Musculoskeletal Ultrasound in Systemic Lupus Erythematosus: Systematic Literature Review by the Lupus Task Force of the OMERACT Ultrasound Working Group

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ABSTRACT. ***Objective.*** To identify and synthesize the best available evidence on the application of musculoskeletal (MSK) ultrasound (US) in patients with systemic lupus erythematosus (SLE) and to present the measurement properties of US in different elementary lesions and pathologies.

Methods. A systematic literature search of PubMed, Embase, and the Cochrane Library was performed. Original articles were included that were published in English between August 1, 2014, and December 31, 2018, reporting US, Doppler, synovitis, joint effusion, bone erosion, tenosynovitis, and enthesitis in patients with SLE. Data extraction focused on the definition and quantification of US-detected synovitis, joint effusion, bone erosion, tenosynovitis, enthesitis, and the measurement properties of US according to the OMERACT Filter 2.1 instruments selection.

Results. Of the 143 identified articles, 15 were included. Most articles were cross-sectional studies (14/15, 93%). The majority of the studies used the OMERACT definitions for ultrasonographic pathology. Regarding the measurement properties of US in different elementary lesions and pathologies, all studies dealt with face validity, content validity, and feasibility. Most studies achieved construct validity. Concerning the reliability of image reading, 1 study (1/15, 7%) assessed both intraobserver and interobserver reliability. For image acquisition, 4 studies (4/15, 27%) evaluated interobserver reliability and none had evaluated intraobserver reliability. Criterion validity was assessed in 1 study (1/15, 7%). Responsiveness was not considered in any of the studies.

Conclusion. This literature review demonstrates the need for further research and validation work to define the involvement of US as an outcome measurement instrument for the MSK manifestations in patients with SLE. (First Release August 1 2019; J Rheumatol 2019;46:1379–87; doi:10.3899/jrheum.181087)

Key Indexing Terms:
ULTRASOUND SYSTEMIC LUPUS ERYTHEMATOSUS OMERACT

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Systemic lupus erythematosus (SLE) is a pleomorphic autoimmune disease involving many organ systems including the musculoskeletal (MSK) system. MSK symptoms and signs are common, affecting up to 95% of patients at some stage during the course of their disease[1]. Although the disease activity scores for SLE, the British Isles Lupus Assessment Group Index and the SLE Disease Activity Index, are broadly accepted as validated measures, they include arthritis only and therefore may underestimate the more subtle MSK manifestations, e.g., subclinical joint, tendon, bone, or entheseal involvement, which may reduce the quality of life of patients with SLE[2,3,4].

Ultrasound (US) is a versatile, multiplanar, and inexpensive bedside imaging modality with high patient acceptability. Although the body of reports analyzing the use of MSK US in SLE is growing, the significance of these findings remains difficult to interpret because no uniform terminology regarding the definition for ultrasonographic pathology has been used and some abnormalities are present in healthy persons[5,6]. Further, data are lacking regarding the validity and the discriminant capability of this tool for the management of patients with SLE. To standardize the use of US as a potential outcome measure for the evaluation of patients with SLE, a task force within the Outcome Measures in Rheumatology (OMERACT) US Working Group was formed.

Our research question, which is addressed in this systematic literature review, is whether there are sufficient data available proving that US may serve as an outcome measurement instrument for the diagnosis and monitoring of MSK manifestations in patients with SLE. More specifically, the objectives of this literature review were 3-fold: to determine (1) which pathologies and elementary lesions were studied by US in patients with SLE; (2) which US definitions and scoring systems were used for SLE MSK pathologies and elementary lesions; and (3) the measurement properties of US in evaluating the MSK domains of inflammation and structural damage in SLE, according to the OMERACT Filter 2.1 Instrument Selection Algorithm (OFISA)[7].

