

## Observational Study

# Fantastic Four: Age, Spinal Cord Stimulator Waveform, Pain Localization and History of Spine Surgery Influence the Odds of Successful Spinal Cord Stimulator Trial

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**Background:** There is a dearth in our understanding of the factors that are predictive of successful spinal cord stimulator (SCS) trials and eventual conversion to permanent implants. Knowledge of these factors is important for appropriate patient selection and treatment optimization.

**Objectives:** Although previous studies have explored factors predictive of trial success, few have examined the role of waveform in trial outcomes. This study sought to establish the relationship of neuraxial waveform and related measures to trial outcomes.

**Study Design:** This study used a retrospective chart review design.

**Methods:** Data were retrospectively collected on 174 patients undergoing SCS trials upon institutional review board approval of the study protocol. Indications for SCS were: complex regional pain syndrome, failed back surgery syndrome with radicular symptoms, peripheral neuropathy, and axial low back pain. Descriptive statistics and logistic regression analyses were used to assess the association of demographic and clinical variables with SCS trial outcomes.

**Results:** The study population comprised 56% women, had a median age of 55 (interquartile range [IQR], 44-64), and 32 of 174 (18%) patients failed SCS trials. Individuals with successful trials ( $\geq 50\%$  pain relief) were significantly younger and had a median age of 54 years (IQR, 42-60) compared to those who failed SCS trials (median age 66 years; IQR, 50-76;  $P = .005$ ). Adjusting for age, gender, number of leads, pain category, and diagnoses: surgical history (odds ratio [OR] = 4.4; 95% confidence interval [CI], 1.3-15.8) and paresthesia-based tonic-stimulation (OR = 10.3; 95% CI, 1.7-62.0), but not burst or high frequency, were significantly associated with successful trials. Of note, the number of leads (whether dual or single), pain duration, characteristics, and category (nociceptive vs neuropathic) were not significant factors. An interaction between surgical spine history and lower extremity pain was significantly associated with a positive trial ( $P = .005$ ).

**Limitations:** This study was limited by its retrospective nature and focus on a patient population at a single major academic medical center.

**Conclusions:** Paresthesia-based tonic stimulation, age, and surgical history have significant effects on SCS trials. Prospective and randomized controlled studies may provide deeper insights regarding impact on costs and overall outcomes.

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**Keywords:** Pain duration, pain location, spinal cord stimulator trial, stimulator waveform, surgical history

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**M**ore than 100 billion health care dollars are spent every year on chronic back and limb pain, far exceeding the annual costs of heart disease, cancer, or diabetes (1-3). Emerging evidence continues to underscore spinal cord stimulation as an effective intervention for chronic back and limb pain (4). However, with the rise in costs of spinal cord stimulator (SCS) trials – costing approximately \$10,900 in US Medicare dollars (5-7) – there is increasing pressure from third-party payers to demonstrate appropriate allocation of this intervention for the right patient cohort (8,9). One of the major challenges in the field of neuromodulation is the dearth in our understanding of the factors that are predictive of successful trials and eventual conversion to permanent implants. Knowledge of these determinants is important as it informs appropriate patient selection and treatment.

To provide insight into patient selection, our group sought to address whether patient-specific vs treatment-related factors are associated with successful SCS trials. Recently, the development of novel SCS waveforms has made it possible to perform paresthesia-free (PF) vs paresthesia-based (PB) trials (10). Yet, it is not precisely clear to what degree SCS waveforms affect the success or failure of trials. To date, the rate of success vs failure of trials reported in the literature has been highly variable, ranging from 40% to greater than 80% (11,12). Part of this variability presumably stems from latent prognostic factors, which have been surmised to influence outcomes (12-14). Gaps in our understanding of how disease and treatment-related metrics influence trial outcomes have implications for the costs and permanent utilization of SCS as a treatment modality.

In this retrospective study, the authors sought to fill gaps in the literature by evaluating the role of treatment factors, such as novel SCS waveforms, which have not been previously studied. Based on our review of the literature, our working hypothesis was that treatment-related factors (type of waveform and trial duration) rather than patient-specific factors (for example, age, body mass index (BMI), smoking, etc.) would be significantly associated with successful SCS trials. In the context of the urgent need to find non-opioid interventions for patients with chronic pain (13), we anticipate that findings from this study could potentially impact utilization of SCS as a non-opioid treatment alternative (14). The findings from this study would serve as a basis for larger prospective and randomized trials that would provide guidance to clinicians and policymakers interested in utilization of SCS.

## **METHODS**

### **Data Collection**

This was a retrospective chart review of patients undergoing SCS trials at the Massachusetts General Hospital in the study period from August 1, 2015 through December 31, 2018. Using Current Procedural Terminology (CPT) codes and electronic health records, data were collected on all patients undergoing SCS trials using a pre-approved data collection form. Indications for SCS were: complex regional pain syndrome (CRPS), failed back surgery syndrome (FBSS) with radicular symptoms, peripheral neuropathy, radiculopathy, and chronic axial low back pain.

Inclusion criteria for SCS trials were: age  $\geq$  18 years, with chronic pain lasting 6 months or more, and failure of medical management or other more conservative treatment modalities. Typical exclusion criteria were applied including coagulopathy, systemic or local infections, and use of pacemakers. Psychological screening was performed in each patient before proceeding to the SCS trial.

