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RESEARCH

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MMP expression and its clinical significance in intervertebral disc destruction of spinal tuberculosis, Brucellar spondylitis, and pyogenic spondylitis

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Abstract

Objective This study is designed to investigate the roles of MMP-2, MMP-9, and MMP-13 in intervertebral disc destruction resulting from different types of spinal infections and their correlations with clinical quantitative data.

Methods Disc tissue samples were collected from 60 patients with spinal infections (20 cases each of STB, BS, and PS in the infection group) and 20 patients with intervertebral disc herniation (control group). The expressions of MMP-2, MMP-9, and MMP-13 were detected by RT-qPCR. Correlation analysis was carried out with clinical quantitative data such as preoperative erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), and related blood routine indicators in the infection group.

Results In the analysis between the infection group and the control group, MMP-13 was expressed in the diseased intervertebral disc tissue of STB patients, but the result was not statistically significant ($P=0.2172$). There was a significant difference in the expression of MMP-13 in the diseased intervertebral discs of BS and PS patients. The expressions of MMP-9 and MMP-2 were markedly increased in the diseased intervertebral disc tissue of STB, BS, and PS patients (all $P<0.05$). In the inter-group analysis of the infection group, the expression of MMP-13 in the diseased intervertebral disc tissue of PS patients was significantly different from that of STB and BS ($P<0.0001$), while there was no significant difference between the STB and BS groups ($P=0.2393$). The expression of MMP-9 in the diseased intervertebral disc tissue of STB patients was significantly different from that of BS and PS ($P<0.0001$), but there was no statistically significant difference between the BS and PS groups ($P=0.9643$). There was no statistically significant difference in the expression of MMP-2 among the STB, BS, and PS groups. In the correlation analysis with clinical quantitative data, MMP-13 was positively correlated with CRP, ESR, IL-6, WBC, and NEUT levels (r values were 0.7346, 0.3465, 0.3326, 0.6347, and 0.5152 respectively), and negatively correlated with LYM level ($r=-0.5152$, $P<0.05$), and had no correlation with PCT and MXD levels. MMP-9 was positively correlated with ESR level ($r=0.3412$, $P<0.05$) and had no correlation with CRP, IL-6, PCT, WBC, NEUT, and LYM levels. MMP-2 was positively correlated with NEUT and

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LYM levels (r values were 0.3021 and 0.3306 respectively, $P < 0.05$) and had no correlation with ESR, CRP, IL-6, PCT, and WBC levels.

Conclusion MMP-2, MMP-9, and MMP-13 play crucial roles in intervertebral disc destruction due to spinal infections. The differential expression of MMPs may be one of the reasons for the varying degrees of intervertebral disc destruction in different types of spinal infections. Moreover, when clinical indicators such as CRP, ESR, IL-6, WBC, and NEUT increase, it suggests that the expression of MMP-13 in the intervertebral disc at the lesion site significantly rises, and it may become a new target for the treatment of spinal infections in the future.

Keywords Spinal infection, Intervertebral disc destruction, Inflammatory reaction, Matrix metalloproteinase

Introduction

Spinal infections are caused by various pathogenic microorganisms and can be classified into two main categories: non-specific infections and specific infections. Non-specific infections, also referred to as purulent spondylitis (PS), and specific infections include spinal tuberculosis (STB) and Brucella spondylitis (BS), collectively accounting for approximately 2–7% of systemic musculoskeletal infections [1, 2]. The invasion of pathogenic microorganisms into the spine initially leads to damage of the intervertebral discs and adjacent vertebrae, with intervertebral disc injury being a hallmark feature [1, 3]. MRI examinations and surgical interventions (Figs. 1, 2 and 3) have revealed that intervertebral disc destruction is more pronounced in patients with non-specific infections compared to those with specific infections, particularly STB. This variation in the extent of intervertebral disc damage across different types of spinal infections merits further investigation.

The intervertebral disc is composed of an outer annulus fibrosus, an inner nucleus pulposus, and upper and lower cartilaginous endplates, and is rich in extracellular matrix components such as collagen and proteoglycans [4, 5]. Matrix metalloproteinases (MMP) are a family of zinc- and calcium-dependent proteolytic enzymes. Upon being released in their pro-forms, they can be activated by various tumor and inflammatory factors, leading to the degradation of the extracellular matrix and contributing to disease pathogenesis [6–7]. The MMP family consists of over 20 members in humans [7, 9]. Castagna A et al. [8] found significantly elevated levels of MMP-1, MMP-2, MMP-3, TIMP-1, and TIMP-2 in tendon samples from 13 patients who underwent arthroscopic repair of rotator cuff tears. Bayar Muluk et al. [9] found that MMP-2 and MMP-9 are significantly expressed by neutrophils and mast cells in nasal polyps, resulting in extracellular matrix degradation. Additionally, recent research by Liu Yuxuan et al. [10] demonstrated that MMP-13, along with inflammatory factors such as TGF-β and Smad3, is highly expressed in the synovial fluid and articular cartilage of knee osteoarthritis patients, suggesting a close relationship between MMP-2, MMP-9, MMP-13, and the development of extracellular matrix and inflammatory responses. Given that intervertebral discs are primarily composed of extracellular matrix, these factors may play a crucial role in the disc degeneration associated with spinal infections; however, substantial evidence remains limited. The objective of this study is to investigate the roles of MMP-2, MMP-9, and MMP-13 in intervertebral disc destruction in STB, BS, and PS, while also analyzing their correlations with clinical data. This research aims to provide novel insights for the clinical diagnosis and management of spinal infections.

