Patient Profiling Can Identify Spondylolisthesis Patients at Risk for Conversion from Nonoperative to Operative Treatment

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Background: Factors that are relevant to the decision regarding the use of surgical treatment for degenerative spondylolisthesis include disease-state severity and patient quality-of-life expectations. Some factors may not be easily appraised by the surgeon. In prospective trials involving patients undergoing nonoperative and operative treatment, there are instances of crossover in which patients from the nonoperative group undergo surgery. Identifying and understanding patient characteristics that may influence crossover from nonoperative to operative treatment will aid understanding of what motivates patients toward pursuing surgery.

Methods: Patients with degenerative spondylolisthesis who were randomized to nonoperative care in a prospective, multicenter study were evaluated over 8 years of enrollment. Two cohorts were defined: (1) the surgery cohort (patients who underwent surgery at any point) and (2) the nonoperative cohort (patients who did not undergo surgery). A Cox proportional hazards model, modeling time to surgery, was used to explore demographic data, clinical diagnoses, and patient expectations and attitudes after adjusting for other variables. A subanalysis was performed on surgery within 6 months after enrollment and surgery >6 months after enrollment.

Results: One hundred and forty-five patients who had been randomized to nonoperative treatment, 80 of whom crossed over to surgery, were included. In analyzing baseline differences between the 2 cohorts, patients who underwent surgery were younger; however, there were no significant difference between the cohorts in terms of race, sex, or comorbidities. Treatment preference, greater Oswestry Disability Index score, marital status, and no joint problems were predictors of crossover to surgery. Clinical factors, including stenosis, neurological deficits, and listhesis levels, did not show a significant relationship with crossover. At the time of long-term follow-up, the surgery cohort showed significantly greater long-term improvement in health-related quality of life ($p < 0.001$). The difference was maintained throughout follow-up.

Conclusions: Neurological symptoms and diagnoses, including listhesis and stenosis severity, did not predict crossover from nonoperative care to surgery. Attitudes toward surgery, greater Oswestry Disability Index score, marital status, and no joint problems were independent predictors of crossover from nonoperative to operative care. Certain demographic characteristics were associated with higher rates of crossover, although they were connected to patient attitudes toward surgery.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

Disclosure: Funding for SPORT (Spine Patient Outcomes Research Trial) was awarded by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) (U01-AR45444) and the Office of Research on Women's Health, the National Institutes of Health, the National Institute of Occupational Safety and Health, and the Centers for Disease Control and Prevention. The Multidisciplinary Clinical Research Center in Musculoskeletal Diseases is funded by NIAMS (P60-AR048094 and P60-AR062799). On the **Disclosure of Potential Conflicts of Interest** forms, which are provided with the online version of the article, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and "yes" to indicate that the author had a patent and/or copyright, planned, pending, or issued, broadly relevant to this work (<http://links.lww.com/JBJSOA/A43>).

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Degenerative spondylolisthesis is defined as the forward translation of 1 vertebra relative to another¹⁻³. Most commonly seen in women over the age of 50 years, degenerative spondylolisthesis is frequently asymptomatic but may cause neurogenic claudication associated with spinal stenosis⁴.

Nonoperative treatment, typically involving physical therapy and nonsteroidal anti-inflammatory drugs (NSAIDs), is widely accepted as the most common first line of care for degenerative spondylolisthesis. The decision to proceed with operative or nonoperative treatment is made jointly by the surgeon and patient on the basis of the risks and benefits of treatment, symptom severity, treatment expectations, complication potential, and quality of life⁵. Decompression and fusion to stabilize the spondylolisthesis and relieve stenosis is commonly indicated for patients with degenerative spondylolisthesis⁶. However, distinguishing patients who would most benefit from operative treatment is frequently unclear. Accordingly, the evaluation of baseline patient characteristics as they relate to disease progression and treatment prognosis is essential in order to optimize clinical decision-making.

The relationship between surgical timing (immediate or delayed by initial nonoperative care) and the associated impact on patient outcomes is understudied. Villavicencio et al., in a recent study of patients undergoing transforaminal lumbar interbody fusion, found that shorter duration of symptoms was a significant predictor of better radicular pain resolution⁷. The clinical value of encouraging continued nonoperative treatment lies in the hope that symptomatic resolution can be achieved without the risk of surgery; however, this approach has inherent risk as well in that the long-term outcomes may be affected as a result of worsening of symptoms.

