

ORIGINAL ARTICLE

Serum Interleukin-1 β and High-Sensitivity C-Reactive Protein Across Schizas Morphological Grades in Degenerative Lumbar Spinal Stenosis: An Exploratory Cross-Sectional Study

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ABSTRACT

Background: In degenerative lumbar spinal stenosis (LSS), symptom severity often bears little relation to the narrowing seen on imaging, and inflammation may contribute.**Objective:** To determine whether the Schizas grade of the dural sac is associated with serum interleukin-1 β (IL-1 β) and high-sensitivity C-reactive protein (hs-CRP) after confounder control.**Methods:** Thirty non-obese patients with LSS (body mass index [BMI] <30 kg/m²) at Dr. Mohammad Hoesin General Hospital, Palembang, were studied after a verified 7-day anti-inflammatory washout. Two blinded radiologists graded axial T2-weighted magnetic resonance imaging (MRI): Grade A, n = 10; B, n = 11; C/D, n = 9 (κ = 0.84). Morning IL-1 β and hs-CRP were compared with Kruskal–Wallis tests and bootstrapped regression.**Results:** BMI (p = 0.312) and sex (p = 0.927) were similar across grades, but age and symptom duration rose with grade (both p < 0.001). IL-1 β medians climbed from 5.60 [4.90–6.40] pg/mL in Grade A to 8.45 [7.20–9.50] pg/mL in Grade B and 11.20 [9.10–13.80] pg/mL in Grade C/D (p < 0.001); hs-CRP medians were 2.15 [1.80–2.60], 3.40 [2.90–4.10] and 4.90 [3.80–6.20] mg/L (p = 0.003). With age and BMI in the model, grade remained associated with IL-1 β (B = 2.05, β = 0.46, p = 0.012, R^2 = 0.41) and hs-CRP (B = 1.12, β = 0.49, p = 0.009, R^2 = 0.44); no variance inflation factor reached 2.5.**Conclusion:** Greater dural sac compression went with higher serum IL-1 β and hs-CRP, independent of age and BMI. Larger longitudinal cohorts are needed before these markers are used alongside MRI.

1. Introduction

Degenerative lumbar spinal stenosis (LSS) is a leading indication for spinal decompression surgery in older adults and a substantial and growing cause of musculoskeletal disability, loss of walking independence and tertiary health-care expenditure.^{1,2} As populations age in both industrialized and developing nations, contemporary epidemiological syntheses estimate that symptomatic LSS affects approximately 11% of the general older adult population and 25%–39% of clinical cohorts with chronic lower extremity or axial spinal complaints.^{2,3} Historically, the pathophysiological framework for LSS diagnosis and surgical decision-making has rested on a static, structural and biomechanical model.^{4,5} In this model, progressive degeneration of the three-joint complex, comprising intervertebral disc desiccation and bulging, facet osteophytosis and capsular thickening, and buckling and hypertrophy of the ligamentum flavum (LFH), encroaches on the central canal, lateral recesses and neural foramina.^{5,6} This osseoligamentous constriction compresses the dural sac and the enclosed cauda equina rootlets, compromising intraneural arterial inflow and microcirculatory perfusion and producing neurogenic intermittent claudication, radicular pain and progressive sensorimotor deficits.^{2,7} Clinical evaluation has therefore relied heavily on static supine magnetic resonance imaging (MRI) to quantify canal dimensions, on the assumption that the geometric severity of anatomical narrowing determines the clinical severity of disability.^{8,9}

Surgical utilization and revision rates show the clinical size of this diagnostic gap.^{2,10} Over the past two decades, decompressive laminectomy, performed alone or with instrumented posterolateral or interbody fusion, has increased rapidly to become one of the most frequent elective orthopedic and neurosurgical procedures in adults aged 60 years and older in North America, Europe and the Asia-Pacific region.^{2,11,12} Yet randomized trials and prospective cohort studies, including the Swedish Spinal Stenosis Study (Karlsson et al.), the NORDSTEN Degenerative Spondylolisthesis (NORDSTEN-DS) trial (Austevoll et al. and, at five years, Kgomotso et al.) and the Swiss Lumbar Stenosis Outcome Study (LSOS; Ulrich et al.), show that a substantial proportion of patients, reported as 20%–35%, continue to have residual neurogenic claudication, persistent radicular dysesthesia or suboptimal functional recovery two to five years after technically successful decompression.^{10,13–16} Furthermore, Hermansen et al. and Zhou et al. found broadly comparable average outcomes across midline-preserving, microscopic and endoscopic decompression techniques, and Inose et al. found comparable long-term outcomes after decompression with or without fusion or stabilization.^{17–19} Part of the outcome variance that static cross-sectional canal dimensions cannot capture may therefore come from factors other than the extent of decompression, possibly including biological heterogeneity in the neural and peridural microenvironment.

Daily spine practice repeatedly challenges this linear structural assumption through the well-documented clinical-radiological paradox.^{20,21} Multicenter trials such as NORDSTEN, and single-center cohorts, report a marked mismatch between MRI stenosis grade and validated patient-reported outcome measures, among them the Oswestry Disability Index (ODI), the Zurich Claudication Questionnaire (ZCQ) and the visual analog scale (VAS) for leg and back pain.²⁰⁻²² Older patients whose axial T2-weighted images show severe, high-grade obliteration of the dural sac are often only mildly symptomatic and still walk well.^{9,21} The reverse is also common: many patients with only moderate radiological narrowing have disabling neurogenic claudication, cramping at night and refractory radicular pain, with a marked loss of quality of life.^{21,23} Were static compression the only determinant of neural dysfunction, pain intensity would rise steadily as dural sac cross-sectional area falls. It does not, which implies that structural narrowing is a necessary condition rather than a sufficient explanation for symptomatic LSS.^{20,24}

Resolving this dilemma may require moving from a purely mechanical view of canal constriction toward an integrated mechanobiological and inflammatory model.^{6,24} In the healthy lumbar canal, cerebrospinal fluid (CSF) forms a pressurized hydraulic cushion inside the dural sac, allowing the cauda equina rootlets to float freely while preserving low-resistance venous drainage through Batson's internal vertebral venous plexus.^{7,25} When progressive ligamentum flavum hypertrophy and facet arthropathy deplete this CSF reserve, crowding is thought to compress the thin-walled, valveless epidural and intraneural venules before the higher-pressure radicular arteries are occluded.^{6,26,27} The resulting venous outflow obstruction can produce microvascular congestion, intraneural edema, raised endoneurial fluid pressure and localized hypoxia within the compressed rootlets and adjacent ligamentum flavum.^{26,27} Hypoxia inhibits prolyl hydroxylase domain enzymes and stabilizes hypoxia-inducible factor-1 α (HIF-1 α) in microvascular endothelial cells, Schwann cells, fibroblasts and infiltrating CD68⁺ macrophages.²⁸⁻³⁰ Activated HIF-1 α may act with nuclear factor kappa B (NF- κ B) to prime the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing protein 3 (NLRP3) inflammasome, triggering caspase-1-mediated cleavage of pro-interleukin-1 β into mature, biologically active interleukin-1 β (IL-1 β).^{30,31}

This biological heterogeneity is closely linked to the pathobiology of the degenerating posterior spinal elements, notably the ligamentum flavum and the epidural neurovascular interface.^{6,32} Under physiological conditions, the ligamentum flavum is a specialized, highly elastic connective tissue composed of approximately 80% elastin and 20% type I and type III collagen, providing elastic recoil during lumbar flexion-extension while maintaining a smooth dorsal boundary of the central canal.³³ Under repetitive biomechanical microtrauma, segmental instability and axial loading, resident ligamentum flavum fibroblasts undergo myofibroblastic transdifferentiation with alpha-smooth muscle actin (α -SMA) expression, accompanied by infiltration of CD68⁺ macrophages.^{6,30,34} Reviews and experimental studies by Silwal et al., Jiang et al., Burt et al. and Lee et al. report macrophage infiltration and increased expression of IL-1 β , interleukin-6 (IL-6), transforming growth factor-beta 1 (TGF- β 1) and secreted protein acidic and rich in cysteine (SPARC) in hypertrophied ligamentum flavum, together with matrix metalloproteinase (MMP)-2 and MMP-9 activity that degrades elastin bundles and their replacement by disorganized, densely cross-linked type I and type III collagen.^{6,30,34,35} Ligamentum flavum hypertrophy is

therefore not a passive mechanical folding of senescent tissue but an active fibro-inflammatory lesion in direct anatomical contiguity with the dorsal epidural venous plexus and dural sac.^{6,32}

Within the stenotic spinal canal, IL-1 β is a candidate mediator linking structural degeneration with nociceptive sensitization.^{30,36} Locally, IL-1 β stimulates ligamentum flavum fibroblasts to express MMP-2, MMP-9 and collagen, while TGF- β 1 and SPARC promote further fibrosis, accelerating elastic fiber fragmentation and collagenous fibrosis that further thicken the ligamentum flavum in a self-amplifying loop.^{6,34,35} At the same time, IL-1 β sensitizes transient receptor potential vanilloid 1 (TRPV1) channels and the voltage-gated sodium channels Nav1.7 and Nav1.8 on dorsal root ganglion neurons, lowering mechanical and thermal nociceptive thresholds.^{36,37} A key translational question is whether this compartmentalized intraspinal cytokine response remains behind the meninges or crosses the blood-spinal cord barrier (BSCB) to leave a measurable footprint in peripheral venous blood.^{38,39} Experimental models of BSCB and blood-brain barrier dysfunction show that sustained exposure to IL-1 β and tumor necrosis factor-alpha (TNF- α) downregulates the tight-junction proteins claudin-5, occludin and zonula occludens-1 (ZO-1), inducing paracellular hyperpermeability across the microvascular endothelium.^{38,40,41} If the BSCB is compromised, locally produced IL-1 β may reach the systemic venous circulation and, with IL-6, stimulate hepatocyte signal transducer and activator of transcription 3 (STAT3) signaling and the synthesis of C-reactive protein, measured clinically as high-sensitivity C-reactive protein (hs-CRP).⁴²

Despite the biological plausibility of this venous stasis, cytokine and hepatic acute-phase axis, earlier clinical studies of circulating biomarkers in LSS have given inconsistent results, which may reflect three methodological limitations.²⁴ First, most studies related serum cytokines directly to subjective pain scores (VAS or ODI), which are strongly confounded by central sensitization, affective comorbidity, pain catastrophizing and paraspinal sarcopenia.⁴³⁻⁴⁵ Second, planimetric measurement of dural sac cross-sectional area (DSCSA) on MRI may not capture the functional tightness of neural compression, because dural sac capacity may vary with stature and ethnicity;^{46,47} the qualitative Schizas grading system instead evaluates the ratio of rootlets to CSF across Grades A to D and may better reflect loss of the CSF buffer and venous stasis.^{7,48} Third, and most important, earlier biochemical cohorts rarely combined exclusion of clinical obesity (body mass index [BMI] ≥ 30 kg/m²) with a standardized washout of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.^{24,49,50} Because visceral adipose tissue secretes pro-inflammatory adipocytokines that raise baseline hs-CRP, whereas analgesic or epidural corticosteroid use suppresses cyclooxygenase and NF- κ B pathways, studies without these controls cannot separate spinal inflammation from metabolic or pharmacological effects.^{49,51-53}

To address these gaps, this prospective exploratory study evaluated the relationship between Schizas morphological severity on axial T2-weighted MRI and peripheral venous IL-1 β and hs-CRP in patients with degenerative LSS selected to limit confounding. With a 7-day pharmacological washout of all NSAIDs and corticosteroids, exclusion of obese individuals (BMI ≥ 30 kg/m²), standardized morning venipuncture to limit diurnal cytokine variation, and multivariable regression with 1,000 bootstrap resamples to adjust for age and BMI, we tested the hypothesis that greater Schizas grade, from Grade A to

Grades C/D, is associated with a stepwise elevation in serum IL-1 β and hs-CRP independent of age and BMI.

