Ultrasonographic Features of Arthritis in Patients With Primary Sjögren's Syndrome and Its Clinical Significance

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Research

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Abstract

Background: This study aim to observe the feature of joint involvement in the patients with primary Sjögren's syndrome (pSS) by musculoskeletal ultrasound (US) and analyze its relationship with clinical manifestations and disease activity.

Methods: US examinations were performed in a total of 1200 joints of 40 patients with pSS. A semi-quantitative grading method (0 to 3) for scoring synovial hyperplasia, PD synovitis, bone erosion, tenosynovitis was used. The clinical and laboratory data were collected, disease activity was assessed. The correlation between US lesions and disease activity assessment and clinical manifestations were analyzed.

Results: The musculoskeletal ultrasound lesions in patients with pSS mainly involved the small joints of the hands and wrists, and the lesions were mild. The semi-quantitative score of musculoskeletal US was positively correlated with ESSPRI. The occurrence of musculoskeletal US lesions was associated with immunological abnormalities and inflammatory markers, and patients with high IgG, RF, and inflammatory markers were prone to abnormal US findings.

Conclusion: The incidence of arthritis in patients with pSS is high, and the musculoskeletal US has its characteristics. The musculoskeletal ultrasound semi-quantitative method can effectively evaluate arthritis in patients with pSS, and the US score of arthritis has a certain correlation with the overall disease activity. US can provide reference for the diagnosis of arthritis and disease activity assessment in patients with pSS.

1. Background

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease. In addition to the characteristic invasion of exocrine glands leading to dry mouth and dry eyes, it can also involve extra-glandular organs and cause systemic damage [1, 2]. About 15–90% of patients with pSS have musculoskeletal symptoms such as myalgia, morning stiffness, arthralgia, arthritis manifestation in 40–50%, and about 37% of patients are diagnosed with pSS due to arthritis [3, 4]. Given the hidden onset of pSS and the complex clinical manifestations, the early detection and identification of arthritis are helpful for the early diagnosis and treatment of pSS. At present, there are controversies about the distribution and nature of pSS arthritis. Some studies based on X-ray examinations consider pSS arthritis to be mild, non-erosive, and oligoarthritis [5, 6], while other studies suggest serious polyarthritis [7]. In recent years, there has been a growing interest in rheumatology to implement US as an instrument for the routine assessment of different rheumatic conditions. Compared with X-ray and nuclear magnetic resonance, ultrasound has significant sensitivity to synovitis and bone erosion and has the advantages of real-time and dynamic. It has been used to detect and evaluate various diseases such as rheumatoid arthritis, spinal arthritis, and systemic lupus erythematosus [8–11]. In this context, US may represent a useful imaging technique to elucidate the paradigm of the nonerosive nature of joint involvement in inflammatory arthritis, including

pSS. However, there is still a lack of studies on the ultrasound pattern of arthritis involvement in patients with pSS. The present study aimed to characterize the US pattern of joint involvement in patients with pSS, and analyzed its correlation with clinical manifestations and disease activity of pSS.

2. Materials And Methods

2.1. Patients.

A total of 40 patients with pSS diagnosed from January 2018 to June 2019 were randomly recruited. There were 3 males and 37 females, aged 23–70 years, with an average of (45.7 ± 17.5) years old. Patients were included as trial participants who (1) met the 2016 ACR/EULAR classification criteria for pSS [12]; (2)were between 18 and 70 years old; (3) signed written informed consent. The exclusion criteria were as follows: (1) patients diagnosed with secondary SS; (2) patients with liver dysfunction (ALT, AST, and TBIL more than 1.5 times the upper limit of normal)or kidney dysfunction (serum creatinine ≥ 133 mmol/L); (3) patients with neutrophil levels less than 3.0×10^9/L, severe anemia (hemoglobin less than 80 g/L), or platelet counts less than 80×10^9/L; (4) combined with other connective diseases. Patients were interviewed by three experienced rheumatologists and detailed clinical history data were collected, including gender, age, duration of disease, and clinical manifestations. The study was conducted following the Declaration of Helsinki and local regulations. The Ethics Committees of the Chongqing Hospital of Traditional Chinese Medicine approved the study protocol (approval number 2019-ky-15). All participants signed an informed consent format.

