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Assessment of Serum Interleukin-19 and C-Reactive Protein in Patients with Acne Vulgaris

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ABSTRACT

Background: Acne vulgaris (AV) is an inflammatory skin lesion affecting the pilosebaceous unit. Interleukin-19 (IL-19) is a pro-inflammatory cytokine produced by epithelial cells. C-reactive protein (CRP) level was found to be increased in AV when there is extensive local inflammation.

Aim: Estimation of serum level of IL-19 and CRP in AV patients, comparing them with healthy controls (HC).

Patients and Methods: This case control study was conducted on 4 groups, group 1 included patients with mild AV, group 2 included patients with moderate AV, group 3 included patients with severe AV, and group 4 included HC matched in age and sex. AV assessment was carried out by using the Global acne grading system (GAGS). Assessment of serum CRP level and serum IL-19 was conducted by using ELIZA. **Results**: There was a significant difference between both groups regarding serum IL-19 and CRP ($P<0.05$) with increasing levels of AV patients. There was no significant correlation between the severity groups of AV and age, sex, duration (years), body mass index (BMI) (kg/m^2), and CRP. The mean IL-19 level was highest in the severe group (58.22). There was a significant correlation between IL-19 and GAGS score. Regarding the validity of IL-19 and CRP for predicting severe acne vulgaris from mild and moderate acne vulgaris, IL-19 showed higher accuracy (84.85%) compared to CRP (63.64%).

Conclusion: Serum levels of IL-19 and CRP are increased in AV and correlated with the disease severity. IL-19 showed higher accuracy compared to CRP in discriminating mild from severe cases.

Keyword: Interleukin-19, C-Reactive Protein, Acne Vulgaris, GAGS.

INTRODUCTION

Acne vulgaris (AV) is an inflammatory skin lesion affecting of the pilosebaceous unit among teenagers [1]. Its pathogenesis is associated with an increase in sebum formation, inflammation, follicular hyperproliferation, and the proliferation of Propionibacterium acne. It has been demonstrated that since inflammation persists in all stages of AV, it has a central part in the development of inflammatory and non-inflammatory lesions. [2].

Propionibacterium acne activates keratinocytes to discharge proinflammatory cytokines [3]. Additionally, IL-6, IL-8, and IL-12 are recorded to have a central role in terms of AV pathogenesis [4]. IL-19 is a pro-inflammatory cytokine produced by epithelial cells [5]. It is characterized by its capability for giving a positive feedback loop that amplifies its own presence during stimulation in the inflammatory process [6].

It has been demonstrated that IL-19 levels significantly differed between moderate and severe AV. The expression of IL-19 will increase with the severity of the inflammation [7]. These findings are in agreement with another study that displayed that IL-19 formation is mainly reliant on the comprised cells and expressing cell microenvironment, and as a result, the expression of IL-19 will increase with the severity of the inflammation [8]. Moreover, IL-1, IL-6 and TNF-α that are demonstrated in the AV lesions are main inducers of hepatic CRP formation [9]. As a result, CRP level was found to be increased in AV when there is extensive local inflammation [10].

Based on the latest EAACI/GA2LEN/EDF/WAO guidelines for urticaria, CRP evaluation has to be conducted in cases with chronic urticaria and could aid in its diagnosis. Additionally, CRP has been suggested as a potential biomarker of chronic spontaneous urticaria (CSU) activity/severity and the response of CSU cases to management. On the other hand, evidence and data in support of these recommendations are rare and inconsistent [11]. There are limited data concerning the correlation between serum CRP and AV degree.

AIM OF WORK

Estimation of serum level of IL-19 and CRP in AV patients, comparing them with healthy controls and searching for any correlation between the level of IL-19 and CRP and severity of AV.

PATIENTS AND METHODS

This case control study was conducted on 33 cases with AV and 11 healthy age and sex matched controls for one year starting at May 2023 at the outpatient clinic of Dermatology, Andrology and STDs Department, Mansoura University Hospitals, Egypt.

The study population was divided into 4 groups, group 1 (n=11) included patients with mild AV, group 2 (n=11) included patients with moderate AV, group 3 (n=11) included patients with severe AV, and group 4 (n=11) included HC matched in age and sex. This study included patients from both sexes with age more than 18-year-old, with acne vulgaris all grades, mild, moderate and severe, with no history of systemic medications for acne for the last 6 weeks before the study, and with no past of topical medications of acne for the last 2 weeks before the study. But we excluded lactating patients, patients with cosmetics induced acne, patients on systemic medications for acne in last 6 weeks, patients with other dermatological conditions

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(eczema, psoriasis and vitiligo), patients with topical medications for acne in last 2 weeks, patients with chronic diseases (HTN, DM or cardiac patients) and patients with immunological diseases (SLE, RA) or with depilating diseases like cancer.

