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Coletto, L.A.; Steenbergen, H.W.V.; Mario, C. di; Gessi, M.; Tolusso, B.; Campobasso, D.; ... ; Alivernini, S.

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Rheumatoid arthritis

Minimally invasive retrieval and characterisation of tenosynovial tissue in rheumatoid arthritis: a novel approach to study at-risk, active, and remission stages

Lavinia Agra Coletto[1,2,3], Hanna W. van Steenbergen[4], Clara Di Mario[5], Marco Gessi[1,6], Barbara Tolusso[5], Denise Campobasso[5], Domenico Somma[3], Pierluigi Rizzuti[1], Dario Bruno[7], Pietro Rubortone[1], Beatrice Fresch[1], Tommaso Hubert[1], Natacha Goulas[1], Luca Petricca[2], Maria Rita Gigante[2], Viviana A. Pacucci[2], Simone Perniola[7], Aziza Elmesmari[3], Carlo Tur[1], Roberta Benvenuto[6], Elisa Gremese[1,5,7], Mariola Kurowska-Stolarska[3], Marco Maria Lizzio[2], Maria Antonietta D'Agostino[1,2,5], Annette H.M. van der Helm-van Mil[4], Stefano Alivernini[1,2,3,5,*]

[1] *Università Cattolica del Sacro Cuore, Rome, Italy*
[2] *Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[3] *Research into Inflammatory Arthritis Centre Versus Arthritis (RACE), University of Glasgow, Glasgow, United Kingdom*
[4] *Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands*
[5] *Immunology Research Core Facility, Gemelli Science and Technology Park (GSTeP), Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[6] *Institute of Pathology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*
[7] *Division of Clinical Immunology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy*

ARTICLE INFO

ABSTRACT

Objectives: Tenosynovial inflammation is a hallmark of rheumatoid arthritis (RA), even in the preclinical phase. However, tenosynovium retrieval and characterisation is beyond the current state-of-the-art. We aimed to (1) assess the rate of magnetic resonance imaging (MRI)-detected tenosynovitis in the wrists of patients with preclinical and clinical RA; (2) develop a technique for tenosynovium retrieval; and (3) characterise its cellular composition across disease phases, including the comparison to adjacent synovium.

Methods: In total, 834 MRI wrist scans were analysed to assess extensor/flexor tendon tenosynovitis rate (168 autoantibody-positive clinical suspect arthralgia (CSA), 473 naïve to treatment RA, and 193 healthy controls). An ultrasound-guided minimally invasive technique was developed to collect tenosynovium from the wrist extensor tendons in an independent cohort: 16 autoantibody-positive CSA patients, 41 RA patients (14 of whom with adjacent synovium with comparable ultrasound-detected inflammation), and 8 osteoarthritis (OA) patients. Tissue representativity, lining hyperplasia, and inflammatory infiltrate degree were assessed by haematoxylin and eosin staining and immunohistochemistry (CD55, CD68, CD3, CD20, CD138, and CD21). Safety and tolerability were assessed.

*Correspondence to Prof. Stefano Alivernini, Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168, Rome, Italy.

E-mail address: stefano.alivernini@unicatt.it (S. Alivernini).

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Results: Tenosynovitis of the wrist extensors/flexor tendons was observed in 34% of CSA and 68% of RA patient compared to 8% in healthy. Tenosynovium was successfully retrieved in 89.7% of cases without severe adverse events. Tenosynovial lining hyperplasia and inflammatory infiltrate were significantly higher in active RA than CSA patients without ultrasound-detected subclinical inflammation and RA remission, and comparable to inflamed adjacent synovium. CSA patients with subclinical inflammation showed early $CD3^{pos}$ and $CD55^{pos}$ cells enrichment compared to OA controls.
Conclusions: Tenosynovium is frequently inflamed and readily accessible in CSA and RA. Future molecular studies of tenosynovial biopsies will advance understanding of the transition from pre-RA to RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

• Human and animal studies have identified tenosynovitis as an early, sensitive, and specific sign of inflammation in the preclinical stages of rheumatoid arthritis (RA). Although molecular characterisation of tenosynovium could advance understanding of RA onset, no techniques to biopsy tenosynovial tissue have been previously described.

WHAT THIS STUDY ADDS

• This study introduces a safe, well-tolerated and effective minimally invasive ultrasound-guided technique for retrieving tenosynovium from the extensor compartments of the wrist. It shows that tenosynovial tissue is accessible across RA phases, including at-risk and remission stages.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

• In the context of preventive studies, in depth characterisation of tenosynovium may help to clarify mechanisms driving the progression from preclinical stages to established RA, possibly identifying new targets or biomarkers for early intervention.

INTRODUCTION

Tenosynovium consists of 2 layers of synovial sheaths that surround tendons in areas subjected to increased pressure, with the primary function of minimising friction during movement [1]. Tenosynovitis, as the inflammation of tendon-synovial sheaths, is becoming increasingly relevant in rheumatoid arthritis (RA) [2]. Magnetic resonance imaging (MRI) studies in patients with clinically suspect arthralgia (CSA) [3] and early clinical arthritis have detected tenosynovitis around the tendons of hands and feet—particularly near the joints as wrist, metacarpophalangeal and/or metatarsophalangeal joints—as an early frequent feature and specifically predictive of RA development [4–7]. Due to its sensitivity and specificity, tenosynovitis is now considered the third hallmark feature of RA, next to synovitis and bone erosions [2]. It causes typical symptoms [8] and functional impairment [9] both at RA diagnosis and in the preceding symptomatic risk stage. Furthermore, an experimental model of murine arthritis has shown that tenosynovitis is the first joint tissue to become inflamed [10].

The early onset of tenosynovial inflammation in both human and animal models increased the interest in understanding the cellular and molecular features of human tenosynovium in health and disease [11]. This requires the ability to retrieve biopsies from the tenosynovium. Although synovial tissue biopsies are frequently obtained using minimally invasive ultrasound-guided techniques, which have revealed novel cellular and molecular players with putative prognostic values in RA [12–15], there have been no techniques developed or described to biopsy tenosynovial tissue. Access to tenosynovial specimens could help elucidate the unresolved cellular composition of this tissue and identify targetable pathways or biomarkers involved in the transition from pre-RA to RA.

Based on these issues, we aimed to (1) assess the rate of MRI-detected tenosynovitis in each tendon compartment of the wrist in both CSA and RA patients, (2) establish novel minimally invasive ultrasound-guided technique to retrieve tenosynovial tissue from all extensor tendon compartments of the wrist, (3) characterise the cellular composition of tenosynovium from CSA to active RA phases, and (4) compare tenosynovial tissue to paired adjacent synovial tissue.