2.2 Ultrasound examination and assessment

US examinations were performed with an Esaote MyLabGamma equipped with SL2325, 6–18 MHz multi-frequency linear array transducer. All scans were performed by two rheumatologists who had undergone musculoskeletal ultrasound training for 6 months. They were blinded to clinical, radiographic, and laboratory data. Initially, each joint was scanned in grey scale to detect morphostructural changes and subsequently with the power Doppler (PD) technique to detect intra-articular blood perfusion. All US examinations were performed using a multiplanar scanning technique according to EULAR guidelines for musculoskeletal US in rheumatology [13]. The following anatomical areas were scanned bilaterally: metacarpophalangeal joints (MCP); proximal interphalangeal joints (PIP); wrist, elbow, shoulder, knee, ankle joints, and tendons associated with joints. Blood flow assessment was performed with settings standardized as follows: pulse repetition frequency = 860 Hz; Doppler frequency = 7-9.3 MHz; and wall filter = 3. PD gain was adjusted to avoid the display of random noise. For assessment of small joints, a plentiful quantity of gel was used and care was taken not to compress tissues under examination to avoid “blanching” of the PD signal due to transducer pressure.

Ultrasound detection of joint lesions follows guidelines for musculoskeletal ultrasound (US) in rheumatology developed and disseminated by European League Against Rheumatism in 2017 [14]. The following abnormalities were recorded: synovitis, bone erosions, and presence of intra-articular PD signal.

Synovitis was defined as the presence of either synovial hypertrophy or joint effusion, or both. Synovial effusion was defined as abnormal hypo or anechoic (relative to subdermal fat) intra-articular material that is displaceable and compressible, but that does not exhibit a PD signal. Synovial hypertrophy was defined as abnormal hypoechoic (relative to subdermal fat) intra-articular tissue that is nondisplaceable and poorly compressible and that may exhibit a PD signal. Semi-quantitative classification of synovial hyperplasia and energy Doppler semi-quantitative classification of synovitis refer to EULAR-OMERACT combined evaluation criteria of ultrasound synovitis. According to the degree of synovial hyperplasia, it can be divided into 0–3 grades. Doppler signal of synovitis was classified into 0–3 grades [15]. Bone erosion was defined as definite intra-articular cortical interruption with a step-down contour defect visible in both longitudinal and transverse views. The severity of bone erosions is classified as 0 to 3 grades using semi-quantitative measurements [16]. Tenosynovitis is defined as an abnormal tendon sheath that exhibits an echo-free and/or hypoechoic signal and may display a Doppler signal. Tenosynovitis is graded from 0 to 3 according to the degree of expansion of the tendon sheath and the semi-quantitative signal of energy Doppler [17]. The total score of each joint lesion was added to the final score.

2.3 Laboratory Assessment.

Peripheral blood was collected from the patients, and blood tests, urine routine, liver and kidney function, Antinuclear antibodies (ANA), anti-SSA antibody, anti-SSB antibody, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and immunoglobulin G (IgG) were collected. High-resolution CT and pulmonary function tests identify lung lesions. Urine routine and kidney function identify kidney lesions. Nerve conduction examination identifies peripheral neuropathy.

2.4 Disease activity assessment

The EULAR Sjogren's Syndrome patients report index (ESSPRI), a validated tool for subjective self-assessment of pSS disease activity, was used. It comprises three domains: dryness, fatigue, and pain (joint and/or muscle pain), with a 0–10 numerical scale for each. The final score is obtained by averaging the scores of the three domains: (dryness + fatigue + pain). The final ESSPRI score ranges from 0 to 10 [18]. The EULAR Sjogren's Syndrome disease activity index (ESSDAI), a validated tool for the global assessment of pSS disease activity for use by experienced clinicians, was also used. It includes 12 domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system, hematological, and biological. For each domain, features of disease activity are classified into four levels (0 = no activity; 1 = low; 2 = moderate; 3 = high) according to their severity. Each domain has a weight that ranges from 1 to 6. The final score is obtained by multiplying the disease domain by the domain weight and then summing the scores of all domains. The ESSDAI score ranges from 0 to 123 [19]. A prospective international 6-month duration validation study was conducted in 2015. The conclusion was that ESSDAI and ESSPRI had good construct validity. All scores were reliable. Systemic scores had a large sensitivity to change in patients whose disease activity improves. Patient scores had a small sensitivity to change, however, significantly better for ESSPRI. Systemic and patient scores poorly correlated, suggesting that they are two complementary components that should be both evaluated, but separately [20].

