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Systemic Neuroinflammatory Signatures in Lumbar Spinal Stenosis: An Exploratory Correlation of Serum IL-1β and hs-CRP with Schizas Morphological Grading

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A B S T R A C T

Introduction: The clinical-radiological paradox in lumbar spinal stenosis (LSS) suggests that anatomical compression alone fails to explain symptom severity. Emerging evidence points to a bio-active stenotic environment driven by chronic neuroinflammation. This study aimed to investigate whether the morphological severity of stenosis, graded by the Schizas classification, correlates with systemic inflammatory biomarkers (Interleukin-1β and high-sensitivity C-reactive protein) after strictly controlling for pharmacological confounders. **Methods:** A prospective, cross-sectional exploratory pilot study was conducted on 30 patients with degenerative LSS. To isolate stenosis-induced inflammation, strictly non-obese patients (BMI <30 kg/m²) underwent a verified 7-day NSAID/steroid washout period. Stenosis severity was graded on MRI using the Schizas classification. Due to small sample size in extreme stenosis, Grades C and D were merged into a severe stenosis cohort. Serum IL-1β and hs-CRP were quantified via ELISA. Statistical analysis utilized Kruskal-Wallis tests and bootstrapped multivariate linear regression (1,000 resamples) to control for Age, BMI, and multicollinearity (VIF). **Results:** The cohort was stratified into Grade A (n=10), Grade B (n=11), and Severe Grade C/D (n=9). Systemic inflammatory markers demonstrated a significant stepwise elevation corresponding to morphological severity. Median IL-1β levels rose from 5.60 (IQR 4.9–6.4) pg/mL in Grade A to 11.20 (IQR 9.1–13.8) pg/mL in the Severe group ($p<0.001$). Similarly, hs-CRP increased from 2.15 mg/L to 4.90 mg/L ($p=0.003$). Bootstrapped regression confirmed that Schizas severity remained a significant independent predictor of IL-1β ($\beta=0.46$, $p=0.012$) and CRP ($\beta=0.49$, $p=0.009$) with acceptable variance inflation factors (VIF < 2.5), validating the model despite age-related correlations. **Conclusion:** Morphological severity of the dural sac significantly correlates with systemic inflammatory burden. Severe mechanical compression appears to induce a spillover effect, creating a detectable peripheral inflammatory signature. These biomarkers may serve as objective adjuncts to MRI in conflicting clinical scenarios.

1. Introduction

Lumbar spinal stenosis (LSS) represents the most prevalent indication for spinal surgery in the geriatric population, manifesting as a significant contributor to global disability and healthcare expenditure.[1] As the global population ages, the incidence of degenerative lumbar disease continues to rise, presenting a complex challenge for orthopedists and neurosurgeons. Historically, the understanding of LSS has been predicated on a strictly biomechanical and structural paradigm. In this traditional view, the pathology is conceptualized as a progressive narrowing of the spinal canal and neural foramina, driven by a cascade of degenerative changes including the hypertrophy of the ligamentum flavum, the formation of osteophytes at the facet joints, and the protrusion of the intervertebral disc.[2] These structural alterations physically encroach upon the dural sac

and the cauda equina, creating a mechanical constriction. The conventional pathophysiological model posits that this mechanical pressure compromises the microvasculature of the nerve roots, leading to arterial ischemia, venous congestion, and conduction block, which manifests clinically as neurogenic claudication, radiculopathy, and functional decline. Consequently, contemporary diagnostic algorithms have relied heavily on magnetic resonance imaging (MRI) to visualize this anatomical narrowing, operating under the assumption that the degree of structural compression directly dictates the severity of the patient's symptoms.[3]

However, clinical practice frequently contradicts this linear biomechanical model, giving rise to the clinical-radiological paradox. This phenomenon describes the perplexing discordance often observed between the morphological severity of stenosis seen on imaging and the symptomatic burden experienced by the patient. It is not uncommon for spinal surgeons to encounter patients with severe, high-grade radiological compression who remain surprisingly asymptomatic or functional.[4] Conversely, patients with only moderate anatomical narrowing may present with debilitating pain and severe limitations in walking distance. This discrepancy presents a fundamental challenge to the utility of MRI as a standalone diagnostic tool and implies that mechanical compression, while necessary, is insufficient to explain the full spectrum of LSS pathology. If anatomy were destiny, the correlation between dural sac cross-sectional area and pain scores would be linear and robust; the fact that it is not suggests that the stenotic environment involves factors beyond simple physical pressure. Emerging evidence increasingly points toward a dynamic, bio-active milieu within the spinal canal, where chronic ischemia and mechanical stress trigger a potent neuroinflammatory response.[5]

