Title

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Operative versus nonoperative treatment for adult symptomatic lumbar scoliosis at 5-year follow-up: durability of outcomes and impact of treatment-related serious adverse events

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OBJECTIVE Although short-term adult symptomatic lumbar scoliosis (ASLS) studies favor operative over nonoperative treatment, longer outcomes are critical for assessment of treatment durability, especially for operative treatment, because the majority of implant failures and nonunions present between 2 and 5 years after surgery. The objectives of this study were to assess the durability of treatment outcomes for operative versus nonoperative treatment of ASLS, to report the rates and types of associated serious adverse events (SAEs), and to determine the potential impact of treatment-related SAEs on outcomes.

METHODS The ASLS-1 (Adult Symptomatic Lumbar Scoliosis–1) trial is an NIH-sponsored multicenter prospective study to assess operative versus nonoperative ASLS treatment. Patients were 40–80 years of age and had ASLS (Cobb angle ≥ 30° and Oswestry Disability Index [ODI] ≥ 20 or Scoliosis Research Society [SRS]–22 subscore ≤ 4.0 in the Pain, Function, and/or Self-Image domains). Patients receiving operative and nonoperative treatment were compared using as-treated analysis, and the impact of related SAEs was assessed. Primary outcome measures were ODI and SRS-22.

RESULTS The 286 patients with ASLS (107 with nonoperative treatment, 179 with operative treatment) had 2-year and 5-year follow-up rates of 90% (n = 256) and 74% (n = 211), respectively. At 5 years, compared with patients treated nonoperatively, those who underwent surgery had greater improvement in ODI (mean difference −15.2 [95% CI −18.7 to −11.7]) and SRS-22 subscore (mean difference 0.63 [95% CI 0.48–0.78]) (p < 0.001), with treatment effects (TEs) exceeding the minimum detectable measurement difference (MDMD) for ODI (7) and SRS-22 subscore (0.4). TEs at 5 years remained as favorable as 2-year TEs (ODI −13.9, SRS-22 0.52). For patients in the operative group, the incidence rates of treatment-related SAEs during the first 2 years and 2–5 years after surgery were 22.38 and 8.17 per 100 person-

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years, respectively. At 5 years, patients in the operative group who had 1 treatment-related SAE still had significantly greater improvement, with TEs (ODI −12.2, SRS-22 0.53; p < 0.001) exceeding the MDMD. Twelve patients who received surgery and who had 2 or more treatment-related SAEs had greater improvement than nonsurgically treated patients based on ODI (TE −8.34, p = 0.017) and SRS-22 (TE 0.32, p = 0.029), but the SRS-22 TE did not exceed the MDMD.

CONCLUSIONS The significantly greater improvement of operative versus nonoperative treatment for ASLS at 2 years was durably maintained at the 5-year follow-up. Patients in the operative cohort with a treatment-related SAE still had greater improvement than patients in the nonoperative cohort. These findings have important implications for patient counseling and future cost-effectiveness assessments.

W E are undergoing an unprecedented and accelerating global shift toward an older population.[1] Decreased natality, improved longevity, and the aging of larger cohorts from times of higher birth rates will produce a global population of more than 2 billion individuals at least 60 years of age by 2050.[2] Although the aging of the population is most advanced in high-income countries, its pace in many developing countries is faster than that of developed countries in the past.[2]

As the global population ages, there will be marked shifts in disease burden, including greater prevalence of musculoskeletal disorders.[3] In a recent review, Diebo and colleagues focused on the significant global impact and treatment disparities of adult spinal deformity (ASD).[4] ASD most commonly develops de novo as a result of degenerative changes and the aging process, but it may also arise from progressive changes in the setting of preexisting childhood or adolescent spinal deformities or following previous spine surgery.[4] ASD is highly prevalent, especially among older individuals, with up to 68% of those at least 70 years of age affected.[5] When symptomatic, ASD can have a profound impact on health-related quality of life, including pain, disability, and neurological deficits.[6] Adult symptomatic lumbar scoliosis (ASLS) is the most common form of symptomatic ASD.

Optimal treatment approaches for ASD remain unclear. Current reports suggest that nonoperative treatments offer limited benefit and may not improve quality of life.[7–11] Although surgical treatment may offer the potential for improved quality of life,[7,8,10–12] these procedures are costly and have high complication rates.[12–17] Few studies provide direct comparisons between nonoperative and operative treatment for ASD[7,8,10,11] and most are limited by retrospective designs, single-surgeon or single-center cohorts, relatively short or poor follow-up, and/or heterogeneous patient populations.[7,8,10,11,18]

The ASLS-1 (Adult Symptomatic Lumbar Scoliosis–1) study is a prospective multicenter trial with randomized and observational cohorts that was designed to compare the outcomes of operative and nonoperative treatment at primary presentation (no prior fusion) among patients with ASLS.[10] We have previously reported the short-term outcomes (2 years) for this trial.[10] The crossover rate from nonoperative to operative care in the randomized cohort was high (64%), which limited meaningful intention-to-treat analysis of the randomized cohort. As-treated analysis of the observational cohort demonstrated that surgery, although associated with high rates of complications, was superior to nonoperative care in improving health-related quality of life. However, the durability of both treatment approaches remains unclear, especially for operative treatment, because the majority of implant failures and nonunions present between 2 and 5 years after surgery.[19] Although nonoperative treatments cumulatively consume significant resources, operative treatment requires substantial upfront investment, from both economic and risk and recovery perspectives, that requires years of sustained benefit to be recouped. Longer outcomes of nonoperative versus operative treatment for ASD, which have not been previously reported, are critically needed to facilitate meaningful patient counseling and to aid health systems globally in effective allocation of healthcare resources for these increasingly common conditions.

We present an as-treated analysis of the ASLS-1 trial based on a combined cohort of randomized and observational patients with a 5-year follow-up. Our objectives were to assess the durability of treatment outcomes for operative versus nonoperative treatment of ASLS, to report the rates and types of associated serious adverse events (SAEs), and to determine the potential impact of treatment-related SAEs on outcomes.

