

# Role of Shear Wave Elastography of Synovium to Differentiate Rheumatoid and Tubercular Arthritis

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## Abstract

**Background:** Synovitis is the underlying pathology in various arthritis, and sometimes, it is difficult to differentiate various arthritis clinically or even by imaging. The purpose of our study was to use shear wave elastography (SWE) to evaluate rheumatoid arthritis (RA) and tubercular (TB) arthritis and to differentiate them using synovial stiffness. **Methods:** The prospective study was performed on Supersonic Imagine Aixplorer Ultrasound (USG) machine using a linear array probe SL10-2 (2–10 MHz). A total of 29 participants, 15 of RA (ACR/EULAR criteria) and 14 of proven TB arthritis were included. Region of interest of 1 mm was applied on the hypertrophied synovium and quantitative SWE data in form of elasticity (kPa) and velocity (m/s) were measured. Discrete categorical data were presented as *n* (%). Mean values were recorded along with standard deviation and the range of values. To find a maximal cutoff value of elasticity and velocity - receiver operating characteristic curve were plotted. **Results:** The mean elasticity and velocity values were  $54.81 \pm 10.6$  kPa and  $4.2 \text{ m/s} \pm 0.42$  for RA and  $37 \pm 10$  kPa and  $3.4 \pm 0.47$  m/s for TB group. Significant difference ( $P < 0.001$ ) was seen in elastic modulus values between rheumatoid and TB group with cutoff of 43.6 kPa to differentiate the two groups (sensitivity – 86.7% and specificity – 80%). Similar significant ( $P < 0.001$ ) results were seen with velocity values, with cutoff of 3.76 m/s (sensitivity – 86.7% and specificity – 80%). **Conclusion:** SWE shows the potential to be a useful adjunct to gray scale and color Doppler USG in differentiating various arthritis on the basis of elastic properties of the synovium. Elastic modulus and velocity are useful SWE quantitative parameters for synovial evaluation and can differentiate RA and TB arthritis.

**Keywords:** Arthritis, elastography, infectious, rheumatoid, synovium

## INTRODUCTION

Tubercular (TB) arthritis is a chronic infectious disease involving peripheral joints and usually presents as a monoarticular disease with preferential involvement of large (hip and knee) joints.<sup>[1]</sup> True incidence of osteoarticular tuberculosis is not known; however, data suggest that in endemic areas musculoskeletal (MSK) TB accounts for 1%–3% of tuberculous infections, 30% of which present as peripheral arthritis.<sup>[1,2]</sup> Rheumatoid arthritis (RA), on the other hand, is a chronic inflammatory disease usually presenting as polyarticular symmetric arthritis affecting 1% of the population worldwide with preferential involvement of small joints of the hands and feet.<sup>[3]</sup> These both generally present as subacute or chronic arthritis (symptoms more than 3 months) with synovial involvement and may share common features such

as periarticular soft-tissue swelling, synovitis, bone erosions, and joint effusions.<sup>[4]</sup> For accurate diagnosis of arthritis, we generally rely on clinical information of presentation of respective arthritis, the distribution of radiographic abnormalities, and supportive laboratory and radiological investigations.

RA at times may present as a monoarticular disease to start with or may remain so for a long period.<sup>[4]</sup> Furthermore, early asymmetric oligoarticular RA is not uncommon. Adding to the confusion, there are case reports suggesting multiple joint involvements in tuberculosis.<sup>[5,6]</sup> Furthermore, there are case

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Received: 09-04-2021 Revised: 16-05-2021 Accepted: 24-05-2021 Available Online: 27-12-2021

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**How to cite this article:** Chandel K, Prakash M, Sinha A, Sharma A, Chouhan DK, Sandhu MS. Role of shear wave elastography of synovium to differentiate rheumatoid and tubercular arthritis. *J Med Ultrasound* 2022;30:30-5.

reports where due to slow progression of disease, TB arthritis has been misdiagnosed as RA or juvenile RA.<sup>[7-10]</sup> Hence, monoarticular or oligo-arthritis may present as a diagnostic challenge. This is of particular interest in developing countries like ours where the incidence of tuberculosis is high, and at times, we see an atypical presentation of TB arthritis in form of multiple joint involvements, small joint involvements, or long-standing disease which may be difficult to differentiate from RA and these indeterminate cases usually require tissue diagnosis. An attempt has been made using magnetic resonance imaging (MRI) to differentiate between RA and TB arthritis.<sup>[4,11]</sup>

