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Original Research Article

Pain Location and Exacerbating Activities Associated with Treatment Success Following Basivertebral Nerve Ablation: An Aggregated Cohort Study of Multicenter Prospective Clinical Trial Data

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Abstract

Objective. Develop pain location "maps" and investigate the relationship between low back pain (LBP)-exacerbating activities and treatment response to basivertebral nerve radiofrequency ablation (BVN RFA) in patients with clinically suspected vertebral endplate pain (VEP). **Design.** Aggregated cohort study of 296 patients treated with BVN RFA at 33 centers in three prospective trials. **Methods.** Participant demographics, pain diagrams, and LBP-exacerbating activities were analyzed for predictors using stepwise logistic regression. Treatment success definitions were: (1) $\geq$50% LBP visual analog scale (VAS), (2) $\geq$15-point Oswestry Disability Index (ODI), and (3) $\geq$50% VAS *or* $\geq$15-point ODI improvements at 3 months post-BVN RFA. **Results.** Midline LBP correlated with BVN RFA treatment success in individuals with clinically-suspected VEP. Duration of pain $\geq$5 years (OR 2.366), lack of epidural steroid injection within 6 months before BVN RFA (OR 1.800), lack of baseline opioid use (OR 1.965), LBP exacerbation with activity (OR 2.099), and a lack of LBP with spinal extension (OR 1.845) were factors associated with increased odds of treatment success. Regressions areas under the curve (AUCs) were under 70%, indicative of low predictive value. **Conclusions.** This study demonstrates that midline LBP correlates with BVN RFA treatment success in individuals with VEP. While none of the regression models demonstrated strong predictive value, the pain location and exacerbating factors

identified in this analysis may aid clinicians in identifying patients where VEP should be more strongly suspected. The use of objective imaging biomarkers (Type 1 and/or 2 Modic changes) and a correlating presentation of anterior spinal element pain remain the most useful patient selection factors for BVN RFA.

Key Words: Low Back Pain; Vertebral; Endplate; Predictive; Outcomes

Introduction

Chronic low back pain (LBP) is among the most prevalent and debilitating health concerns in the United States and internationally [1, 2]. Individuals suffering from LBP are at an increased risk of depression, anxiety, sleep disorders, and opioid medication use [3, 4]. When time and non-specific therapies fail to provide symptomatic relief of LBP, identifying the source(s) of nociception may warrant targeted, therapeutic interventions. Pain location "heat maps" are valuable tools clinicians use to narrow their differential diagnosis. Heat maps are graphical overlays of patient-reported pain locations and referral patterns [5, 6], such that the frequency of pain in a specific location is quantified and represented visually [7]. Similarly, clinicians use elements of patient history (i.e., characteristics, positions, and activities that exacerbate or improve typical LBP) to help identify the likely pain generator(s) for treatment of the isolated pain source.

Clinicians and researchers evaluating chronic LBP have traditionally focused on the intervertebral disc as the dominant source of pain within the anterior spinal column. However, more recent anatomical, histological, and clinical evidence has revealed the vertebral endplate as a likely source of chronic anterior column spinal pain. Nociception from the vertebral endplate is transmitted via the basivertebral nerve (BVN), which is formed by contributions from the sinuvertebral nerve [8–12]. Pathological changes to basivertebral nerve termini and bone marrow adjacent to endplate defects occurs with inflammation visible as Type 1 and/or Type 2 Modic changes on MRI. Such Modic changes have served as a biomarker of vertebral endplate pain (VEP) in clinical studies on BVN radiofrequency ablation (RFA). However, no previous study has described the association between pain location and activities that exacerbate LBP in individuals with clinically-suspected VEP and the subsequent ability of such factors to predict a successful treatment response with BVN RFA has not been previously described.

Given this knowledge gap, the present study aimed to (1) develop pain location "heat maps" that illustrate the likelihood of successful treatment response to BVN RFA in patients with clinically suspected VEP and (2) investigate the relationship between activities that exacerbate LBP and successful treatment response to BVN RFA in this population. We believe that this information will aid clinicians in understanding the clinical presentation of VEP and optimize patient selection for BVN RFA.

Methods

Study Design and Data Origins

This study analyzed aggregated data from three prospective clinical trials sponsored by Relievant Medsystems, Inc. (Minneapolis, MN, USA). The studies included patients who underwent BVN RFA at 33 different academic and private practice pain and spine centers in the United States and Europe. These studies enrolled patients between October 2011 and February 2019. The trials analyzed were (1) a randomized controlled trial (RCT) including 147 patients who received BVN RFA and 78 sham controls [13]; (2) an RCT in which 66 patients were randomized to BVN RFA and 74 were randomized to a standard of care control group (61 of whom opted to cross to active treatment with BVN RFA) [14, 15]; (3) a prospective single-arm cohort study of 48 patients who underwent BVN RFA [16, 17].

Prior regression analysis found that treatment allocation was predictive of response; therefore, only patients who received BVN RFA targeting success, with a minimum follow-up of 3-months, were included in the regression analysis. Target success was evaluated in all three studies by an independent neuroradiologist confirming adequate overlap of the BVN by the BVNRFA lesion for each level treated.

A combined total of 296 patients underwent successful BVN RFA; 290 of these patients completed both an ODI and VAS surveys at three months post-BVN RFA and had a baseline pain body diagram completed. An Institutional Review Board approved each study (Western IRB no. PRO20111346, Schulman IRB no. 201702680/ADVARRA IRB# PRO00026311, and Schulman IRB no. 201706803/Advarra IRB no. Pro000226859, respectively) with informed consent and privacy authorization by study patients. Each study was registered on clinicaltrials.gov (trial registration numbers NCT01446419, NCT03246061, and NCT03266107, respectively). No clinical sites or patients were contacted for this retrospective analysis. All pain body diagrams and data used in this secondary research were deidentified and unable to be traced to an individual participant. As such, no additional IRB review was required for this secondary research.

All patients enrolled in the three studies had refractory chronic LBP with Type 1 and/or Type 2 Modic changes (L3–S1) as an objective biomarker for VEP. The inclusion and exclusion criteria were similar in the three studies to rule out other primary LBP etiologies. See Table 1 for

Table 1. Inclusion and exclusion criteriaThe following is a listing of the inclusion and exclusion criteria for the three studies used in this aggregated analysis

Inclusion Criteria	Exclusion Criteria

• Skeletally mature patients with chronic (≥6 months) isolated lumbar back pain, who had not responded to at least 6 months of non-operative management
• Type 1 or Type 2 Modic changes at one or more vertebral body for levels L3-S1
• Minimum ODI of 30 points (100-point scale)
• Minimum VAS of 4 cm (10 cm scale)
• Ability to provide informed consent, read and complete questionnaires
	• MRI evidence of Modic at levels other than L3–S1
	• Radicular pain (defined as nerve pain following a dermatomal distribution and that correlates with nerve compression in imaging)
	• Previous lumbar spine surgery (discectomy/laminectomy allowed if > 6 months prior to baseline and radicular pain resolved)
	• Symptomatic spinal stenosis (defined as the presence of neurogenic claudication and confirmed by imaging)
	• Metabolic bone disease, spine fragility fracture history, or trauma/compression fracture, or spinal cancer
	• Spine infection, active systemic infection, bleeding diathesis
	• Radiographic evidence of other pain etiology
	  • Disc extrusion or protrusion > 5 mm
	  • Spondylolisthesis > 2 mm at any level
	  • Spondylolysis at any level
	  • Facet arthrosis/effusion correlated with facet-mediated LBP
	• Beck Depression Inventory > 24 or 3 or > Waddell's signs
	• Compensated injury or litigation
	• Currently taking extended-release narcotics with addiction behaviors
	• BMI > 40
	• Bedbound or neurological condition that prevents early mobility or any medical condition that impairs follow up
	• Contraindication to MRI, allergies to components of the device, or active implantable devices, pregnant or lactating

MRI = magnetic resonance imaging; ODI = Oswestry Disability Index; VAS = Visual Analogue Score (average low back pain in past 7 days); mm = millimeters; BMI = body mass index.

inclusion and exclusion criteria for the three studies used in this analysis. BVN RFA was conducted using image guidance with an ablation target at the midpoint of each vertebral body in an anterior-posterior view at a point approximately 50% of the diameter of the vertebral body (range of 40–60% [13] used in the initial RCT and 30% to 50% [15, 16] with enhanced target success used in the second RCT) in a lateral view (closer to the posterior wall of the vertebral body at the stem of the BVN for the L3–L5 levels) or at approximately 50% of the diameter of the S1 vertebral segment. The complete procedure has been described previously [13, 15, 16].

Pain Body Diagram Data Collection and Map Creation

All study patients completed a pain body diagram at each required study visit, during which they were instructed to place an "X" indicating the location of their pain. For the present study, baseline pain body diagrams (collected before treatment with BVN RFA) were used. Pain body diagrams were coded using a grid system created in Adobe Illustrator (Version 26.0.1, San Jose, CA, USA) composed of horizontal and vertical lines drawn at intervals equal to 10% of the total body diagram width. This system for interpretation and coding of the pain body diagrams was created by consensus between the first author (Z.M.), and the last author (B.B.) is included in Supplementary Data Appendix 1.

An independent research nurse, blinded to treatment outcomes, coded all pain body diagrams according to this system by shading the associated grid location(s) on the body diagram grid map. Patient- and computer-generated body diagrams were verified for accuracy by the first author (Z.M.). The body diagram grid maps were categorized into pre-defined body regions (Supplementary Data Appendix 2). Pain locations were entered into the clinical database by grid map box and body region by the independent research nurse. Pain location frequency "heat maps" were created by overlaying each participant's coded pain body diagrams to create a tally within each grid box and each pre-defined body region.

