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Clinical Study

Lumbar high-intensity zones on MRI: imaging biomarkers for severe, prolonged low back pain and sciatica in a population-based cohort

Masatoshi Teraguchi, MD, PhD[a,b,c,*], Jason P.Y. Cheung, MBBS, MMedSc, FRCSE, FHKCOS, FHKAM[a], Jaro Karppinen, MD, PhD[d,e], Cora Bow, MCMSc, BHSa[a], Hiroshi Hashizume, MD, PhD[c], Keith D.K. Luk, FRCSE, FRCSG, FRACS, FHKAM[a], Kenneth M.C. Cheung, MBBS, MD, FRCS, FHKCOS, FHKAM[a], Dino Samartzis, DSc[f,g,**]

[a] *Department of Orthopaedics and Traumatology, The University of Hong Kong, Hong Kong, SAR, China*
[b] *Spine Care Center, Wakayama Medical University, Kihoku Hospital, Ito, Wakayama, Japan*
[c] *Department of Orthopaedic Surgery, Wakayama Medical University, Wakayama, Japan*
[d] *Medical Research Center Oulu, Oulu University Hospital and University of Oulu, Oulu, Finland*
[e] *Finnish Institute of Occupational Health, Oulu, Finland*
[f] *Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL, USA*
[g] *International Spine Research and Innovation Initiative, RUSH University Medical Center, Chicago, IL, USA*
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ABSTRACT

BACKGROUND CONTEXT: There is often discrepancy between clinical presentation and lumbar magnetic resonance imaging (MRI) findings.
PURPOSE: The purpose of this study was to assess the relationship of high-intensity zones (HIZs) on MRI with low back pain (LBP), sciatica, and back-related disability.
STUDY DESIGN: Cross-sectional, population-based Southern Chinese cohort study.
PATIENT SAMPLE: Of 1,414 possible participants, data from 1,214 participants (453 males, 761 females; mean age of 48.1±6.3 years) were included.
OUTCOME MEASURES: Presence of single-level, homogeneous multilevel (same type HIZs of morphology and topography) and heterogeneous multilevel (mixed type HIZs of morphology and topography) HIZs and other MRI phenotypes were assessed at each level with T2-weighted 3T sagittal MRI of L1–S1. Associations with LBP, sciatica and Oswestry Disability Index were correlated with HIZ profiles.
RESULTS: In all, 718 individuals had HIZs (59.1%). Disc degeneration/displacement were more prevalent in HIZ individuals (p<.001). HIZ subjects experienced prolonged severe LBP more frequently (39.6% vs. 32.5%; p<.05) and had higher Oswestry Disability Index scores (10.7±13.7 vs. 8.9±11.3; p<.05). Posterior multilevel HIZ were significantly associated with prolonged severe

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*Corresponding author. Spine Care Center, Wakayama Medical University, Kihoku Hospital, 219 Myoji, Katsuragi Town, Ito, Wakayama, Japan-
**Corresponding author. Department of Orthopedic Surgery, Rush University Medical Center, Orthopaedic Build, Room 204-G, 1611 W. Harrison St, Chicago, IL 60612, USA

E-mail addresses: m-tera@wakayama-med.ac.jp (M. Teraguchi), Dino_Samartzis@rush.edu (D. Samartzis).

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LBP (OR: 2.18; 95% CI:1.42−3.37; p<.05) in comparison to anterior only, anterior/posterior or other patterns of HIZ. Multilevel homogeneous or heterogeneous HIZs were significantly associated with prolonged, severe LBP (OR: 1.53−1.57; p<.05). Individuals with homogeneous HIZs had a higher risk of sciatica (OR: 1.51, 95% CI: 1.01-2.27; p<.05).

CONCLUSIONS: This is the first large-scale study to note that lumbar HIZs, and specific patterns therein, are potentially clinically-relevant imaging biomarkers that are independently and significantly associated with prolonged/severe LBP and sciatica. HIZs, especially homogenous multilevel HIZ, should be noted in the global pain imaging phenotype assessment.

Keywords: High intensity zone; HIZ; Low back; Lumbar; MRI; Pain; Phenotype; Spine

Introduction

Low back pain (LBP) causes functional impairment, diminished quality of life, work disability, potential psychological distress, and increased health-care costs [1−3]. Magnetic resonance imaging (MRI) of the lumbar spine is a useful tool used to identify the potential source of the LBP and to help guide management [4,5]. However there is often discrepancy and critique between the clinical profile and MRI findings [6,7]. Furthermore, inappropriate decision-making based on the lack of understanding of lumbar MRI phenotypes (e.g. black disc, end plate abnormalities, and Modic changes) may explain the relatively high incidence of failed spinal surgeries and poor outcomes in LBP patients [5,8]. Such lumbar phenotypes have been reported to interact with pain pathways or be pain generators; thereby, having the potential to possess novel clinical utility in the decision-making process and further underscoring the importance of imaging phenotype profiling [8−14].

