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Does tenosynovitis of the hand detected by B-mode ultrasound predict loss of clinical remission in rheumatoid arthritis? Results from a real-life cohort

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Keywords

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remission;
flare

Abstract

Objective: The role of US-detected tenosynovitis (USTS) in the management of rheumatoid arthritis remains controversial. The aim of this study was to investigate whether tenosynovitis can predict a flare in rheumatoid arthritis patients in remission in a real-life cohort. **Methods:** Rheumatoid arthritis patients from the Swiss Clinical Quality Management cohort were included in this study if they were in clinical remission, defined by 28-joint disease activity score (DAS28-ESR) <2.6, and had an available B-mode tenosynovitis score. The patients were stratified according to the presence or absence of tenosynovitis (USTS+ vs. USTS–). Cox proportional hazard models were used for time-to-event analysis until the loss of remission, after adjustment for multiple confounders. The impact of baseline US performed early in remission and the advent of flares at different fixed time periods after baseline were investigated in sensitivity analysis. **Results:** Tenosynovitis was detected in 10% of 402 rheumatoid arthritis patients in remission. At baseline, USTS+ patients in remission had significantly higher DAS28-ESR (mean (SD): USTS– 1.8 (0.5) versus USTS+ 2.0 (0.5); $p = 0.0019$) and higher additional disease activity parameters, such as physician global assessment, and simplified- and clinical-disease activity index. Joint synovitis detected by B-mode US was associated with tenosynovitis (mean (SD) 7.2 (6.3) in USTS– versus 9.0 (5.4) in USTS+, respectively; $p = 0.02$). A disease flare was observed in 69% of remission phases, with no differences in the time to loss of remission between USTS+ and USTS– groups. **Conclusion:** While US-detected tenosynovitis was associated with higher disease activity parameters in rheumatoid arthritis patients in clinical remission, it was not able to predict a flare.

Introduction

While rheumatoid arthritis (RA) characteristically presents with synovitis of the small joints of the hands and feet, evidence is accumulating that associated tendon sheaths are also frequently inflamed (i.e. tenosynovitis (TS)), with a prevalence of up to 80%^(1,2). TS seems to be a very early manifestation of RA and represents an independent predictor for developing RA in patients with undifferentiated arthritis⁽²⁾. While these findings originate from magnetic resonance imaging (MRI) and ultrasound (US) studies, accompanying TS at the level of small joints seems difficult to differentiate from isolated synovitis in routine clinical practice⁽³⁾. At least, the absence of palpable tendon friction rubs has not been integrated in the definition of clinical remission in RA, a definition that has evolved over time⁽⁴⁾. Evidence for a role of TS detected by US or MRI for the management of established RA with regards to the treat-to-target principle or to the prediction of remission or of disease flares, remains scarce⁽⁵⁾. Several studies have evaluated subclinical synovitis for RA management. While randomised controlled trials have failed to demonstrate an additional value of US to clinical evaluation during treat-to-target interventions so far^(6,7), subclinical synovitis of the tendons might predict disease flares in patients having reached clinical remission^(8,9).

In our hands, US-detected synovitis had a moderate predictive value for the loss or remission⁽¹⁰⁾. The aim of the current study was to investigate whether US-detected TS also could predict disease flares in RA in a real-life cohort.

Methods

Study population

We included disease-modifying antirheumatic drugs (DMARD)-experienced patients diagnosed by the rheumatologist as having RA in the Swiss clinical Quality Management (SCQM) cohort⁽¹¹⁾ if a) they were in clinical remission (defined as a Disease Activity Score on 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) <2.6), b) an US examination – via standardised SCQM SONAR score⁽¹²⁾ – was available during remission with data on TS entered in the database and c) at least one clinical follow-up visit was available. All patients signed an informed consent prior to the inclusion in SCQM, and the study was approved by the ethics committee of the Canton of Vaud (CER-VD Switzerland: 89/14).

US operators/machines

Rheumatologists with Swiss board-certification to perform US are authorised to enter the established SONAR score into the SCQM database after passing a specific training⁽¹³⁾. A reliability study of the SONAR score including 12 physicians after standardised training showed satisfying results⁽¹⁴⁾. The US assessments were performed with

different machine types and, as most operators represented the treating rheumatologist, they were not blinded to the clinical examination. Taken together, these circumstances represented real-life conditions.

