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Defining inflammatory musculoskeletal manifestations in systemic lupus erythematosus

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ABSTRACT

Objective: To define the prevalence and clinical associations of clinical and imaging definitions of synovitis in unselected SLE patients with musculoskeletal symptoms.

Methods: 112 patients with SLE (excluding RF and CCP positive patients); 88 consecutive with inflammatory musculoskeletal symptoms and 24 asymptomatic SLE controls were recruited. Patients had clinical assessment (BILAG, SLEDAI, joint counts, patient and physician VAS), routine laboratory tests and ultrasound of two hands and wrists (synovitis and tenosynovitis, OMERACT definitions).

Results: Overall 68% (60/88) of symptomatic patients had US inflammation (GS≥2 and/or PD≥1 or tenosynovitis) compared with 17% (4/23) of asymptomatic patients. In symptomatic patients, clinical inflammation was seen defined by BILAG A or B in 38% (34/88) or defined by the SLEDAI-MSK criterion in 32% (28/88). BILAG A/B had sensitivity (95% CI) of 56% (41,69%) and specificity of 89% (72,96%) for US-confirmed inflammation. SLEDAI-MSK criterion had sensitivity of 44% (31,59%) and specificity of 89% (72,96%). In patients with inflammatory symptoms, 27% (24/88) had subclinical inflammation (abnormal US but no clinically swollen joints) and 35% (31/88) had no clinical or US inflammation. Subclinical tenosynovitis and PD were

associated with significantly higher IgG, physician VAS, tender joint count.

Conclusion: In SLE patients with musculoskeletal symptoms, a large proportion of objective, clinically meaningful inflammation is only identifiable by ultrasound. The existing classification of musculoskeletal SLE using disease activity instruments based on joint swelling is inaccurate to guide patient selection for clinical trials, biologic therapy, or treat-to-target protocols.

Key words: Systematic lupus erythematosus, Ultrasonography, Synovium, Tendons and Ligaments, Outcome measures

Key messages

1. More than 1 in 4 SLE patients with inflammatory musculoskeletal symptoms had objective inflammation not detected by clinical instruments
2. BILAG and SLEDAI have high specificity but low sensitivity for ultrasound-confirmed synovitis
3. Ultrasound-only inflammation is associated with worse clinical symptoms and serology

INTRODUCTION

Defining active disease in SLE is challenging for both clinical trials and routine practice. In clinical trials, the difficulty with defining active disease has been illustrated by a series of recent negative trials of promising new treatments. For example, in the belimumab programme, a negative phase II trial was followed by positive phase III data after the target population and primary endpoint were revised [1]. In routine practice, there is an increasing emphasis on defining active disease. First, because of the need to decide on biologic prescription. Second, for treat-to-target strategies that aim to treat to a target of low disease activity while minimising glucocorticoid exposure[2].

Inflammatory musculoskeletal symptoms are common in SLE, being the first presenting symptom in around 50% of cases and affecting up to 95% of patients at some time [3, 4]. Joint pain in SLE impacts on quality of life and results in loss of

function [5-7]. Accordingly, musculoskeletal disease is a common reason for inclusion into clinical trials. For example, in the phase III ILLUMINATE study, at baseline 81% of patients had musculoskeletal activity defined by SLE Disease Activity Index (SLEDAI) [8].

Currently musculoskeletal disease activity is defined using MSK items in the SLEDAI[9] and British Isles Lupus Assessment Group (BILAG 2004)[10]. Although both are validated, there are face validity problems with these tools. They were designed to assess multi-organ system disease and therefore capture less detail on an individual organ system compared to organ-specific instruments such as the DAS28 used in rheumatoid arthritis[11]. For example, SLEDAI scores 4 points for arthritis affecting 2 or more joints, and none for lesser degrees of arthritis. Therefore, there is no difference in score between a swollen joint count of 28 and 2. Joints are considered affected if there is tenderness, warmth, swelling or effusion. The BILAG index allows differentiation of severe synovitis (BILAG-A), moderate synovitis (BILAG-B) and inflammatory arthralgia (BILAG-C), as well as reduction of A and B scores to B and C respectively if symptoms are improving. Importantly, because of the need to assess a wide spectrum of symptoms in SLE, assessors must determine whether features are due to SLE or another pathology for both indices.

