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Original Research Article

Magnetic Resonance Imaging Characteristics Associated with Treatment Success from Basivertebral Nerve Ablation: An Aggregated Cohort Study of Multicenter Prospective Clinical Trials Data

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Abstract

Objective. Investigate associations between endplate and motion segment magnetic resonance imaging (MRI) characteristics and treatment outcomes following basivertebral nerve radiofrequency ablation (BVN RFA) in patients with clinically suspected vertebral endplate pain (VEP). **Design.** Aggregated cohort study of 296 participants treated with BVN RFA from three prospective clinical trials. **Methods.** Baseline MRI characteristics were analyzed using stepwise logistic regression to identify factors associated with treatment success. Predictive models used three definitions of treatment success: (1) $\geq$50% low back pain (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.** The presence of lumbar facet joint fluid (odds ratio [OR] 0.586) reduced the odds of BVN RFA treatment success in individuals with clinically suspected VEP. In patients with a less advanced degenerative disc disease (DDD) profile, a $>$50% area of the endplate with bone marrow intensity changes (BMIC) was predictive of treatment success (OR 4.689). Both regressions areas under the curve (AUCs) were under 70%, indicating low predictive value. All other vertebral endplate, intervertebral disc, nerve roots facet joint, spinal segmental alignment, neuroforamina, lateral recesses, and central canal MRI characteristics were not associated with BVN RFA success. **Conclusions.** In patients with vertebrogenic low back pain with Modic changes, the presence of degenerative findings of the anterior and posterior column was not associated with a clinically important impact on BVN RFA treatment success. None of the models demonstrated strong predictive value, indicating that the use of objective imaging biomarkers (Type 1 and/or 2 Modic changes) and a correlating presentation of pain remain the most useful patient selection factors for BVN RFA.

Key Words: Low Back Pain; Vertebral; Endplate; Disc Degeneration; Imaging

Introduction

Chronic low back pain (LBP) is the most common condition causing pain and disability in the United States and internationally [1]. In the United States alone, direct costs related to LBP treatments are estimated at $90 billion annually [2]. Historically, "discogenic" pain was considered the most common identifiable cause of CLBP, accounting for 39–42% of cases [3]. However, recent anatomic, histologic, and clinical evidence have revealed vertebral endplate pain (VEP) as an important source of CLBP [4].

Vertebral endplate pain is caused by biologic cross talk between vertebrae and discs at sites of vertebral endplate damage that stimulates inflammation and fibrovascular changes in the vertebral bone marrow [5]. Endplate inflammatory factors produce nociception via the basivertebral nerve (BVN), formed by contributions from the sinuvertebral nerve [6–8]. The inflammatory mediators increase vascular and nerve ingrowth and cause nearby vertebral body dysmyelopoiesis [8–11]. These vascular and marrow changes can be observed on magnetic resonance imaging (MRI) as Type 1 and Type 2 Modic changes. Modic changes were first described radiologically by Modic et al. in 1988 and categorized as a fibrovascular replacement (Modic type 1), fatty marrow replacement (Modic type 2), or sclerosis of the vertebral endplate and vertebral body (Modic type 3) [12]. Immunohistochemical studies of vertebral endplates from patients with clinically suspected discogenic pain associated with Modic type 1 and 2 changes have shown increased quantities of protein gene product (PGP) 9.5 immunoreactive nerve fibers and tumor necrosis factor (TNF) immunoreactive cells compared to normal vertebral endplates [13]. Additionally, the utility of Modic 1 and 2 changes as radiographic biomarkers of LPB is clinically demonstrated by their strong association with provocation discography (odd ratio [OR] of 4.01 [1.52–10.61] [14] and persistence of LPB following discectomy surgery [15].

Basivertebral nerve radiofrequency ablation (BVN RFA) was developed to disrupt afferent pain signaling from painful VEPs. The BVN RFA procedure involves unilateral transpedicular access and a bipolar electrode to deliver high-frequency alternating current, resulting in basivertebral nerve denaturing. Two randomized controlled trials (RCTs) and four single-arm prospective cohort study have found BVN RFA to be an effective and durable (up to five years) treatment option to decrease VEP pain [16–28]. To date, all BVN RFA study participants have been selected by the presence of both subjective complaints consistent with anterior spinal element pain and Modic 1 and/or Modic 2 changes within the L3–S1 vertebral bodies. Though Modic changes strongly correlate with VEP, the association between other lumbar MRI biomarkers and BVN RFA success is unknown.

Given this knowledge gap, the current study aimed to catalog MRI characteristics from the three BVN RFA clinical trials to identify MRI variables associated with a successful treatment outcome following BVN RFA. Identifying such variables may help clinicians identify patients more likely to respond to BVN RFA and provide a more informed discussion with patients considering this intervention.

Methods

Study Design

This study aggregated data from three distinct prospective clinical trials that included individuals who underwent treatment with BVN RFA. All three clinical trials were sponsored by Relievant Medsystems, Inc. The aggregated data originated from 33 different centers, representing both academic and private practices in the United States and Europe. Patients were enrolled into the three clinical trials between October 2011 and February 2019, which included (1) an explanatory randomized controlled trial (RCT) of 147 individuals who underwent BVN RFA and 78 sham controls [17]; (2) a pragmatic RCT of 66 individuals who were randomized to treatment with BVN RFA and 74 individuals who were randomized to a standard of care control group (61 of whom crossed to active treatment with BVN RFA) [18, 27]; (3) a prospective cohort study of 48 individuals treated with BVN RFA [19, 26]. The three studies had similar inclusion/exclusion criteria to identify primary vertebrogenic pain and to exclude patients with other primary sources of pain. To evaluate the impact of study blinding differences (one study being double blinded and two studies being open label), individual study regressions were conducted and compared to aggregate results. No notable differences in overall regression findings were noted.

All three clinical trials required informed consent and privacy authorization by study participants. An Institutional Review Board approved all three clinical trials (Western IRB no. PRO20111346, Schulman IRB no. 201702680/ADVARRA IRB no. PRO00026311, and Schulman IRB no. 201706803/Advarra IRB no. Pro000226859, respectively). 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 study data and MRIs used in this secondary research were deidentified and

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 nonoperative 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.

unable to be traced to an individual patient. As such, no additional IRB review was required for this research.

Participant Inclusion and Exclusion Criteria

All patients enrolled in the three studies had chronic, refractory LBP with Type 1 and/or Type 2 Modic changes between L3-S1, and each study's inclusion and exclusion criteria were similar to rule out other LBP etiologies. Patients were excluded for >5-mm disc protrusion, >2-mm spondylolisthesis, and symptomatic stenosis. See Table 1 for the full inclusion exclusion criteria for these studies.

For the present study, a minimum follow-up of 3-months with the collection of ODI and/or VAS was required for inclusion in the regression analysis. In addition, prior regression analysis for the two RCTs [17, 27] demonstrated that treatment accuracy predicted response; therefore, only individuals who received BVN RFA where the BVN was successfully targeted were included in this study. Successful targeting was defined as adequate overlap of the ablation lesion with the BVN foramen adjudicated by a single independent neuroradiologist on post-ablation MRI review. In each study BVN RFA was performed with the Intracept ® System (Relievant Medsystems, Minneapolis, MN USA) under image guidance. The radiofrequency ablation target was located at the midpoint of each vertebral body in an anterior-posterior view, and at or posterior to the midpoint in a lateral view (distance from posterior to anterior vertebral body wall of 40–60% [17] used in the initial RCT and 30% to 50% [18, 19] used in the second RCT with enhanced targeting success). The procedure has been described in greater detail, previously [17–19].