Few studies have evaluated the specific characteristics of patients who initially are assigned to nonoperative care and subsequently undergo surgery. In prospective randomized trials involving operative and nonoperative treatment, crossovers between treatment groups can be quite common⁸⁻¹⁰. These crossovers give a unique perspective on why patients undergo surgery with respect to timing, symptom severity, and quality-of-life considerations¹¹. In analyzing patients who initially pursue nonoperative management but subsequently move to surgical intervention, it is likely that certain baseline patient-related factors predispose the decision for or against surgery. Identifying and understanding parameters that may influence patient decision-making would aid surgeons in defining what patients consider to be their most important burden and in refining the treatment algorithm for spondylolisthesis.

The purpose of the present study of patients who had been randomized to nonoperative treatment of degenerative spondylolisthesis was to compare the profiles of patients who continued to receive nonoperative care with those of patients who instead crossed over to the operative group. Risk factors increasing the likelihood of treatment transition may uncover groups of patients who are most likely to cross over. Given the high cost associated with ineffective health care, characterizing patients who are at risk to cross over from nonoperative to

operative treatment may facilitate further understanding of the drivers of conversion to surgical intervention and potentially allow for more efficient patient counseling and more cost-effective treatment.

Materials and Methods

Study Design

The present study involved a retrospective review of the results of a prospective, randomized multicenter clinical trial (ClinicalTrials.gov NCT00000410). Patients from 13 participating U.S. sites were enrolled in the trial between 2000 and 2005. Patients were randomized to either nonoperative care or standard posterior laminectomy with or without bilateral single-level fusion (using iliac crest bone-grafting with or without instrumentation). Eligible patients who declined treatment randomization were invited to participate within the nonoperative study arm. Institutional review board approval was obtained at each participating site prior to patient enrollment.

Eligibility Criteria and Patient Groups

The present investigation included randomized patients ≥ 18 years of age who had had symptoms for at least 12 weeks (pseudoclaudication or radicular pain with associated neurological deficit or spinal stenosis at the level of listhesis [L3 to L4 or L4 to L5] with or without adjacent-level stenosis) and radiographically confirmed degenerative spondylolisthesis (degenerative forward slippage of the L3 vertebral body relative to the L4 vertebral body or the L4 vertebral body relative to the L5 vertebral body in the sagittal plane as seen on a lateral view). Primary analysis stratified patients into 2 cohorts: (1) the surgery cohort (patients who underwent surgery at any point) and (2) the nonoperative cohort (patients who continued to receive nonoperative treatment). Secondary analysis compared early-crossover patients (those electing surgery within 6 months after enrollment) with late-crossover patients (those electing surgery after receiving >6 months of nonoperative treatment). The 6-month cutoff was

TABLE I Surgery Rates by Time Period for Cohort Randomized to Nonoperative Treatment

Time Period	No. of Patients (N = 145)
6 wk	11 (8%)
3 mo	35 (24%)
6 mo	55 (38%)
1 yr	64 (44%)
2 yr	71 (49%)
3 yr	77 (53%)
4 yr	79 (54%)
5 yr	79 (54%)
6 yr	79 (54%)
7 yr	80 (55%)
8 yr	80 (55%)

TABLE II Patient Baseline Demographic Characteristics, Comorbidities, and Health Status Measures for Patients Randomized to Nonoperative Treatment, According to Treatment Received within 8 Years After Enrollment*

