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Diagnostic and immunophenotypic contribution of ultrasound-guided synovial biopsy in inflammatory arthritis: Real-world experience from a tertiary rheumatology center

Enflamatuvar artritte ultrasonografi eşliğinde sinovyal biyopsinin tanısal ve immünofenotipik katkısı: Üçüncü basamak bir romatoloji merkezinden gerçek yaşam deneyimi

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Abstract

Objective: Synovial tissue-based assessment has re-emerged as a useful approach for characterizing disease heterogeneity in inflammatory arthritis; however, real-world data on the diagnostic and immunophenotypic contribution of ultrasound-guided synovial biopsy (USGSB) in routine rheumatology practice remain limited. We aimed to evaluate the diagnostic contribution, procedural feasibility, and immunophenotypic characteristics of USGSB in patients undergoing tissue sampling for suspected inflammatory arthritis at a tertiary rheumatology center.

Methods: This single-center retrospective observational study included 53 consecutive adults who underwent USGSB for persistent synovitis and diagnostic uncertainty. Histopathological evaluation was performed using hematoxylin-eosin staining and Krenn synovitis scoring. Immunohistochemical analyses included CD3, CD20, CD68, CD138, and CD31. Synovial pathotypes were classified as lympho-myeloid, diffuse-myeloid, or pauci-immune/fibroid when tissue and staining qualities were sufficient. Biopsy contribution was defined as biopsy-supported diagnostic reclassification or the identification of a clinically actionable alternative etiology beyond standard clinical, laboratory, and imaging assessments.

Results: Final diagnostic attribution was available for 51 of 53 patients. Inflammatory arthritis was the most frequent diagnostic category (39/51,

Özet

Amaç: Sinovyal doku temelli değerlendirme, enflamatuvar artritte hastalık heterojenitesini karakterize etmek için yararlı bir yaklaşım olarak yeniden önem kazanmıştır; ancak ultrasonografi eşliğinde sinovyal biyopsinin (USGSB) rutin romatoloji pratiğindeki tanısal ve immünofenotipik katkısına ilişkin gerçek yaşam verileri sınırlıdır. Bu çalışmada, üçüncü basamak bir romatoloji merkezinde enflamatuvar artrit şüphesiyle doku örneklemesi yapılan hastalarda USGSB'nin tanısal katkısını, prosedürel uygulanabilirliğini ve immünofenotipik özelliklerini değerlendirmeyi amaçladık.

Yöntem: Bu tek merkezli retrospektif gözlemsel çalışmaya, persistan sinovit ve tanısal belirsizlik nedeniyle USGSB uygulanan ardışık 53 erişkin hasta dahil edildi. Histopatolojik değerlendirme hematoksilen-eozin boyama ve Krenn sinovit skorlaması kullanılarak yapıldı. İmmünohistokimyasal analizlerde CD3, CD20, CD68, CD138 ve CD31 değerlendirildi. Doku ve boyama kalitesi yeterli olduğunda sinovyal patotipler lenfo-miyeloid, diffüz-miyeloid veya pauci-immün/fibroid olarak sınıflandırıldı. Biyopsi katkısı, standart klinik, laboratuvar ve görüntüleme değerlendirmelerinin ötesinde biyopsi destekli tanısal yeniden sınıflandırma veya klinik olarak eyleme geçirilebilir alternatif bir etiyolojinin saptanması olarak tanımlandı.

Bulgular: Elli üç hastanın 51'inde nihai tanısal değerlendirme mevcuttu. Enflamatuvar artrit en sık tanı kategorisiydi (39/51, %76,5) ve romatoid artrit en büyük alt grubu oluşturdu (25/51, %49,0). Enfeksiyöz artrit, dejeneratif

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Abstract

76.5%), with rheumatoid arthritis representing the largest subgroup (25/51, 49.0%). Alternative diagnoses or management-relevant diagnostic reclassifications were identified in 12 of 51 patients (23.5%), including infectious arthritis, degenerative joint disease, systemic inflammatory diseases, crystal-induced arthritis, and synovial lipoma. Among histologically assessable specimens (n=50), high-grade synovitis was observed in 34 cases (68.0%). CD68-positive macrophage infiltration was the most frequent immunohistochemical finding (48/53, 90.6%), followed by CD3-positive T lymphocytes (42/53, 79.2%), CD20-positive B cells (26/53, 49.1%), CD138-positive plasma cells (21/53, 39.6%), and CD31 positivity (37/53, 69.8%). Definitive pathotype classification was possible in 44/53 cases (83.0%). No major procedure-related complication was documented.

Conclusion: In this real-world cohort, USGSB provided useful diagnostic refinement and tissue-level immunophenotypic characterization in selected patients with suspected inflammatory arthritis. Biopsy-based treatment stratification remains exploratory and requires validation.

Keywords: Inflammatory arthritis, ultrasound-guided synovial biopsy, synovial tissue, immunophenotype, histopathology, diagnostic yield

Özet

eklem hastalığı, sistemik enflamatuvar hastalıklar, kristal artropati ve sinovyal lipom dahil olmak üzere 12/51 hastada (%23,5) alternatif tanılar veya tedavi açısından anlamlı tanısal yeniden sınıflandırma saptandı. Histolojik olarak değerlendirilebilir örnekler arasında (n=50), 34 olguda (%68,0) yüksek dereceli sinovit izlendi. En sık immünohistokimyasal bulgu CD68-pozitif makrofaj enfiltrasyonuydu (48/53, %90,6); bunu CD3-pozitif T lenfositler (42/53, %79,2), CD20-pozitif B hücreleri (26/53, %49,1), CD138-pozitif plazma hücreleri (21/53, %39,6) ve CD31 pozitifliği (37/53, %69,8) izledi. Kesin patotip sınıflandırması 44/53 olguda (%83,0) yapılabildi. Majör işlem ilişkili komplikasyon kaydedilmedi.

