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Clinical classification criteria for radicular pain caused by lumbar disc herniation: the RAPIDH criteria (RAdicular PaIn caused by Disc Herniation)

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Abstract

Context

Classification criteria are recommended for diseases that lack specific biomarkers in order to improve homogeneity in clinical research studies. Since imaging evidence of lumbar disc herniations (LDH) may not be associated with symptoms, clinical classification criteria based upon patient symptoms and physical examination findings are required.

Purpose

This study aimed to produce clinical classification criteria to identify patients with radicular pain caused by LDH.

Study Design

Two stage process. Phase 1: Delphi process; Phase 2 cohort study.

Patient sample

Outpatients recruited from spine clinics in 5 countries

Outcome Measures

Items from history and physical examination

Methods

In Phase 1: Seventeen spine experts participated in a Delphi process to select symptoms and signs suggesting radicular pain caused by LDH. In Phase 2: Nineteen different clinical experts identified patients they confidently classified as presenting with: 1) Radicular pain caused by LDH, 2) neurogenic claudication (NC) caused by lumbar spinal stenosis (LSS), or 3) non-

specific low back pain (NSLBP) with referred leg pain. Patients completed survey items and specialists documented examination signs. A score to predict radicular pain caused by LDH was developed based on the coefficients of the multivariate model.

An unrestricted grant of less than 15000 USD was received from MSD: It was used to support the conception of the Delphi, data management and statistical analysis. No fees were allocated to participating spine specialists.

Results

Phase 1 generated a final list of 74 potential symptoms and signs. In phase 2, 209 patients with pain caused by LDH (89), neurogenic claudication (63), or NSLBP (57) were included. Items predicting radicular pain caused by LDH ($p<0.05$) were: monoradicular leg pain distribution, patient-reported unilateral leg pain, positive straight leg raise test <60° (or femoral stretch test), unilateral motor weakness and asymmetric ankle reflex. The score had an AUC of 0.91. An easy to use weighted set of criteria with similar psychometric characteristics is proposed (specificity 90.4%, sensitivity 70.6%).

Conclusion

Classification criteria for identifying patients with radicular pain caused by LDH are proposed. Their use could improve the homogeneity of patients enrolled in clinical research studies.

Keywords: classification criteria, lumbar radicular pain, sciatica, disc herniation

INTRODUCTION

Low back pain (LBP) is a common symptom leading patients to visit primary care and musculoskeletal specialty providers [1]. Many individuals with LBP also report associated leg pain that may indicate nerve root involvement. A lumbar disc herniation (LDH) is the most frequently identified cause of radicular pain [2]. However, disc herniations may be found on imaging tests of asymptomatic individuals [3]. Guideline recommendations to decrease use of spinal imaging in patients with acute LBP, including radicular leg pain without signs suggesting serious etiologies, emphasize the role of history and physical examination findings as key to guiding initial management [4-6]. Therefore, the diagnosis of radicular pain is predominately clinically based.

In musculoskeletal diseases, the need for classification criteria was recognized 30 years ago as an important step to identify and distinguish patients with a specific disease from those without disease in order to create homogenous groups of patients for clinical or population studies [7]. In the field of LBP, the Quebec Task Force recognized the necessity to differentiate LBP patients with leg pain and neurological signs from other categories of LBP patients [8]. Although clinicians are trained to identify patients with radicular pain caused by LDH, no consensus has emerged to produce classification criteria for these patients [9]. As a consequence, researchers use a wide range of eligibility criteria leading to considerable heterogeneity among patients enrolled in these studies [10]. Classification criteria are useful in clinical research to ensure that study participants have the disease in question and that different centers are studying patients with the same clinical condition [11]. When classification criteria are accepted internationally, they can encourage use of uniform disease definitions and ensure that studies from divergent locations evaluate the same disease entity [12]. For several musculoskeletal diseases (e.g. rheumatoid arthritis, spondyloarthropathy),

widespread adoption of classification criteria has been a key factor leading to improved patient selection and treatment [13]. The absence of such classification criteria for several low back related conditions has been identified as a limitation in terms of understanding the physiopathology and evaluating new treatments [9, 10].

In view of the large economic burden related to LBP syndromes [14], there is an urgent need to develop classification criteria for LBP-related syndromes [10]. During a workshop at the 11th Forum for Primary Care Research in Low Back Pain in Boston (MA), a multidisciplinary, international group proposed developing classification criteria for LBP related neurological leg symptoms.