High-intensity zones (HIZs) are one such phenotype characterized as hyperintense regions of the intervertebral disc noted on T2-weighted (T2W) MRI (Fig. 1). Initially reported in 1992 by Aprill and Bogduk [15] as potential imaging biomarkers for identifying symptomatic discs, the clinical relevance of HIZs with regards to LBP has been debated and scrutinized in the past 2 decades [15−23]. Some proposed its role as a diagnostic biomarker for LBP based on a concordant pain response on discography [15,17,18,22], while others did not find similar associations [16,19−21,23]. Nevertheless, the prevalence of HIZ in symptomatic and asymptomatic subjects varies greatly among these reports [15−23]. Additional controversies exist with regards to pathology, natural history, morphology, and topography of HIZs [15−23]. The failure to reach a consensus can be attributed to the lack of standardized imaging and clinical phenotyping, poor resolution of particular MRI sequences, inappropriate subject sampling from variable demographics, and insufficient statistical analyses, consideration of interactions with occupational/lifestyle factors and other spinal phenotypes [15−23]. However, recently, the understanding of the HIZ phenotype has been significantly broadened with the detailed classification of six types of HIZ based on a large-scale population-based study (Fig. 1) [24]. HIZs may manifest in different locations throughout the disc, have varied morphologies and may involve more than one lumbar disc level [24]. With refined understanding of HIZs, and the clinical role of other MRI phenotypes, the crucial debate between HIZs and their clinical relevance needs to be revisited.

Due to the aforementioned issues surrounding HIZs and their clinical relevance, the following large-scale study addressed if distinct types of lumbar HIZs are significantly associated with LBP, as well as back-related disability and sciatica, in a population-based cohort.

Materials and methods

Study population and design

This was a cross-sectional analysis based on the Hong Kong Disc Degeneration Population-Based Cohort of Southern Chinese volunteers [10−13],[25,26,27−31]. Informed consent was obtained from all subjects and ethics was approved by the local institutional review board. Subjects were recruited by open invitation using newspaper

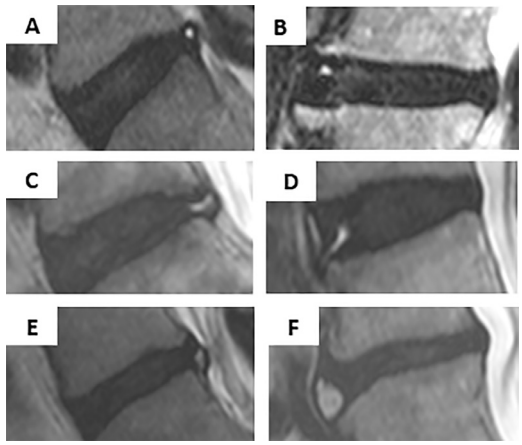

Fig. 1. High-intensity zone classification. High Intensity Zones (HIZ) were defined as a high intensity signal (white) surrounded by low intensity (black) located in the annulus fibrosus on T2-weighted sagittal MRI. Six types of HIZs were created based on the shape (round type, fissure type, vertical type, rim type, and giant type), and location within the disc (posterior or anterior). The images represent (A) posterior round type, (B) anterior round type, (C) posterior fissure type, (D) anterior rim type, (E) posterior vertical type, and (F) anterior enlarged type. (Adapted from Teraguchi et al. [24]).

