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CLINICAL ARTICLE

Does reduction of the Meyerding grade correlate with outcomes in patients undergoing decompression and fusion for grade I degenerative lumbar spondylolisthesis?

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OBJECTIVE Reduction of Meyerding grade is often performed during fusion for spondylolisthesis. Although radiographic appearance may improve, correlation with patient-reported outcomes (PROs) is rarely reported. In this study, the authors' aim was to assess the impact of spondylolisthesis reduction on 24-month PRO measures after decompression and fusion surgery for Meyerding grade I degenerative lumbar spondylolisthesis.

METHODS The Quality Outcomes Database (QOD) was queried for patients undergoing posterior lumbar fusion for spondylolisthesis with a minimum 24-month follow-up, and quantitative correlation between Meyerding slippage reduction and PROs was performed. Baseline and 24-month PROs, including the Oswestry Disability Index (ODI), EQ-5D, Numeric Rating Scale (NRS)–back pain (NRS-BP), NRS-leg pain (NRS-LP), and satisfaction (North American Spine Society patient satisfaction questionnaire) scores were noted. Multivariable regression models were fitted for 24-month PROs and complications after adjusting for an array of preoperative and surgical variables. Data were analyzed for magnitude of slippage reduction and correlated with PROs. Patients were divided into two groups: < 3 mm reduction and ≥ 3 mm reduction.

RESULTS Of 608 patients from 12 participating sites, 206 patients with complete data were identified in the QOD and included in this study. Baseline patient demographics, comorbidities, and clinical characteristics were similarly distributed between the cohorts except for depression, listhesis magnitude, and the proportion with dynamic listhesis (which were accounted for in the multivariable analysis). One hundred four (50.5%) patients underwent lumbar decompression and fusion with slippage reduction ≥ 3 mm (mean 5.19, range 3 to 11), and 102 (49.5%) patients underwent lumbar decompression and fusion with slippage reduction < 3 mm (mean 0.41, range 2 to −2). Patients in both groups (slippage reduction ≥ 3 mm, and slippage reduction < 3 mm) reported significant improvement in all primary patient reported outcomes (all $p < 0.001$). There was no significant difference with regard to the PROs between patients with or without

ABBREVIATIONS MCID = minimal clinically important difference; NASS = North American Spine Society; NRS = Numeric Rating Scale; NRS-BP = NRS for back pain; NRS-LP = NRS for leg pain; ODI = Oswestry Disability Index; PRO = patient-reported outcome; QOD = Quality Outcomes Database.

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intraoperative reduction of listhesis on univariate and multivariable analyses (ODI, EQ-5D, NRS-BP, NRS-LP, or satisfaction). There was no significant difference in complications between cohorts.

CONCLUSIONS Significant improvement was found in terms of all PROs in patients undergoing decompression and fusion for lumbar spondylolisthesis. There was no correlation with clinical outcomes and magnitude of Meyerding slippage reduction.

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KEYWORDS lumbar; spondylolisthesis; listhesis reduction; slip reduction; Quality Outcomes Database; patient-reported outcomes; degenerative

Degenerative lumbar spondylolisthesis is a commonly encountered condition, affecting an estimated 13.6% of the United States population.[1] The condition is associated with degenerative changes and may result from a combination of disc degeneration with disc height collapse, ligamentous hypertrophy or buckling, facet degeneration, and/or osteophyte proliferation.[2–4] For a subset of well-selected patients in whom nonoperative management fails,[5] surgery may be appropriate and may take the form of either decompression alone or decompression with fusion.[6–9] For the latter, surgeons must decide whether to reduce the spondylolisthesis intraoperatively or to fuse the spine in situ (i.e., in the slipped position). The ideal strategy remains controversial.[10–20] Proponents of slip reduction suggest that reduction is associated with improved back pain and recovery.[14] However, other studies have found no clinical differences in patients with and without slippage reduction after surgery.[11] Proponents for in situ fusion suggest that stresses during reduction maneuvers may carry risks (e.g., screw loosening/pullout during reduction[17,18]) with unclear clinical benefit. The optimal approach remains unclear.

To this end, we used data from the prospective, multicenter Quality Outcomes Database (QOD) spondylolisthesis study group to assess the impact of spondylolisthesis reduction on 24-month patient-reported outcome (PRO) measures after decompression and fusion surgery for Meyerding[21] grade I degenerative lumbar spondylolisthesis.