METHODS

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Frequency of MRI-detected tenosynovitis in CSA and recent-onset RA patients

MRI data from the Leiden University Medical Center CSA and Early Arthritis Clinic cohorts (n = 834), collected between April 2012 and April 2021, were analysed. The dataset included 168 patients with CSA who were positive for anti-citrullinated peptide antibodies (ACPA) and/or rheumatoid factor (RF) [5], as well as 473 naïve to treatment RA patients [16,17] fulfilling the 2010 European Alliance of Associations for Rheumatology (EULAR)/American College of Rheumatology (ACR) classification criteria [18]. All patients underwent unilateral wrist MRI to assess the frequency of tenosynovitis in different wrist compartments using the Outcome Measures in Rheumatology (OMERACT) RA Magnetic Resonance Imaging Score (RAMRIS) scoring system [19,20]. The analysis evaluated both extensor (I-VI) and flexor compartments (namely flexor carpi ulnaris, ulnar bursa including flexor digitorum profundus and superficialis tendon quartets and flexor pollicis longus in radial bursa or flexor carpi radialis). A comparison group of 193 healthy individuals was included, with MRI scans assessing the same anatomical sites [21].

Patient enrolment for ultrasound-guided minimally invasive tenosynovial biopsy

Between June 2021 and December 2023, a total of 68 patients were recruited for minimally invasive ultrasound-guided tenosynovial tissue biopsy targeting the extensor tendons

of the wrist at the SYNGem Synovial Tissue Biopsy Unit of the Division of Rheumatology of the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome. Inclusion criteria consisted of patients with CSA (as defined by the Leiden criteria [3]) presenting with wrist arthralgia, patients with active RA fulfilling the 2010 EULAR/ACR classification criteria [18] and exhibiting clinical or subclinical tenosynovitis in the extensor compartment, and patients with RA in remission without evidence of clinical or subclinical tenosynovitis. Of these, 65 patients (96%) consented to undergo the procedure, while 3 declined. Thus, the cohort comprised 16 ACPA^{pos} and/or RF^{pos} patients with CSA (n = 3 with and n = 13 without ultrasound-detected subclinical inflammation) and 41 RA patients (n = 10 naïve to treatment, n = 14 resistant to conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs), n = 13 resistant to biological or synthetic targeted DMARDs, and n = 4 in sustained clinical and ultrasound remission [22]). As a comparison group, n = 8 patients with hand osteoarthritis (OA) presenting mechanical arthralgia without ultrasound-detected subclinical inflammation and 4 samples obtained from surgical removal of tenosynovial cysts were included. All patients provided informed consent before the procedure, which was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore (protocol no. 0040408/20). Demographic, clinical and laboratory data were collected at enrolment. After a comprehensive rheumatological clinical examination, each patient underwent bilateral ultrasound assessment of the extensor tendons synovial sheaths of the wrist using a real-time scanner (Esaote MyLab XPro80). For each location, synovial hypertrophy and vascularisation were scored using Grey-scale (B-mode) and Power Doppler according to OMERACT Ultrasound Task Force recommendations [23]. The purpose was to identify the anatomical references for guiding needle position and target areas of maximum inflammation for biopsy.

A subset of active RA patients (n = 14) with clinically evident synovitis in an adjacent joint to the tendon of interest with comparable ultrasound features underwent paired minimally invasive ultrasound-guided synovial tissue biopsy from the same joint (n = 11 radio-ulnar-carpal joint and n = 3 metacarpophalangeal joint respectively) following the previously published protocol [22,24].

Histological and immunohistochemical analysis of tenosynovial tissue samples

Tenosynovial and synovial specimens were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 4 μm, and stained for haematoxylin and eosin (H&E). In particular, sections were deparaffinised in xylene, rehydrated in a series of graded ethanol, stained in haematoxylin, counterstained in eosin/phloxine, and mounted with Bio Mount (Bio-Optica). Immunohistochemistry (IHC) was performed to assess macrophages (CD68-clone KP1, DAKO), T cells (CD3-clone LN10, Leica), B cells (CD20-clone L26, Leica), follicular dendritic cells (CD21-clone 2G9, Leica), fibroblast (CD55-clone EPR6689, abcam) and plasma cell (CD138-clone MI15, Leica) infiltrates using immunostainer BOND MAX III (Leica). Each entire section was manually examined under a light microscope (Leica DM 2000) by a trained pathologist experienced in synovial tissue assessment and blinded to the patient data.

Inflammation severity was evaluated based on (1) H&E staining, assessing synovial lining hyperplasia and inflammatory infiltrate using a semiquantitative scale (0-3) adapted from synovitis assessment [25], and the presence/absence of perivascular lymphocytic aggregates (defined as ≥10 lymphocytes around blood vessels) and (2) IHC staining for CD55^{pos} (only for tenosynovium) and/or CD68^{pos} cells in the lining layer (scored on a 4-point semiquantitative scale as follows: score 1 = 1-3 layers, score 2 = 3-5 layers, score 3 = 5-10 layers, score 4 = >10 layers under a 20 × magnification) and the sublining infiltration of CD68^{pos}, CD3^{pos}, CD21^{pos},CD20^{pos}, and CD138^{pos} cells (scored on a 5−points scale as follows: grade 0 = no stained cells, grade 1 = 0% to 25% positive cells per field, grade 2 = 25% to 50% positive cells per field, grade 3 = 50% to 75% positive cells per field, and grade 4 ≥75% positive cells per field under 20 × magnification).

Assessment of tenosynovial biopsy yield, safety, and tolerability

The procedure was considered successful if the anatomical representativeness of the tissue was ensured. A sample was considered representative if it included all the anatomical area of interest, as lining and sublining layers, in at least 1 tissue fragment. Lining layer presence was confirmed by IHC for CD68 and CD55, with a scores ≥1 considered adequate (Supplementary Fig S1).

Before the procedure, patients completed a prebiopsy questionnaire to self-assess their level of fear (0-10 scale) and explain their concerns. Postprocedure, patients were observed for 1 hour to monitor short-term adverse events. A questionnaire was administered to assess (1) pain experienced at each stage of the procedure (anaesthesia and sample collection) on a scale from 0 to 10; (2) the improvement/worsening of expectations regarding the procedure using a 5-point Likert scales (eg, way better, better, as expected, worst, way worst); and (3) their willingness to undergo another biopsy if necessary (eg, sure, very likely, most likely, neutral, most unlikely, very unlikely).

Patients were instructed to contact the biopsy unit in case of any postprocedure discomfort, and all underwent a follow-up visit 4 weeks after the procedure to document any late adverse events.

Statistical analysis

The statistical analyses were conducted using GraphPad Prism. Categorical and quantitative variables were described using frequencies, percentages, and mean ± SEM. Comparisons between groups were performed using the nonparametric Mann −Whitney U test, with multiple comparisons corrected using Tukey test. The Wilcoxon signed-rank test was used for paired samples where appropriate.

