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ORIGINAL RESEARCH PAIN MANAGEMENT

Estimation of interleukin-6 level and atherogenic indices as predictors of severity of rheumatoid arthritis in Iraqi patients

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ABSTRACT

Background & Objective: Rheumatoid Arthritis (RA) is an inflammatory illness that causes joint degeneration and inflammation of the synovial membrane, leading to significant disability over time. Interleukin-6 (IL-6) is a widely distributed pro-inflammatory cytokine that has a variety of roles in several pathophysiologic systems, most notably in the RA development. The purpose of this study was to assess the blood levels of IL-6 and the severity and activity of RA in patients, and to assess the association of atherogenic indices with IL-6 as a predictor of severity in RA disease.

Methodology: This study was a case control observational study involving 300 participants diagnosed with RA by the rheumatologists in accordance with American College of Rheumatologists (ACR)/ European League Against Rheumatism (EULAR) 2010 criteria. Serum levels of IL-6, CRP, RF and ACPA were measured by using ELISA technique. While, lipid profile was determined with spectrophotometry. Receiver operating curve (ROC) was used to study the opportunity of using atherogenic indices and IL-6 as diagnostic tools for RA.

Results: The results indicated a higher IL-6 level in RA patients in comparison to the control group, e.g., 28.55 (18.76-41.07) pg/mLvs 10.19 (6.11-12.50) pg/ml. High atherogenic index of plasma (AIP) risk > 0.24 in RA patients parameters (GDF-15, IL-6), the lipid profile parameters and atherogenic indices (TC, TG, VLDL-C**,** LDL-C, CRI-I, CRI-II, AIP, and AC) were compared with moderate atherogenic risk (AIP < 0.24) in RA patients. While a significant decrease was recorded in the HDL-C and BMI levels, it had significantly high atherogenic risk (AIP > 0.24) compared with moderate atherogenic risk (AIP < 0.24) in RA patients. The ROC results analysis showed that the top 5 highly sensitive predictors for RA, e.g., CRI-I, AC, AIP, CRI-II followed by IL-6, have a relatively good sensitivity and specificities for predictors for RA.

Conclusion: Increase in interleukin-6 may indicate the activity and severity of the disease. This biomarker could be helpful for early disease detection. The results showed a higher IL-6 in RA patients as well as increased dyslipidemia and atherogenicity in RA patients. Elevation of serum IL-6 and atherogenic indices are the best predictors for RA patients with a higher risk of atherosclerosis than other biomarkers. There is an important correlation between atherogenic indices parameters and the immunological biomarkers IL-6 indicating a significant role of the inflammation in the incidence of atherogenic indices in RA.

Abbreviations: AUC- Area Under Curve; ACPA - Anti Cyclic Citrullinated Peptide Antibodies; CRP- C-Reactive Protein; ESR- Erythrocyte Sedimentation Rate; RF- Rheumatoid Factor; BMI- Body Mass Index; GDF-15 -Growth Differentiation Factor-15; DAS28-CRP- Disease Activity Score-28-C-Reactive Protein; TC- Total Cholesterol; TG-

Triglyceride; HDL-C -High Density Lipoprotein Cholesterol; LDL-C -Low Density Lipoprotein Cholesterol; VLDL-C-Very Low Density Lipoprotein Cholesterol; AC-Atherogenic Coefficient; AIP-Atherogenic Index of Plasma; CR-I, CR-II-Castelli's Risk Indexes.

Keywords: Rheumatoid Arthritis, Interleukin-6, Atherogenic Indices.

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic auto-immune disease that causes pain, swelling, and inflammation in the joints.[1] RA is characterized by joint stiffness, damage, and destruction of bone.[2] Females have a higher incidence (2:1–3:1). Old age, smoking, obesity, and genetic and epigenetic factors are other risk factors.[3] Common symptoms of RA include swelling, joint pain, and stiffness in the morning. In addition, nonspecific symptoms including fatigue, fever and malaise are common. The patients may have numb hands, dry eyes, subcutaneous rheumatoid nodules, and xerostomia and feet, as well as dyspnea.[4] The World Health Organization estimates that RA affects 0.5 to 1% of people and is a factor in functional impairment.[5] The estimated prevalence of RA in the Iraqi population is 1%.[6]

