Refining synovial inflammation assessment: A modified General Synovitis Score for active rheumatoid arthritis

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Abstract. The General Synovitis Score (GSS) is a well-established method for scoring synovial inflammation. Despite its widespread use, the GSS does not fully capture the inflammatory manifestations characteristic of the synovium in rheumatoid arthritis (RA). To address this limitation, the modified GSS (mGSS) was developed. The present study compared the correlation of the mGSS and the GSS with clinical disease activity. The aim was to provide a more precise histopathological scoring system based on hematoxylin and eosin (H&E) staining for assessing synovial inflammation in patients with active RA. In this cross-sectional study, synovial tissues were obtained from 60 patients with RA using a novel synovial biopsy device. Sections from synovial tissues were stained with H&E, and were assessed using the GSS and the mGSS. Neovascularization was observed in 56 patients (93.3%) and was significantly correlated with disease activity score in 28 joints-C-reactive protein (DAS28-CRP) (ρ=0.49; P<0.001), erythrocyte sedimentation rate (ESR) (ρ=0.44; P<0.001) and CRP (ρ=0.51; P<0.001). In addition, patients with severe neovascularization had significantly higher DAS28-CRP, ESR and CRP levels than those with mild-to-moderate neovascularization (P<0.05). Synoviocyte detachment, which occurred in nine patients (15.0%), was associated with higher DAS28-CRP, ESR and CRP levels than in the patients with synoviocyte proliferation (P<0.05). Furthermore, the mGSS was more strongly correlated with DAS28-CRP (ρ=0.62; P<0.001) than the GSS (ρ=0.37; P=0.003). These findings indicated that neovascularization and synoviocyte detachment, which are critical yet often overlooked aspects in the traditional GSS, are important in RA. Incorporating these elements into the mGSS may enhance the assessment of disease activity, providing a more precise and accurate evaluation of the synovial histopathology in patients with RA.

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Abbreviations: RA, rheumatoid arthritis; GSS, General Synovitis Score; mGSS, modified General Synovitis Score; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibody; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TJC-28, Tender 28-Joint Count; SJC-28, Swollen 28-Joint Count; PGA, patient global assessment; DAS28-CRP, disease activity score in 28 joints-C-reactive protein

Key words: RA, synovial histopathology, GSS, neovascularization

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that significantly impacts global health and affects ~1% of the population (1). This disease is characterized by persistent synovitis, which progressively destroys joint structures and results in substantial loss of function. Effective management of synovitis, the primary pathological manifestation of RA, is crucial for preventing joint erosion and mitigating disability in patients (2).

Histopathological examination of synovial biopsies remains the most direct method of assessing the severity of synovitis. The General Synovitis Score (GSS) is a widely used literature-supported method for scoring synovial inflammation based on histopathological changes observed in the synovium with hematoxylin and eosin (H&E) staining (3). It primarily evaluates three aspects: Synovial hyperplasia, stromal activation and inflammatory infiltration. Each aspect is semi-quantitatively scored from 0-3, with a total score >4 indicating inflammatory arthritis. Previous studies have confirmed a definite correlation between the GSS and the activity level of RA (4,5).

Studies of the histopathological features of the synovium in patients with RA have consistently found that the synovium exhibits characteristic features, including synovial hyperplasia, stromal activation, inflammatory infiltration, neovascularization and ectopic lymphoid neogenesis (6-8). However, the GSS

omits one of the most crucial histopathological features of the RA synovium: Neovascularization. This omission may result in the GSS failing to fully capture the inflammatory characteristics of the RA synovium.

Observations at the Rheumatology and Immunology Department of the First Affiliated Hospital of Nanchang University (Nanchang, China) on RA synovial pathology have revealed that most patients exhibit varying degrees of neovascularization. Although synovial hyperplasia is widely acknowledged as a hallmark pathological change in almost all RA cases (8,9), some patients with RA exhibit thinning of the synovial lining, a decrease in the number of synoviocytes, loosening of the arrangement, or even complete synovial disappearance. This phenomenon is referred to as synoviocyte detachment. Patients with synoviocyte detachment typically have high levels of inflammatory markers, indicating increased disease activity (10). In such cases, the GSS often fails to accurately reflect disease activity. For example, in the present study, one RA patient with moderate to severe disease activity had a GSS of only 1 (Fig. 1).

To address this problem, the present study added neovascularization and synoviocyte detachment to the GSS items, resulting in an enhanced scoring system: The modified GSS (mGSS). This system semi-quantitatively assesses five key aspects of RA synovitis: Synovial hyperplasia, synoviocyte detachment, stromal activation, inflammatory infiltration and neovascularization (Fig. 2).