Methods

Data Source

The QOD is a prospective registry that contains data on patient demographics, comorbidities, clinical characteristics, operative parameters, and baseline and follow-up PRO scores (Oswestry Disability Index [ODI], Numeric Rating Scale [NRS] for back pain [NRS-BP], NRS for leg pain [NRS-LP], EuroQol-5D [EQ-5D], and North American Spine Society [NASS] patient satisfaction questionnaire).

Twelve high-enrolling QOD sites participate in the lumbar spondylolisthesis module/study group[6,22–38] formed to investigate the effectiveness of fusion for grade I degenerative lumbar spondylolisthesis.[6] For this data set, patients who underwent single-segment surgery for Meyerding[21] grade I degenerative lumbar spondylolisthesis from July 2014 through June 2016 were enrolled. Standing or dynamic preoperative plain radiographs were evaluated by surgeons at each participating site to confirm the diagnosis of grade I spondylolisthesis. In addition to QOD exclusion criteria,[39] we excluded patients who had spondylolisthesis that was higher than grade I. Data elements for all patients were audited for data element accuracy. We compared the outcomes for patients who had a reduction of listhesis ≥ 3 mm (reduced) with those who had a reduction of < 3 mm (not reduced). This cutoff was decided a priori and was based on the definitions of instability described by Posner et al., which defined instability as 3 mm or more.[40]

Primary and Secondary Outcomes

Using validated questionnaires, we assessed outcomes at 24 months. The primary outcome of interest was ODI score (range 0–100, with higher scores indicating more disability related to back pain[41]). An ODI improvement of 14.3 was considered the minimal clinically important difference (MCID).[22] Secondary outcomes of interest included NRS-BP score (range 0–10, with higher scores indicating more back pain disability[42]), NRS-LP score (range 0–10, with higher scores indicating more leg pain disability[42]), EQ-5D (range −0.11 to 1, with scores relaying a preference-based quality-of-life outcome metric and higher scores indicating less disability[43]), and NASS patient satisfaction questionnaire.[44] The NASS satisfaction questionnaire is scored 1 through 4, respectively: 1, surgery met my expectations; 2, I did not improve as much as I had hoped but I would undergo the same operation for the same results; 3, surgery helped but I would not undergo the same operation for the same results; and 4, I am the same or worse as compared to before surgery. Other outcomes included estimated blood loss, operative time, length of hospitalization, discharge disposition, 3-month readmission rate, cumulative reoperation rate (within 24–36 months), and 30-day complication rate. Readmissions and reoperations were recorded if deemed related to surgery. Radiographic outcomes for radiographic fusion and reduction in listhesis were determined by a neuroradiologist not affiliated with the study team.

Statistical Analysis

Descriptive statistics were reported as frequencies and percentages and means and standard deviations where appropriate. For univariate analyses, paired and unpaired t-tests were used as appropriate for continuous variables. For categorical variables, chi-square analyses were performed, and Yates' correction was applied where appropriate. If a cell count assumed the value of zero, then the Fisher exact test was used. For multivariable analyses, multivariable linear regression models were fitted for ODI, NRS-BP, NRS-LP, and EQ-5D 24-month values and

24-month change scores (i.e., 24-month value minus baseline value). For each model, covariates included factors reaching $p < 0.20$ on univariate comparisons of the cohorts with and without reduction in listhesis. A logistic regression model was fit for ODI MCID after controlling for covariates reaching $p < 0.20$ on univariate comparisons. An ordinal logistic regression model (R package *polr*) was fit for 24-month NASS patient satisfaction questionnaire scores after controlling for covariates reaching $p < 0.20$ on univariate comparisons. This analysis was conducted using R 2.15.2 (R Foundation for Statistical Computing). Missing values in the data were imputed using the "missForest" R package; p values were two-tailed, and an alpha of 0.05 was considered statistically significant.