Modern imaging has brought a greater understanding to rheumatoid arthritis and explained the discrepancies in clinical and objective imaging-defined synovitis. In low disease activity states, such as early arthritis or remission, musculoskeletal ultrasound (US)-detected synovitis has been shown to explain long term adverse consequences. [12, 13].

Data on musculoskeletal US in SLE are limited and US is not commonly used in practice or trials. In a systematic review we found that several studies reported US-detected abnormalities in SLE but were inconsistent with their reported prevalence of abnormality [14] probably due to methodological differences such as failure to clearly separate rhupus from “pure” SLE, controlling for NSAIDs and glucocorticoids, and reporting Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) criteria. Furthermore, no study has confirmed the clinical significance of US synovitis.

We therefore studied a large cohort of patients with objective measures of synovitis

in order to define the population of patients who should be included in clinical trials and receive escalation, tapering or avoidance of glucocorticoids, conventional and biologic therapies in routine practice. In order to be able to estimate the prevelance of each clinical and ultrasound presentation in a general lupus population, we recruited unselected, consecutive patients with inflammatory MSK symptoms. We addressed the issues with previous US studies by, controlling for rhupus, NSAID and glucocorticoid therapy and reporting OMERACT grades of abnormality.

METHODS

Patients

A cross-sectional observational study was conducted in consecutive patients with active inflammatory musculoskeletal symptoms in two UK centres (Leeds and Southampton). 307 patients enrolled in observational research studies were clinically assessed. We invited all patients with musculoskeletal symptoms to participate in the present study. The inclusion criteria were: adults over 16 years old, meeting the 2012 Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC)[15] for SLE, and active inflammatory musculoskeletal symptoms scoring BILAG A-C (need not be swollen but deemed due to active SLE by investigators due to distribution, morning stiffness etc). Patients were excluded if they had immunological evidence of Rhupus (anti-Anti-Cyclic Citrullinated Peptide(CCP) antibodies or Rheumatoid Factor), recent change immunosuppressive drugs (either conventional or biological), NSAIDs or glucocorticoids in the past 6 weeks. Patients with improving disease were excluded; this allowed grouping of symptomatic patients into three BILAG-Categories: severe clinical synovitis with loss of function (musculoskeletal (MSK) BILAG-A), mild to moderate synovitis (MSK-BILAG-B), inflammatory symptoms but no synovitis (MSK-BILAG-C). An additional group of patients who had SLE and previous musculoskeletal involvement but no current inflammatory musculoskeletal symptoms (MSK-BILAG-D) were recruited as a control group.

Clinical assessment

Clinical assessments were performed by rheumatologists blinded to the US assessment with training and experience in relevant indices. Overall disease activity

was assessed using BILAG-2004 [10], SLEDAI-2K[9] and damage was assessed using the Systemic Lupus International Collaborating Clinics (SLICC-DI) [16]. Musculoskeletal components of BILAG-2004 and SLEDAI-2K were summarized separately as MSK-BILAG (A-E) and MSK-SLEDAI (0 or 4 points) in analyses. Joint disease was also assessed using 66/68 tender and swollen joint counts, symptomatic joint count, physician global visual analogue score (VAS, 0-100mm) and patients' disease activity VAS (0-100mm) and DAS28-ESR (four variables).

Laboratory Assessment

C-reactive protein (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/hr), rheumatoid factor (RF, IU/ml), Cyclic citrullinated peptide antibodies (CCP, IU/ml), complements (C3 and C4, g/L), antinuclear antibody (ANA), extracted nuclear antibodies (ENA) including anti-dsDNA, anti Ro, anti La, anti-chromatin, anti Sm, anti-RNP (using Bioplex 2200) and immunoglobulins (IgA, IgM, IgG, using nephelometry) were measured on the visit date in an accredited clinical diagnostic laboratory.

Ultrasound assessment

Ultrasonography (grey scale (GS) and power Doppler (PD)) was performed using high resolution ultrasound machines (US); General Electric (GE) Logiq E9 US with multi-linear 6-15 MHz transducer in Leeds and Esaote MyLab 70 US with multi-linear 5.0-13.0MHz transducer in Southampton. All sonographers (one in Southampton and two in Leeds) were trained in musculoskeletal US and blinded to clinical status. PD was assessed with the highest gain level without background noise, PRF of 750 Hz and medium wall filter.

