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Role of Cathepsin G in Rheumatoid Arthritis Diagnosis and Disease Activity Evaluation

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ABSTRACT

Background: *"Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 1% of the global population and results in chronic synovitis and joint destruction." It is believed that elevated serum level of cathepsin G (CTSG), a serine protease, contribute to RA pathogenesis and exacerbate disease activity. However, the data about the potential role of CTSG in the diagnosis of RA and disease activity evaluation are limited. The objective of this research is to determine whether CTSG could serve as a potential biomarker for the diagnosis and evaluation of RA activity.* ***Methods:*** *One hundred and thirty-two patients with inflammatory arthritis from the Rheumatology Department at Al-Sader Medical City in Al-Najaf City participated in this cross-sectional study from July 2023 to September 2023. The study included 121 females and 11 males, ranging in age from 18 to 70 years. The level of CTSG and anti-citrullinated peptide antibodies (ACPA) in the serum was assessed using ELISA. Other routine tests were evaluated, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and rheumatoid factor (RF).* ***Results:*** *The mean of CTSG was significantly lower in RA patients (110.53 pg/ml ± 49.959) than in those with other types of inflammatory arthritis (132.65 pg/ml ± 30.199). According to "DAS-28 ESR" and "DAS-28 CRP", the study found no significant difference in CTSG levels across the four disease activity groups (P = 0.585, P = 0.823, respectively). Additionally, CTSG had a significant negative correlation with diabetes mellitus and treatment intake in newly diagnosed RA (P = 0.009, P = 0.041, respectively). This study is the first to evaluate CTSG as an RA diagnostic tool, showing a sensitivity of 70.1% and a specificity of 60.0% at a cut-off value of ≤133.33 pg/ml.* ***Conclusions:*** *The study results suggest that CTSG has potential as a diagnostic biomarker for RA when used alongside other clinical and laboratory criteria. However, it should not be solely relied upon for evaluating RA activity.*

Key words: Rheumatoid Arthritis , Cathepsin G , DAS-28 ESR, DAS-28 CRP, Disease activity.

Article Information

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INTRUDUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that causes inflammation and affects the synovial joints, leading to joint destruction and deformity [(1)]. The cause of RA is unknown[(2)]. This condition can affect people of all ages, but it is more common in women between the third and fifth decades of life [(3)].

Early diagnosis and treatment are critical for a better prognosis, as well as preventing irreversible joint damage and disability. In fact, up to 90% of patients can avoid or significantly delay disease progression with early intervention. Late diagnosis of RA and lack of treatment can cause severe damage to multiple tissues and organs, leading to high disability, reduced quality of life, and mortality [(4).]

The RA occurrence rate is consistently around 0.5–1.0% across the world [3]. In Iraq, a study conducted between 2014 and 2019 reported increased RA incidence from 1.1 in 2014 to 1.7 in 2019, with a cumulative risk of 10.0 [5]. Rheumatoid arthritis is a complicated condition that exhibits several clinical symptoms and varying therapeutic responses. However, as researchers have gained a better understanding of the underlying pathogenesis of the disorder, there has been a growing interest in identifying biomarkers that could help diagnose and monitor its progression at various stages [6]. "Biomarkers play a crucial role in guiding the clinical and therapeutic management of all phases of RA because they can help predict disease development in individuals at risk, improve diagnosis by closing the serological gap, provide prognostic information for treatment choices, assess treatment responses and outcomes, and monitor disease activity and progression" [7].

When comparing RA diagnostic criteria, the significant role of biomarkers can be seen [6]. Rheumatoid factor is the only biomarker for the "American College of Rheumatology (ACR) 1987 criteria " [8]. Four serological tests (ACPA, RF, ESR, and CRP) are used in the "American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR) 2010 criteria " for the diagnosis of RA [4,8].

There are certain limitations to the biomarkers that are frequently used to diagnose RA. For example, RF is found in 80% of patients with RA, but it can also be found in healthy individuals and those with other diseases [9]. The ACPA test is more accurate, but both ACPA and RF still fail to detect 20-25% of RA-negative patients. Moreover, ESR is not specific and can be affected by various factors [10]. Furthermore, CRP levels can be normal in 40% of RA patients and elevated in others diseases [11]. Despite some progress in including ACPA in the updated criteria, there remains a clear need for new biomarkers in the diagnosis of RA [12].

Cathepsin G (CTSG) is a serine protease that is produced in the bone marrow and stored in azurophilic neutrophil granules. It's can also be found in other myeloid cells. When activated, CTSG is released into the extracellular space and plays a role in degrading chemokines and extracellular matrix proteins, as well as regulating pro-inflammatory cytokines. It has been linked to chronic inflammatory diseases and was found to be highly active in the synovial fluid of rheumatoid arthritis patients [13,14]. Cathepsin G is thought to be involved in inflammation and immune reactions by facilitating immune cell movement [14], making it a potential biomarker or therapeutic target for autoimmune diseases [15].

