BMC Musculoskeletal Disorders

RESEARCH

Open Access

Serum and synovial fluid levels of CSF-1 and in knee osteoarthritis and its clinical significance

Yuanchi Huang[1], Wenjie Pan[1], Huanli Bao[1], Chao Xu[1*] and Jianbing Ma[1*]

Abstract

Objective To investigate the serum and synovial fluid levels of CSF-1 in patients with knee osteoarthritis (KOA) and evaluate its clinical significance.

Methods We selected 143 patients with KOA who received treatment at our hospital from June 2021 to August 2024. Enzyme-linked immunosorbent assay (ELISA) was used to determine the levels of CSF-1, IL-6, IL-1β, CRP, and HIF-1α in the serum of all study subjects, as well as the levels of these markers in the synovial fluid of all KOA patients. The Kellgren and Lawrence (KL) grading system was used to assess the radiographic severity of all KOA patients. Additionally, we also collected the Visual Analog Scale (VAS) scores and the Western Ontario McMaster University Osteoarthritis Index (WOMAC). Western blot (WB) was used to detect the expression levels of inflammatory factors in macrophages after CSF-1 stimulation.

Results Compared to healthy volunteers, KOA patients exhibited significantly elevated levels of serum CSF-1, IL-6, IL-1β, CRP, and HIF-1α ($p < 0.05$). The advanced group of KOA patients had significantly higher levels of serum and synovial fluid CSF-1 compared to the early group. Synovial fluid CSF-1 levels were associated with inflammation and disease severity in KOA patients. CSF-1 stimulation significantly increased the expression of CSF-1R, IL-6, TNF-α, IL-1β, HIF-1α, and MMP-3 in macrophages. Moreover, synovial fluid and serum CSF-1, synovial fluid HIF-1α, and synovial fluid IL-6 were identified as risk factors for advanced KOA.

Conclusion Our findings indicated that the serum and synovial fluid levels of CSF-1 were significantly increased in KOA patients, even higher in patients with KL grade 3–4. Moreover, CSF-1 was identified as a risk factor associated with advanced stage KOA.

Keywords Colony stimulating factor-1, Cytokines, Knee osteoarthritis, Synovial fluid

*Correspondence:
Chao Xu
383697196@qq.com
Jianbing Ma
JianbingMa2023@163.com
[1]Department of Joint Surgery, Honghui Hospital, Xi'an Jiaotong University, 555 East Friendship Road, South Gate, Xi'an 710054, China

Introduction

Clinical studies have shown that the incidence of OA is significantly increasing and developing at a younger age. Effective prevention and control of OA is also one of the important topics of current clinical research [1, 2, 3]. However, at present, the clinically effective treatment plan for OA still needs to be further clarified [4]. The pathogenesis of osteoarthritis (OA) remains unclear, involving a complex interplay of systemic and local factors [5]. The important pathological feature of OA is the degradation of articular cartilage, in which chondrocyte apoptosis plays a key role [6, 7]. Articular cartilage, similar to other avascular cartilaginous tissues, relies on nutrient diffusion for maintenance and repair. Aging and degenerative changes impair the diffusion of oxygen and nutrients, leading to progressive cartilage degradation and extracellular matrix loss, key features in the pathogenesis of KOA [8]. Coupled with pressure and inflammation, the extracellular matrix related to articular cartilage tissue will also gradually decrease [9].

Colony-stimulating factor-1 (CSF-1) is one of the most common pro-inflammatory cytokines that can contribute to various inflammatory diseases [10]. CSF-1 is an important signal transduction factor in the inflammatory environment of synovial membrane in osteoarthritis, which can induce a variety of inflammatory factors and participate in the inflammatory response of the body [11]. A study based on synovial fluid datasets from osteoarthritis patients identified high expression of the CSF-1 receptor (CSF-1R) through the computational construction and analysis of the protein-protein interaction (PPI) network [12]. Furthermore, research has demonstrated that targeting macrophage CSF-1 to regulate macrophages can promote the regeneration of the temporomandibular joint, thereby serving a therapeutic role in arthritis [13]. However, no clinical studies have focused on the levels of serum as well as synovial fluid CSF-1 in patients with knee osteoarthritis (KOA). In order to further clarify the clinical significance of CSF-1 in KOA patients, serum and synovial fluid from patients with KOA were collected in this study, and the results are reported as follows.

Data and methods

General information

We selected 143 patients with KOA who received treatment at our hospital from June 2021 to August 2024. All KOA patients were over 18 years old and diagnosed with primary knee osteoarthritis according to the criteria of the American College of Rheumatology [14]. Exclusion criteria included: (a) secondary osteoarthritis; (b) patients who received intra-articular injections or local blockade therapy within one week; (c) patients who received immunotherapy or anti-inflammatory treatment within one month; (d) patients with comorbid metabolic diseases such as diabetes, chronic kidney disease, or thyroid disease; (e) patients with severe infections, malignant tumors, or cardiac, hepatic, or renal dysfunction. In addition, we also enrolled 100 healthy volunteers who underwent physical examinations at our hospital during the same period as controls. Age, gender, and BMI of all study participants were collected. The study complied with the Helsinki Declaration, and informed consent was obtained from all study subjects. The research was approved by the Ethics Committee of Honghui Hospital, Xi'an Jiaotong University.

Enzyme-linked immunosorbent assay

Prior to treatment, knee joint fluid was extracted from KOA patients during arthroscopic examination. The patients were positioned in a sitting position with knee flexed at 90°, and the needle was inserted at the medial and lateral sides below the patella. A 5 mL disposable syringe was used to enter the joint cavity, and after aspiration with no blood reflux, synovial fluid was collected. The synovial fluid samples were collected and immediately centrifuged at 2000 g for 15 min at 4 °C to separate the supernatant, which was stored at -70 °C for further analysis. Hyaluronidase treatment was not applied during sample preparation. Additionally, fasting venous blood samples (5 mL) were collected from all study participants and stored at -70℃ after centrifugation at 2000 g for 15 min. The levels of CSF-1, IL-6, IL-1β, CRP, and HIF-1α in the serum of all study participants, as well as in the synovial fluid of all KOA patients were measured using enzyme-linked immunosorbent assay (ELISA). The analysis was performed according to the instructions provided by the commercially available assay kits (CFS-1, MBS705004, IL-6, MBS175877, IL-1β, MBS175901, CRP, MBS2505217, HIF-1α, MBS2022610, MyBioSource, California, USA).