### **SCS Trial**

Trial electrodes were placed in the epidural space using standardized protocols. Briefly, SCS leads were inserted between T12-L1 and L2-3 and threaded up to T8-12 to cover the lower extremities, while threading up to C5-T1 allowed for upper extremity coverage. Electrodes from multiple manufacturers were used (Boston Scientific Inc., Natick, MA; Medtronic Inc., Minneapolis, MN; Nevro Corp, Redwood City, CA; and Abbott St. Jude's Medical Inc., St. Paul, MN). Multiple waveforms (tonic, high frequency, burst) were utilized. Trial duration ranged from 3 to 14 days. Pain scores (1-11) were obtained prior to, and at the end of the trial period. Successful trials were defined as  $\geq$  50% pain relief based on the numeric rating scale (NRS-11).

### **Statistical Analysis**

Descriptive statistics and logistic regression analyses were used to assess the association of demographic and clinical variables with SCS-trial outcomes. Chi-square ( $\chi^2$ ) and Fisher exact tests were used to analyze the percent distribution and proportion of categorical covariates for each trial outcome (success vs failure). Missing data were assessed via maximum likelihood estimation models. All statistical analyses were performed via SAS Version 9.3 (SAS Institute, Inc., Cary, NC), using a 2-sided hypothesis test with probability of a type 1 error set at .05.

**RESULTS**

The study population comprised 174 patients undergoing SCS trials and 56% women, with a median age of 55 (interquartile range [IQR], 44-64). Of the total study population: 18% failed SCS trials (n = 32), 10% were on worker's compensation (n = 17), 53% had a history of spine surgery (n = 92), and on average, the study cohort had a mean pain duration of 17 years at the time of SCS trial. In addition, 35% (n = 61) were

obese (average BMI of 29), 20% (n = 34) had diabetes, 12% (n = 21) reported use of cannabinoids, and 26% (n = 45) and 43% (n = 75) reported cigarette and opioid use, respectively.

**Treatment vs Patient-Specific Measures**

Table 1 illustrates demographic and clinical variables stratified by SCS trial outcome. Individuals with successful trials ( $\geq 50\%$  pain relief) were significantly

Table 1. Factors associated with SCS trial success vs failure.

Parameter	Success ( $\geq 50\%$ Pain Relief) n = 142	Failure (< 50% Pain Relief) n = 32	P Value
Age in Years (mean $\pm$ SD)	53 $\pm$ 13	64 $\pm$ 14	< .001*
Gender (% male)	44	37.5	.56
Gender (% female)	56	62.5	
BMI (mean $\pm$ SD)	29 $\pm$ 6.0	28.5 $\pm$ 5.3	.66
Obese (BMI $\geq$ 30)			.32
Yes	54	9	
No	88	23	
Employed (% Yes)	28.9	25	.83
Worker's Compensation (% Yes)	10.6	6.3	.74
History of Diabetes (%Yes)	12.7	21.9	.26
History of Spine Surgery (%Yes)	54.9	37.5	.08
THC/Cannabinoids Use (% Yes)	12	12.5	1.0
Smoker (%Yes)	26.8	21.9	.66
Alcohol Use (% Yes)	45.1	34.4	.32
Opioid Use (% Yes)	67.6	68.8	1.0
Morphine Equivalent Dose (mean $\pm$ SD)	34.5 $\pm$ 47.4	46.6 $\pm$ 53.7	.24
Duration of Pain in Years (mean $\pm$ SD)	7.5 $\pm$ .34	9.3 $\pm$ 9.4	.32
Pain Diagnosis			.77
CRPS	15	3	
FBSS	59	10	
Axial low back pain	13	3	
Radiculopathy/Neuropathy	51	15	
Other (ischemic, refractory angina)	4	1	
Pain Category			.803
Nociceptive pain	27	5	
Neuropathic pain	115	27	
Allodynia (%Yes)	15.5	21.9	.42
Hyperalgesia (% Yes)	12	9.4	1
Pain Characteristics			.646
Burning	30	6	
Sharp/Stabbing/Shooting	50	9	
Throbbing/Aching/Dull	62	17	
Primary Pain Site			.032*
Upper Extremity only	11	3	
Lower Extremity only	122	22	
Upper + Lower Extremity	6	3	
Trunk	2	3	
Abdomen	1	1	

Table 1 (cont.). Factors associated with SCS trial success vs failure.