Ultrasound (USG) shear wave elastography (SWE) is an USG-based method widely in use for imaging these days. It allows qualitative as well as quantitative measurements of the elastic properties of the tissue.<sup>[12]</sup> In MSK imaging, it is being used currently to study muscles, tendons, nerves, ligaments, and various tumors.<sup>[12-16]</sup>

Lalitha *et al.* in their initial experience with elastography in MSK applications have described the application of SWE to differentiate between inflammatory and TB arthritis.<sup>[14]</sup> They have shown their experience with the application of SWE on synovium in TB arthritis and RA.<sup>[17]</sup> We found no other study regarding this in the literature. The purpose of this study was to determine SWE findings of RA and tuberculous arthritis with special emphasis on the evaluation of synovial elasticity and any difference in synovial stiffness of the two.

## MATERIALS AND METHODS

### Subjects

This was a prospective study between January 2017 and May 2018 (study period of 1.5 years) in our institute. Ethical clearance was taken from our Institutional Ethical Committee for the study (INT/IEC/2018/00926). Informed consent was obtained from all the patients who underwent ultrasound. 40 patients (22 clinically diagnosed RA with the active disease according to ACR/EULAR criteria and not on treatment and 18 with suspected TB arthritis) underwent SWE in the two groups. Eleven patients were however excluded (7 in the RA group, who had minimal synovitis and was difficult for SWE evaluation, and 4 in the TB group where no tissue diagnosis could be made). Finally, a total of 29 patients were included, and a total of 30 joints ( $n = 30$ ) were evaluated. Fifteen patients with RA ( $n = 15$ ) and 14 patients with TB arthritis were included in the study (total of 15 observations [ $n = 15$ ] were made, in one of the patients with disseminated TB two joints were involved and both were included). Confirmation of TB was done by either biopsy, TB – polymerase chain reaction, or culture of joint fluid aspirate. The experienced clinician examined the patients in the rheumatology and orthopedic departments. Patients of RA visiting the rheumatology department who were on treatment follow-up, were having deformities were not considered for inclusion.

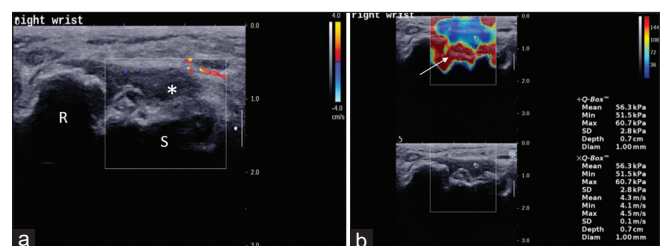
### Imaging

The sonographic examinations were done on a Supersonic Imagine Aixplorer USG machine (SuperSonic Imagine, 510 rue René Descartes, Les Jardins de la Duranne Bât. F, 13857, Aix-en-Provence, France) using a linear array probe SL10-2 (2–10 MHz). USG examination was carried out by an experienced MSK radiologist with more than 10 years of experience. In case of doubt, help was taken from another MSK radiologist, and any issues were settled by consensus of the two. The radiologists were not aware of the initial diagnosis and carried out the examination and noted the results. The results were compiled and evaluated later by another fellow radiologist, who was also not aware of the patient details. Gray scale (GS) USG, Color Doppler, and SWE were done [Figures 1 and 2]. On GS, the maximal synovial thickness was measured. On Color and Power Doppler increased or no color flow was documented.

No defined presets were available for the elasticity of the synovium so the range of elastic modulus was set between 0 and 180 for color scale. The GS USG images were displayed alongside the elastography images and were ensured that the assessment was made in the area of interest. For recording the SWE data, a standard region of interest (ROI) with a diameter of 1 mm was applied. Proper care was taken to place the ROI in the synovium (at the area of max thickness), away from the adjacent bones, soft tissues, and from fluid (in cases with effusion) to avoid reading errors. To avoid any sort of selection bias, three values at three different locations (in the area of max thickness) were taken using an ROI of 1 mm, and the mean of these three values was evaluated for each patient. Two quantitative variables (elasticity and velocity) were calculated using SWE. Quantitative values of elasticity and velocity were expressed in kilopascal (kPa) and m/s. Qualitative data were recorded as color. The scale ranges from blue for the components with the softest components and red for those with the hardest components.