Baseline Magnetic Resonance Imagining Data Collection, Interpretation, and Adjudication

To confirm established MRI-related inclusion/exclusion criteria, all clinical trial participants had an MRI within 3 months before BVN RFA. For the current study, the baseline MRI of every qualifying participant was interpreted by a single independent fellowship-trained, board-certified, Pain Medicine physician (Conor O'Neil MD, University of California San Francisco) who was blinded to treatment outcomes. The vertebral endplates, intervertebral discs, nerve roots, facet joints, spinal segmental alignment, neuroforamina, lateral recesses, and central canal were graded at all lumbosacral spinal levels (L1–S1) according to a pre-defined scheme (Supplementary Data Appendix A). A second blinded review was performed by a fellowship-trained, board-certified Orthopedic Surgeon (Jeffrey Fischgrund, MD, Beaumont Hospital) if there was discordance noted between the original medical monitor's vertebral bodies with Modic changes and the intensity changes identified by the independent reviewer for this study. In cases of disagreements between reviewer 1 and reviewer 2, ties were broken by the first author, a fellowship-trained, board-certified, Pain Medicine physician (Z.M.).

Treatment Success Definitions

To determine the association between MRI findings and BVN RFA success, treatment "success" was defined by three different definitions 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. These definitions are consistent with commonly accepted clinically meaningful thresholds used to assess pain and functional outcomes of treatments for LBP [29, 30].

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 four stepwise regression models fit using the three responder definitions analyzed in this study.

Data Included in the Analysis

The analysis included the endplate and motion segment MRI characteristics measured in the independent radiologic review (Supplementary Data Appendix A). Potential predictive variables were pre-identified for this exploratory analysis by an independent vertebrogenic pain steering committee comprised of orthopedic surgeons, interventional radiologists, and pain management physicians. Endplate and motion segment imaging characteristics that were selected for the models represent severity of endplate damage and/or possible mixed pain sources and were felt by the steering committee to have the greatest potential impact on response to BVN RFA. Endplate variables included in the regression models were bone marrow intensity change (BMIC) type, BMIC height of the vertebral body, BMIC width of the endplate, presence of an endplate defect, type/shape of endplate defect, and endplate defect size (measured as the width of the endplate). Motion segment variables included in the regression models were degree of degenerative disc disease (DDD) by Pfirrmann Grade [31], nuclear signal, disc height, presence of annular high intensity zones, disc contour, nerve root compromise, facet joint arthropathy, presence or absence of facet joint fluid, olisthesis, and degree of foraminal, central canal, and lateral recess stenosis (see Supplementary Data Appendix A for details of grading). All endplate and motion segment factors identified by the steering committee were analyzed for each regression model stratification using the three BVN RFA treatment success/responder definitions and were summarized descriptively. Endplate and motion segment characteristics were either included or excluded in the final model based on pre-specified thresholds. Regression models details and the appropriate statistical methods are described in more detail in the following sub-sections.

Regression Models

For the first regression model, the endplate with the *greatest* height of BMIC, as measured in the sagittal plane on MRI, was selected to represent that study patient. BMIC height was deemed as representing endplate damage severity by the steering committee, with clinical rationale that greater BMIC height is indicative of greater endplate damage and should be most responsive to BVN RFA. In the event the patient's greatest height was the same for all treated endplates, the endplate with the greatest BMIC width was then selected. If both the BMIC height and BMIC width were the same for all treated endplates, the endplate with the greatest defect size (width of the endplate) was chosen to be used in the models. The model was fit with the selected predictors of BMIC type, BMIC height, BMIC width, endplate defect size, and endplate defect shape for the selected patient-representative endplate.

For motion segment variables evaluated in this first regression model, the adjacent motion segment to the selected "most severely damaged" endplate (the endplate with the greatest BMIC height) was used. The model was fit for degree of DDD/Pfirrmann Grade, nuclear signal, disc height, the presence of disc high-intensity zones, disc contour/herniation, nerve root compromise, facet joint arthropathy, presence or absence of facet joint fluid, Olisthesis, and the degree of foraminal, central canal, and lateral recess stenosis, as predictors.

For the second regression model, the endplate with the *least* height of BMIC, as measured in the sagittal plane on MRI, was selected to represent that study patient. The least BMIC height was used to identify the treated level with the least severely damaged endplate(s) and most likely not to respond to BVN RFA. In the event the patient's least height was the same for all treated endplates, the endplate with the least width of BMIC was selected. If a third variable was necessary, the least defect size (width of the endplate) was used to identify the endplate to be used in the models. The model was fit with the selected predictors of BMIC type, BMIC height, BMIC width, endplate defect size, and endplate defect shape for the selected patient-representative endplate.

For motion segment variables evaluated in this second regression model, the adjacent motion segment to the selected "least severely damaged" endplate treated (the endplate with the least BMIC height) was used to represent the patient. The model was fit for degree of DDD/Pfirrmann Grade, nuclear signal, disc height, the presence of disc high-intensity zones, disc contour/herniation, nerve root compromise, facet joint arthropathy, presence of facet joint fluid, Olisthesis, and the degree of foraminal, central canal, and lateral recess stenosis, as predictors.

For a third regression model, only patients with one motion segment treated were included in the analyses. This was done to represent the patient profile that was believed by the steering committee to most likely to

respond to BVN RFA (most advanced DDD) and the least likely to respond BVN RFA (least advanced DDD). The most advanced DDD model included the Pfirrmann grade (for the treated segment), the adjacent endplate (superior or inferior) with the greatest BMIC height, and the adjacent endplate with the greatest BMIC width were included as individual predictors in the model.

The fourth regression model in this analysis included only patients with one motion segment treated. In this least advanced DDD model, the Pfirrmann grade (for the treated segment), the adjacent endplate with the least BMIC height, and the adjacent endplate with the least BMIC width were included as individual predictors in the model.

Statistical Analysis

Descriptive statistics for individual endplate and motion segment variables are presented by response status (responder/nonresponder) for patients in the study cohort (successfully treated BVN RFA patients with a baseline MRI and a minimum of a 3-month follow-up with a VAS and/or ODI questionnaire collected). Statistical comparisons between the proportion of responders and nonresponders for each individual variable were made using a Fisher's exact test. A threshold of $P < .05$ was used for significance for the descriptive summaries.

According to the responder definitions outlined above, stepwise logistic regression was conducted to identify the best imaging predictors (endplate and motion segment characteristics) of positive response to successful treatment with BVN RFA. The stepwise regression used forward selection and backward elimination regression methods. An intercept was entered for the model, and then the model was fit using a .05 entry criterion and a .10 stay criterion with P values calculated used the score chi-square test to assess each variable for entry into the model. The predictor with the smallest P value, less than the prespecified .05 entry criteria, was entered into the model at each iteration. After each predictors' entry, the model was fit by assessing for statistical significance of each predictor in the model. Each predictor required a P value of less than the prespecified .10 stay criteria to remain in the model with P values calculated used the Wald chi-square test. These iterations continued until no further predictors were removed or added into the model. All descriptive statistics and modeling were carried out using SAS version 9.4 (SAS Cary, NC, USA).

After fitting the logistic regression model, the sensitivity and specificity of the model were plotted using a receiver-operating characteristics (ROC) curve. For this curve, the independent variable (predictors) estimates were used to calculate the probability of treatment success. To translate the probability of treatment success into a binary yes/no, we can choose a threshold value for the probability. For example, if we use .5 for the probability threshold, when the predicted probability of success was greater than the .5 threshold, that individual patient was predicted as a treatment success. When the predicted probability of success was less than .5, the patient was predicted as a treatment failure.

Each patient's predicted success/failure from the model estimates was compared to the known actual success/failure from the patients' clinical trial data. A count of the number of patients that true positives (successes), true negatives (failures), false positives, and false negatives based on their actual values and model predicted values was performed. The sensitivity of the threshold is the rate of true positives, and the specificity is the rate of true negatives. The y-axis of sensitivity and the x-axis of (1-specificity) are depicted on the receiver-operating characteristics (ROC) curve graphs for varying probability threshold values.

In interpreting the area under the ROC curve (AUC), a value ranging from 0 to 1 is used, where 0 indicates a perfectly inaccurate model classification of treatment success, and a 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. An AUC above 0.5 indicates a reasonable ability to predict treatment success. Values between 0.5 and 0.7 indicate some predictive ability, while values between 0.7 and 0.8 indicate good predictive ability, and values above 0.8 are deemed excellent predictive ability [32].

Results

The study CONSORT diagram is shown in Figure 1. In the three individual studies, a total of 322 participants underwent BVN RFA, including 61 controls that crossed over to active treatment.

