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Lumbar sacralization and L_4-L_5 microdiscectomy, a prospective cohort study on radiologic and clinical outcomes

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ABSTRACT

Aim: To evaluate the role of lumbar sacralization (LS) on the surgical outcomes of L4-L5 microdiscectomy.
Methods: This prospective cohort study was conducted in a university referral hospital. The patients with L4-L5 disc herniation and eligible for microdiscectomy were enrolled and allocated in G1 (with LS) and G2 (no LS). After the L4-L5 microdiscectomy patients were followed, clinical and radiological parameters were collected to investigate the influence on the outcomes. Recurrence, low back outcome score (LBOS), and the Oswestry disability index (ODI) were defined as main outcomes.
Results: Two hundred and forty patients (n = 120, each), were reviewed in the final analysis. There was no difference between groups regarding baseline characteristics. Postoperative radicular and back pain was more severe in LS($P < 0.05$). Univariate analysis showed recurrence was significantly higher in LS with a direct correlation with postoperative back pain persistence and low LBOS ($p = 0.001$). Age had a negative impact on G2 recurrence($p = 0.008$). LS had a negative impact on LBOS and ODI scores. Postoperative radicular pain and higher lumbar lordosis were associated with a higher disability (ODI) index.
Conclusion: L4-L5 microdiscectomy in patients with lumbar sacralization was associated with higher recurrence rates, worse ODI and LBOS scores, persistent postoperative axial back pain, and radicular pain. Postoperative axial back pain and poor LBOS results could effectively predict a higher recurrence rate following L4-L5 microdiscectomy in lumbar sacralization.

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1. Introduction

Lumbosacral transitional vertebra (LSTV) or lumbar sacralization (LS) is denoted to L5 anatomical variation. L5 endplates slope and anatomical features of the L5 vertebra go to the sacrum and in one word, assimilate to S1. Castellvi classified LSVT into 4 major groups and

Abbreviations: Low Back Outcome Score, (LBOS); Low back pain, (LBP); lumbar sacralization, (LS); Lumbosacral transitional vertebra, (LSTV); Magnetic resonance imaging, (MRI); Oswestry Disability Index, (ODI); Patient Satisfaction Index, (PSI); visual analog scale, (VAS).

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reported a higher incidence of degenerative discopathy with it.[1] In 1985, Mario Bertolotti depicted an association between LSTV and low back pain (LBP).[2]

The prevalence of LS in 6%–37% of patients with LBP and 30% with a herniated lumbar disc is an interesting finding denoting a possible association between LS and lower lumbar degeneration.[3] Recent studies found that lumbar sacralization increases the chance of developing LBP, the severity, and the probability of lumbar disc herniation.[4–6] However, the role of lumbar sacralization in the development and outcome of LBP and disc degeneration is questioned by other studies.[5,6]

Regarding the surgical outcomes of microsurgical discectomy, the anatomical location of the herniated disc is an important indicator.L5-S1 are deemed to have less favorable surgical outcomes than L4-L5(7). One possible hypothesis is the sheer forces and axial stress are not equally transferred to an oblique disc (L5-S1) rather than a more horizontally set disc(L4-L5), thus resulting in mechanical failure and herniation. This unbalanced force distribution results in a higher sheer force of the L5-S1 complex, causing higher recurrence and lower clinical outcomes. LS causes the L5 to play a similar mechanical role as S1, thus shifting the mechanical properties of the lumbar spine to 1 level below the counted vertebra. This anatomical shift causes L4-L5 in LS to participate in its biomechanical roles as L5-S1 in non-sacralized patients.

In the review of the literature, LS is suggested as a vertebral co-morbidity that worsens the outcome of surgical management and results in more recurrence.[8,9] However, there are multiple clinical and statistical controversies requiring well-designed studies on this challenging entity.

The current study was conducted to evaluate the role of lumbar sacralization on the surgical outcomes of L4-L5 standard micro-discectomy and to investigate the exact role of this anatomical and radiological variation on microsurgical discectomy (MD) outcomes.

