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Does the high-intensity zone of lumbar intervertebral disc at magnetic resonance imaging have diagnostic value for discogenic low back pain? A meta-analysis

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Abstract

Objective The correlation between high-intensity zone (HIZ) of lumbar disc magnetic resonance imaging (MRI) and discogenic low back pain (DLBP) is currently controversial, this study aimed to systematically evaluate the correlation between HIZ of lumbar disc MRI and positive discography, as well as its diagnostic value for DLBP.

Method Databases were searched to include research literature on high intensity zone (HIZ) related to discography and DLBP diagnosis. HIZ is a separate small, confined area of high signal located at the posterior border of the annulus fibrosus on MRI T2-weighted images of the lumbar spine, which is separated from the nucleus pulposus but has a higher signal than the nucleus pulposus. Studies on the correlation of HIZ with discography and DLBP diagnosis were searched in the Pubmed, EMBASE, Cochrane Central, Science Direct, China Knowledge Network, Wanfang Database, and China Biomedical Literature Databases, Scopus from January 1992 to June 2024. The outcomes were diagnostic values of HIZ for DLBP. The risk assessment was performed by Deeks' funnel methods in the Stata 17.0 software after 2 investigators independently screened the literature, extracted information and evaluated the risk of bias of the included studies.

Results A total of 25 studies including 5889 patients were included. meta-analysis showed that the sensitivity of HIZ for the diagnosis of DLBP was (0.49, 95% CI [0.37,0.61]) and specificity was (0.89, 95% CI [0.85,0.93]); the positive likelihood ratio was (4.52, 95% CI [3.28,6.25]) and the negative likelihood ratio was (0.58, 95% CI [0.46,0.71]). The diagnostic ratio was (7.87, 95% CI [5.05,12.26]).

Conclusion The available evidence suggests that HIZ has acceptable sensitivity and high specificity in the diagnosis of DLBP. Due to the limitation of the number and quality of included studies, the above conclusions need to be validated by more high-quality studies.

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Keywords Magnetic resonance imaging, HIZ, Discogenic low back pain, Diagnosis, Meta-analysis

Introduction

Discogenic low back pain (DLBP) refers to low back pain symptoms whose clinical manifestations are not dominated by nerve tissue compression (except for lumbar spinal stenosis, lumbar disc herniation, etc.), and which are mainly related to lumbar disc degeneration [1]. Crock [2] first suggested in 1970 that abnormalities in the internal structure and metabolic function of the disc could cause low back pain, and in 1986 [3] further described it as intervertebral disc disruption. In 1987, Milette [4] suggested that discogenic chronic pain is often not caused by mechanical compression of a nerve root by a disk fragment; rather, such pain results from a small tear in the annulus accompanied by an inflammatory reaction and minimal herniated material that puts the posterior longitudinal ligament under tension in young individuals. At present, the pathogenesis of DLBP has not been fully elucidated, and there is still a lack of specific methods for diagnosis. Discography is currently recognized as the comparative standard for the diagnosis of DLBP and can clarify the responsible disc. According to the International Academy of Pain Classification, the criteria for diagnosing discogenic pain should include that the painful symptoms should be induced by discography and that the diseased disc should be detectable on computed tomography (CT) scan. At the same time, there should be at least one disc that does not induce painful symptoms in response to the same stimulus as the control. According to this criterion, discography requires a control negative disc, which requires at least one normal disc to be contrasted as a negative disc, indirectly creating a disruption to the negative disc and likely inducing a negative disc herniation. Thus, as an invasive operation, disc pin puncture has the potential to cause and accelerate damage to the annulus fibrosus and nucleus pulposus, which may accelerate lumbar disc degeneration. Therefore, effective methods and examinations applied to the diagnosis of DLBP are a hot concern for most clinical practitioners.

The high intensity zone (HIZ) on MRI of the lumbar spine was first reported by Aprill [5] in 1992 and refers to a small, independent and confined high signal zone located at the posterior edge of the annulus fibrosus on T2-weighted images of the lumbar spine, which is separated from the nucleus pulposus but has a higher signal than the nucleus pulposus, as shown in Fig. 1. Aprill's clinical study found that the spillage of contrast agent during discography in HIZ patients due to rupture of the annulus fibrosus induced pain in about 90% of cases, and that this pain replicated the patient's usual lower back pain symptoms, the so-called pain replication, thus suggesting that HIZ is an important sign for the diagnosis of painful disc rupture. Since Aprill's discovery of HIZ, scholars at home and abroad have conducted a large number of related studies around HIZ, and many more scholars have conducted studies by comparing MRI and discography, but their understanding of this is not consistent, and there have been endless debates about its role and significance. Since HIZ is non-invasive and actionable as a nuclear magnetic imaging index, and it is currently considered to have a high correlation with disc degeneration; therefore, our study revolves around a Meta-analysis of its diagnostic value in intervertebral discogenic low back pain, with the aim of providing reliable clinical evidence for the clinic.