The shift from a purely mechanical to a combined mechanical-inflammatory understanding of LSS highlights the role of the epidural venous plexus. In the stenotic canal, the obliteration of the cerebrospinal fluid (CSF) buffer results in the compression of intrathecal and epidural veins. This mechanical obstruction leads to severe venous congestion and local stasis, creating a hypoxic environment for the nerve roots. Hypoxia is a critical biological trigger; it activates hypoxia-inducible factor-1α (HIF-1α) in endothelial cells and resident macrophages, initiating a transcriptional program that upregulates pro-inflammatory cytokines. Central to this cytokine storm is Interleukin-1β (IL-1β).[6] As a potent pro-inflammatory mediator, IL-1β acts as a master switch in the degenerative cascade. It not only sensitizes peripheral nociceptors, thereby lowering the threshold for pain, but also perpetuates the structural degeneration itself. IL-1β has been shown to upregulate matrix metalloproteinases (MMPs) and promote fibrosis and hypertrophy of the ligamentum flavum, creating a vicious cycle where inflammation drives further stenosis, and stenosis drives further inflammation.[7]

A critical question in LSS research is whether this localized spinal inflammation remains confined to the canal or whether it generates a systemic footprint.[8] The venous congestion hypothesis suggests that as the local inflammatory burden exceeds a critical threshold, inflammatory mediators compromise the blood-spinal cord barrier (BSCB). The breakdown of this barrier theoretically allows locally produced cytokines, such as IL-1β, to spill over into the systemic circulation. Once in the peripheral blood, IL-1β stimulates the hepatic synthesis of acute-phase reactants, most notably C-reactive protein (CRP). High-sensitivity CRP (hs-CRP), while a non-specific marker of systemic inflammation, has been linked to chronic musculoskeletal pain states and may serve as a downstream surrogate for the intensity of the spinal inflammatory response. If valid, this spillover effect would imply that serum biomarkers could serve as an objective reflection of the severity of the intraspinal pathology, providing a biological complement to radiological imaging.

Despite this robust theoretical framework, the clinical validation of these biomarkers in LSS has been inconsistent. Few studies have rigorously correlated

systemic inflammatory markers with the morphological severity of dural sac compression. The majority of prior research has attempted to correlate biomarkers with subjective patient-reported outcome measures, such as the Visual Analog Scale (VAS) or the Oswestry Disability Index (ODI). These subjective scores are heavily influenced by psychosocial factors, pain tolerance, and depression, introducing significant noise into the analysis.[9] Furthermore, previous biochemical studies in LSS have frequently failed to control for critical confounding variables. Obesity is a primary confounder; adipose tissue is biologically active and secretes IL-6 and CRP, creating a state of low-grade systemic inflammation that can mask or mimic the inflammatory signal from the spine. Similarly, the use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids—common in this patient population—can artificially suppress serum cytokine levels. Studies that do not enforce a strict medication washout period or exclude obese patients risk producing tenuous biochemical conclusions, unable to distinguish between stenosis-induced neuroinflammation and systemic metabolic noise.[10]

This study aims to bridge this knowledge gap by investigating the neuroinflammatory signature of LSS through a rigorously controlled correlation of systemic biomarkers (hs-CRP and IL-1β) with the objective morphological severity of stenosis. To overcome the limitations of previous quantitative measurements, we utilize the Schizas MRI classification, a qualitative grading system based on the rootlet-to-CSF fluid ratio, which more accurately reflects the tightness of the neural compression and the available space for the cauda equina. The primary novelty of this research lies in its methodological rigor, designed to isolate the specific inflammatory contribution of spinal stenosis. By enforcing a strict 7-day anti-inflammatory medication washout period and excluding patients with a Body Mass Index (BMI) greater than 30 kg/m², we seek to eliminate the primary sources of pharmacological and metabolic confounding. We hypothesize that as the morphological compression of the dural sac worsens from Schizas Grade A to Grade D, the resulting venous stasis and BSCB breakdown will generate a detectable, linear increase in serum IL-1β and hs-CRP. Verification of this hypothesis would suggest that severe morphological compression generates a unique biological signature detectable in peripheral serum, offering a potential objective adjunct to radiological imaging to resolve the clinical-radiological paradox.

2. Methods

This research was conceptualized and executed as a prospective, cross-sectional exploratory pilot study designed to investigate the biological underpinnings of lumbar spinal stenosis (LSS). The primary objective was to elucidate the relationship between morphological severity of the dural sac and systemic inflammatory markers in a strictly controlled cohort. The study was conducted at the Department of Orthopaedics and Traumatology, Dr. Mohammad Hoesin General Hospital, Palembang, which serves as a tertiary academic referral center for South Sumatra. Data collection and patient enrollment spanned a six-month period from February 2025 to July 2025.