Parameter	Success ( $\geq 50\%$ Pain Relief) n = 142	Failure ( $< 50\%$ Pain Relief) n = 32	P Value
Adjuvant Medications			
Anticonvulsants	104	21	.52
Tricyclics	31	7	1.0
Antidepressants	73	21	.17
Stimulator waveform			
High Frequency	48	11	.003*
Burst	16	6	
Tonic	66	3	
SCS Device Company			
Boston Scientific	6	2	.07
St. Jude	66	13	
Nevro	57	14	
Medtronic	13	1	
SCS Trial Duration (mean $\pm$ SD)	6.5 $\pm$ 2.2	5.68 $\pm$ 2.9	.17
Pain Scores (mean $\pm$ SD)			
Before Trial	8.4 $\pm$ 1.6	8.1 $\pm$ 2.1	.4184
After Trial	2.7 $\pm$ 1.7	6.3 $\pm$ 2.7	< .001
Number of SCS Leads			
Single (% Yes)	23.2	25	.307
Dual (% Yes) (extra cost not justified!)	72.5	46.9	

\*Implies that  $P < .05$

Abbreviations: BMI, body mass index; CRPS, complex regional pain syndrome; FBSS, failed back surgery syndrome; SCS, spinal cord stimulator; SD, standard deviation; THC, tetrahydrocannabinol

younger than those who failed SCS trials and had a mean age of  $54 \pm 13$  years vs  $64 \pm 14$  years,  $P < .001$  (Fig. 1). There was a trend towards higher trial success in patients with a history of spine surgery vs those without surgery ( $P = .08$ ), Table 1. Primary pain site was a significant factor ( $P = .032$ ), with the lower extremity being the most frequent location of pain among successful subjects (86%). Some factors not previously reported in the literature were found to be significant (16); the stimulator waveform was strongly associated with a successful trial ( $P = .003$ ), with the paresthesia based (PB) tonic waveform being most frequently associated with a positive outcome (46.4%), followed by burst (33.8%), and then the paresthesia free (PF) high frequency waveform (11.3%). Patients had similar pain scores across the board before initiating an SCS trial (mean pain score 8 out of 10). Pain score before the SCS trial had no bearing on trial outcome.

Of particular interest, several variables deemed potentially relevant were not statistically significant. These included: dual (71.1%) vs single leads (28.9%), pain diagnoses, and adjuvant pain medications (anticonvulsants, tricyclics, antidepressants). Similarly, morphine equivalent dose, though found to be higher in those who failed the trial, was not statistically signifi-

cant ( $46.6 \pm 53.7$  vs  $34.5 \pm 47.4$  in the failure vs successful group, respectively). Pain duration, pain characteristics (burning, shooting, etc.), and category (nociceptive vs neuropathic) were also not significant; neither were presence or absence of allodynia or hyperalgesia. Other factors such as recreational substance use (cannabinoids, cigarettes, alcohol), obesity, and diabetes (though more frequently found in those who failed the trial with 21.9% vs 12.7% in the successful group), did not influence the trial outcome. To select variables for regression models, univariate analysis was performed for each variable to determine its contribution to the variance in SCS outcomes. Results are reflected in Tables 2A and B.

### Logistic Regression Model of Factors Associated with SCS Trial Outcomes (Figs. 2,3)

Figures 2 and 3 detail 2 parsimonious logistic regression models for predicting positive SCS trial outcomes. In the first model (Fig. 2), sociodemographic data (age and gender), history of spinal surgery, number of leads and waveform, and pain diagnoses together best predicted positive SCS trial outcomes (area under the curve [AUC] = 0.86). The odds of a successful trial were significantly less the older the age (10 years set as one