Of the BVN RFA group, 292 were treated successfully and had confirmed BMIC changes at treated levels per independent radiologic review. These individuals comprised the cohort for this analysis. Five patients provided VAS but did not complete an ODI questionnaire, and 4 patients provided ODI but did not complete a VAS at three months post-BVN RFA. As such, 287 patients had a minimum of a 3-month follow-up with ODI or VAS scores reported and are included in each regression model pending the response definition.

Table 2 shows the descriptive summaries for patients by the *greatest* BMIC height endplate and the adjacent motion segment stratified by responder/nonresponder for each of the imaging characteristics collected in the study. The presence of facet fluid demonstrated significant differences between responders and nonresponders for Response Definition no. 1 of VAS $\geq$50% improvement at P value .03. There were no endplate or adjacent motion segment characteristics that demonstrated significant differences between responder and nonresponders for the Response Definition no. 2 of ODI $\geq$15-point

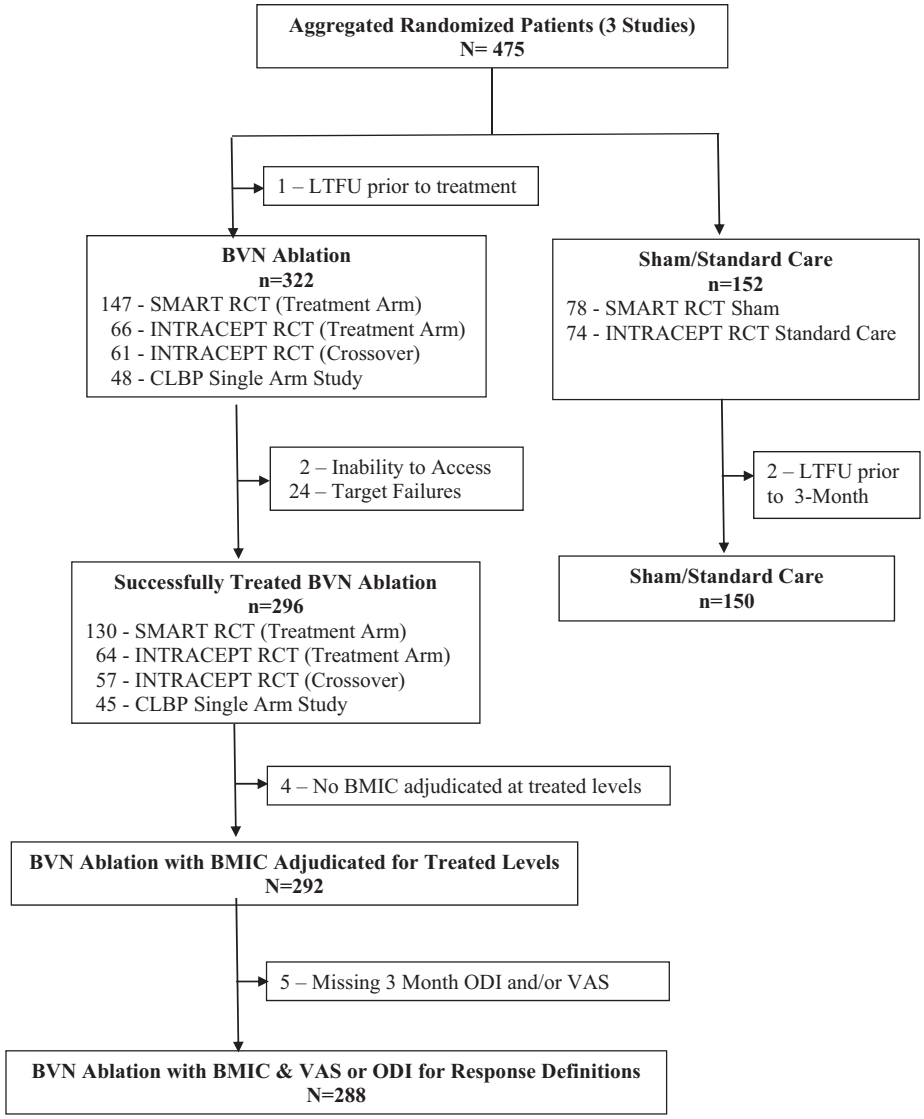

Figure 1. CONSORT diagram of the aggregate cohort included in the analysis. In sum, 475 participants from the three individual studies had a minimum data set, as defined in the methods section and were included in regression analyses to identify potential MRI predictors of treatment success (322 participants underwent BVN RFA, including 61 controls that crossed over to active treatment). Of the BVN RFA group, 296 were treated successfully, and 292 had confirmed BMIC changes at treated levels per independent radiologic review. These individuals comprised the cohort for this analysis. Of these, 288 and had a minimum of a 3-month follow-up with ODI or VAS scores reported and are included in each regression model pending the response definition. BVN RFA = basivertebral nerve radiofrequency ablation; CLBP = chronic low back pain; LTFU = lost to follow-up; RCT = randomized controlled trial; BMIC = bone marrow intensity change; ODI = Oswestry Disability Index; VAS = Visual Analog Scale

improvement or Response Definition no. 3 of VAS $\geq$50% OR ODI $\geq$ 15-point improvement.

Table 3 shows the descriptive summaries for patients by the endplate with the *least* BMIC height and the adjacent motion segment stratified by responder/nonresponder for each of the imaging characteristics collected in the study. The presence of facet fluid demonstrated significant differences between responders and nonresponders for Response Definition no. 1 of VAS $\geq$50% improvement at *P* value .04. Endplate defect shape and foraminal stenosis were approaching significant differences between responders/nonresponders for Response Definition no. 1 at *P* value of .06 and .05, respectively. There were no endplate or adjacent motion segment characteristics that demonstrated significant differences between responder and nonresponders for the Response Definition no. 2 of ODI $\geq$15-point improvement or Response Definition no. 3 of VAS $\geq$50% OR ODI $\geq$ 15-point improvement.

Table 4 **Regression Model 1** includes the results for the stepwise logistic regression model building using the *greatest* BMIC height treated endplate as the patient-level predictor set. The steering committee pre-identified full set of predictors for the selected endplate included:

Table 2. Descriptive summaries by patient and endplate with greatest bone marrow intensity changes (BMIC) height

