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Original article

Serum Clusterin Levels in Patients with Rheumatoid Arthritis and its Implication in the Disease Activity and Severity

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Abstract:

Background: Rheumatoid arthritis (RA) is a multifactorial autoimmune disease, Clusterin (CLU) is an 80 kDa glycoprotein that exhibits chaperone-like. Aim: To measure the serum level of CLU in RA cases and to correlate its level with the different disease parameters to determine its potential role and implication in the disease activity and severity. **Methods:** This is a case-control study, investigation enrolled 60 participants from Benha University Hospital's Rheumatology Department. All participants underwent comprehensive clinical evaluation The history covered personal data, present illness, past medical history, and family history. Physical examination. Disease activity and VAS scores. Functional disability. All participants underwent standardized laboratory testing including inflammatory markers, complete blood count, autoantibody testing, and serum CLU measurement. Radiographic evaluation of hands and wrists. **Results:** There was a non-significant difference between RA cases and controls regarding age (p=0.11). RA cases had median disease duration of 10.5 years, Laboratory assessments revealed elevated inflammatory markers and moderate activity Radiological evaluation showed 40% had moderate joint damage, functional assessment indicated 63.3% maintained normal daily activities .CLU levels were higher in RA cases than control, CLU showed negative correlations with disease duration (r=-0.757) and radiographic damage (r=-0.549), but positive associations with disease activity (DAS28 r=0.364) and swollen joint (r=0.46). **Conclusion** CLU shows promising potential as a biomarker for differentiating RA from controls, with sensitivity 63.3%, a specificity of 66.7% and a total accuracy 65%. Negative correlations of clusterin level with X ray score, positive correlations of clusterin level were observed with DAS28

Keywords: rheumatoid arthritis, clusterin, biomarker, disease activity.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disorder that primarily manifests through persistent inflammation of the synovial joints. However, its clinical presentation is not limited to joint structures alone. The disease may also involve various extra-articular systems, including the cardiovascular, pulmonary, renal, and integumentary systems. Although significant advances have been made in understanding the pathophysiology of RA, its exact etiology remains uncertain. One of the prevailing hypotheses suggests that aberrant citrullination of self-proteins may initiate the synthesis of anti-citrullinated protein antibodies (ACPAs), which contribute to the development of autoimmune reactions and subsequent tissue damage [(1)]. Clinically, RA often follows a relapsing-remitting course, marked by intermittent flare-ups and periods of remission. In the absence of adequate therapeutic control, the disease can progress to irreversible joint destruction, resulting in functional limitations and significant psychological distress. Additionally, systemic complications associated with RA can increase the risk of comorbid conditions and contribute to reduced overall life expectancy [(2)].

Clusterin (CLU) is a glycoprotein with an approximate molecular weight of 80 kilodaltons, composed of disulfide-linked heterodimeric subunits. It is extensively expressed in a wide range of tissues and is particularly concentrated at fluid-tissue interfaces, such as secretory surfaces and biological barriers [(3)]. Dysregulation of CLU expression has been implicated in a variety of pathological conditions, including malignancies [(4)], Crohn's disease [(5)], osteoarthritis (OA) [(6)], and RA [(7)].

From a functional perspective, CLU acts similarly to small heat shock proteins, serving as a molecular chaperone that provides cytoprotection under conditions of cellular stress. It also inhibits apoptotic signaling pathways, thereby supporting cell survival. Furthermore, CLU interacts with several matrix metalloproteinases (MMPs), particularly MMP-2, MMP-3, MMP-7, and MMP-9. Through this interaction, it may suppress excessive proteolytic activity and thus regulate extracellular matrix remodeling, a key factor in both tissue maintenance and pathological degradation [(8)].

Among its various biological roles, CLU has garnered particular interest for its involvement in the regulation of osteoclastogenesis. Experimental studies suggest that CLU inhibits the differentiation and activity of osteoclasts by interfering with intracellular signaling pathways mediated by macrophage colony-stimulating factors (M-CSF), especially those involving extracellular signal-regulated kinases (ERKs). This regulatory effect implies a potential role for CLU in preserving bone structure and preventing pathological bone resorption, particularly in inflammatory diseases characterized by skeletal degradation [(9)].

