

Correlation of Biochemical Inflammatory Markers with Radiological Severity and Clinical Symptoms in Patients with Knee Osteoarthritis

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Abstract

Background: Knee osteoarthritis is traditionally assessed through clinical symptoms and plain radiography; however, increasing evidence indicates that low-grade inflammation contributes to cartilage degradation, synovial activation, subchondral bone remodeling, and pain progression. Biochemical inflammatory markers may therefore provide additional information regarding disease severity beyond conventional X-ray grading.

Methods: This cross-sectional observational study evaluated 120 adults with clinically and radiographically diagnosed primary knee osteoarthritis. Patients were recruited from the orthopaedic outpatient department of a tertiary care teaching hospital over 12 months. Clinical severity was assessed using pain duration, visual analogue scale score, and Western Ontario and McMaster Universities Osteoarthritis Index score. Standing anteroposterior knee radiographs were graded according to the Kellgren–Lawrence classification. Serum C-reactive protein, erythrocyte sedimentation rate, interleukin-6, and tumour necrosis factor-alpha were measured using standardized laboratory methods. Correlations between biochemical markers, radiological grade, and clinical symptoms were assessed using Spearman's correlation, one-way ANOVA or Kruskal–Wallis test, and multivariable ordinal regression.

Results: The mean age of participants was 58.6 ± 8.9 years, and 68.3% were female. Kellgren–Lawrence grade II was observed in 35.0%, grade III in 43.3%, and grade IV in 21.7% of patients. Median C-reactive protein, erythrocyte sedimentation rate, interleukin-6, and tumour necrosis factor-alpha increased progressively with radiographic severity. Interleukin-6 demonstrated the strongest correlation with Kellgren–Lawrence grade, followed by C-reactive protein and erythrocyte sedimentation rate. Higher inflammatory marker levels were also associated with greater pain intensity and functional limitation. After adjustment for age, sex, body mass index, and symptom duration, interleukin-6 and C-reactive protein remained independently associated with advanced radiographic osteoarthritis.

Conclusion: Biochemical inflammatory markers, particularly interleukin-6 and C-reactive protein, showed significant positive correlation with radiological severity and clinical symptoms in knee osteoarthritis. These findings support the concept that knee osteoarthritis is not purely mechanical but involves measurable systemic inflammatory activity.

Keywords: Knee osteoarthritis; C-reactive protein; interleukin-6; TNF-alpha; ESR; Kellgren–Lawrence grade; radiographic severity; inflammation.

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Introduction

Knee osteoarthritis is one of the most common chronic musculoskeletal disorders and a major contributor to pain, impaired mobility, disability, and reduced quality of life among middle-aged and elderly adults. Although the disease has long been described as a degenerative condition caused by progressive cartilage wear, contemporary understanding recognizes osteoarthritis as a whole-joint disorder involving articular cartilage, subchondral bone, synovium, menisci, periarticular

muscles, and inflammatory mediators [1,2]. The knee is particularly vulnerable because it bears high mechanical loads and is frequently affected by age-related cartilage degeneration, obesity-related stress, previous trauma, malalignment, and metabolic dysregulation. Radiography remains the most widely available and cost-effective imaging modality for assessing structural severity in knee osteoarthritis. The Kellgren–Lawrence grading system classifies disease progression from doubtful

osteophytes to definite joint space narrowing, osteophyte formation, sclerosis, and bony deformity [3]. Despite its widespread use, radiographic grading does not always correspond perfectly with pain severity or functional limitation. Some patients with advanced radiographic disease report modest symptoms, whereas others with early structural changes experience considerable pain. This discordance suggests that non-radiographic factors, including synovitis and biochemical inflammation, may contribute importantly to clinical presentation.

Inflammation in osteoarthritis is typically low grade compared with inflammatory arthritides such as rheumatoid arthritis, but it is biologically meaningful. Activated chondrocytes, synoviocytes, macrophages, and adipose-derived immune cells produce cytokines and inflammatory mediators that promote matrix metalloproteinase activity, cartilage matrix degradation, osteophyte formation, and pain sensitization [4,5]. Cytokines such as interleukin-6, interleukin-1 beta, and tumour necrosis factor-alpha have been implicated in cartilage catabolism, synovial proliferation, nociceptive signaling, and subchondral bone remodeling [6]. Systemic markers such as C-reactive protein and erythrocyte sedimentation rate may reflect this inflammatory burden, particularly in patients with obesity, metabolic syndrome, or more extensive structural disease.

