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# Comparison of Ultrasound, Radiography, and Clinical Investigations in the Diagnosis of Early Rheumatoid Synovitis in Patients with Nonspecific Musculoskeletal Symptoms: A Multicenter Cross-Sectional Study

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** Early diagnosis and treatment of rheumatoid synovitis can reduce the progression of rheumatoid arthritis (RA). However, in the early stages of rheumatoid synovitis, patients may only have non-specific musculoskeletal symptoms, and plain film radiographs may not detect early synovial changes. The aim of this study was to compare the sensitivity and specificity of ultrasound with radiography, and clinical investigations in the detection of rheumatoid synovitis in patients presenting with nonspecific musculoskeletal symptoms.

**Material/Methods:** This was a non-randomized, cross-sectional, clinical study that included 189 patients who had nonspecific musculoskeletal symptoms. All patients underwent clinical investigations, postero-anterior and dorsal radiographic imaging, and bilateral grey-scale ultrasound examinations of the third and second metacarpophalangeal (MCP) joints, the third and the second proximal interphalangeal (PIP) joints, the second and the fifth metatarsophalangeal (MTP) joints, and the wrist.

**Results:** There was no clear predictive value for detection of early synovitis by clinical investigations alone. Plain film radiography of patients only provided accurate information of joint erosions but less information for synovitis. Grey-scale ultrasound was more effective at detecting early synovitis compared with clinical investigations ( $p=0.00015$ ;  $q=4.548$ ) and compared with plain film radiography ( $p=0.0002$ ;  $q=4.537$ ), and quantified the synovial changes. The predictive values of plain film radiography and clinical investigations had 0.43 and 0.24 sensitivity and 0 specificity compared with ultrasound.

**Conclusions:** The findings of this study support the use of grey-scale ultrasound in the detection of early rheumatoid synovitis of the fingers and the wrist.

**MeSH Keywords:** **Metacarpophalangeal Joint • Metatarsophalangeal Joint • Radiography • Synovitis • Ultrasonography • Wrist Joint**

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## Background

Early diagnosis and treatment of synovitis in rheumatoid arthritis (RA) reduce the progression of the disease, reduce the loss of joint function, joint damage, and inflammation [1]. Therefore, there is a need for identification of synovitis in RA at an early stage [2].

There are currently evidence-based clinical guidelines available for the clinical diagnosis and management of early RA, including the 2010 guidelines from the American College of Rheumatology (ACR), and the 2013 guidelines from the European League Against Rheumatism (EULAR) [3]. Detection of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are used for the diagnosis of RA [4]. In addition to clinical laboratory investigations, plain film radiography can detect bone erosion and is helpful in the diagnosis of advanced joint disease [5]. However, in the very early stage of RA, patients have non-specific musculoskeletal symptoms only, and symptoms and signs of synovitis may not be easy to detect, inflammatory biomarkers may not be detectable, and X-ray films can be found to be normal [6].

The use of ultrasound is non-invasive and does not cause discomfort to patients, it is cheap, and widely accessible [7]. Also, ultrasound can assess of synovitis by quantifying the thickening of the synovial membrane [8], including targeted tendon sheaths, bursae, and joints [9] by B-mode (grey-scale) ultrasound [10]. Ultrasound has site-specific sensitivity [11], and has been reported to have 44% sensitivity and 99% specificity, which compare favorably with magnetic resonance imaging (MRI), which is considered to be the 'gold-standard' method for evaluating tenosynovitis in RA [12].

Ultrasound is more accurate and sensitive in identifying rheumatoid synovitis than clinical laboratory investigations alone [13,14] and than X-rays [15]. Ultrasound with grey-scale imaging can also evaluate joint effusion and thickening of the synovium can be characterized and quantified. Doppler ultrasound, particularly power Doppler, facilitates the recognition of synovial tissue hyperemia [16]. Also, ultrasound is a more reliable diagnostic modality than plain film radiography in RA and can detect inflammation in RA as well as joint erosions [15]. Ultrasound has a high sensitivity for the detection of small bone erosions and high specificity for the detection of tenosynovitis, synovitis, bursitis, and clinical swelling [17]. At this time, there have been no previously reported studies that have followed the 2015 Standards for Reporting Diagnostic Accuracy (STARD) guidelines (<http://www.stard-statement.org>) in a cross-sectional study on the diagnosis of rheumatoid synovitis using grey-scale ultrasound radiography, without reference to ACR and EULAR guidelines [3,17].