Assessment of severity in patients with KOA

The Kellgren and Lawrence (KL) grading system was used to assess the radiographic severity of all KOA patients [15]. The KL grades are as follows: Grade 0 represents no changes (normal); Grade I represents mild osteophytes; Grade II represents moderate osteophytes without joint space narrowing; Grade III represents moderate osteophytes with moderate joint space narrowing and some sclerosis; Grade IV represents extensive osteophytes with significant joint space narrowing and subchondral bone sclerosis. Additionally, we also utilized the Visual Analog Scale (VAS) [16] to evaluate the pain intensity of KOA patients' knee joints and the Western Ontario McMaster University Osteoarthritis Index (WOMAC) [17] to assess the severity of OA symptoms.

Macrophage isolation and culture from OA synovial fluid

Synovial fluid samples were collected under aseptic conditions and immediately transferred to the laboratory for processing. Synovial fluid mononuclear cells (SFMCs) were isolated using density gradient centrifugation with Ficoll-Paque™ PLUS (GE Healthcare, Piscataway, NJ). Cell debris and dead cells were removed using a dead cell exclusion kit (Miltenyi Biotec). Macrophages were then isolated from SFMCs using a monocyte isolation kit (Miltenyi Biotec) according to the manufacturer's protocol. The purity of the isolated macrophages was confirmed by flow cytometry using an anti-CD14 antibody, which demonstrated a high purity of ≥ 95% CD14 + cells (Supplementary Fig. 1). The isolated macrophages were cultured in RPMI-1640 medium (Gibco, Thermo Fisher Scientific, USA) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin at 37 °C with 5% CO_2 for subsequent experiments.

CSF-1 stimulation protocol

Macrophages were divided into two experimental groups: a control group (no CSF-1 stimulation) and a treatment group stimulated with CSF-1. In the CSF-1 group, recombinant human CSF-1 (PeproTech, USA) was added at a concentration of 50 ng/mL. Cells were incubated for 24 h under standard culture conditions to allow for adequate stimulation.

Western blot analysis

Macrophages were harvested post-stimulation, lysed in RIPA buffer containing protease and phosphatase inhibitors (Thermo Fisher Scientific, USA). Protein concentrations were quantified using a BCA assay kit (Pierce, Thermo Fisher Scientific, USA). Samples were resolved on 10% SDS-PAGE gels and transferred to PVDF membranes (Millipore, USA). Membranes were blocked with 5% BSA and probed overnight at 4 °C with primary antibodies against CSF-1R (Abcam, USA), IL-6, TNF-α, IL-1β, HIF-1α, MMP-3 and GAPDH (Cell Signaling Technology, USA), diluted at 1:1000. Secondary antibodies (anti-rabbit IgG, Cell Signaling Technology) were applied, and bands were visualized using an ECL substrate (Thermo Fisher Scientific, USA). Densitometric analysis was performed using ImageJ software to compare protein expression levels across groups.

Table 1 Demographic and clinical data of all subjects

Variable	KOA patients, n=143	Healthy, n=100	p
Age, y	59 (45-73)	60 (48-71)	0.358
Sex, female (%)	81 (56.6)	59 (59.0)	0.731
BMI	25.74±2.28	25.14±2.30	0.077
Serum CSF-1 (pg/mL)	116.12±16.89	79.59±6.09	<0.001
Serum IL-6 (pg/mL)	19.18±3.79	11.03±1.77	<0.001
Serum IL-1β (pg/mL)	20.43±2.50	8.83±1.54	<0.001
Serum CRP (ng/mL)	11.47±2.17	4.70±1.17	<0.001
Serum HIF-1α (ng/mL)	3.97±0.65	2.14±0.29	<0.001
VAS scores	4.65±1.50		
WOMAC	39.14±14.14		
K-L	3 (2-4)		

Statistical treatment

All data used SPSS 26.0 to analysis. The comparison between two groups with a normal distribution was conducted using the Mann-Whitney test. For the comparison between two groups with a non-normal distribution, the Student's *t*-test was employed. The Chi-square test was used for comparing ratios. Spearman's rank correlation was used for correlation analysis. ROC curve analysis was used to analyze the value of blood and synovial fluid CSF-1 in the diagnosis of KOA patients with advanced stage (KL grade 3 or 4). Multivariable logistic regression analysis was performed to identify risk factors associated with advanced stage in KOA patients. $P < 0.05$ regarded as a significant difference.

Results

Clinical characteristics of all participants

We first compared the demographic data and serum biomarkers levels between KOA patients and healthy volunteers. The results were shown in Table 1; Fig. 1, we found no significant differences in age, gender, and BMI between KOA patients and healthy volunteers. However, compared to healthy volunteers, KOA patients exhibited significantly elevated levels of serum CSF-1, IL-6, IL-1β, CRP, and HIF-1α ($p < 0.05$).

The serum and synovial fluid levels of CSF-1 in KOA patients with different KL grade

Subsequently, we performed radiographic examinations and assessed the KL grading in all KOA patients. Based on previous studies [18], we categorized all KOA patients into the advanced group (KL grade 3 or 4, $n = 82$) and the early group (KL grade 2, $n = 61$). When comparing the levels of serum and synovial fluid markers between the two groups, we found that the advanced group of KOA patients had significantly higher levels of serum (Fig. 2) and synovial fluid (Fig. 3) CSF-1 compared to the early group ($p < 0.05$). Additionally, the synovial fluid levels of IL-6, IL-1β, and HIF-1α were also significantly elevated in the advanced group ($p < 0.05$). No differences were observed between the two groups in terms of serum levels of IL-6, IL-1β, CRP, and HIF-1α.

