

ROLE OF ULTRASOUND IN EARLY DIAGNOSIS OF RHEUMATOID ARTHRITIS- A VALIDATION STUDY

Hamza Javed¹, Faiza Akram^{*2}, Hassan Majeed³, Tayyaba Alam⁴, Alina Farooq⁵, Hafsa Bibi⁶^{1,4,5}MBBS Resident Radiologist, Radiology Department- ATH, Abbottabad^{*2}MBBS, FCPS (Radiology) Professor, Radiology Department- ATH, Abbottabad³MBBS, FCPS (Radiology) Senior Medical Officer, Radiology Department- ATH, Abbottabad.⁶MBBS, FCPS (Radiology) Assistant Professor, Radiology Department- ATH, Abbottabad¹hjk37@gmail.com, ²drfaizafayyaz@gmail.com, ³hassanfiv@yahoo.com, ⁴tayyabalam.92@gmail.com, ⁵alinafarooqlibra@gmail.com, ⁶mrsrafatullah@gmail.comDOI: <https://doi.org/10.5281/zenodo.21882818>**Keywords**

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Corresponding Author: *

Faiza Akram

Abstract

Background: Rheumatoid arthritis (RA) is a common autoimmune disorder that can cause irreversible joint damage if not diagnosed and treated early. While clinical criteria and laboratory tests are commonly used for RA diagnosis, imaging techniques like ultrasound (US) have emerged as valuable tools for early detection, offering advantages in terms of sensitivity, specificity, and cost-effectiveness.

Objective: This study aims to validate the role of ultrasound in the early diagnosis of rheumatoid arthritis, using clinical diagnosis as the gold standard.

Methods: A cross-sectional validation study was conducted at Ayub Teaching Hospital, Abbottabad. A total of 146 patients with clinical suspicion of RA were recruited between December 2024 to November 2025. All participants underwent a clinical assessment based on the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for RA. Subsequently, ultrasound examinations were performed by an experienced radiologist to assess features indicative of RA, such as synovial hypertrophy and increased blood flow. The diagnostic performance of ultrasound was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using the clinical diagnosis as the reference.

Results: Of the 146 participants, 93 (63.7%) were clinically diagnosed with RA, and 74 (50.7%) had positive ultrasound findings. The most common indicator on ultrasound for RA was synovial fluid presence, seen in 83 (56.8%) followed by synovitis seen in 78 (53.4%). The sensitivity of ultrasound for detecting RA was 83.8%, with a specificity of 56.9%. The PPV was 66.8%, and the NPV was 77.4%. The area under the ROC curve (AUC) was 0.720, indicating a moderate diagnostic accuracy of ultrasound.

Conclusion: Ultrasound demonstrated moderate diagnostic performance in the early detection of rheumatoid arthritis. Its high sensitivity makes it a valuable tool for identifying patients with RA, though its specificity suggests that further refinements or complementary tests may be necessary. Ultrasound offers a promising adjunct to clinical criteria in the early diagnosis of RA, particularly in resource-limited settings where cost and radiation exposure are concerns.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease marked by synovial tissue proliferation, pannus formation, cartilage destruction, and systemic complications. Its pathogenesis involves autoreactive CD4⁺ T cells, B cells, macrophages, inflammatory cytokines, chemokines, and autoantibodies. Despite significant progress, the precise interactions and triggers remain unclear¹. RA is the most common inflammatory joint disorder, affecting about 1% of the global population². The disease's pathogenesis involves genetic, epigenetic, and environmental factors, leading to polyarticular synovitis with a symmetrical pattern affecting both small and large joints. Most RA patients have detectable autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, which are specific markers for RA. Chronic, uncontrolled inflammation results in destructive changes to joint cartilage and bone².

