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ORIGINAL RESEARCH

Ultrasound-detected inflammation and structural changes in the joints, tendons and entheses of patients with cancer who developed arthritis or arthralgia after exposure to immune checkpoint inhibitors

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ABSTRACT

Objectives To explore the prevalence and distribution of ultrasound-detected inflammation and structural damage in the joints, tendons and entheses of patients who developed new-onset arthritis or arthralgia following exposure to immune checkpoint inhibitor (ICI) therapy, including a comparison between those with ICI-induced arthritis and those with ICI-induced arthralgia.

Methods Patients with cancer who developed clinical arthritis or arthralgia (ie, joint pain without clinical synovitis) after receiving ICIs were consecutively recruited from six international centres. Patients underwent a full clinical assessment and ultrasound evaluation of 18 joints, 15 tendons and 5 entheses bilaterally, using the Outcome Measures in Rheumatology definitions.

Results A total of 101 patients were included: 53 (52.5%) had ICI-arthralgia (absent clinical synovitis). Among them, 25 (47.2%) had ultrasound-detected subclinical synovitis, 10 (18.9%) tenosynovitis, 1 (1.9%) digital extensor peritendinitis and 13 (24.5%) enthesitis. In the 48 patients with ICI-arthritis, ultrasound-detected synovitis was more prevalent than in ICI-arthralgia (93.8% vs 47.2%, p<0.001), particularly in the wrists (56.3% vs 20.8%, p<0.001) and the knees (54.2% vs 13.2%, p<0.001), which were the most frequently affected joints. Tenosynovitis (52.1% vs 18.9%, p<0.001), peritendinitis (10.4% vs 1.9%, p=0.099) and bone erosions (25% vs 7.5%, p=0.027) were also more frequent in ICI-arthritis. 'Active' enthesitis was similar between groups (31.3% vs 24.5%), with no significant differences.

Conclusions This multicentre study reveals a higher burden of ultrasound-detected changes in ICI-arthritis compared with ICI-arthralgia, with diverse patterns across joints, tendons and entheses in both subtypes. Significant subclinical inflammation suggests that many cases of non-specific ICI-arthralgia may benefit from targeted interventions.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune checkpoint inhibitors (ICIs) are known to cause musculoskeletal toxicities, including arthritis and arthralgia, but there are limited imaging data on these conditions.

⇒ Most existing studies focus on clinical symptoms, often overlooking subclinical inflammation that could indicate underlying inflammatory disease.

WHAT THIS STUDY ADDS

⇒ This study revealed significant subclinical inflammation and structural damage in ICI-arthralgia patients, which suggests that they may have underlying inflammatory joint disease.

⇒ The study showed that ICI-induced joint manifestations present with diverse inflammatory patterns, many resembling conditions like rheumatoid arthritis and psoriatic arthritis.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study highlights the importance of using ultrasound for early detection of inflammation in ICI-treated patients, potentially improving diagnosis and management.

⇒ It highlights the need for more longitudinal research to understand the long-term impact of subclinical inflammation and whether early intervention can prevent progression to overt arthritis and more severe disease outcomes.

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionised the oncological approach to

treating certain cancers, providing many patients with significantly improved disease outcomes.[1] In normal, non-cancerous settings, immune checkpoint activation helps maintain self-tolerance and prevents autoimmunity by regulating physiological immune responses.[2] ICIs, such as those targeting cytotoxic T lymphocyte antigen 4, programmed cell death 1 and programmed cell death 1 ligand 1, work by preventing cancer cells from exploiting an immune environment that tolerates tumour growth.[3]

While ICIs are beneficial for controlling cancer, they carry the risk of breaching self-tolerance, thereby increasing the likelihood of immune-related adverse events (irAEs)—a well-recognised complication of ICI use.[3] Musculoskeletal (MSK) toxicities secondary to ICIs are common but often underappreciated.[4] Clinically evident ICI-induced arthritis (ICI-arthritis) in the form of clinical synovitis is reported in about 7% of patients, while arthralgia (ICI-arthralgia) occurs in up to 43% of patients receiving ICIs.[5] Both ICI-arthritis and ICI-arthralgia can persist even after cessation of immunotherapy, significantly impacting patients' quality of life.[6]

Despite ICI-induced MSK irAEs being a relatively new phenomenon following the introduction of ICIs in 2011, numerous studies have attempted to explore these events.[7 8] Points to consider in the diagnosis and management of these patients have been developed by the European Alliance of Associations for Rheumatology (EULAR).[9] However, the majority of these studies are primarily based on clinical findings. Given the limitations of clinical assessment (including its subjectivity), it is important to evaluate disease burden in terms of inflammatory changes and structural damage using imaging, which offers superior diagnostic sensitivity and accuracy.[10] Indeed, relying exclusively on clinical examination may fail to capture the full extent of the disease, making imaging necessary for a comprehensive evaluation.

A key unmet need in the assessment of MSK irAEs is the limited understanding of the underlying inflammatory processes—an area where imaging could play a pivotal role.[11] Currently, the scarcity of imaging data contributes to under-diagnosis and may falsely reassure clinicians, particularly in patients with subclinical inflammation that is not evident on clinical examination but who may still benefit from targeted therapies. This raises an important question: do a significant number of patients exposed to ICIs develop subclinical autoimmunity that remains undetected?

Recent findings from our group using whole-body MRI (WB-MRI) in patients with cancer receiving ICI therapy with MSK symptoms support this hypothesis, demonstrating widespread subclinical disease.[12] However, while WB-MRI offers comprehensive, whole-body insight into inflammatory burden, its limited availability, cost and complexity restrict its use in routine clinical practice. In contrast, MSK ultrasound is already embedded in many rheumatology services, is highly sensitive for detecting early or subclinical synovitis and allows dynamic, bedside assessment of joints, tendons and entheses. It is also cost-effective, widely accessible and ideal for serial monitoring.[10]

Despite these advantages, current ultrasound data in the context of ICI-induced arthritis and arthralgia are sparse and largely limited to small case series or cohorts.[11] Moreover, most studies have focused only on symptomatic joints, failing to capture the broader pattern of disease distribution and associated structural damage. A more comprehensive, systematic ultrasound approach could offer new insights into the extent and nature of inflammation in this patient population, helping to refine diagnosis and guide management.