The correlation of synovial fluid levels of CSF-1 with cytokines and disease severity in KOA patients

We used Spearman rank correlation analysis to evaluate the correlation between synovial fluid CSF-1 levels,

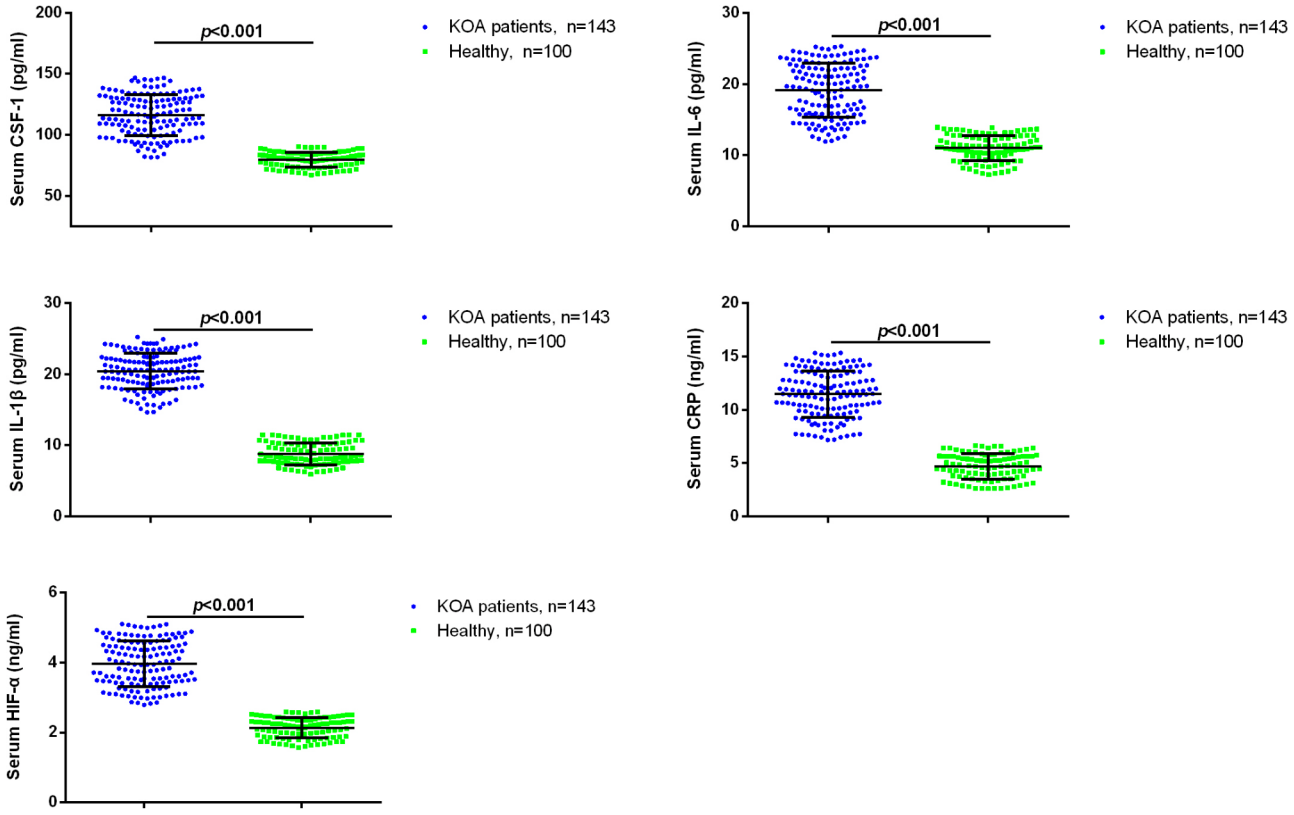

Fig. 1 Serum levels of cytokines in all subjects

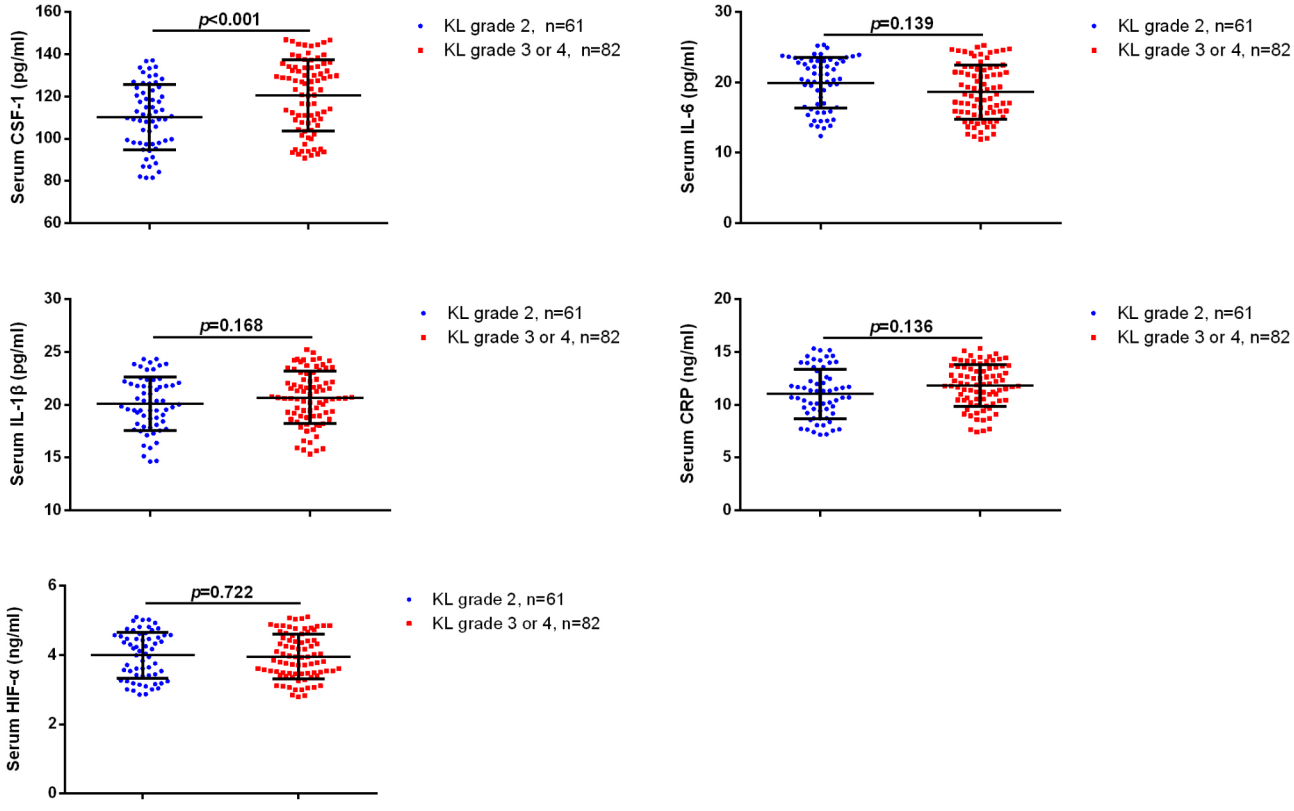

Fig. 2 Serum levels of cytokines in KOA patients

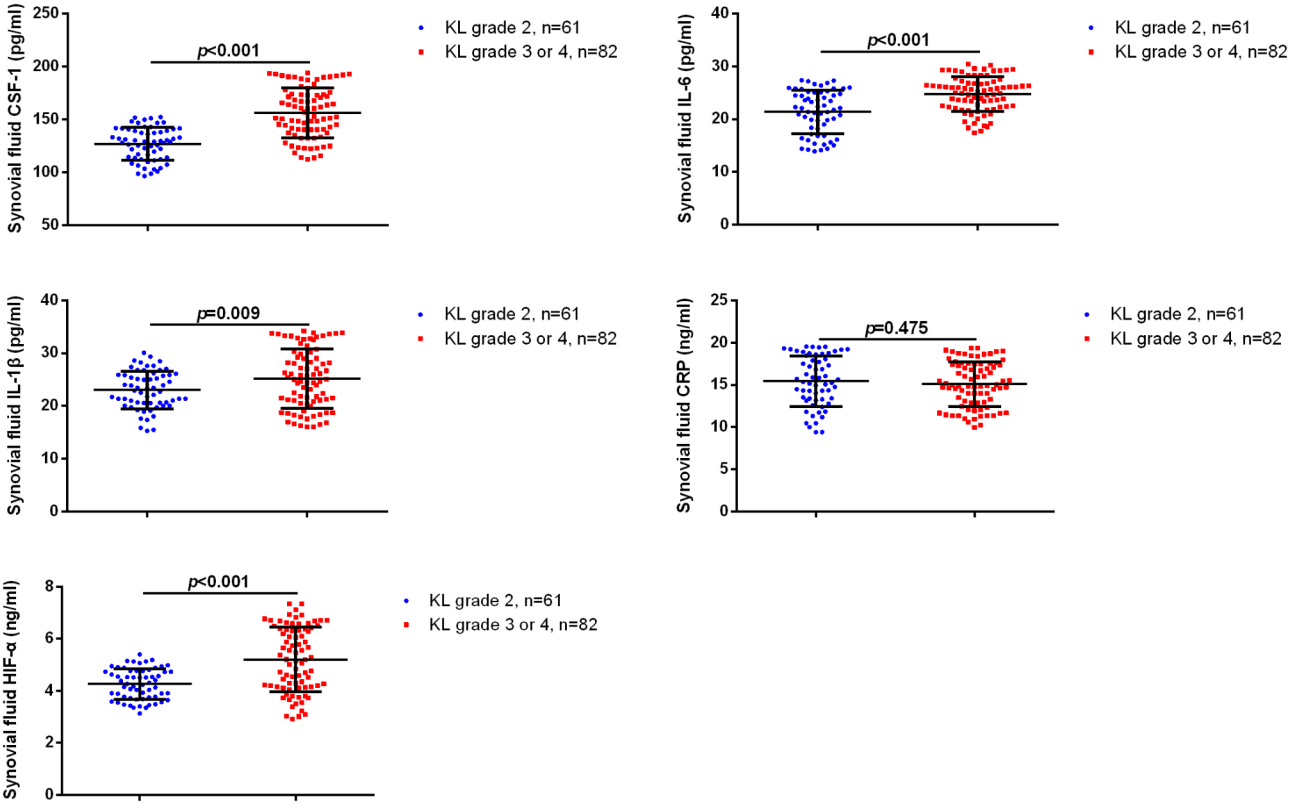

Fig. 3 Synovial fluid levels of cytokines in KOA patients

Table 2 Correlation between synovial fluid levels of CSF-1 with cytokines and disease severity in KOA patients

Variable	CSF-1 in SF	
	Spearman's correlation	P
IL-6 in SF	0.200	0.017
IL-1β in SF	0.155	0.065
CRP in SF	-0.070	0.403
HIF-1α in SF	0.226	0.007
VAS scores	0.465	<0.001
WOMAC index	0.510	<0.001

cytokine levels, and disease severity. The results were shown in Table 2 and Fig. 4, indicating a positive correlation between synovial fluid CSF-1 and cytokines IL-6. Additionally, synovial fluid CSF-1 was positively correlated with KOA patients' VAS scores, and WOMAC index. This suggested that synovial fluid CSF-1 levels were associated with inflammation and disease severity in KOA patients. Moreover, the Western blot analysis revealed that CSF-1 stimulation significantly increased the expression of CSF-1R, IL-6, TNF-α, IL-1β, HIF-1α, and MMP-3 in macrophages compared to the control group. These findings suggest that CSF-1 promotes an inflammatory response in macrophages (Fig. 5).