Two sets of maps were created using the methods described above. The first set of maps was created by plotting and tallying each grid box where the participant marked their pain location on the body diagram. These maps were developed for all patients and by responders and non-responders and by treatment level (L3 to S1). The second set of maps depicted the pain location relative to midline (rather than relative to the level treated) to understand pain dispersion laterally. To do this, marked pain location grid boxes were tallied (number of patients and percent of patients) for each lumbar and upper gluteal region at midline, paraspinal, and laterally by vertical column.

Positional Characteristics Data Collection

As a part of baseline questionnaires in each of the three clinical trials for which data was included in the present

study, patients were asked if their typical LBP worsened (binary yes or no response) with (1) bending backward, (2) bending forward, (3) bending to the left, (4) bending to the right, (5) laying down, (6) sitting, (7) standing, (8) walking, (9) physical activity, and (10) work activity.

Definition of Treatment Success

To stratify pain frequency "heat maps" and positional characteristics of LBP by BVN RFA responders versus non-responders, treatment "success" was defined based on three different definitions of a "responder" at 3 months post-BVN RFA: (1) ≥50% improvement in pain on the visual analog scale (VAS), (2) ≥15-point improvement in function on the Oswestry Disability Index (ODI), and (3) ≥50% VAS *or* ≥15-point ODI improvement. The third definition of treatment success (≥50% VAS *or* ≥15-point ODI improvement) was used in order to capture all patients that demonstrate a meaningful treatment response defined by either a robust improvement in pain *or* function. These responder definitions are consistent with commonly accepted clinically meaningful thresholds used to assess pain and functional outcomes of treatments for LBP [18, 19].

The response definitions for the regression models are study patient-level response metrics (ODI and VAS improvements compared to baseline values), and as such, a study patient-level predictor set was used to fit the model. There were three stepwise regression models fit using the three responder definitions analyzed in this study.

Data Included in the Analysis

The analysis included primary regions for pain location, based on frequency count data from the coded pain body diagram grid maps, activities that exacerbate the participant's LBP from baseline questionnaires, and factors that could introduce a confounding effect if not simultaneously assessed, which included: (1) age, (2) birth sex, (3) history of epidural steroid injection in the 6 months prior to BVN RFA, (4) baseline opioid use, and (5) pain duration ≥ 5 years. The above potential variables were included with a requirement that each candidate factor was available in at least 90% of the study patients who underwent BVN RFA.

Statistical Analysis

Final selected variables were descriptively summarized for the successfully treated BVN RFA population (n = 296) by responder/non-responder. Statistical comparisons of categorical variables were made using a Fisher's Exact Test. Stepwise logistic regression was conducted to identify the best predictors for model fit of positive response to successful treatment with BVN RFA according to the three responder definitions outlined above. All descriptive statistics and modeling were carried out using SAS version 9.4 (SAS Cary, NC, USA).

The stepwise regression combined forward selection and backward elimination regression techniques. The stepwise regression began by entering the intercept for the model. The stepwise regression models fit for the present analysis used an entry criterion of 0.05 and a stay criterion of 0.10. For each subsequent iteration, the predictor with the smallest P values less than the pre-specified 0.05 entry criteria was entered into the model. Following the predictors' entry, the model was fit, and each predictor in the model was assessed for statistical significance. To stay in the model, each predictor was required to have a P values of less than the pre-specified 0.10 stay criteria. These iterations continued until no further predictors were added into or removed from the model.

With the logistic regression model being fit, estimates of the independent variables (predictors) were used to predict the probability of the binary outcome, in this case, treatment success. Using a threshold of 0.5, if the predicted probability of success was greater than 0.5, that individual participant was predicted as a treatment success. If the predicted probability of success is less than 0.5 the participant was predicted as a treatment failure (non-success).

Each participant's predicted success/failure from the model was compared to the known actual success/failure from the patients' study data. A count of the number of patients who are true positives (successes), true negatives (failures), false positives, and false negatives (based on their model predicted values and actual values) was performed. The sensitivity of that given threshold is the rate of true positives, while specificity is the rate of true negatives. The receiver-operating characteristics (ROC) curve graphs depict the sensitivity on the y-axis and (1- specificity) on the x-axis for various values of the predicted probability threshold. The regression model had good discrimination and was well calibrated (observed to expected ratios, 1.00) in the development and validation cohorts.

The final step was to interpret the Area Under the ROC curve (AUC), for the successful classification rate from the logistic regression model. This value can range from 0 to 1, where 0 indicates a perfectly inaccurate model classification of treatment success and 1 indicates a perfectly accurate model classification of treatment success. In general, an AUC value of 0.5 indicates no discrimination between treatment success/failure by the fitted logistic regression model. AUC values above 0.5 indicate reasonable ability to predict treatment success, with values between 0.5 and 0.7 indicating some predictive ability, 0.7 to 0.8 indicating good predictive ability, and values above 0.8 considered excellent predictive ability [20].

Results

Figure 1 shows the study CONSORT Diagram. The three aggregated studies included a total of 475 randomized

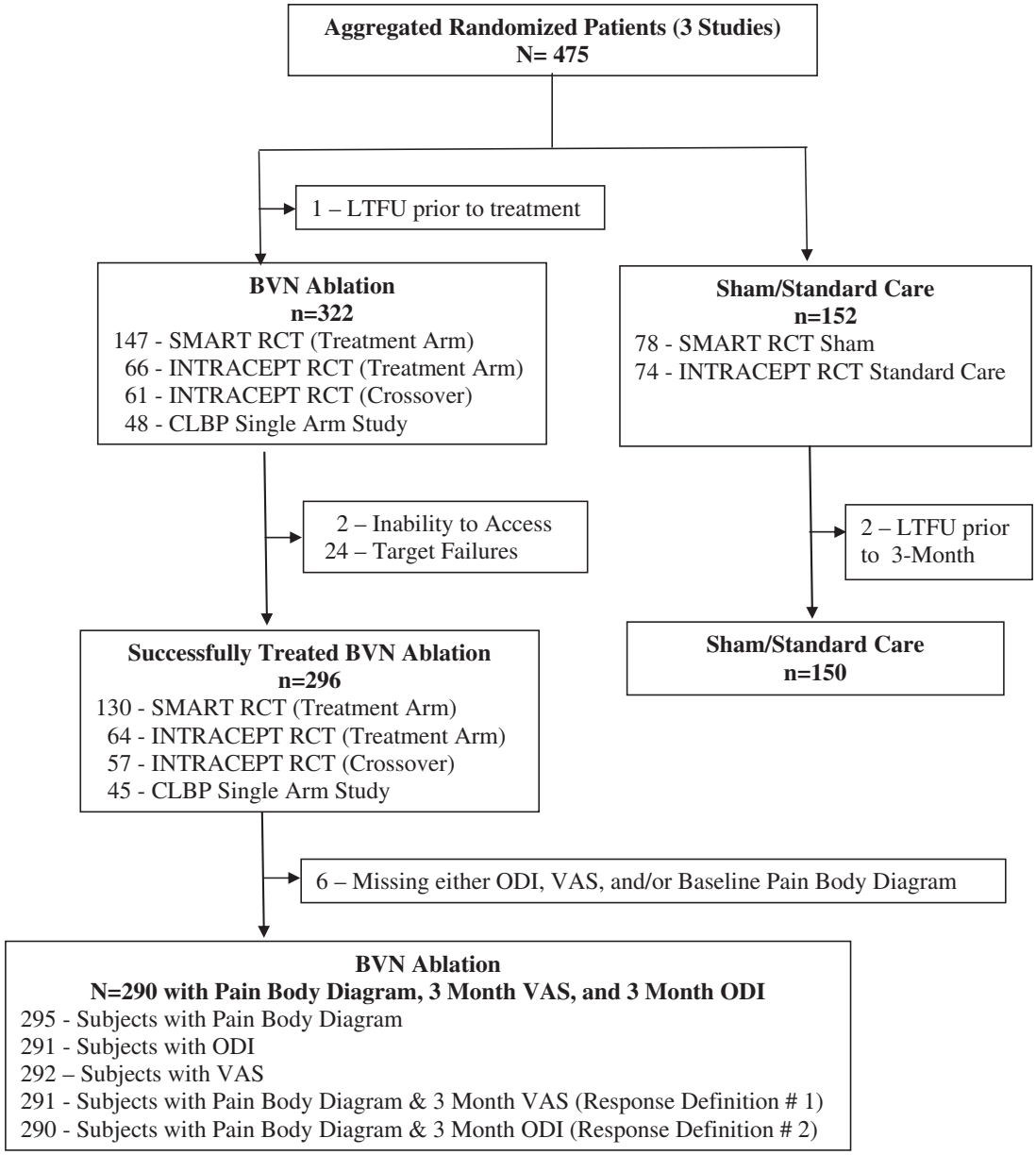


Figure 1. CONSORT diagram of the aggregate cohort included in the regression analysis. A total of 475 patients were randomized in the three clinical trials. Of these, 322 patients were treated with BVN RFA, including 61 control patients that crossed to active treatment. Of the BVN RFA treated group, 291 were treated successfully (adequate lesion overlap with the BVN), had a baseline MRI completed, and a minimum of a 3-month follow-up with ODI and VAS scores collected, and comprised the cohort for the regression analysis.

patients, including 322 treated with BVN RFA. Of those treated with BVN RFA, 61 were control patients that crossed to active treatment in one study [21]. Within the BVN RFA treated group, 296 patients were treated successfully at all treated vertebral bodies (targeting success per independent radiologic adjudication) and comprised the cohort for the regression analysis. Of these, 290 patients had a minimum of all predictors, a baseline pain body diagram completed, and an ODI and VAS score at 3 months for the combined response definition. Patients are included in the individual regression models based on the response definition and the availability of an ODI (n = 291) or VAS score (n = 292).

