Original Article

AO SPINE

Global Spine Journal
2022, Vol. 12(5) 829–839

DOI: 10.1177/2192568220966328
journals.sagepub.com/home/gsj

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High-Intensity Zones on MRI of the Cervical Spine in Patients: Epidemiology and Association With Pain and Disability

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Abstract

Study Design: Retrospective cohort study.

Objectives: This study aimed to address the prevalence, distribution, and clinical significance of cervical high-intensity zones (HIZs) on magnetic resonance imaging (MRI) with respect to pain and other patient-reported outcomes in the setting of patients that will undergo an anterior cervical discectomy and fusion (ACDF) procedure.

Methods: A retrospective cohort study of ACDF patients surgically treated at a single center from 2008 to 2015. Based on preoperative MRI, HIZ subtypes were identified as either traditional T2-hyperintense, T1-hypointense ("single-HIZs"), or combined T1- and T2-hyperintense ("dual-HIZs"), and their level-specific prevalence was assessed. Preoperative symptoms, patient-reported outcomes, and disc degeneration pathology were assessed in relation to HIZs and HIZ subtypes.

Results: Of 861 patients, 58 demonstrated evidence of HIZs in the cervical spine (6.7%). Single-HIZs and dual-HIZs comprised 63.8% and 36.2% of the overall HIZs, respectively. HIZs found outside of the planned fusion segment reported better preoperative Neck Disability Index (NDI; $P = .049$) and Visual Analogue Scale (VAS) Arm ($P = .014$) scores relative to patients without HIZs. Furthermore, patients with single-HIZs found inside the planned fusion segment had worse VAS Neck ($P = .045$) and VAS Arm ($P = .010$) scores. In general, dual-HIZ patients showed no significant differences across all clinical outcomes.

Conclusions: This is the first study to evaluate the clinical significance of HIZs in the cervical spine, noting level-specific and clinical outcome–specific variations. Single-HIZs were associated with significantly more pain when located inside the fusion segment, while dual-HIZs showed no associations with patient-reported outcomes. The presence of single-HIZs may correlate with concurrent spinal pathologies and should be more closely evaluated.

Keywords

high-intensity zones, HIZ, disc, MRI, neck pain, cervical, degenerative, disease, low back pain

Introduction

Various magnetic resonance imaging (MRI) phenotypes of the spine have been associated with clinical symptoms and outcomes.[1-4] High-intensity zones (HIZs) are a specific spinal imaging phenotype that may have implications on the development of discogenic pain.[5-10] HIZs have been largely studied in the lumbar spine and have been traditionally characterized as focal T2-weighted hyperintensities in the posterior annulus of the intervertebral disc on MRI.[11] Aprill and Bogduk[12] originally described

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this phenomenon in 1992, where identification of an HIZ had an 86% positive predictive value for a painful annulus disruption. Subsequent histological studies of HIZs in the lumbar spine appear to support this hypothesis, having identified vascularized granulation tissue in the outer region of the annulus fibrosus, suggestive of a healing response to annular disruption.[8,13-15]

In a recent systematic review, Teraguchi et al[4] assessed associations between low back pain and lumbar HIZs, noting no conclusive relationship could be inferred due to small sample sizes, heterogeneous populations, and unclear imaging methodology. This suggests the relationship between HIZs and patient symptomatology may not be as concrete as proposed by Aprill and Bogduk,[12] but rather, may represent an understudied entity with unclear clinical value.[16-18] Furthermore, outside of the thoracolumbar spine, little is known about HIZs, with a gross paucity of studies having specifically examined the cervical intervertebral segments. In practice, HIZs are frequently identified in the cervical spine, and it is unclear if these imaging findings may lead to similar associations with axial neck pain and/or patient-reported outcomes before and after surgery.

As other studies have reported HIZs in asymptomatic cohorts, some investigators have begun to question whether different subtypes of HIZs exist.[4,19-21] For example, a recent study examined lumbar HIZs on both T1- and T2-weighted MRI, noting 2 distinct HIZ phenotypes: a traditional T2-intense and T1-hypointense "single-HIZ" and another T1- and T2-intense "dual-HIZ."[8,22] They further reported a significant difference in the patients' pain response associated with each subtype, noting that dual-HIZs were generally less symptomatic, and may represent calcified or ossified tissues in contrast to the annular disruption that is observed in the conventional single-HIZ. In addition, a population-based cohort study by Teraguchi et al[23] evaluated the lumbar spine MRIs of 1214 volunteer subjects. Of these individuals, 59% had HIZ and 41% did not. The study noted that specific patterns of HIZ were more associated with the development and severity of low back pain than others. However, whether similar HIZ patterns exist in the cervical spine remains unknown.

According to recent Global Burden of Disease studies, neck pain is considered one of the world's most disabling conditions.[24,25] Patients seeking medical consultation for cervical spine–related ailments is not uncommon and can have detrimental socioeconomic consequences to many stakeholders. Therefore, understanding pain generators is critical. With respect to HIZs located in the cervical spine, their manifestation and clinical relevance remains largely unknown. As such, the main purpose of this study was to characterize the prevalence and distribution of HIZs on MRI in the cervical spine in patients with degenerative cervical conditions indicated for an anterior cervical discectomy and fusion (ACDF) and to assess the nature of dual-HIZs and how they may clinically manifest in comparison to the traditional single-HIZ.

Methods

This was a retrospective cohort study of all patients indicated and surgically treated for an ACDF at a single academic institution from 2008 to 2015. Patients were deemed eligible for study if preoperative T1- and T2-weighted MRI studies of the cervical spine were obtainable, and proper visualization of HIZs could be made. Patients were excluded if they were undergoing surgery for the treatment of a tumor, trauma, or infection, and/or if the patient was under 18 years of age at the time of operation.

Patients' medical records were reviewed for demographics including age, body mass index (BMI), sex, smoking history, and ageless Charlson Comorbidity Index (CCI). The CCI is a well-validated metric that estimates 10-year mortality risk based upon a list of baseline medical comorbidities.[26] Baseline clinical and operative characteristics such as preoperative symptomatology (radiculopathy, myelopathy, myeloradiculopathy, neck pain, arm pain, sensory deficits, and weakness) duration of preoperative symptoms (months) and number of fused vertebral levels were collected.

Both T1- and T2-weighted MRI studies of the cervical spine were assessed for presence of HIZs throughout C2-T1, with documentation of the overall number, intervertebral disc level, location (anterior or posterior) within the disc, and location of HIZs in relation to the planned operative levels. Single-HIZs were identified as conventional T2-weighted signal intensities while dual-HIZ subtypes were identified as combined T1- and T2-weighted hyperintensity findings (Figure 1). HIZ subtype and location stratifications were subsequently assessed for association with baseline symptomatology and preoperative patient-reported outcomes (Neck Disability Index [NDI], Visual Analog Scale [VAS] Neck, VAS Arm).