MATERIALS AND METHODS

Data source and search strategy. A population, intervention, comparator, and outcome-structured search of articles was performed in the PubMed, Embase, and Cochrane Library databases for the period August 1, 2014, to December 31, 2018. The starting date of August 1, 2014, was used because a previous review by Zayat, *et al* had already studied the articles published from January 1, 1950, to August 1, 2014, examining the involvement of US in assessing MSK symptoms of SLE[8]. The medical subject heading (MeSH) terms used were (ultrasonography OR ultrasonography, Doppler) AND (lupus erythematosus, systemic) AND (synovitis OR tenosynovitis OR enthesopathy). The following keywords were used for the search: (ultrasound OR ultrasonographic OR ultrasonography OR sonography OR sonographic OR Doppler), (systemic lupus erythematosus OR SLE OR lupus), (synovial hypertrophy OR synovitis OR joint effusion OR bone erosion OR tenosynovitis OR tendinitis OR tendonitis OR paratendinitis OR paratendonitis OR tendinopathy OR enthesitis OR enthesopathy). Studies included had to be on humans and published in English. Titles, abstracts, and full reports of the articles identified were systematically screened by 1 author (PW) regarding inclusion and exclusion criteria. Further, a manual search of secondary sources including article references was also performed. If an abstract was selected, the full-text article was retrieved and subsequently screened for eligibility criteria prior to selection for review. The inclusion criteria were (1) original research on the use of US for the assessment of MSK manifestations in patients with SLE, and (2) patients who fulfilled the American College of Rheumatology classification criteria for SLE[9,10]. The exclusion criteria were (1) editorials, reviews, case reports, letters to the editor, and conference abstracts, and (2) studies reporting only on patients with rhupus [coexistence of rheumatoid arthritis (RA) and SLE].

Data selection and extraction. All selected studies were independently reviewed by 2 authors (PW and GB). The interreader agreement between the 2 authors for selection of the studies was 1.0. All data were extracted using a standardized template that was specifically designed for this review, based on work previously done by the OMERACT US Working Group[11]. Each included study was analyzed to determine whether the measurement properties of US fulfilled the criteria according to the OFISA[7].

Quality assessment of included studies. The methodological quality of each study was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) instrument[12].

RESULTS

The search yielded 143 citations, of which 125 were excluded after reviewing the titles and abstracts. Eighteen full-text articles were reviewed to determine whether they met the inclusion criteria. Fifteen studies were included in the final analysis. Figure 1 shows the flow chart of the article selection process.

Characteristics of studies. Table 1 shows the characteristics of the 15 studies[13–27]. The majority of the studies were cross-sectional (14/15, 93%)[13,14,15,16,18–27]. One study (1/15, 7%) was a 5-year prospective study with a followup visit every 6 months[17]. There were 7 studies (7/15, 47%)[13,17,20,21,24,26,27] that included control group(s), 4 of them with healthy controls[13,17,21,27], 1 with patients with RA[20], 1 with both patients with psoriatic arthritis (PsA) and healthy controls[24], and 1 with mixed connective tissue disease[26]. Most of the patients were women. The mean age ranged from 29 to 54 years. The mean disease duration ranged from 4 to 21 years, with 1 study investigating treatment-naive patients with early SLE with a mean disease duration of < 1 year[20]. Most studies (12/15, 80%)[13-17,19,20,22-24,26,27] categorized patients into 3 subtypes of SLE arthropathy as proposed by van Vugt, *et al*, i.e., rhupus, Jaccoud arthropathy (JA), and mild deforming arthropathy[28]. Two studies (2/15, 13%) investigated patients with JA[18,25]. One study (1/15, 7%) excluded patients with any 1 of the 3 subtypes and included patients with the non-deforming, nonerosive type of arthropathy only[21].

Table 2 summarizes the US pathology reported, as well as the US definition and the scoring system used in each study. All studies examined at least 1 of the following pathologies or elementary lesions: synovitis, joint effusion, bone erosion, and/or tenosynovitis[13–27]. Two studies (2/15, 13%) assessed enthesitis[23,24]. One study (1/15, 7%) focused on the entheseal involvement of the lower limbs[24]. Supplementary Table 1 shows the frequency of US pathology (available with the online version of this article).

