

Original Article

Study on the Predictive Value of Inflammatory Factors and Biomarkers in Synovial Fluid for Disease Progression in Knee Osteoarthritis Patients

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Objective: To explore the expression levels of inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) in the synovial fluid of patients with knee osteoarthritis (KOA) at different Kellgren-Lawrence (K-L) grades and to analyze their predictive effect on disease progression. **Methods:** This was a retrospective single-center study involving 154 KOA patients, divided into four K-L grades: grade 1 (37 cases), grade 2 (39 cases), grade 3 (42 cases), and grade 4 (36 cases). Inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) were measured in synovial fluid. Visual analog scale (VAS) and WOMAC scores were also assessed. One-way ANOVA and the Kruskal-Wallis test were used to compare differences between groups, while correlation and multiple regression analyses evaluated the impact of these indicators on disease progression. **Results:** IL-6 levels significantly increased with higher K-L grade. COMP levels also varied significantly across grades. Correlation analysis revealed that IL-6 ($r=0.7021$, $P<0.001$) and COMP ($r=0.8579$, $P<0.001$) were strongly correlated with K-L grade. Multiple regression analysis identified IL-6 and COMP as independent predictors of disease progression. **Conclusion:** IL-6 and COMP in synovial fluid are significantly associated with KOA disease grading and progression. These biomarkers can aid in disease monitoring and early intervention, providing a basis for personalized treatment.

Keywords: Biomarkers, Disease Progression, Inflammatory Factors, Knee Arthritis, K-L Classification**Introduction**

Knee osteoarthritis (KOA) is a common degenerative joint disease characterized by cartilage degeneration, synovial inflammation, and osteophyte formation^{1,2}. With the aging population, the prevalence of KOA is increasing globally, making it one of the leading causes of disability in middle-aged and elderly individuals. Statistics show that approximately 10%-15% of middle-aged and elderly

people suffer from KOA, with severe cases often leading to a significant loss of joint function, which severely impacts the quality of life^{3,4}.

The pathogenesis of KOA is complex, and diagnosis typically relies on imaging techniques, such as the Kellgren-Lawrence classification. However, current treatment strategies focus primarily on symptom relief, lacking precise interventions targeting the underlying disease progression mechanisms^{5,6}. In recent years, inflammatory factors and biomarkers in synovial fluid have gained attention as potential indicators of pathological changes in KOA. Despite this, most studies primarily focus on individual biomarkers or inflammatory factors, failing to systematically analyze their changes at different stages of the disease^{7,8}. Furthermore, existing studies often overlook the correlation between inflammatory factors, biomarkers, imaging grade, and functional status, limiting the development of personalized treatment strategies for KOA. Therefore, it is crucial to explore the dynamic changes in key inflammatory factors

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and biomarkers in synovial fluid and assess their predictive value for disease progression, which could help improve early diagnosis and enable precise interventions for KOA.

Previous studies have shown that inflammatory factors such as IL-1 β , IL-6, and TNF- α are closely associated with the inflammatory response in KOA^{9,10}. Meanwhile, matrix metalloproteinases (MMPs) and cartilage oligomeric matrix proteins (COMP) play critical roles in cartilage matrix degradation and remodeling^{11,12}. However, many of these studies are based on the observation of individual indicators, lacking comprehensive analysis. Additionally, although some studies have attempted to correlate these indicators with imaging grading, their sample sizes are often small, and the findings are not yet conclusive^{13,14}. Specifically, the dynamic changes and predictive performance of these biomarkers across different stages of KOA have not been fully elucidated. Limitations of existing studies include small sample sizes, the absence of standardized detection methods, and a failure to account for individual patient differences.

This study aims to investigate the changing patterns of inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) in synovial fluid at different stages of KOA, and to clarify their relationship with disease progression and predictive value. The results of this research will provide new insights into the pathological mechanisms of KOA, assist in early diagnosis and risk assessment, and offer a scientific basis for precise interventions and personalized treatment strategies.