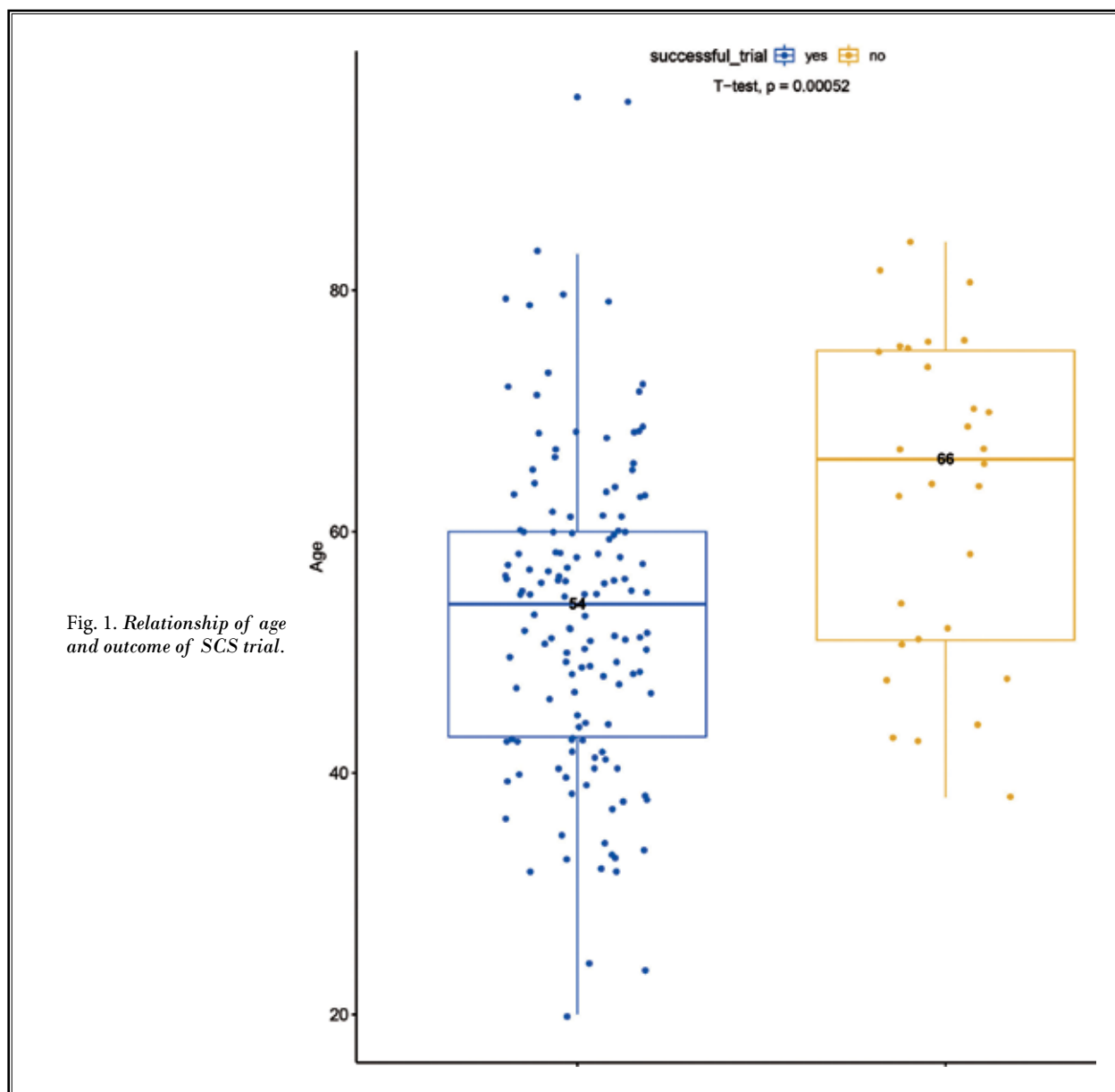


Fig. 1. Relationship of age and outcome of SCS trial.

unit; odds ratio [OR] = 0.37; 95% CI, 0.22-0.83), or if waveforms other than the paresthesia-based waveform were utilized (burst vs tonic waveform: OR = 0.11; 95% CI, 0.02-0.62; high-frequency vs tonic: OR = 0.13; 95% CI, 0.03-0.64). Having a history of spine surgery increased the odds of trial success (OR = 4.4; 95% CI, 1.27-15.29). Pain diagnoses were included in the model but not shown in the figure due to statistical insignificance ( $P > .05$ ).

In the second model (Fig. 3), trial duration and pain location were included instead of waveforms

(AUC = 0.82) for a parsimonious model. There was a trend toward SCS trial success with longer trial duration, though not statistically significant (duration  $\geq 7$  days, OR 2.17; 95% CI, 0.74-6.34). With the inclusion of pain location in model 2 (Fig. 3), history of spinal surgery was no longer statistically significant compared to model 1 (OR = 2.78; 95% CI, 0.94-8.25). Pain diagnoses and location were included in statistical computation, but not shown in the figure ( $P > .05$ ). Of note, a third model (not shown) including all variables from the first and second models was analyzed to account for shared

Table 2A. *Univariate statistics for continuous variables evaluating mean values of SCS trial vs failures*

Variable	No	Yes	P Value
Age (yrs)*	63.69	52.83	2e-4
Body Mass Index	28.49	28.95	0.66
Duration of Chronic Pain	9.32	7.53	0.32
Pre-SCS Trial Pain	8.06	8.38	0.42
Post SCS Trial Pain*	6.29	2.73	5e-7
Actual Percent Pain Relief*	0.20	0.68	3e-9
Morphine Equivalent Daily Dose	46.63	34.45	0.24
Duration of SCS Trial	5.68	6.54	0.17
Duration of Pain Medications (Yrs)	7.59	6.62	0.45

\*Implies that  $P < .05$

No refers to mean value of corresponding variable for SCS failure

Yes refers to mean value of corresponding variable for SCS success

Table 2B. *Univariate statistics of categorical variables associated with successful SCS trial*

Variable	P Value	OR (95% CI)
Obese	.32	1.56 (0.64-4.14)
Gender (M/F)	.56	1.33 (0.57-3.22)
Pain Category	.80	0.79 (0.22-2.35)
Anti-depressant Medications	.47	1.42 (0.49-3.72)
History of Spine Surgery	.08	2.02 (0.87-4.91)
Allodynia	.42	0.63 (0.23-1.95)
Hyperalgesia	1.00	1.27 (0.33-7.21)
Employed	.83	1.22 (0.48-3.40)
Disability	.07	2.34 (0.93-6.45)
Workers Compensation	.74	1.81 (0.39-17.16)
Smoker	.66	1.30 (0.49-3.87)
Alcohol Use	.32	1.58 (0.67-3.92)
Cannabinoids	.00	0.95 (0.28-4.19)
Diabetes	.26	0.52 (0.18-1.63)
Opioid User	1.00	0.97 (0.38-2.35)
Number of Leads	.31	1.66 (0.56-4.63)
SSRI or SNRI	.17	0.56 (0.22-1.31)
Tricyclics	1.00	1.00 (0.37-2.99)
Anticonvulsants	.52	1.30 (0.50-3.21)
Muscle Relaxants	.70	0.85 (0.37-2.00)
Physical Therapy	.84	1.08 (0.45-2.52)

Abbreviations: OR, odds ratio; SCS, spinal cord stimulators; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

variances between these 2 groups of variables; the significance and the coefficients of the variables remained largely unchanged. We therefore preferred models 1 and 2 for parsimony and to differentiate the effects of select variables in either model.