The present cross-sectional study was conducted to demonstrate the efficacy and reliability of the mGSS in assessing RA synovitis. The present study investigated the association of synovial neovascularization and synoviocyte detachment with disease activity in patients with RA and compared the correlations of the GSS and the mGSS with clinical disease activity.

Patients and methods

Patients. Between March 2023 and December 2023, 60 patients diagnosed with RA who underwent synovial biopsy at the Rheumatology and Immunology Department of The First Affiliated Hospital of Nanchang University (Nanchang, China) were enrolled. All patients met the 2010 American College of Rheumatology/European Alliance of Associations for Rheumatism diagnostic criteria for RA (11). The present study was approved by the Ethical Review Board of The First Affiliated Hospital of Nanchang University [ethics approval number IIT (2023); clinical ethics review no. 011]. Written informed consent was obtained from all patients before they underwent synovial biopsy. Clinical data, including sex, age, disease duration, medication history, anti-citrullinated protein antibody (ACPA), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Tender 28-Joint Count (TJC-28), Swollen 28-Joint Count (SJC-28) and patient global assessment (PGA) were collected (12). The disease activity score in 28 joints CRP (DAS28-CRP)=0.56 x TJC-28 + 0.28 x SJC-28+ 0.36 x ln (CRP + 1) + 0.014 x PGA + 0.96.

Synovial biopsy and tissue processing. A novel synovial biopsy device was used in the present study (Fig. 3). A negative-pressure device was attached to the synovial biopsy needle to assist in capturing synovial tissue. The needle biopsy process is illustrated in Fig. 4. The biopsy sites were distributed as follows: 45 knee joints (75.0%), nine wrist joints (15.0%), two elbow joints (3.3%) and four ankle joints (6.7%). A total of six fragmented synovial pieces, each measuring ~3x6 mm, were obtained from the joint of each patient. These samples were fixed in 10% formalin with 0.01 mol/l phosphate buffer at room temperature (20-25˚C) for 24 h. Fixed samples were dehydrated through a graded ethanol series, cleared in xylene and embedded in molten paraffin wax at 60˚C. The paraffin-embedded tissues were sectioned at a thickness of 4 μm. H&E staining of sections was performed and the samples were examined under light microscopy (objective lens 10x). The sections were stained with hematoxylin (1%) at room temperature (~25˚C) for 8 min, differentiated for 5 sec, blued for 30 sec and counterstained with eosin (1%) for 2 min at room temperature. The slides were independently reviewed by two experienced histopathologists and disagreements were referred for further evaluation by a senior specialist.

Histopathology assessment. Histopathological examination assessed synovial lining hyperplasia, stromal activation, inflammatory infiltration and neovascularization, with each aspect scored semi-quantitatively from 0-3. Synoviocyte detachment was scored as 4. The GSS includes synovial lining hyperplasia, stromal activation and inflammatory infiltration, with a total score ranging from 0-9. The mGSS incorporates synovial hyperplasia (0-3) or synoviocyte detachment (4), stromal activation (0-3), neovascularization (0-3) and inflammatory infiltration (0-3), resulting in a total score ranging from 0-13 (Fig. 2). Synovial hyperplasia, stromal activation and inflammatory infiltration were scored as per the GSS (13).

As for neovascularization, both Tak *et al* (14) and de Bois *et al* (15) assessed the severity of neovascularization by evaluating vascular density, using the number of blood vessels counted under high-power fields and defining thresholds at 3, 9, 16 and 22. Inspired by this methodology, the present study adopted a similar approach and found it effective. Specifically, neovascularization was scored based on the number of blood vessels in synovial tissue, using the following criteria: 0: 0-3; 1: 4-9; 2: 10-15; 3: ≥16 vessels per field under a 20x objective lens using light microscopy. For this scoring system, capillaries, venules and arterioles were equally weighted to ensure a comprehensive evaluation.

Statistical analysis. Statistical analyses were performed using SPSS 26.0 (IBM Corp.). The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous data are presented as the mean (standard deviation). Unpaired two-tailed Student's t-test was used to analyze the differences between two normally distributed groups. Categorical data such as sex are presented as the number of subjects (percentage). For comparisons between two groups, the Mann-Whitney U test was applied for non-normally distributed data. For comparisons involving more than two groups, one-way ANOVA was applied for normally distributed continuous data, followed by Bonferroni's post hoc test. For non-normally distributed data,

