



## ORIGINAL ARTICLE

# Associations between radiographic features, clinical features and ultrasound of thumb-base osteoarthritis: A secondary analysis of the COMBO study

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## Funding information

This work was supported by the National Health and Medical Research Council (NHMRC) Program (No. APP1091302) and the Lincoln Center for Bone and Joint Diseases. DJH is supported by an NHMRC Practitioner Fellowship.

## Abstract

**Aim:** To investigate the associations of ultrasound and radiographic features of thumb-base osteoarthritis (OA) with thumb-base pain and hand function at baseline and 12 weeks.

**Method:** Data from a randomized controlled trial conducted in participants with symptomatic radiographic thumb-base OA were analyzed. Participants who finished follow up were included in this secondary analysis. Pain and hand function were assessed using self-reported measures. All participants underwent ultrasound examinations for synovitis, power Doppler signal (PDS), and osteophytes, and underwent radiography for osteophytes, joint space narrowing (JSN), and subchondral bone sclerosis at baseline. Hand pain and function were reassessed after the 12-week follow up. The associations of ultrasound and radiographic findings with clinical features were further evaluated, using linear regression analyses, after adjustment for relevant confounding factors.

**Results:** A total of 166 participants (average age 66.2 years; 76.5% female) were included. At baseline, radiographic JSN and subchondral bone sclerosis were associated with hand function. There was a significant association between ultrasound-detected PDS and patient's global assessment (PGA) at baseline. Baseline radiographic JSN was significantly associated with the changes in stiffness and PGA from baseline to 12 weeks. There was no association between ultrasound features and changes in the clinical outcomes over 12 weeks.

**Conclusion:** This study indicates that radiographic features significantly correlate with hand function, and ultrasound PDS is closely related to the PGA at baseline in thumb-base OA. Radiographic JSN may be a predictor for stiffness and PGA in thumb-base OA.

## KEYWORDS

arthritis, hand osteoarthritis, thumb-base joint, ultrasound, X-ray

**Trial Registration:** Registered at Australian New Zealand Clinical Trials Registry (ANZCTR), <http://www.anzctr.org.au/>, ACTRN12616000353493

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## 1 | INTRODUCTION

Hand osteoarthritis (OA) is a common musculoskeletal disorder that may cause pain, stiffness, and disability.<sup>1</sup> It typically affects the distal interphalangeal joints, proximal interphalangeal joints, and the first carpometacarpal joints.<sup>1,2</sup> Thumb-base OA is defined as OA in the first carpometacarpal joint with or without involvement of the scaphotrapezoid joint.<sup>3</sup> Among the joints affected in people with symptomatic hand OA, pain and disability are more common in the thumb-base OA than in the interphalangeal joint OA.<sup>4</sup> Currently, there are few safe and effective treatments for hand OA, despite its high prevalence and deleterious effects.<sup>5</sup> It is imperative to improve the current understanding of the pathogenesis of hand OA and to develop early diagnostic strategies for hand OA.

Radiography has been widely used in the diagnosis of hand OA and it is currently accepted as the reference standard for the assessment of most predominant structural abnormalities in hand OA.<sup>6</sup> Cartilage loss and marginal bony enlargements have been studied mainly by conventional X-ray and they are manifested as joint space narrowing (JSN), osteophytes, and subchondral bone sclerosis.<sup>7</sup> However, X-ray is unable to visualize soft tissue changes such as synovitis and effusion. Ultrasonography is a non-invasive tool and allows for evaluations of soft tissues. In recent years, ultrasonography has been increasingly used in the assessment of hand OA as a supplementary tool for the clinical evaluation of synovitis and osteophytes. Some ultrasound studies have indicated that synovitis is related to hand pain and limitation of function in people with hand OA.<sup>8,9</sup> In people with knee OA, ultrasound scores revealed significant associations with pain severity.<sup>10</sup>

