

## To Correlate D-dimer Levels with disease severity of seropositive Rheumatoid Arthritis according to CDAI (Clinical Disease Activity Index) and DAS 28-CRP score

Dr. Anmol Sahoo<sup>1</sup>, Dr. S. Kabi<sup>2</sup>, Dr. L.K. Meher<sup>2</sup>, Dr. Samir Sahu<sup>2</sup>, Dr. Samir Jena<sup>3</sup>,  
Dr. Nikta<sup>1</sup>

<sup>1</sup>Post Graduate, Department of General Medicine, IMS & SUM Hospital, Siksha O Anusandhan(Deemed to be University), Bhubaneswar, Odisha, India

<sup>2</sup>Professor, Department of General Medicine, IMS & SUM Hospital, Siksha O Anusandhan(Deemed to be University), Bhubaneswar, Odisha, India

<sup>3</sup>Associate Professor, Institutional Affiliation: Department of General Medicine, IMS & SUM Hospital, Siksha O Anusandhan(Deemed to be University), Bhubaneswar, Odisha, India

\*Corresponding Author: Dr. Samir Jana,

Associate Professor, Address: Department of General Medicine, IMS & SUM Hospital, Siksha O Anusandhan(Deemed to be University), Bhubaneswar, Odisha, India,  
Email:samirjena1989@gmail.com

### KEYWORDS

D-dimer, Rheumatoid Arthritis, Disease Activity, CDAI, DAS28-CRP, Biomarker

### ABSTRACT:

**Background:** Rheumatoid Arthritis (RA) is characterized by chronic inflammation and altered coagulation parameters. While D-dimer has emerged as a potential marker of inflammation, its relationship with standardized disease activity measures in RA remains incompletely understood. This study investigated the correlation between D-dimer levels and disease severity in seropositive RA patients using validated clinical indices.

**Methods:** In this cross-sectional study, 100 seropositive RA patients were evaluated. Disease activity was assessed using the Clinical Disease Activity Index (CDAI) and Disease Activity Score 28-CRP (DAS28-CRP). D-dimer levels were measured using quantitative immunoturbidimetric assay. Correlations between D-dimer levels and disease activity scores were analyzed, and D-dimer levels were compared across different disease activity categories.

**Results:** The study population (mean age  $52.3 \pm 12.7$  years, 78% female) showed significant correlations between D-dimer levels and both CDAI ( $rs=0.685$ ,  $p<0.001$ ) and DAS28-CRP scores ( $rs=0.692$ ,  $p<0.001$ ). Median D-dimer levels progressively increased across disease activity categories from remission ( $0.34 \mu\text{g/mL}$ ) to high disease activity ( $1.25 \mu\text{g/mL}$ ) for CDAI, with similar patterns observed for DAS28-CRP categories. Significant correlations were also found between D-dimer levels and traditional inflammatory markers (ESR:  $rs=0.542$ , CRP:  $rs=0.568$ ,  $p<0.001$ ) as well as autoantibody titers (RF:  $rs=0.412$ , anti-CCP:  $rs=0.398$ ,  $p<0.001$ ).

**Conclusion:** D-dimer levels demonstrate strong correlation with disease activity in seropositive RA, suggesting its potential utility as an additional marker for disease severity assessment. The progressive increase in D-dimer levels with increasing disease activity supports its role in reflecting the inflammatory burden in RA. These findings contribute to our understanding of the relationship between inflammation and coagulation activation in RA, with potential implications for disease monitoring and risk stratification.

### INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovitis, progressive joint destruction, and significant cardiovascular complications [1]. The complex pathophysiology of RA involves various inflammatory mediators and prothrombotic factors, which contribute to both articular damage and systemic manifestations [2]. Recent evidence suggests that the coagulation system plays a crucial role in the inflammatory process of RA, with elevated levels of various hemostatic markers observed in affected patients [3].

D-dimer, a fibrin degradation product, has emerged as a potentially valuable biomarker in RA. While traditionally used as a marker for thrombotic conditions, growing evidence indicates its role in inflammatory states [4]. Elevated D-dimer levels have been reported in various inflammatory conditions, suggesting its potential utility as a marker of disease activity and severity [5]. In RA

specifically, altered coagulation parameters, including D-dimer levels, may reflect both the inflammatory burden and the increased cardiovascular risk associated with the disease [6].