The diagnosis of RA combines symptoms, imaging, and laboratory tests. Clinical presentation often includes symmetric swelling of small joints, with about 25% of patients experiencing an acute or subacute onset. Other presentation patterns include palindromic onset (recurrent oligoarthritis with no residual damage), monoarticular presentation (affecting a single joint), extra-articular synovitis (inflammation around the joint), and polymyalgic-like onset (resembling polymyalgia rheumatica in elderly patients)³. The latest criteria, established in 2010 by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for clinical diagnosis of RA include large joint involvement (scored 0-3), small joint involvement (scored 0-2), seropositivity for RF or anti-CCP antibodies (scored 0-1), duration of morning stiffness (>60 minutes, scored 1), and symmetric joint involvement (scored 1)^{4,5}.

Recent classification criteria suggest using imaging techniques such as ultrasonography (US) for additional diagnostic information in clinically suspected arthritis cases^{3,4}. US has significantly advanced the early diagnosis of RA, providing better disease activity assessment and prognosis⁶. US complements clinical examinations in

diagnosing early RA and assessing remission, offering precise and cost-effective detection of early synovitis in finger joints and the wrist⁶. Although US cannot detect bone marrow edema, it effectively assesses synovitis with effusion, power Doppler signals (indicating active inflammation), and synovial hypertrophy, all specific to RA⁷.

Zheng et al. confirmed that US is feasible and capable of predicting RA disease activity⁸. Studies show that US has high sensitivity and specificity for detecting synovitis in various joints^{9,10}. This study aims to assess the value of ultrasound in the early diagnosis of RA, emphasizing its cost-effectiveness, high sensitivity and specificity, and ability to reduce radiation exposure, ultimately leading to improved patient management and treatment. As no such study has been conducted in this region in the past five years, therefore no recent data is available regarding the validity of ultrasound for the diagnosis of rheumatoid arthritis. Thus, we aim to assess the diagnostic utility of ultrasound in the early diagnosis of rheumatoid arthritis due to its cost-effectiveness, high sensitivity, and specificity, as well as its ability to reduce radiation exposure. Ultrasound facilitates early detection, leading to improved management and treatment of rheumatoid arthritis, ultimately benefiting patients.

METHODOLOGY

This study aims to validate the role of US in the early diagnosis of rheumatoid arthritis (RA), with clinical diagnosis serving as the gold standard. To achieve this, a cross-sectional validation study design was employed, conducted at the Department of Radiology, Ayub Teaching Hospital, Abbottabad. The data collection started after approval from medical ethics committee and college of physicians and surgeons (CPSP) Pakistan in December 2024 and continued until November 2025 (one year period), at which point the required sample size was achieved. Non-probability consecutive sampling was used to recruit participants, ensuring that all patients who were clinically suspected of having RA and referred for ultrasound screening were eligible for inclusion.

The study included 146 patients aged between 18 and 60 years who presented with symptoms suggesting rheumatoid arthritis, specifically polyarthralgia and morning stiffness lasting more than 30 minutes. These clinical symptoms, combined with the presence of multiple small joint pain, were key criteria for enrolment in the study. The exclusion criteria were applied to ensure that participants did not have other known rheumatic diseases, such as psoriatic arthritis or systemic lupus erythematosus (SLE), and that pregnant females were also excluded from the study to avoid potential complications. The sample size of 146 was calculated using the sample size formula for validation study taking sensitivity of ultrasound for the diagnosis for RA associated small joint inflammation to be 87.9% and specificity to be 74% and an expected prevalence of RA in the study sample to be 77.5%.¹⁰ The absolute precision was taken at 15% and the confidence interval at 95%.

Upon inclusion in the study, participants underwent a detailed clinical examination followed by an ultrasound assessment of the affected joints. The ultrasound procedure was performed by a consultant radiologist with at least five years of post-fellowship experience. The ultrasound examination specifically focused on detecting early synovitis, synovial hypertrophy, and increased blood flow in the affected joints, as these features are characteristic of rheumatoid arthritis. The ultrasound diagnosis was based on the presence of at least two of the following features: increased synovial fluid, thickening of the synovial membrane, and a positive Doppler signal indicating increased blood flow.

The clinical diagnosis of RA was established by a rheumatologist with at least five years of post-fellowship experience, adhering to the 2010 ACR and EULAR classification criteria for rheumatoid arthritis. Patients with a total score of 6 or higher on the ACR criteria were diagnosed with RA. These clinical criteria served as the gold standard for comparison with the ultrasound findings.