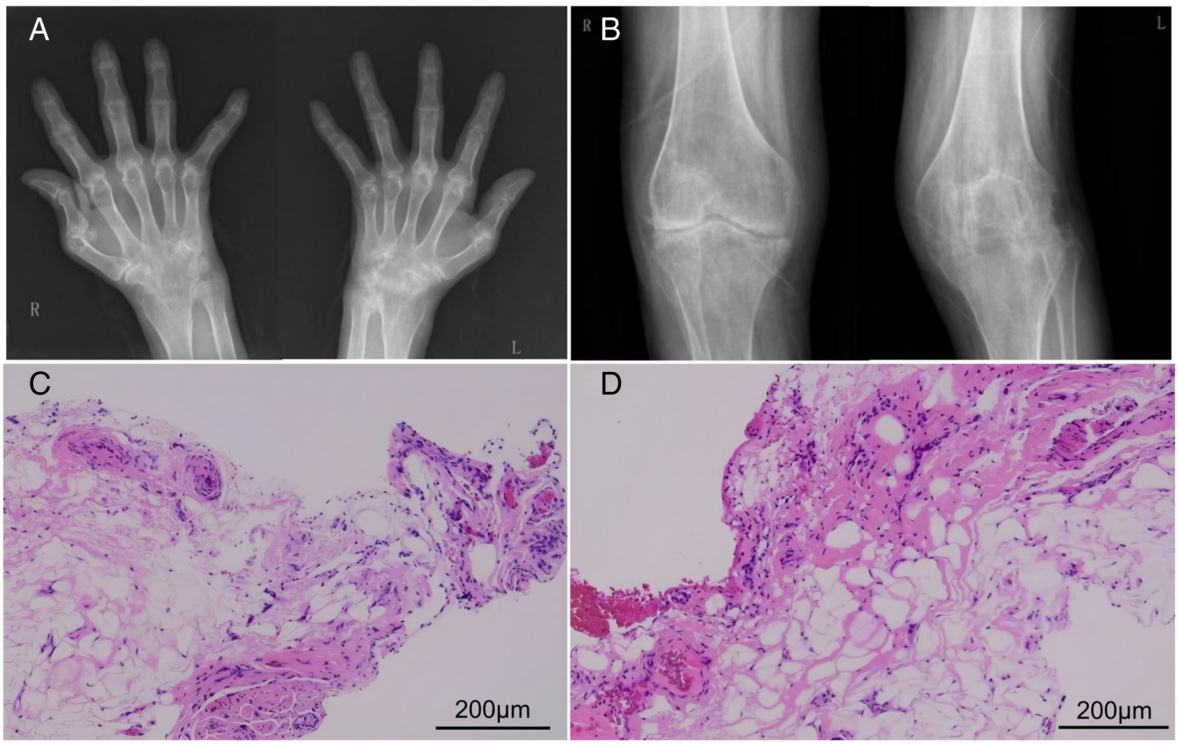

Figure 1. Synoviocyte detachment in a representative patient with RA. A 58-year-old female patient was diagnosed with active RA with an 18-year disease duration. The patient had an erythrocyte sedimentation rate of 98 mm/h, C-reactive protein of 78.12 mg/l and a high rheumatoid factor level. X-ray plain films show severe joint destruction in the (A) wrist and (B) knee. Hematoxylin and eosin staining of the synovium from the (C) wrist and (D) knee show synoviocyte detachment, thickening of the vascular walls, neovascularization and minimal lymphocyte infiltration. The disease activity score in 28 joints-C-reactive protein indicated moderate disease activity (4.68); however, the GSS was only 1, whereas the modified GSS was 8. RA, rheumatoid arthritis; GSS, General Synovitis Score.