Methods

Trial Design and Oversight

The ASLS-1 trial included randomized and observational cohorts of patients enrolled at 9 centers in North America.[10] Institutional review board approval was obtained at each site prior to enrollment. Data were collected by investigators, and the final submission was approved by all contributing authors. This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration number is NCT00854828.

Patient Population

Those eligible for trial inclusion were patients 40–80 years of age who had ASLS, which was defined as either idiopathic or de novo lumbar scoliosis with a Cobb angle ≥ 30° and an Oswestry Disability Index (ODI) score ≥ 20 or a Scoliosis Research Society (SRS)–22 subscore ≤ 4.0 in the domains of Pain, Function, and/or Self-Image. Only patients deemed to be surgical candidates were offered enrollment.

Exclusion criteria included excessive medical comorbidities, pregnancy, osteoporosis (femoral neck dual-energy x-ray absorptiometry t-score < −3.0), previous

thoracolumbar fusion, prior multilevel thoracolumbar decompression, high-grade spondylolisthesis, congenital spine anomalies, neuromuscular scoliosis, or a high risk of operative failure or morbidity. Enrollment began in April 2010 and was closed by July 2014.

Based on previous assessment of 2-year outcomes, the randomized cohort had a high rate of crossover that limited intention-to-treat analysis.[10] By the 2-year follow-up, 64% of patients randomized to nonoperative treatment had crossed over to surgical treatment. Therefore, for the present study, analyses were focused on a combined single cohort of observational and randomized arms (as-treated analysis).

Trial Interventions

In order to make results more generalizable, a "usual care" approach was used.[20,21] Surgical treatment included instrumented fusion with laminectomies for decompression in symptomatic spinal stenosis. In order to provide some degree of standardization of nonoperative care, a single nonoperative spine specialist at each site directed treatments. In general, back pain was treated with a combination of physical therapy, facet injections, NSAIDs, and judicious use of opioids. Nonoperative treatments for leg pain included activity modification, gabapentin, steroid injections, and physical therapy.

Trial Outcomes

The a priori primary outcomes were the ODI and SRS-22 subscore. Secondary outcomes included the numeric rating scale (NRS) scores for back and leg pain. The ODI ranges from 0 to 100, with higher scores reflecting greater disability.[22] The SRS-22 is a disease-specific (spine deformity) measure of health status with 5 domains (Function, Pain, Self-Image, Mental Health, and Satisfaction) that are each scored from 1 (worst) to 5 (best).[23] All domains of the SRS-22 excluding Satisfaction are summarized with a single score (SRS-22 subscore) that ranges from 1 to 5, with 5 corresponding to the best status. The NRS score ranges from 0 to 10, with 0 reflecting no pain and 10 corresponding to the worst pain. Outcome measures were assessed at 3-month intervals for the first 2 years and then at 6-month intervals until the last follow-up. The mean differences in outcomes at 5 years posttreatment (defined as the latest follow-up available in a window of 60–72 months) were evaluated as the primary measure of treatment effects (TEs). The TEs were also compared between 2-year and 5-year posttreatment outcomes for assessment of treatment durability.

Each site monitored patients for SAEs. As defined by the primary study sponsor (NIH),[24] SAEs were as follows: death or any event that was life-threatening, caused significant or permanent disability, resulted in new or prolonged hospitalization, or was unexpected but reasonably related to treatment intervention. Notably, SAEs represent more serious and less common events than complications not further specified. Sites classified SAEs as definitely, probably, possibly, or not related to treatment, and these classifications were centrally reviewed. The tendency was to err on the side of inclusion with regard to classifying

SAEs as being related to treatment. For example, although recent literature disfavors an association between use of recombinant human bone morphogenetic protein–2 and increased risk of neoplasm,[25] since the issue is not definitively settled, we included new cancer diagnosis as an SAE possibly related to operative treatment if recombinant human bone morphogenetic protein–2 was used. Only SAEs considered definitely, probably, or possibly related to treatment were used to assess for impact on outcomes.

Statistical Analysis

Baseline characteristics between patients who received operative treatment and those who only received nonoperative treatment were compared using the chi-square test or Fisher exact test for categorical variables and the Student t-test or Wilcoxon rank-sum test for continuous variables. An as-treated analysis was performed for the combined randomized and observational cohorts using generalized linear mixed models (GLMMs) controlling for baseline outcome measure scores and inclusion of treatment as a time-varying covariate. Baseline outcome measure scores were reset for the crossover group at the time of crossover, and outcome time was measured based on the time the patient was followed in the final as-treated group assignment. The noninferiority margin was defined as the minimum detectable measurement difference (MDMD; ODI 7.0, SRS-22 subscore 0.4).[26] Baseline characteristics, defined a priori as important outcome predictors or identified as associated with treatment in initial analyses, were considered for inclusion in the mixed models to account for potential confounding.[10] The GLMM used outcomes from all follow-up time points available, with missing data treated as missing at random. For patients in the operative group, the potential impact of treatment-related SAEs on the primary outcome measures was assessed using GLMMs.

To evaluate the statistical power available to detect TEs for operative versus nonoperative treatment in the combined randomized and observational cohorts, we calculated the power to detect significant differences in the mean change in SRS-22 subscore. Based on the initial study period, the mean change in SRS-22 subscore was 0.75 for the operative group and −0.12 for the nonoperative group, with a standard deviation of approximately 0.50. To provide a conservative estimate of statistical power at later time points, we assumed a smaller mean difference in SRS-22 subscore between treatment groups (0.30), a higher standard deviation (0.60), and a larger loss to follow-up of 40%. Under this scenario, we estimated 86% power to detect TEs.

All statistical analyses were performed using SAS software (version 9.4; SAS Institute). All tests were 2-sided and statistical significance was determined based on an alpha value of 0.05.

