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Preliminary 12-Month Safety and Efficacy Outcomes for the Treatment of Cervical Radiculopathy and Myelopathy with the STALIF C Integrated Interbody Fusion Device

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ABSTRACT

Anterior cervical discectomy and fusion (ACDF) has been widely utilized as the workhorse approach for the surgical treatment of cervical degenerative pathology. Minimal high-level evidence data exists on the efficacy and safety of integrated cage-screw implants. A prospective, non-randomized clinical study utilizing STALIF C-Ti® integrated cage-screw implants was performed in 145 patients. 12-month outcome scores demonstrated significant improvements in all patient reported outcome scores collected ($p<0.05$ for all), including NDI, VAS neck, VAS left arm, and VAS right arm. Patients receiving STALIF C-Ti integrated cage-screw implants demonstrated significant improvements in clinical outcome scores with minimal overall complication rate.

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Introduction

The anterior cervical discectomy and fusion (ACDF) approach initially described by Smith and Robinson has been widely utilized as the workhorse approach for the surgical treatment of cervical radiculopathy and myelopathy [1]. The addition of anterior cervical plating has been a more recent development, with the benefits of avoiding hard collar immobilization postoperatively, allowing more rapid mobilization, and has been shown to improve fusion rates in multilevel fusions [2,3]. However, anterior cervical plating has been shown to have multiple downsides relating to postoperative outcomes. Yang and colleagues' meta-analysis of standalone cages compared with anterior cervical plating for ACDF reported significantly decreased dysphagia rates at all time points of follow-up with zero-profile cages [4]. While uncommon, multiple studies have suggested anterior cervical plating as a possible contributing cause of esophageal injury [5,6]. Furthermore, Kim and colleagues reported anterior cervical plates placed within 5mm of the adjacent disc increased the risk of adjacent level ossification [7]. During revision surgical procedures, treatment of adjacent segment disease with ACDF using anterior cervical plates often requires additional surgical dissection and existing plate exposure with removal.

Integrated cage-screw implants, also known as "stand-alone" cages, allow for segmental stabilization without additional anterior cervical plating, addressing many of the drawbacks of anterior cervical plating. Multiple studies have supported comparable clinical outcomes of stand-alone cages compared with anterior cervical plating for the treatment of cervical myelopathy and radiculopathy [8-10]. A recent meta-analysis of 12 publications performed by Katsuura and colleagues found no difference in Neck Disability Index (NDI) postoperative score improvements between traditional ACDF and stand-alone ACDF [11]. Shousha and colleagues' single institution experience with 2,078 stand-alone cages reported an overall acceptably low reoperation rate, with an overall 2.07% early reoperations (within 90 days of index surgery) and 3.56% late reoperation (over 90 days) rate [12]. Despite the abundance of available data evaluating stand-alone

ACDF techniques, high-level, prospective data for integrated cage-screw implants is limited. This manuscript reviews the experience of the STALIF C-Ti (Centinel Spine® LLC, West Chester, PA) prospective, open label clinical study in regards to clinical and radiographic outcomes (Figure 1).

Figure 1: Clinical photo of the STALIF C® Ti-surfaced PEEK integrated cage-screw implants.

Methods

Preliminary results of the prospective, non-randomized STALIF C-Ti clinical study were reviewed. Final endpoint analysis was performed with 12-month data, although long term surveillance data continues to be collected and 24-month clinical data was available for reporting at the time of manuscript preparation. Primary objectives of the analysis include safety and efficacy endpoints, including adverse event monitoring, clinical outcome scores using VAS and NDI patient reported outcome scores, changes in neurological status, radiographic outcomes, and dysphagia.

Inclusion criteria for the study allowed males and non-pregnant females between 21 and 65 years of age to be enrolled. Patients with degenerative disc disease (DDD) at one or two contiguous levels between C2 and T1 were allowed and were required to have a minimum of 6 weeks of symptoms, have a minimum VAS (Visual Analog Scale) score of 40mm, and complete appropriate nonoperative management at the discretion of the treating surgeon. Exclusion criteria included osteoporosis, benign cervical spine tumors, malignancies (not including superficial skin cancers), active systemic or localized infection, traumatic fracture or injury at the operative levels, and spinal trauma resulting in neurological deficits. Furthermore, patients with central neurologic system disorders, terminal illnesses, history of drug abuse or chemical dependency, significant psychiatric comorbid conditions, allergies to polyetheretherketone (PEEK), Titanium, or Tantalum, and inability to comply with evaluation requirements were excluded.