### Statistical analysis

Statistical analysis was carried out with IBM (USA) SPSS Statistics Version 22. Discrete categorical data were presented



**Figure 1:** Grey scale and shear wave elastography images of wrist joint in a rheumatoid arthritis patient. (a) Grey scale shows diffuse synovial hypertrophy (Asterisk), R- Radius, S- Scaphoid (b) shear wave elastography showing color Elastogram as blue region depicting synovium with adjacent bone showing red color (arrow). In the image below Region of interest (circle) in hypertrophied synovium shows elastic modulus measuring 56.3 kPa and mean velocity was 4.3 m/s

as  $n$  (%). Mean values were recorded along with standard deviation and the range of values. Kolmogorov–Smirnov test was applied to see the distribution of the quantitative data. The student's  $t$ -test was used to examine the relationship between the two groups ( $n = 30$ ). To find a maximal cutoff value of elasticity and velocity - Receiver operating characteristic (ROC) curve were plotted. All the statistical tests were two-sided and were performed at a significance level of  $\alpha = 0.05$ .

## RESULTS

The data were normally distributed for age, GS thickness, mean elasticity, and mean velocity as confirmed by the Kolmogorov–Smirnov test. The mean age for RA was  $40.60 \pm 11.8$  years and TB arthritis was  $35.5 \pm 15.49$  years. Age, sex, duration of symptoms, and distribution of joint involvement of the two groups are compared in Tables 1 and 2, Respectively. No significant difference was noted in age and sex between the two groups. The duration of symptoms was more for RA group ( $2.48 \pm 2.4$  years) as compared to TB arthritis ( $0.81 \pm 0.56$ ).

## Imaging

### Gray scale and color Doppler

The average mean thickness of the hypertrophied synovium was  $3.10 \pm 0.86$  mm and  $3.73 \pm 1.81$  mm for RA and TB groups, respectively. On GS, synovium was hypoechoic to

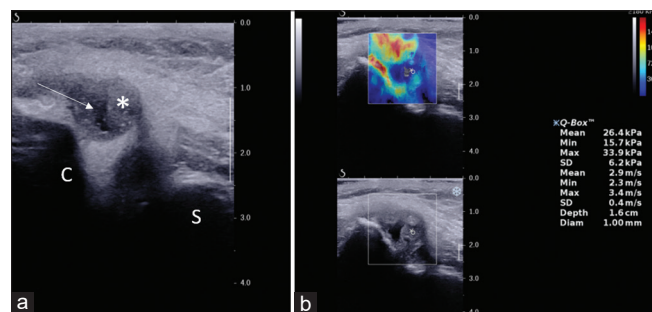
isoechoic (compared to subdermal fat). The increased color flow was observed in a total of 17 out of 30 joints (~57%). In RA 9 out of 15 (~60%) and in TB arthritis 8 out of 15 joints (~53%) showed increased color flow on Doppler. No significant difference was noted among the two groups for GS and Doppler findings [Table 1].

## Sonoelastography

The qualitative index was evaluated on basis of color for different amounts of elasticity, but no difference based on color between the groups was observed and synovium appeared blue in all the patients in both groups in our study. The mean elasticity and velocity of cases in the two groups are given in Table 3. The mean elasticity obtained in the RA group was  $54.81 \pm 10.60$  kPa and in the TB arthritis group was  $37.00 \pm 10.00$  kPa. Comparing the mean elasticities of these groups, a statistically significant difference was noted ( $P < 0.001$ ).

The ROC curve was drawn for the diagnostic performance of SWE for the differentiation between the two groups. The area under the ROC curve was 0.896. To find the optimal quantitative criteria in SWE, the ROC curve [Figure 3a] was used to compute the best cutoff that would achieve the greatest total of sensitivity and specificity. The elasticity cutoff value obtained was 43.60 kPa, and this cutoff was found to have a sensitivity of 86.70% and specificity of 80.00%.