Currently, clinical studies on thumb-base OA are lacking, and most of them are cross-sectional. In a recent study by our group, results showed the presence of power Doppler signal (PDS) was significantly associated with pain severity in 93 participants with thumb-base OA.<sup>11</sup> Kroon et al<sup>12</sup> found that osteophytes were more associated with thumb-base pain than inflammatory features. The associations of radiographic and ultrasound features with clinical findings are still poorly understood in thumb-base OA. In addition, whether imaging features can predict the clinical outcome of thumb-base OA has never been studied. In the present study, data from a randomized controlled trial conducted in participants with thumb-base OA were further analyzed, aiming to examine the associations of ultrasound and radiographic features of OA with changes in pain and hand function within 12 weeks.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

Cross-sectional and longitudinal data were derived from the Efficacy of Combined Conservative Therapies on Clinical Outcomes in Patients with Thumb Base Osteoarthritis (COMBO) trial starting in May 2016 (Trial registration No: ACTRN12616000353493).<sup>13</sup>

The inclusion criteria were as follows: (a) participants aged over 40 years; (b) thumb-base pain for at least half of the days in the past month; (c) average pain  $\geq 40$  on a 0-100 mm Visual Analogue Scale (VAS)<sup>14</sup> over 48 hours before enrollment; (d) Functional Index for Hand Osteoarthritis (FIHOA, range 0-30) score  $\geq 6$ <sup>15</sup>; (e) Kellgren Lawrence grade (KLG)<sup>16</sup>  $\geq 2$  in the index thumb-base joint; and (f) informed consent obtained before the study.

Exclusion criteria were as follows: participants diagnosed with (a) crystal-related arthritis (eg, gout); (b) autoimmune arthritis (eg, rheumatoid arthritis), hemochromatosis or fibromyalgia; (c) significant injury to the index joint in the past 6 months; or (d) any other self-reported hand condition that is likely to cause pain at the thumb base (eg, scaphoid fracture).

The most symptomatic hand, as defined by more severe pain on the VAS score or worst function over the previous 48 hours if the same VAS score in both hands, was included in cases of bilateral symptomatic thumb-base OA.

This study was approved by the local Ethics Committee (HREC/15/HAWKE/479). All participants underwent clinical assessment, and ultrasound and radiographic evaluations at baseline and clinical assessment at 12-week follow up between May 2016 and October 2018. Two hundred and four participants were enrolled in the original trial, and 166 completed the follow-up assessment and were included in the present study.

### 2.2 | Clinical assessments

Demographic data such as age, gender, height, weight, and duration of symptoms were collected at baseline.

The primary outcomes were the pain at the thumb base and hand function. Pain at the thumb base was scored on a 0-100 mm VAS. Hand function was assessed using the FIHOA (0-30) questionnaire, which includes 10 self-reported items scored on a four-point Likert scale: 0 (possible without difficulty) to 3 (impossible). The outcomes were assessed with the instruments recommended for the clinical evaluation of hand OA in clinical trials.<sup>17</sup>

Secondary outcomes included grip and pinch strength, quality of life, duration of stiffness, and patient's global assessment (PGA). Bilateral grip and tip-pinch strength were measured in kilogram-force (kg-F) using the hand dynamometer (Jamar Hand Dynamometer, Model: A7291; Patterson Medical, Glossop, UK) and pinch gauge (Model: PG-30; B&L Engineering, Santa Ana, CA, USA), respectively. Participants were asked to sit with both feet flat on the ground and the elbow flexed at 90 degrees and were instructed to use their maximum force; the maximum score of the three measurements was used in the analysis. The change in patient global disease assessment was assessed in response to the question "Considering all the ways in which your thumb arthritis affects you, how have you been during the last 48 hours?" on a VAS (0-100, where 0 is very well and 100 is very poor). Change in the duration of thumb-base stiffness was assessed by the question "What is the duration of stiffness at the base of your thumb in the morning?" (expressed



in minutes). Health-related quality of life changes were assessed by the Assessment of Quality of Life-4D instrument (AqoL-4D), which is a 12-item tool with good validity and reliability<sup>18</sup> including questions related to independent living, mental health, relationship, and senses, and scored from -0.04 to 1.00, with 1.00 indicating full health.<sup>19</sup>