The aim of this cross-sectional clinical study was to compare the sensitivity and specificity of ultrasound with radiography, and clinical laboratory investigations in the detection of rheumatoid synovitis in the fingers and the wrist of patients presenting with nonspecific musculoskeletal symptoms. This study was designed using the STARD guidelines but without using ACR and EULAR remission criteria [3,17].

## Material and Methods

### Ethical approvals, patients consents, study registrations, and study guidelines

This clinical study, and its design were approved by the Rencheng District First Maternal and Child Health Care Hospital Review Board (Registration No. RD/Re/Hu/15/14; dated 15 December 2014) and was approved for clinical research in human subjects. The study was registered in the Research Registry (<http://www.researchregistry.com>), (UID No. 3486; dated 16 December 2014). The protocol of the study adhered to the legal requirements of the Peoples' Republic of China, the 1964 Declaration of Helsinki, and the 2015 Standards for Reporting Diagnostic Accuracy (STARD) guidelines (<http://www.stard-statement.org>). All patients signed an informed consent form before radiology and pathology investigations. All patients enrolled in the study signed an informed consent to have their clinical data analyzed and used in a manuscript for publication, and provided consent for the analysis and use of radiological images and data in all formats.

### Inclusion criteria

A total of 189 patients were included in the study, who had been referred to the Department of Rheumatology of the Rencheng District First Maternal and Child Health Care Hospital, Heze Municipal Hospital, Heze, Yanzhou Hospital of Traditional Chinese Medicine, Yanzhou, and Jining No.1 People's Hospital, Jining, China between January 2015 to December 2017. Patients who were >18 years-of-age and who presented with nonspecific musculoskeletal symptoms were included in the study. The demographical characteristics of enrolled patients are presented in Table 1.

### Exclusion criteria

Patients who had a diagnosis of systemic lupus erythematosus (SLE) were excluded from the study. Patients with no joint tenderness, stiffness, pain, or joint swelling, detected by a medical interview and physical examinations by a rheumatologist, were excluded. Patients who had confirmed rheumatoid arthritis but who did not sign an informed consent form, who had a history of joint surgery, joint trauma, crystal-associated

**Table 1.** Demographical characteristics and working habits of enrolled patients.

Characters		Population (n=189)
Age (year)	18–40	11 (6)
	41–45	60 (31)
	46–50	55 (29)
	51–55	54 (29)
	56–60	6 (3)
	≥61	3 (2)
Gender	Female	112 (59)
	Male	77 (41)
BMI (kg/m <sup>2</sup> )		22.48±1.71
Nonspecific musculoskeletal symptoms time (days)		56±17
Ethnicity	Chinese	185 (98)
	Non-Chines	4 (2)
Systemic lupus erythematosus		41 (22)
Morning stiffness		11 (6)
Evening stiffness		7 (4)
VAS		1.08±0.72
Overall hand function*		82.76±8.56
Daily living activity#		80.96±9.84
Hand grip strength (kg)	Nondominant	23.43±3.44
	Dominant	33.4±4.58
Sensation of tingling		35 (19)
Laptop/desktop usage (h/day)	No	17 (9)
	<3	87 (46)
	3–5	58 (31)
	≥5	27 (14)
Driving (h/day)	<1	75 (40)
	1–2	89 (47)
	≥3	25 (13)

Continuous parameters are represented as mean ±SD and constant parameters are represented as number (percentage). BMI – Body Mass Index; VAS – Visual analog scale, 0: Absent pain, 10: Possible worst pain. \* 0–100 scale, 0: worst function, 100: Normal function. # 0–100 scale, 0: worst activity, 100: Normal activity.

peri-arthritis, and infective bursitis in the previous year, were excluded from the study. Patients who had been already taken pain medication or steroids, or who were being treated for organ failure were excluded from the study.

**Study design**

All 189 patients who were enrolled in the study participated in a clinical non-randomized cross-sectional study. The STARD 2015 flow diagram of the study is presented in Figure 1.