RESULTS

Distribution of MRI-detected subclinical tenosynovitis in wrist tendon compartments of ACPA^{pos} and/or RF^{pos} CSA and naïve to treatment RA patients

Demographic, clinical and immunological characteristics of the patient cohorts enrolled in the MRI study are summarised in Supplementary Table S1. The overall frequency of MRI-detected extensor/flexor tenosynovitis was significantly higher in ACPA^{pos} and/or RF^{pos} CSA (34%) and treatment-naïve RA patients (68%) compared to healthy controls (8.8%, $P < .0001$ for both comparisons). In health, contrast enhancement was primarily localised to the extensor compartment VI of the wrist [21] (Fig 1A-F). Subclinical tenosynovitis rates in ACPA^{pos} and/or RF^{pos} CSA patients were distributed across tendon

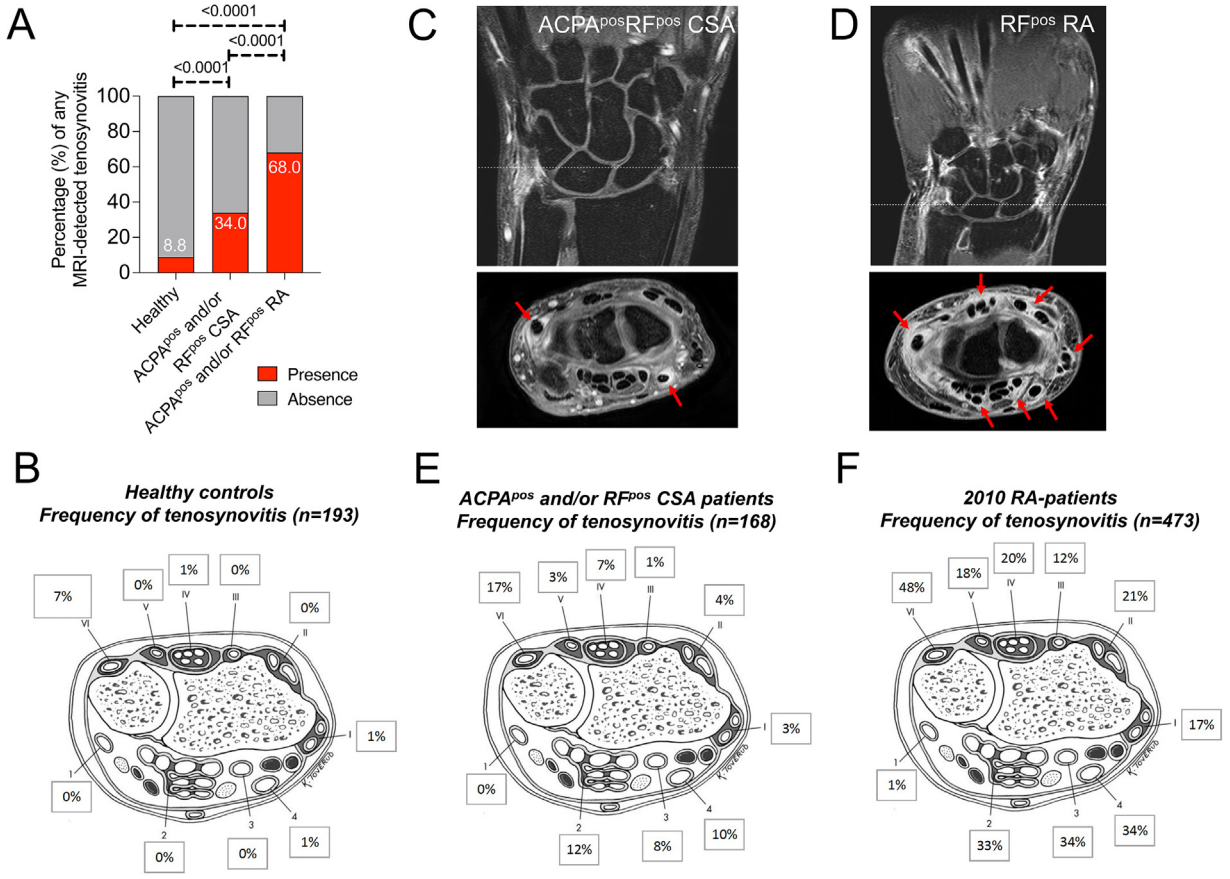

Figure 1. Distribution of MRI-detected subclinical tenosynovitis in the tendon compartments of the wrist in healthy controls, ACPA^{pos} and/or RF^{pos} CSA and naïve to treatment RA patients. A, Rates of MRI-detected tenosynovitis in any tendon compartment of the wrist in healthy controls, ACPA^{pos} and/or RF^{pos} CSA and naïve to treatment RA patients. Each enrolled subject might have multiple tenosynovial sites involved at once. B, Schematic overview of the extensor and flexor tendons compartments of the wrist highlighting the frequency of subclinical tenosynovitis in each compartment in healthy controls. C,D, MRI example T1 images with contrast enhancement (coronal above, axial below) of tenosynovitis (red arrows) in the tendon compartments of the wrist of an ACPA^{pos} and RF^{pos} CSA patient showing tenosynovitis of the extensor compartment VI and flexor compartment IV (T1graded) (C) and in naïve to treatment RF^{pos} RA patient showing tenosynovitis of multiple wrist tendon sheaths (all extensor and flexor compartments) (D). E-F, Schematic of the extensor and flexor tendon compartments of the wrist highlighting the frequency of subclinical tenosynovitis in each compartment in ACPA^{pos} and/or RF^{pos} CSA patients (E) and in naïve to treatment RA patients (F). Graphic of the lower panel was adapted from www.karitoverud.com. ACPA, anti-citrullinated peptide antibodies; CSA, clinical suspect arthralgia; MRI, magnetic resonance imaging; RA, rheumatoid arthritis; RF, rheumatoid factor.

compartments as follows: extensor tendons, 3% (I), 4% (II), 1% (III), 7% (IV), 3% (V) and 17% (VI); flexor tendons, 0% (flexor carpi ulnaris), 12% (flexor digitorum profundus and superficialis), 8% (flexor pollicis longus) and 10% (flexor carpi radialis). In naïve to treatment RA patients, the rates were as follows: extensor tendons, 17% (I), 21% (II), 12% (III), 20% (IV), 18% (V) and 48% (VI); flexor tendons, 1% (flexor carpi ulnaris), 33% (flexor digitorum profundus and superficialis), 34% (flexor pollicis longus) and 34% (flexor carpi radialis). These results indicate that tenosynovitis is common in the wrists of CSA and RA patients, with extensor tendons representing the most accessible biopsy sites due to their superficial location and lower risk of damaging delicate structures, as nerves and blood vessels.