Sonuç: Bu gerçek yaşam kohortunda USGSB, enflamatuvar artrit şüphesi olan seçilmiş hastalarda yararlı tanısal netleştirme ve doku düzeyinde immünofenotipik karakterizasyon sağladı. Biyopsi temelli tedavi sınıflandırması halen araştırma düzeyindedir ve doğrulanmaya ihtiyaç duymaktadır.

Anahtar Kelimeler: Enflamatuvar artrit, ultrasonografi eşliğinde sinovyal biyopsi, sinovyal doku, immünofenotip, histopatoloji, tanısal verim

Introduction

Inflammatory arthritis comprises a heterogeneous group of disorders in which clinical phenotype, serology, and imaging do not always enable confident etiological classification at presentation. In real-world practice, this diagnostic uncertainty is particularly pronounced in seronegative, oligoarticular, monoarticular, or undifferentiated presentations and may delay appropriate disease-modifying treatment or obscure alternative diagnoses such as infection, crystal-associated disease, degenerative disease, or atypical systemic inflammatory disorders. In this context, synovial tissue offers direct assessment of the target organ in which immune activation, stromal remodeling, and vascular changes converge.[1]

Historically, synovial tissue acquisition was largely restricted to arthroscopy. Over the last decade, however, ultrasound-guided minimally invasive synovial biopsy has improved feasibility in routine rheumatology practice. Ultrasound guidance allows targeted sampling of clinically involved synovium across large and small joints and can provide tissue suitable for histopathology and immunohistochemistry (IHC).[2-4] Methodology-focused studies and European Alliance of Associations for Rheumatology (EULAR) points to consider have also emphasized standardized reporting, transparent sampling procedures, and harmonized histological evaluation in synovial tissue research.[3,5]

Standardized histopathological assessment provides a structured framework for interpreting synovial inflammation. The Krenn synovitis score evaluates lining layer hyperplasia, stromal cellularity, and inflammatory infiltrates and can help distinguish inflammatory from low-grade or degenerative patterns.[5] In parallel, immunohistochemical profiling has shown that synovial inflammation is not uniform but includes distinct immune-cell patterns, commonly described as lympho-myeloid, diffuse-myeloid, and pauci-immune/fibroid pathotypes.[7-9]

Although synovial pathotypes are increasingly discussed in precision medicine frameworks, their role in routine treatment selection has not been established in most clinical settings. Trials and translational programs have examined tissue-based treatment-response prediction, but prospective validation is still required before synovial biopsy can be used confidently as a therapeutic decision tool.[8-10] Therefore, real-world studies should clearly distinguish between diagnostic contribution, biological characterization, and unproven treatment-predictive utility.

The present study aimed to evaluate the diagnostic and immunophenotypic contributions of ultrasound-guided synovial biopsy (USGSB) in patients with suspected inflammatory arthritis who were managed at a tertiary rheumatology center. The primary focus was the role of biopsy in diagnostic refinement and tissue-level characterization in clinically challenging cases. Associations with clinical, serological, ultrasonographic, and patient-reported measures were considered descriptive and hypothesis-generating rather than confirmatory.

Materials and Methods

Study Design and Patients

This study was a single-center, retrospective, observational study conducted at a tertiary rheumatology referral center. The study protocol for retrospective data analysis was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-150, date: 10.02.2026), and all procedures were performed in accordance with the principles of the Declaration of Helsinki. Written informed consent for the biopsy procedure was obtained from all participants before tissue sampling.

Consecutive adult patients who underwent USGSB for

suspected inflammatory arthritis between January 2025 and February 2026 were included. Eligible participants were required to be at least 18 years of age and to have clinical evidence of persistent synovitis warranting tissue sampling. Indications for biopsy included undifferentiated inflammatory arthritis, seronegative arthritis with ongoing synovitis, atypical clinical presentation with monoarticular or oligoarticular involvement, treatment-refractory synovitis, or persistent diagnostic uncertainty despite standard clinical, laboratory, and imaging evaluation.

Patients were excluded from the diagnostic analysis if final clinical attribution was unavailable or clinical data were insufficient for interpretation. Importantly, specimens with insufficient synovial tissue were not excluded from the overall feasibility and safety analyses. These cases were retained in the total biopsy cohort and were reported separately as histologically inadequate for Krenn scoring and as unclassifiable or insufficient for pathotype assignment. This approach allowed procedural adequacy, safety, and diagnostic attribution to be treated as distinct outcomes.

Ultrasound-guided Synovial Biopsy Procedure

Synovial biopsies were performed using ultrasound-guided minimally invasive needle biopsy in accordance with EULAR reporting recommendations and standardized procedural literature.[5,11] All procedures were carried out by an experienced rheumatologist trained in musculoskeletal ultrasonography. Musculoskeletal ultrasonography was performed using a high-resolution ultrasound system equipped with a linear-array transducer. Gray-scale (GS) and power Doppler (PD) imaging were used to evaluate synovial hypertrophy, joint effusion, and Doppler activity in clinically involved joints. Synovial hypertrophy, effusion, and PD activity were graded on 0-3 semiquantitative scales, with higher scores indicating greater structural or inflammatory activity. Biopsy specimens were preferentially obtained from joints demonstrating at least grade 2 GS synovial hypertrophy.

After sterile preparation and local anesthesia with 1% lidocaine, synovial tissue samples were obtained using a 14-18G semi-automatic core biopsy needle under continuous real-time ultrasound guidance. Multiple tissue fragments were obtained from different areas of the synovium to reduce sampling variability. A minimum of 6-8 tissue cores per joint were targeted as the procedural standard; additional cores were obtained at the operator's discretion when tissue appeared macroscopically scant. Biopsies were performed on both large and small joints, depending on clinical involvement. No routine peri-procedural antibiotic prophylaxis was administered. Patients were observed for immediate complications and followed clinically for adverse events.

