

Original Article

Serum Neuroinflammatory Biomarkers in Lumbar Disc Herniation: A Diagnostic Perspective

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Received: 03 February 2026

Revised: 12 February 2026

Accepted: 06 March 2026

Published: 15 March 2026

HOW TO CITE

Shamsiya Naseem et al. 2026. Serum Neuroinflammatory Biomarkers in Lumbar Disc Herniation: A Diagnostic Perspective. Journal of Health, Wellness and Community Research. 4, 5 (Mar. 2026), 1–8. DOI:<https://doi.org/10.61919/m66hc505>

ARTICLE INFORMATION

Author Contributions	Concept: MI, SN; Design: MI, SZTR, YI; Data Collection: SN, SZTR, MS, SSQ; Analysis: MI, YI, SSQ; Drafting: SN, SZTR, YI, MS, MI, SSQ
Ethical Approval	The study was approved by research ethical board of MTI Lady Reading Hospital, Peshawar, Pakistan
Informed Consent	Written informed consent was obtained from all participants
Conflict of Interest	The authors declare no conflict of interest.
Funding	No external funding.
Data Availability	Available from the corresponding author on reasonable request.
AI Declaration	No generative AI was used for conceptualization, analysis, or content generation. AI use was limited to language refinement, and the authors remain fully responsible for the accuracy, originality, validity, and integrity of the manuscript's content.

ABSTRACT

Background The interplay between mechanical and inflammatory processes has been implicated in the pathogenesis of radicular symptoms and disability attributed to the herniated lumbar disc (LLH). Circulating inflammatory mediators, or cytokines, may be indicative of systematic inflammatory responses that develop during symptomatic LLH. **Objective** To determine levels of circulating serum interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), in adults presenting with symptomatic MRI-proven LLH, as well as evaluate associations of these inflammatory mediators with perceived pain, functional limitation, and Pfirrmann grade of disc degeneration. **Methods** From August 2025 to January 2026, 85 adults (25–60 years old) with symptomatic LLH that was confirmed on MRI in Balochistan, Pakistan, were prospectively enrolled. Measurements were made of visual analog scale pain (VAS), Oswestry Disability Index (ODI), Pfirrmann grade by MRI, and serum IL-6 and TNF- α by enzyme linked immunosorbent assay (ELISA). The one way analysis of variance and person correlation analyses were conducted by use of IBM SPSS Statistics version 26.0. **Results** The mean IL-6 and TNF- α Concentration were 18.4 $\pm$ 5.2 pg/mL and 22.1 $\pm$ 6.8 pg/mL. Inflammatory marker concentrations were significantly different by Pfirrmann grade III–V. ((F (2,82) = 29.17, p<0.001 (IL-6); F (2,82) = 22.65, p<0.001 (TNF- α) respectively. Interleukin-6 was positively correlated with VAS (r=0.68) and ODI (r=0.62), whereas TNF- α was positively correlated with VAS (r=0.71) and ODI (r=0.65); all p-values <0.001. **Conclusion** Elevated levels of serum IL-6 and TNF- α were correlated with higher grades of disc degeneration, increased perceived pain, and the manifestation of increased functional limitations among the study participants who were diagnosed with symptomatizing LLH. The results provide support for the role of circulating inflammatory mediators as potential clinical indicators of LLH, though more research is needed; no determination of diagnostic value or the existence of a causal or prognostic relationship is indicated by these cross-sectional results. **Keywords** Biomarkers; IL-6; LLH; ODI; Pfirrmann classification

INTRODUCTION

Lumbar radicular pain and dysfunction due to intervertebral disc herniation are common conditions in adults. It has long been proposed that the pathological bulging of nucleus pulposus tissue through the annulus fibrosus in lumbar

disc herniation can mechanically irritate or compress adjacent neural elements. The correlation between these objective structural abnormalities and the severity of subjective pain is often weak, suggesting other, less understood mechanisms contribute to the symptomatology (1).

It has been established that the extent of morphological abnormality associated with symptomatic lumbar disc disease can correlate with both circulating inflammatory mediators and pain severity; however, extensive characterization of lumbar disc tissue has affirmed the role for specific cytokines to explain the neurochemical and pain abnormalities seen in symptomatic disease (2).