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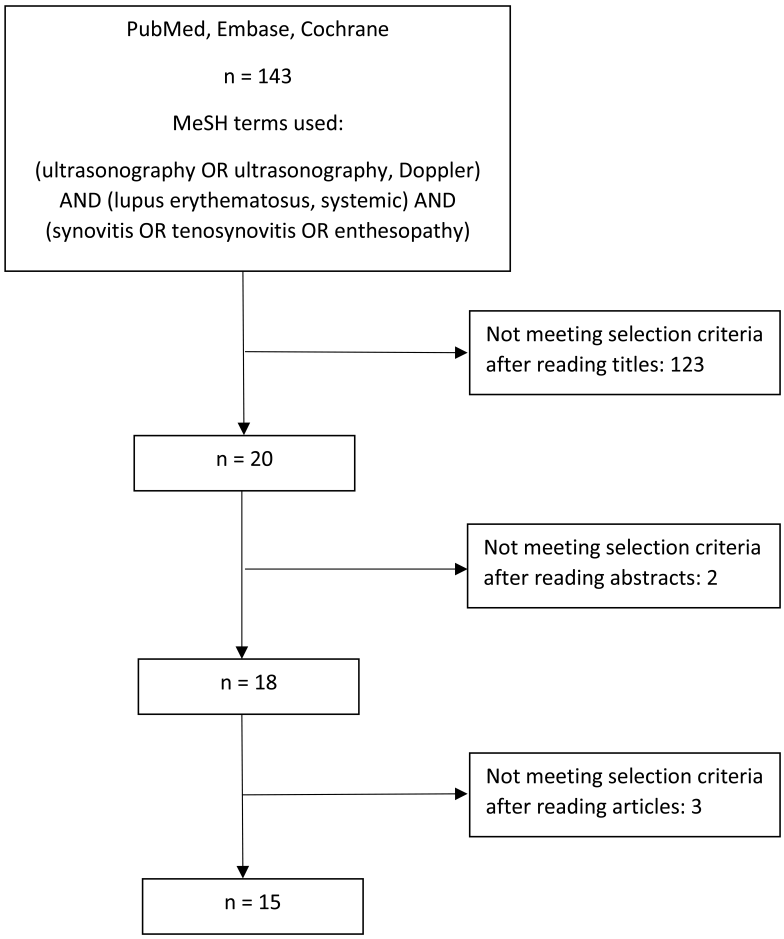

Figure 1. Flow chart of the article selection.

Synovitis. Synovitis was examined in 13 studies (13/15, 87%)[13,14,15,17-23,25,26,27]. In the vast majority of these studies, the choice of the anatomical sites and structures to be examined seemed arbitrary. Hand and wrist were most frequently studied, with the second and third metacarpophalangeal joints assessed in all the studies (13/13, 100%)[13,14,15,17-23,25,26,27]. One study (1/13, 8%) assessed the metatarsophalangeal joint and the forefoot bursa, which were comparatively less reported, particularly by US examination[15]. The OMERACT 2005 definition of synovial hypertrophy[29] was adopted by 11 studies (11/13, 85%)[13,14,17-23,25,26]. Two studies (2/13, 15%) used the definition given by the author[15,27]. Eight studies (8/13, 62%) used a semiquantitative scoring system for synovial hypertrophy[14,15,17,19-22,25], while 5 studies (5/13, 38%) used a binary scoring system[13,18,23,26,27].

Joint effusion. Joint effusion was examined in 4 studies (4/15, 27%)[14,18,22,23]. The OMERACT 2005 definition of joint effusion[29] was used in all 4 studies (4/4, 100%)[14,18,22,23]. Three studies (3/4, 75%) used a binary scoring system to quantify joint effusion[18,22,23] while 1 study (1/4, 25%) used a semiquantitative method[14]. The prevalence of joint effusion varied from 17% to 88.2%[14,18,22].

Bone erosion. Bone erosion was examined in 12 studies (12/15, 80%)[13-19,22,23,24,25,27]. The OMERACT 2005 definition of bone erosion[29] was used in 10 studies (10/12, 83%)[13,14,16,17,18,22,23,24,25,27], of which 2 (2/12, 17%) used their own definitions[15,19]. Ten studies (10/12, 83%)[13,14,15,17,18,22,23,24,25,27] used a binary scoring system, and 1 (1/12, 8%) used a semiquantitative method[16].

Tenosynovitis. Tenosynovitis was examined in 11 studies (11/15, 73%)[13,14,17-20,22,23,25,26,27]. All studies (11/11, 100%)[13,14,17-20,22,23,25,26,27] assessed the flexor and extensor tendons of the hands and wrists, with 1 study (1/11, 9%) assessing 2 lower limb tendons as well[22]. The OMERACT 2005 definition of tenosynovitis[29] was used in 9 studies (9/11, 82%)[13,14,17,18,20,22,23,25,26]. Two studies (2/11, 18%) used the definition of tenosynovitis given by the authors[19,27]. Six studies (6/11, 56%)[13,14,18,23,26,27] used a semiquantitative score while 5 studies (5/11, 46%) used a binary scoring in the

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Table 1. Characteristics of studies.