The research aimed to determine the potential of CTSG as a biomarker for diagnosis rheumatoid arthritis and distinguishing it from other types of inflammatory arthritis, as well as investigate the role of CTSG in assessing RA activity.

Samples Collection and Methods

A cross-sectional study was conducted on 132 patients with inflammatory arthritis. In this study, all participants were pioneers in the Rheumatology Department at Al-Sader Medical City in Al-Najaf City from July 2023 to September 2023.The study involved 107 patients had RA and 25 patients who had other types of inflammatory arthritis such as systemic lupus erythematosus (15 patients), Sjögren's syndrome (3 patients), Behçet's disease (2 patients), polymyalgia rheumatica (2 patients), psoriatic arthritis (1 patient), palindromic rheumatism (1 patient), and monoarticular arthritis (1 patient). The study included 121 females and 11males participants, ranging in age from 18 to 70 years. Based on the inclusion criteria, patients with other inflammatory arthritis and those diagnosed with RA by a physician using the "2010 ACR/EULAR" diagnostic criteria for RA were included. However, the study excluded patients who were under 18 or over 70 years old, as well as those

with any other autoimmune diseases, central nervous system diseases, acute local inflammation, wounds, recent surgeries, cancer, chronic infections, or immunodeficiency diseases.

The participants were randomly selected and divided into two groups. The first group consisted of patients with RA classified into various disease activity levels, "remission, mild, moderate, or severe, based on their disease activity score (DAS-28 ESR and DAS-28 CRP)". The second group included patients with other types of inflammatory arthritis. The patients completed a questionnaire providing information on their name, age, gender, BMI, contraceptive pill use, the family history of RA, as well as any history of chronic diseases like diabetes mellitus, hypertension, and other relevant details.

During the patient examination, a specialist evaluated the number of tender and swollen joints used to determine the disease activity score. In addition, serum levels of CTSG and ACPA were measured in patients with inflammatory arthritis using the ELISA kit from Sunlong, China. The study also measured the ESR using the Westergren method, assessed RF using the sandwich immunodetection method from Boditech, Korea, and measured CRP using a particle-enhanced immune-turbidimetry assay from Cobas, Germany.

STATISTICAL ANALYSIS

The data was analyzed using Statistical Package of Social Science (SPSS) software version 21 (San Diego, California, USA). Continuous variables were presented as means and SD, while categorical variables were expressed as frequency and percentage. The chi-square test was used to determine the significance of categorical variables. Pearson and Spearman correlations were used to measure the correlation between nominal and ordinal scales. An independent t-test and an ANOVA test were used to measure serological parameters between study groups and assess the significance level of different clinical and laboratory parameters. Median ± IQR was reported when variance was not found. Furthermore, ROC curves were used to evaluate the diagnostic utility of CTSG, RF, and ACPA. Sensitivity, specificity, PPV, and NPV were calculated for inflammatory arthritis patients. A significance level of $P<0.05$ was considered statistically significant, while $P<0.01$ was deemed highly significant.

RESULTS

A cross-sectional study was conducted on 132 patients with inflammatory arthritis, including 107 patients with RA and 25 patients with other types of inflammatory arthritis. The age mean and SD (46.85 year ±10.564) of patients with RA were significantly higher than those of patients with other types of inflammatory arthritis (39.48 year ±12.460), indicating a significant difference (P = 0.003) between the two groups. However, RA patients had higher BMI means and SD (29.93 kg/m2 ±5.424) than those with other types of inflammatory arthritis (27.40 kg/m2 ±5.874); this difference was statistically significant (P = 0.04). Furthermore, the smoking index means and SD of RA patients (15.24±14.629) and those of patients with other types of inflammatory arthritis (40.00±0.0) did not differ significantly (P = 0.141). Also, there were no significant differences between the two groups of patients in terms of sex (P = 0.999), hypertension (P = 0.099), smoking (P = 0.152), or contraceptive pill use (P = 0.744). However, a significant difference was observed (P = 0.005) between the two patient groups

according to diabetes mellitus, as shown in Tab.1.