2. Methods

Study design and setting

This was a prospective, observational, cross-sectional exploratory study of serum IL-1 β and hs-CRP across Schizas grades of dural sac compression in degenerative LSS. Clinical enrollment, standardized radiological grading and venous sampling were conducted at the Spine Division of the Department of Orthopaedics and Traumatology, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, the primary tertiary academic referral center for South Sumatra and the teaching hospital of the Faculty of Medicine, Universitas Sriwijaya. Recruitment and clinical data collection spanned six months, from February to July 2025. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies.

Participants and eligibility

A consecutive series of 42 ambulatory patients presenting to the orthopedic spine outpatient clinic with symptoms suggestive of degenerative lumbar canal stenosis was screened for eligibility (Figure 1A). Eligibility was restricted to adults aged 40 years or older with a documented history of neurogenic intermittent claudication, defined as posture-dependent buttock or lower extremity pain, paresthesia, cramping or motor fatigue exacerbated by walking or upright lumbar extension and relieved by sitting or forward flexion, or chronic lumbar radiculopathy lasting at least three consecutive months.^{2,54,55} The three-month threshold was used to exclude transient acute discogenic sprains and self-limiting radicular irritation. All participants required confirmatory 1.5-Tesla lumbar MRI showing degenerative osseoligamentous or disco-vertebral pathology at one or more lumbar motion segments (L1–S1), together with documented willingness and clinical stability to complete a supervised 7-day anti-inflammatory washout before phlebotomy. To separate intraspinal inflammation from systemic metabolic, infectious, autoimmune and pharmacological influences, four exclusion criteria were applied. First, patients with clinical obesity, defined as a BMI of 30.0 kg/m² or greater (body weight in kilograms divided by height in meters squared), were excluded ($n = 5$) because visceral adipocytes and adipose-resident macrophages secrete IL-6 and TNF- α , which raise circulating CRP and would inflate baseline serum inflammatory markers.⁵¹ Second, to remove pharmacological suppression of cyclooxygenase-2 (COX-2), phospholipase A2 and NF- κ B signaling, all prospective participants taking oral or parenteral NSAIDs (such as diclofenac, meloxicam, celecoxib or ibuprofen), oral or epidural corticosteroids or disease-modifying antirheumatic drugs completed a verified 7-day pharmacological washout (more than five elimination half-lives) before venipuncture.^{49,52,53} Only acetaminophen up to 2,000 mg/day was permitted, until 24 hours before blood sampling; patients who required rescue anti-inflammatory analgesia or could not safely tolerate the washout were excluded ($n = 4$). Third, patients with systemic inflammatory, infectious, metabolic or neoplastic comorbidities, including diabetes mellitus, rheumatoid arthritis, ankylosing spondylitis, gouty arthropathy, chronic kidney or liver disease, malignancy, clinical infection or a peripheral leukocyte count above 1.1×10^4 cells/ μ L, were excluded ($n = 2$). Fourth, a history of lumbar trauma, vertebral fracture, or any spinal surgery or invasive epidural procedure within the preceding six months led to exclusion ($n = 1$), because postoperative tissue remodeling

could confound the measurements. That left 30 patients who met every inclusion and confounder-control criterion; they formed the analytical cohort (Table 1; Figure 1A).

MRI protocol and Schizas classification

All 30 participants underwent standardized multiparametric lumbar spine MRI on a single 1.5-Tesla superconducting clinical scanner (Magnetom Sempra/Avanto, Siemens Healthineers, Erlangen, Germany) with a dedicated phased-array spine surface coil. The protocol comprised sagittal T1-weighted turbo spin-echo (repetition time [TR] 450–600 ms; echo time [TE] 10–14 ms; slice thickness 4.0 mm), sagittal T2-weighted turbo spin-echo (TR 3,200–4,000 ms; TE 95–110 ms; slice thickness 4.0 mm), sagittal short tau inversion recovery (STIR; TR 3,500 ms; TE 40 ms; inversion time 150 ms) and high-resolution axial T2-weighted turbo spin-echo sequences (TR 3,500–4,200 ms; TE 100–115 ms; slice thickness 3.0 mm; interslice gap 0.3 mm; field of view 180 $\times$ 180 mm) oriented parallel to each intervertebral disc space from L1–L2 to L5–S1. Morphological evaluation was performed on the axial T2-weighted slice with the greatest dural sac constriction at the level corresponding to the patient's primary symptomatic dermatome or claudication level.⁷ All DICOM datasets were anonymized and evaluated independently by two board-certified senior musculoskeletal radiologists with more than 10 years of spine imaging experience, who were blinded to patient demographics, symptom duration and serum biomarker concentrations. Dural sac morphology was categorized with the validated four-grade qualitative system of Schizas et al.⁷ Grade A (no or minor stenosis), with clearly visible hyperintense CSF inside the dural sac and dark rootlets lying dorsally or occupying less than half of the dural sac area (sub-grades A1–A4); Grade B (moderate stenosis), in which the rootlets occupy the whole cross-sectional area of the dural sac but can still be individualized, with some CSF still present and a grainy (marbled) appearance; Grade C (severe stenosis), with no CSF signal and the compressed rootlets packed into a homogeneous gray mass in which individual rootlets cannot be recognized, although dorsal epidural fat remains visible; and Grade D (extreme stenosis), in which neither individual rootlets nor posterior epidural fat can be identified.^{7,9,25} Inter-observer agreement between the two blinded radiologists across all 30 scans was quantified with Cohen's unweighted kappa (κ), which was 0.84 (95% confidence interval [CI] 0.71–0.97; $p < 0.001$), indicating strong agreement; the two discordant readings, both between Grade B and Grade C, were resolved by consensus review. Because outpatient cross-sectional cohorts rarely include extreme Grade D cases before urgent decompression (Grade C: $n = 7$ [23.3%]; Grade D: $n = 2$ [6.7%]), Grades C and D were merged according to an a priori analytical rule into a single Grade C/D group ($n = 9$ [30.0%]), alongside Grade A ($n = 10$ [33.3%]) and Grade B ($n = 11$ [36.7%]), to avoid unstable estimates in very small groups (Table 1; Figure 1A).

Rationale for morphological grading and sample size

We chose the qualitative Schizas classification rather than linear anteroposterior canal diameter (APCD) or quantitative DSCSA planimetry.^{7,9,25} Although DSCSA thresholds (such as <100 mm² for moderate and <75 mm² for severe stenosis) have been widely used in radiological studies, comparative analyses by Seo and Lee and by Spinnato et al., together with normative data on dural sac dimensions, point to three limitations of absolute area measurement.^{25,46–48} First, absolute DSCSA does not normalize for constitutional variation in bony canal dimensions across sex, body height and Southeast Asian versus European skeletal morphometry.^{46,47} Second, area planimetry treats the dural sac as a uniform cylinder and ignores the spatial arrangement of the cauda equina rootlets relative to the surrounding CSF reserve.

Third, from a fluid-mechanics (Starling resistor) standpoint, epidural venous plexus compression and endoneurial ischemia may be triggered not by a fixed millimeter threshold but by exhaustion of the compliant CSF buffer, the transition that the Schizas grades describe from a patent CSF sleeve (Grade A) through rootlets filling the sac with residual CSF (Grade B) to incompressible rootlet packing with effacement of epidural fat (Grades C/D) (Table 1; Figure 1A).^{7,48} The exploratory sample of 30 patients ($n = 10, 11$ and 9) was constrained by the 7-day NSAID/corticosteroid washout and the BMI < 30.0 kg/m² eligibility ceiling. The effect sizes observed across Schizas grades were large: for serum IL-1 β , the omnibus ANOVA effect size was $\eta^2 = 0.682$ (Cohen's $f = 1.46$) and the Kruskal–Wallis $\epsilon^2 = 0.737$ (Table 2); for serum hs-CRP, $\eta^2 = 0.618$ (Cohen's $f = 1.27$) and $\epsilon^2 = 0.401$; and for the multivariable regression models, Cohen's f^2 was 0.695 for IL-1 β ($R^2 = 0.41$; Table 3) and 0.786 for hs-CRP ($R^2 = 0.44$; Table 4). With three predictors, the regression models met the benchmark of 10 participants per covariate.