Information and methods

Literature search strategy

Literature from PubMed, EMBASE, Cochrane Library, Science Direct, China Knowledge Network, Wanfang Database, and China Biomedical Literature Database was searched from January 1992 to June 2024. Chinese search terms include: "discogenic low back pain", "diagnosis", "nuclear magnetic high intensity-zone", "discography"; English search terms include: "discogenic low back pain, HIZ or high intensity-zone(s)", and "discography". Studies on the correlation of HIZ with discography and DLBP diagnosis were collected. The search was conducted using a combination of subject terms and free terms, and was adjusted to the characteristics of each database. References included in the study were also searched to supplement access to relevant information. Meta-analysis was performed using Stata 17.0 software after 2 investigators independently screened the literature, extracted information and evaluated the risk of bias of the included studies.

Study selection

Studies assessed the diagnostic accuracy test were included for the selection process. Studies with the following items were included for the meta-analysis: (1) Population: Patients with suspected DLBP who underwent discography were referred to the diagnostic criteria of Fischgrund [6]; The studies observed the correlation between HIZ and coherent pain induced by intercalated discography. HIZ is a separate small, confined area of high signal located at the posterior border of the annulus fibrosus on MRI T2-weighted images of the lumbar spine, which is separated from the nucleus pulposus but has a higher signal than the nucleus pulposus. (2) Diagnostic criteria: The accepted discography was used as the comparative standard, and the diagnostic criteria were referred to Fischgrund's diagnostic criteria; (3) Endpoint

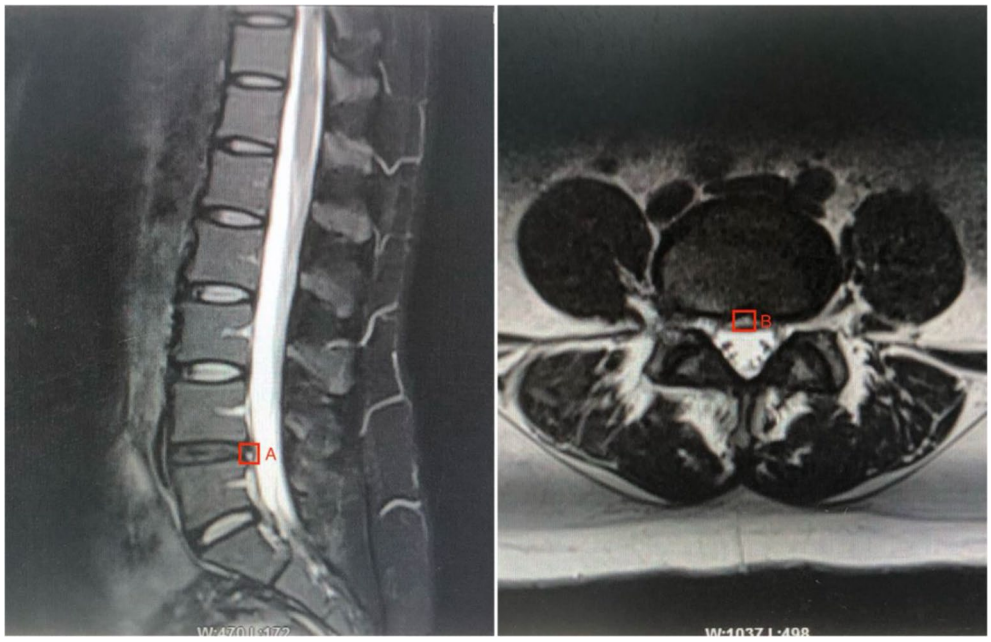

Fig. 1 Lumbar disc HIZ nuclear magnetic image. **A**, a lumbar disc HIZ sagittal imaging; **B**, a lumbar disc HIZ axial imaging

indicators: (a) sensitivity; (b) specificity; (c) positive likelihood ratio; (d) negative likelihood ratio; (e) diagnostic odd ratio (DOR); (f) summary receiver operating characteristic (SROC) area under curve (AUC). The exclusion criteria were as follows: (1) studies without interstitial discography and description of correlation with HIZ; (2) studies for which the four-grid table or raw data could not be extracted; (3) repeatedly published studies; (4) non-Chinese and English studies.

Data extraction

The literature was screened, extracted and cross-checked by 2 researchers independently. In case of disagreement, it was resolved through discussion or consultation with a third party. The literature was screened by first reading the title of the text and, after excluding apparently irrelevant literature, further reading the abstract and full text to determine inclusion. If needed, the authors of the original studies were contacted by email and telephone to obtain information that was not identified but was important to this study. Data extraction included: (1) basic information about the included studies: first author, year of publication, country of study, type of study, sample size, mean age of patients, sex, interstitial discography pain replication results, and device field strength; (2)Enter the number of patients with HIZ and interstitial discography replication pain, and finally collate the information to form a four-grid table (true positive, false positive, false negative and true negative) for statistical analysis [7].