Characteristics	Successfully Treated Patients (n = 292)	VAS ≥50% Improvement		*P* value*	ODI ≥15 Point Improvement		*P* value*
		Responders	Non Responder		Responders	Non Responders	
BMIC							
Yes	100.0% (292)	54.2% (156/288)	45.8% (132/288)		67.2% (193/287)	32.8% (94/287)	
BMIC type				.42			.58
Type 1	54.8% (160)	56.1% (88/157)	43.9% (69/157)		69.4% (109/157)	30.6% (48/157)	
Type 2	44.5% (130)	51.2% (66/129)	48.8% (63/129)		64.3% (83/129)	35.7% (46/129)	
Type 3	0.7% (2)	100.0% (2/2)	0.0% (0/2)		100.0% (1/1)	0.0% (0/1)	
BMIC height				.24			.78
Localized to endplate only	27.7% (81)	60.5% (49/81)	39.5% (32/81)		71.6% (58/81)	28.4% (23/81)	
Less than 25% of vertebral body height	35.3% (103)	49.5% (50/101)	50.5% (51/101)		65.3% (66/101)	34.7% (35/101)	
25 to 50% of vertebral body height	31.5% (92)	56.7% (51/90)	43.3% (39/90)		66.3% (59/89)	33.7% (30/89)	
More than 50% vertebral body height	5.5% (16)	37.5% (6/16)	62.5% (10/16)		62.5% (10/16)	37.5% (6/16)	
BMIC area				.54			.68
Less than 25% of endplate area	28.1% (82)	55.6% (45/81)	44.4% (36/81)		65.4% (53/81)	34.6% (28/81)	
25 to 50% of endplate area	26.7% (78)	58.4% (45/77)	41.6% (32/77)		71.4% (55/77)	28.6% (22/77)	
More than 50% of endplate area	45.2% (132)	50.8% (66/130)	49.2% (64/130)		65.9% (85/129)	34.1% (44/129)	
Endplate defect				.25			.13
No	22.3% (65)	47.6% (30/63)	52.4% (33/63)		58.7% (37/63)	41.3% (26/63)	
Yes	77.7% (227)	56.0% (126/225)	44.0% (99/225)		69.6% (156/224)	30.4% (68/224)	
Endplate defect shape				.50			.63
Sharp, angular	1.8% (4)	25.0% (1/4)	75.0% (3/4)		50.0% (2/4)	50.0% (2/4)	
Schmorl's node	4.4% (10)	60.0% (6/10)	40.0% (4/10)		80.0% (8/10)	20.0% (2/10)	
Irregular	93.8% (213)	56.4% (119/211)	43.6% (92/211)		69.5% (146/210)	30.5% (64/210)	
Endplate defect size				.41			.15
Less than 1/3 endplate area	22.9% (52)	59.6% (31/52)	40.4% (21/52)		71.2% (37/52)	28.8% (15/52)	
Between 1/3 and 2/3 endplate area	22.5% (51)	62.0% (31/50)	38.0% (19/50)		80.0% (40/50)	20.0% (10/50)	
More than 2/3 endplate area	54.6% (124)	52.0% (64/123)	48.0% (59/123)		64.8% (79/122)	35.2% (43/122)	
Degenerative disc disease				.60			.12
Homogeneous disc structure with bright white disc (Pfirrmann Grade 1)	0.0% (0)	0.0% (0/0)	0.0% (0/0)		0.0% (0/0)	0.0% (0/0)	
Inhomogeneous structure with or without horizontal bands (Grade 2)	1.4% (4)	75.0% (3/4)	25.0% (1/4)		75.0% (3/4)	25.0% (1/4)	
Inhomogeneous structure with gray disc (Grade 3)	21.6% (63)	47.5% (29/61)	52.5% (32/61)		55.7% (34/61)	44.3% (27/61)	
Inhomogeneous structure with gray to black disc (Grade 4)	39.7% (116)	55.7% (64/115)	44.3% (51/115)		73.0% (84/115)	27.0% (31/115)	
Inhomogeneous structure with black disc (Grade 5)	37.3% (109)	55.6% (60/108)	44.4% (48/108)		67.3% (72/107)	32.7% (35/107)	
Nuclear signal				.27			.44
Normal, pure white signal on T2-weighted images	1.4% (4)	50.0% (2/4)	50.0% (2/4)		75.0% (3/4)	25.0% (1/4)	
Moderate loss, intermediate between normal and severe	20.2% (59)	44.8% (26/58)	55.2% (32/58)		60.3% (35/58)	39.7% (23/58)	
Severe loss, homogenous black signal	78.4% (229)	56.6% (128/226)	43.4% (98/226)		68.9% (155/225)	31.1% (70/225)	
Disc height				.61			.22
Normal, less than 10% loss of expected height	12.7% (37)	47.2% (17/36)	52.8% (19/36)		58.3% (21/36)	41.7% (15/36)	
Moderate narrowing, 10–50% loss	33.9% (99)	56.7% (55/97)	43.3% (42/97)		63.9% (62/97)	36.1% (35/97)	
Severe narrowing, 50% loss	53.4% (156)	54.2% (84/155)	45.8% (71/155)		71.4% (110/154)	28.6% (44/154)	
High intensity zone				.74			.49
No	84.2% (246)	53.7% (131/244)	46.3% (113/244)		66.3% (161/243)	33.7% (82/243)	
Yes	15.8% (46)	56.8% (25/44)	43.2% (19/44)		72.7% (32/44)	27.3% (12/44)	
Disc contour				.89			.63
Normal, no extension beyond the interspace	3.4% (10)	60.0% (6/10)	40.0% (4/10)		50.0% (5/10)	50.0% (5/10)	
Bulge, circumferential, symmetrical disc extension	81.2% (237)	54.5% (127/233)	45.5% (106/233)		67.4% (157/233)	32.6% (76/233)	
Protrusion, focal or asymmetrical disc extension	15.1% (44)	50.0% (22/44)	50.0% (22/44)		69.8% (30/43)	30.2% (13/43)	

(continued)

Table 2. continued

Characteristics	Successfully Treated Patients (n = 292)	VAS ≥50% Improvement			ODI ≥15 Point Improvement		
		Responders	Non Responder	*P* value*	Responders	Non Responders	*P* value*
Extrusion, focal disc extension beyond the interspace	0.3% (1)	100.0% (1/1)	0.0% (0/1)		100.0% (1/1)	0.0% (0/1)	
Nerve root compromise				.15			.30
No nerve root contact	94.5% (276)	53.3% (145/272)	46.7% (127/272)		67.2% (182/271)	32.8% (89/271)	
Nerve root contact without deviation	3.8% (11)	63.6% (7/11)	36.4% (4/11)		63.6% (7/11)	36.4% (4/11)	
Nerve root deviation	1.4% (4)	100.0% (4/4)	0.0% (0/4)		100.0% (4/4)	0.0% (0/4)	
Nerve root compression/deformation	0.3% (1)	0.0% (0/1)	100.0% (1/1)		0.0% (0/1)	100.0% (1/1)	
Facet joint arthropathy				.47			.62
Normal facet joint space (2–4 mm width)	8.9% (26)	44.0% (11/25)	56.0% (14/25)		60.0% (15/25)	40.0% (10/25)	
Narrowing of the FJ space (<2 mm) and/or small osteophytes	60.6% (177)	57.4% (101/176)	42.6% (75/176)		69.3% (122/176)	30.7% (54/176)	
Narrowing of the FJ space and/or moderate osteophytes	28.8% (84)	51.2% (42/82)	48.8% (40/82)		65.9% (54/82)	34.1% (28/82)	
Narrowing of the FJ space and/or large osteophytes	1.7% (5)	40.0% (2/5)	60.0% (3/5)		50.0% (2/4)	50.0% (2/4)	
Facet joint fluid				.03			.42
No	66.4% (194)	58.6% (112/191)	41.4% (79/191)		68.9% (131/190)	31.1% (59/190)	
Yes	33.6% (98)	45.4% (44/97)	54.6% (53/97)		63.9% (62/97)	36.1% (35/97)	
Olisthesis				.80			.78
No	94.5% (276)	54.4% (148/272)	45.6% (124/272)		67.5% (183/271)	32.5% (88/271)	
Yes	5.5% (16)	50.0% (8/16)	50.0% (8/16)		62.5% (10/16)	37.5% (6/16)	
Congenital stenosis				.34			.10
No	98.6% (288)	54.6% (155/284)	45.4% (129/284)		67.8% (192/283)	32.2% (91/283)	
Yes	1.4% (4)	25.0% (1/4)	75.0% (3/4)		25.0% (1/4)	75.0% (3/4)	
Foraminal stenosis				.11			.46
Normal foramina with normal dorsolateral border	33.6% (98)	49.5% (47/95)	50.5% (48/95)		62.1% (59/95)	37.9% (36/95)	
Slight foraminal stenosis and deformity of the epidural fat	53.1% (155)	52.6% (81/154)	47.4% (73/154)		68.2% (105/154)	31.8% (49/154)	
Marked foraminal stenosis and deformity of the epidural fat	12.0% (35)	71.4% (25/35)	28.6% (10/35)		76.5% (26/34)	23.5% (8/34)	
Advanced stenosis with obliteration of the epidural fat	1.4% (4)	75.0% (3/4)	25.0% (1/4)		75.0% (3/4)	25.0% (1/4)	
Central spinal stenosis				.65			.59
No constriction of thecal sac	95.5% (279)	53.8% (148/275)	46.2% (127/275)		67.3% (185/275)	32.7% (90/275)	
Mild constriction of thecal sac with minimal loss of CSF	2.7% (8)	62.5% (5/8)	37.5% (3/8)		71.4% (5/7)	28.6% (2/7)	
CSF diminished but still present	1.4% (4)	75.0% (3/4)	25.0% (1/4)		75.0% (3/4)	25.0% (1/4)	
Complete loss of CSF in the thecal sac	0.3% (1)	0.0% (0/1)	100.0% (1/1)		0.0% (0/1)	100.0% (1/1)	
Lateral regions spinal stenosis				.25			.55
No nerve root contact	99.0% (289)	53.7% (153/285)	46.3% (132/285)		66.9% (190/284)	33.1% (94/284)	
Nerve root contact without deviation	1.0% (3)	100.0% (3/3)	0.0% (0/3)		100.0% (3/3)	0.0% (0/3)	
Nerve root deviation	0.0% (0)	0.0% (0/292)	0.0% (0/292)		0.0% (0/0)	0.0% (0/0)	