169 patients were screened with 14 not meeting eligibility criteria and 8 patients withdrawing prior to surgical management, for a total of 147 patients included in the Intent-To-Treat analysis set. Two patients were excluded intraoperatively, with 145 patients receiving the STALIF C-Ti implant (Figure 2 & 3).

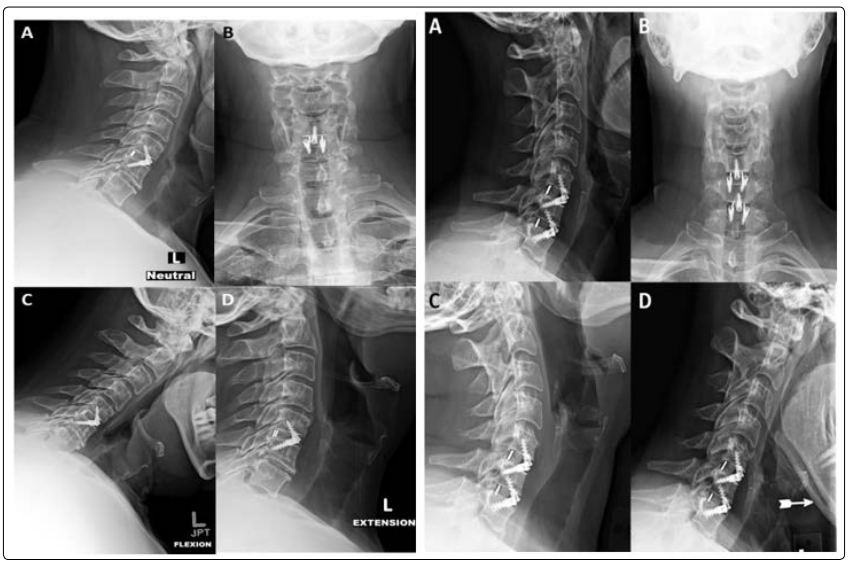

Figure 2: Postoperative x-rays of a single level STALIF C-Ti implant at C5-6, demonstrating upright lateral (image A), anteroposterior (image B), extension (image C), and flexion (image D) views.

Patient reported outcome data was available for 119 patients at the 12 months follow-up timepoint. Evidence-based minimally clinically important difference (MCID) relating to cervical spine pathology were reviewed to quantify the clinical significance of postoperative improvements in patient reported outcomes. MCID thresholds for NDI (Neck Disability Index) reported in the literature range from 7.5 to 18 [13-15]. Similarly, MCID thresholds for VAS (based on 100 point scale) reported in the literature range from 4.6 to 40 for VAS neck pain and 1.1 to 42 for VAS arm pain [1,16,17]. It is important to note the significant ranges in MCID can be attributable to the multiple methods used to calculate MCID as well as heterogeneity of cervical conditions studied in the existing literature. Therefore, we avoid attributing subjective clinical significance or relevance to patient reported outcomes unless the scores are in the upper range or exceed the MCID threshold ranges.

Continuous values at baseline and each follow-up, and the change from baseline were characterized using descriptive statistics (unadjusted mean values with 95% Confidence intervals). Counts and percentages characterize the categorical neurological status. A nominal two-sided paired t-test p-value was calculated to test the research hypothesis that the mean change from baseline was larger than zero. Graphical analysis included Paired Profiles depicting all individual changes from baseline in all subjects. All analysis was conducted use SAS Version 9.4.

Patient's preoperative and postoperative motor and sensory neurological exam scores were used to create a composite outcome score to descriptively assess global neurologic outcomes. Strength testing using Medical Research Council (MRC) grading system (0 to 5) and sensory testing (0- absent, 1- impaired, 2- normal) were reported for the bilateral upper extremities at all time points. Composite outcomes of motor, sensory, and global (motor + sensory) were created for each time point through summation of the exam scores. Patients' neurological scores were followed longitudinally from preoperative through all postoperative time points and postoperative scores were analyzed against their preoperative scores. Three possible outcomes were interpreted from longitudinal assessment of motor, sensory, and global scores: postoperative improvement from baseline, stable to baseline, or a decline from baseline.

