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Original Research Article

Evaluation of Interleukin-33, Interleukin-10 Levels in Rheumatoid Arthritis Patients on Long Term Therapy of Disease-Modifying Antirheumatic Drugs

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Abstract: ***Background*:** Rheumatoid arthritis is a prevalent, long-term, inflammatory autoimmune illness with a wide range of extra-articular symptoms that affects 0.24% of people worldwide. Finding new, RA-specific biomarkers may help in early diagnosis, treatment, and monitoring of the severity and response to therapy of the disease. ***Objective*:** Determining of (IL-33, IL-10) levels in blood of both patients on long term therapy, early diagnosis patients and healthy control groups by using ELISA technique. ***Method*:** A case-control study in the following study groups consisted of three group. Group 1 included (50) patients on medications (DMARDs), Group 2 included (50) early diagnosed patients without medication and group 3 included (50) healthy individuals. ***Result:*** The mean of serum IL-33 concentration was significantly difference in rheumatoid arthritis (157.15 ± 24.88) in treated patients, (513.11 ± 113.01), and in patients with early diagnosis (185.75 ± 30.71) compared to the healthy control group (P = 0.000). But Mean levels of serum IL-10 were 320.27 ± 37.82, 180.24 ± 12.68 and 493.80 ± 68.94 pg/ml in patients on treatment, early diagnosis patients and healthy control group respectively; the level was highly significant lower than in early diagnosis patients with RA in comparison with patient on treatment and healthy control and the IL-10 level in healthy control was highly significant higher than in Patients on treatment, but in Patients on treatment higher than in early diagnosis patients, (P = 0.000). ***Conclusion*:** IL-33 and IL-10 is regarded as a useful biomarker for the diagnosis of RA and for assessing the severity of the illness.

Keywords: Rheumatoid arthritis; IL-33; IL-10; Anti-citrullinated protein antibodies; Rheumatoid factor; DMARDs; ELISA.

BACKGROUND

Rheumatoid arthritis (RA) is a long-term autoimmune condition that mostly affects the synovial joints, causing inflammation in the synovium and damage to the joints. The condition is mostly characterized by swelling, discomfort, stiffness, and other joint symptoms. It most frequently affects the tiny joints in the hands and feet. Morning stiffness is among the most common clinical manifestations [1]. It is a multifactorial disease in which multiple signaling pathways controlled by numerous cells are activated. Among these, T lymphocytes are considered the main conductors of the inflammatory orchestra. CD8 cells, which make up a large proportion of the synovial compartment and are increased in circulation in patients with early diagnosed rheumatoid arthritis, have been largely ignored in the pathogenesis. CD8 T cells are not a homogeneous group and, like CD4 T cells, can also be divided into CD8+ IFNγ+, CD8+ IL4+ and CD8+ IL17+ cells based on cytokine production [2].

RA causes joint destruction over time, resulting in cartilage loss and bone erosion. Rheumatoid arthritis with symptoms that last less than six months is called “early RA,” and if symptoms last longer than six months, it is called “persistent RA” [3]. Rheumatoid arthritis, if left untreated, is a progressive disease with increased morbidity and mortality [4].

The prevalence of rheumatoid arthritis worldwide is surprisingly consistent at around 0.5–1.0%, although it is higher in some populations, such as the indigenous population of North America. Rheumatoid

arthritis can occur at any age, but the highest incidence occurs between the third and fifth decades of life and the disease is two to three times more common in women than in men [5].

Despite advances in the diagnosis and treatment of patients with rheumatoid arthritis, studies have shown that 20–40% of the patients do not respond to treatment after initiation of biologic therapy. High costs and risk to patients due to serious side effects has recognized the need to identify new biomarkers that can be used for early diagnosis, to overcome the limitations of routine testing in diagnosing rheumatoid arthritis, and to distinguish between pretreatment responders and non-responders. Over time, several potential biomarkers have been tested and linked to this role [6].