Moreover, the median (IQR) of ESR level was higher in RA patients [38.00 mm/hr (30.00)] than the median (IQR) [30.00 mm/hr (32.50)] of patients with other types of inflammatory arthritis. However, the difference between these two groups was not significant. However, the median (IQR) of CRP, RF, and ACPA levels were higher in RA patients [5.49 mg/L (9.31), 18.00 IU/mL (32.00), 12.896 U/ml (5.042), respectively] than the median (IQR) [1.68 mg/L (4.46), 8.00 IU/mL (4.00), 5.884 U/ml (2.572), respectively] of patients with the other types of inflammatory arthritis. There was a significant difference (P = 0.01, P = 0.001, and P = < 0.001, respectively) in these levels between the two groups of patients. On the other hand, the mean and standard deviation (SD) of CTSG level were lower in patients with RA (110.53 pg/ml ± 49.959) compared to those with other types of inflammatory arthritis (132.65 pg/ml ± 30.199). There was a significant difference between the two groups of patients (P = 0.006), as shown in Tab.1. There was no significant difference (P = 0.727) in CTSG level between RA patients with a disease duration of less than six months (113.379 pg/ml ±37.064) and those with more than six months (109.520 pg/ml ±53.461). Rheumatoid arthritis patients with a good response to treatment had a higher mean of CTSG (113.41 pg/ml ± 50.155) than those with a poor response (102.27 pg/ml ± 55.288), but the difference was not significant (P = 0.311). Similarly, untreated newly diagnosed RA patients had a higher mean of CTSG (123.00 pg/ml ± 22.68) compared to those with long-term regularly treated RA (113.52 pg/ml ± 54.03). However, the two groups had no significant difference (P = 0.55). In addition, untreated newly diagnosed RA patients had a significantly (P = 0.031) higher mean of CTSG (123.00 pg/ml ± 22.68) compared to those with regularly treated newly diagnosed RA (97.30 pg/ml ± 40.019), as shown in Tab. 2.

According to the DAS-28 ESR and DAS-28 CRP indices, there was no statistically significant difference in CTSG level among the four disease activity groups (P = 0.585 and P = 0.823, respectively), as shown in Tab.3. Additionally, there was no significant correlation between CTSG and RA activity according to DAS-28 ESR and DAS-28 CRP (R = -0.011, P = 0.911; R = -0.032, P = 0.742, respectively), as shown in Fig.1 and Fig.2.

However, CTSG had a significant negative correlation with diabetes mellitus and treatment intake in newly diagnosed RA (P = 0.009, P = 0.041, respectively). There was no significant correlation with other factors such as age, sex, hypertension, smoking index, BMI, family history, disease duration, regularity of treatment intake, response to treatment, untreated newly diagnosed RA/treated long-term RA, and contraceptive pill use (P = 0.598, P = 0.518, P = 0.727, P = 0.992, P = 0.973, P = 0.865, P = 0.316, P = 0.531, P = 0.263, P = 0.194, P = 0.835, respectively), as shown in Tab.4. As well, CTSG showed no significant correlation with hemoglobin level, WBC, or platelet count [(P = 0.765), (P = 0.199), and (P = 0.95), respectively], as shown in Tab.5.

Furthermore, CTSG had a non-significant correlation with ESR, CRP, RF, and ACPA (P > 0.05). On the other hand, ESR had a statistically significant correlation with CRP (P < 0.001). Furthermore, CRP had a low positive correlation with RF but was statistically insignificant (P = 0.059). However, RF had a highly statistically significant correlation with ACPA (P < 0.001), as shown in Tab.6.

The study evaluated the diagnostic performance of CTSG compared to RF and ACPA in distinguishing between patients with RA and other types of inflammatory arthritis using the Receiver Operator Characteristic (ROC) Curve, as shown in Fig.3. The cut-off value for CTSG was determined to be ≤133.33

pg/ml, and the AUC of CTSG was 0.656. Additionally, ACPA showed excellent diagnostic performance with an AUC of 0.813, which was highly significant (P < 0.001). Rheumatoid factor also had good diagnostic performance, with an AUC of 0.743, which was highly significant. Cathepsin G has a sensitivity of 70.1%, almost equal to the sensitivity of RF (72.0%) and lower than the sensitivity of ACPA (85.0%). CTSG has a specificity of 60.0%, lower than the specificities of RF (84.0%) and ACPA (80.0%), as shown in Tab.7.