Diagnostic value of CSF-1 in patients with advanced KOA

To evaluate the diagnostic value of CSF-1 for advanced KOA patients, we constructed ROC curves. The results showed that compared to serum CSF-1, synovial fluid CSF-1 had a better diagnostic value for advanced KOA patients (Fig. 6). The AUC for CSF-1 in diagnosing advanced KOA patients was 0.834, with a cutoff value of 139.74 pg/ml, a sensitivity of 75.6%, and a specificity of 75.4%.

Identification of risk factors for advanced KOA using logistic regression analysis

To identify risk factors for advanced KOA, we performed multivariate logistic regression analysis using the enter method. The results showed that synovial fluid and serum CSF-1, synovial fluid HIF-1α, and synovial fluid IL-6 were identified as risk factors for advanced KOA (Table 3).

Discussion

At present, the main clinical feature of KOA patients is the degenerative change of knee cartilage. Knee osteoarthritis (KOA) affects the cartilage, underlying bone, and synovial tissue. Pathological changes in any part of the tissue are an important mechanism for the initiation of OA, and the final result is damage to articular cartilage [19, 20]. At present, the specific pathogenesis of the

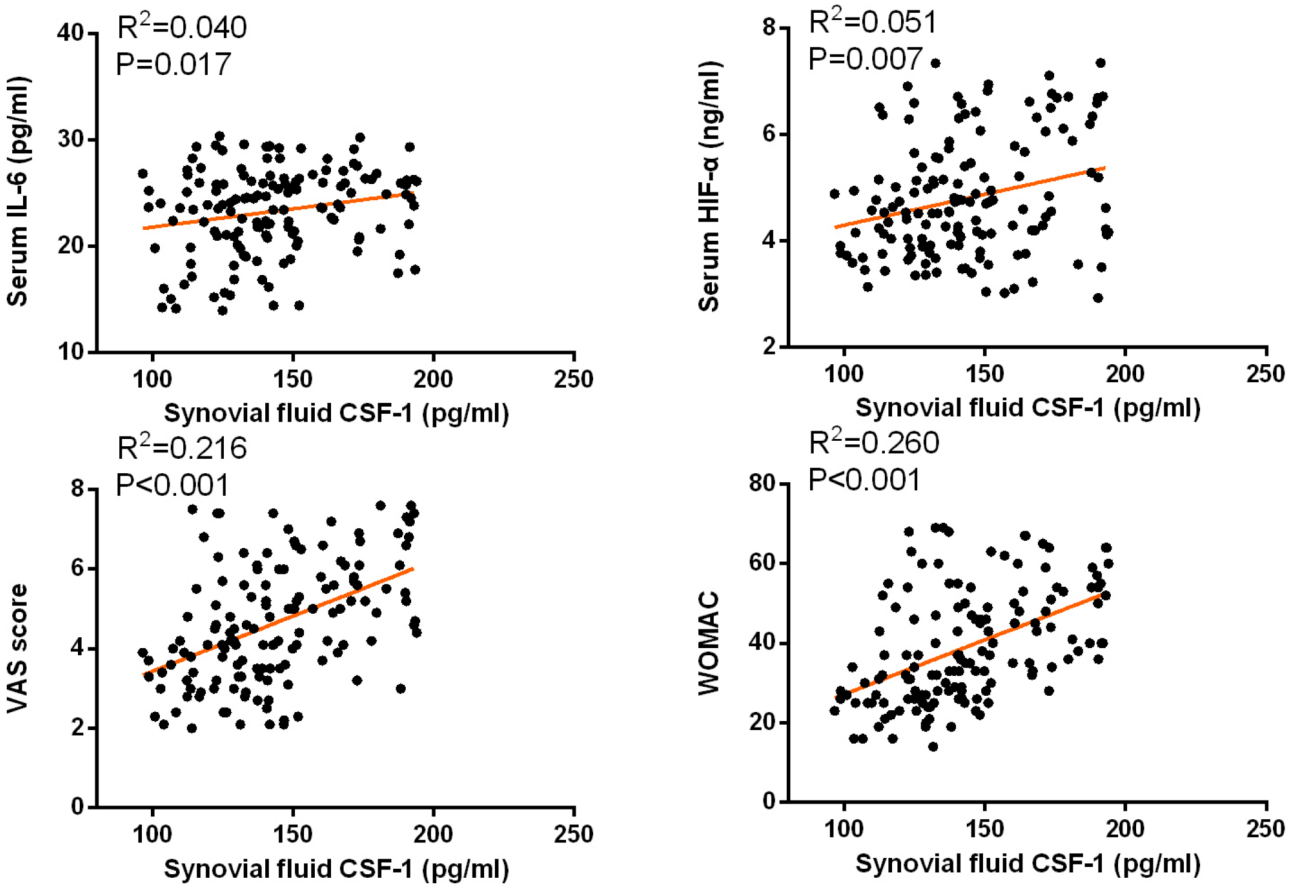

Fig. 4 Scatter plot of correlation analysis of synovial fluid levels of CSF-1 with cytokines and disease severity in KOA patients

