

# A single indicator joint in non-systemic juvenile idiopathic arthritis whose ultrasound scores are correlated with disease activity

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## Research article

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# Abstract

**Background:** Musculoskeletal ultrasound (MSUS) has been used worldwide in adult patients with rheumatoid arthritis (RA) but not in juvenile idiopathic arthritis (JIA). The aim of this study was to investigate the application of MSUS findings of a single indicator joint in JIA to assess the disease activity and classify disease subtype.

**Methods:** Thirty-five non-systemic JIA patients with a total of 62 visits were retrospectively recruited in this study. Among involved joints, the one with highest value of grey scale (GS) plus power Doppler (PD) (=GSPD) was selected as the indicator joint of each visit. The correlations between MSUS parameters of indicator joints and the Physician Global Assessment (PGA) score, The Childhood Health Assessment Questionnaire-disability index (CHAQ-DI), and laboratory data were analyzed. The ultrasound features in different subtypes of JIA were also compared.

**Results:** PD was weakly correlated with the PGA score ( $\rho=0.323$ ,  $p=0.010$ ), while both GS and GSPD were moderately correlated with the PGA score ( $\rho=0.405$ ,  $p=0.001$ ;  $\rho=0.434$ ,  $p=0.000$ ). On the other hand, GS, PD, and GSPD were weakly correlated with CHAQ-DI. Although erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) had a weak correlation with PGA, they were not statistically correlated with GS, PD, or GSPD. The proportions of effusion, synovial hypertrophy, and enthesopathy in 3 different subtypes, showed significant differences (Fisher's exact test,  $p=0.037$ ;  $p=0.004$ ;  $p=0.019$ ). Enthesopathy was only seen in joints of enthesitis-related arthritis (ERA) but not in joints of polyarthritis and oligoarthritis.

**Conclusions:** MSUS seems to be an acceptable non-invasive tool for JIA, particularly for non-systemic JIA patients, that could assist disease classification, and whose parameters of the indicator joints may potentially contribute to the disease activity evaluation.

## Background

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory arthritis that causes arthralgia and decreased ability to function in daily life in pediatric patients [1]. The diagnosis could be difficult and delayed in children who may not clearly express the complaints. Because the joint pain could cause variable problems, including abnormal gaits, refusing to use the affected joint, or a posture of guarding the joints [2, 3], close observation is always necessary. Besides, the severity of pain sometimes was not easily evaluated, which could be influenced by many factors, including sex, age, pain threshold, family pain culture, and coping strategies [4]. Together, these could make the parents hard to objectively evaluate and report the disease severity [5]. Instead of severity evaluation by JIA patients and/or caregivers, a questionnaire is designed for them as The Childhood Health Assessment Questionnaire (CHAQ) to evaluate physical functions of JIA patients.

The Physician Global Assessment (PGA) has been widely used to evaluate the disease activity [6], and it is simple for physician to perform. However, the result could be influenced by the reaction and reporting

of pain, discomfort and physical symptoms according to the child's experience of medical personnel [7]. In our clinical experience, PGA was sometimes hard to be successfully conducted in those patients who could not cooperate well with the physicians in physical examinations, especially in the young children and toddlers. Therefore, it would be better if an objective, quick and non-invasive tool that could be applied in disease activity assessment for JIA patients.

Musculoskeletal ultrasound (MSUS) has been widely employed in adult patients with rheumatoid arthritis (RA). MSUS could help physicians to make diagnosis of synovitis in RA. MSUS findings have good correlations with classical measures of clinical activity [8]. However, the utility of MSUS in children with JIA has been just gradually emphasized in recent years, and the correlations between MSUS findings and clinical features are still under investigation [9, 10].

In this study, to evaluate the clinical utility of MSUS in JIA, we retrospectively collected the JIA patients' records including the values of PGA and CHAQ, laboratory data, and their concomitant MSUS parameters in National Taiwan University Children's Hospital (NTUCH). The MSUS features in different subtypes of JIA were compared. We then analyzed the correlations between MSUS parameters, particularly the parameters of a single selected indicator joint, and the results of PGA and CHAQ, and various laboratory data.