Results

Demographics

Of the 608 patients undergoing surgery for Meyerding grade I degenerative lumbar spondylolisthesis, 206 patients (33.9%) underwent both neutral upright lumbar radiography imaging at baseline and latest follow-up. Of these patients, 104 (50.5%) had a reduction in listhesis of at least 3 mm (mean 5.19, range 3 to 11) (reduced), and 102 (49.5%) did not have a reduction in listhesis (mean 0.41, range 2 to –2) (reduction between 3 and –2 mm) (not reduced). Table 1 compares the baseline characteristics of the two cohorts. Radiographically, those achieving reduction had a higher mean magnitude of listhesis at baseline (5.1 ± 2.1 vs 0.4 ± 1.3 mm, $p < 0.001$) and higher proportion with dynamic listhesis preoperatively (36.8% vs 20.7%, $p = 0.04$). Surgery including an interbody graft was performed in a higher proportion of patients in the reduced cohort (99.0% vs 92.2%, $p = 0.04$). There was a smaller percentage of patients with depression in the reduced cohort (16.3% vs 31.4%, $p = 0.01$). Otherwise, the cohorts were comparable for the remaining demographic, clinical, surgical, and socioeconomic variables.

Perioperative Outcomes, Fusion Rates, Readmission, Reoperation, and 30-Day Complications

Perioperative outcomes, including blood loss, operative time, length of stay, discharge disposition, 3-month readmission, cumulative reoperation (within 24–36 months), and 30-day complications, did not differ significantly ($p > 0.05$) (Table 2). There was no difference in rates of radiographic fusion (98.8% in the reduced group vs 95.5% in the not-reduced group, $p = 0.41$). There were 4 (3.8%) reoperations in the reduced spondylolisthesis group for adjacent-segment disease (n = 2; 1.9%) and surgical site infection (n = 2; 1.9%). Of note, there were no cases of implant failure requiring reoperation. There were 5 (4.9%) reoperations in the not-reduced group for adjacent-segment disease (n = 3; 2.9%), excision of suture granuloma (n = 1; 1.0%), and surgical site infection (n = 1; 1.0%).

Patient-Reported Outcomes

Table 3 compares the PROs for the cohorts. Both cohorts improved significantly from baseline at 24 months for ODI, NRS-BP, NRS-LP, and EQ-5D ($p < 0.001$ for all comparisons) regardless of spondylolisthesis reduction. The 24-month mean ODI did not differ significantly between those with spondylolisthesis reduction (16.0 ± 17.8) and those without reduction (21.4 ± 20.5) ($p = 0.05$). Similarly, the ODI improvement (i.e., change in ODI value from baseline) did not differ at 24 months ($p = 0.87$). The proportion of patients reaching MCID were similar for those with (76.1%) and without (73.1%) spondylolisthesis reduction ($p = 0.64$). The 24-month NRS-BP, NRS-LP, and EQ-5D scores did not differ between the cohorts ($p > 0.05$). The distribution of NASS patient satisfaction scores did not differ between the cohorts at 24 months (75.0% [reduced] vs 70.0% [not reduced] with a NASS score of 1; $p = 0.78$).

In multivariable adjusted analyses, spondylolisthesis reduction was not associated with different outcomes for 24-month ODI, ODI MCID, NRS-BP, NRS-LP, EQ-5D, and NASS patient satisfaction scores (Table 4). This finding remained despite assignment of reduction magnitude as a continuous variable in multivariable modeling (i.e., change in listhesis between pre- and postoperatively) (Table 5). Additionally, we assessed for the influence of minimally invasive techniques on these findings and observed no association between spondylolisthesis reduction and 24-month outcomes with inclusion of minimally invasive techniques as a covariate in multivariable analyses ($p > 0.05$).

Discussion

To our knowledge, this is the largest study to compare long-term clinical outcomes for patients undergoing listhesis reduction versus nonreduction fusion for Meyerding grade I degenerative lumbar spondylolisthesis. In an investigation of 206 patients undergoing single-segment surgery, we found that 50.5% of patients had a reduction in listhesis, whereas 49.5% did not have a reduction in listhesis at latest follow-up. Regardless of listhesis reduction, surgical decompression and fusion was associated with 1) significant improvements in disability, back pain, leg pain, and quality of life; 2) similar rates of reaching an MCID in disability; and 3) similar levels of satisfaction for both cohorts at 24 months. The two cohorts shared similar outcomes for readmission, reoperation, 30-day complications, and radiographic fusion. In multivariable adjusted analyses, slip reduction was not associated with different 24-month outcomes for disability, back pain, leg pain, quality of life, patient satisfaction, or the ability to reach a minimum clinically important improvement in disability.