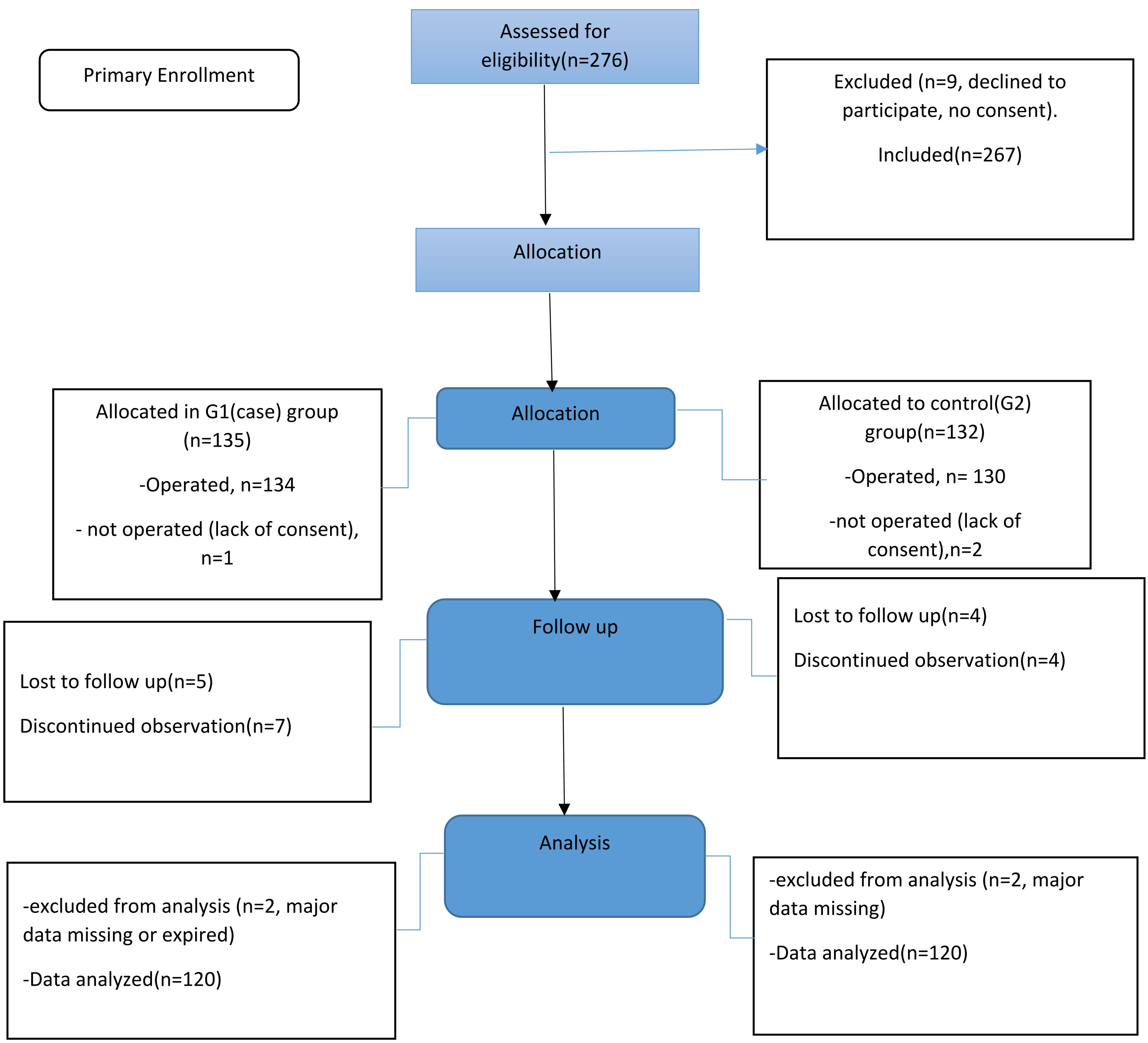

Fig. 1. Brief flow diagram demonstrating enrollment, exclusion, allocation, and follow-up sequences in the current research.

2. Methods

2.1. Study design

This study was designed as a prospective cohort study conducted in Kashani Referral University Hospital, Isfahan, Iran, from January 2020 to September 2022. This study was reviewed, approved, and supervised by the Isfahan University of Medical Sciences Ethics Committee and the neurosurgery department of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.666).