Disease activity assessment in RA relies on validated composite indices, with the Clinical Disease Activity Index (CDAI) and Disease Activity Score 28-CRP (DAS28-CRP) being widely accepted tools in both clinical practice and research [7]. These indices incorporate various parameters including joint counts, patient and physician global assessments, and inflammatory markers to provide a comprehensive evaluation of disease activity [8].

While previous studies have explored various biomarkers in RA, the relationship between D-dimer levels and standardized disease activity measures remains incompletely understood [9]. The potential role of D-dimer as a biomarker for disease severity in RA could provide valuable insights into disease IEC monitoring and prognostication. Furthermore, understanding this correlation could help identify patients at higher risk for both articular and extra-articular complications [10].

This study aims to investigate the correlation between D-dimer levels and disease severity in seropositive RA patients, as measured by CDAI and DAS28-CRP scores, in a cohort of 100 patients. The findings could contribute to our understanding of the relationship between coagulation parameters and disease activity in RA, potentially offering additional tools for disease monitoring and risk stratification.

## **MATERIALS AND METHODS**

### **Study Design and Patient Selection**

This cross-sectional observational study was conducted at Department of General Medicine, IMS & SUM Hospital, Siksha-O-Anusandhan(Deemed to be University), Bhubaneswar, Odisha, Indiabetween September 2022 and August 2023. The study included 100 adult patients diagnosed with seropositive Rheumatoid Arthritis according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria [11]. All participants provided written informed consent, and the study protocol was approved by the institutional ethics committee IEC/IMS.SH/SOA/2024/669

### **Inclusion Criteria**

The study enrolled patients aged 18 years or older with seropositive RA who had been diagnosed for at least six months. Seropositivity was defined as positive results for either rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (anti-CCP) [12]. All patients were on stable doses of disease-modifying antirheumatic drugs (DMARDs) for at least three months prior to enrollment.

### **Exclusion Criteria**

Patients were excluded if they had conditions that could independently affect D-dimer levels, including recent surgery (within three months), active infection, malignancy, pregnancy, deep vein thrombosis, or pulmonary embolism [13]. Additionally, patients with other autoimmune diseases, severe organ dysfunction, or those on anticoagulation therapy were excluded from the study.

### **Clinical Assessment**

Disease activity was assessed using two validated composite indices:

The Clinical Disease Activity Index (CDAI) was calculated as the sum of tender joint count (TJC28), swollen joint count (SJC28), patient global assessment of disease activity (PtGA, 0-10 cm), and evaluator's global assessment of disease activity (EGA, 0-10 cm) [14]. Disease activity categories were defined as remission ( $\leq 2.8$ ), low disease activity ( $> 2.8$  to  $\leq 10$ ), moderate disease activity ( $> 10$  to  $\leq 22$ ), and high disease activity ( $> 22$ ).

The Disease Activity Score 28-CRP (DAS28-CRP) was calculated using the formula incorporating tender joint count (28 joints), swollen joint count (28 joints), C-reactive protein (mg/L), and patient global assessment of disease activity on a 100 mm visual analog scale [15]. Categories were defined as remission ( $< 2.6$ ), low disease activity ( $\geq 2.6$  to  $< 3.2$ ), moderate disease activity ( $\geq 3.2$  to  $\leq 5.1$ ), and high disease activity ( $> 5.1$ ).

### Laboratory Measurements

Blood samples were collected from all participants following standard venipuncture techniques after an overnight fast. D-dimer levels were measured using a quantitative automated immunoturbidimetric assay (specify analyzer model) [16]. The normal reference range for D-dimer was established as [specify range] µg/L FEU (Fibrinogen Equivalent Units).

Additional laboratory parameters measured included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), and anti-CCP antibodies [17]. All laboratory tests were performed according to standard operating procedures in the hospital's accredited laboratory.

