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Expressions of insulin-like growth factor-1, interleukin-1β, and matrix metalloproteinase-13 in patients with knee osteoarthritis and their associations with the severity

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ABSTRACT

Background: A key factor in the pathogenesis of osteoarthritis is an imbalance in cytokines, favoring proinflammatory activity. This study aimed to explore the expressions of insulin-like growth factor-1 (IGF-1), interleukin-1β (IL-β) and matrix metalloproteinase-13 (MMP-13) in patients with knee osteoarthritis (KOA), as well as their associations with the severity.

Methods: Subjects (166 in total) were recruited from KOA patients treated between January 2021 and June 2023. Their clinical data were collected, disease severity was assessed by Kellgren-Lawrence (K-L) grades, and venous blood was drawn to measure the serum levels of IGF-1, MMP-13, and IL-1β. Factors affecting the severity of KOA were analyzed by multivariate logistic regression model incorporating the aforementioned information.

Results: There were more cases of disease course >1 year, body mass index (BMI) >25 kg/m2, heavy physical labor, and osteoporosis in the severe group (P<0.05). Multivariate logistic regression analysis revealed that disease course >1 year, BMI >25 kg/m2, heavy physical labor, osteoporosis, lowly expressed MMP-13, and lowly expressed IL-1β were risk factors for the severity of KOA [odds ratio (OR) >1, P<0.05], while highly expressed IGF-1 was a protective factor (OR<1, P<0.05). The areas under the receiver operating characteristic (ROC) curves (95% confidence interval) of IGF-1, MMP-13, and IL-1β levels and their combination for assessing the severity of KOA were 0.883 (0.823-0.942), 0.880 (0.827-0.934), 0.895 (0.847-0.943), and 0.923 (0.877-0.968), respectively.

Conclusions: IGF-1 is lowly expressed, whereas MMP-13 and IL-1β are highly expressed. The combined application of the three indicators has the highest value for assessing the severity of KOA.

Keywords: expression, insulin-like growth factor, interleukin, knee osteoarthritis, matrix metalloproteinase

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INTRODUCTION

In China, knee osteoarthritis (KOA) has a prevalence rate of 68% in the elderly aged over 65 years old, and it also has a high disability rate, with limb dysfunction found in about 53% of all patients diagnosed with KOA [1]. In the early stage, KOA is easily overlooked since there are no obvious symptoms, but as the disease progresses, symptoms such as redness, swelling, snapping, stiffness, and soreness gradually occur, even resulting in activity limitations in severe cases [2]. KOA is mainly characterized by degenerative pathological changes, accompanied by osseous hyperplasia, cartilage damage, etc. [3]. In clinical practice, corresponding therapeutic regimens are formulated based on the disease severity. At present, the severity of KOA is mainly assessed by the Kellgren-Lawrence (K-L) grades, which, however, lack reliable predictors. Hence, finding effective predictors is of great significance for disease evaluation and prognosis improvement.

The multifactorial pathogenesis of KOA involves a complex interplay among synovial inflammation, subchondral bone changes, and mechanical factors, all of which contribute to joint degeneration and functional impairment [4]. Synovial inflammation is recognized as a key driver in the early stage of KOA. Pro-inflammatory cytokines, such as interleukin-1β (IL-1β), initiate and maintain the inflammatory cascade within the joint, leading to the degradation of cartilage and subsequent pain and swelling [5,6]. Besides, insulin-like growth factor-1 (IGF-1) plays an anabolic role by promoting chondrocyte proliferation and matrix synthesis, which may help counteract the deleterious effects of mechanical stress and inflammation [7,8]. In contrast, matrix metalloproteinase-13 (MMP-13) is a key enzyme involved in

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the breakdown of extracellular matrix components in both cartilage and subchondral bone, making it a key mediator in the degenerative process [9].

Despite the well-established roles of these mediators in cartilage homeostasis and joint integrity, their expressions in KOA and their associations with disease severity remain largely unknown. Given this, the present study elucidated these relationships by evaluating serum levels of IGF-1, MMP-13, and IL-1β in KOA patients and correlating these biomarkers with radiographic severity as determined by the K-L classification. By focusing on the contributions of synovial inflammation, subchondral bone changes, and mechanical factors, we aimed to provide a more comprehensive understanding of KOA progression and to identify potential targets for early intervention and therapeutic monitoring.