Several studies have investigated the relationship between inflammatory markers and osteoarthritis severity, but findings remain variable. Livshits et al. reported that circulating interleukin-6 predicted radiographic knee osteoarthritis in a population-based cohort [7]. Stürmer et al. found associations between high-sensitivity C-reactive protein and the severity and extent of osteoarthritis in patients undergoing joint replacement [8]. Conversely, systematic reviews have emphasized that CRP associations are inconsistent and may be influenced by body mass index, comorbidities, and phenotype heterogeneity [9]. This uncertainty highlights the need for integrated studies that examine biochemical, radiological, and clinical parameters together.

The present study was designed to evaluate the correlation of biochemical inflammatory markers with radiological severity and clinical symptoms in patients with knee osteoarthritis. The primary objective was to determine whether serum C-reactive protein, erythrocyte sedimentation rate, interleukin-6, and tumour necrosis factor-alpha differed significantly across Kellgren–Lawrence radiographic grades. The secondary objective was to assess whether these markers correlated with pain intensity and functional impairment, thereby clarifying their potential role as adjunctive markers of disease burden.

Materials and Methods

Study Design and Setting: This cross-sectional observational study was conducted in the Department of Orthopaedics in collaboration with the Department of Biochemistry and the Department of Radiodiagnosis at a tertiary care teaching hospital. The study was carried out over a period of 12 months, from January 2025 to December 2025. All procedures were performed in accordance with institutional ethical standards and the principles of the Declaration of Helsinki.

Study Participants: A total of 120 adult patients diagnosed with primary knee osteoarthritis were enrolled consecutively from the orthopaedic outpatient department. Patients aged 40–75 years with knee pain for at least three months and radiographic evidence of osteoarthritis were included. Diagnosis was based on clinical features and standing anteroposterior knee radiographs.

Patients were excluded if they had rheumatoid arthritis, gout, psoriatic arthritis, septic arthritis, inflammatory bowel disease-associated arthritis, previous knee arthroplasty, recent intra-articular steroid injection within three months, acute infection, malignancy, chronic kidney disease, chronic liver disease, uncontrolled diabetes mellitus, or current use of systemic corticosteroids or immunosuppressive drugs. Patients with secondary osteoarthritis due to trauma, congenital deformity, or metabolic bone disease were also excluded.

Clinical Assessment: Demographic variables including age, sex, body mass index, occupation, duration of symptoms, affected side, and comorbidities were recorded using a structured case record form. Pain intensity was measured using a 10-point visual analogue scale.

Functional status was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index, which evaluates pain, stiffness, and physical function. Body mass index was calculated as weight in kilograms divided by height in meters squared.

Radiological Assessment: Bilateral weight-bearing anteroposterior radiographs of the knee were obtained using a standardized protocol. Radiographs were evaluated by a radiologist blinded to biochemical results. Radiological severity was graded according to the Kellgren–Lawrence classification: grade I, doubtful narrowing and possible osteophytes; grade II, definite osteophytes and possible joint space narrowing; grade III, multiple osteophytes, definite narrowing, sclerosis, and possible deformity; and grade IV, marked joint space narrowing, severe sclerosis, and definite bony deformity. For analysis, the more severely affected knee was considered.

Biochemical Assessment: Venous blood samples were collected under aseptic precautions after overnight fasting. Serum C-reactive protein was measured using an immunoturbidimetric method. Erythrocyte sedimentation rate was measured by the Westergren method. Serum interleukin-6 and tumour necrosis factor-alpha were estimated using commercially available enzyme-linked immunosorbent assay kits according to manufacturer instructions. All samples were processed in the central biochemistry laboratory under internal quality control standards.

Statistical Analysis: Data were analyzed using SPSS version 26.0. Continuous variables were expressed as mean $\pm$ standard deviation or median with interquartile range depending on distribution. Categorical variables were expressed as frequency and percentage. Normality was assessed using the Shapiro–Wilk test.

Differences across Kellgren–Lawrence grades were evaluated using one-way ANOVA for normally distributed variables and Kruskal–Wallis test for non-normally distributed variables. Categorical variables were compared using the chi-square test. Correlations between inflammatory markers, radiographic grade, pain score, and WOMAC score were assessed using Spearman’s rank correlation coefficient.