Table 1: Demographic and clinical characteristics of the Inflammatory Arthritis Patients (n= 132)

Characteristic	RA patients (n=107)	Other inflammatory arthritis patients (n=25)	Characteristic
Demographics			
Age, mean (year) ±S.D.	46.85±10.564	39.48±12.460	0.003**
Sex [females/males (% of females)]	98/9 (91.6%)	23/2 (92.0%)	0.999
BMI, mean (kg/m2) ±S.D.	29.93±5.424	27.40±5.874	0.04*
Hypertension [Hypertensive/Non-hypertensive (% of Hypertensive)]	42/65 (39.3%)	7 /18 (28.0%)	0.099
Diabetes mellitus [Diabetic/Non-diabetic (% of Diabetic)]	17 /90 (15.9%)	1 /24 (4.0%)	0.005**
Smoking [Smoker/Non-smoker (% of Smoker)]	10 /97 (9.3%)	1 /24 (4.0%)	0.152
Smoking index, mean pack per year ±S.D.	15.24±14.629	40.00±0.0	0.141
Contraceptive pill use [user/Non-user (% of Contraceptive pills user)]	6 /91 (6.2%)	1 /21 (4.5%)	0.744
Clinical data			
ESR level (mm/hr), median (IQR)	38.00 (30.00)	30.00 (32.50)	0.657
CRP level (mg/L), median (IQR)	5.49 (9.31)	1.68 (4.46)	0.01*
RF level (IU/mL), median (IQR)	18.00 (32.00)	8.00 (4.00)	0.001**
ACPA level (U/ml), median (IQR)	12.896 (5.042)	5.884 (2.572)	<0.001**
CTSG level (pg/ml), mean ±S.D.	110.53± 49.959	132.65± 30.199	0.006**

BMI body mass index, ESR erythrocyte sediment rate, CRP C-reactive protein, RF rheumatoid factor, ACPA anti-citrullinated peptide antibody, CTSG cathepsin G, IQR interquartile range, S.D standard deviation *: significant difference, **: highly significant difference.

Table 2: Comparison of CTSG According to the Disease Duration and Features of Treatment Intake		
Characteristic	CTSG mean ± SD (pg/ml)	P-value
Less than 6 months (n=28)	113.379±37.064	0.727
More than 6 months (n=79)	109.520±53.461	
Good response to treatment (n= 57)	113.41 ± 50.155	0.311
Poor response to treatment (n= 38)	102.27 ± 55.288	
Untreated newly diagnosed RA (n=12)	123.00 ± 22.68	0.55
Long-term regularly treated RA (n=54)	113.52 ± 54.03	
Untreated newly diagnosed RA (n=12)	123.00 ± 22.68	0.031*
Regularly treated newly diagnosed RA (n=13)	97.30 ± 40.019	
CTSG cathepsin G. *: significant difference		

Table 3: CTSG comparison among RA patients' disease activity groups using DAS-28 ESR and DAS-28 CRP				
DAS-28 ESR of RA patients (n=107)				
CTSG level (pg/ml), mean ±S.D.				
Remission (n =2)	Low activity (n =2)	Moderate activity (n =33)	High activity (n =70)	P-Value
149.61±22.237	80.13±51.942	109.95±39.846	110.55±54.594	0.585
DAS-28 CRP of RA patients (n=107)				
CTSG level (pg/ml), mean ±S.D.				
Remission (n = 6)	Low activity (n = 6)	Moderate activity (n = 61)	High activity (n = 34)	P-Value
97.01±49.416	123.59±36.756	111.63±46.993	108.64±57.942	0.823
CTSG cathepsin G, DAS28 disease activity score, ESR erythrocyte sediment rate, CRP C-reactive protein.				