Study	Yr	Type of Study	No. Patients	No. Controls	Mean Age, Yrs	Mean Disease Duration, Yrs	Subtypes of SLE Arthropathy	Joints	Tendons	Entheses
Dreyer, *et al*[13]	2015	CS, CC	33	11	41.8	—	All	Wrist, MCP 1–5	Finger flexors, finger extensors, APL	—
Mosca, *et al*[14]	2015	CS	102	—	42.5	15	All	Wrist, MCP 2–5, PIP 2–5	Finger flexors, finger extensors	—
Mukherjee, *et al*[15]	2016	CS	20	—	53.6	12.1	All	MCP, MTP, forefoot bursa	—	—
Piga, *et al*[16]	2016	CS	26	—	49.4	16	All	Ulnar head, radiocarpal, MCP 2–5	—	—
Piga, *et al*[17]	2016	PC, CC	94	60	30.7	10.5	All	Wrist, MCP 2–3	Wrist extensors, FPL, FCR, FDS 2–5, FDP 2–5	—
Ceccarelli, *et al*[18]	2017	CS	17	—	50.7	20.6	JA	Radio-ulno-carpal, MCP 1–5, PIP 2–5	Wrist extensors, finger flexors 2–5	—
Lins, *et al*[19]	2017	CS	64	—	42.9	—	All	Radiocarpal, MCP 2–4, PIP 2–4	Finger flexors 2–4	—
Ogura, *et al*[20]	2017	CS, CC	15	15 (RA)	53	0.6	All	Wrist, MCP 1–5, thumb IP, PIP 2–5	Wrist flexors, wrist extensors, finger flexors 1–5, finger extensors 1–5	—
Ruano, *et al*[21]	2017	CS, CC	36	10	41.5 (asymptomatic), 45 (symptomatic)	9 (asymptomatic), 12.5 (symptomatic)	Nondeforming, nonerosive	Radiocarpal, ulnar head, MC head 2–5	—	—
Salliot, *et al*[22]	2018	CS	151	—	45.6	11.9	All	Shoulder, elbow, wrist, MCP 1–5, PIP, knee, ankle, MTP 1–5	Finger flexors 1–5, finger extensors 1–5, fibular and tibialis posterior	—
Di Matteo, *et al*[23]	2018	CS	25	—	43.7	4	All	Clinically involved in physical examination and/or joints reported as painful in patient's medical history	Clinically involved in physical examination and/or joints reported as painful in patient's medical history	Clinically involved in physical examination and/or joints reported as painful in patient's medical history
Di Matteo, *et al*[24]	2018	CS, CC	65	50 (PsA), 50 (HC)	41.8	7.9	All	—	—	Patellar insertion of quadriceps tendon, patellar insertion (proximal) of patellar tendon, tibial insertion of patellar tendon, calcaneal insertion of Achilles tendon, plantar fascia
Lins, *et al*[25]	2018	CS	40	—	44	16.3	JA	Radiocarpal, ulnocarpal, MCP 2–4, PIP 2–4	Finger flexors 2–4, finger extensors 2–4	—
Gunashekar, *et al*[26]	2018	CS, CC	40	40 (MCTD)	32	3.7	All	Wrist, MCP 1–5	Finger flexors 1–5, finger extensors 1–5	—
Abdel-Magied, *et al*[27]	2018	CS, CC	30	20	28.9	8.9	No JA or rhupus	Wrist, MCP 1–5, PIP 1–5, MTP 1–5	Wrist flexors, wrist extensors, ankle tendons	—

SLE: systematic lupus erythematosus; CS: cross-sectional; CC: case-control; PC: prospective cohort; RA: rheumatoid arthritis; PsA: psoriatic arthritis; HC: healthy controls; MCTD: mixed connective tissue disease; JA: Jaccoud's arthropathy; MCP: metacarpophalangeal; PIP: proximal interphalangeal; MTP: metatarsophalangeal; IP: interphalangeal; MC: metacarpal; APL: abductor pollicis longus; FPL: flexor pollicis longus; FCR: flexor carpal radialis; FDS: flexor digitorum superficialis; FDP: flexor digitorum profundus.

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Table 2. Definition and scoring system of ultrasound pathology.