In Figs. 1, 2 and 3, (a), (b), (c), and (d) represent sagittal T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), T2-weighted fat-suppressed imaging (T2FS), and axial T2-weighted imaging, respectively, in MRI. Figure (e) shows the intraoperative specimen.

Materials and methods

Study population

The study cohort comprised 60 patients who were clinically diagnosed with spinal infection and subsequently underwent surgical intervention at the General Hospital of Ningxia Medical University between June 2022 and June 2024. This cohort was subdivided into three groups based on the etiology of spinal infection: 20 cases of spinal tuberculosis (STB), 20 cases of brucellar spondylitis (BS), and 20 cases of pyogenic spondylitis (PS). A control group was also established, consisting of 20 patients diagnosed with intervertebral disc herniation (IDH) who were treated during the same timeframe. Informed consent was obtained from all participants prior to their inclusion in the study.

Criteria for inclusion and exclusion

Inclusion Criteria: (1) Patients are included if they have been diagnosed with STB, BS, or PS based on a thorough evaluation that includes clinical manifestations, laboratory findings, imaging results, bacterial analyses, and pathological examinations; (2) All confirmed patients must have clear surgical indications and have undergone surgical intervention; (3) The duration from the onset of symptoms to the surgical treatment should not exceed three months; (4) Only patients with comprehensive and intact clinical records are considered for inclusion.

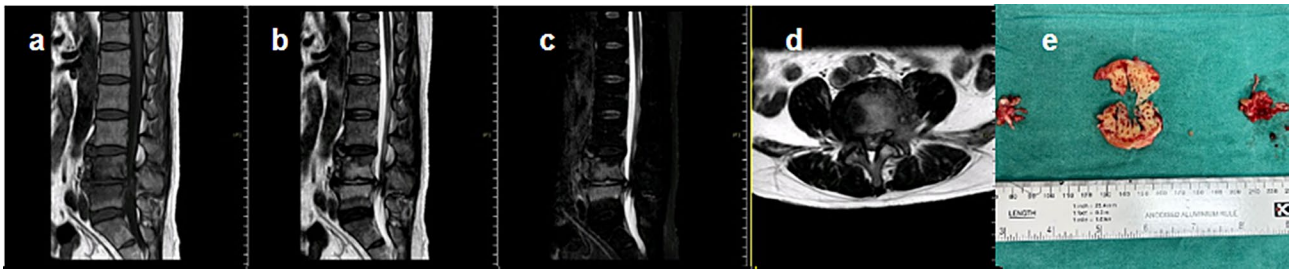

Fig. 1 The patient is a 55-year-old male with L4-5 vertebral tuberculosis. (**a**-**d**) show MRI images indicating mild bone erosion of the L4-5 vertebral bodies, with preservation of intervertebral disc height and no significant disc damage. (**e)** depicts a large excised piece of cartilage endplate (center) and partially intact intervertebral disc tissue removed during surgery

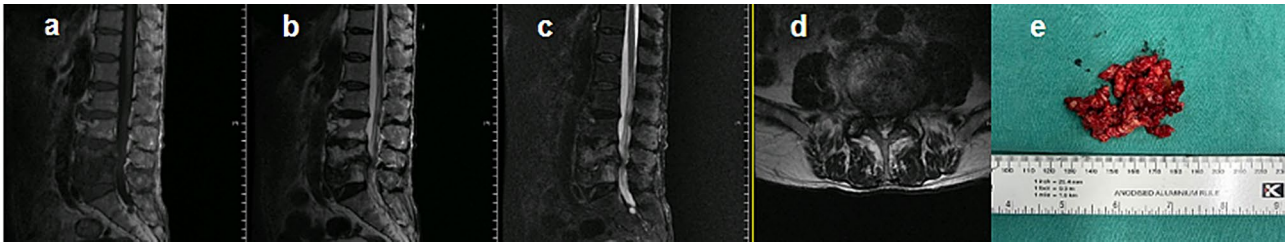

Fig. 2 The patient is a 49-year-old male with L4-5 brucellar spondylitis. (**a-d**) show MRI images revealing bone destruction at the L4-5 level, decreased intervertebral disc space, and notable disc deterioration. (**e**) shows the fragmented intervertebral disc and granulation tissue that were surgically debrided

