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ORIGINAL ARTICLE

Lower urinary tract symptoms (LUTS) as a clinical feature of lumbar spinal stenosis (LSS): a prospective study with lumbar spine morphometry analysis

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ABSTRACT

Aim To investigate clinical and morphometric characteristics of patients with lower urinary tract symptoms (LUTS) due to lumbar spinal stenosis (LSS).

Methods This study evaluated LSS patients using clinical assessments of motor, sensory, bladder, and bowel functions, and functional disability scores from the Oswestry Disability Index (ODI) and Swiss Spinal Stenosis Questionnaire (SSSQ). Morphometric analysis included MRI measurements of the anteroposterior diameter of the intervertebral disc and dural sac, and the modified Torg-Pavlov ratio (mTPR), with follow-up re-evaluations at 6 months.

Results Of 159 patients, 49 (30.8%) had LUTS and 110 (69.2%) were in the control group. LUTS patients had a significantly higher prevalence of neurogenic claudication (100% vs. 47.3%; p<0.001), lower back pain (93.9% vs. 77.3%; p=0.011), and lower extremity pain (57.1% vs. 34.5%; p=0.008). The LUTS group also had higher ODI (54.0 vs. 50.0; p=0.019) and SSSQ score (44.0 vs. 34.0; p<0.001). Morphometric analysis showed significantly lower mTPR in LUTS patients (median 0.31 vs. 0.45; p<0.001), with an AUC of 0.704 (95%CI 0.627-0.774). mTPR≤0.31 predicted surgical revision within 6 months (OR:3.4, CI: 1.2-9.8), motor deficiency (OR:2.1, 95%CI: 1.4-5.2), and persistent LUTS post-surgery (OR:4.5, 95%CI: 1.1-18.9). mTPR≤0.34 was associated with worse follow-up outcome, including increased ODI (β:3.2; 95%CI: 1.1-5.3; p=0.004) and SSSQ score (β:4.8; 95%CI:2.1-7.5).

Conclusion LUTS patients with LSS exhibit more severe symptoms and poorer outcome, with mTPR≤0.34 being a predictor of adverse clinical outcome and the need for surgical revision within 6 months.

Keywords: back pain, neurogenic bladder, spinal stenosis, urological manifestations, urinary tract diseases

INTRODUCTION

Lumbar spinal stenosis (LSS) involves the narrowing of the spinal canal in the lumbar region, primarily due to degenerative process, which is exacerbated by aging, chronic wear and tear, and trauma (1). This condition, which is prevalent among the elderly, is a leading cause of disability and often necessitates spinal surgery in individuals over the age of 65. In addition, body mass index (BMI) plays a critical role by influencing lumbar spine degeneration, underscoring the importance of weight management as a preventive measure (2,3).

The LSS can lead to severe clinical entities such as cauda equina syndrome (CES) or conus medullaris syndrome (CMS), which are characterized by back pain, bowel or bladder dysfunction (including urinary retention or incontinence), saddle anaesthesia, sudden bilateral lower limb weakness, and sexual dysfunction (4). However, there is no established consensus on the diagnostic criteria for CES, particularly regarding whether it requires one or more of these clinical signs (5).

Urinary incontinence (UI), which involves involuntary leakage of urine, includes various types such as stress urinary

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incontinence, urge urinary incontinence, functional incontinence, mixed incontinence, and overflow incontinence (6,7). The UI is observed in compression syndromes of the spinal cord above the L1 level (8). Conversely, urinary retention (UR), characterized by the inability to voluntarily pass urine, is frequently caused by obstruction, notably benign prostatic hyperplasia (BPH), which accounts for the majority of cases (9). Neurological, infectious, inflammatory, and iatrogenic factors also contribute to UR, especially in compressive syndromes of the spinal cord below the L1 level (8). In any case, all symptoms originating from lower urinary tract, including UI and UR, are known as lower urinary tract symptoms (LUTS).

There is a pronounced literature gap concerning the relationship between clinical and morphometric characteristics and the condition of patients who develop LUTS due to LSS. To the best of our knowledge, this is the first study combining clinical and morphometric characteristics of patients with LUTS caused by LSS.