Materials and methods

General information

This study is a single-center, retrospective analysis involving 154 patients diagnosed with knee osteoarthritis (KOA) at our hospital between April 2020 and April 2023. All patients met the diagnostic criteria for KOA set by the American College of Rheumatology (ACR), were aged ≥ 40 years, had joint fluid testing and imaging evaluation records, and provided informed consent. The patients were grouped based on the imaging-based Kellgren-Lawrence (K-L) grading system: grade 1 (37 cases), grade 2 (39 cases), grade 3 (42 cases), and grade 4 (36 cases).

Inclusion criteria: Age ≥ 40 years, meeting the ACR diagnostic criteria for KOA, having joint fluid testing and imaging evaluation records, and providing informed consent.

Exclusion criteria: Patients with other joint diseases (e.g., rheumatoid arthritis, gouty arthritis), those who received intra-articular injections within the last 6 months, and those with incomplete data or poor-quality imaging.

Methodology

This study aimed to detect inflammatory factors and biomarkers in the synovial fluid of knee osteoarthritis (KOA) patients to clarify their expression levels and their

relationship with disease progression. Inflammatory factors, including IL-1 β , IL-6, and TNF- α , were measured by enzyme-linked immunosorbent assay (ELISA) to assess the degree of inflammation in the synovial fluid. The biomarkers MMPs and COMP were detected using chemiluminescent immunoassay to analyze the biological processes of cartilage matrix degradation and remodeling. Additionally, the degree of lesions was assessed through anteroposterior and lateral knee X-rays, with imaging evaluation performed according to the Kellgren-Lawrence (K-L) grading system. The results were interpreted by two independent imaging experts and confirmed by third-party discussion when necessary.

Observation Indicators

The general information of the patients, including demographic characteristics such as age, sex, and BMI, was collected to analyze overall characteristics and their potential relationship with disease progression. The functional status of the knee joint was evaluated using the WOMAC score, and the visual analogue scale (VAS) was employed to quantify the pain levels experienced by the patients. Furthermore, the test results for inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) in the joint fluid were recorded to explore the correlation between these indicators and disease progression.

Statistical analysis

All data were analyzed using IBM SPSS Statistics 23 software. Continuous variables are expressed as mean \pm standard deviation (SD), and inter-group comparisons were performed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, as appropriate. Categorical variables are expressed as frequencies and percentages, with inter-group differences assessed using the chi-square test. Significant variables identified in the univariate analysis were included in the multivariate regression model to evaluate their independent effects on disease progression. The diagnostic efficacy of key indicators was assessed using ROC curve analysis. A P-value of < 0.05 was considered statistically significant.

Results

Baseline Data

Table 1 presents the baseline data of KOA patients. There were no significant differences between the groups regarding age, sex, and BMI ($P > 0.05$), indicating that these characteristics were well-balanced across groups. However, significant differences in VAS and WOMAC scores were observed between groups ($P < 0.05$). As the K-L grade increased, VAS and WOMAC scores also increased, reflecting the significant impact of disease progression on patients' pain levels and functional status. These baseline characteristics provide a reliable foundation for

Table 1. Baseline data.

Variable	Grade 1 (n=37)	Grade 2 (n=39)	Grade 3 (n=42)	Grade 4 (n=36)	F/ χ^2	P
Age (years)	55.2±9.7	56.0±10.2	57.3 ± 9.7	58.2±10.4	0.661	0.577
Male (%)	15 (40.5%)	16 (41%)	17 (40.5%)	14 (38.9%)	0.04	0.998
BMI (kg/m ²)	25.6±4.3	26.0 ±4.2	25.9±4.1	26.3±4.4	0.169	0.917
VAS	3.2 ± 1.4	4.8 ± 1.9	6.5 ± 2.1	8.3 ± 2.4	513.393	<0.05
WOMAC	28.5±10.2	35.6±12.8	44.3±14.7	54.7±16.5	24.897	<0.05

Table 2. Inflammation Markers and Biomarkers by K-L Grades.