Polyfunctional T cells in human rheumatological autoimmune diseases. Polyfunctional T cells are characterized by the ability to simultaneously produce multiple cytokines to alleviate the complex local inflammatory environment and are molecularly different from monofunctional cells [7].

Interleukins (ILs) are cytokines that stimulate the differentiation of T- and B-lymphocytes and the development of hematopoietic cells. Interleukins and their receptor genes have been identified as having several genetic variants associated with RA [8].

IL-33 has a conflicting function in autoimmune disorders. Cytokine production in mast cells, basophils, eosinophils, NK cells, and T lymphocyte cells is stimulated by IL-33 through the ST2 receptor. It has been shown that IL-33 plays a critical function as an active component that results in abnormal local and systemic damage in a variety of inflammatory illnesses and immune-mediated pathological states, including multiple sclerosis, RA, SLE, and others. The IL-33/ST2 axis can increase the release of pro-inflammatory cytokines in autoimmune disorders; on the other hand, IL-33 may be an anti-inflammatory cytokine in various metabolic diseases, such as type 1 diabetes [9].

In general, STAT5-regulated Th0 cell differentiation into Th2 cells is induced by IL-33. In a Th2 cell polarizing culture system, IL-33 increases the production of IL-5, IL-13, and IFN-γ during human antigen-dependent and independent T cell responses [10].

Pliotropic in nature, IL-10 is a key player in both regulating inflammation and preserving cellular homeostasis. Its main function as a cytokine that reduces inflammation keeps the body safe from an unchecked immunological reaction. Proinflammatory cytokine production from CD4+ T cells, including IL-2, interferon gamma (IFNc), and tumor necrosis factor alpha (TNFa), as well as from monocytes and macrophages, including IL-1, IL-6, TNFa, and IL-12, is inhibited by IL-10. IL-10 reduces memory and effector responses of CD4+ T helper cells [11].

The heterodimeric IL-10 receptor is responsible for the immunosuppressive effects of IL-10 (IL-10R1, IL-10R2). Despite the fact that a wide variety of cell types express the IL-10 receptor complex to differing degrees, monocytes and macrophages seem to be the main targets of IL-10 [12].

MATERIAL AND METHOD

A case-control study was conducted in the following study groups between November 2023 and the end of January 2024. In this study, the study groups consisted of three groups. Group 1 included (50) patients on medications (DMARDs), of which (43) were female and (7) were male. Group 2 included (50) early diagnosed patients without medication, including (49) women and (1) men. Group 3 included (50) healthy individuals, (45) women and (5) men with no history of systemic diseases who were considered clinically healthy and were included as a control group in this study. All participant groups aged 20 to 70. This study was conducted at Al-Sadr Medical City. The doctor clinically diagnosed the patient with rheumatoid arthritis. Patients were interviewed directly using an anonymous questionnaire that included age, gender, place of residence, family history of rheumatoid arthritis, disease duration, treatment duration, and smoking. Study compliance with the ethical guidelines of Al-Sadr Medical City and verbal informed consent were obtained from participants. The aim of this study was to evaluate IL-33, IL-10 markers using ELISA. Utilizing the Statistical Package for the Social Sciences (SPSS) software, version 26, created by Inc. in Chicago, USA, all data from both research groups were gathered and examined.

Inclusion Criteria

- Every patient who receives a rheumatologist diagnosis of RA based on the 2010 ACR/EULAR Criteria.
- Healthy people without any diseases which can effect on immunological cells and markers.

Exclusion Criteria

- Patients with any other autoimmune diseases.
- Patients with the central nervous system diseases.
- Patients with cardiovascular diseases.
- Individuals who have had recent wound care, surgery, or acute local inflammation.
- Patients who are under 20 years old and older than 70 years old.
- Patients with any disease that can affect serum biomarkers such as immunodeficiency disease, malignancy, and chronic infections.