## Methods

### Patients

Based on the International League of Associations for Rheumatology (ILAR) diagnostic criteria, children with JIA receiving regular treatment and follow-up at NTUCH from March 2018 to August 2019 would be retrospectively recruited into this study. The inclusion criteria included those JIA patients visited pediatric rheumatic clinics and evaluated by the same pediatric rheumatologist (Dr. Yang YH); CHAQ assessment was completed by patient itself and/or caregiver at the same visit; MSUS examination and blood tests were then arranged and performed. Of note, above physician's evaluation, CHAQ assessment, MSUS examination and blood tests are routine practices at pediatric rheumatic clinics, NTUCH. The patients with shoulder joints, axial skeleton joints, and hip joints involvement were excluded, because the ultrasound scale we currently used could not access these joints. Besides, considering the extra-articular symptoms and signs are more complicated in systemic JIA that may affect the overall disease activity evaluation, those children with such subtype were also excluded in this study. This study has been approved by National Taiwan University's Hospital Research Ethics Committee (IRB approval number: [202003066RINB](#)).

### Clinical and laboratory assessments

The following basic data including sex, age, and ILAR category were recorded for each patient. Disease activity evaluation was performed by one pediatric rheumatologist who has worked in this field for more than 20 years. He rated overall disease activity by PGA according to chief complaints, symptoms, signs, and the findings of physical examinations. The PGA was given as a numerical score on a visual analogue scale (VAS) of 0–100 mm (where 0= no disease activity and 100= maximum disease activity). The CHAQ has been adapted from the Stanford Health Assessment Questionnaire for assessing functional ability in JIA patients [11]. It comprised 30 questions in eight domains: dressing and grooming; arising; eating; walking; hygiene; reach; grip; and activities. Each question had four possible answers: without any difficulty (score 0), with some difficulty (score 1), with much difficulty (score 2), and unable to do (score 3). The items with the highest score determined the score for that domain. The highest score in each domain was averaged into a summary score called CHAQ-disability index (DI), which ranged from 0 to 3. The laboratory tests included white cell count (WBC), platelet count (PLT), hemoglobin (Hb), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement (C)3, and C4.

## **MSUS evaluation**

The pediatric rheumatologist arranged MSUS for the involved joints only. The examination was then conducted by one rheumatologist (Dr. Li KJ) with more than 15 years of experience of MSUS, who didn't know the exact disease status of these JIA patients. Toshiba Xario XG ultrasound system machine was used with a broadband 7.2-18 MHz linear array transducer and identical settings optimized for power Doppler (PD) in superficial joints. We recorded the MSUS findings including effusion, synovial hypertrophy, and enthesopathy (Figure 1). The severity of effusion and synovial hypertrophy was rated by gray-scale (GS) from 0 to 3, and the severity of power signal was rated by PD from 0 to 3. This scoring system was according to the definition by the Outcomes Measure in Rheumatology (OMERACT) pediatric ultrasound task force [12, 13]. Subsequently, we calculated the sum of GS and PD as GSPD. Among the involved joints of the same subject, the joint with highest GSPD was selected as the indicator joint. The GS, PD, and GSPD of this indicator joint were evaluated for their correlations with other parameters and disease status.

## **Statistical analysis**

The statistical analyses were performed using SPSS statistics version (International Business Machines Corp., Armonk, New York, USA). The age, clinical assessment (PGA score and CHAQ-DI), MSUS parameters (GS, PD, and GSPD), and laboratory data were expressed as mean  $\pm$  standard deviation (SD). Correlations among clinical assessment and MSUS parameters and laboratory data were calculated by Spearman's rank correlation. Correlations were considered to be strong, moderate, or weak when absolute values of correlation coefficient ( $|r_{ho}|$ ) were  $>0.7$ ,  $0.4-0.7$ , or  $<0.4$ , respectively. The scatterplot pictures were used to show the relation among PGA score and CHAQ-DI. One-way analysis of variance (ANOVA)

test was used for comparison of the PGA score among the JIA subtypes. The MSUS features in different subtypes of JIA were examined using the Fisher's exact test. In these statistical analyses, a p value < 0.05 was considered to be statistically significant.