Quality assessment

The risk of bias of the included studies was evaluated independently by 2 investigators and the results were cross-checked. The risk of bias was evaluated using the Quality Assessment Tool for Diagnostic Accuracy Studies (QUADAS-2) recommended by the Cochrane Collaboration Network [8].

Statistical analysis

This is a single-arm meta-analysis of diagnostic tests performed by the MIDAS module of Stata 17.0 software. Heterogeneity between the results of the included studies was analyzed using the $\chi 2$ test (test level $\alpha = 0.1$), while the size of the heterogeneity was determined quantitatively in combination with I^2 [9], Heterogeneity was significant with $I^2 > 50\%$. If there was no statistical heterogeneity among the findings, Meta-analysis was performed using a fixed-effects model; if there was statistical heterogeneity among the findings, the source of heterogeneity was further analyzed and Meta-analysis was performed using a random-effects model after excluding the effect of obvious clinical heterogeneity. The combined diagnostic efficacy measures calculated included: combined sensitivity, combined specificity, combined positive likelihood ratio, combined negative likelihood ratio, and combined DOR, with 95% confidence interval (CI) provided for all combined effect measures. Using a bivariate mixed effects model for Meta-analysis of diagnostic tests [10–12], forest plots and ROCs were drawn by logit transformation of true positive and false positive rates, and the strength of diagnostic efficacy was evaluated using AUC, the closer the AUC to 1.0, the higher the

diagnostic efficacy was suggested. The presence of publication bias was assessed by Deek's asymmetric regression test [13]. Fagan plots were drawn to evaluate the value of the clinical use of diagnostic tests.

Results

Literature screening process and results

A total of 1835 relevant literature was obtained from the initial review, and after stratification screening, 25 studies [5, 14–37] were finally included, including 5889 patients. The literature screening process and results are shown in Fig. 2.

Basic characteristics of the included studies and the results of the risk of bias evaluation

The basic characteristics of the included studies are shown in Table 1. Of the 25 studies, 12 were conducted in China, 7 in America, 2 in UK, 2 in Korea, 1 in Australia and 1 in Germany. 17 studies were case-control designed, 7 studies were retrospective cohort study, while 1 study was prospective cohort study. 1.5T magnetic field intensity were used in most of the included studies (15/25). The sample size, mean age and gender distributions were described in the Table 1. And the results of the risk of bias evaluation are shown in Table 2.