Role of the Funding Sources

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) division of the NIH had a role in study design, but not in data collection, data analysis, data interpretation, or writing of the report. The SRS
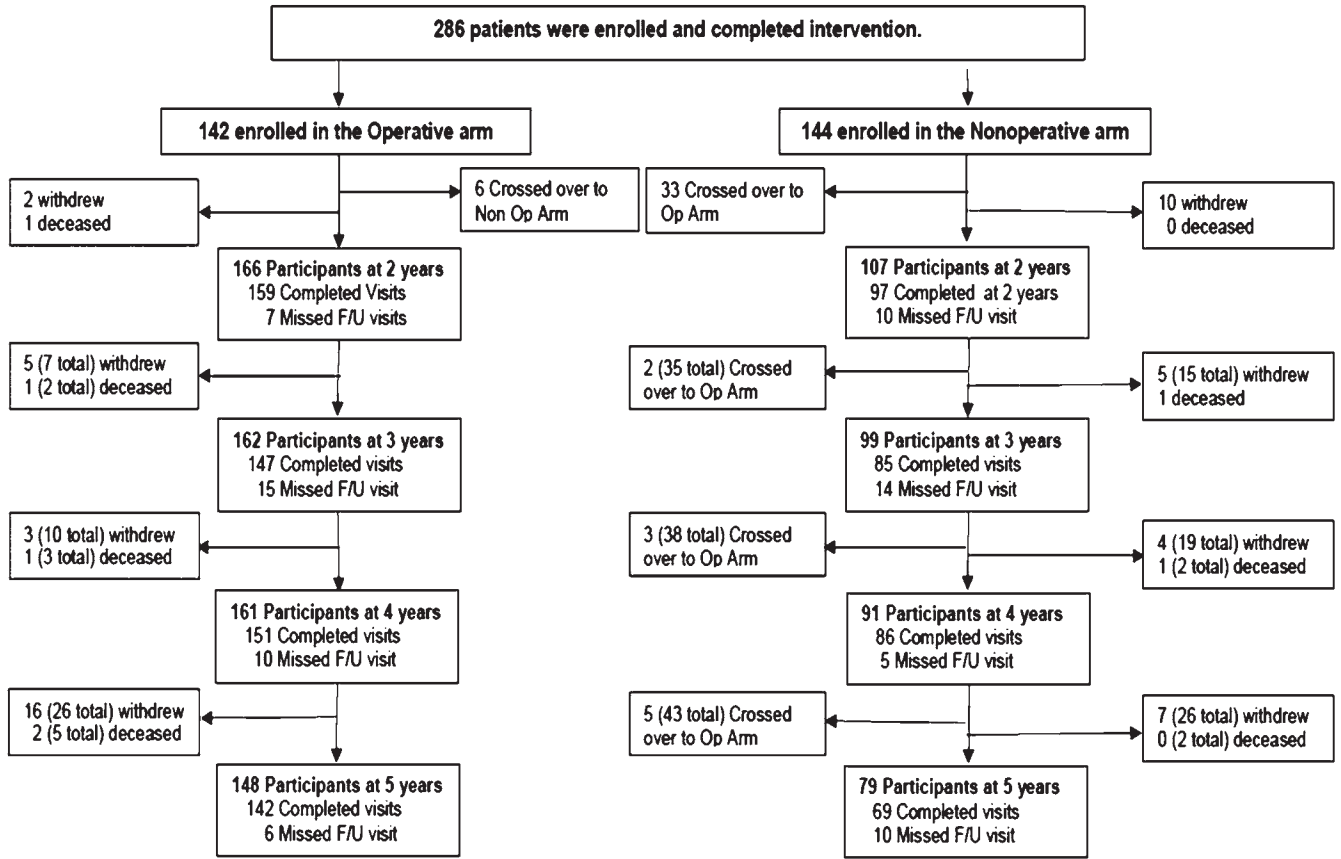
FIG. 1. Flow of participants from enrollment through 5-year follow-up (F/U, defined as the latest follow-up time point available within the window of 60–72 months), with randomized and observational cohorts combined. Enrollment arm (operative or nonoperative) reflects initial treatment approach, either as randomized or as selected for the observational cohort. Follow-up time points indicate the time since first treatment occurred. When patients crossed over to a different treatment, they were counted in the new treatment arm for all subsequent time points. Cumulative numbers of those who withdrew, died, or underwent surgery across follow-up time points are given in parentheses. Individuals who opted for surgery outside of the study were counted as withdrawals at the time of surgery. Withdrawal counts do not include deaths.

had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The senior author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Patient Population and Characteristics

A total of 286 patients were enrolled, including 63 in the randomized cohort and 223 in the observational cohort. Combining the randomized and observational cohorts, 142 patients initially enrolled with plans for operative treatment and 144 initially enrolled with plans for nonoperative treatment (Fig. 1). The follow-up rates for the combined operative and nonoperative cohorts at 2 years and 5 years were 90% (256/286) and 74% (211/286), respectively.

Baseline patient characteristics are summarized in Table 1 for the 179 patients who ever received operative treatment and the 107 patients who only received nonoperative treatment. The only demographic assessed that was significantly different between these 2 cohorts was the

presence of depression, anxiety, or other psychiatric disorder, with patients in the operative group having a higher prevalence (32.4% vs 17.8%, p = 0.0069). Patients treated operatively had modestly but significantly worse spinal deformity compared with nonoperatively treated patients. Operatively treated patients also had significantly worse pain, disability, and self-image compared with patients who only received nonoperative treatment.