MATERIAL AND METHODS

This study was designed according to rules defined by Fries et al. for constructing classification criteria [15], and focused on radicular pain caused by LDH and neurogenic claudication caused by lumbar spinal stenosis. Here, we report on the development and validation of a clinical classification criteria for radicular pain caused by a LDH.

Selection of potential items

A convenience sample of 17 spine specialists (see Appendix A) participated in the item selection, phase 1, of the study. They were selected according to their background in the field of spine care and research, and a range of individuals in terms of country of origin and their specialties were recruited to increase generalizability. A list of patient-reported symptoms and clinical signs considered useful in diagnosing radicular pain caused by LDH or neurogenic claudication caused by spinal stenosis was generated from a structured literature review with additional items suggested by the participants.

Delphi Process

A Delphi consensus process consisting of rounds of expert review [16, 17] was then conducted using a computer-based survey program to reduce the list of items to those deemed potentially important for the diagnosis of each syndrome. When relevant, a precise definition of the test was provided in a separate booklet. For each round, the spine specialists rated the usefulness of each criterion "to differentiate patients with radicular pain caused by LDH from all others" on a 7 point Likert-type scale ranging from 1 (useless) to 7 (very useful). No other framing was provided for the other numbers available.

For round 1, items were excluded if they had a mean score <3, had a rating of 1 by more than 25% of the participants, or if more than 50% of reviewers answered "don't know". For round 2, retained items were re-scored. Items were selected for the clinical phase if the mean score was ≥ 4.5 and the difference between the two rounds was ≤ 1. Additional rounds were planned until all items were either included or excluded.

Clinical Study

In phase 2, nineteen spine specialists (surgeon and non-surgeon), working in English or French speaking countries (see Appendix A) and who did not participate in the item selection phase, screened patients presenting at their clinics with back related leg pain for study eligibility. Clinical signs were precisely defined and, when needed figures demonstrating the technique were provided, to decrease heterogeneity during the testing. The case report form was translated from English into French following the rules defined for cross-cultural adaptation and validation [18].

Patients were included if the spine specialist diagnosed the patient with radicular pain caused by LDH. As a comparison group, patients with neurogenic claudication caused by LSS or non-specific LBP (NSLBP) with referred leg pain were also recruited [19]. Exclusion criteria were: patients younger than 18 years, LBP without any leg pain, leg pain not related to a spinal problem, unable to read or understand the native language of the country, or declined study participation. As recommended for the development of classification criteria [20], spine specialists were asked to enroll similar numbers of patients from each of the three diagnostic groups. Spine specialists were not compensated for their participation in the item selection or clinical phases of the study.

Human subjects' approval was obtained from the ethical committee of the Geneva University Hospitals, Switzerland with additional approval obtained from each participating institution. Potentially eligible patients consulting participating spine specialists were approached about the study and informed consent was obtained prior to enrollment. During the same visit, patients completed a patient survey and physicians provided information on the presence of symptoms and documented physical examination findings on the provided case report form. Spine specialists also categorized patients into one of the 3 diagnosis groups using any diagnostic test or procedure felt necessary as part of routine practice and rated their degree of confidence with the diagnosis on a visual analog scale from 0 (not confident at all) to 10 (extremely confident). The participating spine specialists were blinded to the study's planned exclusion of patients diagnosed with a level of confidence below 7.

Sample size calculation

To accurately estimate the coefficients of potential items included in logistic regression models to develop a classification criteria to predict LDH, at least 10 patients per item were

needed. Assuming a total of 10 items in the final model, the required sample size was 100 patients. However, because patients recruited by the same expert are not independent, we multiplied this sample size by a design effect, assuming an intraclass correlation of 0.05 and an average number of patients per physician (cluster size) of 15 [21]. This led to a final sample size of 170 (100 x [1+(15-1)x0.05]). Assuming similar numbers of recruited patients per diagnosis (60 patients with radicular pain caused by LDH, 60 patients with neurogenic claudication related to LSS, and 50 patients with NSLBP, this sample size allowed for estimating a 95% confidence interval around a sensitivity of 80% with a half-interval of 10.1% (i.e., 69.9% and 90.1%), and a specificity of 80% with a half-interval of 7.5% (72.5% and 87.5%).