A secondary analysis was performed to determine association of HIZs and their subtypes with concurrence of other disc pathologies (disc degeneration, disc space narrowing, disc displacement) overall and at the same cervical vertebral levels. Degenerative discs were identified as Pfirrmann Grade V hypointense black discs on T2-weighted MRI.[27] This designation was used to promote inter- and intraobserver reliability, so as to prevent ambiguity when presented with partially degenerated disc imaging findings. Disc space narrowing was defined as a 30% decrease in disc height relative to adjacent healthy disc spaces. Last, disc displacement was measured if protrusion of disc material was observed either anteriorly or posteriorly at a given intervertebral level. Three readers independently assessed all images, and after a short training period, intra- and interobserver reliability was deemed to be good to excellent (intraclass coefficient constant [ICC] > 0.80). ICC cutoffs were established as ≤ 0.50 for poor reliability, 0.51 to ≤ 0.74 for moderate, 0.75 to 0.89 for good, and ≥ 0.90 for excellent.[28]

Statistical Analysis

The collected data was analyzed using the statistical software STATA version 15.1 (StataCorp). Continuous baseline variables are reported as mean $\pm$ standard deviation (SD). Baseline patient demographics and operative characteristics were compared using 2-way t tests and χ^2 analysis for continuous

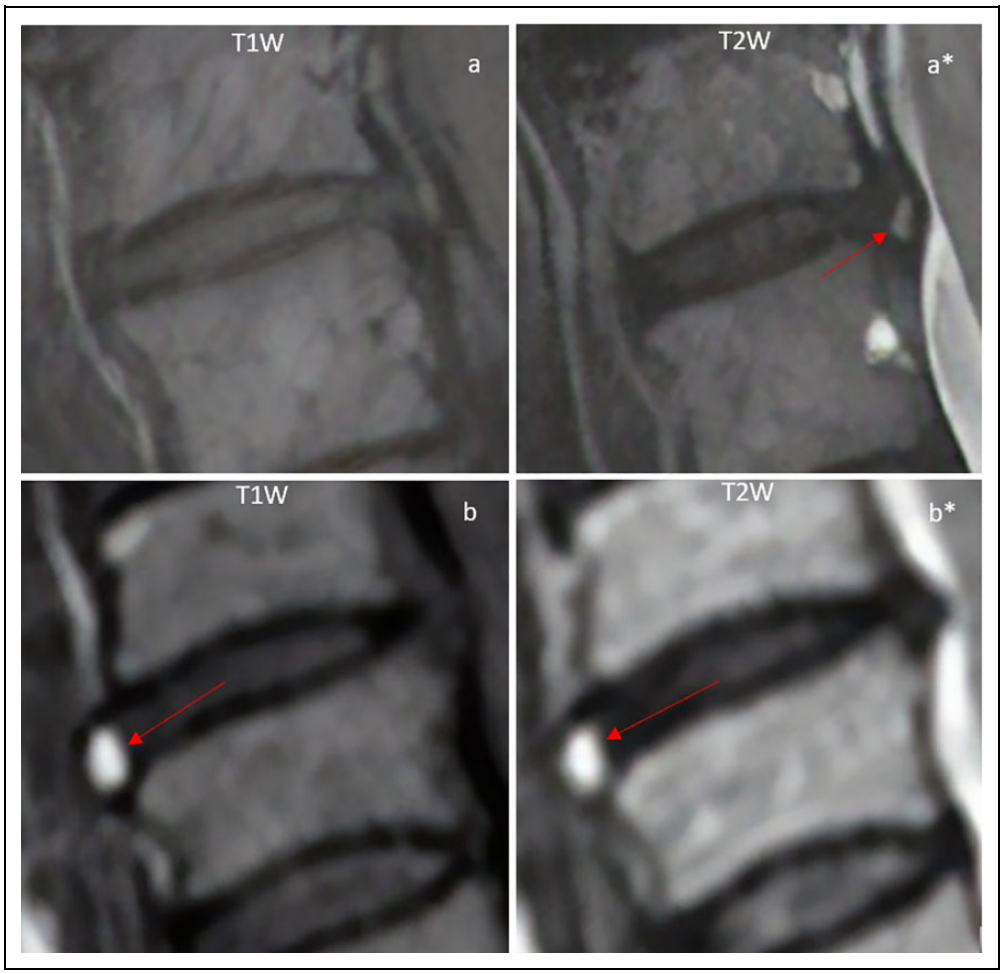

Figure 1. T1- and T2-weighted images of single- and dual-HIZ subtypes. (a, a*) T1-weighted image (left) without evidence of a HIZ, and corresponding T2-weighted image (right) with a single-HIZ in the posterior annulus of C5-C6 (arrow). (b, b*) T1-weighted image (left) showing the distinct morphology and intensity of a dual-HIZ in the anterior annulus of C6-C7 (arrow), with corresponding T2-weighted image (right) depicting a similar lesion (arrow).

and categorical outcome variables, respectively. Multivariate logistic regression was used to determine the association of preoperative cervical HIZs with baseline patient symptomatology and degenerative disc pathology. Multivariate linear regression was used to assess the relationship with patient-reported outcomes. Statistical models were built by incorporating all baseline demographic and operative characteristics in addition to the HIZ variable to be examined. Beta coefficients, odds ratios (ORs), and corresponding 95% confidence intervals (CIs) were also assessed for each covariate within multivariate linear and logistic regression. A P value of $<.05$ was used to determine statistical significance.

Results

A total of 861 patients indicated for an ACDF for degenerative pathology with a preoperative cervical MRI were identified from 2008 to 2015. The incidence of patients with HIZs within this surgical cohort was 6.7% (58/861). There were no demographic differences observed between either cohort (Table 1).

Within the 861 patients, 58 patients had HIZs. When stratifying by HIZ subtype, the incidence of single-HIZs and dual-HIZs was 63.8% and 36.2%, respectively. Patients with dual-HIZs were significantly older, with a mean age of 57.1 $\pm$ 11.8 years when compared to single-HIZ patients, with a mean age of 49.9 $\pm$ 11.7 years ($P = .029$). No other demographic differences were observed between HIZ subtypes (Table 2).

In regard to specific location, most HIZs were seen in the posterior annulus (45/58; 78.0%) and outside the operative segment (34/58; 58.6%). The greatest number of overall HIZ observations was seen at C4-C5 (16/58; 27.6%), and C6-C7 (16/58; 27.6%), followed by C5-C6 (13/58; 22.4%). The fewest HIZs were observed at C2-C3 (2/58; 3.45%) and C7-T1 (1/58; 1.7%). Dual-HIZs were more frequently found in the anterior annulus (9/21 = 42.9%) when compared to single-HIZs (4/37 = 10.8%). Conversely, single-HIZs were more frequently observed in the posterior annulus (33/37 = 89.2%) than dual-HIZs (12/21; 57.1%). A similar distribution was observed between single- and dual-HIZ cohorts along the length of the cervical spine, with the greatest number observed between C3-

Table 1. Baseline Patient Demographic and Operative Characteristics.