Description of a novel minimally invasive ultrasound-guided tenosynovial biopsy technique

Demographic, clinical and immunological characteristics of the patient cohorts enrolled in the biopsy study are summarised in Supplementary Table S2. Biopsies were performed on the extensor tendon compartments of the wrist (n = 54 IV compartment, n = 5 II, n = 2 VI, n = 2 III, n = 1 I, and n = 1 V) (Fig 2A-F) by 4 operators for active settings [1 with short-term (<1 year), 1 with med-term (<5 years) and 2 with long-term (>10 years) experience in Ultrasound (US)-guided synovial tissue (ST) biopsy] and for the CSA or remission settings by 2 operators (with long-term experience). Each patient received a facemask, and the procedure was carried out under sterile conditions. The skin was disinfected twice with iodine solution, covering an area from the needle entry to 15 cm proximally and distally. As shown in Figure 2A-F, guided by ultrasound, and with careful assessment of nearby delicate structures (vessels and nerves), the needle entry point was identified distally to the wrist's extensor retinaculum, directly over the tendon of interest. The needle was directed proximally, following a longitudinal course along to tendon's length. For patients with active tenosynovitis (Fig 3A-D, upper panel), after aspirating any peritendinous fluid, the tendon sheaths, subcutaneous tissue, and skin were anesthetized using 1% to 2% lidocaine/mepivacaine (4-6 mL, depending on the space allowed by each anatomical site) (Fig 3C, upper panel). For patient with quiescent conditions such as CSA, OA or RA in remission (Fig 3A-D, lower panel), the anaesthetic was injected to expand the peritendinous space between the visceral and parietal layers, improving visualisation of the tenosynovial surface (Fig 3C, lower panel).

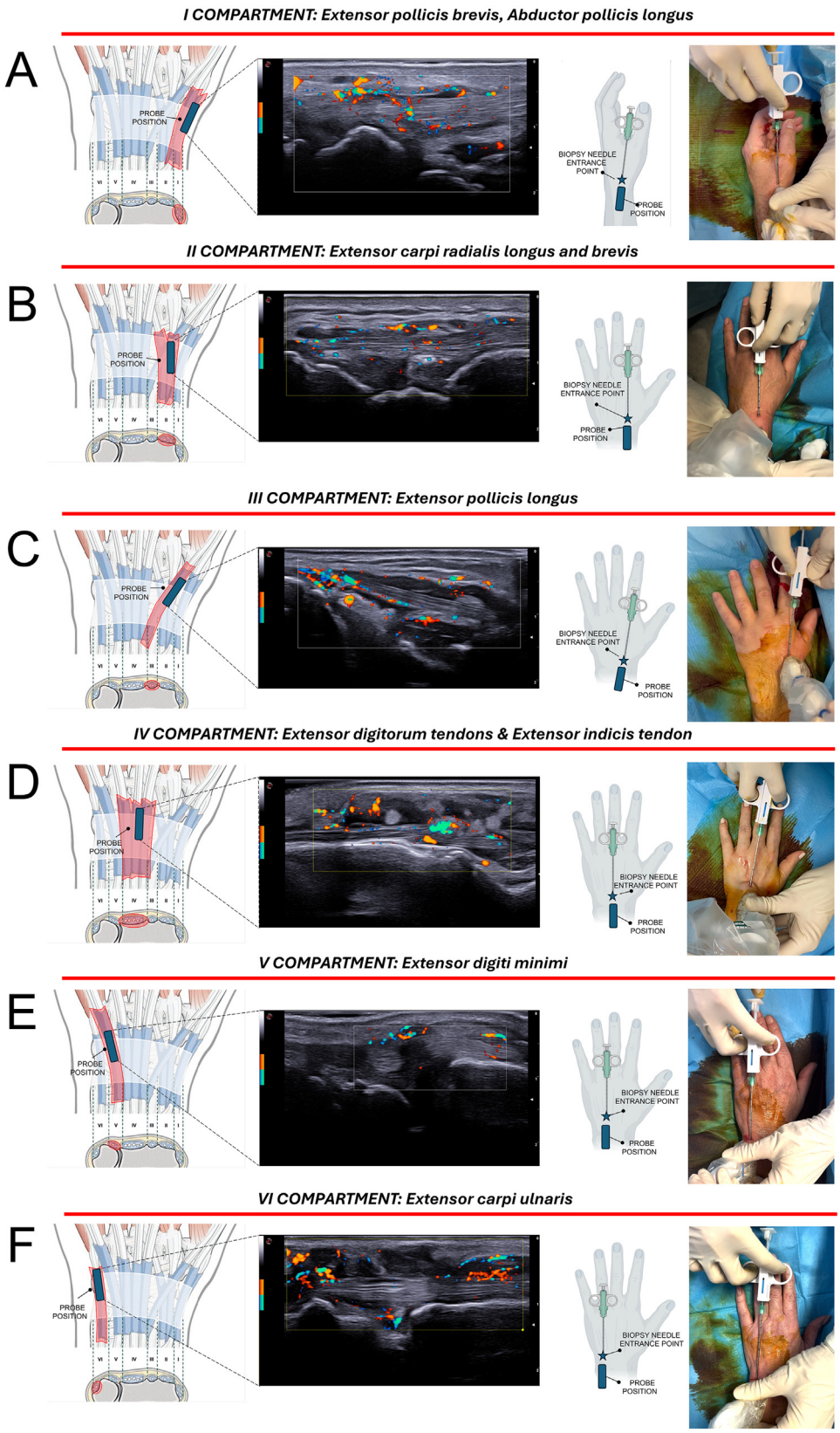

Figure 2. Minimally invasive ultrasound-guided tenosynovial tissue biopsy in inflamed extensor tendon compartments of the wrist of RA patients. A-F, Each row shows sequentially for each extensor tendon compartments (I-VI) the schematic representation of the tendon compartment, the ultrasound longitudinal scan of tenosynovitis with the Power Doppler signal, the reference point for the biopsy needle entry, the ultrasound probe position and the corresponding live photo. Schematic of the wrist extensor tendons was adapted from AO Surgery Reference, https://surgery.reference.aofoundation.org/orthopedic-trauma/adult-trauma/carpal-bones/approach/dorsal-approach-to-the-scaphoid#surgical-anatomy. Copyright by AO Foundation, Switzerland. AO, Association of Osteosynthesis; RA, rheumatoid arthritis.