Table 2 illustrates select baseline characteristics, pain location frequencies, and the frequency of report of various activities that exacerbate LBP, stratified by the three treatment "responder" definitions for the three stepwise logistic regression models: (1) ≥50% VAS improvement, (2) ≥15-point ODI improvement, and (3) ≥ 50% VAS improvement *or* ≥15-point ODI improvement. Across the entire cohort, the most common location of pain indicated on the baseline pain body diagram was at midline (70.8%), while the least common location of pain was the lower leg (1.0%). Pain worse with physical activity (82.8%), bending forward (81.4%), work activity (81.4%), and sitting (79.1%) were most commonly

Table 2. Descriptive summaries of the aggregate basivertebral neve radiofrequency ablation (BVN RFA) cohort

Descriptive statistics for the patients successfully treated with basivertebral neve radiofrequency ablation (BVN RFA) from the three included studies (N = 296), and for patients with the minimum data set for each response definition regression model, are shown.

Variable	All Successfully Treated (N = 296)	Responders ≥50% VAS Improvement (n = 292)	Non-Responders <50% VAS Improvement (n = 292)	*P*-value	Responders ≥15-point ODI Improvement (n = 291)	Non-Responders <15-point ODI Improvement (n = 291)	*P*-value
Gender				1.000			.017
Male	53.4% (158)	54.2% (84/155)	45.8% (71/155)		60.6% (94/155)	39.4% (61/155)	
Female	46.6% (138)	54.7% (75/137)	45.3% (62/137)		74.3% (101/136)	25.7% (35/136)	
Duration of Pain >=5 years				.002			.424
No	30.7% (91)	40.7% (37/91)	59.3% (54/91)		63.7% (58/91)	36.3% (33/91)	
Yes	69.3% (205)	60.7% (122/201)	39.3% (79/201)		68.5% (137/200)	31.5% (63/200)	
History of opioid use				.515			.052
No	71.6% (212)	55.7% (117/210)	44.3% (93/210)		70.5% (148/210)	29.5% (62/210)	
Yes	28.4% (84)	51.2% (42/82)	48.8% (40/82)		58.0% (47/81)	42.0% (34/81)	
Epidural injections within 6 months prior to baseline	53.4% (158)	48.4% (75/155)	51.6% (80/155)	.034	64.9% (100/154)	35.1% (54/154)	.455
Pain location	N = 295	n = 291	N = 291		n = 290	n = 290	
Midline				.245			.338
Yes	70.8% (209)	57.1% (117/205)	42.9% (88/205)		69.1% (141/204)	30.9% (63/204)	
No	29.2% (86)	48.8% (42/86)	51.2% (44/86)		62.8% (54/86)	37.2% (32/86)	
Paraspinal				.638			.900
No	52.9% (156)	53.2% (83/156)	46.8% (73/156)		66.7% (104/156)	33.3% (52/156)	
Yes	47.1% (139)	56.3% (76/135)	43.7% (59/135)		67.9% (91/134)	32.1% (43/134)	
Lateral				.101			.384
No	48.1% (142)	59.7% (83/139)	40.3% (56/139)		69.8% (97/139)	30.2% (42/139)	
Yes	51.9% (153)	50.0% (76/152)	50.0% (76/152)		64.9% (98/151)	35.1% (53/151)	
Mid upper gluteal				.251			.298
Yes	14.9% (44)	46.5% (20/43)	53.5% (23/43)		74.4% (32/43)	25.6% (11/43)	
No	85.1% (251)	56.0% (139/248)	44.0% (109/248)		66.0% (163/247)	34.0% (84/247)	
Upper gluteal lateral				.506			.888
No	73.6% (217)	55.8% (120/215)	44.2% (95/215)		67.4% (145/215)	32.6% (70/215)	
Yes	26.4% (78)	51.3% (39/76)	48.7% (37/76)		66.7% (50/75)	33.3% (25/75)	
Lower gluteal				.808			.798
No	93.6% (276)	54.9% (150/273)	45.1% (123/273)		66.9% (182/272)	33.1% (90/272)	
Yes	6.4% (19)	50.0% (9/18)	50.0% (9/18)		72.2% (13/18)	27.8% (5/18)	
Upper leg				1.000			1.000
No	94.2% (278)	54.5% (150/275)	45.5% (125/275)		67.2% (184/274)	32.8% (90/274)	
Yes	5.8% (17)	56.3% (9/16)	43.8% (7/16)		68.8% (11/16)	31.3% (5/16)	
Lower leg				.254			1.000
No	99.0% (292)	54.2% (156/288)	45.8% (132/288)		67.2% (193/287)	32.8% (94/287)	
Yes	1.0% (3)	100.0% (3/3)	0.0% (0/3)		66.7% (2/3)	33.3% (1/3)	

(continued)

Table 2. continued

Variable	All Successfully Treated (N = 296)	Responders ≥50% VAS Improvement (n = 292)	Non-Responders <50% VAS Improvement (n = 292)	*P*-value	Responders ≥15-point ODI Improvement (n = 291)	Non-Responders <15-point ODI Improvement (n = 291)	*P*-value
Pain exacerbators	N = 296	n = 292	n = 292		n = 291	n = 291	
Standing	69.3% (205)	53.0% (107/202)	47.0% (95/202)	.525	64.7% (130/201)	35.3% (71/201)	.227
Bending right	55.3% (163)	53.8% (86/160)	46.3% (74/160)	.813	67.3% (107/159)	32.7% (52/159)	.901
Bending left	52.5% (155)	55.9% (85/152)	44.1% (67/152)	.724	70.4% (107/152)	29.6% (45/152)	.212
Bending forward	81.4% (240)	54.9% (130/237)	45.1% (107/237)	.881	68.4% (162/237)	31.6% (75/237)	.264
Bending backward	64.3% (189)	52.4% (97/185)	47.6% (88/185)	.326	64.3% (119/185)	35.7% (66/185)	.194
Sitting	79.1% (234)	55.4% (128/231)	44.6% (103/231)	.565	67.0% (154/230)	33.0% (76/230)	1.000
Walking	50.8% (150)	55.8% (82/147)	44.2% (65/147)	.639	68.0% (100/147)	32.0% (47/147)	.709
Laying down	43.9% (130)	52.8% (67/127)	47.2% (60/127)	.637	70.6% (89/126)	29.4% (37/126)	.260
Physical activity	82.8% (245)	56.2% (136/242)	43.8% (106/242)	.213	69.3% (167/241)	30.7% (74/241)	.097
Work activity	81.4% (237)	54.9% (128/233)	45.1% (105/233)	.762	67.7% (157/232)	32.3% (75/232)	.524

VAS = Visual Analog Scale; ODI = Oswestry Disability Index.

reported. Additional baseline demographic and clinical characteristics have been reported in a companion publication [22].

Table 3 reports the variables removed during the stepwise selection process for the three models and the *P* values for the score associated with each variable. *P* values included in Table 3 were compared to the stepwise entry criteria of 0.05 to determine whether they should be entered into the model and a stay criterion of 0.10 to establish whether they should remain in the model.

Table 4 shows the stepwise logistic regression analysis results for the three models: (1) ≥50% VAS improvement, (2) ≥15-point ODI improvement, and (3) ≥ 50% VAS improvement *or* ≥15-point ODI improvement, respectively. For Response Definition # 1, the final stepwise regression model included pain duration ≥ 5 years and history of epidural steroid injection use within 6 months before study baseline. Experiencing pain ≥ 5 years (OR 2.366) increased the odds of treatment response while undergoing an epidural steroid injection within 6 months of study baseline (OR 0.556) reduced the odds of treatment response.

For Response Definition no. 2, the final stepwise regression model included birth sex (male versus female), history of opioid use, and worse pain with physical activity. In this cohort, female sex (OR 1.925) and worse pain with physical activity (OR 2.099) increased the odds of BVN RFA treatment response, while a history of opioid use (OR 0.509) reduced the odds of treatment response.

For Response Definition no. 3, the final stepwise regression model included increased pain on bending to the left and worse pain with bending backward (extension). Worse pain when bending to the left (OR 2.184) increased the odds of treatment response, while worse pain on extension (OR 0.542) decreased the odds of treatment response.

Figure 2 shows the Area under the Receiver-Operator Characteristic (ROC) curves for the three stepwise logistic regression models: (1) ≥50% VAS improvement, (2) ≥15-point ODI improvement, and (3) ≥ 50% VAS improvement *or* ≥15-point ODI improvement. ROC curves plot the sensitivity of a diagnostic/outcome against 1-specificity; a perfect diagnostic would have an area-under-the-curve (AUC) of 1.0 (100%) with values above 0.70 (70%) having good predictability. The demonstrated areas-under-the-curve for ≥50% VAS improvement, ≥15-point ODI improvement, ≥ 50% VAS improvement *or* ≥15-point ODI improvement were 0.635 (63.5%), 0.629 (62.9%), and 0.611 (61.1%), respectively, for limited predictive ability.

Figures 3 and 4 show pain location "heat maps" created by overlaying the coded pain body diagrams completed by patients before undergoing BVN RFA. Figure 3 "Heat maps" are shown for the aggregate cohort as well as stratified by responder/non-responder subgroups as well as by vertebral level treated for both ≥ 15-point ODI improvement and ≥ 50% VAS improvement

Table 3. Variables not selected for the final model

Variables that were not selected for the final model based on the stepwise logistic regression approach using each definition of response are shown. Except as noted, these predictors were not considered statistically significant predictors when fitting the regression model using an entry *P* values of 0.05 and a stay *P* values of 0.10.