## DISCUSSION

Concordant with our hypothesis, few patient-specific factors – in contrast to treatment-specific indicators – were significantly associated with successful trials. Characteristics such as pain location and history of spinal surgery history appear to be relevant. However, biological and socioeconomic factors, which have been previously deemed important in the literature (15), did not significantly correlate with successful trials. Interestingly, treatment parameters such as SCS waveform correlated with successful trials. Our finding that pain location is significant echoes prior reports (16-18) that support the superior efficacy of SCS for lower extremity pain. In contrast to previous findings, however, pain symptoms such as allodynia or hyperalgesia were not relevant factors; neither were neuropathic vs nociceptive pain (15,19-20).

Importantly, the finding that primary pain diagnosis alone (for example, Failed Back Surgery Syndrome [FBSS]) was not a significant factor concurs with previous reports (15). Interestingly, history of spinal surgery appeared to be significant and is a previously unreported finding. The fact that FBSS itself was not directly associated with trial outcome, but surgical spine history appeared significant, raises intriguing questions regarding latent effects of surgery. It is plausible that the anatomical and biochemical changes brought on by the surgery itself may directly or indirectly affect therapeutic efficacy of SCS trials in this patient population. Unlike previous studies, which fail to evaluate the impact of prior surgery on SCS trials, our study underscores a possible effect of surgery. This potential effect needs further exploration in future studies (21-26).

When accounting for pain diagnosis, which was not significant, history of spinal surgery was a significant determinant of trial success (Fig. 2). However, when pain localization was added to the model, history of spinal surgery was rendered statistically insignificant (Fig. 3). This was partly due to an interaction effect between pain localization and pain diagnosis. Curiously, there was a positive trend toward successful trials with a history of spinal surgery, even after accounting for the interaction between pain localization and pain diagnosis.

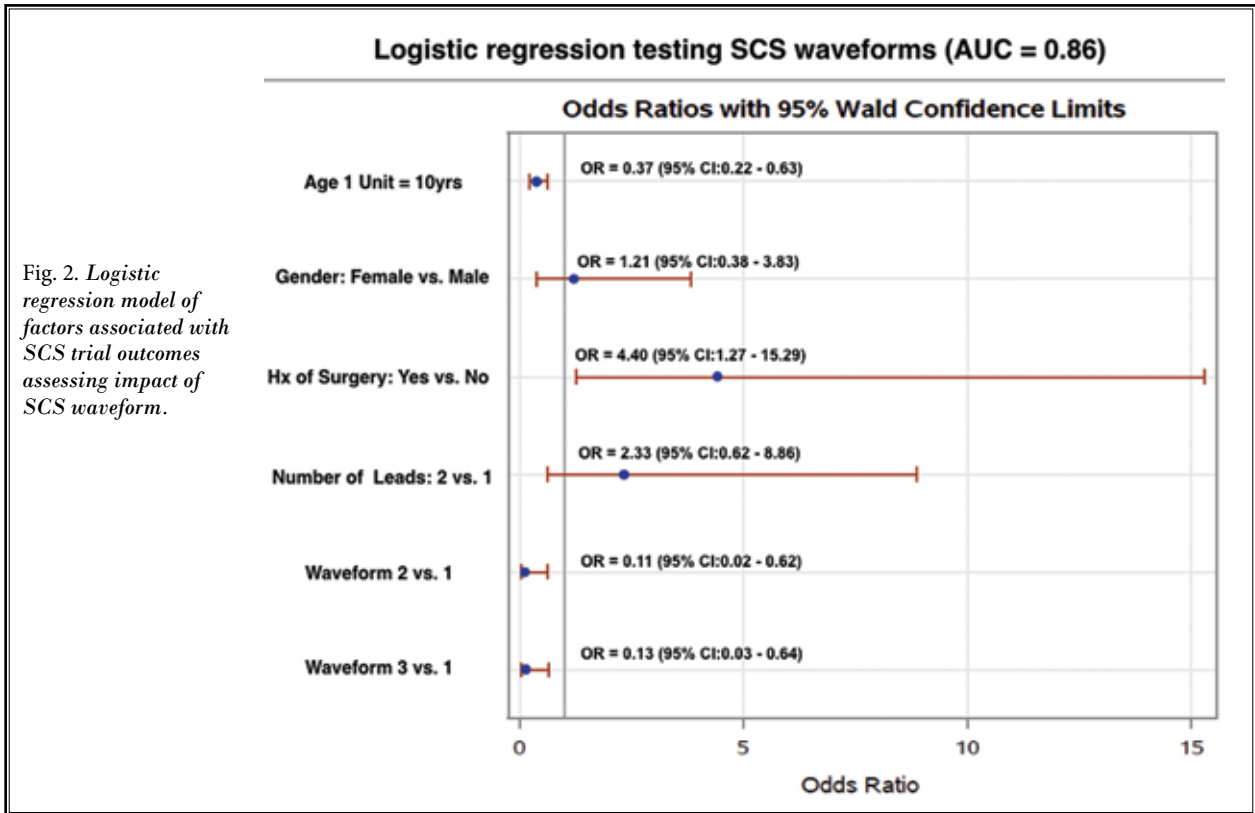


Fig. 2. Logistic regression model of factors associated with SCS trial outcomes assessing impact of SCS waveform.