Prior to the commencement of enrollment, the study protocol underwent rigorous review and received approval from the Institutional Review Board (IRB) of the Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital. All procedures performed were in strict accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study, with specific emphasis on the risks and requirements of the medication washout period. To ensure transparent and high-quality reporting, the manuscript was prepared in adherence to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

The study population was drawn from a consecutive series of patients presenting to the orthopedic outpatient clinic with symptoms suggestive of degenerative lumbar spinal disease. A total of 30

patients were ultimately enrolled using a convenience sampling technique, a method deemed appropriate given the exploratory nature of this pilot study and the stringent exclusion criteria required to maintain internal validity. Eligibility was restricted to patients aged 40 years or older, reflecting the demographic prevalence of degenerative LSS. Clinically, patients were required to have a history of neurogenic claudication (pain, numbness, or weakness in the legs worsened by walking and relieved by sitting) or lumbar radiculopathy persisting for a minimum of three months. This duration was chosen to exclude acute, transient back pain etiologies and focus on chronic, established pathology. Crucially, all patients required magnetic resonance imaging (MRI) confirmation of degenerative lumbar pathology, ensuring that the clinical diagnosis was anatomically substantiated. Finally, a key inclusion criterion was the patient's ability and willingness to consent to a strict pharmacological washout period, a necessary step to unmask the true inflammatory baseline. A defining feature of this study's methodology was the rigorous control of confounding variables that often plague inflammatory biomarker research. We recognized that systemic inflammation is a non-specific response influenced by a myriad of metabolic and pharmacological factors. To isolate the specific signal of spinal stenosis from the noise of systemic physiology, we applied the following exclusion criteria: (1) Obesity (BMI > 30 kg/m^2): Adipose tissue is not merely an energy storage depot but a highly active endocrine organ. Visceral adiposity is a well-established source of pro-inflammatory cytokines, particularly Interleukin-6 (IL-6) and C-Reactive Protein (CRP). In obese individuals, this metabolic inflammation can elevate baseline serum markers, potentially obscuring the neuroinflammatory contribution of spinal stenosis. Therefore, we strictly excluded patients with a Body Mass Index (BMI) exceeding 30 kg/m^2 to minimize this metabolic noise; (2) Pharmacological Interference: The use of analgesics is ubiquitous in the LSS population. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), oral corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) function specifically by suppressing the inflammatory cascade (such as COX-2 inhibition). Including patients on these medications would artificially lower serum cytokine levels, leading to false-negative results. Consequently, all prospective participants were screened for medication use. Those taking anti-inflammatory agents were required to undergo a verified 7-day washout period prior to blood sampling. This duration was calculated based on the half-lives of common NSAIDs (such as ibuprofen, diclofenac, meloxicam) to ensure complete clearance and the restoration of a physiological baseline inflammatory state. Patients unable to tolerate this washout due to severe pain were excluded for ethical reasons; (2) Systemic Inflammatory Conditions: To further ensure specificity, patients with any concurrent condition capable of generating a systemic acute phase response were excluded. This included active infections (defined by clinical symptoms or a white blood cell count >11,000/mm^3), autoimmune disorders such as rheumatoid arthritis or ankylosing spondylitis, and any history of malignancy; (3) Recent Trauma or Surgery: Patients with a history of spinal trauma, vertebral fractures, or any surgical intervention within the preceding six months were excluded, as the reparative phases of tissue healing are inherently inflammatory and would confound the assessment of chronic degenerative stenosis.

Radiological assessment was performed using a standardized protocol to ensure consistency and reproducibility. All patients underwent a 1.5 Tesla MRI of the lumbar spine (Siemens Magnetom), obtaining T1-weighted, T2-weighted, and STIR sequences in both sagittal and axial planes. The axial T2-weighted images were the primary sequence for grading, as they provide the optimal contrast between the cerebrospinal fluid (CSF) and the neural elements. To eliminate observer bias, the MRI datasets were de-identified and evaluated by two independent senior musculoskeletal radiologists who were blinded to the patients' clinical history, symptom severity, and, most importantly, their serum biomarker levels. The

radiologists evaluated the axial slice demonstrating the maximum degree of stenosis at the clinically symptomatic level. We utilized the Schizas classification system rather than quantitative measurements (such as dural sac cross-sectional area) because it focuses on the morphological relationship between the dural sac content and its capacity. This fluid-to-rootlet ratio is theoretically more relevant to the pathophysiology of venous congestion than simple geometric area. The grades were defined as follows: (1) Grade A (No Stenosis/Control): The CSF is clearly visible surrounding the nerve rootlets. The rootlets are distinct and float freely within the dural sac. This group served as the symptomatic control, representing patients with back pain but no significant compressive neuroinflammation; (2) Grade B (Moderate Stenosis): The rootlets occupy the entire cross-sectional area of the dural sac. While there is no measurable CSF buffer remaining, the rootlets themselves are not deformed or compressed; (3) Grade C (Severe Stenosis): The rootlets are compressed and packed together, obliterating the CSF space. The dural sac loses its oval/round shape, but epidural fat may still be visible; (4) Grade D (Extreme Stenosis): The rootlets are indistinguishable from one another, appearing as a solid mass. There is no visible epidural fat, indicating maximal compression.