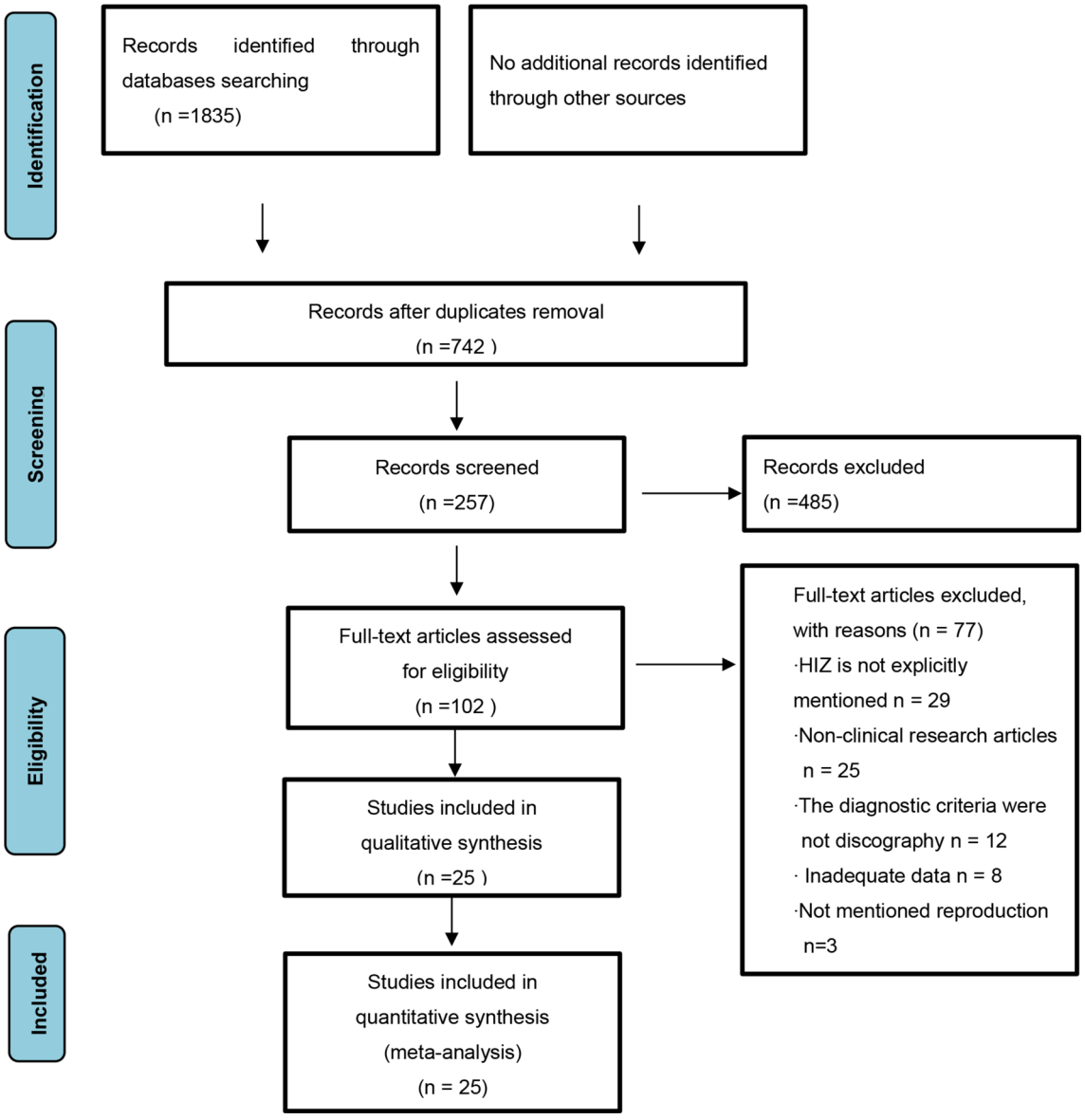

Fig. 2 Flow diagram of the study selection process. The identification, screening, eligibility, included of studies

Table 1 Basic characteristics of the included studies

Study	Country	Study design	Magnetic field intensity	Sample size disc number	Mean age	Gender		Diagnostic criteria
						male	female	
Aprill 1992	Australia	CS	0.6T	118	NA	357	143	Discography
Ricketson 1996	America	CCT	NA	80	40.9	17	12	Discography
Schellhas 1996	America	RA	1.5T	167	37.5	NA	NA	Discography
Saifuddin 1998	UK	RA	0.5-1.5T	152	42	31	27	Discography
Smith 1998	America	RA	1.5T	152	46	36	36	Discography
Ito 1998	America	CCT	1.5T	101	37	17	22	Discography
Carragee 2000	America	RA	1.5T	109	36.4	25	17	Discography
Lam 2000	UK	RA	1.5T	155	42	52	21	Discography
Lim 2005	Korea	CCT	1.5T	97	43	20	27	Discography
Kang 2009	Korea	RA	1.5T	178	46	NA	NA	Discography
Chen 2011	China	CCT	1.5T	256	40.11	64	29	Discography
William 2012	Germany	CCT	NA	35	43.2	10	21	Discography
Wang 2017	China	CCT	NA	98	37.8	26	11	Discography
Chelala 2019	America	CCT	NA	2457	43	367	338	Discography
Guo 2008	China	CCT	NA	134	NA	25	30	Discography
Ma 2009	China	CCT	1.5T	43	37.8	18	25	Discography
Li 2011	China	CCT	1.5T	106	51.2	40	26	Discography
Peng 2012	China	CCT	NA	289	41	146	61	Discography
Liu 2013	China	CCT	1.5T	216	39.3	52	24	Discography
Liu 2014	China	CCT	1.5T	152	22.3	39	15	Discography
Liu 2016	China	CCT	1.0T	228	51.36	48	34	Discography
Liu WB 2016	China	CCT	1.5T	79	45.3	30	20	Discography
Qiu 2017	China	CCT	1.5T	112	38.9	20	28	Discography
Liu 2022	China	CCT	3.0T	275	40.5	44	58	Discography
Bartynski 2023	America	RA	1.5T	100	43.1	19	25	Discography

CS, cohort study; RA, retrospective analysis; CCT, case-control study; NA, not available

Meta-analysis results

Combined effect size

As shown in Fig. 3, meta-analysis results showed a combined sensitivity of 0.49 ([95%CI=0.37–0.61] I^2=95.32) and a combined specificity of 0.89 ([95%CI=0.85–0.93] I^2=96.49) of HIZ for diagnosis of DLBP. Univariable meta-regression and subgroup analysis indicated that the study design (index), comparative standard selection and description (reftest), study population (subject) to be evaluated showed no significant influence for the sensitivity and specificity (Fig. 4). As summarized in Table 3, HIZ had a positive likelihood ratio of 4.52 [95%CI=3.28–6.25], a negative likelihood ratio of 0.58 [95%CI=0.46–0.71], and a diagnostic ratio of 7.87 [95%CI=5.05–12.26] in the diagnosis of DLBP.

ROC graph

Meta-analysis results showed that the AUC area of HIZ ROC curve plot was 0.82 [95%CI=0.79–0.85] in the diagnosis of DLBP (Fig. 5).

Literature publication bias test

Deek's funnel plot asymmetry test is shown in Fig. 5, and the study showed that the study sites were largely symmetrical, suggesting a low likelihood of publication bias (p=0.70, Fig. 6).

Fagan diagram

The results of the Meta-analysis showed that the HIZ Fagan plot is shown in Fig. 7, and its likelihood ratio dot plot is shown in Fig. 8, suggesting that the diagnostic accuracy of a positive HIZ as a confirmatory diagnosis of DLBP may be relatively good.

