

Patients at the Highest Risk for Reherniation Following Lumbar Discectomy in a Multicenter Randomized Controlled Trial

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Background: The purposes of the present study were to (1) confirm the risk of recurrent lumbar disc herniation in patients with a large anular defect who had undergone limited discectomy and (2) assess potential risk factors within this population.

Methods: The patient population was extracted from the control cohort of a prospective, randomized, multicenter controlled trial investigating the efficacy of an anular closure device following standard limited discectomy. All control patients underwent limited discectomy for the treatment of a single-level symptomatic posterior or posterolateral lumbar disc herniation. Only patients presenting with a large anular defect (6 to 10 mm wide by 4 to 6 mm long) were included in the study (n = 278). Baseline demographic, clinical, and surgical characteristics were recorded. Follow-up evaluations were performed at 6 weeks and at 3, 6, 12, and 24 months. Imaging modalities included magnetic resonance imaging, low-dose computed tomography, and radiographs. Symptomatic recurrent lumbar disc herniation was defined as any symptomatic postoperative herniation on either side of the index level. A multivariate logistic regression analysis of demographic and surgical variables associated with the incidence of recurrent lumbar disc herniation was performed.

Results: The mean anular defect area (and standard deviation) was 39.3 ± 9.1 mm², and the mean excised nuclear tissue volume was 1.3 ± 0.8 mL. At 2 years, the incidence of symptomatic recurrent lumbar disc herniation was 25.3% (64 of 253), with the herniation occurring at a mean of 264 days after the index procedure. Of the 64 patients with recurrent lumbar disc herniation, 36 underwent a subsequent surgical procedure. Logistic regression analysis identified an increased risk for recurrent lumbar disc herniation in females (odds ratio, 2.2) and in patients with greater anular defect widths (odds ratio, 1.3). Furthermore, multivariate logistic regression analyses revealed a significant interaction between age and sex (p = 0.005).

Conclusions: The outcomes of the present study provide the most substantial evidence to date in confirming previous reports of a high risk of reherniation among patients with large anular defects. Among those with large anular defects (width, ≥ 6 mm), females ≤ 50 years of age had the highest risk (up to ~ 10 times higher) of recurrent lumbar disc herniation. It is recommended that an anular repair or closure should be performed after limited discectomies in patients with large anular defects.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Surgical discectomy is an effective treatment for lumbar intervertebral disc herniation. Discectomy techniques have evolved markedly since they were originally described in 1934 by Mixer and Barr¹. Initially, a “complete” or “radical” discectomy involving curettage of both the intervertebral disc space and the cartilaginous end plates was advocated². Most

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TABLE I Notable Inclusion and Exclusion Criteria

Inclusion criteria

1. Age of 21 to 75 years and skeletally mature (male or female)
2. Posterior or posterolateral disc herniation at one level between L1 and S1 with confirmation of neural compression on MRI*
3. Minimum posterior disc height of 5 mm at index level
4. Radiculopathy (with or without back pain) with positive straight leg raise (0°-60°) (L4-L5, L5-S1) or femoral stretch test (L1-L2, L2-L3, L3-L4 only)
5. ODI score of at least 40/100 at baseline
6. VAS pain score of at least 40/100 at baseline (1 or both legs)

Exclusion criteria

1. Spondylolisthesis of grade II or higher (≥25% slip)
2. Requires spinal surgery other than a discectomy (with or without laminotomy) to treat leg/back pain (scar tissue and osteophyte removal allowed)
3. Back or nonradicular leg pain of unknown etiology
4. Prior surgery at the index lumbar vertebral level
5. Clinically compromised vertebral bodies in the lumbosacral region due to any traumatic, neoplastic, metabolic, or infectious pathology
6. Pathological fractures of the vertebra or multiple fractures of the vertebra or hip
7. Scoliosis of >10° (both angular and rotational)
8. Morbidly obese, defined as a body mass index of >40 kg/m² or weighing >100 lb (45 kg) over ideal body weight

*Intraoperatively, only post-discectomy anular defects between 4 and 6 mm long and 6 and 10 mm wide qualified for inclusion.

recently, Spengler described a more “limited” discectomy that eliminates curettage by means of excising only fragments and loose disc material via a pituitary rongeur alone³.