The table shows the descriptive summaries for patients by the *greatest* BMIC height endplate and the adjacent motion segment stratified by responder/nonresponder by Response Definition no. 1 (VAS ≥50% improvement) and Response Definition no. 2 (ODI ≥15-point improvement) for each of the endplate and motion segment imaging characteristics collected in the study. The presence of facet fluid demonstrated significant differences between responders and nonresponders for Response Definition no. 1 - VAS ≥50% improvement at *P* values 0.03. There were no endplate or adjacent motion segment characteristics that demonstrated significant differences between responder and nonresponders for Response Definition no. 2 - ODI ≥15-point improvement. BMIC = bone marrow intensity change; MRI = magnetic resonance imaging; ODI = Oswestry Disability Index; VAS = Visual Analogue Score (average low back pain in past 7 days).

**P* values calculated using a Fisher exact test.

BMIC type, BMIC height, BMIC width of the endplate, presence of an endplate defect, endplate defect width of the endplate, and endplate defect shape, for the selected endplate. After removing study patients that had missing outcome or predictor values (with the most common missing variables being endplate defect shape and size), 225/292 patients remained for Response Definition no. 1—VAS ≥50% improvement, 224/292 patients remained for ODI Response Definition no. 2—ODI ≥15-point improvement, and 225/292 patients remained for the Response Definition no. 3—VAS ≥50% OR ODI ≥ 15-point improvement. There were no predictors that had a *P* value below .05, and as such none were included in the final fitted models across all response definitions.

Table 3. Descriptive summaries by patient and endplate with least bone marrow intensity changes (BMIC) height

Characteristics	Successfully Treated Patients (n = 292)	VAS ≥50% Improvement			ODI ≥15 Point Improvement		
		Responders	Non Responder	*P* value*	Responders	Non Responders	*P* value*
BMIC							
Yes	100.0% (292)	54.2% (156/288)	45.8% (132/288)		67.2% (193/287)	32.8% (94/287)	
BMIC type				.29			.58
Type 1	53.8% (157)	56.5% (87/154)	43.5% (67/154)		69.5% (107/154)	30.5% (47/154)	
Type 2	45.5% (133)	50.8% (67/132)	49.2% (65/132)		64.4% (85/132)	35.6% (47/132)	
Type 3	0.7% (2)	100.0% (2/2)	0.0% (0/2)		100.0% (1/1)	0.0% (0/1)	
BMIC height				.48			.46
Localized to endplate only	56.8% (166)	56.4% (93/165)	43.6% (72/165)		67.9% (112/165)	32.1% (53/165)	
Less than 25% of vertebral body height	30.5% (89)	51.7% (45/87)	48.3% (42/87)		70.1% (61/87)	29.9% (26/87)	
25 to 50% of vertebral body height	12.0% (35)	52.9% (18/34)	47.1% (16/34)		57.6% (19/33)	42.4% (14/33)	
More than 50% vertebral body height	0.7% (2)	0.0% (0/2)	100.0% (2/2)		50.0% (1/2)	50.0% (1/2)	
BMIC area				.25			.37
Less than 25% of endplate area	46.2% (135)	59.4% (79/133)	40.6% (54/133)		68.4% (91/133)	31.6% (42/133)	
25 to 50% of endplate area	22.9% (67)	50.8% (33/65)	49.2% (32/65)		72.3% (47/65)	27.7% (18/65)	
More than 50% of endplate area	30.8% (90)	48.9% (44/90)	51.1% (46/90)		61.8% (55/89)	38.2% (34/89)	
Endplate defect				.26			.29
No	34.2% (100)	49.5% (48/97)	50.5% (49/97)		62.9% (61/97)	37.1% (36/97)	
Yes	65.8% (192)	56.5% (108/191)	43.5% (83/191)		69.5% (132/190)	30.5% (58/190)	
Endplate defect shape				.06			.55
Sharp, angular	5.2% (10)	30.0% (3/10)	70.0% (7/10)		80.0% (8/10)	20.0% (2/10)	
Schmorl's node	4.2% (8)	87.5% (7/8)	12.5% (1/8)		87.5% (7/8)	12.5% (1/8)	
Irregular	90.6% (174)	56.6% (98/173)	43.4% (75/173)		68.0% (117/172)	32.0% (55/172)	
Endplate defect size				.87			.19
Less than 1/3 endplate area	34.4% (66)	59.1% (39/66)	40.9% (27/66)		74.2% (49/66)	25.8% (17/66)	
Between 1/3 and 2/3 endplate area	18.2% (35)	54.3% (19/35)	45.7% (16/35)		77.1% (27/35)	22.9% (8/35)	
More than 2/3 endplate area	47.4% (91)	55.6% (50/90)	44.4% (40/90)		62.9% (56/89)	37.1% (33/89)	
Degenerative disc disease				.33			.44
Homogeneous disc structure with bright white disc (Pfirrmann Grade 1)	0.0% (0)	0.0% (0/0)	0.0% (0/0)		0.0% (0/0)	0.0% (0/0)	
Inhomogeneous structure with or without horizontal bands (Grade 2)	2.1% (6)	83.3% (5/6)	16.7% (1/6)		66.7% (4/6)	33.3% (2/6)	
Inhomogeneous structure with gray disc (Grade 3)	23.3% (68)	47.0% (31/66)	53.0% (35/66)		59.1% (39/66)	40.9% (27/66)	
Inhomogeneous structure with gray to black disc (Grade 4)	42.5% (124)	55.3% (68/123)	44.7% (55/123)		70.7% (87/123)	29.3% (36/123)	
Inhomogeneous structure with black disc (Grade 5)	32.2% (94)	55.9% (52/93)	44.1% (41/93)		68.5% (63/92)	31.5% (29/92)	
Nuclear signal				.21			.56
Normal, pure white signal on T2-weighted images	2.1% (6)	66.7% (4/6)	33.3% (2/6)		66.7% (4/6)	33.3% (2/6)	
Moderate loss, intermediate between normal and severe	22.0% (64)	44.4% (28/63)	55.6% (35/63)		61.9% (39/63)	38.1% (24/63)	
Severe loss, homogenous black signal	75.9% (221)	56.4% (123/218)	43.6% (95/218)		68.7% (149/217)	31.3% (68/217)	
Disc height				.76			.15
Normal, less than 10% loss of expected height	15.1% (44)	48.8% (21/43)	51.2% (22/43)		58.1% (25/43)	41.9% (18/43)	
Moderate narrowing, 10–50% loss	36.1% (105)	55.3% (57/103)	44.7% (46/103)		64.1% (66/103)	35.9% (37/103)	

(continued)