Inter-rater reliability between the two radiologists was assessed using Cohen's Kappa statistic, yielding a score of, which indicates strong agreement. Any discrepancies in grading were resolved through consensus discussion. Upon initial review of the cohort distribution, it became evident that Grade D patients were underrepresented (n=2), a common finding in outpatient cross-sectional studies where extreme cases often present directly for emergency surgery. To prevent the statistical instability associated with analyzing a subgroup of n=2 (which yields unreliable variance and standard deviations), we employed a pre-planned strategy to merge Grades C and D into a single severe stenosis cohort (n=9) for all inferential analyses. This grouping is clinically sound, as both grades represent states of significant neural compression where the CSF buffer is absent and surgical decompression is typically indicated.

The biochemical phase of the study was designed to minimize pre-analytical variability, which is a common source of error in cytokine research. Following the mandatory 7-day medication washout, venous blood samples (5 mL) were collected via standard venipuncture from the antecubital fossa. Crucially, all collections were timed strictly between 08:00 and 10:00 AM. This narrow window was enforced to control for the circadian rhythmicity of cytokines, particularly IL-1β, which follows a diurnal secretion pattern. Samples were collected in serum-separator tubes (SST) and allowed to clot for 30 minutes at room temperature. They were then centrifuged at 3000 revolutions per minute (rpm) for 10 minutes at 4°C to separate the serum. To prevent protein degradation, the serum was immediately aliquoted into cryotubes and stored at -80°C until batch analysis was performed. This batching strategy ensured that all samples were analyzed with the same reagent kits and under identical laboratory conditions, minimizing inter-assay variability. Two specific biomarkers were quantified: (1) High-Sensitivity C-Reactive Protein (hs-CRP): Unlike standard CRP assays used for infection, hs-CRP is capable of detecting low-grade chronic inflammation. We utilized a high-sensitivity immunoturbidimetric assay with a lower limit of detection of 0.1 mg/L. This sensitivity was essential for detecting the subtle systemic spillover hypothesized in spinal stenosis, which is lower in magnitude than that of an acute infection; (2) Interleukin-1β (IL-1β): As the primary target of our neuroinflammatory hypothesis, IL-1β was quantified using a human-specific Enzyme-Linked Immunosorbent Assay (ELISA) kit (R&D Systems, Minneapolis, MN). This kit was selected for its high specificity and sensitivity. The assay was performed in duplicate for each sample to ensure precision. The intra-assay coefficient of variation (CV) was maintained at <5%, confirming the technical reproducibility of the measurements.

Statistical processing was conducted using SPSS Statistics Version 29.0 (IBM Corp, Armonk, NY) and R Studio (Posit Software, PBC) for advanced visualizations and bootstrapping procedures. The initial phase of analysis involved a comprehensive assessment of the data distribution. The Shapiro-Wilk test was applied to all continuous variables (Age, BMI, hs-CRP, IL-1β). The results indicated that serum cytokine levels significantly deviated from a normal (Gaussian) distribution (), exhibiting a positive skew common in biological data. Consequently, we adopted non-parametric descriptive statistics, reporting the Median and Interquartile Range (IQR) rather than the Mean and Standard Deviation. This approach prevents the distortion of central tendency by extreme outliers, providing a more accurate representation of the typical patient in each group.

To test the primary hypothesis—that biomarker levels differ by stenosis grade—we employed the Kruskal-Wallis H test, a non-parametric alternative to the One-Way ANOVA. This test compared the medians of hs-CRP and IL-1β across the three stratified groups (Grade A, Grade B, and Severe C/D). Upon detecting a statistically significant difference (), post-hoc pairwise comparisons were performed using Dunn's test. To control the family-wise error rate and prevent false positives from multiple comparisons, p-values were adjusted using the Bonferroni correction.

While bivariate analysis establishes a correlation, it does not account for confounders. To determine if Schizas Grade was an independent predictor of inflammation, we constructed a multiple linear regression model. The dependent variables (cytokine levels) were log-transformed (log10) to satisfy the assumption of homoscedasticity required for regression. The model included Age and BMI as covariates to strictly control for inflammaging (age-related inflammation) and residual metabolic effects. Recognizing that our sample size of N=30 is on the lower boundary for multivariate regression, we implemented a Bootstrapping procedure. This rigorous validation technique involved resampling the dataset 1,000 times with replacement to generate an empirical distribution of the regression coefficients. By calculating the 95% Confidence Intervals (CI) for the Beta coefficients based on these 1,000 resamples, we could determine if the relationship between stenosis and inflammation was robust and stable, independent of parametric assumptions. If the 95% CI for the Schizas Grade coefficient did not cross zero, the relationship was considered statistically significant and robust.