	Surgery Cohort (N = 80)	Nonoperative Cohort (N = 65)	P Value
Age (yr)	63.6 ± 10.7	68.1 ± 10.1	0.009
Female	53 (66%)	46 (71%)	0.69
Ethnicity: not Hispanic†	80 (100%)	64 (98%)	0.92
Race: white†	74 (93%)	56 (86%)	0.33
Education: at least some college	56 (70%)	49 (75%)	0.59
Marital status: married	63 (79%)	36 (55%)	0.005
Work status			0.75
Full or part-time	31 (39%)	22 (34%)	
Disabled	5 (6%)	5 (8%)	
Retired	35 (44%)	27 (42%)	
Other	9 (11%)	11 (17%)	
Compensation: any‡	5 (6%)	1 (2%)	0.32
BMI§	28.9 ± 5.2	29.2 ± 6.4	0.74
Smoker	7 (9%)	5 (8%)	0.94
Comorbidities			
Hypertension	34 (43%)	34 (52%)	0.31
Diabetes	9 (11%)	8 (12%)	0.95
Osteoporosis	3 (4%)	7 (11%)	0.18
Heart problem	12 (15%)	14 (22%)	0.42
Stomach problem	17 (21%)	10 (15%)	0.49
Bowel or intestinal problem	5 (6%)	3 (5%)	0.95
Depression	16 (20%)	13 (20%)	0.83
Joint problem	41 (51%)	44 (68%)	0.067
Other#	30 (38%)	21 (32%)	0.63
PROMs			
Time since most recent episode >6 mo	51 (64%)	36 (55%)	0.39
SF-36 scores**			
Bodily pain score	32.2 ± 18.7	35.5 ± 18.4	0.29
Physical functioning score	34.6 ± 21	33.9 ± 22.3	0.85
MCS score	49.9 ± 11.9	50.9 ± 11.1	0.58
ODI††	44.2 ± 15.4	40.3 ± 18.6	0.17
Stenosis Frequency Index‡‡	14.2 ± 5.2	13.8 ± 5.6	0.65
Stenosis Bothersomeness Index§§	15.1 ± 5.4	13.3 ± 5.5	0.063
Back Pain Bothersomeness##	4.1 ± 1.9	3.8 ± 1.9	0.36
Leg Pain Bothersomeness***	4.7 ± 1.7	4.3 ± 1.8	0.17
Satisfaction with symptoms: very dissatisfied	61 (76%)	38 (58%)	0.035
Problem getting better or worse			0.027
Getting better	3 (4%)	7 (11%)	
Staying about the same	23 (29%)	27 (42%)	
Getting worse	53 (66%)	29 (45%)	
Missing data	1 (1%)	2 (3%)	
Treatment preference			<0.001
Preference for nonoperative treatment	18 (23%)	44 (68%)	
Not sure	36 (45%)	10 (15%)	
Preference for surgery	26 (33%)	10 (15%)	

continued

TABLE II (continued)

	Surgery Cohort (N = 80)	Nonoperative Cohort (N = 65)	P Value
High expectation of being free of pain with nonoperative treatment†††	10 (13%)	14 (22%)	0.22
High expectation of being free of pain with surgery†††	49 (61%)	27 (42%)	0.028
Pseudoclaudication: any	67 (84%)	57 (88%)	0.66
Straight-leg-raising test or femoral-tension sign	16 (20%)	12 (18%)	0.98
Dermatomal pain radiation: any	67 (84%)	53 (82%)	0.90
Any neurological deficit	45 (56%)	39 (60%)	0.78
Reflexes: asymmetrically depressed	24 (30%)	20 (31%)	0.94
Sensory: asymmetric decrease	20 (25%)	19 (29%)	0.70
Motor: asymmetric weakness	24 (30%)	23 (35%)	0.61
Listhesis level			0.67
L3-L4	7 (9%)	8 (12%)	
L4-L5	73 (91%)	57 (88%)	
Stenosis levels			
L2-L3	7 (9%)	9 (14%)	0.48
L3-L4	34 (43%)	36 (55%)	0.17
L4-L5	77 (96%)	62 (95%)	0.87
L5-S1	5 (6%)	9 (14%)	0.21
Moderate or severe stenotic levels			0.15
None	2 (3%)	0 (0%)	
1	51 (64%)	33 (51%)	
2	23 (29%)	25 (38%)	
≥3	4 (5%)	7 (11%)	
Stenosis locations			
Central	72 (90%)	60 (92%)	0.85
Lateral recess	77 (96%)	59 (91%)	0.31
Neuroforamen	31 (39%)	27 (42%)	0.86
Stenosis severity			0.27
Mild	2 (3%)	0 (0%)	
Moderate	34 (43%)	23 (35%)	
Severe	44 (55%)	42 (65%)	
Spinal instability	8 (10%)	6 (9%)	0.90
Opioid use	32 (40%)	17 (26%)	0.11
Taking antidepressants	6 (8%)	3 (5%)	0.71
Taking NSAIDs	36 (45%)	29 (45%)	0.90
Had physical therapy	58 (73%)	39 (60%)	0.16
Had injection	46 (58%)	25 (38%)	0.035