The type and frequency of postoperative radiographic examinations obtained were left to the discretion of the operating surgeon. Surgeons who obtained postoperative flexion-extension x-rays were evaluated for fusion status. Twelve-month follow up radiographic images were available in 77 patients (98 levels), with 63 patients (80 levels) who had additional lateral flexion extension views. Radiographic data was reviewed by Medical Metrics, Inc. (Houston, TX, USA) for qualitative analysis and fusion assessment. Available flexion-extension views were analyzed for angular motion at the index surgical site, bridging bone at the interbody space, device subsidence, device migration, and device fracture. Device subsidence was reported as a binary outcome (yes versus no), with any radiographically discernible subsidence reported as the presence of subsidence. Device fracture was a derived composite endpoint if any evidence of hardware disassembly, fracture, or loosening was present.

Results

Average patient age was 50.11 years (SD 9.54 years) with 45% male subjects. Average patient weight was 196.3 pounds (SD 44.16) with an average BMI of 31.07 (SD 7.89). Baseline patient reported outcomes were collected prior to surgical management. Reported baseline patient reported outcomes are as follows: NDI: 52.5, VAS Neck: 71.93, VAS Right Arm: 51.45, and VAS Left Arm: 44.09. 70% of patients were employed, with 10% reporting "sick leave" or disability status, and 20% were unemployed. 21% of patients reported active smoking status preoperatively. One- and two-level procedures were performed in 70% and 30%, respectively, with an average surgery time of 72.7 minutes (SD 27 minutes). C5-6 and C6-7 were the most common treated single levels (35% and 24% of overall procedures, respectively), and C5-7 was the most common treated two-level procedure (23% of overall procedures).

All patient reported outcome scores demonstrated statistically significant improvements at 6 weeks follow-up and were maintained out to 12-month follow-up. Six weeks follow-up NDI decreased to 33.30 ($p<0.001$, 18.30-point decrease), VAS Neck decreased to 29.89 ($p<0.001$, 41.34-point decrease), VAS Right Arm decreased to 21.43 ($p<0.001$, 30.04-point decrease), and VAS Left Arm decreased to 18.73 (SD $p<0.001$, 26.6-point decrease). Twelve-month outcome scores maintained statistically significant improvement over baseline preoperative values. Statistically significant improvements ($p<0.001$) were maintained out to 12-month follow-up for all patient reported outcome scores: NDI 22.48 (29.77-point decrease), VAS Neck 22.48 (48.43-point decrease), VAS Right Arm 18.77 (32.48-point decrease), and VAS Left Arm 16.67 (26.93-point decrease). Furthermore, 12-month NDI and VAS neck pain scores exceeded the MCID threshold range and VAS arm pain scores were in the upper 50% of reported MCID threshold ranges, suggesting clinically significant improvements in the observed patient reported outcome scores (Tables 1-4).

Table 1: Neck Disability Index Value and Change Score Analysis

Value over time					Change from baseline*				
Visit	**N**	**Estimate**	**LB**	**UB**	**N**	**Estimate**	**LB**	**UB**	**p**
Pre-Op	145	52.50	49.79	55.20					
Week 06	122	33.30	29.64	36.95	122	-18.30	-21.68	-14.91	<.001
Month 03	121	25.24	21.32	29.15	121	-27.55	-30.92	-24.19	<.001
Month 06	116	23.43	19.64	27.23	116	-28.38	-32.01	-24.75	<.001
Month 12	120	22.48	18.62	26.34	120	-29.77	-32.97	-26.56	<.001
Month 24	24	16.75	9.89	23.61	24	-38.42	-46.30	-30.53	<.001

*Paired t-test p-value.
Source: Manuscript_Analysis.sas; Analyzed: 03SEP2020

Table 2: VAS Neck Value and Change Score Analysis

Value over time					Change from baseline*				
Visit	**N**	**Estimate**	**LB**	**UB**	**N**	**Estimate**	**LB**	**UB**	**p**
Pre-Op	145	71.93	68.70	75.17					
Week 06	122	29.89	24.96	34.83	122	-41.34	-46.81	-35.88	<.001
Month 03	119	25.01	20.21	29.81	119	-47.06	-52.38	-41.73	<.001
Month 06	116	26.44	21.32	31.56	116	-44.51	-50.17	-38.85	<.001
Month 12	120	22.48	17.63	27.34	120	-48.43	-53.86	-43.01	<.001
Month 24	24	18.75	7.68	29.82	24	-53.96	-65.13	-42.79	<.001