Biospecimen handling and immunoassays

To minimize pre-analytical variability and to control for the circadian secretory rhythm of pro-inflammatory cytokines, which is regulated by the hypothalamic–pituitary–adrenal axis, fasting peripheral venous blood samples (5.0 mL) were drawn from the median cubital vein between 08:00 and 10:00 on the morning after completion of the 7-day washout.^{56,57} Whole blood was collected into sterile vacuum serum-separator tubes (BD Vacutainer SST II Advance, Becton Dickinson, Franklin Lakes, NJ, USA) and allowed to clot upright for 30 minutes at room temperature (22–24 °C). Tubes were then centrifuged at approximately $1,500 \times g$ (3,000 rpm) for 10 minutes at 4 °C in a refrigerated swing-bucket centrifuge. The serum was aspirated with pyrogen-free micropipette tips, divided into 500 μ L polypropylene cryovials to avoid repeated freeze–thaw cycles and stored at -80 °C until single-batch analysis. All 30 specimens were thawed simultaneously and analyzed in a single batch with identical reagent lots by laboratory personnel blinded to radiological grade. Serum hs-CRP was quantified with a latex-enhanced high-sensitivity immunoturbidimetric assay on an automated clinical chemistry analyzer (Cobas c501, Roche Diagnostics, Mannheim, Germany), with a lower limit of detection of 0.10 mg/L, a functional linearity range of 0.15–20.0 mg/L and an intra-assay coefficient of variation (CV) below 3.2%. Serum IL-1 β was measured in duplicate with a high-sensitivity human-specific quantitative sandwich enzyme-linked immunosorbent assay (ELISA; Quantikine HS ELISA Human IL-1 β /IL-1F2 Immunoassay, R&D Systems, Minneapolis, MN, USA) read at 450 nm with wavelength correction at 540 nm on a microplate spectrophotometer (BioTek Epoch 2, Agilent Technologies, Santa Clara, CA, USA).⁴⁹ Calibration curves were fitted with four-parameter logistic regression ($R^2 = 0.999$), with a minimum detectable dose of 0.057 pg/mL and an intra-assay CV below 5.0% (mean duplicate CV 3.6%).

Statistical analysis

Statistical analyses and visualizations were performed with IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA) and with Python 3.11 and R (RStudio; Posit Software, PBC, Boston, MA, USA). The normality of all continuous variables (age, BMI, symptom duration, serum IL-1 β and serum hs-CRP) was assessed within each group and in the pooled sample with the Shapiro–Wilk W test and Q–Q plots. Because age ($W = 0.968$, $p = 0.485$), BMI ($W = 0.974$, $p = 0.652$) and symptom duration ($W = 0.951$, $p = 0.182$) met the assumption of normality, they were summarized as mean $\pm$ standard deviation (SD) with 95% CIs and compared across the three Schizas groups by one-way

analysis of variance (ANOVA; F statistic and eta-squared [η^2]), whereas sex was reported as counts and percentages and compared with Pearson's chi-square (χ^2) test with Cramér's V (Table 1). Because pooled serum IL-1 β ($W = 0.914$, $p = 0.019$) and hs-CRP ($W = 0.921$, $p = 0.028$) were positively skewed, as is typical of circulating cytokines, biomarker outcomes were reported as median and interquartile range (IQR, 25th–75th percentile), supplemented by mean $\pm$ SD [95% CI] in Table 2 to aid meta-analytic pooling. Differences across Grade A, Grade B and Grade C/D were tested with the Kruskal–Wallis H test ($df = 2$) with epsilon-squared effect size ($\epsilon^2 = H/[(N^2 - 1)/(N + 1)]$), followed by Dunn's post hoc pairwise comparisons with Bonferroni correction (p_{adj}). The bivariate association between IL-1 β and hs-CRP was quantified with Spearman's rank correlation coefficient (ρ) and Pearson's correlation coefficient (r). To determine whether Schizas grade was associated with circulating biomarker levels independently of age-related inflammation and residual adiposity, we fitted multiple linear regression models with Schizas grade, age (years) and BMI (kg/m²) entered simultaneously (Tables 3 and 4). Because a sample of 30 is near the lower limit for multivariable linear regression (10 participants per covariate for three covariates), we used non-parametric bias-corrected and accelerated (BCa) bootstrapping with 1,000 resamples with replacement to derive empirical 95% CIs and bootstrap p values free of distributional assumptions. Multicollinearity between age and stenosis severity was assessed with the variance inflation factor ($VIF = 1/[1 - R_j^2]$), with an a priori threshold of $VIF < 2.5$. Finally, exploratory receiver operating characteristic (ROC) analyses assessed the ability of serum IL-1 β , hs-CRP and a combined logistic index of both markers to discriminate Grade C/D stenosis ($n = 9$) from Grades A/B ($n = 21$), with optimal cut-offs identified by Youden's index ($J = \text{sensitivity} + \text{specificity} - 1$) (Table 5). All tests were two-tailed, with statistical significance set at $\alpha = 0.05$.

Ethical approval

Before participant screening, the study protocol, patient information sheets and the safety-monitoring procedures for the pharmacological washout were reviewed and approved by the Health Research Ethics Committee (Institutional Review Board) of the Faculty of Medicine, Universitas Sriwijaya / Dr. Mohammad Hoesin General Hospital (Reference No.2025/227). All clinical, radiological and biochemical procedures complied with the ethical principles of the Declaration of Helsinki and its later amendments. Written informed consent was obtained from every participant before the 7-day washout began.

3. Results

Screening, baseline characteristics and confounder balance

Between February and July 2025, 42 consecutive patients with chronic neurogenic claudication or lumbar radiculopathy were screened, of whom 12 (28.6%) were excluded because of BMI ≥ 30.0 kg/m² ($n = 5$), inability to complete the 7-day NSAID/corticosteroid washout ($n = 4$), systemic inflammatory comorbidity or leukocytosis $> 1.1 \times 10^4$ cells/ μ L ($n = 2$) or previous lumbar spine surgery ($n = 1$), leaving 30 patients with 100.0% protocol adherence (Figure 1A). Independent grading of axial T2-weighted MRI by the two blinded musculoskeletal radiologists showed strong agreement (Cohen's $\kappa = 0.84$, 95% CI 0.71–0.97, $p < 0.001$) and assigned 10 patients (33.3%) to Grade A (no or minor stenosis with an intact CSF buffer), 11 (36.7%) to Grade B (moderate stenosis with residual CSF and distinct rootlets) and 9 (30.0%) to Grade C/D, comprising Grade C ($n = 7$; 23.3%) and Grade D ($n = 2$; 6.7%) (Table 1). In the total

cohort, mean age was 55.2 ± 8.4 years (95% CI 52.1–58.3); 22 patients (73.3%) were women and 8 (26.7%) men; mean BMI was 26.4 ± 2.0 kg/m² (95% CI 25.6–27.1); and mean symptom duration was 15.6 ± 8.2 months (95% CI 12.6–18.7) (Table 1). The groups were comparable in BMI and sex. Mean BMI was 25.8 ± 1.9 kg/m² (95% CI 24.4–27.2) in Grade A, 26.2 ± 2.3 kg/m² (95% CI 24.7–27.7) in Grade B and 27.2 ± 1.6 kg/m² (95% CI 26.0–28.4) in Grade C/D (one-way ANOVA $F(2,27) = 1.22$, $\eta^2 = 0.083$, $p = 0.312$; Figure 1C), and women made up 70.0% (7/10), 72.7% (8/11) and 77.8% (7/9) of the three groups ($\chi^2(2) = 0.151$, Cramér's $V = 0.071$, $p = 0.927$; Figure 1D). Age

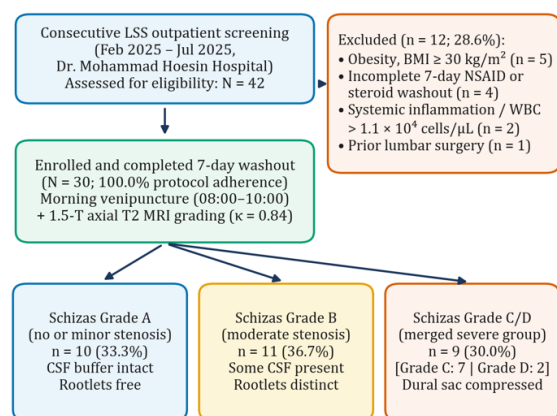
and symptom duration, by contrast, rose significantly with grade (Table 1; Figure 1B). Patients with Grade C/D averaged 64.3 ± 4.5 years (95% CI 60.8–67.8), against 54.1 ± 6.2 years (95% CI 49.9–58.3) in Grade B and 48.2 ± 5.4 years (95% CI 44.3–52.1) in Grade A ($F(2,27) = 20.68$, $\eta^2 = 0.605$, $p < 0.001$). Symptoms had lasted 8.4 ± 2.1 months (95% CI 6.9–9.9) in Grade A, 14.2 ± 4.5 months (95% CI 11.2–17.2) in Grade B and 25.4 ± 6.8 months (95% CI 20.2–30.6) in Grade C/D, a threefold difference ($F(2,27) = 31.45$, $\eta^2 = 0.700$, $p < 0.001$). This gradient fits the slow progression of degenerative canal remodeling and is the reason the regression models were adjusted for age.

Table 1. Baseline demographic, anthropometric and clinical characteristics by Schizas grade (N = 30).

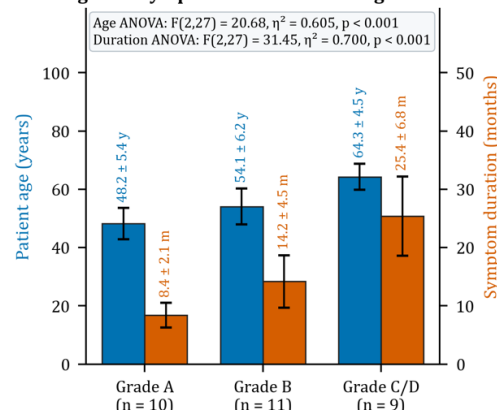
Variable	Total cohort (N = 30; 100.0%)	Grade A (n = 10; 33.3%)	Grade B (n = 11; 36.7%)	Grade C/D (n = 9; 30.0%)	Test statistic and effect size	p value†
Age (years), mean ± SD [95% CI]	55.2 ± 8.4 [52.1–58.3]	48.2 ± 5.4 [44.3–52.1]	54.1 ± 6.2 [49.9–58.3]	64.3 ± 4.5 [60.8–67.8]	$F(2,27) = 20.68$ $\eta^2 = 0.605$	<0.001*
Sex: female, n (%)	22 (73.3%)	7 (70.0%)	8 (72.7%)	7 (77.8%)	$\chi^2(2) = 0.151$ $V = 0.071$	0.927
Sex: male, n (%)	8 (26.7%)	3 (30.0%)	3 (27.3%)	2 (22.2%)		
BMI (kg/m ²), mean ± SD [95% CI]	26.4 ± 2.0 [25.6–27.1]	25.8 ± 1.9 [24.4–27.2]	26.2 ± 2.3 [24.7–27.7]	27.2 ± 1.6 [26.0–28.4]	$F(2,27) = 1.22$ $\eta^2 = 0.083$	0.312
Symptom duration (months), mean ± SD [95% CI]	15.6 ± 8.2 [12.6–18.7]	8.4 ± 2.1 [6.9–9.9]	14.2 ± 4.5 [11.2–17.2]	25.4 ± 6.8 [20.2–30.6]	$F(2,27) = 31.45$ $\eta^2 = 0.700$	<0.001*
Schizas sub-grade, n (% of total cohort)	Grade A: 10 (33.3%) Grade B: 11 (36.7%) Grade C: 7 (23.3%) Grade D: 2 (6.7%)	Grade A: 10 (100.0%)	Grade B: 11 (100.0%)	Grade C: 7 (77.8%) Grade D: 2 (22.2%)	$\kappa = 0.84^\ddagger$ [0.71–0.97]	<0.001*

Continuous variables meeting the Shapiro–Wilk normality criterion ($p > 0.05$) are presented as mean ± standard deviation (SD) with 95% confidence intervals (CI); categorical variables as frequency (n) and percentage (%). †Omnibus test: one-way analysis of variance (ANOVA; F statistic with eta-squared, η^2) for continuous variables and Pearson's chi-square test (χ^2 with Cramér's V) for sex. ‡Cohen's κ for agreement between the two radiologists (not a between-group test). * $p < 0.05$ (two-tailed). BMI, body mass index.

