RMD Open
Rheumatic & Musculoskeletal Diseases

SHORT REPORT

Histological synovitis and radiographic damage in knee osteoarthritis: insights from a comprehensive analysis of ultrasound-guided synovial biopsies in 161 patients

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To cite: Rubortone P, De Lorenzis E, Leone F, *et al*. Histological synovitis and radiographic damage in knee osteoarthritis: insights from a comprehensive analysis of ultrasound-guided synovial biopsies in 161 patients. *RMD Open* 2025;**11**:e006011. doi:10.1136/rmdopen-2025-006011

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/rmdopen-2025-006011).

Received 12 June 2025
Accepted 30 July 2025

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ABSTRACT

Objective Synovial inflammation plays a crucial role in osteoarthritis (OA) by producing key cytokines that mediate synovium–cartilage interaction and drive damage progression. In this study, we aimed to evaluate relationships between histological features of synovitis, radiographic damage and patients' clinical characteristics.

Methods This observational cross-sectional study included consecutive patients with knee OA from 2016 to 2022. Enrolled patients were aged between 40 and 90 years, had chronic knee pain lasting at least 3 months and showed ultrasound evidence of synovitis. All patients underwent a general rheumatological evaluation, including the collection of clinical and laboratory data and ultrasound (US)-guided minimally invasive synovial tissue biopsy. The severity of synovitis was assessed by histology using the Krenn Synovitis Score (KSS).

Results A total of 161 patients were considered for the analysis. The multivariate analysis showed that both US effusion and Kellgren-Lawrence (KL) grade were positively associated with histological synovitis. In contrast, age, sex, body mass index, levels of inflammatory markers, pain intensity and cardiovascular risk factors were not associated with histological synovitis. A strong positive correlation was found between KL grades and the KSS. A moderate positive correlation emerged between KL grades and the proportion of patients with lymphocytes and plasma cells in synovial tissue.

Conclusions More severe histological synovitis in patients with non-end-stage knee OA is associated with worse radiographic structural damage. In the advanced stages of structural damage, the likelihood of detecting a lymphoplasmacytic inflammatory infiltrate in the synovial membrane increases. US-detected effusion serves as a marker of histological synovitis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although synovial membrane inflammation is typically considered low-grade, it plays a key role in osteoarthritis (OA) pathogenesis, contributing to pain and structural damage through the production of proinflammatory cytokines.

WHAT THIS STUDY ADDS

⇒ In patients with knee OA, more severe synovitis, assessed through ultrasound-guided synovial biopsy and graded using a semiquantitative histological approach, is associated with more severe radiographic structural damage. Lymphocytic infiltration of the synovial membrane is already present in the early stages of the disease, while in advanced stages, the likelihood of detecting a lymphoplasmacytic synovial infiltrate is quite high. Moreover, ultrasound-detected effusion serves as a clinical marker of histological synovitis in knee OA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Classifying patients with knee OA based on a combination of imaging and histological findings may improve patient stratification, allowing for more targeted and effective treatment strategies.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disorder,[1] with the knee being one of the most commonly affected joints. Accumulating evidence highlights the central role of synovitis in the progression of OA.[2] Low-grade synovial tissue (ST) inflammation contributes to the progression of radiographically evident lesions and worsening of pain.[3 4] The presence of synovitis at baseline, detected using MRI or ultrasound (US), is associated with a worsening of the Kellgren-Lawrence (KL) score,[5] joint space narrowing, erosive OA of the hands and accelerated knee OA.[6–8]

Furthermore, the majority of key cytokines involved in the pathogenesis of OA are expressed by fibroblast-like synoviocytes.[9]

The role of synovitis in OA progression is not fully understood, as the majority of histological studies investigating the synovial composition in the OA spectrum have been conducted on final stages of the disease and on residual tissues from arthroplasty procedures.[2]

Based on these issues, this study aimed to (1) dissect the histological composition of synovial membrane in patients with OA using minimally invasive US-guided biopsies, (2) identify the clinical characteristics of patients associated with histologically confirmed OA synovitis and (3) evaluate the association between OA synovitis degree and structural radiographic damage.