2.1.1. Patients enrollment

The inclusion criteria were radiologically proven L4-L5 disc herniation, age< 60 years old, who failed conservative treatment and were scheduled for elective MD. To control confounding factors, the patients who had a history of diabetes mellitus, any preexisting neuropathy not attributable to disc herniation, cardiovascular diseases, history of smoking, previous lumbar surgery, low back trauma, any concurrent spinal diseases(spondylolisthesis, spondylolysis, canal stenosis or disc herniation in other discs, metabolic, infectious, inflammatory and non -metabolic spinal diseases, concurrent discopathies in other levels) and those who refused to participate were excluded from the study (Fig. 1).

The case group (G1) was defined as the patients with radiologically proven lumbar sacralization (LS) and the control group (G2) was those without lumbar sacralization. Figs. 2 and 3 display a typical G1 and G2 case, respectively.

2.1.2. Radiologic assessments

The diagnosis of lumbar sacralization was based on radiologic imaging, including oblique and lateral views of the spine x-ray images, and MRI T1 and T2 weighted images. LSTV categorization was reported according to Castellvi's classification system as described by Castellvi el. al.[1] To determine the exact index vertebrae, we used both regular lumbar-sacral counting and counter-counting of the cervical vertebrae back to lumbosacral regions (double-counting method). Disc degeneration severity was assessed by Pfirrmann's classification system.[10] Those with concurrent discopathies in the sub-axial spine were excluded from the study. Spine biometrics such as lumbar lordosis(LL), pelvic incidence (PI), sacral slope(SS), and pelvis tilt(PT) were measured in each case. A typical illustration of spine biometrics is provided in Fig. 4 for better understanding. This validation was reproduced by two independent specialized investigators with inter-rater reliability (IRR) of 1(100% agreement).

2.1.3. Microsurgical discectomy

All the operations were performed by a senior neurosurgeon (SA). Under a unified general anesthesia protocol, in a prone position, after prep and drape in a sterile fashion, and under the C-arm fluoroscopy, the index level (L4-L5 disc space) was identified. Through a midline incision and unilateral paravertebral muscle sharp dissection, we gained access to L4-L5 space. Using Kerrison punch a small laminostomy (<1 cm^2) in L4 lamina was performed, PLL was dissected, and dura and root were identified. Medial hemifacet and facet joint were not violated. Under microscopic visualization, L4-L5 disc herniation was identified, incised, and removed. The amount of disc removal was restricted to nucleus polposus, herniated disc material, and loose tissues. This approach opted to preserve the annulus fibrosus and biomechanical properties of the disc.

Those who required more extensive surgery or any alternative techniques during the operation were excluded from the study and treated accordingly. Obvious sources of bleeding such as engorged veins were coagulated by bipolar electrocautery and cotton patty hemostasis. No drain was inserted. After proper irrigation with sterile room temperature normal saline, muscle, fascia, and the skin were repaired in anatomic layers.

2.1.4. Postoperative care

All the patients were transferred to the neurosurgery ward with routine and equal postoperative orders. All of them received cefazolin 1 g every 6 h and Acetaminophen 500 mg every 6 h PRN. All of them received elastic lumbar braces and then were encouraged to mobilize 24 h postoperation. All of them were discharged within 48 h postoperation.

2.1.5. Follow-up

The patients were visited in outpatient management settings in the university clinics 2 weeks postoperation and then in 1, 3,6, and 12-month intervals. Medical records were collected in each phase by the neurosurgical team and documented appropriately. Postoperative pain or the persistence of neurological deficits were managed by routine medications and physical rehabilitation. Those who failed the conservative treatment and had significant symptoms were re-evaluated by MRI. We defined the clinical recurrence as the relapse of disc herniation symptoms within 12 months postoperation corresponding to an attributable new disc herniation in the operated L4-L5 site.

2.1.6. Surgical complications

To control postoperative events, we sought every single post-operative complication and reported them upon occurrence. Post-operative cerebrospinal fluid leakage, nerve root injuries, new focal neurological deficits, iatrogenic spinal instabilities, infectious processes, wound dehiscence, recurrence, intractable and exacerbated pain, and any unpredictable surgery-associated complications were considered