## 2.3 | Ultrasound assessment

Ultrasound examination was performed at baseline only. Ultrasound examination was performed by the same physician (WMO, 6 years of experience in musculoskeletal ultrasonography and certified with musculoskeletal ultrasonography in rheumatology [RhMSUS] by the American College of Rheumatology) for the clinical assessment using the Philips Sparq Model detection system with a multi-frequency (4-12 MHz) linear array transducer. The thumb-base joint was scanned in the longitudinal and transverse planes of the palmar and dorsal sites according to the OMERACT ultrasound definitions and as previously reported.<sup>20,21</sup> PDS was assessed with a frequency of 12 MHz and low wall filter, using minimal pressure during the scanning. The gain was adjusted until the background signal was removed. The ultrasonographer was blinded to clinical outcomes (eg, pain scores, PGA).

Effusion was defined as the presence of hypoechoic or anechoic fully compressible materials, and synovial hypertrophy was defined as the presence of echogenic or hypoechoic slightly compressible or non-compressible intra-articular tissues.<sup>22</sup> The presence of synovial hypertrophy and effusion was considered together as "synovitis", which was graded on a 0-3 scale (absent, mild, moderate and severe) as suggested by Keen et al.<sup>21</sup> PDS was defined as a pulsating color spot within the synovial structure,<sup>2</sup> and was graded with a binary score (present/absent). Osteophytes were defined as cortical protrusions at the joint margin seen in two planes,<sup>20</sup> and the severity of osteophytes was scored semi-quantitatively (0-3) using the atlas reported by Mathiessen et al,<sup>23</sup> based on the largest osteophyte independent of the number, size, and location of other osteophytes. An electronic evaluation form was used to document the ultrasonographic findings.

The intra-rater reliability and inter-machine reliability have been reported previously,<sup>11</sup> showing good reliability—a kappa value of 0.77 (0.60-0.94) for synovitis and 0.79 (0.63-0.96) for osteophytes, and an unweighted kappa value of 0.89 (0.69-1.00) for power Doppler. PABAK (Prevalence And Bias-Adjusted Kappa) values were 0.81 (0.65-0.97; percentage agreement 87.5%) for synovitis, 0.78 (0.60-0.95; percentage agreement 85%) for osteophytes, and 0.60 (0.34-0.86; percentage agreement 80%) for power Doppler).

## 2.4 | Radiographic assessments

Radiographic examination was performed at baseline. Bilateral hand radiographs (posteroanterior view) were taken to score KLG.<sup>16</sup>

Osteophytes (0-3) and JSN (0-3) were graded with semi-quantitative scores (absent, mild, moderate, and severe) and subchondral bone sclerosis was graded with a binary score (present/absent) according to the Osteoarthritis Research Society International (OARSI) atlas.<sup>24</sup> Radiographic KLG, OARSI osteophytes, JSN, and subchondral bone sclerosis were graded by the same rheumatologist (LD) and the rheumatologist grading radiographic changes was blinded to clinical outcomes.

The intra-rater reliability was assessed in 20 randomly selected cases with a 6-month interval between two sessions. There were good reliabilities demonstrated by the weighted kappa of 0.76, 0.72, 0.78, and 0.74 for KLG, OARSI osteophytes, OARSI JSN, and OARSI subchondral bone sclerosis, respectively.

## 2.5 | Statistics

We investigated the associations of ultrasound and radiographic features with pain, function, and AqoL-4D at baseline using linear regression after adjustment for age, sex, body mass index, and duration of disease. The results of linear regression were reported as coefficient values.

To examine the relationships of ultrasound and radiographic features with the changes in the severity of pain, function, and AqoL-4D from baseline to 12 weeks, we used linear regression after adjustment for age, sex, body mass index, duration of disease, and self-baseline radiographic or ultrasound features. The results of linear regression were reported as coefficient values.

Statistical analysis was performed using STATA version 15.0 (StataCorp, College Station, TX, USA), and a value of *P* less than 0.05 was considered statistically significant.

## 3 | RESULTS

### 3.1 | Study population

Two hundred and four participants with thumb-base OA were included in the study and 166 completed the follow up (81.37%). Thirty-eight participants were excluded from the study: one had no information about body mass index, 19 participants refused to participate in the study, and 18 participants were not assessed by ultrasound examination. Baseline characteristics of participants are shown in Table 1. The mean age was 66.2 years and 76.5% were female. The mean VAS pain and FIHOA scores were  $57.11 \pm 13.27$  and  $10.43 \pm 3.72$ , respectively.