Ethical Considerations

An informed consent was received from all subjects. The study design was approved by Mansoura Medical Ethics Research Committee (MMERC) of Faculty of Medicine and according to the Declaration of Helsinki. Confidentially was respected.

METHODS

All subjects were subjected to personal history (name, age, BMI, skin type, and occupations), present history (Onset, course, duration of AV), past history of any medications and family history of AV. Determination of BMI was done by measuring the weight of the patients in kilograms (KG) and the height in meters square (m^2). Full general examinations included general appearance, localizations of lesions, chronic diseases (HTN, DM and cardiac), inflammatory diseases, systemic diseases, malignant diseases and associated autoimmune diseases.

Full cutaneous examinations included diagnosis of AV that was conducted based on the history and the classic features of noninflammatory lesions (closed and open comedones) and inflammatory lesions (papule, pustule, nodule, and/or cyst). The lesional distribution (faces, back, and/or shoulders) and the presence or absence of scarring or hyperpigmentation were also observed. The grade of AV lesions (mild, moderate, or severe) was assessed. Determination of acne vulgaris severity was done by the GAGS [12]. All participants underwent full routine investigations, including CBC, urea, serum creatinine, ALT, AST, and ESR. Five ml of venous blood was withdrawn from all subjects by venipuncture using a sterile syringe and put in a plain tube. The tube was kept at 22°C for half an hour till coagulation and then was centrifuged (at 1500 r.p.m. for 15 min). The resultant serum was stored at -80°C for further analysis. Assessment of serum CRP level and serum IL-19 was done by ELIZA.

Statistical Analysis

The collected data were revised, coded, and tabulated using SPSS (Released 2017. Version 25.0.). Mean±SD, median, and range were used for numerical data. Frequency and percentage were used for non-numerical data. Shapiro-Wilk test was done to test the normality of data distribution. Student T Test and Mann-Whitney U test were utilized to assess the significance of the difference of parametric variable and a non-parametric variable between two study groups respectively. In contrast, in terms of nonparametric variables among more than 2 groups, we used Kruskal Wallis test. Chi-Square test was used to assess the relationship between two qualitative variables. Fisher Exact or Monte-Carlo test: was used to assess the correlation between two qualitative variables when over 20% of cells have an expected count of less than 5. A p value was considered significant if <0.05.

RESULTS

Table **(1)** displays that there were insignificant differences in sex, age, weight, height or BMI between AV patients and the control group. There was a significant difference between both groups regarding serum IL-19 and CRP with increasing levels of AV patients. Table **(2)** shows the mean score for acne severity was 27.52 with a standard deviation of 16.35.

Table (1): Comparison of patients with AV and the control group regarding personal history, anthropometric data, IL-19, CRP

	AV patient n = 33		**Control n = 11**		**Test**	**p**
	No.	**%**	**No.**	**%**		
Sex						
Male	8	24.2	6	54.5	X^2=3.492	FE 0.132
Female	25	75.8	5	45.5		
Age (years)						
Mean ± SD.	21.36 ± 4.51		23.64 ± 3.44		U=253.5	0.151
Median	20.0		22.0			
Min. – Max.	15.0 – 36.0		20.0 – 30.0			
Weight (kg)						
Mean ± SD.	75.06 ± 16.35		78.27 ± 12.17		t=0.597	0.554
Median	75.0		80.0			
Min. – Max.	49.0 – 117.0		55.0 – 95.0			
Height (m)						
Mean ± SD.	1.66 ± 0.09		1.73 ± 0.10		t=2.174	0.035*
Median	1.65		1.78			
Min. – Max.	1.50 – 1.85		1.55 – 1.85			
BMI (kg/m^2)						
Mean ± SD.	27.03 ± 5.24		26.07 ± 3.60		U=176.0	0.894
Median	26.12		26.23			
Min. – Max.	18.86 – 41.45		19.49 – 31.22			
IL-19						
Mean ± SD.	32.91 ± 29.50		6.86 ± 5.69		U=30.50	<0.001 *
Median	20.59		5.20			
Min. – Max.	3.95 – 114.6		1.87 – 21.84			
CRP						
Mean ± SD.	8.67 ± 2.63		5.59 ± 1.93		U=57.0	<0.001 *
Median	9.85		5.17			
Min. – Max.	2.0 – 11.45		2.09 – 8.42			

U: Mann Whiteny, X^2: Chi Square, FE: Fisher Exact, *: Significant p value.

