectively), as shown in Table 2.

In patients with AS, no significant difference was observed among the disease activity groups according to BASDAI and ASDAS-CRP indices in the mean and Std. Error levels of MMP-3 (P=0.297 and P=0.796, respectively). While, based on the ASDAS-ESR index, there was a significant difference (P=0.005), as shown in Table 3.

According to the BASDAI, ASDAS-CRP, and ASDAS-ESR indices, there was no significant correlation between MMP-3 level and AS activity [(r=0.060, P=0.382), (r=-0.258, P=0.093), and (r=-0.284, P-value=0.071), respectively], as shown in Fig. 1, Fig. 2, and Fig.3.

Furthermore, MMP-3 had no significant correlation with age, sex, hypertension, diabetes mellitus, BMI, smoking index, family history, age of the AS onset, duration of biological treatment, response to treatment, and contraceptive pill use (P=0.318, P=0.613, P=0.495, P=0.823, P=0.313, P=0.104, P=0.135, P=0.438, P=0.534, P=0.762, and P=0.998, respectively), as shown in Table 4.

However, MMP-3 had a significant negative correlation with hemoglobin level and RBC count (P=0.049 and P=0.020, respectively), while it had no significant correlation with WBC count and platelet count (P=0.322 and P=0.170, respectively), as shown in Table 5.

As well, MMP-3 had no significant correlation with CRP and ESR (P=0.227 and

P=0.373, respectively). In addition, CRP had no significant correlation with ESR (P=0.145), as shown in Table 6.

The receiver operative characteristics (ROC) curve is used as a diagnostic tool for MMP-3 and CRP to distinguish the AS patients from healthy persons, as shown in Table 7. At the cut-off value 191 pg/ml, MMP-3 showed an AUC of 0.396, with 61.8% sensitivity and 62.5% specificity. In addition, at a cut-off value of 46.5 pg/ml, CRP showed an AUC of 0.244, with 84.5% sensitivity and 72.2% specificity. Furthermore, the diagnostic performance of MMP-3 and CRP in distinguishing the AS patients from the CBP patients was demonstrated in Table 8. At the cut-off value of 104.5 pg/ml, MMP-3 revealed the AUC of 0.400 with 54.2% sensitivity and 52.8% specificity. While at the cut-off value 54.2 pg/ml, CRP shows an AUC of 0.235 with 61.8% sensitivity and 65.4% specificity.

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.

Table 2: Levels of ESR, CRP, and MMP-3 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
MMP-3 (pg/ml)	221.92± 68.10	193.29± 25.02	279.17± 80.44	0.699	0.587

MMP-3 matrix metalloproteinase-3, ESR erythrocyte sedimentation rate, CRP C-reactive protein, **: highly significant difference.

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

Characteristics	AS activity index				
MMP-3, 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
	89.67± 0.0	77.89± 7.36	483.58± 364.23	202.42± 38.79	0.297
	ASDAS-CRP index of AS patients (n=30)				
	Inactive n=11	Low activity n=15	High activity n=4	Very high activity	P- value
	282.95± 184.33	195.89± 42.38	148.61± 35.34	-	0.796
	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
	1023.19± 915.06	99.26± 17.10	192.06± 39.83	133.19± 43.52	0.005**

MMP-3 matrix metalloproteinase-3, BASDAI bath ankylosing spondylitis disease activity index, ASDAS ankylosing spondylitis disease activity score, CRP C-reactive protein, ESR erythrocyte sedimentation rate **: Highly Significant difference