*Patients were classified according to whether they received surgical treatment or only nonoperative treatment during the first 8 years after enrollment. Values in this table are expressed as the mean and the standard deviation or as the number of patients with the percentage in parentheses. †Race or ethnic group was self-assessed. Whites and blacks could be either Hispanic or non-Hispanic. ‡This category includes patients who were receiving or had applications pending for Workers' Compensation, Social Security compensation, or other compensation. §The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. #Other = problems related to stroke, cancer, fibromyalgia, chronic fatigue syndrome (CFS), posttraumatic stress disorder (PTSD), alcohol, drug dependency, lung, liver, kidney, blood vessels, nervous system, migraine, or anxiety. **The SF-36 scores range from 0 to 100, with higher scores indicating less-severe symptoms. ††The Oswestry Disability Index (ODI) ranges from 0 to 100, with lower scores indicating less-severe symptoms. †††The Stenosis Frequency Index ranges from 0 to 24, with lower scores indicating less-severe symptoms. §§The Stenosis Bothersomeness Index ranges from 0 to 24, with lower scores indicating less-severe symptoms. ##The Low Back Pain Bothersomeness Scale ranges from 0 to 6, with lower scores indicating less-severe symptoms. ***The Leg Pain Bothersomeness Scale ranges from 0 to 6, with lower scores indicating less-severe symptoms. ††††Patient expectation of being free of pain with surgery or with nonoperative treatment was dichotomized as "certain" or "big chance," "no chance," "small chance," or "moderate chance."

TABLE III Results of Cox Proportional Hazards Model for Variables Predicting Time to Surgery (Treatment Preference Involved)*

Variable	Hazard Ratio (95% CI)
Oswestry Disability Index (ODI) per point	1.01 (1.0-1.03)
Married versus not married	1.76 (1.01-3.07)
Had joint problem vs. no joint problem	0.63 (0.4-1.0)
Treatment preference	
Not sure vs. preference for nonoperative	3.75 (2.08-6.76)
Preference for surgery vs. preference for nonoperative	4.33 (2.31-8.12)

*Candidate predictor variables were age; sex; race; education; marital status; work status; body mass index; smoking status; hypertension; diabetes; osteoporosis; heart problem; stomach problem; depression; joint problem; time since most recent episode; patient's self-assessment of health trend; patient dissatisfaction with symptoms; expectation of being free of pain with surgery; expectation of being free of pain with nonoperative treatment; opioid use; injections; had physical therapy; taking antidepressants; taking NSAIDs; Low Back Pain Bothersomeness Index; Leg Pain Bothersomeness Index; Stenosis Bothersomeness Index; Oswestry Disability Index (ODI); SF-36 Bodily Pain, Physical Functioning, MCS, and Physical Component Summary (PCS); neurogenic claudication; pain on straight-leg raising or femoral-nerve tension sign; dermatomal pain radiation; any neurological deficit; asymmetric reflexes; asymmetric sensory decrease; asymmetric motor weakness; moderate or severe stenotic levels; stenosis location; stenosis severity; spinal instability; and treatment preference.

selected on the basis of the distribution of crossover times. Additional methodological information is provided in the original report outlining the details of the trial¹².

Outcomes Definitions

Patient outcomes were evaluated at all postoperative intervals (6 weeks, 3 months, 6 months, 1 year, 2 years, 3 years, and 4 years) with use of the following patient-reported outcomes measures (PROMs): Short Form 36 (SF-36) Bodily Pain Score, Physical Functioning Score and Mental Component Summary (MCS); Oswestry Disability Index (ODI); Stenosis Frequency Index; Stenosis Bothersome Index, Back Pain Bothersomeness Index; and Leg Pain Bothersomeness Index.