Nonoperative and Operative Treatments

Nonoperative treatments included NSAIDs or gabapentin (89%), opioids (56%), physical therapy (89%), and steroid injections (39%), with percentages based on 149 patients who were managed nonoperatively for part or all of their time in the study. A total of 43 patients crossed over from nonoperative to operative treatment and were followed for operative outcomes (Fig. 1). Additionally, 4 had surgery outside the trial and were considered withdrawn from the study. One patient randomized to the surgical group decided to have surgery outside the trial and was also considered withdrawn. Six patients assigned to

TABLE 1. Baseline characteristics of 286 patients with ASLS by as-treated group

Patient Characteristic	Ever Received Op Treatment, n = 179	Only Received Nonop Treatment, n = 107	p Value*
Age, median (IQR)	60.2 (53.8, 66.6)	61.7 (53.9, 68.9)	0.2875
Female sex	158 (88.3%)	100 (93.5%)	0.1530
Race			0.0747
White	172 (96.1%)	96 (89.7%)	
Black	5 (2.8%)	9 (8.4%)	
Other	2 (1.1%)	2 (1.9%)	
Ethnicity			0.3526
Hispanic	3 (1.7%)	0 (0%)	
Non-Hispanic	169 (94.4%)	101 (94.4%)	
Did not report	7 (3.9%)	6 (5.6%)	
Education			0.1763
Less than high school	7 (3.9%)	2 (1.9%)	
High school diploma or graduate equivalent degree	45 (25.1%)	31 (29%)	
Technical or associate's degree	34 (19%)	16 (15%)	
Bachelor's degree	38 (21.2%)	34 (31.8%)	
Graduate degree	55 (30.7%)	24 (22.4%)	
Income per yr			0.3557
<$20,000	10 (5.6%)	7 (6.5%)	
$20,000–39,999	22 (12.3%)	9 (8.4%)	
$40,000–74,999	32 (17.9%)	28 (26.2%)	
$75,000+	86 (48%)	51 (47.7%)	
Did not report	29 (16.2%)	12 (11.2%)	
Tobacco use			0.7703
Current	11 (6.1%)	6 (5.6%)	
Former	57 (31.8%)	30 (28.0%)	
Never	111 (62.0%)	71 (66.4%)	
Body mass index, median (IQR)	26.2 (23.4, 30.1)	25.1 (22, 29.8)	0.1714
Osteopenia/osteoporosis			0.6846
None/does not apply	67 (37.4%)	45 (42.1%)	
T-score –1 to –1.5	51 (28.5%)	24 (22.4%)	
T-score –1.6 to –2.4	47 (26.3%)	28 (26.2%)	
T-score –2.5 or worse—or vertebral compression fracture	14 (7.8%)	10 (9.3%)	
Hypertension—uncontrolled or requiring medications			0.3278
No	104 (58.1%)	67 (62.6%)	
Yes, controlled w/ diet & exercise	8 (4.5%)	1 (0.9%)	
Yes, controlled w/ medication	66 (36.9%)	39 (36.4%)	
Yes, poorly controlled w/ medication	1 (0.6%)	0 (0%)	
Diabetes—uncontrolled or requiring medications			0.8065
No	169 (94.4%)	103 (96.3%)	
Yes, controlled w/ diet	1 (0.6%)	1 (0.9%)	
Yes, controlled w/ oral hypoglycemics	7 (3.9%)	2 (1.9%)	
Yes, insulin-dependent	2 (1.1%)	1 (0.9%)	
Depression/anxiety/psychiatric disorder	58 (32.4%)	19 (17.8%)	0.0069
Duration of back symptoms in mos, median (IQR)	48 (24, 132)	60 (12, 180)	0.6671
Duration of leg symptoms in mos, median (IQR)	32.5 (12, 72)	12 (5, 72)	0.1547
Baseline imaging findings			
Lumbar Cobb angle, median (IQR)	54° (43°, 67°)	49° (40°, 57°)	0.0301
Lumbar lordosis, T12–sacrum, median (IQR)	–37° (–49°, –25°)	–45° (–56°, –30°)	0.0087

TABLE 1. Baseline characteristics of 286 patients with ASLS by as-treated group

Patient Characteristic	Ever Received Op Treatment, n = 179	Only Received Nonop Treatment, n = 107	p Value*
Baseline imaging findings (*continued*)			
Sagittal balance, absolute value in mm, median (IQR)†	26.5 (2, 59)	20 (−11, 55)	0.0284
Coronal balance, absolute value in mm, median (IQR)†	−2 (−22, 18)	−6 (−18, 13)	0.4386
Pelvic incidence–lumbar lordosis mismatch, median (IQR)‡	18° (4°, 32°)	13° (1°, 28°)	0.0342
No. of stenosis levels			0.0012
0	82 (45.8%)	72 (67.3%)	
1	29 (16.2%)	14 (13.1%)	
2+	68 (38.0%)	21 (19.6%)	
Listhesis	164 (91.6%)	90 (84.1%)	0.0513
Baseline PROs, all median (IQR)			
ODI score	38 (26, 48)	30 (20, 40)	<0.001
SRS subscore	3.1 (2.7, 3.5)	3.4 (3.1, 3.7)	<0.001
SRS Pain	2.8 (2.3, 3.2)	3 (2.6, 3.6)	0.0014
SRS Function	3.2 (2.6, 3.8)	3.4 (3.2, 4)	<0.001
SRS Self-Image	2.8 (2.3, 3.2)	3.2 (2.7, 3.7)	<0.001
SRS Mental Health	3.8 (3, 4.2)	3.8 (3.4, 4.3)	0.4361
SRS Satisfaction	3 (2, 3.5)	3 (2.5, 3.5)	0.0536
NRS back pain	7 (5, 8)	5 (4, 7)	0.0032
NRS leg pain	4 (1, 6)	2 (0, 5)	0.0198
Mental component score	51.4 (41.8, 59.8)	50.3 (43.7, 58.3)	0.7545
Physical component score	32.9 (26.4, 39.9)	39.2 (29.2, 46.7)	<0.001

Values are expressed as either the number of patients (%) or the median (IQR).

* For categorical variables Fisher exact tests were used if one category included fewer than 5 people, and otherwise chi-square tests were used. For continuous variables Wilcoxon rank-sum tests were used when distributions were nonnormal, and otherwise Student t-tests were used.

† Information on sagittal and coronal balance was missing for 1 patient in the operative group because baseline films were done at an outside facility and did not include scales to permit linear measures.

‡ Information on pelvic incidence–lumbar lordosis mismatch was missing for 17 patients, because femoral heads were not visible on radiographs.

operative treatment crossed over to nonoperative treatment and were followed for nonoperative outcomes. On average, the operative time was 385 minutes, 10.9 vertebral levels were fused, and the estimated blood loss was 2066 mL.