Discussion

The results of this study showed that HIZ has a strong diagnostic value in the diagnosis of discogenic low back pain. The combined sensitivity was 0.49, combined specificity was 0.89, positive likelihood ratio was 4.52, negative likelihood ratio was 0.58, and the AUC area of the ROC plot was 0.84.

Currently, there are no clear diagnostic criteria for DLBP. Because of the variety of anatomic and pathophysiologic causes of chronic low back pain, it is a difficult diagnosis for clinicians to make. Lumbar provocation discography is a procedure that is used to characterize the pathoanatomy and architecture of the disc and to determine if the disc is a source of chronic low back pain. Recent systematic reviews have concluded that there is

Table 2 Risk of bias evaluation of the included studies

Study	Biased evaluation				Clinical applicability		
	Case selection	Trial to be evaluated	Gold Standard	Case flow and progression	Case selection	Trial to be evaluated	Gold Standard
Aprill 1992	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ricketson 1996	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Schellhas 1996	High Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Saifuddin 1998	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Smith 1998	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ito 1998	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Carragee 2000	High Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Lam 2000	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Lim 2005	High Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Kang 2009	Low Risk	High Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Chen 2011	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Not sure	Low Risk
William 2012	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Wang 2017	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Chelala 2019	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Guo 2008	High Risk	Not sure	Low Risk	Low Risk	Not sure	Low Risk	Low Risk
Ma 2009	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Li 2011	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Peng 2012	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Liu 2013	High Risk	Low Risk	Low Risk	Low Risk	Not sure	Low Risk	Low Risk
Liu 2014	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Liu 2016	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Liu WB 2016	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Not sure	Low Risk
Qiu 2017	Low Risk	Not sure	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Liu 2022	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Bartynski 2023	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

strong evidence that lumbar discography can identify the subset of patients with chronic discogenic pain [38, 39]. The term discogenic low back pain, which is currently used in the literature, is in fact a specific IDD-induced low back pain. At present, IDD has been described as a distinct clinical entity to be distinguished from other painful processes, such as degenerative disc disease and segmental instability [40].

The diagnostic criteria for internal disc disruption (IDD) established by the International Association for the Study of Pain include emergence of a concordant pain response during discography, internal annular disruption demonstrated by computed tomography after discography and at least one adjacent disc without concordant pain [41, 42].Magnetic resonance imaging (MRI) usually demonstrates degeneration of the disc, the socalled black disc syndrome. MRI usually shows high signal area behind the annulus fibrosus, which has an important diagnostic value. It usually indicates annulus fibrosus rupture, histologically representing vascularized granulation tissue [43].

Since Aprill's discovery of the HIZ, scholars have conducted research around the HIZ, and by comparing MRI and discography, they have disagreed with the HIZ, and the debate about the role and significance of the HIZ has continued. Jha SC [44], Schellhas KP [14], Lam KS [15], Peng Baojian [45] and other scholars believe that HIZ is an imaging sign of disc annulus fibrosus tear and DLBP, and point out that a single-segment disc with low signal on MRI and HIZ behind the annulus fibrosus is likely to be the source of the pain symptoms. Horton W [46] and others found that discs with neither signal reduction nor HIZ changes could be excluded as a source of pain in 95% of discs. However, researchers such as Chen ZY [47] disagreed with the above opinion on the actual diagnostic value of HIZ in DLBP and concluded that HIZ has limitations.

As early as 1986, Crock et al. [3] proposed the theory of "internal rupture of the intervertebral disc", which suggested that the inflammatory response and the growth of nerve fibers into the intervertebral disc were the main pathological basis of DLBP, and many scholars also studied the mechanism of low back pain caused by HIZ from this perspective. Ren et al. [48] found that a large number of proliferating chondrocytes and vascular endothelial cells were seen in the annulus fibrosus in the region where HIZ was located, and the expression levels of tumor necrosis factor-α (TNF-α) and CD68