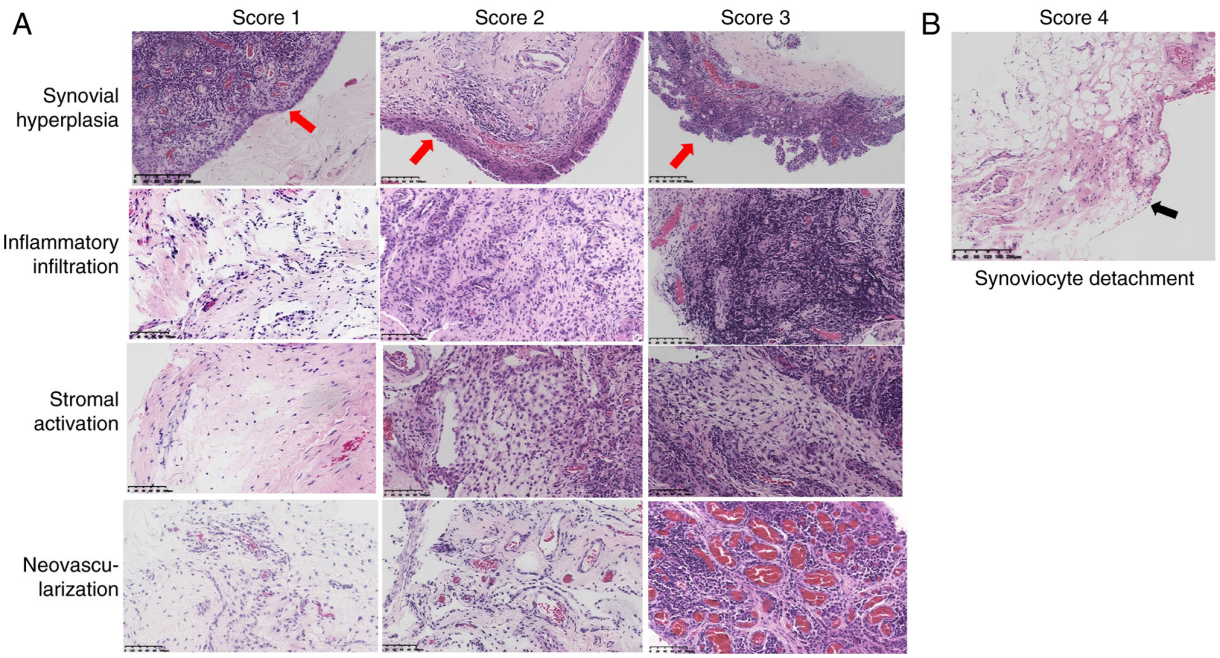

Figure 2. mGSS assessment was performed at x200 magnification using hematoxylin and eosin staining. (A) Synovial hyperplasia (red arrow), stromal activation, inflammatory infiltration and neovascularization are shown in order of increasing severity of the disease and are each scored semi-quantitatively from 0 to 3 based on severity. (B) Synoviocyte detachment (black arrow), was assigned a score of 4, if present. Combining the scores from A and B, the mGSS ranges from 0 to 13. mGSS, modified General Synovitis Score.

the Kruskal-Wallis test was used, with Dunn's post hoc test for multiple comparisons. Parametric data underwent correlation analyses using Spearman's correlation coefficient. $P<0.05$ was considered to indicate a statistically significant difference.

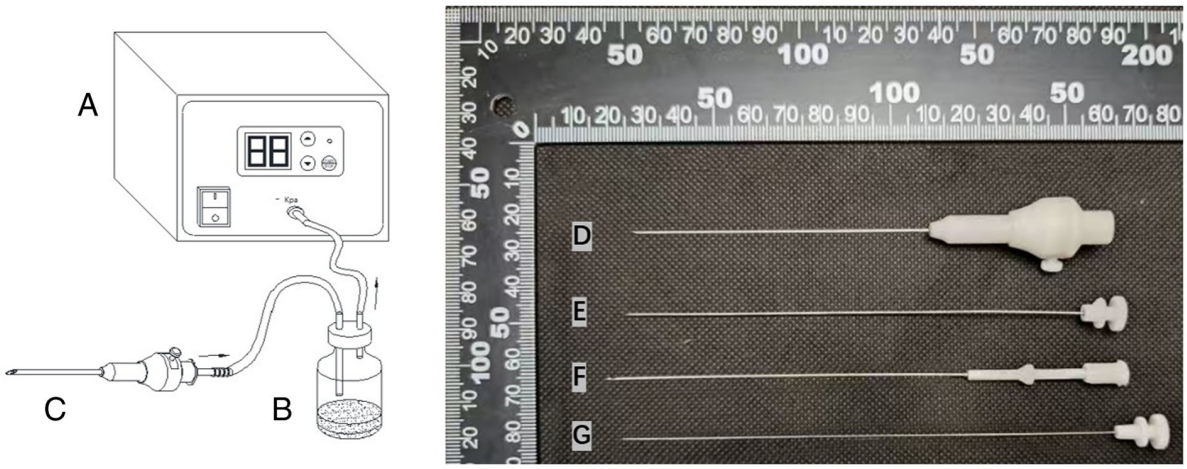

Figure 3. Structure of the novel synovial biopsy device. The novel synovial biopsy device mainly consists of (A) a negative pressure pump, (B) a negative pressure suction bottle and (C) a synovial biopsy needle. The components of the synovial biopsy needle include the (D) puncture sheath needle, (E) puncture inner core, (F) sampling needle and (G) sampling needle core.