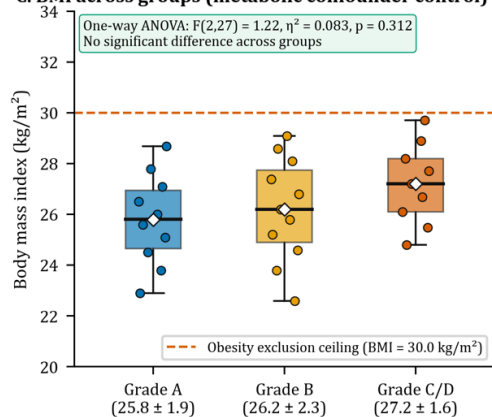
A. Cohort screening and confounder washout protocol



B. Age and symptom duration across grades



C. BMI across groups (metabolic confounder control)



D. Sex distribution and MRI inter-rater reliability

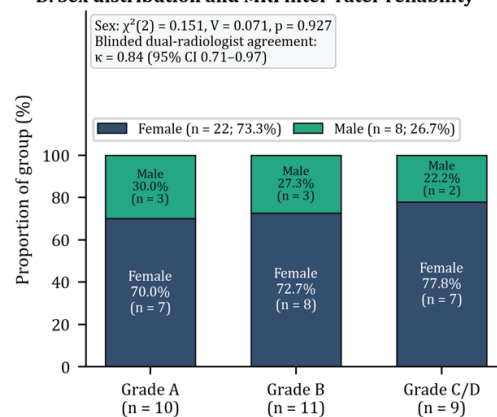


Figure 1. Study flow, demographic progression and confounder balance (N = 30). (A) STROBE flowchart: consecutive outpatient screening (N = 42), exclusions (n = 12), 7-day NSAID/corticosteroid washout and allocation to Schizas Grade A (n = 10), Grade B (n = 11) and merged Grade C/D (n = 9). (B) Age ($F = 20.68$, $p < 0.001$) and symptom duration ($F = 31.45$, $p < 0.001$) across grades (mean ± SD). (C) BMI across groups (BMI < 30 kg/m²; $F = 1.22$, $p = 0.312$); boxes show median and interquartile range, whiskers the range and diamonds the mean. (D) Sex distribution ($\chi^2 = 0.151$, $p = 0.927$) and agreement between the two blinded radiologists ($\kappa = 0.84$).

Serum IL-1 β and hs-CRP across Schizas grades

Serum IL-1 β and hs-CRP concentrations increased across Schizas grades (Table 2; Figure 2). In the pooled cohort, median serum IL-1 β was 8.35 [IQR 5.90–10.60] pg/mL (mean 8.39 $\pm$ 2.86 pg/mL, 95% CI 7.32–9.46) and median serum hs-CRP was 3.35 [IQR 2.30–4.60] mg/L (mean 3.51 $\pm$ 1.48 mg/L, 95% CI 2.96–4.06). Median IL-1 β was 1.51-fold higher in Grade B (8.45 [IQR 7.20–9.50] pg/mL; mean 8.36 $\pm$ 1.38 pg/mL, 95% CI 7.43–9.29) than in Grade A (5.60 [IQR 4.90–6.40] pg/mL; mean 5.68 $\pm$ 0.92 pg/mL, 95% CI 5.02–6.34) and 2.00-fold higher in Grade C/D (11.20 [IQR 9.10–13.80] pg/mL; mean 11.42 $\pm$ 2.45 pg/mL, 95% CI 9.54–13.30) (Kruskal–Wallis $H = 21.38$, $df = 2$, $\epsilon^2 = 0.737$, $p < 0.001$; ANOVA $F(2,27) = 28.91$, $p < 0.001$; Figure 2A). Dunn–Bonferroni comparisons showed significant differences in IL-1 β between Grade A and Grade B ($Z = -2.74$, $p_{adj} = 0.018$), between Grade B and Grade C/D ($Z = -2.43$, $p_{adj} = 0.045$) and between Grade A and Grade C/D ($Z = -4.61$, $p_{adj} < 0.001$). Serum hs-CRP followed a parallel pattern: median concentrations were 1.58-fold higher in Grade B (3.40 [IQR 2.90–4.10] mg/L; mean 3.48 $\pm$ 0.78 mg/L, 95% CI 2.96–4.00) than in Grade A (2.15 [IQR 1.80–2.60] mg/L; mean 2.18 $\pm$ 0.54 mg/L, 95% CI 1.79–2.57) and 2.28-fold higher in Grade C/D (4.90 [IQR 3.80–6.20] mg/L; mean 5.04 $\pm$ 1.36 mg/L, 95% CI 3.99–6.09) (Kruskal–Wallis $H = 11.62$, $df = 2$, $\epsilon^2 = 0.401$, $p = 0.003$; ANOVA $F(2,27) = 21.84$, $p < 0.001$; Figure 2B). For hs-CRP, the Dunn–Bonferroni comparison was significant between Grade A and Grade C/D ($Z = -3.40$, $p_{adj} = 0.002$) but not between Grade A and Grade B ($Z = -2.39$, $p_{adj} = 0.050$) or between Grade B and Grade C/D after Bonferroni correction ($Z = -1.89$, $p_{adj} = 0.176$). Values for Grades C and D

separately are reported in the sensitivity analysis below. Across all 30 patients, serum IL-1 β and hs-CRP were strongly correlated (Spearman's $\rho = 0.784$, 95% CI 0.589–0.892, $p < 0.001$; Pearson's $r = 0.778$, $p < 0.001$; Figure 2C).

Sensitivity analysis by Schizas sub-grade

We also checked whether combining Grade C ($n = 7$) and Grade D ($n = 2$) had shaped the results, repeating the analysis across all four original Schizas grades with both parametric and non-parametric estimators (Table 2). IL-1 β medians rose without exception from Grade A ($n = 10$; 5.60 [IQR 4.90–6.40] pg/mL) through Grade B ($n = 11$; 8.45 [IQR 7.20–9.50] pg/mL) and Grade C ($n = 7$; 10.60 [IQR 9.05–12.40] pg/mL; mean 10.64 $\pm$ 1.98 pg/mL) to Grade D ($n = 2$; 14.15 [range 13.80–14.50] pg/mL; mean 14.15 $\pm$ 0.49 pg/mL), with a four-group Kruskal–Wallis H of 22.84 ($df = 3$, $p < 0.001$). The same ordering held for hs-CRP: 2.15 [IQR 1.80–2.60] mg/L in Grade A, 3.40 [IQR 2.90–4.10] mg/L in Grade B, 4.60 [IQR 3.75–5.60] mg/L in Grade C (mean 4.63 $\pm$ 1.12 mg/L) and 6.45 [range 6.20–6.70] mg/L in Grade D (mean 6.45 $\pm$ 0.35 mg/L) ($H = 13.08$, $df = 3$, $p = 0.004$). Dropping the two Grade D patients and refitting the bootstrapped regression in the remaining 28 (Grades A–C) left Schizas grade significantly associated with serum IL-1 β ($B = 1.84$, bootstrapped 95% CI 0.52–3.18, $\beta = 0.43$, $p = 0.016$, VIF = 2.1) and with serum hs-CRP ($B = 0.98$, bootstrapped 95% CI 0.29–1.69, $\beta = 0.45$, $p = 0.014$, VIF = 2.1). The association between canal narrowing and serum inflammatory markers (Tables 2–4) therefore does not appear to depend on how Grade D was handled, and it is consistent with a gradient across the range of dural sac compression.

Table 2. Serum IL-1 β and hs-CRP concentrations across Schizas MRI grades ($N = 30$).

Schizas group	n (%)	IL-1 β (pg/mL) median [IQR]	IL-1 β (pg/mL) mean $\pm$ SD [95% CI]	hs-CRP (mg/L) median [IQR]	hs-CRP (mg/L) mean $\pm$ SD [95% CI]
Grade A (no or minor stenosis)	10 (33.3%)	5.60 [4.90–6.40]	5.68 $\pm$ 0.92 [5.02–6.34]	2.15 [1.80–2.60]	2.18 $\pm$ 0.54 [1.79–2.57]
Grade B (moderate stenosis)	11 (36.7%)	8.45 [7.20–9.50]	8.36 $\pm$ 1.38 [7.43–9.29]	3.40 [2.90–4.10]	3.48 $\pm$ 0.78 [2.96–4.00]
Grade C/D (merged)	9 (30.0%)	11.20 [9.10–13.80]	11.42 $\pm$ 2.45 [9.54–13.30]	4.90 [3.80–6.20]	5.04 $\pm$ 1.36 [3.99–6.09]
• Grade C ($n = 7$)	7 (23.3%)	10.60 [9.05–12.40]	10.64 $\pm$ 1.98 [8.81–12.47]	4.60 [3.75–5.60]	4.63 $\pm$ 1.12 [3.59–5.67]
• Grade D ($n = 2$)	2 (6.7%)	14.15 [13.80–14.50] [§]	14.15 $\pm$ 0.49 [9.70–18.60]	6.45 [6.20–6.70] [§]	6.45 $\pm$ 0.35 [3.27–9.63]
Total cohort	30 (100.0%)	8.35 [5.90–10.60]	8.39 $\pm$ 2.86 [7.32–9.46]	3.35 [2.30–4.60]	3.51 $\pm$ 1.48 [2.96–4.06]
Kruskal–Wallis test (H , $df = 2$, ϵ^2)	—	$H = 21.38$, $\epsilon^2 = 0.737$ $p < 0.001^*$	One-way ANOVA: $F(2,27) = 28.91$, $p < 0.001^*$	$H = 11.62$, $\epsilon^2 = 0.401$ $p = 0.003^*$	One-way ANOVA: $F(2,27) = 21.84$, $p < 0.001^*$
Dunn–Bonferroni pairwise:					
• Grade A vs Grade B	—	$Z = -2.74$, $p_{adj} = 0.018^*$	Fold difference: B vs A: 1.51-fold	$Z = -2.39$, $p_{adj} = 0.050$	Fold difference: B vs A: 1.58-fold
• Grade A vs Grade C/D		$Z = -4.61$, $p_{adj} < 0.001^*$	C/D vs A: 2.00-fold	$Z = -3.40$, $p_{adj} = 0.002^*$	C/D vs A: 2.28-fold
• Grade B vs Grade C/D		$Z = -2.43$, $p_{adj} = 0.045^*$		$Z = -1.89$, $p_{adj} = 0.176$	

Median [interquartile range, IQR, 25th–75th percentile] is the primary descriptor because of positive skewness on Shapiro–Wilk testing (IL-1 β : $W = 0.914$, $p = 0.019$; hs-CRP: $W = 0.921$, $p = 0.028$); mean $\pm$ standard deviation (SD) [95% confidence interval, CI] is given for meta-analytic comparability. Omnibus tests compared the three primary groups (Grade A, Grade B, Grade C/D): Kruskal–Wallis H test with epsilon-squared ($\epsilon^2 = H/[(N^2 - 1)/(N + 1)]$) and Dunn's post hoc comparisons with Bonferroni adjustment (p_{adj}).