METHODS

Subjects

This study was approved by the ethics committee of our hospital, and written informed consent was obtained from all patients. A total of 166 KOA patients hospitalized for treatment herein between January 2021 and June 2023 was enrolled in this study, including 70 males and 96 females. Besides, 75 patients aged <60 years old and 91 patients aged ≥60 years old were recorded. As to disease course, there were 78 cases with disease course <1 year and 85 cases with disease course ≥1 year. Regarding body mass index (BMI), 74 cases of BMI ≤25 kg/m^2 and 92 cases of >25 kg/m^2 were observed. Moreover, 84 patients engaged in heavy physical labor, while the remaining 82 ones did not.

Inclusion and exclusion criteria

The following inclusion criteria were utilized: 1) patients meeting the diagnostic criteria for KOA [10], 2) those diagnosed with KOA by X-ray examinations, 3) those with unilateral knee affected, 4) those with morning stiffness time <0.5 h, 5) those with good compliance, 6) those with normal cognitive function, 7) those with normal coagulation function, and 8) those voluntarily signing the informed consent to the study.

The exclusion criteria involved: 1) patients complicated with rheumatoid arthritis, 2) those with arthritic symptoms caused by other factors, 3) those complicated with autoimmunodeficiency diseases, 4) those with severe hepatic or renal insufficiency, 5) those complicated with other infectious diseases, 6) those with disability before developing the disease, 7) those with a history of knee surgery, 8) pregnant or lactating females, or 9) those complicated with malignancies.

Grouping method

All subjects were evaluated for K-L grades, and a mild-to-moderate group (patients with K-L grades I-II) and a severe group (patients with K-L grades III-IV) were set up. The K-L grading was independently performed by two experienced radiologists who were blinded to the patients' clinical information. The inter-observer agreement was calculated using Cohen's kappa statistic, which showed good agreement (kappa = 0.80). In the case of discrepancies, a consensus was reached through discussion.

IGF-1, MMP-13, and IL-1beta measurement

Fasting venous blood (4 mL) was collected into an anticoagulant-free tube from all subjects in the early morning of the first day after admission, left still for 20 min and centrifuged at 3500 r/min (radius: 12 cm) and 4°C for 10 min. Afterwards, the upper layer serum was separated and stored in a refrigerator at -20°C. Next, the serum levels of IGF, MMP-13, and IL-1β were measured by enzyme-linked immunosorbent assay kits purchased from Wuhan Bioswamp Co., Ltd. (China) strictly following relevant instructions.

Collection of clinical data

The sex (male or female), age (<60 years old or ≥60 years old), disease course (<1 year or ≥1 year), BMI (≤25 kg/m2 or >25 kg/m2), heavy physical labor (yes or no), drinking history (yes or no), smoking history (yes or no), and osteoporosis (yes or no) of all subjects were recorded.

Statistical analysis

SPSS 25.0 software was employed for statistical analysis. Measurement data were expressed in the format of (mean ± SD) and subjected to the independent-samples t-test. Count data were represented as [n (%)] and examined through the $\chi 2$ test. Factors affecting the severity of KOA were analyzed through multivariate logistic model. The receiver operating characteristic (ROC) curves were plotted, based on which the areas under the curve (AUCs) were yielded to analyze the values of IGF-1, MMP-13, and IL-1β levels for predicting the severity of KOA. P<0.05 denoted a statistically significant difference.

RESULTS

K-L grades

Among the 166 KOA subjects, K-L grades I, II, III, and IV were found in 30, 39, 75, and 22 subjects, respectively. The mild-to-moderate group consisted of 69 patients with grade I-II, while the severe group was composed of 97 patients with grade III-IV.

IGF-1, MMP-13, and IL-1beta levels

The severe group had a lower IGF-1 level and higher MMP-13 and IL-1β levels than those of the mild-to-moderate group (p<0.05) (Table 1).

Clinical data

The sex, age, drinking history, and smoking history were comparable between the two groups (p>0.05). The severe group had more patients with disease duration >1 year, BMI >25 kg/m2, heavy physical labor, and osteoporosis (p<0.05) (Table 2).

Multivariate logistic regression analysis

Multivariate logistic regression analysis was carried out with the severity of KOA (severe/mild-to-moderate =1/0) as the dependent variable and the items showing differences in Table 1 and 2 as the independent variables. The results showed that the disease course >1 year, BMI >25 kg/m2, heavy physical labor, osteoporosis, lowly expressed MMP-13, and lowly expressed IL-1β were all risk factors affecting the severity of KOA [odds ratio (OR) >1, p<0.05], while highly expressed IGF-1 was a protective factor (OR<1, p<0.05) (Table 3 and Figure 1).

