CLINICS

CLINICAL SCIENCE

Is painless synovitis different from painful synovitis? A controlled, ultrasound, radiographic, clinical trial

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OBJECTIVE: This study compares the clinical, ultrasonography, radiography, and laboratory outcomes of painless and painful chronic synovitis in patients with established rheumatoid arthritis.

METHODS: This cross-sectional study involved 60 patients with rheumatoid arthritis and synovitis in the metacarpophalangeal joints; 30 of the patients did not experience pain, and 30 had experienced pain for at least 6 months prior to the study. The radiocarpal, distal radioulnar, and metacarpophalangeal joints were evaluated using the ultrasound gray scale, power Doppler, and radiography. Past and present clinical and laboratory findings were also evaluated.

RESULTS: There were no statistically significant differences between the groups for most of the outcomes. The group with pain scored worse on the disease activity indices (e.g., DAS 28 and SDAI), function questionnaires (HAQ and Cochin), and pinch strength test. A logistic regression analysis revealed that the use of an immunobiological agent was associated with a 3-fold greater chance of belonging to the group that experienced pain. The painless group had worse erosion scores in the second and fifth metacarpophalangeal with odd ratios (ORs) of 6.5 and 3.5, respectively. The painless group had more cartilage with grade 4 damage in the third metacarpophalangeal.

CONCLUSIONS: The rheumatoid arthritis patients with both painless and painful synovitis exhibited similar disease histories and radiographic and ultrasound findings. However, the ultrasonography evaluation revealed worse scores in the second and fifth metacarpophalangeal of the synovitis patients who did not experience pain.

KEYWORDS: Rheumatoid Arthritis; Synovitis; Pain; Ultrasound; Radiographic.

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INTRODUCTION

The clinical presentation of rheumatoid arthritis (RA) varies, but most patients have intermittent polyarthritis with swelling and tenderness to palpation (1). Some patients exhibit persistent chronic synovitis, which is marked by joint swelling (2) and may or may not be accompanied by pain. The reason for the absence of pain despite the persistent joint swelling is unknown. Moreover, little is known about the predictive factors of painless synovitis or its relationship to the past progression of the disease, ultrasound inflammatory findings (e.g., power Doppler), or the degree of joint damage (erosion).

Ultrasonography (US) allows the early detection of bone and cartilage damage and the evaluation of synovitis (gray scale [GS-US] and power Doppler [PD-US]). US is more sensitive than a clinical examination and simple radiography (X-ray) (3-8). PD-US enhances the specificity of US (9), assists in the diagnosis of active synovitis (10), and predicts joint damage (11).

No previous studies have addressed the importance of painless chronic synovitis in RA. Thus, the present study compared the clinical, US, radiographic, and laboratory outcomes of patients with established RA and chronic synovitis with or without pain.

PATIENTS AND METHODS

Study design

This cross-sectional study evaluated RA patients. The study was approved by the Human Research Ethics Committee of the *Universidade Federal de São Paulo/Escola Paulista de Medicina* (Brazil). All patients provided written informed consent.

No potential conflict of interest was reported.

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Table 1 - Semiquantitative scores for synovitis, PD-US, bone-erosion and cartilage.

	Synovitis (19):		PD-US (19):
0	no synovial thickening	0	no flow in the synovium
1	minimal synovial thickening	1	single vessel signals
2	moderate synovial thickening with capsule distension	2	confluent vessel signals in less than half of the area evaluated
3	synovial thickening, extending to bone diaphysis	3	vessel signals in more than half of the evaluated area
	Bone erosion (19):		**Cartilage (22):**
0	regular bone surface	0	normal hyaline cartilage
1	bone surface irregularity	1	loss of the sharpness of the cartilage margin
2	bone surface defect on 2 planes	2	partial thickness defect of the cartilage layer
3	bone defect with bone destruction	3	full thickness of the cartilage layer
		4	grade 3 + subchondral bone involvement

The sample size of 30 individuals in each group was considered appropriate, and the PD-US was the primary study outcome. The study had a standard deviation (SD) of 0.4, a power of 90%, and a 5% significance level.