MATERIALS AND METHODS

This was a retrospective observational study based on cross-sectional data. Consecutive patients who fulfilled the classification criteria for knee OA according to the American College of Rheumatology[10] were included at the Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore (Rome, Italy), from 2016 to 2022. Given the exploratory nature of the study, no formal sample size calculation was performed. Instead, all eligible patients within this time frame were included to enhance statistical power and support exploratory analyses of histological and radiological associations in knee OA. Enrolled patients were (1) adults aged from 40 to 90 years, (2) with chronic knee pain (≥3 months) and (3) evidence of synovitis graded ≥1 on US, as defined by the European Alliance of Associations for Rheumatology (EULAR)-Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) semiquantitative scoring system.[11] Exclusion criteria were (1) concomitant inflammatory arthritis and connective tissue disease; (2) contraindication to performing ST biopsy; (3) any intra-articular injection in the previous 12 weeks; (4) inability to provide informed consent and (5) concomitant disease-modifying antirheumatic drug therapy within 6 months. All patients provided signed informed consent.

Patients' clinical assessment

At study entry, each patient underwent a comprehensive rheumatological evaluation in which demographic, clinical and laboratory data were collected, including age, sex, weight, height, body mass index (BMI), smoking habit, Visual Analogue Scale pain (before the procedure), primary systemic hypertension, diabetes, fibromyalgia, concomitant use of non-steroidal anti-inflammatory drugs, painkillers and antidepressants/gabapentinoids (at least 7 days/month). Moreover, for each patient, peripheral blood values of erythrocyte sedimentation rate and C reactive protein were assessed.

US and radiographic evaluation

Each patient underwent a knee US evaluation performed by two experienced rheumatologists (MML and SA), blinded to clinical and laboratory data, using a real-time scanner (MyLabTwice, Esaote, Genoa, Italy) with a 4–15 MHz probe. The suprapatellar recess was assessed in the sagittal plane at midline with the knee flexed at 30°, while the medial and lateral parapatellar recesses were evaluated in the mid-patellar transverse plane (approximately 90° to the sagittal midline) with the knee extended, using the retinacula as anatomical landmarks. Joint effusion was defined as abnormal anechoic or hypoechoic intra-articular material that was displaceable and compressible but lacked a Doppler signal.[12] Effusion was considered present when the maximal anteroposterior measurement was ≥3.6 mm in the suprapatellar recess or ≥2.4 mm in the parapatellar recesses[13] and was then categorised dichotomously as 'absent' or 'present'. Synovitis was scored using the EULAR-OMERACT semiquantitative 0–3 grading system (0=normal, 1=minimal, 2=moderate and 3=severe), applied to both grey scale (GS) and power Doppler (PD) findings.[11] The Doppler signal was recorded only in the medial and lateral parapatellar recesses.

Each enrolled patient underwent bilateral knee X-rays within 12 weeks of the synovial biopsy to assess structural damage using the anteroposterior KL scoring system.[5]

ST biopsy performance and histological synovitis score assessment

Each patient underwent US-guided minimally invasive ST biopsy of the knee according to a published protocol.[14] All ST specimens obtained (at least 6–8 fragments) were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm and stained with H&E/phloxine. Slides were examined using a light microscope (Leica DM2000) by a trained pathologist (MG) who was unaware of the patients' characteristics. Synovitis severity was graded according to the Krenn Synovitis Score (KSS).[15] The values were interpreted as follows: a score of 0–1=no synovitis, 2–4=low-grade synovitis and 5–9=high-grade synovitis. In addition, the presence/absence of lymphocytes, plasma cells, granulocytes and crystals at polarised light analysis was recorded.