The aim of this study was to investigate the clinical and morphometric characteristics of patients experiencing LUTS due to LSS, thereby enhancing our understanding and treatment strategies for this complex clinical entity.

PATIENTS AND METHODS

Patients and study design

This prospective study evaluated LUTS in LSS patients at the Department of Neurosurgery, Canton Hospital Zenica, Bosnia and Herzegovina, from January 2018 to April 2023. The patients were divided into two groups: LUTS and control (without LUTS). Inclusion criteria were: diagnosed lumbar spinal stenosis based on clinical and radiological findings, surgically treated, age 40-80 years, and signed informed consent. Patients with history of lumbar spine surgery, lumbar disc herniation, spondylolisthesis, spinal tumours and history of urinary tract disorders were excluded.

Ethical approval has been obtained from the Ethics Committee of Cantonal Hospital Zenica.

Methods

All patients underwent detailed anamnestic and neurological assessments. Gender, age, and LUTS duration were recorded from anamnestic data. Neurological examination included motor, sensory, urinary, and bowel function assessments. Motor strength was evaluated using the Medical Research Council (MRC) muscle power scale: 0 - no visible contraction, 1 - visible minimal contraction, 2 - movement without overcoming gravity, 3 - active movement with overcoming gravity, 4 - movement with some resistance, 5 - normal strength (4). Sensory impairment was assessed using the sensitivity assessment scale (SAS) for L1-S3 dermatomes: 0 - absent, 1 - reduced, 2 – normal (4). Bladder and bowel functions were categorized into three levels: 0 - complete dysfunction, 1 - incomplete dysfunction, 2 - normal function (4). Motor deficiency was defined as MRC <5, and sensory deficiency as SAS <2. Bladder and bowel functions were categorized into three levels (either incontinence or retention): 0 - complete dysfunction, 1 - incomplete dysfunction, and 2 - normal function (4).

Additionally, patients completed the Oswestry Disability Index (ODI) (10) and Swiss Spinal Stenosis Questionnaire (SSSQ) (11) forms upon admission. The ODI assessed functional disability in patients with lower back pain using ten sections, each with two statements scored from 0 (no disability) to 5 (severe disability); scores are summed to a total of 0 to 100, with higher scores indicating greater disability (10). The SSSQ consists of 12 questions, with the first 7 on symptom severity and 8-12 on physical functioning. Responses are scored 1-5, or 1-4 for some questions. Total scores range from 12 to 55, with higher scores indicating more severe symptoms (11). The Visual Analogue Scale (VAS) was employed to evaluate pain levels in the back and leg, with scores ranging from 0 to 10, where higher scores indicate greater pain intensity (4).

All patients received preoperative lumbar spine magnetic resonance imaging (MRI; Magnetom Avanto 1.5 T, Siemens, Erlangen, Germany) to detect the vertebral level, dominant side of LSS, presence of intervertebral disc degeneration, dural sac compression, foraminal stenosis, or facet joint degeneration. Morphometric analysis included measuring the anteroposterior diameter of the intervertebral disc (AP_{IVD}) and dural sac (AP_{DSC}), expressed in mm, to determine the modified Torg-Pavlov ratio (mTPR) (Figure 1) using the relation $mTPR=AP_{DSC}/AP_{IVD}$.

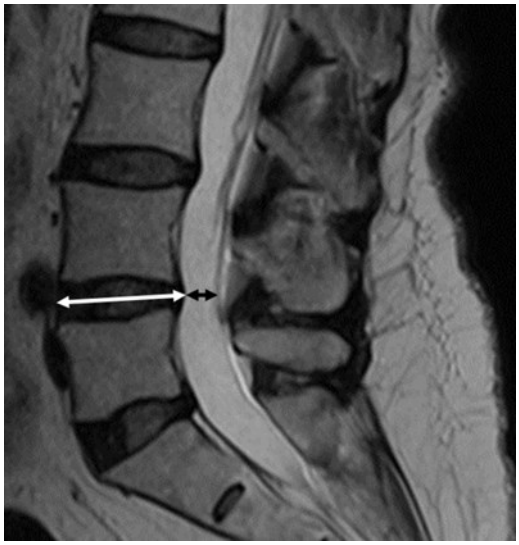

Figure 1. Modified Torg-Pavlov ratio (mTPR). White arrow depicts antero-posterior diameter of intervertebral disc (AP_{IVD}). Black arrow depicts antero-posterior diameter of dural sac (AP_{DSC}) (Department of Neurosurgery, Cantonal Hospital Zenica, 2023)