Study	Yr	Synovial Hypertrophy	Synovial Hypertrophy Definition	Synovial Hypertrophy Scoring	Joint Effusion	Joint Effusion Definition	Joint Effusion Scoring	Bone Erosion	Bone Erosion Definition	Bone Erosion Scoring	Teno-synovitis	Teno-synovitis Definition	Teno-synovitis Scoring	Enthesitis	Enthesitis Definition	Enthesitis Scoring
Dreyer, *et al*[13]	2015	Yes	OM	Bin.	–	–	–	Yes	OM	Bin.	Yes	OM	Bin.	–	–	–
Mosca, *et al*[14]	2015	Yes	OM	SQ	Yes	OM	SQ	Yes	OM	Bin.	Yes	OM	Bin.	–	–	–
Mukherjee, *et al*[15]	2016	Yes	*	SQ	–	–	–	Yes	*	Bin.	–	–	–	–	–	–
Piga, *et al*[16]	2016	–	–	–	–	–	–	Yes	OM	SQ	–	–	–	–	–	–
Piga, *et al*[17]	2016	Yes	OM	SQ	–	–	–	Yes	OM	Bin.	Yes	OM	SQ	–	–	–
Ceccarelli, *et al*[18]	2017	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	Bin.	–	–	–
Lins, *et al*[19]	2017	Yes	OM	SQ	–	–	–	Yes	*	–	Yes	*	SQ	–	–	–
Ogura, *et al*[20]	2017	Yes	OM	SQ	–	–	–	–	–	–	Yes	OM	SQ	–	–	–
Ruano, *et al*[21]	2017	Yes	OM	SQ	–	–	–	–	–	–	–	–	–	–	–	–
Salliot, *et al*[22]	2018	Yes	OM	SQ	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	SQ	–	–	–
Di Matteo, *et al*[23]	2018	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	Bin.	Yes	OM	–
Di Matteo, *et al*[24]	2018	–	–	–	–	–	–	Yes	OM	Bin.	–	–	–	Yes	OM	SQ
Lins, *et al*[25]	2018	Yes	OM	SQ	–	–	–	Yes	OM	Bin.	Yes	OM	SQ	–	–	–
Gunashekar, *et al*[26]	2018	Yes	OM	Bin.	–	–	–	–	–	–	Yes	OM	Bin.	–	–	–
Abdel-Magied, *et al*[27]	2018	Yes	*	Bin.	–	–	–	Yes	OM	Bin.	Yes	*	Bin.	–	–	–

*Definition was given by author. SQ: semiquantitative; OM: Outcome Measures in Rheumatology; Bin.: binary.

assessment[17,19,20,22,25]. The prevalence of tenosynovitis ranged from 10% to 93%[13,14,17,20,22,25,26,27].

Enthesitis. Enthesitis was examined in 2 studies (2/15, 13%)[23,24]. The OMERACT 2005 definition of enthesopathy[29] and the standardized US definition of enthesitis and its elementary components in spondyloarthritis[30] were used in both studies[23,24]. In 1 study (1/2, 50%), a binary score was used to report the entheseal abnormalities while a semiquantitative scale was used to grade the power Doppler signal of the enthesitis[24]. The prevalence of entheseal involvement was 67.7%[24]. US enthesitis was mainly found at the distal insertion of the patellar tendon[24].

US scanning techniques and settings. Supplementary Table 2 (available with the online version of this article) shows the characteristics of the US scanning techniques and settings. Bilateral US examination was performed in most studies (12/15, 80%)[15–25,27] except in 3 (3/15, 20%) that performed unilateral US examination only[13,14,26]. The scanning techniques including dorsal and volar sides as well as longitudinal and transverse planes were reported in 9 studies (9/15, 60%)[13,15,16,19,20,21,23,24,25]. Two-thirds of the studies (10/15, 67%) used both greyscale and power Doppler modes[14,15,17,18,20,21,22,23,24,27]. Color Doppler mode was used in 1 study (1/15, 7%)[13]. Three studies (3/15, 20%) evaluated greyscale only[19,25,26]. The US settings regrading the Doppler frequency, power Doppler pulse repetition frequency, wall filter, and color gain were reported in 6 studies (6/15, 40%)[13,18,20,21,23,24]. The majority of the studies reported the US machine brand[13-21,23,24,25,26,27], US transducer[13-18,20,21,23,24,26,27], and the frequency of US transducer[13–27].

Measurement properties of US. Table 3 shows the measurement properties of US for the elementary lesion of joint effusion and the key pathologies including synovitis, bone erosion, tenosynovitis, and enthesitis according to the OMERACT Filter 2.1 Instrument Selection Algorithm.

Validity. Supplementary Table 3 (available with the online version of this article) shows the association between US findings and the clinical, laboratory, and other imaging assessments. Clinical assessment was performed in all studies (15/15, 100%)[13–27], but the construct validity of US as related to clinical assessment was reported in only 11 studies (11/15, 73%)[13,14,15,16,17,19,20,21,22,24,27]. Laboratory assessment was performed in 14 studies (14/15, 93%)[13-18,20-27] and the construct validity of US as related to laboratory assessment was reported in 4 studies (4/15, 27%)[14,17,24,27]. Six studies (6/15, 40%)[14,16,17,20,22,26] performed another imaging technique including 1 study with magnetic resonance imaging[14], 1 study with computer tomography[16], and 4 studies with radiography[17,20,22,26]. However, only 1 study (1/15, 7%) compared the findings obtained in US with the additional imaging technique[16]. The criterion validity as related to histology was not performed in any of the studies. Table 3 summarizes all the measurement properties of US.