RESULT AND DISCUSSION

ELISA results expressed as mean concentration of immune markers, the comparison of serum IL-33 level between patients with RA on treatment, early diagnosis patients and healthy control subjects has been completed, and the table (1-1) and figure (1-1) show the results. Mean levels of serum IL-33 were 157.15 ± 24.88, 513.11 ± 113.01 pg/ml and 185.75 ± 30.71 pg/ml in patients on treatment, early diagnosis patients and healthy control subjects respectively; the level was highly significant higher than in early diagnosis patients with RA in comparison with patient on treatment and healthy control and the IL-33 level in healthy control was highly significant higher than in Patients on treatment, but lower than in early diagnosis patients, (P = 0.000).

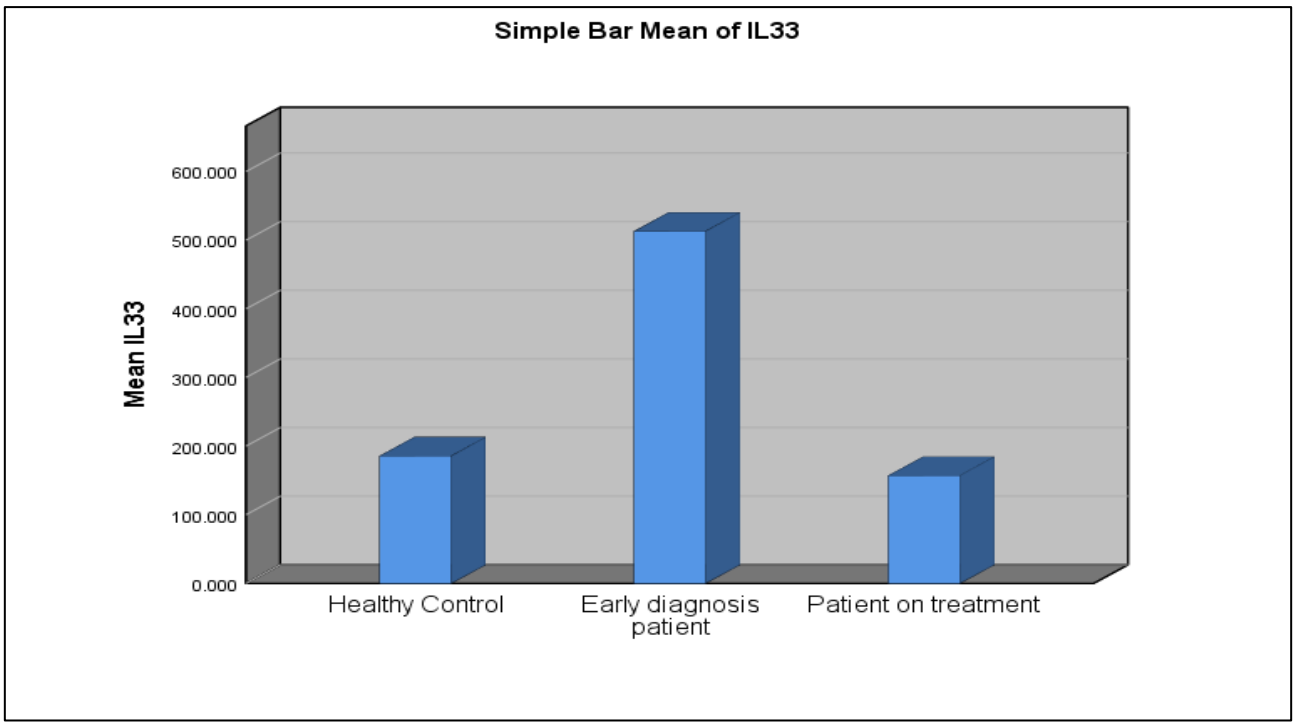

Figure 1-1: Mean Bar showing comparison of Mean serum IL-33 level among study groups

Table 1-1: Comparison of Serum IL-33 level in study groups

Characteristic	Patients on treatment Drug/ n = 50	Early diagnosis Patients Drug/ n = 50	Healthy control/ n = 50	P-value
IL – 33 (pg/ml)				
Mean ± SD	157.15 ± 24.88	513.11 ± 113.01	185.75 ± 30.71	0.001** A
Range	122.78 - 190.23	340.30 - 652.76	154.64 - 228.81	

n: number of cases; **SD**: standard deviation; **A**: ANOVA test; *significant at **P** ≤ 0.05: **significant at **P** < 0.01.