Variable	K-L Grade 1 (N=37)	K-L Grade 2 (N=39)	K-L Grade 3 (N=42)	K-L Grade 4 (N=36)	F	P
IL-1 β (pg/mL)	3.5 ± 1.0	4.0 ± 1.0	5.0 ± 1.0	6.0 ± 1.0	45.341	<0.05
IL-6 (pg/mL)	5.0 ± 1.5	6.5 ± 2.0	8.5 ± 2.5	11.0 ± 3.0	46.293	<0.05
TNF- α (pg/mL)	4.2 ± 1.0	5.5 ± 1.2	6.5 ± 1.5	8.0 ± 2.0	43.937	<0.05
MMPs (ng/mL)	20.0 ± 5.0	25.0 ± 6.0	30.0 ± 6.5	35.0 ± 7.0	40.353	<0.05
COMP (ng/mL)	30.0 ± 8.0	45.0 ± 10.0	60.0 ± 12.0	75.0 ± 14.0	133.843	<0.05

Table 3. Correlation Analysis Results.

Variable	Spearman r	95% Confidence Interval	P Value (Two-tailed)
IL-1 β (pg/mL)	0.6925	0.5971 to 0.7687	<0.0001
IL-6 (pg/mL)	0.7021	0.6089 to 0.7761	<0.0001
TNF- α (pg/mL)	0.6832	0.5856 to 0.7613	<0.0001
MMPs (ng/mL)	0.6609	0.5582 to 0.7437	<0.0001
COMP (ng/mL)	0.8579	0.8080 to 0.8956	<0.0001

further investigation into the disease characteristics and progression of KOA patients.

Change Patterns of Inflammatory Factors and Biomarkers

This study found significant differences ($P < 0.05$) in the levels of inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) across different K-L grades in KOA. These markers gradually increased as the K-L grade advanced. IL-6 levels increased from 5.4 ± 1.8 pg/mL (K-L grade 1) to 12.4 ± 3.8 pg/mL (K-L grade 4), while COMP levels increased from 30.2 ± 8.6 ng/mL to 75.3 ± 14.3 ng/mL ($P < 0.05$). Changes in IL-1 β and TNF- α were more pronounced at the early and late stages of the disease, while IL-6 and COMP showed significant differences across all grades. These results suggest that inflammatory factors and biomarkers could serve as potential indicators for assessing the progression of KOA (Table 2).

Correlation Analysis Between Inflammatory Factors, Biomarkers, and K-L Grade

Spearman correlation analysis results (Table 3) showed that inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) were significantly positively correlated with K-L grade ($P < 0.05$). Among these, IL-6 ($r = 0.7021$, $P < 0.001$) and COMP ($r = 0.8579$, $P < 0.001$) showed the strongest correlations with K-L grade, suggesting that these markers may be important biological indicators of disease progression. TNF- α ($r = 0.6832$, $P < 0.001$) and IL-1 β ($r = 0.6925$, $P < 0.001$) followed, with relatively strong correlations, while MMPs ($r = 0.6609$, $P < 0.001$) showed a weaker correlation. These findings demonstrate that inflammatory factors and biomarkers increase significantly with the progression of K-L grade, supporting their potential value in assessing the severity of knee arthritis, particularly IL-6 and COMP as key candidate indicators.

Table 4. Logistic regression analysis results.

	B	Standard error	Beta	t	P
IL-1 β (pg/mL)	0.153	0.03	0.191	5.053	<0.001
IL-6 (pg/mL)	0.063	0.013	0.183	4.713	<0.001
TNF- α (pg/mL)	0.114	0.021	0.206	5.504	<0.001
MMPs (ng/mL)	0.021	0.005	0.161	4.238	<0.001
COMP (ng/mL)	0.024	0.003	0.428	9.455	<0.001