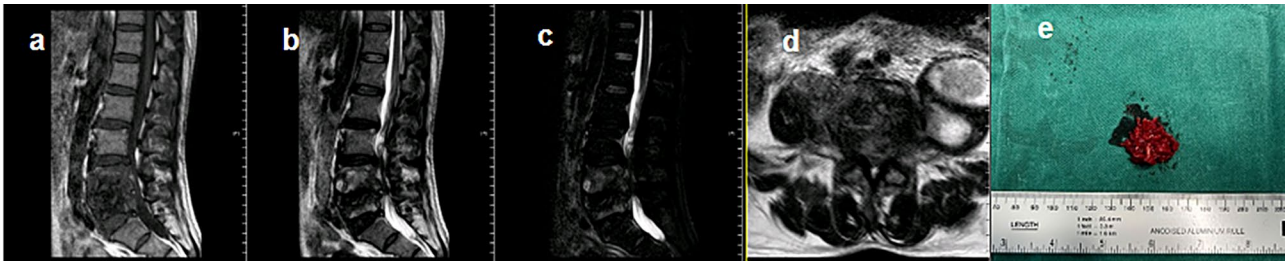

Fig. 3 The patient is a 51-year-old female with L4-5 pyogenic spondylitis. (**a-d**) show MRI images indicating bone destruction at the L4-5 vertebral level, vertebral collapse, and loss of intervertebral disc height, with severe disc damage. (**e**) illustrates the purulent necrotic material containing granulation tissue and remnants of the intervertebral disc that were surgically evacuated

Exclusion Criteria: (1) Patients with concurrent active pulmonary tuberculosis, malignancies, or other significant comorbid conditions; (2) Individuals diagnosed with other types of spinal infections, such as syphilitic spondylitis or fungal spondylitis; (3) Cases where clinical data is incomplete or missing.

Clinical data and sample collection

Laboratory examination data of patients with spinal infection included in the study were collected, including preoperative ESR, CRP, IL-6, PCT and related indicators of blood routine tests. Additionally, intervertebral disc samples were collected from all patients during the surgical procedure. After removal, the intervertebral disc tissues were carefully washed with normal saline, placed into sample preservation tubes, and then immersed in liquid nitrogen for rapid freezing. Following freezing, the samples were stored in a -80 °C freezer for subsequent analysis.

Reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay

A sample of 10 mg of the pulverized intervertebral disc tissue was lysed in PBS buffer to prepare a homogenate. To this homogenate, 1 ml of Trizol reagent was added, and the mixture was incubated at -30 °C for a period of 5 min. Following this, 0.2 ml of chloroform was introduced, vortexed for 15 s, and then allowed to separate at room temperature for 3 min. The sample was subjected to centrifugation at 4 °C for two rounds to facilitate the removal of the supernatant and the subsequent extraction of total RNA. The isolated RNA was then reverse transcribed into cDNA using 0.2 μL of reverse transcription reaction mixture, in accordance with the protocol provided by the manufacturer, to amplify the target

Table 1 Primer sequences for reverse transcription quantitative polymerase chain reaction (RT-qPCR)

Gene	Primer sequence (5'→3')
MMP-2	H-MMP-2-S：AGTGGATGATGCCTTTGCTCG
	H-MMP-2-A：CAAGGTCCATAGCTCATCGTCAT
MMP-9	H-MMP-9-S: GCACGACGTCTTCCAGTACC
	H-MMP-9-A: GGTTCAACTCACTCCGGGAA
MMP-13	H-MMP-13-S: AATGCAGTCTTTCTTCGGCTTAG
	H-MMP-13-A: CAGAATGAGTCATATCAGGGGTGT
GAPDH	H-GAPDH-S: GGAAGCTTGTCATCAATGGAAATC
	H-GAPDH-A: TGATGACCCTTTTGGCTCCC

Exegesis: S(sense primer) -A(antisense primer)

genes MMP-2, MMP-9, and MMP-13.The expression levels of MMP-2, MMP-9, and MMP-13 were quantified using RT-PCR. The RT-qPCR reaction mix was prepared with specific primers for MMP-2, MMP-9, and MMP-13 (Sevier Biotech, Wuhan, China). The qPCR protocol included a UDG pretreatment step at 50 °C for 2 min, an initial denaturation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 15 s, annealing at 95 °C for 30 s, and extension at 72 °C for 30 s. The relative mRNA expression was calculated using the 2-ΔΔCT method. To ensure the reliability of the results, the RT-qPCR was conducted in triplicate, and the mean value was recorded for statistical analysis (Table 1 and 2)

Statistical analysis

The data were statistically analyzed and visualized using SPSS 26.0, GraphPad Prism 8.0 software (GraphPad Software, La Jolla, CA, USA), and OriginPro 2024b. Regarding the baseline data, the non-parametric rank sum test is used for inter-group comparisons. Categorical variables are described by the number of cases and percentage or rate. The chi-square test and Fisher's exact probability test are used for inter-group comparisons, and the Wilcoxon rank sum test is used for intra-group comparisons.For comparative analysis, the t-test was employed for pairwise comparisons between two groups, while one-way ANOVA was utilized for evaluating differences across multiple groups and perform a Tukey post-mortem test. To explore the associations between PCR outcomes and clinical parameters, Spearman's correlation analysis and linear regression were applied following an assessment of normality. Statistical significance was set at a P-value of less than 0.05.