Table 1-2: Comparison of IL-33 levels according to some characteristics

Characteristic		Median	Range	P-value
Sex	Male, n = 5	340.306	190.2 - 340.3	0.937 M
	Female, n = 95	190.234	122.7 - 652.7	
Occupation	Housewife, n = 50	340.306	130.0 - 652.7	0.044* K
	employee, n = 41	190.234	122.7 - 652.7	
	Self-employment, n = 9	138.350	130.0 - 633.9	
Family history	Positive, n = 35	190.234	138.3 - 633.9	0 .928 M
	Negative, n = 65	355.580	122.7 - 652.7	
Smoking	Yes, n = 15	190.234	130.0 - 190.2	0.11 M
	No, n = 85	340.306	122.7 - 652.7	
Severity	Mild, n = 46	522.785	340.3 - 652.7	0.001** K
	Moderate, n = 43	163.567	122.7 - 602.9	
	Severe, n = 11	144.502	122.7 - 178.4	

n: number of cases; **M**: Mann–Whitney U test; **K**: kruskal wallis test; *significant at **P** ≤ 0.05; **highly significant at **P** ≤ 0.01.

The comparison of serum IL-10 level between patients with RA on treatment, early diagnosis patients and healthy control subjects has been completed, and the table (1-3) and figure (1-2) show the outcomes. Mean levels of the serum IL-10 were 320.27 ± 37.82, 180.24 ± 12.68 and 493.80 ± 68.94 pg/ml in patients on treatment, early diagnosis patients and healthy control respectively; the level was highly significant lower than in early diagnosis patients with RA in comparison with patient on treatment and healthy control and the IL-10 level in healthy control was highly significant higher than in Patients on treatment, but in Patients on treatment higher than in early diagnosis patients, (P = 0.000).

Table 1-3: Comparison of Serum IL-10 level in study groups

Characteristic	Patients on treatment Drug/ n = 50	Early diagnosis Patients Drug/ n = 50	Healthy control/ n = 50	P-value
IL – 10 (pg/ml)				
Mean ± SD	320.27 ± 37.82	180.24 ± 12.68	493.80 ± 68.94	0.001**
Range	269.56 - 377.78	165.13 - 199.17	400.64 - 575.91	**A**

n: number of cases; **SD**: standard deviation; **A**: ANOVA test; *significant at **P** ≤ 0.05: **significant at **P** ≤ 0.01.