Neuroinflammation and mechanisms involving peripheral neuroimmune responses that influence neural root sensitization have also been increasingly suggested as factors associated with injury or expulsion of intervertebral disc material. Contact between nucleolus pulposus and epidural tissue might trigger immune responses. Such responses might activate pro-inflammatory cytokines, chemokine and other mediators that sensitize neural tissue and exacerbate pain signaling. Imbalances in certain cytokines were subsequently hypothesized to a likely biologically characteristic of intervertebral disc degeneration-related symptomatic condition (3).

Regarding mediators proposed to mediate both chronic neuropathic and radicular pain, tumor necrosis factor alpha TNF- has gained focus on role for neural inflammatory changes and neural axonal dysfunction that leads to pain sensitization (4).

Interleukin-6 IL-6 has also been strongly linked with the inflammatory processes in degenerated spinal disease, though system response of these cytokines might vary considerably among patient population as well as the clinical significance. Research on neuroinflammation on human pain studies in literature involved analysis of specific cytokine in the cerebrospinal fluid, the intervertebral disc tissues and peripheral blood, of the latter two the systemic circulating cytokines can easily be measured among the patient groups. Nevertheless, studies on CSF provide better support for pro-inflammatory immune activation of nerve root pain, and the more readily accessible serum analysis may be useful to detect chronic inflammatory presence within the nerve roots of these patients even if its relation to symptoms has not fully established (5).

Lumbar radiculopathy serum cytokine concentration can be abnormally elevated in subjects with symptomatic lumbar disc disease: however, changes may not be specific to the pathology, instead attributed to other psychological and clinical factors (6). Concentrations of local mediators such as chemokines in herniated lumbar discs were also noted to positively correlate with severity of sciatic pain and indirectly contribute with their own relation to the underlying disc pathologies (7). In spite of the many existing observational data, exact associations have not been properly established between peripheral inflammatory biomarkers concentrations and symptoms or radiological severity among studies due to variety of tests and imaging methods.

Evidence from genetically studies, meta-analyses suggested involvement of inflammation, but relation between peripheral cytokine concentrations and clinical disease severity has not been definitively shown (8).

Additionally, distinguish between 'degeneration' of intervertebral discs and anatomical 'herniation' is important, and Pfirrmann scale measures disc degeneration, not disc size or the magnitude of nerve root compression, but measures that are related indirectly, hence measurement of serum variables and the Pfirrmann scale indicates correlation to disc degeneration rather than specific assessment of nerve compression. From these information, analysis of Lumbar disc degeneration and relevant cytokines, specifically TNF- and IL-6, associated with symptoms such as pain and dysfunction appears a valuable cross-sectional study to detect association regardless the causality and accurate diagnosis. Cross-sectional analyses like the current one are cannot identify causal relationship between diseases process, diagnose accurately patient or indicate prognosis; However, it might verify objective measurable relation among systemic cytokines concentrations with symptoms or imaging results. Therefore, current study was designed to quantify circulating IL-6 and TNF- concentrations of asymptomatic, MRI confirmed, Lumbar Radicular Pain patients that could determine associations with Visual Analogue Scale for Pain severity and with Oswestry Disability Index, and also as compared to Pfirrmann scale reflecting the level of LLD, assuming higher concentration will be found in those patients with more pain, higher degree of function impairment and higher grade of LLD.

MATERIAL AND METHODS

A cross-sectional observational study of adults presenting with symptomatic lumbar disc herniation, assessing the relation between neuroinflammatory circulating markers and clinical features at that time including those on MRI was carried out from August 2025 to January 2026 in Balochistan Pakistan. Adults aged 25–60 yr symptoms of lumbar radiculopathy and an MRI proven lumbar disc herniation were recruited in the study. Patients satisfying the criteria between the date were screened, and data from 85 eligible patients were used for final analysis cohort. The number of patients for the present study was chosen based on literature evidence based on a similar study that investigated relationship between serum inflammatory marker (cytokines) and the clinical picture of patients in Lumbar Radiculopathy (1, 6) and found a clinically meaningful relationship between them.