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Table 3. Measurement properties of ultrasound according to the OMERACT Filter 2.1 Instrument Selection Algorithm.

Target Pathology	Study	Year	Face	Validity			Reliability				Responsiveness	Feasibility
				Content	Construct	Criterion	Intraobserver Image Reading	Interobserver Image Reading	Intraobserver Image Acquisition	Interobserver Image Acquisition		
Synovitis	Dreyer, *et al*[13]	2015	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Mosca, *et al*[14]	2015	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Mukherjee, *et al*[15]	2016	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Piga, *et al*[16]	2016	—	—	—	—	—	—	—	—	—	—
	Piga, *et al*[17]	2016	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Ceccarelli, *et al*[18]	2017	Yes	Yes	No	No	No	No	No	No	No	Yes
	Lins, *et al*[19]	2017	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Ogura, *et al*[20]	2017	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
	Ruano, *et al*[21]	2017	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Salliot, *et al*[22]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[23]	2018	Yes	Yes	No	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[24]	2018	—	—	—	—	—	—	—	—	—	—
	Lins, *et al*[25]	2018	Yes	Yes	No	No	No	No	No	Yes	No	Yes
	Gunashekar, *et al*[26]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Abdel-Magied, *et al*[27]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
Summary			13/13	13/13	10/13	0/13	1/13	1/13	0/13	3/13	0/13	13/13
Joint effusion	Dreyer, *et al*[13]	2015	—	—	—	—	—	—	—	—	—	—
	Mosca, *et al*[14]	2015	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Mukherjee, *et al*[15]	2016	—	—	—	—	—	—	—	—	—	—
	Piga, *et al*[16]	2016	—	—	—	—	—	—	—	—	—	—
	Piga, *et al*[17]	2016	—	—	—	—	—	—	—	—	—	—
	Ceccarelli, *et al*[18]	2017	Yes	Yes	No	No	No	No	No	No	No	Yes
	Lins, *et al*[19]	2017	—	—	—	—	—	—	—	—	—	—
	Ogura, *et al*[20]	2017	—	—	—	—	—	—	—	—	—	—
	Ruano, *et al*[21]	2017	—	—	—	—	—	—	—	—	—	—
	Salliot, *et al*[22]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[23]	2018	Yes	Yes	No	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[24]	2018	—	—	—	—	—	—	—	—	—	—
	Lins, *et al*[25]	2018	—	—	—	—	—	—	—	—	—	—
	Gunashekar, *et al*[26]	2018	—	—	—	—	—	—	—	—	—	—
	Abdel-Magied, *et al*[27]	2018	—	—	—	—	—	—	—	—	—	—
Summary			4/4	4/4	2/4	0/4	0/4	0/4	0/4	0/4	0/4	4/4
Bone erosion	Dreyer, *et al*[13]	2015	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Mosca, *et al*[14]	2015	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Mukherjee, *et al*[15]	2016	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Piga, *et al*[16]	2016	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes
	Piga, *et al*[17]	2016	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Ceccarelli, *et al*[18]	2017	Yes	Yes	No	No	No	No	No	No	No	Yes
	Lins, *et al*[19]	2017	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Ogura, *et al*[20]	2017	—	—	—	—	—	—	—	—	—	—
	Ruano, *et al*[21]	2017	—	—	—	—	—	—	—	—	—	—
	Salliot, *et al*[22]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[23]	2018	Yes	Yes	No	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[24]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Lins, *et al*[25]	2018	Yes	Yes	No	No	No	No	No	Yes	No	Yes
	Gunashekar, *et al*[26]	2018	—	—	—	—	—	—	—	—	—	—
	Abdel-Magied, *et al*[27]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
Summary			12/12	12/12	9/12	1/12	0/12	0/12	0/12	4/12	0/12	12/12
Tenosynovitis	Dreyer, *et al*[13]	2015	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Mosca, *et al*[14]	2015	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Mukherjee, *et al*[15]	2016	—	—	—	—	—	—	—	—	—	—
	Piga, *et al*[16]	2016	—	—	—	—	—	—	—	—	—	—
	Piga, *et al*[17]	2016	Yes	Yes	Yes	No	No	No	No	Yes	No	Yes
	Ceccarelli, *et al*[18]	2017	Yes	Yes	No	No	No	No	No	No	No	Yes
	Lins, *et al*[19]	2017	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Ogura, *et al*[20]	2017	Yes	Yes	Yes	No	Yes	Yes	No	No	No	Yes
	Ruano, *et al*[21]	2017	—	—	—	—	—	—	—	—	—	—
	Salliot, *et al*[22]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes

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Table 3. Continued.