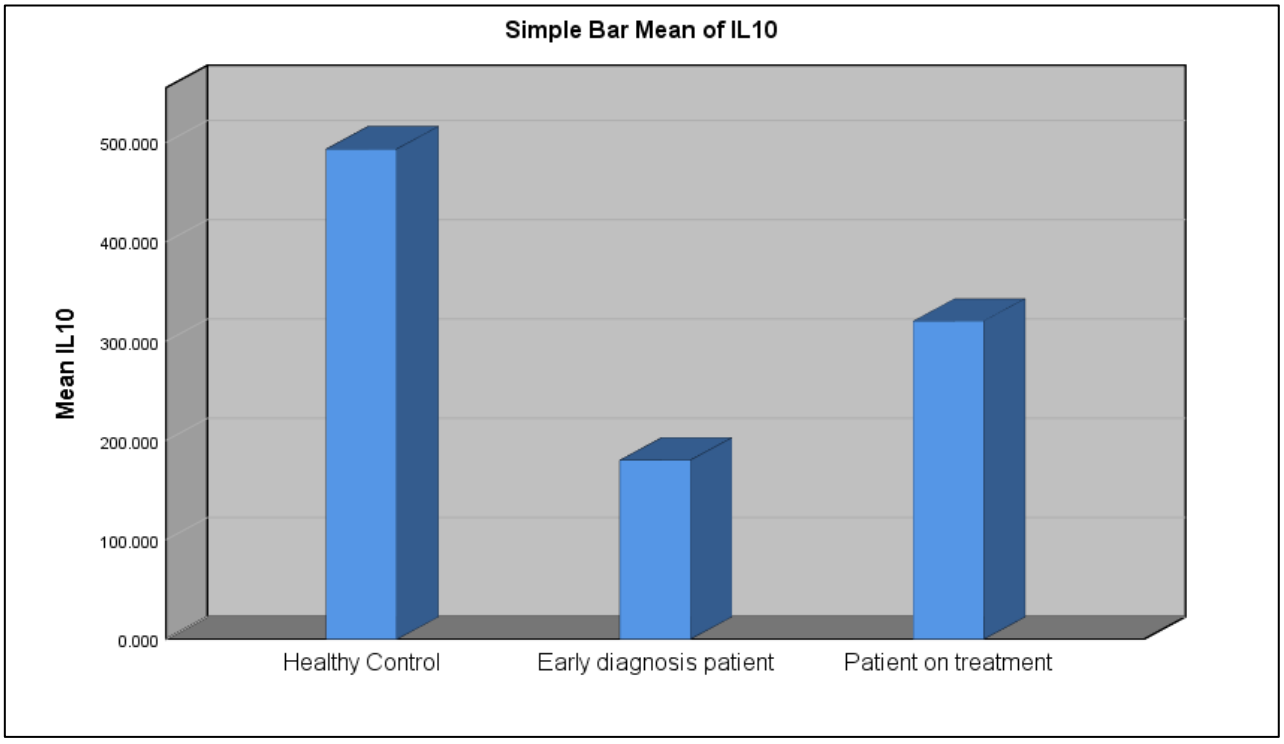

Figure 1-2: Mean bar showing comparison of Mean serum IL-10 level among study groups

Table 1-4: Comparison of IL-10 levels according to some characteristics

Characteristic		Mean ± SD	Range	P-value
Sex	Male, n = 5	262.01 ± 86.05	199.1 - 356.2	0.724
	Female, n = 95	249.63 ± 75.64	165.1 - 377.7	I
Occupation	Housewife, n = 50	239.50 ± 77.75	165.1 - 377.7	0.086
	employee, n = 41	252.51 ± 72.07	165.1 - 377.7	A
	Self-employment, n = 9	299.69 ± 67.28	184.3 - 377.7	
Family history	Positive, n = 35	294.31 ± 76.81	169.0 - 356.2	0 .001**
	Negative, n = 65	226.53 ± 64.11	165.1 - 377.7	I
Smoking	Yes, n = 15	363.45 ± 10.48	356.2 - 377.7	0.001**
	No, n = 85	230.28 ± 63.67	165.1 - 340.9	I
Severity	Mild, n = 46	180.61 ± 12.92	165.1 - 199.1	0.001**
	Moderate, n = 43	309.30 ± 59.26	169.0 - 377.7	A
	Severe, n = 11	310.66 ± 38.25	269.5 - 377.7	

n: number of cases; **SD**: standard deviation; I: independent samples t-test; **A**: ANOVA test; *significant at **P** ≤ 0.05; ** highly significant at **P** ≤ 0.01.

3.9.2 ROC curve analysis to diagnostic between RA patients and healthy control.

Receiver operator characteristic (ROC) curve analysis was used to assess the biomarkers (IL-33 and IL-10) cutoff value as well as to predict the RA as diagnostic tests or adjuvant diagnostic tests. The results are displayed in table (1-5), and figure (1-3). The IL-33 cutoff value was ≥ 189.288 pg/ml with sensitivity, specificity, PPV, NPV, and AUC 86%, 80%, 89%, 74% and 0.791 (0.712-0.870), and the IL-10 cutoff value was ≤ 494.329 pg/ml with sensitivity, specificity, positive PPV, NPV, and AUC, 86%, 92%, 97%, 70% and 0.886 (0.831-0.941).