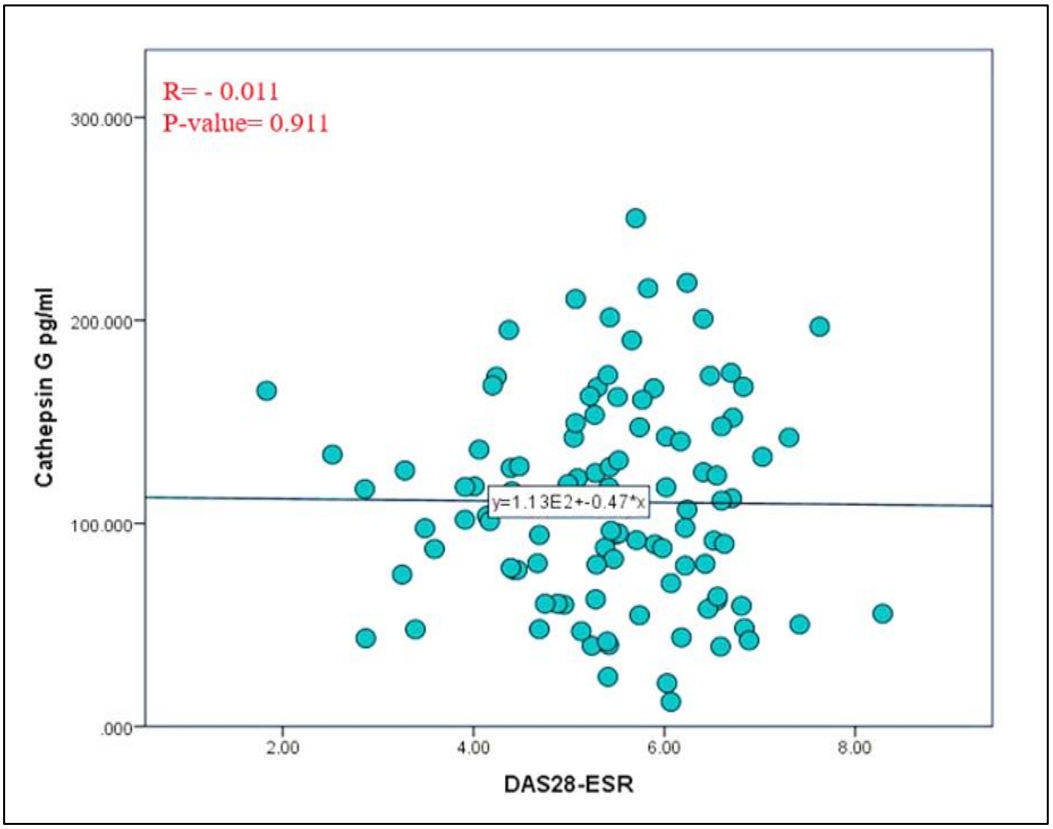

Figure 1: Correlations of CTSG with RA Activity According to DAS-28 ESR.

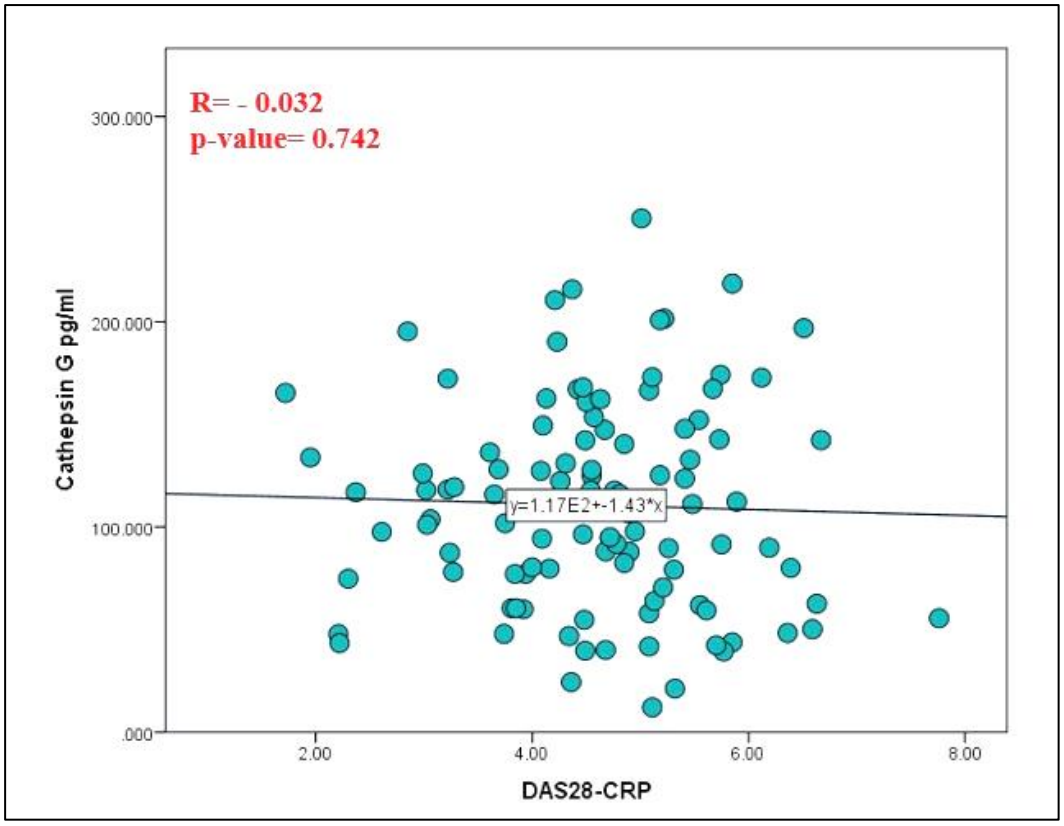

Figure 2: Correlations of CTSG with RA Activity According to DAS-28 CRP.