Whether slippage reduction should be a primary goal of spondylolisthesis surgery is controversial,[10–16,19,20] with comparative investigations demonstrating mixed results depending on the etiology and grade of spondylolisthesis. Audat et al. conducted a randomized trial of 41 adult patients with low-grade isthmic spondylolisthesis undergoing fusion, comparing reduction versus in situ fixation.[10] The study observed significant improvements in ODI at the 3-year follow-up for both groups but lower mean ODI in the cohort undergoing reduction at the 3-month, 1-, 2-, and 3-year postoperative time points. However, other similarly sized randomized trials comparing reduction with in situ fixation found no difference in clinical outcomes for dysplastic and isthmic spondylolisthesis cohorts.[11,17]

TABLE 1. Characteristics of patients undergoing surgery for grade I lumbar spondylolisthesis

	Reduced (n = 104)	Not Reduced (n = 102)	p Value
Age in yrs, mean ± SD	61.3 ± 9.5	63.7 ± 12.6	0.18
Female, n (%)	60 (57.7)	63 (61.8)	0.55
BMI, mean ± SD	31.0 ± 6.1	31.3 ± 6.1	0.73
Smoker, n (%)	9 (8.7)	15 (14.7)	0.18
Comorbidities, n (%)			
Diabetes mellitus	19 (18.3)	13 (12.7)	0.27
Coronary artery disease	13 (12.5)	9 (8.8)	0.39
Anxiety	20 (19.2)	27 (26.5)	0.22
Depression	17 (16.3)	32 (31.4)	**0.01**
Listhesis in mm, mean ± SD	5.1 ± 2.1	0.4 ± 1.3	**<0.001**
Dynamic listhesis, n (%)	28/76 (36.8)	12/58 (20.7)	**0.04**
Dominant presenting symptom, n (%)			0.79
Back pain dominant	34 (32.7)	38 (37.3)	
Leg pain dominant	12 (11.5)	11 (10.8)	
Back pain = leg pain	58 (55.8)	53 (52.0)	
Motor deficit present at presentation, n (%)	20 (19.2)	19 (18.6)	0.91
Independently ambulatory, n (%)	96 (92.3)	90 (88.2)	0.32
Symptom duration in mos, n (%)			0.48
<3	0 (0)	1 (1.0)	
>3	103 (99.0)	94 (92.2)	
ASA class, n (%)			0.76
I or II	55 (52.9)	59 (57.8)	
II or IV	41 (39.4)	34 (33.3)	
Surgical characteristics			
Use of interbody, n (%)			**0.04**
No interbody	1 (1.0)	8 (7.8)	
Interbody	103 (99.0)	94 (92.2)	
Use of minimally invasive techniques, n (%)	47 (45.2)	40 (39.2)	0.39
Surgical approach			0.63
Posterior only	95 (91.3)	95 (93.1)	
Other than posterior only (anterior, lateral, & 2-stage)	9 (8.7)	7 (6.9)	
Ethnicity, n (%)			
Hispanic or Latino	5 (4.8)	4 (3.9)	>0.99
Education level, n (%)			
4-yr college education or more	35 (33.7)	31 (30.4)	0.65
Employed or employed & on leave, n (%)	50 (48.1)	50 (49.0)	0.89
Private insurance, n (%)	61 (58.7)	57 (55.9)	0.69
Use of workers' compensation, n (%)	8 (7.7)	9 (8.8)	>0.99
Baseline ODI, mean ± SD	46.4 ± 16.2	50.5 ± 15.8	0.07
Baseline NRS-BP, mean ± SD	7.1 ± 2.6	6.8 ± 2.2	0.45
Baseline NRS-LP, mean ± SD	6.7 ± 3.0	6.7 ± 2.6	0.89
Baseline EQ-5D, mean ± SD	0.56 ± 0.23	0.51 ± 0.23	0.09
>2-yr follow-up rate, n (%)	94 (90.4)	93 (91.2)	0.84

ASA = American Society of Anesthesiologists.
Boldface type indicates statistical significance.