[§]Range ($n = 2$). IL-1 β and hs-CRP were strongly correlated (Spearman's $\rho = 0.784$, $p < 0.001$; Pearson's $r = 0.778$, $p < 0.001$). ANOVA, analysis of variance; hs-CRP, high-sensitivity C-reactive protein; IL-1 β , interleukin-1 β . * $p < 0.05$.

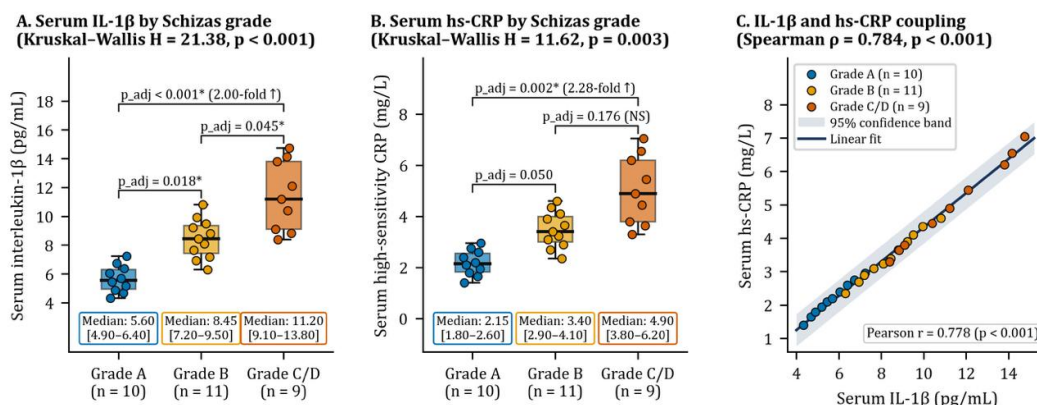


Figure 2. Serum IL-1 β and hs-CRP across Schizas grades. (A) Individual serum IL-1 β values with box plots (median and interquartile range; whiskers, range): Grade A 5.60 [4.90–6.40] pg/mL vs Grade C/D 11.20 [9.10–13.80] pg/mL (2.00-fold; Kruskal–Wallis $H = 21.38$, $p < 0.001$). (B) Serum hs-CRP: Grade A 2.15 [1.80–2.60] mg/L vs Grade C/D 4.90 [3.80–6.20] mg/L (2.28-fold; $H = 11.62$, $p = 0.003$). Brackets show Dunn–Bonferroni adjusted p values (p_{adj}). (C) Correlation between IL-1 β and hs-CRP (Spearman $\rho = 0.784$, Pearson $r = 0.778$, $p < 0.001$) with linear fit and 95% confidence band.

Bootstrapped multivariable regression and multicollinearity

Because the groups differed in age, we examined whether age rather than dural sac compression could explain the biomarker differences. Multiple linear regression models adjusted for age and BMI were fitted and validated with 1,000 non-parametric bootstrap resamples (Tables 3 and 4; Figures 3 and 4). For serum IL-1 β (Table 3; Figure 3A), the three predictors together accounted for 41.0% of the variance ($R^2 = 0.41$, adjusted $R^2 = 0.34$, $F(3,26) = 6.02$, $p = 0.003$). Schizas grade remained significantly associated with serum IL-1 β (unstandardized $B = 2.05$, bootstrapped 95% CI 0.65–3.45; standardized $\beta = 0.46$; $t = 2.71$; bootstrapped $p = 0.012$; constant $B = 1.18$, bootstrapped 95% CI 0.45–2.80, $p = 0.160$), whereas neither age ($B = 0.03$, 95% CI -0.01 to 0.08 , $\beta = 0.17$, $t = 1.28$, $p = 0.210$) nor BMI ($B =$

0.11 , 95% CI -0.05 to 0.28 , $\beta = 0.09$, $t = 0.77$, $p = 0.450$) was significant with Schizas grade in the model. The model for serum hs-CRP (Table 4; Figure 3B) explained 44.0% of the variance ($R^2 = 0.44$, adjusted $R^2 = 0.38$, $F(3,26) = 6.81$, $p = 0.002$). In this model, Schizas grade was associated with hs-CRP ($B = 1.12$, bootstrapped 95% CI 0.38–1.86; $\beta = 0.49$; $t = 2.83$; $p = 0.009$; constant $B = -0.64$, 95% CI -2.40 to 1.12 , $p = 0.462$), whereas age ($B = 0.02$, 95% CI -0.01 to 0.05 , $\beta = 0.15$, $t = 1.20$, $p = 0.240$) and BMI ($B = 0.06$, 95% CI -0.04 to 0.17 , $\beta = 0.11$, $t = 0.87$, $p = 0.390$) were not. In both models, all VIFs were below the a priori threshold of 2.5 (Schizas grade 2.2; age 2.1; BMI 1.1; Figure 3C). At the cohort means (age 55.2 years; BMI 26.4 kg/m ^{2}), covariate-adjusted estimated marginal means of serum IL-1 β were 5.82 pg/mL in Grade A, 8.39 pg/mL in Grade B and 11.21 pg/mL in Grade C/D, and those of hs-CRP were 2.26, 3.49 and 4.93 mg/L (Figure 4A and 4B).

Table 3. Bootstrapped multiple linear regression predicting serum IL-1 β , adjusted for age and BMI (1,000 bootstrap resamples; $N = 30$).

Predictor	Unstandardized coefficient B	Bootstrapped 95% CI [lower, upper]	Standardized β	t statistic	Bootstrapped p value	Variance inflation factor (VIF)
(Constant)	1.18	[0.45, 2.80]	—	1.44	0.160	—
Schizas grade (ordinal)	2.05	[0.65, 3.45]	0.46	2.71	0.012*	2.2
Age (years)	0.03	[-0.01 , 0.08]	0.17	1.28	0.210	2.1
BMI (kg/m ^{2})	0.11	[-0.05 , 0.28]	0.09	0.77	0.450	1.1

Model summary: $R^2 = 0.41$, adjusted $R^2 = 0.34$, $F(3,26) = 6.02$, $p = 0.003$. Non-parametric bias-corrected and accelerated (BCa) bootstrapping with 1,000 resamples with replacement. VIF = $1/[1 - R_j^2]$; values < 2.5 were taken to indicate no distorting multicollinearity between age and Schizas grade. BMI, body mass index; CI, confidence interval; IL-1 β , interleukin-1 β . * $p < 0.05$.

Table 4. Bootstrapped multiple linear regression predicting serum hs-CRP, adjusted for age and BMI (1,000 bootstrap resamples; $N = 30$).

Predictor	Unstandardized coefficient B	Bootstrapped 95% CI [lower, upper]	Standardized β	t statistic	Bootstrapped p value	Variance inflation factor (VIF)
(Constant)	-0.64	[-2.40 , 1.12]	—	-0.75	0.462	—
Schizas grade (ordinal)	1.12	[0.38, 1.86]	0.49	2.83	0.009*	2.2
Age (years)	0.02	[-0.01 , 0.05]	0.15	1.20	0.240	2.1
BMI (kg/m ^{2})	0.06	[-0.04 , 0.17]	0.11	0.87	0.390	1.1

Model summary: $R^2 = 0.44$, adjusted $R^2 = 0.38$, $F(3,26) = 6.81$, $p = 0.002$. Non-parametric bootstrapping with 1,000 resamples. Schizas grade remained independently associated with hs-CRP ($B = 1.12$ [0.38, 1.86], $\beta = 0.49$, $p = 0.009$, VIF = 2.2) after adjustment for age ($p = 0.240$) and BMI ($p = 0.390$). BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein. * $p < 0.05$.

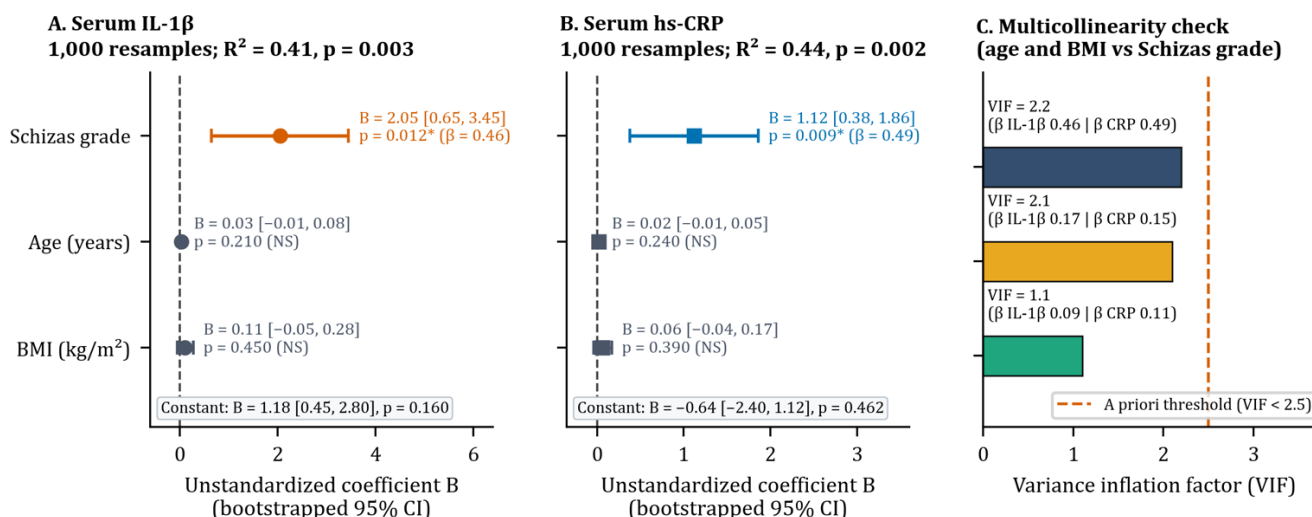


Figure 3. Bootstrapped multivariable linear regression (1,000 resamples). (A) Unstandardized coefficients (B) with bootstrapped 95% CI for serum IL-1 β ($R^2 = 0.41$, $p = 0.003$); Schizas grade $B = 2.05$ [0.65, 3.45], $\beta = 0.46$, $p = 0.012$. (B) Corresponding model for serum hs-CRP ($R^2 = 0.44$, $p = 0.002$); Schizas grade $B = 1.12$ [0.38, 1.86], $\beta = 0.49$, $p = 0.009$. (C) Variance inflation factors (Schizas grade 2.2, age 2.1, BMI 1.1) against the a priori threshold of 2.5.

