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# Apoptosis Inhibitor of Macrophage/CD5L in Rheumatoid Arthritis Correlation with Disease Activity and Severity

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**Abstract**
**Background:** Rheumatoid Inflammation of the synovial joints causes damage to the joints and functional impairment in people with arthritis (RA), a chronic autoimmune illness. Apoptotic process dysregulation in immune cells, especially macrophages, may contribute to RA pathophysiology. An intriguing protein that has recently come to light as a possible contributor to the onset and development of RA is Apoptosis Inhibitor of Macrophage (AIM)/CD5L. Evidence from research points to a link between AIM/CD5L expression and RA disease activity. Serum and synovial tissues from people with active RA show higher levels of AIM/CD5L, suggesting that it may be a biomarker for disease activity. Methods: The 120 participants in this case control research were split into three groups according on their diagnoses: group A consisted of 60 patients with RA, group B of 30 patients with OA, and group C of 30 seemingly healthy individuals who were age and sex matched to the other two groups. People were scouted from Benha University Hospitals' rheumatology, physical medicine, and rehabilitation outpatient clinics and patient departments. The results showed a statistically significant difference ($P<0.001$) in the mean serum AIM levels in RA patients (1292.1 ng/ml), OA patients (691.7 ng/ml), and healthy controls (483.7 ng/ml). With a diagnostic capacity at its peak at 654.09ng/ml, serum AIM may distinguish between RA patients and healthy persons with remarkable specificity and sensitivity. In conclusion, serum AIM has the potential to become a novel RA biomarker.

**Keywords:** Synonyms for "RASS" include "RAS," "DAS28-ESR," "Apoptosis Inhibitor of Macrophage/CD5L," and "Modified Larsen's Score."

## 1. Introduction

Rheumatoid Progressive disability, untimely mortality, and financial difficulties are connected with arthritis, a chronic systemic autoimmune disease that disproportionately affects females. The illness mainly damages the lining of the synovial joints [1].

Disabilities, including loss of cartilage and bone, develop due to symmetrical inflammation of afflicted joints [2].

Although AIM/CD5L is a multi-functional protein, its ability to prevent cell death is its most conserved and unified feature. This is how it helps macrophages and other cells survive exposure to different kinds of apoptosis-inducing agents [3].

Whether it's an infection, cancer, or another immunological disorder, apoptosis inhibitor of macrophages (AIM) may modify the signals involved in the inflammatory response. New research indicates that AIM, similar to interleukin-10 (IL-10), has a role in the polarisation of alternatively activated (M2) macrophages [4].

By releasing IL-1β and TNF, macrophages facilitate the recruitment of monocytes in the RA synovium. Th17 cells are activated by IL-23 released by macrophages, while Th1 cells are activated by IL-12 and TNF secreted by macrophages, both of which play significant roles in the RA process [5].

The purpose of this research was to determine if there was a correlation between the blood levels of apoptosis inhibitor of macrophage (AIM) and clinically and radiologically assessed measures of disease activity and severity in RA patients.

## 2. Methods

This The 120 participants in the case control study were split into three groups according on their diagnoses: group A consisted of 60 patients with RA, group B of 30 patients with OA, and group C of 30 seemingly healthy individuals who were age and sex matched to the other two groups. Individuals were scouted from the inpatient and outpatient departments of Benha University Hospitals' Rheumatology, Rehabilitation, and Physical Medicine departments.

Inclusion criteria included being at least 18 years old, meeting the 1986 ACR criteria for osteoarthritis, and meeting the American College of Rheumatology/European League against Rheumatism (ACR/EULAR) Classification criteria for rheumatoid arthritis [6].

Individuals who did not meet the inclusion criteria were those who were under the age of 18, had a history of infection, fibromyalgia, cancer, diabetes mellitus, hypertension, heart, lung, gastrointestinal, renal, endocrine, or neuropsychiatric disease, or an infectious disorder such as septic, viral, or fungal arthritis.

The study was authorised by the local ethics committee at Benha College of Medicine, and all participants were required to provide

written informed consent before they were recruited.

Clinical evaluations were conducted on all patients, which included taking detailed medical histories and doing physical examinations. The assessment of disease activity was based on a 28-joint count. The disease severity may be assessed using the Rheumatoid Arthritis Severity Scale (RASS) [9] and the Modified Larsen's Score [10]. The Disease Activity Score (DAS28-ESR) [8] is one such measure.

Status of the patient's functional abilities as assessed by the Modified Health Assessment Questionnaire (MHAQ) [11]. Visual Analogue Scale for pain [12].