### 3.2 | Ultrasound findings

There were 85 participants (51.2%) without ultrasound-detected synovitis (grade 0). PDS was shown in 24 participants (14.5%) on ultrasound examination. All the participants had osteophytes and

**TABLE 1** Baseline characteristics of participants in the study (n = 166)

Characteristics	Mean ± SD
Age, mean ± SD; years	66.25 ± 8.28
Female, %	127 (76.51)
BMI, mean ± SD; kg/m <sup>2</sup>	28.54 ± 6.67
VAS pain, mean ± SD	57.11 ± 13.27
FIHOA, mean ± SD	10.43 ± 3.72
Pinch strength, mean ± SD, kg-F	3.22 ± 1.18
Grip strength, mean ± SD, kg-F	21.21 ± 9.08
Duration of stiffness: mean ± SD, min	8.41 ± 18.84
PGA, mean ± SD	38.93 ± 22.03
AqoL-4D, mean ± SD	84.69 ± 8.97
Disease duration, mean ± SD; years	2.95 ± 1.06
Kellgren Lawrence grade, %	
II	88 (42.17%)
III	80 (40.36%)
IV	36 (17.47%)

Abbreviations: AqoL-4D, Assessment of Quality of Life-4D instrument; BMI, body mass index; FIHOA, Functional Index for Hand Osteoarthritis; JSN, joint space narrowing; OARSI, Osteoarthritis Research Society International; PGA, patient's global assessment; SD, standard deviation; VAS, visual analogue scale.

more than half of participants had severe osteophytes (grade 3) (n = 108, 65.1%). The frequencies of different ultrasound features are shown in Table 2.

### 3.3 | Radiographic findings

Most participants had KLG 2 (n = 88, 42.2%) or 3 (n = 80, 40.4%) and 36 had KLG 4 (17.5%) (Table 1). Similar to the ultrasound findings, radiographic osteophytes were identified in most of the participants (159; 95.8%). Radiographic JSN was absent in 54 participants (32.5%) and subchondral bone sclerosis was found in 115 participants (69.3%). The frequencies of all radiographic findings are shown in Table 2.

### 3.4 | Associations of ultrasound and radiographic findings with primary clinical outcomes at baseline and change over 12 weeks

At baseline, significant associations were found between radiographic JSN and baseline FIHOA (coefficient = 0.90,  $P = 0.02$ ), and between radiographic subchondral bone sclerosis and baseline FIHOA (coefficient = 1.89,  $P = 0.03$ ), respectively. No significant association was detected between ultrasound features with baseline pain or FIHOA and between ultrasound features and change in the pain or FIHOA from baseline to 12 weeks (Table 3).

**TABLE 2** Baseline ultrasound and radiographic features of participants (n = 166)

Ultrasound and radiographic features	n (%)
Ultrasound-detected synovitis	
0	85 (51.20)
I	61 (36.75)
II	20 (12.05)
III	0 (0)
Ultrasound-detected PDS	24 (14.46)
Ultrasound-detected osteophytes	
0	0 (0)
I	13 (7.83)
II	45 (27.11)
III	108 (65.06)
Radiographic joint space narrowing	
0	54 (32.53%)
I	37 (22.29%)
II	45 (27.11%)
III	30 (18.07%)
Radiographic osteophytes, %	
0	7 (4.22%)
I	79 (47.59%)
II	38 (22.89%)
III	42 (25.30%)
Radiographic subchondral bone sclerosis, n (%)	115 (69.27%)

Abbreviation: PDS, power Doppler signal.

### 3.5 | Associations of ultrasound and radiographic findings with secondary clinical outcomes at baseline and change over 12 weeks

There was a significant association between ultrasound-detected PDS and PGA at baseline (coefficient = -9.92,  $P = 0.04$ ). Radiographic JSN was significantly associated with the change in the duration of stiffness (coefficient = 5.57,  $P = 0.01$ ) and change in the PGA (coefficient = 4.28,  $P = 0.01$ ) from baseline to 12 weeks, after adjustment for the confounding factors. There were no significant associations between ultrasound features and changes in other secondary clinical outcomes from baseline to 12 weeks. Radiographic features were not associated with baseline secondary clinical outcomes (Table 4).