However, despite refinement in approach and technique, the incidence of reoperation persists at 13% to 25%, with symptomatic recurrent disc herniation presenting as the primary contributor, with reported rates of 3% to 18%⁴⁻¹⁷. Robust predictive metrics and/or risk factors associated with recurrent lumbar disc herniation have yet to be clearly defined.

Considerable efforts continue to be made to best characterize recurrent lumbar disc herniation with respect to both the type of herniation and the size of the anular defect. Particular focus has been given to patients exhibiting “large” or “massive” anular defects (≥6 mm), as first classified by Carragee et al.⁵. However, while both Carragee et al. and Kim et al. demonstrated that large anular defects were significantly predisposed to recurrent lumbar disc herniation, specifically following limited discectomy, additional risk factors for this subpopulation remain unclear^{5,18}. Given the substantial morbidity, chronic disability, and economic burden associated with recurrent lumbar disc herniation (estimated direct costs, \$34,242; estimated indirect costs, \$3,778), further delineation of demographic risk is imperative¹⁹.

The purpose of the present study was to prospectively confirm the risk of recurrent lumbar disc herniation and to evaluate associated factors in a population of patients with a large anular defect who had undergone limited discectomy. We hypothesized that the observed incidence of recurrent lumbar disc herniation would coincide with those in the historical reports by Carragee et al. (27.3%) and Kim et al. (18.0%)^{5,18}. We further hypothesized that logistic analyses of the incidence of

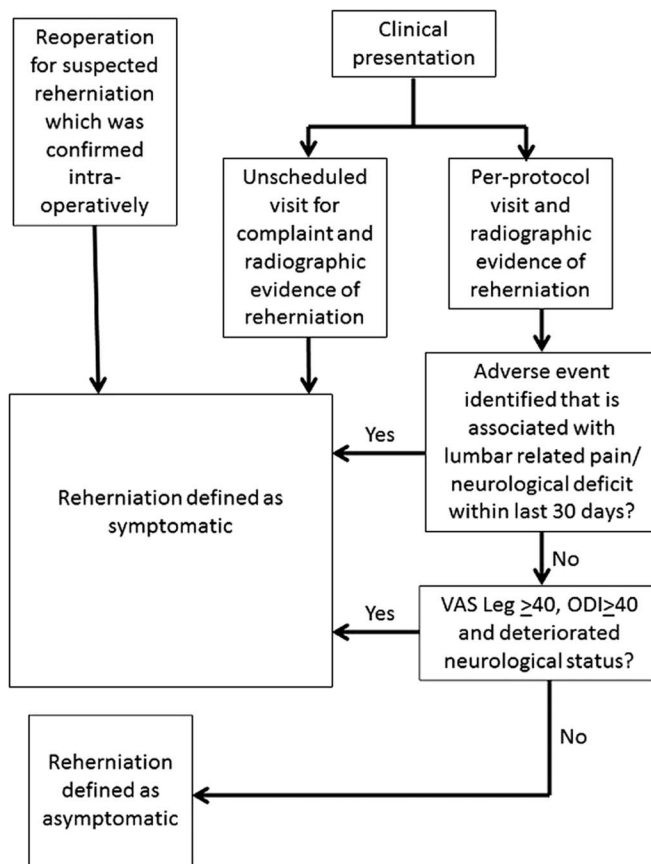


Fig. 1 Algorithm for determination of symptomatic recurrent lumbar disc herniation on the basis of reoperation or clinical presentation.