Statistical analysis

Categorical variables are presented as numbers and percentages, while continuous variables are reported as the mean±SD or median with IQR, based on data normality, assessed through inspection of quantile–quantile plots. Univariate logistic regression analysis examined predictors of histological synovitis, defined as a Krenn score ≥2. Two adjusted models were then proposed: one including predictors with a p value of <0.1, and the other also including age and BMI due to their expected clinical impact on the outcome. Associations are expressed as OR with 95% CI. Spearman's rank correlation coefficient was used to assess monotonic relationships between ordinal

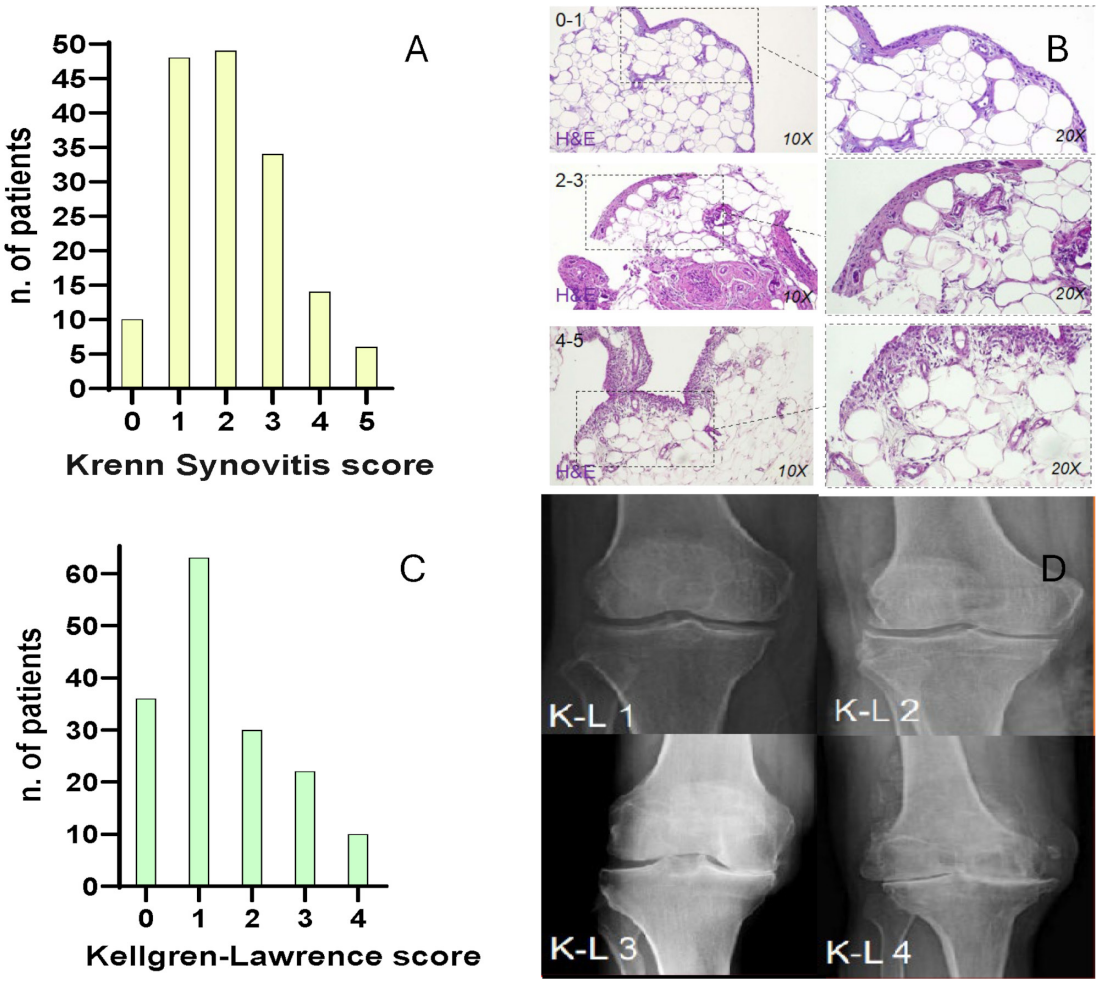

Figure 1 (A) Distribution of KSS in patients with knee OA. (B) Light microscope images of samples obtained from patients in our cohort with different KSS (top to bottom: KSS 0–1, KSS 2–3 and KSS 4–5). (C) Distribution of the KL score in patients with knee OA. (D) Representative radiographic images of the KL score. KL, Kellgren-Lawrence; KSS, Krenn Synovitis Score; OA, osteoarthritis.

and binary/ordinal variables. Statistical significance was defined as a p value of less than 0.05 for all analyses; all tests were two-tailed. Data analysis was performed using RStudio (V.2023.03.0).