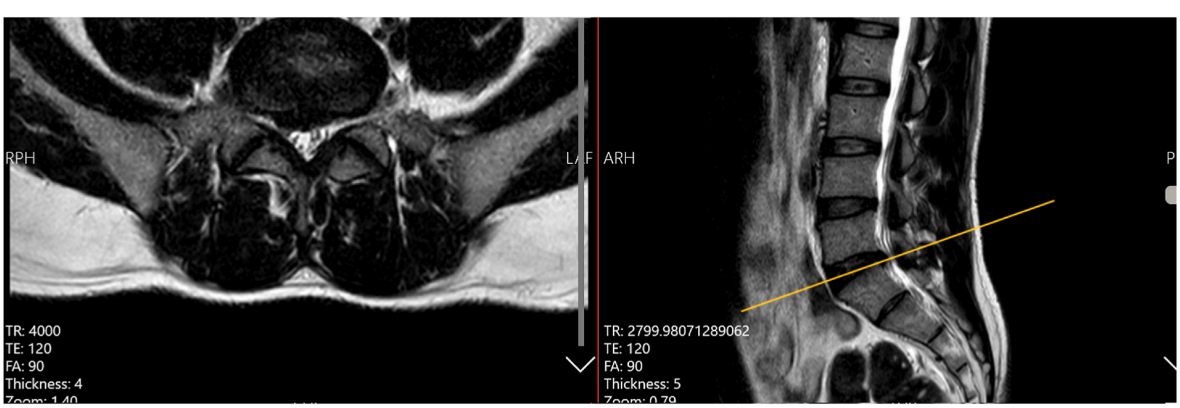

Fig. 2. A patient with lumbar sacralization (G1) and L4-L5 disc degeneration presented with right radicular pain due to right paracentral herniation. Please notice the fused true L5-S1 disc space. Considering the functional and anatomical perspectives, true L4-L5 in LS plays the role of true L5-S1 disc space in non-LS patients. Please notice the normal L4-L5 horizontal plane in LS is sloped(yellow line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

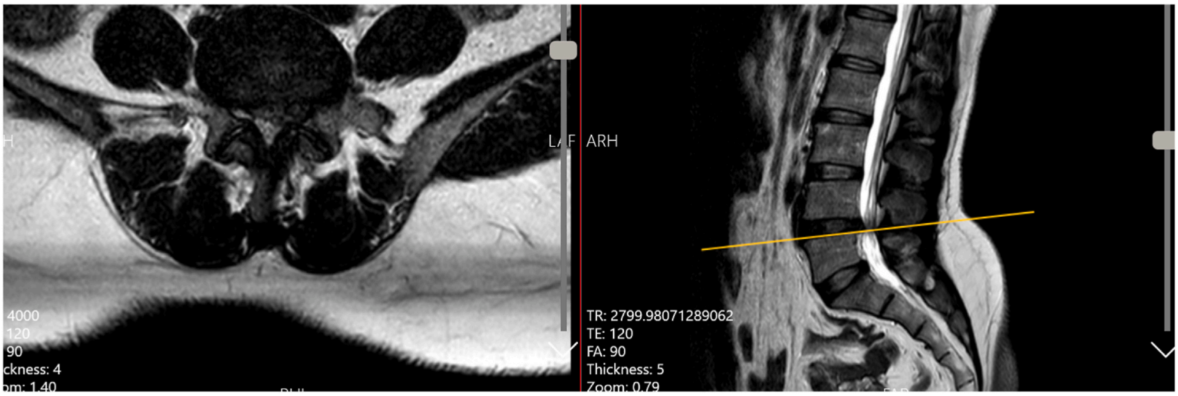

Fig. 3. A patient with normal spine anatomy(G2, without LSTV), presented with left radicular pain due to central-para central disc herniation. Please compare the horizontal plane at L4-L5 disc space in Fig. 1 and 2 together.

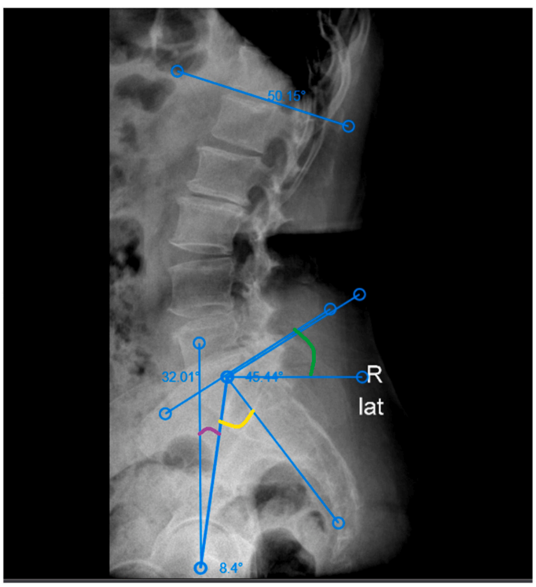

Fig. 4. a classic spine biometrics illustration used in the study. Purple angle: pelvic tilt(8.4°), green angle: sacral slope(32.01°), yellow angle; pelvic incidence(45.44°), and lumbar lordosis: 50.15°, is measured by the angle between superior end plates of S1 and L1. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

major postoperative adverse events. The observation period was defined until the end of the follow-up interval.