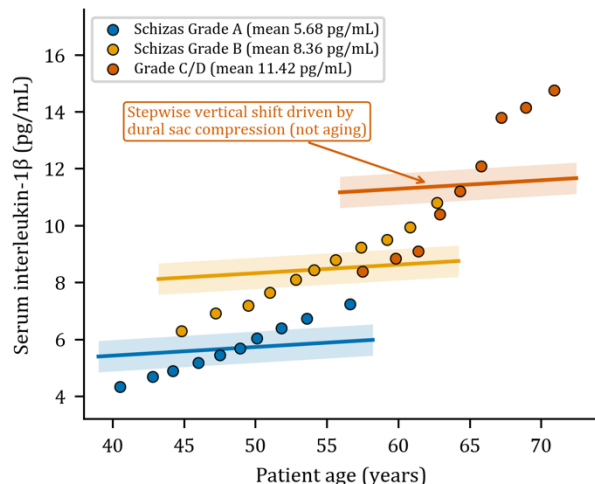
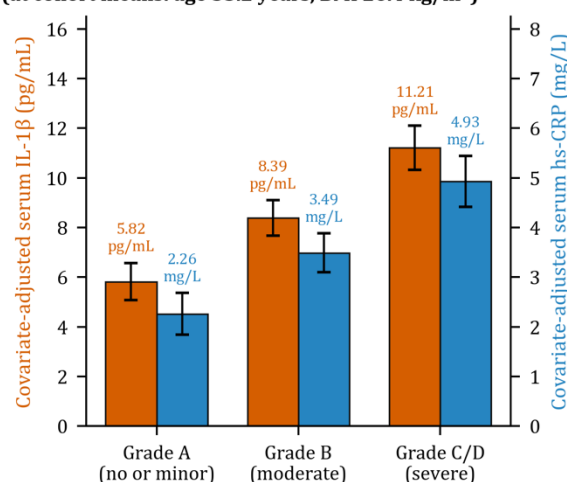
A. Serum IL-1 β by age within Schizas grades(Schizas $\beta = 0.46$, $p = 0.012^*$ vs age $\beta = 0.17$, $p = 0.210$)**B. Estimated marginal means adjusted for age and BMI**(at cohort means: age 55.2 years, BMI 26.4 kg/m²)

Figure 4. Serum IL-1 β and hs-CRP in relation to age, BMI and Schizas grade. (A) Serum IL-1 β by age within Schizas grades, with within-grade fitted lines and bands (age $p = 0.210$ in the regression model). (B) Estimated marginal means adjusted for age and BMI at the cohort means (age 55.2 years, BMI 26.4 kg/m²): IL-1 β 5.82 to 11.21 pg/mL and hs-CRP 2.26 to 4.93 mg/L.

Exploratory diagnostic discrimination for Grade C/D stenosis

Exploratory ROC analyses assessed the ability of serum IL-1 β and hs-CRP to discriminate Grade C/D stenosis ($n = 9$) from Grades A and B ($n = 21$) (Table 5; Figure 5). Serum IL-1 β had an apparent area under the curve (AUC) of 0.915 (95% CI 0.812–1.000, $p < 0.001$); at the Youden-optimal cut-off of ≥ 9.05 pg/mL ($J = 0.746$), its sensitivity was 88.9% (8/9), specificity 85.7% (18/21), positive predictive value (PPV) 72.7% and negative

predictive value (NPV) 94.7% (Figure 5A). Serum hs-CRP had an AUC of 0.857 (95% CI 0.714–1.000, $p = 0.002$); at ≥ 3.75 mg/L ($J = 0.587$), sensitivity was 77.8% (7/9), specificity 81.0% (17/21), PPV 63.6% and NPV 89.5% (Figure 5B). The combined logistic index of both markers had an apparent AUC of 0.942 (95% CI 0.858–1.000, $p < 0.001$), with 88.9% sensitivity (8/9), 90.5% specificity (19/21), 80.0% PPV and 95.0% NPV at a predicted-probability cut-off of ≥ 0.42 ($J = 0.794$) (Table 5; Figure 5). Because the cut-offs were derived and evaluated in the same 30 patients, these estimates are optimistic.

Table 5. Exploratory receiver operating characteristic (ROC) performance of serum biomarkers for discriminating Schizas Grade C/D ($n = 9$) from Grades A/B ($n = 21$).

Biomarker / index	Optimal Youden cut-off	AUC [95% CI]	Sensitivity % (n/N)	Specificity % (n/N)	PPV / NPV (%)	Youden's index (J)	p value
Serum interleukin-1 β (IL-1 β)	≥ 9.05 pg/mL	0.915 [0.812–1.000]	88.9% (8/9)	85.7% (18/21)	72.7% / 94.7%	0.746	<0.001*
Serum high-sensitivity CRP (hs-CRP)	≥ 3.75 mg/L	0.857 [0.714–1.000]	77.8% (7/9)	81.0% (17/21)	63.6% / 89.5%	0.587	0.002*
Combined index (logistic composite: IL-1 β + hs-CRP)	Probability ≥ 0.42	0.942 [0.858–1.000]	88.9% (8/9)	90.5% (19/21)	80.0% / 95.0%	0.794	<0.001*

AUC, area under the ROC curve; CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value. Optimal cut-offs maximize Youden's index ($J = \text{sensitivity} + \text{specificity} - 1$). Given the exploratory sample ($N = 30$), these thresholds are hypothesis-generating benchmarks that require prospective validation in larger multicenter cohorts. *AUC significantly > 0.50 ($p < 0.05$).

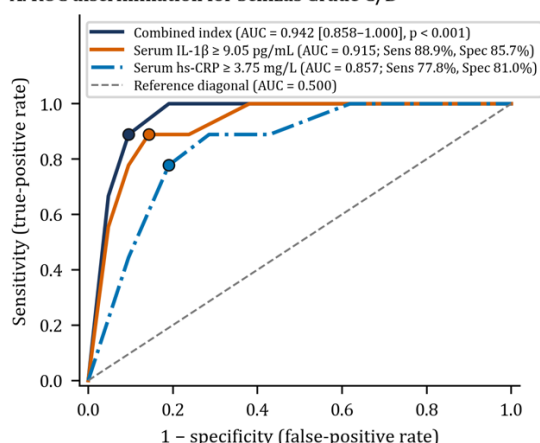
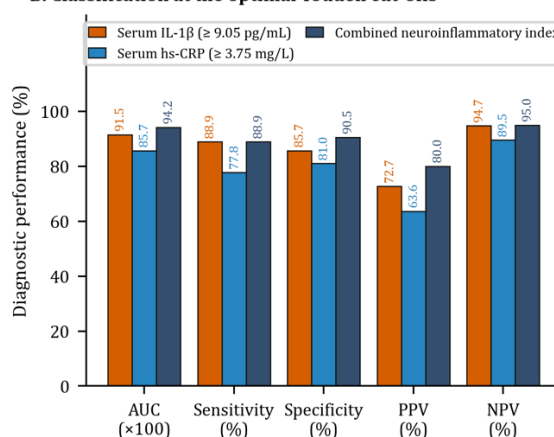
A. ROC discrimination for Schizas Grade C/D**B. Classification at the optimal Youden cut-offs**

Figure 5. Exploratory receiver operating characteristic (ROC) analysis for Schizas Grade C/D vs Grades A/B. (A) ROC curves for serum IL-1 β (AUC = 0.915), serum hs-CRP (AUC = 0.857) and the combined index (AUC = 0.942); circles mark the Youden-optimal cut-offs. (B) Sensitivity, specificity, positive and negative predictive values (PPV, NPV) at the optimal cut-offs (IL-1 β ≥ 9.05 pg/mL; hs-CRP ≥ 3.75 mg/L), with AUC $\times 100$ for comparison. Values are apparent (in-sample) estimates.