Therefore, the primary objective of this study was to explore the prevalence and distribution of ultrasound findings of active inflammation and structural damage across the joints, tendons and entheses of patients who developed joint symptoms after ICI therapy exposure, analysing the differences between ICI-arthritis and ICI-arthralgia patients. A secondary objective was to explore the correlation between ultrasound inflammatory findings and the demographic, clinical and serological characteristics in both ICI-arthritis and ICI-arthralgia patients.

MATERIALS AND METHODS

We conducted an observational, multicentre cohort study involving six rheumatology centres internationally. Patients were enrolled consecutively and eligible if they were adults over 18 years old, currently or previously treated with ICIs for cancer, and had developed new MSK symptoms, specifically new-onset arthritis or arthralgia, either during ICI therapy or within 12 months of stopping treatment. While patients with previously diagnosed inflammatory rheumatic diseases were excluded, no formal exclusion was made for other pre-existing MSK conditions such as osteoarthritis or rotator cuff syndrome. This is because such conditions are common, often underdiagnosed, and might have been present but asymptomatic prior to ICI therapy. Importantly, only patients with new symptoms were referred to rheumatology by their oncologists and subsequently enrolled in the study. No other specific exclusion criteria were applied.

At the baseline visit, detailed clinical data were gathered, including demographic information (age and sex), cancer-related data (diagnosis, ICI treatment and other ICI-irAEs), time between joint symptom(s) onset and ICI therapy, joint symptom(s) duration, early morning stiffness duration, disease activity scoring (tender joint count (TJC) and swollen joint count (SJC) using the joints included in the disease activity score-28 joints,[13] as well as other symptomatic joints), current or previous skin psoriasis and medication history (current and previous use of disease-modifying anti-rheumatic drugs (DMARDs) and corticosteroids, defined as prednisolone equivalent equal or higher than 5 mg/day). Laboratory tests included C reactive protein (CRP), rheumatoid factor

(RF), anti-cyclic citrullinated peptide (anti-CCP) and anti-nuclear antibodies (ANA).

Patients were defined as having ICI-arthritis if they experienced joint pain, joint tenderness and swelling (ie, clinically apparent synovitis) on physical examination. They were classified as having ICI-arthralgia if they had joint pain, with or without joint tenderness, but without joint swelling on physical examination (ie, no clinically apparent synovitis) in at least one joint.

For patients with ICI-arthritis, further classifications were based on SJC, with monoarthritis defined as SJC=1, oligoarthritis as SJC=2–4 and polyarthritis as SJC>4. Clinical presentation consistent with polymyalgia rheumatica (PMR), defined for this study as bilateral shoulder and/or hip girdle pain and stiffness, with or without elevated inflammatory markers and in the absence of prominent peripheral joint synovitis, was recorded based on the assessing rheumatologist's evaluation.

All patients underwent an extensive ultrasound scanning protocol of joints, tendons and entheses by a rheumatologist with at least 10 years of experience in the use of MSK ultrasound, who was blinded to the patients' clinical data. The ultrasound scans were performed using B-mode and Power Doppler (PD) modalities, employing longitudinal and transverse scans, according to the EULAR guidelines.[14]

The following joints were evaluated for the presence of synovitis: shoulders (ie, glenohumeral joints), elbows, wrists (ie, radiocarpal and intercarpal joints, with a global score based on the highest grades in both joints), metacarpophalangeal (MCP) joints 1–5, proximal interphalangeal (PIP) joints 2–5, knees, ankles and metatarsophalangeal (MTP) joints 2–5. Additionally, bone erosions were assessed in the wrists (including the ulnar styloid), MCP joints 1–5, PIP joints 2–5 and MTP joints 2–5. The first MTP joint was excluded from the analyses because ultrasound abnormalities are commonly observed at this site in non-inflammatory joint conditions, such as osteoarthritis, as well as in asymptomatic healthy individuals.[15]

The tendons assessed for tenosynovitis and tendon damage included the extensor carpi ulnaris (ECU), the 4th extensor compartment, the flexor digitorum superficialis and profundus, flexor tendons 2–5, the anterior compartment of the ankle (tibialis anterior, extensor hallucis longus and extensor digitorum longus tendons), the lateral compartment of the ankle (peroneus longus and peroneus brevis tendons) and the medial compartment of the ankle (MC) (tibialis posterior and flexor digitorum longus tendons). The presence of extensor tendon peri-tendinitis was also evaluated in both thumbs and fingers 2–5 at the level of the MCP joint.

The entheses evaluated included the lateral epicondyle (insertion of the extensor tendons at the lateral epicondyle of the humerus), quadriceps tendon (insertion at the superior pole of the patella), proximal patellar tendon (insertion at the inferior pole of the patella), distal patellar tendon (insertion at the tibial tuberosity) and Achilles' tendon (insertion at the calcaneus). The plantar fascia was not included in the enthesis assessment because inflammatory conditions at this site rarely show PD signal.[16]

Grey scale (GS) changes and PD signal in the joints and tendons were scored semi-quantitatively (0–3) according to the Outcome Measures in Rheumatology (OMERACT) scoring system.[17] The OMERACT definitions for elementary lesions of enthesitis were also scored according to OMERACT guidelines.[18]

Ultrasound synovitis was defined as either GS≥1+PD ≥1 (in small joints and large joints) or GS≥2±PD (large joints), using the Global OMERACT-EULAR Synovitis Score.[19] US tenosynovitis was defined as GS≥1+PD ≥1.[15] Ultrasound detected bone erosions and tendon damage were scored as present/absent according to the OMERACT definitions.[17] Ultrasound 'active' enthesitis was defined as PD grade ≥1 at the enthesis plus entheseal thickening and/or hypoechoic areas, or PD at the enthesis grade >1.[16 20] Peritenon extensor tendon inflammation (ie, 'active' peritendinitis) was defined as a hypoechoic swelling surrounding the extensor digitorum tendon with PD signal.[21] The ultrasound machines used at each centre were 'high-end', the details of which are reported in online supplemental table 1.

