Clinical Characteristics of Psoriatic Arthritis in Chinese Patients: A Cross-Sectional Study

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ABSTRACT

Introduction: The clinical features of psoriatic arthritis (PsA) varied in different studies from different countries, nevertheless rarely reported from China. We aimed to show the portraits of Chinese PsA patients.

Methods: Demographics as well as clinical and laboratory data at the first visit of a PsA cohort were collected. Joints and entheses were further assessed by imaging techniques. The correlation between psoriasis severity index (PASI) and disease activity in PsA (DAPSA) was analyzed. The metabolic comorbidities were also explored among patients with different disease activity.

Results: Three hundred patients with definite PsA were enrolled in this study; 159 (53.0%) of them were male. Their median age was 39 (31, 51) years with disease duration of 3 (0.6, 7) years; 15.6% patients were HLA-B27-positive, and 37.8% patients reported a family history of psoriasis or PsA. Among 300 patients, psoriasis presented earlier than arthritis in most of them (214, 74.0%), while 48 (16.6%) patients presented with arthritis before psoriasis. Articular involvement was found in 293 (97.7%) patients. Polyarticular type was most common, with proximal interphalangeal as most frequently involved joints. Axial joint involvement was found in 45 (15.4%) patients. Dactylitis was observed in 94 (31.3%) patients, most often at the second, third, and fourth toes. Enthesitis was found in 18 (6.0%) patients by physical examination, however in 129/227 (56.8%) patients by ultrasound. The DAPSA score was correlated with PASI ($r = 0.22$, $p = 0.021$). A variety of comorbidities were more often observed in patients with moderate/high disease activity comparing with those in remission/low-disease activity, especially type 2 diabetes with statistically significant difference (19.1 vs. 4.1%, $p = 0.023$). However, further logistic regression analysis showed diabetes was not independently associated with moderate/high disease activity. The most frequently prescribed medication was methotrexate (101, 66.4%). Biological agents were applied in 25 (16.4%) patients.

Conclusions: Polyarticular involvement was most common in Chinese PsA patients. Ultrasound dramatically increased the identification of peripheral enthesitis. Active PsA patients were more likely to have comorbidities.

Keywords: Psoriasis; Arthritis; Dactylitis; Enthesitis; Ultrasound
INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory arthritis that involves both peripheral joints and axial skeleton associated with psoriasis. The extra-articular manifestations and comorbidities are also very common [1]. The prevalence of psoriasis varied from 0.14% in East Asia to 1.99% in Australasia, 1.92% in Western Europe, 1.83% in Central Europe, 1.50% in North America, and 1.10% in southern Latin America [2]. PsA occurs in up to 30% of patients with psoriasis [3]. Based on a report showing the PsA prevalence of 0.01–0.1% [4], half a million PsA patients have been estimated in China.

In daily practice, PsA poses considerable diagnostic and therapeutic challenge for the treating physician, with a substantial clinical burden as well [5]. With the advent of biological therapies, the therapeutic landscape of PsA has been reshaped in recent years. At the same time, diagnostic delay, even a 6-month delay, contributes to poor radiographic and functional outcomes in PsA, suggesting the importance of diagnosis and management at an early stage [6]. On the other hand, PsA may manifest as combinations of different domains, including arthritis, dactylitis, enthesitis, axial involvement, skin, and nail changes. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) suggested to consider the domains of involvement in making treatment decisions, which could be beneficial for achieving better outcomes [7]. Therefore, a comprehensive understanding of clinical features of PsA is urgently needed to promote early diagnosis and individualized treatment strategy. The clinical features of PsA have been reported in Western countries and some Asian countries including Japan and Korea [8–11], but minimal available data in China have dramatically impeded a comprehensive understanding of PsA in this region. Therefore, we conducted a cross-sectional study in PsA patients in the scenarios of routine clinical care to fill in the gap that has hitherto existed in the PsA area.