Demographic and clinical data were collected from each participant, including age, gender, body mass index (BMI), and medical history, including hypertension and diabetes status. The duration of symptoms was also recorded, and detailed clinical assessment notes were documented. Additionally, data regarding the number of joints showing synovitis on ultrasound were collected, as well as information about the clinical diagnosis of RA. All the data were recorded in a specially designed proforma for consistency and reliability.

Data analysis was conducted using SPSS software version 27.0. Continuous variables, such as age and BMI, were analyzed using mean $\pm$ standard deviation (SD) after conforming for normality using the Shapiro-Wilk test. Categorical variables, such as gender, hypertension, and diabetes status, were analyzed using frequencies and percentages. The diagnostic performance of ultrasound for RA diagnosis was assessed by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. A 2x2 contingency table was constructed to compare the clinical diagnosis and ultrasound results.

Receiver operating characteristic (ROC) curves were constructed to determine the optimal threshold values for the ultrasound features indicative of RA. The study also addressed potential effect modifiers, such as age, gender, and duration of symptoms, by stratifying the data and performing post-stratification analyses using chi-square tests, with a significance level set at $p \leq 0.05$.

Ethical approval for the study was obtained from the Medical Ethics Committee of Ayub Teaching Hospital, Abbottabad (RC-EA-2024/187). All participants provided written informed consent before enrolling in the study. The confidentiality of participant data was strictly maintained, with all personal information de-identified and stored securely. Participants were informed that they could withdraw from the study at any time without affecting the quality of care they received.

RESULTS

Table 1: Demographic and Clinical Characteristics of Study Participants

Demographic and Clinical Characteristics of Study Participants		N (%)
Gender	Male	38 (26.0%)
	Female	108 (74.0%)
Duration of Symptoms (Months)	≤3 Months	75 (51.4%)
	>3 Months	71 (48.6%)
BMI Categories	Normal weight	53 (36.3%)
	Over Weight	57 (39.0%)
	Obese	36 (24.7%)
Hypertension	Negative	104 (71.2%)
	Positive	42 (28.8%)
Diabetes	Negative	122 (83.6%)
	Positive	24 (16.4%)
Synovitis	Not Seen	68 (46.6%)
	Seen	78 (53.4%)
Synovial Fluid	Not Seen	63 (43.2%)
	Seen	83 (56.8%)
Increased Blood flow	Not Seen	88 (60.3%)
	Seen	58 (39.7%)
Ultrasound Screened cases of Rheumatoid Arthritis	Negative	72 (49.3%)
	Positive	74 (50.7%)
Clinically Diagnosed cases of Rheumatoid Arthritis	Negative	53 (36.3%)
	Positive	93 (63.7%)
Continuous characteristics	Mean ± SD	Minimum - Maximum
Age (n=146)	48.51 ± 8.45	24 - 60
BMI (n=146)	26.89 ± 4.80	18.0- 40.0

This table provides the distribution of study participants based on key demographic and clinical characteristics. Of the 146 participants, 74% were female (n=108), and 26% were male (n=38). Regarding symptom duration, 51.4% (n=75) had symptoms for ≤3 months, while 48.6% (n=71) had symptoms for >3 months. The BMI categories showed that 36.3% (n=53) were of normal weight, 39.0% (n=57) were overweight,

and 24.7% (n=36) were obese. Hypertension was present in 28.8% (n=42), and 16.4% (n=24) of participants had diabetes. The most common indicator on ultrasound for RA was synovial fluid presence, seen in 83 (56.8%) followed by synovitis seen in 78 (53.4%). On ultrasound screening, 50.7% (n=74) were positive for RA, while 63.7% (n=93) were clinically diagnosed with RA.