Assessment value

The ROC curves were plotted with the severity of KOA (severe/mild-to-moderate =1/0) as the state variable and the IGF-1, MMP-13, and IL-1β levels as the test variables. It was found that the AUCs [95% confidence interval (95% CI)] of IGF-1, MMP-13, and IL-1β levels and their combination for assessing the severity of KOA reached 0.883 (0.823-0.942), 0.880 (0.827-0.934), 0.895 (0.847-0.943), and 0.923 (0.877-0.968), respectively (Table 4, Figure 2).

Table 1. IGF-1, MMP-13, and IL-1β levels

Group	IGF-1 (ng/mL)	MMP-13 (pg/mL)	IL-1β (pg/mL)
Mild-to-moderate (n=69)	85.25 ± 10.37	135.26 ± 12.47	71.26 ± 8.12
Severe (n=97)	68.43 ± 6.37	172.12 ± 15.36	111.56 ± 15.35
t	12.919	16.444	19.906
p value	< 0.001	< 0.001	< 0.001

Abbreviations: IGF-1 – insulin-like growth factor-1, IL-1β – interleukin-1beta, MMP-13 – matrix metalloproteinase-13

Table 2. Demographic and clinical data [n (%)]

Item		Severe group (n=97)	Mild-to-moderate group (n=69)	χ^2	p value
Sex	Male	40 (41.24)	30 (43.48)	0.083	0.773
	Female	57 (58.76)	39 (56.52)		
Age (year)	≥60	55 (56.70)	36 (52.17)	0.334	0.564
	<60	42 (43.30)	33 (47.83)		
Disease course (years)	>1	60 (61.86)	25 (36.23)	9.049	0.003
	≤1	37 (38.14)	41 (59.42)		
Body mass index (kg/m^2)	>25	63 (64.95)	29 (42.03)	8.573	0.003
	≤25	34 (35.05)	40 (57.97)		
Heavy physical labor	Yes	59 (60.82)	25 (36.23)	9.756	0.002
	No	38 (39.18)	44 (63.77)		
Drinking history	Yes	28 (28.87)	14 (20.29)	1.569	0.210
	No	69 (71.13)	55 (79.71)		
Smoking history	Yes	25 (25.77)	15 (21.74)	0.359	0.549
	No	72 (74.23)	54 (78.26)		
Osteoporosis	Yes	55 (56.70)	23 (33.33)	8.839	0.003
	No	42 (43.30)	46 (66.67)		

Table 3. Results of multivariate logistic regression analysis

Factor	Assignment	β	SE	Wald χ^2	p value	OR	95%CI
Disease course	≤1 year = 0, >1 year = 1	0.978	0.329	8.852	0.003	2.659	1.396-5.066
Body mass index	≤25 kg/m2 = 0, >25 kg/m2 = 1	0.938	0.324	8.404	0.004	2.556	1.355-4.820
Heavy physical labor	No = 0, Yes = 1	1.005	0.326	9.534	0.002	2.733	1.444-5.173
Osteoporosis	No =0, Yes =1	0.963	0.327	8.647	0.003	2.619	1.379-4.976
IGF-1	Original value input	0.236	0.035	45.783	0.000	0.790	0.738-0.846
MMP-13	Original value input	0.204	0.035	33.491	0.000	1.226	1.145-1.314
IL-1β	Original value input	0.219	0.039	32.062	0.000	1.244	1.154-1.342

Abbreviations: IGF-1 – insulin-like growth factor-1, IL-1β – interleukin-1beta, MMP-13 – matrix metalloproteinase-13.