Patients eligible must have symptoms and signs of lumbar radiculopathy and recent findings consistent on imaging of the lumbar disc herniation. Patients were excluded if any previous surgery on the spine was performed or if the participant suffered from autoimmune disease, for example Rheumatoid Arthritis; a recent epidural injection into the spine was given, severe Trauma and infection. These possible exclusions could lead to alternative sources that could increase or decrease the circulating inflammatory factors (biomarkers) and also to remove bias from systemic inflammation activity as best as possible. Informed written consent was sought from each participant prior to data collection.

Base demographic data and clinical information were taken from participants at entry in the study. Subjective Pain on Visual Analogue scale from 0–10 where 10 indicating most pain was measured using VAS. The Lumbar Disability Scale known as Oswestry Disability Index (ODI) was performed with answers as percentage where 100% indicates most disability, from which functional limitation due to lumbar condition was assessed. Duration of symptoms along with demographic & occupational data were asked. Primary biochemical markers were IL-6 & TNF-serum concentration. Primary clinical parameters were VAS pain score and ODI.

MRI of the lumbar spine was evaluated, where disc degeneration on MRI was categorized using The Pfirrmann grading system, categorizing advancing levels of morphological and signal change in intervertebral disc. Participants were categorized within each examination and graded with Pfirrmann grade III, IV or V for purpose of this study and thus this scale was used as a surrogate for overall extent of disc degeneration. As intended in original study, this was not a measurement of size of herniation nor of magnitude of nerve compression. The spinal imaging was independently graded by an experienced musculoskeletal radiologist blinded to subject clinical data on lumbar spinal image quality and severity/size of the disc herniation. MR based structural measure, along with data regarding circulating levels of cytokines in patients who have symptom of lumbar disc herniation have also been used before (1).

For biochemical examination 5mls of peripheral venous blood sample was drawn aseptically then the serum was extracted by centrifuging at higher speed, stored in suitable vials at -80(0)C prior to analysis of IL-6 & TNF- by commercially available kits of enzyme-linked immunosorbent assay of high sensitivity.

All tests regarding incubation, washing, estimation and evaluation of cytokines in serum sample were done as per manufacturer instructions, and Serum IL-6 & TNF were quantified using enzyme linked immunosorbent assays and a clinically relevant relation was shown between the concentrations of cytokines in the serum and the pain score in lumbar radiculopathy. Serum cytokine determination has been applied for profiling systemic inflammatory condition previously too (6).

All statistical tests carried out explored the differences in serum IL-6 & TNF-levels across each category of Pfirrmann grade, and association between cytokines levels, and patient related factors namely pain & disability, were evaluated. Descriptive measures that included mean $\pm$ SD were used to summarize continuous variables, and frequencies (%) were used to describe categorical variables.

All continuous variables used, which were explored initially with Shapiro–Wilk test for determining their appropriateness for statistical analysis and then found normally distributed for further analysis using parametric method was applicable (e.g. For mean, SD; Correlation). Mean IL-6 & TNF- were compared in groups namely III, IV and V Pfirrmann grading with ANOVA. The correlations between variables were calculated using Pearson product-moment correlation. Interpretation of the correlation coefficient was made in regard to its direction and magnitude. P-value <0.05 was regarded as statistically significant. Statistical analyses were performed using IBM SPSS version 26.0.

Ethical approval for the study protocol was obtained by the local institutional review board before commencement of participant recruitment. Participant written informed consent was obtained prior to enrolment and, following protocol, was used for the purposes of this study.

RESULTS

Out of 102 patients, 17 were excluded for the following reasons; prior spinal surgery (n 10), receipt of an epidural steroid injection in the last six months (n 5) or outright refusal to be included in the study (n 2), yielding a total for final analysis. Eighty five study patients (Mean age 42.4 ± 8.7 years; 52/85, 61.2% were males) have been accounted. Sixty eight point two percent of the patients (58/85) performed a physically heavy workload and the remain 31.8% (27/85) were performing their work while sitting or light workload based. Mean symptom duration was 4.5 ± 2.1 months (Table 1).

Participants presented with a mean VAS pain score of 6.8 ± 1.4 and a mean ODI of 48.5 ± 12.2%. Regarding their MRI, Pfirrmann classification was Grade III in 29/85 patients (34.1%), IV in 41/85 patients (48.2%) and V in 15/85 patients (17.6%). The total mean concentration of IL-6 and TNF- α were 18.4 ± 5.2 pg/mL and 22.1 ± 6.8 pg/mL respectively (Table 1).