Bilateral wrists, hands, ankles and feet were assessed in all patients. All joints in the hand and wrists were examined using a standard approach of examining the following; radio-carpal (RCJ), inter-carpal (ICJ), ulnar-carpal joints (UCJ) and 1^{st} to 5^{th} metacarpo-phalangeal joints (MCP) and 1^{st} to 5^{th} proximal inter-phalangeal joint joints (PIP). Bilateral tendon sheaths including the 1^{st}-6^{th} extensor tendons compartments of the wrist and 2^{nd} to 5^{th} flexor digitorum tendon sheaths of the hands were assessed for tenosynovitis. Bilateral ankles and feet were examined including 1^{st} to 5^{th} metatarso-phalangeal joints (MTP). Ankle tendons including tibialis anterior,

extensor hallucis longus, extensor digotrium, tibialis posterior, flexor digitorum, flexor hallucis longus, and peroneal tendons were assessed for tenosynovitis. The synovitis GS and PD were scored using the OMERACT definitions and proposed semiquantitative 0-3 scale [17-20]. The GS scoring was as follows; 0 = no synovial hypertrophy, 1 = mild hypertrophy, 2 = moderate hypertrophy, and 3 = severe hypertrophy. The PD scoring was as follows; 0 = absence of signal, no intra-articular flow; 1 = mild hyperemia, one or two vessels signal (including one confluent vessel); 2 = moderate hyperemia, (>grade 1) and less than 50% of GS area; 3 = marked hyperemia, vessels signal in more than half of the synovial area. Tenosynovitis was defined according to the OMERACT criteria [19] and the GS and PD signal scored using semi-quantitative 0-3 scale system (0= normal, 1=mild, 2=moderate and 3= severe) [21].

Statistical analysis

Patients were classified according to BILAG groups (MSK-BILAG=A, B, C and D/E) and SLEDAI groups (MSK-SLEDAI = 0 or 4 points). Overall clinical characteristics (demographics, therapies, clinical joint assessments and immunological parameters) and ultrasound characteristics were summarised for each group using proportions of patients or median and interquartile range as appropriate. US abnormalities were calculated as total grey scale (GS), PD, erosions and tenosynovitis as well as numbers of joints with abnormal GS (≥2), PD (≥1), erosions or tenosynovitis (as any GS and/or PD abnormality in the tendon sheath). Association of BILAG grade and erosions with patient groups were tested using Fisher's exact test.

Level of agreement between clinical assessment and US when detecting synovitis was quantified as the proportion of joints in which both methods exactly agreed over the presence or absence of synovitis (percentage exact agreement [PEA]), proportions of category-specific negative and positive agreement (Sp0 and Sp1 for absence and presence of synovitis, respectively), and the proportions of joints where clinical examination (CE) and US disagreed in either direction (US>CE, US<CE). Category-specific agreement was defined as the proportion of the total number of positive or negative ratings (CE=US) that were concordant; it represents the conditional probability that US would place a patient in category X, given than CE had placed them in that category, and vice versa. The kappa statistic was also

calculated and supplemented with the prevalence-adjusted bias-adjusted kappa (PABAK) to give an indication of the extent to which differences in the overall level of synovitis identified by each assessment method together with imbalances in the proportions of joints with and without synovitis affected the calculated value of kappa.

Patients with inflammatory symptoms without clinical joint swelling (MSK-BILAG-C) were divided into "subclinical synovitis" and "normal" groups based on: GS≥2 in ≥1 joint; PD ≥1 in ≥1 joint; GS≥1 or PD≥1 in ≥ 1 tendon sheath. For each abnormality, we compared: clinical (patient- and physician-VAS, tender and symptomatic joint count, DAS28-ESR); immunological parameters that differed in BILAG groups (total serum IgG, ESR); and ultrasound erosions, using Mann-Whitney-U tests.

All tests were conducted at two-sided 5% level of significance. Statistical analyses were performed using IBM SPSS Statistics v24.