Table 3. continued

Characteristics	Successfully Treated Patients (n = 292)	VAS ≥50% Improvement			ODI ≥15 Point Improvement		
		Responders	Non Responder	*P* value*	Responders	Non Responders	*P* value*
Severe narrowing, 50% loss	48.8% (142)	54.6% (77/141)	45.4% (64/141)		72.1% (101/140)	27.9% (39/140)	
High intensity zone				1.00			.47
No	85.6% (249)	53.8% (133/247)	46.2% (114/247)		66.3% (163/246)	33.7% (83/246)	
Yes	14.4% (42)	55.0% (22/40)	45.0% (18/40)		72.5% (29/40)	27.5% (11/40)	
Disc contour				.33			.60
Normal, no extension beyond the interspace	4.1% (12)	66.7% (8/12)	33.3% (4/12)		50.0% (6/12)	50.0% (6/12)	
Bulge, circumferential, symmetrical disc extension	80.8% (235)	55.0% (127/231)	45.0% (104/231)		67.5% (156/231)	32.5% (75/231)	
Protrusion, focal or asymmetrical disc extension	14.8% (43)	44.2% (19/43)	55.8% (24/43)		69.0% (29/42)	31.0% (13/42)	
Extrusion, focal disc extension beyond the interspace	0.3% (1)	100.0% (1/1)	0.0% (0/1)		100.0% (1/1)	0.0% (0/1)	
Nerve root compromise				.15			.32
No nerve root contact	94.5% (276)	53.3% (145/272)	46.7% (127/272)		66.8% (181/271)	33.2% (90/271)	
Nerve root contact without deviation	3.8% (11)	63.6% (7/11)	36.4% (4/11)		72.7% (8/11)	27.3% (3/11)	
Nerve root deviation	1.4% (4)	100.0% (4/4)	0.0% (0/4)		100.0% (4/4)	0.0% (0/4)	
Nerve root compression/deformation	0.3% (1)	0.0% (0/1)	100.0% (1/1)		0.0% (0/1)	100.0% (1/1)	
Facet joint arthropathy				.69			.89
Normal facet joint space (2–4 mm width)	9.6% (28)	44.4% (12/27)	55.6% (15/27)		63.0% (17/27)	37.0% (10/27)	
Narrowing of the FJ space (<2 mm) and/or small osteophytes	60.6% (177)	56.3% (99/176)	43.8% (77/176)		68.8% (121/176)	31.3% (55/176)	
Narrowing of the FJ space and/or moderate osteophytes	28.4% (83)	53.1% (43/81)	46.9% (38/81)		65.4% (53/81)	34.6% (28/81)	
Narrowing of the FJ space and/or large osteophytes	1.4% (4)	50.0% (2/4)	50.0% (2/4)		66.7% (2/3)	33.3% (1/3)	
Facet joint fluid				.04			.50
No	67.8% (198)	58.5% (114/195)	41.5% (81/195)		68.6% (133/194)	31.4% (61/194)	
Yes	32.2% (94)	45.2% (42/93)	54.8% (51/93)		64.5% (60/93)	35.5% (33/93)	
Olisthesis				.60			.58
No	94.9% (277)	54.6% (149/273)	45.4% (124/273)		67.6% (184/272)	32.4% (88/272)	
Yes	5.1% (15)	46.7% (7/15)	53.3% (8/15)		60.0% (9/15)	40.0% (6/15)	
Congenital stenosis				.34			.10
No	98.6% (288)	54.6% (155/284)	45.4% (129/284)		67.8% (192/283)	32.2% (91/283)	
Yes	1.4% (4)	25.0% (1/4)	75.0% (3/4)		25.0% (1/4)	75.0% (3/4)	
Foraminal stenosis				.05			.27
Normal foramina with normal dorsolateral border	35.6% (104)	48.5% (49/101)	51.5% (52/101)		61.4% (62/101)	38.6% (39/101)	
Slight foraminal stenosis and deformity of the epidural fat	51.4% (150)	53.0% (79/149)	47.0% (70/149)		68.5% (102/149)	31.5% (47/149)	
Marked foraminal stenosis and deformity of the epidural fat	11.6% (34)	73.5% (25/34)	26.5% (9/34)		78.8% (26/33)	21.2% (7/33)	
Advanced stenosis with obliteration of the epidural fat	1.4% (4)	75.0% (3/4)	25.0% (1/4)		75.0% (3/4)	25.0% (1/4)	
Central spinal stenosis				.50			1.00
No constriction of thecal sac	95.9% (280)	53.3% (147/276)	46.7% (129/276)		67.0% (185/276)	33.0% (91/276)	
Mild constriction of thecal sac with minimal loss of CSF	2.7% (8)	75.0% (6/8)	25.0% (2/8)		71.4% (5/7)	28.6% (2/7)	

(continued)

Table 3. continued

Characteristics	Successfully Treated Patients (n = 292)	VAS ≥50% Improvement			ODI ≥15 Point Improvement		
		Responders	Non Responder	*P* value*	Responders	Non Responders	*P* value*
CSF diminished but still present	1.0% (3)	66.7% (2/3)	33.3% (1/3)		66.7% (2/3)	33.3% (1/3)	
Complete loss of CSF in the thecal sac	0.3% (1)	100.0% (1/1)	0.0% (0/1)		100.0% (1/1)	0.0% (0/1)	
Lateral regions spinal stenosis				.13			.53
No nerve root contact	98.3% (287)	53.4% (151/283)	46.6% (132/283)		66.7% (188/282)	33.3% (94/282)	
Nerve root contact without deviation	1.4% (4)	100.0% (4/4)	0.0% (0/4)		100.0% (4/4)	0.0% (0/4)	
Nerve root deviation	0.3% (1)	100.0% (1/1)	0.0% (0/1)		100.0% (1/1)	0.0% (0/1)	

The table shows the descriptive summaries for patients by the *least* BMIC height endplate and the adjacent motion segment stratified by responder/nonresponder by Response Definition no. 1 (VAS ≥50% improvement) and Response Definition no. 2 (ODI ≥15-point improvement) for each of the endplate and motion segment imaging characteristics collected in the study. The presence of facet fluid demonstrated significant differences between responders and nonresponders for Response Definition no. 1 (VAS ≥50% improvement at *P* value .04). Endplate shape and foraminal stenosis were nearing significance for difference in responder/nonresponders for Response Definition no. 1. There were no endplate or adjacent motion segment characteristics that demonstrated significant differences between responder and nonresponders for Response Definition no. 2 (ODI ≥15-point improvement). BMIC = bone marrow intensity change; MRI = magnetic resonance imaging; ODI = Oswestry Disability Index; VAS = Visual Analogue Score (average low back pain in past 7 days).

**P* values calculated using a Fischer's exact test.

An additional stepwise logistic regression model using the *greatest* BMIC height treated endplate as the patient-level predictor set with a reduced variable set removing the endplate defect size and shape variables from the model was performed to increase the sample to 288/292, 287/292, and 288/292 patients for the three response definitions, respectively. The regression analysis with the increased sample did not identify any additional predictors with the larger sample.

Regression Model 1 also includes the results for the stepwise logistic regression for the adjacent motion segment of the selected endplate with the *greatest* BMIC height as the patient-level predictor set. The pre-identified full set of motion segment predictors evaluated for inclusion in the model included DDD by Pfirrmann Grade, nuclear signal, disc height, the presence of disc high intensity zones, disc contour/herniation, nerve root compromise, facet joint arthropathy, presence of facet joint fluid, Olisthesis, and degree of foraminal, central canal, and lateral recess stenosis for the adjacent motion segment. After removing study patients that had missing outcome or predictor values, 288/292 patients remained for Response Definition no. 1—VAS ≥50% improvement, 287/292 patients remained for ODI Response Definition no. 2—ODI ≥15-point improvement, and 288/292 patients remained for the Response Definition no. 3—VAS ≥50% OR ODI ≥ 15-point improvement. Only one variable met the stay criterion for Response Definition no. 1 (VAS ≥50% improvement) and was selected in the stepwise regression, the presence of facet fluid (*P* value .03). Table 4 depicts the results of the final regression model. While the presence of facet fluid reduced the odds of treatment success (OR 0.586) the AUC of 0.5597 demonstrates this to be a weak predictor.

Regression Model 2 includes the results for the stepwise logistic regression model building using the *least* BMIC height treated endplate as the patient-level predictor set. The full set of pre-identified endplate predictors included were: BMIC type, BMIC height, BMIC width of the endplate, presence of an endplate defect, endplate defect width of the endplate, and endplate defect shape, for the selected endplate, and Pfirrmann Grade, presence of disc high intensity zones, disc contour/herniation, nerve root compromise, facet joint arthropathy, presence of facet joint fluid, Olisthesis, and degree of foraminal, central canal, and lateral recess stenosis for the adjacent motion segment. When using the *least* BMIC height endplate as the patient-level predictor set, the numbers of patients without endplate defects is greater than when using *greatest* BMIC height endplate as the patient-level predictor set. After removing study patients that had missing outcome or predictor values (with the most common missing variables being endplate defect shape and size), 191/292 patients remained for Response Definition no. 1—VAS ≥50% improvement, 190/292 patients remained for ODI Response Definition no. 2—ODI ≥15-point improvement, and 191/292 patients remained for the Response Definition no. 3—VAS ≥50% OR ODI ≥ 15-point improvement. There were no predictors that had a *P* value below .05, and as such none were included in the final fitted models across all response definitions. In the model fit for response definition no. 1—VAS ≥50% improvement, endplate defect shape was marginally significant with a *P* value of .05.