Furthermore, a systematic review of retrospective studies found no reduction-related clinical benefits in studies including patients with isthmic spondylolisthesis.[19] As for high-grade spondylolisthesis, a recent meta-analysis observed that slip reduction was associated with a greater overall improvement in ODI compared with in situ fusion.[16] For degenerative spondylolisthesis, Kawakami et al. observed an association between listhesis reduction

TABLE 2. Operative data for patients undergoing surgery for grade I lumbar spondylolisthesis

	Reduced (n = 104)	Not Reduced (n = 102)	p Value
EBL in ml, mean ± SD	198.0 ± 145.4	226.5 ± 235.0	0.31
Op time in mins, mean ± SD	203.3 ± 76.2	193.0 ± 67.5	0.31
Length of hospitalization in days, mean ± SD	3.2 ± 1.5	3.2 ± 1.7	0.92
Discharge disposition			
Home or home health care, n (%)	99 (95.2)	93 (91.2)	0.25
3-mo readmission, n (%)	1 (1.0)	1 (1.0)	0.49
24- to 36-mo reop, n (%)	4 (3.8)	5 (4.9)	0.97
30-day complications, n (%)	6 (5.8)	4 (3.9)	0.77

EBL = estimated blood loss.

and improved clinical outcomes.[14] However, our present investigation—representing a much larger sample size of patients and multiple surgeons' experiences across the United States—failed to observe an association between degenerative spondylolisthesis reduction and long-term clinical outcomes. Indeed, the need for reduction in patients undergoing surgery for degenerative spondylolisthesis remains unclear.

Spondylolisthesis reduction is not trivial, as reduction maneuvers may be associated with surgical complications. For instance, increased index-level stress during reduction may be associated with screw loosening and pullout[17,18] for unclear clinical benefit. However, we did not observe any complications related to instrumentation failure in either cohort. Moreover, the similar cumulative reoperation rates observed presently suggests that spondylolisthesis reduction was not associated with significant adverse effects. With modern techniques, including teriparatide treatment[45–47] and methylmethacrylate screw augmentation,[48–50] surgeons may gain additional confidence using reduction techniques in osteopenic or osteoporotic populations. Further contemporaneous studies may shed light on the modern complication profile associated with listhesis reduction.

One explanation for the inconsistent clinical findings associated with listhesis reduction is the heterogeneity of populations and surgical techniques across the multiple prior single-center investigations on the topic. Herein lies the strength of our study, as it represents a multicenter registry effort with standardized reporting procedures, data elements, and inclusion criteria. By using a registry designed specifically for Meyerding grade I degenerative lumbar spondylolisthesis, we reduce the variability of numerous disease processes while also maintaining a large

TABLE 3. Outcomes for patients undergoing surgery for grade I lumbar spondylolisthesis

	Reduced (n = 104)	Not Reduced (n = 102)	p Value
ODI			
MCID	92	93	0.64
Reached	70 (76.1)	68 (73.1)	
Not reached	22 (23.9)	25 (26.9)	
Score at 24 mos, mean ± SD	16.0 ± 17.8	21.4 ± 20.5	0.05
Change in score, mean ± SD	–29.0 ± 18.9	–28.5 ± 19.9	0.87
NRS-BP			
Score at 24 mos, mean ± SD	3.1 ± 3.1	3.2 ± 3.0	0.76
Change in score, mean ± SD	–4.1 ± 3.4	–3.7 ± 3.2	0.37
NRS-LP			
Score at 24 mos, mean ± SD	2.2 ± 3.1	2.2 ± 2.9	0.93
Change in score, mean ± SD	–4.5 ± 4.0	–4.5 ± 3.6	0.98
EQ-5D			
Score at 24 mos, mean ± SD	0.80 ± 0.17	0.76 ± 0.22	0.16
Change in score, mean ± SD	+0.22 ± 0.27	+0.24 ± 0.26	0.61
NASS satisfaction score, n (%)	92	90	0.78
1	69 (75.0)	63 (70.0)	
2	15 (16.3)	17 (18.9)	
3	1 (1.1)	7 (7.8)	
4	7 (7.6)	3 (3.3)	

TABLE 4. Association between reduction of listhesis and 24-month outcomes after surgery for grade I lumbar spondylolisthesis

24-Mo Outcome	Adjusted β Coefficients (95% CI)*	p Value
ODI change	–1.1 (–6.4 to 4.1)	0.67
NRS-BP change	–0.3 (–1.2 to 0.6)	0.53
NRS-LP change	0.1 (–1.0 to 1.1)	0.90
EQ-5D change	–0.002 (–0.06 to 0.05)	0.94
	Adjusted OR (95% CI)*	p Value
ODI MCID	1.2 (0.6 to 2.6)	0.58
NASS satisfaction	1.0 (0.5 to 1.9)	0.92