	HIZ		No HIZ		
	#/Mean	%/(SD)	#/Mean	%/(SD)	*P* value
Overall total	58	6.86	803	93.14	
Demographics					
Age	52.47	(12.15)	52.50	(11.29)	.980
BMI	28.70	(6.23)	29.13	(6.19)	.624
Female sex	24	41.4	382	47.99	.330
Current smoker	5	9.62	104	15.25	.271
CCI	1.18	(1.81)	0.92	(1.48)	.235
Operative					
Duration of preoperative symptoms (months)	27.15	(40.35)	22.22	(36.55)	.338
Number of vertebral levels fused	1.90	(0.88)	1.90	(0.75)	.972

Abbreviations: HIZ, high-intensity zone; BMI, body mass index; CCI, Charlson Comorbidity Index.

Table 2. Baseline Patient Demographic and Operative Characteristics.

	Single-HIZ		Dual-HIZ		
	#/Mean	%/(SD)	#/Mean	%/(SD)	*P* value
Overall total	37	63.79	21	36.21	
Demographics					
Age	49.86	(11.71)	57.05	(11.82)	**.029**
BMI	28.23	(6.64)	29.57	(5.45)	.468
Female sex	16	43.24	8	38.1	.702
Current smoker	4	11.76	1	5.56	.47
CCI	1.09	(1.91)	1.33	(1.68)	.659
Operative					
Duration of preoperative symptoms (months)	23.01	(21.90)	34.60	(61.14)	.308
Number of vertebral levels fused	1.90	(0.88)	1.89	(0.90)	.967

Abbreviations: HIZ, high-intensity zone; BMI, body mass index; CCI, Charlson Comorbidity Index.
Bolded values indicate statistical significance with $p < 0.05$.

Table 3. Distribution and Location of High-Intensity Zones.

	HIZ		Single-HIZ		Dual-HIZ		*P* value[a]
	#	%	#	%	#	%	
Disc location							
Anterior	13	22.41	4	10.81	9	42.86	**.005**
Posterior	45	77.59	33	89.19	12	57.14	**.005**
Relation to operative level(s)							
Inside operative level(s)	24	41.37	15	40.54	9	42.86	.863
Outside operative level(s)	34	58.62	22	59.46	12	57.14	.863
Cervical vertebral level							
C2-C3	2	3.45	1	2.70	1	4.76	.680
C3-C4	10	17.24	5	13.51	5	23.80	.318
C4-C5	16	27.59	10	27.03	6	28.57	.899
C5-C6	13	22.41	9	24.32	4	19.05	.643
C6-C7	16	27.59	11	29.73	5	23.80	.628
C7-T1	1	1.72	1	2.70	0	0.00	.447

Abbreviation: HIZ, high-intensity zone.
[a]Calculation of *P* values was performed using χ^2 test. Bolded values indicate statistical significance at $P < .05$.

C7 (single-HIZ: 35/37, 94.6%; dual-HIZ: 20/21; 95.2%; Table 3). The distribution of HIZs by cervical vertebral level are illustrated graphically in Figure 2.

Evaluating preoperative symptomatology and patient-reported outcomes, HIZs were generally associated with better outcomes when found outside of the planned fusion segment. Specifically, patients reported better preoperative NDI ($P = .049$; Coeff. $= -11.63$; 95% CI: -23.2 to 0.04) and VAS Arm ($P = .014$; Coeff $= -2.56$; 95% CI: -4.60 to -0.53) scores relative to patients without HIZs. However, when stratified by HIZ subtype, patients with single-HIZs within the fusion segment were found to have significantly worse VAS Neck ($P = .045$; Coeff. $= 3.34$; 95% CI: 0.07 to 6.60) and VAS Arm ($P = .010$; Coeff. $= 4.90$; 95% CI: 1.20 to 8.60) scores compared to patients without HIZs. Interestingly, dual-HIZ patients did not demonstrate any significant differences relative to patients without HIZs across all patient-reported outcomes. There was no association with preoperative symptoms with HIZs or HIZ subtypes (Table 4).

When assessing relationships between HIZs and other disc pathologies, anterior HIZs and HIZs inside the area of fusion were significantly associated with lower odds of disc

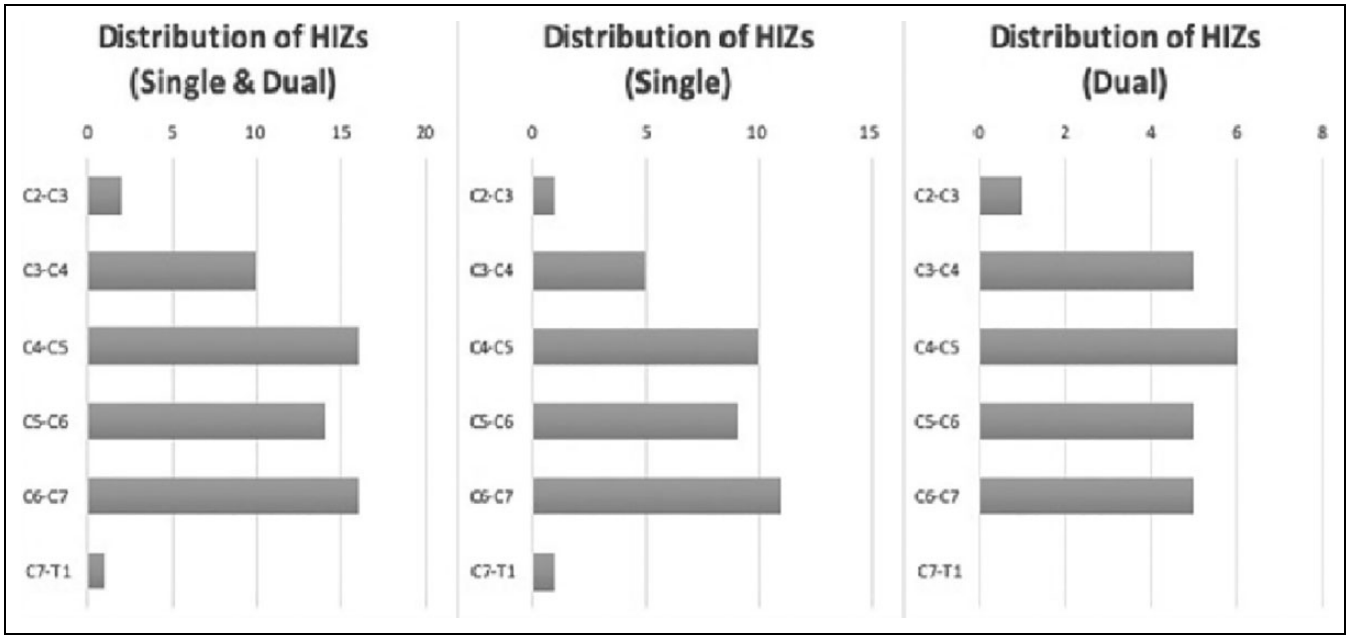

Figure 2. Distribution of high-intensity zones (HIZs) by cervical intervertebral level. *X*-axis = Count data for number of HIZs observed per level; *Y*-axis = Cervical intervertebral level.