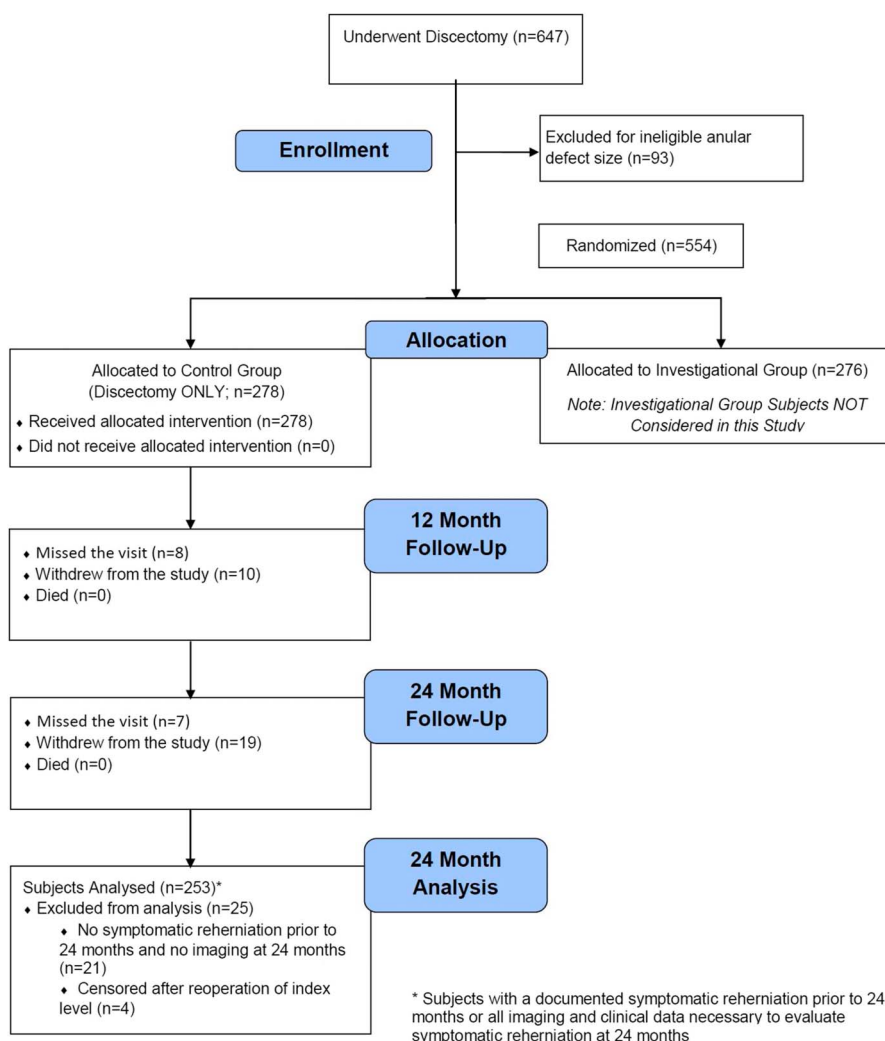


Fig. 2

Flowchart diagram summarizing patient allocation and follow-up retention.

recurrent lumbar disc herniation within this cohort would identify unique demographic variables demonstrating elevated risk. To our knowledge, the present study is the first to assess risk stratification in this discrete population, leveraging a large sample size with high data accountability.

Materials and Methods

Patient Sample Selection

The patient sample included the entire control cohort of a prospective randomized controlled trial (RCT) investigating the efficacy of a novel anular closure device following standard limited discectomy (Clinicaltrials.gov ID: NCT01283438). The RCT protocol has been published previously in its entirety and in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 guidelines for reporting parallel-group randomized trials^{20,21}.

Patients in the RCT were randomly assigned to limited discectomy (control group) or limited discectomy and treatment with the anular closure device (investigational group) via an

Internet-based randomization platform following completion of the discectomy. The comprehensive randomization methodology and sample-size determinations are detailed in the aforementioned protocol publication²⁰. All enrolled patients provided informed consent, as approved by a local Medical Ethics Commission. Study enrollment ($n = 554$) took place across 21 sites between December 2010 and October 2014.

Inclusion and Exclusion Criteria

All subjects were managed with a standard limited discectomy for the treatment of a single-level symptomatic posterior or posterolateral lumbar disc herniation (L1 to S1). Neural compression was confirmed with magnetic resonance imaging (MRI). A minimum posterior disc height of 5 mm was required for inclusion. All subjects were diagnosed with a “large” or “massive” anular defect, measuring 6 to 10 mm wide by 4 to 6 mm long. All measurements were recorded intraoperatively. Full inclusion/exclusion criteria are summarized in Table I.