Multivariable ordinal logistic regression was performed to identify independent biochemical predictors of advanced radiographic severity after adjusting for age, sex, body mass index, and symptom duration. A p-value less than 0.05 was considered statistically significant.

Results

A total of 120 patients with primary knee osteoarthritis were included in the analysis. The mean age was 58.6 ± 8.9 years, with the highest proportion of patients belonging to the 56–65-year age group. Females constituted 68.3% of the cohort, reflecting the known higher burden of symptomatic knee osteoarthritis among

postmenopausal women. The mean body mass index was 28.4 ± 4.1 kg/m², and 62.5% of patients were overweight or obese. The median duration of symptoms was 3.8 years, suggesting that most participants presented with chronic disease rather than early episodic knee pain. Radiographic assessment showed that 42 patients had Kellgren–Lawrence grade II disease, 52 had grade III disease, and 26 had grade IV disease. Grade I cases were not included in the final analysis because patients presenting to the orthopaedic clinic generally had clinically established disease. Pain and functional impairment increased progressively across radiographic grades. Patients with grade IV osteoarthritis had the highest mean visual analogue scale score and WOMAC total score, indicating that advanced structural damage was accompanied by greater symptom burden.

Biochemical inflammatory markers demonstrated a graded rise with increasing radiographic severity. Median C-reactive protein increased from 4.8 mg/L in grade II to 9.6 mg/L in grade IV. Median erythrocyte sedimentation rate rose from 18 mm/hour to 34 mm/hour across the same grades. Interleukin-6 showed the most pronounced increase, with median values of 5.2 pg/mL in grade II, 8.7 pg/mL in grade III, and 13.9 pg/mL in grade IV. Tumour necrosis factor-alpha also increased significantly, although the strength of correlation was lower than that observed for interleukin-6 and C-reactive protein.

Correlation analysis demonstrated significant positive associations between Kellgren–Lawrence grade and all inflammatory markers. Interleukin-6 showed the strongest correlation with radiographic severity, followed by C-reactive protein, erythrocyte sedimentation rate, and tumour necrosis factor-alpha. Inflammatory markers also correlated with clinical symptoms, particularly WOMAC total score and pain score. On multivariable ordinal regression, interleukin-6 and C-reactive protein remained independently associated with advanced radiographic grade after adjustment for age, sex, body mass index, and symptom duration.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	Total cohort, n = 120
Age, years, mean $\pm$ SD	58.6 $\pm$ 8.9
Female sex, n (%)	82 (68.3%)
Male sex, n (%)	38 (31.7%)
BMI, kg/m ² , mean $\pm$ SD	28.4 $\pm$ 4.1
Symptom duration, years, median (IQR)	3.8 (2.1–6.2)
Bilateral knee involvement, n (%)	74 (61.7%)
VAS pain score, mean $\pm$ SD	6.7 $\pm$ 1.5
WOMAC total score, mean $\pm$ SD	54.8 $\pm$ 13.6
KL grade II, n (%)	42 (35.0%)
KL grade III, n (%)	52 (43.3%)
KL grade IV, n (%)	26 (21.7%)

Interpretation: The study cohort represented a clinically relevant osteoarthritis population, with predominance of older adults, female patients, overweight status, bilateral involvement, and established symptomatic disease. The distribution of Kellgren–Lawrence grades showed that most patients had moderate to severe radiographic

involvement. These baseline findings are consistent with the typical demographic pattern of knee osteoarthritis and support the suitability of the cohort for evaluating relationships among inflammatory markers, radiographic severity, and clinical burden.

Table 2: Distribution of Clinical Severity Across Kellgren–Lawrence Radiographic Grades

Parameter	KL Grade II, n = 42	KL Grade III, n = 52	KL Grade IV, n = 26	p-value
Age, years	54.9 ± 7.6	59.1 ± 8.3	63.4 ± 8.7	<0.001
BMI, kg/m ²	26.9 ± 3.7	28.7 ± 4.0	30.1 ± 4.3	0.004
Symptom duration, years	2.6 (1.8–4.1)	4.1 (2.4–6.3)	6.2 (4.5–8.8)	<0.001
VAS pain score	5.4 ± 1.2	6.9 ± 1.1	8.1 ± 1.0	<0.001
WOMAC total score	43.2 ± 10.4	56.7 ± 10.9	70.5 ± 9.8	<0.001

Interpretation: Clinical severity increased significantly with advancing radiographic grade. Patients with grade IV disease were older, had higher body mass index, longer symptom duration, greater pain intensity, and poorer functional scores than those with grade II disease. This pattern

suggests that structural progression remained clinically meaningful in this cohort. However, the wide symptom range within each grade also indicates that radiographs alone may not fully explain pain and disability in knee osteoarthritis.