Procedural adequacy was defined separately from pathotype assignment. Histological adequacy required the presence of identifiable synovial lining and/or sublining tissue. Pathotype adequacy required both sufficient synovial tissue and interpretable immunohistochemical staining. Complications were categorized as major (infection, hemarthrosis requiring intervention, neurovascular injury, hospitalization, or any event requiring invasive treatment) or minor (self-limited pain, bruising, vasovagal symptoms, transient sensory symptoms, or transient swelling).

Histopathological Assessment

Synovial tissue specimens were fixed in 10% neutral-buffered formalin and embedded in paraffin. Serial sections (3-4 µm) were stained with hematoxylin and eosin for routine histopathological evaluation.[6]

Histological assessment focused on synovial lining layer hyperplasia, density and distribution of inflammatory infiltrates, stromal activation and fibrosis, and vascular proliferation or endothelial activation. Inflammatory activity was quantified using the Krenn synovitis score, which evaluates three domains: enlargement of the synovial lining cell layer, density of resident stromal cells, and intensity of inflammatory infiltrates.[6] Each domain was scored from 0 to 3, yielding a total score from 0 to 9. Synovitis was classified as absent/minimal (0-1), low-grade (2-4), or high-grade (5-9). Krenn scoring was performed only on specimens that met the histological adequacy criteria for synovial tissue.

Immunohistochemical Analysis

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded sections using standardized protocols. The predefined panel included CD3 for T lymphocytes, CD20 for B lymphocytes, CD138 for plasma cells, CD68 for macrophages, and CD31 for vascular/endothelial structures. CD34 and CD38 were excluded from the final quantitative analysis to maintain consistency among the methods, results, and figures.

For each marker, staining patterns and cellular distribution were evaluated by experienced observers, and relative abundance was assessed using a semiquantitative approach. Staining was recorded as present or absent and graded on a 0-3 scale when applicable (0=absent or background-level staining; 1=mild/focal staining; 2=moderate/multifocal staining; 3=dense/diffuse staining or organized aggregates). Scoring was performed separately for lining and sublining compartments when tissue orientation permitted. Immunophenotypic features were integrated with routine histopathological findings to support dominant pathotype assignment and to describe the synovial inflammatory microenvironment.

Antigen retrieval and staining were performed according to the manufacturer's recommendations. Appropriate positive and negative controls were included in each staining run. Immunostaining was evaluated by observers blinded to clinical data. To improve interobserver standardization, representative sections were reviewed in a calibration session before final classification, and ambiguous or borderline cases were re-reviewed jointly by rheumatology and pathology investigators. Discrepant interpretations were resolved by consensus.

Synovial Pathotype Classification

Based on integrated histological and immunohistochemical findings, synovial tissue samples were categorized into predefined pathotypes according to previously described classification frameworks.[7-9] The lympho-myeloid pathotype was defined by dense B-cell aggregates, lymphoid organization (ectopic lymphoid-like structures), or prominent infiltration by CD20-positive B cells and CD138-positive plasma cells. The diffuse-myeloid pathotype was characterized by dominant diffuse CD68-positive macrophage infiltration with limited lymphoid organization and absent or low CD20/CD138 staining. The pauci-immune/fibroid pathotype was characterized by marked stromal fibrosis, low inflammatory cell density, and minimal immune cell marker expression. A separate mixed category was not used for quantitative reporting. Samples with overlapping features with no clearly dominant pattern, limited tissue or IHC quality, or inadequate histological evidence of synovial tissue were classified as unclassifiable or insufficient for pathotype analysis.

EULAR Reporting Standards and Quality Control

The study adhered to the EULAR points to consider for minimal reporting requirements in synovial tissue research. Key methodological aspects were systematically documented, including ultrasound guidance, rationale for joint selection, number of tissue fragments targeted, fixation and processing procedures, scoring systems, and immunohistochemical markers. To minimize interobserver variability, representative sections were reviewed jointly by rheumatologists and pathologists experienced in synovial tissue evaluation, and discrepant cases were resolved by consensus.[5]

Patient-reported Outcome Measures and Pain-related Assessments

Validated patient-reported outcome measures and pain-related assessments were analyzed descriptively to capture patient-centered disease impact. Functional status was evaluated using the Health Assessment Questionnaire (HAQ), which ranges from 0 to 3, with higher scores indicating greater functional impairment.[12] Neuropathic pain-related symptom burden was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, which ranges from 0 to 24.[13] Central sensitization-related symptom burden was evaluated using the Central Sensitization Inventory-9 (CSI-9) short form.[14,15] Patient global assessment, physician global assessment, and fatigue severity were recorded using 0-100 mm visual analogue scales, with higher scores reflecting greater perceived disease activity or symptom burden.[16] These measures were not used for formal pathotype-related inference.

Diagnostic Contribution and Management-relevant Outcomes

Diagnostic contribution was operationally defined as biopsy-supported diagnostic reclassification or the identification of a clinically actionable alternative etiology beyond routine clinical, laboratory, and imaging assessments. Management-relevant biopsy contribution was considered present when tissue-based evaluation supported infection-directed investigation or treatment, reduced the likelihood of inappropriate immunosuppressive escalation, or refined the differential diagnosis toward degenerative, crystal-related, systemic inflammatory, or structural synovial disease. The term "biopsy contribution" was used to indicate support for the final diagnostic interpretation after multidisciplinary integration; it was not used to imply that all diagnoses were established by histology alone. Longitudinal treatment-response prediction was not analyzed because medication-response data were not systematically collected.