RESULTS

A total of 182 consecutive patients were enrolled in the study. Among these, 21 patients were excluded: 14 because of radiographic (meniscal calcifications) or histological findings consistent with crystal-induced arthritis and seven due to X-ray unavailability. Thus, 161 patients were then considered for the analysis.

Online supplemental table 1 summarises the clinical and demographic characteristics of the enrolled cohort. The mean age (±SD) was 63 (±11) years; the mean BMI was 27.2 (±4.6), and 80% of the patients were female. As shown in figure 1A, B, 103 (64%) patients had histological synovitis (KSS ≥2), of which six (6%) had high-grade synovitis (KSS ≥5). The distribution of KSS values was as follows: 10 patients with KSS=0, 48 with KSS=1, 49 with KSS=2, 34 with KSS=3, 14 with KSS=4 and 6 with KSS=5 (figure 1). The mean (±SD) KSS value was 2.08±1.18. The distribution of the KL score was 36 patients with KL=0, 63 with KL=1, 30 with KL=2, 22 with KL=3 and 10 with KL=4. The median (IQR) KL score was 1 (1–2).

Predictive factors of OA-related synovitis

Univariate logistic regression analysis (table 1) revealed that US effusion (OR 8.23, 95% CI 3.80 to 19.59, p<0.001), PD signal (PD ≥1; OR 6.08, 95% CI 2.25 to 21.34, p=0.001), US-detected synovial hypertrophy (SH) (OR 2.03, 95% CI 1.32 to 3.2, p=0.016) and KL grade (OR 4.03, 95% CI 2.54 to 6.99, p<0.001) were associated with the presence of histological synovitis defined as KSS ≥2. The multivariate model, adjusted for predictors with p<0.1 in the univariate analysis, confirmed that US effusion and KL grade were independently associated with the presence of histological synovitis, with ORs of 4.76 (95% CI 1.99 to 12.27, p<0.001) and 3.27 (95% CI 1.97 to 5.93, p<0.001), respectively. In the second model, age and BMI were included as covariates due to their well-established association with OA. Their inclusion aimed to

Table 1 Predictors of histological synovitis (Krenn Synovitis Score ≥2): univariate and multivariate logistic regression analyses

	Unadjusted analysis		Adjusted analysis 1		Adjusted analysis 2	
Characteristic	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Age, years	1.02 (0.99 to 1.05)	0.2	–	–	0.96 (0.92 to 1.01)	0.13
Male sex	1.30 (0.58 to 3.09)	0.6	–	–	–	–
Smoke (current)	0.59 (0.22 to 1.56)	0.3	–	–	–	–
Body mass index	1.05 (0.98 to 1.13)	0.2	–	–	1.01 (0.92 to 1.1)	0.89
Systemic hypertension	1.14 (0.60 to 2.20)	0.7	–	–	–	–
Ischaemic heart disease	0.55 (0.15 to 2.07)	0.4	–	–	–	–
Diabetes	0.95 (0.33 to 2.94)	>0.9	–	–	–	–
Fibromyalgia	0.52 (0.26 to 1.05)	0.069	0.72 (0.29 to 1.70)	0.4	0.68 (0.27 to 1.67)	0.41
C reactive protein >5 mg/L	1.22 (0.56 to 2.83)	0.6	–	–	–	–
Erythrocyte sedimentation rate >20 mm/hour	1.19 (0.62 to 2.29)	0.6	–	–	–	–
US effusion	**8.23 (3.80 to 19.59)**	**<0.001**	**4.51 (1.86 to11.72)**	**0.001**	**4.34 (1.8 to 11.4)**	**0.002**
US-synovial hypertrophy	**2.03 (1.32 to 3.2)**	**0.016**	1.41 (0.82 to 2.45)	0.21	1.3 (0.72 to 2.24)	0.41
Power Doppler signal	**6.08 (2.25 to 21.34)**	**0.001**	1.67 (0.47 to 6.9)	0.4	1.97 (0.53 to 8.92)	0.34
Kellgren-Lawrence grading	**4.03 (2.54 to 6.99)**	**<0.001**	**3.21 (1.91 to 5.86)**	**<0.001**	**3.79 (2.14 to 7.31)**	**<0.001**
Pain severity on Visual Analogue Scale	1.15 (0.94 to 1.42)	0.2	–	–	–	–
Paracetamol*	1.29 (0.65 to 2.61)	0.5	–	–	–	–
Gabapentinoids/antidepressants	1.28 (0.51 to 3.54)	0.6	–	–	–	–
Non-steroidal anti-inflammatory drugs*	0.96 (0.47 to 1.93)	0.9	–	–	–	–