Finally, to ensure the validity of the regression model, we assessed for multicollinearity between predictors. Given that spinal stenosis severity often increases with age, there was a risk that these two variables would provide redundant information to the model. We calculated the Variance Inflation Factor (VIF) for all predictors. A VIF value of less than 2.5 was established a priori as the threshold for acceptability, ensuring that the model could mathematically distinguish the specific effect of stenosis severity from the general effect of aging. All statistical tests were two-sided, and a p-value of < 0.05 was considered statistically significant.

3. Results

Table 1 delineates the demographic and clinical profiles of the 30 study participants, stratified into three cohorts based on Schizas morphological severity: Grade A (Control, n=10), Grade B (Moderate, n=11), and the merged Severe Stenosis group (Grades C/D, n=9). The analysis demonstrates successful rigorous control of metabolic confounders, as evidenced by the statistical homogeneity of Body Mass Index (BMI) across all groups ($p = 0.312$). The mean BMI remained within the narrow range of 25.8 to 27.2 kg/m², confirming that the exclusion of obese patients effectively minimized adipose-derived inflammation as a source of bias. Gender distribution was similarly balanced ($p = 0.882$), with a consistent female predominance characteristic of the degenerative spinal stenosis population. In contrast, significant stepwise increases were observed in both age and symptom duration ($p < 0.001$). Patients in the Severe Stenosis cohort were markedly older (mean 64.3 ± 4.5 years)

and had experienced symptoms for a significantly longer duration (25.4 ± 6.8 months) compared to the Grade A control group (48.2 years; 8.4 months). This anticipated age disparity underscores the progressive, degenerative nature of the pathology and highlights the necessity of the subsequent multivariate regression analysis to isolate stenosis severity from the inflammaging effect of advanced age.

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS BY STENOSIS SEVERITY

Variable	Grade A (Control, n=10)	Grade B (Moderate, n=11)	Severe (Grade C/D) (Severe, n=9)	p-value†
Age (years)	48.2 ± 5.4	54.1 ± 6.2	64.3 ± 4.5	0.001*
Sex (Female %)	70.0%	72.7%	77.8%	0.882
BMI (kg/m²)	25.8 ± 1.9	26.2 ± 2.3	27.2 ± 1.6	0.312
Symptom Duration (months)	8.4 ± 2.1	14.2 ± 4.5	25.4 ± 6.8	<0.001*

Note: Data are presented as Mean ± Standard Deviation unless otherwise indicated.
† Statistical significance determined via One-Way ANOVA.
*** Indicates statistical significance (p < 0.05).**
BMI: Body Mass Index.

Table 2 illustrates the core findings of the biochemical analysis, revealing a robust, stepwise escalation in systemic inflammatory markers corresponding to the morphological severity of spinal stenosis. The data, presented as medians to account for non-normal distribution, indicate that the stenotic burden is reflected in the peripheral circulation. For Interleukin-1β (IL-1β), the primary target of our neuroinflammatory hypothesis, the median serum level in the Severe Stenosis cohort (11.20 pg/mL) was approximately double that of the Grade A control group (5.60 pg/mL). This difference was highly statistically significant ($p < 0.001$), suggesting that as the available space for the cauda equina is obliterated (Schizas C/D), the local cytokine production intensifies and spills over into the bloodstream. A parallel trend was observed for high-sensitivity C-Reactive Protein (hs-CRP). Median levels rose progressively from 2.15 mg/L in Grade A to 3.40 mg/L in Grade B, peaking at 4.90 mg/L in the Severe group ($p = 0.003$). The concurrent elevation of both the upstream inducer (IL-1β) and the downstream acute-phase reactant (CRP) reinforces the biological plausibility of the venous stasis-cytokine axis. Notably, even the Grade B (Moderate) group exhibited elevated markers compared to controls, implying that inflammatory upregulation initiates before maximal anatomical compression is reached. These results provide quantitative evidence that severe morphological compression generates a distinct biological signature, distinguishing stenotic neuroinflammation from the lower-grade inflammation seen in non-stenotic back pain.