The mean velocity obtained in the RA group was  $4.20 \pm 0.42$  m/s, and it was significantly low in the TB arthritis group ( $3.40 \pm 0.47$  m/s). The difference in mean velocities was statistically significant ( $P < 0.001$ ). The area under the ROC curve was 0.876 [Figure 3b]. To find the optimal quantitative criteria in SWE, the ROC curve was used to compute the best cutoff that would achieve the greatest total of sensitivity and specificity. The velocity cutoff value obtained was 3.76 m/s, and this cutoff was found to have a sensitivity of 86.70% and specificity of 80.00%.



**Figure 2:** Grey scale and shear wave elastography images of a case of sternoclavicular joint tuberculosis. (a) Grey scale showing SC joint with synovial hypertrophy (Asterisk) and minimal fluid (Arrow), C-Clavicle, S-Sternum (b) shear wave elastography showing color Elastogram (Blue) in the region of hypertrophied synovium, Region of interest (Circle) shows mean elastic modulus measuring 26.4 kPa and mean velocity -2.9 m/s

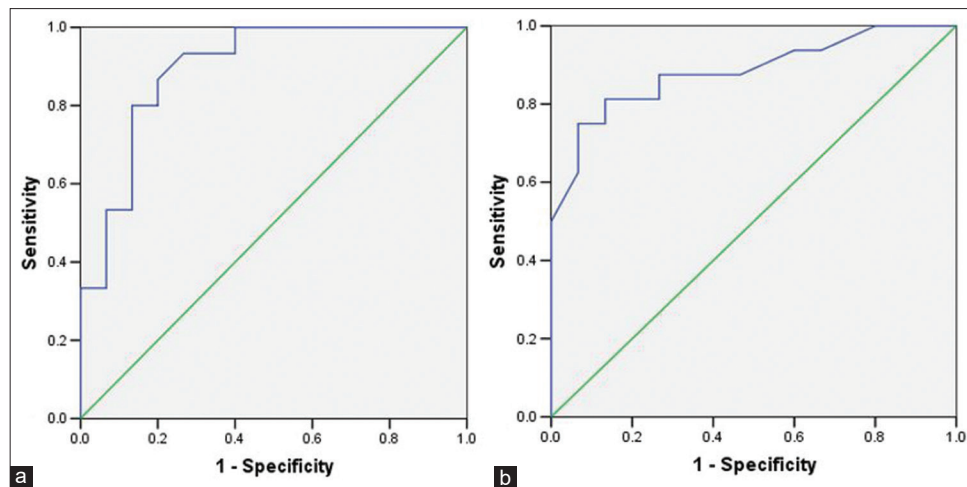
## DISCUSSION

The indeterminate chronic monoarticular disease poses a diagnostic challenge. They are multiple infectious and inflammatory differentials with infectious causes being the most common.<sup>[18,19]</sup> Conventional radiography, USG, and

**Table 1: Comparison of mean age, sex, symptoms duration, Grey Scale thickness and color flow on doppler between the two groups**

	Rheumatoid arthritis	Tubercular arthritis	P
Age (years $\pm$ SD)	40.6 $\pm$ 11.80	35.5 $\pm$ 15.49	0.326 <sup>‡</sup>
Sex			
Male, $n$ (%)	2 (13.3)	6 (42.9)	0.109 <sup>‡</sup>
Female, $n$ (%)	13 (86.7)	8 (57.1)	
Duration of symptoms (years $\pm$ SD)	2.48 $\pm$ 2.41	0.81 $\pm$ 0.56	0.001*
GS thickness (mm $\pm$ SD)	3.09 $\pm$ 0.86	3.73 $\pm$ 1.81	0.222 <sup>‡</sup>
Color flow on doppler, $n$ (%)	9 (60)	8 (53)	0.713 <sup>‡</sup>

\*Significant difference, <sup>‡</sup> No significant difference. SD: Standard deviation,  $n$ : Frequency within group, GS: Grey Scale



**Figure 3:** Receiver operating characteristic curve between rheumatoid arthritis and tubercular arthritis group for (a) Mean elasticity (b) Mean velocity

**Table 2: Distribution of joint involvement in rheumatoid arthritis and tubercular arthritis**

	RA, n (%)	TB, n (%)
Knee	3 (20)	8 (53.3)
Wrist	11 (73.3)	-
Hip	-	4 (26.7)
Shoulder	-	1 (6.7)
Sternoclavicular	-	1 (6.7)
Proximal interphalangeal	1 (6.7)	-
Mid foot	-	1 (6.7)
Total	15	15

n: Frequency of joints involved, Percentage: Within group,  
TB: Tubercular, RA: Rheumatoid arthritis