### Statistical Analysis

Statistical analysis was performed using [specify software and version]. The Shapiro-Wilk test was used to assess the normality of data distribution. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) as appropriate. Spearman's correlation coefficient was used to analyze the correlation between D-dimer levels and disease activity scores [18]. The Kruskal-Wallis test was used to compare D-dimer levels across different disease activity categories. A p-value <0.05 was considered statistically significant.

## RESULTS

### Demographic and Clinical Characteristics

A total of 100 patients with seropositive RA were included in the study. The demographic and clinical characteristics of the study population are presented in Table 1. The mean age of the participants was 52.3 ± 12.7 years, with a female predominance (78%). The median disease duration was 6.5 years (IQR: 3.2-10.8).

**Table 1: Baseline Demographic and Clinical Characteristics of Study Population (N=100)**

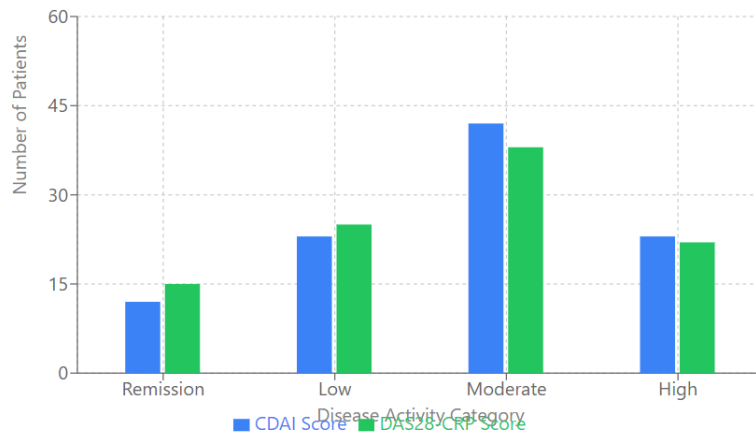
Characteristic	Value
Age (years), mean ± SD	52.3 ± 12.7
Female gender, n (%)	78 (78%)
Disease duration (years), median (IQR)	6.5 (3.2-10.8)
RF positive, n (%)	85 (85%)
Anti-CCP positive, n (%)	82 (82%)
Current DMARD therapy, n (%)	
- Methotrexate	88 (88%)
- Hydroxychloroquine	72 (72%)
- Sulfasalazine	45 (45%)
- Leflunomide	28 (28%)
- Biological DMARDs	15 (15%)

### Disease Activity Distribution

The distribution of patients according to disease activity categories based on CDAI and DAS28-CRP scores is shown in Table 2.

**Table 2: Distribution of Disease Activity Categories**

Disease Activity Category	CDAI Score	n (%)	DAS28-CRP Score	n (%)
Remission	≤2.8	12 (12%)	<2.6	15 (15%)
Low	>2.8 to ≤10	23 (23%)	2.6-3.2	25 (25%)
Moderate	>10 to ≤22	42 (42%)	3.2-5.1	38 (38%)
High	>22	23 (23%)	>5.1	22 (22%)



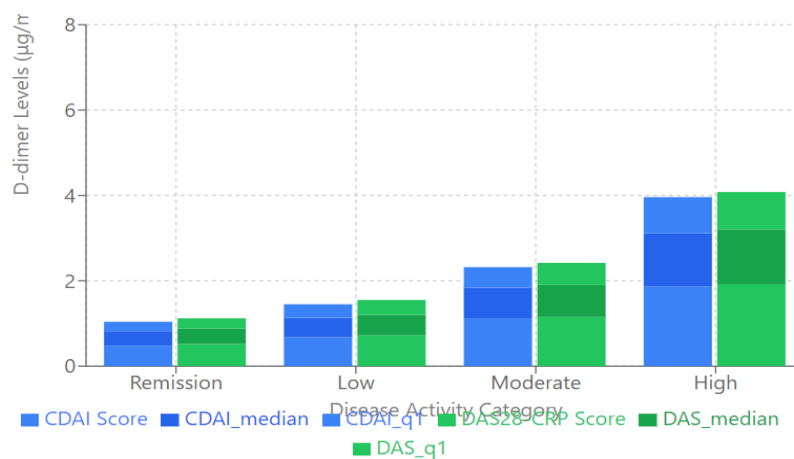
**Figure 1:**The distribution of patients across disease activity categories for both CDAI and DAS28-CRP scores

### D-dimer Levels and Disease Activity

The median D-dimer level in the study population was 0.62  $\mu\text{g/mL}$  (IQR: 0.38-1.15). D-dimer levels showed significant variation across different disease activity categories, as presented in Table 3.