Patients

Adult patients who fulfilled the 1987 American College of Rheumatology criteria for RA (12) were eligible for the study if they also met the following criteria: joint swelling in at least 4 metacarpophalangeal (MCP) joints for at least 6 consecutive months, female gender, and stable use of disease-modifying antirheumatic drugs (DMARDs) in the previous 3 months. The visual analogue scale (VAS), which ranges from 0 to 10 cm, was used for the pain criteria; the VAS score was at least 4 cm in the painful group and 0 in the painless group. The following exclusion criteria were used: overlap syndromes, irreducible deformation and MCP surgery, and comorbidities, such as uncontrolled hypothyroidism, uncontrolled fibromyalgia or diabetic neuropathy.

Data collection

Sixty patients were selected from the rheumatology outpatient clinic of the *Universidade Federal de São Paulo/ Escola Paulista de Medicina* (Brazil) between July 2011 and July 2012. The patients were recruited consecutively and assigned to the painful synovitis group or the painless synovitis group. The groups were age matched.

We collected the demographic data, life habits, and information about both the past and present progression of RA using a questionnaire.

Clinical examinations were performed by a rheumatologist who was ''blinded'' to each patient's history and the results of the imaging exams. The evaluation included a patient and a medical global assessment (on a 0-100 scale), grip strength using a Jamar®, and pinch strength using a Preston Pinch Gauge®; the 28-joint Disease Activity Score (DAS 28) (13), Clinical Disease Activity Index (CDAI) (14), Simplified Disease Activity Index (SDAI) (15), Stanford Health Assessment Questionnaire (HAQ) (16), and Cochin Hand Function Scale (CHFS) were also used (17).

The transverse US exam included the dorsal side of the radiocarpal (RC) and the palmar and dorsal sides of MCPs 1 to 5; the longitudinal US exam included the dorsal radioulnar (DRU), according to a quantitative synovitis measurement (in mm) in the largest synovial bursa and semiquantitative scores, as described above (Table 1).

Furthermore, a transverse evaluation of the cartilage of the dorsal side of MCPs 1 to 5 was performed with flexion of the fingers.

US was performed bilaterally on the hands and wrists by a ''blinded'' musculoskeletal sonographer with 5 years of experience, using the ESAOTE MyLab 60 Xvision, with a multi-frequency linear transducer (6-18 MHz). The sonographer followed the guidelines for musculoskeletal US recommended by the European League Against Rheumatism (18).

The US were measured based on the definitions published in the Outcome Measures in Rheumatology Clinical Trials (except cartilage) (19).

Semiquantitative synovitis, bone erosion, and PD-US were each evaluated using a 4-grade scale ranging from 0 to 3. The scores were defined as follows.

Grades 0-1 for bone erosion and synovitis were considered normal (Score I), whereas grades 2-3 indicated pathological changes (Score II) (20).

For the PD-US signal, grade 0 was considered to be normal (Score I), whereas grades 1-3 were considered to be pathological (Score II) (20,21).

Joint cartilage was evaluated using a semi-quantitative 5-grade score with the aforementioned categories (22,23).

The inter-observer reliability for the US evaluation was determined based on the image evaluations recorded on 20% of the overall sample in the RC (a total of 52 joint recess). The evaluation was performed by a blinded rheumatologist trained in musculoskeletal US.

The radiological evaluation (plain X-ray of the hands and wrists) was performed by a single experienced radiologist who was unaware of the clinical or US findings. The evaluation used the modified method proposed by van der Heijde and collaborators (24).

STATISTICAL ANALYSIS

The data were analyzed in SPSS v.17.0. We express the quantitative parameters as the mean, standard deviation, and range. Any value of $p<0.05$ was consider significant.

The data were compared using either the Student's t-test or the Mann-Whitney test.

The categorical variables were measured in percentages and were compared between the groups, using either the chi-squared or Fisher's exact tests. The correlations between variables were evaluated using either Pearson's or Spearman's correlation coefficients. Cohen's Kappa index and the intraclass correlation coefficient were used to evaluate the inter-observer reliability.

A subanalysis of the 2 groups was performed on the US findings for the joints that exhibited swelling in the clinical examination. Logistic regression analysis was applied to the semi-quantitative US variables to assess the ability of the

Table 2 - Group characteristics.