By definition, patients classified as having ICI arthritis exhibited clinical synovitis on physical examination. Therefore, while ultrasound findings were documented in this group, synovitis was considered clinically evident rather than subclinical. In contrast, the term 'subclinical synovitis' specifically refers to findings in the ICI-arthralgia group, where patients presented with MSK symptoms but lacked clinical synovitis.

Statistical methods

Statistical analyses were conducted using standard descriptive and inferential methods. Continuous variables were reported as means with SD or medians with IQR, depending on normality, assessed using the Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Differences between groups (eg, ICI-arthritis vs ICI-arthralgia) were assessed using Student's t-test or Mann-Whitney U test for continuous variables, depending on distribution, and χ^2 test or Fisher's exact test for categorical variables.

To account for multiple comparisons, the Benjamini-Hochberg correction was applied within each hypothesis set, adjusting p values based on the number of comparisons performed while maintaining statistical power. Adjusted p values are presented for relevant comparisons, with statistical significance defined as $p<0.05$. Statistical analyses were performed using SPSS (V.28).

RESULTS

Overall, 101 patients with ICI-induced arthritis or arthralgia were included in the study, with 48 (47.5%) classified as having ICI-arthritis (based on the presence of joint pain, tenderness and swelling on physical

Table 1 Main demographic and clinical characteristics of the included patients in the overall population and divided by ICI-arthritis and ICI-arthralgia

	Overall (n=101)	Arthritis (n=48)	Arthralgia (n=53)	P value* (arthritis and arthralgia)
Age, mean (SD)	63.6 (13.3)	69.4 (9.8)	64.4 (12.8)	0.065
Female gender, n (%)	44 (44.4)	23 (48.9)	21 (40.4)	0.683
TJC, mean (SD)	4.6 (6.3)	6 (6.8)	3.3 (5.7)	0.091
SJC, mean (SD)	2 (3.8)	4.2 (4.5)	0.0	**0.013**
Time between ICI therapy and symptom onset, mean (SD), months	7.7 (10)	8.2 (11.5)	7.2 (8.1)	0.618
Duration of symptoms, mean (SD), months	13.1 (21)	15.7 (21.9)	10.6 (20)	0.446
CRP (mg/L), mean (SD)	14.5 (30.2)	19.5 (39.8)	9.8 (16.1)	0.182
EMS duration (min), mean (SD)	63.3 (99)	65.9 (123.7)	60.5 (64.9)	0.840
Anti-CCP positivity, n (%)	4 (4.7)	3 (6.2)	1 (2.6)	0.806
RF positivity, n (%)	8 (9)	5 (10.6)	3 (7.1)	0.840
ANA positivity, n (%)	10 (11.6)	8 (16.7)	2 (5.1)	0.217
PMR-like presentation, n (%)	5 (4.9)	1 (2.1)	4 (7.5)	0.365
Psoriasis, n (%)	8 (8.1)	3 (6.2)	5 (9.4)	0.718
DMARD use	5 (4.9)	5 (10.4)	0 (0)	**0.022**
Sulfasalazine, n (%)	4 (80)	4 (8.3)	0 (0)	**0.047**
Hydroxychloroquine, n (%)	1 (20)	1 (2.1)	0 (0)	0.475
GC use, n (%)	45 (45)	28 (58.3)	17 (32.7)	0.059

Bold indicates statistically significant results.
*P values were adjusted using the Benjamini-Hochberg method for multiple comparisons, based on the number of hypotheses tested within each table.
ANA, antinuclear antibodies; CCP, cyclic citrullinated peptide; CRP, C reactive protein; DMARD, disease-modifying anti-rheumatic drug; EMS, early morning stiffness; GC, glucocorticoid; ICI, immune checkpoint inhibitor; PMR, polymyalgia rheumatica; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count.

examination) and 53 (52.5%) as having ICI-arthralgia (joint pain, with or without tenderness, but without swelling).

Table 1 shows the main demographic and clinical characteristics of the included patients, highlighting significant differences between ICI-arthritis and ICI-arthralgia. Among the cohort, 96/101 (95.0%) patients were currently receiving ICI therapy at the time of symptom onset, while 5 (5.0%) patients had completed ICI treatment prior to developing arthritis or arthralgia. Patients with ICI-arthritis tended to be older and had higher TJC, with significantly greater use of DMARDs and a tendency toward glucocorticoid use compared with those with ICI-arthralgia. However, CRP levels and the presence of autoantibodies were similar between the two groups. Online supplemental table 2 illustrates the cancer diagnoses, ICI therapy and other irAEs in the included population.

In the overall patient population, synovitis was the most common ultrasound finding, affecting nearly 70% of patients, with the wrists and knees being the most frequently involved joints (37.6% and 32.7%, respectively) (table 2). Tenosynovitis was observed in about one-third of the population, primarily in the ECU and ankle MC tendons (15.8% and 13.9%, respectively). Enthesitis was detected in 31.3% of patients, with the lateral epicondyle being the most frequently involved site (22.9%). As shown in online supplemental table 3, 'active' peritendinitis of the finger extensor tendons was found in 5.9% of patients.

A high proportion of ICI-arthralgia patients had ultrasound-detected subclinical synovitis (47.2%), tenosynovitis (18.9%) and enthesitis (24.5%) despite the absence of clinically apparent joint swelling (table 2).

Synovitis was significantly more frequent in ICI-arthritis than in ICI-arthralgia (93.8% vs 47.2%, p<0.001), particularly in the wrists (56.3% vs 20.8%, p<0.001), knees (54.2% vs 13.2%, p<0.001) and ankles (27.1% vs 5.7%, p=0.036). Overall, tenosynovitis was also significantly more common in ICI-arthritis (52.1% vs 18.9%, p<0.001), especially in the ankle MC tendons (22.9% vs 5.7%, p=0.08). Enthesitis showed no significant difference between the two groups (31.3% vs 24.5%, p=0.51). Peritendinitis was infrequent in both groups, particularly in ICI-arthralgia, with no statistically significant difference in frequency between ICI-arthritis and ICI-arthralgia (10.4% vs 1.9%, p=0.099) (online supplemental table 3).