Risk Factors

Patient demographic characteristics, comorbidities, clinical characteristics, and expectations and attitudes toward surgery were assessed as risk factors for crossover from nonoperative to operative treatment of lumbar degenerative spondylolisthesis. Patient attitudes and expectations were evaluated with questions related to dissatisfaction with symptoms (options: "very dissatisfied with symptoms" or "not dissatisfied"), whether the problem was getting better or worse (options: "getting better," "staying about the same," or "getting worse"), treatment preference (options: "definitely prefer non-surgical treatment," "probably prefer non-surgical treatment," "not sure," "probably prefer surgery," or "definitely prefer surgery"), and whether the patient had a high expectation of being free of pain with surgery/nonoperative care (options: "yes" or "no"). The baseline PROMs were also assessed as risk factors for surgical crossover.

Statistical Analysis

Baseline demographic characteristics, comorbidities, expectations and attitudes toward surgery, and PROMs were assessed for normality. Parametric and nonparametric comparisons between the 2 groups were used as appropriate (e.g., chi-square tests for categorical variables and t tests for normally distributed continuous variables). To analyze risk factors for conversion

TABLE IV Mean Change in Scores Over 4 Years (Area Under the Curve), According to Treatment Received*

	Change in Score Compared with Baseline†		Treatment Effect‡	P Value
	Surgery (N = 80)	Nonoperative (N = 65)		
SF-36 scores§				
Bodily pain	34.2 ± 1.7	15.1 ± 1.8	19.1 (15, 23.2)	<0.001
Physical functioning	27.6 ± 1.9	9.2 ± 1.9	18.4 (14.5, 22.3)	<0.001
MCS	4.2 ± 0.8	0.8 ± 0.8	3.4 (1.6, 5.2)	<0.001
Physical component summary	11.7 ± 0.7	4.4 ± 0.7	7.3 (5.6, 9)	<0.001
Oswestry Disability Index#	-26 ± 1.4	-9 ± 1.4	-17 (-20.1, -13.9)	<0.001
Stenosis Bothersomeness Index**	-8.9 ± 0.5	-3.3 ± 0.5	-5.6 (-6.9, -4.3)	<0.001

*Scores are adjusted for age, sex, race, marital status, problem getting better or worse, treatment preference, and baseline score (for SF-36, Oswestry Disability Index, and Stenosis Bothersomeness Index). †The values are given as the mean and the standard error. ‡Treatment effect is the difference between the surgical and nonoperative mean change from baseline. The 95% CI is given in parentheses. §The SF-36 scores range from 0 to 100, with higher scores indicating less-severe symptoms. #The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less-severe symptoms. **The Stenosis Bothersomeness Index ranges from 0 to 24, with lower scores indicating less-severe symptoms.

Fig. 1

Line graph showing the mean changes in scores over 4 years (area under the curve), according to treatment received. Error bars represent the standard error of the mean.

from nonoperative to surgical treatment, a Cox proportional hazards model incorporating time to crossover was used. The final model selection was based on the Akaike information criterion (AIC).

The effect of surgical treatment on PROM scores was assessed with a mixed-effects longitudinal regression model using PROM score changes from baseline at each follow-up interval (6 weeks, 3 months, 6 months, 1 year, 2 years, 3 years, and 4 years). This model incorporated a random individual effect to account for correlation between repeated measurements within individuals. In these as-treated analyses, the treatment indicator was a time-varying covariate, allowing for

variable times of surgery. Follow-up times were measured from the time of surgery for the surgical group and the time of enrollment for the nonoperative group; baseline covariates were updated to the follow-up immediately preceding the time of surgery for surgical visits. This procedure has the effect of including all changes from baseline prior to surgery in the estimates of the nonoperative treatment effect and all changes after surgery in the estimates of the surgical treatment effect. The analyses were adjusted for age, sex, race, marital status, whether the problem was getting better or worse, treatment preference, and baseline scores (SF-36, ODI, and Stenosis Bothersomeness Index). Across the 4 years of follow-up, overall

TABLE V Mean Change in Scores Over 4 Years (Area Under the Curve), According to Surgery Within 6 Months After Enrollment*