Statistical analysis

We used all items (for both radicular pain caused by LDH and neurogenic claudication caused by LSS) to identify the best criteria set for radicular pain caused by LDH using the expert clinical diagnosis as the gold standard. We first used univariable generalized estimating equation (GEE) models (logit link) with patients categorized as radicular pain caused by LDH versus the combined LSS and NSLBP groups as the outcome and each item as the predictor. The GEE model with an exchangeable correlation matrix was used to account for the multicenter study. Items were included in the multivariable models if the univariable p-value was <0.1 but excluded if selected in 10 patients or fewer. We then ran two multivariable GEE models, one with the remaining specialist-reported items, and the other with the remaining patient-reported items. For items which were very similar and thus highly correlated (e.g. different angle limits for straight leg raise [SLR] test to be considered positive, see Appendix B), we introduced each version separately in the multivariable model and chose the model based on the lowest value of the quasi-information criteria. The next step

combined all items retained in step 2 (p-value <0.1) in a single GEE model (M1, logit link, exchangeable correlation matrix). Sensitivity analyses were then performed to attempt to simplify the models while retaining good sensitivity and specificity (Models S1 to S7). To test the appropriateness of model selection, we also used the least absolute shrinkage and selection operator (LASSO) method and compared the criteria retained using this statistical model selection with the sequential model selection described above. Finally, based on the coefficients of the last GEE model, we assigned a weight to each criterion retained, and derived the RAPIDH criteria set (RAdicular PaIn caused by Disc Herniation). To determine the score cutoff, we used receiver operating characteristic (ROC curve) and area under the curve (AUC). This score and cutoff were then used to compute sensitivity, specificity, with their respective 95% confidence intervals. All analyses were done using R v3.2.3, with libraries geepack for the GEE analysis, MESS for the quasi-information criterion, and the glmnet library for the LASSO model selection.

RESULTS

Delphi process

The literature review and items identified by spine specialists resulted in a list of 236 potential items for spine-related leg pain symptoms and physical examination findings, including 145 associated with radicular pain caused by a LDH. The large number of items reflected an inclusive list generation phase with multiple items reflecting small variations among similar concepts (e.g. Lasègue Sign / Straight Leg Raise Test items including 5 different angles and with 3 different wording). In the 1st round, 23 items were excluded, all based on mean scores of <3, leaving 213 items. In the 2nd round, 118 additional items were excluded. Among items assessing the same concept, we chose the ones with the highest average score, thus deleting 21 additional items.

Of the 74 remaining items included in the clinical study, 28 were patient-reported symptoms and 46 were physician-reported findings (see Appendix B). As all had a stable evaluation (≤1 point difference between rounds on the usefulness scale), the Delphi process ended.

Clinical study

There were 213 patients (average 10.7 patients enrolled per expert) enrolled in the clinical phase. Four patients were excluded as the spine specialist rated <7/10 their confidence in their diagnosis, leaving 209 patients included the statistical analysis: 89 with radicular pain caused by LDH, 63 with neurogenic claudication caused by LSS, and 57 with NSLBP with referred leg pain (Table 1). Tests employed by spine specialists to reach a diagnosis with confidence included MRI or CT scan for 203 of 209 patients (86/89 for patients diagnosed as radicular pain caused by LDH) and EMG for 25 of 209 patients.

In univariable analyses, 26 of 74 items were significantly associated with a diagnosis of radicular pain caused by LDH, including 8 patient-reported and 18 specialist-reported items (see Appendix B). Overlapping items were combined to create single variables (e.g. leg pain increased by either sneezing, coughing or straining). In addition, items reported only by ten patients or fewer were dropped from the final analyses.

Multivariable analysis was conducted separately for patient-reported items and specialist-reported items. Items with p-value < 0.1 were included in a second multivariable analysis leading to the identification of 5 items (Table 2). The score derived from this model (M1, Table 3) had an AUC of 0.91 (Figure 1), and the cutoff to obtain a specificity of ≥90% resulted in a sensitivity of 74%. Simplifying the model by collapsing response categories for retained items (e.g., combining bilateral muscle weakness with absence of muscle weakness) resulted in little loss in AUC, sensitivity and specificity (Table 3). The final model retained

patient reported pain in one leg, and physician assessed monoradicular leg pain distribution, unilateral motor weakness (vs. no weakness or bilateral weakness), positive SLR test <60° or positive femoral traction test, and asymmetrical ankle reflex (vs. normal reflex or decreased reflex in both legs) (Table 4). The Lasso method resulted in the same five items and confirmed the strength of the results.