	PAINLESS GROUP mean ± SD (%) (N = 30)	PAINFUL GROUP mean ± SD (%) (N = 30)	*p*-value
Age (in years)	59.9 ± 11.5	56.8 ± 14.0	*0.441**
Skin color White(%)/Brown(%)/Black(%)	16(55)/10(35)/3(10)	11(41)/11(41)/5(18)	*0.496***
Smoking	2 (7)	9 (30)	***0.042****
Alcohol use	0 (0)	1 (3)	*0.500****
Dominant right hand	28 (93)	27 (90)	*1.000****
Arterial hypertension	15 (50)	23 (77)	***0.032****
Dyslipidemia	8 (27)	15 (50)	*0.063***
Other comorbidities OP/Fibromyalgia/Others	8(27)/1(3)/1(3)	5(17)/0(0)/4(13)	*0.319***
Disease duration (years)	17.7 ± 9.4	15.1 ± 10.2	*0.185*∞*
Duration of the absence or presence of MCP pain (months)	30.3 ± 32.6	50.9 ± 74.6	*0.740*∞*
Rheumatoid factor positive	13 (43)	13 (43)	*1.000 **
Anti-CCP positive	23 (77)	19 (63)	*0.269 **
Use of MTX	17 (57)	20 (67)	*0.426***
Use of Leflunomide	18 (60)	13 (43)	*0.196***
Use of Hydroxychloroquine	1 (3)	4 (13)	*0.353****
Use of CS via oral	11 (37)	16 (53)	*0.194***
***Dose of CS via oral** (in mg)*	2.08 ± 3.09	5.00 ± 6.76	*0.097*∞*
Use of immunobiological agent	5 (17)	11 (37)	*0.080***
DMARD association	9 (30)	11 (37)	*0.584***
Morning stiffness (minute)	4.7 ± 13.3	24.8 ± 29.0	*<**0.001**∞*
ESR	31.7 ± 21.8	31.5 ± 25.9	*0.723*∞*
CRP (mg/dl)	0.75 ± 1.00	0.68 ± 0.69	*0.706*∞*
MDGA	33.3 ± 15.6	48.3 ± 14.9	*<**0.001**∞*
PGA	30.7 ± 26.8	60.0 ± 19.3	*<**0.001**∞*
N painful joints	1.5 ± 2.3	13.6 ± 6.1	*<**0.001**∞*
N swollen joints	8.4 ± 3.0	9.6 ± 3.9	*0.246*∞*
DAS 28 by ESR	3.75 ± 0.83	5.57 ± 0.94	*<**0.001****
DAS 28 by CRP (mg/L)	3.06 ± 0.86	4.90 ± 0.95	*<**0.001****
SDAI	16.17 ± 6.74	30.21 ± 9.52	*<**0.001****
CDAI	15.3 ± 6.5	28.9 ± 9.1	*<**0.001****

SD: standard deviation; * Student's t-test; ** chi-squared test; ∞ Mann-Whitney U-test; *** Fisher's exact test; OP: osteoporosis; MCPs: metacarpophalangeal joints; T: time; Anti-CCP: anti-cyclic citrullinated peptide; MDGA: physician's global assessment; PGA: patient's global assessment; N: number; DAS-28: 28-Joint Disease Activity Score; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate (mm/h); mg: milligrams; CS: corticosteroid (mg); MTX: methotrexate; DMARDs: disease-modifying antirheumatic drugs; DMARD association: ≥2.

variables to predict painful or painless synovitis and to identify the variables that were likely to be predictive of painless synovitis.

RESULTS

The sample consisted of 60 patients with established RA, for a total of 120 hands and wrists and 600 MCFs. The mean duration of the absence of joint pain in the painless group and the presence of joint pain in the painful group was, respectively, 30.3 ± 32.6 months and 50.9 ± 74.6 months ($p = 0.740$). There were no statistically significant differences between the groups for the majority of the demographic variables and laboratory findings or in the disease progression (Tables 2, 3).

Two patients in the painless group (7%) and 9 patients (30%) in the painful group were smokers ($p = 0.042$) (Table 2).

The medical diagnosis for RA took 13.2 ± 23.6 months in the painless group and 21.2 ± 26.1 months in the painful group ($p = 0.028$) (Table 3). The majority of patients were initially treated with monotherapy consisting of a DMARD associated with a corticosteroid. Furthermore, the majority of patients were primarily treated with a combination of DMARDs (Table 3).

There were statistically significant between-groups differences in the current DAS-28 measurement (using erytrocyte sedimentation rate-ESR) and for all variables influenced by the presence of joint pain, with higher scores in the painful group ($p<0.05$) (Tables 2 and 4). However, there was no statistically significant difference between the groups in the number of swollen joints.