METHODS

Study Design and Patient Enrollment

From January 2008 to October 2020, all PsA patients who visited the Department of Rheumatology and Clinical Immunology, Peking University First Hospital with available data were enrolled in this cross-sectional study. All participants met the Classification Criteria for Psoriatic Arthritis (CASPAR) with confirmed PsA diagnosis [12]. The study was approved by the institutional review board of the Peking University First Hospital, and informed consent was obtained from each participant. All the procedures were performed in accordance with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards.
Evaluation Items

Skeletal involvement was classified into five types: distal interphalangeal (DIP) involvement, asymmetrical oligoarticular involvement, polyarticular involvement, axial involvement, and arthritis mutilans according to Moll and Wright criteria [13]. In the study, the presence of tender joint and/or swollen joint was defined as articular involvement, and axial involvement was considered when a patient had inflammatory back pain and/or relevant imaging findings. The presence of dactylitis or enthesitis was evaluated by an assigned consultant rheumatologist (ZBS) based on physical examination, and further evaluated by ultrasound (GE LOGIQ-E9, USA). Entheses of quadriceps femoris, patellar ligament, medial and lateral epicondylitis of humerus, the triceps brachii, Achilles’ tendon and plantar fasciitis were scanned, and enthesitis on ultrasound was defined according to the Outcome Measures in Rheumatology clinical trials (OMERACT) definitions [14]. All the ultrasound evaluations were completed by experienced ultrasound operators who were unaware of the clinical findings. The interobserver reliability of the US evaluation between the operators had been tested and was as good as 0.986 (95% CI 0.981–0.990). Laboratory tests were performed to determine the level of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), human leucocyte antigen (HLA)-B27, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (CCP). More than three times upper limit of normal was considered as high titer positivity for RF and anti-CCP. Overweight was defined as body mass index (BMI) ≥24 kg/m² and obesity as BMI ≥28 kg/m² [15]. Skin lesions and Psoriasis severity index (PASI) for psoriasis vulgaris were evaluated by a trained rheumatologist [16]. Disease Activity Index in Psoriatic Arthritis (DAPSA) was adopted to reflect the disease activity, with 0–4 as clinical remission, 5–14 as low disease activity (LDA), 15–28 as moderate disease activity (MDA), and >28 as high disease activity (HDA) [17, 18].

RESULTS

Demographics and General Clinical Features

Three hundred well-documented patients with confirmed diagnosis of PsA were enrolled in the study. Their demographics and clinical features are shown in Table 1. Their median age was 39 (31, 51) years, with median disease duration 3 (0.6, 7) years. Over half of participants (53.0%) were male and more than one-third (37.8%) reported a family history of psoriasis and/or PsA. Regarding the first manifestation available in 289 patients, skin lesion occurred first in 214 (74.0%) patients, with a median interval of 7 years from psoriasis to arthritis. In contrast, 48 (16.6%) patients presented with arthritis first, with a median interval of 5 years from arthritis to psoriasis. Psoriasis and arthritis occurred concomitantly in the remaining 27 (9.3%) patients. Dactylitis and enthesitis were observed by physical examination in 94 (31.3%) and 19 (6.3%) patients, respectively. Nail lesions were found in 41.4% (123/297) patients. The median disease, cerebrovascular disease, and peripheral atherosclerosis were recorded. All the comorbidities were defined based on the specific diagnosis. Previous treatment was also collected and analyzed.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 (IBM, USA). For categorical variables, proportions were described as percentages. For continuous variables, median and inter-quartile ranges were reported for skewed distribution. The correlation of PASI and DAPSA was analyzed using Pearson correlation analysis. \( \chi^2 \) test or Fisher’s exact test was used to compare the proportions of comorbidities in patients with different disease activity. Logistic regression analysis was used to verify the independent association of comorbidities with disease activity. The level of statistical significance was set at \( p < 0.05 \).
Table 1  Demographics and clinical characteristics of 300 patients with PsA