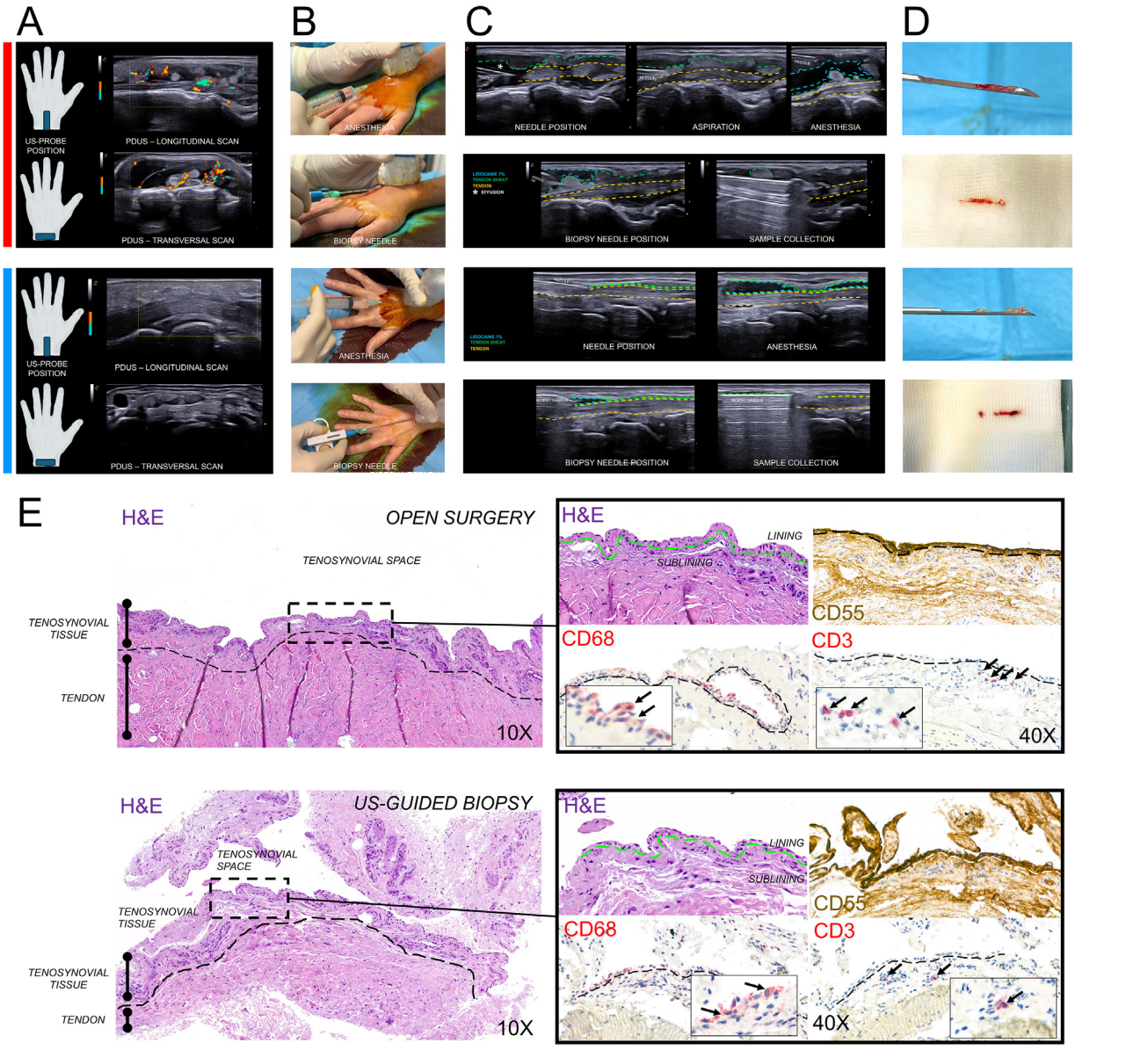

Figure 3. Minimally invasive ultrasound-guided tenosynovial tissue biopsy in active and quiescent stages and histological evaluation. A-D, The upper panels represent the procedure on the inflamed IV compartment of the extensor tendons of the wrist; the lower panels represent the procedure on the same anatomical location in quiescent state (preclinical). A, Longitudinal and transversal ultrasound scans showing tenosynovitis of the IV compartment of the extensor tendons of the wrist or normal features in the quiescent state. B, Example photos showing the reference point for the anaesthesia and the biopsy needle entrance. C, Longitudinal ultrasound scans showing the sequential steps of the procedure (eg, the aspiration of tenosynovial effusion (only for the inflamed condition), the injection of the anaesthetic to visualise tenosynovial tissue surface, the insertion of the biopsy needle and the sample collection). D, Macroscopic appearance of the tenosynovial tissue fragments. E, Comparative histological analysis of healthy tenosynovial tissue collected using open surgery (upper panel) and tenosynovial tissue of patients with mechanical arthralgia collected using the developed ultrasound-guided minimally invasive procedure (lower panel). Example images of H&E and IHC stainings for CD68 (RED), CD55 (DAB) and CD3 (RED) of tenosynovial tissue collected by open surgery or ultrasound-guided minimally invasive procedure. Of note, tendon retrieval was a rare event (3.1%). H&E, haematoxylin and eosin; IHC, immunohistochemistry; US, ultrasound; PDUS, Power Doppler.

Following anaesthesia, a 14G needle (Precisa 1410-HS Hospital Service Spa, Italy) was inserted along the same path as the anaesthetic needle into the peritendinous space, resting on the visceral layer parallel to the tendon (Fig 3C). B-mode ultrasound was used to visualise the tenosynovium, ensuring the sampling of representative tissue, particularly in cases of synovial hypertrophy. For both inflamed and quiescent conditions, tissue samples were collected from various locations using the portal-assisted needle device (Supplementary Video S1). At least 5 tissue fragments were obtained from the IV compartment and at least 4 from the others (Fig 3D). The macroscopic appearance of the fragments was recorded, showing clear distinctions between tenosynovium (yellow/white, soft, and similar to synovial tissue) and tendon (white, hard, unintentionally rarely retrieved, Supplementary Fig S2).

The quality of ultrasound-guided biopsy samples is comparable to open surgery

Histological and immunohistochemical analyses confirmed that the anatomical composition and the quality of tenosynovial tissue obtained by ultrasound-guided biopsy in quiescent conditions (ie, OA and CSA patients without US-detected subclinical inflammation) were comparable to those retrieved by

open surgery in the context of tendon cysts excision. Both methods yielded samples that showed comparable microscopic tissue anatomy in terms of lining layer, predominantly expressing CD55^{pos} and to a lesser extent CD68^{pos} cells, and a sublining layer with scattered CD68^{pos} and CD3^{pos} cells (Fig 3E).

Yield, safety and tolerability of tenosynovial biopsy

Tenosynovial tissue was retrieved in 100% of procedures, with 89.7% considered representative based on the presence of both lining and sublining layers. Safety and follow-up data were available for all the procedures. No serious adverse events were reported. A total of 12.3% of patients experienced self-limiting arthralgia, and 7.7% reported local pain requiring analgesia, leading to transient wrist dysfunction (≤7 days) in 4.6% of patients. Local hematoma occurred in 2 (3%) patients but resolved after topic treatment without any long-term complications, such as persistent pain, impaired function or infections. Tendon tissue fragments were involuntarily retrieved in 3.1% patients, all in quiescent settings. A clinical evaluation conducted 28 days after the biopsy showed complete resolution of any procedure-related pain, if present, and no signs of functional discomfort (eg, joint stiffness, tendon rupture, or neurological complaints due to nerve damage), regardless of tendon tissue fragment retrieval. No significant differences in terms of safety and tissue quality were seen comparing operators with different expertise.

Patients-rated pain during the biopsy was 3.8/10 on average, with anaesthesia being reported as the most painful phase (visual analogue scale [VAS] 3.7 ± 2.6) compared to sample collection (VAS 2.7 ± 2.2, $P = .0041$) and 1 hour postprocedure (VAS 2.7 ± 2.5, $P = .0013$; see Supplementary Fig S3A).