Target Pathology	Study	Year	Face	Validity: Content	Validity: Construct	Validity: Criterion	Reliability: Intraobserver Image Reading	Reliability: Interobserver Image Reading	Reliability: Intraobserver Image Acquisition	Reliability: Interobserver Image Acquisition	Responsiveness	Feasibility
	Di Matteo, *et al*[23]	2018	Yes	Yes	No	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[24]	2018	–	–	–	–	–	–	–	–	–	–
	Lins, *et al*[25]	2018	Yes	Yes	No	No	No	No	No	Yes	No	Yes
	Gunashekar, *et al*[26]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Abdel-Magied, *et al*[27]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
Summary			11/11	11/11	8/11	0/11	1/11	1/11	0/11	3/11	0/11	11/11
Enthesitis	Dreyer, *et al*[13]	2015	–	–	–	–	–	–	–	–	–	–
	Mosca, *et al*[14]	2015	–	–	–	–	–	–	–	–	–	–
	Mukherjee, *et al*[15]	2016	–	–	–	–	–	–	–	–	–	–
	Piga, *et al*[16]	2016	–	–	–	–	–	–	–	–	–	–
	Piga, *et al*[17]	2016	–	–	–	–	–	–	–	–	–	–
	Ceccarelli, *et al*[18]	2017	–	–	–	–	–	–	–	–	–	–
	Lins, *et al*[19]	2017	–	–	–	–	–	–	–	–	–	–
	Ogura, *et al*[20]	2017	–	–	–	–	–	–	–	–	–	–
	Ruano, *et al*[21]	2017	–	–	–	–	–	–	–	–	–	–
	Salliot, *et al*[22]	2018	–	–	–	–	–	–	–	–	–	–
	Di Matteo, *et al*[23]	2018	Yes	Yes	No	No	No	No	No	No	No	Yes
	Di Matteo, *et al*[24]	2018	Yes	Yes	Yes	No	No	No	No	No	No	Yes
	Lins, *et al*[25]	2018	–	–	–	–	–	–	–	–	–	–
	Gunashekar, *et al*[26]	2018	–	–	–	–	–	–	–	–	–	–
	Abdel-Magied, *et al*[27]	2018	–	–	–	–	–	–	–	–	–	–
Summary			2/2	2/2	1/2	0/2	0/2	0/2	0/2	0/2	0/2	2/2

OMERACT: Outcome Measures in Rheumatology.

Reliability. Reliability of US can be divided into image reading and image acquisition. Regarding image reading, both intraobserver and interobserver reliability were assessed in only 1 study (1/15, 7%), which reported excellent agreement[20]. Regarding image acquisition, no intraobserver reliability was measured, while interobserver reliability was assessed in 4 studies (4/15, 27%), with poor to excellent agreement[13,16,17,25].

Responsiveness. None of the studies evaluated the ability of US to change after an intervention.

Feasibility. US was considered highly acceptable to both patients and physicians; no side effects or complications were reported in any studies[13–27]. Though the time spent on US examination was not quantified in any of the studies, and it varied according to the number of anatomical sites and structures examined, it was regarded as acceptable by both patients and physicians.

Quality assessment of studies. The signaling questions used for the quality assessment of the included studies are listed in Supplementary Table 4 (available with the online version of this article). The risk of bias in patient selection was high in most studies (12/15, 80%)[13,14,16,17,19-24,26,27], because patients with rhupus were either not separated or were excluded in the final analysis, in which the US findings in patients with SLE could have been affected. The risk of bias in index test was low in most studies (9/15, 60%), given that the sonographer was blinded to the clinical and laboratory data of the patients and the US scoring method was prespecified[13,14,17,18,21-25]. Only 2 studies (2/15, 13%) compared the US findings with another imaging method, which served as a reference standard[14,16]. US was performed at the same time with the clinical reference standard test in most studies (11/15, 73%)[13-17,20-25], with 4 studies not stating the US timing (4/15, 27%)[18,19,26,27]. Regarding concerns about the applicability of patient selection and the index test of each study to the proposed research question, all studies were rated as low. The applicability concerns for reference standard were high in all studies (15/15, 100%), despite 2 studies having compared US findings with a concomitant imaging method as a reference standard[14,16]. Supplementary Table 5 shows the analysis of the quality assessment of each study.