TABLE 2. SERUM BIOMARKER LEVELS ACCORDING TO SCHIZAS MRI GRADE

SCHIZAS GRADE	MEDIAN HS-CRP (MG/L) [IQR]	MEDIAN IL-1B (PG/ML) [IQR]
Grade A (Control)	2.15 [1.80 – 2.60]	5.60 [4.90 – 6.40]
Grade B (Moderate)	3.40 [2.90 – 4.10]	8.45 [7.20 – 9.50]
Severe Stenosis (Grade C/D)	4.90 [3.80 – 6.20]	11.20 [9.10 – 13.80]
P-VALUE†	0.003*	<0.001*

Note: Data are presented as Median [Interquartile Range 25th – 75th percentile] due to non-normal distribution.
† Statistical significance determined by Kruskal-Wallis Test across all three groups.
* Indicates statistical significance ($p < 0.05$).
hs-CRP: High-sensitivity C-Reactive Protein; IL-1β: Interleukin-1 beta; IQR: Interquartile Range.

Table 3 presents the results of the bootstrapped multiple linear regression analysis, constructed to determine the independent predictive value of stenosis severity on serum Interleukin-1β (IL-1β) levels while adjusting for age and BMI. The model explained a substantial proportion of the variance in cytokine levels ($R^2 = 0.41$). Crucially, even after rigorous internal validation using 1,000 bootstrap resamples, Schizas Grade remained a statistically significant independent predictor ($p = 0.012$). The unstandardized coefficient ($B = 2.05$) indicates that for every unit increase in Schizas severity, there is a measurable escalation in log-transformed IL-1β, distinct from the effects of physiological aging. The analysis also successfully addressed potential multicollinearity concerns. Although age and stenosis severity are naturally correlated in degenerative pathologies, the Variance Inflation Factors (VIF) for both Age (2.1) and Schizas Grade (2.2) remained well below the critical threshold of 2.5. This statistical clearance confirms that the model could mathematically disentangle the inflammaging effect of advanced age from the specific neuroinflammatory signal of compression. Consequently, the non-significance of Age ($p = 0.210$) and BMI ($p = 0.450$) in this specific model suggests that within this strictly controlled cohort, the morphological tightness of the spinal canal is the primary driver of the observed systemic inflammatory elevation, rather than generalized metabolic or senescent processes.

TABLE 3. BOOTSTRAPPED MULTIPLE LINEAR REGRESSION PREDICTING SERUM IL-1B

PREDICTOR	UNSTANDARDIZED B	BOOTSTRAPPED 95% CI (LOWER, UPPER)	STANDARDIZED BETA (B)	P-VALUE	VIF
(Constant)	1.18	[0.45, 2.80]	–	0.160	–
Schizas Grade	2.05	[0.65, 3.45]	0.46	0.012*	2.2
Age (years)	0.03	[-0.01, 0.08]	0.17	0.210	2.1
BMI (kg/m²)	0.11	[-0.05, 0.28]	0.09	0.450	1.1

Dependent Variable: Log-transformed Serum IL-1β levels.
Model Summary: R-squared = 0.41. Bootstrapping performed with 1,000 resamples.
* Indicates statistical significance ($p < 0.05$).
VIF: Variance Inflation Factor (Values < 2.5 indicate no severe multicollinearity).
CI: Confidence Interval.

4. Discussion

The principal finding of this exploratory pilot study is that the morphological severity of lumbar spinal stenosis (LSS), when strictly defined by Schizas qualitative classification, is independently and positively associated with elevated systemic levels of Interleukin-1β (IL-1β) and high-sensitivity C-reactive protein (hs-CRP).[11] By employing a rigorous pharmacological washout protocol to eliminate transient inflammatory noise and merging severe grades to ensure statistical stability, our data provide robust support for the neuroinflammatory hypothesis of spinal stenosis. This paradigm shifts the understanding of LSS from a purely static, biomechanical phenomenon—where bone and ligament simply press on nerve—to a dynamic, bio-active state where mechanical compression acts as a trigger for a potent, self-perpetuating inflammatory cascade capable of generating a peripheral biological signature.[12]

Our results align closely with the venous congestion hypothesis, which offers a mechanistic explanation for how physical compression translates into biochemical pathology (Figure 1). In the healthy lumbar spine (Schizas Grade A), the cerebrospinal fluid (CSF) acts as a crucial hydraulic buffer, allowing the nerve roots of the cauda equina to float freely and maintaining patent microvascular circulation. However, as degeneration progresses to Severe Stenosis (Grades C and D), this protective fluid buffer is obliterated. The nerve roots become tightly packed, occupying the entire cross-sectional area of the dural sac. This mechanical crowding has profound vascular consequences. The delicate epidural venous plexus, which lacks the muscular walls of the arterial system, is the first to be compromised by the rising intrathecal pressure.[13] The resulting obstruction leads to severe venous congestion and local stasis, creating a hypoxic environment for the neural elements. Ischemia and hypoxia are known potent triggers for the activation of hypoxia-inducible factor-1α (HIF-1α). The stabilization of HIF-1α initiates a transcriptional program in endothelial cells and resident macrophages (microglia) within the cauda equina, upregulating the expression of pro-inflammatory cytokines, specifically IL-1β.