A stepwise logistic regression model using the *least* BMIC height treated endplate as the patient-level predictor set with a reduced variable set removing the endplate defect size and shape variables from the model was performed to increase the sample to 288/292, 287/292, and 288/292 patients for the three response definitions, respectively. The regression analysis did not identify any additional predictors with the larger sample.

Table 4. Regression model 1 - motion segment predictors of BVN RFA treatment success according to the treated vertebral endplate with the greatest height of bone marrow intensity change

Model	Variable Included	OR	*P* value*	Pseudo R^2	Area Under ROC Curve
Treated subjects N = 296, N = 288 used for selection, N = 288 used for final model	Facet Joint Fluid (Yes vs No)	0.586	.0333	0.0157	0.5567

The table shows the results for the stepwise logistic regression model for motion segment characteristics using the motion segment that is adjacent to the endplate with the *greatest* BMIC height treated as the patient-level predictor set. One predictor, the presence of facet joint fluid, had a *P* value of .03 for the response definition no. 1—VAS ≥ 50% improvement, and was included in the final fitted models across all response definitions. While the presence of facet joint fluid reduced the odds of treatment success (OR 0.586) with the response definition no. 1—VAS ≥ 50% improvement, the AUC was 0.5567 for weak predictability. VAS = Visual Analogue Score (average low back pain in past 7 days); OR = Odds Ratio; ROC = Receiver-Operating Characteristics.

**P* values calculated used Wald χ^2 test.

Table 5. Regression model 2: motion segment predictors of BVN RFA treatment success according to the treated vertebral endplate with the least height of bone marrow intensity change

Model	Variable Included	OR	*P* value*	Pseudo R^2	Area Under ROC Curve
Treated subjects N = 296, N = 287 used for selection, N = 288 used for final model	Facet Joint Fluid (Yes vs No)	0.585	0.0349	0.0154	0.5586

The table shows the results for the stepwise logistic regression model building using the motion segment that is adjacent to the endplate with the *least* BMIC height treated as the patient-level predictor set. One predictor, the presence of facet joint fluid, had a *P* value of *.03* for the response definition no. 1—VAS ≥ 50% improvement, and was included in the final fitted models across all response definitions. While the presence of facet joint fluid reduced the odds of treatment success (OR 0.585) with the response definition no. 1—VAS ≥ 50% improvement, the AUC was 0.5586 for weak predictability. VAS = Visual Analogue Score (average low back pain in past 7 days); OR = Odds Ratio; ROC = Receiver-Operating Characteristics.

**P* values calculated used Wald chi-square test.

Regression Model 2 also includes the results for the stepwise logistic regression for the adjacent motion segment of the selected endplate with the *least* BMIC height as the patient-level predictor set. The full set of preidentified motion segment predictors evaluated for inclusion in the model included Pfirrmann Grade, nuclear signal, disc height, the presence of disc high intensity zones, disc contour/herniation, nerve root compromise, facet joint arthropathy, presence of facet joint fluid, Olisthesis, and degree of foraminal, central canal, and lateral recess stenosis for the adjacent motion segment. After removing study patients that had missing outcome or predictor values, 288/292 patients remained for Response Definition no. 1—VAS ≥50% improvement, 287/292 patients remained for ODI Response Definition no. 2—ODI ≥15-point improvement, and 288/292 patients remained for the Response Definition no. 3—VAS ≥50% OR ODI ≥ 15-point improvement. Only one variable met the stay criterion for Response Definition no. 1 (VAS ≥50% improvement) and was selected in the stepwise regression, the presence of facet fluid (*P* value .03). Table 5 depicts the results of the final regression model. While the presence of facet fluid reduced the odds of treatment success (OR 0.585) the AUC of 0.5586 demonstrates this to be a weak predictor.

Regression Model 3 includes the results for the stepwise logistic regression model building using the most severe DDD endplate in a subset of patients with only one motion segment that was successfully treated (N = 227). Of these, five patients were missing either a 3-month ODI or VAS outcome and were excluded from the model depending on the response definition. The steering committee prespecified predictors included in this model representing most advanced DDD were Pfirrmann Grade of the treated motion segment, the greatest BMIC height for an adjacent endplate, and the greatest BMIC width for an adjacent endplate. There were no significant predictors across the three response definitions.

Regression Model 4 includes the results for the stepwise logistic regression model building using the least severe DDD endplate in a subset of patients with only one motion segment that was successfully treated (N = 227). Of these, five patients were missing either a 3-month ODI or VAS outcome and were excluded from the model depending on the response definition. The prespecified predictors included in this model representing least severe DDD were Pfirrmann Grade of the treated motion segment, the greatest BMIC height for an adjacent endplate, and the greatest BMIC area for an adjacent endplate. There was one predictor for the response Response Definition no. 3 VAS ≥50% OR ODI ≥ 15-point improvement that met the stay criterion, BMIC area (*P* value .13) and was selected in the stepwise regression. Table 6 depicts the results of the final regression model. While BMIC area increased the odds of treatment success (OR 1.418 when comparing <25% BMIC area of the

Table 6. Regression model 4: MRI predictors of BVN RFA treatment success according in a single treated motion segment by the least severe degenerative disc disease (DDD)

Model	Variable Included	OR	P^*	R^2	Area Under ROC Curve
Treated subjects	BMIC Area	1.418	0.2295	0.0478	0.6196
N = 231	(<25% vs >50%)	4.689	0.0061		
N = 233 used for selection	(25% to 50% vs >50%)				
N = 223 used for final model					

The table shows the results for the stepwise logistic regression model building using the *least severe* DDD endplate in a subset of patients with only one motion segment that was successfully treated (N = 227). Five of these patients were missing either a 3-month ODI or VAS outcome and were excluded from the model depending on the response definition. There was one predictor for the Response Definition no. 3 VAS ≥50% OR ODI ≥ 15-point improvement that met the stay criterion, BMIC area (*P* value .13) and was selected in the stepwise regression. While BMIC area increased the odds of treatment success (OR 1.418 when comparing <25% BMIC area of the endplate to >50% BMIC area and OR 4.689 when comparing 25% to 50% and >50%), the AUC of 0.6196 demonstrates this to be a weak predictor. VAS = Visual Analogue Score (average low back pain in past 7 days); ODI = Oswestry Disability Index; OR = Odds Ratio; ROC = Receiver-Operating Characteristics; BMIC = Bone Marrow Intensity Changes.

*P values calculated used Wald chi-square test.

endplate to >50% BMIC area and OR 4.689 when comparing 25% to 50% and >50%), the AUC of 0.6196 demonstrates this to be a weak predictor.

Discussion

This study represents the first comprehensive analysis of the association between MRI characteristics and treatment success following BVN RFA in patients with clinically suspected VEP. In summary, no specific endplate or motion segment MRI characteristic was strongly predictive of treatment outcome after BVN RFA. Although statistically significant, the presence of facet fluid only marginally reduced the odds of achieving >50% pain improvement (OR 0.578 for greatest BMIC model and OR 0.586 for least BMIC model) and had no association with treatment outcome for >15-point ODI improvement. The AUC was 0.5609 for the greatest BMIC height model and 0.586 for the least BMIC height model, suggesting that the presence of facet fluid on MRI was a weak predictor of failure to achieve >50% pain reduction (values between 0.5 and 0.7 indicate some predictive ability) [32].