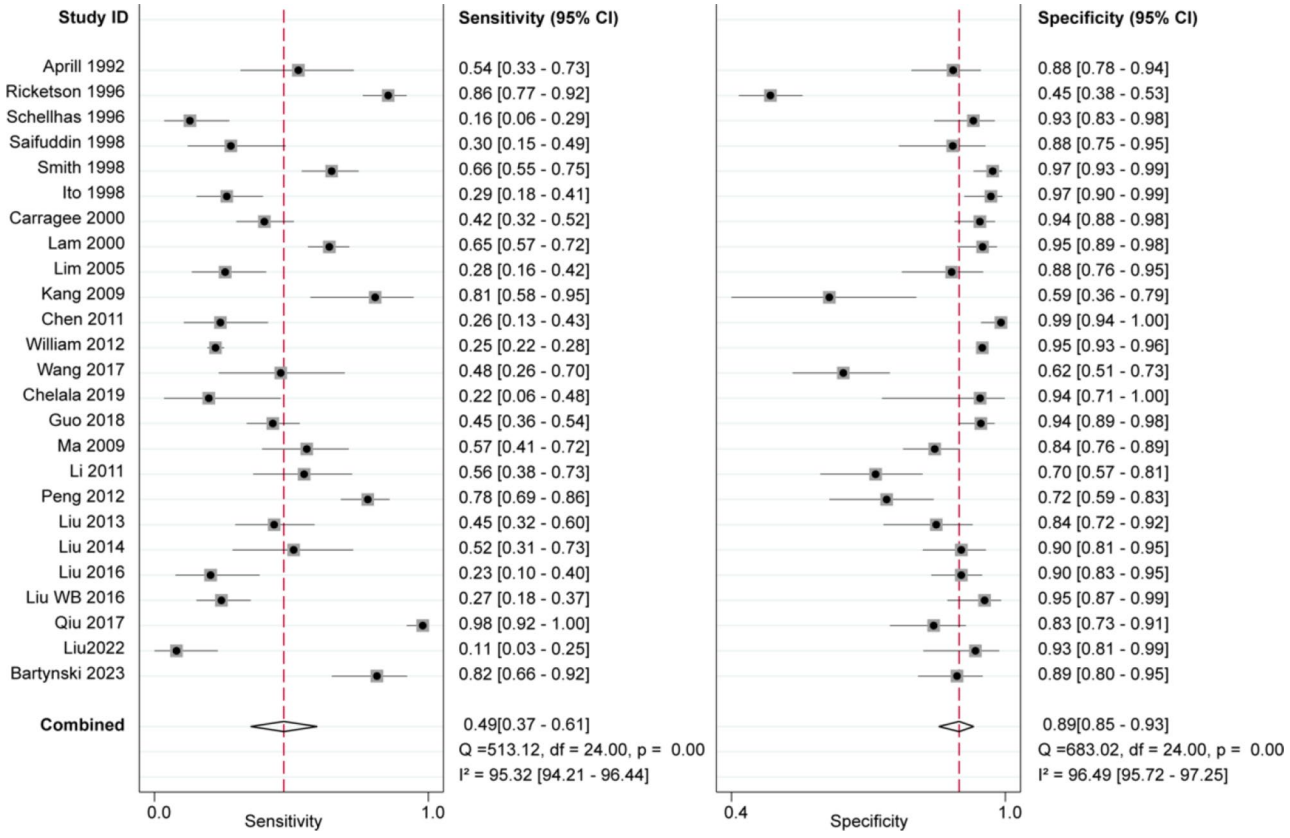

Fig. 3 Combined sensitivity and specificity map of MRI high-intensity zone (HIZ). Sensitivity and specificity results from 25 studies were included

immunopositive cells were significantly higher than those in the surrounding annulus fibrosus, while controls had little or no expression. Peng BG et al. [49] concluded that the widely distributed granulation tissue strip area within the HIZ was the site of origin of discography pain and DLBP by discography pain provocation test. Wang Huadong et al. [50] found a significant correlation between the presence of HIZ and the grade of annulus fibrosus rupture in intervertebral discography. The higher the degree of rupture, the higher the proportion of high-signal areas appeared on MRI, indicating a high degree of rupture of the annulus fibrosus with high-signal areas and a low degree of rupture of the annulus fibrosus without high-signal areas. The presence of HIZ suggests a high likelihood of vertebral annulus fibrosus rupture; HIZ is associated with the main pathological parenchyma which may be inflammatory granulation tissue in the fissure of the annulus fibrosus injury, and foci of calcification or ossification of the annulus fibrosus. Therefore, HIZ is highly correlated with DLBP.

Limitations of this study: ① HIZ-positive patients are mostly a high-risk population included in the retrospective study, and there may be a selective bias towards patients. ② The included literature contains only Chinese and English, and to some extent there is language bias.

In summary, the available evidence suggests that HIZ has acceptable sensitivity and high specificity in the diagnosis of DLBP. Due to the limitation of the number and quality of included studies, future research could focus on the correlation between the development of HIZ and annulus fibrosus rupture, as well as the correlation between the degree of HIZ development and pain.