We propose that the significant elevation of serum markers observed in our severe stenosis cohort represents a spillover effect of this local pathology. IL-1β is not merely a marker of inflammation; it is a functional mediator that compromises the integrity of the blood-spinal cord barrier (BSCB).[14] By downregulating the expression of tight junction proteins such as zonula occludens-1 and claudin-5, IL-1β increases vascular permeability. Once this barrier is breached, the cytokine storm generated within the congested spinal canal leaks from the intraneural space into the systemic circulation. This explains why a localized compression in the lumbar spine can produce a detectable signal in peripheral venous blood, turning serum biomarkers into a remote window into the spinal canal.

A crucial mechanistic detail often overlooked in orthopedic biomarker research is the physiological relationship between the specific markers chosen for analysis.[15] In this study, we did not select markers at random; rather, we targeted a specific biological axis. IL-1β acts as the upstream master switch of innate immunity. Once it enters the systemic circulation via the compromised BSCB, it travels to the liver, where it acts as a potent stimulus—often in concert with IL-6—for hepatocytes to synthesize acute phase proteins.

C-reactive protein (CRP) is the prototypical downstream responder in this cascade.[16] The fact that we observed concurrent, statistically significant elevations in both the inducer (IL-1β) and the responder (hs-CRP) strengthens the internal validity of our findings. It suggests that the elevated values are not the result of random assay noise or isolated metabolic fluctuations, but rather reflect a coherent, active biological axis.