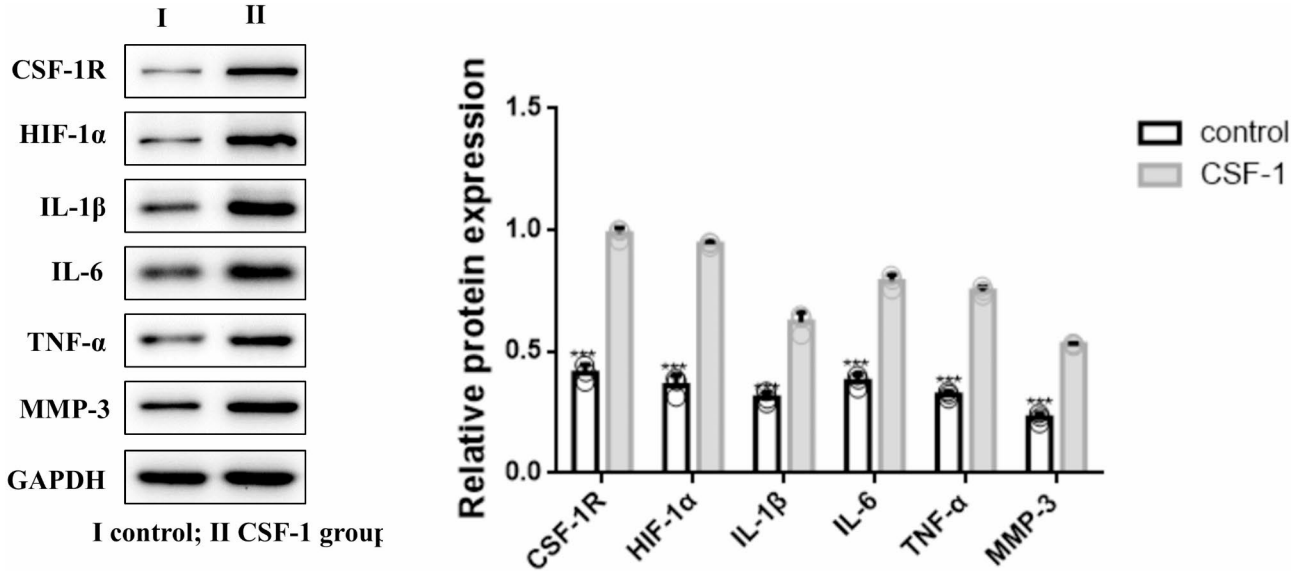

Fig. 5 Western blot analysis was performed to measure the expression of CSF-1R, IL-6, TNF-α, IL-1β, HIF-1α, and MMP-3 in macrophages isolated from OA synovial fluid. Data were presented as mean ± SD, ***$p < 0.001$ compared to the CSF-1 group

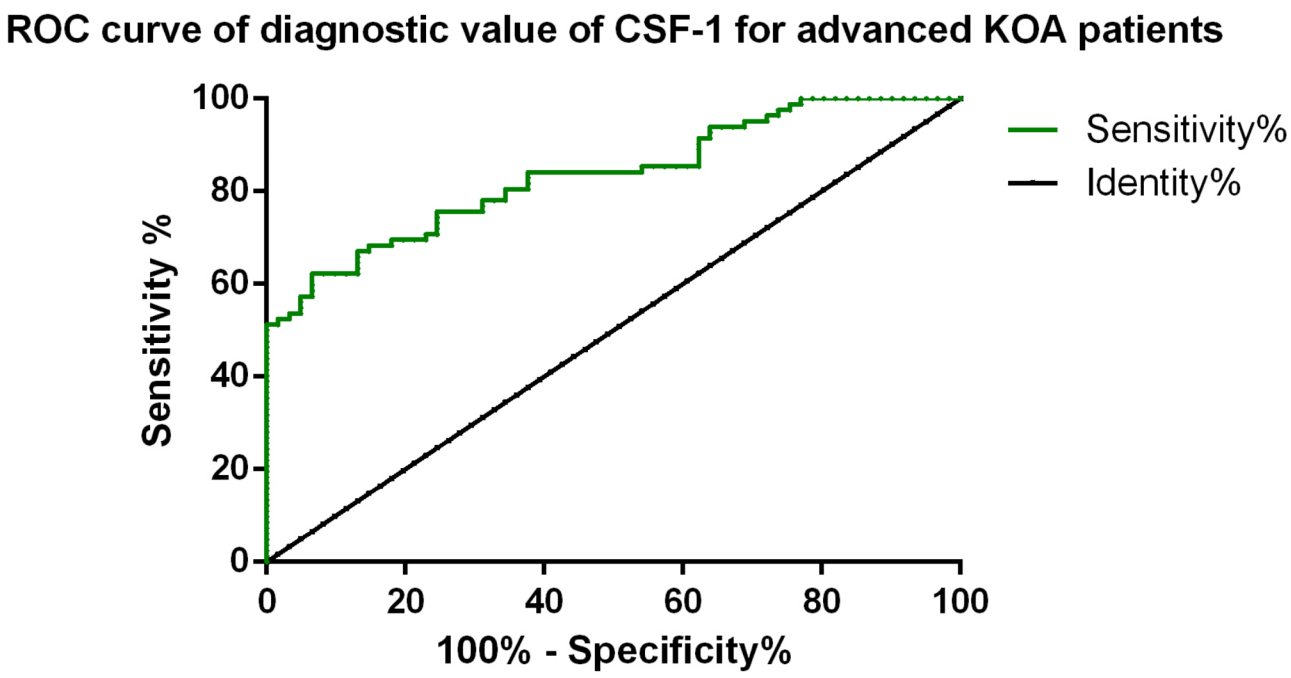

Fig. 6 ROC curves of CSF-1 in patients with advanced KOA

Table 3 Logistic regression of risk factors for advanced KOA

Variables	Wald	Odds ratio	95% CI	P
Age	0.633	0.967	0.889-1.051	0.426
Sex	0.225	1.331	0.408-4.345	0.635
BMI	0.710	0.894	0.688-1.161	0.399
Serum CSF-1	8.160	1.064	1.020-1.110	0.004
Serum IL-6	0.188	1.012	0.678-1.971	0.223
Serum IL-1β	0.021	1.019	0.793-1.309	0.885
Serum CRP	0.443	1.095	0.837-1.433	0.506
Serum HIF-1α	0.022	1.071	0.430-2.668	0.882
IL-6 in SF	10.768	1.371	1.136-1.656	0.001
IL-1β in SF	1.735	1.089	0.959-1.237	0.188
CRP in SF	0.001	1.003	0.807-1.246	0.980
HIF-1α in SF	9.177	3.124	1.495-6.529	0.002
CSF-1 in SF	19.678	1.112	1.061-1.165	<0.001