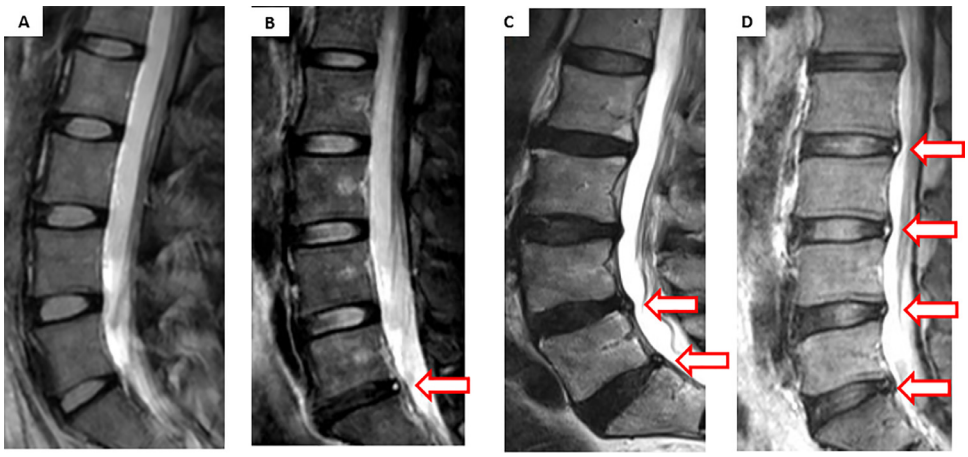

Fig. 2. Morphologic and topographic variables of high-intensity zones (HIZs): (A) normal lumbar indicating no HIZ; (B) single-level HIZ indicating only one HIZ in the entire lumbar spine; (C) multilevel homogenous HIZs indicating multiple HIZs of the same type; and (D) multilevel heterogeneous HIZs indicating multiple HIZs of variable types.

advertisements, posters, and e-mails. Subjects with LBP or sciatica were not actively recruited. The study recruited individuals irrespective of sex-type and who were cognitively capable to participate. Subjects with known spine tumors, fractures, metabolic diseases, infections, chronic inflammatory conditions, marked/severe spinal deformities, and recent spine surgery were not asked to enroll. The invitation to participate did not discriminate with regards to social or economic demographics. Participants were not recruited based on the presence or absence of LBP. However, in an effort to assess for selection bias for LBP in our sample, microsatellite marker frequencies were conducted [23]. The outcome of this comparison demonstrated that the sample was representative of the general population. The study sample and recruitment procedures have been previously described in further detail elsewhere [10−13],[25,26,27−31].

Low back pain, sciatica, and LBP-related disability

Duration of LBP and sciatica were recorded as pain in the past year with 0, 1 to 7, 8 to 30 days, over 30 days, or daily LBP. The worst past LBP experience was recorded by visual analog scale (VAS). For analysis purposes, duration of LBP was divided into under or over 30 days [13]. Severity of LBP was divided into 3 categories: no or mild pain (VAS<3), moderate pain (VAS 3−5.9), and severe pain (VAS >6) [10]. Prolonged severe LBP was defined as severe LBP lasting at least 30 days. Sciatica was also defined as pain radiating down one or both of the lower extremities beyond the knee and lasting over 30 days which was marked as the worst past sciatica experience. LBP-related disability was evaluated using the Oswestry Disability Index (ODI) [32] and was defined as scores ≥15% [10].

Magnetic resonance imaging protocol

3T sagittal T2W lumbar (L1−S1) MRIs (Siemens, Berlin and Munich, Germany; Phillips, Amsterdam, and Netherlands) without fat suppression were obtained for all subjects. The following protocol was adopted: repetition time: 3,320 ms, echo time: 85 ms, 5 mm slice thickness, 1 mm slice gap, field of view: 280×240 mm, and imaging matrix: 448×336. HIZs were defined as a bright white signal located in the substance of the annulus fibrosus (AF), which was clearly dissociated from the signal of the nucleus pulposus (NP). It was also surrounded by the low-intensity (black) signal of the AF and in turn was appreciably of similar brightness as the cerebrospinal fluid signal of the same level on T2- weighted sagittal MRI [15,16].

Evaluation of magnetic resonance imaging

Evaluation of a detailed HIZ classification and their relationship to other MRI phenotypes was performed. The HIZ classification [24] adopted was based on the disc level, shape (round type, fissure type, vertical type, rim type, and enlarged type), and location within disc (posterior or anterior) (Fig. 1). Furthermore, morphologic and topographic variables (Fig. 2) were defined including no HIZs, single-level or multilevel HIZs. Multilevel HIZs (i.e. 2 or more lumbar levels) were further defined as homogeneous (same morphologic type and location) or heterogeneous, also known as “mixed type” (variable morphologic types and location).

Morphologic HIZ variables were assessed by a board certified orthopedic surgeon (MT) who was blinded to subject information. Intra- and interobserver reliability were performed for HIZ. Reliability assessment of other MRI phenotypes have been reported elsewhere and were noted as good to excellent [26]. Two separate sets of 50 randomly selected MRIs were scored by two readers (MT and JC) for HIZ intra-observer and interobserver reliability. The assessments were performed more than 1 month apart independently and blinded to subject information. Reliability was evaluated by kappa analysis and were 0.99 and 0.83 ($p<.001$, 95% confidence interval (CI): MT; 0.98−0.99, JC;

0.73−0.91), respectively for intraobserver reliability, and was 0.94 (p<.001, 95% CI: 0.88−0.96) for interobserver reliability. Kappa of >0.90 were considered excellent, 0.80 to 0.90 were considered good, 0.60 to 0.80 were considered fair, and <0.60 were considered poor [33],[34]. Any disagreements in classification were settled by consensus after reliability assessments were completed.