Statistical Analysis

Normality of continuous variables was assessed visually and, where appropriate, using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for approximately normally distributed variables and as median with interquartile range (IQR) for skewed variables; categorical variables were presented as number and percentage. Krenn synovitis scores were summarized for histologically adequate specimens only. LANSS and CSI-9 scores were analyzed as continuous variables and summarized descriptively. Because of the modest sample size, uneven distribution of pathotypes, and 9 unclassifiable or insufficient cases, formal inferential comparisons between synovial pathotypes and clinical variables were not performed. Relationships between pathotype, serological findings, inflammatory markers, ultrasonographic activity, and PROMs were interpreted descriptively and as hypothesis-generating. Statistical analyses were performed using SPSS version 25.0 (IBM Corp.).

Results

Baseline Characteristics of the Study Population

A total of 53 patients undergoing USGSB were included in the biopsy cohort. The mean age was 47.7±13.6 years. Women constituted the majority of the study population, with 34 women (64.2%) and 19 men (35.8%). The mean body mass index was 28.0±6.8 kg/m^2. Baseline demographic and clinical characteristics are summarized in Table 1.

Comorbidity Profile and Analytical Denominators

Comorbid conditions were frequently observed among the study participants. Hypertension was the most prevalent comorbidity (14/53, 26.4%), followed by diabetes mellitus (9/53, 17.0%), thyroid disorders (6/53, 11.3%), and chronic lung disease (4/53, 7.5%). No patient had a documented history of malignancy at the time of synovial biopsy. Final diagnostic attribution was available for 51 of 53 patients. Histologically adequate synovial tissue for Krenn scoring was available in 50 of 53 specimens; the remaining 3 specimens did not meet adequacy criteria. Definitive pathotype classification could be assigned in 44 of 53 cases after the integration of histology and IHC. Thus, final diagnosis, Krenn scoring, procedural adequacy, and pathotype classification were analyzed using their respective denominators.

Final Diagnostic Distribution and Biopsy-supported Diagnostic Contribution

Following synovial biopsy, a wide spectrum of final diagnoses was identified (Figure 1). Final diagnoses were available for 51 patients, while final diagnostic attribution was missing for two patients, who were excluded from the diagnostic distribution analysis. Overall, inflammatory arthritis remained the predominant diagnostic category, identified in 39 of 51 patients (76.5%). Within this group, rheumatoid arthritis (RA) was the most frequent diagnosis (25/51, 49.0%), and two additional patients were classified as having RA with overlap features (RA with antisynthetase syndrome, n=1; RA with suspected immunoglobulin G4-related disease, n=1). Other inflammatory arthritis diagnoses included spondyloarthritis (5/51, 9.8%), psoriatic arthritis (3/51, 5.9%), juvenile idiopathic arthritis (2/51, 3.9%), and undifferentiated/inflammatory arthritis (2/51, 3.9%).

Table 1. Baseline characteristics of the study population

Characteristics	Mean ± SD or n (%)
Age, years	47.7±13.6
Female sex	34 (64.2)
Male sex	19 (35.8)
Body mass index, kg/m^2	28.0±6.8
Hypertension	14 (26.4)
Diabetes mellitus	9 (17.0)
Thyroid disorders	6 (11.3)
Chronic lung disease	4 (7.5)
History of malignancy	0 (0)

SD: Standard deviation

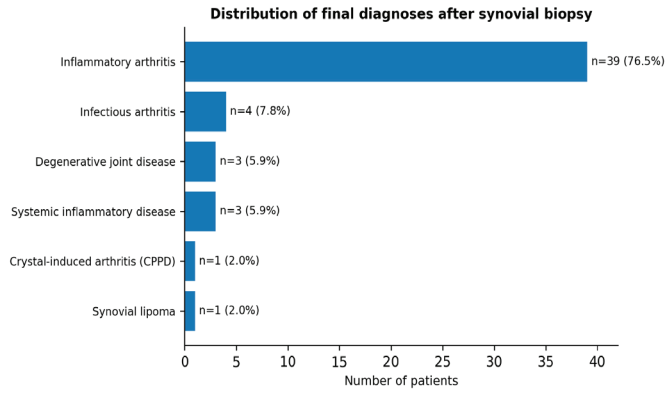

Figure 1. Distribution of final diagnoses following ultrasound-guided synovial biopsy. Final diagnostic attribution was available for 51 patients. Inflammatory arthritis constituted the predominant diagnostic category. Alternative etiologies included infectious arthritis, degenerative joint disease, systemic inflammatory diseases, crystal-induced arthritis, and synovial lipoma

A biopsy-supported diagnostic contribution was identified in 12 of 51 patients (23.5%). These cases included infectious arthritis in 4/51 patients (7.8%; septic arthritis, n=1; tuberculous arthritis, n=1; fungal arthritis, n=2), degenerative joint disease in 3/51 patients (5.9%), systemic inflammatory diseases in 3/51 patients (5.9%; Behçet disease, familial Mediterranean fever, and connective tissue disease; each n=1), crystal-induced arthritis in 1/51 patient (2.0%), and synovial lipoma in 1/51 patient (2.0%). In these patients, tissue-based evaluation contributed to the final diagnostic interpretation after integration with clinical, laboratory, imaging, and microbiological data. The alternative diagnoses, biopsy-supported diagnostic contributions, and management-relevant implications are summarized in Table 6. Therefore, the findings should be interpreted as diagnostic and management-relevant observations rather than evidence of longitudinal treatment-response benefit.