Table 1. Demographic, Clinical, Radiological, and Biochemical Characteristics of Participants (N=85)

Variable	Category	Value
Age, years	—	42.4 ± 8.7
Sex	Male	52 (61.2%)
	Female	33 (38.8%)
Occupation	Heavy manual labor	58 (68.2%)
	Sedentary/light work	27 (31.8%)
Symptom duration, months	—	4.5 ± 2.1
VAS score, 0–10	—	6.8 ± 1.4
ODI, %	—	48.5 ± 12.2
Pfirrmann disc degeneration grade	III	29 (34.1%)
	IV	41 (48.2%)
	V	15 (17.6%)
Serum IL-6, pg/mL	—	18.4 ± 5.2
Serum TNF- α , pg/mL	—	22.1 ± 6.8

Values are mean ± SD or n (%), as appropriate. VAS, Visual Analog Scale; ODI, Oswestry Disability Index; IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha.

Table 2. Serum IL-6 and TNF- α Concentrations Across Pfirrmann Disc Degeneration Grades

Biomarker	Grade III (n=29), mean ± SD	Grade IV (n=41), mean ± SD	Grade V (n=15), mean ± SD	F (2,82)	p-value	η^2
IL-6, pg/mL	14.1 ± 3.4	19.5 ± 4.2	23.6 ± 5.1	29.17	<0.001	0.416
TNF- α , pg/mL	17.3 ± 4.5	23.2 ± 5.6	28.4 ± 6.3	22.65	<0.001	0.356

F-statistics and η^2 were derived from the reported group sample sizes, means, and SDs using one-way analysis of variance. IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha; η^2 , eta squared.

Table 3. Pairwise Differences in Serum Biomarker Concentrations Across Pfirrmann Grades

Biomarker	Comparison	Mean difference, pg/mL	95% CI	Adjusted p-value
IL-6	Grade IV – Grade III	5.4	3.01 to 7.79	<0.001
IL-6	Grade V – Grade III	9.5	6.37 to 12.63	<0.001
IL-6	Grade V – Grade IV	4.1	1.13 to 7.07	0.004
TNF- α	Grade IV – Grade III	5.9	2.78 to 9.02	<0.001
TNF- α	Grade V – Grade III	11.1	7.01 to 15.19	<0.001
TNF- α	Grade V – Grade IV	5.2	1.32 to 9.08	0.005

Pairwise estimates, simultaneous 95% confidence intervals, and multiplicity-adjusted p-values were derived using Tukey-Kramer comparisons based on the pooled error variance from the corresponding one-way ANOVA. CI, confidence interval; IL-6, interleukin-6; TNF- α , tumor necrosis factor-alpha.

Table 4. Correlations of Serum Neuroinflammatory Biomarkers With Pain and Functional Disability (N=85)

Biomarker	Clinical outcome	Pearson r	95% CI	p-value
IL-6	VAS	0.68	0.55 to 0.78	<0.001
IL-6	ODI	0.62	0.47 to 0.74	<0.001

Biomarker	Clinical outcome	Pearson r	95% CI	p-value
TNF- α	VAS	0.71	0.59 to 0.80	<0.001
TNF- α	ODI	0.65	0.51 to 0.76	<0.001

Reported are the two sided values for Pearson correlation coefficients, using the study population of 85 individuals. CI's reported for r-to-z correlation and Fisher's r-to-z transformation Fisher's r-to-z, CI; VA S, Visual analog scale; ODI, Oswestry Disability Index; IL-6, interleukin-6; T N F - α , tumor necrosis factor-alpha; C I, confidence interval.