Disc degeneration was evaluated using the Pfirrmann classification, ranging in score from 1 (normal) to 5 (most severe) for each disc [35]. Disc displacement was evaluated as a disc bulge, protrusion, or extrusion. Disc bulge was defined as disc displacement posteriorly beyond the line linking the posterior edges of adjacent vertebral bodies. Disc protrusion was noted as nucleus displacement beyond the confines of the AF. Disc extrusion was recognized when the distance between edges of the disc material beyond the disc space was greater than the distance between edges of the base of the disc material [11,31,36,37]. Modic change was defined as high-signal intensity at the vertebral end plates. The presence of Modic change was defined as one or more Modic changes in the entire lumbar spine. Since only T2W MRIs were utilized, we did not distinguish between different Modic types. Disc degeneration summary score was calculated by adding the individual scores of all 5 lumbar levels (L1−S1) and further divided into 2 categories: disc degeneration score <16 was considered normal to mild degeneration, whereas a score ≥16 was regarded as moderate to severe degeneration [6]. Disc displacement score was considered per disc with 1 point for bulge/protrusion and 2 points for extrusion. The disc displacement summary score was calculated by adding all 5 lumbar levels and divided into 2 categories for analysis: <2 was considered normal to mild disc displacement, and ≥3 was considered moderate to severe disc displacement.

Lifestyle factors

Height (m), weight (kg) and body mass index (BMI) (kg/m^2) were measured. The factor of smoking was classified as being nonsmokers, smoking ≦10, and smoking >10 pack-years during one's lifetime. Pack-years were calculated based on the frequency (cigarettes smoked per day) and duration (years) of smoking in the context of the number of cigarettes within a pack. Physical workload was assessed based on occupation, further characterized as sedentary, light, medium, heavy, or very heavy on a scale of 1 to 4 [12].

Statistical analyses

All statistical analyses were performed using JMP version 8 (SAS Institute Japan, Tokyo, Japan). The descriptive statistics were calculated for all variables, and compared with HIZ using *t* test (age, BMI), Mann-Whitney *U* test (LBP intensity, ODI, disc degeneration, and disc displacement scores), and chi-square test (sex, smoking, heavy/very heavy workload, prolonged severe LBP, prolonged sciatica, back-related disability, and presence of Modic change). Data were presented as mean±standard deviation. Logistic regression was used to analyze the associations of prolonged severe LBP, sciatica and back-related disability with single-level, multilevel homogeneous, and multilevel heterogeneous HIZs. Unadjusted odds ratios (ORs) and 95% CIs were calculated to estimate the crude association between each HIZ and prolonged severe low back pain, sciatica, and back-related disability comparing with no HIZ. The multivariable logistic regression models were evaluated the association between each HIZ and outcome variables comparing with no HIZ after adjustment for age, sex and BMI, moderate disc degeneration, moderate disc displacement, and presence of Modic change. Furthermore, multivariate logistic regression analysis evaluated the association between single level HIZ, anterior multilevel HIZs, posterior multilevel HIZs, and anterior/ posterior multilevel HIZs to that of prolonged severe LBP. The threshold for statistical significance was established at p<.05 and the corresponding 95% CIs were assessed.

Results

Study population characteristics

Imaging was available for 1,414 subjects. However, only 1,214 (86%) subjects who attended the interview and examination were included in the analysis. There were 761 (63%) females and 453 (37%) males with mean age of 48.1±6.3 years (Table 1). Mean BMI was 23.4±3.5 kg/m^2 and 72 (5.9%) subjects smoked more than 10 pack-years during their lifetime. Heavy or very heavy workload was reported by 96 (7.9%) subjects.

Prevalence of HIZs

HIZs were noted in 59.1% (n=718) of all subjects and its location was posterior, anterior, and both posterior/anterior in 50.7% (n=364), 29.5% (n=212), and 19.8% (n=142), respectively. Of these 718 subjects, 53.3% had single HIZ (n=383), 32.5% had 2 HIZs (n=233), 11.1% had 3 HIZs (n=80) and 3.1% had 4 HIZs (n=22). For the 335 multilevel HIZs subjects, 40.0% had homogeneous HIZs (n=134) and 60.0% had heterogeneous HIZs (n=201). And, the percentage of anterior and posterior of homogeneous HIZ was 40.3% (n=54) and 59.7% (n=80) of 134 subjects with homogenous HIZ.