4. Discussion

In this prospective exploratory study, patients with more severe dural sac compression on the Schizas scale had stepwise higher serum IL-1 β and hs-CRP, and the association was independent of age and BMI (Tables 2–4). Several design choices reduced confounding: obesity was excluded with a BMI ceiling of 30.0 kg/m², NSAIDs and corticosteroids were withdrawn for a verified 7 days, blood was drawn in the morning to limit circadian variation, and the bootstrapped models adjusted for age and BMI.^{24,49} From Grade A to Grade C/D, median IL-1 β doubled (5.60 to 11.20 pg/mL; $p < 0.001$) and median hs-CRP rose 2.28-fold (2.15 to 4.90 mg/L; $p = 0.003$; Figure 2). Schizas grade was the only covariate significantly associated with either marker in the bootstrapped regression (IL-1 β : $B = 2.05$, $\beta = 0.46$, $p = 0.012$, $R^2 = 0.41$; hs-CRP: $B = 1.12$, $\beta = 0.49$, $p = 0.009$, $R^2 = 0.44$), and all VIFs were below 2.5 (1.1–2.2; Figures 3 and 4). Taken together, the results fit a mechanobiological model of LSS, in which high-grade obliteration of the dural sac is accompanied by measurable systemic inflammation, better than a purely localized, static mechanical entrapment.^{6,24,38}

Placed in the context of spine biomarker research, these findings show why confounder control matters when peripheral inflammatory signals are sought in degenerative LSS.^{24,49,50,58} A 2026 systematic review of inflammatory biomarkers in degenerative LSS by Noma, Djuric and Vleggeert-Lankamp found sparse and heterogeneous evidence, including one CSF study that linked IL-6 to dural sac area, and called for adjustment for confounding and standardized protocols; a systematic review of blood biomarkers in non-specific low back pain by Pinto et al. also reported heterogeneous findings.^{24,50} CSF studies have reported elevated mitochondrial reactive oxygen species (ROS) in an experimental model of LSS and higher CSF lysophosphatidic acid concentrations in patients with more severe stenosis,^{59,60} whereas peripheral blood studies have given variable results, possibly because cohorts were not stratified by medication use or metabolic status.²⁴ Kwon et al. found significantly lower CSF IL-6, Her1 and MCP-1 concentrations in patients with persistent neuropathic pain after lumbar stenosis surgery,⁵⁸ and Hong et al. found elevated mitochondrial ROS in the CSF of rats with experimental LSS and proposed it as an early index of canal compromise.⁵⁹ However, lumbar puncture for CSF sampling is invasive, carries risks of post-dural puncture headache and epidural hematoma⁶¹ and is impractical for routine outpatient surgical screening. In contrast, Chalermkitpanit et al. reported in 2025 that serum IL-1 β , IL-6, interferon-gamma (IFN- γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF) decreased significantly after lumbar epidural steroid injection in clinical responders with lumbosacral radiculopathy.⁴⁹ Our study complements CSF profiling with routine peripheral venipuncture: with masking by NSAIDs and corticosteroids limited by a 7-day washout and adipose-derived cytokine effects limited by a BMI < 30.0 kg/m² criterion, serum IL-1 β and hs-CRP differed approximately two-fold between Grade A and Grade C/D and tracked with Schizas grade (Table 2; Figure 2).^{24,49}

Our biochemical results are consistent with the venous congestion and hypoxia-cytokine hypothesis of neurogenic claudication, summarized as a hypothesized pathway in Figure 6, although this study did not test the pathway directly.^{6,26,27} In a morphologically preserved canal (Schizas Grade A), the hyperintense CSF sleeve acts as a hydrodynamic cushion that

distributes mechanical loads and maintains venous drainage through Batson's internal vertebral venous plexus.^{7,25} As ligamentum flavum buckling, facet capsule hypertrophy and disc bulging progress to Grade B (moderate stenosis), the CSF reserve is reduced and the cauda equina rootlets crowd the dural sac; when pathology reaches Grades C and D, the rootlets are compressed into an undifferentiated mass and posterior epidural fat is effaced.^{7,9} Because intraspinal and radicular venules have thin, non-muscular walls and low intraluminal pressure, they are thought to collapse at compression pressures far below mean arterial pressure.^{26,62} Venous outflow obstruction across multisegmental or severe single-level stenosis may then produce chronic venous hypertension, endoneurial microvascular stasis and intraneural hypoxia (reduced pO₂) (Figure 6, stage 2).^{6,26} In hypoxic endothelial cells, Schwann cells and ligamentum flavum fibroblasts, low oxygen tension prevents von Hippel-Lindau-mediated proteasomal degradation of HIF-1 α , allowing HIF-1 α dimerization and nuclear translocation.²⁸ Stabilized HIF-1 α may cooperate with mechanosensitive NF- κ B and mitochondrial ROS to activate the NLRP3 inflammasome in infiltrating CD68⁺ macrophages and dorsal root microglia, driving caspase-1-dependent maturation and secretion of bioactive IL-1 β (Figure 6, stage 3).^{30,31,59}

A closer look at the molecular events in the hypothesized venous stasis-HIF-1 α -IL-1 β -BSCB axis suggests how mechanical stress at the L3–S1 motion segments could translate into systemic hepatocyte activation (Figure 6).^{6,38,39} Anatomically, Batson's internal vertebral venous plexus forms a rich, valveless anastomotic network around the dural sac in the epidural space and drains the radicular veins that accompany each cauda equina root through the intervertebral foramina.²⁶ When ligamentum flavum hypertrophy and facet osteophytes reduce or obliterate the CSF space in Schizas Grades B, C and D, the elevated intrathecal and extradural tissue pressure may exceed venular transmural pressure (typically 8–12 mmHg),^{7,9,63} collapsing the periradicular veins while higher-pressure radicular arterioles continue to perfuse the capillary bed.⁶² In a rat model of cranial venous outflow obstruction after traumatic brain injury, Wang et al. found that venous obstruction promoted tight-junction loss and ADAM17/soluble TNF- α /NF- κ B-mediated neuroinflammation;⁶³ by analogy, venous hypertension in the stenotic canal might cause endothelial shear stress, microvascular stasis and pericapillary fibrin cuff deposition that impair oxygen diffusion and lower intraneural partial pressure of oxygen (pO₂).²⁶ In the ischemic rootlets and adjacent hypertrophied ligamentum flavum, hypoxia stabilizes HIF-1 α ²⁸ and may uncouple the mitochondrial electron transport chain, generating bursts of mitochondrial ROS such as those documented in the CSF of rats with experimental LSS by Hong et al.^{6,59} Concurrently, mechanical stretching and compression of ligamentum flavum fibroblasts activate mitogen-activated protein kinase (MAPK) and NF- κ B signaling⁶ and possibly mechanosensitive Piezo1 ion channels and focal adhesion kinase (FAK),^{64,65} which may converge with HIF-1 α on NF- κ B p65 to drive transcription of NLRP3 and pro-IL-1 β .³¹ Within infiltrating CD68⁺ macrophages, which Jiang et al. identified in hypertrophied human ligamentum flavum (predominantly of the M2 phenotype), potassium efflux and mitochondrial ROS can trigger assembly of the NLRP3-ASC-pro-caspase-1 inflammasome complex, cleaving pro-IL-1 β into mature 17-kDa IL-1 β that is released into the epidural and intrathecal interstitial fluid.^{30,31}

STAGE 1: MORPHOLOGICAL DURAL SAC ENCROACHMENT (Schizas Grade A → B → Severe C/D)

Facet osteophytosis, intervertebral disc bulging, and ligamentum flavum hypertrophy (LFH) progressively reduce the cerebrospinal fluid (CSF) hydraulic buffer (Grade B) and pack cauda equina rootlets into a solid mass (Grades C/D).

STAGE 2: EPIDURAL VENOUS PLEXUS CONGESTION, ISCHEMIA & HIF-1 α STABILIZATION

Thin-walled Batson's internal vertebral venous plexus collapses under elevated intrathecal pressure → venous stasis, microvascular hypertension, and intraneural hypoxia ($\downarrow$ pO₂) → stabilization of endothelial & Schwann cell HIF-1 α .

STAGE 3: NLRP3 INFLAMMASOME ACTIVATION & INTRATHECAL IL-1 β CYTOKINE CASCADE

HIF-1 α & NF- κ B prime NLRP3 inflammasome in infiltrating CD68⁺ macrophages and dorsal root microglia → caspase-1 cleavage of pro-IL-1 β into bioactive IL-1 β → MMP-2/9 & TGF- β 1 upregulation (fibrotic LFH feedback loop) + nociceptor sensitization.

STAGE 4: BLOOD-SPINAL CORD BARRIER (BSCB) TIGHT-JUNCTION DISRUPTION & VENOUS SPILLOVER

Intrathecal IL-1 β degrades endothelial tight-junction proteins (Claudin-5, Occludin, ZO-1) via RhoA/ROCK & MMP-9 signaling → paracellular BSCB hyperpermeability → systemic spillover of IL-1 β into peripheral venous circulation (Median 11.20 vs. 5.60 pg/mL, $p < 0.001^*$).

STAGE 5: HEPATIC ACUTE-PHASE AMPLIFICATION & CLINICAL DIAGNOSTIC SIGNATURE

Circulating IL-1 β (synergistically with IL-6) activates hepatocyte STAT3/C/EBP β transcription → systemic hs-CRP synthesis (Median 4.90 vs. 2.15 mg/L, $p = 0.003^*$; $\beta = 0.49$, $p = 0.009^*$) → candidate biological adjunct for the clinical-radiological paradox.

Figure 6. Hypothesized venous stasis-HIF-1 α -IL-1 β -BSCB pathway in degenerative lumbar spinal stenosis. Schematic, not tested in this study (only serum IL-1 β and hs-CRP were measured), of how dural sac obliteration (Schizas Grades C/D) might compress Batson's epidural venous plexus and lead to intraneural hypoxia, HIF-1 α stabilization, NLRP3 inflammasome activation, tight-junction degradation (claudin-5, occludin, ZO-1) across the blood-spinal cord barrier (BSCB), peripheral venous IL-1 β spillover and hepatic hs-CRP synthesis.

The higher cytokine concentrations in antecubital venous blood with greater lumbar dural sac compression may be explained by cytokine-mediated disruption of the BSCB and the blood-nerve barrier (BNB) (Figure 6, stages 4 and 5).^{38,39,66} Under homeostatic conditions, the BSCB restricts the paracellular flux of hydrophilic macromolecules between the intrathecal compartment and the systemic vasculature through endothelial tight junctions composed of claudin-5, occludin and the cytoplasmic scaffolding proteins ZO-1 and ZO-2.^{38,39} Experimental studies of brain microvascular endothelium show that IL-1 β downregulates claudin-5 and related tight-junction proteins,^{40,41} and signaling through the endothelial interleukin-1 receptor type 1 (IL-1R1), p38 MAPK, RhoA/Rho-associated protein kinase (ROCK) and MMP-9 has been proposed to internalize and proteolytically cleave claudin-5 and ZO-1.³⁸ Once tight-junction integrity is breached, the high concentration gradient of IL-1 β generated within the congested canal and hypertrophied ligamentum flavum could allow diffusion across the hyperpermeable microvascular endothelium into the perivertebral venous plexus and systemic venous circulation.³⁸ Furthermore, we did not observe an isolated rise in IL-1 β ; serum IL-1 β correlated positively with serum hs-CRP (Spearman's $\rho = 0.784$, $p < 0.001$; Figure 2C). Physiologically, circulating IL-1 β acts as an upstream inducer that, together with IL-6, activates hepatic STAT3 and CCAAT/enhancer-binding protein beta (C/EBP β) transcription factors and triggers de novo synthesis and release of acute-phase CRP into the peripheral blood.⁴² The parallel elevation of IL-1 β and hs-CRP is consistent with a systemic acute-phase response.