Table 1-5: ROC curve for determine the important biomarkers to diagnostic between RA patients and control groups

Characteristic	IL-33	IL-10
Optimal Cutoff Value	≥ 189.288	≤ 494.329
AUC	0.813	0.886
Sensitivity %	84%	86%
Specificity %	64%	92%
(95% CI)	0.743 - 0.883	0.831-0.941
Sig	0.0001	0.0001
SE	0.036	0.028
PPV %	81%	97%
NPV %	70%	70%
Accuracy	77%	88%

* Significant at P-value< 0.05, ** Highly Significant at P-value< 0.01, **AUC**, Area under the Curve, **SE**, Standard Error, Positive Predictive Value, Negative Predictive Value, and Confidence Interval

During this study was Interleukin 10, had RA higher than the cut off value (≤ 494.329), but the difference was extremely significant (P = 0.0001), For these cytokines, the receiver operating characteristic (ROC) AUC, (CI) was 0.886 (0.831 - 0.941), implying that the degree of RA disease might be predicted using these cytokines.

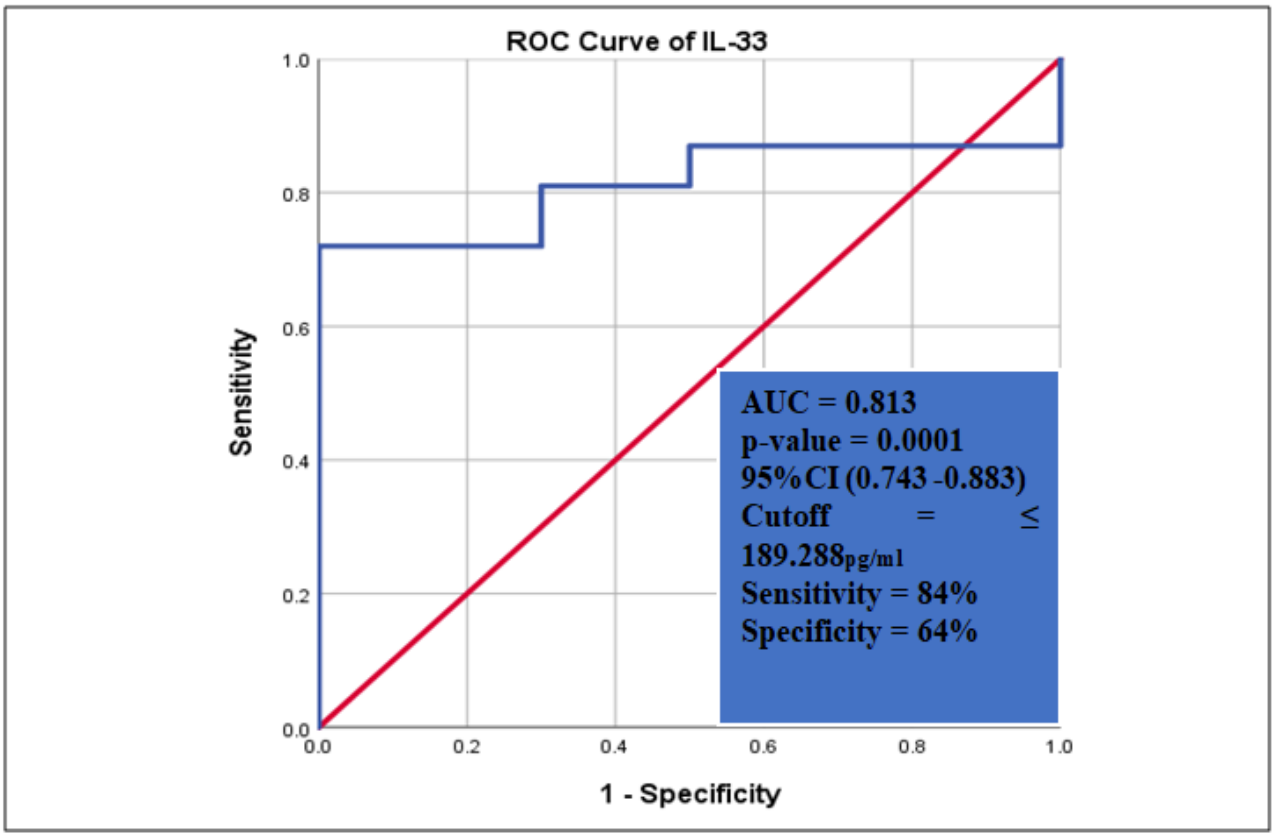

Figure 1-3: Receiver operating curve characteristics (ROC) curves of Interleukin 33 for diagnostic of RA in patients N=100 and control N=50