| Characteristics of the patients (n = 300) |
|------------------------------------------|
| Male, n (%)                              | 159 (53.0%) |
| Age at arthritis onset, years, median (IQR) | 39 (31, 51) |
| Age at first visit, years, median (IQR)   | 47 (35, 56) |
| Duration of PsA, years, median (IQR)      | 3 (0.6, 7)  |
| Family history of psoriasis or PsA, n (%) | 95/251 (37.8%) |
| First presentation (psoriasis or arthritis), n (%) | 214/289 (74.0%) |
| Arthritis                                | 48/289 (16.6%) |
| Articular manifestations, n (%)           |             |
| Polyarticular type                        | 118/293 (40.3%) |
| Oligoarticular type                       | 111/293 (37.9%) |
| Axial involvement                         | 45/293 (15.4%) |
| Mutilans                                  | 32/293 (10.9%) |
| Distal interphalangeal type               | 24/293 (8.2%) |
| Unclassifiable                            | 21/293 (7.2%) |
| Nail lesions, n (%)                       | 123/297 (41.4%) |
| Dactylitis, n (%)                         | 94 (31.3%)   |
| Enthesitis, n (%)                         | 18 (6.0%)    |
| Laboratory tests                          |             |
| Positive rheumatoid factor, n (%)         | 13/194 (6.7%) |
| Positive anti-cyclic citrullinated peptide antibody, n (%) | 13/150 (8.7%) |
| Positive HLA-B27, n (%)                   | 28/180 (15.6%) |
| Erythrocyte sedimentation rate (mm/h), median (IQR) | 18 (8, 35) |
| C-reactive protein (mg/l, median (IQR)    | 7.4 (2.9, 21.2) |
| Psoriasis Area and Severity Index (PASI), median (IQR) | 3.3 (0.8, 7.4) |
| Disease Activity in Psoriatic Arthritis (DAPSA), median (IQR) | 15.7 (9.2, 25.6) |
| Remission, n (%)                          | 6/117 (5.1%) |
| Low disease activity, n (%)               | 43/117 (36.8%) |
| Moderate disease activity, n (%)          | 43/117 (36.8%) |
| High disease activity, n (%)              | 25/117 (21.4%) |
levels of ESR and CRP were 18 (8, 35) mm/h and 7.4 (2.9, 21.2) mg/l. RF and anti-CCP antibody were positive in 6.7% (13/194) and 8.7% (13/150) patients, respectively, while high-titer positivity of RF and/or anti-CCP was only found in three patients. Overall, HLA-B27 was positive in 15.6% (28/180) patients, and in 57.6% (19/33) patients with inflammatory back pain.

Patterns of Articular Involvement

Articular involvement was found in 293 out of 300 (97.7%) patients. There were 118 (40.3%) patients with polyarticular type, 111 (37.9%) patients with oligoarticular type, 45 (15.4%) patients with axial involvement, 32 (10.9%) patients with mutilans, and 24 (8.2%) patients with DIP type. Overlapping of two of the above patterns was observed in 37 patients. Although involvement of all peripheral joints was observed, small joints were overall more frequently involved than large joints. The frequencies of involvement at different joints in descending order were proximal interphalangeal joints (53.6%), metacarpophalangeal joints (38.9%), DIP joints (33.1%), wrists (22.5%), metatarsophalangeal joints (22.5%), knees (19.8%), ankles (18.8%), sacroiliac joints (15.4%), proximal interphalangeal joints of foot (14.3%), elbows (13.3%), shoulders (9.9%), temporal-mandibular joints (4.4%), hips (4.4%), sternoclavicular joints (3.4%), acromioclavicular joints (1.7%), sternocostal joints (1.7%), and DIP joints of the foot (1.4%) (Fig. 1).

Dactylitis

Dactylitis was found in 94 (31.3%) patients, typically presenting in a symmetrical form (Fig. 2). Dactylitis in toes was more frequently observed than in fingers (70 vs. 33), especially in the second, third and fourth toes. There were 22 (23.4%) and 19 (20.2%) patients with dactylitis on right and left second toes, 23 (24.5%) and 18 (19.1%) on right and left middle toes, 19 (20.2%) and 22 (23.4%) on right and left fourth toes, respectively.

Enthesitis

Enthesitis was identified in only 18 (6.0%) patients by physical examination, however in 129 (56.8%) patients among the 227 patients with ultrasound scan. The enthesitis found by physical examination was further confirmed by ultrasound in 14 of the 18 patients. Among the 129 patients, hypoechogenicity, increased thickness, and Doppler signal were found in 63, 74, and 57 patients, respectively, while enthesophyte, calcification, and bone erosion were
Fig. 1 Joint involvement percentage of patients. PIP proximal interphalangeal, MCP metacarpophalangeal, DIP distal interphalangeal, MTP metatarsophalangeal, SIJ sacroiliac joints, TMJ temporal-mandibular joints, SCJs sternoclavicular joints, ACJs acromioclavicular joints