## 4 | DISCUSSION

This study showed that radiographic JSN and subchondral bone sclerosis were significantly related to baseline hand function (FIHOA), and ultrasound PDS was closely associated with baseline PGA in participants with thumb-base OA. Over a 12-week period, baseline radiographic JSN was significantly associated with the changes in the duration of stiffness and PGA. Ultrasound features could not predict



TABLE 3 Associations of ultrasound and radiographic features with primary clinical outcomes

	Baseline <sup>a</sup>		Change from baseline to 12 week <sup>b</sup>	
	Coefficient (95% CI) <sup>c</sup>	P	Coefficient (95% CI) <sup>c</sup>	P
<b>Pain</b>				
Ultrasound-detected synovitis	0.42 (-2.61, 3.45)	0.78	3.14 (-2.14, 8.42)	0.24
Ultrasound-detected PDS (Yes/No)	-5.16 (-11.02, 0.71)	0.08	-6.23 (-16.63, 4.17)	0.24
Ultrasound-detected osteophyte	0.23 (-3.23, 3.69)	0.90	2.47 (-3.57, 8.51)	0.42
Radiographic JSN	1.44 (-0.64, 3.51)	0.17	3.41 (-0.22, 7.03)	0.07
Radiographic osteophytes	-1.22 (-3.57, 1.14)	0.31	-0.82 (-4.96, 3.32)	0.70
Radiographic subchondral bone sclerosis (Yes/No)	-2.62 (-7.15, 1.90)	0.25	-4.12 (-12.37, 4.13)	0.33
<b>FIHOA</b>				
Ultrasound-detected synovitis	0.58 (-0.25, 1.41)	0.17	-0.34 (-1.24, 0.55)	0.45
Ultrasound-detected PDS (Yes/No)	-0.79 (-2.42, 0.83)	0.34	-1.08 (-2.82, 0.65)	0.22
Ultrasound-detected osteophyte	0.82 (-0.13, 1.76)	0.09	-0.37 (-1.40, 0.65)	0.47
Radiographic JSN	<b>0.90 (0.34, 1.45)</b>	<b>0.02</b>	0.42 (-0.21, 1.05)	0.19
Radiographic osteophytes	0.45 (-0.19, 1.10)	0.17	0.31 (-0.39, 1.01)	0.39
Radiographic subchondral bone sclerosis (Yes/No)	<b>1.89 (0.67, 3.10)</b>	<b>0.03</b>	-0.66 (-2.07, 0.75)	0.36

Abbreviations: CI, confidence interval; FIHOA, Functional Index for Hand Osteoarthritis; JSN, joint space narrowing; PDS, power Doppler signal. The significance of bold values represent positive values ( $P < 0.05$ ).

<sup>a</sup>Adjustment for age, sex, body mass index, and duration of disease.

<sup>b</sup>Adjustment for age, sex, body mass index, course of disease, and baseline symptoms.

<sup>c</sup>95% confidence interval.

changes in clinical outcomes within a 12-week period in participants with thumb-base OA.

In contrast to previous studies<sup>8,25,26</sup> on multifocal hand OA, the present study was focused on thumb-base OA. The thumb base is a unique complex articulation within the hand, and thumb-base OA has been hypothesized to comprise a separate hand OA subset because it is associated with different risk factors and outcomes than interphalangeal OA.<sup>27</sup> Kroon et al<sup>12</sup> found that osteophytes were more strongly associated with thumb-base pain than synovitis. In our study, no significant associations were observed between ultrasound features and baseline pain VAS or hand function (FIHOA) in participants with thumb-base OA. Our results support other findings in thumb-base OA, including that ultrasound features were not associated with pain.<sup>12,28</sup> Kroon et al<sup>12</sup> showed that the presence of osteophytes was associated with pain and speculated that, in the thumb base, a mechanical effect likely played a prominent role. Our study also showed an association between radiographic OA and hand function (FIHOA) in thumb-base OA, but not with pain. This discrepancy may be due to the different characteristics of patient cohorts. Compared with the previous thumb-base OA study,<sup>12,28</sup> participants in the present study were older, had more severe OA of the thumb-base joint, as supported by the KLG  $\geq 2$  at baseline in all the participants, and had a fairly high VAS pain and functional disability of the hand (FIHOA). In addition, pain induced by the compression of the thumb column during pinching may also cause functional disability.<sup>29</sup> Therefore, our findings may be explained as the thumb-base joint with moderate to severe radiographic OA being more susceptible to have an impairment in hand function.