## Results

### Patients and joints characteristics

Thirty-five patients were enrolled in this study with a total of 62 visits. Among 35 patients, there were 21 girls and 14 boys; 13 patients were oligoarthritis, 15 patients were polyarthritis including rheumatoid factor (RF) positive and RF negative, while the other 7 patients were enthesitis-related arthritis (ERA). In each visit, a single joint with highest GSPD among all involved active joints was selected as the indicator joint. Therefore, 62 indicator joints were finally recruited for the analysis. Twenty-four joints were derived from JIA patients with oligoarthritis, 29 joints from polyarthritis, and 9 joints from ERA. Among these, 8 joints were elbows, 18 were wrists, 2 were fingers, 27 were knees, 6 were ankles, and 1 was a toe. The average age on the visiting day was 14.09 years old, and the gender ratio (female: male) was 40:22 (Table 1).

Table 1  
Demographic and clinical characteristics of 62 visits

<b>Age (years): mean ± SD</b>	<b>14.09 ± 5.30</b>
Gender: female/male	40/22
JIA subtype: n (%)	
Oligoarthritis	24 (38.7%)
Polyarthritis	29 (46.8%)
ERA	9 (14.5%)
Selected indicator joint: n (%)	
Elbow	8 (12.9%)
Wrist	18 (29%)
Finger	2 (3.2%)
Knee	27 (43.5%)
Ankle	6 (9.7%)
Toe	1 (1.6%)
JIA: juvenile idiopathic arthritis; ERA: enthesitis-related arthritis.	

### Disease activity and physical function scores

JIA disease activity was shown as PGA score, while the physical function was presented as CHAQ-DI. The PGA score and CHAQ-DI of 62 visits were  $18.77 \pm 22.41$  and  $0.14 \pm 0.88$ , respectively. The PGA score among the JIA subtypes showed no significant difference ( $F=2.043$ ,  $p=0.139$ ). As can be seen in figure 2, the disease activity parameter PGA score had a positive correlation with the physical function parameter CHAQ-DI ( $\rho=0.692$ ), that indicated the status of disease activity evaluated by a physician was consistent with the reported functional disability in JIA patients.

### **The MSUS features of indicator joint in different subtypes of JIA**

Effusion, synovial hypertrophy, and enthesopathy are main MSUS features of involved joints of JIA. Figure 3 summarized the presence of above 3 features in joints of different subtypes. Of 62 indicator joints, all joints (29/29) of polyarthritis were characterized by the presence of effusion and synovial hypertrophy. Twenty-one of 24 joints (87.5%) and 19 of 24 joints (79.2%) of oligoarthritis were detected respectively with effusion and synovial hypertrophy. Compared with polyarthritis and oligoarthritis, effusion and synovial hypertrophy were less seen in joints of ERA, 7 of 9 (77.8%) and 6 of 9 (66.7%), respectively. However, enthesopathy was only seen in joints of ERA (2/9) but not in joints of polyarthritis (0/29) and oligoarthritis (0/24).

### **The correlations between MSUS parameters of indicator joints and laboratory data**

The values of GS, PD, and GSPD of 62 indicator joints were  $1.74 \pm 0.89$ ,  $0.56 \pm 0.84$ , and  $2.31 \pm 1.46$ . Since chronic inflammation usually leads to leukocytosis, anemia, thrombocytosis, and elevated ESR, CRP, C3, and C4, laboratory tests including WBC, Hb, PLT, ESR, CRP, C3, and C4 are routinely performed at our clinics to provide another objective parameters for JIA evaluation. The data of 62 visits showed WBC:  $7.93 \pm 2.19 \times 10^3/\mu\text{L}$ , Hb:  $12.62 \pm 1.67$  g/dL, PLT:  $340 \pm 94 \times 10^3/\mu\text{L}$ , CRP:  $0.53 \pm 0.99$  mg/dL ESR:  $25.22 \pm 19.63$  mm/hr, C3:  $119.3 \pm 32.5$  mg/dL, C4:  $25.4 \pm 18.0$  mg/dL. We then analyzed the relationship between MSUS parameters (GS/PD/GSPD) and above laboratory data. As shown in Table 2, GS was weakly correlated with WBC, PLT, C3, and C4. PD had a weak negative correlation with Hb and a weak positive correlation with C4. Moreover, GSPD had a weak positive correlation with WBC and C3, a weak negative correlation with Hb, while had a moderate positive correlation with C4. ESR and CRP, the two common inflammatory parameters, however, were not significantly correlated with GS, PD, or GSPD.