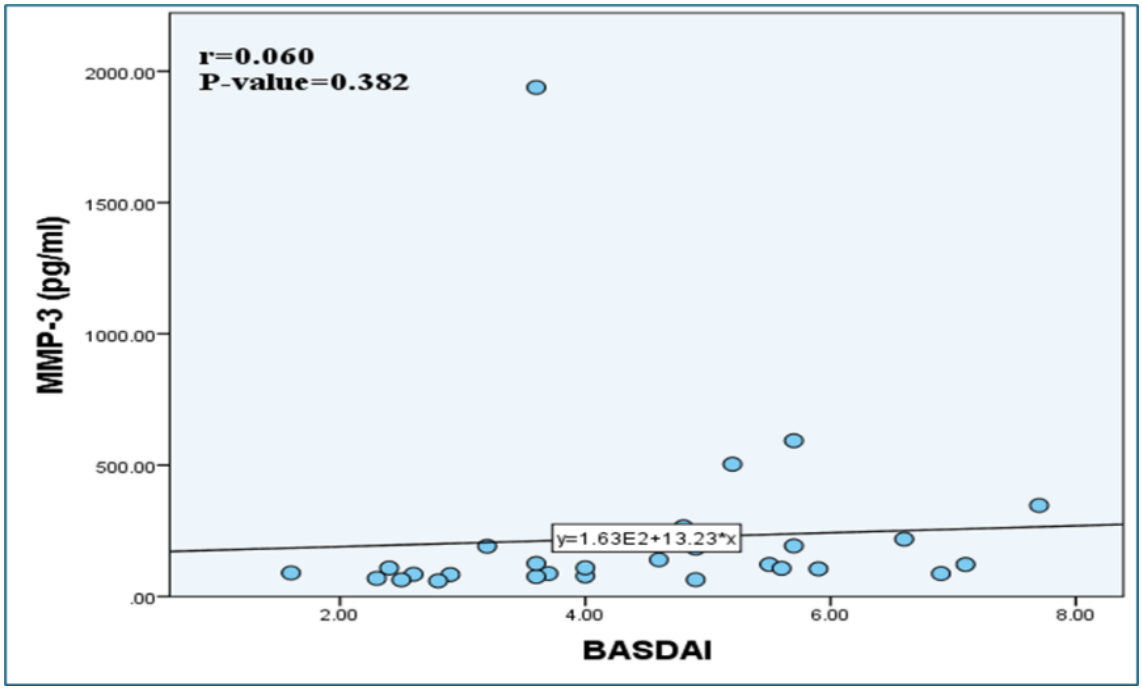

Figure 1: Correlation of MMP-3 Level with AS Activity Based on BASDAI.

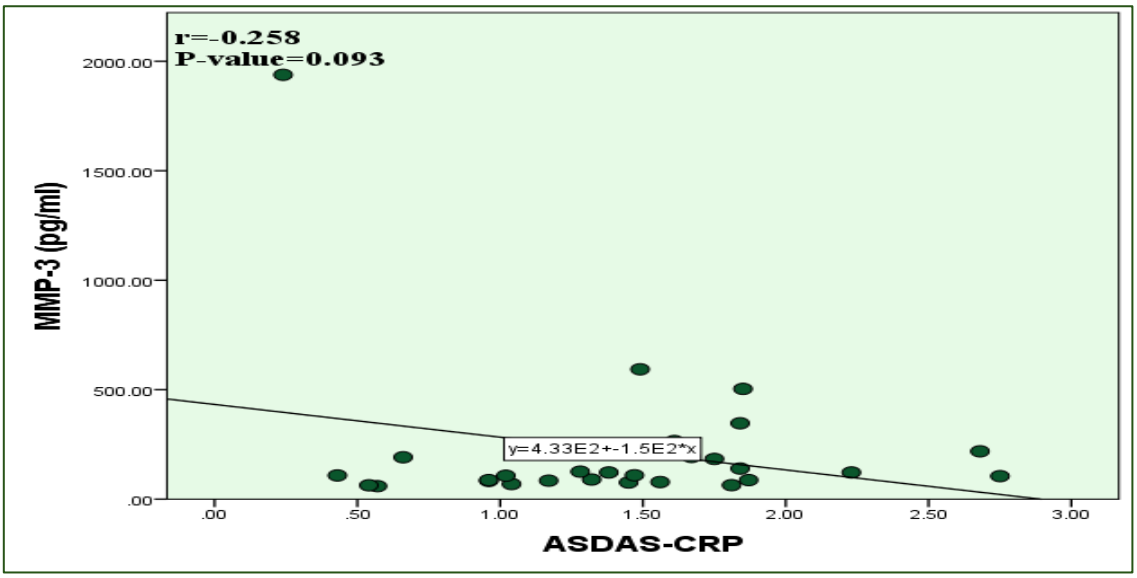

Figure 2: Correlation of MMP-3 Level with AS Activity Based on ASDAS-CRP.