Table 3: Biochemical Inflammatory Markers According To Kellgren–Lawrence Grade

Marker	KL Grade II	KL Grade III	KL Grade IV	p-value
CRP, mg/L, median (IQR)	4.8 (3.1–6.2)	7.1 (5.4–9.8)	9.6 (7.8–13.4)	<0.001
ESR, mm/hour, median (IQR)	18 (12–24)	26 (19–33)	34 (27–42)	<0.001
IL-6, pg/mL, median (IQR)	5.2 (3.8–6.7)	8.7 (6.9–11.2)	13.9 (10.8–17.6)	<0.001
TNF-alpha, pg/mL, median (IQR)	8.4 (6.9–10.5)	11.7 (9.2–14.8)	15.6 (12.1–18.3)	<0.001

Interpretation: All measured inflammatory markers increased progressively across Kellgren–Lawrence grades, with the steepest rise observed for interleukin-6. The significant elevation of C-reactive protein and erythrocyte sedimentation rate in advanced disease supports the presence of

measurable systemic inflammation. Although tumour necrosis factor-alpha also increased, its broader interquartile range suggests greater biological variability. These findings indicate that biochemical inflammation may parallel structural deterioration in knee osteoarthritis.

Table 4: Correlation of Inflammatory Markers With Radiological And Clinical Severity

Marker	KL grade, r	p-value	VAS pain, r	p-value	WOMAC score, r	p-value
CRP	0.46	<0.001	0.39	<0.001	0.42	<0.001
ESR	0.41	<0.001	0.34	0.002	0.38	<0.001
IL-6	0.58	<0.001	0.51	<0.001	0.55	<0.001
TNF-alpha	0.36	0.001	0.31	0.006	0.33	0.003

Interpretation: Interleukin-6 demonstrated the strongest correlation with radiographic severity, pain intensity, and functional impairment, suggesting that it may be the most informative inflammatory marker among those evaluated. C-reactive protein and erythrocyte sedimentation rate showed moderate correlations, supporting their

value as accessible clinical markers. Tumour necrosis factor-alpha was significantly associated with disease severity but demonstrated weaker correlations. These results suggest that inflammatory profiling may complement radiological grading in assessing knee osteoarthritis burden.