HIZs and demographic factors

Subjects with HIZs were older (48.8±6.3 vs. 47.2±6.1, p<.0001). Sex-type, BMI, smoking >10 pack-years, and heavy/very heavy workload had no significant association with presence of HIZs (Table 2).

HIZs and other MRI phenotypes

Subjects with HIZ had significantly higher disc degeneration score (13.3±2.7 vs. 11.8±3.5, p<.001) and disc displacement score (3.8±2.1 vs. 2.4±2.1, p<.0001) (Table 2).

Table 1
Characteristics of the study population

	Overall	Male	Female
No. of participants	1,214	453	761
Age, years	48.1±6.3	48.2±6.3	48.1±6.2
Body mass index (kg/m2)	23.4±3.5	24.2±3.0	22.8±3.6
Prevalence of lifestyle/occupation characteristics, N (%)			
Smoking habit			
No	1,079 (88.9%)	334 (73.7%)	745 (97.9%)
1−10 pack-year	63 (5.2%)	54 (11.9%)	9 (1.2%)
>10 pack year	72 (5.9%)	65 (14.3%)	7 (0.9%)
Workload			
Sedentary/light	619 (51.0%)	239 (52.8%)	380 (49.9%)
Medium	499 (41.1%)	168 (37.1%)	331 (43.5%)
Heavy/Very heavy	96 (7.9%)	46 (10.2%)	50 (6.6%)
Prevalence of clinical profile, N (%)			
LBP lasting for at least 30 days in the past year	838 (69%)	320 (70.6%)	518 (68.0%)
LBP intensity			
No pain/ mild pain (VAS <30)	454 (37.4%)	165 (36.4%)	289 (38.0%)
Moderate pain (VAS 30−59)	261 (21.5%)	93 (20.5%)	168 (22.1%)
Severe pain (VAS ≥60)	499 (41.1%)	195 (43.1%)	304 (39.9%)
Prevalence of prolonged severe LBP ODI score	445 (36.7%)	174 (38.4%)	271 (35.6%)
<15%	904 (74.5%)	377 (83.2%)	527 (69.3%)
≥15%	310 (25.5%)	76 (16.8%)	234 (30.7%)
Lasting sciatica for at least 30 days in the past year	502 (41.4%)	168 (37.1%)	334 (43.9%)

LBP, low back pain; ODI, Oswestry Disability Index; VAS, visual analog scale.

Prolonged severe LBP defined as lasting for at least 30 days in the past year and most severe VAS experienced at least 6 out of 10. Sciatica was also defined as pain radiating down one or both of the lower extremities beyond the knee and lasting over 30 days which was marked as the worst past sciatica experience.

However, this relationship was not observed for Modic change (17.7% vs. 14.1%, p=.09).

HIZs and clinical parameters

Subjects with HIZs had experienced prolonged severe LBP more frequently (39.6% vs. 32.5%, respectively; p=.011). However, this association was not observed for prolonged sciatica nor LBP-related disability. As shown in Table 3, higher risk of prolonged severe LBP was observed for both homogeneous (OR: 1.57; 95% CI: 1.10−2.23) and heterogeneous HIZs (OR: 1.53; 95% CI: 1.02−2.31). Single-level HIZ did not demonstrate significant risk of prolonged severe LBP in the fully adjusted multivariable

Table 2
The association of high-intensity zones with subject demographics and clinical/imaging phenotypes

	No HIZ	Presence of HIZ	p Value
No. of participants	496	718	
Age	47.2±6.1	48.8±6.3	<.0001
Female sex; N (%)	307 (61.9%)	454 (63.2%)	.64
BMI	23.4±3.9	23.4±3.1	.97
Smoking >10 pack-yea; N (%)	26 (5.2%)	46 (6.4%)	.5
Heavy/ very heavy workload; N (%)	33 (6.7%)	63 (8.8%)	.18
Symptoms			
Prolonged severe LBP; N (%)	161 (32.5%)	284 (39.6%)	<.05
ODI score	8.9±11.3	10.7±13.7	<.05
Prolonged sciatica	198 (39.9%)	304 (42.3%)	.4
Other Imaging Phenotypes			
Disc degeneration score	11.8±3.5	13.3±2.7	<.001
Disc displacement score	2.4±2.1	3.8±2.1	<.0001
Presence of Modic change; N (%)	70 (14.1%)	127 (17.7%)	.09

HIZ, high-intensity zone; BMI, body mass index; LBP, low back pain; ODI, Oswestry Disability Index; VAS, visual analog scale.

Prolonged severe LBP defined as lasting for at least 30 days in the past year and most severe VAS experienced at least 6 out of 10. Prolonged sciatica defined as pain radiating down one or both of the lower extremities beyond the knee and lasting over 30 days which was marked as the worst past sciatica experience.