displacement ($P = .019$; OR = 0.03; 95% CI: <0.01 to 0.54) and disc degeneration ($P = .049$; OR: 0.31; 95% CI: 0.10 to 0.99). However, when stratified further by cervical vertebral level, HIZs were found to be associated with increased odds of disc displacement at C3-C4 ($P = .002$; OR = 2.93; 95% CI: 1.50 to 5.70). Comparably, anterior annulus HIZs at C6-C7 was still significantly associated with lower odds of disc degeneration (at C6-C7; $P = .036$; OR: 0.27; 95% CI: 0.08 to 0.92). When stratified by subtype, single-HIZs were similarly associated with lower odds of disc displacement when found in the anterior annulus ($P = .011$; OR: <0.01; 95% CI: <0.01 to 0.30) or within the planned fusion segment ($P = .026$; OR: 0.04; 95% CI: <0.01 to 0.68). Again, the relationship between single-HIZs and disc displacement reversed when considering cervical vertebral level at C3-C4 ($P = .019$; OR = 2.65; 95% CI: 1.18 to 6.00), while odds of disc degeneration remained decreased at C7-T1 ($P = .017$; OR = 0.34; 95% CI: 0.14 to 0.82). Dual-HIZs were not significantly associated with any other disc phenotype, unless stratified by vertebral level. Specifically, dual-HIZs had lower odds of disc degeneration at C4-C5 within the fusion segment ($P = .011$; OR = 0.16; 95% CI: 0.037 to 0.65), greater odds of disc space narrowing at C3-C4 outside of the fusion segment ($P = .031$; OR = 7.28; 95% CI: 1.20 to 44.00), and greater odds of disc displacement at C3-C4 ($P = .024$; OR = 3.67; 95% CI: 1.20 to 11.00; Table 5).

Discussion

Previous studies have examined the association of lumbar HIZs and low back pain, but similar investigations have largely evaded application in the cervical spine.[4,6,9] Thus, we sought to characterize HIZs in the cervical spine and determine their association with preoperative symptoms and clinical outcomes. In this study, we have demonstrated a unique and significant association between cervical HIZ subtypes and subjective reports of neck and arm pain. Specifically, the traditional imaging definition of the HIZ (single-HIZs) when located inside the area of planned fusion was associated with self-reported pain symptoms, though dual-HIZs bore no relationship with subjective outcomes before surgery. This finding provides evidence that when located inside the area of fusion, HIZs may somehow contribute to symptoms of pain. Furthermore, both HIZ subtypes demonstrated patterns of association with other disc imaging findings different than previously reported in the lumbar literature. As such, this study provides new evidence on the possible significance of HIZs and suggests that associated clinical manifestations may largely relate to the subtype and location within the cervical spine.

The findings of the present study discussing HIZ subtypes and patient symptomatology may explain why the relationship between HIZs and pain is inconclusive. In a systematic review by Teraguchi et al,[4] they noted the clinical relevance of HIZs in the lumbar spine was inconclusive, largely due to small sample size, heterogeneous study populations, and lack of standardized imaging protocols. However, the studies they reviewed did not discuss the presence or significance of HIZ subtypes. Shan et al[22] originally introduced this concept in their examination of HIZs in the lumbar spine, and remains the only other study to perform such an analysis. Similarly, in their study, they found a difference in pain response between the 2 HIZ subtypes, noting a greater pain response in those with single-HIZs. Given this, the single-HIZ appears to resemble the clinical and imaging features of the traditional HIZ and suggests the dual-HIZ is likely a different phenomenon. To this point, histological

Table 4. Multivariate Analyses of High-Intensity Zones With Preoperative Symptoms and Patient-Reported Outcomes.[a]

	No stratification			Anterior			Posterior			Inside fusion segment			Outside fusion segment		
	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value
HIZ															
Preoperative symptom															
Radiculopathy	1.26	0.25-6.40	.784	0.52	0.08-3.4	.488	—	—	—	0.73	0.13-4.30	.729	—	—	—
Myelopathy	1.23	0.43-3.50	.695	2.11	0.47-9.5	.327	0.77	0.17-3.50	.738	0.79	0.15-4.00	.773	1.77	0.48-6.60	.394
Myeloradiculopathy	1.32	0.58-3.00	.507	1.20	0.25-5.8	.816	1.31	0.52-3.30	.570	1.18	0.37-3.80	.777	1.41	0.47-4.20	.539
Neck pain	0.96	0.28-3.40	.951	0.94	0.11-7.8	.957	1.03	0.23-4.60	.972	0.70	0.15-3.30	.658	1.44	0.18-11.0	.731
Arm pain	0.74	0.35-1.60	.424	0.38	0.11-1.3	.113	1.08	0.42-2.80	.866	0.47	0.19-1.20	.118	1.40	0.40-4.90	.601
Sensory deficits	0.86	0.44-1.70	.672	0.69	0.20-2.4	.551	0.96	0.44-2.10	.928	0.65	0.26-1.60	.344	1.16	0.42-3.20	.773
Weakness	0.97	0.52-1.80	.928	0.53	0.16-1.8	.316	1.11	0.55-2.20	.778	0.89	0.38-2.10	.795	1.05	0.45-2.50	.905
Patient-reported outcomes															
NDI	−7.63	−17.0 to 1.40	.096	−11.0	−27 to 4.7	.168	−5.99	16.0 to 4.40	.256	−2.85	−17.0 to 11.0	.68	**−11.63**	−23.0 to 0.04	**.049**
VAS Neck	0.03	−1.40 to 1.40	.962	−1.63	−4.00 to 0.70	.169	1.01	−0.58 to 2.60	.211	0.31	−1.9 to 2.50	.78	−0.27	−2.00 to 1.50	.755
VAS Arm	−0.61	−2.20 to 1.00	.463	−0.71	−3.30 to 1.90	.593	−0.18	−2.10 to 1.70	.857	2.13	−0.36 to 4.60	.09	**−2.56**	−4.60 to −0.53	**.014**
Single-HIZ															
Preoperative symptom															
Radiculopathy	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—	1.00	—	—
Myelopathy	1.18	0.26-5.40	.834	7.76	0.60-100.0	.116	0.64	0.08-5.00	.668	1.00	—	—	2.42	0.49-12.0	.279
Myeloradiculopathy	1.58	0.59-4.20	.360	0.76	0.05-12.0	.846	1.72	0.61-4.90	.302	1.25	0.28-5.60	.765	1.90	0.52-6.90	.330
Neck Pain	0.75	0.16-3.50	.717	1.00	—	—	0.65	0.14-3.00	.582	0.66	0.08-5.60	.701	0.80	0.10-6.70	.840
Arm Pain	1.09	0.39-3.10	.871	0.54	.043-6.80	.632	1.22	0.40-3.80	.726	0.58	0.16-2.00	.387	3.05	0.38-24.0	.292
Sensory deficits	0.84	0.36-2.00	.701	0.19	.016-2.20	.178	1.05	0.40-2.70	.927	0.60	0.19-1.90	.378	1.22	0.33-4.50	.770
Weakness	1.30	0.60-2.80	.510	0.60	.053-6.80	.679	1.42	0.62-3.20	.404	0.87	0.29-2.60	.795	1.95	0.64-6.0	.243
Patient-reported outcomes															
NDI	−4.38	−17.0 to 8.40	.501	−24.67	−62.0 to 13.0	.198	−1.82	−15.0 to 12.0	.791	8.86	−10.0 to 28.0	.363	−14.95	−32.0 to 2.00	.084
VAS Neck	−0.16	−2.20 to 1.90	.873	−4.43	−10.0 to 1.10	.117	0.47	−1.70 to 2.60	.668	**3.34**	0.07 to 6.60	**.045**	−2.23	−4.70 to 0.26	.079
VAS Arm	0.62	−1.90 to 3.10	.623	−4.86	−11.0 to 1.50	.130	1.57	−1.10 to 4.20	.245	**4.90**	1.20-8.60	**.010**	−2.57	−5.80 to 0.60	.111
Dual-HIZ															
Preoperative symptom															
Radiculopathy	0.75	0.13-4.30	.742	0.49	.073-3.30	.462	—	—	—	0.46	0.07-3.20	.435	—	—	—
Myelopathy	1.29	0.32-5.30	.721	1.32	0.22-8.00	.764	0.99	0.11-8.80	.993	1.39	0.22-8.70	.723	1.13	0.13-10.0	.912
Myeloradiculopathy	0.88	0.22-3.50	.856	1.54	0.24-10.0	.649	0.49	0.06-4.20	.516	1.06	0.18-6.40	.951	0.69	0.08-6.10	.742
Neck pain	1.38	0.17-11.0	.760	0.72	0.08-6.30	.765	—	—	—	0.72	0.08-6.40	.770	—	—	—
Arm pain	0.48	0.17-1.40	.172	0.33	0.08-1.30	.120	0.87	0.17-4.50	.869	0.38	0.09-1.60	.180	0.63	0.12-3.30	.582
Sensory deficits	0.87	0.30-2.50	.796	1.17	0.24-5.90	.845	0.78	0.20-3.10	.725	0.72	0.17-3.00	.655	1.08	0.22-5.30	.924
Weakness	0.58	0.21-1.60	.296	0.51	0.12-2.10	.354	0.54	0.13-2.20	.391	0.92	0.24-3.60	.904	0.34	0.07-1.70	.189
Patient-reported outcomes															
NDI	−11.00	−23.0 to 1.20	.078	−8.15	−25.0 to 9.10	.351	−11.93	−28.0 to 3.70	.134	−14.78	−34.0 to 4.60	.134	−8.93	−25.0 to 6.70	.261
VAS Neck	0.12	−1.70 to 1.90	.899	−1.06	−3.60 to 1.50	.415	1.60	−0.70 to 3.90	.173	−2.04	−4.90 to 0.83	.163	1.40	−0.90 to 3.70	.231
VAS Arm	−1.47	−3.5 to 0.60	.163	0.14	−2.70 to 3.0	.923	−1.86	−4.50 to 0.80	.170	0.06	−3.20 to 3.30	.971	−2.48	−5.10 to 0.15	.064