*Paired t-test p-value.
Source: Manuscript_Analysis.sas; Analyzed: 03SEP2020

Table 3: VAS Right Arm Value and Change Score Analysis

Value over time					Change from baseline*				
Visit	**N**	**Estimate**	**LB**	**UB**	**N**	**Estimate**	**LB**	**UB**	**p**
Pre-Op	145	51.45	45.85	57.05					
Week 06	122	21.43	16.25	26.61	122	-30.04	-36.78	-23.31	<.001
Month 03	119	18.82	13.85	23.80	119	-31.65	-38.52	-24.77	<.001
Month 06	116	17.01	12.34	21.67	116	-34.53	-40.78	-28.29	<.001
Month 12	120	18.77	13.68	23.85	120	-32.48	-39.53	-25.44	<.001
Month 24	24	10.04	2.30	17.78	24	-48.00	-63.99	-32.01	<.001

*Paired t-test p-value.
Source: Manuscript_Analysis.sas; Analyzed: 03SEP2020

Table 4: VAS Left Am Value and Change Score Analysis

Value over time					Change from baseline*				
Visit	**N**	**Estimate**	**LB**	**UB**	**N**	**Estimate**	**LB**	**UB**	**p**
Pre-Op	145	44.09	38.41	49.77					
Week 06	122	18.73	13.98	23.47	122	-26.61	-34.46	-18.77	<.001
Month 03	119	16.47	11.96	20.99	119	-27.93	-35.45	-20.42	<.001
Month 06	116	17.69	13.18	22.20	116	-25.83	-33.24	-18.41	<.001
Month 12	120	16.67	12.46	20.87	120	-26.93	-34.17	-19.70	<.001
Month 24	24	9.46	2.26	16.65	24	-36.21	-53.06	-19.35	<.001

*Paired t-test p-value.
Source: Manuscript_Analysis.sas; Analyzed: 03SEP2020

At 6 weeks postoperatively, 61.3% of patients improved and 29.0% maintained their global neurologic scores with 9.7% reporting a deterioration in neurologic scores. 12-month follow-up demonstrated an overall similar distribution with 54.2%, 37.5%, and 8.3% reporting an improved, maintained, and deteriorated global neurologic status compared to preoperative status, respectively. Evaluation of motor scores specifically revealed similar data at early and long-term follow-up. At 6 weeks postoperatively, 45.2% of patients improved and 46.8% maintained their neurologic scores with 8.1% reporting a deterioration in neurologic scores. 12-month follow-up demonstrated an overall similar distribution with 41.7% and 54.2%, reporting an improved and maintained neurologic status and 4.2% reporting a deterioration in neurologic scores compared to preoperative status. Neurologic motor score decline from baseline was uncommon at 12 months, with only 4.2% reporting 12-month deterioration from baseline. Of the reported motor score deteriorations, no severe deteriorations were found at 24 month followup. The lowest reported MRC score for any tested myotome at the 24 month timeframe was 4 (Tables 5 & 6).

Table 5: Neuro Overall Status at each visit compared to baseline

Descriptive Statistics for Neurological Overall (Motor + Sensory) Status* Primary Analysis Set (N= 145)										
	Week 06		**Month 03**		**Month 06**		**Month 12**		**Month 24**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Subjects with data	124	--	124	--	111	--	112	--	24	--
Improved	76	61.3%	75	60.5%	69	62.2%	71	63.4%	13	54.2%
Maintained	36	29.0%	35	28.2%	31	27.9%	29	25.9%	9	37.5%
Deteriorated	12	9.7%	14	11.3%	11	9.9%	12	10.7%	2	8.3%

*Defined as a change from baseline of +/- 1 in all Motor and Sensory tests collapsed across anatomical levels.
Source: Create Neuro 3-level.sas; Analyzed: 20SEP2020

Table 6: Neuro Motor Status at each visit compared to baseline

Descriptive Statistics for Neurological Overall (Motor + Sensory) Status* Primary Analysis Set (N= 145)										
	Week 06		**Month 03**		**Month 06**		**Month 12**		**Month 24**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Subjects with data	124	--	124	--	112	--	113	--	24	--
Improved	56	45.2%	52	41.9%	51	45.5%	53	46.9%	10	41.7%
Maintained	58	46.8%	60	48.4%	54	48.2%	55	48.7%	13	54.2%
Deteriorated	10	8.1%	12	9.7%	7	6.3%	5	4.4%	1	4.2%
*Defined as a change from baseline of +/- 1 in all Motor tests collapsed across anatomical levels. **Source:** Create Neuro 3-level.sas; Analyzed: 20SEP2020										

Of the 77 patients who had 12-month radiographic images available for review, 66 patients (83 levels) had adequate AP and lateral images to assess for device subsidence, migration, or fracture. Obscured anatomy limited review for one C6-7 and one C7-T1 integrated cage-screw implant and AP views were unavailable in 9 patients (13 levels). Device subsidence was identified in one patient (1-level) and no evidence of device migration or fracture was identified. Of the 66 patients (83 levels), 63 patients (80 levels) had adequate lateral flexion extension imaging to determine fusion status. Out of 80 levels, 39 levels (48.8%) demonstrated less than 2 degrees of motion on flexion extension imaging and 21 levels demonstrated clear evidence of radiographic bridging bone on lateral views. Further analysis of angular motion at the surgical levels found 72.5% and 82.5% of levels demonstrated less than 3 degrees and 4 degrees of motion, respectively.