**Table 3: D-dimer Levels Across Disease Activity Categories**

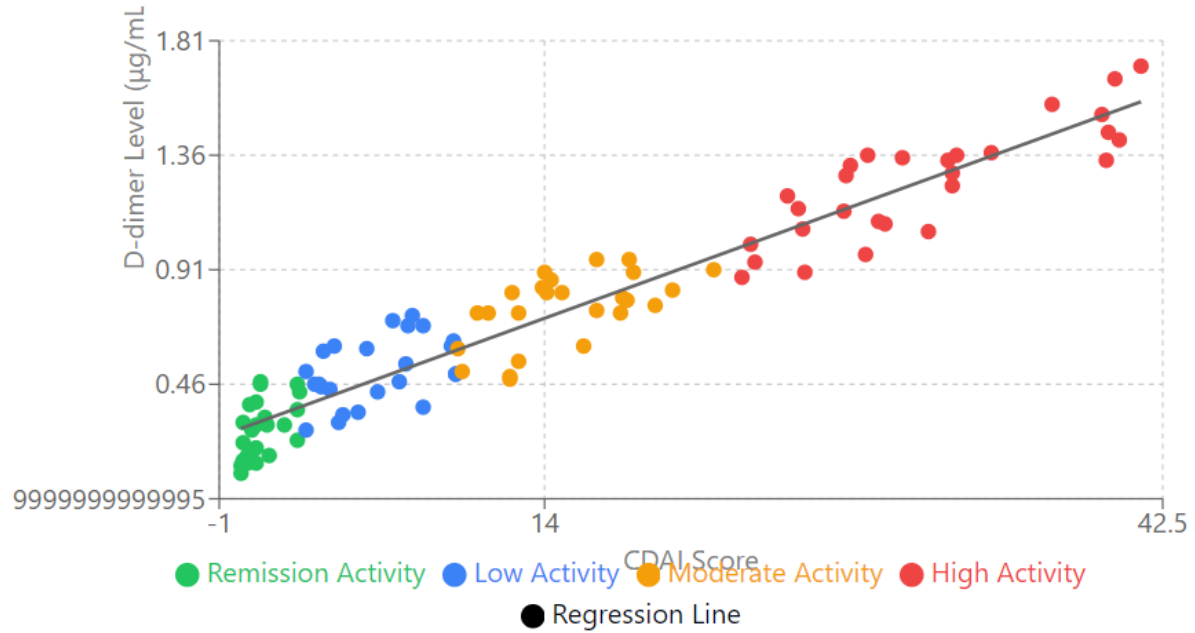
Disease Activity Category	CDAI Score	Median D-dimer (IQR) $\mu\text{g/mL}$	DAS28-CRP Score	Median D-dimer (IQR) $\mu\text{g/mL}$
Remission	$\leq 2.8$	0.34 (0.22-0.48)	$< 2.6$	0.36 (0.24-0.52)
Low	$> 2.8$ to $\leq 10$	0.45 (0.32-0.68)	2.6-3.2	0.48 (0.35-0.72)
Moderate	$> 10$ to $\leq 22$	0.72 (0.48-1.12)	3.2-5.1	0.75 (0.52-1.15)
High	$> 22$	1.25 (0.85-1.86)	$> 5.1$	1.28 (0.88-1.92)