**Clinical laboratory investigations**

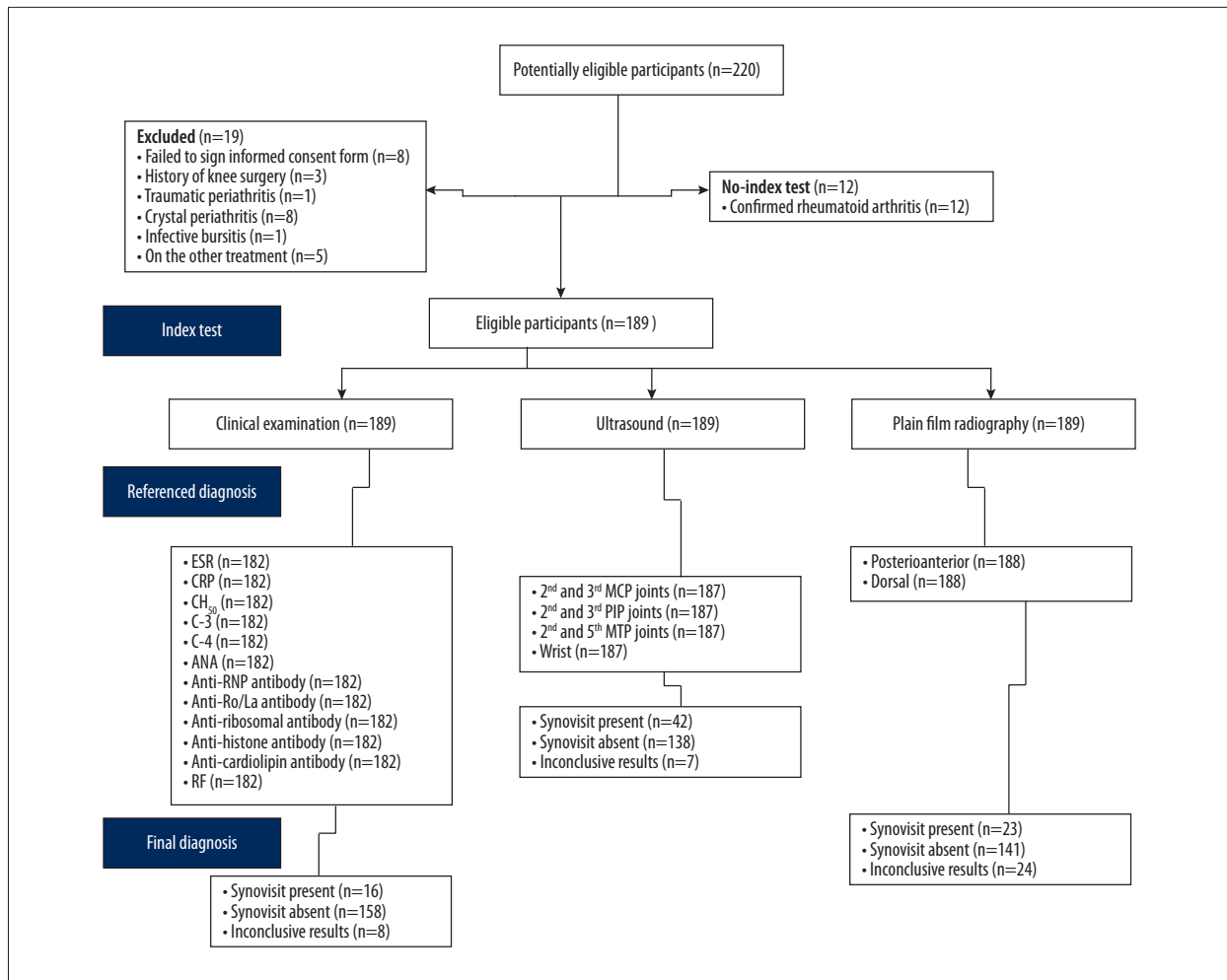
A venous blood sample was obtained from each study participant, which was stored in citrate-containing ampoules and used for the detection of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), 50% hemolytic complement activity of serum (CH<sub>50</sub>), complement components C1, C3, C4. An enzyme-linked immunosorbent assay (ELISA) was used to measure serum antibodies to ribonucleoprotein (anti-RNP), antibodies to double-strand DNA (anti-dsDNA), anti-Ro/La antibody, antibody to smooth muscle (anti-Sm), anti-ribosomal P antibody, anti-β2 glycoprotein 1 (GPI) antibody, anti-cardiolipin antibody, anti-histone antibody, and rheumatoid factor (RF) [13].