Table 4: Correlations of Demographic Characteristics, BMI and Features of Treatment Intake with CTSG Values in the RA Patients		
Characteristic of RA Patients		CTSG
Age (years)	r	-0.052
	P	0.598
Sex	r	-0.063
	P	0.518
Hypertension	r	-0.034
	P	0.727
Diabetes Mellitus	r	-0.252
	P	0.009**
Smoking index, (pack per year)	r	0.001
	P	0.992
BMI	r	0.003
	P	0.973
Family History	r	-0.017
	P	0.865
Disease Duration	r	-0.097
	P	0.316
Regularity of treatment intake	r	-0.061
	P	0.531
Response to Treatment	r	0.115
	P	0.263
Untreated newly diagnosed RA/ treated long-term RA	r	-0.137
	P	0.194
Untreated, newly diagnosed/Regularly treated, newly diagnosed RA	r	-0.410
	P	0.041*
Contraceptive pill use	r	0.021
	P	0.835
CTSG cathepsin G, *BMI* body mass index, *r* correlation coefficient, *P* P-value. *: Significant, **: highly significant		

Table 5: Correlations of Haematological Parameters with CTSG Values in the RA Patients		
Characteristic of RA patients		CTSG
Haemoglobin level (mg/dl)	r	-0.029
	p	0.765
WBC Count (x 10^9/liter)	r	-0.125
	p	0.199
Platelets Count (x 10^9/liter)	r	-0.006
	p	0.95
CTSG cathepsin G, *WBC* white blood cell, *r* correlation coefficient, *P* P-value		

Table 6: Correlations between Biomarkers in the RA patients						
Parameters		CTSG	ESR (mm/h)	CRP (mg/L)	RF (IU/mL)	ACPA(U/ml)
CTSG	P	1				
	r	-				
ESR (mm/h)	r	-0.056	1			
	P	0.566	-			
CRP (mg/L)	r	0.05	0.537	1		
	P	0.609	<0.001**	-		
RF (IU/mL)	r	-0.096	0.097	0.183	1	
	P	0.328	0.318	0.059	-	
ACPA (U/ml)	r	0.073	0.061	0.006	0.549	1
	P	0.453	0.534	0.949	<0.001**	-
CTSG cathepsin G, *ESR* erythrocyte sediment rate, *CRP* C-reactive protein, *RF* rheumatoid factor, *ACPA* anti-citrullinated peptide antibody, *r* Correlation Coefficient, *P* P-value. **: highly significant						