RA is characterized by an abnormally higher level of cytokines that promote inflammation, which gradually damage and enlarge joints.[7,8] Cytokines control a wide range of numerous inflammatory mechanisms that are involved in the pathogenesis of RA.[9] In patients with RA, elevated levels of cytokines, such as interleukin-6 (IL-6), have been demonstrated to be indicative of inflammation and to be predictive of treatment outcomes, fatigue, pain, and depression.[10] IL-6 is a proinflammatory cytokine that plays essential role in the pathogenesis and physiology of inflammatory and autoimmune diseases, such as rheumatoid arthritis.[11]

IL-6 is a main pro-inflammatory cytokine with pleiotropic functions.[12,13] It is a glycoprotein with a molecular weight of 26 kD and an inflammatory cytokine with a four-helix bundle structure.[14] IL-6 plays a key role in RA; it is involved in acute inflammation as the primary stimulator of the production of the majority of acute-phase proteins,[15] and in a variety of innate and adaptive immune responses.[16]

2. METHODOLOGY

We enrolled 150 RA patients, 121 females and 29 males, and 150 age-matched healthy control subjects, 31 males and 119 females, in the present case control study conducted from November 2022 to July 2023. All the patients were diagnosed with RA, who visited the rheumatology department in the Marjan Teaching Hospital in Babylon Province, Iraq. The age range of the patients was 20–79 y. Weight, height, gender, age, residency, family history were noted. All patients fulfilled the 2010 ACR/EULAR RA classification.[17] According to these diagnostic criteria, each patient should have a score > 6 depending upon the number and location of painful joints, favorable serologic findings (ACPA) and rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and duration of RA symptoms. These criteria were found to be more accurate in predicting the likelihood of RA and have a higher specificity. The duration of RA disease in patients included in this study was a maximum of 30 y and a minimum of six months. Information was noted from the rheumatologist questionnaires filled up by patients with RA, and DAS-28-CRP, the online (DAS28-CRP) calculator was utilized to compute the disease activity score. https://www.mdcalc.com/disease-activity-score-28-rheumatoid-arthritis-crp-das28-crp. We divided patients into low disease activity as indicated by a DAS28 of 2.6–3.2, moderate disease activity indicated by 3.2–5.1, and high disease activity indicated by >5.1.[18] The body mass index (BMI) was calculated.[19]

2.1. Inclusion Criteria

The inclusion criteria were patients aged 20−79 y, diagnosed with RA by a rheumatologist based on the 2010 ACR/EULAR criteria and had a score ≥ 6.

2.2. Exclusion Criteria

Patients with diabetes mellitus, hypertension, hyperthyroidism, or liver or renal disorders, and cardiovascular events were excluded. Patients with recent surgical procedures, open wounds, or sudden localized inflammation, patients suffering from immunodeficiency disorders, cancer, and recurring infections were also excluded. Furthermore, those with a BMI ≥ 30 and those on prescription drugs for lipid-lowering agents, beta-blockers, thyroxin, estrogen, vitamin E, and progestin were also excluded. Additionally, patients on biological therapy and smokers were not included.

2.3. Measurements

A sample of 5 mL of venous blood was taken from each participant; 3 mL of the gel sample and 2 mL of the EDTA sample were collected from patients and control group after overnight fasting for 12−14 h. The blood samples were divided into two parts: the first portion (2 mL) was collected in an ethylene diamine tetra acetic acid (EDTA) tube and used the same day to measure the erythrocyte sedimentation rate (ESR) by the Westergren method, while the second portion (3 mL) was collected in a gel tube and allowed to clot at room temperature before being centrifuged at 1500 xg for 10 min to collect serum. The sera were divided into three aliquots and placed in Eppendorf tubes to be stored in a deep freezer, serum samples were stored at a temperature of −20 ºC until the time of analysis.

Human CRP, Human ACPA-Ab, Human IL-6 kit by ELISA (BioTek™ EL_X800^{TM}, USA Absorbance Microplate Readers, ELISA washer BioTek™ EL_X50^{TM}, USA) were used for analysis. All kits were described by the manufacturer (Elabscience, Biotechnology Inc. USA), and were based on a sandwich technique and showed an inter-assay Coefficient of Variability (CV) of less than 10%. The steps were carried out precisely as directed by the manufacturer. Estimation of serum lipid profile (total cholesterol, triglyceride and HDL-C were measured by enzymatic reactions using commercial analytical kits from BIOLABO (02160 Miazy, made in France) were determined using spectrophotometric. The levels of LDL-C, and VLDL-C were calculated using the Friedewald's equations.[20] Atherogenic ratios were calculated from the lipid profile parameters following established formulas:

1. Atherogenic Coefficient (AC) = (TC – HDL-C)/HDL-C
2. Atherogenic Index of Plasma (AIP) = $\log_{10}$(TG/HDL-C)
3. Castelli's Risk Index-I (CRI-I) = TC/HDL-C
4. Castelli's Risk Index-II (CRI-II) = LDL-C/HDL-C

Based upon previous studies, the cut-off values of atherogenic indexes were determined to assess the cardiovascular risk. We further divided the patients of RA into a high AIP group and a moderate AIP group based on the cut-off values of atherogenic indexes were determined to assess the cardiovascular risk. [21] The high atherogenic risk group AIP > 0.24 compared with moderate atherogenic risk group AIP < 0.24 in RA patients.[21]

2.4. Statistical analysis

The statistical program SPSS (version 26, SPSS Inc. Chicago, Illinois, USA) was utilized to analyze the data. Based on the statistical distribution, the analysis's findings divided the variables into two groups: normally distributed variables and nonparametric variables identified by the results of the Kolmogorov-Smirnov test. The mean ± standard deviation (SD) was used to represent results that followed a normal distribution. To compare the patient and control groups, the pooled t test was employed. The nonparametric variables' values are displayed as medians and 25%–75% percentiles. The Mann-Whitney U test was used to compare the parameters between the control groups, the divided groups, and the patients itself. Using receiver operating characteristics (ROC) analysis, the measured biomarkers' capacity for diagnosis was investigated. Youdin's statistic J, cut-off values, sensitivities, specificities, and area-under-the-curve (AUC) were computed.

3. RESULTS

3.1. Comparison of IL-6

The results of serum IL-6 in HC and RA patients are presented in Figure 1. The results showed that there is a statistically significant difference (P < 0.001) in IL-6 concentration between RA patients 28.55 (18.76-41.07) pg/mL compared to the control group 10.19 (6.11-12.50) pg/mL.

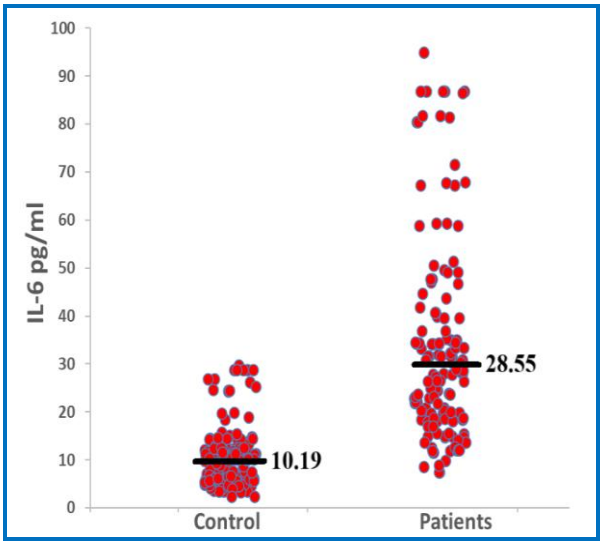

Figure 1: IL-6 concentration in healthy controls (HC) and RA patients.

3.2. Comparison between high and moderate atherogenic risk RA groups

The results of comparison between high and moderate atherogenic risk RA patient groups in the RA group are presented in Table 1.

Table 1: Comparison between moderate and high atherogenic risk RA patients

Parameters	AIP < 0.24*	AIP > 0.24**	F/χ^2	df	P-value
IL-6 (pg/ml)	25.68 (17.58-34.95)	34.21 (21.72-57.84)	MWUT	-	0.002
TC (mM)	4.90 ± 1.01	5.43 ± 0.98	10.607	1/148	0.001
TG (mM)	1.30 ± 0.26	1.97 ± 0.42	128.393	1/148	< 0.001
HDL-C (mM)	0.96 ± 0.14	0.84 ± 0.13	26.577	1/148	< 0.001
VLDL-C (mM)	0.60 ± 0.12	0.89 ± 0.19	128.393	1/148	< 0.001
LDL-C (mM)	3.35 ± 0.10	3.69 ± 1.03	4.203	1/148	0.042
CRI-I	5.21 ± 1.30	6.64 ± 1.70	32.269	1/148	< 0.001
CRI-II	3.58 ± 1.29	4.56 ± 1.65	15.677	1/148	< 0.001
AIP	0.145 (0.07-0.20)	0.35 (0.29-0.45)	MWUT	-	< 0.001
AC	4.21 ± 1.30	5.64 ± 1.70	0.293	1/148	<0.001
Age (y)	45.21 ± 9.97	46.12 ± 10.60	0.007	1/148	0.589
BMI (kg/m^2)	28.22 ± 3.64	28.17 ± 3.44	32.269	1/148	0.936
Sex (F/M)	58/10	63/19	1.708	1	0.191
ACPA (IU/ml)	161.98 (24.81-272.26)	181.82 (32.04-293.89)	MWUT	-	0.373
CRP (mg/dl)	10.44 (5.85-12.17)	9.28 (4.47-11.29)	MWUT	-	0.060
ESR (mm/h)	33.50 (20-49.5)	33.50 (20.00-45.00)	MWUT	-	0.706
RF (U/ml)	25.75 (9.97-34.12)	27.68 (10.90-35.99)	MWUT	-	0.632
RA duration (y)	6.00 (3-9)	6.00 (3-9)	MWUT	-	0.267
DAS-CRP	4.40 (3.41-5.36)	4.29 (3.43-5.31)	MWUT	-	0.751