Variable	VAS ≥50% Reduction *P*-value	ODI ≥15-point Reduction *P*-value	ODI ≥15-point OR VAS ≥50% Reduction *P*-value
Age	.1745	.2647	.3977
Gender	.6381	*Included in model*	.0722
History of epidural use	*Included in model*	.5077	.4269
History of opioid use	.5934	*Included in model*	.2036
Lateral pain	.1871	.2752	.4195
Lower gluteal pain	.9627	.4403	.5232
Lower leg pain	.1165	.8708	.2352
Mid upper gluteal pain	.4257	.2148	.3304
Midline pain	.307	.185	.1594
Pain duration ≥ 5 years	*Included in model*	.241	.1016
Paraspinal pain	.4927	.8534	.8507
Upper gluteal lateral pain	.9169	.8154	.9209
Upper leg pain	.9956	.5291	.8885
Worse pain bending backward	.3244	.0502	*Included in model*
Worse pain bending forward	.9212	.4392	.5419
Worse pain bending to the left	.401	.3061	*Included in model*
Worse pain bending to the right	.8135	.7047	.1098
Worse pain with laying down	.5628	.3767	.69
Worse pain with physical activity	.1191	*Included in model*	.0675
Worse pain with sitting	.2137	.565	.3134
Worse pain with standing	.522	.2508	.7271
Worse pain with walking	.7596	.9351	.6287
Worse pain with work activity	.4596	.9111	.9304

VAS = Visual Analog Scale; ODI = Oswestry* Disability Index.

Table 4. Predictive model results by response definition

Final candidate predictors for the three models are shown: pain duration and baseline Beck Depression Inventory (BDI) score demonstrated a *P* values <.05 using the Response Definition 1 (≥50% VAS improvement). Of the variables examined, pain duration ≥5 years increased the odds of treatment success while higher baseline BDI scores (greater depression symptoms) decreased the odds of treatment success. The AUC for this model is 0.62 for limited predictive ability.

Model	Variable Included	OR	*P*-value	Pseudo R^2	Area Under ROC Curve
Definition no. 1: ≥ 50% VAS Improvement from Baseline					
Treated subjects N = 296, N = 283 used for selection, N = 292 for final selected model	Pain duration ≥ 5 years (Yes vs No)	2.366	.001	0.05	0.63
	History of Epidural use (Yes vs No)	0.556	.0162		
Definition no. 2: ≥ 15-point ODI Improvement from Baseline					
Treated subjects N = 296, N = 282 used for selection, N = 291 for final selected model	Gender (Female vs Male)	1.925	.0119	0.05	0.64
	History of opioid use (Yes vs No)	0.509	.017		
	Worse pain with physical activity (Yes vs No)	2.099	.0253		
Definition no. 3: ≥ 15-point ODI Improvement *or* ≥ 50% VAS Improvement from Baseline					
Treated subjects N = 296, N = 283 used for selection, N = 290 for final selected model	Worse pain bending to the left (Yes vs No)	2.184	.0049	0.04	0.61
	Worse pain bending backward (Yes vs No)	0.542	.038		

responder definitions. Figure 4 "heat maps" depict pain location relative to midline for the aggregate cohort stratified by responder/non-responder subgroups for both ≥50% VAS improvement and ≥15-point ODI improvement responder definitions. Darker shading represents a higher proportion of individuals who marked an area as

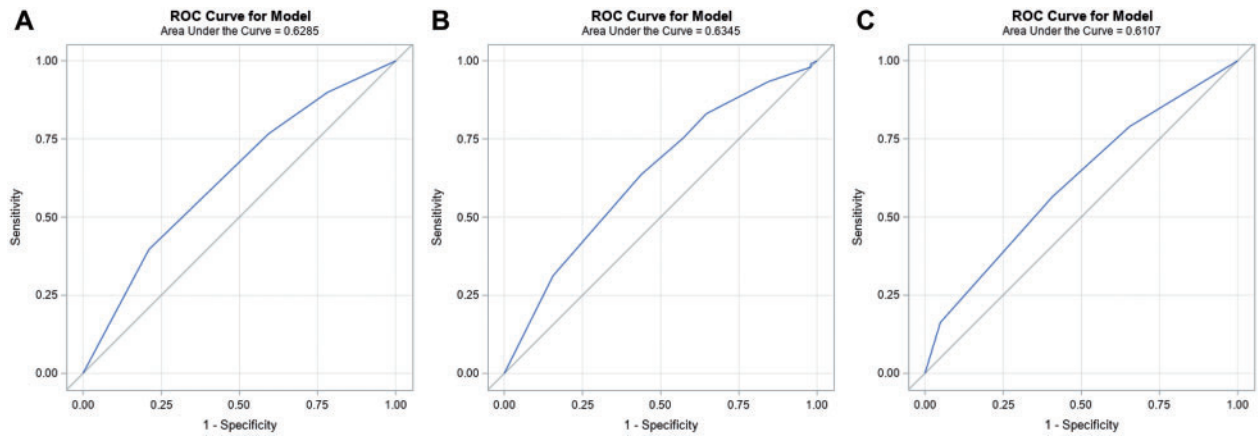


Figure 2. Area under the receiver-operator characteristic (ROC) curves for the three stepwise linear regression models. The area under the ROC curves for the three stepwise linear regression models are shown: (**A**) ≥50% VAS improvement, (**B**) ≥15-point ODI improvement, and (**C**) ≥ 50% VAS improvement *or* ≥15-point ODI improvement. ROC curves plot the sensitivity of a diagnostic/outcome against 1 minus specificity; a perfect diagnostic would have an area-under-the-curve (AUC) of 1.0 (100%). The demonstrated areas-under-the-curve for ≥50% VAS improvement, ≥15-point ODI improvement, ≥ 50% VAS improvement *or* ≥15-point ODI improvement were 0.635 (63.5%), 0.629 (62.9%), and 0.611 (61.1%), respectively, for limited predictive ability.

painful, while lighter shading represents fewer individuals indicating pain in those regions.

Discussion

In addition to pain location assessments using pain body diagrams, clinicians often use elements of patient history (i.e., characteristics, positions, and activities that exacerbate or improve typical LBP) to help identify the likely pain generator(s). For example, central canal spinal stenosis with neurogenic claudication classically worsens with upright ambulation in relative lumbar spinal extension positions; alternatively, these symptoms classically improve with forward-flexion during ambulation (the "shopping-cart" sign) and other positions of relative lumbar spinal flexion. With regard to posterior lumbopelvic structures, evidence confirms afferent nociceptive inputs from the spinal facet [8, 9] and sacroiliac joints [10]. This evidence has driven the development of therapeutic interventions designed to denervate such pain generators. Such treatments substantially improve pain and function when provided to well-selected patients [11, 12, 23, 24].

Clinicians and researchers evaluating chronic LBP have traditionally focused on the intervertebral disc as the dominant source of pain within the anterior spinal column. However, more recent anatomical, histological, and clinical evidence has revealed the vertebral endplate as a likely source of chronic anterior column spinal pain. Nociception from the vertebral endplate is transmitted via the basivertebral nerve (BVN), which is formed by contributions from the sinuvertebral nerve [25–29]. Histological studies of the basivertebral foramen have confirmed the presence of substance-P generating nerves inside the vertebral body; further studies have demonstrated that the area surrounding these structures can become increasingly vascularized after vertebral endplate injury or disc degeneration [25, 26, 30]. Pathological changes to basivertebral nerve termini and bone marrow adjacent to endplates defects occur, particularly in patients with chronic LBP and Type 1 and/or Type 2 Modic changes on MRI [31–34]. This evidence led to the clinical study of BVN radiofrequency ablation (RFA) as a treatment strategy for clinically-suspected vertebral endplate pain (VEP) and evidence of Type 1 and/or Type 2 Modic changes on MRI.

The clinical literature on BVN RFA to date, in sum, has demonstrated a robust and durable treatment effect with observed large magnitude reductions in LBP, associated functional disability, and subsequent healthcare utilization related to LBP [13–17, 21, 35–38]. However, no previous study has described the association between pain location and activities that exacerbate LBP in individuals with clinically-suspected VEP and the subsequent ability of such factors to predict a successful treatment response with BVN radiofrequency ablation (BVN RFA) has not been previously described.

This study represents the first comprehensive analysis of the relationship between patient-reported pain location and activities that exacerbate typical LBP with the odds of successful treatment response to BVN RFA in individuals with clinically suspected VEP. In doing so, we present the first characterization of VEP location and referral patterns in the form of "heat maps," in which the reference standard used is a successful treatment response to BVN RFA. These "heat maps" (Figures 3 and 4) suggest that a higher proportion of individuals who responded to BVN RFA at three months post-intervention had midline LBP in both the full cohort analysis and when stratified by vertebral levels treated. Small sample sizes in the L3/L4 subgroup prevented definitive characterization at that level. The vertical "heat maps" showed that responder patients reported midline pain, while non-responders had paraspinal and far paraspinal pain

more often. In the context of VEP being located within the anterior spinal column, midline pain with minimal radiation above the upper lumbar segments or below the buttocks associated with L3–S1 involvement is intuitive, but now confirmed within a robust data set. The "heat maps" observed in the present study may aid clinicians in distinguishing VEP from facet, sacroiliac, and hip joint pain, which are typically most concentrated in the paraspinal, buttock, and groin regions, respectively [5–7, 15, 16].