Studies conducted in a controlled environment: A complete blood count (CBC), rheumatoid factor (RF), antibodies to cyclic citrullinated peptides (anti-CCP), the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and measurement of serum AIM using the Enzyme Linked Immunosorbent Technique (ELISA) technique were all performed on five millilitres of venous blood drawn from each participant under meticulous aseptic conditions. After 30 minutes of letting the sample coagulate in serum separation tubes, it was centrifuged. The AIM measurement was performed using the separated serum. Following the manufacturer's instructions, the findings were expressed in ng/ml.

We took digital plain radiographs of the patient's hands and wrists as part of our radiological examination.

Data was carefully revised, coded, and tabulated using IBM SPSS Statistics for statistical analysis (Version 25.0). Mean, standard deviation (± SD), median, and range were used to evaluate numerical data, whilst frequency and percentage calculations were used for non-numerical data. An assortment of statistical tests were used, including One Way ANOVA for multiple parametric variables, the Kruskal-Wallis test for non-parametric variables among more than two groups, and the Mann Whitney Test (U test) for non-parametric variables between two groups. Quantitative links between variables were assessed using correlation analysis, while qualitative correlations were investigated by chi-square and Monte-Carlo testing. The ROC Curve determined the best cutoff values by analysing the specificity and sensitivity of diagnostic measurements. Categorical outcomes were predicted using logistic regression, which provided odds ratios (OR) that indicated the strength of the link. The accuracy of the OR was evaluated using a 95% confidence interval (CI), and p-values were considered significant if they were less than 0.05 across the CI.

## 3. Results

**This study was carried out on 120 subjects were divided into:**

**Group (A) involved sixty RA** patients with a disease duration ranging from one to twenty-two years and ages ranging from twenty-three to seventy-one. There were 57 female patients and 3 male patients.

The thirty OA patients who made up Group (B) had illness durations ranging from one to twenty years and ages ranging from thirty-seven to seventy. Of the patients, 26 were female and 4 were male.

Thirty individuals who seemed to be in good health made up Group (C). Their ages varied from thirty-one to sixty years. There were 28 girls and 2 males.

(B) and (C) were the control groups that participated in the research.

The distribution tables for the groups under study showed no statistically significant differences in age (P=0.712) or sex (P=0.430) (1).

**Table (1)** Socio-demographic characteristics of the groups under study compared

| | **RA n = 60** | | **OA n = 30** | | **Healthy Control n = 30** | | **Test** | **P** |
|---|---|---|---|---|---|---|---|---|
| | ***No.*** | ***%*** | ***No.*** | ***%*** | ***No.*** | ***%*** | | |
| **Sex** | | | | | | | | |
| Male | 3 | 5.0 | 4 | 13.3 | 2 | 6.7 | $X^2$= | MC |
| Female | 57 | 95.0 | 26 | 86.7 | 28 | 93.3 | 2.039 | 0.430 |
| **Age (years)** | | | | | | | | |
| Mean ± SD. | 47.47 ± 10.62 | | 49.0 ± 9.43 | | 47.17 ± 6.89 | | F= 0.341 | 0.712 |
| Median | 47.50 | | 46.0 | | 45.50 | | | |
| Min. – Max. | 23.0 – 71.0 | | 37.0 – 70.0 | | 31.0 – 60.0 | | | |

Definitions: F: One Way ANOVA test, SD: Standard deviation, Min.: Minimum, and Max.: Maximum. Chi-Square (X2) and Monte-Carlo (MC) are two types of statistical techniques Analysis of RA, OA, and control groups.

AKA Rheumatoid Arthritis and Osteo-Arthritis, respectively.

The results of the comparison between the RA and control groups in terms of serum AIM levels demonstrated that the former had significantly higher levels (P<0.001) than the latter. The average levels found in the RA group were 1292.1 ± 59.58, the OA group 691.7 ± 6.78, and the healthy control group 483.7 ± 23.22. Data set (2). The first figure is seen here.

**Comparison of AIM/CD5L among the groups that were investigated (Table 2):**

| | **RA n = 60** | **OA n = 30** | **Healthy Control n = 30** | **Test** | **P1** | **Pairwise** |
|---|---|---|---|---|---|---|
| **AIM /CD5L (ng/ml)** | | | | | | |
| Mean ± SE. | 1292.1 ± 59.58 | 691.7 ± 6.78 | 483.7 ± 23.22 | H= 94.844 | <0.001 * | P2<0.001* |
| Median | 1193.0 | 684.7 | 519.6 | | | P3<0.001* |
| Min. – Max. | 564.1 – 2251.7 | 610.1 – 755.7 | 111.6 – 745.9 | | | P4=0.001* |

The acronyms SE, Min., Max., and H stand for the Kruskal Wallis test.
P1: Examining the status of control, RA, and OA patients Comparing RA with OA is P2.
P3: We compare the RA group to the control group. P4: Control and OA comparison.
Purpose: Molecule that Prevents Macrophage Death, AKA Rheumatoid Arthritis and Osteo-Arthritis, respectively.