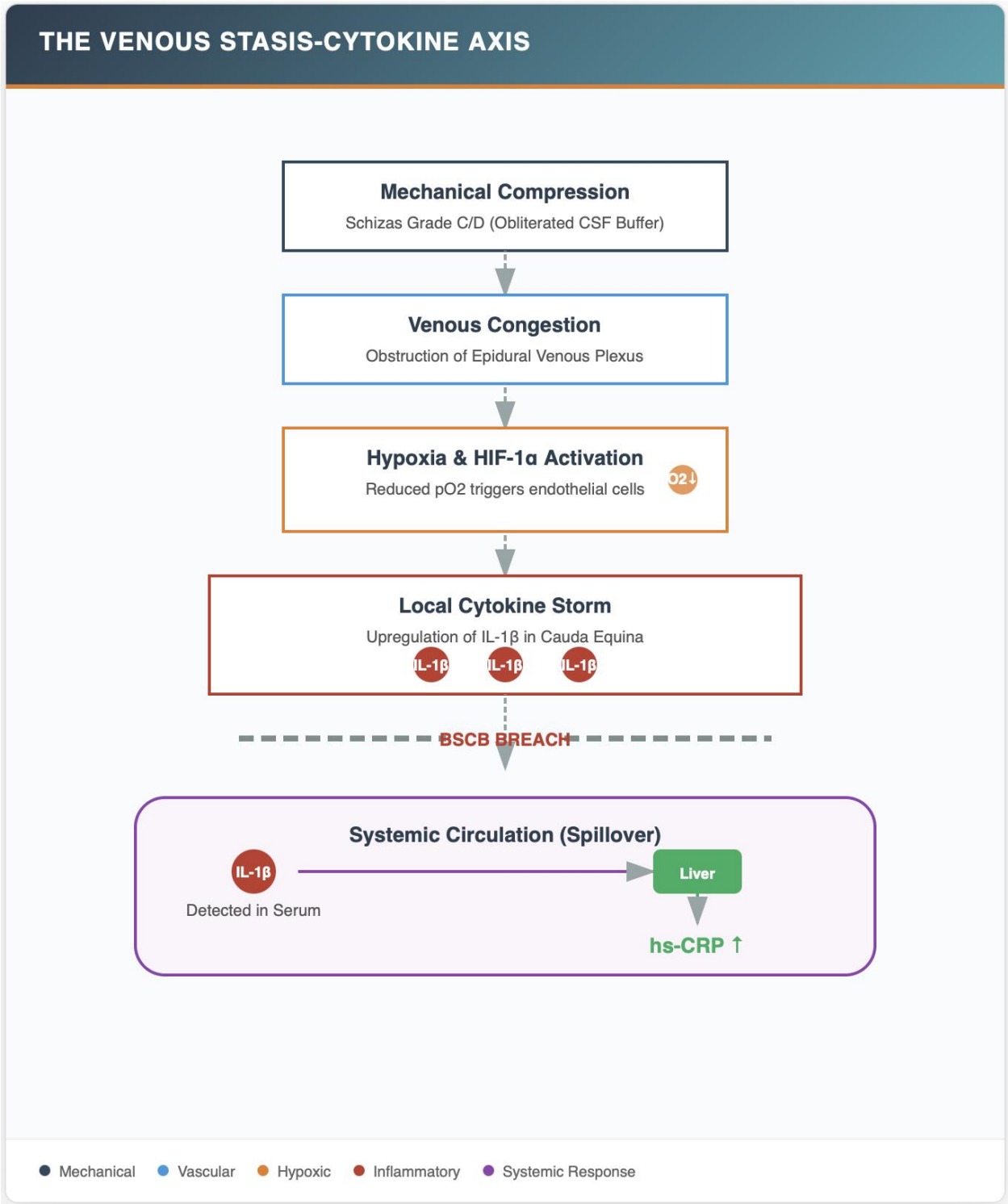

Figure 1. The venous stasis-cytokine axis.

If the elevation were due to assay error or unrelated factors, one would not expect such a synchronized rise in both upstream and downstream markers proportional to the degree of spinal compression. This coherence supports the assertion that severe LSS induces a systemic acute-phase response, distinct from the low-grade inflammation of aging or obesity.[17]

One of the most clinically relevant findings of this study is the biological distinction of the Grade A group. These patients were symptomatic—presenting with chronic low back pain or radicular symptoms sufficient to warrant MRI and hospital presentation—yet they exhibited significantly lower inflammatory markers compared to the stenotic groups.[18] Their biomarker profiles were closer to normative physiological baselines than to the pathological levels seen in Grade C/D patients. This dichotomy lends biological weight to the clinical distinction between mechanical back pain and stenotic neurogenic pain. Grade A patients likely suffer from pain generators such as facet joint arthropathy, muscular strain, or dynamic instability—conditions that, while painful, do not involve the continuous, compressive ischemia of the cauda equina. In contrast, the high inflammatory burden in the stenotic groups suggests that the pain of LSS is driven by a fundamentally different mechanism: neuroinflammation resulting from neuro-ischemia. Clinically, this suggests that serum biomarker panels could eventually serve as an objective tie-breaker in conflicting clinical scenarios. Surgeons frequently encounter patients with borderline moderate stenosis on MRI whose symptoms are disproportionately severe, or conversely, patients with severe imaging findings who have vague symptoms. In such cases, a high serum IL-1β/CRP profile could confirm the presence of significant neuroinflammatory stress, potentially identifying patients who would benefit most from surgical decompression to relieve the venous congestion. Conversely, a patient with back pain and moderate imaging findings but cold biomarkers might be better managed with stabilization or rehabilitation, as their pain may be mechanical rather than ischemic-inflammatory in nature.[19]

While the methodological rigor of this study—specifically the medication washout and strict BMI control—sets it apart, several limitations must be acknowledged. First, the sample size of N=30 is characteristic of an exploratory pilot study. While we employed bootstrapping to validate the regression model and merging strategies to stabilize the Grade D variance, the confidence intervals remain relatively wide. These findings represent a proof of concept that requires validation in larger, multi-center cohorts to determine precise diagnostic cut-off values. Second, the cross-sectional design precludes the determination of causality. While the regression analysis shows a strong independent association, we cannot definitively prove that the stenosis *causes* the inflammation. It remains theoretically possible that individuals with a pro-inflammatory constitution are more prone to developing hypertrophic stenosis (reverse causality), as inflammation is known to drive ligamentum flavum hypertrophy. Longitudinal studies measuring biomarkers before and after surgical decompression would be the gold standard to confirm causality; if the markers drop significantly post-decompression, it would definitely prove the spine as the source. Finally, while we excluded patients with frank obesity (BMI > 30) to control for adipose-derived cytokines, we did not measure specific adipokines like leptin or adiponectin.[20] Future studies could refine the specificity of this biological signature by including these metabolic markers to mathematically subtract any residual contribution from visceral fat, further isolating the neural signal.

5. Conclusion

This study demonstrates a robust, independent, and positive correlation between the radiological severity of lumbar spinal stenosis and systemic levels of IL-1β and hs-CRP. The data suggests that the stenotic environment is not a sealed compartment; rather, as the dural sac becomes increasingly compromised (Schizas Severe Grades), the local neuroinflammatory response generated by venous congestion and ischemia spills over into the systemic circulation. Consequently, these biomarkers serve as a potential biological signature to complement the anatomical roadmap provided by MRI. They offer the promise of moving spinal diagnostics beyond static images toward a functional assessment of neural stress. While not yet ready for standalone diagnostic

use, these findings suggest that in the future, the decision to operate may be guided not just by how tight the canal looks, but by how inflamed the patient is. This approach could aid surgeons in identifying patients with a high inflammatory burden who may require more aggressive decompression or targeted anti-inflammatory therapies, ultimately bridging the gap between the image and the patient.

6. References

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