disease is still not fully understood. Clinical treatment of OA is mainly to relieve joint pain, improve function and artificial joint replacement, but there is still a need to explore new therapeutic targets as well as integrated approaches to treat KOA [20]. Our study found that the levels of serum and synovial fluid CSF-1 were significantly elevated in KOA patients, and these levels were even higher in patients with KL grading 3–4.

In recent years, increasing attention has been given to the differential expression of biomarkers in the serum or synovial fluid of KOA patients. Chen et al. found that the plasma level of MFG-E8 in KOA patients was significantly lower than that in the healthy control group, and it was inversely correlated with the radiographic severity of knee OA [21]. Udomsinprasert et al. demonstrated that the levels of glypican-3 in the plasma and synovial fluid of KOA patients were significantly lower than those in the healthy control group, suggesting that glypican-3 could be a potential biomarker reflecting the severity of knee OA [22]. Furthermore, studies have confirmed that serum CRP and IL-6 are significantly elevated in KOA patients and can predict the progression of the disease [23, 24]. Our study yielded consistent results, as we also found significantly enhanced levels of serum cytokines in KOA patients, with IL-6 and IL-1β being even higher in KL grade 3–4 KOA patients. Additionally, we observed a significant increase in the levels of serum and synovial fluid CSF-1 and HIF-1α in KOA patients.

HIF-1α is an important regulator of cell adaptation to hypoxic environment and a nuclear regulator of gene transcription. Studies have shown that HIF-1α is finely regulated by intracellular oxygen partial pressure, and HIF-1α expression increases under tissue hypoxia [25]. When OA occurs, the hypoxia in the knee joint is more obvious, which promotes the continuous increase of HIF-1α expression [25]. Therefore, its important position in the occurrence and development of OA cannot be denied. CSF-1 is a heterodimer structure, which is formed by the combination of glycoprotein and α-helical bundle structure [26]. It can stimulate the growth and differentiation of granulocytes and macrophages. Currently, some scholars have found that CSF-1 can also stimulate the maturation of immune cells. Meanwhile, osteoarthritis is accompanied by chronic inflammation of joints, and inflammatory cells will play a role in the erosion process [27]. A clinical study by Menke et al. suggested that the

serum levels of CSF-1 in lupus patients are increased and correlated with the activity of lupus [28]. Moreover, a study collected serum samples from KOA patients and analyzed 92 inflammatory markers in each sample using Proximity Extension Array (PEA) technology and discovered that macrophage CSF-1 is an important independent parameter for the intensity of patient pain [29]. Our study confirmed these findings as we observed a positive correlation between synovial fluid CSF-1 levels and VAS scores and WOMAC scores in KOA patients. Additionally, both serum and synovial fluid CSF-1 were identified as risk factors for advanced-stage KOA patients.

There are certain limitations to our study that should be acknowledged. Firstly, the sample size was relatively small, which may limit the generalizability of our findings. Secondly, our analysis only assessed a limited number of biomarkers. Lastly, we did not investigate the molecular mechanisms by which CSF-1 contributes to the development of KOA. Further in-depth research is needed to elucidate these mechanisms and provide a more comprehensive understanding of CSF-1's role in KOA progression.

In conclusion, our findings indicated that the serum and synovial fluid levels of CSF-1 were significantly increased in KOA patients, even higher in patients with KL grade 3–4. Moreover, CSF-1 was identified as risk factor associated with advanced stage KOA. Further investigation into the role of CSF-1 in KOA might provide new targets and a comprehensive approach to treatment in KOA patients.

Supplementary information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08537-8.

Supplementary Fig. 1. Flow Cytometry Analysis of CD14 + Cells in Isolated Macrophages. Flow cytometry was performed to determine the proportion of CD14 + cells in the isolated macrophage population

Author contributions

Yuanchi Huang designed the study and wrote the manuscript, Wenjie Pan performed the ethical approval and informed the patients of their informed consent, Huanli Bao collected and analyzed the data, and Chao Xu and Jianbing Ma reviewed and revised the manuscript.

Funding

This work was supported by: 1. General Research Projects of Xi'an Municipal Health Commission (2023yb28). 2. The Program for Innovation Team of Shaanxi Province (2023-CX-TD-73).

Data availability

All data can be requested and received from Jianbing Ma. The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Honghui Hospital, Xi'an Jiaotong University. The study complied with the Helsinki Declaration, and informed consent was obtained from all study subjects.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Received: 3 June 2024 / Accepted: 17 March 2025
Published online: 10 April 2025