DISCUSSION

Our systematic literature review shows a very high heterogeneity in almost all aspects of the published articles on US assessment of patients with SLE. These aspects included the elementary lesions (synovial hypertrophy and joint effusion), key pathologies (synovitis, bone erosion, tenosynovitis, and enthesitis), definitions of these elementary lesions and pathologies, measurement properties of US including the construct validity (types of comparator), intraobserver and interobserver reliability, and the US scanning protocol (anatomical sites taken, scanning technique, US mode, US

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setting, US transducer, and its frequency). Another important limitation in evaluating US for the assessment of patients with SLE is that no study assessed the responsiveness to change. Moreover, the overall quality assessment of the included studies as assessed by the QUADAS-2 instrument showed a high risk of bias.

We found a great heterogeneity in the US evaluation of the different pathologies. Only 4 studies (4/15, 27%) evaluated all 4 key pathologies of interest at the same time[14,18,22,23]. The majority of the studies used a binary scoring system in reporting joint effusion (3/4, 75%)[18,22,23] and bone erosion (10/12, 83%)[13,14,15,17,18,22-25,27]. Tenosynovitis was unexpectedly found with a high prevalence in patients with SLE too. Other tendon abnormalities such as para-tendonitis, tendon thinning, tendon dislocation, tendon rupture, etc., were not reported at all, although they might play certain roles in the MSK abnormalities of patients with SLE.

One study with both patients with PsA and healthy subjects included focused on the study of entheses in patients with SLE[24]. The results showed that patients with SLE had a higher prevalence of active enthesitis than healthy controls but a lower prevalence in comparison with PsA patients. This is the first study focusing on enthesitis, which is traditionally not considered among the targeted pathologies in patients with SLE. It provides new insight into the evaluation of patients with SLE that might have been missed previously.

We found only one 5-year prospective study with patients prospectively assessed by US to predict MSK flare[17]. This highlights an important lack of longitudinal followup studies investigating MSK US manifestations and treatment outcome measures in patients with SLE. Compared with the treat-to-target and tight control treatment strategies in RA, the warranted attention to the MSK manifestations in patients with SLE seems to fall short. Another methodological concern is that most studies recruited a rather small number of patients and lacked a control group.

Most studies examined the hand and wrist joints as well as the flexor and extensor tendons of the fingers and wrists for the reason of accessibility. Only 4 studies (4/15, 27%) examined different anatomical sites and structures of the lower limbs including the knees, ankles, metatarsophalangeal joints, forefoot bursa, and various entheses[15,22,23,24]. This suggests that either inadequate attention is being paid to the lower limbs of patients with SLE, or MSK pathologies are limited to the upper limbs, which seems improbable.

The US scanning techniques were briefly mentioned in most studies, with inadequate details to allow comparisons to be made between studies. There was neither standardization nor consistency in the scanning methodology. In general, most studies provided some information about the US settings. However, the characteristics and the resolution of the US machines, details of the US setting variables, and the presets of the US transducers were either unaddressed or only partially addressed.

Compared with the results obtained in the systematic literature review by Zayat, *et al*[8], there were new studies examining the presence of joint effusion[14,18,22,23] and enthesitis[23,24] in patients with SLE, and the association between US findings and imaging techniques other than conventional radiography[16].

We identified a high heterogeneity regarding the methodological reporting of US findings in patients with SLE. These include a paucity of specific imaging recommendations to evaluate MSK manifestations in patients with SLE, and a lack of recommendations for the sites and pathologies of interest to be examined. Moreover, there appears to be a lack of uniformity regarding the definitions used for the US abnormalities. OMERACT definitions[29] were used in most studies but not all[13,14,16,17,18,20-25]. These observations limit the use of US for the assessment of MSK manifestations in patients with SLE. According to the OMERACT methodology for imaging outcome measurement tools recently published by the US working group[31], the future research agenda for MSK US in SLE should (1) define which anatomical sites and pathologies should be examined, (2) apply the developed definitions for US elementary lesions and pathologies[32], (3) test their reliability, and (4) apply them in clinical longitudinal trials to develop a body of evidence for OFISA assessment. Improved standardization may help incorporate US in the assessment of SLE patients with MSK symptoms.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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