RESULTS

Patient characteristics

Patient recruitment is shown in Supplementary Figure S1, available at *Rheumatology* online. Of consecutive patients clinically assessed, 184 had musculoskeletal symptoms deemed to be inflammatory. Rates of BILAG abnormality in the overall group were BILAG A: 25/184 (13.5%); BILAG B: 44/184 (24%); BILAG C: 114/184 (61.9%). A further 116 patients had no active musculoskeletal symptoms (101 with previous involvement recorded, 87%). 112 consecutive SLE patients were recruited into the musculoskeletal study (Leeds: 92; Southampton: 20). These included 89 consecutive patients with active MSK symptoms who consented to participate. We also recruited 23 of the patients with prior MSK involvement. 100% were ANA positive. They were predominantly female (108/112, 96%). Median (IQR) age was 46.5 (34,57) and disease duration 60 (24,168). Median SLICC damage index was 0 (0,1). 46/112 patients (41%) were treated with hydroxychloroquine alone. 43/112 (38%) received oral immunosuppressants with or without hydroxychloroquine (Methotrexate = 15, Azathioprine = 10, Mycophenolate Mofetil = 18). 13 had received previous rituximab and 42/112 were on low-dose glucocorticoid. Rates of -MSK-BILAG abnormalities in the musculoskeletal study group were very similar to the

overall group; BILAG A: 14/89 (15.7%); BILAG B: 20/89 (22.5%); BILAG C: 54/89 (60.7%). Other baseline demographics and clinical characteristics are presented in table 1.

Most symptomatic patients do not have clinical synovitis

In this consecutive series, most patients with active musculoskeletal symptoms (as defined above) did not have clinical synovitis on examination (and therefore did not meet levels of BILAG and SLEDAI criteria usually required for entry into clinical trials or to start biologic therapy). Of 88 patients deemed by clinicians to have symptoms due to active inflammatory SLE, clinical inflammation was seen defined by BILAG A or B in 38% (34/88) or defined by the SLEDAI-MSK criterion in 32% (28/88). The others were classified as BILAG-C or MSK-SLEDAI = 0.

Ultrasound reveals a large group of patients with subclinical synovitis

We next compared ultrasound findings according to clinical assessment (Table 2). This revealed a large group of patients with subclinical synovitis confirmed on ultrasound that was not detected clinically.

Overall 68% (60/88) of symptomatic patients had US inflammation (GS≥2 and/or PD≥1 or tenosynovitis) compared with 17% (4/23) of asymptomatic patients. Therefore, in patients with inflammatory symptoms, we observed three major groups: (1) Clinical synovitis: (38%) 34/88 patients had one or more swollen joint, scoring BILAG A or B; (2) Subclinical synovitis (27%) 24/88 patients had no swollen joint but confirmed US abnormality; (3) No confirmed synovitis, with no swollen joint and no significant US abnormality in 30/88 (34%).

Sensitivity and Specificity of clinical definitions of active disease

Overall, there was US-confirmed joint inflammation defined by BILAG A or B in (38%) 34/88; defined by SLEDAI-MSK criterion (32%) 28/88; and defined by GS≥2 and/or PD≥1 or tenosynovitis in (61%) 54/88. Only 4/88 patients were reported to have clinical joint swelling not confirmed by US.

BILAG A/B had sensitivity (95% CI) of 56% (41,69%) and specificity of 89% (72,96%). SLEDAI-MSK criterion had sensitivity of 44% (31,59%) and specificity of

89% (72,96%)

Validation of BILAG A and B

US validated the distinction between BILAG-A and B musculoskeletal disease. All BILAG-A patients had moderate to severe PD synovitis compared to only 35% of BILAG-B ($p<0.0001$).

Erosions

US showed erosive disease in non-rhupus SLE (Figure 1). The presence of erosions correlated with clinical synovitis (29% of MSK-BILAG-A vs.4% of MSK-BILAG-C, $p=0.0126$; 25% of MSK-SLEDAI=4 vs. 5% of MSK-SLEDAI=0, $p=0.005$). Erosions tended to be mild and not affecting multiple joints (Table 2).

Joint by joint agreement between clinical and ultrasound assessment

Overall agreement between clinical and US assessment on joint by joint analysis, as measured by Kappa and prevalence-adjusted-bias-adjusted Kappa (PABAK), was reasonably good (Supplementary table S1, available at *Rheumatology* online). However, when analysing specific agreement for presence or absence of synovitis there was considerable disagreement, indicating a degree of inaccuracy of clinical assessment in SLE against US as gold standard. For the absence of synovitis, agreement between clinical assessment and US appeared generally good across all joints assessed. However, this is because most joints were normal by both techniques. For presence of synovitis agreement was poor. Therefore, there is no joint in which US-confirmed synovitis can be reliably detected using clinical assessment. Even in the joints with best agreement (2^{nd} and 3^{rd} PIP joints) there was only approximately 50% chance that if US detected synovitis were present it would be detected clinically.