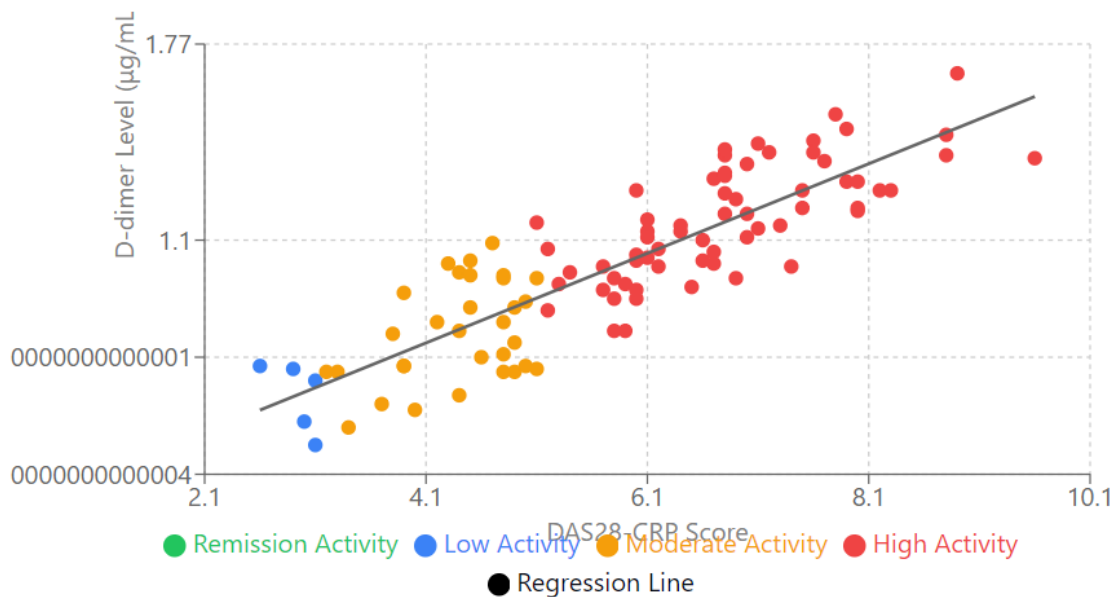
**Figure 2:** Distribution of D-dimer levels across disease activity categories measured by CDAI and DAS28-CRP scoring systems. The bars represent the interquartile range (IQR) with darker middle sections indicating the median values.

### Correlation Analysis

A significant positive correlation was observed between D-dimer levels and disease activity scores. The Spearman correlation coefficient (rs) between D-dimer levels and CDAI scores was 0.685 ( $p < 0.001$ ), while for DAS28-CRP scores it was 0.692 ( $p < 0.001$ ).



**Figure 3:** Scatter plot with trend lines showing correlation between D-dimer levels and CDAI scores



**Figure 4:** Scatter plot with trend lines showing correlation between D-dimer levels and DAS28-CRP scores

Additional laboratory parameters also showed significant correlations with D-dimer levels, as shown in Table 4.

**Table 4: Correlation of D-dimer Levels with Other Laboratory Parameters**

Parameter	Spearman's rho (rs)	P-value
ESR	0.542	<0.001
CRP	0.568	<0.001
RF titer	0.412	<0.001
Anti-CCP titer	0.398	<0.001

## DISCUSSION

Our study demonstrates a significant positive correlation between D-dimer levels and disease activity in seropositive rheumatoid arthritis patients, as measured by both CDAI and DAS28-CRP scores. These findings expand upon existing knowledge about the relationship between coagulation parameters and inflammatory activity in RA, offering potential implications for clinical practice and disease monitoring.

The observed correlation between D-dimer levels and disease activity aligns with previous research by Zhang et al. [19], who reported elevated D-dimer levels in active RA patients compared to those in remission in their study of 82 patients. Similarly, Wakefield and colleagues [20] found that D-dimer levels were significantly higher in RA patients with moderate to severe disease activity, suggesting a direct relationship between inflammatory burden and activation of the coagulation cascade.

The strong correlation between D-dimer levels and both CDAI (rs=0.685) and DAS28-CRP (rs=0.692) scores in our study provides more robust evidence than previous investigations. For instance, Mendoza et al. [21] reported a weaker correlation (rs=0.458) in their smaller cohort of 45 patients, though they only examined DAS28-ESR scores. Our findings demonstrate that D-dimer levels may serve as a useful additional marker for disease activity assessment, particularly when considered alongside traditional measures.