Table 2  
The correlations between MSUS parameters and laboratory data

	Mean ± SD	GS rho (p)	PD rho (p)	GSPD rho (p)
WBC (10 <sup>3</sup> /μL)	7.93 ± 2.19	0.335 (0.013)	0.174 (0.209)	0.315 (0.020)
Hb (g/dL)	12.62 ± 1.67	-0.200 (0.148)	-0.282 (0.039)	-0.280 (0.040)
PLT (10 <sup>3</sup> /μL)	340 ± 94	0.300 (0.028)	0.151 (0.277)	0.264 (0.054)
CRP (mg/dL)	0.53 ± 0.99	0.151 (0.275)	0.093 (0.502)	0.154 (0.267)
ESR (mm/hr)	25.22 ± 19.63	0.193 (0.162)	0.211 (0.126)	0.232 (0.091)
C3 (mg/dL)	119.3 ± 32.5	0.322 (0.031)	0.186 (0.221)	0.300 (0.045)
C4 (mg/dL)	25.4 ± 18.0	0.392 (0.008)	0.322 (0.031)	0.428 (0.003)†
† Moderate correlation (0.4 ≤ rho ≤ 0.7).				
GS: grey scale, PD: power Doppler, GSPD: the sum of grey scale and power Doppler, WBC: white blood cell, Hb: hemoglobin, PLT: platelet, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, p = p value.				

### The correlations between MSUS/laboratory parameters and JIA disease status

In each visit, there were 10 objective parameters of one JIA patient including GS, PD, and GSPD of the indicator joint and 7 laboratory data (WBC, Hb, PLT, ESR, CRP, C3, and C4). Their relationship with JIA disease status that included disease activity (PGA score) and physical function (CHAQ-DI) were further elucidated. The results showed PD, WBC, ESR, CRP, and C4 had a weak positive correlation with the PGA score, while GS and GSPD had a moderate positive correlation with the PGA score. On the other hand, GS, PD, GSPD, CRP, and C4 were weakly correlated with CHAQ-DI. The other parameters had no significant correlations with CHAQ-DI (Table 3).

Table 3.  
The correlations between MSUS/laboratory parameters and disease status

	PGA rho (p)	CHAQ rho (p)
GS	0.405 (0.001)†	0.257 (0.047)
PD	0.323 (0.010)	0.305 (0.018)
GSPD	0.434 (0.000)†	0.332 (0.010)
WBC (10 <sup>3</sup> /μL)	0.28 (0.04)	0.237 (0.084)
Hb (g/dL)	-0.193 (0.161)	-0.264 (0.054)
PLT (10 <sup>3</sup> /μL)	0.045 (0.748)	0.069 (0.622)
CRP (mg/dL)	0.374 (0.005)	0.368 (0.006)
ESR (mm/hr)	0.313 (0.021)	0.215 (0.118)
C3 (mg/dL)	0.283 (0.059)	0.214 (0.158)
C4 (mg/dL)	0.365 (0.014)	0.391 (0.008)

† Moderate correlation ( $0.4 \leq |\text{rho}| \leq 0.7$ ).

PGA: Physician Global Assessment, CHAQ: Childhood Health Assessment Questionnaire, GS: grey scale, PD: power Doppler, GSPD: the sum of grey scale and power Doppler, WBC: white blood cell, Hb: hemoglobin, PLT: platelet, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, p=p value.

## Discussion

The PGA is a simple and easy tool to assess the disease activity [5], and it can also be used to evaluate the treatment outcome in JIA [14, 15]. However, it is a subjective evaluation. The results may be varied from physician to physician. MSUS is well accepted not only by children but also their parents. It is a quick and friendly tool and can be performed at clinics without sedation and general anesthesia [9, 16]. This tool does not have limitations on language or culture. In clinical assessment, it can detect subclinical synovitis more frequently than the physical examination [10, 17]. However, the studies about the relationship between MSUS findings and JIA disease activity are few.