2.5. Statistical Analysis.

Data analysis was performed using SPSS 20.0 statistical software. Forty patients were divided into two groups according to the presence or absence of ultrasound lesions. Sixteen patients with abnormal ultrasonographic findings were divided into one group and the others into another group. The clinical manifestations of age, sex, IgG, RF, CRP, ESR, anti-SSA, anti-SSB, and organ involvement were compared between the two groups. Measurement data were expressed as mean ± standard deviation (), and group t-tests were used for comparison between groups. Count data is expressed as a percentage, and Chi-square test is used for comparison between groups. Correlation between variables was analyzed using Pearson correlation analysis. All analyses were two-tailed, and significance was set at $p < 0.05$.

3. Results

3.1. US imaging features.

A total of 1200 joints were evaluated by US in 40 patients with pSS. 16 patients were found to have at least 1 joint with ultrasound imaging abnormalities, with an incidence of 40%. According to the symptoms of joint pain combined with high inflammatory index, 14 patients (35%) were clinically diagnosed with arthritis. Ultrasound examination found synovial hyperplasia, PD synovitis, bone erosion, tenosynovitis (≥ grade 1) were defined as ultrasound imaging abnormalities. There were 486 joints showing abnormalities in US, with an incidence of 40.5%. They were as follows: MCP (133 cases), wrist (125 cases), PIP (70 cases), shoulder (60 cases), knee (46 cases), ankle (38 cases), elbow (14 cases). The types of US lesions and the joints involved are shown in Table 1. Abnormal US findings were in the order of the number of occurrences: tenosynovitis (222 cases), synovial hypertrophy (187 cases), PD synovitis (70 cases), bone erosion (7 cases). The semi-quantitative scores of various types of lesions are shown in Table 2. The typical images of ultrasound lesions are shown in Fig. 1.

Table 1
Joint distribution with US lesions (number of cases)

Joint Lesion	MCP	wrist	PIP	shoulder	knee	ankle	elbow
Tenosynovitis	68	40	41	50	0	23	0
Synovial hypertrophy	41	58	20	8	34	15	11
PD synovitis	21	24	9	2	12	0	2
Bone erosion	3	3	0	0	0	0	1
Total	133	125	70	60	46	38	14

Table 2
The semi-quantitative score of US lesions (number of cases)

Grade Lesion	Level 1	Level 2	Level 3	Total
Tenosynovitis	159	57	6	222
Synovial hypertrophy	121	53	13	187
PD synovitis	52	16	2	70
Bone erosion	5	2	0	7

3.2 The relationship between semi-quantitative scores of US lesions and overall disease activity.

The semi-quantitative scores of 486 joints showing ultrasound lesions were mainly 1 to 2 points, with a total score of 1 to 28 points, with an average of (10.0 ± 8.5) points. It is suggested that the lesion is generally mild. Pearson correlation analysis showed that the semi-quantitative score of musculoskeletal ultrasound was positively correlated with ESSPRI score (r = 0.448, $p = 0.0421$), as shown in Fig. 2. The semi-quantitative score of musculoskeletal ultrasound has no obvious correlation with ESSDAI score (r = 0.236, $p = 0.406$).

3.3 The relationship between US performance and clinical manifestations.

Forty patients with pSS were divided into two groups according to the presence or absence of ultrasound lesions. 16 patients with abnormal ultrasound imaging findings were found to be in one group, and the remaining patients were in another group. The clinical manifestations of age, gender, IgG, RF, CRP, ESR, anti-SSA, anti-SSB, and organ involvement were compared between the two groups. IgG, RF, CRP, and ESR were found to be statistically different between the two groups ($p < 0.05$), suggesting that the occurrence of musculoskeletal ultrasound lesions is associated with immunological abnormalities and inflammatory markers. Patients with high IgG, RF, and inflammatory markers are prone to abnormal ultrasound findings. See Table 3.