Laboratory, Serological, and Patient-reported Measures

Laboratory and serological findings are summarized in Table 2. The mean white blood cell count was 8.77±2.30 ×10^9/L, hemoglobin level was 12.78±2.49 g/dL, and platelet count was 321.69±102.36 ×10^9/L. The median erythrocyte sedimentation rate and C-reactive protein levels were 17.0 mm/h (IQR 9.75-24.25) and 7.5 mg/L (IQR 1.97-17.27), respectively. Rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies were positive in 18/53 (34.0%) and 17/53 (32.1%) patients, respectively, while antinuclear antibodies were detected in 15/53 (28.3%) patients.

Patient-reported outcome measures and pain-related assessments are summarized descriptively in Table 3. These variables were retained to describe the clinical burden of the

cohort but were not used to draw formal pathotype-related conclusions. The HAQ score indicated mild-to-moderate functional impairment. LANSS, CSI-9, global assessment, and fatigue scores suggested a substantial symptom burden in the available dataset.

Ultrasonographic Findings and Biopsy Sites

Ultrasonographic findings are summarized in Table 4. The mean GS synovitis score was 2.04±0.62, indicating moderate to severe synovial hypertrophy in most patients selected for biopsy. The mean joint effusion score was 1.89±0.78, and the mean PD score was 1.08±0.92, reflecting heterogeneous inflammatory activity across the cohort.

Synovial biopsies were performed across a broad range of joints, reflecting heterogeneous clinical involvement patterns (Figure 2). The knee was the most commonly sampled joint (27/53, 50.9%), followed by the wrist (12/53, 22.6%), ankle (5/53, 9.4%), elbow (3/53, 5.7%), small joints (3/53, 5.7%), shoulder (2/53, 3.8%), and hip (1/53, 1.9%).

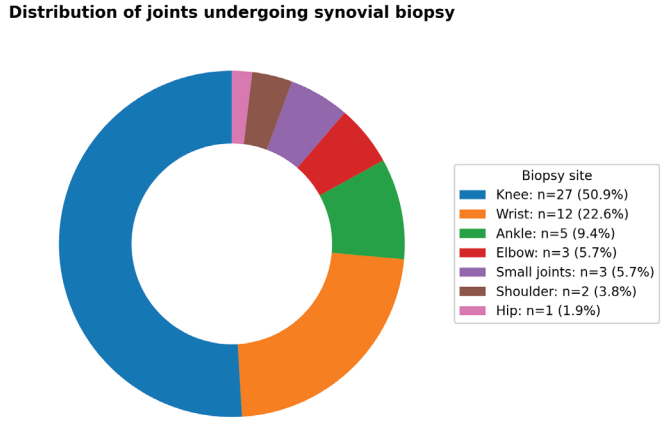

Figure 2. Distribution of joints undergoing synovial biopsy. Values are reported as patient-level biopsy sites in the total biopsy cohort (n=53)

Table 2. Laboratory and serological characteristics of the study population

Hematological and inflammatory parameters	Mean ± SD or median (IQR)
White blood cell count (×10⁹/L)	8.77±2.30
Hemoglobin (g/dL)	12.78±2.49
Platelet count (×10⁹/L)	321.69±102.36
Erythrocyte sedimentation rate (mm/h)	17.0 (9.75-24.25)
C-reactive protein (mg/L)	7.5 (1.97-17.27)
Rheumatoid factor positivity	18 (34.0)
RF titer	35.0 (15.5-59.8)
Anti-CCP positivity	17 (32.1)
Anti-CCP titer	144.0 (89.2-214.2)
Antinuclear antibody positivity	15 (28.3)

CCP: Cyclic citrullinated peptide, IQR: Interquartile range, RF: Rheumatoid factor, SD: Standard deviation

Histopathological and Immunohistochemical Findings

Histopathological evaluation demonstrated variable degrees of synovial inflammatory activity (Table 5). Krenn scoring was performed only on histologically adequate specimens (n=50). The mean synovial lining layer thickness score was 1.92±0.71, the mean sublining stromal cellularity score was 1.84±0.68, and the mean inflammatory infiltrate density score was 2.01±0.74. The mean total Krenn synovitis score was 5.77±1.86. High-grade synovitis (score ≥5) was observed in 34/50 assessable specimens (68.0%), while 16/50 (32.0%) showed low-grade synovitis. Three specimens did not meet histological adequacy criteria for Krenn scoring.

Krenn scoring was performed only in histologically adequate specimens (n=50). Three specimens lacked adequate synovial tissue and were therefore not included in Krenn-grade percentage calculations.

Immunohistochemical analysis demonstrated prominent macrophage and T-cell infiltration. CD68-positive macrophages were detected in 48/53 cases (90.6%) and represented the

Table 3. Patient-reported outcomes and pain-related assessments

Parameter	Mean ± SD
HAQ	0.92±0.74
LANSS total score (0-24)	14.6±4.5
CSI-9 score	19.48±0.44
VAS patient global assessment (0-100)	64.34±21.10
VAS physician global assessment (0-100)	52.64±21.50
VAS fatigue (0-100)	65.28±26.65

Higher scores indicate greater disability or symptom burden. These outcomes were analyzed descriptively
CSI-9: Central Sensitization Inventory-9, HAQ: Health Assessment Questionnaire, LANSS: Leeds assessment of neuropathic symptoms and signs, SD: Standard deviation, VAS: Visual analogue scale

Table 4. Ultrasonographic findings of the study population

Ultrasonographic parameter	Mean ± SD
Gray-scale synovitis score (0-3)	2.04±0.62
Joint effusion score (0-3)	1.89±0.78
Power Doppler score (0-3)	1.08±0.92