The broad spectrum of CLU's physiological functions, including protein stabilization, inhibition of protease activity, and control of bone metabolism, suggests that it may serve as a valuable therapeutic target. This is especially relevant in disorders associated with chronic inflammation, accelerated tissue breakdown, or dysregulated cellular survival mechanisms. CLU's multifunctional profile highlights its importance in maintaining cellular homeostasis and tissue integrity, positioning it as a candidate of interest for therapeutic exploration [(10)].

In view of these diverse biological functions, this investigation was designed to quantify the serum level of CLU in cases diagnosed with RA and to examine the relationship between CLU level and various clinical and biochemical disease markers, with the objective of assessing its potential involvement in disease activity and severity.

Patients and Methods

This case-control study investigation included a total of 60 participants, consisting of 30 cases diagnosed with RA and 30 healthy individuals serving as a control group. The control subjects were matched to the patient group based on age and sex to minimize potential confounding factors. All participants were recruited from both the outpatient and inpatient clinics affiliated with the Rheumatology, Rehabilitation, and Physical Medicine Department at Benha University Hospital from 2023 to 2024. Ethical committee (20-8-2023).

A comprehensive clinical evaluation was conducted for each subject, which comprised a detailed medical history and a full physical examination. Individuals younger than 16 years of age or those previously diagnosed with other autoimmune or rheumatic diseases were excluded to ensure the specificity of the sample. The history-taking process included demographic data, current illness characteristics—such as joint symptoms and any extra-articular manifestations—past medical events, and relevant family history. The physical examination focused on general systemic health and included a thorough assessment of the musculoskeletal system. This involved the evaluation of all major joints through inspection, palpation, and assessment of range of motion.

Cases were diagnosed with RA employing the standardized criteria introduced in 2010 by the collaborative efforts of the American College of Rheumatology and the European League Against Rheumatism. [(11)].

In this investigation, disease activity among cases diagnosed with RA was evaluated employing the modified Disease Activity Score based on the assessment of 28 joints (DAS-28). This validated composite index incorporates both clinical and laboratory parameters, including the number of tender joints (TEN 28), the number of swollen joints (SW 28), erythrocyte sedimentation rate (ESR), and the patient's self-perceived general health (GH), which is assessed employing a Visual Analogue Scale (VAS) [(12)]. The DAS-28 score was computed employing the following formula: **DAS-28=0.56 × tender joint count + 0.28 × swollen joint count + 0.70 × Ln (ESR) + 0.14 × GH score**.

Once calculated, the DAS-28 scores were interpreted according to established thresholds to classify the level of disease activity. A score of less than 2.6 was indicative of remission. Scores ranging from 2.6 to below 3.2 represented low disease activity, while values between 3.2 and 5.1 were considered to reflect moderate disease activity. Scores exceeding 5.1 were interpreted as indicative of high disease activity. This stratification provides a standardized approach for evaluating and monitoring disease progression and treatment response in RA cases.

The global health component of the DAS-28 was measured employing a 10-centimeter VAS. Participants were asked to place a mark along the scale that best represented their current perception of general health or pain intensity, with the left endpoint labeled as “no pain” and the right endpoint labeled as “worst imaginable pain.” The distance from the origin of the line to the patient’s mark was measured in centimeters to yield a numerical pain score. These values were then categorized into four levels of pain intensity: 0.0 to 2.4 cm was classified as Grade 1 (minimal pain), 2.5 to 4.4 cm as Grade 2 (mild pain), 4.5 to 6.4 cm as Grade 3 (moderate pain), and 6.5 to 10.0 cm as Grade 4 (severe pain) [(13)].

Functional status was assessed through the application of the Health Assessment Questionnaire (HAQ) [(14)], a widely recognized and validated instrument for evaluating disability in individuals with rheumatoid arthritis. This self-administered questionnaire is designed to capture the patient’s perceived level of

difficulty in performing routine daily activities essential for independent living. The HAQ encompasses eight functional domains, which include dressing and grooming, arising from a seated or lying position, eating and drinking, ambulation or walking, personal hygiene tasks, reaching for objects, gripping or grasping items, and participation in activities outside the home environment.

Each item within these domains is rated by the participant based on the degree of difficulty experienced during task performance. Responses are scored on a four-point Likert scale: a score of 0 indicates no difficulty; 1 reflects some difficulty; 2 signifies considerable or much difficulty; and 3 denotes inability to perform the activity altogether. After all responses are recorded, the final HAQ score is calculated by averaging the scores across all completed items. The resulting composite score ranges from 0 to 3, with higher values indicating greater level of functional impairment and reduced ability to carry out basic or complex daily functions independently.

