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LETTER

Prediction of histology by B-mode and PD-mode ultrasound across different joint locations and diseases

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A few studies have investigated the predictive value of ultrasound (US) regarding specific histological findings and no study so far assessed the respective impact of different joint locations and diseases.[1–3] Thus, the aim of this study was to investigate whether US—using grey scale (B)-mode and power Doppler (PD)-mode—can predict synovial characteristics in patients with specific inflammatory rheumatic diseases across different joint locations.

Ultrasound guided synovial biopsy (USGB) and histological examination were performed according to EULAR guidelines[4 5] including questionnaires on tolerability and side effects before and after the procedure; ethical approval as well as informed consent was obtained (KEK2021-00092). Histology included quality control, Krenn Score,[6] synovial pathotype according to Humby *et al*,[7] and vascularisation based on the mean number of ERG positive blood vessels over five randomly selected visual fields (×20 magnification). B-mode and PD-mode US were scored semiquantitatively according to OMERACT definitions.[8] Patients fulfilled classification criteria for the respective diseases. Statistical analyses included univariable and multivariable linear and multinomial logistic regression analysis (goodness-of-fit by likelihood ratio χ^2 test) and were performed with R V.4.1.3.

A total of 33 joints with available US scores and representative histology were assessed from 33 patients with the following diseases: rheumatoid arthritis (RA; n=12), psoriatic arthritis (PsA; n=13), spondyloarthritis (n=4) and undifferentiated arthritis (UA; n=4). USGB was very well tolerated with no side effects, and all patients would repeat the procedure, if necessary. Participants' ages ranged from 20 to 79 years (mean 51, SD=13.75) and 64% of patients were female. The following joint locations were included: 10 wrists, 3 metacarpophalangeal, 18 knee joints, 1 sternoclavicular and 1 metatarsophalangeal joint. Median B-mode and PD-mode score were 2. A significant positive relationship between B-mode US and total Krenn score (figure 1A), and between PD-mode US and vascularisation (figure 1B) was found in univariate linear regression analysis. This effect remained significant in the adjusted analysis, including age, sex (reference men), disease (reference RA) and location (reference knee) as covariables (online supplemental table S1). In addition, PsA was related to significantly higher vascularisation in the multivariable model (estimate 3.27; 95% CI 0.19 to 6.36; p=0.039), a finding previously described.[9] A multinomial logistic regression model using B-mode US as independent variable showed a high likelihood ratio for prediction of pathotype (LRT 11.76, p<0.01). Low B-mode US scores increased the probability of having a pauci-immune pathotype, while patients with high B-mode US scores had a high probability of having a lympho-myeloid pathotype (figure 1C). Adding total Krenn Score as additional variable to the multinomial model, B-mode US likelihood ratio diminished to 4.06 (p=0.13) suggesting the possible role of Krenn Score as mediator for the capability of B-mode US Score to predict the synovial pathotype.

In conclusion, this study suggests, that B-mode and PD-mode US scores according to definitions introduced for hand joints by OMERACT[8] can predict the grade of histological synovitis and vascularisation independent of the disease analysed or of