As shown in table 3, in the overall population, bone erosions were found in 15.8% of patients, with the wrists and MTP5 joints being the most commonly affected sites (10.9% and 4%, respectively). Bone erosions were more

Table 2 Prevalence and distribution of ultrasound findings of active inflammation (synovitis, tenosynovitis and enthesitis) in the overall population, and divided by ICI-arthritis and ICI-arthralgia

	Overall (n=101)	Arthritis (n=48)	Arthralgia (n=53)	P value* (arthritis and arthralgia)
Synovitis				
Wrists, n (%)	38 (37.6)	27 (56.3)	11 (20.8)	**<0.001**
MCP1, n (%)	15 (14.9)	9 (18.8)	6 (11.3)	0.554
MCP2, n (%)	19 (18.8)	14 (29.2)	5 (9.4)	0.08
MCP3, n (%)	15 (14.9)	10 (20.8)	5 (9.4)	0.285
MCP4, n (%)	12 (11.9)	10 (20.8)	2 (3.8)	0.067
MCP5, n (%)	11 (10.9)	9 (18.8)	2 (3.8)	0.083
PIP2, n (%)	13 (12.9)	9 (18.8)	4 (7.5)	0.28
PIP3, n (%)	13 (12.9)	8 (16.7)	5 (9.4)	0.547
PIP4, n (%)	9 (8.9)	8 (16.7)	1 (1.9)	0.067
PIP5, n (%)	7 (6.9)	6 (12.5)	1 (1.9)	0.141
Shoulder, n (%)	13 (12.9)	10 (20.8)	3 (5.7)	0.115
Elbow, n (%)	14 (13.9)	10 (20.8)	4 (7.5)	0.206
Knee, n (%)	33 (32.7)	26 (54.2)	7 (13.2)	**<0.001**
Ankle, n (%)	16 (15.8)	13 (27.1)	3 (5.7)	**0.036**
MTP2, n (%)	5 (5)	4 (8.3)	1 (1.9)	0.285
MTP3, n (%)	8 (7.9)	6 (12.5)	2 (3.8)	0.284
MTP4, n (%)	8 (7.9)	5 (10.4)	3 (5.7)	0.604
MTP5, n (%)	7 (6.9)	6 (12.5)	1 (1.9)	0.141
Overall (≥1 joint), n (%)	70 (69.3)	45 (93.8)	25 (47.2)	**<0.001**
Tenosynovitis				
EC4th, n (%)	10 (9.9)	7 (14.6)	3 (5.7)	0.285
ECU, n (%)	16 (15.8)	11 (22.9)	5 (9.4)	0.212
FDSaP, n (%)	6 (5.9)	3 (6.3)	3 (5.7)	1
FT2, n (%)	9 (8.9)	5 (10.4)	4 (7.5)	0.773
FT3, n (%)	10 (9.9)	6 (12.5)	4 (7.5)	0.612
FT4, n (%)	10 (9.9)	7 (14.6)	3 (5.7)	0.285
FT5, n (%)	5 (5)	3 (6.3)	2 (3.8)	0.731
Ankle AC, n (%)	5 (5)	4 (8.3)	1 (1.9)	0.285
Ankle LC, n (%)	5 (5)	3 (6.3)	2 (3.8)	0.731
Ankle MC, n (%)	14 (13.9)	11 (22.9)	3 (5.7)	0.08
Overall (≥1 tendon), n (%)	35 (34.7)	25 (52.1)	10 (18.9)	**<0.001**
Enthesitis				
Lateral epicondyle, n (%)	21 (20.8)	11 (22.9)	10 (18.9)	0.731
Quadriceps, n (%)	3 (3)	3 (6.3)	0 (0)	0.212
Proximal patellar, n (%)	6 (5.9)	3 (6.3)	3 (5.7)	1
Distal patellar, n (%)	8 (7.9)	5 (10.4)	3 (5.7)	0.604
Achilles, n (%)	3 (3)	3 (6.3)	0 (0)	0.212
Overall (≥1 entheses), n (%)	28 (27.7)	15 (31.3)	13 (24.5)	0.51

The maximum score observed bilaterally is reported.
Bold indicates statistically significant results.
*Refers to arthritis and arthralgia. P values were adjusted using the Benjamini-Hochberg method for multiple comparisons, based on the number of hypotheses tested within each table.
Ankle AC, ankle anterior compartment; Ankle LC, ankle lateral compartment; Ankle MC, ankle medial compartment; EC4th, fourth extensor compartment; ECU, extensor carpi ulnaris; FDSaP, flexor digitorum superficialis and profundus; FT, flexor tendon; ICI, immune checkpoint inhibitor; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

Table 3 Prevalence and distribution of ultrasound findings of structural damage (bone erosions, tendon damage, entheseal bone erosions) in the overall population, and divided by ICI-arthritis and ICI-arthralgia

	Overall (n=101)	Arthritis (n=48)	Arthralgia (n=53)	P value* (arthritis and arthralgia)
Bone erosions				
Wrists, n (%)	11 (10.9)	8 (16.7)	3 (5.7)	0.457
MCP1, n (%)	1 (1)	1 (2.1)	0 (0)	0.623
MCP2, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
MCP3, n (%)	1 (1)	1 (2.1)	0 (0)	0.623
MCP4, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
MCP5, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
PIP2, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
PIP3, n (%)	1 (1)	1 (2.1)	0 (0)	0.623
PIP4, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
PIP5, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
Shoulder, n (%)	NA	NA	NA	NA
Elbow, n (%)	NA	NA	NA	NA
Knee, n (%)	NA	NA	NA	NA
Ankle, n (%)	NA	NA	NA	NA
MTP2, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
MTP3, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
MTP4, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
MTP5, n (%)	4 (4)	3 (6.3)	1 (1.9)	0.612
Overall (≥1 joint), n (%)	16 (15.8)	12 (25)	4 (7.5)	**0.027**
Tendon damage				
EC4th, n (%)	0 (0)	0 (0)	0 (0)	NA
ECU, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
FDSaP, n (%)	2 (2)	1 (2.1)	1 (1.9)	1
FT2, n (%)	0 (0)	0 (0)	0 (0)	NA
FT3, n (%)	0 (0)	0 (0)	0 (0)	NA
FT4, n (%)	0 (0)	0 (0)	0 (0)	NA
FT5, n (%)	0 (0)	0 (0)	0 (0)	NA
Ankle AC, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
Ankle LC, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
Ankle MC, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
Overall (≥1 tendon), n (%)	5 (5)	4 (8.3)	1 (1.9)	0.19
Entheseal bone erosions				
Lateral epicondyle, n (%)	3 (3)	3 (6.3)	0 (0)	0.457
Quadriceps, n (%)	2 (2)	2 (4.2)	0 (0)	0.457
Proximal patellar, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
Distal patellar, n (%)	3 (3)	2 (4.2)	1 (1.9)	0.623
Achilles, n (%)	4 (4)	3 (6.3)	1 (1.9)	0.612
Overall (≥1 entheses), n (%)	8 (7.9)	6 (12.5)	2 (3.8)	0.15