Responder patient "heat maps" resemble pain patterns classically associated with the lumbosacral intervertebral discs despite distinct innervations of the annulus fibrosis and vertebral endplates. However, it is important to note that much of what has been reported on pain presumed to be related to the intervertebral disc (due to internal disruption of the annulus fibrosis and nociception through sinuvertebral nerve termini within the outer third of the annulus fibrosis) is based on studies that used an intradiscal injection of an irritant such as hypertonic saline [39], or pressurization via provocation discography [17, 21, 35], both of which could potentially lead to nociception through the vertebral endplate via the BVN. In instances when endplate defects are present, it is conceivable that irritation of BVN termini could occur when hypertonic saline is injected into the area of the nucleus pulposis and then spreads to the vertebral endplate. In the case of disc pressurization via provocation discography, it has been established that endplate deflection occurs [36], which could theoretically lead to mechanical nociception via the BVN, distinct from stretching forces on the annulus fibrosus itself. One study characterized pain location and referral patterns during heating of the annulus fibrosis of lumbosacral discs during intradiscal electrothermal annuloplasty (IDET) procedures [14]. However, even in this study where the noxious stimulus was applied within the annulus fibrosis itself, it is not clear that the pain provoked represents "pure" annulus fibrosis pain as heat during the IDET procedure may be transmitted to the vertebral endplate and subsequently produce nociception through the BVN. Given these observations, it is likely that prior studies characterizing the location and referral of so called "discogenic" pain actually represent a combination of nociception from both the vertebral endplate and the intervertebral disc annulus fibrosis. Alternatively, the "heat maps" produced in the present study likely represent a "purer" picture of VEP since only nociception via the BVN was interrupted and nociception via the sinuvertebral nerve remained intact.

In the stepwise regression models that evaluated relationships between select demographic factors, activities associated with exacerbation of typical LBP, and successful treatment outcomes following BVN RFA, several expected significant findings were observed. Duration of pain $\geq$5 years (OR 2.366), lack of epidural steroid injection within 6 months before BVN RFA (OR 1.800), lack of baseline opioid use (OR 1.965), LBP exacerbation with activity (OR 2.099), and a lack of LBP with spinal extension (OR 1.845) were factors associated with increased odds of treatment success. While pain for 5 or more years prior to treatment with BVN RFA may not initially be intuitive, it is likely that patients with a longer duration of pain already had alternative sources of pain ruled-out and/or treated, since they were recruited from spine or pain specialty clinics (as opposed to a primary care setting). Additionally, the study population, including a trial with randomization to a sham control, likely favored patients with more chronic LBP who had expended all other available options. It is interesting and perhaps unsurprising that LBP exacerbation when bending backward (spinal extension)—an activity classically associated with facet loading—was associated with a reduced odds (OR 0.542) of treatment success following BVN RFA. The involved clinical studies did not require a medial branch block in addition to clinical assessment to rule out facet joint pain. Trial inclusion only required the primary source of LBP to be VEP and therefore are representative of a typical spine patient.

Increased pain with physical activity increasing the odds of treatment success with BVN RFA (OR 2.099) suggests that mechanical forces on the endplate likely cause VEP when pressure is loaded onto the vertebral column [40, 41]. Although such pressures have classically been thought to be received by the intervertebral discs, vertebral endplates may also be impacted to an extent that nociception via the BVN occurs.

Other findings from the regression models were not anticipated. The finding that female sex is associated with an increased odds of positive response to BVN RFA (OR 1.925) for the response definition 2 (ODI $\geq$ 15-point improvement), is inconsistent with other literature suggesting roughly equal treatment responses by sex for other interventional procedures to address low back pain [37, 38]; Based on the authors' cumulative experience with this procedure, we suspect that additional study will likely reveal parity between men and women who undergo BVN RFA.

Similarly, we did not anticipate that a history of lumbar epidural steroid injection in the 6 months prior to BVN RFA would predict lower odds (OR 0.556) of treatment response. To speculate, patients who had undergone lumbar epidural steroid injection were likely being treated for radicular pain, which presumably would have largely resolved prior to enrollment in one of the three included clinical trials. Each of these patients would have had unresolved chronic axial LBP with associated Type 1 and/or Type 2 Modic changes and clinically-suspected VEP in order to be enrolled in the three respective trials. It is possible that following BVN RFA, VEP may have largely resolved the low back pain, but radicular pain could have reemerged given the expected therapeutic duration of epidural steroid injections in the lumbar region [42].

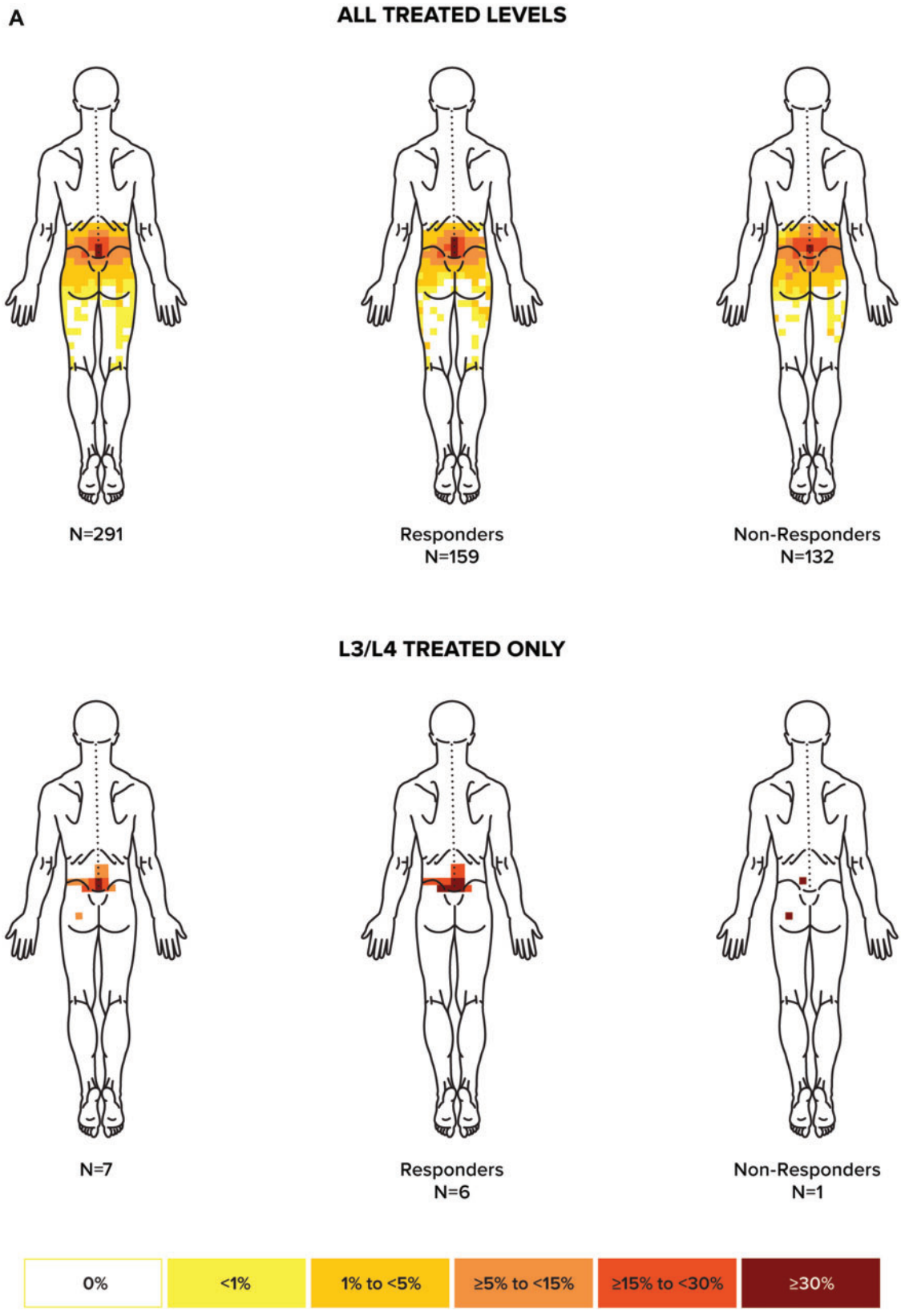
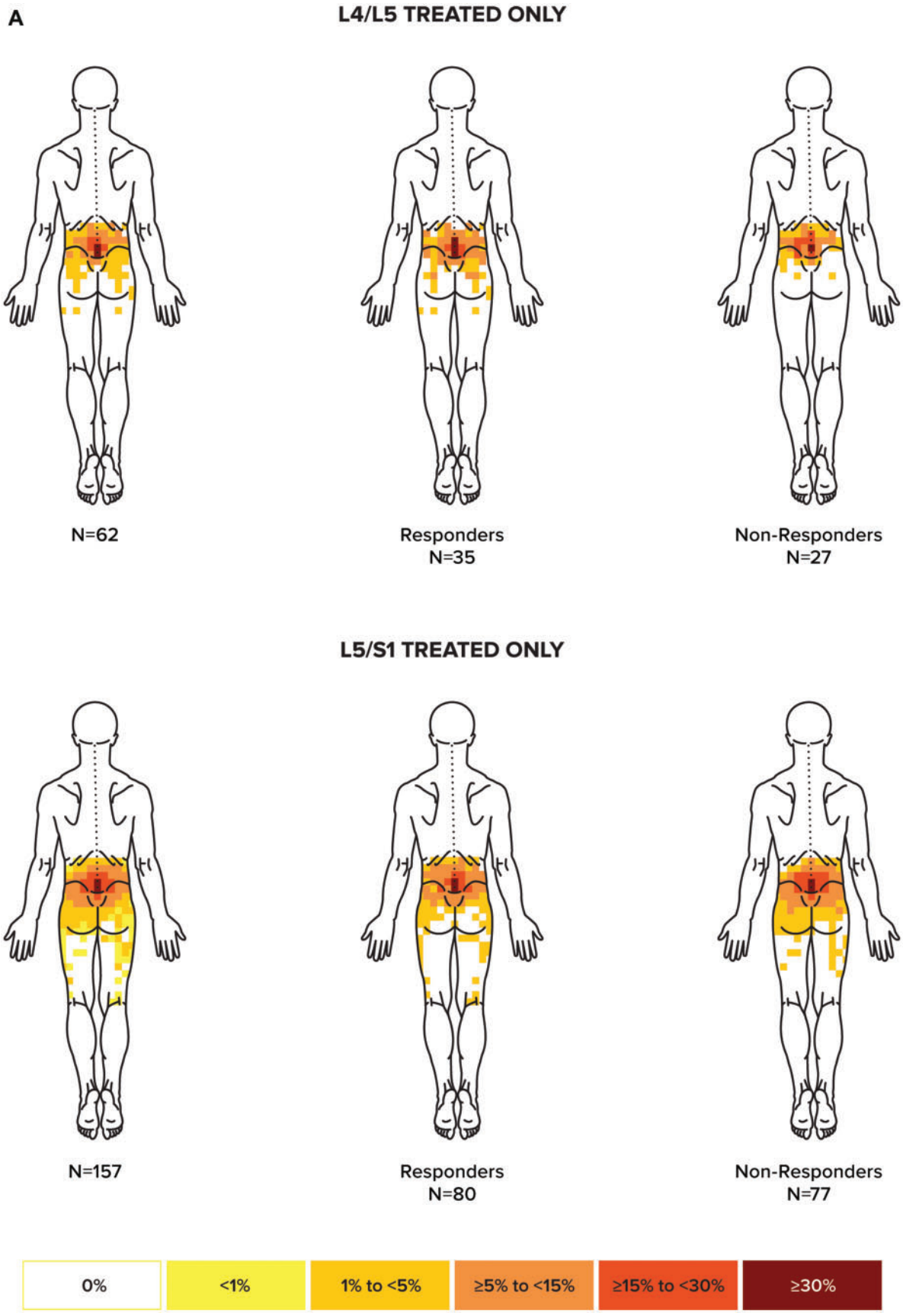