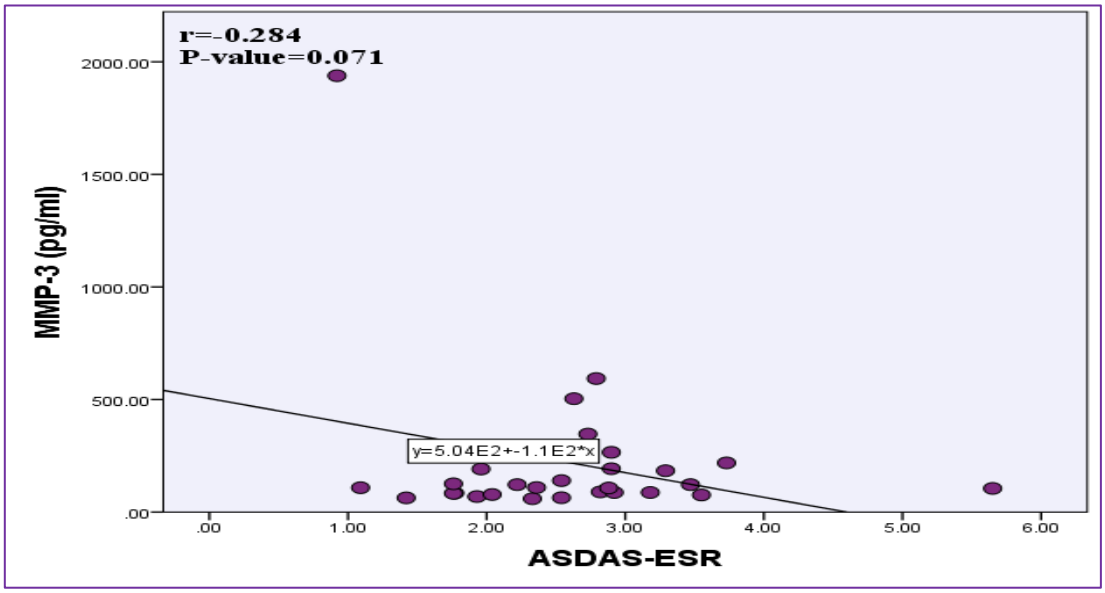

Figure 3: Correlation of MMP-3 Level with AS Activity Based on ASDAS-ESR.

Table 4: Correlations of MMP-3 Levels with Demographic Characteristics, BMI, and Features of Treatment History in the AS Patients.

Characteristics	AS patients, n=30	
	MMP-3	
Age, years	r	-0.093
	P	0.318
Sex	r	0.001
	P	0.613
Hypertension	r	-0.002
	P	0.495
Diabetes mellitus	r	0.001
	P	0.823
BMI, kg/m^2	r	-0.096
	P	0.313
Smoking index, pack per year	r	-0.500

Characteristics	AS patients, n=30	
	MMP-3	
	P	0.104
Family history	r	0.007
	P	0.135
Age of AS onset, year	r	-0.031
	P	0.438
Duration of biological treatment, years	r	0.123
	P	0.534
Response to treatment	r	-1.042
	P	0.762
Contraceptive pill use	r	0.077
	P	0.998

MMP-3 matrix metalloproteinase-3, BMI body mass index, r correlation coefficient, P P-value.

Table 5: Correlations of MMP-3 Levels with the Hematological Parameters in the AS Patients.