A follow-up was conducted after 6 months (±15 days) and included re-evaluation of MRC (score of <5 considered as motor deficiency), SAS (score of <2 considered as sensitive deficiency), LUTS, bowel dysfunction, ODI, and SSSQ.

Statistical analysis

Data are presented as medians and interquartile range (IQR) for continuous variables, considering distribution normality determined by the Kolmogorov-Smirnov test, while categorical variables were shown as frequencies (N) and percentages (%). Differences among the groups for continuous variables were assessed using the Mann-Whitney U test, and for categorical variables using Pearson's χ^2 test. Diagnostic accuracy of morphometric characteristics was evaluated using receiver operating character-

istic (ROC) curves and area under the curve (AUC) indices, with cut-off values defined by the Youden index and multivariate regression analysis. Statistical significance was set at p<5%.

RESULTS

The total number of patients was 159, with 49 (30.8%) in the LUTS and 110 (69.2%) in the control group. The LUTS group had a significantly higher proportion of males, 35 (71.4%) compared to the control group, 46 (41.8%) (p=0.001). Age distribution was similar between the groups (p=0.482). The LUTS group exhibited higher ODI (54.0 vs. 50.0; p=0.019) and SSSQ (44.0; IQR:28.0–48.0 vs. 34.0; IQR:12.0–39.0; p<0.001) (Table 1A). Neurogenic claudication was presented in all LUTS patients (100%) comparing to controls (p<0.001). Lower back pain and lower extremity pain were more prevalent in the LUTS group, 46 (93.9%) vs. 85 (77.3%) (p=0.011) and 28 (57.1%) vs. 38 (34.5%), respectively (p=0.008).

Motor deficiency was universal and more severe in LUTS patients (p<0.001). The SAS scale indicated greater deficiency in the LUTS group (p=0.035). VAS pain score was higher for lower back (7.0 vs. 6.0; p=0.042) and lower extremity (8.0 vs. 5.0; p<0.001) in LUTS patients. Bowel dysfunction was also more common in LUTS patients (8.2% vs. 0.9%, p=0.037) (Table 1B).

The vertebral level of LSS was predominantly at L4/L5 in 40 (81.6%) of the LUTS group compared to 60 (54.5%) in the control group (p<0.001). The LSS affected the right side in 9 (18.4%) of the LUTS group versus 53 (48.2%) of the control group (p<0.001) (Table 1B).

AP_{IVD} was significantly higher in the LUTS group (median 52.6, IQR 45.4-55.3) compared to controls (median 45.8, IQR 39.4-50.3 mm) (Figure 2A), with an AUC of 0.696 (CI:0.618-0.767) (Figure 2B) and a cut-off >43.01 showing high sensitivity (95.92%) but lower specificity (40.91%) and an OR of 2.41 (CI:1.42-4.24). AP_{DSC} did not show a significant difference between groups (Figure 2C) (p=0.220) with AUC of 0.562 (CI:

Table 1A. Baseline and clinical patients' data

Variable	LUTS (N = 49; 30.8%)	Control (N = 110; 69.8%)	p*	OR or β coefficient (95%CI)	p†
Gender (No; %)					
Male	35 (71.4)	46 (41.8)	0.001	4.24 (2.11; 8.23)	<0.001
Female	14 (28.6)	64 (58.2)		reference	
Median (IQR)					
Age (years)	50.0 (46.0 - 56.0)	51.0 (43.0 - 61.0)	0.482	0.37 (0.19; 0.78)‡	<0.001
ODI score	54.0 (42.0 - 59.0)	50.0 (37.0 - 59.0)	0.019	0.14 (0.10; 0.22)‡	<0.001
SSSQ score	44.0 (28.0 - 48.0)	34.0 (12.0 - 39.0)	<0.001	0.45 (0.31; 0.59)‡	<0.001
No (%) of patients					
Neurogenic claudication	49 (100.0)	52 (47.3)	<0.001	2.47 (1.89; 4.21)	<0.001
Lower back pain	46 (93.9)	85 (77.3)	0.011	1.80 (1.04; 3.99)	<0.001
Pain in lower extremity	28 (57.1)	38 (34.5)	0.008	4.55 (1.16; 17.83)	<0.001
VAS score (Median; IQR)					
Lower back	7.0 (4.0 - 9.0)	6.0 (3.0 - 8.0)	0.042	0.27 (-0.22; 0.42)‡	0.583
Lower extremity	8.0 (5.0 - 9.0)	5.0 (3.0 - 8.0)	<0.001	0.68 (0.42; 0.85)‡	<0.001

*Pearson's χ^2; †regression-analysis based p-value (LUTS vs. control); ‡β coefficient based on linear regression analysis (otherwise logistic regression analysis); LUTS, lower urinary tract symptoms; IQR, interquartile range; OR, odds ratio; CI, confidence interval; ODI, Oswestry disability index; SSSQ, Swiss spinal stenosis questionnaire; VAS, visual analogue scale;

Table 1B. Patients' motoric and sensory deficiencies

Variable	LUTS (N=49; 30.8%)	Control (N=110; 69.8%)	p*	OR or β coefficient (95%CI)	p‡
	No (%) of patients				
Motor deficiency	49 (100.0)	51 (61.8)	<0.001	22.73 (5.49; 94.12)	<0.001
MRC score					
0	3 (6.1)	6 (5.5)	<0.001	-0.39 (-0.68; -0.24)†	<0.001
1	14 (28.6)	0 (0.0)			
2	0 (0.0)	0 (0.0)			
3	15 (30.6)	8 (7.3)			
4	17 (34.7)	54 (49.1)			
5	0 (0.0)	42 (38.2)			
SAS score					
0	46 (93.9)	85 (78.0)	0.035	-0.58 (-0.37; -0.36)†	<0.001
1	3 (6.1)	16 (14.7)			
3	0 (0.0)	8 (7.3)			
Bladder dysfunction level					
0	12 (24.4)	0 (0)	<0.001	-0.80 (-0.42; -0.94)†	<0.001
1	37 (76.6)	0 (0)			
2	0 (0)	110 (100.0)			
Bowel dysfunction level					
0	4 (8.2)	1 (0.9)	0.037	-0.22 (-0.35; 0.24)†	0.524
1	12 (24.4)	27 (24.6)			
2	33 (67.4)	82 (74.5)			

*Pearson's χ^2; †β coefficient based on linear regression analysis (otherwise logistic regression analysis); ‡regression analysis-based p-value (LUTS vs. control); LUTS, lower urinary tract symptoms; IQR, interquartile range; OR, odds ratio; CI, confidence interval; LSS, lumbar spinal stenosis; MRC, Medical Research Council muscle power scale; SAS, sensitivity assessment scale; VAS, visual analogue scale;

0.481-0.641) (Figure 2D), a cut-off ≤6.3 with low sensitivity (22.45%) and high specificity (100%), and OR of 0.49 (CI:0.24-1.95). For mTPR, the LUTS group had a significantly lower median (0.31; IQR 0.30-0.36) than controls (0.45; IQR 0.36-0.49) (Figure 2E), with an AUC of 0.704 (CI:0.627-0.774) (Figure 2F), a cut-off ≤0.34 showing high sensitivity (85.71%) and moderate specificity (55.45%), and OR of 2.21 (CI:1.52-7.42).