	Change in Score Compared with Baseline†		Treatment Effect‡	P Value
	Surgery Within 6 Mo After Enrollment (N = 55)	Surgery >6 Mo After Enrollment (N = 25)		
SF-36 scores§				
Bodily pain	34.5 ± 3.2	31.2 ± 4.6	3.3 (−8.2, 14.8)	0.57
Physical functioning	27.5 ± 3	24.5 ± 4.5	3.0 (−8.4, 14.4)	0.61
MCS	4.1 ± 1.5	2.4 ± 2.1	1.7 (−3.6, 7)	0.52
Physical component summary	11.1 ± 1.3	10 ± 1.8	1.1 (−3.4, 5.6)	0.62
Oswestry Disability index#	−27.2 ± 2.4	−22.5 ± 3.5	−4.8 (−13.5, 3.9)	0.28
Stenosis Bothersomeness index**	−8.6 ± 0.8	−8.3 ± 1.1	−0.3 (−3.1, 2.5)	0.84

*Scores are adjusted for age, sex, race, marital status, problem getting better or worse, treatment preference, and baseline score (for SF-36, Oswestry Disability Index, and Stenosis Bothersomeness Index). †The values are given as the mean and the standard error. ‡Treatment effect is the difference between the mean change from baseline for patients with surgery within 6 months after enrollment and the mean change from baseline for patients with surgery >6 months after enrollment. The 95% CI is given in parentheses. §The SF-36 scores range from 0 to 100, with higher scores indicating less-severe symptoms. #The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less-severe symptoms. **The Stenosis Bothersomeness Index ranges from 0 to 24, with lower scores indicating less-severe symptoms.

comparisons of the “area under the curve” between groups were performed with use of the Wald test. Computations were performed with use of the SAS procedure PROC MIXED for continuous data (SAS, version 9.2; SAS Institute).

Hazard ratios are reported along with 95% confidence intervals (CIs). The level of significance was defined as $p < 0.05$ on the basis of a 2-sided hypothesis test, with no adjustments made for multiple comparisons.

Results

Surgery and Nonoperative Cohorts

Overall, 145 patients with degenerative spondylolisthesis (average age, 65.6 years; 68% female) were randomized to receive nonoperative treatment. Of these, 80 patients (55.2%) crossed over to surgical treatment during the 8 years of study enrollment; these patients constituted the surgery cohort (Table I). Of the 80 patients in the surgery cohort, 55 underwent surgery within 6 months after enrollment (early surgery subgroup) and 25 underwent surgery >6 months after enrollment (late surgery subgroup). The 65 patients who had been randomized to nonoperative treatment and remained in the nonoperative treatment arm for all 8 years of the study constituted the nonoperative cohort.

Crossover to Surgical Treatment

Analysis of the baseline demographic characteristics demonstrated that the patients in the nonoperative cohort were older than those in the surgery cohort (mean age, 68.1 compared with 63.6 years; $p = 0.009$) (Table I). There were no significant differences between cohorts in terms of race or sex. There also were no significant differences in terms of hypertension, diabetes, osteoporosis, heart problems, stomach problems, bowel or intestinal problems, depression, joint problems, or other comorbidities (Table II).

Patients who crossed over were more likely to be “very dissatisfied with symptoms” ($p = 0.035$) and were more likely

to have defined their preoperative treatment preference as “probably prefer surgery” or “definitely prefer surgery” ($p < 0.001$). Conversely, patients who did not cross over were more likely to have chosen “probably prefer non-surgery” or “definitely prefer non-surgery” ($p < 0.001$). There were no significant differences between the surgery and nonoperative cohorts in terms of the validated PROMs (SF-36 Bodily Pain score, Physical Functioning score, and MCS; ODI; Stenosis Frequency Index; Stenosis Bothersomeness Index; Back Pain Bothersomeness Index; and Leg Pain Bothersomeness Index) ($p > 0.05$ for all). All PROMs displayed normal distributions, with the exception of SF-36 Bodily Pain at 1 year, SF-36 Bodily Pain at 3 years, and SF-36 Physical Functioning at 4 years.