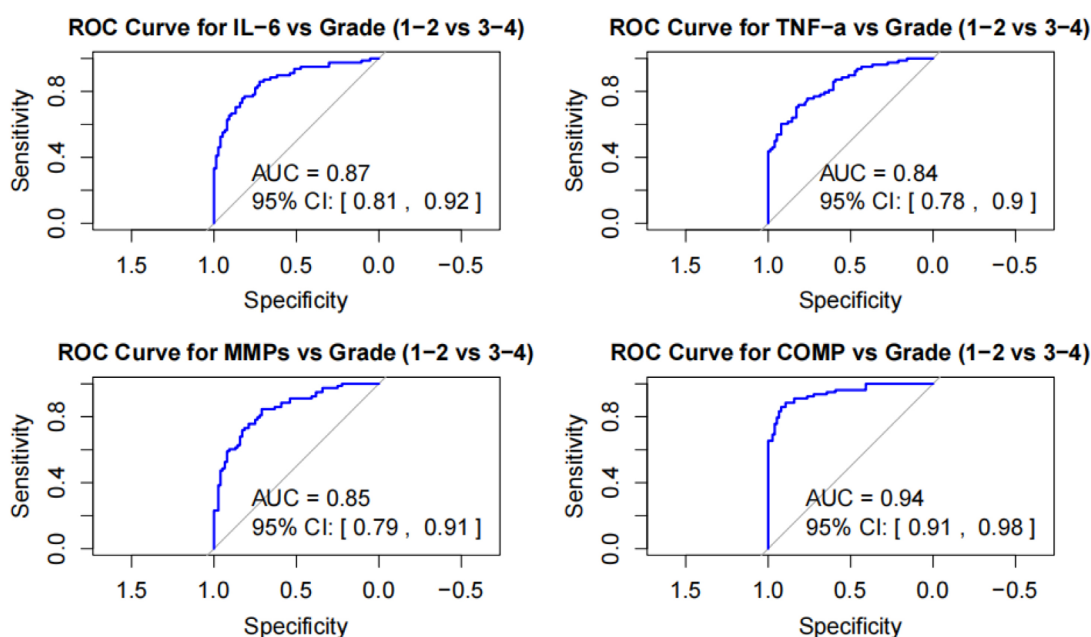


Figure 1. ROC curve analysis results of different inflammatory factors and biomarkers in different K-L grades of KOA (grade 1-2 vs. grade 3-4). Note: The ROC curve of IL-6 showed good classification ability, with an AUC of 0.87 (95% CI: [0.81, 0.92]), indicating that IL-6 has high sensitivity in distinguishing patients with K-L grades 1-2 and 3-4. The ROC curve of TNF- α showed an AUC of 0.84 (95% CI: [0.78, 0.90]), which also showed good classification efficiency, suggesting that TNF- α also has reference value in the evaluation of K-L grading. The ROC curve of MMPs showed an AUC of 0.85 (95% CI: [0.79, 0.91]), indicating its effectiveness in classifying K-L grading of KOA patients. The ROC curve of COMP had the highest AUC, reaching 0.94 (95% CI: [0.91, 0.98]), emphasizing that COMP has the strongest classification ability in the prediction of K-L grading.

Logistic Regression to Assess the Predictive Power of Key Indicators

The logistic regression analysis results revealed that multiple inflammatory factors and biomarkers significantly influence KOA K-L grading (Table 4). The regression coefficient for IL-1 β was 0.153 ($P < 0.001$), indicating that the K-L grade significantly increased with each 1 pg/mL increase in IL-1 β . IL-6 showed a regression coefficient of 0.063 ($P < 0.001$), demonstrating a positive correlation

with disease severity. TNF- α had a regression coefficient of 0.114 ($P < 0.001$), reflecting a moderate positive effect. MMPs showed a regression coefficient of 0.021 ($P < 0.001$), indicating a relationship with K-L grade. The regression coefficient for COMP was 0.024 ($P < 0.001$), which had the most significant impact, suggesting that the increase in COMP levels is strongly associated with disease progression. These findings emphasize the importance of IL-1 β , IL-6, TNF- α , MMPs, and COMP in assessing the severity of KOA.