Table 3
Multivariate regression analyses of the association between prolonged, severe low back pain and high-intensity-zones

	N (%) with/without prolonged severe LBP		OR (95%CI)	
	Yes	No	Unadjusted (vs. no HIZ)	Adjusted (vs. no HIZ)
Presence of HIZ	284 (63.8%)	434 (56.4%)	1.36 (1.07−1.73)*	1.35 (1.05−1.74)*
Single HIZ	140 (31.5%)	245 (31.9%)	0.85 (0.64−1.12)	0.84 (0.63−1.12)
Homogenous multilevel HIZs	57 (12.8%)	75 (9.8%)	1.57 (1.06−2.32)*	1.53 (1.02−2.31)*
Heterogenous multilevel HIZs	86 (19.3%)	114 (14.8%)	1.56 (1.11−2.18)*	1.57 (1.10−2.23)*

Adjusted; adjusted for age, sex, BMI, moderate disc degeneration, moderate disc displacement, and presence of Modic change.

Presence of HIZ; at least one HIZ in the lumbar spine, single HIZ; only one HIZ in the lumbar, Homogenous HIZ; same type of multilevel HIZs in the lumbar, Heterogenous HIZ; different type of multilevel HIZs in the lumbar.

Prolonged severe LBP defined as lasting for at least 30 days in the past year and severest VAS at least 6 out of 10 on a 10-cm VAS.

OR, odds ratio; CI, confidence interval; VAS, visual analog scale; LBP, low back pain; HIZ, high intensity zone; BMI, body mass index.

* p<.05.

Table 4
Multivariate regression analyses of the association between prolonged sciatica and high-intensity-zones

	N (%) with/without prolonged Sciatica		OR (95%CI)	
	Yes	No	Unadjusted (vs. no HIZ)	Adjusted (vs. no HIZ)
Presence of HIZ	304 (60.1%)	414 (58.2%)	1.28 (0.98−1.68)	1.09 (0.85−1.39)
Single HIZ	147 (29.3%)	238 (33.4%)	0.92 (0.70−1.21)	0.94 (0.70−1.24)
Homogenous multilevel HIZs	67 (13.4%)	65 (9.1%)	1.54 (1.05−2.27)*	1.51 (1.01−2.27)*
Heterogenous multilevel HIZs	89 (17.7%)	111 (15.6%)	1.20 (0.86−1.67)	1.17 (0.82−1.66)

Adjusted; adjusted for age, sex, BMI, moderate disc degeneration, moderate disc displacement, and presence of Modic change.

Presence of HIZ; at least one HIZ in the lumbar spine, single HIZ; only one HIZ in the lumbar, Homogenous HIZ; same type of multilevel HIZs in the lumbar, Heterogenous HIZ; different type of multilevel HIZs in the lumbar.

Prolonged sciatica defined as lasting for at least 30 days in the past year.

OR, odds ratio; CI, confidence interval; HIZ, high intensity zone; BMI, body mass index.

* p<.05.

Table 5
Multivariate regression analyses of the association between back-related disability and high-intensity-zones

	N (%) with/without back-related disability		OR (95%CI)	
	Yes	No	Unadjusted (vs. no HIZ)	Adjusted (vs. no HIZ)
Presence of HIZ	197 (63.6%)	521 (57.6%)	1.28 (0.98−1.68)	1.16 (0.88−1.55)
Single HIZ	98 (31.6%)	287 (31.8%)	0.87 (0.64−1.19)	0.93 (0.67−1.28)
Homogenous multilevel HIZs	40 (12.9%)	92 (10.2%)	1.46 (0.94−1.96)	1.31 (0.83−2.04)
Heterogenous multilevel HIZs	58 (18.7%)	142 (15.7%)	1.37 (0.94−1.98)	1.21 (0.81−1.77)

Adjusted; adjusted for age, sex, BMI, moderate disc degeneration, moderate disc displacement, and presence of Modic change.

Presence of HIZ; at least one HIZ in the lumbar spine, single HIZ; only one HIZ in the lumbar, Homogenous HIZ; same type of multilevel HIZs in the lumbar, Heterogenous HIZ; different type of multilevel HIZs in the lumbar.

Back-related disability defined as scores ≥15%.

OR, odds ratio; CI, confidence interval; HIZ, high intensity zone; BMI, body mass index.

regression analysis (OR: 0.84; 95% CI: 0.63−1.12). Moreover, posterior multilevel HIZs were significantly associated with prolonged severe LBP (OR: 2.18; 95% CI: 1.42−3.37), but anterior multilevel HIZs and anterior/ posterior multilevel HIZs were not significantly associated with prolonged severe LBP (OR: 1.09; 95% CI: 0.66−1.80, OR: 1.46, 95% CI: 0.97−2.19).