Spârchez et al. identified the area with the most pronounced PD activity in 32 patients and they found a high level of agreement between PGA and PD score by Kappa statistics [18]. They didn't investigate the relationship between GS and PGA in the study. Algergawy et al. selected the knee joints as their objective and detected the synovial thickness and effusion volume in 20 JIA patients by ultrasound, and they found synovial thickness had a strong correlation with disease activity score of 28 joint count (DAS28) but did not have a correlation with PGA, and effusion volume had a strong correlation with DAS28 and a

moderate correlation with PGA [19]. Synovial thickness and effusion volume, like GS, were tools to quantify the severity of synovial hypertrophy and effusion. Their study, however, did not evaluate PD activity and may be useful only in JIA patients with knee involvement. In our study, we simultaneously analyzed GS, PD, and GSPD for their correlations with disease activity, and found GS and GSPD of the indicator joints had a moderate correlation with the PGA score.

In contrast to our results, Magni-Manzoni et al. showed poor correlations between MSUS parameters and PGA, and even the Juvenile Arthritis Disease Activity Score of 52 joint count (JADAS52) in 32 JIA patients [10]. In that study, they used the sum of MSUS parameters of 52 joints of each patient to compare the clinical parameters, but we used the MSUS parameters of the indicator joint to analyze. In fact, JIA is a disorder comprising a clinically heterogeneous group of chronic arthritis with different subtypes and affected joint count [20]. One study showed the initial average active joint count in persistent oligoarthritis and in RF negative polyarthritis were 1 and 8 [21]. In our clinical experience, although the affected joint count in oligoarthritis was fewer than that in polyarthritis, the disease severity in oligoarthritis may not be less than that in polyarthritis. Therefore, usage of the sum of MSUS parameters of involved joints may underestimate the disease severity in the subtypes with less affected joints. To avoid this possibility, we used one single indicator joint in this study rather than all active joints for subsequent analysis.

PD signal in synovial tissue reflexes hypervascularization of the synovial tissue, which is considered as active state [22]. Magni-Manzoni et al. found the JIA patients with persistent inactive disease had a greater frequency of PD signal at the beginning of study than the patients with synovitis flare, which suggested PD signal did not predict subsequent synovitis flare [23]. Recently, Miotto e Silva et al. found the risk of flare was five times higher in JIA patients with positive PD signal in clinical remission than in patients without positive PD signal [24]. The uncertain role of PD signal in JIA may be due to the different sensitivity of PD signal in younger children and adolescent and due to the difference in immunopathological mechanism between JIA and seropositive RA [24, 25]. In our study, the combination of PD score and GS score (GSPD) seemed to have a better correlation than single MSUS parameter (GS or PD) with disease activity (Table 3), which suggested evaluation of PD in JIA was still important and may have a synergistic effect with GS on disease evaluation. Actually, the similar combination score has been introduced in RA by EULAR-OMERACT US Taskforce [26]. To our knowledge, our study is the first one to use the highest GSPD score of involved joints to assess disease activity in JIA.

Previously, some laboratory parameters, particularly ESR and CRP have been used to assist the evaluation of JIA disease activity [27, 28]. In our study, however, there was no any strong or moderate correlations between laboratory parameters and disease activity. Similar results were noted in the study of Berntson et al [6]. Among all parameters, although some correlations existed between laboratory and MSUS parameters, GSPD presented a best correlation with the PGA score (with highest rho value). It indicated that MSUS may be a better tool to detect disease activity than laboratory tests.

In addition to disease activity evaluated by PGA, daily physical functions of JIA patients were assessed in our study by patient itself and/or caregiver. Several studies showed the CHAQ was useful for assessing functional ability rather than disease activity [14, 29, 30]. Of note, a moderate correlation was found between CHAQ-DI and PGA score (Fig. 2). Together, although evaluated by different perspectives, tools, and investigators, the overall JIA disease status was likely to be consistent in this study. Thus, we also evaluated the relationship between each parameter and physical function, and found that although not strongly associated, 3 MSUS parameters, GS, PD, and GSPD of the indicator joints and 2 laboratory parameters, CRP and C4 had weak positive correlations with CHAQ-DI.

