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Clinicopathological Study of Rheumatoid Arthritis with Association with C-reactive Protein Levels; As a Potential Biomarker of Cartilage Damage

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ABSTRACT

Objective: To explore the association between rheumatoid arthritis (RA) and C-reactive protein (CRP) levels as a potential biomarker of cartilage damage.

Methodology: This case control study was done at Department of pathology Ziauddin University Clifton Campus, Karachi from June 2018 to May 2019. Patients diagnosed with rheumatoid arthritis (RA) according to established criteria, aged 18 years or older and both male and female participants were included. Clinical data was collected through medical record review and direct patient interviews. Blood samples were collected from participants for CRP measurement using standard laboratory assays. Serum CRP levels were quantified using high-sensitivity CRP assays in a certified clinical laboratory. CRP levels was defined based on established cutoff values, typically exceeding 3 mg/L. Statistical Analysis: Statistical analysis will be performed using SPSS version 26.

Results: Mean age of patients was 43.38±.56 years, while control group subjects had a slightly lower mean age of 42.33±6.93 years (p = 0.412). Gender distribution showed a predominant female representation, with 76 female patients (88.4%) and 75 female controls (87.2%) (p = 0.816). There was a strong positive correlation was observed between DAS28 and CRP levels, with a Pearson correlation coefficient of r= 0.745 and (p < 0.01), indicating a significant association between disease activity and CRP concentration. Conversely, the correlation between DAS28 and ESR was weaker and not statistically significant (r = 0.123, p = 0.258).

Conclusion: Study revealed that the significant elevation of serum CRP levels in RA patients compared to healthy individuals. The positive correlation between serum CRP levels and the extent of joint damage observed radiographically, suggesting CRP's potential as a biomarker for estimating disease severity and cartilage deterioration in RA.

Key words: Ketamine, Propofol, Ketofol, Homodynamic effect.

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Introduction

Rheumatoid arthritis (RA) stands out as a prevalent chronic autoimmune rheumatic condition, impacting around 1.5% of the global population. It leads to bone and joint deterioration, often resulting in severe osteoporosis and disability, significantly compromising patients' quality of life.[1] The existing treatments for RA are limited in number and often come with significant adverse effects.[2] RA impacts about 1% of the populace, with a female-to-male ratio of roughly 2.5–1 and its occurrence rises with age, typically striking women aged 40–60 years.[3,4] Inadequate treatment may result in the disease progressing to gradual joint deterioration and distortion, leading to chronic pain, prolonged disability, and premature

mortality.[5] In contrast to common perception, these illnesses are becoming more common in low- and middle-income countries (LMIC), where the burden of both non-communicable and infectious diseases is doubled.[6] The healthcare facilities in low-income countries (LMICs) are insufficiently funded, and this results in limited treatment, which predominantly impact the working age population and have a detrimental effect on household earnings and inequalities.[6] Multiple factors contribute to the complex pathophysiology and diverse symptoms of RA, including genetic and environmental influences.[7,8] The considerable variability in RA presentations makes precise diagnosis challenging and time-consuming. Early and accurate diagnosis is crucial for effective treatment and symptom management in RA.[7]

Individuals receive a diagnosis typically characterized by a history of morning stiffness lasting over thirty minutes and pain in the small joints of their hands.[9] Examination of the musculoskeletal system reveals symmetrical synovitis in multiple joints. To confirm the diagnosis, tests for rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP), erythrocyte sedimentation rate (ESR), and C-reactive protein are conducted.[9] In rheumatoid arthritis (RA), CRP is frequently measured as a measure of systemic inflammation. But it's also an immune modulator that contributes significantly to RA-related inflammatory pathways and atherogenic consequences. In addition, CRP has been positively linked to an increased risk of depressive disorders, diabetes, cardiovascular disease, metabolic syndrome, and pulmonary illnesses.[10] Comorbidities linked to chronic inflammatory conditions are frequent in RA. Systemic inflammation, CRP, and comorbidities in RA have a complicated relationship, making it difficult to predict how shifting CRP levels could impact the development or risk of these comorbidities.[10]

Recently, it has been noted that biomarkers play a valuable role in clinical practice for diagnosing RA, monitoring treatment progress, and forecasting prognosis.[11] However, additional research is recommended by recent studies,[11-13] To explore new biomarkers that can identify patients likely to respond well to treatment before therapy initiation, facilitating precision medicine in this field. This study, however, aims to assess the association between rheumatoid arthritis and C-reactive protein (CRP) as a potential biomarker of cartilage damage.