2.1.7. Data collection

Demographic data were recorded the day before the operations and clinical data were recorded before operations, 1, 3,6, and 12 months postoperative. The demographic data, clinical and neurological findings, the interval between pain initiation and operation, body-mass index (BMI), presence of paresthesia, low back pain, and radicular pain, Pfirrmann's disc degeneration grading, Castellvi gradings, surgical notes, complications, visual analog scale (VAS) for radicular and back pain, Oswestry Disability Index (ODI), Patient Satisfaction Index (PSI), Low Back Outcome Score (LBOS), spine radiographic measurements (vertebral slip degree, pelvic incidence, lumbar lordosis, and sacral slope), recurrence and all collectable data were recorded.[11–14] The outcomes were defined as VAS scores, postoperative ODI, recurrence, postoperative neurological deficits, postoperative LBOS, PSI, surgical complications, and spinal biometric values.

Statistical section.

Considering the previous publications and the rarity of the situation, to obtain a type I error as low as 0.05 and a study power>85%, we considered a minimum number of 30 patients to be assigned to each group.[14] Due to the high volume of referrals in our center, we could enroll over 130 patients in each arm.

IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp used for statistical analysis. Data expressed with mean ± standard deviation(sd.) and median for quantitative variables. We have determined qualitative variables by frequencies and percentages. The Chi-square test, independent *t*-test, Mann–Whitney test, and Pearson correlation test were used for determining associations. Logistic regression analyses were used to assess the predictors of the dependent outcome. $P < 0.05$ was defined as significant.

3. Results

Two hundred and forty patients were reviewed for the final data analysis. The overall number of the case (G1, $n = 120$) and control group (G2, $n = 120$) showed equal allocation in each group. Demographic and baseline medical data showed equal distribution in both groups (Table 1). The interval between symptom initiation and operation was not significantly different among groups (P-value = 0.076). Preoperative disc degeneration degenerative status such as Pfirrmann's grading, biomechanical parameters of the spine, and LSTV categorization data had no group superiority and, thus not provided.

Tables 2 and 3 summarizes the preoperative and postoperative clinical data. Preoperative radicular pain and back pain in both groups were 9 and 8, respectively. Regarding the preoperative radicular and back pain both groups had equal VAS scores, reflecting normal statistical distribution in case–control groups (Table 2). According to pre and postoperative VAS scores, it is apparent that MD had a dramatic and continuous effect on pain reduction and is considered an effective cure for such inflicting pain.

Postoperative and follow-up VAS score results showed that radicular

Table 1
The general characteristics of the patients, by study group. Statistical results show equal group distribution.

Variable	Sacralization		P-value
	G1	G2	
Age, years (Mean±SD)	46.6 ± 7.09	48.14 ± 7.06	0.075[1]
Sex (Male), n(%)	66 (55%)	78 (65%)	0.074[2]
BMI (kg/m^2) (Mean±SD)	24.49 ± 3.30	23.74 ± 4.08	0.062[1]
The interval from symptom initiation and operation, weeks (Mean±SD)	6.69 ± 2.33	5.53 ± 2.07	0.076[1]

1. Independent *t*-test
2. Chi-square test

Table 2
Inter-group and intra-group analyses of pre and post-operative radicular and back pain VAS scores. Please notice dramatic pain reduction after surgery.

Variable		VAS scores G1 Median (IQR)	VAS scores G2 Median (IQR)	P-Value[1]
Radicular Pain	**Before**	$9^{8,9}$	$9^{8,9}$	0.204
	One month later	$7^{6,7}$	$6^{6–8}$	0.015
	Three months later	$5^{4–6}$	$4^{3–6}$	<0.001
	Six months later	$3^{2–5}$	$2^{2–5}$	<0.001
P-Value[2]		0.002	0.001	
Back Pain	**Before**	$8^{7–9}$	$8^{7,8}$	0.870
	One month later	$8^{6–8}$	$7^{6,7}$	0.001
	Three months later	$4^{3–5}$	$3^{2–6}$	0.003
	Six months later	$2^{2–4}$	$2^{2–5}$	<0.001
P-Value[2]		0.002	0.001	

All comparisons performed using the Mann–Whitney test

Table 3
Surgical outcomes in both G1 and G2 groups. Statistical results show efficient clinical benefit of the surgery, regardless of anatomical variations.