Subclinical synovitis is associated with objective and symptomatic evidence of inflammation

In the subclinical synovitis group, substantial numbers (30% of MSK-BILAG=C and 26% of MSK-SLEDAI=0) had moderate-severe power Doppler (a severe and specific abnormality). Tenosynovitis was common in the subclinical synovitis group, affecting

just under half of patients.

To analyse the clinical significance of subclinical synovitis, we selected patients without joint swelling. Because most abnormities were detected in the hands and wrists, and to compare with a 28-joint count and DAS28, we analysed US data in the hands and wrists only. We analysed physician VAS, and IgG and ESR, which were associated with clinical synovitis in the whole cohort. We compared these variables according to the presence or absence of US synovitis, as well as the main categories of abnormality: GS, PD and tenosynovitis (Table 3). Subclinical synovitis was associated with serological evidence of disease activity: IgG titre was significantly higher in the presence of overall synovitis (p=0.002), GS synovitis (p=0.003) and PD/tenosynovitis (p=0.045). Patients with tenosynovitis or PD synovitis also had higher tender joint count (p=0.024) and showed some evidence of higher physician VAS (p=0.056), and DAS28-ESR (p=0.061). Although the difference in DAS28 was not significant at alpha=0.05 the large descriptive difference between patients with/without PD/tenosynovitis (median 4.82 vs 3.09) warrants investigation in a larger cohort.

DISCUSSION

In this study we report results from a large cohort of patients. We demonstrate that more than a quarter of SLE patients with inflammatory musculoskeletal symptoms have proven synovitis, which is associated with worse serological and clinical assessments, but not detected by validated disease activity instruments. These results are important for the treatment of this common manifestation of SLE, as well as for conduct and interpretation of clinical trials.

A EULAR taskforce has recommended that in order to achieve the best long-term outcomes, SLE patients should be treated to a target of low disease activity measured using validated instruments while minimising glucocorticoid exposure[24]. BILAG and SLEDAI are the instruments most commonly used. Our results show the limitation of directing treatment according to these tools in musculoskeletal SLE and their likely consequences. In patients with ongoing inflammatory symptoms but not meeting SLEDAI musculoskeletal criteria or BILAG A/B, therapy might not be

escalated despite definite synovitis. Quality of life and work disability are impaired in SLE despite current therapy, and musculoskeletal symptoms are one of the strongest determinants of this [25, 26]. Failure to escalate therapy is therefore likely to result in serious adverse long term outcomes.

Conversely, the treat to target recommendation emphasises the need to minimise gluococorticoid exposure. This is because there is a dose-related association between glucocorticoid exposure and accrual of damage[27, 28]. We show that imaging can identify 35% of patients who present with seemingly inflammatory symptoms (attributed to SLE activity and rated BILAG C) in whom there is no objective evidence of synovitis and glucocorticoids would therefore not be appropriate. Better tools to assess musculoskeletal disease activity would therefore help physicians to reduce prescribing of glucocorticoids.

Treat-to-target regimens have been shown to be effective in RA using clinical criteria, but not in more recent studies using an ultrasound target [Grigor et al. 2004, Paulshus et al 2018]. However, there are significant differences between these diseases and protocols. In RA all patients have joint swelling at some time (to meet criteria) while in SLE this is not essential for a diagnosis. Also, in RA the DAS28 captures any tender joint regardless of aetiology, as well as patient VAS. Whereas in SLE, only symptoms deemed to represent SLE disease activity by a physician are rated. Therefore in RA the DAS28 maximises sensitivity over specificity, whilst in SLE there is a greater emphasis on specificity for true joint inflammation, which has important implications in comparison to US for treating-to-target.

Identifying active disease is essential to produce reliable clinical trial results. Placebo response rates in SLE trials are notably high, sometimes more than 40% for SRI-4 in recent phase II and III trials [29, 30]. Although we found that joint swelling is usually indicative of ultrasound-proven synovitis, this is not always required for entry into clinical trials; the SLEDAI allows scoring for arthritis based on warmth, tenderness or swelling reported by the patient in the past 30 days rather than measured on clinical examination. These criteria have not been independently validated. Further work is required to determine whether superior clinical instruments could be defined using ultrasound as a gold standard.