The maximum score observed bilaterally is reported.
Bold indicates statistically significant results.
*Refers to arthritis and arthralgia. P values were adjusted using the Benjamini-Hochberg method for multiple comparisons, based on the number of hypotheses tested within each table.
Ankle AC, ankle anterior compartment; Ankle LC, ankle lateral compartment; Ankle MC, ankle medial compartment; EC4th, fourth extensor compartment; ECU, extensor carpi Ilnaris; FDSaP, flexor digitorum superficialis and profundus; FT, flexor tendon; ICI, immune checkpoint inhibitor; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

prevalent in the ICI-arthritis group (25%) compared with the ICI-arthralgia group (7.5%) (p=0.027). Conversely, there was no significant difference between the two groups in terms of tendon damage or entheseal bone erosions (p values >0.05).

Clinically, in our cohort, ICI-arthritis clinical presentation was evenly balanced between monoarthritis, oligoarthritis and polyarthritis. The main demographic and clinical characteristics of the ICI-arthritis patients, divided by monoarthritis, oligoarthritis and polyarthritis, are presented in online supplemental table 4. From a sonographic perspective, the distribution of inflammation and damage detected in involved joints, tendons and entheses was similar in patients who presented clinically with monoarthritis, oligoarthritis and polyarthritis, with more frequent involvement of MCP and PIP joints in patients with polyarthritis compared with the other subgroups (tables 4 and 5). Of the 18 patients with monoarthritis—based on physical examination findings alone—7 (38.9%) and 3 (16.7%) would be reclassified as having oligoarthritis and polyarthritis, respectively, if joints with ultrasound-detected synovitis were included in the joint count. Additionally, 1 out of 15 patients (6.7%) with oligoarthritis would be reclassified as having polyarthritis based on ultrasound findings.

As shown in online supplemental table 5, in the overall population, patients with ultrasound-detected synovitis were significantly older (67.7 vs 63.4 years, p=0.05), had higher TJC (5.7 vs 2.1, p<0.001) and SJC (2.8 vs 0.2, p<0.001) and had experienced symptoms for a longer duration (15.7 vs 7.1 months, p=0.006). Patients with tenosynovitis had a higher TJC (7.2 vs 3.2, p=0.004) and SJC (4 vs 1, p=0.001) and tended to have higher CRP levels (24.4 vs 8.8 mg/L, p=0.053). They were less likely to have other irAEs (p=0.046). Patients with peritendinous inflammation were older but not significantly so (72.3 vs 65.6 years, p=0.067), and had higher TJC (6.8 vs 1.4, p=0.016). They also had longer symptom duration (13.3 vs 3.4 months, p=0.008) and a lower frequency of other irAEs (50.6% vs 9.1%, p=0.009). Patient with 'active' enthesitis had higher TJC (7.1 vs 3.6, p=0.024), shorter disease duration (7.3 vs 15.2 months, p=0.014) and a lower frequency of irAEs (28.6% vs 52.9%, p=0.029). Conversely, there was no association between tendon damage and patient characteristics (data are not presented here). The small subset of patients with entheseal bone erosions (n=8 patients) were older (74.5 vs 65.7 years, p=0.046), but no other significant correlations were found.

Finally, no significant difference was observed in the prevalence of synovitis, tenosynovitis, peritendinitis or enthesitis between patients on or off glucocorticoid therapy in the ICI-arthritis and ICI-arthralgia populations (data not presented here).

Table 4 Prevalence and distribution of ultrasound findings of active inflammation (synovitis, tenosynovitis and enthesitis) in ICI-arthritis patients divided by monoarthritis, oligoarthritis and polyarthritis

	Monoarthritis (n=18)	Oligoarthritis (n=15)	Polyarthritis (n=15)
Synovitis			
Wrists, n (%)	10 (55.6)	4 (26.7)	13 (86.7)
MCP1, n (%)	1 (5.6)	1 (6.7)	7 (46.7)
MCP2, n (%)	1 (5.6)	0 (0)	13 (86.7)
MCP3, n (%)	1 (5.6)	0 (0)	9 (60)
MCP4, n (%)	1 (5.6)	0 (0)	9 (60)
MCP5, n (%)	1 (5.6)	0 (0)	8 (53.3)
PIP2, n (%)	1 (5.6)	2 (13.3)	6 (40)
PIP3, n (%)	1 (5.6)	0 (0)	7 (46.7)
PIP4, n (%)	1 (5.6)	0 (0)	7 (46.7)
PIP5, n (%)	1 (5.6)	1 (6.7)	4 (26.7)
Shoulder, n (%)	5 (27.8)	1 (6.7)	4 (26.7)
Elbow, n (%)	4 (22.2)	1 (6.7)	5 (33.3)
Knee, n (%)	10 (55.6)	9 (60)	7 (46.7)
Ankle, n (%)	5 (27.8)	3 (20)	5 (33.3)
MTP2, n (%)	1 (5.6)	0 (0)	3 (20)
MTP3, n (%)	1 (5.6)	1 (6.7)	4 (26.7)
MTP4, n (%)	1 (5.6)	1 (6.7)	3 (20)
MTP5, n (%)	1 (5.6)	1 (6.7)	4 (26.7)
Overall (≥1 joint), n (%)	16 (88.9)	14 (93.3)	15 (100)
Tenosynovitis			
EC4th, n (%)	0 (0)	2 (13.3)	5 (33.3)
ECU, n (%)	3 (16.7)	0 (0)	8 (53.3)
FDSaP, n (%)	1 (5.6)	1 (6.7)	1 (6.7)
FT2, n (%)	1 (5.6)	1 (6.7)	3 (20)
FT3, n (%)	1 (5.6)	1 (6.7)	4 (26.7)
FT4, n (%)	2 (11.1)	1 (6.7)	4 (26.7)
FT5, n (%)	0 (0)	0 (0)	3 (20)
Ankle AC, n (%)	2 (11.1)	1 (6.7)	1 (6.7)
Ankle LC, n (%)	2 (11.1)	0 (0)	1 (6.7)
Ankle MC, n (%)	4 (22.2)	2 (13.3)	5 (33.3)
Overall (≥1 tendon), n (%)	7 (38.9)	7 (46.7)	11 (73.3)
Enthesitis			
Lateral epicondyle, n (%)	2 (11.1)	4 (26.7)	5 (33.3)
Quadriceps, n (%)	2 (11.1)	1 (6.7)	0 (0)
Proximal patellar, n (%)	3 (16.7)	0 (0)	0 (0)
Distal patellar, n (%)	3 (16.7)	0 (0)	2 (13.3)
Achilles, n (%)	1 (5.6)	1 (6.7)	1 (6.7)
Overall (≥1 entheses), n (%)	5 (27.8)	5 (33.3)	5 (33.3)