Pre-procedure, patients' self-assessed fear scored 5.58 ± 3.08 on a 10-point scale (Supplementary Fig S3B), driven by concerns about pain (37.5%), anxiety (27.5%), and not knowing what the procedure entailed (32.5%, Supplementary Fig S3C). Postprocedure, 87.7% of patients found the experience to be better (44.6%) or much better (43.1%) than expected, and 94.4% indicated a willingness to undergo the biopsy again if necessary (15.8% most likely, 21.4% very likely and 57.2% extremely likely, see Supplementary Fig S3C). These data confirm the feasibility, safety, and patient tolerability of the developed tenosynovial biopsy procedure.

Inflammation degree in tenosynovial tissue is associated with RA stage

All tenosynovial tissue samples were graded to assess the degree of inflammation using histological (H&E) and IHC techniques, evaluating markers such as CD55, CD68, CD3, and CD20 to assess lining hyperplasia and inflammatory infiltrate (Fig 4A-H). In the OA control group, tenosynovial tissue displayed no signs of inflammation, with a thin lining layer (score ≤ 1 in H&E and CD55/CD68 evaluations), no inflammatory infiltrate, and no detectable perivascular lymphocytic infiltrates in the sublining layer, with minimal presence of CD3^{pos} and CD68^{pos} cells. In CSA patients without ultrasound-detected subclinical inflammation, a slightly higher inflammatory profile was observed, with 30.8% of samples showing perivascular lymphocytic infiltrates and higher scores for other inflammatory markers, although these did not reach statistical significance compared to the OA control group. In contrast, CSA patients with ultrasound-detected subclinical inflammation exhibited a moderate increase in inflammatory scores across all evaluated parameters, and perivascular lymphocytic infiltrates were detected in 66.6% of samples. In particular, these patients had significant higher thickening of the lining layer, indicated by elevated CD55^{pos} cells and a significant higher enrichment of CD3^{pos} cells in the sublining layer compared to both OA controls and CSA patients without subclinical inflammation ($P < .05$ for all comparisons). Additionally, all parameters in these patients were comparable to those observed in treatment-naïve RA patients ($P > .05$, Fig 4F and H).

Active RA patients, including those who were treatment-naïve and those resistant to cs-/b-DMARDs, demonstrated significantly higher scores of lining hyperplasia (detected by H&E, CD55, and CD68) and inflammatory infiltrates up to the formation of germinal centre like structures (detected by H&E, CD68, CD3, CD20 and CD138) (Supplementary Fig S4) compared to OA, CSA patients without subclinical inflammation, and remission RA ($P < .05$ for all comparisons). The latter group showed a significant reduction of tenosynovial inflammation scores similar to those in CSA patients without subclinical inflammation and OA controls ($P > .05$ for all comparisons).

These findings demonstrate that the degree of inflammation in tenosynovial tissue, as assessed by both H&E and IHC, correlates with disease activity and that early inflammatory changes may already be present in CSA patients.

Comparison between inflamed tenosynovium and adjacent synovial tissue

Comparative analysis of tenosynovium and adjacent synovial tissue retrieved from RA patients (n = 14) with clinically evident tenosynovitis and adjacent synovitis, both with comparable ultrasound findings (Fig 5A,B), revealed no significant differences in lining hyperplasia ($P = .6250$) or inflammatory infiltrate scores ($P = .7656$) (Fig 5C). Immunohistochemical analysis showed comparable enrichment of CD68^{pos} cells in both lining and sublining layers, as well as similar enrichment of CD20^{pos} and CD3^{pos} cells in the sublining layer, between tenosynovium and adjacent synovial tissue in both naïve to treatment and cs-/b-DMARD-resistant RA patients ($P > .05$ across all comparisons) (Fig 5D). In particular, paired tissues showed similar rates of lympho-myeloid and diffuse-myeloid pathotypes [26] ($P > .05$ for both comparisons). These data indicate that inflamed adjacent tenosynovial and synovial tissues exhibit similar histological and immunohistochemical profiles in RA, suggesting a consistent inflammatory pattern across these anatomical sites.

DISCUSSION

This is the first study to develop, describe, and evaluate a minimally invasive method for retrieving tenosynovial tissue from the extensor compartments of the wrist at various stages of RA. We showed that the presented procedure is effective, well-tolerated and yields high-quality tissue, even in quiescent conditions. In addition, inhere we present the first cellular characterisation of the tenosynovium in different stages of RA.

Tenosynovitis is common in RA, particularly in the wrist, where it occurs in 68% of autoantibody-positive RA patients and 34% of CSA patients. Tenosynovitis underpins several of RA's typical signs and symptoms [8]. Its predictive of RA development in CSA patients: the greater the number of affected tendon sheaths, the higher the likelihood of progression towards defined RA [27]. Longitudinal MRI studies indicate that tenosynovitis is the first inflamed joint tissue to resolve—compared