Reported postoperative dysphagia decreased from 23.0% at week 6 to 3.3% at 12-month follow-up. Adverse events were reported in 51 subjects (34.7% of patients) with a total of 113 events reported. Unspecified pain was the most common reported adverse event, reported by 26 patients (17.7%). 5 serious adverse events (2.7%) and 3 device related adverse events (2.0%) were reported during the available follow-up. Serious adverse events included myocardial infarction, severe recurrent lumbar back pain, clinically symptomatic pseudarthrosis, lumbar compression fracture after syncopal fall, and internal injuries after a fall requiring blood transfusion (specific etiology unknown). Attributed device-related complications included incisional rash (of which the implant could not be ruled out as an allergic etiology), postoperative C5 palsy, and delayed union. Furthermore, two reoperations, both for the same patient, and three fractures were reported as adverse events.

Discussion

Anterior cervical discectomy and fusion has been widely considered the work-horse approach for cervical degenerative disc disease resulting in radiculopathy and/or myelopathy. Although the anterior cervical plate offers advantages of immediate stability and mobilization and improved fusion rates, stand-alone cervical cages were designed to potentially address issues of stability while avoiding the drawbacks of soft tissue damage, dysphagia, adjacent segment degeneration or ossification, and dysphonia. Although integrated cage-screw implants are an increasingly utilized option for ACDF, extensive high-quality data supporting the safety and efficacy of the implant is not available. We report 12-month safety and efficacy outcomes for the STALIF C-Ti integrated cage-screw implant, with outcomes that are comparable and consistent with traditional ACDF procedures with anterior cervical plating [10,18,19]. At 12-month follow-up, we report statistically significant improvements in all patient reported outcome metrics (NDI, VAS arm and VAS neck) beginning at 6 weeks postoperatively, and maintained out to 1 year follow-up. Furthermore, the rate of adverse events is comparable to traditional ACDF with anterior cervical plating [20].

Controversy continues to exist within published large systematic reviews on the clinical effectiveness of ACDF with anterior plating versus integrated cage-screw implants. A recent meta-analysis performed by Oliver and colleagues, reviewing 15 studies with 3 RCTs, found comparable NDI and VAS arm outcomes and dysphagia for traditional ACDF with anterior cervical plating compared to integrated cage-screw implants. However, they did report improved fusion rates (OR 1.98), lower subsidence rates (OR 0.31), and improved VAS neck scores (MD 0.59) with anterior cervical plating [21]. Conversely, a meta-analysis from Zhang and colleagues similarly reviewing 15 studies found no difference in clinical outcomes with JOA (Japanese Orthopedic Association) or NDI scores as well as no difference in fusion rate or subsidence. The integrated cage-screw implant did demonstrate lower rates of dysphagia, shorter surgical times, and shorter hospital stay [22]. Our publication supports the available literature, suggesting statistically significant and clinically meaningful improvements in clinical outcome scores with the STALIF C-Ti implant.

While understanding clinical and radiographic outcomes is common focus of research efforts, minimizing complications is critical to the evaluation of new techniques. One of the most common issues with anterior cervical plating is plate prominence and concern for dysphagia [23]. Dysphagia is a common occurrence after ACDF, with reported rates between 10% and 71% [23-25]. While dysphagia is commonly transient and mild in severity, occasionally it can result in severe symptoms requiring further interventions or feeding tube placement. Although recent literature is controversial in regards to dysphagia related to plate prominence of anterior cervical plates, the presence of the plate may be itself a risk factor for dysphagia and notably for high anterior cervical fusions [26]. Our data suggests a clinically acceptable low rate of postoperative dysphagia with the integrated cage-screw implant.