Though radiographic OA correlated with FIHOA at baseline, it was not significantly correlated with other clinical outcomes. Radiographic JSN at baseline was correlated to a very small increase in the FIHOA (coefficient 0.90; 95% confidence interval [CI] 0.34-1.45). The relationship between radiographic OA and clinical severity at baseline in thumb OA remains debatable. Further studies may help to understand this relationship but currently radiographic OA cannot predict most clinical severity.

Clinically, ultrasound PDS is frequently used as a marker of active synovitis. Our previous study, which had a smaller sample size ( $n = 93$ ), showed that PDS was significantly related to the severity of pain in people with thumb-base OA.<sup>11</sup> We further examined the correlations of ultrasonic features with baseline hand pain and function after increasing the sample size ( $n = 166$ ) and the results showed that PDS was not significantly associated with most clinical outcomes except PGA. Sample size may account for the discrepancy between our previous study and the present study. Several studies have shown, in patients with rheumatoid arthritis (RA), that PDS is related to the clinical activity of RA,<sup>30,31</sup> and therefore PDS may be used as a marker of disease activity in individuals with RA.<sup>32</sup> Recent OA studies indicate that ultrasound-detected synovitis and PDS are significantly associated with radiographic progression, indicating a role for inflammation in the etiology of structural damage in hand OA.<sup>33-35</sup> In addition, Mancarella et al<sup>36</sup> showed that synovitis detected by PDS was associated with new bone erosions. In the present study, the positive association between ultrasound PDS and PGA was for the first time described in thumb-base OA. PGA was found to be associated with objective measures of disease

**TABLE 4** Association between ultrasound and radiographic features and the secondary clinical outcomes at baseline and changes for 12 weeks