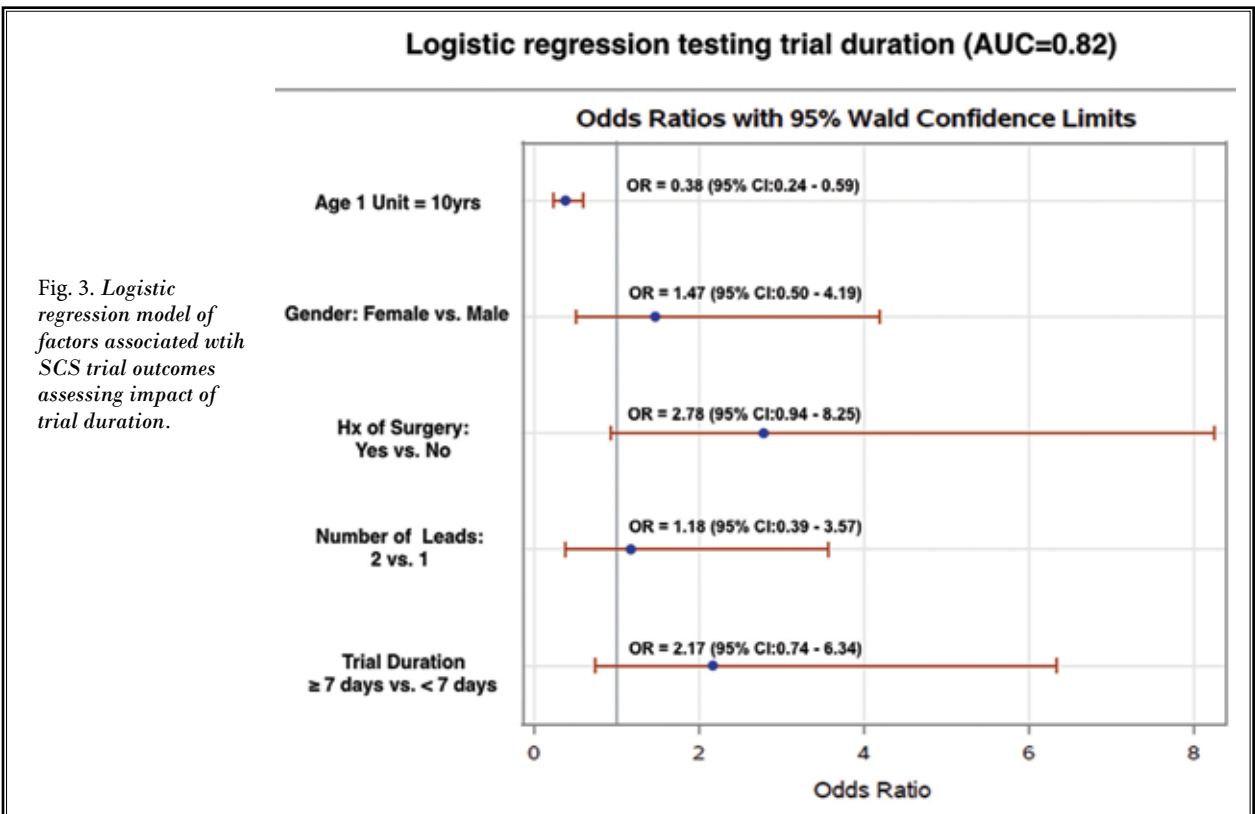
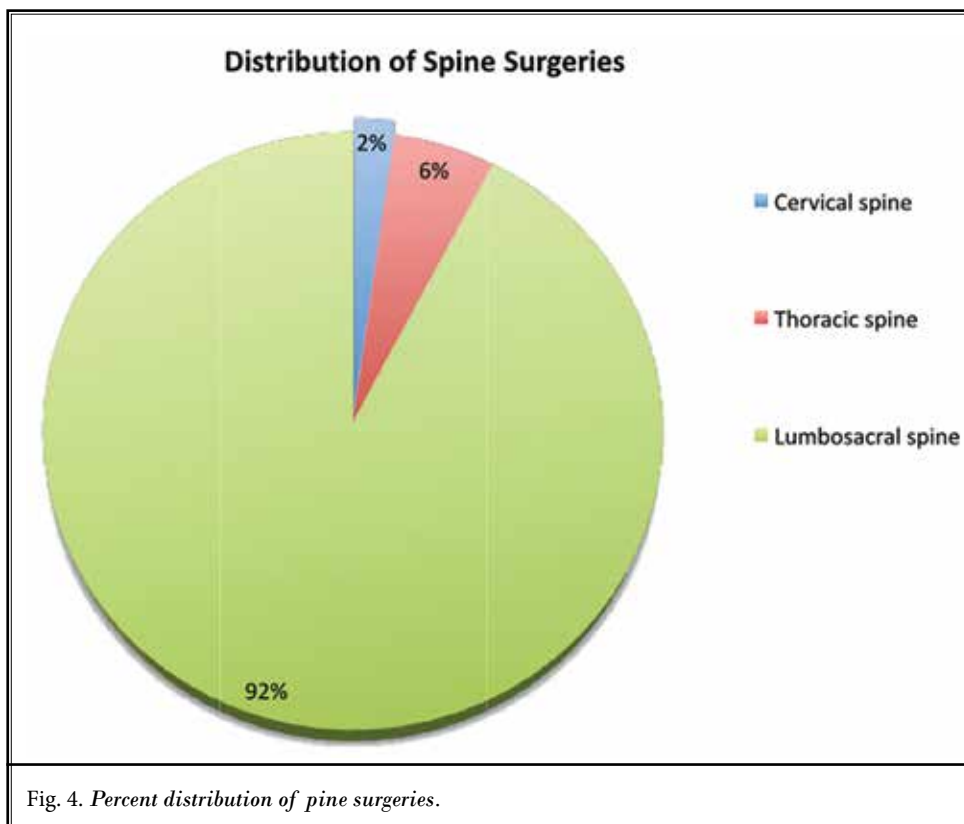