Table (2): Severity of acne vulgaris by the GAGS

	AV patients n = 33	
	No.	**%**
Severity of acne vulgaris		
Mild	11	33.3
Moderate	11	33.3
Severe	11	33.3
Score		
Mean ± SD.	27.52 ± 16.35	
Median	24.0	
Min. – Max.	6.0 – 72.0	

Table (3) and figure 1 show that there was insignificant association between the severity of AV and age, sex, duration (years), BMI (kg/m^2), and CRP. The mean IL-19 level was highest in the severe group (58.22), followed by the moderate group (22.94) and mild group (17.57). The statistical test indicated a statistically significant difference in IL-19 levels among the severity groups. Pairwise comparisons showed that level of IL-19 is significantly higher in severe group than in mild group and a slightly higher in sever group than in moderate group.

Table (3): Association between the severity of AV and personal history, duration (years), BMI (kg/m^2), CRP, and IL-19

	Severity of acne vulgaris						**Test**	**p**
	Mild n = 11		**Moderate n = 11**		**Severe n = 11**			
	No.	**%**	**No.**	**%**	**No.**	**%**		
Sex								
Male	1	9.1	3	27.3	4	36.4	X^2= 2.303	MC 0.462
Female	10	90.9	8	72.7	7	63.6		
Age (years)								
Mean ± SD.	21.09 ± 4.46		21.36 ± 3.88		21.64 ± 5.48		H= 0.374	0.829
Median	20.0		22.0		20.0			
Min. – Max.	16.0 – 30.0		15.0 – 28.0		16.0 – 36.0			
Duration (years)								
Mean ± SD.	1.04 ± 0.67		0.73 ± 0.33		1.92 ± 1.94		H= 1.957	0.376
Median	1.0		1.0		2.0			
Min. – Max.	0.25 – 2.0		0.25 – 1.0		0.08 – 6.0			
BMI (kg/m^2)								
Mean ± SD.	25.99 ± 4.57		26.41 ± 4.66		28.70 ± 6.38		H= 0.739	0.691
Median	25.71		26.12		26.12			
Min. – Max.	18.86 – 34.60		20.03 – 35.44		22.09 – 41.45			
CRP								
Mean ± SD.	8.89 ± 2.44		7.42 ± 1.35		9.71 ± 1.43		H= 2.388	0.303
IL-19								
Mean ± SD.	17.57 ± 3.27		22.94 ± 4.47		58.22 ± 6.65		H= 15.685	p<0.001* p2=0.112 p3<0.001* p4=0.019*

H: Kruskal Wallis test, X^2: Chi Square, MC: Monte Carlo, p: Comparing the different categories, p2: Comparing mild and moderate, p3: Comparing mild and severe, p4: Comparing moderate and severe, *: Significant p value.

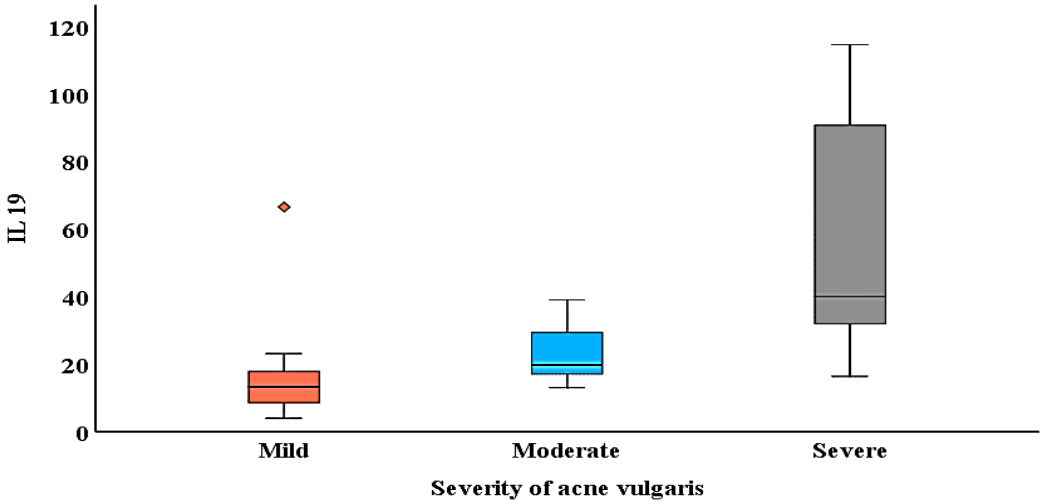

Figure 1: Boxplot chart for association between the severity of acne vulgaris and IL-19.