Table 3
Comparison of clinical manifestations between the two groups of patients

Clinical indicators	US lesion		t/χ^2	p
	Have(n = 16)	No(n = 24)		
Age(,year)	50.7 ± 3.5	43.6 ± 2.9	1.984	0.097
Gender[n(%), male]	1(6.2)	2(8.3)	0.857	0.549
RF(,IU/mL)	56.8 ± 9.8	20.3 ± 4.0	4.159	0.001
IgG(,mg/L)	25.2 ± 2.1	13.4 ± 2.0	4.765	0.001
CRP(,mg/L)	22.4 ± 6.3	12.5 ± 4.3	3.178	0.005
ESR(,mm/H)	48.2 ± 5.6	30.4 ± 2.9	2.976	0.012
SSA [n(%)]	15(93.7)	20(83.3)	0.009	1.034
SSB [n(%)]	11(68.7)	12(50.0)	0.429	0.694
Lung involvement[n(%)]	7(43.7)	8(33.3)	0.987	0.516
Kidney involvement[n(%)]	6(37.5)	5(25.0)	1.520	0.189

4. Discussion

PSS is a systemic immune disease. Muscle and joint pain are the most common manifestations except for dry mouth and dry eyes. Inflammation of joints, tendons and tendon sheaths around the joints is a common cause of pain in patients with pSS, and it is also a common first symptom of patients visiting the clinic. Arthritis is both a common clinical manifestation of pSS and one of the indicators of disease activity assessment. As a sensitive and reliable imaging method, ultrasound can evaluate the morphological changes of joints, and it can detect abnormal signs of musculoskeletal ultrasound in some asymptomatic patients, even in the subclinical stages of various rheumatoid immune inflammations [21–23]. In recent years, ultrasound has been used more and more in rheumatology, which has improved the accuracy of musculoskeletal clinical examination and played an active role in the diagnosis and management of rheumatism [24]. However, the application of US in pSS arthritis is currently inconclusive. This study found that the incidence of inflammation of joints and soft tissue around joints was 40.5% in patients with pSS, which was higher than that of clinical diagnosis of arthritis (35%), suggesting that the sensitivity of musculoskeletal ultrasound in the diagnosis of pSS arthritis might be higher. Ultrasound as a convenient, inexpensive, non-invasive, non-radiative examination method can be used as the first choice for the diagnosis of pSS arthritis, providing an objective basis for clinicians.

To date, a small number of studies have observed the ultrasound manifestations of pSS arthritis, which reported synovial hyperplasia, joint effusion, PD synovitis [25, 26], and several cases of bone erosion were

also found [27]. The existing reports on the ultrasonographic manifestations of arthritis in patients with pSS are mostly limited to the description of single joint lesions. There is no unified quantitative standard to measure the degree of arthritis damage. The main concern is the occurrence of joint erosion, and there is controversy. The musculoskeletal semi-quantitative scoring system can score various joint lesions such as joint effusion, synovial hyperplasia, tenosynovitis, and bone erosion. It has been mainly used in the diagnosis and activity evaluation of RA. In this study, the semi-quantitative score of musculoskeletal ultrasound was applied to pSS arthritis, and the degree of damage and overall activity of arthritis were objectively evaluated using quantitative criteria. Through musculoskeletal ultrasonography, we found that the lesions in the pSS patients were most common in the MCP, mainly involving the MCP, wrist joints, and PIP, while the knee joints and ankle joints were less, suggesting joint inflammation in patients with pSS. Small joints involving the hands and wrists are more common. The most common abnormalities of musculoskeletal ultrasound are tenosynovitis, followed by synovial hyperplasia, active PD synovitis is rare, and the incidence of bone erosion is low. The semi-quantitative ultrasound score is mainly graded 1, a small number of grade 2, the overall score is low, suggesting that the degree of lesion is light. Mainly involving the small joints of the hands and wrists and the milder lesions may be characteristic of arthritis in patients with pSS.