Items retained in the final model demonstrated fractional weights that varied two-fold (see the respective scores, Table 4). In order to translate these weights into an easy to use scoring method, the score of each item was determined by multiplying by 2 and rounding the results to the nearest integer. Hence, in the RAPIDH criteria, a weight of 6 is attributed to monoradicular leg pain distribution, 4 to unilateral decrease of ankle reflex, positive SLR<60° or femoral traction, and 3 to the other items so that the total score range from 0 to 20 (Table 5). Setting the cutoff at 10, provided an AUC of 0.90, with a sensitivity of 70.6% [95%CI: 59.6% – 79.7%] and a specificity of 90.4% [95%CI: 83.2% – 94.9%] (Table 3, model S7).

DISCUSSION

A multidisciplinary, international team developed and validated clinical classification criteria for radicular pain caused by LDH. The proposed criteria contain a majority of items relating to the clinician’s examination rather than patient-reported symptoms, and differentiated patients with radicular pain caused by LDH from those with LSS or non-NSLBP with referred leg pain. We propose an easy to use weighted score of retained items, the RAPIDH criteria, to identify individuals with radicular pain caused by LDH for use in clinical and population-based research studies.

Despite the large number of items collected at the beginning of this study, it is notable that the five included in the final classification criteria are classic signs and symptoms of nerve root involvement [22]. The item with the highest weight was monoradicular leg pain distribution. This pattern of pain distribution has been classically reported as characterizing nerve root pain [23, 24], although a study using pain drawing did not confirm this statement [25]. This item might be influenced by physician's expertise and has a component of subjectivity as reflected by poor reproducibility [26, 27]. The other items from physical examination have moderate to good reproducibility with kappa values ranging from 0.5 to 0.7 [28]. Only one item is derived from patient history (i.e. unilateral leg pain), and has not been previously reported for the diagnosis of radicular pain caused by LDH [28-31].

The 5 items in the classification criteria derived from the statistical analysis had a different impact on the diagnosis of radicular pain caused by LDH precluding a non-weighted set of items. For ease of use, a weighted set of items with rounded figures was derived (RAPIDH score) without significantly altering the performance (AUC 0.903 vs. 0.909). In creating our clinical classification criteria, we sought high specificity in order to avoid the inclusion of falsely positive cases in the research setting. Thus the RAPIDH score should not be used as a diagnostic tool since it might misdiagnose individuals with atypical presentations of radicular pain. In clinical practice where sensitivity may be equally important, different clinical criteria may be needed [10].

There have been a few studies focusing on the diagnosis of radicular pain caused by LDH,[29, 30, 32, 33] but none of them set the goal of defining classification criteria. All these studies were conducted in single center and none used a specific method to select the items that were clinically tested. One study focused on patients undergoing surgery and used "relief of

sciatica at 2 years" as the reference point [33]. Another focused on items from patient reported symptoms [30], and a third one explored the value of needle EMG [29]. The study most similar to the current one [34], used imaging (MRI showing nerve root compression by disc material) as the gold standard, without considering clinical correlation. As nerve root compression on imaging has been reported in asymptomatic individuals [3], its presence does not ascertain that it is the cause of the symptoms.

Strengths

The methods used in this study complied with published recommendations [9]. In particular, in the absence of valid objective criteria the diagnosis relied on expert opinion, and two different panels of spine specialists were involved in the item selection process and the clinical evaluation. The items included in the RAPIDH score are frequently reported in clinical research [10] and are in agreement with published guidelines [35], thus supporting face validity. The content validity of this classification criteria is also good as the studied population included patients with radicular pain involving L3 to S1 nerve roots. The inclusion of a heterogeneous population of patients with back and associated leg pain at baseline helps ensure that this classification criteria has good construct validity.

Limitations

Although expert opinion was used as the gold standard for the patient's diagnosis in the absence of pathognomonic tests, it represents an intrinsic bias. In the present study, it is likely that the physician report of findings was influenced by what they thought was the final diagnosis. Moreover, these results only apply to evaluations performed by spine specialists. In particular, as the item "monoradicular leg pain distribution" has the highest weight in the final

classification criteria, the use of the item in a population assessed by non-specialist physicians, less familiar with this concept, might decrease the accuracy of the final criteria.

The use of items focused on a specific nerve root deserves specific consideration. The presence of "unilateral ankle reflex decrease" in the final set increases the diagnostic probability of S1 radiculopathy compared to other levels of lumbar radiculopathy, and lowers the sensitivity of the RAPIDH criteria. L5 nerve root reflex has been reported [36], but is rarely acknowledged in the literature [26]. This may explain why it was not selected by the spine specialists during the Delphi process. The "unilateral patellar reflex decrease" (assessing L3 or L4 nerve roots) was more frequently found in patients with radicular pain caused by LDH (see Appendix B) but did not remain statistically significantly associated with the diagnosis when integrated in the model (Table 3, S3). It is however important to note that RAPIDH criteria apply to any radicular pain from L3 to S1.