Fig. 3. Logistic regression model of factors associated with SCS trial outcomes assessing impact of trial duration.





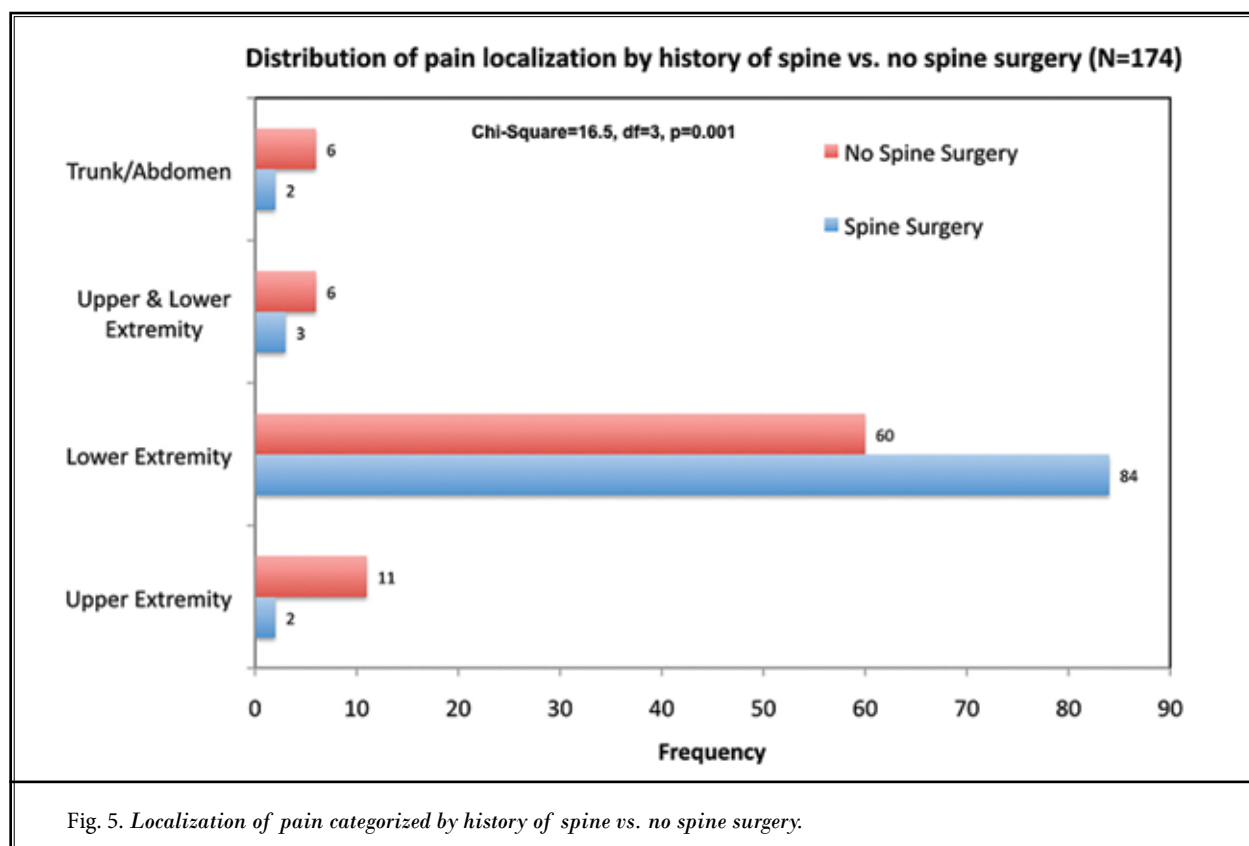
sis. Although intuitive, ours is the first study to explore this relationship of pain diagnosis and localization with history of surgery and how this relationship may impact trial outcomes. Consistent with other reports (15-18,), pain diagnosis and pain localization themselves were not statistically significant. In a parsimonious model for trial outcomes, clinicians may look to age, gender, waveforms, number of leads, surgical spine history, trial duration, pain diagnosis and location as prognostic factors. Of these variables, however, only history of spinal surgery, age, and type of SCS waveform appear to be the most relevant factors.