All individuals enrolled in the investigation were subjected to a series of standardized laboratory investigations to evaluate systemic inflammation and immune response, as well as general hematologic status. The laboratory tests included measurement of inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both of which are commonly elevated in inflammatory and autoimmune conditions. A complete blood count (CBC) was performed to assess overall hematologic health, including red and white blood cell indices.

Autoantibody testing was also conducted to provide immunological profiling. This included analysis for rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, and anti-citrullinated protein antibodies (anti-ACPA), which are commonly used in the diagnostic evaluation and classification of RA. Additionally, serum concentrations of clusterin (CLU) were measured employing the enzyme-linked immunosorbent assay (ELISA), a sensitive and specific technique widely used for quantifying protein level in biological fluids.

Radiographic imaging was performed to assess the extent of joint involvement and structural damage. Standard plain radiographs, taken in both posteroanterior and lateral views, were obtained for the hands and wrists of all participants. The severity of radiographic damage was evaluated employing the Larsen scoring system, a validated method for grading joint erosion and destruction. Each joint assessed was assigned a score ranging from 0 (normal) to 5 (severe damage), depending on the degree of joint space narrowing and erosion observed.

The Larsen scoring method was systematically applied to several specific joint groups, including the interphalangeal (IP) joints, metacarpophalangeal (MCP) and wrist joints of both hands, in addition to the 2nd through 5th metatarsophalangeal (MTP) joints of the feet. A cumulative score was calculated by summing the individual joint scores, resulting in a total possible score ranging from 0 to 100. Greater total scores are indicative of more extensive joint destruction and reflect greater disease severity and progression over time.

Data and Statistical Analysis

To evaluate the data effectively, statistical analyses were carried out employing SPSS version 26 (SPSS Inc., Chicago, IL, USA). Normality of continuous variables was first assessed employing the Shapiro-Wilk test, guiding the choice of descriptive and inferential methods. Normally distributed data were reported as mean ± standard deviation, while non-normally distributed data were summarized as median and interquartile range. Categorical variables were described employing frequencies and percentages. Group comparisons were conducted employing the Chi-square test for categorical data, the student's *t*-test for

continuous parametric variables, and the Mann-Whitney U test for their non-parametric counterparts. Associations between ordinal or non-normally distributed variables were explored employing Spearman's rank correlation. Receiver operating characteristic (ROC) curve analysis was applied to assess the discriminatory performance of continuous variables, with optimal cut-off values determined based on sensitivity and specificity. Diagnostic accuracy, including predictive values and overall classification performance, was further evaluated through cross-tabulation. Statistical significance was defined as a p-value less than 0.05 [(16)].

Results

Clinical and socio-demographic features of the participants:

The present investigation involved 30 individuals diagnosed with RA and 30 healthy controls, matched for demographic characteristics. The two groups were comparable in terms of age (p=0.11) and sex distribution (p=0.739) as presented in (**Table 1).**

Articular involvement was the predominant clinical feature among the studied RA cases. Arthritis emerged as the most prevalent manifestation, observed in 36.7% of cases. Extra-articular observations were comparatively less frequent; with subcutaneous nodules and pleurisy each reported in 10% of the cases. Furthermore, the median duration of morning stiffness was 37.5 minutes, ranging from 10 to 90 minutes (**Table 2).**

Laboratory observations among studied RA cases

The inflammatory profile of the RA group reflected active systemic inflammation. The mean ESR was markedly elevated at 60.33 ± 32.17 mm/hr., with a median value of 54 mm/hr. (range: 20–140). Similarly, CRP levels were significantly raised, with a mean of 15.95 ± 17.75 mg/L and a median of 12 mg/L (range: 4.0–96.0). Hemoglobin level was decreased, indicating anemia of chronic disease, with a mean value of 11.30 ± 1.33 g/dL and a median of 11.45 g/dL. RF was positive in most cases (83.3%, n=25), while 16.7% (n=5) were RF-negative.