US assessment

TS scoring was performed according to OMERACT definitions⁽¹⁵⁾. TS grade was assessed in longitudinal and transverse planes, and defined as abnormal anechoic and/or hypoechoic (relative to tendon fibres) tendon sheath widening (either corresponding to tenosynovial abnormal fluid and/or hypertrophy). TS was semi-quantitatively assessed in B-mode from 0 to 3: grade 0, normal; grade 1, minimal; grade 2, moderate; grade 3, severe (Fig. 1).

The following tendons were scanned bilaterally: all flexor tendons at the level of the finger, flexor carpi radialis and extensor tendons at the level of the wrist. Only the highest score for TS at any location was entered in the database (with 0 entered if no TS was present). The database does not include information about individual tendons. Relevant TS was present if a TS score of 2 or 3 was identified.

Definition of residual time of remission

Baseline was defined as the first visit with an available TS US score during clinical remission. Loss of remission was assumed in the following situations: an increase in DAS28-ESR ≥ 2.6 , drug discontinuation due to insufficient effectiveness, start/change of a conventional (c-) or biologic (b-) DMARD 60 days after baseline, and start or dose increase of at least 5 mg of glucocorticoids. As the date of clinical examination did not necessarily correspond to the start of remission, we applied left and right imputation to estimate the true remission phase (Supp. Fig. 1). We analysed patients separately as per time-point of the US; “early” was applied if the US was performed ≤ 6 months after the start of clinical remission. In addition, subanalyses were performed for different follow-up time-points: 3, 6, 12, and 24 months. The main analysis included only the initial remission phase. Additionally, two sensitivity analyses were performed: 1) inclusion of several remission phases per patient, as multiple US examinations were possible during remission in many patients, and 2) restriction of the definition of flare to DAS28-ESR ≥ 2.6 in the context of only one remission phase per patient. The earliest US examination in remission was performed in September 2009, and the latest in September 2019.

Statistics

Baseline disease and patient characteristics were compared between patients with US-detected TS (TS+) and those without TS (TS-) using Kruskal-Wallis test and Fisher exact test, as appropriate. Log-rank test was used to compare the median remission time between TS+ and TS- patients. We applied Cox proportional hazard models,