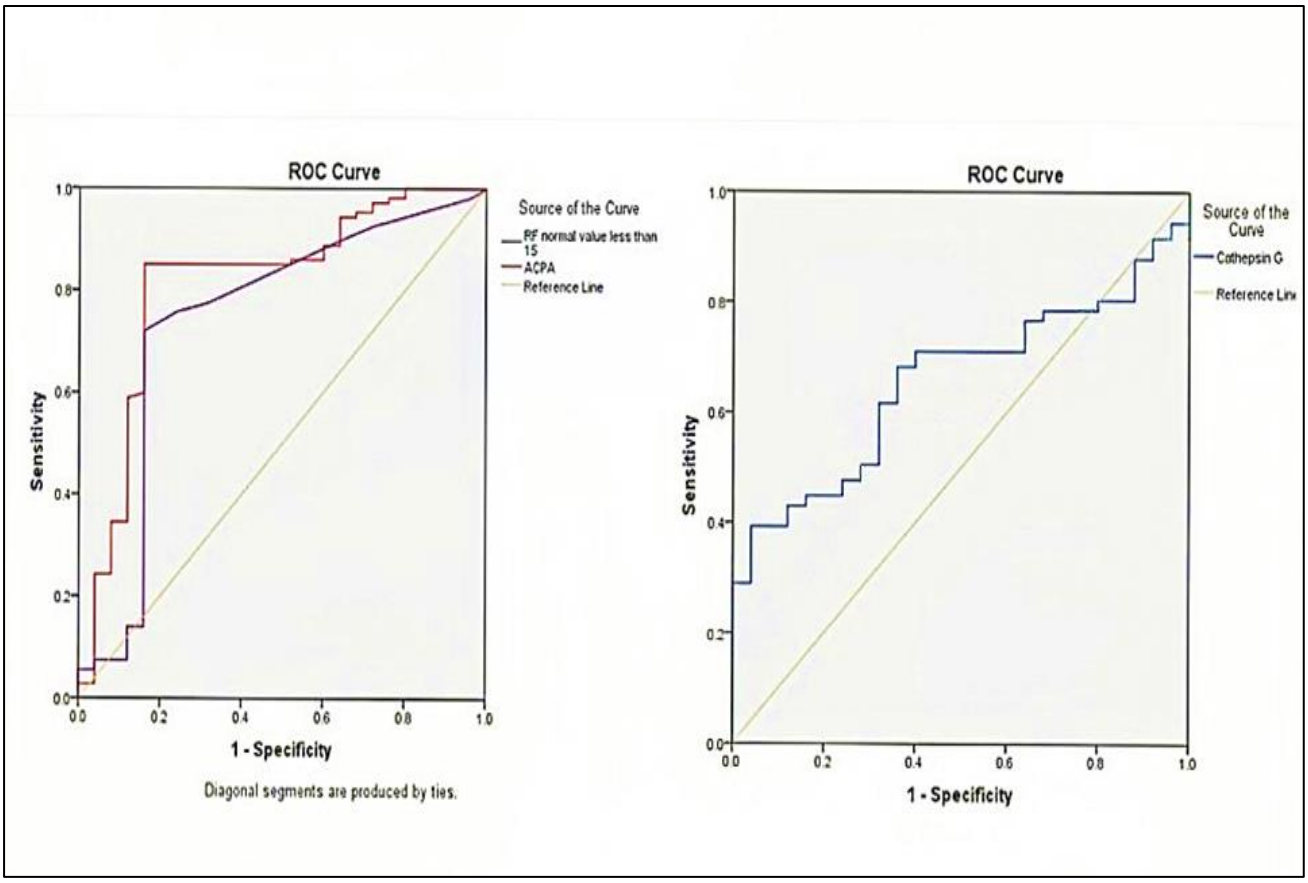

Figure 3: The Diagnostic Performance of RF, ACPA, and CTSG.

Table 7: Receiver Operator Characteristic (ROC) Curve for Biomarkers of Patients with Inflammatory Arthritis

Characteristic	CTSG	RF	ACPA
AUC	0.656	0.743	0.813
SE	0.050	0.063	0.053
Sig.	0.015*	<0.001**	<0.001**
95% confidence interval	0.559-0.754	0.619 -0.867	0.709 -0.917
Optimal cut-point value (pg/ml)	133.33	12.500	9.920
Sensitivity (%)	70.1%	72.0%	85.0%
Specificity (%)	60.0%	84.0%	80.0%
PPV (%)	88.2%	71.96%	85.04%
NPV (%)	31.9%	84%	80%
Diagnostic effectiveness (accuracy)	68.18%	74.24%	84.09%
Youden's index	0.3	0.56	0.65

CTSG cathepsin G, *RF* rheumatoid factor, *ACPA* anti-citrullinated peptide antibody *AUC* area under the curve, *SE* standard error *Sig* significant, *PPV* positive predictive value, *NPV* negative predictive value. *: Significant difference, **: highly significant difference

DISCUSSION

The current study found that the mean level of CTSG was significantly lower in patients with RA compared to patients with other types of inflammatory arthritis. Although previous studies have shown a correlation between CTSG levels and many other inflammatory arthritis or autoimmune diseases, such as psoriatic arthritis (PsA) and systemic lupus erythematosus (SLE), there have been no studies specifically comparing CTSG levels between RA and other types of inflammatory arthritis.

Popova-Belova et al. [16] found significantly higher CTSG levels in patients with PsA compared to a control group of gouty arthritis patients and healthy controls. Kida et al. [17] found that CTSG is the main antigen for anti-neutrophil cytoplasmic antibodies in systemic SLE. They reported that patients with active SLE displayed considerably higher levels of CTSG antibodies in their serum than those with inactive SLE or healthy controls. These high levels decreased rapidly after corticosteroid therapy. Patients with other types of inflammatory arthritis have higher levels of CTSG compared to those with RA. These high levels are potentially due to CTSG's contribution to the development of autoimmune disorders characterized by cytokine production and neutrophil infiltration in the joints. However, additional studies are required to understand CTSG's involvement in different types of inflammatory arthritis.

The relatively small sample size of patients with other types of inflammatory arthritis compared to those with RA may contribute to the lower levels of CTSG in RA patients. Furthermore, in the present study, SLE patients dominated the other inflammatory arthritis group. As previously mentioned, CTSG is known to impact SLE and is linked to disease activity. Despite this lower level of CTSG in RA patients, Gao et al. [15] found that the synovial fluid of RA patients has a higher level of CTSG than that of healthy controls, which leads this study to suspect a

higher level of CTSG in those patients compared to healthy controls. It is also believed that this increase in CTSG level may be due to the release of a protease enzyme by neutrophils during inflammation [18].