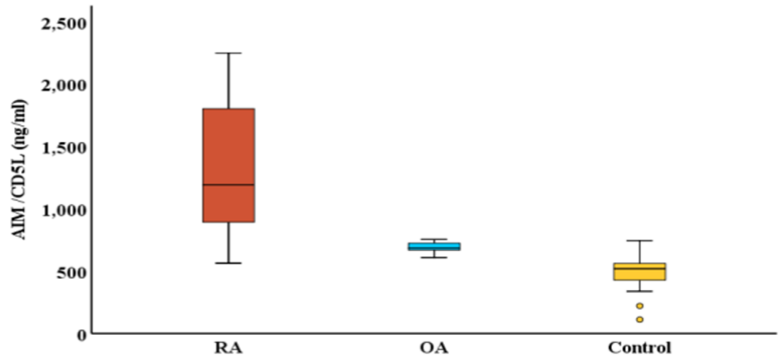


**Fig. (1)** shows a boxplot chart comparing AIM/CD5L levels among the groups that were analysed.

You can see the results of the patients' tests in the table (3).
In the RA group, the following are the CBC characteristics, acute phase reactants, and serological markers: Table 3.

| | **RA n = 60** |
|---|---|
| **Haemoglobin (g/dl)** | |
| Mean ± SD. | 11.11 ± 1.91 |
| Median (Min. – Max.) | 11.55 (4.0 – 13.50) |
| **RBCS ($10^6$/$mm^3$)** | |
| Mean ± SD. | 4.42 ± 0.48 |
| Median (Min. – Max.) | 4.50 (2.60 – 5.50) |
| **WBCS ($10^3$/$mm^3$)** | |
| Mean ± SD. | 6.40 ± 1.93 |
| Median (Min. – Max.) | 5.95 (3.10 – 11.40) |
| **Platelets ($10^3$/$mm^3$)** | |
| Mean ± SD. | 285.5 ± 70.14 |
| Median (Min. – Max.) | 268.0 (140.0 – 443.0) |
| **ESR (mm/h)** | |
| Mean ± SE. | 42.57 ± 3.66 |
| Median (Min. – Max.) | 35.0 (7.0 – 120.0) |
| **CRP (mg/I)** | |
| Negative | 12 (20%) |
| Positive | 48 (80%) |
| Mean ± SE. | 22.84 ± 4.58 |
| Median (Min. – Max.) | 12.0 (2.0 – 192.0) |
| **RF (IU/ml)** | |
| Negative | 2(3.3%) |

| | |
|---|---|
| Positive | 58(96.7%) |
| **ANTICCP** | |
| Negative | 33(55.0%) |
| Positive | 27(45.0%) |

RA stands for rheumatoid arthritis, SD for standard deviation, min and max for minimum and maximum, and RBCS and WBCS, respectively, for red and white blood cell counts. RF stands for rheumatoid factor, CRP stands for C-reactive protein, and ESR is for erythrocyte sedimentation rate. RA stands for rheumatoid arthritis, while ANTICCP stands for anti-cyclic citrullinated peptides. The serum AIM/CD5L ROC curve for RA patient discrimination compared well to the OA + healthy control group, with a high accuracy area under the curve (AUC) of 0.987 and a 95% confidence interval (CI) of 0.966 to 1.000. It also demonstrated good specificity and sensitivity at the best cutoff value of 755.71. (Image 2)

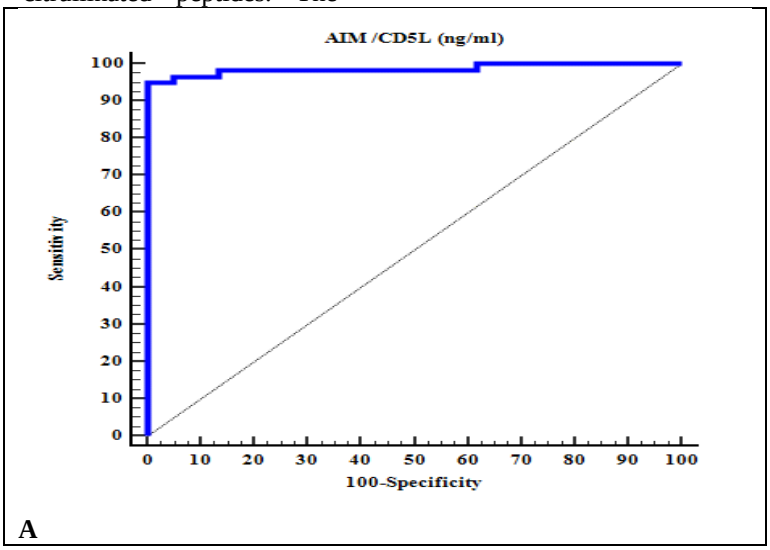


**Fig.(2)** Receiver Operating Characteristic (ROC) Curve for AIM/CD5L for (A) discriminating between OA + control group and RA patients.