The mean DAS28was 4.59 ± 0.58, suggesting moderate disease activity. Tender joint counts showed variability, with a median of 2 (range: 0–6); notably, 43.3% of cases had two tender joints, while 33.3% had four. Swollen joint counts were generally lower, with a median of 0 (range: 0–4), and most cases (63.3%) presented without any swollen joints **(Table 3).**

Radiological assessment of studied cases

33.3% of studied cases had moderate damage, 26.7% had mild damage, 30 % had severe damage and 10% had very sever damage by X rays. **(Figure 1)**

Among the studied cases, 63.3% of studied cases had score 0 HAQ, 16.7% score 1, 13.3% score 2 and 6.7% score 3 **(Figure 2)**

Comparison of Clusterin level between cases and control groups

Median CLU level was significantly higher among RA cases than control group. **(Table 4)**

Statistical analysis revealed significant negative correlations between serum CLU level and both disease duration and radiographic score (r=–0.757, –0.549; p=0.001, 0.002, respectively), indicating that diminished CLU levels were associated with longer disease duration and greater joint damage. Conversely, significant positive correlations were observed between CLU levels and DAS28 scores as well as the number of swollen joints (r=0.364, 0.460; p=0.048, 0.01, respectively), suggesting a relationship between elevated CLU levels and increased disease activity. **(Table 5).**

A statistically significant difference in mean sCLU level was observed in cases presenting with arthritis (p=0.03), indicating elevated level in this subgroup. In contrast, no significant differences in sCLU levels were exhibited in cases with

extra-articular manifestations, including those with subcutaneous nodules (p=0.557) or pleurisy (p=0.604).

The AUC for CLU level showed its potential to distinguish RA cases from controls. Employing a cut-off value of ≥5.8 ng/mL, the test achieved 63.3% sensitivity, 66.7% specificity, and 65% overall accuracy. **Figure 3**

Table 1: Demographic characteristics of the studied groups

	Cases group N=30	Control group N=30	Test of significance
Age / years			t=1.62
Mean±SD	46.77±11.21	42.07±11.25	p=0.110
Sex N (%)			
Male	5(16.7)	6(20.0)	x^2=0.111
Female	25(83.3)	24(80.0)	P=0.739

t: Student t test, x2= Chi-Square test, N=Number, p>0.05 insignificant, p<0.05 significant.

Table 2: Clinical features of RA cases

Variable			No. (%)
Clinical manifestations	**Articular and Extra-articular**	**Arthritis**	**11(36.7)**
		SC nodules	**3(10.0)**
		Pleurisy	**3(10.0)**
	Morning stiffness duration Median (min-max)	37.5(10-90)	

Table (3): DAS-28 score, tender & swollen joints count of the studied RA cases.

	N=30	%
DAS28	4.59± 0.58	**DAS28**
Tender joint		
0	3	10.0
1	1	3.3
2	13	43.3
3	2	6.7
4	10	33.3
6	1	3.3
Median (min-max)	2(0-6)	
Swollen joint		
0	19	63.3
1	3	10.0
2	6	20.0
4	2	6.7
DAS Median (min-max)	0(0-4)	

Table (4) Comparison of Clusterin level between cases and control groups

Clusterin level / ng/ml	Cases group N= 30	Control group N= 30	Test of significance	Odds ratio (95%CI)
Median (range)	8.54(0.682-28.87)	3.92(1.06-19.92)	Z=1.50, p=0.133	1.08(1.01-1.16)

Z: Mann Whitney U test, N= Number, p>0.05= insignificant, p<0.05= significant.

Table (5): Correlation between Clusterin level and other parameters in the studied cases

	Clusterin	
	r	P
Age (years)	-0.280	0.134
Disease duration (years)	**-0.757**	**0.001***
ESR	0.219	0.246
CRP	-0.347	0.06
DAS28	**0.364**	**0.048***
HAQ	-0.189	0.316
Morning stiffness duration(min)	0.06	0.771
radiological Larsen score	**-0.549**	**0.002***
Swollen joints(n.)	**0.460**	**0.01***
Tender joints(n.)	0.339	0.067
Platelet count	0.256	0.171
HB	-0.151	0.427
RBCS	0.017	0.927
WBCS	-0.180	0.350

r: Spearman correlation coefficient, *statistically significant, ESR=Erythrocyte sedimentation rate, CRP= C-reactive protein, DAS28= disease activity score, HAQ= Health Assessment Questionnaire, HB= Hemoglobin, RBCs= Red blood cells, WBCS= White blood cells, p>0.05 insignificant, p<0.05 significant.