Twenty-seven patients (90%) in the painless group and 13 (43%) patients in the painful group were classified as having mild dysfunction (HAQ scores 0 and 1, respectively) (25) ($p = 0.001$). There were statistically significant between-group differences for the CHFS, lateral pinch, and tripod pinch ($p<0.001$, $p<0.001$, and $p = 0.039$, respectively), with better scores in the painless group. The Jamar and pulp-to-pulp pinch scores were similar between the groups. There were no statistically significant between-group differences in the degree of joint deformities or in the number of prior surgeries (Table 3).

The most frequently used DMARDs in both groups at the time of the study were methotrexate and leflunomide. More than half of the painful group used corticosteroids but at a low mean dose of 5.0 mg ± 6.76 mg (Table 2). Eleven patients in the painful group and 5 patients in the painless group used immunobiological agents ($p = 0.080$).

In the univariate logistic regression analysis, only the variable ''used an immunobiological agent after one year of the disease'' was associated with painful synovitis; however, it was associated with a 3-fold increase in the odds of the patient belonging to the painful group (odds ratio [OR] = 3.0, 1.00-9.37, $p = 0.049$).

A total of 1.560 joint recesses were examined in the US evaluation. In the semi-quantitative analysis, there were no

Table 3 - Past disease variables of the groups.

	PAINLESS GROUP mean ± SD (%) (N = 30)	*PAINFUL GROUP mean ± SD (%) (N = 30)*	*p*-value
Use of MTX initially	12 (41)	13 (43)	0.879*
Dose of MTX initially	4.91 ± 7.29	5.89 ± 8.17	0.675**
Monotherapy initially	20 (67)	18 (60)	0.592*
DMARD association initially	6 (20)	6 (20)	1.000*
Use of CS initially	21 (70)	21 (70)	0.611*
Dose of CS initially	7.04 ± 7.24	9.28 ± 9.20	0.413**
Time of use of CS initially (months)	70.1 ± 98.1	33.7 ± 57.5	0.504**
Monotherapy during > part of the disease	11 (37)	6 (21)	0.176*
DMARD association during > part of the disease	18 (60)	22 (76)	0.192*
Use of NSAID during > part of the disease	5 (17)	1 (3)	0.105***
Use of biological agent after 1 year of the disease	7 (23)	14 (48)	**0.045***
Change of biological agent	6 (20)	7 (24)	0.701 *
Use of MTX any T of disease	29 (97)	27 (96)	1.000***
Use of HDQ any T of disease	24 (80)	19 (68)	0.291*
Use of Leflunomide any T of disease	24 (80)	22 (79)	0.893*
Use of SSZ any T of disease	7 (23)	9 (32)	0.453 *
Joint impairment initially Polyarticular/Monoarticular	26 (87)/04(13)	22 (73)/08(27)	0.333***
Joints initially affected: Hands/Hands and feet/Lower limbs	13(45)/11(38)/5(17)	15(53)/6(21)/4(14)	0.548*
T until seeking physician (months)	7.9 ± 22.2	9.7 ± 23.0	0.526**
T until diagnosis (months)	13.2 ± 23.6	21.2 ± 26.1	**0.028****
N° of past IAI	3.9 ± 3.2	4.3 ± 3.8	0.942**
N° of IAI in hand joints	1.6 ± 2.5	2.5 ± 3.7	0.940**
Deformity in hands	19 (63)	20 (69)	0.599 *
Deformity in feet	7 (23)	7 (25)	0.562 *
Joint surgeries	4 (13)	4 (13)	0.362 *

SD: standard deviation; MTX: methotrexate; * chi-squared test; ** Mann-Whitney U-test; *** Fisher's exact test; CS: corticosteroid; T: time; NSAID: non-steroidal anti-inflammatory drug; SSZ: sulfasalazine; N: number; IAI: intra-articular injection; HDQ: hydroxychloroquine.

statistically significant between-group differences for the presence of synovitis (at least grade 2) or positive PD-US (Figure 1) in the majority of the joint recesses studied. Bone erosion (at least grade 2) was similar in the 2 groups, but the painless group had worse scores in some joints (Table 5). Statistically significant differences were found in the cartilage evaluation, with more scores of 4 in the third MCP in the painless group ($p<0.004$) and more scores of 2 in the second MCP ($p<0.022$) and 1 in the fourth MCP ($p<0.004$) in the painful group.

Fifty-eight percent of the wrists in the painful group had pain on clinical examination, and 83% of the wrists in the painless group had no pain.