TABLE II Demographic Data, Surgical Approach, and Disc Characteristics

Variable	No. of Patients or Mean Value (and Standard Deviation)
Sex (n = 278)	
Female	107 (38.5%)
Male	171 (61.5%)
Age (yr)	44.0 ± 10.4
BMI (kg/m ²)	26.3 ± 4.1
Smoking (n = 278)	
Not current	155 (55.8%)
Current	123 (44.2%)
Index level (n = 278)	
L2-L3	1 (0.4%)
L3-L4	5 (1.8%)
L4-L5	101 (36.3%)
L5-S1	171 (61.5%)
Spondylolisthesis (n = 253)	
Grade 0	245 (96.8%)
Grade I	8 (3.2%)
Disc height at index level (mm)	8.9 ± 2.2
Modic changes (n = 267)	
None	115 (43.1%)
Type I	30 (11.2%)
Type II	121 (45.3%)
Type III	1 (0.4%)
Disc degeneration (n = 276)	
None	3 (1.1%)
Doubtful	126 (45.7%)
Minimal	107 (38.8%)
Moderate	38 (13.8%)
Severe	2 (0.7%)
Pfirrmann grade (n = 271)	
Grade III	218 (80.4%)
Grade IV	53 (19.6%)
Defect dimensions	
Height (mm)	4.9 ± 0.7
Width (mm)	8.0 ± 1.3
Area (mm ²)	39.3 ± 9.1
Herniation type (n = 278)	
Contained fragment	76 (27.3%)
Extruded fragment	103 (37.1%)
Sequestered fragment	98 (35.3%)
None	1 (0.4%)
Nucleus material removed (mL)	1.3 ± 0.8
Surgical approach (n = 278)	
Through existing defect	169 (60.8%)
Through new created defect	109 (39.2%)

Surgical Technique and Intraoperative Defect Measurement

All surgeons were experienced in performing standard limited discectomy. General anesthesia was administered, and disc access was achieved under direct visualization with magnification through an interlaminar approach. Annular defects were measured with a set of dedicated measurement devices. A limited discectomy was then performed with a pituitary rongeur, whereby only extruded fragments and loose pieces of disc material in the disc space were removed. No curettage of either the disc or cartilaginous end plates was performed. Discectomy was followed by standard incision closure.

Follow-up and Outcome Metrics

Follow-up evaluations were performed at 6 weeks and at 3, 6, 12, and 24 months, with MRI, low-dose computed tomography (CT), and flexion-extension radiographs being made at 12 and 24 months. Imaging also was performed outside of these per-protocol visits if symptoms suggestive of reherniation were reported. Baseline demographic, clinical, and surgical characteristics were recorded, including annular defect area and excised nuclear material volume. Preoperative and postoperative follow-up imaging was performed to assess both angular and translational motion as well as presence of disc degeneration, Modic changes, and Pfirrmann grade. Imaging modalities included MRI, low-dose CT, and radiographs. All radiographic assessments and measurements were performed by radiologists who were board-certified.

Symptomatic Recurrent Lumbar Disc Herniation

Recurrent lumbar disc herniation was defined as any postoperative herniation on the ipsilateral or contralateral side relative to the index operation. Symptomatic herniation was confirmed on the basis of (1) patient complaints of radiculopathic pain and radiographic evidence of reherniation, (2) radiographic evidence of reherniation and an adverse event associated with documented lumbar-related pain or neurological deficit within the last 30 days, or (3) radiographic evidence of reherniation and documented deterioration of the neurological status, a visual analog scale (VAS) score of ≥40 for leg pain, or an Oswestry Disability Index (ODI) of ≥40. All radiographs were assessed by an independent group of radiologists who were blinded to the clinical outcomes. Reherniations were visually confirmed at the time of reoperation. The algorithm for defining a symptomatic recurrent lumbar disc herniation is detailed in Figure 1. Asymptomatic recurrent lumbar disc herniations that were observed on CT or MRI were excluded.