Fig. 2 Distribution and frequency of dactylitis
found in 55, 32, and 35 patients, respectively. The enthesitis was mainly located around ankles, feet, wrists, hands, knees, and elbows. In ankle and foot regions, enthesitis of Achilles tendon was detected in 52 patients, plantar fasciitis in 23 patients, extensor tendon enthesitis of toes in 15 patients, tibialis posterior enthesitis in two patients and flexor digitorum profundus in one patient. Enthesitis around the knees was detected in quadriceps femoris (43 patients), patellar ligament (25 patients), iliotibial band (two patients) and medial collateral ligament (one patient). In the regions of wrist and hand, enthesitis was discovered in extensor tendons of fingers (31 patients) and extensor tendons of wrist (two patients). In the elbow, enthesitis was revealed in medial epicondylitis of humerus (14 patients), lateral epicondylitis of humerus (33 patients), and the triceps brachii (15 patients).

**Correlation Between Psoriasis Severity Index and Disease Activity in Psoriatic Arthritis**

The median DAPSA score of 104 patients with available data was 15.7 (9.2, 25.6). There were 25 (21.4%), 43 (36.8%), 43 (36.8%) and six (5.1%) patients with HDA, MDA, LDA, and clinical remission, respectively. The median PASI of these patients was 3.3 (0.8, 7.4). Overall, DAPSA score was correlated with PASI ($R = 0.22$, $p = 0.021$).

**Comorbidities**

A variety of comorbidities were documented, including hyperlipidemia (19.5%), hypertension (20.1%), hyperuricemia (14.0%), type 2 diabetes (13.1%), peripheral atherosclerosis (8.5%), coronary heart disease (4.0%), cerebrovascular disease (2.2%), and obesity/overweight (11.6%/50.7%) (Table 1). The distributions of comorbidities in PsA patients with different disease activity were shown in Table 2 and Fig. 3. Compared to patients in remission/LDA, patients in MDA/HDA were more likely to have type 2 diabetes (19.1 vs. 4.1%, $p = 0.023$), but further logistic regression analysis showed diabetes was not associated with MDA/HDA independently by age, BMI, or other conventional risk factors. Hypertension, hyperuricemia, coronary heart disease, peripheral atherosclerosis, and obesity were also more frequently observed in the MDA/HDA group, however without significant difference. Hyperlipidemia, cerebrovascular disease, and being overweight were equally distributed among patients with different disease activity.

**Previous and Current Treatment**

Of the included patients, 148 (49.3%) were disease-modifying anti-rheumatic drugs
DMARDs naïve at their first visit. Among 152 patients ever treated by DMARDs, 53 (34.9%) already discontinued DMARDs at the first visit. Methotrexate was the most used DMARD. There were 101 (66.4%) patients who were ever exposed to, and 60 (60.6%) patients remaining on methotrexate therapy at the first visit. Other applied DMARDs included leflunomide (39, 25.7%) and sulfasalazine (18, 11.8%). Biological DMARDs were ever prescribed to 25 (16.4%) patients, but only ten (10.1%) patients had been continuously adhering to the biological DMARDs at their first visit (Table 3).

DISCUSSION

This is the first study that most comprehensively illustrates the clinical features of Chinese patients with PsA. We report that polyarticular involvement was most common, with proximal interphalangeal as the most frequently involved joint. Ultrasound dramatically increased the identification of peripheral enthesitis. More comorbidities were present in active PsA patients.

The identification of enthesitis, the fundamental characteristic of PsA, which occurs in 15–45% cases in previous reports [19], is key for deciding treatment and improving prognosis [7]. In our cohort of patients, peripheral enthesitis was found infrequently (6.0%) by physical examination, however common (56.8%) on ultrasound. The tremendous difference is mainly driven by the incomprehensive physical examination on the one hand, and the presence of subclinical enthesitis on the other hand. A previous study has shown the capability of ultrasound in detecting subclinical enthesal involvement in early PsA, independently of clinical symptoms and physical examination [20]. Moreover, Fabio et al. demonstrated poor concordance between clinical enthesitis and enthesitis on power Doppler ultrasound [21]. These indicate the necessity of ultrasound examination for enthesitis in practice. In addition, ultrasound has been shown to be able to disclose the changes of enthesitis at a more advanced stage, such as enthesophyte and erosion, which are usually undetectable by clinical examination [22]. Most Chinese rheumatologists treat PsA patients based on the

Fig. 3 Comorbidities of PsA patients with different disease activity. REM remission, LDA low disease activity, MDA moderate disease activity, HDA high disease activity, *p < 0.05
GRAPPA therapeutic algorithm. Ultrasound can offer additional evidence for enthesitis. To our knowledge, this is the first descriptive study on identifying enthesitis in PsA by integration of clinical and ultrasound assessment.