In the US subanalysis of the joints with swelling, there were no statistically significant between-group differences in the quantitative synovitis, the semi-quantitative synovitis, or the PD-US in the MCPs. The bone erosion scores were worse in the painless group for the palmar and lateral sides of the second MCP ($p<0.022$ and $p<0.004$, respectively). Regarding the joint cartilage, only the third MCP had more 0 scores in the painful group ($p<0.030$).

The univariate logistic regression revealed a greater likelihood of patients belonging to the painless group based on worse US scores for the following variables (Figure 2): the semiquantitative synovitis in the DRU, the PD-US in the RC, the erosion on the dorsal face of the 2nd MCP and the dorsal face of the 5th MCP, and the DRU (OR = 2.5, 1.09-5.64, $p = 0.029$; OR = 2.3, 1.07-5.16, $p = 0.034$; OR = 6.5, 1.76-23.77, $p = 0.005$; OR = 3.5, 1.06-11.57, $p = 0.040$; and OR = 5.7, 1.54-20.98, $p = 0.009$, respectively). The interobserver reliability was moderate to strong (Kappa = 0.435 to 1.00; $p<0.018$) for all US measures and strong for the PD-US (Kappa = 0.655 to 0.783, $p = 0.001$).

No statistically significant differences were found in the radiographic evaluation, except for the proximal interphalangeal (PIP) joint, for which the painless group had a worse

Table 4 - Current functional assessment of the groups.

	PAINLESS GROUP mean ± SD % (N = 30)	**PAINFUL GROUP mean ± SD % (N = 30)**	*p*-value
HAQ	0.43 ± 0.41	1.10 ± 0.56	<0.001∞
HAQ categorized Mild/mod/severe dysfunction	27 (90)/3 (10)/0 (0)	13 (43)/16 (53)/1(3)	0.001**
Functional Class 1/2/3	17(57)/10(35) 2 (7)	11(37)/19(63)/0 (0)	0.048**
Cochin	8.2 ± 9.9	24.8 ± 15.9	<0.001∞
Jamar	20.35 ± 12.80	18.42 ± 13.89	0.284∞
Lateral pinch	4.69 ± 1.45	3.71 ± 1.59	<0.001∞
Pulp-to-pulp pinch	2.92 ± 1.27	2.56 ± 1.21	0.069∞
Tripod pinch	3.45 ± 1.44	2.99 ± 1.55	0.039∞

SD: standard deviation; mod: moderate; ∞ Mann-Whitney U-test; ** chi-squared test; HAQ: Stanford Health Assessment Questionnaire; CHFS: Cochin Hand Function Scale.

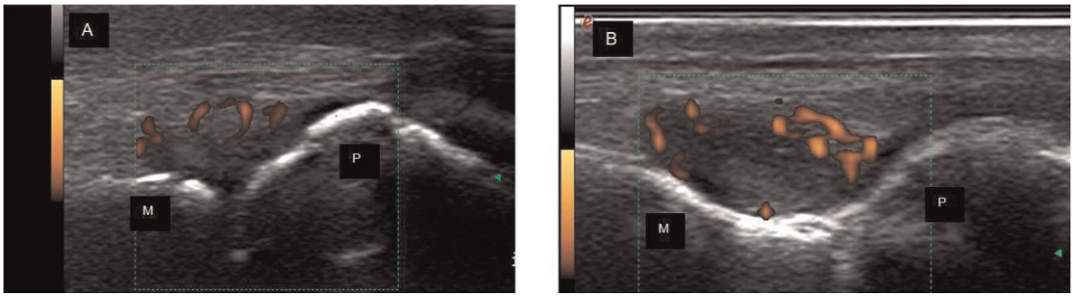

Figure 1 - Dorsal longitudinal image of 2nd MCP; (A) Patient in group without pain with synovial hypertrophy and positive PD signal; (B) Patient in Painful group with synovial hypertrophy and positive PD signal; M = metacarpal; P = phalange.

joint space reduction score ($p = 0.018$). The mean total Sharp score was 93.2 ± 61.6 in the painless group and 65.4 ± 40.6 in the painful group ($p = 0.114$).

DISCUSSION

Pain control is a priority in 90% of patients with RA. However, in a prospective study, Lee et al. (26) demonstrated that the number of joints with swelling at baseline was negatively associated with the presence of pain in a 1-year follow-up period. The perception of pain is highly subjective and may be influenced by a number of issues, including socio-cultural factors (27-29).