β coefficients for change scores are reported such that a negative value for ODI, NRS-BP, and NRS-LP and a positive value for EQ-5D represent superior outcomes at 24 months. ORs are reported such that an OR < 1.0 for NASS satisfaction represents greater satisfaction at 24 months.
* Multivariable models adjusted for factors with p < 0.20 on univariate comparisons of those with and without reduction of listhesis, including age, smoking status, depression, use of interbody graft, baseline ODI, baseline EQ-5D, average baseline millimeters of listhesis, and dynamic listhesis at baseline.

TABLE 5. Association between change in listhesis in millimeters (treated as a continuous variable) and 24-month outcomes after surgery for grade I lumbar spondylolisthesis

24-Mo Outcome	Adjusted β Coefficient (95% CI)*	p Value
ODI change	0.3 (–0.6 to 1.2)	0.53
NRS-BP change	0.1 (–0.1 to 0.2)	0.45
NRS-LP change	0.05 (–0.1 to 0.2)	0.61
EQ-5D change	0.002 (–0.01 to 0.01)	0.75
	Adjusted OR (95% CI)*	
ODI MCID	0.9 (0.8 to 1.1)	0.37
NASS satisfaction	1.0 (0.9 to 1.1)	0.90

β coefficients for change scores are reported such that a negative value for ODI, NRS-BP, and NRS-LP and a positive value for EQ-5D represent superior outcomes at 24 months. ORs are reported such that an OR < 1.0 for NASS satisfaction represents greater satisfaction at 24 months.
* Multivariable models adjusted for factors with p < 0.20 on univariate comparisons of those with and without reduction of listhesis, including age, smoking status, depression, use of interbody graft, baseline ODI, baseline EQ-5D, average baseline millimeters of listhesis, and dynamic listhesis at baseline.

sample size for one specific pathology: degenerative spondylolisthesis.

There are limitations to our study. First, this is a retrospective analysis of a prospective registry and holds the associated limitations. Second, as a registry study, we could not control for surgical decision-making or operative technique. Although there were data for each enrollment site, there was no granularity in identifying specific surgical preferences for each surgeon in this study. Specifically, we are unable to retrospectively adjudicate whether observed reductions were actively pursued with reduction techniques or incidentally induced by patient positioning or interbody graft placement. This may have introduced a selection bias, and the data should be interpreted with this caveat. Third, as a nonrandomized study, patients undergoing listhesis reduction versus no reduction differed in several baseline characteristics. However, we attempted to adjust for several of these baseline differences using multivariable analyses. Fourth, not all patients in our registry had postoperative radiographs to analyze. Because we used complete case analysis—and selected only patients having pre- and postoperative radiographs for inclusion—it is important to recognize that this represents a selected sample (i.e., selection bias), and the results should be interpreted accordingly. Furthermore, although our registry contains multiple radiographic parameters (e.g., millimeters of listhesis, dynamic listhesis, fusion status), it remains without other parameters, including sagittal and spinopelvic measurements and measurements of central, lateral recess, and foraminal stenosis. Future investigations may assess the interaction of these parameters on spondylolisthesis reduction and outcomes. Lastly, our prospective registry includes only patients with Meyerding grade I degenerative lumbar spondylolisthesis. Thus, our findings are not intended to be generalized to higher grades of spondylolisthesis. Despite these limitations, to our knowledge, this study represents the largest investigation that compares outcomes for patients with and without listhesis reduction after surgery for degenerative spondylolisthesis.

Conclusions

In an analysis of the prospective, QOD registry, we compared 24-month clinical outcomes for patients with and without spondylolisthesis reduction after single-segment surgery for grade I degenerative spondylolisthesis. There was no difference in 24-month outcomes for disability, back pain, leg pain, quality of life, patient satisfaction, and the ability to reach a minimum clinically important improvement in disability with or without reduction of spondylolisthesis. Additionally, the two cohorts shared similar outcomes for reoperation and radiographic fusion. These data fail to provide evidence that listhesis reduction is associated with improved long-term clinical outcomes following surgery.

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Supplemental Information

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