Nonoperative Versus Operative Treatment Outcomes

Based on as-treated analysis, operative treatment was associated with greater improvement compared with nonoperative treatment at 5 years posttreatment in the ODI (adjusted mean difference −15.2 [95% CI −18.7 to −11.7]; p < 0.001) and SRS-22 subscore (adjusted mean difference 0.63 [95% CI 0.48–0.78]; p < 0.001) (Table 2 and Fig. 2A and B), with TEs that exceeded the MDMD for both primary outcome measures. Operative treatment was also associated with greater improvement compared with nonoperative treatment in back pain NRS score (adjusted mean difference −2.42 [95% CI −3.05 to −1.79]; p < 0.001) and leg pain NRS score (adjusted mean difference −1.17 [95% CI −1.83 to −0.51]; p < 0.001) (Table 2 and Fig. 2C and D). All SRS-22 domains were improved to a significantly greater degree with operative compared with nonoperative treatment at 5 years posttreatment. TEs favoring operative over nonoperative treatment remained at least as favorable

at 5 years posttreatment as the corresponding TEs at 2 years posttreatment across all of the patient-reported outcome (PRO) measures assessed (Table 2).

SAEs and Impact on Outcomes

Total SAEs (related and unrelated) for the patients in the operative and nonoperative groups are summarized in Table 3. SAEs that were classified as definitely, probably, or possibly related to treatment are summarized in Table 4. The incidence rates of related SAEs for surgically treated patients during the first 2 years and at 2–5 years following surgery were 22.38 and 8.17 SAEs per 100 person-years, respectively. During the first 2 years and between 2 and 5 years after surgery, there were 34 revisions in 28 patients and 40 revisions in 37 patients, respectively, with an overall total of 74 revisions in 55 patients (Table 5).

At 5 years after initial surgery, patients with 1 treatment-related SAE still had significantly greater improvement in primary outcome measures compared with patients treated nonoperatively, with TEs that exceeded the MDMD (ODI −12.2, SRS-22 subscore 0.53; p < 0.001 for both) (Table 6). Twelve patients who were treated operatively and who had 2 or more treatment-related SAEs had

TABLE 2. Effect of operative versus nonoperative treatment on patient outcomes

| | As-Treated Effect (op – nonop)* | | | |
| | 2 Yrs | | 5 Yrs† | |
PRO	Mean Difference (95% CI)	p Value	Mean Difference (95% CI)	p Value
ODI	−13.9 (−16.9, −10.8)	<0.001	−15.2 (−18.7, −11.7)	<0.001
SRS subscore	0.52 (0.40, 0.65)	<0.001	0.63 (0.48, 0.78)	<0.001
SRS Pain	0.64 (0.47, 0.81)	<0.001	0.79 (0.58, 1.01)	<0.001
SRS Function	0.51 (0.37, 0.65)	<0.001	0.60 (0.42, 0.79)	<0.001
SRS Self-Image	0.59 (0.42, 0.76)	<0.001	0.69 (0.49, 0.90)	<0.001
SRS Mental Health	0.23 (0.08, 0.39)	0.004	0.31 (0.14, 0.49)	<0.001
SRS Satisfaction	0.50 (0.28, 0.72)	<0.001	0.71 (0.44, 0.98)	<0.001
NRS back pain	−1.63 (−2.17, −1.08)	<0.001	−2.42 (−3.05, −1.79)	<0.001
NRS leg pain	−0.75 (−1.31, −0.18)	0.015	−1.17 (−1.83, −0.51)	<0.001

Estimates are from GLMMs accounting for the correlation among repeated measures using a heterogeneous autoregressive covariance matrix. Results are adjusted for the baseline value of each outcome. All models are also adjusted for these baseline characteristics: age, body mass index, depression/anxiety/psychiatric disorder, lumbar Cobb angle, lumbar lordosis, stenosis levels, education, osteoporosis, SRS subscore, ODI, NRS back pain, and physical component score.

* Data reported for the 2- and 5-year time points represent those subjects who spent 2 and 5 years in that specific treatment group (operative or nonoperative), not necessarily time from enrollment.

† Defined as the latest follow-up time point available within the window of 60–72 months.

significantly greater improvement compared to the nonoperative group based on ODI (TE −8.34, p = 0.017) and SRS-22 (TE 0.32, p = 0.029), but the SRS-22 TE did not exceed MDMD.

Discussion

ASD is a highly prevalent and impactful disease, especially among the rapidly expanding elderly population. Primary treatment options for ASD can be broadly grouped into nonoperative and operative approaches. Although these 2 approaches differ substantially with regard to invasiveness, recovery, and cost, it remains unclear whether one provides better benefit than the other, and whether treatment benefits are durable. The numbers of patients seeking treatment for symptomatic ASD will markedly increase over the decades ahead, and the ability to appropriately counsel patients and allocate resources for their care will be a growing concern globally.[4,27]

The present study was designed to compare operative versus nonoperative treatment for ASLS, the most common form of ASD. The study results show that the significantly greater improvement in health-related quality of life with operative treatment versus nonoperative treatment observed in as-treated cohorts at 2 years is durably maintained at 5 years. This is important because the majority of implant failures and bony nonunions present between 2 and 5 years after surgery.[19] Patients who underwent operative treatment and those who had a single treatment-related SAE experienced only a limited impact on outcomes and maintained significantly greater improvement than did patients who only received nonoperative treatment. For the small subset of surgically treated patients who had 2 or more treatment-related SAEs, the TEs were more substantially reduced.