Our study has a number of limitations. Even in this larger patient group, it is difficult to reliably assess the symptomatic impact of subclinical synovitis and longitudinal follow-up is required. Confirmation that US positive patients respond better to therapy is needed to confirm that US synovitis should be an indication for immunosuppressive therapy. Longitudinal data after treatment is also needed to determine relative responsiveness of US and BILAG/SLEDAI to determine whether existing instruments are underestimating the effectiveness of therapy in clinical trials.

Several previous studies assessed musculoskeletal ultrasound in SLE but we identified limitations and inconsistencies that the present study was designed to resolve [14, 31-39]. Since our systematic review, one additional study has reported clinical and ultrasound findings in a large cohort of patients [Salliot et al 2018]. There were unusually high rates of ultrasound abnormality, e.g. in 85% of asymptomatic patients with PD in 37% of asymptomatic patients. The reason for these unusually high rates is not clear (although some rhupus patients were included). However, because so few patients had normal ultrasound it was not possible to address the central objective of our study in their dataset: to describe the prevalence and clinical associations of ultrasound synovitis in patients without joint swelling compared to patients with swelling, and those with active symptoms but normal ultrasound. Strengths of our study were recruitment of consecutive patients to allow estimates of prevalence, exclusion of rhupus, control for NSAID and glucocorticoid use and reporting OMERACT grades of US abnormality. There are a number of choices of OMERACT grades of abnormality to be reported. These may vary by clinical site – for example, GS change is commonly seen in the feet in healthy individuals. We chose to use GS>2 or PD>1 based on OMERACT definitions and data in other inflammatory arthritides and provide the first analysis of the clinical significance of these definitions against symptoms and serology in SLE our paper, as well as a joint-by-joint comparison with clinical evaluation.

In summary, our results demonstrate the limitations of current classification of active musculoskeletal SLE based on joint swelling, BILAG and SLEDAI and that a new classification of proven musculoskeletal inflammation may allow improvement in outcomes of immunosuppressive therapy.

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Ethical Approval

All individuals provided informed written consent and this research was carried out in compliance with the Declaration of Helsinki. The study was approved by National Research Ethics Committee Yorkshire and Humber–Leeds East reference 10/H1306/88. All procedures were performed in accordance with relevant guidelines and regulations. The University of Leeds was contracted with administrative sponsorship.

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Table 1: Clinical and serological characteristics according to musculoskeletal disease status

	All Patients	Patients with MSK Symptoms					No MSK Symptom
		BILAG			SLEDAI		
		MSK-BILAG=A	MSK-BILAG=B	MSK-BILAG=C	MSK-SLEDAI=4	MSK-SLEDAI=0	MSK-BILAG=D and MSK-SLEDAI=0
No. of patients	112[a]	14	20	54	28	61	23
Disease duration	60 (24–168)	36 (12–180)	36 (18–180)	84 (24–168)	84 (24–168)	51 (21.5–168)	108 (53.3–171)
Age mean(range)	46.5 (34–57)	49 (36–59)	46.5 (33–55)	49 (37.5–58)	45 (18–73)	41.5 (31.2–51.7)	35 (26–53)
Therapy							
Steroid, N (%)	42/112 (38)	3/14 (21)	10/20 (50)	17/54 (30)	19/28 (68)	38/61 (62)	12/23 (52)
HCQ only, N (%)	55/112 (49)	7/14 (50)	9/20 (45)	32/54 (58)	15/28 (54)	33/61 (54)	7/23 (30)
Oral Immunosuppressant, N (%)	42/112 (38)	4/14 (29)	9/20 (45)	20/54 (36)	9/28 (32)	24/61 (39)	9/23 (31)
Rituximab, N (%)	13/118 (27)	2/14 (14)	2/20 (10)	5/54 (9)	3/28 (11)	6/61 (10)	4/23 (17)
Clinical Assessment							
TJC	5 (1–11)	9 (5–18)	7(2–13)	7 (2–12)	5 (9–13)	6 (2–12)	0 (0–0)
SJC	0 (0–2)	4 (3–9)	2 (1–2)	0 (0–0)	3(2–5)	0(0–0)	0 (0–0)
Patients arthritis VAS	50 (23.5–70)	70 (40–84)	57 (46–70)	50 (40–70)–71)	63 (43–77)	20 (8.5–31)	0 (0–22)
Physician VAS	20 (2.5–50)	67 (55–76)	50 (32–60)	15 (7–22)	60 (35–70)	50 (40–70)	0 (0–0)
Symptomatic joints	5 (0–13)	10 (5–20)	9 (2–17)	7 (2–13)	10 (5–17)	6.5 (1–13)	0 (0–0)
Total SLEDAI	4 (0–6)	6 (4–8)	6.0 (4–8)	2 (0–5.5)	6 (4–8)	5.5 (4–8)	0(0–2)
SLICC-DI	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–0)
CRP	5 (5–8)	5 (5–11)	5 (5–10)	5 (5–10)	5 (5–15)	5 (5–7.5)	5 (5–5)
ESR	20 (9–41.5)	47 (11–81)	31 (12–42)	14 (9–40)	32 (10–58)	16 (9–41)	12 (4–23)
Serology							