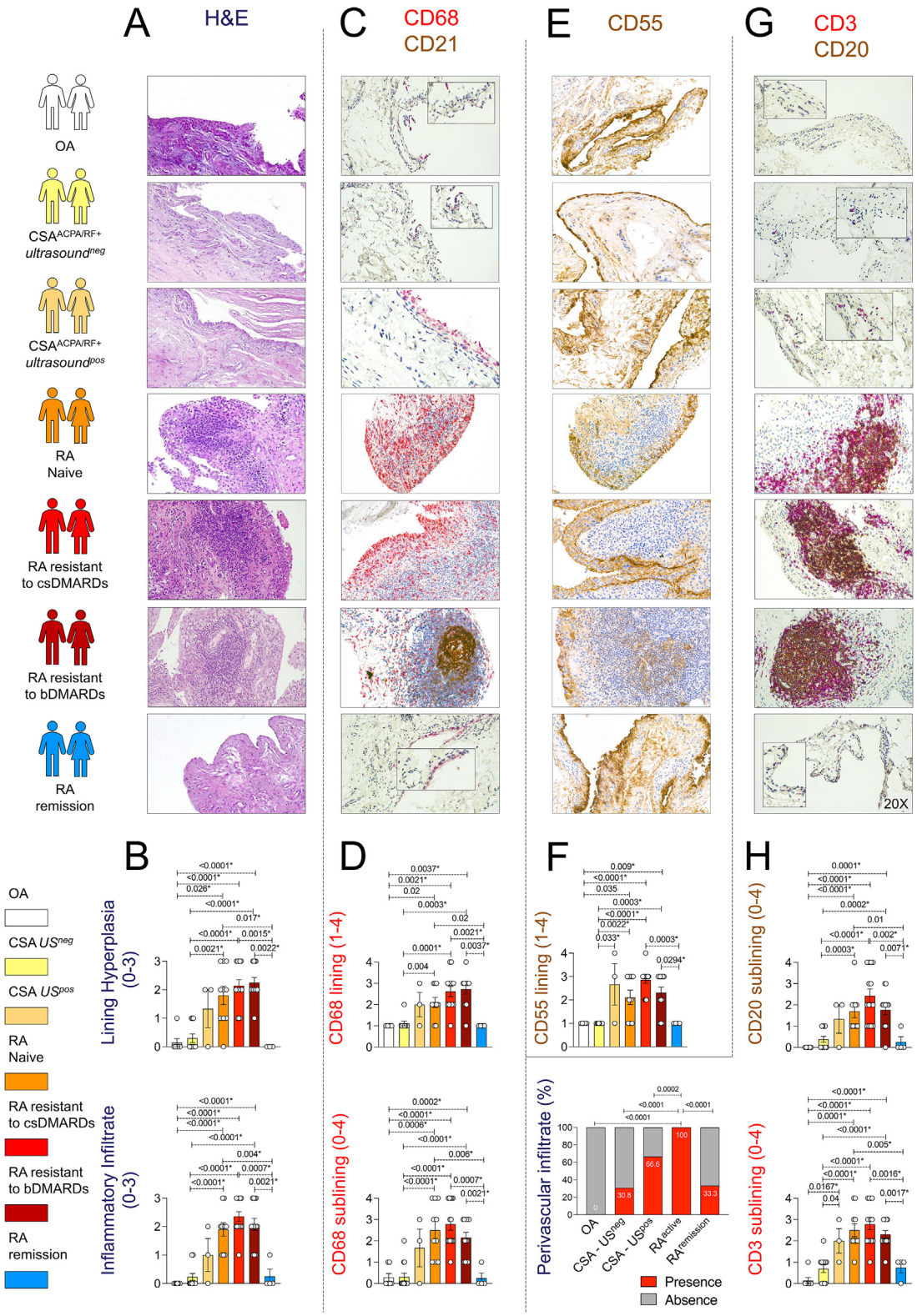

Figure 4. Inflammation degree of the tenosynovial tissue across RA stages. A, H&E staining of tenosynovial tissue across RA stages. B, Scatter dot plot representing the scores of lining hyperplasia and inflammatory infiltrate. Each dot represents a patient, the error bars represent SEM, the edge of the box represents the mean. C, IHC staining of CD68 (RED) and CD21 (DAB) in tenosynovial tissue across RA stages. D, Scatter dot plots representing the scores of lining and sublining $CD68^{pos}$ cells across RA stages. E, IHC staining of CD55 (DAB) in tenosynovial tissue across RA stages. F, Scatter dot plots representing the scores of lining $CD55^{pos}$ cells across RA stages. G, IHC staining of CD3 (RED) and CD20 (DAB) in tenosynovial tissue across RA stages. H, Scatter dot plots representing the scores of sublining $CD3^{pos}$ and $CD20^{pos}$ cells across RA stages. Rates of perivascular lymphocytic inflammatory infiltrates at H&E assessment in tenosynovial tissue across RA stages. Exact *P* values are shown, Mann–Whitney or multiple comparisons with Tukey correction (marked with * when multiple conditions compared). CSA, clinical suspect arthralgia; DAB, 3,3'-diaminobenzidine; H&E, haematoxylin and eosin; IHC, immunohistochemistry; OA, osteoarthritis; RA, rheumatoid arthritis; bDMARDs, biologic-Disease Modifying Anti-Rheumatic Drugs; csDMARDs, conventional-synthetic-Disease Modifying Anti-Rheumatic Drugs; US, ultrasound.

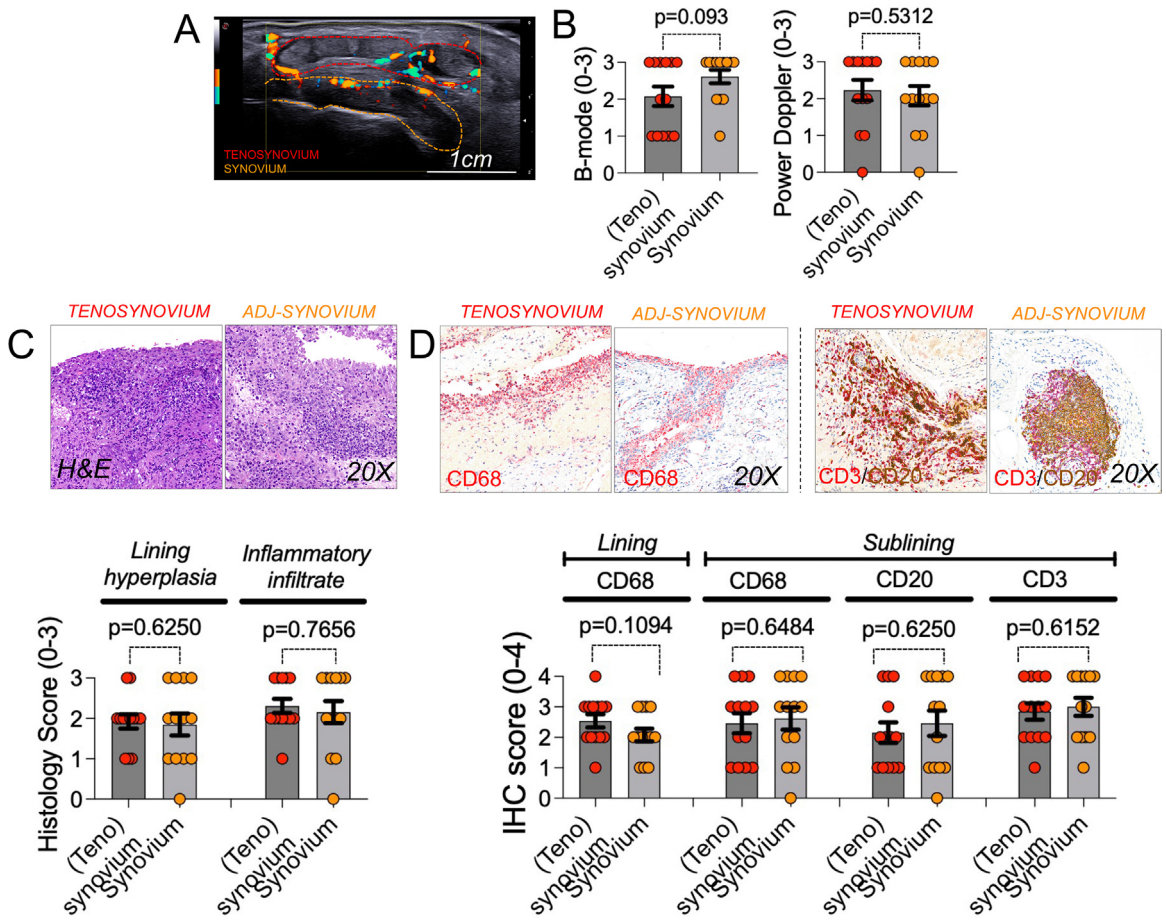

Figure 5. Comparative analysis of inflammation degree of the tenosynovial and adjacent synovial tissue in active RA. A, Example picture of ultrasound assessment of wrist tenosynovial and synovial compartments; Red dotted line highlights the tenosynovial III and IV compartments of the extensor tendons and the orange dotted line highlights the synovial compartment of the wrist. B, B-mode and Power Doppler scores of tenosynovium and adjacent synovium in active RA patients (n = 14). C, H&E staining of tenosynovium and adjacent synovial tissue in active RA for comparative analysis of synovial hyperplasia and inflammatory infiltrate. D, IHC staining for lining CD68 (RED) and sublining CD68 (RED), CD3 (RED), and CD20 (DAB) of tenosynovium and adjacent synovial tissues in active RA. Magnification 20 ×. ADJ, adjacent. DAB, 3,3'-diaminobenzidine; H&E, haematoxylin and eosin; IHC, immunohistochemistry; RA, rheumatoid arthritis.

to concomitant synovitis and osteitis—when CSA patients experience spontaneous resolution of joint pain [28,29]. Thus, tenosynovial tissue plays a key role in RA, acting as an early site of either inflammatory changes or resolution during the preclinical stage.