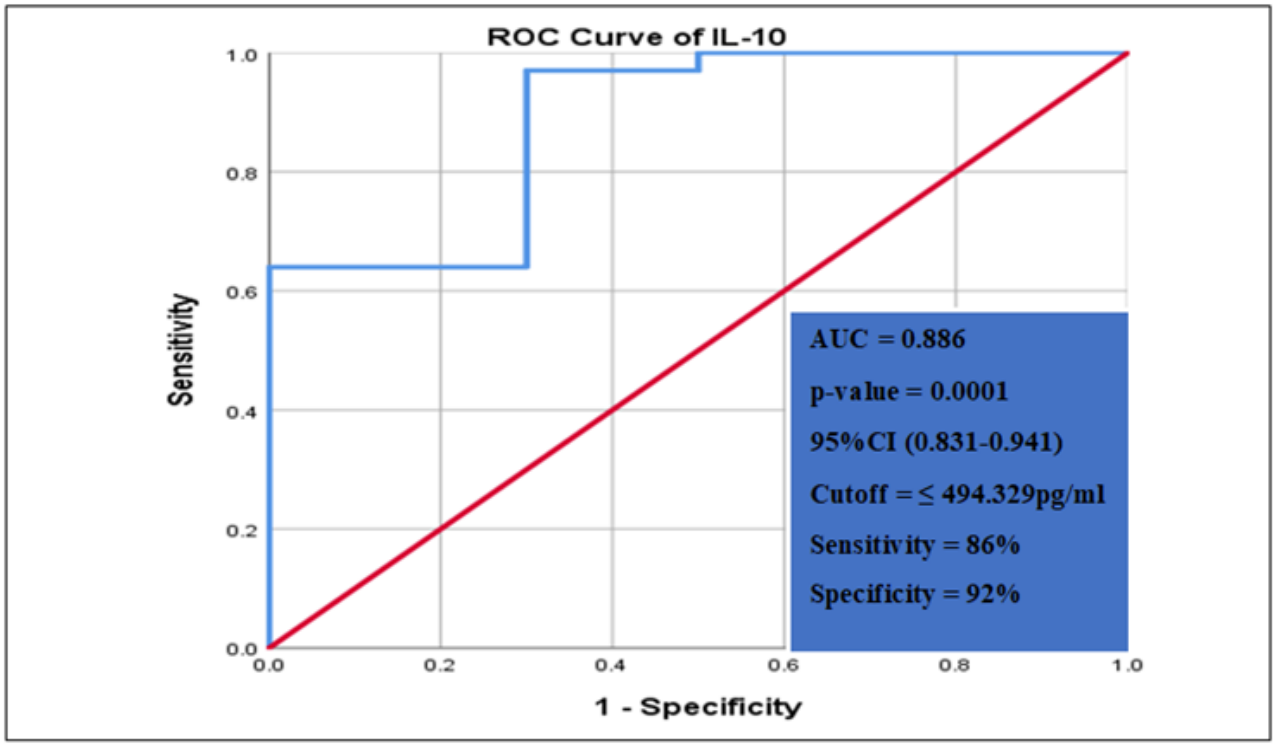

Figure 1-4: Receiver operating curve characteristics (ROC) curves of Interleukin 10 for diagnostic of RA in patients N=100 and control N=50

Correlations between Different Parameters: The correlations between immunological parameters levels are shown in table (1-6).