Baseline data

Results

Result 1: Increased expression of MMP-13, MMP-9, and MMP-2 in lesional intervertebral discs of spinal infection patients

In our quest to understand the role of matrix metalloproteinases (MMP) in the degradation of intervertebral

Table 2 General information and clinical quantitative data of patients

	STB	BS	PS	IDH	*P* value
n	20	20	20	20	
Age $[(x \pm s)]$	58.00 ± 15.58	60.00 ± 9.48	61.80 ± 9.62	56.70 ± 10.48	0.525
Gender [n/(%)]					
Males	9/45%	17/85%	15/75%	8/40%	0.006
Females	11/55%	3/15%	5/25%	12/60%	
ESR(mm/h) $[(x \pm s)]$	39.92 ± 30.21	29.90 ± 17.20	56.85 ± 32.13	-	0.010
CRP(mg/h) $[(x \pm s)]$	32.08 ± 40.64	43.49 ± 44.56	75.36 ± 67.98	-	0.032
IL-6(pg/ml) $[M(Q_L, Q_U)]$	15.30(9.90,23.23)	16.66(4.40,8.64)	27.60(15.70,54.09)	-	0.058
PCT(ng/ml) $[M(Q_L, Q_U)]$	0.06(0.05,0.12)	0.06(0.03,0.09)	0.07(0.05,0.13)		0.576
WBC($*10^9$) $[(x \pm s)]$	5.06 ± 1.99	6.14 ± 2.27	9.48 ± 4.84		0.001
NEUT(%) $[(x \pm s)]$	62.97 ± 8.05	55.67 ± 12.65	71.21 ± 11.57		0.001
LYM(%) $[(x \pm s)]$	25.34 ± 7.11	33.00 ± 11.52	18.14 ± 9.30		0.001
MXD(%) $[(x \pm s)]$	8.78 ± 1.83	9.47 ± 2.42	8.63 ± 2.95		0.511

Exegesis: Measurement data are expressed as mean ± standard deviation $[(x \pm s)]$. Measurement data that do not follow a normal distribution are presented as median (interquartile range) [M(QL, QU)].

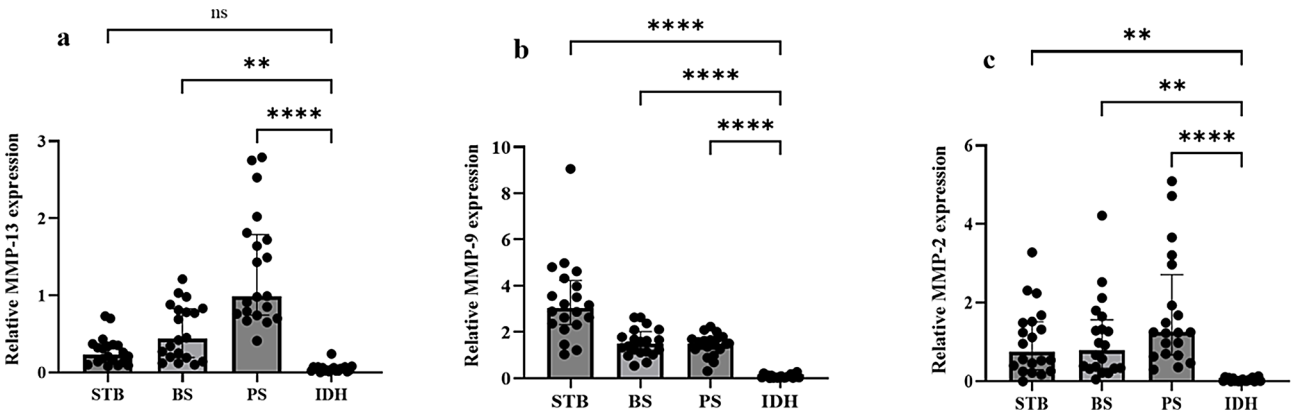

Fig. 4 (**a-c**): Comparative analysis of MMP-13, MMP-9, and MMP-2 mRNA expression levels in intervertebral disc tissue from the infection groups (STB, BS, and PS) versus the control group (IDH)