PSS is a systemic immune disease that progresses slowly and is relatively stable. The disease often recurs, manifested as alternating periods of stable and active disease. Assessing the activity and injury of the disease is extremely important for the treatment options, assessment of efficacy, and prognosis of the disease. The ESSPRI score and the ESSDAI score are currently commonly used. Both evaluation systems include joint and muscle performance, but this part of the score is strongly correlated with the evaluator, subject to subjective factors and bias [28], while imaging and laboratory-assisted examination can reduce the error. Musculoskeletal ultrasound can directly and objectively evaluate the soft tissue lesions around the joints and joints. Understanding the ultrasound image features of musculoskeletal bone in patients with pSS can increase the accuracy of diagnosis and provide an effective basis for accurate assessment of disease activity in patients with pSS. This study found the semi-quantitative score of musculoskeletal ultrasound in patients with pSS was positively correlated with ESSPRI score, but lacked correlation with ESSDAI score. Limb pain accounts for a large proportion of the ESSPRI scoring system, and the ESSDAI scoring system focuses more on the evaluation of systemic injuries such as lungs and kidneys. Therefore, musculoskeletal ultrasonography, which reflects the symptoms of joint and muscle, is related to the ESSPRI score and cannot be accurate to reflect involvement of other organs.

Not all patients with pSS develop arthritis. Which patients are prone to joint inflammation? In this study, the correlation between the musculoskeletal ultrasound performance and the clinical symptoms and laboratory indicators of patients was investigated. The results showed that the occurrence of abnormal musculoskeletal ultrasound was related to IgG, RF, CRP, and ESR, which means that IgG, RF, CRP, and ESR of pSS patients with arthritis were higher than those without arthritis. It is suggested that there are hyperimmune globulinemia and hyperimmune inflammatory reaction in pSS patients with arthritis. PSS is a systemic immune system disease. The presence of multiple autoantibodies in the serum and hyperimmunoglobulinemia are the main immunological changes. The increase in immunoglobulin is

seen in 70% of patients with pSS, of which the increase in IgG is the most common [29]. High immunoglobulin is associated with extra-glandular manifestations in patients with pSS and plays a role in arthrosis. Positive RF is a common manifestation in pSS, but its diagnostic specificity for pSS is far less significant than in RA, and its significance in pSS with arthritis is less than that of anti-cyclic citrullinated peptide antibody (ACPA) [30, 31]. The high level of CRP and ESR inflammation reflects the high activity of inflammation in the whole lesion, and may also be a direct reaction of joint inflammation. The correlation between increased inflammation indicators and arthritis may be reciprocal causation. Anti-CCP antibodies were detected in three pSS patients with bone erosion. Anti-CCP antibody is highly specific for RA. However, it is also found in 5–10% of pSS. Studies have suggested that a median follow-up of ACPA-positive patients with pSS revealed that nearly half of them had RA, especially in the case of elevated acute phase reactants. Close monitoring of radioactivity in these patients allows early detection of aggressive lesions and early effective treatment. These ACPA-positive pSS patients may actually have RA or SS secondary to RA [32].

In summary, the incidence of arthritis in patients with pSS is high, and the musculoskeletal ultrasound has its characteristics. Musculoskeletal ultrasound semi-quantitative scoring method can effectively evaluate arthritis in patients with pSS, and the ultrasound score of arthritis has a certain correlation with the overall disease activity. Ultrasonographic features can provide reference for the diagnosis of arthritis and disease activity assessment in patients with pSS. The development of arthritis in patients with PSS may be associated with elevated levels of IgG, RF, CRP, and ESR. However, this study also has certain limitations for example small sample size, the next step is to include a larger sample for further research.

Declarations

Ethics approval and consent to participate

Ethics committee approval for our study was obtained from the ethics committee of the Chongqing City Hospital of Traditional Chinese Medicine (No: 2019-ky-15).

Consent for publication

Not applicable.

Availability of data and material

The datasets are available upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Qin Shao designed this study and wrote the manuscript. Shasha Wang and Bin Wu collected data and analyzed data. Both authors read and approved the final manuscript.