Once extracellular IL-1 β accumulates within the stenotic canal, it may act through two parallel programs: local tissue remodeling with nociceptive sensitization, and microvascular barrier breakdown allowing systemic spillover (Figure 6, stages 3–5).^{38,39,66} At the local level, Burt et al. and Lee et al. reported upregulation of TGF- β 1, connective tissue growth factor (CTGF) and SPARC with collagen deposition in hypertrophied ligamentum flavum, and IL-1 β binding to IL-1R1 on ligamentum flavum fibroblasts, with MMP-2 and MMP-9 induction, may perpetuate elastin degradation and type I/III collagen deposition;^{6,34,35} IL-1 β also acts on dorsal root ganglion nociceptors to phosphorylate TRPV1 and tetrodotoxin-resistant Nav1.8 sodium channels, generating ectopic discharges perceived clinically as radicular pain and neurogenic claudication.^{36,37} At the microvascular interface, reviews and experimental studies of the BSCB by Chopra et al., Huang et al. and Xie et al. describe NF- κ B-driven inflammation, MMP activity and loss of claudin-5, occludin and ZO-1 in barrier dysfunction.^{38,39,66} Huang et al. showed that M01, an inhibitor of claudin-5 interactions, reduced inflammatory factor release, ZO-1 degradation and vasogenic edema after BSCB dysfunction, and Xie et al. showed in 2026 that exogenous IL-33, by suppressing NF- κ B signaling, promoted BSCB repair and neural functional recovery.^{39,66} In severe LSS (Schizas Grades C and D), cytokine-induced BSCB/BNB hyperpermeability, together with raised hydrostatic pressure in the congested epidural venous plexus, might allow convective and diffusive paracellular transport of intrathecal IL-1 β into the ascending lumbar and azygos venous systems. On reaching the hepatic sinusoids, circulating IL-1 β , acting with endothelial and hepatic IL-6, activates hepatocyte JAK/STAT3 and C/EBP β transcriptional complexes,⁴² which

would be consistent with the higher hs-CRP observed in Grade C/D (median 4.90 vs 2.15 mg/L in Grade A, $p = 0.003$; Table 2; Figure 2B).

The biomarker profiles of Grade A (no or minor stenosis) and Grade B (moderate stenosis) are also informative (Table 2). All 10 patients with Grade A presented to our tertiary spine clinic with chronic axial low back pain or non-compressive pseudoradicular complaints lasting a mean of 8.4 ± 2.1 months (Table 1), yet their median serum IL-1 β (5.60 pg/mL) was significantly lower than in Grade B (8.45 pg/mL; $p_{\text{adj}} = 0.018$) and Grade C/D (11.20 pg/mL; $p_{\text{adj}} < 0.001$), and their median hs-CRP (2.15 mg/L) was significantly lower than in Grade C/D ($p_{\text{adj}} = 0.002$). This difference may be relevant to the clinical-radiological paradox reported in the NORDSTEN and Japanese cohorts,²⁰⁻²² although symptom severity was not measured in this study. In Grade A patients, pain may arise predominantly from facet joint capsular strain, interspinous ligament sprain or paraspinal myofascial fatigue, nociceptive processes that do not obliterate the CSF buffer or induce cauda equina venous ischemia.^{44,67} Conversely, the higher IL-1 β already present in Grade B (8.45 pg/mL) suggests that inflammatory activity is increased at a stage when the rootlets fill the dural sac but some CSF remains, before the rootlets lose their individual outline on static supine MRI.⁷ Because supine MRI underestimates the dynamic canal narrowing that occurs during upright axial loading and lumbar extension,⁶⁸ some patients with morphologically moderate Grade B stenosis may experience substantial dynamic venous congestion during walking.²⁶ In such borderline scenarios, in which a surgeon must choose between decompressive laminectomy or endoscopic flavectomy and conservative rehabilitation for a patient with moderate Grade B stenosis on supine MRI,^{17,19} the exploratory ROC results (serum IL-1 $\beta \geq 9.05$ pg/mL: AUC 0.915, sensitivity 88.9%, specificity 85.7%; hs-CRP ≥ 3.75 mg/L: AUC 0.857; combined index: AUC 0.942; Table 5; Figure 5) suggest that serum markers merit evaluation as an adjunct in prospective studies; cut-offs derived in-sample require external validation before clinical use.^{24,49}

From a clinical standpoint, combining serum IL-1 β and hs-CRP with standard axial T2-weighted MRI could help address three common diagnostic dilemmas in spine surgery if the associations are confirmed.^{17,20,22} The first concerns the symptomatic patient with borderline moderate stenosis (Schizas Grade B) on supine MRI. The NORDSTEN investigators (Aaen et al., Tronstad et al. and Hermansen et al.) and Minetama et al. have described the uncertainty over whether levels with moderate stenosis should be decompressed or managed with structured physical therapy and gait rehabilitation,^{17,20-22,69} and static supine MRI may underestimate the functional narrowing that develops during upright posture and walking.⁶⁸ In our cohort, Grade B patients had an intermediate median IL-1 β of 8.45 [IQR 7.20–9.50] pg/mL and hs-CRP of 3.40 [IQR 2.90–4.10] mg/L (Table 2). Grade B patients with values above the exploratory Youden cut-offs (IL-1 $\beta \geq 9.05$ pg/mL or hs-CRP ≥ 3.75 mg/L; Table 5; Figure 5) could be studied prospectively to test whether they differ clinically or respond differently to treatment; venous congestion and barrier leakage were not measured here. Epidural corticosteroid injection and minimally invasive decompression are options for selected patients with LSS, and minimally invasive techniques such as unilateral biportal endoscopic (UBE) and arthroscopic-assisted uni-portal decompression differ in paraspinal muscle injury and postoperative CRP response.^{19,70-72} The second dilemma involves older patients with multilevel MRI abnormalities in whom the primary pain generator, neurogenic claudication

from central stenosis or mechanical axial back pain from facet arthropathy, paraspinal sarcopenia or multifidus fatty infiltration, remains unclear.⁴³⁻⁴⁵ Regev et al. found that multifidus fatty infiltration, but not psoas-defined sarcopenia, predicted the improvement in disability after minimally invasive decompression; Schönnagel et al. related axial muscle wasting to the severity of stenosis; and Virk et al. found poorer lumbar muscle health in patients with spondylolisthesis undergoing surgery for stenosis.⁴³⁻⁴⁵ Whether a low serum biomarker profile, such as values below the Grade A upper quartiles in Table 2 (IL-1 $\beta < 6.40$ pg/mL and hs-CRP < 2.60 mg/L), identifies patients whose symptoms are predominantly mechanical or myogenic rather than neuro-ischemic is a question for future studies; if so, such patients might be directed toward targeted core rehabilitation and non-operative management, as recommended in the clinical practice guideline of Bussi  res et al. and supported by the systematic review of Ammendolia et al.^{54,55} The third application lies in postoperative biomarker surveillance and digital phenotyping: serial serum IL-1 β and hs-CRP combined with wearable gait sensors (reviewed by Morimoto et al.) could help quantify the biological effect of decompression and identify persistent neuropathic inflammation before irreversible neural fibrosis develops.^{58,73}

Several limitations should be considered. First, the sample of 30 patients, with 9 in Grade C/D and only 2 in Grade D (Tables 1 and 2), reflects an exploratory single-center design. Although bootstrapping supported the stability of the regression coefficients and the VIF diagnostics did not indicate multicollinearity (VIF 1.1–2.2; Tables 3 and 4), the bootstrapped CIs remain moderately wide, and the ROC cut-offs (IL-1 $\beta \geq 9.05$ pg/mL; hs-CRP ≥ 3.75 mg/L; Table 5) must be interpreted as hypothesis-generating rather than as clinical decision rules until they are externally validated in larger multicenter cohorts.²⁴ Second, the cross-sectional design precludes causal inference about the direction of the relationship between inflammation and stenosis. Because macrophage-derived IL-1 β stimulates TGF- β 1, SPARC and collagen synthesis in the ligamentum flavum, local inflammation and mechanical stenosis may reinforce each other; longitudinal studies with paired serum IL-1 β and hs-CRP measured before and 3–6 months after decompression (for example, UBE decompression or microscopic tubular laminotomy) are needed to test whether relief of venous congestion normalizes peripheral biomarker levels.^{6,19,72} Third, although clinical obesity (BMI ≥ 30.0 kg/m²) was excluded and BMI did not differ significantly across groups ($p = 0.312$; Table 1; Figure 1C), visceral adipose mass was not measured by dual-energy X-ray absorptiometry, circulating adipokines such as leptin and adiponectin were not measured, and peripheral sampling was not paired with intrathecal CSF sampling or with pain and function questionnaires (ODI, ZCQ) to model the full pathway between MRI morphology, serum cytokines and claudication distance.^{58,60}

5. Conclusion

In this prospective exploratory study with confounder restrictions, greater dural sac compression on Schizas MRI grading was associated with stepwise increases in serum IL-1 β and hs-CRP in degenerative LSS. The association held after obesity was excluded (BMI < 30.0 kg/m²), a 7-day NSAID and corticosteroid washout was verified, and age and BMI were adjusted for in bootstrapped regression (all VIF < 2.5): Schizas grade was associated with both IL-1 β ($B = 2.05$, $\beta = 0.46$, $p = 0.012$) and hs-CRP ($B = 1.12$, $\beta = 0.49$, $p = 0.009$). These findings are consistent with, but do not test, the hypothesis that venous stasis, hypoxia-induced cytokine production and blood–spinal cord barrier leakage link severe canal compression to a

measurable peripheral inflammatory response. If they are confirmed in larger multicenter cohorts with sampling before and after decompression, serum IL-1 β and hs-CRP could become accessible adjuncts to structural MRI that help spine surgeons interpret discordant imaging and symptoms and select patients for surgical or rehabilitative care.

6. Declarations

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya and Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia (Reference No.2025/227). All procedures were conducted in accordance with the Declaration of Helsinki and its later amendments. Written informed consent was obtained from all 30 participants before the 7-day pharmacological washout and venipuncture.

Consent for Publication

Not applicable; the article contains no individually identifiable data, images or clinical details.

Availability of Data and Materials

The anonymized analytical dataset supporting the findings of this study is available from the corresponding author on reasonable request.

Artificial Intelligence Use Statement

No artificial intelligence tools were used in preparing this article.

Author Contribution Statement

A.G.P.: Conceptualization, Investigation, Project administration, Formal analysis, Writing – original draft. R.L.: Supervision, Investigation, Validation, Writing – review & editing. T.: Methodology, Formal analysis, Validation, Supervision, Writing – review & editing. All authors read and approved the final manuscript.

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Conflict of Interest / Competing Interests

The authors declare no financial or non-financial competing interests.

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