Few studies have assessed painless synovitis in RA. The absence of pain in patients with juvenile idiopathic arthritis can delay the disease diagnosis, which could lead to greater joint damage and disability (30,31). The significance of painless synovitis for physicians and patients remains unknown.

In the present study, the majority of both the past and present variables were similar in the patients with and without pain. The time until the RA diagnosis was longer for patients in the painful group. Pain or the absence of pain may not be constant for each patient throughout the disease course. Smoking is an aggravating factor for RA (32); this issue was also observed in this study through the association between smoking and painful synovitis.

The painful group had worse disease activity indices (DAS 28, SDAI, and CDAI), a greater number of painful joints, and worse overall evaluations by both the physician and patient. However, the DAS 28 may not be a good measure of disease activity (33) because joint pain is weighted twice as swelling in the DAS 28 score.

Felson et al. (33) have argued that joint swelling is the true predictor of late radiographic progression in RA. In a prospective cohort study, Lukas et al. (34) have found that

Table 5 - Ultrasound findings for each joint.

	QUANTITATIVE SYNOVITIS in mm Mean (SD)			*ABNORMAL SYNOVITIS SCORES (2-3) N (%)*			*ABNORMAL POWER DOPPLER SCORES (1-3) N (%)*			ABNORMAL BONE EROSION SCORES (2-3) *N (%)*		
JR	PAINLESS N = 60	PAINFUL N = 60	*p-value*	PAINLESS N = 60	PAINFUL N = 60	*p-value*	PAINLESS N = 60	PAINFUL N = 60	*p-value*	PAINLESS N = 60	PAINFUL N = 60	*p-value*
RC	3.0 (2.0)	2.8 (2.2)	*0.308*	22 (36.7)	18 (30.0)	*0.439*	25 (41.7)	14 (23.3)	***0.032***	57 (95.0)	53 (88.3)	*0.186*
DRU	3.3 (2.3)	3.0 (2.1)	*0.542*	23 (38.3)	12 (20.0)	*0.027*	25 (41.7)	16 (26.7)	*0.083*	56 (94.9)	46 (76.7)	***0.004***
1st MCP												
P	1.7 (1.6)	1.4 (1.8)	*0.312*	36 (60.0)	29 (48.3)	*0.200*	15 (25.0)	8 (13.3)	*0.104*	51 (85.0)	42 (70.0)	***0.049***
D	1.7 (1.7)	1.4 (1.5)	*0.298*	35 (58.3)	30 (50.0)	*0.360*	13 (21.7)	12 (20.0)	*0.822*	47 (78.3)	40 (66.7)	*0.152*
2nd MCP												
P	2.2 (2.0)	1.9 (1.9)	*0.304*	27 (45.0)	19 (31.7)	*0.133*	13 (21.7)	11 (18.3)	*0.648*	53 (88.3)	44 (73.3)	***0.037***
D	2.6 (2.1)	2.4 (1.9)	*0.404*	34 (56.7)	24 (40.0)	*0.068*	27 (45.0)	17 (28.3)	*0.058*	54 (90.0)	51 (85.0)	*0.408*
L										57 (95.0)	44 (74.6)	***0.002***
3rd MCP												
P	1.5 (1.8)	1.4 (1.7)	*0.694*	20 (33.3)	15 (25.0)	*0.315*	09 (15.0)	08 (13.3)	*0.793*	42 (70.0)	42 (70.0)	*1.000*
D	1.9 (1.8)	1.9 (1.8)	*0.850*	21 (35.0)	18 (30.0)	*0.559*	16 (26.7)	14 (23.3)	*0.673*	51 (85.0)	43 (71.7)	*0.076*
4th MCP												
P	1.3 (1.7)	0.9 (1.3)	*0.274*	14 (23.3)	09 (15.0)	*0.246*	03 (5.0)	03 (5.0)	*1.000*	34 (57.6)	29 (49.2)	*0.356*
D	1.4 (1.7)	1.4 (1.9)	*0.993*	23 (38.3)	19 (31.7)	*0444*	09 (15.0)	10 (16.7)	*0.803*	33 (55.0)	28 (46.7)	*0.361*
5th MCP												
P	1.4 (2.2)	1.2 (1.6)	*0.906*	14 (3.7)	13 (21.7)	*0.827*	06 (10.0)	6 (10.2)	*0.976*	33 (55.0)	22 (37.3)	*0.053*
D	2.1 (2.0)	1.9 (2.1)	*0.616*	23 (38.3)	19 (31.7)	*0.444*	11 (18.3)	11 (18.3)	*1.000*	56 (93.3)	48 (80.0)	***0.032***

JR: joint recesses; RC: radiocarpal; DRU: distal radioulnar; P: palmar; D: dorsal; L: lateral; MCP: metacarpophalangeal; Statistical tests – Pearson's chi-squared test; Mann-Whitney U-test.