SD: Standard deviation

Table 5. Histopathological characteristics of synovial biopsies

Histopathological parameter	Mean ± SD or n/N (%)
Synovial lining layer thickness (0-3), mean ± SD	1.92±0.71
Sublining stromal cellularity (0-3), mean ± SD	1.84±0.68
Inflammatory infiltrate density (0-3), mean ± SD	2.01±0.74
Total Krenn synovitis score (0-9), mean ± SD	5.77±1.86
High-grade synovitis (score ≥5), n/N (%)	34/50 (68.0)
Low-grade synovitis (score 2-4), n/N (%)	16/50 (32.0)
Not assessable for Krenn scoring	3/53 (5.7)

SD: Standard deviation

dominant immune cell population. CD3-positive T lymphocytes were observed in 42/53 patients (79.2%), frequently located in the sublining and perivascular regions. CD20-positive B-cell infiltration was present in 26/53 patients (49.1%), and CD138-positive plasma cells were identified in 21/53 patients (39.6%). CD31 positivity, reflecting vascular/endothelial structures, was observed in 37/53 patients (69.8%). CD34 and CD38 were not included in the final quantitative marker analysis.

Diagnostic and Procedural Contribution

Safety outcomes were assessed retrospectively from procedure and follow-up records. Very mild or delayed symptoms may have been under-recorded because of the retrospective design. Procedural adequacy, feasibility, and safety outcomes are summarized in Table 7. No major procedure-related complication, bleeding event, infection, neurovascular injury, hospitalization, or repeat biopsy due to an adverse event was documented.

Synovial Pathotype Distribution

Based on combined histological and immunophenotypic features, 44/53 cases (83.0%) were classifiable into predefined synovial pathotypes (Table 8). Percentages were reported using the total biopsy cohort (n=53) as the primary denominator, and the classifiable denominator (n=44) was also provided to aid interpretation. The lympho-myeloid pathotype was the most frequent, identified in 25/53 patients (47.2%; 25/44, 56.8% of classifiable cases), followed by diffuse-myeloid synovitis in 10/53 patients (18.9%; 10/44, 22.7%), and pauci-immune/fibroid synovitis in 9/53 patients (17.0%; 9/44, 20.5%). Nine cases (17.0%) were unclassifiable or insufficient: three specimens did not meet histological criteria for adequate synovial tissue, and 6 had limited tissue or IHC quality or overlapping non-dominant features.

The primary denominator for percentages is the total biopsy cohort (n=53); percentages among classifiable cases use n=44. Unclassifiable or insufficient cases were excluded from definitive pathotype-specific interpretation.

Pathotype-stratified immunophenotypic analysis demonstrated distinct cellular compositions among synovial tissue subtypes. Lympho-myeloid synovitis showed higher expression of B-cell and plasma-cell markers, including CD20 and CD138, whereas diffuse-myeloid synovitis was characterized by predominant infiltration of CD68-positive macrophages. Pauci-immune/fibroid synovitis exhibited low expression of immune cell markers. Because of small subgroup sizes and the unavailability of definitive pathotype assignment in 9 cases, formal inferential comparisons were not performed; these findings are presented descriptively and as hypothesis-generating. The revised heatmap includes only markers specified in the final IHC panel (Figure 3).

Collectively, these findings demonstrate substantial heterogeneity in clinical characteristics, ultrasonographic activity, serological profiles, and synovial tissue immunophenotypes among patients undergoing synovial biopsy. However, because the study was cross-sectional and did not include longitudinal

Table 6. Alternative diagnoses and biopsy-supported diagnostic contribution

Final diagnostic category	n/51 (%)	How biopsy contributed to the diagnostic work-up	Management-relevant implication
Infectious arthritis: septic arthritis, tuberculous arthritis, fungal arthritis	4 (7.8)	Tissue-based evaluation supported an infectious differential and prompted or complemented infection-directed microbiological work-up after integration with clinical data	Supported antimicrobial or infection-directed management and reduced the risk of inappropriate immunosuppressive escalation
Degenerative joint disease	3 (5.9)	Histological and clinical-radiological integration favored a non-primary inflammatory explanation for synovitis-like symptoms	Reduced the risk of over-classifying degenerative presentations as active inflammatory arthritis
Systemic inflammatory diseases: Behcet disease, familial Mediterranean fever, connective tissue disease	3 (5.9)	Biopsy findings did not establish these diagnoses alone but contributed to exclusion/refinement of competing etiologies in a multidisciplinary diagnostic assessment	Supported extension of the differential diagnosis beyond primary inflammatory arthritis
Crystal-induced arthritis (gout, CPPD, etc.)	1 (2.0)	Tissue-based evaluation contributed to recognition of a crystal-associated inflammatory process in the final integrated diagnosis	Supported crystal-focused management rather than escalation for seronegative inflammatory arthritis alone
Synovial lipoma	1 (2.0)	Tissue morphology supported a structural/non-inflammatory synovial lesion	Redirected the diagnostic interpretation toward a structural synovial disorder
Total biopsy-supported alternative etiology or diagnostic reclassification	12 (23.5)	Contribution was defined as support for final diagnostic interpretation after integration with clinical, laboratory, imaging, and microbiological data	Indicates diagnostic refinement, not longitudinal treatment-response benefit

The term biopsy-supported indicates contribution to the final diagnostic interpretation; it does not imply that all diagnoses were established by histology alone
CPPD: Calcium pyrophosphate deposition disease

treatment-response data, tissue-based findings should be interpreted as supporting diagnostic refinement and biological characterization rather than proving biopsy-guided treatment selection.