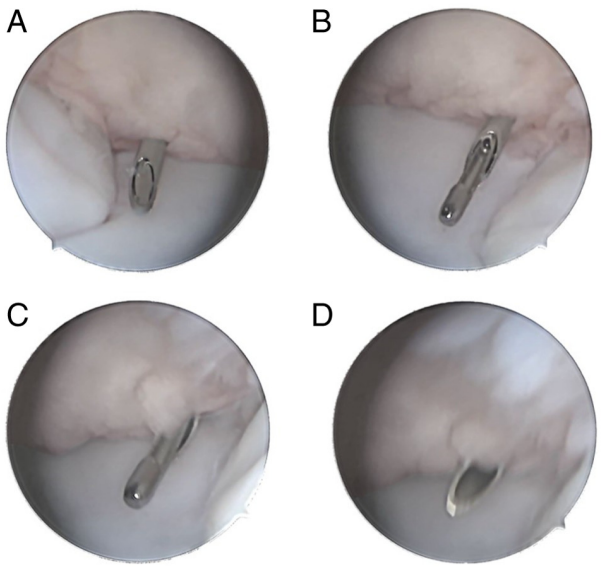

Figure 4. Procedure of the novel synovial biopsy device for tissue sampling of the joint. (A) First, a puncture inner core was inserted into the puncture sheath needle and the joint cavity was punctured. (B) Next, the inner core of the puncture was removed, the sample needle was inserted and the needle was secured in the rebound position. (C) The negative-pressure device was then connected and negative-pressure aspiration was performed. (D) Finally, the trigger was pressed, causing the sample needle to quickly rebound and the synovial tissue that has been aspirated into the sampling port was cut off.

Table I. Baseline characteristics of all patients.

Characteristic	All patients (n=60)
Age, years	53.9±11.3
Sex, female, n (%)	53 (88.3%)
Disease duration, months	97.6±84.9
ACPA positive, n (%)	38 (63.3)
RF positive, n (%)	45 (75.0)
ESR, mm/h	45.57±29.51
CRP, mg/l	34.96±35.13
TJC-28	5.33±3.74
SJC-28	4.93±3.73
PGA	66.22±11.54
DAS28-CRP	4.71±1.02

Data are presented as the mean ± standard deviation or n (%). ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TJC-28, Tender 28-Joint Count; SJC-28, Swollen 28-Joint Count; PGA, patient global assessment; DAS28-CRP, disease activity score in 28 joints-C-reactive protein.

Results

Demographic and disease characteristics of all patients. The baseline characteristics of the 60 patients enrolled in the present study are summarized in Table I. Among the patients, 53 (88.3%) were female, with a mean age of 53.9 years and a mean disease duration of 97.6 months. Serological tests indicated that 38 (63.3%) patients were ACPA-positive and 45 (75.0%) were RF-positive. The mean DAS28-CRP score was 4.71±1.02.

Correlation between synovial neovascularization and clinical activity in patients with RA. The synovial histopathology of the 56 patients with RA (93.3%) had varying degrees of neovascularization. Among these, 23 had mild neovascularization (score, 1), 16 had moderate neovascularization (score, 2) and 17 had severe neovascularization (score, 3) (Fig. 5A). Patients with severe neovascularization had significantly higher DAS28-CRP, ESR and CRP levels than those with mild or moderate neovascularization ($P<0.05$) (Fig. 5B, E and F). However, no significant statistical difference was observed in ACPA levels across the mild, moderate and severe neovascularization groups (Fig. 5C). The mean RF level in patients with severe neovascularization was higher than that in patients with moderate neovascularization ($P<0.05$; Fig. 5D). The severity of neovascularization was significantly correlated with DAS28-CRP, ESR and CRP levels (all $P<0.001$) with correlation coefficients of 0.49, 0.44 and 0.51, respectively (Table II).

Table II. Correlation between synovial neovascularization and disease activity indicators in patients with rheumatoid arthritis.

Neovascularization	ACPA, IU/ml	RF, IU/ml	ESR, mm/h	CRP, mg/l	DAS28-CRP
None (Score 0)	74.15 (0.58-309.50)	34.45 (11.63-76.15)	17.50 (4.50-46.25)	5.73 (2.03-14.47)	3.90±1.10
Mild (Score 1)	35.90 (12.0-306.83)	73.55 (37.50-230.16)	30.00 (17.00-65.00)	16.85 (5.73-29.46)	4.40±0.78
Moderate (Score 2)	7.78 (0-117.78)	48.57 (13.78-91.06)	30.50 (20.25-35.00)	9.80 (6.36-39.28)	4.60±1.09
Severe (Score 3)	40.10 (0-555.50)	216.47 (37.42-574.71)	64.00 (47.50-98.00)	70.10 (27.69-105.77)	5.53±0.71
Correlation coefficient, ρ	0.08	0.22	0.44	0.51	0.49
P-value	0.570	0.085	<0.001	<0.001	<0.001

Data are presented as the mean ± standard deviation or median (interquartile range). ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28-CRP, disease activity score in 28 joints-C-reactive protein.