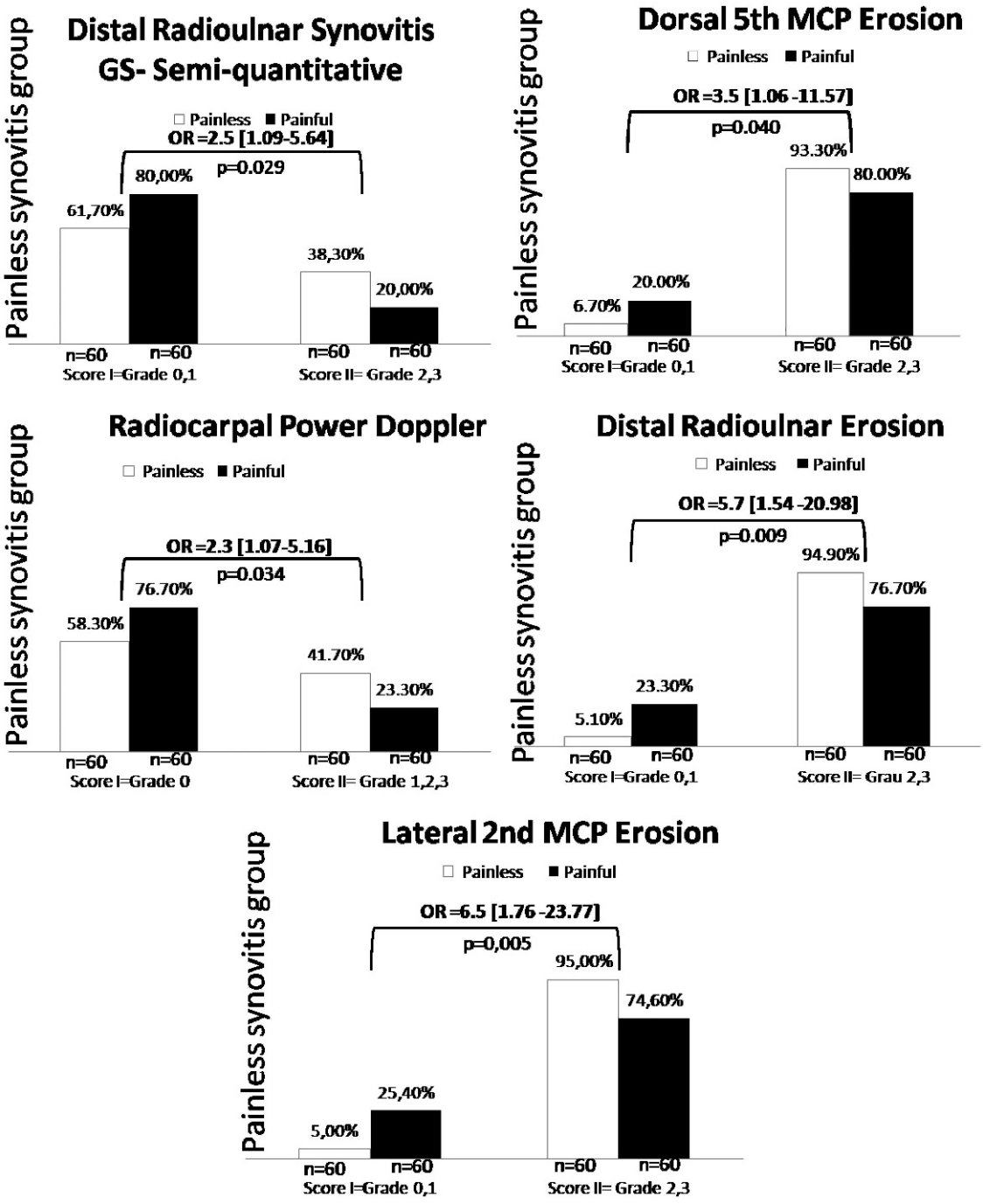

Figure 2 - Probability of belonging to painless synovitis group with presence of Score II semi-quantitative synovial hypertrophy, PD and erosion in relation to Score 1 in joint recesses with statistically significant difference in the previous ultrasonographic evaluation and significant difference in regression analysis ($p < 0.05$); Statistical test: univariate logistic regression; OR = odds ratio; n = number.

joint swelling was the greatest predictor of ''repair'' in radiographic erosion. Studying early arthritis, Filler et al. (35) have also found that the progression of RA was more closely associated with the swollen joint count than with the tenderness joint count (35).