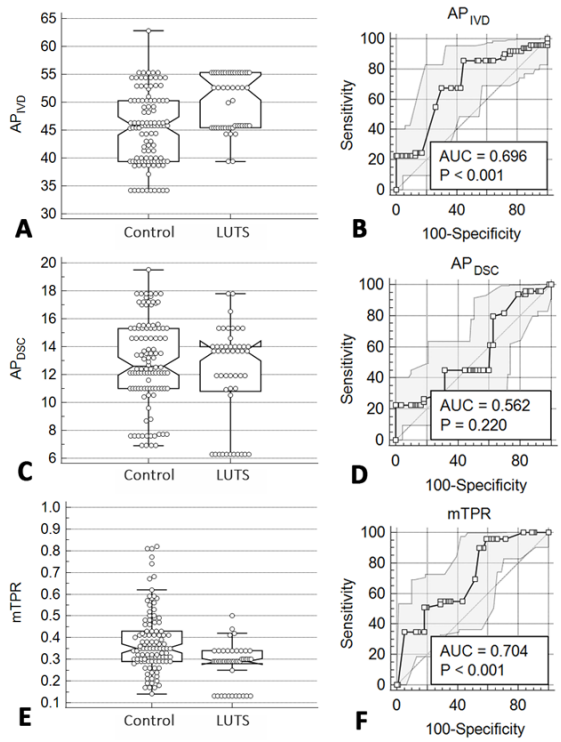

Figure 2. Values and diagnostic accuracy of the antero-posterior diameter of the intervertebral disc (AP_{IVD}), the antero-posterior diameter of the dural sac (AP_{DSC}), and the modified Torg-Pavlov ratio (mTPR). A) Values of AP_{IVD} in the lower urinary tract symptoms (LUTS) and control groups; B) Receiver operating characteristic (ROC) analysis of AP_{IVD} for diagnostic accuracy in LUTS patients; C) Values of AP_{DSC} in the LUTS and control groups; D) ROC analysis of AP_{DSC} for diagnostic accuracy in LUTS patients; E) Values of mTPR in the LUTS and control groups; F) ROC analysis of mTPR for diagnostic accuracy in LUTS patients.

Regression analysis showed males were more likely to have LUTS than females (OR 4.24; CI:2.11-8.23; p < 0.001). Older age (β=0.37; CI: 0.18-0.56; p < 0.001), higher ODI scores (β=0.14; CI:0.01-0.2;, p=0.048), and higher SSSQ scores (β=0.45; CI:0.31-0.59; p<0.001) were linked to a higher likelihood of LUTS. Neurogenic claudication (OR 2.47; CI:1.89-4.21; p<0.001), lower back pain (OR:1.80; CI:1.04-3.99; p<0.001), lower extremity pain (OR:4.55; CI:1.16-17.83; p<0.001), and motor deficiency (OR 22.73; CI:5.49-94.12; p<0.001) were significantly associated with LUTS. Lower MRC scores (β= -0.39; CI:-0.68 to -0.24; p < 0.001), bladder dysfunction (β= -0.80, CI:-0.94 to -0.42;, p < 0.001), and VAS lower extremity pain score (β=0.68; CI:0.42-0.85; p < 0.001) were also associated with LUTS. LUTS was significantly associated with LSS at the L4/L5 vertebral level (OR:1.51; CI:1.08-3.48; p=0.021) and bilateral side involvement (OR:27.5; CI: 8.18-92.53; p<0.001).

The mTPR≤0.34 is a strong predictor of adverse clinical outcomes. Patients with mTPR≤0.34 have higher odds of revision surgery due to cerebrospinal fluid (CSF) leakage, infection or recurrence within 6 months (OR:3.4; CI:1.2-9.8) and motor deficiency (OR: 2.1; CI:1.4-5.2), and are more likely to have LUTS after surgery (OR:4.5, CI: 1.1 - 18.9). mTPR≤0.34 correlates with worse outcomes on the ODI (β: 3.2; CI: 1.1-5.3; p = 0.004), SSSQ (β: 4.8; CI: 2.1-7.5), VAS for lower back pain (β: 1.3; CI: 0.6-2.0), and VAS for lower extremity pain (β: 1.7; CI: 0.82.6) (Table 3).