There were no significant differences between the surgery and nonoperative cohorts in terms of the degenerative spondylolisthesis-related diagnoses that were assessed (pseudo-claudication, neurological deficits, listhesis levels, stenosis levels, stenosis locations [central, lateral recess, foramen], stenosis severity, and spinal instability) ($p > 0.05$). In addition, baseline evaluations of previous treatment methods revealed no difference between the groups in terms of opioid use, antidepressant use, NSAID use, or physical therapy. However, compared with the nonoperative cohort, the surgery cohort had a greater rate of treatment with epidural or facet injections prior to crossing over to surgical treatment (58% versus 38%; $p = 0.035$).

The Cox proportional hazards model adjusted for concurrent demographic predictors of crossover via hazard ratios. Attitudes toward surgery (specifically, a preference for surgery as opposed to a preference for nonoperative treatment [hazard ratio, 4.33; 95% CI, 2.31 to 8.12] and a response of “not sure” as opposed to a preference for nonoperative treatment [hazard ratio, 3.75; 95% CI, 2.08 to 6.76]), greater ODI score (hazard ratio, 1.01 per point; 95% CI, 1.00 to 1.03), and marital status (hazard ratio, 1.76; 95% CI, 1.01 to 3.07) were the only independent predictors of crossover from nonoperative to operative

Fig. 2

Mean change in scores over 4 years (area under the curve), according to time to crossover. Early crossovers received surgery within 6 months after enrollment, and late crossovers received it >6 months after enrollment.

care, and joint problems (hazard ratio, 0.63; 95% CI, 0.40 to 1.00) predicted a lower risk of crossover from nonoperative to operative care (Table III).

Outcomes of Group That Crossed Over to Surgery Compared with Nonoperative and Immediate Surgery Groups

There were no baseline differences between the nonoperative and surgery cohorts in terms of PROM scores (Table II). At 1 year after enrollment, patients in the surgery group had greater improvement in scores relative to the nonoperative group on all health-related quality-of-life measures that were analyzed (Table IV, Fig. 1). Treatment effect, defined as the

mean difference in health-status scores between the nonoperative and surgery groups, was significant (all $p < 0.001$, Table IV). Analysis of treatment effect over time showed that the difference between the groups in health status scores stayed relatively constant over the 4 years of follow-up after enrollment (for the nonoperative group) or surgery (for the surgery group) (Table V).

Outcomes in Early-Surgery and Late-Surgery Subgroups

PROMs were evaluated for the early and late-surgery subgroups with the follow-up times based on the date of surgery (Table V, Fig. 2). While the early-surgery subgroup had a lower

baseline physical function score, this difference was no longer significant after 1 year (mean, 32.3 for the early-surgery subgroup versus 22.3 for the late-surgery subgroup; $p = 0.200$).

Discussion

Surgeons' motivations for recommending surgery are multifactorial, depending on the severity and progression of symptoms, the severity of findings on diagnostic imaging studies, concomitant comorbidities, expectations, and quality of life³. Patients play an equal role in the decision-making process. Their reasons to pursue or not to pursue surgery depend on their current physical and emotional condition and the prospects for their future condition. Studies examining reasons to pursue surgery traditionally have examined rates of surgery in different patient populations, but, to our knowledge, no study has shown a decision-making process examining nonoperative treatment patients who go on to seek surgical treatment¹³. Comparing these baseline considerations as they relate to the disease state is essential for optimizing surgeon decision-making.

In a landmark study, the Spine Patient Outcomes Research Trial (SPORT) examined patients undergoing surgical treatment for degenerative spondylolisthesis compared with conservative care¹⁰. SPORT established recommendations in favor of surgery, with superior outcomes compared with nonoperative care following both short and long-term follow-up; these findings appear to be potentially generalizable and consistent with those in studies involving national cohorts¹⁴. However, the number of crossovers was so great that intention-to-treat analysis was abandoned in favor of as-treated analysis. Evaluation of the predictors of crossover from nonoperative treatment to surgery indicated that those who crossed over were younger, were more often married, were less satisfied with symptoms, and had stronger preferences for surgery¹⁰. The current study examined the decision of those same individuals to seek surgery in greater detail by controlling for confounding factors for crossover and isolating early-stage and late-stage crossovers.