Recently, Dougados et al. (36) have emphasized the importance of persistent synovitis (both clinical and US examination) for predicting subsequent structural deterioration in RA patients. In his study, the level of clinical disease activity was defined by the number of swollen joints. Furthermore, the patients who had synovitis at baseline had more structural progression (OR = 2.01, 1.36-2.98, $p<0.001$) in a 2-year follow-up period (36).

In this study, worse functional and dynamometric scores were found in the painful group. It is unsurprising that individuals with painful joints at the time of evaluation had worse functional scores than those without joint pain (37). Nonetheless, no statistically significant between-group differences were found with respect to the grip strength or the pulp to pulp pinch strength.

Subclinical synovitis may be present in RA remission (8). Furthermore, there is evidence indicating the progression of joint damage in RA patients during clinical remission (11,10), which may be related to residual joint swelling (2). The consideration of persistent joint swelling in RA patients, even in the absence of pain, as in the present study, aligns with the hypothesis that residual swelling causes erosion and is contrary to the notion of ''cold,'' ''fibrous,'' and innocuous synovitis.

US has been proven effective at detecting subclinical synovitis (38,8,5), and PD-US is an important tool for detecting active synovitis (10,39). In this study, no differences were found between the painful and painless groups for the majority of US variables in the MCPs and wrists. The detection of the PD-US signal is a predictor of disease evolution in RA (35) and also of the progression of joint damage (11) and the reactivation of the disease (40). In this sample, PD-US was detected in 21% of the joint recesses analyzed, with no significant between-group differences for the majority of joint recesses. This result suggests that there is no association between active synovitis and the presence of joint pain. US also allows for earlier detection of erosion than plain x-rays. In this respect, US is comparable to magnetic resonance imaging (41-43). In the US analysis of erosion, 5 joint recesses were statistically different between groups, with worse scores in the painless group. For the joint cartilage, poorer scores were found more frequently in the painless group, although the between-group difference did not achieve statistical significance.

The similarities between the painful and painless groups in the quantitative analysis of synovial hypertrophy, semi-quantitative analysis of GS-US variables, PD-US, and bone erosion may mean that painless synovitis can still result in joint damage and disability. Moreover, painless synovitis may make the patient and physician more passive in optimizing treatment. This hypothesis is in agreement with the findings that, after the first year of the disease, the painful group were more likely to use immunobiological agents ($p = 0.045$), and patients with worse US scores in some joint recesses were more likely to be in the painless group.

The radiographic analysis demonstrated that major previous structural damage was similar in both groups, except for IFP scores, which were worse in the painless group. This evidence further indicates that the continual presence of synovitis, instead of joint pain, is an important factor influencing structural damage in RA because both groups had a similar history of radiographic progression. These findings also aligned with the present analysis regarding the identification of joint deformities; there were no statistically significant differences between groups. However, a controlled prospective study with US and radiographic evaluations is needed to compare the evolution of structural joint damage in this sample of patients.

One of the limitations of this study is that was impossible to recruit patients in the painless group who had a complete absence of pain in all joints. The difficulty in obtaining individuals with a constant pain status (presence or absence) throughout the progression of RA constitutes another study limitation. This study is the first to compare patients with RA and painless synovitis with those patients with painful synovitis using clinical, ultrasonographic and radiographic variables. The majority of the findings suggest that patients with painless synovitis exhibit a similar profile to those patients with painful synovitis with respect to the presence of active synovitis and past joint damage.

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AUTHOR CONTRIBUTIONS

Pereira DF recruited the patients, organized the study protocol, and was responsible for the inter-observer reliability for the ultrasonography evaluation. Natour J and Furtado RN coordinated the study and wrote the article. Buosi AL performed the clinical examination. Ferreira FB performed the ultrasonography examination. Fernandes AR performed the radiography evaluation.

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