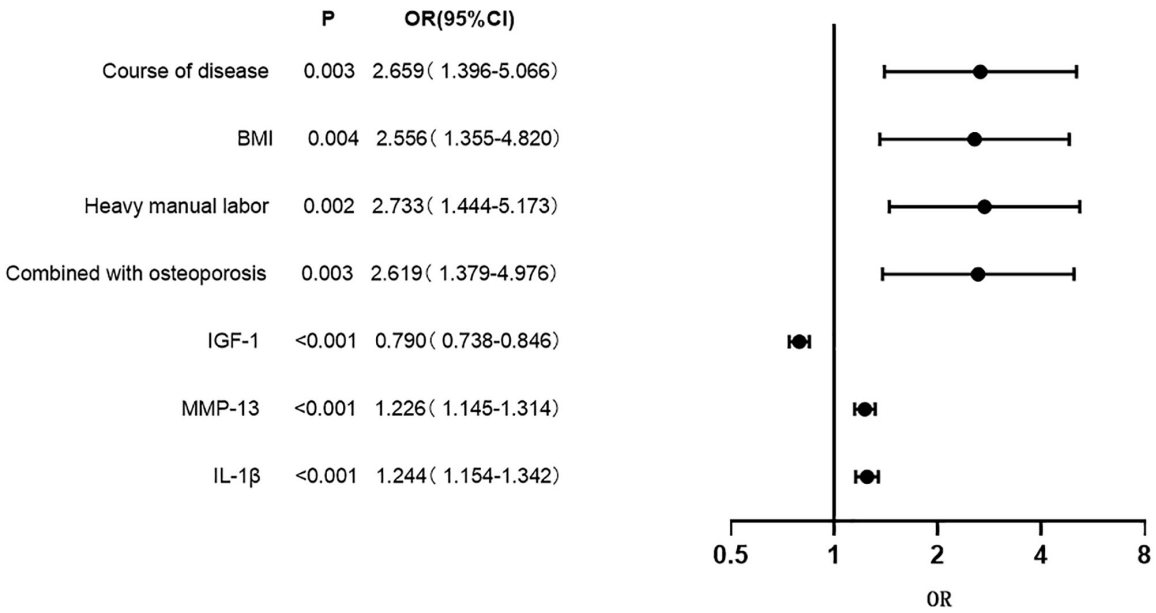

Figure 1. Forest plots of clinical characteristics based on multivariate logistic regression analysis.

Table 4. Value of IGF-1, MMP-13, and IL-1β levels for assessing the severity of KOA

Indicator	AUC	SE	Cut-off	95% CI	*p* value	Specificity	Sensitivity	Youden index
IGF-1	0.883	0.030	102.364	0.823-0.942	0.000	0.841	0.814	0.655
MMP-13	0.880	0.027	162.351	0.827-0.934	0.000	0.783	0.794	0.577
IL-1β	0.895	0.024	95.142	0.847-0.943	0.000	0.826	0.835	0.661
Combination	0.923	0.023	-	0.877-0.968	0.000	0.870	0.887	0.757

Abbreviations: IGF-1 – insulin-like growth factor-1, IL-1β – interleukin-1beta, MMP-13 – matrix metalloproteinase-13.

DISCUSSION

In China, KOA has an increasing prevalence rate with the aggravation of population aging, which has become one of the leading causes of disability in middle-aged and elderly people [11]. In this study, among the 166 KOA patients, 30 patients had K-L grade I KOA, 39 had grade II KOA, 75 had grade III KOA, and 22 had grade IV KOA, suggesting that the majority of KOA patients have progressed to the advanced stage on diagnosis. Therefore, discovering indicators sensitive to KOA is an urgent issue.

Serological detection has become a crucial tool to evaluate KOA in clinical practice since it is simple, reproducible, and highly safe and supports dynamic monitoring. A study reported that both KOA and rheumatoid arthritis are induced by cartilage damage, which is mainly ascribed to the reduction of proteoglycan (PG) and type II collagen in the extracellular matrix. PG exerts the anti-compression and lubricating effects, while type II collagen has supporting and anti-tensile effects, and the decrease in PG is regarded as an initiating factor [12]. As an important member of the growth factor family, IGF-1 is highly similar to the insulin structure, mainly distributed in the local matrix around cartilage tissues, and its expression level is relatively constant [13]. The results of this study revealed that IGF-1 level was lower in the severe group than in the mild-to-moderate group, revealing that a close relationship exists between KOA severity and IGF-1 level. IGF-1 is capable of effectively facilitating the mitosis and proliferation of chondrocytes, as well as the secretion of PG and type II collagen, especially the decomposition of PG caused by inflammatory stimuli, thus increasing the content of PG in chondrocytes and playing a vital role in the repair of cartilage [14]. Moreover, IGF-1 can suppress the activity of MMPs to a certain extent, thereby avoiding further inflammatory factor-induced damage to chondrocytes [15]. However, IGF1