The length and rates of follow-up in the present study far exceed those of previously published reports on ASD. In addition, the present study was a prospective, non–industry-funded, multicenter trial that had a relatively homogeneous patient population, with a focus on ASLS that had not been previously surgically treated, and it was limited to patients at least 40 years of age. Currently only a few reports provide comparisons of operative and nonoperative treatment for ASD.[7,8,10,11,18,28,29] Bridwell and colleagues reported a series of patients with ASD treated operatively or nonoperatively based on a study group registry.[8] Although the investigators also noted greater improvement with surgery compared to nonoperative treatment, the follow-up was limited to 2 years, the patient population was very heterogeneous with regard to types of spinal deformities and history of previous surgical treatment, and their follow-up was poor, with 55% of the patients in the nonoperative cohort lost to follow-up before 2 years. Smith and colleagues also reported results from a study group registry, comparing patients with ASD treated operatively or nonoperatively.[11] They similarly noted improved outcomes with operative versus nonoperative treatment, but the study population was markedly heterogeneous with regard to types of spinal deformity, history of previous spine surgery, and patient age (18–84 years); follow-up was limited to 2 years; and the follow-up rate for patients in the nonoperative cohort was poor (55%). Acaroglu and colleagues also compared operative and nonoperative treatment for ASD based on a study group registry.[7] They noted better outcomes with operative treatment, but their follow-up was very short (1 year), follow-up rates were poor for patients in both the operative (49%) and nonoperative (59%) cohorts, and the study population included a very broad range of deformity types.

The ASLS-1 study design included both randomized and observational treatment arms. Although the advantages of randomized versus observational comparisons in terms of strong protections against confounding are well recognized, the challenges of randomization to surgery versus nonoperative care in this chronic painful condition were numerous. For example, for patients to be eligible for study enrollment in either randomized or observational
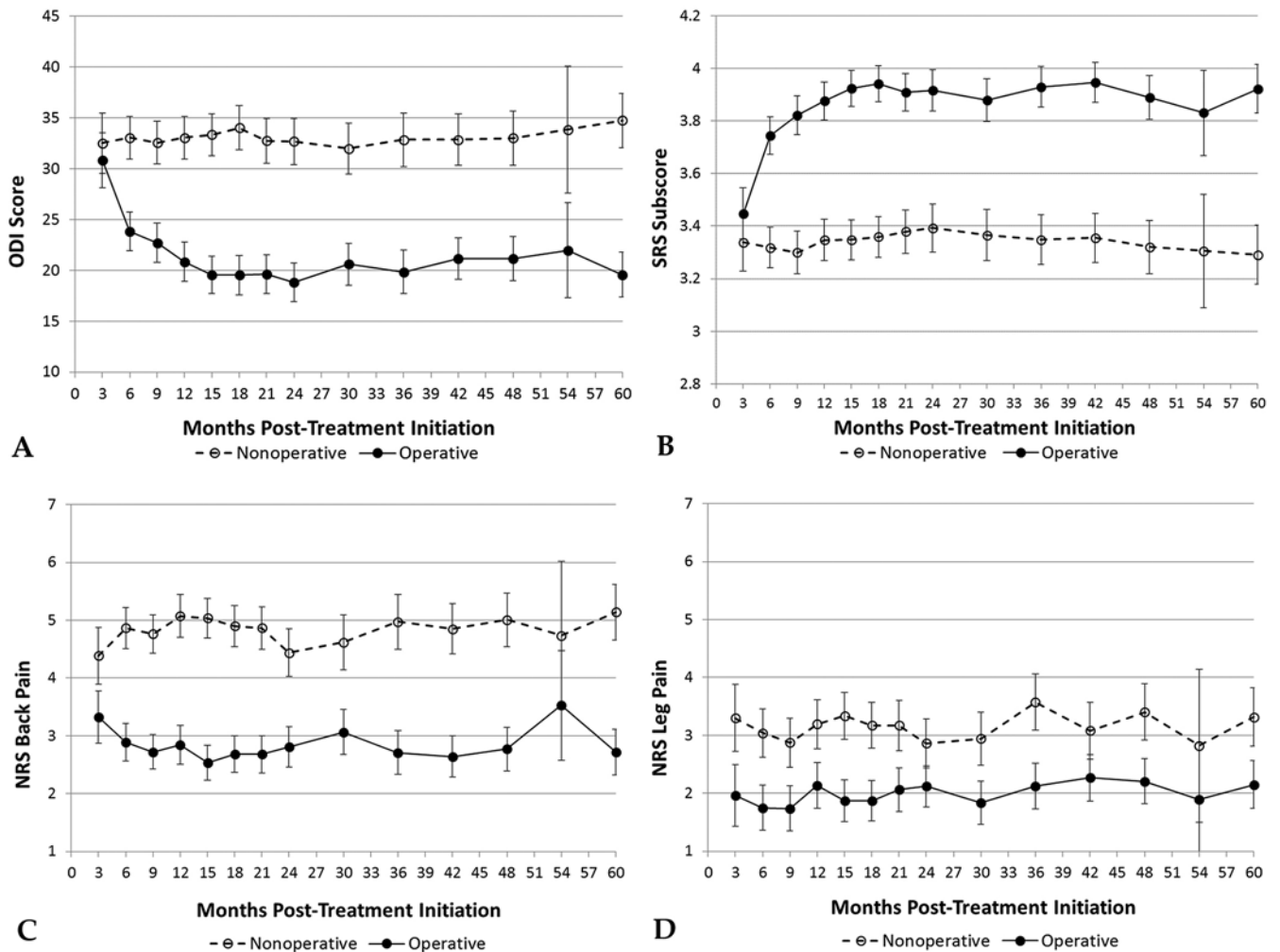
FIG. 2. Comparison of operative versus nonoperative treatment for PROs from as-treated analysis of the combined randomized and observational cohorts. Graphs show results from adjusted GLMMs for the ODI score (**A**), SRS-22 subscore (**B**), NRS score for back pain (**C**), and NRS score for leg pain (**D**). Note that baseline pretreatment values are not shown because the figures represent model-based estimated outcomes that adjust for baseline differences between the treatment groups. Due to these adjustments, these plots are optimized for comparisons between the treatment groups and not for comparisons between raw baseline means with 5-year outcomes within each treatment group.

arms, they had to be a candidate for surgery. Generally, before surgical treatment is considered for ASD, patients receive extensive courses of nonoperative treatments. Thus, the process of enrolling in the randomized arm necessitated convincing patients to elect for randomization that could result in being assigned to nonoperative treatment approaches they may have already tried. In addition, the significant invasiveness of the surgical treatments and the associated high rates of complications make the decision on whether to pursue treatment for ASD highly personal for the patient. Although randomization is a powerful tool to effectively assess many treatments, the challenges of implementing it in the present study demonstrate that its application to some pathologies and treatments may simply not be feasible and that the ability to randomize for study purposes may be an unrealistic expectation for some disease treatments. As a result, the as-treated analyses provided may represent the most rigorous evidence that is

feasible in this condition in which patients rarely exhibit equipoise with regard to such radically different treatment approaches.