The maximum score observed bilaterally is reported.
Ankle AC, ankle anterior compartment; Ankle LC, ankle lateral compartment; Ankle MC, ankle medial compartment; EC4th, fourth extensor compartment; ECU, extensor carpi ulnaris; FDSaP, flexor digitorum superficialis and profundus; FT, flexor tendon; ICI, immune checkpoint inhibitor; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

DISCUSSION

This study represents the largest and most comprehensive imaging evaluation to date of joint and peri-articular

Table 5 Prevalence and distribution of ultrasound findings of structural damage (bone erosions, tendon rupture and entheseal bone erosions) in ICI-arthritis patients, categorised by monoarthritis, oligoarthritis and polyarthritis

	Monoarthritis (n=18)	Oligoarthritis (n=15)	Polyarthritis (n=15)
Bone erosions			
Wrists, n (%)	3 (16.7)	0 (0)	5 (33.3)
MCP1, n (%)	1 (5.6)	0 (0)	0 (0)
MCP2, n (%)	1 (5.6)	0 (0)	1 (6.7)
MCP3, n (%)	1 (5.6)	0 (0)	0 (0)
MCP4, n (%)	1 (5.6)	0 (0)	1 (6.7)
MCP5, n (%)	1 (5.6)	0 (0)	1 (6.7)
PIP2, n (%)	1 (5.6)	1 (6.7)	0 (0)
PIP3, n (%)	1 (5.6)	0 (0)	0 (0)
PIP4, n (%)	1 (5.6)	0 (0)	1 (6.7)
PIP5, n (%)	1 (5.6)	0 (0)	1 (6.7)
Shoulder	NA	NA	NA
Elbow	NA	NA	NA
Knee	NA	NA	NA
Ankle	NA	NA	NA
MTP2, n (%)	1 (5.6)	0 (0)	1 (6.7)
MTP3, n (%)	1 (5.6)	0 (0)	1 (6.7)
MTP4, n (%)	1 (5.6)	0 (0)	1 (6.7)
MTP5, n (%)	1 (5.6)	0 (0)	2 (13.3)
Overall (≥1 joint), n (%)	4 (22.2)	1 (6.7)	7 (46.7)
Tendon damage			
EC4th, n (%)	0 (0)	0 (0)	0 (0)
ECU, n (%)	1 (5.6)	0 (0)	1 (6.7)
FDSaP, n (%)	1 (5.6)	0 (0)	0 (0)
FT2, n (%)	0 (0)	0 (0)	0 (0)
FT3, n (%)	0 (0)	0 (0)	0 (0)
FT4, n (%)	0 (0)	0 (0)	0 (0)
FT5, n (%)	0 (0)	0 (0)	0 (0)
Ankle AC, n (%)	2 (11.1)	0 (0)	0 (0)
Ankle LC, n (%)	2 (11.1)	0 (0)	0 (0)
Ankle MC, n (%)	2 (11.1)	0 (0)	0 (0)
Overall (≥1 tendon), n (%)	3 (16.7)	0 (0)	1 (6.7)
Entheseal bone erosions			
Lateral epicondyle, n (%)	1 (5.6)	2 (13.3)	0 (0)
Quadriceps, n (%)	2 (11.1)	0 (0)	0 (0)
Proximal patellar, n (%)	2 (11.1)	0 (0)	0 (0)
Distal patellar, n (%)	2 (11.1)	0 (0)	0 (0)
Achilles, n (%)	2 (11.1)	0 (0)	1 (6.7)
Overall (≥1 entheses), n (%)	3 (16.7)	2 (13.3)	1 (6.7)

The maximum score observed bilaterally is reported.
Ankle AC, ankle anterior compartment; Ankle LC, ankle lateral compartment; Ankle MC, ankle medial compartment; EC4th, fourth extensor compartment; ECU, extensor carpi ulnaris; FDSaP, flexor digitorum superficialis and profundus; FT, flexor tendon; ICI, immune checkpoint inhibitor; MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

soft tissue involvement in patients with cancer who developed joint-related symptoms after ICI therapy. The findings show a high burden of inflammation in both ICI-arthritis and ICI-arthralgia, suggesting that they are part of the same spectrum rather than distinct clinical presentations.

A striking finding is that nearly half of ICI-arthralgia patients exhibited ultrasound-detected synovitis, with a smaller proportion also displaying tenosynovitis, peritendinitis or enthesitis, even in the absence of clinical synovitis. This suggests that a high burden of inflammation in patients who develop arthralgia after ICI exposure, reinforcing the hypothesis that ICI exposure may trigger a broader spectrum of autoimmunity than previously appreciated.