Variable		Groups G1,	Groups G2	P-Value
Paresthesia, n (%)	**Before**	40 (33.3)	49 (40.8)	0.096
	One month later	30^{25}	38 (31.6)	0.124
	Three months later	14 (11.7)	18^{15}	0.307
	Six months later	7 (5.8)	9 (7.5)	0.965
Infections, n (%)	**Before**	0	0	–
	One month later	0	1 (0.8)	–
	Three months later	0	0	–
	Six months later	0	0	–
Recurrence, n (%)	**Six months later**	5 (4.1)	2 (1.7)	<0.001
ODI (Mean±SD, 12 months)	**Before**	56.2 ± 5.8	57.6 ± 4.2	0.238 *
	Six months later	22.5 ± 5.5	16.3 ± 9.2	0.042 *
LBOS, n (%)	**Excellent**	57 (47.5)	62 (51.7)	<0.001
	Good	36 (30)	41 (34.2)	
	Fair	19 (15.8)	12^{10}	
	Poor	8 (6.7)	5 (4.1)	
PSI, n (%)	**Satisfied**	87 (72.5)	96 (80)	0.639
	Dissatisfied	33 (27.5)	24^{20}	
Radiographic Measurements	**Slip (%)**	26.1	22.3	0.923
	Lumbar lordosis (°)	39.1 ± 9.7	38.9 ± 10.6	0.062 *
	Sacral slope (°)	31.4 ± 7.8	30.8 ± 8.4	0.151 *

All comparisons were performed using the chi-square test.
Independent *t*-test. :*

and low back pain in patients with lumbar sacralization was more prominent than those without sacralization ($P < 0.05$).

The prevalence of lower limb paresthesia was 33.3% and 40.8% in G1 and G2, respectively (Table 3). Postoperative paresthesia persisted in 6.6% of the patients after 6 months of surgery without any group preferences ($P = 0.096$).

There was only 1 case of postoperative discitis in the G2 group that was treated conservatively.

Regarding the clinical recurrence requiring reoperation, the patients with lumbar sacralization had more recurrence rates compared to those with normal lumbar spine anatomy (4.1% vs. 1.7%, P-value<0.001, Table 3). Univariate analysis showed advanced age was associated with a higher recurrence rate in the normal spine (G2 $P = 0.008$) and LS had a protective role in this association (G1P = 0.0625). Regardless of the group allocation, univariate analysis showed postoperative axial back pain was strongly associated with higher recurrence rates ($P < 0.001$, Table 4). Further statistical tests delineated that recurrence was also associated with LBOS but had no clear association with ODI and PSI (Table 5).

On admission ODI, had equal allocation between the two groups ($P = 0.238$). Postoperative ODI scores showed that MD could efficiently restore the patient's function and account a cure for such a debilitating neurosurgical situation. Postoperative ODI (6 months), showed LS had more significant disabilities in patients with LS compared to normal spine (22.5 ± 5.5 vs. 16.3 ± 9.2, $P = 0.042$). Higher ODI scores were associated with persistent postoperative radicular pain and higher lumbar lordosis in LS (Table 4).

Univariate analysis of Low Back Outcome Scores (LBOS) results showed that LS was associated with poor satisfaction outcomes regarding the control group($P < 0.001$). However, PSI results failed to display such differences ($P = 0.639$, Table 3).

Regarding radiographic measurements, the slip means, lumbar lordosis, sacral slope, and pelvis incidence were not different between case and control, denoting their independence considering the anatomical variation in the L5 vertebra ($P = 0.923$, 0.062, and 0.151, respectively). However, under such controlled circumstances, lumbar lordosis in G1 was associated with higher ODI scores. Regression tests failed to reproduce statistically significant results; thus tables were not provided.

Considering the preoperative Castellvi and Pfirrmann's grades and clinical outcomes, statistical analysis showed no significant association between preoperative MRI indices and outcomes (tables not provided).