The nonoperative treatment approach in the present study was based on usual care.[21] Although lack of a highly regimented approach to nonoperative care may be seen as a limitation, this strategy was intentionally chosen and was perceived as a strength, because the usual care approach much better approximates what actually occurs in practice, especially given that ASD pathology, symptoms, and responses to therapies are highly patient specific. In addition, given that many patients seeking surgical consultation already have some experience with nonoperative therapies, they often have biases in favor of or against specific nonoperative treatments. Based on this usual care approach, it appears that a subset of patients with ASLS can be maintained at similar pain and disability levels at the time of initial presentation with nonoperative treatments.

TABLE 3. All SAEs, including those related and not related to treatment, in the as-treated operative and nonoperative treatment groups

All SAEs	Time After Op Treatment					Time During Nonop Treatment					
	0–2 Yrs		2–5 Yrs*		Total	0–2 Yrs		2–5 Yrs*		Total	
	No.	Incidence Rate†	No.	Incidence Rate†	No.	No.	Incidence Rate†	No.	Incidence Rate†	No.	p Value‡
Spine (neuro deficits excluded)	30	8.50	39	6.64	69	1	0.38	0	0.00	1	<0.001
Neuro deficits related to intervention	16	4.53	1	0.17	17	0	0.00	0	0.00	0	0.002
Neuro deficits not related to intervention§	0	0.00	1	0.17	1	0	0.00	1	0.27	1	0.7761
Musculoskeletal (TL spine excluded)	21	5.95	39	6.64	60	12	4.58	10	2.73	22	0.0159
Pulmonary	12	3.40	12	2.04	24	3	1.15	1	0.27	4	0.0101
Gastrointestinal	11	3.12	5	0.85	16	12	4.58	9	2.45	21	0.0422
Cancer	4	1.13	7	1.19	11	3	1.15	9	2.45	12	0.2412
Cardiovascular	6	1.70	7	1.19	13	4	1.53	1	0.27	5	0.2931
Circulatory	4	1.13	4	0.68	8	2	0.76	3	0.82	5	0.9053
Genitourinary	8	2.27	6	1.02	14	6	2.29	2	0.55	8	0.7225
Death	1	0.28	4	0.68	5	0	0.00	2	0.55	2	0.5389
Miscellaneous	10	2.83	9	1.53	19	5	1.91	2	0.55	7	0.1774
Total	123	34.85	134	22.82	257	48	18.32	40	10.90	88	<0.001

Neuro = neurological; TL = thoracolumbar.

* The 5-year time point was defined as the latest follow-up available within the window of 60–72 months.

† Incidence rates are per 100 person-years.

‡ The p values are from Poisson models comparing SAE incidence rates between all time spent in the operative treatment group and all time spent in the nonoperative treatment group (to account for crossover). Exact tests were used when 0 counts were observed.

§ Not spine related (e.g., stroke and traumatic brain injury).

Thus, if a patient presents with ASLS and is satisfied with current spine-related health, it is reasonable to pursue nonoperative therapies and reassess as needed, with the understanding that although improvement is unlikely, deterioration is not inevitable. For patients not satisfied with current spine-related health who desire improvement, operative care should be considered.

The TEs for the NRS leg and back pain scores at 5 years may appear to be modest, but it is important to recognize that not all patients had back or leg pain, and just because the average differences at 5 years are not large does not mean that individual patients are not experiencing larger, more meaningful changes over time. In addition, the NRS scores, which are secondary outcome measures for this

TABLE 4. SAEs definitely, probably, or possibly related to treatment in the as-treated operative and nonoperative treatment groups

Related SAE	Time After Op Treatment					Time During Nonop Treatment					
	0–2 Yrs		2–5 Yrs*		Total	0–2 Yrs		2–5 Yrs*		Total	
	No.	Incidence Rate†	No.	Incidence Rate†	No.	No.	Incidence Rate†	No.	Incidence Rate†	No.	p Value
Spine (neuro deficits excluded)	30	8.50	39	6.64	69	1	0.38	0	0.00	1	<0.001
Neuro deficits	16	4.53	1	0.17	17	0	0.00	0	0.00	0	<0.001
Musculoskeletal (TL spine excluded)	1	0.28	0	0.00	1	0	0.00	0	0.00	0	<0.001
Pulmonary	8	2.27	2	0.34	10	0	0.00	0	0.00	0	<0.001
Gastrointestinal	5	1.42	0	0.00	5	1	0.38	2	0.55	3	<0.001
Cancer	3	0.85	5	0.85	8	0	0.00	0	0.00	0	<0.001
Cardiovascular	3	0.85	0	0.00	3	0	0.00	0	0.00	0	<0.001
Circulatory	4	1.13	0	0.00	4	0	0.00	0	0.00	0	<0.001
Genitourinary	3	0.85	0	0.00	3	1	0.38	0	0.00	1	<0.001
Death	1	0.28	1	0.17	2	0	0.00	0	0.00	0	<0.001
Miscellaneous	5	1.42	0	0.00	5	0	0.00	0	0.00	0	<0.001
Total	79	22.38	48	8.17	127	3	1.15	2	0.55	5	<0.001

* The 5-year time point was defined as the latest follow-up available within the window of 60–72 months.

† Incidence rates are per 100 person-years.