Abbreviations: HIZ, high-intensity zone; OR, odds ratio; CI, confidence interval; NDI, Neck Disability Index; VAS, Visual Analogue Scale.

[a]Beta-coefficents, Odds ratio and *p*-values were calculated using multivariate linear and logistic regression models controlling for patient demographics. Bolded values indicate statistical significance with $p < 0.05$.

Table 5. Multivariate Analyses of High-Intensity Zones With Concurrence of Disc Pathology at Identical Intervertebral Level.[a]

	No stratification			Anterior			Posterior			Inside fusion segment			Outside fusion segment		
	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value
HIZ															
Overall disc phenotype															
Disc degeneration	0.57	0.28-1.20	.128	0.22	0.04-1.10	.065	0.85	0.39-1.90	.681	**0.31**	0.10-1.00	**.049**	0.93	0.37-2.40	.886
Disc space narrowing	1.17	0.61-2.30	.634	0.72	0.20-2.60	.607	1.31	0.63-2.70	.468	1.09	0.44-2.70	.850	1.3	0.51-3.10	.621
Disc displacement	0.11	0.01-1.60	.108	**0.03**	<0.01-0.50	**.019**	—	—	—	0.05	<0.01-1.00	.050	—	—	—
Disc degeneration by cervical vertebral level															
C2-C3	0.87	0.42-1.80	.699	0.66	0.17-2.50	.545	1.00	0.43-2.30	.995	0.79	0.29-2.10	.645	0.93	0.33-2.60	.893
C3-C4	0.92	0.44-1.90	.820	0.44	0.13-1.60	.204	1.24	0.52-3.00	.630	2.01	0.57-7.10	.280	0.51	0.21-1.30	.155
C4-C5	0.67	0.34-1.30	.239	0.48	0.14-1.70	.252	0.78	0.36-1.70	.533	0.46	0.18-1.10	.093	0.98	0.37-2.70	.976
C5-C6	1.17	0.52-2.70	.708	0.93	0.19-4.50	.925	1.29	0.51-3.30	.588	2.63	0.59-12.0	.206	0.68	0.25-1.80	.446
C6-C7	0.74	0.37-1.50	.407	**0.27**	0.08-0.90	**.036**	1.11	0.47-2.60	.807	1.01	0.35-2.90	.992	0.56	0.22-1.40	.225
C7-T1	0.61	0.32-1.20	.137	0.70	0.20-2.40	.577	0.60	0.29-1.30	.182	0.55	0.22-1.40	.214	0.65	0.27-1.60	.342
Disc space narrowing by cervical vertebral level															
C2-C3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C3-C4	0.84	0.18-3.80	.817	—	—	—	1.43	0.30-6.80	.652	—	—	—	2.47	0.50-12.0	.268
C4-C5	1.65	0.66-4.20	.287	2.10	0.46-9.60	.341	1.43	0.46-4.50	.536	1.03	0.27-4.00	.965	2.66	0.80-8.90	.112
C5-C6	1.13	0.57-2.20	.725	1.35	0.37-5.00	.647	1.03	0.47-2.20	.939	0.84	0.33-2.20	.715	1.53	0.60-3.90	.375
C6-C7	0.82	0.39-1.70	.590	0.33	0.07-1.70	.182	1.05	0.47-2.40	.905	0.86	0.33-2.30	.753	0.76	0.26-2.20	.617
C7-T1	1.61	0.51-5.00	.415	2.52	0.49-13.0	0.271	1.09	0.23-5.10	.915	3.28	0.94-11.0	.062	—	—	—
Disc displacement by cervical vertebral level															
C2-C3	0.52	0.12-2.30	.385	0.74	0.09-6.20	.783	0.41	0.05-3.20	.390	0.97	0.21-4.50	.971	—	—	—
C3-C4	**2.93**	1.50-5.70	**.002**	**6.08**	1.30-29.0	**.025**	**2.52**	1.20-5.30	**.014**	1.04	0.42-2.60	.933	**10.1**	3.20-31.0	**.000**
C4-C5	1.63	0.82-3.30	.166	1.01	0.28-3.70	.988	1.76	0.81-3.80	.156	1.02	0.41-2.60	.968	2.63	0.97-7.20	.058
C5-C6	2.71	0.62-12.0	.187	1.49	0.17-13.0	.717	2.00	0.45-8.90	.362	2.09	0.26-17.0	.486	3.28	0.42-26.0	.260
C6-C7	1.20	0.53-2.70	.669	2.09	0.26-17.0	.489	1.09	0.45-2.70	.851	0.96	0.30-3.00	.938	1.42	0.46-4.40	.543
C7-T1	1.25	0.52-3.00	.616	1.43	0.34-6.00	.629	1.08	0.37-3.20	.884	2.13	0.73-6.30	.168	0.52	0.10-2.60	.432
Single-HIZ															
Overall disc phenotype															
Disc degeneration	0.55	0.21-1.40	.223	—	—	—	0.65	0.24-1.70	.391	0.32	0.07-1.60	.158	0.84	0.24-2.90	.777
Disc space narrowing	1.33	0.58-3.00	.502	—	—	—	1.13	0.48-2.70	.781	1.94	0.59-6.30	.273	0.94	0.29-3.00	.913
Disc displacement	0.07	0.005-1.10	.060	<**0.01**	<.01-0.30	**.011**	—	—	—	**0.038**	<0.01-0.68	**.026**	—	—	—
Disc degeneration by cervical vertebral level															
C2-C3	0.95	0.38-2.40	.908	—	—	—	0.82	0.33-2.10	.678	2.12	0.45-10.0	.341	0.52	0.16-1.60	.261
C3-C4	0.82	0.34-2.00	.660	0.61	0.05-7.34	.696	0.85	0.34-2.20	.734	4.70	0.59-37.3	.143	**0.30**	0.10-0.90	**.034**
C4-C5	0.81	0.34-1.90	.620	—	—	—	0.68	0.28-1.60	.388	0.95	0.28-3.20	.935	0.71	0.22-2.30	.558
C5-C6	1.01	0.39-2.60	.980	—	—	—	0.92	0.35-2.40	.871	3.86	0.48-31.0	.203	0.47	0.15-1.50	.203
C6-C7	0.62	0.27-1.40	.260	—	—	—	0.94	0.37-2.40	.888	1.24	0.33-4.70	.753	0.34	0.11-1.0	.059
C7-T1	**0.34**	0.14-0.82	**.017**	0.34	0.03-4.17	.400	**0.34**	0.13-0.86	**.023**	0.54	0.16-1.80	.301	**0.20**	0.05-0.80	**.020**
Disc space narrowing by cervical vertebral level															
C2-C3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