Cox proportional hazards models revealed that patient treatment preference, greater ODI score, marriage, and no joint problems were independent predictors of crossover to surgery. In contrast, diagnosis and clinical differences did not predict crossover to surgery. For example, the number of stenotic levels, stenosis severity, spinal instability, and listhesis levels did not influence time to crossover. Spondylolisthesis symptoms may come and go over long periods of time as inflammation subsides or the disc stabilizes, which can make determining the disease prognosis difficult. Other studies have similarly shown difficulty in using pathology, whether radiographically or clinically defined, for predicting patient symptomology^{15,16}. In fact, MacGregor et al., in a study involving 1,064 twins in total, found that psychological and lifestyle variables were strong predictors for back pain along with magnetic resonance imaging changes¹⁶.

Nonoperative interventions such as opioid use, antidepressant use, NSAID use, and physical therapy did not predict crossover. However, a higher injection rate was noted for patients who crossed over to pursue surgery. Further research is needed to quantify the effect of nonoperative measures on long-term out-

comes. Pearson et al. described better nonoperative treatment outcomes for patients with greater mobility at baseline¹⁷.

The original SPORT trial evaluated patients who had undergone nonoperative or operative treatment on an as-treated basis. The current study evaluated postoperative improvement in patients who crossed over from nonoperative to operative care. In the present analysis, patients randomized to the nonoperative group who received surgery, although delayed, fared significantly better than patients who continued to receive nonoperative treatment, at least until the 4-year time point.

In patients with stenosis who were enrolled in the SPORT trial, significant differences between operative and nonoperative treatment were found at 4 years but not at 8 years¹⁸. Eight-year results on the degenerative spondylolisthesis group have not been published, to our knowledge. However, the current study showed that at 4 years in the assigned-nonoperative cohort, patients who had crossed over to surgery fared significantly better than patients who stayed in the nonoperative group.

A secondary aim of the present study was to evaluate whether delayed surgery affected long-term outcomes. In our analysis of patients who crossed over within and after 6 months of nonoperative care, there was no difference in long-term outcomes according to PROMs.

We recognize that the present study had several limitations. Foremost, at baseline, patients may not have understood the randomized nature of the trial or may not have been committed to the trial but for some reason agreed to be randomized. Also, the surgical procedures that were offered to patients varied, including with regard to the inclusion and method of fusion, which could impact long-term outcomes.

Additionally, although randomized controlled trials (RCTs) can control for known and unknown confounding variables, it is important to recognize the role of confirmation bias as a confounder in the present study, especially as it relates to the randomization of patients into operative and nonoperative study arms. To reduce confirmation bias, the present investigation excluded patients who declined randomization as this refusal may be indicative of a preexisting preference toward a specific treatment arm. Despite this notion, the present investigation could not control for patients' preconceived surgical preferences. It is possible that patients who were randomized to nonoperative treatment possessed the preexisting view of surgery as a necessary intervention following the failure of nonoperative treatment, regardless of the likelihood of postoperative improvement. Such a preexisting conviction could predispose patients toward crossover to surgical intervention, effectively confounding the assessment of factors influencing patients to pursue surgery.

Current spine-specific clinical research is plagued by high operative crossover rates, resulting in a lack of viable control arms and making it extremely difficult to draw long-term outcome conclusions^{19,20}. Having a greater understanding of why patients cross over between treatment arms may help to control for crossover rates in future RCTs, thus providing higher-quality evidence. The present study serves as a good first step toward finding the best evidence for clinical action, especially in light of the marked lack of high-level evidence in spine-specific clinical

research. Still, future research should incorporate data from non-RCT sources, as RCTs can be resource-intensive and only applicable to a specific set of controlled conditions²¹.

In conclusion, neurological symptoms and diagnoses (including listhesis and stenosis severity) did not predict which patients who had been randomized to nonoperative care would cross over to surgery. The only patient baseline characteristics that significantly predicted crossover were the patient desire for surgery, greater ODI score, marital status, and having no joint problems. Patients with certain demographic characteristics crossed over at a higher rate, but crossover was contingent on their baseline attitudes toward surgery. ■

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