The MSUS features in different JIA subtypes were analyzed. Effusion and synovial hypertrophy were most seen in polyarthritis, while least seen in ERA. Enthesopathy was only seen in ERA, although the case number was small (Fig. 3). It suggested MSUS may be helpful to JIA classification. Previous studies also showed the importance of MSUS in ankles to differentiate between synovitis and tenosynovitis and to improve classification in JIA [31, 32]. Jousse-Joulin et al. reported 9.4% (20/213) of enthesal sites had enthesitis in patients with JIA [33], and Weiss et al. reported 57% (17/30) of the patients with ERA had enthesopathy on MSUS examination [34]. The reason why there was only 22.2% (2/9) of ERA joints with enthesopathy might be it was the findings of indicator joints but not all involved joints.

There are some limitations in our study. Only 3 subtypes of JIA, oligoarthritis, polyarthritis, and ERA were recruited. Besides, we excluded the patients with shoulder joints, axial skeleton joints, and hip joints involvement. As a result, the case number was limited. Furthermore, PGA is a simple tool for JIA activity evaluation and is easily applied in daily practice, however, it is just one of core set of JADAS, which has been widely used in many studies. The correlations between MSUS parameters of the indicator joints and JADAS should be investigated in the future.

## Conclusions

Although more cases and further studies are needed, the current study revealed that MSUS parameters of a single indicator joint in non-systemic JIA were well correlated with PGA. MSUS seems to be an acceptable non-invasive tool for JIA patients that could assist disease classification, and whose parameters of indicator joints may potentially contribute to the disease activity evaluation.

## Declarations

### Declarations

**Ethics approval and consent to participate:** This study has been approved by National Taiwan University's Hospital Research Ethics Committee (IRB approval number: [202003066RINB](#)).

**Consent for publication:** All authors have consented to publication of the manuscript. No individual person's data are shown in the paper.

**Availability of data and materials:** The data are available on request to the corresponding author.

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**Authors' contributions:** All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Yang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design:** Huang YH, Yang YH, Li KJ, Chiang BL

**Acquisition of data:** Huang YH, Hu YC, Liao CH, Lu CH, Li KJ

**Analysis and interpretation of data:** Huang YH, Yang YH

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## **Abbreviations**

Juvenile idiopathic arthritis: JIA

Childhood Health Assessment Questionnaire: CHAQ

Physician Global Assessment: PGA

Musculoskeletal ultrasound: MSUS

Rheumatoid arthritis: RA

Visual analogue scale: VAS

Disability index: DI

White cell count: WBC

Platelet count: PLT

Hemoglobin: Hb

Erythrocyte sedimentation rate: ESR

C-reactive protein: CRP

Complement: C

Gray-scale: GS

Power Doppler: PD

Rheumatoid factor: RF

Enthesitis-related arthritis: ERA

Juvenile Arthritis Disease Activity Score: JADAS

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## Figures

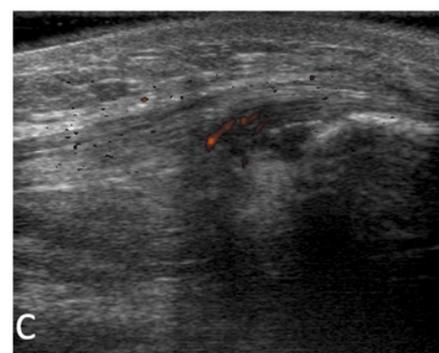
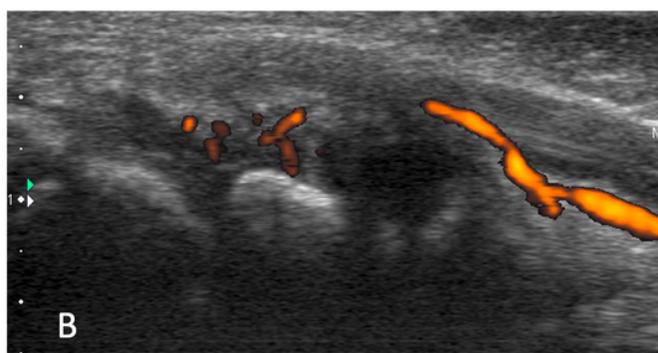


Figure 1

MSUS features in JIA. A. Effusion in the suprapatellar pouch of the knee. B. Synovial hypertrophy with PD signals in the radiocarpal and intercarpal joint. C. Longitudinal ultrasound image of the patellar tendon that shows hypoechogenicity and PD signals inside the enthesis.