(continued)

Table 5. (continued)

	No stratification			Anterior			Posterior			Inside fusion segment			Outside fusion segment		
	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value	Beta/OR	95% CI	*P* value
C3-C4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C4-C5	1.79	0.54-5.90	.337	13.30	0.97-182.68	.053	1.00	0.21-4.70	.996	1.53	0.29-8.0	.613	2.15	0.42-11.0	.358
C5-C6	1.00	0.42-2.40	.993	—	—	—	0.75	0.29-2.00	.566	1.17	0.36-3.80	.796	0.85	0.24-3.10	.800
C6-C7	0.58	0.21-1.60	.294	—	—	—	0.72	0.26-2.10	.545	0.92	0.27-3.20	.900	0.24	0.03-1.90	.173
C7-T1	2.82	0.72-11.0	.135	11.10	0.74-167.60	.082	1.95	0.40-9.70	.412	**6.99**	1.50-33.0	**.014**	—	—	—
Disc displacement by cervical vertebral level															
C2-C3	0.54	0.07-4.30	.557	—	—	—	0.66	0.08-5.30	.697	1.14	0.13-9.80	.901	—	—	—
C3-C4	**2.65**	1.20-6.0	**.019**	3.34	0.28-39.96	.340	**2.61**	1.10-6.10	**.028**	0.67	0.20-2.30	.527	**14.31**	3.0-68.0	**.001**
C4-C5	2.04	0.84-5.0	.115	—	—	—	1.83	0.74-4.50	.190	1.12	0.35-3.60	.852	**3.89**	1.0-15.0	**.049**
C5-C6	3.14	0.41-24.0	.273	—	—	—	3.05	0.39-23.70	.287	1.07	0.13-8.90	.951	—	—	—
C6-C7	0.82	0.33-2.10	.674	—	—	—	0.72	0.28-1.80	.486	0.81	0.21-3.10	.761	0.82	0.24-2.80	.750
C7-T1	1.04	0.29-3.80	.954	—	—	—	1.21	0.33-4.50	.777	1.36	0.27-7.0	.710	0.69	0.09-5.70	.733
Dual-HIZ															
Overall disc phenotype															
Disc degeneration	0.61	0.21-1.80	.366	0.28	0.05-1.50	.143	1.43	0.38-5.30	.598	0.31	0.06-1.68	.172	1.04	0.26-4.10	.955
Disc space narrowing	0.97	0.35-2.70	.956	0.36	0.08-1.70	.204	1.87	0.45-7.80	.389	0.46	0.11-2.00	.297	1.99	0.45-8.80	.364
Disc displacement	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Disc degeneration by cervical vertebral level															
C2-C3	0.75	0.23-2.40	.622	0.40	0.10-1.70	.216	2.06	0.25-17.0	.506	0.25	0.06-1.00	.053	—	—	—
C3-C4	1.15	0.32-4.20	.832	0.40	0.09-1.70	.209	—	—	—	0.77	0.15-4.00	.759	1.85	0.22-15.0	.569
C4-C5	0.50	0.17-1.40	.192	0.25	0.06-1.00	.052	1.20	0.23-6.10	.827	**0.16**	0.04-0.65	**.011**	2.23	0.27-18.0	.457
C5-C6	1.59	0.35-7.30	.553	0.67	0.13-3.50	.635	—	—	—	1.52	0.18-13.0	.701	1.65	0.19-14.0	.649
C6-C7	1.13	0.31-4.20	.856	0.65	0.12-3.40	.605	2.39	0.28-20.0	.425	0.71	0.13-3.90	.694	1.90	0.23-16.0	.555
C7-T1	1.51	0.49-4.60	.473	0.92	0.21-4.10	.915	2.79	0.52-15.0	0.234	0.58	0.13-2.50	.469	5.14	0.61-43.0	.132
Disc space narrowing by cervical vertebral level															
C2-C3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
C3-C4	1.72	0.34-8.60	.511	—	—	—	4.55	0.79-26.0	.089	—	—	—	**7.28**	1.20-44.0	**.031**
C4-C5	1.47	0.37-5.80	.585	0.71	0.07-7.00	.771	2.26	0.42-12.0	.343	0.62	0.07-5.80	.671	3.23	0.56-18.0	.188
C5-C6	1.34	0.48-3.80	.578	0.72	0.15-3.50	.684	1.94	0.50-7.60	.342	0.50	0.11-2.30	.379	3.56	0.78-16.0	.101
C6-C7	1.25	0.44-3.50	.675	0.54	0.10-3.00	.475	2.09	0.55-8.00	.279	0.79	0.18-3.50	.753	1.98	0.47-8.30	.350
C7-T1	0.70	0.08-5.80	.740	1.39	0.15-13.0	.770	—	—	—	1.21	0.13-11.0	.863	—	—	—
Disc displacement by cervical vertebral level															
C2-C3	0.52	0.06-4.20	.535	1.07	0.12-9.60	.954	—	—	—	0.87	0.10-7.60	.900	—	—	—
C3-C4	**3.67**	1.20-11.0	**.024**	**8.74**	1.00-75.0	**.047**	2.43	0.60-9.80	.212	2.08	0.44-9.80	.354	**6.22**	1.20-32.0	**.030**
C4-C5	1.17	0.40-3.40	.776	0.62	0.14-2.70	.515	1.59	0.37-6.80	.529	0.89	0.19-4.10	.876	1.52	0.35-6.60	.576
C5-C6	2.18	0.27-18.0	.469	1.39	0.16-13.0	.766	0.88	0.10-7.90	.906	—	—	—	1.11	0.12-10.0	.929
C6-C7	3.78	0.48-30.0	.205	1.40	0.17-12.0	.758	—	—	—	1.45	0.17-13.0	.736	—	—	—
C7-T1	1.49	0.45-4.90	.515	1.97	0.42-9.20	.387	0.88	0.15-5.30	.891	3.22	0.73-14.0	.123	0.38	0.035-4.10	.423