Data presented as mean ± SD or median (range)

*AIP - atherogenic index of plasma; *Moderate AIP risk < 0.24; **High AIP risk > 0.24*

The study's findings demonstrated that RA patients had significantly high atherogenic risk AIP>0.24 in RA patients parameters (IL-6), the lipid profile parameters and atherogenic indices (TC, TG, VLDL-C**,** LDL-C, CRI-I, CRI-II, AIP, and AC) compared with moderate atherogenic risk AIP < 0.24 in RA patients. While a significant decrease was recorded in the (HDL-C and BMI) level in had significantly high atherogenic risk AIP > 0.24 compared with moderate atherogenic risk AIP < 0.24 in RA patients. While, there were non-significant differences between (Age, BMI, Sex, ESR, CRP, RF, ACPA, and DAS-CRP) in both the two RA patient groups.

3.3. ROC for diagnosis of severity of RA patients by atherogenic indices and IL-6

The analysis of ROC was performed to determine the diagnostic sensitivity and specificity of the atherogenic indices and IL-6 for the diagnosis of severity of RA persons (Figure 2). While, the coordinates of the ROC results and the cut-off of the concentration that produced the best sensitivities and specificities are presented in Table 2. The results show in Table 2. that the increase in CRI-I higher than the cut-off value (5.023), and CRI-II higher than the cut-off value (3.222) indicates that the subjects may have RA. The curve covers a high AUC with a

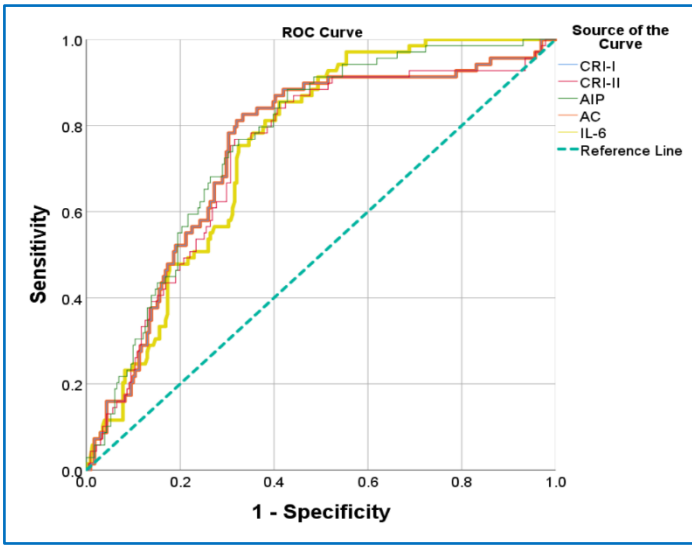

Figure 2: ROC curves of atherogenic indices and IL-6 for diagnosis of severity of RA.

Table 2: ROC- (AUC) analysis of atherogenic indices and IL-6 for diagnosis of severity of RA

Variable	Cut-off	Sensitivity %	Specificity %	Youdin's J Statistic	AUC (95% CI)	p
IL-6 (pg/ml)	21.133	68.0	68.0	0.360	0.75 (0.694-0.806)	< 0.001
CRI-I	5.023	71.0	70.1	0.411	0.746 (0.681-0.811)	
CRI-II	3.222	69.6	69.3	0.389	0.732 (0.665-0.799)	
AIP	0.168	71.0	71.0	0.420	0.767 (0.709-0.824)	
AC	4.023	71.0	70.1	0.411	0.746 (0.681-0.811)	

high Youdins J statistic. The increase in AIP higher than the cut-off value (0.168) and increase in AC higher than the cut-off value (4.023) indicates that the subjects may have RA.