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Figures

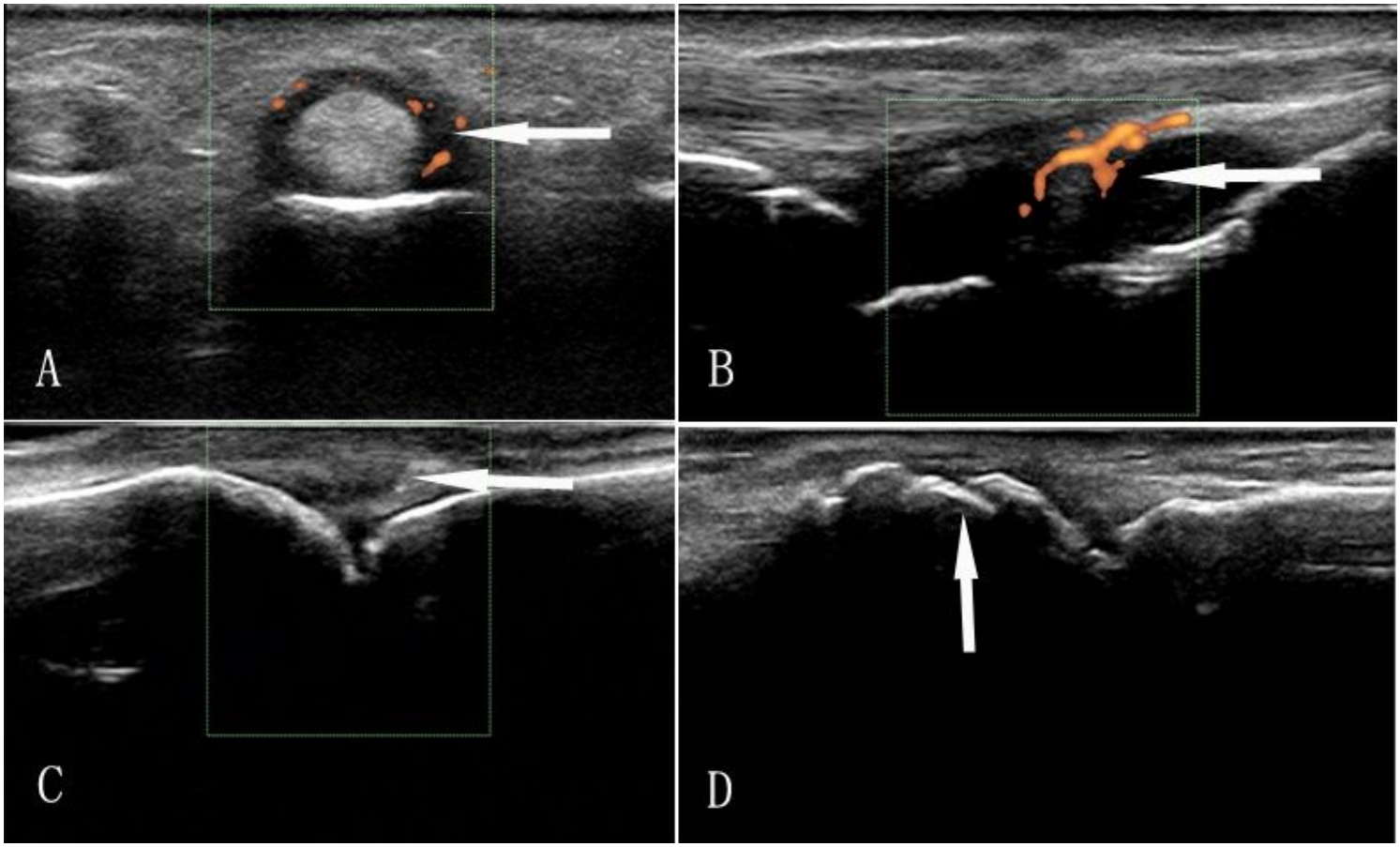

Figure 1

A. Tenosynovitis. Volar transverse scan of PIP2 B. PD synovitis. Dorsal longitudinal scan of wrist joint C. Synovial hypertrophy. Dorsal longitudinal scan of MCP 2 D. Bone erosion. Dorsal longitudinal scan of MCP 2

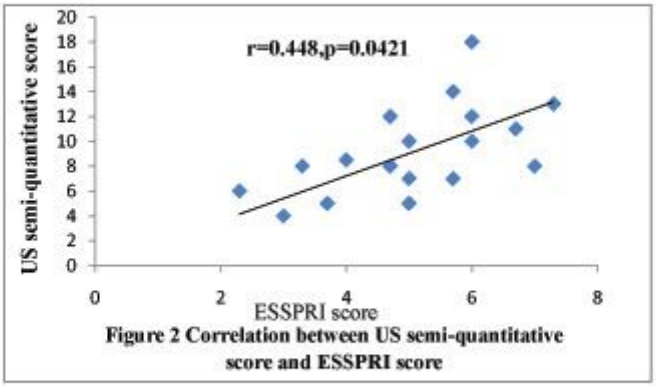

Figure 2

Correlation between US semi-quantitative score and ESSPRI score