Abbreviations: HIZ, high-intensity zone; OR, odds ratio; CI, confidence interval.

[a]Beta-coefficents, Odds ratio and *p*-values were calculated using multivariate linear and logistic regression models controlling for patient demographics. Bolded values indicate statistical significance with $p < 0.05$.

analysis performed by Shan et al[22] demonstrated significantly higher calcium content within the dual-HIZ lesion, suggesting the single-HIZ phenotype may be a different age-related entity.[29] As such, previous studies examining HIZs may be confounded by the presence of 2 distinct HIZ phenotypes, and a description of the true clinical presentation of those with HIZs remains unknown. In a recently submitted population-based cohort study evaluating 496 HIZs in the lumbar spine, it was reported that certain patterns of HIZ phenotypes in the lumbar spine are more associated with the development and severity of low back pain than others. This provides further evidence for the clinical use of HIZs in the lumbar spine and the importance of interpreting phenotype patterns.[23] Future investigations should aim to understand varying HIZ patterns and the pathogenesis of single- and dual-HIZs to evaluate how differing HIZ phenotypes may manifest in the spine.

Given these phenotypic differences, further consideration was given to reported associations of HIZs with other disc pathologies. Previous studies suggest lumbar HIZs are highly associated with disc degeneration.[6,8,20,22,30] The current study analyzed the relationship between cervical HIZs (as well as HIZ subtypes) and other disc pathologies, stratified by concurrence at the same intervertebral level, and by incidence overall from C2-C7. Unexpectedly, cervical HIZs were significantly associated with *lower* odds of concurrent disc degeneration and disc displacement. However, when stratified by subtype and location within the intervertebral disc, single-HIZs showed similarly lower odds of disc displacement, while dual-HIZs were unrelated to all other disc phenotypes. While possibly underpowered to detect findings related to the latter, both subtypes trended toward lower odds of concurrent degenerative disc pathology. Moreover, it may also be that the dual-HIZ has a distinct pathogenesis, such that the calcific nature of the lesion may lead to a different risk profile for other degenerative phenotypes.

In the lumbar spine, Wang and Hu[9] performed an analysis on the risk factors for HIZs, suggesting that these phenomena are part of the natural history of intervertebral disc degeneration. However, they concluded that the association of HIZs with disc degeneration was confounded by associations with older age. Other studies have found the incidence of HIZs in the lumbar spine was greater with higher rates of disc degeneration.[8,10,31] Similar considerations for confounding may also be present in our study, as the population under study was comprised entirely of a surgical cohort awaiting treatment with ACDF. These patients, by default, had a significant level of baseline degenerative findings at other cervical vertebral levels, such that the observed associations may be attributable to other underlying pathologies. Irrespective, these results suggest the potential of cervical HIZs as possible biomarkers for pain and disability, emphasizing the need for further exploration.

Despite providing new evidence surrounding HIZs in the cervical spine, this study has notable limitations. As with all retrospective studies, selection bias may be prevalent, and could have affected the outcomes observed. Similarly, as this study was performed on a degenerative spine cohort at a single academic institution, there may be concerns regarding external validity. Furthermore, patients obtained MRIs from various outside facilities; thus, we could not control for specific differences in MRI techniques/protocols/parameters. In examination of our surgical cohort of ACDF patients, this study is limited as it does not cover all cervical spine pathologies but focuses on a group of patients with a diagnosis that ACDF was indicated to treat. Future studies will aim to address HIZ phenotypes in asymptomatic populations. Additionally, this study was limited by its small sample size and the relatively low incidence of HIZs, which both may contribute to an underpowered analysis. Last, given the number of independent tests utilized in this study, concerns for false positive findings may be prevalent. However, given the lack of previous studies on cervical spine HIZs, and consequently, an unclear historical effect size, corrections for multiple comparisons were omitted to prevent masking of potential associative relationships. Overall, this study aimed to address these shortcomings by performing its analysis on prospectively acquired data, and exploring variations of HIZs in great detail, performing a rigorous assessment of different phenotypes, HIZ location, and association with other degenerative cervical spine pathologies. In addition, this is, to our knowledge, the first study to systematically address HIZs of the cervical spine in a relatively large cohort of cervical spine patients. Findings from this study are meant to raise awareness of the HIZ phenotype that may be further addressed in multicenter projects whose larger sample size may allow further exploration of these imaging findings and their clinical relevance.

Conclusions

This is the first study to evaluate the epidemiology and clinical significance of HIZs in the cervical spine in patients, noting level-specific and clinical outcome–specific variations. In accordance with previous reports on the association of lumbar HIZs with clinical outcomes, HIZs in the cervical spine were also found to be associated with symptoms of pain. However, these results were largely attributable to the single-HIZ, a subtype consistent with the traditional imaging definition. Interestingly, the single-HIZ was associated with increased preoperative pain symptoms when observed inside the planned area of fusion suggesting the presence of single HIZs may correlate with concurrent spinal pathologies and therefore should be more closely evaluated. Furthermore, these findings highlight the need to perform a comprehensive T1- and T2-weighted MRI analysis of HIZs in the cervical spine. In contrast to lumbar spine literature showing at times significant association of HIZs with disc degeneration pathology, the results of the current study showed lower odds of disc degeneration (ie, black disc) in association with cervical HIZs. This provides credence to explore the pathophysiological spatial development of HIZs in the context of disc changes which may vary between cervical and lumbar regions. Given these findings, it is important to consider the different ways that imaging pathology may manifest in different regions of the spine and

further assessments of HIZs should utilize a holistic MRI approach. This may provide a better assessment of the clinical significance of HIZs within the cervical and lumbar spine. However, prospective and longitudinal studies are needed to further validate our findings and to further explore the HIZ phenotype in conservatively managed as well as nonpatient groups.