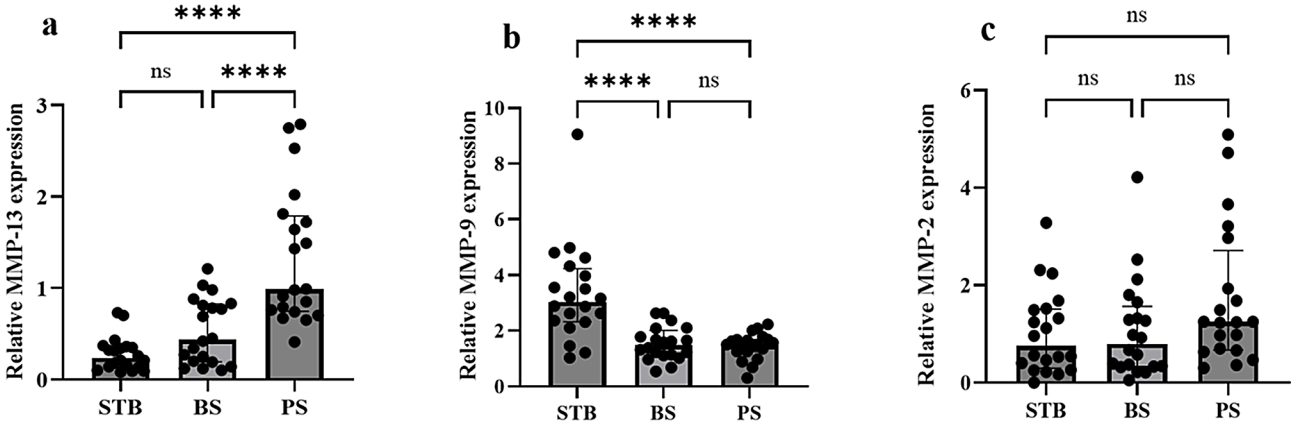

Fig. 5 (**a-c**): The expression of MMP-13, MMP-9, and MMP-2 mRNA among the infected groups (STB, BS, and PS) shows significant differences

discs affected by spinal infection, we utilized RT-qPCR to evaluate the mRNA expression levels of MMP-13, MMP-9, and MMP-2 in intervertebral disc tissue. Our sample comprised 60 cases from the infected group, with 20 cases each from the STB, BS, and PS groups, alongside a control group of 20 cases from the IDH group. The findings indicated a marked elevation in the expression of MMP-13, MMP-9, and MMP-2 in the infected group compared to the controls. As depicted in Fig. 4a, although MMP-13 expression was noted in the intervertebral disc tissue of STB patients, it did not achieve statistical significance ($P = 0.2172$). In contrast, a statistically significant increase in MMP-13 expression was observed in the lesional intervertebral discs of BS and PS patients ($P = 0.0017$ and $P < 0.0001$, respectively). Figure 4b illustrates that MMP-9 expression was significantly elevated across the intervertebral disc tissue of STB, BS, and PS patients (all with $P < 0.0001$). Similarly, Fig. 4c confirms that MMP-2 expression was also significantly higher in the intervertebral disc tissue of STB, BS, and PS patients ($P = 0.0059$, $P = 0.0035$, and $P < 0.0001$, respectively).

Result 2: The expression of MMP-13 and MMP-9 in the lesioned intervertebral disc tissue of patients with different types of spinal infections shows significant differences

Upon establishing the elevated expression of MMP-13, MMP-9, and MMP-2 in the intervertebral disc tissue of patients with spinal infections, we conducted a comparative analysis to explore the differential mRNA expression patterns among the distinct infection categories (STB, BS, and PS). As depicted in Fig. 5a, a significant disparity in MMP-13 expression was observed between the pyogenic spondylitis (PS) group and both the tuberculous spondylitis (STB) and bacterial spondylitis (BS) groups ($P < 0.0001$), whereas no significant difference was noted between the STB and BS groups ($P = 0.2393$). Figure 5b reveals that the expression of MMP-9 in the STB group significantly diverged from that in the BS and PS groups ($P < 0.0001$), with no significant difference detected between the BS and PS groups ($P = 0.9643$). Finally, Fig. 5c illustrates that while MMP-2 expression was augmented across all infection groups, no statistically significant differences in its expression were identified among the STB, BS, and PS groups.

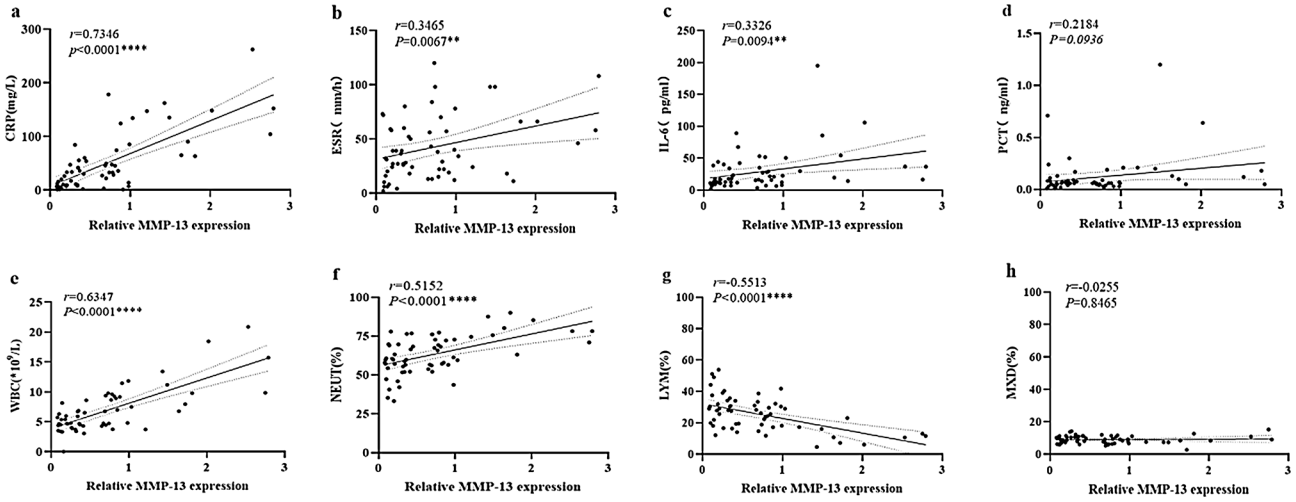

Fig. 6 (**a-h**): Linear regression analysis of MMP-13 expression levels and their correlation with clinical quantitative data including CRP, ESR, IL-6, PCT, WBC, NEUT, and LYM in patients with spinal infection