DISCUSSION

This prospective study highlights morphometric importance in diagnosing LUTS in LSS patients. An mTPR≤0.34 indicated a 2.2-fold higher risk of LUTS development. Additionally, mTPR≤0.34 predicted a 4.5-fold increased likelihood of surgery revision within 6 months.

Our findings revealed significant associations between clinical and morphometric characteristics and the prevalence of LUTS in patients with LSS, highlighting the crucial influence of demographic factors such as age. The increased likelihood of LUTS in older population aligns with autopsy evidence showing that LSS naturally occurs in this population, with prevalence ranging from 90% to 100% (12).

Table 2. Radiological characteristics of patients

Variable	LUTS (N = 49; 30.8%)	Control (N = 110; 69.8%)	p*	OR (95% CI)	p†
	No (%) of patients				
Vertebral level of LSS					
L2/L3	1 (2.0)	10 (9.1)	<0.001	0.10 (0.01-2.10)	0.527
L3/L4	0 (0)	16 (14.5)		0.30 (0.03-2.72)	0.328
L4/L5	40 (81.6)	60 (54.5)		1.51 (1.08-3.48)	0.021
L5/S1	8 (16.3)	24 (21.8)		2.0 (0.81-4.89)	0.098
Dominant side affected by LSS					
Right	9 (18.4)	53 (48.2)	<0.001	0.69 (0.27-1.75)	0.681
Left	27 (55.1)	53 (48.2)		0.76 (0.48-2.21)	0.223
Bilateral	13 (26.5)	4 (3.6)		27.5 (8.18-92.53)	<0.001
Disc degeneration	48 (98.0)	109 (99.1)	0.554	0.82 (0.45-14.83)	0.892
Dural sac compression	49 (100.0)	108 (98.2)	0.342	1.41 (0.74-1.42)	0.875
Lateral recess stenosis	38 (77.6)	95 (86.4)	0.165	0.44 (0.16-1.21)	0.411
Foraminal stenosis	26 (53.1)	62 (56.4)	0.699	1.22 (0.57-2.60)	0.616
Facet joint degeneration	49 (100.0)	107 (98.2)	0.340	1.95 (0.89-6.24)	0.947

*Pearson's χ^2; †multivariate regression analysis;
LUTS, lower urinary tract symptoms; OR, odds ratio; CI, confidence interval

Table 3. Follow-up data 6 months after surgical treatment

Variable	LUTS (N = 49; 30.8%)	Control (N = 110; 69.8%)	p*	OR (95% CI)	p†
No (%) of patients					
Revision within 6 months	7 (14.3)	2 (1.8)	<0.001	3.4 (1.2-9.8)	<0.001
Motor deficiency	11 (22.5)	8 (7.3)	0.014	2.1 (1.4-5.2)	<0.001
Sensitive deficiency	16 (32.6)	23 (20.9)	0.038	1.8 (0.9-3.4)	0.104
LUTS	6 (12.2)	1 (1.0)	<0.001	4.5 (1.1-18.9)	<0.001
Bowel dysfunction	3 (6.1)	9 (8.2)	0.086	0.7 (0.2-2.5)	0.584
Median (IQR)					
ODI **score**	18.0 (12.0-22.0)	14.0 (5.0 - 17.0)	<0.001	3.2 (1.1-5.3)	0.004
SSSQ **score**	21.0 (10.0-34.0)	12.0 (10.0-6.0)	<0.001	4.8 (2.1-7.5)	0.001
VAS score					
Lower back	6.0 (3.4-4.9)	3.0 (2.0-3.0)	<0.001	1.3 (0.6-2.0)	0.015
Lower extremity	5.0 (2.9-7.0)	3.0 (2.0-4.0)	<0.001	1.7 (0.8-2.6)	0.007

*Pearson's χ^2; †univariate logistic regression analysis for modified Torg-Pavlov ratio (mTPR) ≤0.34 mm;
LUTS, lower urinary tract symptoms; IQR, interquartile range; OR, odds ratio; CI, confidence interval; ODI, Oswestry disability index; SSSQ, Swiss spinal stenosis questionnaire; VAS, visual analogue scale;

The increased prevalence of neurogenic claudication, lower back pain, and lower extremity pain among LUTS patients underscores the close association between these symptoms and LSS (13). These findings align with previous studies that have identified neurogenic claudication as a hallmark of LSS, often leading to significant disability and reduced quality of life (14,15). The more severe motor deficiencies observed in the LUTS group in our study are consistent with the understanding that LSS compresses nerve roots, leading to progressive morphological impairment (16,17) and neurological deficits (18,19).