TABLE 5. Details of SAEs requiring revision spine surgery through 5-year follow-up*

SAE	No.	Incidence Rate†	No. w/ 2nd or Higher Revision
During index procedure hospitalization	6	3.37%‡	
Malpositioned screw (or minor neuro deficit)	1	0.56%‡	
Major neuro deficit	2	1.12%‡	1
Wound issues	3	1.69%‡	1
Within 90 days after index procedure	6	13.33	
Proximal junctional kyphosis/breakdown	3	6.67	
Major neuro deficit	1	2.22	
Wound issues	1	2.22	
CSF leak	1	2.22	
91 days–1 yr after index procedure	12	8.91	
Malpositioned screw (or minor neuro deficit)	2	1.49	
Major neuro deficit	1	0.74	
Proximal junctional kyphosis/breakdown	3	2.23	
Implant failure/pseudarthrosis	3	2.23	1
Other implant issues	3	2.23	
1–2 yrs after index procedure	10	5.64	
Proximal junctional kyphosis/breakdown	1	0.56	
Implant failure/pseudarthrosis	9	5.07	3
2–3 yrs after index procedure	17	9.77	
Proximal junctional kyphosis/breakdown	2	1.15	1
Implant failure/pseudarthrosis	13	7.47	5
Wound issues	1	0.57	
Other implant issues	1	0.57	
3–4 yrs after index procedure	9	5.35	
Proximal junctional kyphosis/breakdown	2	1.19	1
Implant failure/pseudarthrosis	6	3.57	1
Other implant issues	1	0.59	1
4–5 yrs after index procedure	14	4.88	
Proximal junctional kyphosis/breakdown	6	2.09	3
Implant failure/pseudarthrosis	8	2.79	1
Total revision procedures	74	7.50	19

* A total of 178 patients had 192 primary surgeries (14 were staged procedures). One patient randomized to the operative treatment group withdrew at intervention (i.e., had surgery outside of the study) and is not included in these numbers. A total of 55 patients had 74 revision procedures: 42 patients required 1 revision; 7 patients required 2 revisions; and 6 patients required 3 revisions. Revisions occurred during surgical admission or required an admission. Outpatient procedures were not included. Some events required 2 revisions (i.e., early neurological deficits or wound issues/incision and drainage). The 5-year time point was defined as the latest follow-up available within the window of 60–72 months.
† Incidence rates are per 100 person-years.
‡ For revisions occurring during the index hospitalization, instead of incidence rates, incidence proportions were calculated as number of revisions divided by the total number of patients in the operative treatment group.

TABLE 6. Comparison of primary outcomes of operatively treated versus nonoperatively treated patients with ASLS with and without a related SAE

5-Yr Follow-Up*	Average Change From Baseline (SE)	Difference in Average Change (95% CI)	p Value
ODI score, group			
Nonop	0.13 (1.40)	Reference	
Op w/ no SAE	−16.3 (1.49)	−16.4 (−20.3, −12.5)	<0.001
Op w/ 1 SAE	−12.0 (2.07)	−12.2 (−17.0, −7.29)	<0.001
Op w/ ≥2 SAEs	−8.21 (3.18)	−8.34 (−15.2, −1.51)	0.017
SRS-22 subscore, group			
Nonop	−0.02 (0.06)	Reference	
Op w/ no SAE	0.63 (0.06)	0.66 (0.50, 0.82)	<0.001
Op w/ 1 SAE	0.51 (0.09)	0.53 (0.33, 0.74)	<0.001
Op w/ ≥2 SAEs	0.29 (0.13)	0.32 (0.03, 0.60)	0.029

SE = standard error.
SAEs include only those that are classified as possibly, probably, or definitely related.
* Defined as the latest follow-up time point available within the window of 60–72 months. Data reported for the 5-year time point represent those subjects who spent 5 years in that specific treatment group (operative or nonoperative), not necessarily time from enrollment.

study, are not the best overall measures to be used for the assessment of benefit to the patient and decision-making compared with the ODI and SRS-22 subscore.

Although operative treatment provided significant improvement in health-related quality of life, it was associated with high complication rates (127 related SAEs in 179 patients in the operative cohort), consistent with the rates in previous reports.[8,11,12,15] In the present study, the incidence rates of treatment-related SAEs are reported in person-years in order to account for time actually spent within the treatment group based on length of follow-up and crossover between treatment groups. The most common related SAEs were revision procedures, with 55 patients undergoing a total of 74 revisions during the first 5 years after surgery. The most common indications for revision were related to implant failures, failure of bone healing, breakdown at the proximal junction of instrumentation, and wound issues. These are well-recognized challenges in adult deformity surgery.[30–42] A single related SAE had very limited impact on long-term outcomes, but with increased numbers of related SAEs, the impact on outcomes became stronger. It should be recognized that although many related SAEs may not impact the ultimate outcomes, these events often do impact patient recovery and increase the cost of care.

Limitations of the present study include the potential for selection, indication, and expertise bias to have influenced the results.[9] Because of these limitations, it is possible that the findings may not be generalizable to all settings beyond the contributing centers. In addition, the data do not permit conclusions based on an intention-to-treat analysis of the randomized cohort due to excessive crossover from nonoperative to operative treatment. Although the 5-year follow-up rates far exceed those previously

published, there were patients lost to follow-up who could have impacted outcome assessment. Last, although the operative and nonoperative patient groups were generally similar, there were baseline differences with the potential for residual confounding despite the use of GLMMs to adjust for measured differences.

Conclusions

This study provides an assessment of the durability of operative versus nonoperative treatment for ASLS based on a prospective multicenter trial. The significantly greater improvement in health-related quality of life with operative versus nonoperative treatment observed at 2 years is durably maintained at the 5-year follow-up. The length and rates of follow-up, as well as the completeness of data collection of the present study, far exceed those of previously published reports on ASD outcomes. Collectively, these findings should prove useful for patient counseling, future cost-effectiveness assessments, and ongoing efforts to improve the safety of patient care.

Acknowledgments

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Disclosures

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