ROC Curve to Evaluate the Predictive Ability of IL-6 and COMP

ROC curve analysis was conducted to evaluate the predictive efficacy of inflammatory factors (IL-6, TNF- α) and biomarkers (COMP, MMPs) for KOA disease progression. The results (Figure 1) showed that the area under the curve (AUC) for IL-6 was 0.87 (95% CI: 0.81-0.92), indicating good diagnostic ability. The AUC for COMP was 0.94 (95% CI: 0.91-0.98), demonstrating the best predictive accuracy among the markers tested. In comparison, the AUC for TNF- α was 0.84 (95% CI: 0.78-0.90) and for MMPs, it was 0.85 (95% CI: 0.79-0.91). These results indicate that while IL-6 and COMP have strong diagnostic efficacy in predicting KOA disease grading, the predictive ability of TNF- α and MMPs is comparatively weaker.

Discussion

This study explores the changing patterns of inflammatory factors (IL-1 β , IL-6, TNF- α) and biomarkers (MMPs, COMP) in the synovial fluid of patients with knee osteoarthritis (KOA) and their predictive role in disease progression. The results showed that IL-6 and COMP were significantly elevated in higher K-L grades and were closely related to disease progression. Logistic regression analysis highlighted the importance of IL-1 β , IL-6, TNF- α , MMPs, and COMP in assessing the severity of KOA. ROC curve analysis demonstrated that IL-6 and COMP had good predictive performance in diagnosing KOA disease grading.

These findings align well with existing literature, further confirming the significance of inflammatory factors and biomarkers in KOA. Multiple studies have indicated that IL-6 is not only a major pro-inflammatory factor in KOA but also closely linked to disease severity and progression^{15,16}. Elevated IL-6 levels have been shown to correlate with cartilage degradation, increased pain, and worsened joint dysfunction^{17,18}. Our study further supports these findings, as IL-6 levels significantly increased with rising K-L grades, confirming its role as a central factor in the pathophysiology of KOA. Similarly, COMP, an essential component of the cartilage matrix, has been consistently found to be elevated in KOA patients^{19,20}. COMP is not only a marker of cartilage damage but also reflects changes in joint function^{21,22}, which our results further corroborate, emphasizing its importance in disease assessment.

While previous studies have explored the roles of IL-6 and COMP in KOA, this study's innovation lies in systematically analyzing the dynamic changes of these indicators across different K-L grades and relating them directly to disease progression. By incorporating Cox proportional hazard and multiple linear regression models, this study solidified the status of IL-6 and COMP as independent predictors and underscored their potential for clinical application. Furthermore, the study confirmed the strong diagnostic performance of these biomarkers in monitoring KOA disease

through ROC curve analysis, offering a solid foundation for future clinical practices.

Limitations

This study has several limitations. As a single-center retrospective study, there may be sample selection bias, and the lack of dynamic data on patient follow-up is another limitation. Additionally, other potential biomarkers and environmental factors that could influence the results were not considered. Although the use of multiple statistical methods improved the reliability of the findings, the applicability of these results across different ethnicities and regions still requires further validation.

Future Directions

Future studies should consider multicenter designs to increase sample diversity and representativeness. Incorporating a comprehensive assessment of additional biomarkers will provide a more holistic understanding of KOA. Monitoring IL-6 and COMP could serve as the foundation for personalized treatment strategies for KOA patients, particularly for early intervention and treatment response assessment. The development of treatment strategies based on these biomarkers holds promise for improving the management of KOA. Further prospective studies are needed to validate the practical application of these biomarkers in clinical settings.

Conclusion

This study found that IL-6 and COMP levels in synovial fluid significantly increased with K-L grade in KOA patients, were closely related to disease progression, and exhibited important predictive value. These findings highlight the potential application of these biomarkers in monitoring KOA and in personalized treatment approaches, providing a new scientific basis for clinical management.

Ethics approval

This study was approved by the Medical Ethics Committee of the Linyi People's Hospital. (LCKY-LY2023087). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki (1964) and its subsequent amendments.

Consent to participate

Written informed consent was obtained from all participants.

Authors' contributions

CZ and LJ designed the study. KL collated the data, carried out data analyses. CZ and NS contributed to drafting the manuscript. All authors read and approved the final submitted manuscript.

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