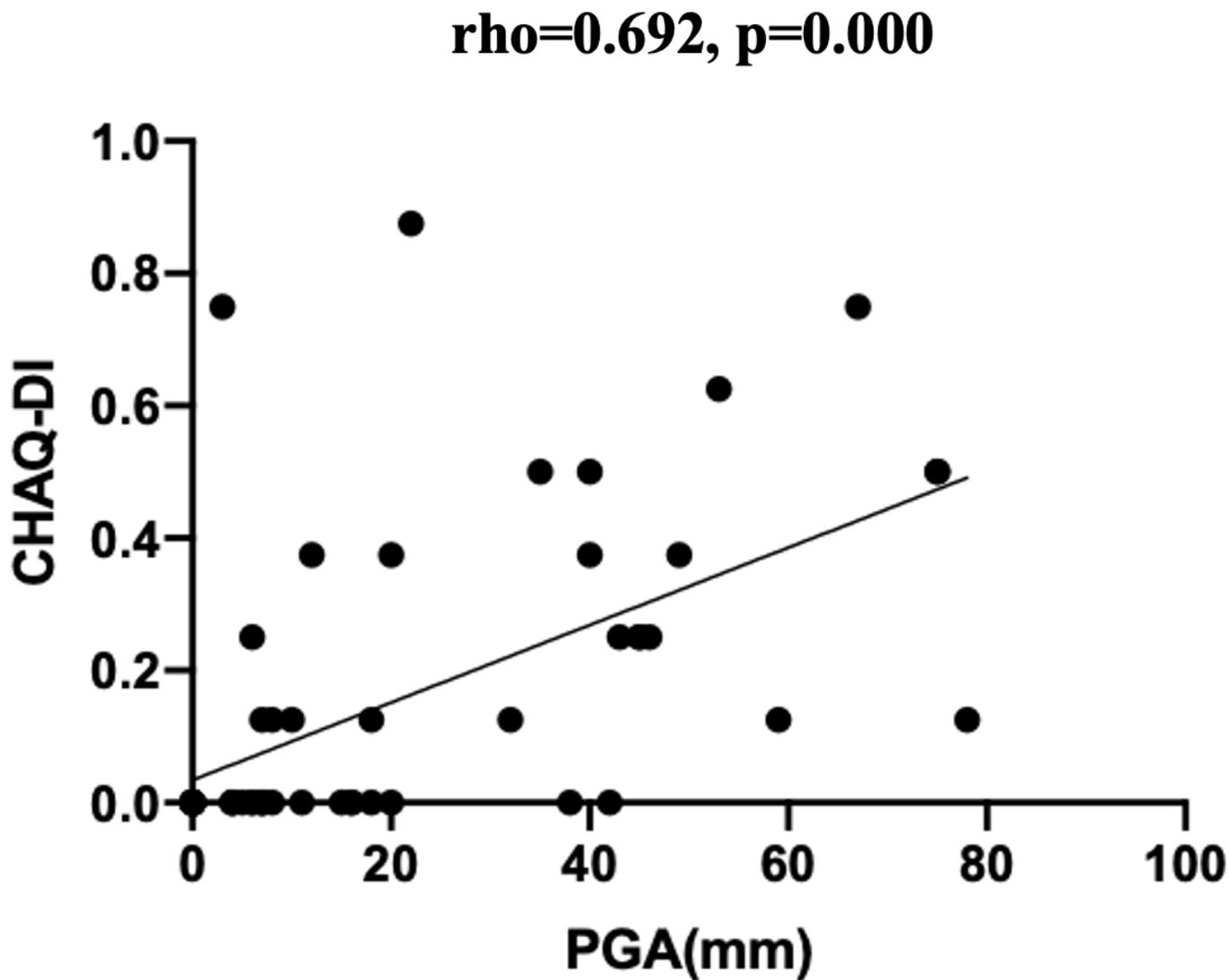
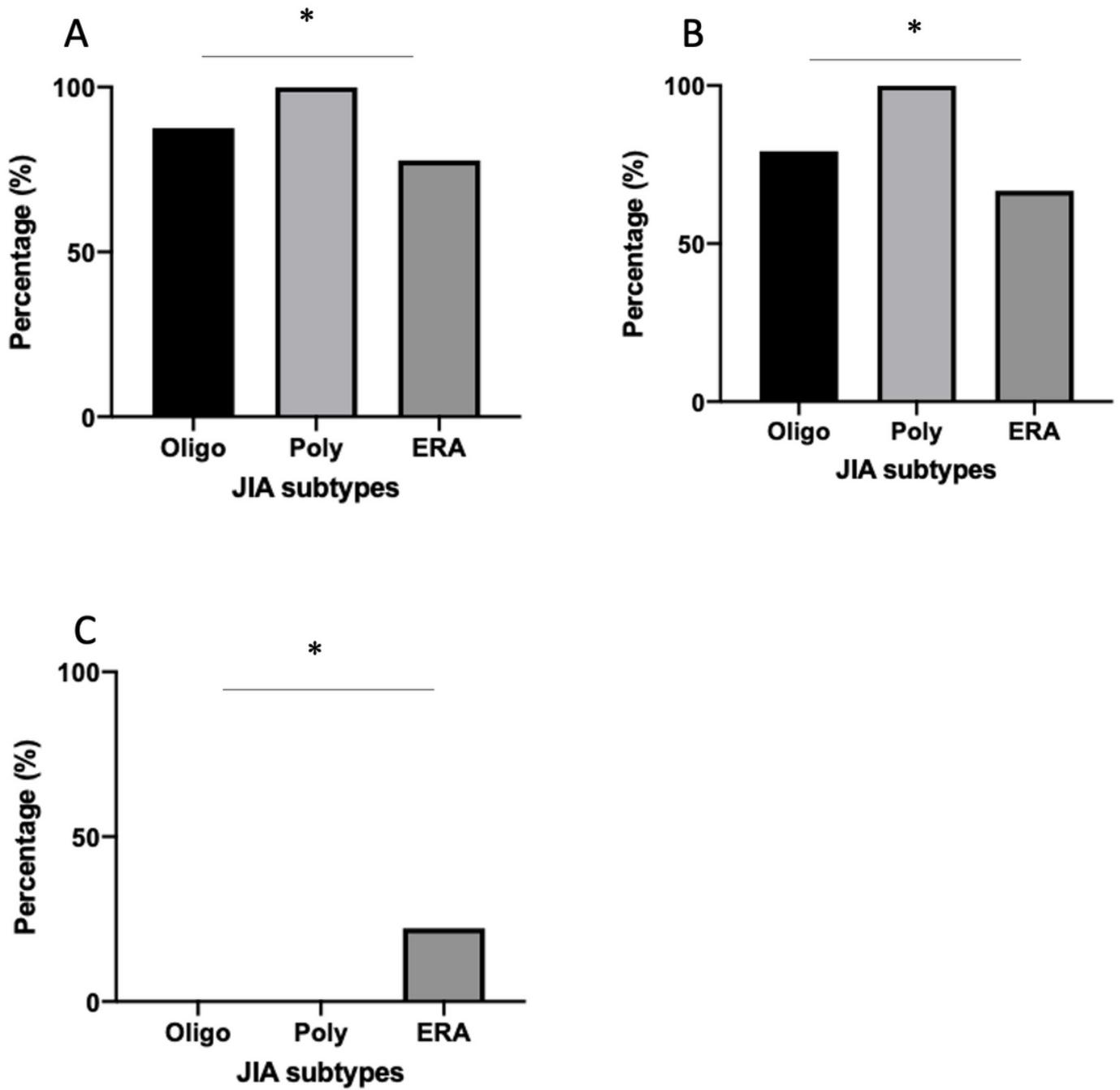


Figure 2

The scatterplot pictures of the correlation between PGA score and CHAQ-DI.



**Figure 3**

The percentage of (A) effusion, (B) synovial hypertrophy, and (C) enthesopathy in different JIA subtypes. \*p<0.05. Oligo: oligoarthritis, Poly: polyarthritis, ERA: enthesitis-related arthritis.