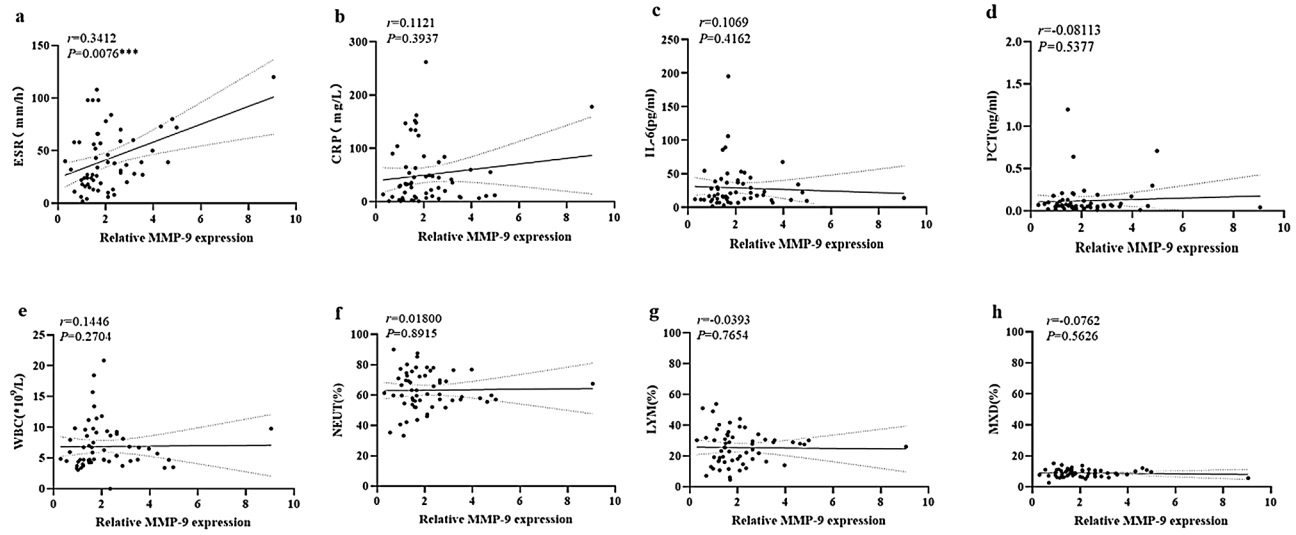

Fig. 7 (**a-h**): Linear regression analysis of MMP-9 expression levels and their correlation with clinical quantitative data including CRP, ESR, IL-6, PCT, WBC, NEUT, and LYM in patients with spinal infections

Result 3: The expression of MMP-13, MMP-9, and MMP-2 is correlated with clinical quantitative data in patients with spinal infection

In the preliminary experiments, we observed an increase in the expression levels of MMP-13, MMP-9, and MMP-2 in the intervertebral discs at the infected sites of patients with spinal infection, and there were differences in expression levels between the STB, BS, and PS groups. To further explore the relationship between these matrix metalloproteinases and the clinical condition of the patients, we collected laboratory examination data and analyzed the correlation between these data and the PCR results. As shown in Fig. 6a-h, the expression of MMP-13 is positively correlated with the levels of CRP, ESR, IL-6, WBC and neutrophil count (NEUT) (correlation coefficients r are 0.7346, 0.3465, 0.3326, 0.6347, and 0.5152, respectively), and negatively correlated with lymphocyte count (LYM) levels (r=-0.5152, P<0.05). There is no significant correlation with the levels of PCT and mid-cell (MXD).

Figure 7a-h shows: MMP-9 is positively correlated with ESR levels ($r = 0.3412$, $P < 0.05$), and there is no correlation with CRP, IL-6, PCT, WBC, NEUT, and LYM levels

Figure 8a-h MMP-2 is positively correlated with the levels of NEUT and LYM (correlation coefficients are 0.3021 and 0.3306, respectively, $P < 0.05$), and there is no correlation with the levels of ESR, CRP, IL-6, PCT, and WBC Fig. 9.