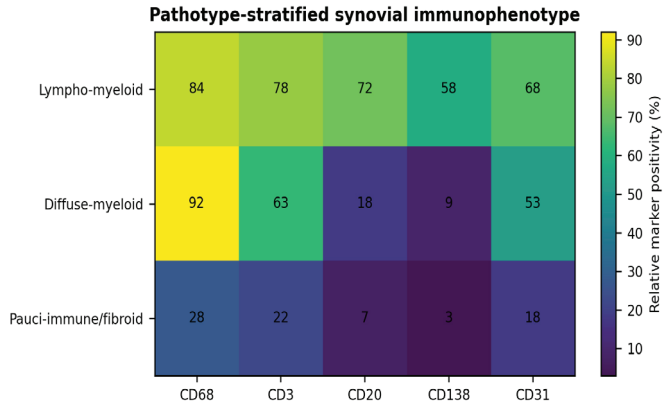

Figure 3. Synovial tissue immunophenotyping and pathotype-specific immune signatures. Values represent descriptive relative marker positivity (%) and are used to visualize pathotype-specific immune-cell patterns. CD38 was removed from the heatmap to maintain consistency with the final immunohistochemical panel. Formal statistical comparisons were not performed

Discussion

In this single-center real-world cohort, USGSB provided clinically useful diagnostic refinement and synovial tissue-level characterization in patients evaluated for suspected inflammatory arthritis. The principal finding was that biopsy-supported evaluation contributed to the final diagnostic interpretation for approximately one-quarter of patients for whom final diagnoses were available. This contribution was most evident in cases ultimately attributed to infectious, degenerative, crystal-related, systemic inflammatory, or structural synovial diseases. The study demonstrated substantial heterogeneity in synovial inflammation within routine tertiary rheumatology practice, identifying macrophage-dominant, lympho-myeloid, and pauci-immune/fibroid patterns.

The novelty of the present study lies less in describing synovial pathotypes themselves, which have been reported previously, and more in showing how tissue sampling functions in a routine care population characterized by diagnostic uncertainty, seronegativity, atypical presentations, and monoarticular or oligoarticular involvement. In such scenarios, synovial biopsy should be considered a complementary diagnostic tool rather than a replacement for clinical reasoning. Our data suggest that its greatest immediate value lies in refining the differential diagnosis and providing tissue-level information that cannot

Table 7. Procedural adequacy, feasibility, and safety outcomes

Indicator	n/N(%)	Interpretation
Final diagnostic attribution available	51/53 (96.2)	Most patients had a final diagnostic classification after biopsy-based evaluation
Alternative etiology or diagnostic reclassification	12/51 (23.5)	Biopsy-supported evaluation provided added diagnostic value beyond routine assessment
Specimens not meeting histological criteria for adequate synovial tissue	3/53 (5.7)	Retained in feasibility/safety analyses and included within the unclassifiable/insufficient pathotype category
Targeted tissue fragments per procedure	Minimum 6-8 cores	Adequacy-oriented sampling protocol was used to reduce sampling error
Definitive pathotype classification	44/53 (83.0)	Sufficient tissue and IHC quality were obtained for definitive pathotype assignment in most cases
Any recorded minor adverse event	18/53 (34.0)	All recorded events were minor and self-limited; no event required hospitalization or invasive intervention
Self-limited post-biopsy pain	17/53 (32.1)	Most frequent minor event; managed conservatively
Vasovagal reaction/transient sensory symptom	1/53 (1.9) / 1/53 (1.9)	Transient events; event counts are not necessarily additive at patient level
Bleeding-related complication	0/53 (0)	No ecchymosis, hemarthrosis, or bleeding event requiring medical intervention was documented
Infection, thrombophlebitis/DVT, or neurovascular/tendon injury	0/53 (0)	No skin/joint infection, thrombophlebitis, deep venous thrombosis, neurovascular injury, or tendon/ligament/muscle injury was documented
Major procedure-related complications	0/53 (0)	No infection, hemarthrosis requiring intervention, neurovascular injury, hospitalization, or invasive treatment was documented
Repeat biopsy because of a procedure-related adverse event	0/53 (0)	No repeat biopsy attributable to a procedural adverse event was documented in the available records

DVT: Deep venous thrombosis, IHC: Immunohistochemistry

Table 8. Synovial pathotype distribution and operational criteria			
Pathotype	**n (%)**	**Operational criteria used for classification**	**Interpretive comment**
Lympho-myeloid	25/53 (47.2); 25/44 (56.8 of classifiable cases)	Dense B-cell aggregates, lymphoid organization/ectopic lymphoid-like structures, or prominent CD20-positive B cells and CD138-positive plasma cells	Adaptive immune-rich inflammatory pattern
Diffuse-myeloid	10/53 (18.9); 10/44 (22.7 of classifiable cases)	Dominant diffuse CD68-positive macrophage infiltration with limited lymphoid organization and low/absent CD20 or CD138 staining	Macrophage/innate immune-dominant pattern
Pauci-immune/fibroid	9/53 (17.0); 9/44 (20.5 of classifiable cases)	Marked stromal fibrosis, low inflammatory-cell density, and minimal immune-cell marker expression	Low-inflammatory or remodeling-dominant pattern
Unclassifiable/insufficient	9/53 (17.0)	Three specimens did not meet histological criteria for adequate synovial tissue; six had limited tissue/IHC quality or overlapping features without a clearly dominant pattern	Excluded from definitive pathotype-specific interpretation A separate mixed category was not used for quantitative reporting

be fully captured by peripheral blood biomarkers, imaging, or clinical scoring systems alone.

The observed distribution of immune-cell markers is consistent with previous work showing that synovial inflammation is biologically heterogeneous.[7,17,18] CD68-positive macrophages were the most frequent cellular component, whereas CD3-positive T-cells, CD20-positive B-cells, and CD138-positive plasma cells showed variable involvement. These patterns support the concept that inflammatory arthritis encompasses distinct tissue microenvironments rather than a single uniform pathological process. Nevertheless, the present study was not designed to test treatment-response prediction, and the findings should not be interpreted as evidence for biopsy-guided therapeutic selection.