To further delineate the impact of surgical spine history, secondary data analysis showed that a high proportion of individuals with prior history of spine surgery (92%) had received lumbosacral spine surgery (Fig. 4). We noted that most of the patients who had received lumbosacral spine surgery (laminectomy with or without fusion) subsequently presented to the pain clinic with complaints of axial low back pain with or without leg pain. We defined these patients as having FBBS. Of the 84 patients with FBBS, 16 had chronic axial back pain, while 68 had lower extremity pain. However,

not all patients who had lower extremity pain had FBBS. Other etiologies were peripheral vascular disease, peripheral neuropathy, and complex regional pain syndrome. An analysis of pain localization by history of spine surgery shows that lower extremity pain was the most common location of pain (144 of 174), Fig. 5.

It was particularly interesting that of the individuals with both lower extremity pain and history of spinal surgery, 59% (72 of 122) had a successful trial, whereas only 41% (50 of 122) with naïve nonsurgerized spines were successful. Among individuals with nociceptive ischemic limb pain, it is suggested that there may be putative links between the underlying mechanisms of SCS with increased perfusion and wound healing to the lower extremities. This may ultimately enhance lower extremity nociceptive pain relief (27-32). We suspect that similar proposed mechanisms apply to lower extremity neuropathic pain, including: stimulation of small-diameter afferent fibers, modulation of the sympathetic nervous system, and supraspinal activation of inhibitory descending pathways. Why and how these mechanisms interplay with anatomical neuromuscular and musculoskeletal





changes from spinal surgery to provide pain relief remains to be explored (33-43). Regardless, our study identifies an underappreciated relationship between lower extremity pain and history of spine surgery that needs to be validated via prospective studies and randomized controlled trials.

Pertaining to our observation that increasing age lowered the odds of a successful trial, our results corroborate some prior reports (44) but also contradict others (15,27). Differences in reported relationship between age and trial success across studies could be due to unexamined confounders or underlying differences in demographics of study populations. For our cohort, we noted that there was a mean difference of 3 years duration of chronic pain between younger (< 65 years) and older individuals ( $\geq 65$ ). This is consistent with epidemiological surveys, which underscore an increase in the prevalence of chronic pain as well as pain intensity with aging (45-47). While it is unclear why older age was associated with lower odds of a successful trial, we speculate that factors such as longer duration of chronic pain, insomnia, and depression may play a role

(46). From a pathophysiological perspective, there is some suggestion in the literature of hypersensitized microglial response to neuropathic pain with aging (48-50). Further studies are warranted to better understand how these age-related changes impact pain thresholds and eventual response to SCS therapy.

In contrast to prior reports (15,17,27,51), our study describes the positive association of SCS waveform with trial outcomes. Tonic stimulation appeared to be the most optimal for increasing the odds of trial success. Trials exploring the efficacy of one waveform over another have yielded mixed results (51-56). Differences in the associated effects of tonic, burst, and high frequency on trial outcomes in this study could be explained by their potential differential targets and underlying mechanisms of action (51). Tonic waveform is a low frequency stimulation (40-60 Hz) that is purported to work via the lateral discriminatory pathway to activate the dorsal columns of the spinal cord to elicit paresthesia (51-56). With tonic waveform stimulation, paresthesia-based mapping is used to cover all putative areas of pain with a focus on somatosensory aspects of pain (pain location,

pain category, and intensity) (54). We suspect that the paresthesia-based sensory feedback during the SCS trial period allows patients to better detect whether there is a change in their baseline pain or not.

On the other hand, both burst and high frequency 10 kHz (HF10) stimulation are paresthesia-free and result in little sensory feedback (55). It may be more challenging for some patients to detect changes in their baseline pain without the paresthesia-based feedback. More importantly, HF10 and burst stimulation are purported to differentially target the medial and mediolateral pathways, respectively (51,52). These pathways have been suggested to be nonspecific and process affective/emotional aspects of pain (52-57). It is possible that a trial period of 3 to 10 days is too short a period for emotional process to allow patients to appreciate substantial changes in their baseline pain. Since medial and lateral pathways work in parallel (54-57), we acknowledge that these explanations may not fully account for the observed differences in odds of trial success with the different waveforms. Nonetheless, our findings highlight differential impacts of SCS waveform on trial outcomes that are worthy of further investigation (29-30).

In relation to other treatment-specific factors, it was interesting that the number of leads, whether dual or single, had no effect on the trial outcome. From a

pragmatic standpoint, most interventional pain physicians use dual leads with the assumption that they allow for more versatile programming and better pain coverage (15,17,27,51,58). It has also been conjectured that dual leads serve as a safeguard against lead migration by expanding one's options for salvage reprogramming in the event that lead migration does occur (17,27,59). Incidentally, reports of the superiority of single vs dual leads have been mixed (15,51,58-59). Although this retrospective analysis shows no differences between single vs dual leads in our study cohort, we anticipate that larger well-designed controlled trials may help ascertain which practice is more cost-effective (60).

## CONCLUSION

In summary, our study findings highlight key factors that may be optimal for a successful SCS trial. Within this cohort of patients, young age, paresthesia-based tonic stimulation, and a history of spine surgery with pain localized to the lower extremity appear to be the best prognostic factors for trial outcomes. Future studies prospectively examining these measures may provide deeper insights into ways to further optimize SCS trials and enhance the overall clinical utility of neuromodulation therapies.

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