Figure 3. (**A**) Pain location "heat maps" for response definition ≥50% VAS improvement. Pain location "heat maps" were created by overlaying the coded pain body diagrams completed by study patients before undergoing BVN RFA. "Heat maps" are shown for the aggregate cohort as well as stratified by responder and non-responder subgroups and by vertebral level treated for the response definition ≥50% VAS improvement. Darker shading represents a higher proportion of individuals who marked an area as painful, while lighter shading represents fewer individuals indicating pain in those regions.



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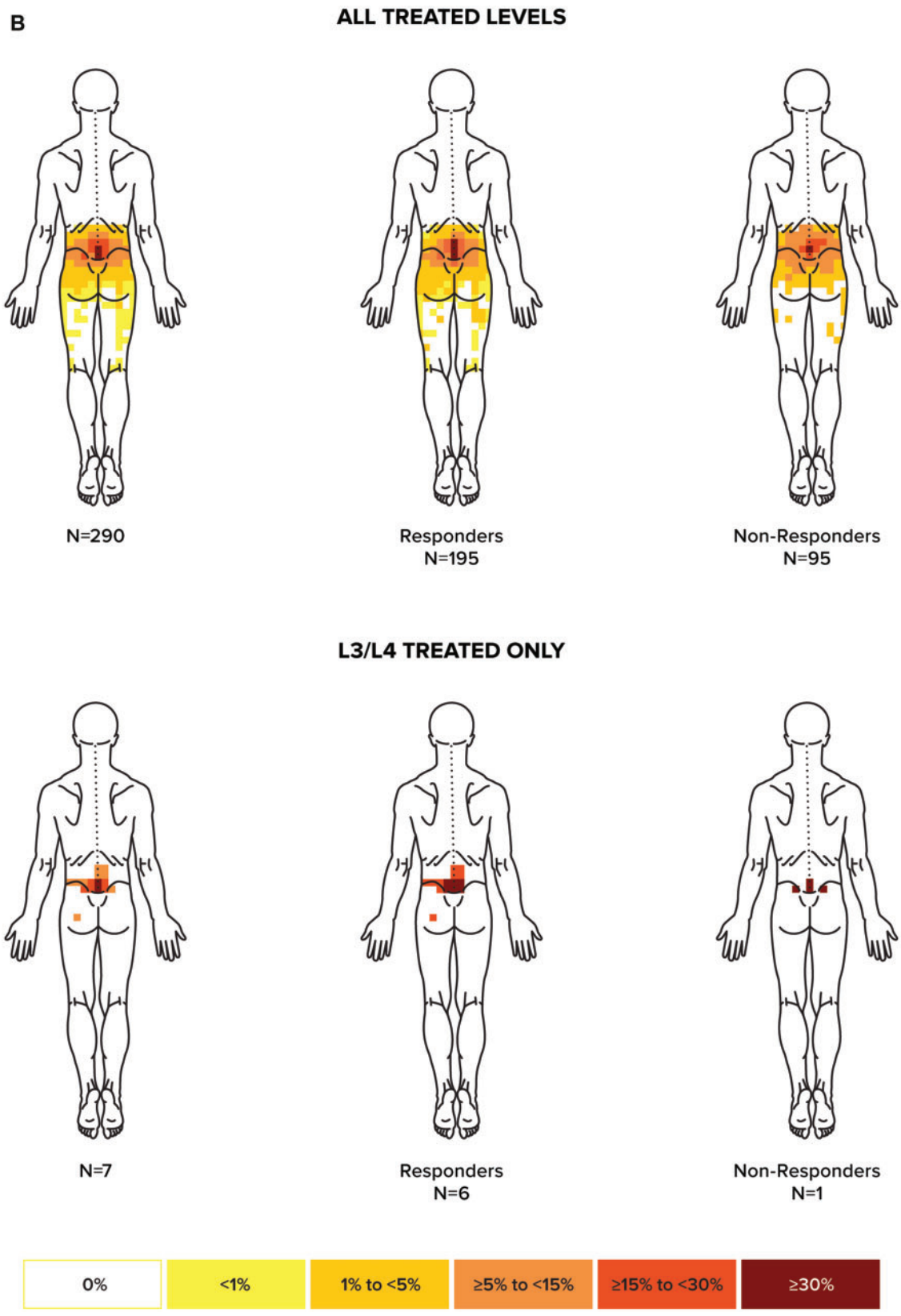
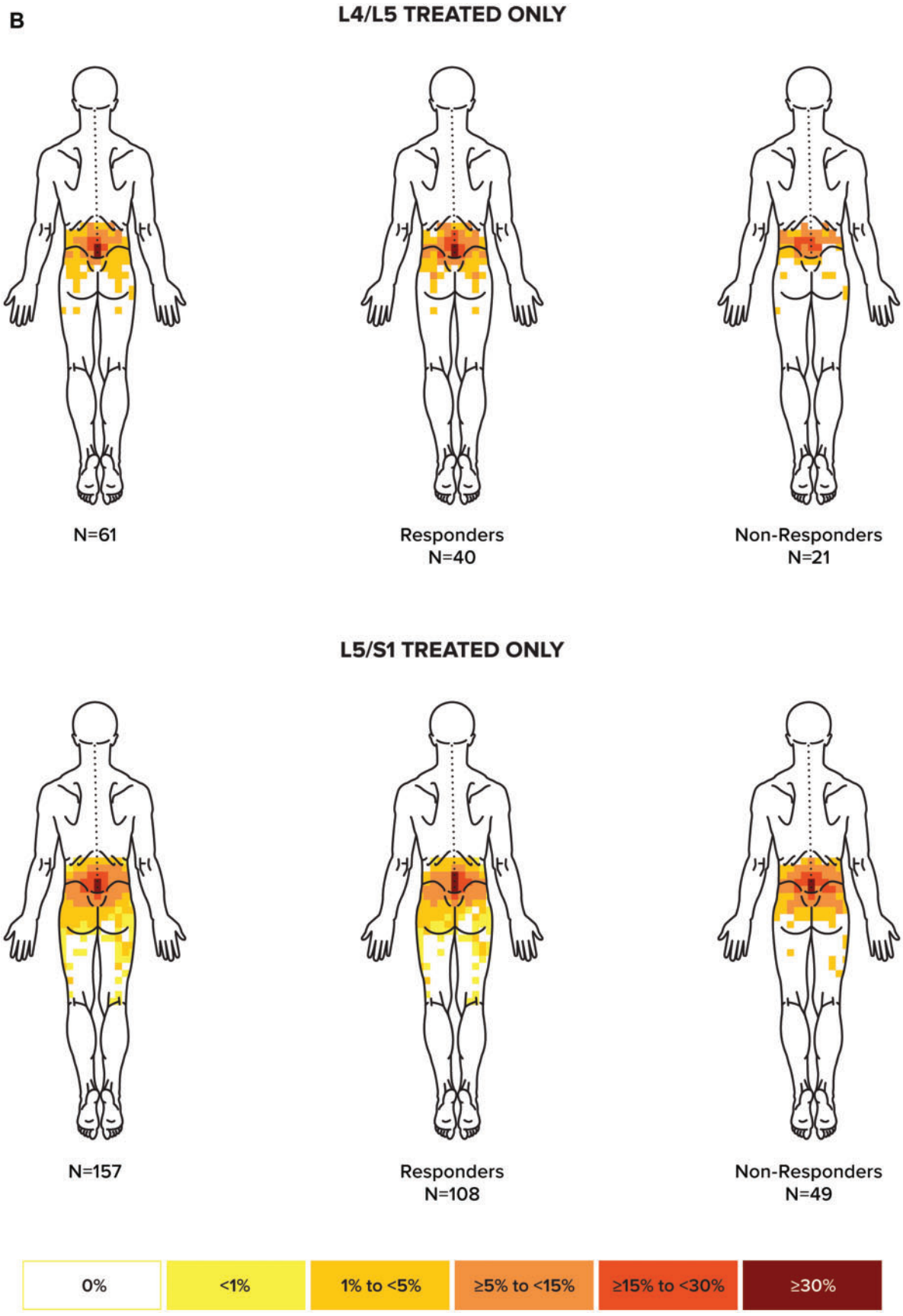


Figure 3. (Continued) (**B**) Pain location "heat maps" for response definition ≥15-point ODI improvement. Pain location "heat maps" were created by overlaying the coded pain body diagrams completed by study patients before undergoing BVN RFA. "Heat maps" are shown for the aggregate cohort as well as stratified by responder and non-responder subgroups and by vertebral level treated for the response definition ≥15-point ODI improvement. Darker shading represents a higher proportion of individuals who marked an area as painful, while lighter shading represents fewer individuals indicating pain in those regions.