IgG	12.6 (9.7,17.5)	13 (10,20)	18 (9,21)	12.7 (11,15)	14 (11,20)	12.5 (10,16)	11 (9,16.5)
Raised Anti-dsDNA, N (%)	36/108 (33)	6/14(43)	5/18 (28)	16/52 (31)	8/27 (30)	19/58(33)	8/23 (35)
Low C3, N (%)	11/104 (11)	3/14 (21)	5/15 (33)	8/52(15)	20/28 (71)	3/58 (5)	7/22 (32)
Low C4, N (%)	20/104 (19)	2/11 (17)	4/14 (21)	8/49 (16)	18/28 (64)	7/58 (12)	8/20 (36)

All values presented are median (IQR) unless otherwise stated . SLICC-DI: SLICC damage index. [a]1 patient with missing BILAG/SLEDAI data was excluded from further analysis.

Table 2: Frequencies of different ultrasound abnormalities in BILAG-And SLEDAI groups

	All patients (n=112)	Patients with MSK symptoms					No MSK symptom
		BILAG			SLEDAI		
		MSK-BILAG=A (n=14)	MSK-BILAG=B (n=20)	MSK-BILAG=C (n=54)	MSK-SLEDAI = 4 (n=28)	MSK-SLEDAI = 0 (n=61)	MSK BILAG=D (n=23)
Overall Synovitis (GS ≥ 2 and/or PD≥1)	57	100	85	53	86	52	17
Total PD synovitis	39	100	65	30	79	36	4
Total mod-severe PD synovitis	26	100	35	13	64	26	4
Total erosions	9	29	20	4	25	4.8	100
Tenosynovitis	25	57	35	24	43	21	0
Hands synovitis	57	100	85	52	86	67	17
Hands mild PD synovitis	50	100	75	44	86	55	9
Hands mod-severe PD synovitis	29	93	50	15	64	31	0
Hand erosions	13	29	20	11	29	12	0
Hands tenosynovitis	18	57	30	11	39	19	0
Feet synovitis	27	44	20	26	43	19	22
Feet mild PD synovitis	9	14	13	13	7	12	0
Feet mod-severe PD synovitis	2	14	0	0	2	0	0
Feet erosions	5	7	10	4	7	5	4
Total GS score, median (IQR)	4 (1–15)	27 (19–41)	11 (4–20)	3.5 (1–7.25)	3(1–8)	4 (1–11)	2 (0–6)
Total PD score, median (IQR)	0 (0–3)	13.5 (6–26)	1 (0–6.8)	0 (0–1)	0 (0–1)	0 (0–2.3)	0 (0–0)
Total Erosion score, median (IQR)	0 (0–0)	0 (0–2)	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Total TS GS score, median (IQR)	0 (0–0)	0 (0–3)	0 (0–0)	0 (0–1)	0 (0–0)	0 (0–0)	0

Total TS PD score, median (IQR)	0 (0–0)	0 (0–2)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
% PD score of 1 in hands	37	86	60	30	68	36	0
% PD score of 2 in hands	29	93	50	15	64	31	0
% PD score of 3 in hands	9	36	10	4	21	7	0
% Erosion=1 in hands	12	21	20	11	29	10	0
% Erosion=2 in hands	5	14	15	2	14	2	0
% Erosion=3 in hands	2	7	5	0	1	2	0