**Table 3: Mean elasticity and velocity among two groups**

Group	n	Mean elasticity (kPa)	Mean velocity (m/s)
RA	15	54.8±10.6	4.2±0.42
TB arthritis	15	37±10	3.29±0.47
P		<0.001*	<0.001*

\*Significant difference. n: Number of joints, TB: Tubercular,  
RA: Rheumatoid arthritis

MRI along with clinical details help in narrowing down the differentials, but still, there are cases which pose diagnostic challenge leaving room for newer advancements. In our research, we looked for the application of SWE to measure elastic properties of the synovium and our result looks promising and may add value to USG to differentiate between tuberculous and RA. The clinical significance of it is abundant as in equivocal cases of arthritis where SWE can be used as an additional adjunctive tool to make the correct diagnosis and even serve as marker for image-guided interventions.

As, both RA and TB arthritis have chronic inflammatory hypertrophied synovium. RA consists of articular manifestations of a disease of immunoregulatory dysfunction. The key inflammatory cascade includes overproduction and overexpression of TNF.<sup>[3]</sup> Many different types of cells, as

well as their variable products (cytokines), proliferative factors contribute to the disease process leading to bulky, hypervascular, and proliferative lesions. On microscopic examination, the synovium of RA is predominantly cellular and shows infiltration by plasma cells, lymphocytes with or without lymphoid follicles, and fibrin deposits which are often seen close to the synovial lining or within the stroma, whereas the synovium in TB arthritis contains necrotic and fibrin like material, caseous areas, and collections of leukocytes and mononuclear phagocytes. Exudation with necrosis and caseation predominates in infective (TB) and dense cellularity is seen within the inflamed synovium, this may result in a difference in stiffness in the two. In patients with RA, we do expect a larger degree of fibrosis as compared to patients presenting with relatively sub-acute symptoms as in the TB group which will have more inflammation with less or no fibrosis at all.<sup>[3,4,20]</sup>

The average elastic modulus (kPa) of the synovium for the RA group was  $54.81 \pm 10.61$  kPa and for TB arthritis was  $37.00 \pm 10.00$  kPa. There was a statistically significant difference seen in the elasticity of synovium of RA as compared to TB arthritis and this difference was independent for age and sex. The mean velocity obtained in the RA was  $4.20 \pm 0.42$  m/s, and it was significantly low in the TB arthritis group ( $3.40 \pm 0.47$  m/s). There was also a statistically significant difference in velocity between the TB group as compared to the RA group. This difference in elastic modulus and velocity was significant.

To find the optimal quantitative criteria in SWE, the ROC curve was used to compute the best cutoff for elasticity and velocity that would achieve the greatest total of sensitivity and specificity between the rheumatoid and TB groups. The elasticity cutoff value obtained was 43.60 kPa, and this cutoff was found to have a sensitivity of 86.7% and specificity of 80%. The velocity cutoff value obtained was 3.76 m/s, and this cutoff was found to have a sensitivity of 86.7% and specificity of 80%.

There was no difference based on color as both groups showed blue color on the elastography images. We believe this



happened because of our set elastography scale parameters, as we were not aware of the elasticity values to expect, the range for the color scale was set from 0 to 180 kPa. All the values observed in our study were in the range of 20–80 kPa. Hence, no obvious appreciable color difference could be observed, probably because of high color scale parameter settings.

The mean duration of symptoms of arthritis in our study for RA was 2.48 years and in the TB group was 8 months. Hence, as expected, a significant number of patients included in the RA group was symptomatic for a longer period. The average thickness of the synovium in the rheumatoid and TB group was 3.1 and 3.7 mm, respectively. There was no statistically significant difference seen among the groups. Synovial thickness was more in the patients with the TB group, this was contrary, as we expected larger synovial volume in RA. We explain this by the fact that larger joints were involved in TB and most of the observations were made in the knee and hip joints compared to the RA group where wrist joints were frequently evaluated.

RA has a propensity for hand and wrist joints and TB affects larger joints. As there is no difference between the synovium of different joints, we believe that the pathological process will determine the changes in the hypertrophied synovium, not the joint subtype. The resultant synovial volume may vary based on the joint size, with larger joints allowing more joint space hence larger synovial volume. As the involved disease process will have a similar type of histopathological changes in the hypertrophied synovium irrespective of the involved joint, therefore, elastic properties of the hypertrophied synovium should not vary across the joints.