Table 1-6: Correlations between immunological parameters and biochemical parameters in patients with RA

Parameters		ACCP	RF	CRP	ESR	IL33	IL10
ACCP	r	1					
	P						
RF	r	0.812**	1				
	P	0.000					
CRP	r	0.783**	0.796**	1			
	P	0.000	0.000				
ESR	r	0.542**	0.406**	0.597**	1		
	P	0.000	0.000	0.000			
IL33	r	0.115	0.309**	0.340**	-0.139	1	
	P	0.160	0.000	0.000	0.090		
IL10	r	-0.655**	-0.775**	-0.720**	-0.260**	-0.665**	1
	P	0.000	0.000	0.000	0.001	0.000	

**Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

The results of the present study showed a strong positive association between RF and IL33. This outcome is in line with [13] research that reveal RA patients' serum and synovial fluid to have significantly elevated levels of IL-33, and that IL-33 levels positively correlate with both rheumatoid factor and the severity of the

disease. And found a significant correlation between IL33 and CRP that in the line with [14] study that show the correlation between IL-33 and CRP in patients with rheumatoid arthritis. This suggests that IL-33 may play a role in the inflammatory process in RA and could be a potential biomarker for disease activity.

Exogenous IL-10 treatment successfully reduces IL-33 synthesis because IL10 is an immunosuppressive agent. When IL10 levels drop, RA development is worse and IL-33 expression is upregulated. Consequently, despite the fact that IL-33 and IL-10 are both involved in the pathophysiology of RA, there is no clear relationship between their levels. [15]. The most effective anti-inflammatory cytokine, IL-10, is generated by nearly all innate and adaptive immune cells. Therefore, the capacity to generate IL-10 from a wide variety of cell types may be required to guarantee its prompt availability at various locations when required. Patients with RA have higher amounts of IL-10 in both serum and synovial fluid; hence, IL-10 appears to have a dual function in RA, inhibiting pro-inflammatory cytokines while also boosting the humoral autoimmune response. The inconsistent findings regarding the therapeutic efficacy of IL-10 in RA are indicative of these competing roles [16].

The results of the current investigation demonstrated a substantial negative association between the blood IL-10 level and the ACPA, ESR, RF, and CRP titers. These results conflict with research of [17] says that there was no significant correlation between IL-10 levels and autoantibodies such as ACPA and RF.

One possible explanation for this correlation between IL-10 and CRP titer, RF titer, ESR level and ACPA level is that IL-10 has been found to decrease the antigen-presenting capacity (APCA) of synovial fluid macrophages in rheumatoid arthritis [18]. The impact of IL-10 on the phenotype of synovial fluid macrophages, including the decrease in the expression of CD40, CD86, and HLA-DR and the increase in the expression of CD14, is another plausible reason for the decrease in APCA [19].

The anti-inflammatory properties of IL-10 in RA may be influenced by the reduction in APCA that IL-10 causes. Furthermore, IL-10 has been demonstrated to counteract the effects of IL-4 and granulocyte/macrophage colony-stimulating factor (GM-CSF) on natural killer (SF) macrophages. SF macrophages are known to express more CD40, CD80, and CD86 and to have an increased ability to stimulate T cells [20].

CONCLUSION

1. Treatment with DMARD decrease the inflammatory markers ESR, RF, CRP, ACPA levels.
2. The serum levels of IL33 were statistically higher in early diagnosed patients with Rheumatoid Arthritis than patients on treatment, this in turn higher than controls, and can be used to predict the disease severity.
3. When comparing patients receiving therapy for Rheumatoid Arthritis to those who were not, the serum level of IL-10 was significantly lower in the former group. Similarly, when comparing patients receiving treatment to controls, IL-10 levels were much lower.
4. 1L33 levels are thought to be useful biomarkers for assessing the course and severity of the disease as well as how well people with rheumatoid arthritis are responding to treatment.

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Conflict of Interest: No conflict of interest is present in the current study.

The Ethical Committee Approval

This study was given ethical permission by the University of Al-Qadisiyah's Faculty of Medicine ethical committee before to starting the research activity. Every patient who took part gave their informed consent, and the Rheumatology Unit granted authorization.

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