**Plain film radiography**

After half an hour of clinical examination and investigations, postero-anterior and dorsal radiographic images were performed for both hands by a radiologist who was unaware of the clinical history or findings, using an Optima XR220amx X-ray machine (GE Healthcare, USA). The specifications for plain film radiography were single-screen, high-resolution, single-emulsion, focus field distance 104 cm (41 inches), 101 mA, 49–56 kV at 301 ms [18]. Any disagreement between radiological interpretation regarding erosion or synovitis was overcome by discussion among radiologists.

**Ultrasound imaging and quantitation**

Ultrasound examinations were performed bilaterally for the third and the second metacarpophalangeal (MCP) joints, the third and the second proximal interphalangeal (PIP) joints, the second and the fifth metatarsophalangeal (MTP) joints, and the wrist using a Logiq P5 ultrasound machine (GE Healthcare, USA) with a linear probe at 6.95–11.95 MHz, and a Doppler frequency of 4.95–6.99 MHz [19]. The probe was kept parallel to the extensor digitorum tendons, and the synovium was examined in the wrist, the third and the second MCP, and PIP joints from palmar, ulnar, and dorsal sides [20]. The area of interest of the ultrasound assessment is shown in Table 2. The synovitis was scored as shown in Table 3, using the German US-7 seven-point scoring index to assess synovitis and erosions in patients with RA [18,21].



**Figure 1.** Study design: the 2015 Standards for Reporting Diagnostic Accuracy (STARD) flow diagram of the cross-sectional study. ESR – erythrocyte sedimentation rate; CRP – C-reactive protein; CH<sup>50</sup> – 50% hemolytic complement activity of serum; C – complement component; ANA – anti-nuclear antibody; RF – rheumatoid factor; MCP – metacarpophalangeal; PIP – proximal interphalangeal; MTP – metatarsophalangeal. The 2015 Standards for Reporting Diagnostic Accuracy (STARD) guidelines (<http://www.stard-statement.org>).

**Table 2.** Grey-scale ultrasound for synovitis.

Condition	Hand		
	Wrist	Fingers	Thumb
Synovitis		MCP 2 <sup>nd</sup> , 3 <sup>rd</sup>	MTP 2 <sup>nd</sup> , 5 <sup>th</sup>
	Dorsal	Palmar	Dorsal
	Palmar	Dorsal	
	Ulnar		
		PIP 2 <sup>nd</sup> , 3 <sup>rd</sup>	
	Palmar		
	Dorsal		
Joint	1	4	2

MCP – metacarpophalangeal; PIP – proximal interphalangeal; MTP – metatarsophalangeal.

**Table 3.** Grading of grey scale for synovitis.

Scale	Condition of maximal potential joint enlargement	Prediction of synovitis
0	0	Absent
1	<1/3	Mild
2	≥1/3 but <1/2	Moderate
3	≥1/2 but <2/3	Moderate to severe
4	≥2/3 but <9/10	Sever
5	≥1/2	Extreme

**Statistical analysis**

One-way analysis of variance (ANOVA), following Tukey's *post hoc* test (considering critical value  $q > 4.143$ ) was performed for predictive values between diagnostic modalities [13]. GraphPad InStat software (GraphPad, USA) was used for statistical analysis. Results were considered significant at 99% confidence level.

**Results**

From the 189 patients who were enrolled in the study and who had blood samples collected for laboratory investigations, seven samples of blood were unsuitable for analysis. The remaining 182 samples underwent laboratory investigation. The results showed that serological findings showed no clear predictive or diagnostic association with the presence of rheumatoid synovitis (Table 4).

Plain film radiographs of one patient were lost, and the sets of radiographs for the remaining 188 patients were used in the analysis. Plain film radiography of patients only provided accurate information of joint erosions but less information regarding the presence or degree of synovitis (Table 5).

Two patients were failed to undergo ultrasound examination, but ultrasound assessment of synovitis in the remaining 187 patients is shown in Table 6.