In the fully adjusted model (Table 4), homogeneous HIZs had a higher risk of prolonged sciatica (OR: 1.51; 95% CI: 1.01−2.27). However, similar findings were not observed for single-level (OR: 0.94; 95% CI: 0.70−1.24) and heterogeneous HIZs (OR: 1.17; 95% CI: 0.82−1.66). The presence of HIZ (Table 5) did not increase the risk of back-related disability (heterogeneous HIZ OR: 1.21; 95% CI: 0.81−1.77; homogeneous HIZ OR: 1.31, 95% CI: 0.83−2.04).

Discussion

To our knowledge, this is the largest study adopting a detailed, systematic and standardized methodology, to assess the relationship of HIZ with LBP, sciatica, and LBP-

related disability. Our large-scale population-based study is the first to note that multilevel homogeneous HIZs of the lumbar spine were significantly and independently associated with prolonged severe LBP and sciatic.

The overall prevalence of HIZs is variable in the literature especially with regards to LBP [15–23]. The prevalence of HIZs is reported as 14% to 63%, yet most of these studies are flawed with no comparative symptomatic groups, lack of controls and utilizing heterogeneous populations [15–23]. The Wakayama Spine Study [24] had previously reported the overall prevalence of HIZs to be 38.0% among 814 Japanese subjects, in comparison to 59.1% with HIZ in the current study. The prevalence variation may be attributed to the older cohort subjects in the Japanese study (63.6 vs. 48.1 years), further supported by previous studies noting similar age-effects in annular tears/HIZs [19,38].

Whether HIZs are symptomatic is under continued debate. Lack of consensus is a result of contradictory evidence from studies which are underpowered, lacking in controls and standardization in assessing heterogeneous populations, and the poorly understood imaging phenotypes and their standardization [15–23]. Some investigators suggest its role as a MRI biomarker for discogenic LBP due to its concordant pain response on provocative discography [15,19,22]. However, others were unable to reproduce these original findings [15–23]. Furthermore, Carragee et al. demonstrated that discographic injections provoked significant pain in approximately 70% of cases irrespective of whether patients had pain or not [16]. This indicates that even though a discographic injection in a disc with an HIZs may produce significant pain, the disc may not be the cause of LBP. Moreover Carragee et al. reviewed, the sensitivity and reliability of discographic injections to diagnose LBP is questionable. Thus, provocative discographic studies are of limited use for determining LBP [16,39] and similar controversies exist in population-based longitudinal studies for relationships between HIZ and LBP [40]. In our study, a thorough assessment using a detailed HIZ classification and assessment with adjustment of confounding lifestyle/environmental and other imaging phenotype factors noted a strong association between multilevel same-type HIZ and prolonged/severe LBP. Furthermore work done by Samartzis et al. and others over the years based on large-scale studies has clearly demonstrated that degeneration of the spine may exist even in asymptomatic subjects; [[5,6],16,39] however, the severity, specific patterning and aggregation of MRI phenotypes may be more telling with regards to the development and severity of pain [40]. This of course does not imply that all single level HIZs present are dormant and nonimportant. There could of course be ethnic, religious, lifetime experience, stressors, pain genetic factors, and others that may play a role in pain expression that need further investigation [40].

Our large-scale population-based study was also able to address the relationship between HIZ and prolonged sciatica. After adjustment for confounding factors, multilevel homogeneous HIZs was a significant risk factor for prolonged sciatica. This is a sensible association based on its pathology. HIZs are in large part fluid-filled zones that represent a portion of detached NP between the lamellae of a torn AF leading to granulation tissue formation or neovascularization by secondary inflammation [21,41]. As a result, proinflammatory cytokines and mediators may be produced to sensitize the nociceptors of spinal nerves. Our study further underscores that specific HIZ types and patterning may be more relevant than others with regards to sciatica.

With regards to disability as based on ODI assessment, we were unable to find any significant relationship with HIZ. Therefore, HIZ may not have a significant impact on disability gauged by ODI as an assessment tool. Such findings illustrated the more acute nature of this imaging phenotype, which needs further investigation.