Table 2: Cross-tabulation of Clinical Diagnosis and Ultrasound Diagnosis of RA

Cross tabulation		Clinical Diagnosed RA		Total	P value
		Negative	Positive		
		N (%)	N (%)	N (%)	
RA on USG	Negative	41 (77.4%)	31 (33.3%)	72 (49.3%)	<0.001
	Positive	12 (22.6%)	62 (66.7%)	74 (50.7%)	
Total		53 (100.0%)	93 (100.0%)	146 (100.0%)	

Sensitivity: 83.8%
Specificity: 56.9%
Positive Predictive Value (PPV): 66.8%
Negative Predictive Value (NPV): 77.4%
Accuracy: 70.6%

This table compares the clinical diagnosis of RA with ultrasound diagnosis, revealing a significant association ($p<0.001$). Among the clinically negative cases, 77.4% ($n=41$) were also negative on

ultrasound, while 22.6% ($n=12$) were positive. Among the clinically positive cases, 33.3% ($n=31$) were negative on ultrasound, while 66.7% ($n=62$) were positive. The sensitivity of ultrasound for RA diagnosis was 83.8%, specificity was 56.9%, positive predictive value (PPV) was 66.8%, negative predictive value (NPV) was 77.4%, and diagnostic accuracy was 70.6%.

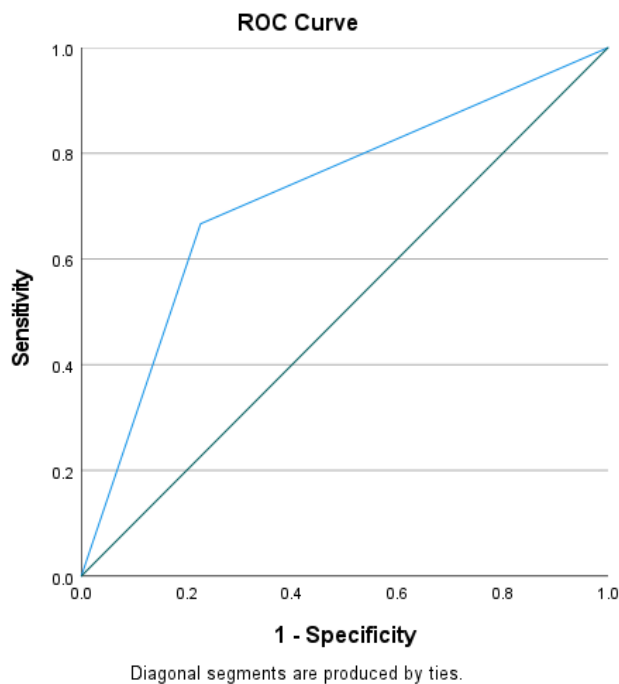


Figure 1: Receiver Operating Characteristic (ROC) Curve for Ultrasound in Diagnosing Rheumatoid Arthritis

This ROC curve illustrates the diagnostic performance of US in detecting RA when compared to clinical diagnosis as the gold standard. The curve shows sensitivity (true positive rate) on the y-axis and 1-specificity (false positive rate) on the x-axis. The area under the curve

(AUC) is 0.720, indicating a moderate ability of ultrasound to differentiate between RA and non-RA cases. The curve demonstrates the trade-off between sensitivity and specificity at various cutoff points, with the optimal balance seen around a sensitivity of 66.7% and specificity of 77.4%.

Table 3: Cross-tabulation of Gender, BMI, Hypertension, and Diabetes with RA Clinical Diagnosis

		RA Clinical Diagnosis				Total		P value
		Negative		Positive				
		N	%	N	%	N	%	
Gender	Male	9	17.0%	29	31.2%	38	26.0%	0.06
	Female	44	83.0%	64	68.8%	108	74.0%	

BMI Categories	Normal weight	21	39.6%	32	34.4%	53	36.3%	0.808
	Over Weight	20	37.7%	37	39.8%	57	39.0%	
	Obese	12	22.6%	24	25.8%	36	24.7%	
Hypertension	Negative	39	73.6%	65	69.9%	104	71.2%	0.636
	Positive	14	26.4%	28	30.1%	42	28.8%	
Diabetes	Negative	47	88.7%	75	80.6%	122	83.6%	0.208
	Positive	6	11.3%	18	19.4%	24	16.4%	

This table outlines the association between gender, BMI, hypertension, and diabetes with clinical diagnosis of RA. There was no significant

association between clinical diagnosis and gender ($p=0.06$), BMI ($p=0.808$), hypertension ($p=0.636$), or diabetes ($p=0.208$).