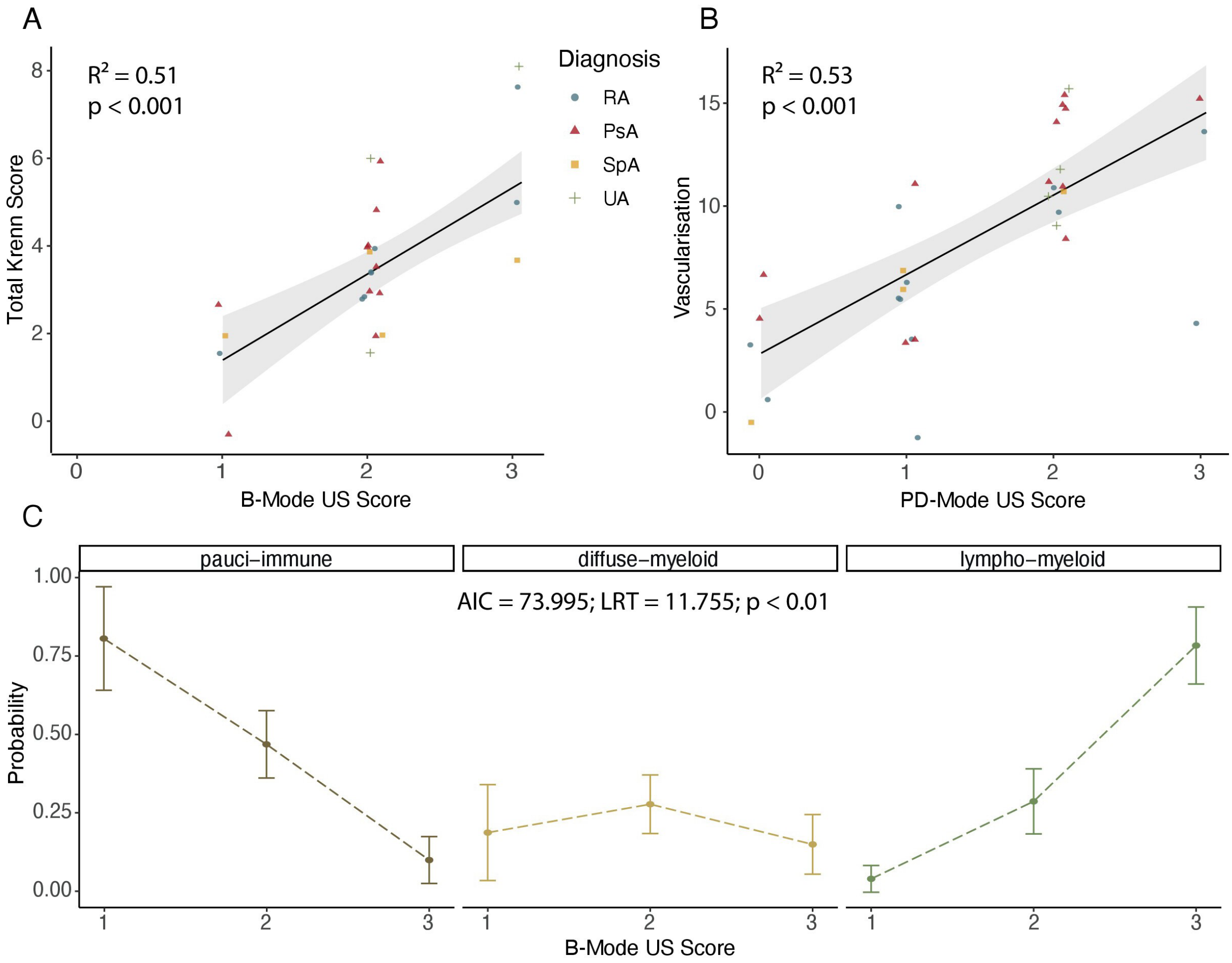

Figure 1 Univariate linear regression between B-mode ultrasound (US) score and total Krenn score (A) and PD-mode score and vascularisation (B). Predicted probabilities (±SE) of different pathotypes (pauci-immune, diffuse-myeloid and lympho-myeloid) based on B-mode US score estimated by multinomial logistic regression model (C). AIC, Akaike information criterion; LRT, likelihood ratio test; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthritis; UA, undifferentiated arthritis.

joint location. Although B-mode showed a high likelihood ratio to predict the synovial pathotype, the identification of the diffuse-myeloid subtype seems to be challenging based on US characteristics alone. Additional clinical/imaging surrogate markers might, therefore, be needed.

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Contributors RM, CO and AC were involved in conception and design of the work. RM performed US examinations and joint biopsies, analysed the data and wrote the manuscript. CP did the histological analysis. PR performed US examinations and joint biopsies. KB organised and assisted all biopsies. OD, CO and AC contributed to the interpretation of the data and development of the manuscript. All authors critically revised the manuscript and approved the final version. CO and AC are joint last authors.

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REFERENCES

1 Andersen M, Ellegaard K, Hebsgaard JB, *et al*. Ultrasound colour Doppler is associated with synovial pathology in biopsies from hand joints in rheumatoid arthritis patients: a cross-sectional study. *Ann Rheum Dis* 2014;73:678–83.

2 Walther M, Harms H, Krenn V, *et al*. Correlation of power Doppler sonography with vascularity of the synovial tissue of the knee joint in patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum* 2001;44:331–8.

3 Ramírez J, Celis R, Usategui A, *et al*. Immunopathologic characterization of ultrasound-defined synovitis in rheumatoid arthritis patients in clinical remission. *Arthritis Res Ther* 2016;18:74.

4 Najm A, Costantino F, Alivernini S, *et al*. EULAR points to consider for minimal reporting requirements in synovial tissue research in rheumatology. *Ann Rheum Dis* 2022;13:annrheumdis-2021-221875.

5 Najm A, Le Goff B, Orr C, *et al*. Standardisation of synovial biopsy analyses in rheumatic diseases: a consensus of the EULAR synovitis and OMERACT synovial tissue biopsy groups. *Arthritis Res Ther* 2018;20:265.

6 Krenn V, Morawietz L, Burmester G-R, *et al*. Synovitis score: discrimination between chronic low-grade and high-grade synovitis. *Histopathology* 2006;49:358–64.

7 Humby F, Lewis M, Ramamoorthi N, *et al*. Synovial cellular and molecular signatures stratify clinical response to csDMARD therapy and predict radiographic progression in early rheumatoid arthritis patients. *Ann Rheum Dis* 2019;78:761–72.

8 D'Agostino M-A, Terslev L, Aegerter P, *et al*. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open* 2017;3:e000428.

9 Fromm S, Cunningham CC, Dunne MR, *et al*. Enhanced angiogenic function in response to fibroblasts from psoriatic arthritis synovium compared to rheumatoid arthritis. *Arthritis Res Ther* 2019;21:297.