	Baseline <sup>a</sup>		Change from baseline to 12 week <sup>b</sup>	
	Coefficient (95% CI)	P	Coefficient (95% CI)	P
<b>Grip strength</b>				
Ultrasound-detected synovitis	-0.23 (-1.75 to 1.29)	0.77	-0.74 (-1.98 to 0.51)	0.25
Ultrasound-detected PDS (Yes/No)	0.88 (-2.08 to 3.85)	0.56	0.49 (-1.95 to 2.93)	0.69
Ultrasound-detected osteophyte	-0.14 (-1.87 to 1.59)	0.87	0.94 (-0.48 to 2.36)	0.19
Radiographic JSN	-0.05 (-1.09 to 1.00)	0.93	0.30 (-0.56 to 1.16)	0.49
Radiographic osteophytes	-0.99 (-2.16 to 0.18)	0.10	-0.41 (-1.39 to 0.57)	0.41
Radiographic subchondral bone sclerosis (Yes/No)	0.40 (-1.87 to 2.68)	0.40	1.23 (-0.70 to 3.16)	0.21
<b>Pinch strength</b>				
Ultrasound-detected synovitis	-0.01 (-0.27 to 0.24)	0.92	-0.12 (-0.34 to 0.10)	0.27
Ultrasound-detected PDS (Yes/No)	0.07 (-0.42 to 0.57)	0.77	-0.05 (-0.48 to 0.37)	0.81
Ultrasound-detected osteophyte	-0.05 (-0.34 to 0.24)	0.72	0.01 (-0.24 to 0.26)	0.94
Radiographic JSN	-0.01 (-0.19 to 0.16)	0.90	-0.00 (-0.15 to 0.15)	0.99
Radiographic osteophytes	-0.01 (-0.20 to 0.19)	0.95	-0.11 (-0.27 to 0.06)	0.21
Radiographic subchondral bone sclerosis (Yes/No)	-0.15 (-0.53 to 0.23)	0.43	-0.02 (-0.36 to 0.32)	0.91
<b>Duration of stiffness</b>				
Ultrasound-detected synovitis	-0.75 (-5.12 to 3.62)	0.74	0.37 (-5.91 to 6.66)	0.91
Ultrasound-detected PDS (Yes/No)	-2.61 (-11.13 to 5.92)	0.55	-5.57 (-17.82 to 6.68)	0.37
Ultrasound-detected osteophyte	-2.93 (-7.90 to 2.03)	0.25	6.14 (-1.00 to 13.28)	0.09
Radiographic JSN	-0.44 (-3.45 to 2.56)	0.77	<b>5.57 (1.33 to 9.80)</b>	<b>0.01</b>
Radiographic osteophytes	-1.27 (-4.67 to 2.14)	0.46	-0.45 (-5.35 to 4.46)	0.29
Radiographic subchondral bone sclerosis (Yes/No)	-0.60 (-7.15 to 5.95)	0.86	5.17 (-4.54 to 14.89)	0.86
<b>PGA</b>				
Ultrasound-detected synovitis	0.11 (-4.89 to 5.12)	0.96	2.29 (-2.31 to 6.89)	0.33
Ultrasound-detected PDS (Yes/No)	<b>-9.92 (-19.56 to 0.28)</b>	<b>0.04</b>	-2.35 (-11.46 to 6.77)	0.61
Ultrasound-detected osteophytes	-0.38 (-6.09 to 5.32)	0.89	3.04 (-2.20 to 8.28)	0.25
Radiographic JSN	0.48 (-2.95 to 3.92)	0.78	<b>4.28 (1.18 to 7.38)</b>	<b>0.01</b>
Radiographic osteophytes	-0.34 (-4.24 to 3.56)	0.87	0.39 (-3.21 to 3.99)	0.83
Radiographic subchondral bone sclerosis (Yes/No)	-0.23 (-7.73 to 7.26)	0.95	-0.90 (-8.05 to 6.25)	0.80
<b>AqoL-4D</b>				
Ultrasound-detected synovitis	-0.59 (-2.51 to 1.33)	0.54	0.86 (-0.53 to 2.25)	0.22
Ultrasound-detected PDS (Yes/No)	1.25 (-2.50 to 4.99)	0.51	0.65 (-2.07 to 3.37)	0.64
Ultrasound-detected osteophytes	-1.77 (-3.94 to 0.41)	0.11	0.21 (-1.39 to 1.81)	0.80
Radiographic JSN	-0.19 (-1.51 to 1.13)	0.77	-0.49 (-1.45 to 0.46)	0.31
Radiographic osteophytes	-0.47 (-1.97 to 1.02)	0.53	0.42 (-0.66 to 1.51)	0.44
Radiographic subchondral bone sclerosis (Yes/No)	-0.66 (-3.53 to 2.22)	0.65	1.61 (-0.54 to 3.75)	0.14

Abbreviations: AqoL-4D, Assessment of Quality of Life-4D instrument; CI, confidence interval; JSN, joint space narrowing; PDS, power Doppler signal; PGA, patient's global assessment. The significance of bold values represent positive values ( $P < 0.05$ ).

<sup>a</sup>Adjustment for age, sex, body mass index and duration of disease.

<sup>b</sup>Adjustment for age, sex, body mass index, course of disease and baseline symptoms.

activity and higher scores of PGA represent a higher level of disease activity.<sup>37</sup> Disease activity is useful to characterize the disease status and risk of progression, which helps with clinical decision-making and management. Our findings might provide evidence on the use of ultrasound-detected inflammatory features to evaluate

the effects of anti-inflammatory medications.<sup>38</sup> However, there was a wide confidence interval (95% CI -19.56 to 0.28) around this estimate, making the statistical significance uncertain. Further studies, including larger samples of patients, are warranted to confirm this finding.