Table 4: Group Statistics for Age and BMI Based on RA Clinical Diagnosis

Clinically Diagnosed cases of RA		N	Mean	Std. Deviation	P value
Age	Positive	93	47.65	9.029	0.083
	Negative	53	50.02	7.162	
BMI	Positive	93	26.848	4.9195	0.887
	Negative	53	26.966	4.6298	

This table presents the group statistics for age and BMI based on the clinical diagnosis of RA. The mean age of clinically diagnosed RA patients was 47.65 (SD = 9.03), compared to 50.02 (SD = 7.16) in non-RA patients, with a p-value of 0.083. The mean BMI for clinically diagnosed RA patients was 26.85 (SD = 4.92), compared to 26.97 (SD = 4.63) for non-RA patients, with a p-value of 0.887.

DISCUSSION

The principal finding of this study is that musculoskeletal ultrasound demonstrated good sensitivity but only moderate specificity for the detection of rheumatoid arthritis when compared with clinical classification. In 146 clinically suspected patients, 93 (63.7%) fulfilled the clinical criteria for RA, while 74 (50.7%) had a positive ultrasound examination. US correctly identified 83.8% of clinically diagnosed cases, with a specificity of 56.9%, PPV of 66.8%, NPV of 77.4%, and overall accuracy of 70.6%. The ROC analysis demonstrated moderate discrimination, with an AUC of 0.720. These findings support ultrasound primarily as an adjunctive test for detecting inflammatory joint disease rather than as

an independent diagnostic substitute for clinical assessment.

The relatively high sensitivity observed in this study is consistent with the established ability of ultrasound to detect synovitis that may be clinically occult. In a systematic review of 15 studies evaluating musculoskeletal ultrasound in patients with early or possible RA, 13 studies reported additional diagnostic value over clinical and laboratory assessment; the benefit appeared particularly relevant in seronegative disease.¹¹ Similarly, a systematic review found ultrasound to be superior to clinical examination for detecting synovitis and predicting progression to persistent arthritis or RA, particularly when the wrists, MCP and MTP joints were assessed.¹² These findings provide a plausible explanation for the sensitivity of 83.8% observed in our cohort, particularly because 75 patients (51.4%) presented within three months of symptom onset, when inflammatory abnormalities may be present before established structural damage becomes radiographically apparent.

The lower specificity of 56.9% requires careful interpretation. Ultrasound demonstrates inflammation rather than RA-specific pathology.

Synovial hypertrophy, effusion and Doppler hyperaemia may occur in several inflammatory arthritides and in other conditions associated with synovial irritation. The literature therefore consistently regards ultrasound findings as complementary to, rather than independent of, clinical and serological assessment. In the present study, 12 of 53 clinically negative patients (22.6%) were ultrasound-positive, whereas 31 of 93 clinically diagnosed patients (33.3%) were ultrasound-negative. This discordance illustrates the biological and methodological limitations of using a single imaging modality against a clinical reference standard.

The nature of the ultrasound criteria used in this study may also have contributed to the moderate specificity. A positive ultrasound diagnosis required at least two of three findings- joint fluid, synovial thickening and increased Doppler flow- rather than a validated semiquantitative scoring system. Contemporary EULAR-OMERACT methodology separates grey-scale synovial hypertrophy from power Doppler activity and provides standardised semiquantitative scoring. Standardised scanning has demonstrated good-to-excellent interobserver reliability, particularly for power Doppler assessment.^{13,14} More recent evidence suggests that this approach may substantially improve diagnostic discrimination. In a 2024 cohort of 411 patients with suspected RA, including 131 patients with seronegative RA, a semiquantitative ultrasound approach incorporating synovial hypertrophy, power Doppler and bone erosion achieved 93.12% sensitivity and 91.30% specificity for seronegative RA when higher-grade Doppler or erosion findings were present.¹⁵ Although these figures cannot be directly compared with our binary diagnostic approach, they suggest that standardised scoring may be an important route to improving specificity.