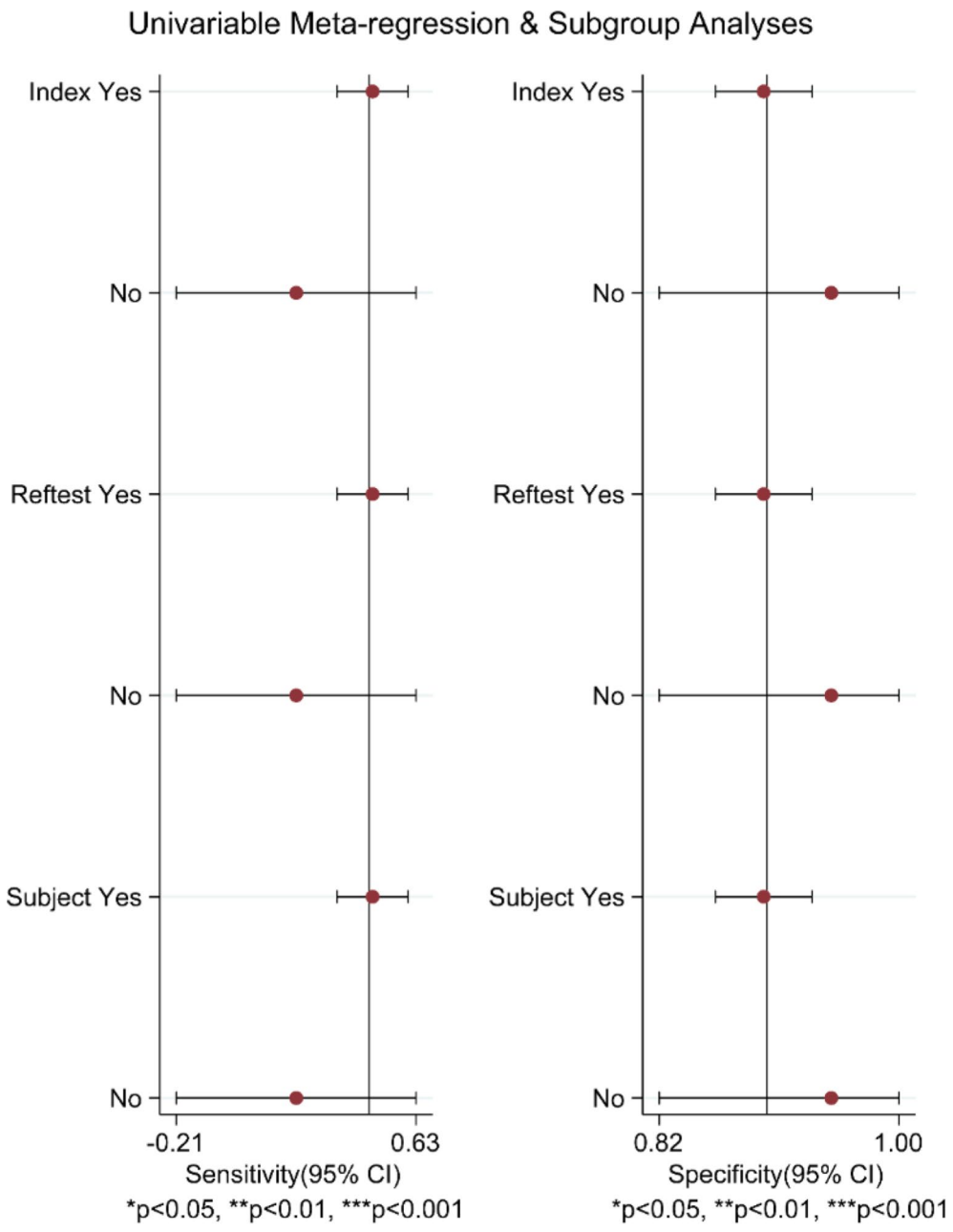

Fig. 4 Univariable meta-regression and subgroup analyses for sensitivity and specificity

Table 3 Results of meta-analysis of the diagnostic value of nuclear magnetic HIZ for DLBP

	Merge Sensitivity(95%CI)	Merged specificity(95%CI)	Diagnostic Ratio(95%CI)	Combined positive likelihood ratio(95%CI)	Combined negative likelihood ratio(95%CI)	AUC
HIZ	0.49[0.37,0.61]	0.89[0.85,0.93]	7.87[5.05,12.26]	4.52[3.28,6.25]	0.58[0.46,0.71]	0.82

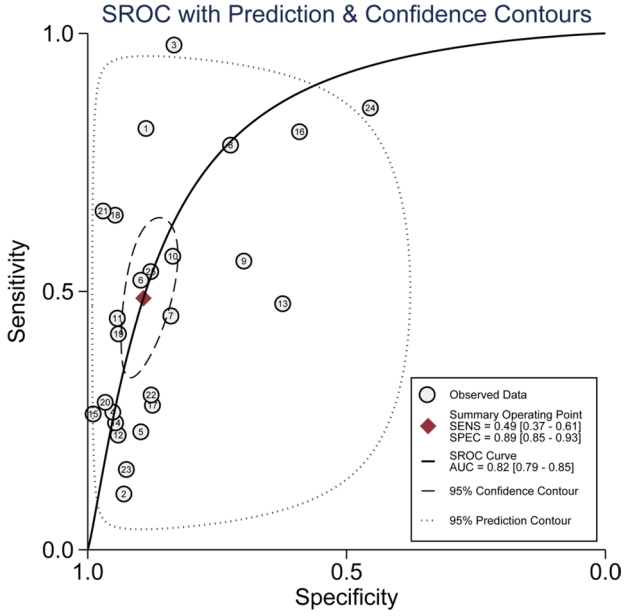

Fig. 5 MRI high-intensity zone (HIZ) ROC curve. SROC curve AUC with prediction 0.82[0.79–0.85], 95% confidence contour with 95% prediction contour are shown in Fig