Despite the relatively short symptom duration (mean 13.1 months), erosive pathology was observed in a quarter of ICI-arthritis patients, suggesting a potentially aggressive disease course in many cases. Moreover, erosive changes in a minority of ICI-arthralgia patients (7.5%) indicate that structural damage can occur even without clinically apparent arthritis. In this context, patients with arthralgia (ie, without clinical synovitis) might otherwise be considered as having 'non-specific' ICI-related symptoms, implying a lack of significant inflammation and potentially leading to false reassurance or treatment with simple analgesia alone. However, the detection of significant inflammation and structural damage in these patients could indicate a need for targeted interventions, such as closer follow-up or specific treatment. Longitudinal data are needed to clarify the prognostic significance of these subclinical features—particularly whether they predict worse outcomes or progression to clinically evident arthritis.

There is a notable lack of studies evaluating ultrasound findings in ICI-induced MSK toxicity. Most prior research on ICI-arthritis consists of case series, small cohort studies[22–24] or retrospective studies that combine multiple imaging modalities but lack standardised imaging protocols. A recent cohort study reported that 62% of 55 patients with de novo ICI-related MSK symptoms had confirmed inflammatory arthritis on ultrasound.[25] Ultrasound findings included synovial thickening, hyperaemia and tenosynovitis, with 71% of patients showing inflammatory features even in the absence of clinically evident synovitis. Notably, seven patients with synovial fluid counts traditionally considered 'non-inflammatory' (<2000 cells/µL) also demonstrated ultrasound evidence of inflammation.[25] However, this study focused primarily on the most symptomatic joints rather than using a systematic imaging approach.[25] In contrast, our study provides a systematic and prospective ultrasound assessment, capturing a broad spectrum of joint, tendon and entheseal inflammation. A retrospective analysis by Ponce *et al*, involving 19 patients and multiple imaging modalities (15 ultrasound, 4 MRI, 2 PET-CT), identified diverse inflammatory patterns, including PMR-like hip synovitis and trochanteric bursitis, rheumatoid arthritis

(RA)-like wrist synovitis and tenosynovitis, and psoriatic arthritis (PsA)-like oligoarthritis.[26] However, imaging tests were performed only on symptomatic joints, the cohort was small, and the absence of a standardised treatment protocol—combined with the fact that many patients were receiving glucocorticoid therapy—may have influenced the results.[26]

The high prevalence of subclinical inflammation detected via ultrasound in the current study aligns with WB-MRI findings of our research group, which demonstrated significant inflammatory changes even in ICI-arthralgia patients without overt clinical synovitis.[12] This further supports the notion that ICI-induced MSK toxicity is likely under-recognised in clinical practice and that many patients presenting with non-specific arthralgia and MSK symptoms may actually have inflammatory joint disease that could benefit from a more targeted intervention.

In ICI-arthritis patients, while monoarthritis was the most frequently observed phenotype, a significant proportion also displayed a pattern of both small and large joint polyarthritis. In patients with monoarthritis and oligoarthritis, knees, wrists and ankles were the most commonly involved joints, resembling the clinical pattern typically seen in seronegative spondyloarthritis/PsA. Additionally, some patients presented with polyarthritis affecting wrists and small joints of hands and feet, similar to RA. This aligns with previous descriptions of ICI-induced arthritis as having features of both RA-like and seronegative inflammatory arthritis.[27] As expected, patients with polyarthritis showed a higher overall burden of active inflammation across joints, tendons and entheses, along with more structural damage, particularly bone erosions, compared with those with mono- or oligoarthritis. A small subgroup of patients (4.9%) demonstrated a PMR-like clinical presentation. The relatively low prevalence observed in our cohort compared with previous reports may reflect differences in study population and imaging focus.[28] Specifically, our study included patients referred for predominantly peripheral joint symptoms and employed an ultrasound protocol that did not systematically assess the shoulder girdle or hip bursae. As such, patients with classical PMR features following ICI exposure may have been under-represented. While patients with pre-existing inflammatory rheumatic diseases were excluded, some may have had underlying MSK conditions such as osteoarthritis or rotator cuff tendinopathy that were undiagnosed. These conditions are common and often asymptomatic until triggered or worsened by systemic immune activation, such as with ICI therapy. Our inclusion criteria, based on the development of new symptoms, reflect real-world clinical practice but may contribute to the subclinical inflammation detected by ultrasound.

From a purely sonographic perspective, the imaging patterns were heterogeneous, with varying involvement of joints, tendons and entheses. This study adds to the growing understanding of ICI-induced joint and periarticular manifestations as distinct yet overlapping disease entities—an observation also reflected in WB-MRI findings from our research group in patients with cancer on ICI therapy with MSK symptoms.[12] The inflammatory patterns observed include RA-like features such as erosive synovitis and tenosynovitis, alongside enthesitis and peritendinitis, which are more typical of PsA and systemic lupus erythematosus.[29–33] These findings reinforce the concept that ICI-arthritis encompasses a diverse spectrum of inflammatory phenotypes. Figure 1 illustrates the spectrum of ultrasound-detected inflammation and structural damage.

Similar to other cohorts, the large majority of our patients were seronegative for anti-CCP antibodies and RF, while a minority had positive ANA.[7 8] No significant correlation was found between ultrasound features and clinical characteristics, except for TJC, SJC and disease duration. An inverse association emerged between ultrasound findings—particularly tenosynovitis, peritendinitis and enthesitis—and other irAEs, suggesting that patients with predominant MSK involvement may exhibit a distinct immune response compared with those with multi-organ irAEs. However, the small number of patients with these findings limits definitive conclusions. This underscores the need for larger, prospective studies to better define the relationship between ultrasound-detected MSK abnormalities and the broader irAE spectrum. These results also inform the ongoing discussion on irAEs and cancer outcomes, as prior studies suggest that patients with irAEs, including MSK toxicity, may experience better cancer responses—raising important considerations for treatment balance.[34 35] While subclinical inflammation in ICI-arthralgia may justify targeted interventions, including immunosuppression to prevent joint damage and disability, clinicians must carefully consider its potential impact on cancer control. Future research should assess whether ultrasound-detected inflammation correlates with different cancer outcomes or irAE profiles, and whether tailored immunosuppressive strategies can preserve both MSK and oncologic benefits.