The predominance of synovial fluid and synovitis in our cohort is also clinically relevant. Synovial fluid was identified in 83 patients (56.8%) and synovitis in 78 (53.4%), whereas increased Doppler flow was demonstrated in 58 (39.7%). Power Doppler is particularly valuable because it provides an imaging correlate of synovial

vascularity and active inflammation. Earlier studies have shown that Doppler activity can identify inflammatory disease that is not fully captured by clinical examination, while subsequent work has demonstrated its prognostic relevance for structural progression and disease activity.^{12,13} The lower frequency of Doppler positivity compared with grey-scale abnormalities in our cohort is therefore not unexpected and reinforces the distinction between structural/effusive abnormalities and active hyperaemia.

Our findings should also be considered in relation to conventional radiography and MRI. Plain radiography remains valuable for documenting established erosions and structural damage, but its sensitivity for early inflammatory abnormalities is limited. Ultrasound provides direct assessment of synovial and periarticular soft-tissue abnormalities without ionising radiation and is considerably more accessible than MRI in many clinical environments. Conversely, MRI remains superior for detecting bone marrow oedema and provides a more comprehensive assessment of intra-articular and osseous inflammatory change.¹⁶ A recent expert review similarly emphasised that ultrasound and MRI are complementary rather than competing modalities: ultrasound is particularly suited to accessible peripheral joints, serial assessment and bedside decision-making, whereas MRI retains advantages for deeper structures and osteitis.¹⁷

The clinical implications are particularly relevant to resource-constrained settings. The study population was predominantly female (74.0%), with a mean age of 48.5 years, reflecting the typical demographic distribution of RA, while more than half of participants had symptoms for three months or less. Ultrasound can therefore provide a practical extension of the physical examination in patients presenting early with inflammatory symptoms. Its portability, absence of ionising radiation and ability to perform dynamic, targeted examinations make it attractive where access to MRI is limited. Current evidence-based recommendations support the use of imaging to increase diagnostic certainty when clinical assessment alone is insufficient.¹⁸

An important finding of the present study is that demographic and selected metabolic variables did not significantly discriminate patients with and without clinically diagnosed RA. There was no significant association with sex ($p=0.060$), BMI ($p=0.808$), hypertension ($p=0.636$) or diabetes ($p=0.208$). Similarly, mean age did not differ significantly between clinically diagnosed RA and non-RA patients (47.65 versus 50.02 years; $p=0.083$), and BMI was virtually identical between groups (26.85 versus 26.97 kg/m²; $p=0.887$). These findings suggest that, within this clinically selected population, ultrasound interpretation should remain centred on articular inflammatory findings rather than demographic or metabolic characteristics.

Several limitations should be considered. First, the study was cross-sectional and conducted at a single tertiary-care centre, limiting generalisability. Second, clinical diagnosis based on the 2010 ACR/EULAR criteria was used as the reference standard, longitudinal clinical outcome or an independent composite reference standard. This is particularly relevant because classification criteria are designed primarily for classification and may not constitute an absolute diagnostic gold standard in every patient. Third, ultrasound assessment was based on predefined binary criteria rather than a validated EULAR-OMERACT semiquantitative score, and interobserver agreement was not assessed. Finally, the study did not evaluate the diagnostic contribution of RF or anti-CCP status, nor did it examine whether ultrasound findings predicted persistence, treatment response or radiographic progression.

CONCLUSIONS

Musculoskeletal ultrasound is a sensitive and clinically useful adjunct in patients with suspected early RA. The sensitivity of 83.8% indicates substantial potential for identifying inflammatory disease, whereas the specificity of 56.9% indicates that ultrasound abnormalities should not be interpreted as disease-specific in isolation. The moderate AUC of 0.720 further supports an adjunctive rather than standalone diagnostic role. Future prospective multicentre studies should incorporate standardised EULAR-OMERACT

scanning protocols, power Doppler semiquantitative scoring, serological status and MRI or longitudinal clinical outcomes as reference standards. Such an approach may better define the patients in whom ultrasound can meaningfully accelerate the diagnosis of RA and facilitate earlier treatment.

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