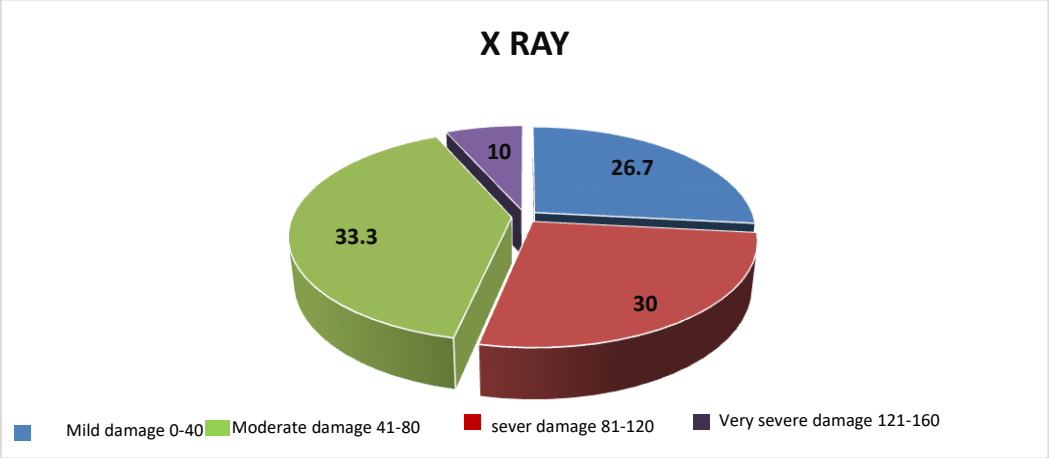

Figure (1) Radiological assessment of the studied RA cases by modified Larsen score

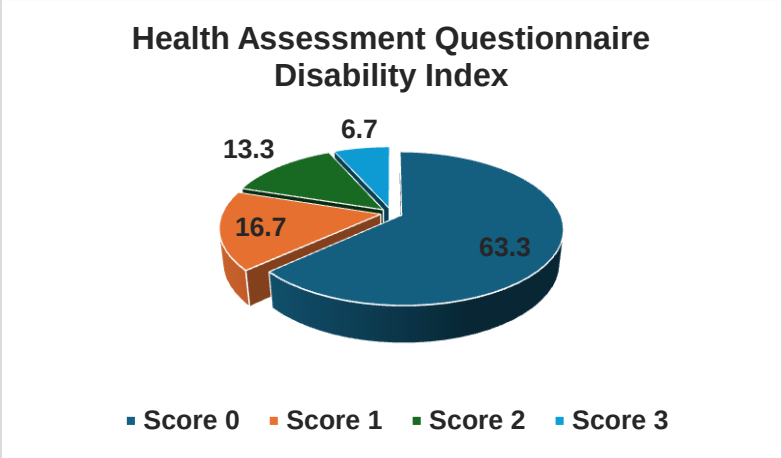

Figure (2): Health Assessment Questionnaire Disability Index amongst studied cases.

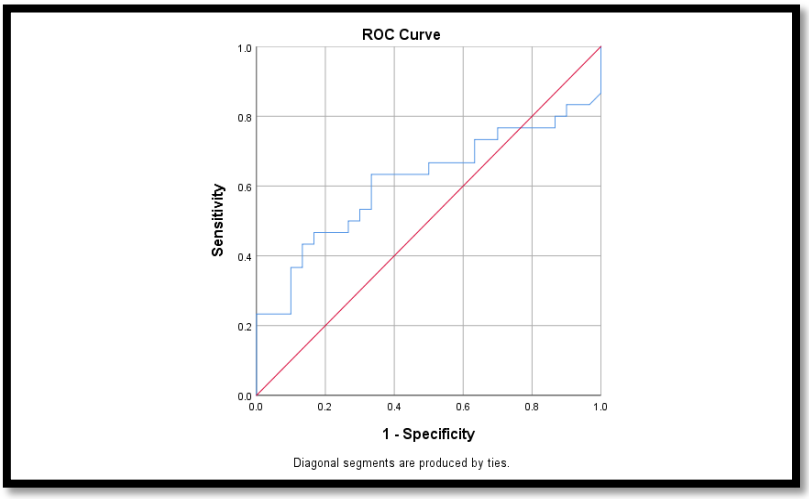

Figure (3): The ROC curve for clusterin level in differentiating RA cases from the healthy control group**.**

Discussion

RA is a persistent autoimmune disorder marked by immune-mediated inflammation of the synovial lining, leading to pain, joint swelling, tissue destruction, and reduced mobility and overall well-being. Advances in research have enhanced insight into its multifaceted pathogenesis and paved the way for innovative treatment approaches [(2).]