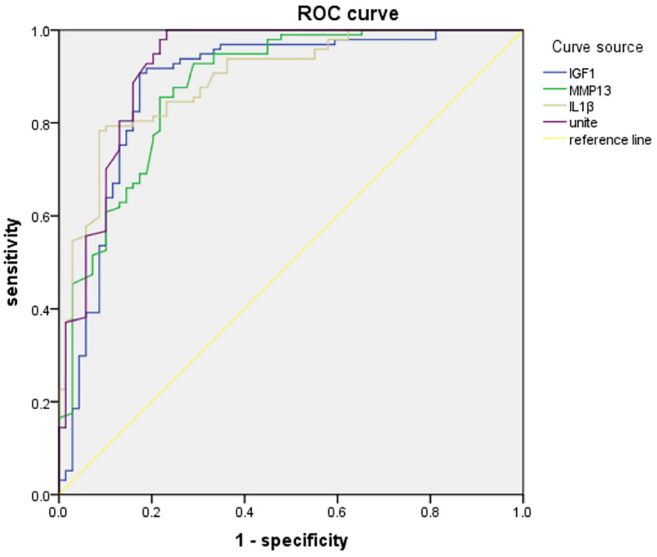

Figure 2. ROC curves for KOA severity assessment

may not always be protective, depending on systemic inflammation and insulin resistance [16]. Hence, further studies are still in need.

Cartilage degeneration has been closely related to the synthesis, degradation, and dysregulation of matrixes, in which MMPs play a dominant role [17]. Notably, MMP-13 has the highest activity and specificity for collagen. Inflammatory responses are implicated in the onset and progression of KOA, and IL-1β is a proinflammatory factor with pivotal functions in the degradation of cartilage [18,19]. In this study, MMP-13 and IL-1β levels rose in the severe group compared to those in the mild-to-moderate group, and highly expressed MMP-13 and IL-1β were risk factors for the aggravation of KOA. Possibly, MMP-13 can directly decompose the triple helix structure of type II collagen, which is essential for stabilizing the structure of cartilages, and the gradual decomposition of type II collagen results in reduced stability of the cartilage structure, giving rise to osteoarticular lesions [20]. Additionally, IL-1β mainly originates from macrophages and monocytes, and its high expression-induced aggravation of KOA is mainly attributed to the following facts. First, IL-1β can up-regulate the expression level of MMPs. Second, it stimulates the release of inflammatory factors such as tumor cell necrosis factor-α and exerts a synergistic effect, further exacerbating inflammatory responses, dissolving cartilage tissues, and promoting disease progression. Third, IL-1β is able to directly stimulate chondrocytes and inhibit PG synthesis, thus facilitating the decomposition of the endochondral matrix and accelerating apoptosis [21,22]. In this study, the AUCs (95%CI) of IGF-1, MMP-13, and IL-1β levels and their combination for assessing the severity of KOA were 0.883 (0.823-0.942), 0.880 (0.827-0.934), 0.895 (0.847-0.943), and 0.923 (0.877-0.968), respectively, demonstrating that the abnormal expressions of IGF-1, MMP-13 and IL-1β had close associations with KOA.

Moreover, this study also showed that the proportions of patients with disease duration >1 year, BMI >25 kg/m2, heavy physical labor, and osteoporosis were higher in the severe group than those in the mild-to-moderate group. Besides, the above-mentioned indicators were identified as risk factors for the severity of KOA. The reasons are as follows. Firstly, with the prolongation of disease course, the degree of joint damage rises, and it is easy to miss the optimal opportunity for treatment, leading to a poor prognosis in most cases. Secondly, patients with BMI >25 kg/m2 are considered obese, and the knee joint, a vital tissue for the body to bear the force, bears more load in this case, resulting in greater wear when walking and going up and down stairs. Thirdly, similar to obese people, patients with heavy physical labor also have faster disease progression, because their knee joints are subject to more wear. Fourthly, osteoporosis influences the bones of the whole body, and KOA patients with this disease have more brittle and thinner bones and joints, and the two diseases interact to accelerate the progression of diseases [23,24]. Hence, it is necessary to record the clinical information and medical history of patients in detail before treatment, actively prevent and treat the above risk factors, and formulate reasonable therapeutic regimens to control disease progression.

Nevertheless, this study is limited. First, the analysis relies only on serum biomarkers without considering synovial fluid or cartilage samples which provide a more direct reflection of local joint pathology. Second, this is a retrospective single-center study. Third, the correlations among IGF-1, MMP-13, and IL-1β are not investigated, and the detailed mechanism remains unclear. Hence, further studies are still required to validate our findings.

CONCLUSIONS

In conclusion, a low expression of IGF-1 and high expressions of MMP-13 and IL-1β are observed in the case of KOA. The combined application of the three indicators is of highest value for assessing the severity of KOA.

ABBREVIATIONS

AUC – area under the curve

BMI – body mass index

IGF-1 – insulin-like growth factor-1

IL – interleukin

K-L – Kellgren-Lawrence

MMP – matrix metalloproteinase

ROC – receiver operating characteristic

CONFLICT OF INTEREST

None to declare.

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