A majority of investigators identified HIZs as a step in the degenerative cascade and hence strongly associated with disc degeneration [16,18,21,24,42]. HIZs are often seen with morphologic changes of the NP and may be related to a faster subsequent nuclear degeneration [42]. However, several investigators are skeptical of these findings due to lack of conclusive evidence [16,41]. In our study, HIZ was found to be strongly associated with disc degeneration. Disc displacement, such as disc bulging and protrusion, are also important phenotypic projections of disc degeneration. Yu et al. [43] has demonstrated that disc bulge is associated with annular tears by cadaveric study. Teraguchi et al. [24] further supported this finding in a population-based cohort. HIZs cause migration of the nucleus relative to the AF and hence, the disc periphery is weakened and at risk of prolapse. Depending on the extent of nucleus migration, bulging or protrusion of the nuclear material may occur [41].

It remains unclear in the current literature what risk factors lead to HIZs. Despite the possible mechanism of traumatic disc disruption, Park et al. [19] showed that 57 out of 99 patients (58%) with HIZ had no previous trauma and only 17 patients with trauma history had experienced high-energy injuries sufficient to cause intervertebral disc disruption. Nevertheless, these findings are based on limited evidence and require further study. Although traumatic incidents were not studied in this population-based cohort, we did not find any significant association between heavy workload and Modic changes, surrogates for traumatic or hyper-loading, and HIZ. No other lifestyle/environmental factors were found to be associated with HIZs.

As with any clinical study, limitations exist. Our study was a cross-sectional study and thus we cannot conclude any causative relationships. Although these volunteers were recruited from the general population, there is an inherent bias and influences with open recruitment. Nevertheless, based on our previous analyses, we have found that our cohort represents a good representation of the general population [30,31,36]. Furthermore, in comparison to other population-based studies assessing similar parameters, our cohort remains more detailed in its assessment of the various demographic, lifestyle/environmental, imaging, and clinical profile dimensions [10–13],[25,26,27–31]. In addition, due to the homogeneity

of the ethnic population, this minimized potential ethnic confounds and biases. Nonetheless, future studies are needed to determine the generalizability of our findings in other ethnic groups. That said, our study is the first to raise awareness and to provide a framework that specific "patterns" and "types" of HIZs should be assessed in the discussion of the clinical imaging profile. However, our study did not include a physical examination or assessment of somatic symptom amplification issues in each volunteer [44]. Then again, our subjects were not patient-based and not recruited on the basis of a pain profile that may further complicate the element of somatic symptom amplification. Finally, the development of LBP is multifactorial and as such can be caused by multiple factors, such as osteoporosis, back muscle strain, psychosocial problems, pain genetics and so on [4,5,8]. Therefore, not all imaging findings are the definitive pain generating sources for LBP. However, due to our very large-scale imaging and clinical profile study as well as our in-depth phenotyping of various MRI findings, we can conclude that HIZs, in particular posterior multilevel HIZs, may have a significant clinical relevance and represent a unique pathologic process that demands attention by researchers and clinicians alike. Such findings need to be further explored and their impact upon clinical decision-making in patients who present with LBP further considered.

In the era of precision medicine and personalized spine care, understanding the "spinal phenotype profile" of individuals is critical. This allows a better identification of the pain source for diagnosis as well as to assist in more precise clinical management algorithms that will ultimately enhance patient outcomes and lead to better cost-effectiveness. Having such an understanding may further enhance novel regenerative disc therapies and patient selection, as well as their respective outcomes. Moreover, HIZ profiling may lead to advanced targeted phenotype therapies or serve as flags in the diagnosis and clinical treatment algorithm of LBP by clinicians. This study stresses the point that specific patterning of HIZs should not be "dismissed" and may be vital MRI biomarkers. This could also be the case that such phenotypes are also heavily associated with disc displacement; however, multilevel posterior HIZs are independently associated with pain profiles and may represent a unique underlying pathologic process that may represent more active disc inflammation and pain generating. With innovations in machine learning and automated imaging analysis, HIZs are a clinically relevant imaging phenotype that should be noted and mapped. Furthermore, our study further provides credence to further investigate the molecular pathogenesis, genetics, and predictive modeling of HIZs.

Authors' contribution

Masatoshi Teraguchi: Imaging analyses, statistical analyses, interpretation of findings, initial draft of paper.

Cora Bow: Data collection, critical editing of paper, interpretation of findings.

Jason PY Cheung: Imaging analyses, critical editing of paper, interpretation of findings.

Jaro Karppinen: Data collection, critical editing of paper, interpretation of findings.

Hiroshi Hashizume: Critical editing of paper, interpretation of findings.

Keith DK Luk: Critical editing of paper, interpretation of findings, obtained funding.

Kenneth MC Cheung: Interpretation of findings, obtained funding.

Dino Samartzis: Conception of study design, data collection, statistical analysis, interpretation of findings, writing of paper, critical edits of paper, administrative support, obtained funding, supervision of study.

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