All values presented as % of patients unless otherwise stated. GS scoring was as follows; 0 = no synovial hypertrophy, 1 = mild hypertrophy, 2 = moderate hypertrophy, and 3 = severe hypertrophy. The PD scoring was as follows; 0 = absence of signal, no intra-articular flow; 1 = mild hyperemia, one or two vessels signal (including one confluent vessel); 2 = moderate hyperemia, (>grade 1) and less than 50% of GS area; 3 = marked hyperemia, vessels signal in more than half of the synovial area [19, 22] The erosion scoring was as follows; 0 = no erosion, 1 = small erosion/ minimal bone surface area affected <1/3 of joint quadrant, 2 = moderate size erosions/ moderate bone surface area affected <2/3 of joint quadrant hypertrophy, and 3 = large size erosion/ severe bone surface area affected ≥2/3 of joint quadrant)[23].

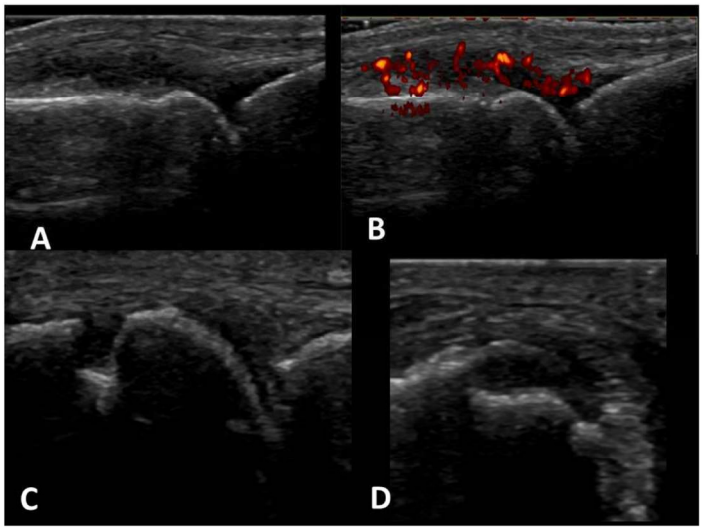
Table 3: Clinical and serological characteristics of symptomatic patients without joint swelling according to ultrasound status

	Overall US Abnormality			Grey Scale			Tenosynovitis or PD		
	No (n=36)	**Yes** (n=17)	***P***	**No** (n=38)	**Yes** (n=15)	***P***	**Both –** (n=43)	**Either +** (n=10)	***P***
Physician VAS	5 (0–16)	10 (0–25)	0.354	5 (0–17)	7 (0–26)	0.668	5 (0–16)	18 (6–26)	0.056
Tender Joint Count	1.5 (0–8)	2 (1–9)	0.310	2 (0–8)	2 (1–10)	0.511	1 (0–7)	7 (3–14)	0.024
IgG	10.9 (9.0–14.0)	14.8 (13.9–16.5)	0.002	11.2 (9.0–14.4)	14.8 (13.6–16.5)	0.003	11.5 (9.3–14.8)	16.2 (13.3–16.5)	0.045
ESR	11 (6-33)	20 (11–34)	0.106	11 (6–33)	20 (11–34)	0.106	13 (8–29)	16 (11–88)	0.417
DAS28-ESR	3.25 (1.48–4.41)	3.43 (2.52–4.96)	0.293	3.25 (1.48–4.41)	3.43 (2.52–4.96)	0.293	3.09 (1.69–4.14)	4.82 (2.85–5.31)	0.061

Analysis of patients with no joint swelling (MSK-SLEDAI=0). Values are median (IQR). Joints assessed by ultrasound in this analysis were hands and wrists. Clinical assessment was 28 joint set. Tenosynovitis GS1 was considered abnormal.

Figure 1: US synovitis and erosions detected in SLE patients

A: Grade 2 GS synovitis in 4th MCP joint, B: grade 3 PD synovitis in 4th MCP joint, C: Longitudinal view of an erosion in a 2nd MCP joint, D: Transverse view of the same erosion seen on C.



A: Grade 2 GS synovitis in 4th MCP joint, B: grade 3 PD synovitis in 4th MCP joint, C: Longitudinal view of an erosion in a 2nd MCP joint, D: Transverse view of the same erosion seen on Figure C

190x274mm (208 x 208 DPI)