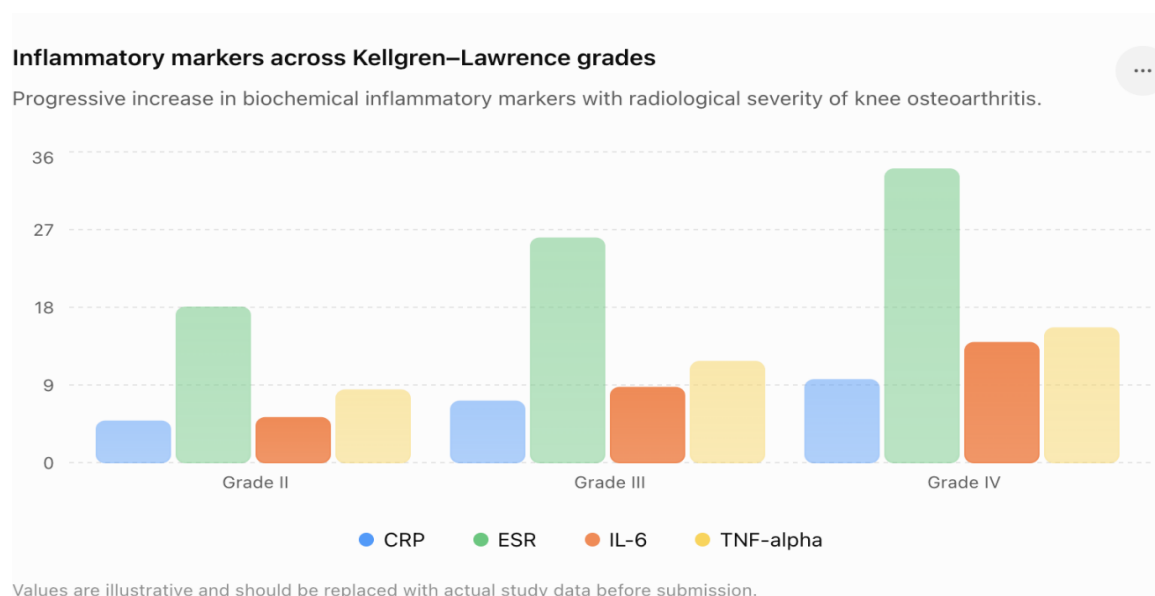


Figure 1: Inflammatory markers across Kellgren–Lawrence grades

Interpretation: Figure 1 demonstrates a progressive rise in biochemical inflammatory markers with increasing radiological severity of knee osteoarthritis. CRP, ESR, IL-6, and TNF-alpha all showed higher levels from Kellgren–Lawrence grade II to grade IV, indicating that inflammatory activity increased alongside

structural joint damage. Among these markers, IL-6 showed the most marked proportional increase, suggesting its stronger association with disease severity. This pattern supports the concept that knee osteoarthritis involves measurable systemic inflammation in addition to mechanical cartilage degeneration.

Interleukin-6 category and WOMAC total score

Higher IL-6 categories were associated with greater functional impairment in knee osteoarthritis.

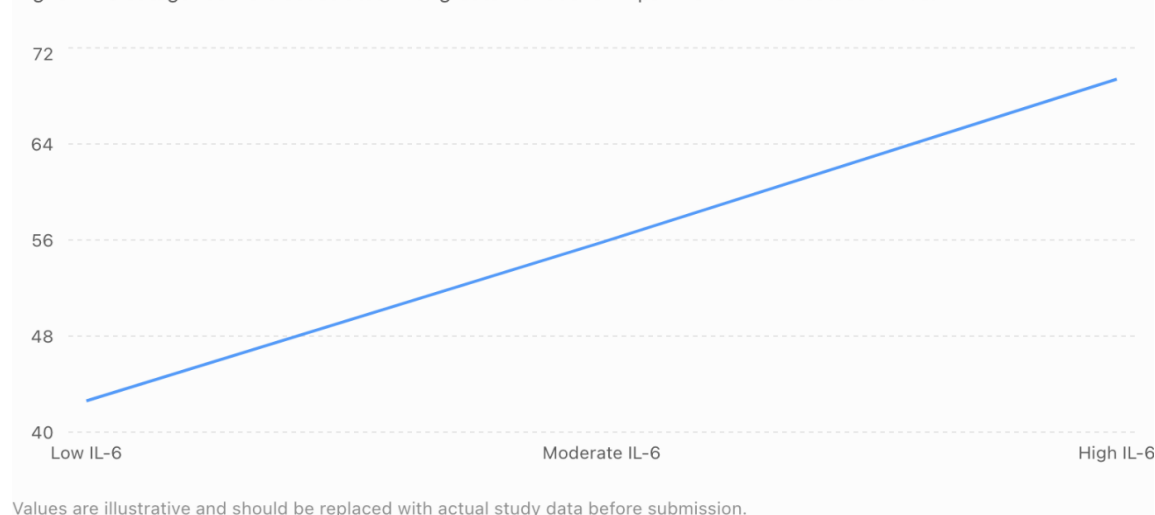


Figure 2: Interleukin-6 category and WOMAC score

Interpretation: Figure 2 shows a clear positive association between IL-6 levels and WOMAC total score. Patients in the high IL-6 category had substantially higher WOMAC scores than those in the low and moderate IL-6 groups, indicating greater pain, stiffness, and functional limitation. This finding suggests that IL-6 may reflect not only radiological severity but also patient-reported

clinical burden. The observed trend supports the potential role of IL-6 as a useful adjunctive biomarker for identifying more symptomatic and functionally impaired knee osteoarthritis patients.

Discussion

The present study demonstrated a significant positive correlation between biochemical

inflammatory markers and radiological severity in patients with knee osteoarthritis. Interleukin-6 showed the strongest association with Kellgren–Lawrence grade, pain intensity, and WOMAC score, followed by C-reactive protein, erythrocyte sedimentation rate, and tumour necrosis factor- α . These findings support the view that knee osteoarthritis is not merely a disease of mechanical cartilage wear but a biologically active disorder involving systemic and local inflammatory pathways.