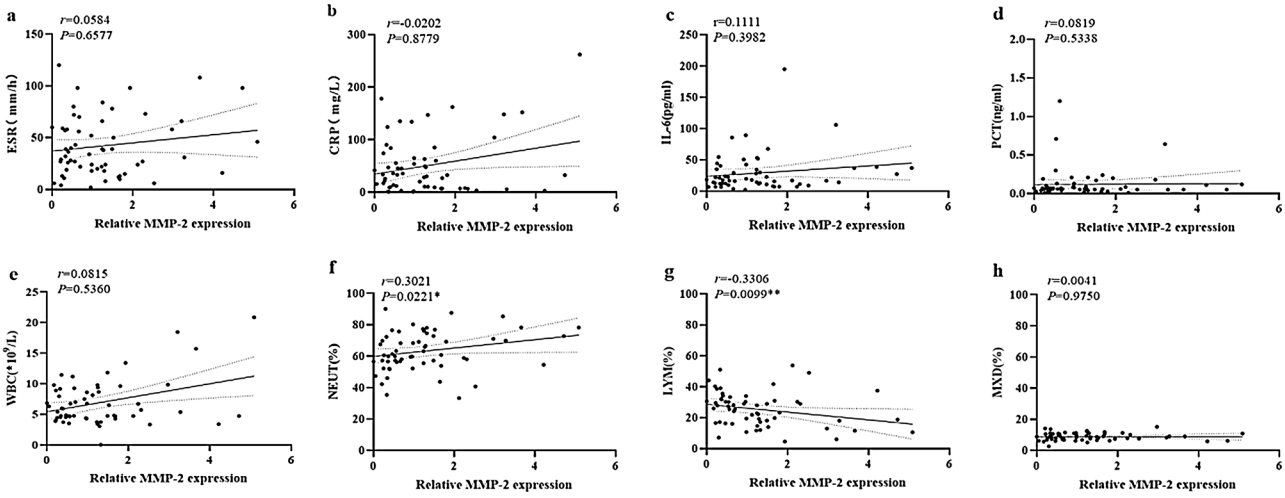

Fig. 8 (**a-h**): Linear regression analysis of MMP-2 expression levels in relation to clinical quantitative data a ~ h, showing the correlation between MMP-2 expression levels and CRP, ESR, IL-6, PCT, WBC, NEUT, and LYM in patients with spinal infections

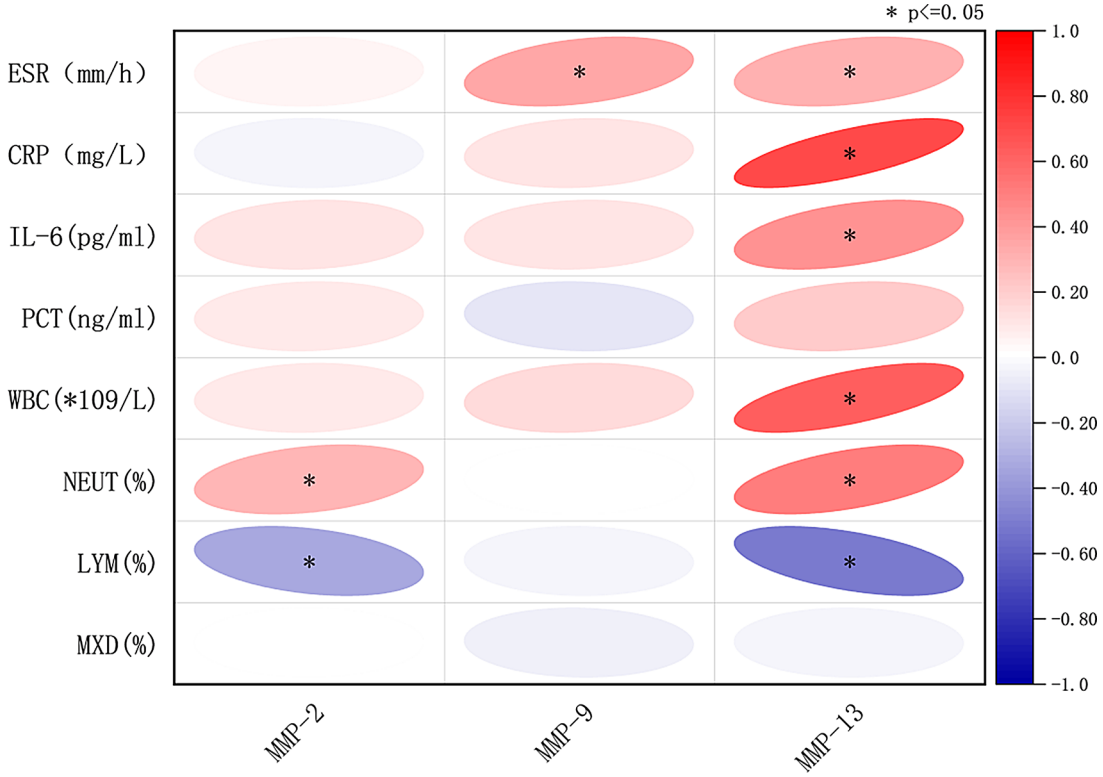

Fig. 9 Heatmap of Spearman correlation analysis between MMP-2, MMP-9, MMP-13, and clinical quantitative data