Correlation was computed between these cytokines and Pfirrmann grades (Table 2 and 3) and correlates of symptoms (Table 4). Circulating serum cytokine concentrations differed by Pfirrmann grades of disc degeneration (Table 2). The average concentration of IL-6 at Pfirrmann Grade III was 14.1 $\pm$ 3.4 pg/mL (grade I V, 19.5 $\pm$ 4.2 pg/mL; grade V, 23.6 $\pm$ 5.1 pg/mL). There was an overall difference in cytokine concentrations at the various Pfirrmann grades ($F(2,82)=29.17$, $P < .001$, $\eta^2=0.416$); serum concentrations of T N F - α Were 17.3 $\pm$ 4.5 pg/mL (grade I V, 23.2 $\pm$ 5.6 pg/mL; grade V, 28.4 $\pm$ 6.3 pg/mL). There was also an overall difference in cytokine concentrations at various Pfirrmann grades ($F(2,82)=22.65$, $P < .001$, $\eta^2=0.356$). Paired comparisons revealed that concentrations for both cytokines were significantly increased in grade I V compared with Grade I I and in grade V compared with Grades III and IV for IL-6 (TABLE 3); grade I V was 5.4 pg/mL greater than Grade III (95% CI 3.01-7.79; $\text{adj } p < .001$). Grade V was 9.5 pg/mL greater than Grade III (95% CI 6.37-12.63; $\text{adj } p < .001$). Grade V was 4.1 pg/mL greater than grade IV (95% CI 1.13-7.07; $\text{adj } p = 0.004$). Concentrations of TNF- α was increased in grades I V and V compared with grades III and I V (TABLE 3). Grade IV was 5.9 pg/mL greater than grade III (95% CI 2.78-9.02; $\text{adj } p < .001$). Grade V was 11.1 pg/mL greater than grade III (95% CI 7.01-15.19; $\text{adj } p < .001$). Grade V was 5.2 pg/mL greater than grade I V (95% CI 1.32-9.08; $\text{adj } p = 0.005$). Both biomarkers of inflammation were positively associated with intensity of pain and functional disability (Table 4). IL-6 was positively related to the VAS score ($r = 0.68$, 95% CI 0.55, to 0.78; $p < 0.001$) and ODI score ($r = 0.62$; 95% CI 0.47 to 0.74; $p < 0.001$). The correlation to be noted here is the strongest that this study produced, between the plasma TNF and the VAS score ($r = 0.71$; 95% CI 0.59 to 0.80; $p < 0.001$), and another positively with the ODI score ($r = 0.65$; 95% CI 0.51 to 0.76; $p < 0.001$). These analyses indicate associations between elevated concentrations of circulating cytokines, and increased Pfirrmann grade of disc degeneration as well as simultaneous pain and disability.

DISCUSSION

There was a strong association between serum IL-6 and TNF- concentrations and both clinical and radiological aspects of symptomatic lumbar disc herniation. The means of each cytokine increased incrementally according to Pfirrmann grade of disc degeneration (III < IV < V), with large differences between grades, and the mean was highly correlated with each pain and disability index. While these findings support the hypothesis of an association between peripheral inflammation and clinical presentation of symptomatic lumbar disc disease, they are not exclusive from the study design (cross-sectional observational).

The findings from this study regarding cytokine association with clinical and radiological parameters parallel an abundance of literature postulating the participation of different inflammatory mediators in pain produced by lumbar disc disease.

For example, in a systematic review assessing the role of macrophage-derived inflammatory factors in lumbar disc herniation, higher levels of many pro-inflammatory mediators (including TNF- and IL-6) were found with increasing level of pain while support for general inflammation was generally limited by heterogeneity (2). In addition, the observation of altering circulating cytokine levels (including IL-6 and TNF-) was observed by Bielewicz et al. In symptomatic patient volunteers scheduled for surgical consultation due to symptomatic lumbar disc herniation, however clinical findings were confounded by a relationship with depressive symptomatology and disability (6). The serum cytokine alteration consists of a level of inflammatory illness greater than or equal to any other clinical variable presented herein and further reinforces that not all cytokine changes are driven by structural bony change alone.

Lastly, while Peng et al. Were unable to achieve statistical significance for a correlation between serum cytokine levels and pain, the study found positive correlations between the expression of local chemokines and pain in lumbar disc herniation (7).