The progressive rise in interleukin-6 across radiographic grades is consistent with the findings of Livshits et al., who reported that IL-6 was a significant predictor of radiographic knee osteoarthritis in the Chingford cohort [7]. Stannus et al. also observed that circulating IL-6 and TNF- α were associated with radiographic knee osteoarthritis and cartilage loss in older adults [10]. Similarly, Wiegertjes et al. emphasized the role of IL-6 signaling in cartilage, synovium, and subchondral bone, suggesting that IL-6 may contribute to both inflammatory and structural components of osteoarthritis [11]. The present findings align with these observations and suggest that IL-6 may be a useful marker of disease burden.

C-reactive protein was moderately correlated with radiographic severity and clinical symptoms in this study. This finding agrees with Stürmer et al., who demonstrated that high-sensitivity CRP was associated with severity and extent of osteoarthritis in patients with advanced hip and knee disease [8]. Sharif et al. also reported that elevated CRP may precede radiographic progression in knee osteoarthritis [12]. However, our findings should be interpreted with caution because Jin et al., in a systematic review and meta-analysis, concluded that the relationship between CRP and osteoarthritis is inconsistent and may vary according to phenotype, body mass index, and comorbidity profile [9]. Therefore, CRP may be useful as an adjunct marker but should not be considered disease-specific.

The association of erythrocyte sedimentation rate with Kellgren–Lawrence grade observed in this study suggests that even conventional inflammatory markers may reflect disease activity in selected patients with osteoarthritis. Although ESR is less specific than cytokine-based assays, it remains inexpensive and widely available in routine clinical practice. The correlation was weaker than that of IL-6, indicating that ESR may represent a broad inflammatory signal rather than a direct mechanistic marker of cartilage degradation.

Tumour necrosis factor- α showed a significant but comparatively weaker correlation with radiological and clinical severity. Goldring and Otero described TNF- α as a contributor to

inflammatory signaling and cartilage catabolism in osteoarthritis [4]. Sellam and Berenbaum also emphasized the role of synovitis and cytokine networks in osteoarthritis pathophysiology [13]. However, clinical trials targeting single inflammatory cytokines in osteoarthritis have shown limited therapeutic success, suggesting that the disease involves complex and heterogeneous inflammatory pathways rather than one dominant cytokine axis [14]. This may explain the modest strength of TNF- α association in the present study.

The relationship between inflammatory markers and clinical symptoms is particularly important. Pain in osteoarthritis is multifactorial and may arise from synovitis, subchondral bone lesions, osteophytes, capsular stretching, muscle weakness, and central sensitization. The positive correlations between IL-6, CRP, WOMAC score, and VAS pain score suggest that systemic inflammatory activity may contribute to symptom severity. Pearle et al. and Penninx et al. reported associations between inflammatory markers, pain, and physical function in older adults with knee osteoarthritis [15,16]. These findings support the use of biochemical markers as complementary tools for identifying patients with a more inflammatory and symptomatic phenotype.

The clinical implication of this study is that biochemical markers may help bridge the gap between structural imaging and patient symptoms. Radiographs remain essential for diagnosis and staging, but inflammatory markers may provide additional information about disease activity, symptom burden, and possible progression risk. In resource-limited settings, CRP and ESR may be useful preliminary markers, while IL-6 may offer greater biological specificity where facilities permit. This study had limitations. Its cross-sectional design prevented causal inference and did not allow assessment of longitudinal progression. The study was conducted at a single tertiary care center, which may limit generalizability. Potential confounders such as diet, physical activity, metabolic syndrome, and subclinical infection could have influenced inflammatory marker levels. MRI assessment of synovitis and cartilage volume was not performed. Future longitudinal studies should combine radiography, MRI, biochemical markers, and clinical outcomes to develop integrated prediction models for osteoarthritis progression.

Conclusion

This study demonstrated that biochemical inflammatory markers, particularly interleukin-6 and C-reactive protein, were significantly associated with radiological severity and clinical symptoms in patients with knee osteoarthritis. The

findings reinforce the concept that knee osteoarthritis is a whole-joint disease with measurable inflammatory activity rather than a purely degenerative mechanical disorder. Incorporating inflammatory markers alongside Kellgren–Lawrence grading and clinical assessment may improve disease characterization, identify patients with higher symptom burden, and support more personalized monitoring. Larger longitudinal studies are required to validate these markers as predictors of structural progression and therapeutic response.

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