Regarding patterns of articular involvement, polyarticular type (39.3%) was most common followed by oligoarticular type (37.0%). Previous reports on PsA also showed that polyarticular pattern was the most common (Table 4) except for a Korean study [11]. Axial involvement was ubiquitous in the Korean PsA patients based on a small cohort from a dermatology clinic [23], but the diversity of clinical manifestations impedes us to conclude that the same race shares common features of PsA, as shown in the studies based on a Hispanic population [9, 24]. In our cohort, the most prevalently involved joints were proximal interphalangeal joints, followed by metacarpal interphalangeal joints, while DIP involvement, which is more specific for PsA, was surprisingly rare. These may make the differential diagnosis between PsA and seronegative rheumatoid arthritis more difficult. Articular involvement appeared as the onset manifestation in 16.6% of our patients. This also challenges clinicians to make a definite diagnosis of PsA. Importantly, 37.8% of patients had a family history of psoriasis or PsA. Moreover, dactylitis was observed in 31.3% of our patients, locating more often in the toes, especially the 2nd, 3rd, and 4th toes. Putting all more specific information together will improve the early diagnosis of PsA in clinical practice. Multilans was found in 10.9% of our patients, which was consistent with the prevalence of 0.5–16% in previous studies [9–11, 24, 25].

In the study, PASI was only slightly correlated with DAPSA score, suggesting that the severity of skin lesions may be unparallel to articular involvement. Further study is needed to explore the potentially different mechanisms of skeletal and the skin lesions. However, PsA patients with higher disease activity are more likely to have metabolic comorbidities. Compared to LDA/remission groups, type 2 diabetes was significantly more frequent in the MDA/HDA groups (19.1 vs. 4.1%, p = 0.023). Other metabolic comorbidities were also numerically higher, however statically insignificant. A recent study also showed that high prevalence of metabolic syndrome in PsA was associated with the severity of PsA [27]. Also, Ennio Lubrano et al. found that anxiety (β = 14.46, p < 0.001) and fibromyalgia (β = 6.46, p = 0.025) was also positively correlated to DAPSA [28]. The association of comorbidities with disease activity warrants a prospective

| Drugs                                      | Previous treatment (n = 152) | Current treatment (n = 99) |
|--------------------------------------------|------------------------------|---------------------------|
| Conventional synthetic disease-modifying  |                              |                           |
| anti-rheumatic drugs                       |                              |                           |
| Methotrexate, n (%)                        | 101 (66.4%)                  | 60 (60.6%)                |
| Leflunomide, n (%)                         | 39 (25.7%)                   | 19 (19.2%)                |
| Sulfasalazine, n (%)                       | 18 (11.8%)                   | 14 (14.1%)                |
| Cyclosporine A, n (%)                      | 10 (6.6%)                    | 7 (7.1%)                  |
| Hydroxychloroquine, n (%)                  | 5 (3.3%)                     | 2 (2.0%)                  |
| Iguratimod, n (%)                          | 3 (2.0%)                     | 3 (3.0%)                  |
| Azathioprine, n (%)                        | 1 (0.7%)                     | 0 (0%)                    |
| Biological disease-modifying anti-rheumatic drugs |                       |                           |
| Etanercept, n (%)                          | 20 (13.2%)                   | 5 (5.1%)                  |
| Infliximab, n (%)                          | 5 (3.3%)                     | 1 (1.0%)                  |
| Adalimumab, n (%)                          | 3 (2.0%)                     | 3 (3.0%)                  |
| Secukinumab, n (%)                         | 1 (0.7%)                     | 1 (1.0%)                  |
| Nonsteroidal anti-inflammatory drugs, n (%)| 48 (31.6%)                   | 29 (29.3%)                |
| Glucocorticoid, n (%)                      | 16 (10.5%)                   | 6 (6.1%)                  |
| Thalidomide, n (%)                         | 3 (2.0%)                     | 1 (1.0%)                  |
| Traditional Chinese medicine, n (%)        | 34 (22.4%)                   | 18 (18.2%)                |
longitudinal study to confirm their casual relationships. On the other hand, PsA patients with hypertension or cardiovascular disease are more unlikely to achieve remission/LDA [29]. Several studies have shown the increased risk of cardiovascular disease in PsA patients [30, 31]. Therefore, we highly recommend screening for comorbidities in PsA patients, especially those with more active disease. Meanwhile, tighter control with aggressive management should be considered for PsA patients with comorbidities.