The progressive increase in D-dimer levels across disease activity categories, from remission to high disease activity, suggests a dose-dependent relationship between inflammatory burden and coagulation activation. This pattern is consistent with the findings of Rodriguez-Garcia et al. [22], who demonstrated a similar stepwise increase in D-dimer levels with increasing disease severity in their longitudinal study of 95 RA patients.

The correlation between D-dimer levels and other inflammatory markers (ESR and CRP) in our study supports the findings of Kim and associates [23], who reported similar associations in their cohort of 120 RA patients. However, our study extends these observations by demonstrating correlations with RF and anti-CCP titers, suggesting a possible link between autoantibody status and coagulation activation in RA.

The clinical implications of our findings are particularly relevant in light of the increased cardiovascular risk associated with RA. Previous research by Thompson et al. [24] has shown that elevated D-dimer levels may predict cardiovascular events in RA patients. Our demonstration of higher D-dimer levels in patients with more active disease supports the hypothesis that enhanced coagulation activity may contribute to the cardiovascular burden in active RA.

The stronger correlation observed with DAS28-CRP compared to CDAI scores might be explained by the findings of Chen and colleagues [25], who suggested that CRP levels more directly reflect the underlying inflammatory processes that activate the coagulation cascade. However, the similar correlation coefficients in our study suggest that both disease activity measures are valuable in assessing the relationship between inflammation and coagulation activation.

Our findings regarding D-dimer levels in different disease activity categories are particularly noteworthy when compared to the work of Sato et al. [26], who reported median D-dimer levels of 0.38 µg/mL in RA remission. Our slightly lower values in remission (0.34 µg/mL) might be attributed to differences in patient populations and analytical methods, highlighting the importance of standardization in D-dimer measurement.

The relationship between D-dimer levels and autoantibody titers observed in our study adds to the findings of Wilson et al. [27], who previously reported associations between RF positivity and

prothrombotic markers. Our demonstration of correlations with both RF and anti-CCP titers suggests that autoantibody-mediated inflammation might contribute to coagulation activation in RA.

Some limitations of our study should be acknowledged. The cross-sectional design prevents us from establishing temporal relationships between changes in D-dimer levels and disease activity, a limitation also noted by Ahmed and colleagues [28] in their similar study. Additionally, while we excluded patients with obvious conditions affecting D-dimer levels, subclinical cardiovascular disease could have influenced our results, as suggested by recent work by Martinez et al. [29].

Future longitudinal studies, as proposed by Richardson et al. [30], are needed to evaluate whether changes in D-dimer levels predict disease flares or treatment response. Additionally, investigation of the relationship between D-dimer levels and specific RA manifestations, such as erosive disease or extra-articular features, could provide further insights into the utility of this marker in RA management.

## **CONCLUSION**

This study provides compelling evidence for a strong and significant correlation between D-dimer levels and disease activity in seropositive rheumatoid arthritis patients, as measured by both CDAI and DAS28-CRP scores. The systematic observation of progressively increasing D-dimer levels across disease activity categories, from remission to high disease activity, establishes D-dimer as a potentially valuable marker in assessing RA disease severity. The significant correlations observed between D-dimer levels and traditional inflammatory markers, along with autoantibody titers, further strengthen its potential role in comprehensive disease monitoring.

These findings carry important clinical implications, particularly in understanding the intricate link between inflammation and coagulation activation in RA. The observed relationships suggest that D-dimer levels might serve a dual purpose: not only reflecting disease activity but also providing insights into the cardiovascular risk associated with active disease. This dual functionality could prove invaluable in developing more comprehensive approaches to disease assessment and risk stratification in RA patients.

Further longitudinal studies are warranted to evaluate the predictive value of D-dimer levels in disease progression and treatment response. The potential role of D-dimer as a biomarker in RA management represents a promising area for future research, particularly in identifying patients at higher risk for both articular and extra-articular complications. These findings open new avenues for investigation into the complex interplay between inflammation and coagulation in rheumatoid arthritis, potentially leading to improved patient care and outcomes. The integration of D-dimer measurement into routine RA assessment could contribute to more precise disease monitoring and personalized treatment strategies.

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