Interpretability of serum cytokine concentrations and Pfirrmann grades is particularly subject to caution. Unlike the present report, Jacobsen et al. Found that MRI determined severity of disc herniation (rather than Pfirrmann grade which they differentiated), and not necessarily Pfirrmann grade, was related to circulating levels of certain cytokines in chronic radicular pain; in fact, Pfirrmann grade was not significantly associated with cytokines at all in their study sample (1). There may be differences in imaging methodology, select cytokines, disease chronicity, patient population, or the exclusion in the present study of Pfirrmann grades I and II or of adjustment for other factors in multivariate models between studies. However, there remains an association in the current data and for relevant reasons it is important to be clear on what kind of spinal pathology is related; we observed a relationship between both serum IL-6 and TNF- concentrations and degree of cumulative degeneration across Pfirrmann grades III-V in patients with at least one MRI confirmed lumbar disc herniation.

There are a number of potentially plausible biologically underlying explanations for this association. Progressive intervertebral disc degeneration involves intricate pathways between pro-inflammatory and anti-inflammatory cytokines with both IL-6 and TNF-pathway components participating in inflammatory signaling and pathogenesis. In particular, TNF-plays a role in both peripheral nerve injury-associated neuroinflammation and neuropathic pain. Experimental studies suggest increased inflammatory activity may even promote faster disc degradation/inflammation. Nevertheless, mechanisms do not constitute "proof" that the specific serum cytokines measured originated from the affected disc nor that these were the drivers for participant pain. Comprehensive reviews on circulating inflammatory mediators in chronic pain report widely differing associations between concentrations and reported pain intensities for multiple mediators including IL-6 and TNF-. The complexity and overlapping pathways of chronic pain-associated inflammation are further evident in recent works that posit combined inflammatory, oxidativ and neural contributions to symptomatology rather than singularly attributed causes. Genetics research has demonstrated some evidence of selective cytokine associations in lumbar disc herniation(8).

This suggests the correlation between serum inflammatory mediator levels, VA/OD index pain scores, and VAS scores are at best one part of a much more complex picture of inflammation and clinical sequelae that also involves numerous other potentially disease associated factors. Interestingly TNF-demonstrated a slightly stronger correlation to patient reported symptoms as a measure of disease activity compared to IL-6, and both mediators were significantly correlated with disability levels-this may provide avenues for stratification of future research to investigate the biological heterogeneity inherent in lumbar disc disease and symptomatic pathology thereof. At this time, there is no definitive diagnostic utility to measurements of IL-6 and TNF- levels given the inclusion criteria (symptomatic MRI confirmed lumbar disc herniation), the absence of a comparison population, lack of differential diagnosis population, absence of ROC, sensitivity/specificity testing, or any sort of receiver threshold of value/importance. Similarly no prognostic application of these measures could be ascertained given they were collected at one point in time without prospectively measuring follow-up, patient recovery, relapse rates, or treatment response.

A key strength of the study is that a measurement of two biologically relevant serum cytokines in the same clinical cohort is interpreted alongside standardized measurements of pain, functional disability, and MRI-defined disc degeneration. All MRI scans were interpreted by a single, experienced musculoskeletal radiologist who was blind to the patients' symptoms, limiting the possibility that knowledge of pain and disability scores affected the radiological grading. The omission of patients with a number of important potential confounding factors: the presence of a significant known inflammatory illness, current active infection, previous spinal surgery, recent major spinal trauma or recent epidural injection service; potentially removed a number of sources of variation in systemic inflammatory activity. The internally consistent increment in both IL-6 and TNF- throughout Pfirrmann classifications III to V; along with corresponding, positive correlations with both VAS and ODI, make for a coherent pattern that warrants future evaluation of systemic inflammatory profiles in symptomatic lumbar disc disease. Despite the strengths there are number of limitations that influence how results should be interpreted. As the design is cross sectional temporal sequencing/causality cannot be evaluated. As there was no control group it is impossible to say whether measurements are truly elevated compared to patients with no signs/symptoms of symptomatic lumbar disc herniation. For the most part the study's results are unadjusted so potential key factors which could affect serum cytokine concentrations, such as age, gender, body mass index, smoking status, metabolic disease, medication, psychopathology or Recent physical activity etc., can not be accounted for in multivariable modelling. Research in human subjects has previously showed how demographic and clinical factors