Methodology

This case control study was done at the department of pathology Ziauddin University Clifton Campus, Karachi. Study was conducted during a period of one year, from June 2018 to May 2019. Patients diagnosed with rheumatoid arthritis (RA) according to established criteria, aged 18 years or older and both male and female participants were included. All the patients diagnosed with gouty arthritis, osteoarthritis or any other form of autoimmune inflammatory arthritis, suffering from any other chronic systemic inflammatory disease, history of recent trauma or surgical interventions affecting joints, obese and smoker patients, patients currently undergoing treatment with disease-modifying anti-rheumatoid arthritis drugs and those who did not willing to take part in the study were excluded. Prior to any study-related procedures, the study protocol was thoroughly explained to each participant, including potential risks and benefits. Written informed consent was obtained from all participants before their inclusion in the study, in accordance with ethical guidelines and institutional regulations.

All enrolled patients underwent a comprehensive clinical examination by trained healthcare professionals. Disease activity was assessed using the Disease Activity Score with 28-joint count (DAS28). DAS28 score > 5.1: High disease activity, DAS28 score between 3.2 and 5.1: Moderate disease activity, DAS28 score between 2.6 and 3.2: Low disease activity and DAS28 score < 2.6: Remission. Clinical data was collected through medical record review and direct patient interviews. Blood samples were collected from participants for CRP measurement using standard laboratory assays. Serum CRP levels were quantified using high-sensitivity CRP assays in a certified clinical laboratory. CRP levels was defined based on established cutoff values, typically exceeding 3 mg/L. The study protocol was approved by the institutional ethics committee or review board, ensuring adherence to ethical principles and guidelines for research involving human subjects. Confidentiality of participant information was strictly maintained throughout the study, with data anonymization and secure storage practices implemented. Statistical Analysis: Statistical analysis will be performed using SPSS version 26.

Results

Mean age of patients was 43.38$\pm$.56 years, while control group subjects had a slightly lower mean age of

42.33±6.93 years (p = 0.412). Regarding rheumatoid factor (RF) levels, patients exhibited a substantially higher mean RF concentration of 66.22±20.43 IU/mL) compared to the control group's mean of 6.99±2.14 IU/mL), with a statistically significant difference (p < 0.001). Similarly, CRP levels was also significantly higher in patients, with a mean of 27.09±25.58 mg/dL, contrasting with controls' mean CRP level of 1.54±0.47 mg/dL (p<0.001). On gender distribution showed a predominant female representation, with 76 female patients (88.4%) and 75 female controls (87.2%), indicating a similar proportion of females in both groups (p = 0.816). Table I

Table I: Demographic and clinical variable values of the patients. (n=172)

Variables		Groups		p-value
		Patients	Control	
Age	**Mean**	43.38 years	42.33 years	
	SD	7.56 years	6.93 years	0.412
RF	**Mean**	66.22 IU/mL	6.99 IU/mL	
	SD	20.43 IU/mL	2.14 IU/mL	0.001
CRP	**Mean**	27.09 mg/dL	1.54 mg/dL	
	SD	25.58 mg/dL	0.47 mg/dL	0.001
Gender	**Females**	76	75	
		88.4%	87.2%	
	Males	10	11	0.816
		11.6%	12.8%	

In a study involving 86 individuals, C-reactive protein (CRP) levels were assessed based on disease severity categories. Patients with low disease activity had a mean CRP level of 12.64±12.49 mg/dL, while individuals with high disease activity showed a significantly higher mean CRP level of 42.22±27.09 mg/dL (p=0.0001), indicating a significant association between CRP levels and the severity of rheumatoid arthritis. Table II

Table II: CRP level according to severity of disease. (n=86)

		CRP		
DAS cat	**N**	**Mean**	**Std. Deviation**	**p-value**
Low disease	44	12.64	12.49	
High disease	42	42.22	27.09	0.0001

A strong positive correlation was observed between DAS28 and CRP levels, with a Pearson correlation coefficient of 0.745 (p < 0.01), indicating a significant association between disease activity and CRP concentration. Conversely, the correlation between DAS28 and ESR was weaker and not statistically significant (Pearson correlation coefficient = 0.123, p = 0.258). These findings suggest that there is a consistent relationship with disease severity as measured by DAS28. Table III

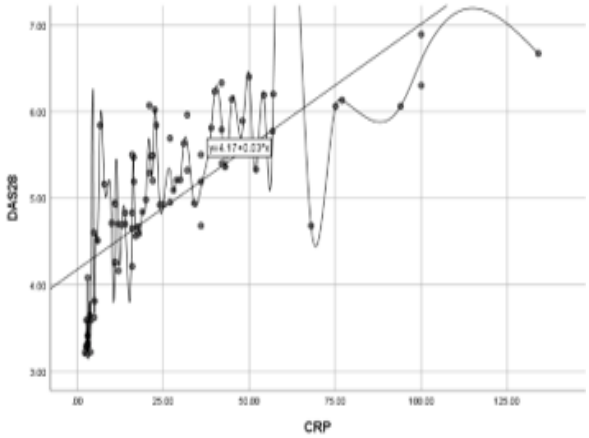

Table III: Pearson Correlation of DAS 28 with CRP and ESR level. (n=172)