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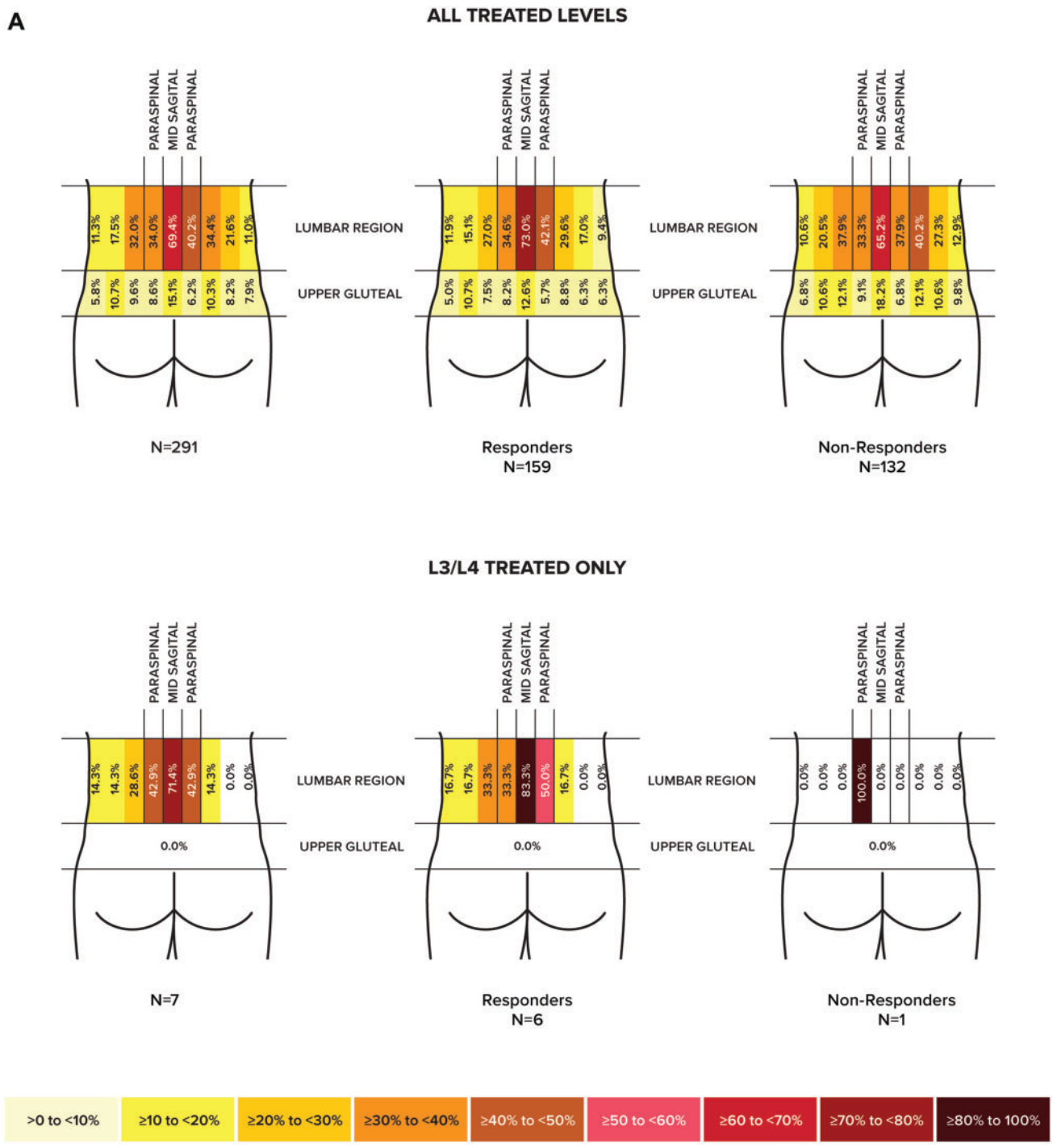
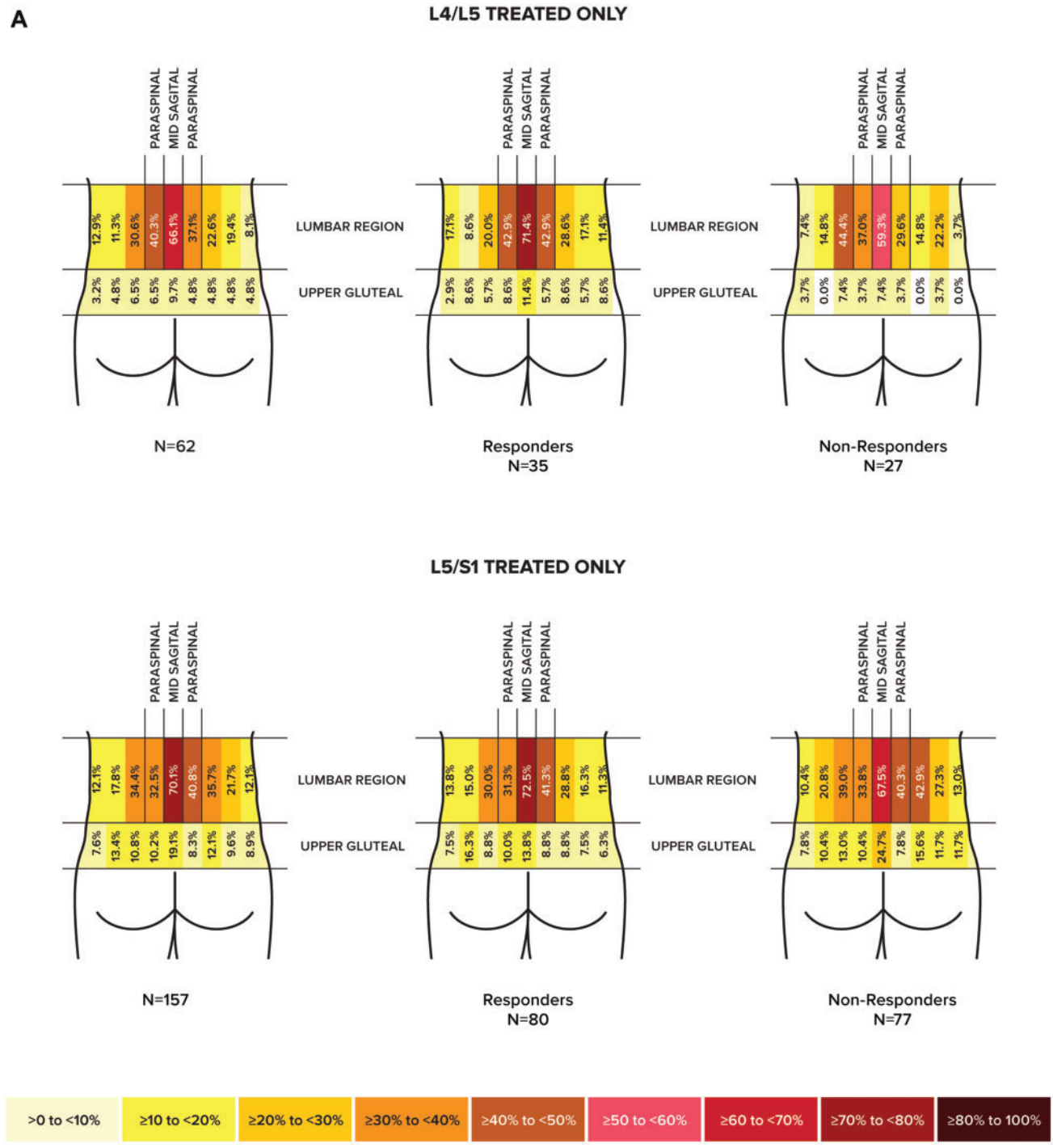


Figure 4. (**A**) Pain location "heat maps" grouped by treated levels *relative to midline* for the response definition ≥50% VAS improvement. Pain location "heat maps" were created by overlaying the coded pain body diagrams completed by study patients before undergoing BVN RFA. "Heat maps" depict pain location grouped by treated levels (all patients, L3–L4, L4–L5, and L5–S1) *relative to midline* for the aggregate cohort stratified by responder and non-responder subgroups for the response definition ≥50% VAS improvement. Darker shading represents a higher proportion of individuals who marked an area as painful, while lighter shading represents fewer individuals indicating pain in those regions.