Characteristics	AS patients n=30	
	MMP-3	
Hemoglobin level, g/dl	r	-0.308
	P	0.049*
WBC count, x 10^9/liter	r	-0.088
	P	0.322
RBC count, x 10^{12}/liter	r	-0.379
	P	0.020*
Platelet count, x10^9/liter	r	0.181
	P	0.170

MMP-3 matrix metalloproteinase-3, WBC white blood cell, RBC red blood cell, r correlation coefficient, P P-value

****: Significant difference.***

Table 6: Correlations between Biomarkers in the AS Patients.

Characteristics	AS patients, n=30			
	MMP-3		CRP	ESR
MMP-3, pg/ml	r	1		
	P	-		
CRP, pg/ml	r	0.142	1	
	P	0.227	-	
ESR, mm/h	r	0.062	-0.200	1
	P	0.373	0.145	-

MMP-3 matrix metalloproteinase-3, CRP C-reactive protein, ESR erythrocyte sedimentation rate, r correlation coefficient, P P-value.

Table 7: The Diagnostic Performance of MMP-3 and CRP in Distinguishing the AS Patients from the Healthy Individuals.

Characteristics	MMP-3	CRP
AUC	0.396	0.244
SE	0.083	0.072
Sig.	0.205	2.22
95% confidence interval	0.233-0.559	0.104-0.384
Optimal cut-point value (pg/ml)	191	46.5
Sensitivity (%)	61.8%	84.5%
Specificity (%)	62.5	72.2%
PPV (%)	70%	70%
NPV (%)	53.57%	85.71%
Diagnostic effectiveness (accuracy)	62.06%	77.58%
Youden's index	0.24	0.57

MMP-3 matrix metalloproteinase-3, CRP C-reactive protein, AUC area under the curve, SE standard error, Sig significant, PPV positive predictive value. NPV negative predictive value.

Table 8: Receiver Operator Characteristic (ROC) Curve of MMP-3 and CRP in Distinguishing the AS Patients from the CBP Patients.

Characteristics	MMP-3	CRP
AUC	0.400	0.235
SE	0.077	0.065
Sig.	0.204	<0.001**
95% confidence interval	0.248- 0.552	0.108- 0.362
Optimal cut-point value (pg/ml)	104.5	54.2
Sensitivity (%)	54.2%	61.8%
Specificity (%)	52.8%	65.4%
PPV (%)	43.3%	70%
NPV (%)	63.3%	56.6%
Diagnostic effectiveness (accuracy)	53.33%	63.3%
Youden's index	0.07	0.27

MMP-3 matrix metalloproteinase-3, 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.

DISCUSSION

The current study indicates that the mean level of MMP-3 in the AS patients was lower than that in healthy controls, with a non-significant difference between them, as in the previous study that performed by Soliman et al. [12], who showed no statistically significant difference between the AS patients and the controls.

According to the CBP group of this study, a lower mean level of MMP-3 was reported compared to that in the AS patients, with no significant difference between them, indicating that MMP-3 was not a specific biomarker for distinguishing between the two groups.

The current study shows a non-significant difference in MMP-3 levels among disease activity groups based on the BASDAI and ASDAS-CRP indices. This result is consistent with a previous study by Dhir et al. [8], which found no significant correlation between serum levels of MMP-3 and disease activity in AS patients, as measured by the BASDAI index. However, in the current study, the ASDAS-ESR index shows a significant difference in MMP-3 levels among disease activity groups. The highest level of MMP-3 was found in the inactive group, which may not be relied upon due to the small size of this activity group (only two patients), followed by the high and very high disease activity groups, while the low activity group showed the lowest level of MMP-3. Matrix metalloproteinase-3 is a protease mainly produced by fibroblasts, synovial cells, and cartilage cells. It can degenerate multiple fibronectins and collagens, which are regarded as proteins found in bone and cartilage [8]. In addition, Yang et al. [13] found that MMP-3 was expressed in the serum and joint fluid of patients with AS, and its level is closely associated with the disease activity. It plays a key role in cartilage damage and joint destruction, and they concluded that serum MMP-3, originating directly from the inflamed joints, could be a specific marker of active inflammation inside the joints [14].