Table **(4)** shows that there were insignificant correlations between IL-19 and age, duration, or BMI but there was a correlation between IL-19 and GAGS score and there were insignificant correlations between CRP and age, duration, BMI, or GAGS score.

Table **(5)** shows that the correlation coefficient between IL-19 and CRP was 0.055, indicating a weak positive correlation. However, the p-value suggests that this correlation was not statistically significant.

Table (4): Correlation between IL-19 and CRP and different parameters among patients with AV

	IL-19		**CRP**	
	Correlation Coefficient	**p**	**Correlation Coefficient**	**p**
Age	0.074	0.680	0.008	0.964
Duration	0.174	0.332	0.295	0.096
BMI	0.124	0.491	-0.218	0.223
GAGS score	0.740	<0.001 *	0.065	0.720

*: Significant p value.

Table (5): Correlation between IL-19 and CRP among patients with AV

	Correlation Coefficient	**p**
IL-19 versus CRP	0.055	0.763

Regarding discrimination between patients with AV and the control group, table (6) and figure 2 shows that IL-19 demonstrated higher accuracy (88.64%) compared to CRP (79.55%). The AUC for IL-19 was 0.916, indicating a high discriminatory power, while the AUC for CRP was 0.843 which indicates a moderate discriminatory power. Both IL-19 and CRP had statistically significant AUC values, suggesting their potential validity as markers for distinguishing AV patients from the control group.

Regarding the validity of IL-19 and CRP for predicting severe acne vulgaris from mild and moderate acne vulgaris, IL-19 showed higher accuracy (84.85%) compared to CRP (63.64%). The AUC for IL-19 was 0.893, indicating significant predictive ability, while the AUC for CRP was 0.649 indicates a poor discriminatory power. The p-value for CRP was not statistically significant, suggesting limited predictive power.

Regarding the validity of IL-19 and CRP for predicting moderate and severe acne vulgaris from mild acne vulgaris, IL-19 demonstrated higher accuracy (87.88%) compared to CRP, which had no statistically significant predictive ability. The AUC for IL-19 was 0.845, indicating moderate discriminatory power, while that of CRP was poor AUC (=0.508) indicating poor discriminatory ability.

Table (6): Validity of IL-19 and CRP for discrimination between patients with AV and the control group, prediction severe acne vulgaris from mild and moderate AV and prediction moderate and severe acne vulgaris from mild AV

	AUC	95% CI	p	Cut off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Discrimination between patients with AV and the control group	**IL-19**								
	0.916	0.818–1.000	<0.001*	>10.5	87.88	90.91	96.67	71.43	88.64
	CRP								
	0.843	0.730–0.956	0.001*	>6.3549	81.82	72.73	90.0	57.15	79.55
Prediction severe acne vulgaris from mild and moderate AV	**IL-19**								
	0.893	0.777–1.000	<0.001*	>27.072	90.91	81.82	71.43	94.74	84.85
	CRP								
	0.649	0.457–0.840	0.169	>9.7862	72.73	59.09	47.06	81.25	63.64
Prediction moderate and severe acne vulgaris from mild AV	**IL-19**								
	0.845	0.686–1.000	0.001*	>15.184	95.45	72.73	87.50	88.88	87.88
	CRP								
	0.508	0.304–0.712	0.939						

AUC: Area under ROC curve, PPV, positive predictive value, NPV, negative predictive value, *: Significant p value.