4. DISCUSSION

The results of this study showed that there was a higher IL-6 concentration in RA patients compared to the control group. This result is in agreement to a study by Gaber et al. (2013).[22,23,24] Increased IL-6 is expressed at sites of inflammation and is thought to be a major factor in chronic inflammation.[22] Due to its pro-inflammatory properties, it is essential for the development and course of RA. According to some research done in Iraq, in RA patients' plasma IL-6 levels are significantly greater than those of healthy individuals', and they can occasionally be undetectable. [25,26] This has been confirmed by other studies as well.[26,27] indicating that a higher IL-6 level is a significant indicator of a disease's quicker progression.[27]

IL-6 is a pleiotropic pro-inflammatory cytokine and has a significant impact on RA and its associated conditions. It has a major role in acute inflammation by stimulating the synthesis of the majority of acute-phase proteins.[15] It has been linked to the pathophysiology of RA and atherosclerosis development in the general population.[9] It is produced by different cells, including immune cells, and causes inflammation. Elevated IL-6 levels are frequently seen in RA joints that are inflamed. There is indication that RA patients have elevated levels of proinflammatory cytokines including TNF-α, IL-1, and IL-6.[24]

Triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C), and the atherogenic index of plasma (AIP) are used to predict the risk of CVD in individuals with RA.[28,29] LDL-C and TG are two of those lipid profiles that may be used as biochemical indicators to control and evaluate the estimation of cardiovascular risk.[2,29] Adverse cardiac events have been connected to elevated (AIP).[30,31] In particular, the study found that patients with moderate atherogenic risk (AIP < 0.24) were less likely to have atherogenic risk than those with high atherogenic risk (AIP > 0.24) due to elevated LDL-C and TG values, as shown in Table 1. These relationships may have multiple underlying explanations. Chronic inflammation is a major factor in the onset and advancement of atherosclerosis and cardiovascular disease in RA patients. Endothelial dysfunction, changes in lipid metabolism, and an increase in the production of pro-inflammatory cytokines, such as IL-6, might result from the chronic systemic inflammation associated with RA. These variables raise the risk of cardiovascular events and aid in the development of atherosclerotic plaques. Elevated TG and LDL-C values, which are parts of the lipid profile, are known to be atherosclerosis risk factors. Dyslipidemia and chronic inflammation together can accelerate the atherogenic process in people with RA. There is growing evidence that inflammation might not only increase the endothelial cells directly, as is hypothesized, but also increase the cardiovascular risk due to lipid profile degradation. This is supported by the demonstration of a decrease in HDL-C levels and an a rise in triglycerides during an acute phase response.[24]

The ROC results analysis showed that the top 5 high sensitive predictors for RA are CRI-I, AC, AIP, CRI-II followed by IL-6, that produce the best sensitivities and specificities are presented in Table 2. ROC results and the cut-off of the concentration produce the best sensitivities and specificities for diagnosis of severity of RA. The results showed increased in IL-6 atherogenic indices (CRI-I, AIP, AC and CRI-II) can indicate severity of RA in RA patients. As a result, this study confirmed that atherogenic indices may play a part in managing and predicting CVD risk in individuals with RA. Heart diseases are the leading cause of death for RA patients.[32]

5. CONCLUSION

Atherogenic index of plasma could serve as a useful biomarker for the early identification of atherosclerosis in RA patients. The results showed a higher IL-6 in RA patients as well as increased dyslipidemia and atherogenicity in RA patients. Elevation of serum IL-6

and atherogenic indices are the best predictors for RA patients with a higher risk of atherosclerosis than other biomarkers. There is an important correlation between atherogenic indices and the immunological biomarkers IL-6 indicating a significant role of the inflammation in the incidence of atherogenic indices in RA.

6. Ethical considerations

All patients provided informed consent, the institutional review board (IRB) of the College of Science, University of Kufa, Iraq (Document No. 8215/2022) and the Babylon Health Directorate Training and Human Development Centre, babil, Iraq (Document No. 1502/2023), which was in accordance with the Helsinki Declaration and the "International Guideline for Human Research" criteria that were set forth.

7. Data Availability

The numerical data generated during this research is available with the authors.

8. Acknowledgments

We value each and every patient, particularly those who accepted the request to participate in the research. We also owe our gratitude to the staff of the rheumatology department of the Marjan Teaching Hospital in Babil City, Babylon Province, Iraq.

9. Conflicts of Interest

There are no conflicts of interest to be mentioned.

10. Authors' Contribution

All authors took equal part in concept, conduct the study, data collection, data analysis. manuscript writing, editing and correction, final approval.

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