The current study found no significant correlation between MMP-3 and various factors such as age, sex, marital status, residency, hypertension, diabetes mellitus, smoking index, BMI, family history, age of AS onset, disease duration, duration of biological treatment, regularity of treatment intake, response to treatment, and contraceptive pill use. According to our knowledge, no previous studies were available to compare these results. However, MMP-3 had a significant negative correlation with hemoglobin level and RBC count. This can be explained by the inflammatory process in AS, marked by elevated cytokines, which contributes to the development of anemia of chronic disease (ACD) by affecting iron metabolism and erythropoiesis. The presence and severity of anemia in AS patients are associated with higher disease activity scores and increased levels of inflammatory markers, suggesting that the inflammatory milieu, potentially exacerbated by elevated MMP-3, contributes to the anemic syndrome. Therefore, MMP-3, through its role in inflammation, may indirectly contribute to anemia in AS patients by perpetuating the inflammatory environment that underlies ACD [14, 15, 16].

In addition, the current study found a non-significant correlation between MMP-3 and CRP, as well as between MMP-3 and ESR. This result is inconsistent with a previous study performed by Chen et al. [14]. This non-significant correlation suggests that the inflammatory pathways in AS might differ from those in other inflammatory diseases, potentially affecting the correlation between MMP-3 and traditional markers like ESR and CRP. Therefore, while MMP-3 may offer some advantages in assessing disease activity, its relationship with ESR and CRP in AS is not straightforward, and these markers may not be directly correlated in all cases. This complexity underscores the need for a multifaceted approach in evaluating disease activity in AS

[17].

In the current study, the receiver operating characteristic (ROC) curve analysis was constructed to quantify the utility of MMP-3 and CRP in the diagnosis of AS patients and distinguish them from healthy individuals or patients with CBP. Furthermore, MMP-3 recorded low diagnostic values with an accuracy of 62.06%, a sensitivity of 61.8%, a specificity of 62.5%, and a low AUC (0.396). These results suggest that MMP-3 has limited value in diagnosing AS. Regarding CRP, it showed higher diagnostic performance than that of MMP-3, with an accuracy of 77.58%, a sensitivity of 84.5%, and a specificity of 72.2%. 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 et al. [18], the sensitivity of CRP was 63.1%, and the specificity was 71.6%. In addition, Sieper & Poddubnyy [19] 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 high sensitivity observed. While Chen et al. [14] demonstrated that MMP-3 was more accurate than ESR and CRP in detecting high disease activity in AS patients, with a sensitivity and specificity of 69.2% and 68.8%, respectively, as determined by ROC plots.

Additionally, the ROC curve analysis was carried out to quantify the utility of MMP-3 and CRP in the diagnosis of AS and to distinguish them from other causes of CBP. Interleukin-17A demonstrated an AUC of o.452, with a sensitivity of 58.3% and a specificity of 55.6%, and its Youden's index was 0.14. The marker did not reach statistical significance (P=0.525), reinforcing its inadequate discriminatory ability for clinical application. Regarding the results of CRP, it exhibited better diagnostic characteristics compared to that of MMP-3. Despite a low AUC value (0.235), CRP achieved the higher sensitivity (61.8%), specificity (65.4%), and PPV (70%). Furthermore, it recorded higher Youden's index (0.27) and it demonstrated a highly significant difference (P <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.

CONCLUSION

The findings showed that MMP-3 plays a significant role in evaluating disease activity in patients with AS based on the ASDAS-ESR index; however, it does not have a diagnostic value and is not involved in the initial diagnosis of the disease.

The limitations of this study are the small sample size, all patients were collected from a single center, disease activity was not assessed by using additional indices such as BASMI and BASFI, and the biomarkers were measured only in serum and not in synovial fluid.

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Ethical approval: Before this study began, ethical approval was obtained from the Ethics Committee of the College of Medicine, 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 to participate in the questionnaire and blood sample collection.

Statement of Permission and Conflict of Interests: We declare that there is no conflict of interest.

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