This was the first prospective, longitudinal study that investigated whether baseline ultrasound and radiographic features were associated with the changes in clinical outcomes of thumb-base OA over time. Cross-sectional studies have shown the associations between imaging features on ultrasound, magnetic resonance imaging, or X-ray and clinical outcomes in OA,<sup>39-43</sup> which supports the findings of this study. Kortekaas et al<sup>9</sup> reported that synovial thickening, effusion and PDS on ultrasonography were all significantly associated with pain upon palpation, both at baseline and 3 months later. However, our longitudinal analyses showed no association between baseline ultrasound features and changes in pain, hand function, and other clinical outcomes. There are several possible explanations. In the present study, the association between baseline ultrasound features and changes in clinical findings was investigated, which was different from previous studies<sup>44</sup> investigating the association between the longitudinal changes in the imaging outcomes and changes in pain and function over 2 years. On the other hand, the sample size of this study was small. Haugen's longitudinal analyses showed that the progression of osteophytes, increased JSN and development of erosions and malalignment were independently associated with the incidence of joint tenderness during 7-year follow up in hand OA.<sup>45</sup> In the present study, baseline JSN was associated with changes in the duration of stiffness and PGA over 12 weeks but not with baseline. This may be attributed to the older age of our study population and higher grade in study selection criteria. It may be explained by the association between severe JSN and most clinical outcomes in the thumb base being considerably weak, which is in line with the previous study.<sup>45</sup> Our study provides evidence that baseline JSN was a predictor for the changes in the duration of stiffness and PGA over the short period of 12 weeks. However, the clinical significance of change in duration of stiffness expressed in minutes may be limited because the cut-off for minutes of stiffness is unclear. Our follow-up period was only 12 weeks and, therefore, changes in the clinical findings were limited. As thumb-base OA has not been extensively studied longitudinally with ultrasound, X-ray, and magnetic resonance imaging to date, the association between imaging features and changes in clinical outcomes is still poorly understood. In our study, participants with severe OA of the thumb-base joint were included, and participants were followed up for only 12 weeks. Future longitudinal studies with longer follow up in different patient populations with less severe OA are warranted to confirm our findings.

There are several limitations to our study. First, this was the secondary exploratory analysis of a clinical trial. However, all the participants with thumb-base joint OA were evaluated, and our findings may provide evidence on the associations of ultrasound and radiographic features with short-term outcomes. Second, the participants in this study were from the community and the majority of patients had advanced radiographic OA. Hence, it remains uncertain whether our findings can be extrapolated to all the patients with thumb-base OA. Third, in the present study, JSN was associated with the changes in the duration of stiffness from baseline to 12 weeks

that were statistically significant (coefficient 5.57; 95% CI 1.33-9.80). However, the clinical significance of change in duration of stiffness expressed in minutes may be limited. Fourth, there were 84 hypotheses being tested in the present study and we did not make any adjustment for multiple comparisons. All of the analyses were predefined, and exploratory in nature. Finally, only baseline PDS scans were performed, so changes in the image features were not assessed. However, as a result of the short-term follow up, these structural features are not likely to change, especially on X-ray. All ultrasound and major radiographic features may be unable to predict the short-term clinical outcomes in thumb-base OA.

Cross-sectionally, the radiographic structural features of thumb-base OA are significantly associated with hand function (FIHOA) severity, and ultrasound PDS is closely associated with PGA in participants with thumb-base OA. In longitudinal analyses, baseline radiographic JSN was associated with changes in the duration of stiffness and PGA over 12 weeks. However, there was no association between ultrasound features and changes in the clinical outcomes over 12 weeks.

#### CONFLICT OF INTEREST

David J. Hunter is a consultant to TLCBio, Pfizer, Lilly, and Merck Serono. LAD declares partial reimbursement of a conference registration by Pfizer.

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**How to cite this article:** Shi Y, Fu K, Oo WM, et al.

Associations between radiographic features, clinical features and ultrasound of thumb-base osteoarthritis: A secondary analysis of the COMBO study. *Int J Rheum Dis*. 2022;25:38-46. doi:[10.1111/1756-185X.14248](https://doi.org/10.1111/1756-185X.14248)