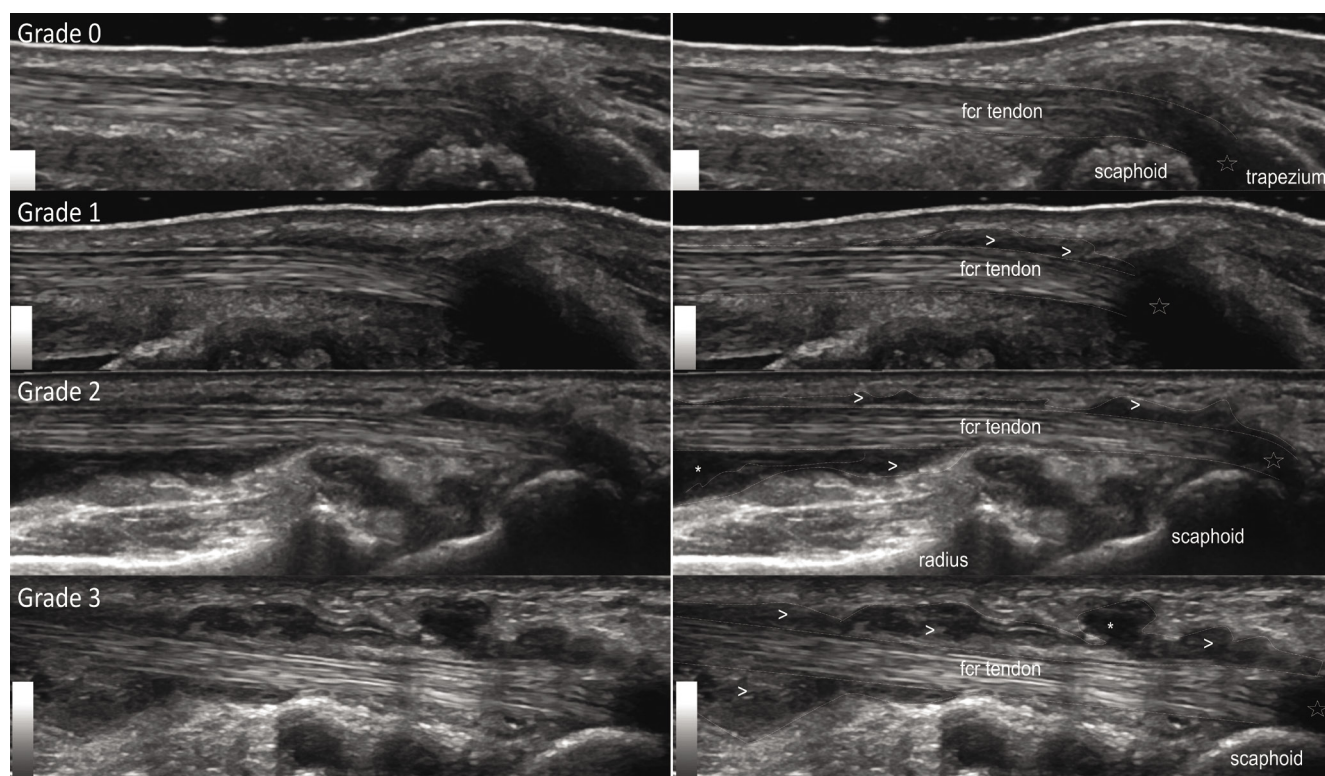


Fig. 1. Examples of grading of tenosynovitis (TS) from 0–3 in B-Mode. Grade 0 – no TS; grade 1 – minimal TS; grade 2 – moderate TS; grade 3 – severe TS. fcr – flexor carpi radialis; arrowhead – synovial thickening, asterisks – anechoic effusion; star – anisotropy of the fcr tendon at the level of the osteofibrous canal

adjusted for baseline levels of potential confounders (age, sex, disease duration, seropositivity (rheumatoid factor and/or anticyclic citrullinated protein antibodies), type of treatment (bDMARD (with or without concomitant csDMARDs), csDMARD, or no DMARD), duration of remission at baseline and presence of synovitis in US), to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of time from baseline US examination to the loss of remission for USTS+ versus USTS– cases. “Presence of US synovitis” was defined as either the detection of two or more joints with a B-mode score ≥ 2 , a total B-mode score > 8 or the presence of any power Doppler (PD).

Results

The baseline demographic and clinical characteristics of 402 patients fulfilling the inclusion criteria are displayed in Tab. 1 (40 patients USTS+ and 362 patients USTS–). Overall, common RA characteristics were present with no significant difference between the two groups: female predominance (73%), mean age of 54 years (standard deviation (SD) 13.5), anti-CCP (73%), and rheumatoid factor positivity (70%). Median (IQR) disease duration was 4.8 (2–10.4) years. Only a minority of patients were in drug-free remission (7%), while biologicals were used in 60%. The presence of US-detected TS at baseline was associated with significantly higher disease activity as assessed by a multitude of parameters including DAS28-ESR, simplified disease activity index (SDAI), clinical disease activity

index (CDAI), and physician global. The tender joint count as well as CRP and ESR did not differ between USTS– and USTS+, but SJC28 showed a significantly higher value in USTS+ (median (IQR): USTS– 0 (0–1) versus USTS+ 1 (0–2.2); $p < 0.001$). Alongside SJC28, US synovitis assessed by B-mode (total B-Mode Score) was significantly more often present in the USTS+ group (mean (SD): USTS– 7.2 (6.3) versus USTS+ 9 (5.4); $p = 0.02$). The percentage of drug tapering between patients with and without US-detected TS is shown in Supp. Tab. 1; USTS had no influence on the tapering behaviour.

The loss of remission occurred in 33 patients with and 249 patients without USTS (82.5% vs. 68.8%, respectively). The main reason for the loss of remission was an elevation of the DAS28-ESR above 2.6 in both groups, followed by the start of a csDMARD and drug discontinuation due to ineffectiveness in the USTS+ group. Starting a bDMARD was the second most common cause of the loss of remission in the USTS– group, followed by drug ineffectiveness (data not shown).

The median duration until the loss of remission was 1.3 years (95% CI 0.7, 2.5) when TS was found, and 2.2 years (95% CI 1.9, 2.4) when US showed no signs of TS (log-rank $p = 0.24$). In the subset of patients with US performed early in remission, right imputation showed a median of 1.3 years (95% CI 0.7, 2.5) for USTS+, and a median of 2 years (95% CI 1.4, 2.2) until the loss of remission (Log-rank $p = 0.65$) for USTS–. In contrast, left imputation revealed a slightly shorter, but non-significant, duration

Tab. 1. Baseline characteristics at first ultrasound in remission in patients with ultrasound-detected tenosynovitis (USTS+) and those without (USTS-)