References

1. Neogi T, Krasnokutsky S, Pillinger MH. Urate and osteoarthritis: evidence for a reciprocal relationship. Joint Bone Spine. 2019;86(5):576–82.
2. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthr Cartil. 2022;30(2):184–95.
3. Alekseeva LI, Taskina EA, Kashevarova NG. Osteoarthritis: epidemiology, classification, risk factors, and progression, clinical presentation, diagnosis, and treatment. Mod Rheumatol J. 2019;13(2):9–21.
4. Böck T, Schill V, Krähnke M, Steinert AF, Tessmar J, Blunk T, Groll J. TGF-β1-Modified hyaluronic acid/poly (glycidol) hydrogels for chondrogenic differentiation of human mesenchymal stromal cells. Macromol Biosci. 2018;18(7):1700390.
5. Tong L, Yu H, Huang X, Shen J, Xiao G, Chen L, Wang H, Xing L, Chen D. Current Understanding of osteoarthritis pathogenesis and relevant new approaches. Bone Res. 2022;10(1):60.
6. Guo Q, Chen X, Chen J, Zheng G, Xie C, Wu H, Miao Z, Lin Y, Wang X, Gao W. STING promotes senescence, apoptosis, and extracellular matrix degradation in osteoarthritis via the NF-κB signaling pathway. Cell Death Dis. 2021;12(1):13.
7. Hu Y, Gui Z, Zhou Y, Xia L, Lin K, Xu Y. Quercetin alleviates rat osteoarthritis by inhibiting inflammation and apoptosis of chondrocytes, modulating synovial macrophages polarization to M2 macrophages. Free Radic Biol Med. 2019;145:146–60.
8. Tudorachi NB, Totu EE, Fifere A, Ardeleanu V, Mocanu V, Mircea C, Isildak I, Smilkov K, Cărăuşu EM. The implication of reactive oxygen species and antioxidants in knee osteoarthritis. Antioxidants. 2021;10(6):985.
9. Chow YY, Chin K-Y. The role of inflammation in the pathogenesis of osteoarthritis. *Mediators of inflammation*. 2020;2020.
10. Mi J, Wu X, Bai X, Yang Y, Yang H. ST2 and CSF-1 as potential druggable targets of inflammatory bowel diseases: results from two-sample Mendelian randomization study. Clin Transl Sci. 2023;16(2):236–45.
11. Lenzo JC, Turner AL, Cook AD, Vlahos R, Anderson GP, Reynolds EC, Hamilton JA. Control of macrophage lineage populations by CSF-1 receptor and GM-CSF in homeostasis and inflammation. Immunol Cell Biol. 2012;90(4):429–40.
12. Zheng M, Li Z, Feng Y, Zhang X. CD14 and CSF1R as developmental molecular targets for the induction of osteoarthritis. Int J Clin Exp Pathol. 2023;16(8):184.
13. Liu Y, Zhang Z, Wang B, Dong Y, Zhao C, Zhao Y, Zhang L, Liu X, Guo J, Chen Y. Inflammation-Stimulated MSC-Derived small extracellular vesicle miR-27b-3p regulates macrophages by targeting CSF-1 to promote temporomandibular joint condylar regeneration. Small. 2022;18(16):2107354.
14. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, Christy W, Cooke TD, Greenwald R, Hochberg M, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and therapeutic criteria committee of the American rheumatism association. Arthritis Rheum Aug. 1986;29(8):1039–49. https://doi.org/10.1002/art.1780290816
15. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis Dec. 1957;16(4):494–502. https://doi.org/10.1136/ard.16.4.494
16. Creamer P, Lethbridge-Cejku M, Hochberg MC. Determinants of pain severity in knee osteoarthritis: effect of demographic and psychosocial variables using 3 pain measures. J Rhuematol. 1999;26(8):1785–92.
17. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring

clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rhuematol. 1988;15(12):1833–40.
18. Zhang K, Ji Y, Dai H, Khan AA, Zhou Y, Chen R, Jiang Y, Gui J. High-Density lipoprotein cholesterol and Apolipoprotein A1 in synovial fluid: potential predictors of disease severity of primary knee osteoarthritis. Cartil Dec. 2021;13(1suppl):s1465–73. https://doi.org/10.1177/19476035211007919
19. Hu J, Yuan L. Inhibition of SDF-1α/CXCR4 signaling pathway could prevent trabecular bone loss and attenuate cartilage degeneration in PTOA mice. Genomics Appl Biology. 2019;38(6):2799–805.
20. Hodgkinson T, Kelly DC, Curtin CM, O'Brien FJ. Mechanosignalling in cartilage: an emerging target for the treatment of osteoarthritis. Nat Rev Rheumatol. 2022;18(2):67–84.
21. Chen F, Liu H, Xia J, Ding X, Fan J, Zhu X, Cui S, Yi H, Gao R, Liu W. Synovial fluid and plasma levels of milk fat globule–epidermal growth factor 8 are inversely correlated with radiographic severity of knee osteoarthritis. J Int Med Res. 2019;47(9):4422–30.
22. Udomsinprasert W, McConachie E, Ngarmukos S, Theerawattanapong N, Tanavalee A, Honsawek S. Plasma and joint fluid glypican-3 are inversely correlated with the severity of knee osteoarthritis. Cartilage. 2021;12(4):505–11.
23. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, Pepys MB. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheumatism: Official J Am Coll Rheumatol. 1997;40(4):723–7.
24. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, Ding C. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthr Cartil. 2010;18(11):1441–7.
25. Li L, Newton PT, Bouderlique T, Sejnohova M, Zikmund T, Kozhemyakina E, Xie M, Krivanek J, Kaiser J, Qian H. Superficial cells are self-renewing chondrocyte progenitors, which form the articular cartilage in juvenile mice. FASEB J. 2017;31(3):1067.
26. Freuchet A, Salama A, Remy S, Guillonneau C, Anegon I. IL-34 and CSF-1, Deciphering similarities and differences at steady state and in diseases. J Leukoc Biol. 2021;110(4):771–96.
27. Hamilton JA. GM-CSF-dependent inflammatory pathways. Front Immunol. 2019;10:2055.
28. Menke J, Rabacal WA, Byrne KT, Iwata Y, Schwartz MM, Stanley ER, Schwarting A, Kelley VR. Circulating CSF-1 promotes monocyte and macrophage phenotypes that enhance lupus nephritis. J Am Soc Nephrology: JASN. 2009;20(12):2581.
29. Giordano R, Petersen KK, Andersen HH, Simonsen O, Arendt-Nielsen L. Serum inflammatory markers in patients with knee osteoarthritis: a proteomic approach. Clin J Pain. 2020;36(4):229–37.

Publisher's note