Despite a wide range of treatment options, a proportion of cases fail to attain remission or maintain low disease activity. The search for a dependable predictive marker remains ongoing. Although numerous biomarkers have been investigated for their potential to reflect disease activity and predict treatment response, their clinical application still requires validation in larger, well-defined populations [(17)].

CLU, a secreted glycoprotein, is involved in several pathological conditions such as malignancies, Crohn's disease, OA, and RA. It exhibits chaperone-like activity, offers cytoprotection, prevents cell death, and suppresses MMP activity [(18)].

In RA, CLU is synthesized via synovial lining cells, although at diminished levels as opposed to OA. Decreased CLU levels have been linked to elevated synthesis of pro-inflammatory cytokines, particularly IL-6 and -8, both of which are key contributors to the chronic inflammatory environment seen in RA. Conversely, CLU overexpression appears to suppress TNF-driven activation of the NF-κB pathway, indicating its potential anti-inflammatory and regulatory role in RA pathogenesis. However, research has primarily focused on intracellular CLU, with limited attention given to circulating sCLU and its potential clinical implications [(19)].

In the present investigation, age and sex were comparable between the RA and control groups, which reinforces the internal validity of the results by reducing the potential impact of demographic conexhibiteders.

Although sCLU levels were elevated in RA cases compared to healthy controls, the levels were comparable between the two groups (p=0.133). Previous research has reported increased sCLU level in treatment-naïve individuals with early RA as opposed to healthy subjects, with a subsequent decline following the initiation of conventional therapy. Moreover, baseline sCLU levels appear to influence treatment outcomes, with higher levels linked to better chances of achieving remission, low disease activity, or a major clinical response, while diminished levels may be associated with worse therapeutic responses [(20)].

In the current analysis, sCLU levels showed significant negative correlations with disease duration and radiographic scores (r=–0.757, –0.549; p=0.001, 0.002, respectively), suggesting that elevated sCLU levels may be associated with earlier stages of RA and milder joint damage. In contrast, no significant correlation was observed between sCLU level and HAQ scores (r=–0.189; p=0.316), indicating that only a subset of cases with high disability scores exhibited elevated sCLU levels.

Remarkably, observations from Falgarone et al [(21)] diverged, reporting that RA cases with higher sCLU levels exhibited more severe clinical manifestations and elevated inflammatory markers. These contrasting results further underscore the complex role of sCLU in RA pathogenesis and highlight the need for continued investigation into its clinical significance.

In alignment with our observations, sCLU levels showed statistically significant positive correlations with RA disease activity, as estimated via DAS28 (r=0.364, p=0.048), and with the number of swollen joints (r=0.460, p=0.01). This observation challenges previous suggestions that diminished sCLU level are associated with higher disease activity and inflammation in RA. In contrast, no significant correlation was exhibited between sCLU levels and morning stiffness (r=0.06, p=0.771).

Our results are also consistent with those of Kropáčková et al [(7)], who reported a significant positive association between sCLU level and DAS28 scores. However, in our investigation, sCLU levels did not significantly correlate with traditional inflammatory markers, including ESR (r=0.219, p=0.246) and CRP (r=-0.347, p=0.06).

Several factors may explain the discrepancy between our observations and previous reports based on joint-specific measurements. CLU is widely expressed across multiple tissues and cell types, and its synthesis is known to increase in a variety of pathological conditions such as aging, cardiovascular disease, diabetes, and neurodegeneration. Consequently, systemic characteristics of RA, beyond localized joint inflammation, may influence circulating sCLU level. [(22)].

Supporting our observations, Johnson et al [(23)] reported elevated sCLU levels in RA cases, which were positively associated with markers of disease activity. Their investigation proposed that sCLU could serve as a useful biomarker for tracking

disease progression and evaluating treatment response in RA.

Ding et al [24], examined the therapeutic potential of CLU in RA management and highlighted evidence indicating that alterations in sCLU expression can impact disease progression. Their review supports the notion that sCLU may serve as a promising target for future therapeutic approaches in RA.

Supporting this perspective, Ungsudechachai et al [25] investigated the involvement of sCLU in joint inflammation and tissue damage associated with RA. Their observations revealed a correlation between sCLU levels and both inflammatory markers and joint structural damage, reinforcing its role in RA pathogenesis, particularly in joint-related pathology.