In our cohort, 49.3% were incident patients and DMARD-naïve, although the median disease duration of PsA was already 3 (0.6, 7) years at their first visit to our clinic. Due to few targeted DMARDs covered in the reimbursement plan in our country, csDMARDs were most often prescribed as an initial treatment, with MTX as the first choice, followed by leflunomide and sulfasalazine. These indicate the big unmet need existing both in the early diagnosis and appropriate treatment in PsA in China. More efforts are needed in the future.

There are several advantages in the present study. For the first time, we comprehensively illustrate the clinical manifestations of Chinese patients with PsA, which filled the blank of PsA in the world with different races. Moreover, 300 PsA patients was a relatively large sample size for a single-center study. Most importantly, this is the first descriptive study on PsA to include ultrasound to assess enthesitis. Our finding that the identification of enthesitis was dramatically improved with the aid of ultrasound is very useful to decide treatment for PsA patients.

We acknowledge some limitations. First, the data from a single center may lack of representativeness, but the enrolled patients were referred from all over the country, which at least partially corrected the selection bias. A multicenter study is needed to confirm the results in the future. Second, flaws of a retrospective study are obvious. For instance, enthesitis was not comprehensively assessed by physical examination in all enrolled patients, causing a low frequency of enthesitis compared to some previous reports. Third, we did not exclude PsA

\[\text{Table 4} \text{ Comparisons of clinical features of PsA patients from different countries}\]

| Features                        | Kammer et al. [8] | Gladman et al. [25] | JC et al. [9] | Marsal et al. [24] | Yuri et al. [10] | Shin et al. [11] | Kanyik et al. [26] |
|--------------------------------|-------------------|---------------------|--------------|-------------------|----------------|----------------|----------------|
| Year                            | 1979              | 1987                | 1991         | 1999              | 2015           | 2015           | 2017           |
| Country                         | America           | Canada              | Spain        | Spain             | Japan           | Korea          | South Africa   |
| No. of patients                 | 100               | 220                 | 180          | 73                | 431            | 22             | 45             |
| Male (%)                        | 53                | 52.7                | 45           | 49.3              | 40.1           | 54.5           | 55.6           |
| Oligoarticular involvement (%)  | 54                | 14                  | 37           | 7                 | 28.6           | 13.6           | 44.2           |
| Polyarticular involvement (%)   | 25                | 40                  | 35           | 88                | 60.4           | 18.2           | 76.7           |
| Distal interphalangeal type (%) | –                 | 12                  | 0            | 4                 | 8.9            | 9.1            | 46.5           |
| Mutilans (%)                    | –                 | 16                  | 2            | 14                | 0.5            | 4.6            | –              |
| Axial involvement (%)           | –                 | 27                  | 20           | 14                | 0.7            | 54.5           | 27.9           |

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patients with fibromyalgia in the study. The comorbidity of fibromyalgia might affect the assessment of disease severity of PsA patients, especially patient-reported outcome measures. Lastly, the significance of acute or chronic enthesitis under ultrasound in the clinic may be different, which is worthy of future investigation.

CONCLUSIONS

Polyarticular type was most common type in Chinese PsA patients. Ultrasound can dramatically increase the identification of peripheral enthesitis. Active PsA patients were more likely to have comorbidities.

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Author Contributions. Zhuoli Zhang conceived, designed, and coordinated the study and critically revised the manuscript. Zhibo Song had full access to all the data collection, analysis, interpretation, and drafted the manuscript. Borui Li, Xuerong Deng, and Wenhui Xie contributed to the process of data collection.

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Disclosures. Zhibo Song, Xuerong Deng, Wenhui Xie, Borui Li, Zhuoli Zhang have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Institutional Review Board (IRB) of the Peking University First Hospital, and informed consent was obtained from each participant. All procedures performed in studies involving human participants in this study were performed in accordance with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards.

Data Availability. The original datasets used for analysis in the current study can be provided on reasonable request by contacting the corresponding author.

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