Statistical Analysis

Logistic analyses of the incidence of symptomatic recurrent lumbar disc herniation were performed on 13 variables related to demographic characteristics, surgical approach, and disc characteristics that were selected a priori. Univariate logistic regression analyses were performed on each variable. Variables that were found to have a significant association with recurrent lumbar disc herniation on univariate

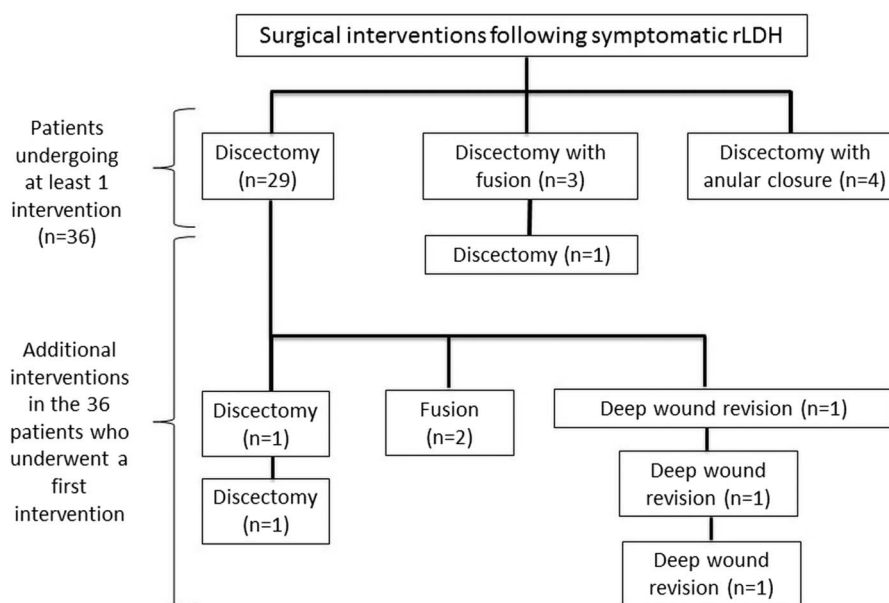


Fig. 3 Flowchart summarizing progression of subsequent surgical interventions following symptomatic recurrent lumbar disc herniation (rLDH).

TABLE III Odds Ratios and 95% Confidence Intervals for Symptomatic Reherniation by Variable*				
Variable	OR	95% CI	P Value	
Sex (female versus male)	2.18	1.22-3.90	0.008	
Age (increase in SD by 10.50 yr)	1.03	0.77-1.37	0.86	
BMI (increase in SD by 4.12 kg/m ²)	0.91	0.68-1.21	0.51	
Smoking				
Current versus never	1.36	0.72-2.58	0.34	
Prior versus never	1.01	0.44-2.30	0.99	
Index level				
L2-L3 or L3-L4 versus L5-S1	0.74	0.08-6.86	0.79	
L4-L5 versus L5-S1	0.98	0.54-1.77	0.94	
Disc height (increase in SD by 2.19 mm)	0.84	0.63-1.13	0.25	
Modic changes				
Type I versus none	2.36	0.95-5.89	0.07	
Type II or III versus none	1.67	0.88-3.16	0.12	
Disc degeneration				
None or doubtful versus minimal	1.50	0.81-2.80	0.20	
None or doubtful versus moderate or severe	1.57	0.66-3.70	0.31	
Pfirrmann grade (Grade III versus IV)	1.36	0.68-2.70	0.38	
Defect dimensions				
Increase in SD of height by 1.29 mm	0.80	0.60-1.07	0.13	
Increase in SD of width by 0.71 mm	1.33	1.00-1.78	0.05	
Increase in SD of area by 8.96 mm ²	1.04	0.78-1.38	0.80	
Herniation type				
Contained versus extruded	1.22	0.59-2.53	0.59	
Sequestered versus extruded	1.41	0.71-2.77	0.32	
Nucleus material removed (increase in SD by 0.82 mL)	1.00	0.75-1.33	0.99	
Surgical approach (through existing defect versus new created defect)	1.45	0.80-2.64	0.22	

*SD = standard deviation.

analysis were then evaluated for interactions in multivariate logistic regression analysis. The level of significance of the odds ratios (ORs) for the incidence of recurrent lumbar disc herniation (and 95% confidence intervals [CIs]) was defined as $p < 0.05$. All analyses were performed with use of SAS 9.4 (SAS Institute) or R version 3.3.2 (R Foundation for Statistical Computing).