Clinically, arthritis is classified based on the location, symmetry, and extent of the joint involvement. RA preferably involves small joints of the hands including metacarpophalangeal, proximal interphalangeal, and wrists and small joints of feet.<sup>[3,21]</sup> Extrapulmonary skeletal tuberculosis generally involves the spine. When peripheral joints are involved, it is usually a monoarticular disease with the propensity for large and medium sized joints.<sup>[1]</sup> Various imaging modalities are available for the evaluation of patients with arthritis. Plain radiographs of joints are widely used for assessing the disease process in arthritis with particular emphasis on the joints of hands and feet in RA and involved joints in tuberculosis. Radiograph shows soft-tissue swelling, osteopenia, joint space narrowing, destruction of joints, erosions of joints, malalignment, and bony ankylosis.<sup>[1]</sup>

They are useful in clinical practice as they can be performed rapidly. There are several limitations of radiographs in clinical practice for the assessment of patient status. Radiographs show the changes slowly, which may take time for the changes to manifest. Furthermore, there is a lack of sensitivity in detecting soft-tissue lesions. Hence, there is renewed interest in newer imaging modalities such as MRI and USG in the assessment of patients with various arthritis whenever the diagnosis is in doubt and to know the disease status. MRI is a better modality

for detecting soft-tissue changes in inflamed joints.<sup>[4,22]</sup> However, the major limitation of MRI is that it is expensive, time-consuming, and not easily available. In contrary to MRI, USG is an easily available, noninvasive imaging modality with high patient acceptability. GS USG assesses the synovial thickness, joint effusions, and bone erosions. Power Doppler shows increased synovial inflammation and soft-tissue vascularity.<sup>[21,23]</sup>

Elastography is a new development in the field of USG. It has been widely used in the thyroid, breast, and prostate to differentiate benign and malignant lesions.<sup>[24]</sup> In the liver, it is used in the assessment of liver fibrosis.<sup>[25]</sup>

SWE is a recent development in elastography USG. SWE allows quantitative evaluation of the elastic properties and stiffness of tissue. This method is based on the principle of generation of shear waves by the USG wave, to obtain elastic modulus. The result generated contains both qualitative data in form of color and quantitative data in form of elastic modulus (kPa).<sup>[12,13]</sup> The challenge in the application of SWE to the synovium is that there are multiple bone tissue interfaces and fluid synovial interfaces in the joint which gave rise to increased chances of fallacious values.

Being first of its kind in concept and design, our study has noteworthy flaws and limitations. Our sample size of 29 Subjects with 15 participants in the RA group and 14 in the TB group was relatively small. The study was technically challenging to perform as there was no consensus regarding the application protocol of SWE for the assessment of synovium. One observer did the USG, and the other observer's help was taken to solve any doubts, the study had no interobserver reproducibility. Elastogram of the MSK system, particularly joints is highly variable as they include a variety of tissue with heterogeneous characteristics from the skin, subcutaneous fat, fascia, muscles to the tendon, nerve, nerve sheath, vessels, and bone. Obtaining good MSK elastogram is technically difficult and requires patience and experience. As synovial tissue is near to the bone and the cartilage, the main limitation of SWE is the fallacious values that may be there near the bones which is the most critical zone for ROI placement to look for hypertrophied synovium. This may lead to loss of signal or false values, and it may not be an actual representation of the synovial pathology. No obvious appreciable qualitative color difference could be observed on Elastograms, probably because of high color parameter settings.

However, one of its kinds, our study can be used for future references, for further research. We could come across only one reference in the literature that has reported the role of SWE in studying the elasticity of synovium.<sup>[5]</sup> There are no other studies to substantiate our study.

We recommend and expect further studies to evaluate the significance of altered elastic modulus (kPa) in synovium in various groups of arthritis.

## CONCLUSION

SWE is a useful modality with clinical implications in various diseases. Our study shows that it may have good sensitivity for differentiating RA from TB arthritis. Furthermore, SWE shows the potential to be a useful adjunct to GS USG in differentiating various arthritis (RA and TB arthritis in our study) on the basis of elastic properties of the synovium. However, further dedicated research is required for further validation of our work.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest

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