Variable	N	Tenosynovitis			P-value
		All (n = 402)	Negative (n = 362)	Positive (n = 40)	
Age in yrs, mean (SD)	402	54 (13.5)	53.8 (13.6)	56 (11.8)	0.44
Male, n (%)	402	110 (27)	99 (27)	11 (28)	1.00
Disease duration in yrs at baseline, median (IQR)	402	4.8 (2–10.4)	4.9 (2.1–10.6)	4.4 (1.7–7.6)	0.21
Anti-CCP, n (%)	381	277 (73)	252 (73)	25 (68)	0.44
RF, n (%)	395	275 (70)	243 (68)	32 (80)	0.15
Synovitis score, mean (SD)					
B-mode score (units/22)	397	7.4 (6.2)	7.2 (6.3)	9 (5.4)	0.02
power-Doppler score (units/22)	373	1.2 (2.2)	1 (2)	2.3 (3.5)	0.06
ESR (mm/h), mean (SD)	376	8.4 (8.1)	8.5 (8.3)	7.7 (6.1)	0.69
CRP (mg/l), mean (SD)	391	3 (6)	3 (6.2)	2.9 (3.9)	0.24
SJC28, median (IQR)	402	0 (0–1)	0 (0–1)	1 (0–2.2)	0.00
TJC28, median (IQR)	402	0 (0–0)	0 (0–0)	0 (0–1)	0.09
DAS28 at baseline, mean (SD)	402	1.8 (0.5)	1.8 (0.5)	2 (0.5)	0.00
Physician global, mean (SD)	379	1.3 (1.1)	1.1 (1.1)	2.2 (1.3)	0.00
Radai, mean (SD)	227	2 (2)	1.9 (2)	2.4 (1.9)	0.15
SDAI, mean (SD)	209	4.5 (4)	4.3 (3.8)	7.7 (4.4)	0.00
CDAI, mean (SD)	214	4.2 (4)	4 (3.8)	7.4 (4.3)	0.00
HAQ, median (IQR)	237	0.1 (0–0.6)	0.1 (0–0.5)	0.2 (0–0.9)	0.24
Smoking status	362				0.86
never smoker, n (%)		172 (48)	156 (47)	16 (52)	
former smoker, n (%)		104 (29)	95 (29)	9 (29)	
current smoker, n (%)		86 (24)	80 (24)	6 (19)	
Body mass index, mean (SD)	340	25.1 (4.9)	25.1 (4.8)	24.9 (5.4)	0.42
Treatment	402				0.57
bDMARD treatment at baseline, n (%)		242 (60)	220 (61)	22 (55)	
csDMARD treatment at baseline, n (%)		132 (33)	118 (33)	14 (35)	
no DMARD treatment at baseline, n (%)		28 (7)	24 (7)	4 (10)	
Yrs in rem. before (left imput., mode 2), median (IQR)	402	1 (0.4–2.1)	1 (0.5–2.1)	0.6 (0.3–1.2)	0.04
Yrs in rem. before (right imput., mode 1), median (IQR)	402	0 (0–0.5)	0 (0–0.6)	0 (0–0)	0.05

A p-value of zero indicates a value of <0.001. P-values are from Kruskal-Wallis test for continuous or discrete variables and from Fisher's exact test for categorical variables. **Rows with p-values <0.05 are in bold.**
 bDMARD – biological disease-modifying antirheumatic drugs; CDAI – clinical disease activity index; csDMARD – conventional synthetic disease-modifying antirheumatic drugs; DAS28 – 28-joint disease activity score; ESR – erythrocyte sedimentation rate; HAQ – health assessment questionnaire; imput. – imputation; IQR – interquartile range; RADAI – rheumatoid arthritis disease activity index; rem. – remission; SDAI – simple disease activity index; SD – standard deviation; yrs – years

until the loss of remission in the USTS- group (1.1 (0.8; 2.1) years vs. 1.3 (0.5; 2.7) years in USTS+; $p = 0.55$).

The adjusted hazard ratios (HR) for the loss of remission are shown for different analyses in Fig. 2 (all vs. early remission phases using the complete and separated follow-up times (3, 6, 12, 24 months)). No statistical difference could be detected between USTS+ and USTS- in all analyses. While a longer duration of remission prior to the baseline US was associated with a lower probability of the loss of remission for all remission phases using left imputation (HR 0.74 (95% CI 0.56, 0.98)), a lack of DMARD treatment at baseline was associated with a higher probability of a flare assessing all remission phases (left imputation HR 2.69 (95% CI 1.02, 7.09; right imputation HR 2.67 (95% CI 1.01, 7.12)), but not in early remission phases.