In the present investigation, significantly higher mean sCLU levels were observed in cases presenting with arthritis (p=0.03), while no significant differences were noted in cases with extra-articular features such as subcutaneous nodules (p=0.557) and pleurisy (p=0.604). These observations suggest that sCLU may be more closely associated with joint-specific inflammation rather than systemic manifestations of RA.

In contrast, Kropáčková et al [7] reported that diminished baseline sCLU levels were predictive of more favorable clinical outcomes, including achieving remission and low disease activity based on CDAI, SDAI, and DAS28 scores at various follow-up intervals. Their ROC curve analysis indicated that reduced sCLU level at baseline were significantly associated with better disease control at 3, 6, and 12 months. However, at the 12-month point, this association did not remain statistically significant, suggesting that the predictive value of sCLU may fluctuate over time.

These differing results may be influenced by variations in investigation methodology, patient characteristics, disease stages, or treatment regimens. Such inconsistencies highlight the complexity of sCLU's involvement in RA and underscore the need for further comprehensive studies to clarify its clinical relevance and potential as a biomarker.

Prochnow et al ([26], reported that CLU exists in multiple isoforms, each with distinct functions and subcellular localizations. The predominant form is the glycosylated secretory variant, which forms a heterodimer with a molecular weight ranging between 75 and 80 kDa and is secreted into the extracellular space. Other isoforms, though less prevalent, are in the cytoplasm or nucleus. The secretory form is typically associated with protective functions against cellular stress, whereas nuclear CLU has been linked to pro-apoptotic activity. These functional and locational differences among isoforms may account for the variability observed in circulating CLU levels in cases with RA.

These observations indicate that sCLU might play a dual role in RA, reflecting both the severity of the disease and the inflammatory processes involved.

Similarly, Ungsudechachai et al [27], exhibited cases with erosive hand OA exhibited diminished concentrations of sCLU as opposed to those with non-erosive forms of the disease. This variation supports the notion that sCLU may offer a protective role in preventing bone erosion, a theory that is also applicable in RA, where CLU may contribute to the maintenance of cartilage and joint structure.

In our current investigation, sCLU levels showed no statistically significant association with variables such as sex (p=0.636), RF status (p=0.278), or age (p=0.134). These results suggest that sCLU expression is not influenced by these demographic or serological factors, implying that sCLU could serve as a reliable biomarker in RA without being affected by sex or RF positivity.

Our observations agree with observations reported by Kropáčková et al [7], who also identified no significant relationships between baseline sCLU level and clinical

variables such as sex, age, body mass index, CRP, ESR, medication doses (prednisone or MTX), or the presence of RF or anti-CCP antibodies. This consistency further supports the idea that CLU may be involved in RA pathogenesis through mechanisms independent of these common clinical and laboratory indicators.

In the present work, sCLU levels were able to discriminate between RA cases and healthy controls. The most effective cut-off value, determined through ROC curve analysis, was ≥5.8 ng/mL, which corresponded to a sensitivity of 63.3%, specificity of 66.7%, and a total diagnostic accuracy of 65%. All RA cases included in the investigation were undergoing treatment, suggesting that CLU levels may be modulated over time due to long-term therapeutic interventions. For instance, it has been demonstrated that treatment with DMARDs and corticosteroids is associated with a notable decrease in synovial macrophage infiltration [(28)]. This change in the inflammatory environment of synovium may contribute to a reduction in sCLU levels after three months of treatment, bringing levels closer to those exhibited in healthy individuals, a trend also observed in our data.

Furthermore, CLU has potential utility as a biomarker for predicting disease activity and therapeutic response in treatment-naïve RA cases. According to Kropáčková et al [(7)], CLU demonstrated superior performance as opposed to CRP, a conventional inflammatory marker, in forecasting both disease activity and treatment outcomes, underscoring its potential value in clinical practice.

Conclusion

CLU shows promising potential as a biomarker for differentiating RA from controls, with a sensitivity 63.3%, a specificity of 66.7% and a total accuracy 65%. Positive correlations with disease activity (DAS28) and swollen joints highlight its potential link to inflammation. However, no significant relationship was exhibited between CLU and sex or rheumatoid factor, indicating its role in RA may be independent of these factors. Further research is needed to better understand its biological mechanisms and clinical utility.

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