One of the key strengths of this study is the use of a standardised, comprehensive ultrasound protocol employing validated OMERACT scoring systems across multiple centres. This approach enhances the generalisability and robustness of the findings by providing consistent and detailed sonographic assessment of joints, tendons and entheses in a large, mostly DMARD-naïve cohort. Unlike prior studies that focused only on limited symptomatic joints, our protocol captures a broader and more representative picture of ICI-induced MSK toxicity.

However, the cross-sectional design of this study limits conclusions about disease progression, particularly whether subclinical inflammation in ICI-arthralgia evolves into overt arthritis or affects long-term outcomes. Longitudinal studies are needed to determine if early intervention improves symptoms, quality of life and reduces the risk of disability. In addition, the absence of a formal inter-rater reliability assessment

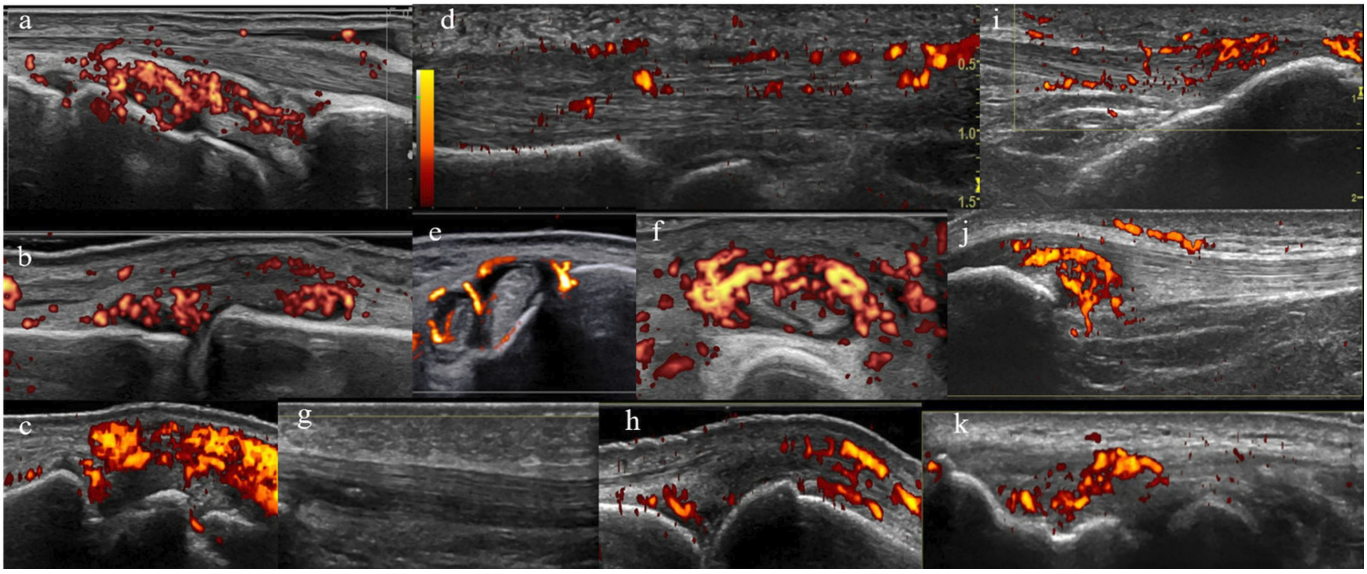

Figure 1 Spectrum of ultrasound-detected inflammatory changes and structural damage across joints, tendons and entheses in patients with ICI-arthritis and ICI-arthralgia. (a) Wrist synovitis (radio-carpal and intercarpal joints). (b) Third metacarpophalangeal joint synovitis. (c) Active synovitis of the second metacarpophalangeal joint with bone erosion on the medial side of the metacarpal head. (d) Second finger flexor tendon tenosynovitis. (e) Peroneal brevis and longus tendon tenosynovitis. (f) Extensor carpi ulnaris tenosynovitis. (g) Focal discontinuity of the peroneal brevis tendon consistent with partial rupture. (h) Synovitis of the second metacarpophalangeal joint and extensor finger tendon peri-tendinitis. (i) Active enthesitis of the distal patellar tendon. (j) Active enthesitis of the proximal patellar tendon. (k) Active enthesitis of the extensor tendons of the forearm. ICI, immune checkpoint inhibitor.

introduces some variability, despite a shared scanning protocol ensuring consistent image acquisition. Another limitation is the use of different ultrasound machines with varying PD settings across centres, which could influence the sensitivity and grading of inflammatory changes. An important limitation of our study is that although ultrasound assessments were performed and analysed at the joint, tendon and enthesis level, we did not systematically record the specific joints—but only the number of joints—identified as clinically involved (ie, swollen or tender) during physical examination. This precludes a direct joint-by-joint comparison between clinical findings and ultrasound-detected synovitis or tenosynovitis. As a result, we are unable to determine the prevalence of subclinical synovitis—defined as sonographic inflammation in joints that were not clinically involved—among patients with ICI-arthritis. We acknowledge this limitation and recognise that a joint-level analysis would have provided valuable insights into the distribution and subclinical nature of inflammatory findings. This represents an important area for future research to better delineate the extent of subclinical joint involvement in this patient population. Finally, although some patients were on corticosteroids, no significant differences in ultrasound findings were observed between treated and untreated groups.

CONCLUSION

This international multicentre cohort represents the largest and most comprehensive ultrasound study of ICI-arthritis and ICI-arthralgia to date. Both groups showed significant inflammatory and structural involvement, with greater burden in those with clinically apparent arthritis, as expected. Notably, the high prevalence of subclinical inflammation in ICI-arthralgia suggests that many patients with cancer with 'non-specific' joint symptoms post-ICI therapy may, in fact, have underlying inflammatory joint disease. These individuals could benefit from earlier rheumatologic evaluation and targeted imaging to support more accurate and timely treatment.

Ultrasound was instrumental in identifying pathology-based phenotypes, revealing inflammation and structural damage even in the absence of clinical arthritis. These insights carry important implications for treatment strategies. Future research should prioritise longitudinal studies to better define the natural course and prognostic significance of subclinical inflammation, and to further investigate its relationship with the broader spectrum of irAEs.

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