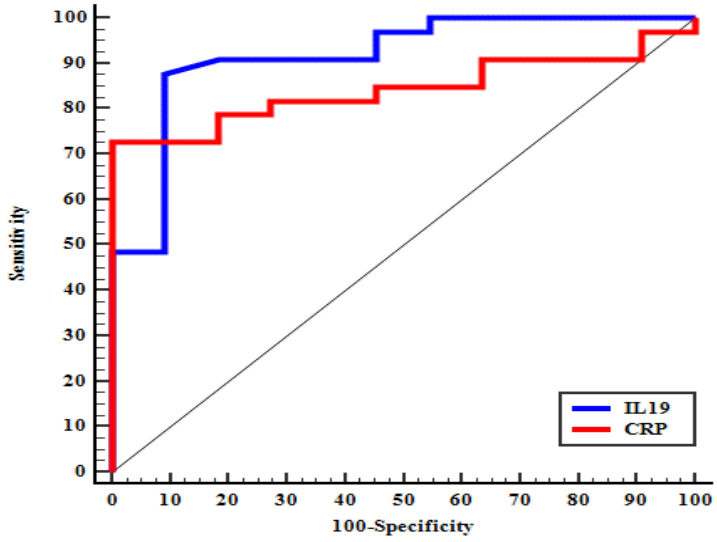

Figure 2: ROC Curve for IL-19 and CRP for discrimination between patients with AV and the control group.

DISCUSSION

Acne vulgaris is a common skin inflammatory disease of the pilosebaceous unit. It is frequently presented by comedones, papules, pustules, or nodules, mostly on the face; however, in addition, it could affect the upper arms, trunk, and back. Although AV frequently affects teenagers [13], its pathogenesis includes the interaction of several factors that eventually cause the formation of its primary lesion, "comedo". The manifestations differ from a limited number of comedones (mild degree) to disfiguring inflammatory manifestations (severe degree), which could be accompanied by hyperpigmentation, scar formation, and negative psychiatric problems [14].

It has been demonstrated that all stages of AV are associated with inflammatory reactions, which could be detected by histopathological and immunologic examination. As a result, IL-19 expression could be detected in keratinocytes (in human and experimental studies) due to the release of proinflammatory cytokines (such asIL-1) [15].

The IL-19 and this locus have a potent correlation with IL-10 as part of a gene cluster. When subjected to pro-inflammatory triggers, monocytes and epithelial cells produce IL-19. As a result, IL-19 augments the pro-inflammatory nature by the creation of a positive feedback loop, encouraging these cells to further amplify their response [16]. CRP is a good indicator of systemic inflammation, as it has no circadian alteration throughout the day. IL-1, IL-6, and TNF-α, detected in the AV lesions, are also main inducers of hepatic CRP production. Therefore, if there is sufficient local inflammation, AV may experience an increase in CRP values [9].

Therefore, the present study aimed to estimate serum level of IL-19 and CRP in AV patients, comparing them with healthy controls and searching for any relationship between the level of IL-19, CRP and severity of AV, as defined by GAGS. The current study was case control study, carried out on 33 patients with AV and 11 HC groups. The 44 subjects were divided into four groups, 11 in each; mild, moderate, and severe AV patients' groups based on AV and apparently HC group with no preceding history of AV.

Regarding demographics of the present study, both groups displayed female predominance with no significant differences between both groups regarding gender, BMI, weight, height or age. Mean age of AV cases and control groups were 21.36± 4.51, and 23.64 ± 3.44 respectively. The mean duration of AV among the cases was 1.23 ± 1.27 years.

In same line with **Mohammed *et al.***, [16] who examined 120 subjects, comprising 80 cases of AV and 40 HC and revealed no significant differences between both groups regarding gender or age. The same study also showed that females (57%) slightly outnumbered males.

In the present study, all patients didn't receive any systemic or topical treatment in the last two months. Regarding severity of acne, the present study showed that 33.3% of AV patients had mild acne, 33.3% had moderate acne, and 33.3% had severe AV. The mean score for acne severity was 27.52 ± 16.35. Similarly **Mohammed *et al.*, [16]** showed that the AV patients were divided into three groups: mild (25%), moderate (50%), and severe (25%).

The mean IL-19 level among AV cases in the current study was higher than the controls with a significant difference (32.91 ±29.50 in AV group versus, 6.86 ±5.69 for control group). Likewise, **Mohammed *et al.* [16]** showed that there was a significant increase in IL-19 level in AV cases compared with HC (mean IL-19 was 14.6 pg versus 2.7 pg in controls).

In the present study, the increase in IL-19 level was significantly correlated with acne severity median IL-19 in mild cases was 13.31, versus 19.76 in moderate cases, 40 in severe cases. Also, **Saleh *et al.* [17]** study was in same line with our results, displayed significant increase in IL-19 levels in AV cases compared to the controls. In addition, the rise in serum interleukin-19 levels had a significant relationship with AV (median IL-19 in controls was 12.5 (10-13) versus 35 (30-60) in mild cases, 85.5 (75-90) in moderate cases, 125 (100-150) in severe cases.