Ethical Approval

Institutional review board approval was obtained by the RUSH University Ethics Committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (RUSH Institutional Review Board + IRB Number 18033101-IRB01) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. Braithwaite I, White J, Saifuddin A, Renton P, Taylor BA. Vertebral end-plate (Modic) changes on lumbar spine MRI: correlation with pain reproduction at lumbar discography. *Eur Spine J*. 1998;7:363-368.
2. Djurasovic M, Carreon LY, Crawford CH 3rd, Zook JD, Bratcher KR, Glassman SD. The influence of preoperative MRI findings on lumbar fusion clinical outcomes. *Eur Spine J*. 2012;21:1616-1623.
3. Luoma K, Vehmas T, Kerttula L, Gronblad M, Rinne E. Chronic low back pain in relation to Modic changes, bony endplate lesions, and disc degeneration in a prospective MRI study. *Eur Spine J*. 2016;25:2873-2881.
4. Teraguchi M, Yim R, Cheung JP, Samartzis D. The association of high-intensity zones on MRI and low back pain: a systematic review. *Scoliosis Spinal Disord*. 2018;13:22.
5. Fang C, Zhang W, Chen L, Li H. The correlation between the high-intensity zone on a T2-weighted MRI and positive outcomes of discography: a meta-analysis. *J Orthop Surg Res*. 2017;12:26.
6. Jha SC, Higashino K, Sakai T, et al. Clinical significance of high-intensity zone for discogenic low back pain: a review. *J Med Invest*. 2016;63:1-7.
7. Lam KS, Carlin D, Mulholland RC. Lumbar disc high-intensity zone: the value and significance of provocative discography in the determination of the discogenic pain source. *Eur Spine J*. 2000;9:36-41.
8. Peng B, Hou S, Wu W, Zhang C, Yang Y. The pathogenesis and clinical significance of a high-intensity zone (HIZ) of lumbar intervertebral disc on MR imaging in the patient with discogenic low back pain. *Eur Spine J*. 2006;15:583-587.
9. Wang ZX, Hu YG. Factors associated with lumbar disc high-intensity zone (HIZ) on T2-weighted magnetic resonance image: a retrospective study of 3185 discs in 637 patients. *J Orthop Surg Res*. 2018;13:307.
10. Yang H, Liu H, Li Z, et al. Low back pain associated with lumbar disc herniation: role of moderately degenerative disc and annulus fibrous tears. *Int J Clin Exp Med*. 2015;8:1634-1644.
11. Fan SW, Fang XQ, Liu YJ, Yu HJ, Lu YJ, Liu C. Reliability and variability in the interpretation of lumbar high intensity zone. *Acta Orthop Traumatol Turc*. 2015;49:606-613.
12. Aprill C, Bogduk N. High-intensity zone: a diagnostic sign of painful lumbar disc on magnetic resonance imaging. *Br J Radiol*. 1992;65:361-369.
13. Carragee EJ, Paragioudakis SJ, Khurana S. 2000 Volvo Award winner in clinical studies: lumbar high-intensity zone and discography in subjects without low back problems. *Spine (Phila Pa 1976)*. 2000;25:2987-2992.
14. Fardon DF, Williams AL, Dohring EJ, Murtagh FR, Rothman SLG, Sze GK. Lumbar disc nomenclature: version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. *Spine J*. 2014;14:2525-2545.
15. Yue JJ, Telles C, Schlösser TP, Hermenau S, Ramachandran R, Long WD 3rd. Do presence and location of annular tear influence clinical outcome after lumbar total disc arthroplasty? A prospective 1-year follow-up study. *Int J Spine Surg*. 2012;6:13-17.
16. Pande KC, Khurjekar K, Kanikdaley V. Correlation of low back pain to a high-intensity zone of the lumbar disc in Indian patients. *J Orthop Surg (Hong Kong)*. 2009;17:190-193.
17. Rankine JJ, Gill KP, Hutchinson CE, Ross ER, Williamson JB. The clinical significance of the high-intensity zone on lumbar spine magnetic resonance imaging. *Spine (Phila Pa 1976)*. 1999;24:1913-1920.
18. Smith BM, Hurwitz EL, Solsberg D, et al. Interobserver reliability of detecting lumbar intervertebral disc high-intensity zone on magnetic resonance imaging and association of high-intensity zone with pain and anular disruption. *Spine (Phila Pa 1976)*. 1998;23:2074-2080.
19. Cheung JPY, Luk KDK. The relevance of high-intensity zones in degenerative disc disease. *Int Orthop*. 2019;43:861-867.
20. Lee TH, Kim SJ, Lim SM. Prevalence of disc degeneration in asymptomatic Korean subjects. Part 2: cervical spine. *J Korean Neurosurg Soc*. 2013;53:89-95.
21. Teraguchi M, Samartzis D, Hashizume H, et al. Classification of high intensity zones of the lumbar spine and their association with other spinal MRI phenotypes: the Wakayama Spine Study. *PLoS One*. 2016;11:e0160111.
22. Shan Z, Chen H, Liu J, Ren H, Zhang X, Zhao F. Does the high-intensity zone (HIZ) of lumbar intervertebral discs always represent an annular fissure? *Eur Radiol*. 2017;27:1267-1276.
23. Teraguchi M, Cheung JPY, Karppinen J, et al. Lumbar high-intensity zones on MRI: imaging biomarkers for severe,

prolonged low back pain and sciatica in a population-based cohort. *Spine J*. 2020;20:1025-1034.
24. Sinnott PL, Dally SK, Trafton J, Goulet JL, Wagner TH. Trends in diagnosis of painful neck and back conditions, 2002 to 2011. *Medicine (Baltimore)*. 2017;96:e6691.
25. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163-2196.
26. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47: 1245-1251.
27. Pfirrmann CW, Metzdorf A, Zanetti M, Hodler J, Boos N. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2001;26:1873-1878.
28. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15:155-163.
29. Chanchairujira K, Chung CB, Kim JY, et al. Intervertebral disk calcification of the spine in an elderly population: radiographic prevalence, location, and distribution and correlation with spinal degeneration. *Radiology*. 2004;230:499-503.
30. Takeuchi M, Nagamachi A, Adachi K, et al. Prevalence of high-intensity zones in the lumbar spine according to age and their correlation with other degenerative findings on magnetic resonance imaging. *Spine Surg Relat Res*. 2018;2:299-303.
31. Brinjikji W, Diehn FE, Jarvik JG, et al. MRI findings of disc degeneration are more prevalent in adults with low back pain than in asymptomatic controls: a systematic review and meta-analysis. *AJNR Am J Neuroradiol*. 2015;36:2394-2399.