Discussion

It is currently understood that spinal infections primarily result from the invasion of pathogenic microorganisms, which disseminate from the primary site of infection through the bloodstream and lymphatic circulation, ultimately affecting the spine and its accessories. The most common types of spinal infections are STB, BS, and PS [11]. Following Mycobacterium tuberculosis infection, macrophages are stimulated to produce inflammatory cytokines such as IL-1α and IL-12, enhancing their antigen-presenting capabilities and simultaneously activating T cells to elicit a cellular immune response. $CD4^+$T cells, upon stimulation, differentiate into various helper T lymphocytes, producing cytokines such as IL-1, IL-6, IL-17, and TNF, which further induce macrophage activation and recruit neutrophils, among other immune cells, to exert their functions [12, 13]. The primary virulence determinant of Brucella species is their type IV

secretion system, which elicits effector Vcec, prompting macrophages and other inflammatory cells to produce cytokines such as IL-6 and TNF-α, promoting granuloma formation at the site of infection [14]. Collectively, both Mycobacterium tuberculosis and Brucella species can activate the macrophage system upon infecting the human body, generating inflammatory cytokines and inducing local granuloma formation. Studies by Ma Hongbao et al. [15], Rammeh et al. [16], and Li Yong'ai et al. [17] on the histopathology of STB and BS have revealed that the intervertebral discs in the affected lesions are predominantly infiltrated by a large number of macrophages and lymphocytes, thereby providing histopathological evidence for the aforementioned content. PS, on the other hand, is primarily caused by pyogenic bacteria such as Staphylococcus aureus and Escherichia coli, which are characterized by their ability to secrete proteinases, rapidly forming local abscesses and producing substantial necrotic material that induces the production of chemokines such as CXCL and CXCR, recruiting neutrophils, macrophages, and lymphocytes. These inflammatory cells then produce a plethora of inflammatory cytokines, including IL-1, IL-2, IL-8, and TNF, triggering a more intense immune response [11, 18].

MMP are categorized into collagenases, gelatinases, stromelysins, matrilysins, membrane-type MMPs, and others that do not fit into these categories. MMP-2 and MMP-9 are classified as collagenases and are capable of targeting and cleaving type II, III, and IV collagens, proteoglycans, and laminin in the extracellular matrix. MMP-13, a gelatinase, also targets these substrates [19]. Research indicates that MMPs play a significant role in the onset and progression of tendinopathy, Tendon tissue is rich in extracellular matrix (ECM), and MMPs are capable of comprehensively degrading various components of connective tissue, particularly the ECM, thereby directly contributing to and driving the pathological progression of tendinopathy [20, 21]. During an inflammatory response, activated macrophages and neutrophils release MMP-2, MMP-9, and MMP-13, while the release of IL-6, TNF, and other inflammatory cytokines stimulates the further release of these MMPs, creating a positive feedback loop [22, 23]. Our study also confirmed elevated expression of MMP-2, MMP-9, and MMP-13 in the intervertebral discs of patients with spinal infections, which plays a significant role in the degradation of the extracellular matrix (Fig. 4a-c). Studies have shown that MMP-13 is the most potent enzyme within the MMP family for degrading the extracellular matrix of articular cartilage, suggesting that its destructive potential on the intervertebral disc extracellular matrix may exceed that of MMP-2 and MMP-9. Our research demonstrated that the expression of MMP-13 in the intervertebral discs of PS patients was higher than that in STB and BS patients (Fig. 5a-c), which partly explains why the disc destruction caused by PS is more severe than that caused by STB and other conditions.

ESR, CRP, IL-6, PCT and related indicators of complete blood count are recognized as crucial laboratory parameters for assessing the magnitude of inflammatory responses in clinical settings. Weng et al. [24] demonstrated that higher levels of serum ESR, CRP, and PCT in children with Mycoplasma pneumoniae infection were associated with an increased risk of severe pneumonia, closely correlating with the severity of the disease. Lorenzo et al. [25] identified that in severe COVID-19 patients, there was a significant elevation of IL-6 and WBC counts, which may serve as markers of critical disease progression. In our study, we observed that patients with elevated CRP, ESR, IL-6, WBC, and neutrophil counts also exhibited increased expression of MMP-13 in the intervertebral disc lesions. This suggests a correlation between MMP-13 expression and the degradation of intervertebral discs, as well as the severity of the condition, potentially positioning MMP-13 as a therapeutic target for spinal infections in the future.

Conclusion

In summary, the expression of MMP-13, MMP-9, and MMP-2 is elevated in the intervertebral disc tissue of patients with spinal infections, playing significant roles in the process of intervertebral disc destruction. The expression of MMP-13 in the intervertebral disc tissue of patients with PS is significantly higher than that in patients with BS and STB, which to some extent explains why the intervertebral disc destruction is more severe in PS. MMP-13 shows a significant positive correlation with CRP, ESR, IL-6, WBC, and NEUT counts. Therefore, when these clinical indicators are elevated, the increased local expression of MMP-13 in the intervertebral disc often suggests a more severe condition. Reducing these clinical indicators may help better control the disease, and this approach could be considered as one of the therapeutic directions for patients with spinal infections in the future. Additionally, our study is the first to demonstrate that the expression of MMP-9 in the intervertebral disc of STB patients is higher than that in BS and PS patients, although the specific reasons for this require further investigation.

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Author contributions

Yuxin Gao: Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing - Original Draft, Specimen collection Xiaojun Ma: Data Curation, Writing - Original Draft, Specimen collection Zhiyun Shi: Data Curation, Methodology Mengqi Zhu: Data analysis Zongqiang Yang: Investigation, Specimen collection Zhengyong Tao: Specimen collection Ningkui Niu: Experimental supervision, Paper revision, Data review #YuXin

Gao and XiaoJun Ma, contributed equally to this work and share the first authorship. These authors contributed equally to this work.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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