Despite increasing evidence of the role of tenosynovitis in RA pathophysiology [30], a minimally invasive technique to study cellular and molecular tissue composition has been lacking. The novel procedure described here was developed at a leading centre for minimally invasive ultrasound-guided synovial tissue biopsies. This centre also offers training programmes aimed at addressing educational needs to support standardisation of synovial tissue research [24] and has used high-throughput technologies to characterise synovial tissue from RA patients in both active and remission phases [12,15,22]. The procedure presented in this study was systematically effective, well-tolerated, and capable of retrieving high-quality tissue, even under quiescent conditions. The yield of this ultrasound-guided procedure, defined by the presence of all anatomically informative structures, was comparable to that of open surgery and ultrasound-guided synovial tissue biopsy reported in several prior studies [31], with a representativeness exceeding 90%. The safety and tolerability of the procedure aligned with previously published data [32], confirming a very low rate of procedure-related complications and high patient compliance. Notably, although up to 50% of patients expressed some fear and anxiety prior the procedure, over 90% reported that the biopsy was better tolerated than expected, and more than 90% was willing to undergo a repeated biopsy, if required. These findings support the feasibility of this technique in centres where ultrasound-guided synovial tissue biopsies are already well-established.

The tissue architecture and composition of the inflammatory infiltrate at different disease stages were assessed. Healthy tenosynovium was characterised by a single- or double-layered lining primarily expressing $CD55^{pos}$ fibroblasts and, to a lesser extent $CD68^{pos}$ macrophages, with the sublining area containing scattered $CD68^{pos}$ macrophages and $CD3^{pos}$ T cells. In the presence of inflammation, the tenosynovium undergoes changes similar to those seen in the synovium [14], with the lining layer thickening due to an increase in $CD68^{pos}$ macrophages and $CD55^{pos}$ cells, while the sublining layer exhibit increased cellularity due to the proliferation and infiltration of inflammatory cells. This cells initially form perivascular infiltrates, which can organise into fully developed germinal centre like ectopic structures. Comparable histological features were observed in tenosynovial and adjacent synovial tissue collected from active RA patients. While confirmation in a larger cohort is necessary, subsequent studies will also be required to determine whether the inflammatory cell populations in these 2 anatomical niches share similar molecular and transcriptomic profiles.

Interestingly, tenosynovium collected from autoantibody-positive CSA with ultrasound-detected subclinical joint inflammation displayed early histological changes, showing intermediate inflammatory characteristics between healthy and pathologic tissue. The most significant changes observed at this stage included an expansion of $CD55^{pos}$ fibroblasts in the lining layer and an enrichment of $CD3^{pos}$ T cells in the sublining perivascular regions. These findings are consistent with a previous study that examined the synovial tissue of autoantibody-positive individuals with arthralgia and showed that $CD3^{pos}$ T cells had a borderline association with subsequent development of arthritis [33]. Although the CSA cohort in our study lacks longitudinal data, the findings suggest that early changes in the tenosynovial niche may precede disease development and align with promising results from preventive studies using abatacept, which has been shown to delay the onset of RA, to reduce the severity of inflammatory symptoms, to improve physical disability and to mitigate MRI-detected inflammation [27–31].

Some of current unmet needs in refractory RA are being addressed by synovial tissue biopsy-driven trials [34,35], which are reshaping the future of precision medicine in RA. While comparable histological features were observed in tenosynovial and adjacent synovial tissue collected from active RA patients, it remains to be seen whether the inflammatory cell populations in these 2 anatomical niches also share similar molecular and transcriptomic profiles. Addressing these shared and niche-specific pathogenic networks will contribute to a better understanding of disease mechanisms. Given the relevance of subclinical tenosynovitis in at-risk RA stages [3,5,9], further characterisation of tenosynovial tissue may be considered in future RA prevention trials. To date, risk stratification of at-risk individuals has been based on clinical, serological and imaging characteristics [36,37]. MRI is the most sensitive imaging method for detecting tenosynovitis [38,39], and a limitation of our study is the absence of MRI data in the biopsy cohort. It is plausible that integrating molecular characterisation of tenosynovium in CSA patients with imaging-detected tenosynovitis could improve risk stratification and help identify the molecular processes critical for the progression from at-risk stage to clinically apparent disease. Although this procedure was developed at a centre with extensive experience in minimally invasive synovial biopsies, the dissemination to other centres could be facilitated through dedicated training programmes tailored to specific needs [24].

In conclusion, this study demonstrates that tenosynovial biopsy is a safe and well-tolerated technique that allows the collection of high-quality tissue across all stages of RA. The degree of tenosynovitis, as assessed histologically, reflects inflammation progression and may help identify preclinical changes in at-risk individuals.

Competing interests

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Contributors

SA designed the study. LAC, HWvS, CDM, MG, BT, DC, DS, PR, DB, PR, BF, TH, NG, LP, MRG, VAP, SP, AE, CT, RB, EG, MK-S, MML, MADA, AHMvdH-vM, and SA were involved in the acquisition and analysis of data. LAC, HWvS, AHMvdH-vM, and SA were involved in the interpretation of data. LAC, HWvS, AHMvdH-vM, and SA created the original draft and data visualisation. AHMvdH-vM and SA acquired resources and oversaw this study. All authors were involved in manuscript preparation and proofreading. SA takes full responsibility for the overall content as guarantors.

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Patient consent for publication

Not applicable.

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Orcid

Lavinia Agra Coletto: http://orcid.org/0000-0001-6613-9468
Hanna W. van Steenbergen: http://orcid.org/0000-0002-3251-0238
Beatrice Fresch: http://orcid.org/0000-0003-2817-6633
Simone Perniola: http://orcid.org/0000-0001-6918-4731
Carlo Tur: http://orcid.org/0009-0003-6241-6116
Mariola Kurowska-Stolarska: http://orcid.org/0000-0003-2124-7777
Stefano Alivernini: http://orcid.org/0000-0002-7383-4212

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