The present study displayed that mean IL-19 level was highest in the severe group (58.22), followed by the moderate group (22.94) and mild group (17.57) with highly significant differences, thus high IL-19 revealed a significant positive correlation with GAGS score. **Mochtar *et al*.** [7] investigated IL-19 levels in cases with AV of different grades and demonstrated results comparable to ours. They demonstrated a significant difference in IL-19 concentration between mild and severe cases and between moderate and severe cases.

The present study showed no significant association between mean IL-19 levels and gender, age, duration, BMI, or history of systemic treatment or local treatment in the past 2 months. Also, **Saleh *et al.*, [17]** displayed that serum IL-19 level wasn't significantly linked to age or sex of subjects, or disease duration. Hence, serum IL-19 level has a direct relationship with the inflammatory process of AV and has no relationship with alteration in the sociodemographic data. Since AV is an inflammatory lesion and IL-19 plays an essential role in its pathogenesis and has a positive correlation with its severity, monoclonal antibodies could antagonize its action and could be considered a promising agent in terms of AV management.

C-reactive protein has been considered the best inflammatory marker, as its value raises rapidly in inflammatory conditions, and its values display no circadian alteration. IL-1, IL-6, and TNF-α implicated in AV pathogenesis have been considered major inducers of hepatic CRP formation. As a result, CRP levels may be increased in AV when there is extensive local inflammation [18].

The present study revealed that AV patients were associated with a significant increase in CRP level

compared to HC (8.67±2.63 in AV group versus 5.59±1.93 in control group). **Alsalem *et al.***, [10] displayed that there was a significant increase in CRP among studied cases of AV compared to HC. Similarly, **Monib *et al.***, [19] displayed that the serum CRP level in the AV cases were significantly increased compared to the HC ($p < 0.001$).

In contrast, **Namazi *et al.***, [9] didn't determine an increase in serum CRP level in their AV cases. The discrepancies in their results could be clarified by the differences between both groups being non-matched as the controls were enrolled from the blood donors.

No significant difference was recorded in the present study regarding severity of disease with other parameters (gender, age, duration of disease, past treatment history and anthropometric data. While **Saleh *et al.,*** [17] found that there was a significant negative relationship between age of cases and grade of AV. On the other hand, no significant relationships were detected between AV severity and gender, or duration of active acne lesions**.**

Also, the current study revealed that mean CRP level was highest in the severe group (9.71), followed by the mild group (8.89) and moderate group (7.42), but with no significant difference in CRP levels among the severity groups. Similarly, **Alsalem *et al.***, [10] found a significant increase in CRP level among cases with severe GAGS grades compared to the group with moderate and the least was determined for the group with mild grades ($p=0.03$).

Our study displayed no significant correlation between mean CRP levels and gender, age, duration, BMI or history of systemic treatment or topical treatment in the last 2 months or GAGS score. Another report by, **Alsalem *et al.***, [10] revealed a significant relationship between CRP and the next: negative with BMI, disease onset and positive relationship with GAGS degree. There was a significant increase in the CRP among cases with severe GAG compared to cases with moderate degree and mild degrees**.**

The present study revealed that IL-19 demonstrated higher accuracy (864%) compared to CRP (79.55%) in discriminating cases with AV from controls. While **Alsalem *et al.,*** [10] displayed that the determination of CRP levels may be utilized as a reliable predictor in the differentiation between AV cases and the controls (cut-off =0.650) with moderate sensitivity and specificity.

Additionally, the present study showed that IL-19 showed higher accuracy (84.85%) compared to CRP (63.64%) in discriminating mild from severe cases. IL-19 remained significantly associated with AV, while Both markers were considered independent predictors for AV susceptibility. Other recent study by **Albalat *et al.,*** [20] proved that there is a significant difference in serum IL-19 between the various grades of acne vulgaris severity. The mean serum level of IL-19 among mild, moderate and severe cases were 162.6 ± 54.7 and 213.4 ± 8.45 and 258.7 ± 61.3 respectively with increased significant difference among moderate and severe cases than mild cases. That means that the increase in serum IL-19 levels was proportional to the increase in the gravidity of AV with a significant difference between the four study groups.

CONCLUSION

In conclusion, serum levels of IL-19 and CRP are increased in AV and correlated with the disease severity. IL-19 showed higher accuracy compared to CRP in discriminating mild from severe cases.

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