Results

Follow-up, Demographics, and Characteristics of Disc Herniation

The study group consisted of 278 subjects, with a 2-year follow-up rate of 91% (253 of 278). A flowchart diagram summarizing patient allocation and follow-up retention is shown in Figure 2. The demographic, surgical approach, and disc characterization variables (all chosen a priori) are summarized in Table II. The mean anular defect area (and standard deviation) was $39.3 \pm 9.1 \text{ mm}^2$, and the mean defect width was $8.0 \pm 1.3 \text{ mm}$. The mean excised nuclear tissue volume was $1.3 \pm 0.8 \text{ mL}$.

Incidence of Recurrent Lumbar Disc Herniation and Associated Risk Factors

At 2 years, the incidence of symptomatic recurrent lumbar disc herniation was 25.3% (64 of 253), with the herniation occurring at a mean of 264 days (range, 2 to 787 days) after the index procedure. In 60 (93.8%) of 64 cases, the reherniation occurred on the side of the index operation. Of the 64 patients with symptomatic recurrent lumbar disc herniation, 36 underwent at least 1 subsequent surgical intervention (Fig. 3).

Univariate analysis identified 2 significant factors associated with the risk of recurrent lumbar disc herniation: sex and defect width (Table III). Females had an increased risk for recurrent lumbar disc herniation in comparison with males (OR, 2.2; $p = 0.008$). Even within this population of patients with large anular defects, those with larger defect widths (those with widths that were increased by ≥ 1 standard deviation) had an increased risk of reherniation (OR, 1.3; $p = 0.05$).

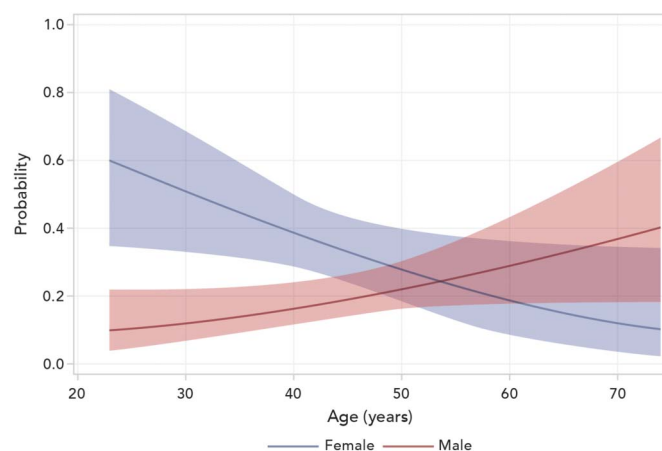


Fig. 4
Line graph showing the probabilities (and 95% CIs) of symptomatic recurrent lumbar disc herniation based on age and sex.

Multivariate logistic regression analysis specifically investigating the relationship between sex and defect width revealed 1 variable combination with significance from among the 13 variables: age and sex. The incidence of recurrent lumbar disc herniation was negatively correlated with age in females but was positively correlated with age in males. The OR showed a higher risk for females in comparison with males, ranging from 1.2 (at the seventy-fifth percentile of age) to 9.6 (at the fifth percentile of age) times higher until an age of ~ 51 years ($p = 0.005$), at which point a crossover occurred, with males experiencing slightly greater risk. The lower bound of the 95% CI for recurrent lumbar disc herniation risk in females did not contain the upper bound of risk for males until an age of ~ 43 years (Fig. 4).

Discussion

The results of the present study demonstrated a high incidence of symptomatic recurrent lumbar disc herniation (25.3%) in a cohort of patients with large anular defects (width, $\geq 6 \text{ mm}$) who had undergone limited discectomy, substantiating the rates previously reported by Carragee et al. (27.3%) and Kim et al. (18.0%)^{5,18}. Even if the definition of recurrent lumbar disc herniation was limited to symptomatic reherniations on the ipsilateral side relative to the index operation, the incidence would decrease only slightly, to 23.7%.