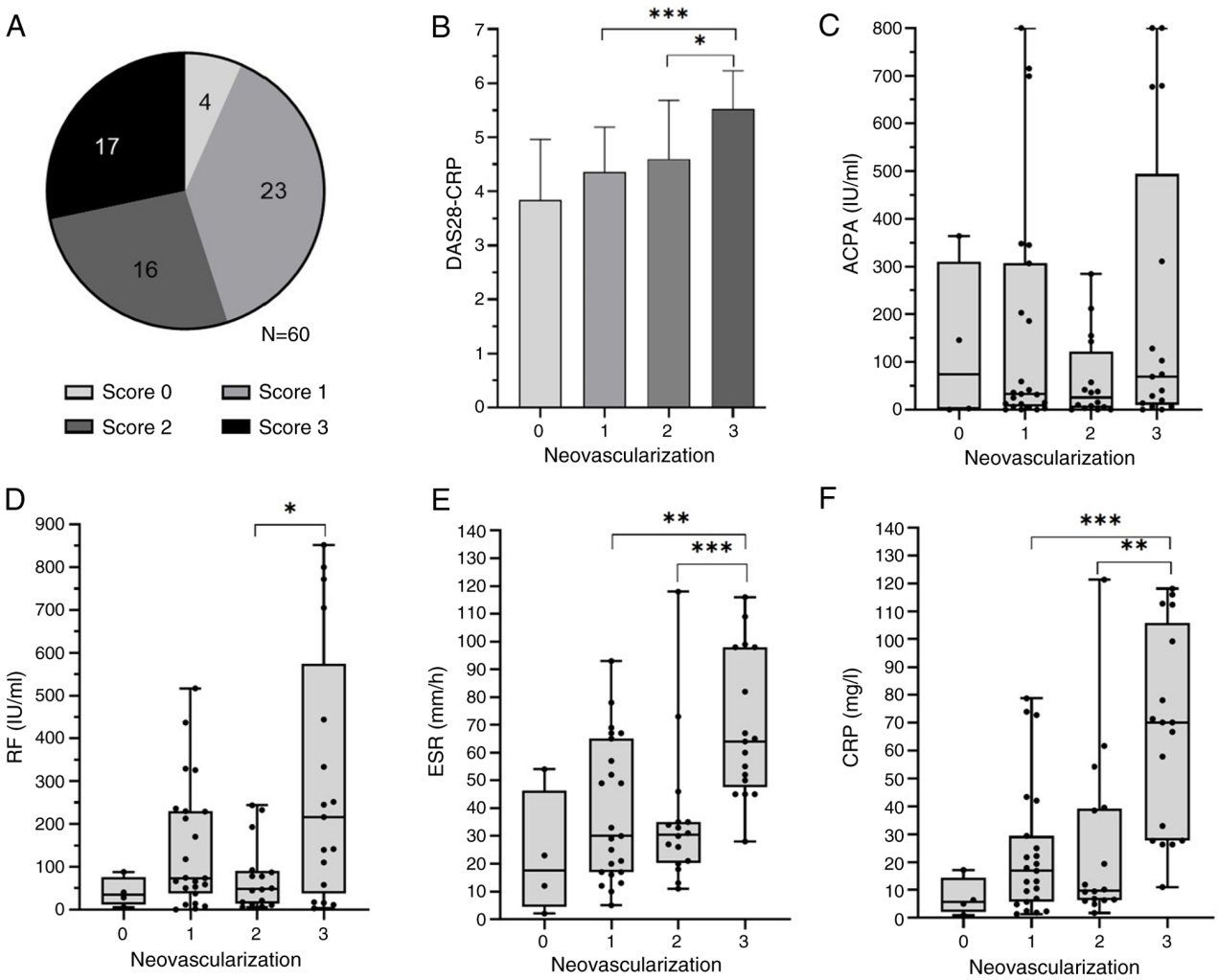

Figure 5. Comparison of clinical and serological parameters with neovascularization scores in patients with rheumatoid arthritis. (A) Severity of neovascularization was scored form 0-3. A score of 0 indicates no neovascularization (four patients), a score of 1 indicates mild neovascularization (23 patients), a score of 2 indicates moderate neovascularization (16 patients) and a score of 3 indicates severe neovascularization (17 patients). Patients with severe neovascularization had significantly higher (B) DAS28-CRP) levels compared to those with mild and moderate neovascularization. (C) ACPA levels showed no statistically significant differences among the mild, moderate, and severe groups. (D) RF level in patients with severe neovascularization was higher than in those with moderate neovascularization. Patients with severe neovascularization had significantly higher (E) ESR and (F) CRP levels compared to those with mild and moderate neovascularization. *P<0.05, **P<0.01, ***P<0.001. DAS28-CRP, disease activity score in 28 joints-C-reactive protein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor.

Comparison of disease activity in patients with synoviocyte proliferation and synoviocyte detachment. Among the patients, 36 (60%) had synoviocyte proliferation, with DAS28-CRP scores ranging from 1.88-5.88. A total of nine

Table III. Comparison of clinical characteristics between patients with rheumatoid arthritis and with synoviocyte detachment and those with synoviocyte proliferation.