		DAS28	CRP	ESR
DAS28	Pearson Correlation	1	.745**	.123
	Sig. (2-tailed)		.000	.258
	N	86	86	86

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

Discussion

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the joints, leading to pain, stiffness, and eventually joint damage. One of the key challenges in managing RA is early detection of joint damage to prevent irreversible disability. In recent years, C-reactive protein (CRP) has emerged as a potential biomarker for assessing severity of disease in RA patients.[14] This study has been done to evaluate the association between rheumatoid arthritis (RA) and C-reactive protein (CRP) levels as a potential biomarker, contains 86 patients of RA and in equal number of healthy controls, with an overall mean age of patients was 43.38±.56 years and controls' was 42.33±6.93 years, with female predominance in both groups, comprising 88.4% of patients and 87.2% of controls. In the comparison of this study Butt NI et al,[15] found that among the 133 patients with active disease, females were in majority 85.0% and remaining15.0% were male, with an overall average age of 40.0 ± 12.8 years and average duration of the disease was 8.3 ± 6.2 years. Furthermore, they found mean DAS-28 score was 5.5 ± 0.9, which was almost similar to this study.

In aligns to this study Khaliq T et al[16] conducted study on rheumatoid arthritis and they found that out of the 63 patients studied, males were 28.6% and females were in majority 71.4% with an average age across the entire study

sample was 43.09 ± 13.03 years, and the mean duration of the disease was reported as 5.05 ± 5.58 years. The prevalence and impact of rheumatoid arthritis (RA) are notably higher in females compared to males and this may because of several factors contribute to this observation, including hormonal influences, genetic predispositions, differences in immune response, and environmental/ lifestyle factors. Estrogen, for example, may play a role in modulating the immune system, potentially increasing the susceptibility of females to autoimmune diseases like RA.

In this study there was a strong positive correlation was observed between DAS28 and CRP levels, with a Pearson correlation coefficient of 0.745 ($p < 0.01$), indicating a significant association between disease activity and CRP concentration. Conversely, the correlation between DAS28 and ESR was weaker and not statistically significant (Pearson correlation coefficient = 0.123, $p = 0.258$). These findings suggested that there was a consistent relationship of CRP with disease severity as measured by DAS28. In the comparison of this study Bagdi R et al[17] observed that the CRP plays vital roles in the management of rheumatoid arthritis (RA), with elevated CRP levels serving as valuable prognostic indicators. Comparisons between erythrocyte sedimentation rate (ESR) and CRP indicate that both tests exhibit similarity and utility in assessing disease activity.

Consistently Dessie G et al[18] reported that the average CRP concentration was significantly higher in the patients 10.54 ± 17.26 compared the controls 3.54 ± 7.60. According to a previous study by Ammitzbøll CG et al,[19] noted that the CRP genotype and haplotype exhibited only slight associations with serum CRP levels and displayed no correlation with the DAS28 score and they suggested that the DAS28, considered a central measure of inflammatory activity in rheumatoid arthritis (RA), can be utilized for clinical decision-making without the need for adjustments based on CRP gene variants.[9] In the line of this series Pope JE et al[10] found a significance of C-reactive protein (CRP) as both a marker and modulator of systemic inflammation in rheumatoid arthritis (RA). Additionally, CRP appears to directly contribute to bone destruction and radiographic progression in RA. Moreover, CRP has been implicated in the development of common comorbidities associated with RA, suggesting its multifaceted involvement in the pathophysiology of the disease.[10] In aligns to the series Shrivastava AK Et al[20] demonstrated that the patients with rheumatoid arthritis (RA) exhibit elevated levels of inflammatory markers. Specifically, RA patients showed significantly higher levels of serum high-sensitivity C-reactive protein (hs-CRP) ($p<0.001$), and there was a positive correlation between hs-CRP levels and DASS28 in these patients ($p<0.001$). Despite the compelling evidence supporting the use of CRP in RA management, it's essential to acknowledge that the current study possess several limitations. Therefore, to validate the findings, larger-scale, multi-center studies with diverse patient cohorts are recommended, to ensure robust and reliable conclusions regarding the clinical utility of CRP in RA diagnosis and management.

Conclusion

Study revealed a robust positive correlation between Disease Activity Score with 28-joint count (DAS28) and CRP levels, indicative of a significant association between disease activity and CRP concentration. Thes findings suggest that CRP concentration consistently reflects disease severity as measured by DAS28, emphasizing its potential utility as a biomarker in the clinical assessment and management of RA.

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