The majority (56%) of patients with recurrent lumbar disc herniation underwent at least 1 subsequent surgical intervention, although the reoperation rate across all patients was lower than that reported by Carragee et al. (14.2% compared with 21.2%)⁵. We hypothesize that this difference was attributable to the lengthier follow-up period in the study by Carragee et al. (median, 6 years)⁵. As follow-up continues on our population, the incidence of reoperation due to recurrent lumbar disc herniation may increase. Taken together, the results of these studies demonstrate an unmet clinical need in a high-risk segment of the population of patients managed with discectomy, in which the rate of reherniation is otherwise $< 10\%$ ^{5,18}.

The most pronounced finding of regression analysis was the relationship between age and sex, with females experiencing as much as a ~ 10 times (OR = 9.6) greater risk of recurrent lumbar disc herniation until ~ 51 years of age. The significantly increased rate of recurrent lumbar disc herniation in young females may be attributable to the effect of differences in premenopausal steroid hormone levels on the collagen biology of the intervertebral disc. Premenopausal steroid hormone levels previously have been implicated in the increased incidence of injuries involving the tendons and ligaments (structures that are also rich in collagen) among young females²².

The findings of the present study suggest that univariate analysis alone is not sufficiently sensitive to characterize those who are at highest risk of reherniation. In addition, while previous studies have explored the risk factors for recurrent lumbar disc herniation, including sex, those analyses have not focused on the particular subpopulation studied here, that is, patients with large anular defects^{4,18,23,24}. Therefore, a substantial

portion of the literature on recurrent lumbar disc herniation may inadvertently mask increased reherniation rates, and patients with critical risk factors, by including high-risk patients with confirmed large anular defects in rate calculations for the broader population of patients who have undergone discectomy²⁴. Improving the standard of care for high-risk patients requires isolation of this high-risk subpopulation for separate multivariate analysis.

Carragee et al., in a study investigating variations in discectomy technique for the management of patients with large anular defects, found that although subtotal discectomy, with its more extensive removal of disc material, substantially decreased the rate of recurrent lumbar disc herniation when compared with the limited discectomy technique (9% compared with 18%), it also led to inferior clinical outcomes and patient satisfaction⁶. Similarly, McGirt et al., in a comprehensive review of the literature, reported a higher rate of recurrent lumbar disc herniation, but a lower rate of long-term recurrent back pain, in association with limited removal of disc material²⁵.

For the high-risk group of patients undergoing discectomy for treatment of intervertebral disc herniation, an optimal surgical outcome necessitates maintaining a maximum amount of disc tissue in order to minimize disc degeneration, loss of intervertebral disc height, and resulting back pain while also mitigating the risk of recurrent disc herniation. Consequently, the treatment goal should be a surgical technique that permits a discectomy with limited nucleus removal, but also effectively repairs or closes the anular defect.

Strengths and Limitations of Present Study

The relative strengths of the present study include the size of the cohort, the prospective enrollment of patients, the collection of data at multiple centers, and the high rate of follow-up at 2 years. Additionally, the consistency of the demographic characteristics of the patients in the present study with those in the studies by both Carragee et al. and Kim et al. offers considerable validation of the rate of recurrent lumbar disc herniation in patients with a large defect and limited discectomy^{5,18}.

The present study had slight variations from the cited studies (e.g., defect measurement technique and duration of

follow-up). However, such nuanced differences do not substantially limit the conclusions of the current study.

In conclusion, the present study offers the most definitive evidence to date in establishing that patients with large anular defects who have undergone limited discectomy are a well-defined, high-risk surgical population. Among those with large anular defects (width, ≥ 6 mm), females ≤ 50 years of age had the highest risk (~ 10 times higher) of recurrent lumbar disc herniation. Further stratification of the risk factors within this cohort may provide additional useful information. It is recommended that an anular repair or closure should be performed after limited discectomy in patients with large anular defects. ■

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