Bold values indicate odds ratios (OR) and p-values that are statistically significant.
*At least 7 days per month.
KSS, Krenn Synovitis Score; US, ultrasound.

adjust for potential unmeasured confounding effects that might bias the associations with other variables. In this model as well, effusion and structural damage were found to be independently associated with synovitis (table 1).

Association between KL grades and ST characteristics in knee OA

A Spearman's rank correlation analysis was conducted to assess the relationship between KL grades, the KSS and the proportion of patients with lymphocyte-, granulocyte- and plasma cell-enriched ST (figure 2). The analysis revealed a strong positive correlation between KL grades and KSS (Rs=0.712, p<0.001), while synovial enrichment of lymphocytes and plasma cells was rare in patients with OA with KL grades 0–1 (figure 2B, C). Patients with OA with KL grades ≥2 were more likely to have synovial

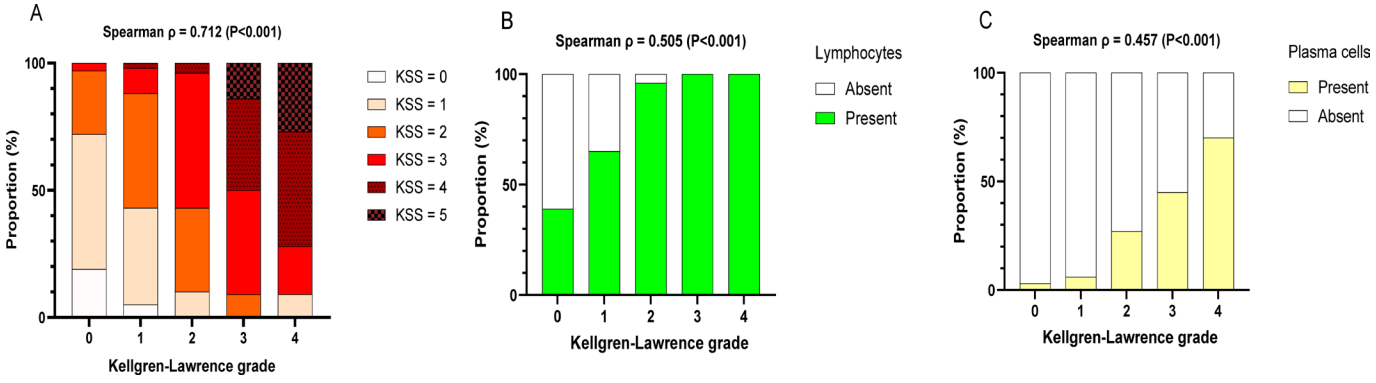

Figure 2 Proportion of patients with synovial inflammatory features across KL grades. (A) Proportional distribution of KSS among patients for each KL grade. (B and C). Proportional distribution of the patients with synovial tissue enriched in lymphocytes (B) and plasma cells (C) for each KL grade. KL, Kellgren-Lawrence; KSS, Krenn Synovitis Score; OA, osteoarthritis.

enrichment of lymphocytes (Rs=0.505, p<0.001) and plasma cells (Rs=0.457, p<0.001).

DISCUSSION

To our knowledge, this is one of the first studies on knee OA using samples not obtained from end-stage disease (arthroplasty) and employing a US-guided minimally invasive biopsy approach. The results obtained indicate that over 60% of patients with painful, non-end-stage knee OA exhibit histologically detectable synovitis, assessed semiquantitatively via US-guided biopsy. Notably, approximately 6% of these patients exhibited high-grade synovitis, and 71% of all patients displayed lymphocytic infiltration in the synovial membrane.