Using multiple remission phases per patient and applying a more stringent definition of remission (only DAS28-ESR

≥ 2.6) did not affect our findings. The respective adjusted HR for a flare with different follow-up times as well as right and left imputations are shown in Supp. Fig. S2 (multiple remission phases per patient) and Supp. Fig. S3 (restriction of flare as DAS28-ESR ≥ 2.6).

Discussion

Our investigation of the role of US-detected TS in RA patients in remission in a real-world population found that TS did not predict a disease flare. This is different from a previous SCQM analysis demonstrating that residual synovitis – detected either by B-Mode or PD-Mode – had a moderate predictive power for the loss of remission in the same setting⁽²⁾.

The absence of PD assessment of TS in SCQM might be regarded as a major limitation. Indeed, the longitudinal analysis of the STARTER cohort⁽⁸⁾ showed that the concomitant

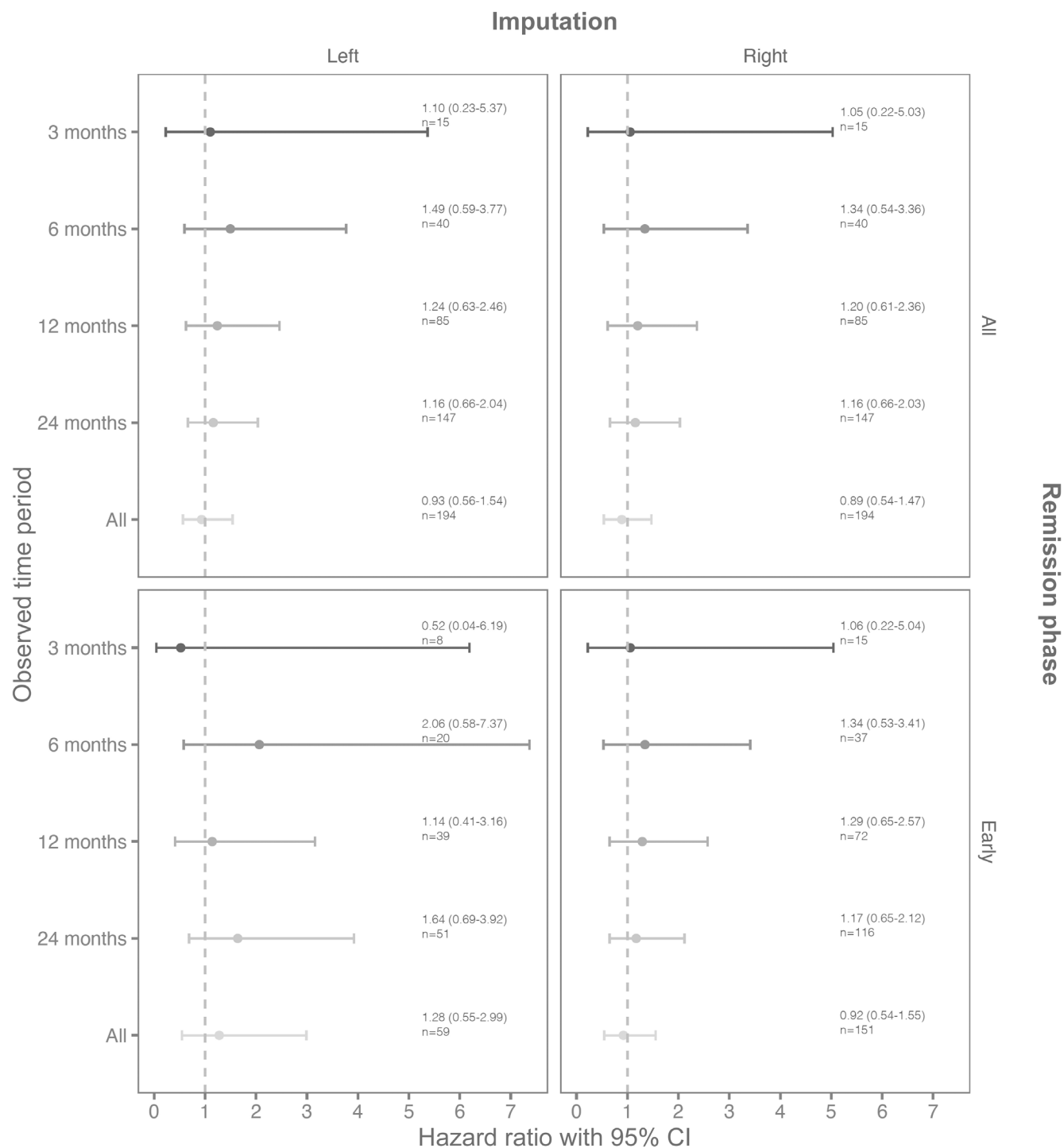


Fig. 2. Multiple adjusted hazard ratios (HR) for time to loss of remission comparing patients with versus without ultrasound-detected TS across different observed time periods and across all and early remission phases using left and right imputation. Progression events after the respective indicated observation time were censored. The numbers on the right of each panel are the HR with 95% confidence interval (CI) in brackets and below the number of occurred events

presence of PD positive TS and joint synovitis predicted a disease flare in crude as well as adjusted analyses. In concordance with our results, TS in B-Mode had no predictive value in this setting. As the SONAR Score was integrated in SCQM as early as 2009, the inclusion of PD TS was not considered and therefore could not be analysed here.

Other methodological issues seem relevant as well. We used a stringent definition of TS (B-mode score ≥ 2) to minimise the proportion of false-positive findings. In contrast, Fillipou *et al.*^(8,9) defined any appearance of tenosynovitis as relevant in the STARTER study. The appropriate differentiation between pathologic and healthy tendon synovial

sheaths, regarding the extent as well as the location of TS, is critical. In STARTER, diverging results were found using different definitions (B-mode and PD-mode ≥ 1 vs. B-mode and PD-mode ≥ 2 , respectively) of pathological US findings. A US study comparing US-detected TS in healthy individuals in comparison to RA patients is needed to define a cut-off for clinically or prognostically relevant TS. It is important to know if a certain extent of TS is related to clinical symptoms (e.g., trigger finger) and findings (palpable tendon friction rubs) in RA. Furthermore, TS can develop due to mechanical stress and crystal arthropathies in the setting of RA as well. As standardised exclusion of possible differential diagnosis (e.g., by fluid aspiration) was not part of our study, misclassification bias is possible.