Grey-scale ultrasound was more effective at detecting early synovitis compared with clinical laboratory investigations ( $p=0.00015$ ;  $q=4.548$ ) and compared with plain film radiography ( $p=0.0002$ ,  $q=4.537$ ), and quantified the synovial changes (Figure 2). The predictive values of plain film radiography and clinical investigations had 0.43 and 0.24 sensitivity and 0 specificity when compared with ultrasound

**Discussion**

The aim of this cross-sectional study was to compare the sensitivity and specificity of ultrasound with radiography, and clinical laboratory investigations in the detection of rheumatoid synovitis in patients presenting with nonspecific musculoskeletal symptoms. There was no clear predictive value for detection of early synovitis by clinical examination and laboratory tests alone. Plain film radiography of patients only provided accurate information of joint erosions but less information for synovitis, but grey-scale ultrasound was more effective at detecting early rheumatoid synovitis compared with clinical investigations and compared with plain film radiography, and quantified the synovial changes

**Table 4.** Clinical examinations of enrolled patients.

Parameter	Reference	Populations (n=182)
ESR (mm/h)	Normal (0–22 for M and 0–29 for F)	180 (99)
	Abnormal (>22 for M and >29 for F)	2 (1)
CRP (mg/dL)	<3	179 (98)
	≥3	3 (2)
CH <sub>50</sub> (U/mL)	>41 but <90	180 (99)
	≥90	2 (1)
C1 (mg/dL)	>16 but <31	181 (99)
	≥31	1 (1)
C-3 (mg/dL)	Normal (≥88 but <252 for M and ≥88 but <206 for F)	179 (98)
	Abnormal (≥252 for M and ≥206 for F)	3 (2)
C-4 (mg/dL)	Normal (≥12 but <72 for M and ≥13 but <75 for F)	180 (99)
	Abnormal (≥72 for M and ≥75 for F)	2 (1)
Anti-nuclear antibody	Positive	0 (0)
	Negative	182 (100)
Anti-RNP antibody	Positive	0 (0)
	Negative	182 (100)
Anti-Ro/La antibody	Positive	0 (0)
	Negative	182 (100)
Anti-Sm antibody	Positive	0 (0)
	Negative	182 (100)
Anti-ribosomal P antibody	Positive	0 (0)
	Negative	182 (100)
Anti-histone antibody	Positive	0 (0)
	Negative	182 (100)
Anti-β2 GPI antibody	Positive	0 (0)
	Negative	182 (100)
Anti-cardiolipin antibody	Positive	0 (0)
	Negative	182 (100)
Rheumatoid factor (IU/mL)	<15	3 (2)
	≥15	179 (98)

Data were represented as number (percentage).  
M – Male; F – Female; ESR – erythrocyte sedimentation rate;  
CRP – C-reactive protein; CH<sub>50</sub> – hemolytic complement;  
C – complement component.

**Table 5.** Plain-film radiographic assessment of enrolled patients.

Parameters	Populations (n=188)	
	Dominant hand	Non-dominant hand
Wrist joints erosion	12 (6)	11 (6)
Hand joints erosion	15 (8)	13 (7)
Wrist and hand joints erosion	4 (2)	3 (2)
Synovitis	13 (7)	7 (4)

Data were represented as number (percentage).

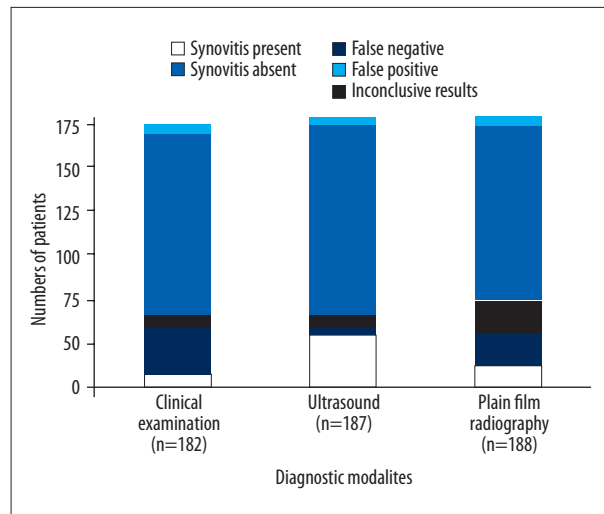
**Table 6.** Ultrasound assessment of enrolled patients.