4. Discussion

Our study results have displayed that LS negatively impacts postoperative outcomes. LS was associated with worse radicular and back pains, higher recurrence rates, and poor satisfaction indices following L4-L5 microdiscectomy. Interestingly, postoperative axial back pain and poor LBOS results could effectively predict a higher recurrence rate in LS. The reason for these findings is buried in the anatomical variation of sacralized lumbar spine. The following discussions are provided for a better understanding of these novel findings.

Ahn et al conducted a retrospective case–control study on the

Table 4
Correlation between Recurrence and ODI in patients with possible predisposing factors. Please notice postoperative low back pain was associated with recurrence in both groups.

variables	Recurrence *(p-value)* G1	Recurrence *(p-value)* G2	Recurrence *(p-value)* Total	ODI *(p-value)* G1	ODI *(p-value)* G2	ODI *(p-value)* Total
age	0.625	**0.008**	0.220	0.414	0.220	0.237
sex	0.681	0.504	0.444	0.380	0.168	0.281
BMI	0.932	0.728	0.155	0.933	0.163	0.158
Paresthesia	0.399	0.731	0.577	0.319	0.636	0.127
Postop radicular pain 1 month	0.342	0.615	0.459	0.929	0.583	0.480
Postop radicular pain 3 month	0.309	0.270	0.324	**0.006**	0.294	0.350
Postop radicular pain 6 month	0.290	0.699	0.326	**0.019**	0.379	0.340
PSI	0.776	0.523	0.433	0.300	0.300	0.447
Slip (%)	0.088	0.951	0.263	0.838	0.208	0.279
Lumbar lordosis (°)	0.287	0.337	0.278	0.047	0.282	0.282
Sacral slope (°)	0.870	0.864	0.213	0.584	0.186	0.223
postoperative axial back pain	<0.001	<0.001	<0.001	0.239	0.252	0.342

Table 5
Comparative univariate analysis between functional scoring tests and recurrence prediction. Only LBOS could reliably predict recurrence rates.

Outcome assessors	p-value
ODI	0.943
LBOS	0.001
PSI	0.256

surgical outcomes of MD in those with and without LS. According to their data, LS negatively impacted the postoperative VAS scores, recurrence rate, and lower functional outcomes(ODI).[15] Although their study had some limitations in study design and a low number of patients, their results were reliable and confirmed by our prospective study. We would like to encourage larger prospective studies on these associations.

Lumbosacral transitional vertebra(LSTV) is a common anatomical variation with an estimated prevalence of 4–36% in the population.[16] This congenital anomaly stems from malformation in the development of the lumbar vertebra at the 3rd week of gestation.[17] Castellvi has categorized LSTV into four major classes with minor modifications in each group. LSTV is an anatomical variation spectrum, ranging from minor dysplastic changes in the L5 transverse process extending to the solid fusion of L5 to S1 in bony elements and biomechanical properties similar to S1. Lumbar sacralization (LS) and LSTV are used interchangeably but there are some obvious differences. To be more specific, LS is denoted to LSTV Castellvi type II-IV that transverse process articulates with sacral ala while L5 is more vertical compared to the horizontal plane and settled as S1. Consequently, the sacralized L4-L5 disc is more vertical compared to normal lumbar segmentation. As a result, the sacralized L4-L5 disc bears mechanical stresses like L5-S1. This causes vertical and shear forces on sacralized L4-L5 disc space to distribute unevenly and promotes disc herniation and lumbar degeneration.[3,18,19] Due to the altered anatomy of this region, some studies have reported errors in the numeric identification of the vertebrae and subsequently, performing surgery at incorrect levels.[20]

It has been suggested that lumbar sacralization could affect the outcomes of lumbar spine surgery and increase complications. A study by Lee et al on 145 patients reported that patients with lumbar sacralization might have worse fusion rates after posterior lumbar interbody fusion (PLIF) surgery at the L4-L5 level compared to patients without lumbar sacralization.[8] Another case report by Hou et al presented a transformation of lumbar sacralization from Castellvi-IIa to Castellvi-IIIa following discectomy.[21]

Another confirmatory study on 102 patients showed that sacralized L5 leads to hypermobility at the L4-L5 segment, which potentially could be associated with L4-L5 disc herniation and anterior slippage.[22] Numerous studies have investigated the correlation between lumbar sacralization and low back pain; however, there is controversy over this subject and requires further controlled studies on such an interesting and naïve field of research.[3,23–26]