Radiology results of our study showed LUTS group predominantly exhibited L4/L5 stenosis, which is consistent with previous findings (20,21). From a morphometric perspective, the predominance of L4/L5 stenosis in the LUTS group aligns with existing literature, which identifies the L4/L5 level as the most commonly affected segment in LSS due to its anatomical and biomechanical characteristics (22,23). The bilateral involvement observed in the LUTS group suggests a more extensive pathological process (24), potentially leading to a greater burden of symptoms and functional impairment (22).

The differences in AP_{IVD} and modified mTPR between the LUTS and control groups of our study are particularly noteworthy as they have not been previously investigated. The higher AP_{IVD} in the LUTS group indicates a greater degree of disc degeneration and bulging (25), contributing to spinal canal narrowing and nerve root compression (26). Conversely, the lower mTPR in the LUTS group reflects a relatively smaller dural sac diameter compared to the intervertebral disc diameter (27), suggesting more severe central canal stenosis.

Higher ODI and SSSQ scores in the LUTS group of our patients support the fact that a more severe clinical form of LSS is associated with LUTS. Reportedly, a mean ODI of 37.8 and a mean SSSQ of 31.1, are both lower than our findings in the LSS population (28). This suggests greater disability in patients who, besides the conventional LSS symptoms, have developed LUTS. However, ODI and SSSQ values obtained in our study, significantly decreased 6 months post-surgery, which is consistent with previous findings (29,30). Another key finding of our study was that mTPR≤0.34 was negatively associated with ODI and SSSQ 6 months post-surgery in LUTS patients, suggesting mTPR can predict patient functionality and symptom relief from LSS. While ODI and SSSQ's predictive roles were confirmed (29), they were not specifically previously investigated in LUTS LSS-related patients.

Overall, morphometric analysis showed diagnostic significance in LSS patients (30,31), mainly focusing on AP_{DSC} values. However, it did not perform well diagnostically in LUTS patients. This is likely due to individual patient characteristics such as age, and gender (3), as well as the high specificity of AP_{DSC} for LSS observed in previous studies (32). Additionally, both the study and control groups in our research had LSS, which explains no statistically significant differences between the groups and diagnostic accuracy for AP_{DSC}.

The presented study has notable strengths, including enhanced diagnostic accuracy through the identification of specific clinical and morphometric characteristics linked to LUTS in LSS patients, and novel insights into their relationship, which aid in developing targeted treatments. It also highlights the potential of morphometric markers for predicting disease outcomes and personalizing treatment. However, the study has limitations, such as the need for validation in larger, more diverse populations, further investigation into long-term outcome, and the exploration of new diagnostic tools based on these markers.

In conclusion, this study highlights the diagnostic and predictive value of the mTPR in LUTS related to LSS. An mTPR≤0.34 is associated with a higher risk of developing LUTS and an increased likelihood of a need for surgery revision within 6 months. Future research should validate these findings in larger populations, explore long-term outcomes, and develop new diagnostic tools.

AUTHOR CONTRIBUTIONS

Conceptualization, H.H., E.B., and H.B.; methodology, H.B., E.B. and N.H.; software, E.B.; validation, I.S., A.P. and R.I.; formal analysis, E.B. and T.Z.; investigation, H.H., E.B., G.L., A.N.; resources, H.B., R.I. and T.Z.; data curation, E.B.; writing—original draft preparation, G.L., H.S., A.J. and H.H.; writing—review and editing, J.R., H.B., H.H. and E.B.; visualization, E.B.; supervision, H.S., H.B. and E.B.; project administration, E.B.; All authors have read and agreed to the published version of the manuscript.

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TRANSPARENCY DECLARATION

Conflict of interests: None to declare.

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