This study confirms that synovitis in knee OA is associated with radiographic structural damage, as evaluated by the KL score. Additionally, we established that an increased severity of synovitis and a richer inflammatory infiltrate are associated with greater radiographic damage. While causality cannot be inferred, growing evidence suggests that synovitis (on US or MRI) is an early event in the pathogenesis of OA and the primary source of proinflammatory cytokines.[9 16–18] Our findings support the hypothesis that synovitis and osteochondral damage may have a bidirectional, self-reinforcing relationship.

Consistent with previous findings,[19] only a few patients in our cohort exhibited a granulocytic infiltrate (4% of cases) in ST. The presence of lymphocytes in more than 90% of synovial samples from patients with incipient OA (KL=2) reinforces the potential early involvement of this cell population in the development and progression of OA.[20] Moreover, the proportion of patients with synovial plasma cell infiltrates increases with the severity of structural damage, further supporting the notion that adaptive immune-mediated dysfunctions play a key role in OA pathogenesis.[21]

Although senescence is a risk factor for OA,[22] age was not predictive of synovitis in our cohort. Synovitis may instead reflect cumulative exposure to various stressors. Additionally, neither BMI nor cardiovascular risk factors were associated with synovitis, suggesting a predominance of local over systemic mechanisms.

The multivariate analysis shows that US-detected effusion is associated with histological synovitis, while PD and US-detected SH are not. This is in line with previous observations.[8] Since inflammation in OA is often mild and may already be present in preclinical stages, both GS and PD modalities might lack the sensitivity to detect subtle inflammatory changes that remain below the threshold of sonographic classification. Conversely, joint effusion is easier to assess and may better reflect the presence of low-grade synovial inflammation.

This study has some limitations, including the lack of OA subtype classification, due to the frequent coexistence of various conditions, as well as unaccounted factors such as other treatments, metabolic status and functional limitation. Further longitudinal cohort studies are needed to confirm such findings.

In conclusion, these findings support the value of integrating complementary and multidimensional assessments to refine the characterisation of knee OA phenotypes. In the absence of effective disease-modifying therapies, this approach may represent a crucial step towards the development of more tailored treatment strategies.

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Acknowledgements We thank the patients with OA who participated in the study. We are grateful to Dr Giusy Peluso, Dr Luca Petricca, Dr Simone Perniola, Dr Maria Rita Gigante (Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy) and Professor Elisa Gremese (Humanitas Research Hospital IRCCS, Milan, Italy) for their support in patients' recruitment.

Contributors MADA is the guarantor of this work. All listed authors meet the criteria for authorship. PR, MML, MADA and SA made substantial contributions to the conception and design of the study. SA, MML, PR, BT and DB performed all joint ultrasounds and synovial biopsies. FL contributed significantly to data acquisition. MG conducted the semiquantitative assessment of the synovitis score in synovial biopsies. EDL made a substantial contribution to data analysis. All authors participated in data interpretation. PR drafted the manuscript, while SA, MML and MADA critically revised the paper, providing essential intellectual input. MADA gave final approval of the version to be published. ChatGPT was used during the drafting of the manuscript for grammar-checking purposes.

Funding This work was supported by Linea D1 (R4124500654) (Università Cattolica del Sacro Cuore #R4124500654) (SA) and Ricerca Finalizzata Ministero della Salute GR-2018-12366992 (SA). The funding sources were not involved in the collection, analysis or interpretation of the data.

Competing interests None declared.

Patient and public involvement statement Patients and members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. Nevertheless, we anticipate that the findings of this study will contribute to improving patient care and outcomes, informing policies and practices that directly benefit the target population.

Patient consent for publication Consent was obtained directly from all patients. Each patient signed an informed consent form to undergo the procedures.

Ethics approval This study involves human participants and was approved by the Ethics Committee of Università Cattolica del Sacro Cuore (approval no. 6334/15). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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