Site	Synovitis detected (Dominant + non-dominant hand)
2 <sup>nd</sup> and 3 <sup>rd</sup> MCP joints	13 (7)
2 <sup>nd</sup> and 3 <sup>rd</sup> PIP joints	6 (3)
2 <sup>nd</sup> and 5 <sup>th</sup> MTP joints	7 (4)
Wrist	9 (5)

Populations (n)=187. Data were represented as number (percentage). MCP – metacarpophalangeal; PIP – proximal interphalangeal; MTP – metatarsophalangeal.

Several previously published diagnostic studies have shown that early detection is required in rheumatoid synovitis to prevent disease progression [1,5,22]. Imaging modalities are useful in the diagnosis of rheumatoid synovitis [13,15,16,23] and are also recommended by current clinical guidelines [17,24]. Clinical and laboratory investigations [13], plain film radiographs [25], ultrasound [20], and magnetic resonance imaging (MRI) [18] are used for the diagnosis of rheumatoid synovitis. However, clinical laboratory investigations and plain film radiographs are not sensitive for the diagnosis of early rheumatoid synovitis [18]. MRI has high signal-to-noise ratio and anatomical coverage [15] but has a high cost and may not be available in all clinical centers [18]. Ultrasound has been shown to have good intra-observer and inter-observer reproducibility and reliability for the detection of rheumatoid synovitis [7], but these properties for MRI are less clear [26]. Also, in the present study, the German US-7 seven-point scoring index to assess synovitis and erosions in patients with rheumatoid arthritis (RA) was used [18, 21]. All the methods used in this clinical study were non-invasive, rapid, non-costly, and reliable for the detection of rheumatoid synovitis.

In this study, a high frequency, linear probe was used for ultrasound diagnosis, whereas previously published ultrasound



**Figure 2.** Comparison between the predictive values of the diagnostic modalities used in the study. The *p*-values and *q*-values of the comparison of clinical laboratory investigations with ultrasound imaging were 0.00015 and 4.548. The *p*-values and *q*-values of the comparison of plain film radiography with ultrasound imaging were 0.0002 and 4.537. One-way analysis of variance (ANOVA), following Tukey's *post hoc* range test, were used for statistical analysis. Values of *p*<0.01 and *q*>4.143 were considered to be statistically significant.

studies have used an L-shaped hockey stick probe (HSP) for real-time diagnostic ultrasonography [7,15,19,23]. Also, ultrasound provides a more sensitive diagnostic imaging technique for the assessment of inflammation [7]. Considering the selection of the ultrasound probe, the probe position, the ultrasound machine configuration, the study was helpful in demonstrating the value of grey-scale ultrasound in the detection of early rheumatoid synovitis.

The predictive values of plain film radiography and clinical laboratory investigations had 0.43 and 0.24 sensitivity and no specificity compared with ultrasound. Until this time, available ultrasound techniques have required an evaluation of seven joints in the wrist and fingers [13] for the diagnosis of rheumatoid synovitis and has required repeated examinations [19]. From the findings of the ultrasound procedure used for this study, the ultrasound method was shown to be rapid, easy to use and interpret, economical, and a reliable method for the diagnosis of early rheumatoid synovitis.

There were several limitations in this study. Color Doppler imaging was not performed and would be important to evaluate in future studies. No inter-observer or intra-observer quality control (QC) checks were performed. The final decision regarding the diagnosis of rheumatoid synovitis was taken by the authors of this study only, and no independent external

expert opinion was sought. Also, this study was limited to RA involving the fingers and wrist only. A comparison between ultrasound and MRI was not undertaken, and if any of the patients had undergone MRI imaging, this data was not included in the study. Because age also has an effect on the onset and progression of rheumatoid synovitis, and this study did not include an analysis of the effect of age on the diagnostic modalities used, future studies should include analysis of the effects of age in the detection of early rheumatoid synovitis.

## Conclusions

The findings of this cross-sectional study support the use of grey-scale ultrasound in the detection of early rheumatoid synovitis of the fingers and the wrist. Clinical laboratory investigations did not provide information regarding joint erosions and synovitis, plain film radiographs provided information of

joint erosions, but did not provide information regarding synovitis. Grey-scale ultrasound is a validated, precise, cheap, and easily available method for the detection of early rheumatoid synovitis of the finger joints and the wrist.

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## Conflict of interest

None.

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