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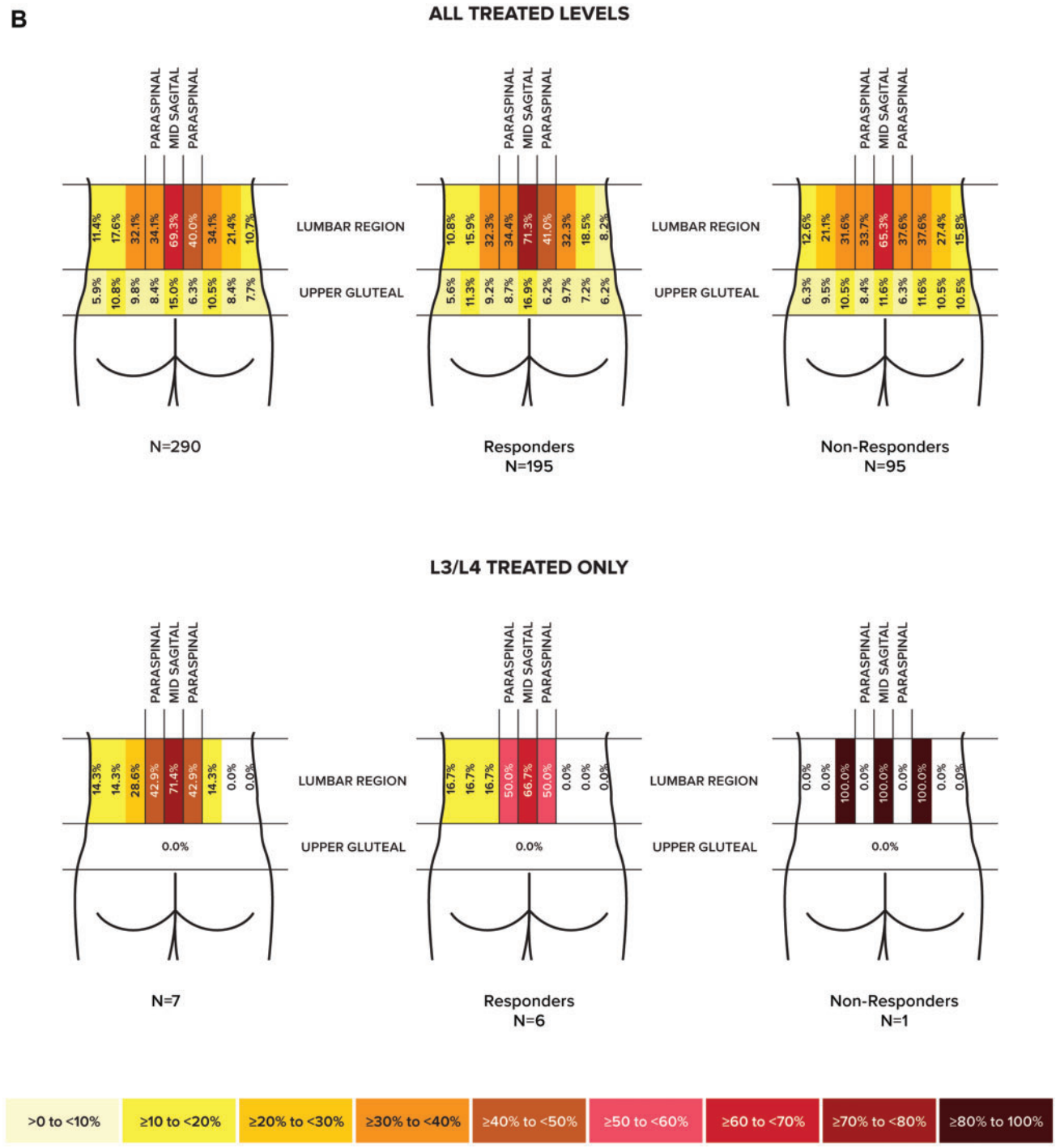

Figure 4. (Continued) (**B**) Pain location "heat maps" grouped by treated levels *relative to midline* for the response definition ≥15-point ODI improvement. Pain location "heat maps" were created by overlaying the coded pain body diagrams completed by study patients before undergoing BVN RFA. "Heat maps" depict pain location grouped by treated levels (all patients, L3–L4, L4–L5, and L5–S1) *relative to midline* for the aggregate cohort stratified by responder and non-responder subgroups for the response definition ≥15-point ODI improvement. Darker shading represents a higher proportion of individuals who marked an area as painful, while lighter shading represents fewer individuals indicating pain in those regions.

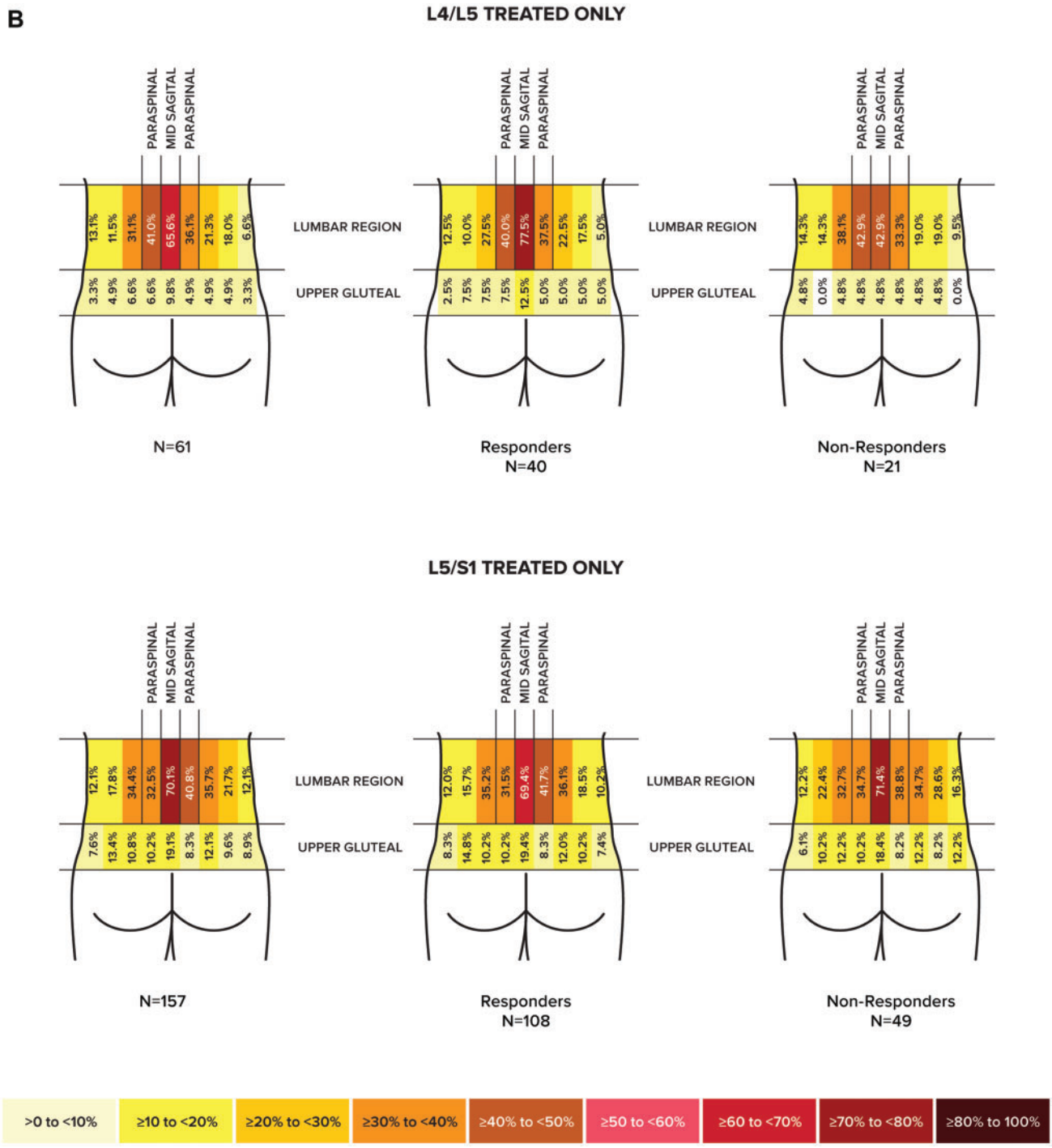

Figure 4. (Continued)

Stepwise regression modeling also suggested that increased pain when bending to the left predicted increased odds (OR 2.184) of BVN RFA success, though exacerbated pain when bending to the right was deemed insignificant during stepwise regression for all three responder criteria and was never included in any predictive model. We suspect this may be due to collinearity between bending to the left and bending to the right. In this instance, these two predictors would be highly correlated and the inclusion of both in the model would be redundant and potentially result in less precise estimates and large standard errors.

Finally, it is important to acknowledge that each of the three stepwise regressions returned AUCs of under 70%, which is indicative of low predictive value. In this context, we recommend that clinicians continue to rely

on inclusion criteria from the three clinical trials analyzed for patient selection for BVN RFA. These include a history of chronic LBP with evidence of Type 1 and/or Type 2 Modic changes on MRI, lack of response to traditional non-operative care, and a correlating clinical presentation of anterior spinal element pain as the dominant source of symptoms.

A strength of this analysis is that all patients were part of a prior clinical trial with similar inclusion/exclusion criteria for a more homogenous population of primary VEP for discerning predictive pain characteristics of BVN RFA. However, this is also a limitation because the cohort does not entirely reflect an LBP population with mixed etiologies. Additionally, the predictive model is limited to the variables collected in the trials, and therefore unknown predictive variables may exist. Finally, these findings represent associations but not causation.

Response to BVN RFA is an imperfect reference standard for VEP, but it is an acceptable clinical point of reference in the absence of a more specific diagnostic approach or a better-established gold standard. The heat maps included in this work offer only a preliminary analysis of the predictive value of pain location on BVN RFA treatment response. Future diagrammatic approaches would be well-advised to incorporate measures of pain intensity and pain location into predictive analyses, as has been done in previous pain-mapping approaches [7]. Doing so may offer a more nuanced insight of overall innervation pathways of the basivertebral nerve and augment the clinical utility of pain maps for both BVN RFA and other interventional pain procedures.

Conclusion

This study demonstrates that midline LBP, with or without a component of paraspinal or gluteal pain, correlates with treatment success at 3 months following BVN RFA in individuals with clinically suspected VEP. Duration of pain greater than 5 years, lack of epidural steroid injection within 6 months before BVN RFA, lack of baseline opioid use, LBP exacerbation with activity, and a lack of LBP with spinal extension are factors associated with increased odds of treatment success. While none of the regression models used in this study demonstrated strong predictive value, the pain location and exacerbators identified in this analysis can aid clinicians in recognizing patients where VEP should be more strongly suspected. The use of objective imaging biomarkers (Type 1 and/or 2 Modic changes) and a correlating presentation of anterior spinal element pain remain the most useful patient selection factors for BVN RFA.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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