Although only weakly predictive of treatment failure, it is notable that nearly 1 in 3 participants in this data set had lumbar facet fluid on MRI. Synovial fluid often accumulates within lumbar facet joints in the context of *unstable* spondylolisthesis. As such, the presence may indicate an unstable spondylolisthesis. It is widely postulated that excessive movement, as is the case with dynamic spondylolisthesis, at any motion segment can alter sheer forces at the discovertebral, facet joints, ligaments, and paraspinal musculature, all of which are sensate and may contribute to a patient's symptom of LBP. A recent systematic review and meta-analysis found that in those with existing spondylolisthesis, the probability of having instability is 8 times greater for those with facet fluid (compared to no facet fluid) and that a dose dependent relationship exists between the size of the effusion and likelihood of instability [33]. In the present study close to 32% of participants were noted to have facet joint fluid on MRI, yet only 5% had any degree of listhesis (Table 1). It is possible, that a subset of patients within these trials had undetected dynamic spondylolisthesis (evidenced by facet joint effusion), as supine MRI may not detect degenerative spondylolisthesis up to 28% of the time [34, 35]. However, this seems unlikely given the extensive exclusion criterion which were used to select participants for these studies. Investigators excluded those with radiographic evidence of spondylolisthesis greater than 2 mm, as well as those with facet arthrosis/effusion (in the presence of clinical suspicion for facet joint pain). Furthermore, disc protrusion > 5 mm and those with any clinical evidence of radicular pain or neurogenic claudication were also excluded. Given that these findings are often comorbid to unstable spondylolisthesis (spinal stenosis, disc protrusion, neurogenic claudication, and radicular pain), it seems improbable that many of those with facet effusion on MRI had unstable spondylolisthesis. Perhaps a more likely explanation is that the facet joint effusion seen in approximately 1/3 of participants simply mirrors the prevalence of that finding in the general population. The Wakayama spine study, a population based cohort study of over 800 participants, found that the prevalence of facet effusion in the lumbar spine was 34% and that there was no correlation between the presence of facet effusion and low back pain or spondylolisthesis (or even LBP in the presence of facet effusion AND spondylolisthesis) [36]. Further, multiple prior studies have found that facet pathology on MRI is either not associated or only weakly associated with the presence of facet joint pain and outcomes after lumbar medial branch RFA [37–39].

Recognizing this, clinicians are encouraged to interpret MRI findings in the clinical context and to investigate facet joint pain or unstable spondylolisthesis when the situation dictates. If lumbar facet mediated pain is clinically suspected in the setting of Modic changes, particularly in the setting of facet joint fluid on MRI, then it may be beneficial to rule this in/out with lumbar facet medial branch blocks before consideration of BVN RFA for VEP. Of note, if VEP is the primary pain generator, then lumbar medial

branch blocks should not result in a high degree of pain relief. Radiofrequency ablation may be appropriate for mixed sources of pain when the dominant source is addressed first (either the VEP or lumbar facet joints). Given the interconnected biomechanical nature of the lumbar spine, nociception arising from only one discrete structure may be less common than recognized clinically. For example, a recent study utilizing a placebo controlled triple block paradigm has suggested that the prevalence of "pure" lumbar facet joint pain may be as low as 15% [40]. Given the robust response to BVN sham treatment seen in the SMART trial, it is difficult to ascertain exactly what the true prevalence of "pure" VEP is in those presenting with CLBP with Modic changes, but it is notable that 31% of participants from the INTRACEPT study reported 100% pain relief at 2 years [28]. Clinicians are encouraged to use their best judgment to determine the *primary* generator of pain accepting that some patients may have pain from multiple sources.

Given the robust analysis of MRI findings, it is remarkable that no finding (other than the presence of Modic changes) significantly impacted the success of BVN RFA in a meaningful way. The presence of annular fissuring was not associated with treatment failure, though this finding has been associated with positive provocation discography in multiple studies [41, 42]. Similarly, although strongly associated with the presence of LBP in other studies [43–45], the presence and size of endplate defects was not significantly associated with treatment response. These findings may be best understood in a disease model that begins with injury to the discovertebral complex and culminates in chronic inflammation and chemical sensitization of the vertebral endplate and bone marrow [46]. Given that 100% of patients in this study had Modic 1 or 2 changes, it is perhaps not surprising that the relatively earlier findings of disc height loss, annular fissuring, and endplate damage did not influence BVN RFA success.

Modic change size and morphology was also not significantly associated with treatment outcome. This highlights that even trace amounts of Modic changes should not be dismissed, as it is likely that Modic changes are a late pain biomarker after vertebral endplate damage. Similarly, anterior localized intensity signals should be considered in the same manner as they are thought to occur from "tidemark avulsions" a form of endplate irregularity wherein the outer disc annulus separates from the vertebra at the enthesis [47]. Taken together, these findings should reassure clinicians that successful treatment response is likely in the majority of patients selected for BVN RFA based on a history of CLBP with evidence of Type 1 or Type 2 Modic changes on MRI, lack of response to traditional nonoperative care, and a correlating clinical presentation of anterior spinal element pain as the dominant source of symptoms.

A strength of this analysis is the homogeneity of the study populations with similar inclusion/exclusion for clinically suspected primary VEP. The MRIs were analyzed by board certified, fellowship trained Orthopedic and Pain Medicine specialists in a blinded fashion. The total N from which these observations were drawn was relatively large which allowed for more precise analysis of any important associations.

Limitations of this study must also be acknowledged. The potential impact of blinding differences between the three studies (one study being double blinded and two studies being open label) needs to be considered. To evaluate this, individual study regressions were conducted and compared to the aggregate results. While there were differences in variables that met the final stepwise regression model inclusion, there were no notable differences in overall regression findings for predictors of BVN RFA treatment success or failure for VEP. Another limitation is the exploratory nature of this study without prespecified hypotheses that were powered due to the set sample of the prior clinical studies that was available. We retrospectively explored the statistical power and found ORs of 1.5 and 2.0 to have a fairly low power (about 22% to 53%), but those of 2.5 and higher had power of at least 85%, and as high at 88% when the OR was 3.0. Therefore, if the effect of the candidate variables was fairly large, there was good power to detect it. Variables that had only a small effect on the probability of response were unlikely to be detected, but usually would be of less clinical interest. Given that the overall prediction was modest, it is likely that some important predictors such as the psychological components of pain, were not included as candidates with this retrospective study and a restricted data set.

Partial response to BVN RFA is an imperfect reference standard for VEP; however, it is a useful clinical point of reference in the absence of a more specific diagnostic approach or a better-established gold standard. Some MRI findings might have been significantly associated with failure to achieve 100% pain reduction after BVN RFA. This was considered an impractical criterion standard, as significant improvements translating to decreased healthcare utilization are noted at lower thresholds. Given the large and enduring nonspecific responses observed after pedicle access alone in the sham group of the SMART trial [17], it is possible this same effect is partially represented in patient reported pain relief after BVN RFA [48]. This would be consistent with findings from systematic reviews describing large placebo effects associated with invasive treatments, where the effects of noxious stimuli are influenced by psychological and social pain processing in the central nervous system [49]. However, in the field of Pain Medicine, it is generally accepted that legitimate treatments will have both specific and nonspecific effects, as is likely the case with BVN RFA.

Future study using advanced imaging sequences that are more sensitive to tissue features suspected in vertebrogenic pain may be useful. A recent systematic review of 26 studies (including >11,000 subjects) noted

moderate quality evidence of an association between structural endplate defects and low back pain [44]. Yet, it is highly suspected that cartilaginous end-plate (CEP) pathologies precede Modic changes and are not detectable by conventional MRI [50]. Bailey et al. used ultrashort time-to-echo (UTE) MRI to assess for the presence of CEP defects and observed that CEP defects were the strongest predictor of CLBP even after adjusting for Modic changes and disc degeneration [51]. Likewise, Kerttula et al. reported that Modic change (type 1) was associated with an adjacent endplate lesion in 96% of the cases [52].

Conclusions

In the setting of presumed vertebrogenic low back pain with Modic changes, the presence of almost any degenerative finding of the anterior and posterior column was not associated with a clinically important impact on treatment success after BVN RFA. None of the models demonstrated strong predictive value, indicating that the use of objective imaging biomarkers (Type 1 and/or 2 Modic changes) and a correlating presentation of pain remain the most useful patient selection factors for BVN RFA.

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Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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