Cathepsin G can change and activate molecules like cytokines, chemokines, and cell surface receptors that are important for the immune system and the inflammatory response [14]. It can also attract more monocytes to the inflammation site. In RA, immune cells such as monocytes and neutrophils infiltrate and lead to inflammation of the synovial tissue that lines the joints [19]. These cells release CTSG and other pro-inflammatory cytokines, which lead to inflammation and joints damage [20]. The high level of CTSG may participate in the RA pathogenesis by recruitment cells to the affected joints and initiating an inflammatory response [14]. It may also be used as an indicator for RA diagnosis and progression. However, additional researches are necessary to clarify the role and effects of CTSG in the pathogenesis of RA.

The current study revealed that RA patients with disease duration less than six months had slightly higher CTSG levels compared to those with disease duration more than six months. However, the difference did not reach statistical significance. According to the researcher's knowledge, there are no studies available to compare this result. Rheumatoid arthritis patients with disease duration less than six months have slightly higher CTSG levels, may due to increased inflammatory immune response in the early stages of RA that stimulates the recruitment and activation of neutrophils in the joints [21]. As part of the immunological response, neutrophils produce and release CTSG [18]. The low levels of CTSG in RA patients with disease duration more than six months may be related to long-term use of medications for RA, which can reduce inflammation and slow disease progression. This may result in decreased CTSG levels.

The current study did not find a significant difference in CTSG level based on response to treatment in RA patients. According to previous study conducted by Miyata et al. [19] , CTSG levels have been found to be affected by RA treatment and decrease after treatment, suggesting that it may be a potential biomarker of response to treatment.

The current study found there was no statistically significant difference in the levels of CTSG between patients with long-term, regularly treated RA and those with newly diagnosed, untreated RA. According to the researcher's knowledge, there are no studies available to compare this result. However, the levels of CTSG were slightly higher in the untreated, newly diagnosed RA group compared to the regularly treated long-term RA group. This increase can be attributed to excessive inflammation and neutrophil infiltration in the joints, which leads to the release of CTSG from various immune cells and neutrophil granules. Cathepsin G also attracts monocytes and regulates immune responses, thus increasing inflammation and joint damage [14].

The study found that regularly treated newly diagnosed RA patients had significantly lower CTSG levels than untreated newly diagnosed RA patients. The reason behind this significantly lower level of CTSG was explained previously. This finding suggests that CTSG could serve as a new diagnostic biomarker or treatment target for RA. This idea is supported by previous studies that found the activity of human leukocyte CTSG can be inhibited by anti-rheumatic drugs. As a result of this finding, the authors recommend CTSG inhibition as a potential therapeutic approach for treating autoimmune diseases such as RA [19,22, 15].

To the best of our knowledge, this is the first study to evaluate the role of CTSG in RA activity. The findings of this study revealed a non-significant association between CTSG and disease activity (according to the DAS-28 ESR and DAS-28 CRP indices). Additionally, a study by Popova-Belova et al. [16] found that CTSG did not show strong associations with disease activity in patients with PsA. Another study by Ruge et al. [23], who work on other types of cathepsins (S and L), also found no significant association between these cathepsins and RA activity, as characterized by DAS-28 ESR. The level of serum cathepsins cannot precisely indicate the level of inflammation present in the joints [24].

The current study showed that CTSG had a significant negative correlation with diabetes mellitus. The findings differ from the study which reported increased CTSG in patients with Type 1 diabetes [25]. Furthermore, this study has shown a negative correlation between CTSG and treatment intake in newly diagnosed RA patients. The elevated CTSG levels observed in RA patients could be attributed to joint inflammation triggering the release of CTSG by immune cells like neutrophils and monocytes as part of the inflammatory process [14]. Conversely, RA medications that reduce immune responses and inflammation may have an impact on the lower levels of CTSG in regularly treated, newly diagnosed RA patients. These results indicate that CTSG might hold potential as a biomarker for monitoring treatment outcomes in diagnosed RA patients and as a target for RA therapy.

This is the first study that used a receiver operator characteristic (ROC) curve analysis to measure the diagnostic value of CTSG and its usefulness in differentiation of RA from other types of inflammatory arthritis. According to the results, CTSG has demonstrated reliable diagnostic performance with an AUC of 0.656 at a cut-off value of ≤133.33 pg/ml, a sensitivity of 70.1%, and a specificity of 60.0%. Cathepsin G had lower accuracy, sensitivity, and AUC than ACPA and RF; the specificity was similar to RF but lower than ACPA.

CONCLUSION

In conclusion, the findings showed that CTSG could be a useful diagnostic biomarker for RA when combined with other clinical and laboratory criteria but is unreliable for RA activity evaluation.

Ethical Approval

Before commencing the study project, the ethical committee of the College of Medicine at the University of Kufa had approved. The Rheumatology Department of Al-Sadr Medical City also granted permission, and the patient's consent was obtained to conduct a questionnaire and collect a blood sample.

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