can significantly affect serum cytokines and disc herniation (1) while in vitro research indicates similar potential effects on disc or neuroimmune response (11). It is likely the study's results cannot be generalizable given relatively small number of relatively young (although this is not stated specifically) people from one part of the USA working in physical labor. Examining only those at Pfirrmann grades III to V likely does not give a representative sample of all disc degeneration: the possibility should be considered that the effects are only seen at this extreme stage of the degeneration and not at stages I-II where, conceptually, there may be fewer physical problems for an inflammatory response to develop at all. Assay performance characteristics along with repeat measure reproducibility were not evaluated, hence were not available for examination, meaning these aspects cannot be factored into the interpretations. Appropriately identified control subjects, careful MRI characterisation (herniation and compression), all potential confounding factors studied and appropriately complex multivariable modelling, standard laboratory protocols including quality control, are required along with follow-up data over time for circulating IL-6 and TNF- to determine if they add to well established clinical and radiological indicators.

CONCLUSION

Higher serum IL-6, and TNF- levels in adult patients presenting with symptomatic, MRI-diagnosed lumbar disc herniation were correlated with higher Pfirrmann disc degeneration grades, and were found to be significant predictors of pain intensity and functional disability at the same time of measurement. In conclusion, it seems that circulating inflammation, assessed by those two markers, is linked with degenerative changes and symptomatology of a symptomatic lumbar disc disease, though there are no grounds to interpret the present cross-section findings in relation to its causal factors, predictive or diagnostic value.

REFERENCES

1. Jacobsen HE, Khan AN, Levine ME, Filippi CG, Chahine NO. Severity of intervertebral disc herniation regulates cytokine and chemokine levels in patients with chronic radicular back pain. *Osteoarthritis Cartilage*. 2020;28(10):1341-50.
2. Djuric N, Lafeber GC, Vleggeert-Lankamp CL. The contradictory effect of macrophage-related cytokine expression in lumbar disc herniations: a systematic review. *Eur Spine J*. 2020;29(7):1649-59.
3. Shnayder NA, Ashhotov AV, Trefilova VV, Nurgaliev ZA, Novitsky MA, Vaiman EE, Petrova MM, Nasyrova RF. Cytokine imbalance as a biomarker of intervertebral disk degeneration. *Int J Mol Sci*. 2023;24(3):2360.
4. Myers RR, Shubayev VI. The ology of neuropathy: an integrative review of the role of neuroinflammation and TNF- α axonal transport in neuropathic pain. *J Peripher Nerv Syst*. 2011;16(4):277-86.
5. Rosenström AHC, Konsman JP, Kosek E. Cytokines in cerebrospinal fluid and chronic pain in humans: past, present, and future. *Neuroimmunomodulation*. 2024;31(1):157-72.
6. Bielewicz J, Daniluk B, Kamieniak P. Altered serum cytokines in patients with symptomatic disk herniation and depressive symptoms. *Front Neurosci*. 2024;18:1366559.
7. Peng ZY, Chen R, Fang ZZ, Chen B, Wang ZH, Wang XY. Increased local expressions of CX3CL1 and CCL2 are related to clinical severity in lumbar disk herniation patients with sciatic pain. *J Pain Res*. 2017:157-65.
8. Yang J, Xu W, Chen D, Liu Y, Hu X. Evidence from Mendelian randomization analysis combined with meta-analysis for the causal validation of the relationship between 91 inflammatory factors and lumbar disc herniation. *Medicine (Baltimore)*. 2024;103(47):e40323.
9. Kim H, Hong JY, Lee J, Jeon WJ, Ha IH. IL-1 β promotes disc degeneration and inflammation through direct injection of intervertebral disc in a rat lumbar disc herniation model. *Spine J*. 2021;21(6):1031-41.
10. Singh M, Kim A, Young A, Nguyen D, Monroe CL, Ding T, Gray D, Venketaraman V. The mechanism and inflammatory markers involved in the potential use of N-acetylcysteine in chronic pain management. *Life*. 2024;14(11):1361.

11. Novais EJ, Ottone OK, Brown EV, Madhu V, Tran VA, Ramteke P, Dighe AS, Solga MD, Manchel A, Lepore AC, Risbud MV. Genetics- and age-driven neuroimmune and disc changes underscore herniation susceptibility and pain-associated behaviors in SM/J mice. *Sci Adv.* 2025;11(17):eado6847.