The latest EULAR recommendations for the management of RA⁽¹⁶⁾ state that treatment should be aimed at reaching a target of sustained remission using Boolean-based and index-based definitions⁽¹⁷⁾. We used a less stringent definition (DAS28-ESR < 2.6) by virtue of the following: it is known that a substantial proportion of RA patients do not reach Boolean-based remission; our goal was to study a patient population reflecting everyday clinical practice, including some patients with remaining low disease activity defined by Boolean- and SDAI-indexes. Furthermore, using more stringent remission criteria would have resulted in significantly fewer patients with USTS+, making statistical analysis even more difficult.

Tendon damage and related functional impairment over a prolonged time period have not been investigated as an outcome in studies assessing the value of US-detected TS in RA. It is likely that untreated TS – apparent or not – does not resolve spontaneously and could lead to tendon damage and consequent disability over time^(18,19). Independently of flare prediction, the assessment of TS by US could, therefore, represent an important tool to prevent secondary harm by early detection of inapparent – but potentially relevant – TS and/or already present tendon damage which might progress.

The strength of our study was the real-world setting investigating a large number of patients with RA in clinical remission. Besides the observational nature of this study, several other limitations need to be addressed. The ultrasonographers had information about clinical data and were most of the time the treating rheumatologists. Knowledge of the clinical situation might have resulted in higher US scores, which might have influenced treatment decisions. We tried to reduce the impact of this potential bias by only including b- and csDMARD starts > 60 days after the baseline

US as a sign of the loss of remission. Furthermore, reducing the definition of a flare as DAS28-ESR ≥ 2.6 did not influence the results. Left- and right imputations were used to overcome the lack of prescheduled visits and the variation between the time-points as the varied among patients. The results were not affected by the different imputation methods.

Conclusion

In conclusion, US-detected B-mode TS in RA patients in remission had no predictive value for future flares in this real-life study. Future investigations should concentrate on the definition of significant US tenosynovitis and test its value for the development of tendon damage and functional disabilities in larger studies of longer duration.

Ethics approval and consent to participate

All patients signed an informed consent prior to the inclusion in SCQM, and the study was approved by the ethics committee of the Canton of Vaud (CER-VD Switzerland: 89/14)

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Declarations

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Conflict of interest

Authors do not report any financial or personal connections with other persons or organisations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

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