There are multiple reporting systems for functional outcomes of spinal disease. ODI is one of the most reliable, reproducible, and valid questionnaires available for multiple spinal situations focusing on pain, daily activities (walking, lifting, sitting, sexual life, and even social interactions), and the travel capacity of patients with spine diseases.[27] LBOS is another outcome measurement tool designed to evaluate functional outcomes of spine diseases with good reliability and clinical applicability.[28] PSI was primarily designed to report clinical outcomes of circumferential lumbar fusion and had lower applicability on simple discectomy.[11,12] There are many controversies regarding the reliability, applicability, and validity of these tests. Many studies have tried to answer some of these questions.

Azimi and Benzel conducted a cross-sectional study of the association between ODI, LBOS, and PSI after discectomy and declared their conclusions based on PSI results. According to their paper, ODI and LBOS had a lower clinical correlation with patient satisfaction while PSI had better predictive values.[29] We would like to mention that their study was a cross-sectional study that used PSI as the basis of the patient's real satisfaction and compared ODI and LBOS with it.[29] The authors would like to imply that PSI, besides its multiple pitfalls and limitations, was designed to cursory categorize a patient's conceptions of the postoperative results of a circumferential fusion surgery not for a simple discectomy. While looking at PSI satisfaction definitions and grading, it is easy to understand that neurosurgical, biomechanical, and real functional aspects of spine surgery are not reflected in this system, and it can be easily biased by the patient and interviewer. In simple terms, PSI is not a reliable and valid outcome assessor following discectomy.

In our prospective case–control study, we have found that the postdiscectomy functional improvement, patient's pain, and real-life functional outcomes were strongly associated with ODI, VAS, and LBOS but had no realistic correlation with PSI. Besides, VAS, ODI, and LBOS could reliably predict recurrence rates after discectomy while this predictive potential was not detected using PSI as an outcome assessor (Tables 3–5).

5. Conclusion

According to our data, L4-L5 microdiscectomy in patients with lumbar sacralization is associated with higher recurrence rates, worse ODI and LBOS scores, persistent postoperative axial back pain, and radicular pain. Postoperative axial back pain and poor LBOS results could effectively predict a higher recurrence rate following L4-L5 microdiscectomy in lumbar sacralization. Regarding the age and recurrence rate, normal patients experienced more recurrence as compared to LS.

5.1. Limitations

This study had multiple pitfalls worth mentioning. Due to the rarity of the variation, we had a limited number of patients, so the preoperative indices and outcomes could be different in larger data samples. A larger study population would be ideal for our data generalizability. Long-term postoperative lumbosacral MRI would be beneficial in terms of disc anatomy comparison and degeneration evolution. The authors would like to encourage future studies on the role of alternative surgical approaches such as tubular discectomy on the surgical outcomes of patients with LS.

Funding

None.

Ethics approval

This study was reviewed, approved, and supervised by the Isfahan University of Medical Sciences Ethic Committee and the neurosurgery department of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1399.666).

Consent to participate

An inform consent was obtained from all the patients.

Consent to publish

We declare that the manuscript complies with all instructions to authors, authorship requirements have been met, all authors approved the final manuscript, and this manuscript has not been published elsewhere and is not under consideration by another journal. All the authors accepted the manuscript to be submitted in this form to the journal.

Availability of data and material

Data and original images in the current study are available from the corresponding author at reasonable request. Authors can confirm that all relevant data are included in the article and/or its supplementary information files.

CRediT authorship contribution statement

Pouya Omidi: Supervision, Formal analysis, Data curation. **Saeid Abrishamkar:** Validation, Resources, Project administration, Methodology, Conceptualization. **Mehdi Mahmoodkhani:** Supervision, Resources, Investigation. **Arman Sourani:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Amin Dehghan:** Writing – original draft, Software, Data curation. **Mina Foroughi:** Writing – original draft, Project administration, Methodology. **Sadegh Baradaran Mahdavi:** Writing – original draft, Validation, Software, Project administration, Methodology. **Donya Sheibani Tehrani:** Software, Methodology, Data curation. **Roham Nik Khah:** Validation, Resources, Methodology, Data curation. **Shaahin Veisi:** Software, Resources, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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