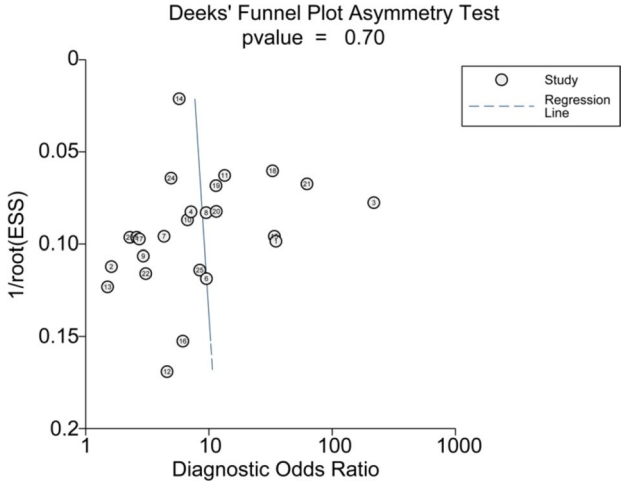

Fig. 6 MRI high-intensity zone (HIZ) Deek's chart. Deek's funnel plot asymmetry test, $p = 0.7$

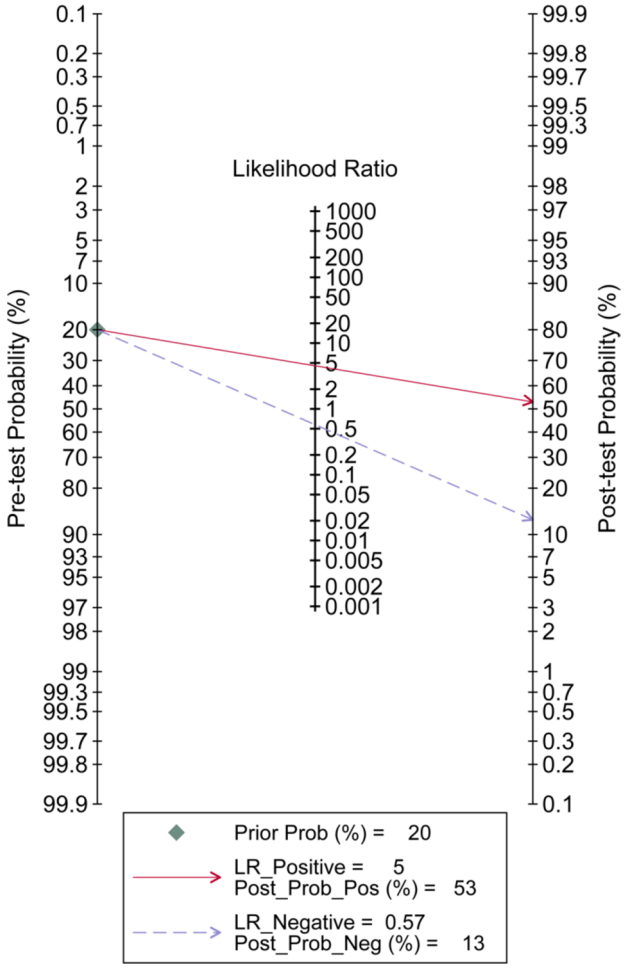

Fig. 7 MRI high-intensity zone (HIZ) Fagan map. Likelihood ratio positive as 5, post-test probability as 53%; likelihood ratio negative as 0.57, post-test probability as 13%

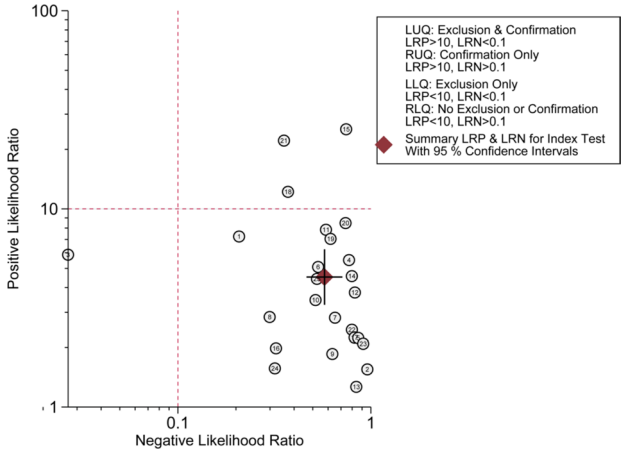

Fig. 8 MRI high-intensity zone (HIZ) likelihood ratio dot plot

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
X.Y. and J.W. conceived and designed the study. L.Y. and L.H. wrote the manuscript. X.Y. and J.W. rewriting the manuscript. L.Y., L.H., H.H., W.L., Y.Y. and H.Z. analyzed and interpreted the data. All authors read and approved the final manuscript.

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Data availability
All the datasets were available from Dr. Lei Yang upon reasonable request.

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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