Characteristic	Synoviocyte detachment (n=9)	Synoviocyte proliferation (n=36)	P-value
Age, years	60.44±7.99	51.86±10.79	0.031
Female, n (%)	8 (88.9)	31 (86.1)	0.823
Disease duration, months	112.67±90.39	89.94±81.14	0.466
Moderate-severe bone erosion, n (%)	8 (77.8)	20 (61.1)	0.047
ACPA positive, n (%)	7 (77.8)	21 (58.3)	0.267
RF positive, n (%)	8 (88.9)	25 (69.4)	0.206
ESR, mm/h	73.44±31.93	40.72±25.04	0.002
CRP, mg/l	62.36±40.95	30.36±29.64	0.010
TJC-28	7.33±5.05	5.69±3.60	0.267
SJC-28	7.33±4.97	5.22±3.43	0.142
PGA	71.11±13.41	65.00±10.89	0.158
DAS28-CRP	5.51±0.95	4.77±1.02	0.046

Data are presented as the mean ± standard deviation or n (%). The P-value indicates the difference between the clinical characteristics of patients with synoviocyte detachment and those with synoviocyte proliferation. ACPA, anti-citrullinated protein antibody; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TJC-28, Tender 28-Joint Count; SJC-28, Swollen 28-Joint Count; PGA, patient global assessment; DAS28-CRP, disease activity score in 28 joints-C-reactive protein.

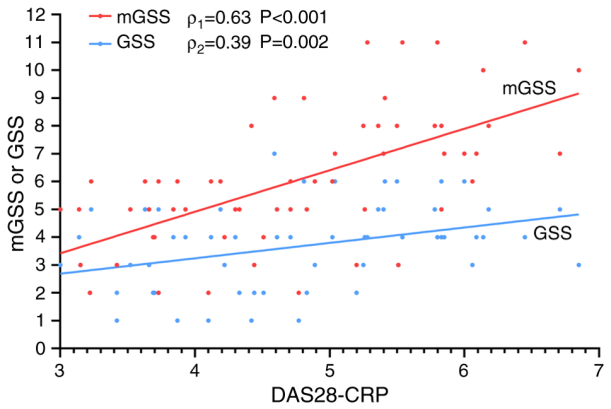

Figure 6. Correlation of mGSS and GSS with DAS28-CRP. Red dots and line represent the mGSS, and blue dots and line represent the GSS. Correlation coefficients (r) and P-values are shown for both scores, indicating the strength and significance of the relationship with DAS28-CRP. Specifically, the mGSS has a stronger correlation (ρ=0.63; P<0.001) with DAS28-CRP than the GSS (ρ=0.39; P=0.002), suggesting that the mGSS may be a more accurate measure of disease activity in rheumatoid arthritis. mGSS, modified General Synovitis Score; GSS, General Synovitis Score; DAS28-CRP, disease activity score in 28 joints-C-reactive protein.

patients (16%) had synoviocyte detachment, corresponding to DAS28-CRP scores ranging from 3.75-5.89. The group with synoviocyte detachment had higher levels of ESR, CRP and DAS28-CRP compared with patients with synovial hyperplasia (P<0.05; Table III).

Comparison of the correlations of DAS28-CRP between GSS and mGSS. Spearman's correlation analysis revealed that the GSS and the mGSS were significantly correlated with the DAS28-CRP level (Fig. 6). However, the mGSS had a stronger correlation (ρ=0.63; P<0.001) than the GSS (ρ=0.39; P=0.002).

Discussion

Neovascularization is considered to be an early and key event in the formation and maintenance of synovial inflammation in RA (16). Persistent inflammation increases oxygen demand, leading to local hypoxia, which induces the expression of pro-angiogenic factors, such as vascular endothelial growth factor (VEGF). This stimulates the formation of new blood vessels, provides oxygen and nutrients to proliferating synovial cells and facilitates inflammatory cell infiltration, thereby exacerbating chronic synovial inflammation (17,18). The increased endothelial surface area also creates a substantial capacity for producing cytokines, adhesion molecules and other inflammatory stimuli. Additionally, the proliferation of new blood vessels in the synovium facilitates tissue invasion, supporting the active infiltration of the synovium into the cartilage, leading to erosion and destruction of the cartilage (19,20).

In a previous study, the serum VEGF level was revealed to be higher in patients with RA than in healthy individuals. Furthermore, the serum VEGF level was correlated with ESR, CRP, RF, the number of tender and swollen joints, Modified Health Assessment Questionnaire and PGA of disease activity in patients with RA (21). Another study revealed that the serum VEGF level at presentation in patients with early RA was significantly correlated with the development of radiographic damage after 1 year, and improvement in the clinical symptoms of RA was associated with a reduced serum VEGF level (22). These findings highlight the pivotal role of neovascularization in fueling the progression and severity of RA. However, by inhibiting neovascularization, particularly through blocking the VEGF signaling pathway, synovial vascular density can be reduced, inflammatory cell infiltration decreased and symptoms alleviated (7,23).