## 4. Discussion

Rheumatoid Arthritis is a systemic autoimmune disease that causes inflammation over time and may lead to disability, complications, and even death at a young age. Inflammation and hyperplasia of the synovium, production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA), abnormalities of the cartilage and bones, and systemic manifestations including disorders of the heart, lungs, skin, and skeleton are all hallmarks of rheumatoid arthritis (RA) [13].

In order to manage rheumatoid arthritis, it is important to identify the illness early on, prescribe DMARD medication, and monitor disease activity regularly until remission is achieved. Identifying active illness allows for better diagnosis and the modification of treatment plans. It is crucial to discover a sensitive and objective biomarker to evaluate the disease activity in RA patients during the active phase, as ESR and CRP are not sensitive enough [14].

One component of innate immunity is the soluble molecular glycoprotein known as Apoptosis Inhibitor of Macrophage (AIM) (CD5L). In addition to its regulatory function in the immune system, this protein affects macrophage activity in a broad variety of contexts, including the pathophysiology of several infectious and inflammatory disorders. Leukocyte recruitment, inflammatory responses, and lipid homeostasis may all be controlled with the help of AIM-CD5L [15].

The inflammatory nature of many human pathologic diseases, including as atherosclerosis, acute kidney damage, lung involvement, and cancer, may be attributed to AIM. In addition, AIM may enhance the release of IL-10 in peripheral blood monocytes while inhibiting the synthesis of TNF and IL-1β. In RA's pathogenic process, TNF, IL-1β, and IL-10 are involved. Thus, AIM may have a role in regulating both host immunological homeostasis and autoimmunity[16].

Our results are in line with those of Wu et al., who discovered that AIM content in RA serum was much greater than in OA serum or the serum of healthy individuals [17]. Balakrishnan et al. found that AIM/CD5L is increased in OA and RA patients and can attach to numerous kinds of immune cells, suggesting it has a regulatory function in the

immune system [18]. Our results are also in line with these findings.

Additionally, Wu et al. demonstrated that CD5L mRNA expression was much greater in PBMC from RA patients compared to OA patients when they studied the expression of CD5L in synovial tissue and peripheral blood mononuclear cells (PBMC) of OA and RA patients, respectively [19].

Our findings suggest that elevated AIM levels may signal the onset of illness. This is in line with the findings published by Wu et al., who also found substantial results [17]. Agreeing with Wu et al., who demonstrated that AIM levels of RA patients with moderate-high activity were considerably greater than those with low activity as determined by DAS28 score, we find that there is a correlation between AIM concentration and disease activity score (DAS28). Additionally, he demonstrated a strong correlation between RF and anti-CCP antibody production in RA patients and blood AIM level [17].

In order to further understand the relationship between AIM and disease severity, Bicho et al. induced CIA in CD5L KO mice and found that these animals had a much greater incidence of RA, more severe illness, and a significantly poorer recovery rate compared to WT mice. In addition to the obvious inflammatory symptoms in KO mice, wild-type animals with RA had elevated CD5L levels relative to the control group, corroboration of the results shown in human samples [20]. Instead of being an inflammatory promoter, Bicho et al. found that CD5L is an essential anti-inflammatory molecule [20].

According to our results, AIM was quite good at differentiating between RA and controls. So, AIM could be a new and sensitive biomarker for severe RA disease activity. The studies cited earlier show that higher CD5L levels are associated with the worsening of RA illness and that CD5L may be a therapeutic target for this disease.

It is important to note, nevertheless, that our research did have certain limitations. To begin with, the remission group did not have a large enough sample size to draw any firm conclusions on AIM expression levels. The majority of patients in our research had a history of RA, and since we only measured disease activity at admission, it may not be reflective of the full extent of chronic inflammation that the patients experienced. Another factor that impacts the effect of our results is that the majority of our patients were already taking their medications.

Evaluation of patients' state at onset based on multicenter studies with long-term follow-up still need further research.

**5. Conclusion**

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