For one and two-level ACDF, biomechanical studies have suggested equal stability between anterior cervical plating and stand-alone cages, but multilevel constructs demonstrated improved stability with anterior cervical plating. Scholz and colleagues compared one-level instrumentation options comparing static and dynamic anterior cervical plates to stand-alone cage implants using non-destructive biomechanical testing in 24 human cadaver spines. They reported comparable biomechanical outcomes with no significant differences in range of motion in flexion/extension, lateral bending, or rotation between implants [27]. However, Paik and colleagues suggested multilevel stand-alone cage constructs

display inferior biomechanical properties compared to anterior cervical plating. One to three-level instrumentation was performed on human cadavers for biomechanical testing, and while stand-alone cage performed similarly to anterior cervical plating for one level instrumentation, two and three-level stand-alone cages demonstrated significantly greater range of motion in all tested planes [28]. It is important to acknowledge that despite findings from biomechanical laboratory testing, its relevance in regards to clinical outcomes is uncertain. Multiple studies have suggested comparable fusion rates for stand-alone cages compared with traditional ACDF with anterior cervical plating [22].

Significant controversy exists with radiographic fusion analysis after ACDF which may partially account for variability in published postoperative fusion rates. Oshina and colleagues reported on the various described methods, with reported methods widely ranging from presence of bridging bone between the endplates, absence of radiolucent lines between the graft and endplates, angulation between the spinous processes ranging from 0mm to 3mm, and angulation between endplates ranging from 0-4 degrees [29]. Using a more lenient cutoff of 4 degrees or less of angular motion to assess fusion status, we found that 82.5% of levels would meet this criteria. Using stringent radiographic criteria to assess for fusion status, the observed fusion rate was lower than previously reported literature fusion rates of 84%-96% [30-32]. While it is important to report short term radiographic data, it is unclear whether the observed fusion rate is clinically significant. Recent literature suggests that fusion can continue to proceed beyond the 2 year mark and delayed fusion can still result in excellent long term clinical outcomes. Lee and colleagues reported a 32.6% (29/83) pseudarthrosis rate after 1-3 level ACDF seen at 1 year postoperatively, but decreased to 9.6% (8/83) with 2 year radiographic follow up [33]. Lee and colleagues reported 9 delayed fusions at 2 years, noting 5/9 patients proceeded to union at 5 year follow up and 3 of 4 persistent nonunions continued to have excellent clinical results [34].

Several limitations are important to review in regards to this clinical study. No matched control arm is available for direct comparison of outcome data and only indirect comparisons to existing comparable literature on traditional ACDF can be made. While 12-month data is available and considered appropriate for primary endpoint analysis, multi-year follow-up would be required to meaningfully capture datapoints such as reoperations for pseudarthrosis or adjacent segment disease. Additionally, assessment of the clinical relevance of the statistically significant improvement in patient reported outcome scores is challenging, as the MCID reported ranges vary widely. Although our reported outcomes were at the upper 50% for VAS arm pain and exceeded MCID thresholds for NDI and VAS neck, attributing clinical significance to the data is limited by the heterogeneity of available MCID thresholds reported. Furthermore, reported neurologic outcomes out to mid-term follow up can be challenging to interpret. While the majority of patients demonstrated stable or improved motor scores, approximately 4% at 12 months reported a decline from baseline motor scores. Due to the summated quality of the global neurologic score and that the study is based on 1-2 level fusion procedures, there is likely a component of early adjacent segment disease with symptomatic radiculopathy at caudal or cephalad segments that is being factored in, in addition to target level complications (C5 palsy, postoperative radiculitis, etc.).

The incomplete dynamic radiographic follow up limits rigorous statistical analysis of the radiographic data, and instead we present our radiographic data in a descriptive manner to avoid selection bias. For future studies, we would recommend standardized postoperative dynamic radiographs across all study sites to eliminate selection bias. One important and notable distinction between this study and other literature reported fusion rates is our utilization of an independent, third party consulting firm for radiographic review in order to minimize observer bias. Furthermore, as the study's design is safety and efficacy, we plan to follow these patients out to at least 24 months with x-rays to assess for interval development of fusion or device-related complications. Despite the limitations to radiographic images available for direct review, the high rate of follow up for clinical outcomes and complication rate suggests that the STALIF C-Ti demonstrates an acceptable safety and efficacy profile in the treatment of cervical degenerative disc disease.

Conclusion

STALIF C-Ti integrated cage-screw implants demonstrated statistically significant and clinically meaningful improvement in all available patient reported outcome scores at 12 months. Although observed fusion rates were lower than reported literature comparisons, no radiographic device related complications and only 1 incidence of subsidence was noted. Furthermore, low rates of both dysphagia and serious/device related adverse events were reported at 12-month data analysis.

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