In the present study, >90% of the patients with RA exhibited varying degrees of neovascularization. The synovial

neovascularization score was significantly correlated with disease activity (DAS28-CRP) and the inflammatory markers, ESR and CRP. This indicates the widespread presence of synovial vascular lesions in RA histopathology and a strong association between increased neovascularization and heightened disease activity in patients with RA. Therefore, these results suggested that neovascularization may be a crucial parameter for assessing disease activity in patients with RA.

Another notable feature of RA synovium is synovial hyperplasia. The normal synovial lining consists of 2-3 layers of synoviocytes. However, in RA, chronic inflammation and aberrant cellular signaling drive the excessive proliferation of synoviocytes, leading to a synovial lining that can expand to 6-10 layers (8,24). This hyperplasia promotes the development of invasive pannus tissue and exacerbates joint damage (25). Consistent with previous studies, the current study found that most patients with RA (60%) had synovial hyperplasia. However, it was observed that some patients with RA did not have synovial hyperplasia and synoviocyte proliferation; by contrast, 16% of the patients had thinning of the synovial lining with synoviocyte detachment.

Physiopathological observations suggest that chronic mild inflammation typically leads to cell proliferation, whereas severe acute inflammation can result in cell necrosis and detachment (26,27). Substantial evidence indicates that chronic persistent inflammation within the synovial membrane leads to synoviocyte proliferation in RA (28). The mechanisms underlying synoviocyte proliferation are multifaceted and include the effects of inflammatory mediators, oxidative-stress-induced DNA damage and the infiltration of bone marrow-derived cells (29,30).

However, long-term chronic inflammation also results in the release of various inflammatory mediators, including TNF-α, IL-1 and IL-6, which can induce apoptosis of synoviocytes (31,32). There are two types of synoviocytes: Macrophage-like synoviocytes and fibroblast-like synoviocytes (FLS), with FLS being the major component of the synovial lining layer. In the early stages of RA, FLS have enhanced proliferative and antiapoptotic capabilities, leading to synovial hyperplasia. However, in later stages, prolonged inflammatory stimulation and cellular metabolic stress may cause these cells to gradually lose their proliferative ability, resulting in synovial thinning (20,33). Thus, synoviocyte necrosis and detachment can occur in two scenarios: During severe inflammation or as a late-stage manifestation. The present study showed that patients with synoviocyte detachment had higher disease activity but did not have longer disease duration than patients with synoviocyte proliferation. Therefore, it was hypothesized that synoviocyte detachment is more closely associated with severe inflammation in patients with RA. Thus, it is proposed that in synovitis scoring, the presence of synoviocyte detachment should be assigned a score of 4, higher than the score of 3 for severe synovial hyperplasia.

In response to these findings, the present study proposed the mGSS, which includes assessments of neovascularization and synoviocyte detachment alongside traditional parameters. The correlation between the mGSS and DAS28-CRP showed a trend towards superiority over the GSS (correlation coefficient, 0.62 vs. 0.37). This suggested that the enhanced scoring system aligns more closely with the clinical realities of RA, offering a more comprehensive assessment tool that can improve disease management strategies.

The present study had some limitations. First, it was a single-center study with a relatively small sample size, which may affect the generalizability of the findings. Second, the local sampling from different sites during minimally invasive synovial biopsy, the selection of synovial histopathology sections and manual readings are susceptible to subjective bias, which may also lead to result bias. Future studies with larger sample sizes are required to ensure the objectivity and accuracy of the results.

In conclusion, although the GSS provides a fundamental framework for evaluating synovial inflammation, it does not fully encompass the intricate histopathology of RA. The mGSS, with its inclusion of neovascularization and synoviocyte detachment, offers a more detailed and clinically relevant evaluation of synovial histopathology. The present study not only highlighted the association of these histopathological features with RA activity, but also set the stage for future research to validate and refine the mGSS, potentially establishing a new standard for assessing and managing RA.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

DW and YD analyzed the data and drafted the initial manuscript. YH, JZ and WL collected the data and confirm the authenticity of all the raw data. YP and ZX independently assessed the pathological slides of the synovium. RW oversaw the entire project, designed the experiment and revised the manuscript draft. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Review Board of the First Affiliated Hospital of Nanchang University [approval no. IIT (2023); clinical ethics review no. 011]. Written informed consent was obtained from all patients/participants, covering both their participation in the procedure and their participation in the study. All procedures were conducted in accordance with The Declaration of Helsinki (as revised in 2013).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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