The lympho-myeloid pathotype was the most common classifiable pattern in our cohort. This pattern has been associated in previous studies with adaptive immune activation, B-cell aggregates, plasma-cell infiltration, and ectopic lymphoid-like organization.[7,17,18] Diffuse-myeloid synovitis, in contrast, reflects macrophage-rich innate immune activation, whereas pauci-immune/fibroid synovitis reflects low-inflammatory or remodeling-dominant tissue features.[7,19] Our findings demonstrate that these patterns are identifiable using conventional histology and IHC in a real-world setting, although their clinical implications require prospective validation.

Serological findings further highlight the limitations of relying solely on peripheral markers. A substantial proportion of patients were seronegative for rheumatoid factor and anti-CCP antibodies, which is expected in undifferentiated, atypical, or early inflammatory arthritis populations.[20] Prior studies have shown that synovial immune phenotypes may diverge from circulating autoantibody status, with lymphoid or plasma-cell-rich infiltrates detectable even in seronegative individuals.[7,19] Thus, tissue-level assessment may add information when serology is non-informative, particularly in selected patients with persistent diagnostic uncertainty.

Patient-reported measures showed a meaningful symptom burden, including functional impairment, fatigue, and pain-related symptoms. These variables were analyzed descriptively and were not used to infer pathotype-specific associations. Their inclusion emphasizes that clinical disease expression is multidimensional: pain, fatigue, disability, synovial inflammation, and imaging activity may not always move in parallel.[21,22] Future studies with larger cohorts should evaluate whether tissue phenotypes relate to pain mechanisms or patient-reported outcomes after controlling for inflammatory activity and comorbidity.

A clinically important aspect of synovial biopsy is its contribution to the differential diagnosis of infectious and non-inflammatory joint disorders. Chronic monoarthritis and oligoarthritis can be diagnostically challenging, particularly when systemic inflammatory markers are modest or synovial fluid studies are inconclusive. Previous studies have demonstrated that synovial tissue examination may support recognition of granulomatous inflammation, crystal-associated disease, amyloid deposition, occult infection, or structural synovial lesions.[23-26] In our cohort, tissue-based evaluation contributed to the work-up of septic, tuberculous, and fungal arthritis cases after integration with clinical and microbiological data. This finding is clinically relevant because delayed recognition of infection may expose patients to inappropriate immunosuppression, whereas early tissue-based investigation may redirect management.

The safety profile observed in this cohort was acceptable. No major procedure-related complications, bleeding events requiring intervention, joint or skin infections, neurovascular injuries, hospitalizations, or repeat biopsies due to adverse events were documented. Minor self-limited events, mostly transient post-biopsy pain, were relatively common but were managed conservatively. Because safety outcomes were assessed retrospectively, very mild or delayed symptoms may have been under-recorded. Nonetheless, the findings are in keeping with

previous reports that USGSB is feasible and generally well tolerated when performed by trained operators.[2,4,11,27,28]

Study Limitations

Several limitations should be acknowledged. First, the study was retrospective and single-center, with a moderate sample size, thereby limiting generalizability. Second, the final diagnostic attribution was unavailable for two patients, and three specimens were histologically inadequate for Krenn scoring. Third, although 44 cases were classifiable by pathotype, subgroup sizes were small, and formal inferential comparisons were intentionally avoided. Fourth, detailed medication changes and longitudinal treatment-response outcomes were not systematically collected, precluding any conclusions about the prediction of therapeutic response. Fifth, molecular analyses, such as transcriptomics, spatial profiling, and single-cell technologies, were not performed. Finally, because the diagnostic contribution was defined pragmatically after multidisciplinary integration, biopsy should be interpreted as supporting, rather than independently establishing, all final diagnoses.

Future multicenter prospective studies should integrate standardized synovial histology, IHC, high-dimensional molecular profiling, predefined diagnostic endpoints, and longitudinal treatment-response outcomes. Such designs will be necessary to determine whether biopsy-based phenotyping can move beyond diagnostic refinement toward validated therapeutic stratification in inflammatory arthritis.

Conclusion

The findings of this study have practical implications for tertiary rheumatology care. First, USGSB can provide objective tissue-level characterization of synovial inflammation in selected patients with persistent diagnostic uncertainty. Second, biopsy-supported evaluation may refine the differential diagnosis in seronegative, undifferentiated, monoarticular, oligoarticular, atypical, or treatment-refractory arthritis. Third, integration of synovial pathology with ultrasonographic, serological, microbiological, and clinical data offers a multidimensional diagnostic framework. However, its role in treatment selection remains investigational and should not be overstated without prospective outcome-driven validation.

Taken together, our results support the selective incorporation of ultrasound-guided synovial biopsy into tertiary rheumatology practice as a feasible and biologically informative procedure when diagnostic uncertainty persists after standard evaluation. The present findings should be viewed as real-world evidence for diagnostic refinement and immunophenotypic characterization, whereas biopsy-based personalized treatment strategies require prospective validation.

Ethics

Ethics Committee Approval: The study protocol for retrospective data analysis was approved by the University of Health Sciences Türkiye, Ankara Etlik City Hospital Clinical Research Ethics Committee (approval no: AEŞH-BADEK2-2026-150, date: 10.02.2026), and all procedures were performed in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent for the biopsy procedure was obtained from all participants before tissue sampling.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.Ç.Y., H.A., H.Ü., G.E.T.K., Concept: G.Ç.Y., H.A., Design: G.Ç.Y., H.A., M.P., C.Ö., E.B.D., Data Collection and Processing: G.Ç.Y., H.A., E.B.D., M.İ.B., Analysis or Interpretation: H.A., A.S., S.C.S., E.G.A.G., E.B.D., Literature Search: G.Ç.Y., Writing: G.Ç.Y., H.A., M.P., C.Ö.

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