CONCLUSION

The present study proposes clinical classification criteria using a set of 5 items with good specificity and sensitivity for identifying patients with radicular pain caused by a LDH. Although this set of items requires validation in different patients and settings, we believe that such criteria represent an important step in the field of spinal pain research and will contribute to improving quality of future studies and the evaluation of future treatments.

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Figure 1. Receiver operating characteristic (ROC curve) of the score obtained using the full model (M1), and the RAPIDH score (S7). There is only minor difference between M1 and the RAPIDH score.

Table 1: Patients' characteristics - Figures are means (standard deviation) unless otherwise specified

	Radicular pain caused by LDH N=89	Other (neurogenic claudication caused by LSS or NSLBP with referred leg pain) N=120	*p*
Age	46.8 (13.0)	55.8 (18.0)	<0.001
Sex (female)	31 (36.9%)	62 (53.0%)	0.03
Duration of back pain (years)	5.1 (7.6)	7.2 (9.1)	0.07
Duration of leg pain (years)	1.8 (4.8)	3.6 (5.5)	0.02
Worst pain location			0.02
Back	14 (16.5%)	29 (26.4%)	
Leg	48 (56.5%)	40 (36.4%)	
Both equally	23 (27.1%)	41 (37.3%)	

Table 2: GEE model with logit link and exchangeable correlation matrix to predict radicular pain caused by lumbar disc herniation

	Estimate	OR	p	score
Intercept	-4.407	0.012	<0.001	-
Monoradicular: not monoradicular	1 (Reference)	1 (Reference)		
Monoradicular L3 or L4	2.983	19.743	<0.001	3.0
Monoradicular L5or S1	2.903	18.221	<0.001	2.9
Decreased ankle reflex: absence of	1 (Reference)	1 (Reference)		
Decreased ankle reflex: unilateral	1.623	5.069	0.02	1.6
Decreased ankle reflex: bilateral	-0.945	0.389	0.15	-0.9
Femoral traction or SLR ≤ 60°	1.878	6.540	<0.001	1.9
Muscle weakness: absence of	1 (Reference)	1 (Reference)		
Muscle weakness: unilateral	1.435	4.200	0.02	1.4
Muscle weakness: bilateral	-0.767	0.465	0.40	-0.8
Patient-reported unilateral leg pain	1.175	3.237	0.03	1.2

SLR: straight leg raise test.
SLR ≤ 60: SLR is positive if typical leg pain is produced between 0 and 60°

Table 3: Sensitivity analysis of full and simplified prediction models, with each model's estimation of AUC, sensitivity and specificity.

	AUC	Se	Spe
M1: full model (see table 2)	0.913	0.74	0.90
S1: combine "monoradicular L3 or L4" with "monoradicular L5 or S1" (vs. non-radicular)	0.911	0.74	0.90
S2: combine "bilateral muscle weakness" with "absence of muscle weakness" (vs. unilateral muscle weakness)	0.912	0.75	0.90
S3: " patellar or ankle decrease reflex" instead of "ankle reflex decrease" (vs. normal reflex)	0.905	0.72	0.92
S4: combine "bilateral ankle decrease reflex" and "absence of decrease ankle reflex" (vs. unilateral ankle reflex decrease)	0.912	0.72	0.90
S5: all S1 to S4 modifications	0.902	0.74	0.88
S6: all S1 to S4 except S3	0.909	0.71	0.90
S7: S6, simplified weighted model*.	0.903	0.71	0.90

AUC: area under curve
M1: full model including all variables. Se: sensitivity. Spe: specificity S: simplified model.
SLR: straight leg raise test. SLR ≤ 60: SLR is positive if typical leg pain is produced between 0 and 60°.
*simplified weighted model (see Table 4).

Table 4: Results of the final (S6) GEE model to predict diagnosis of radiculopathy caused by lumbar disc herniation

	Estimate	OR	p	score
Intercept	-4.69	0.01	<0.001	-
Monoradicular leg pain distribution	2.88	17.89	<0.001	2.9
Unilateral decreased ankle reflex	1.70	5.45	0.01	1.7
SLR ≤ 60° (L5, S1) or positive femoral stretch test (L3, L4)	1.83	6.26	<0.001	1.8
Unilateral muscle weakness (ref. none or bilateral)	1.44	4.24	0.02	1.4
Unilateral patient-reported pain in leg	1.42	4.14	0.003	1.4

SLR: straight leg raise test

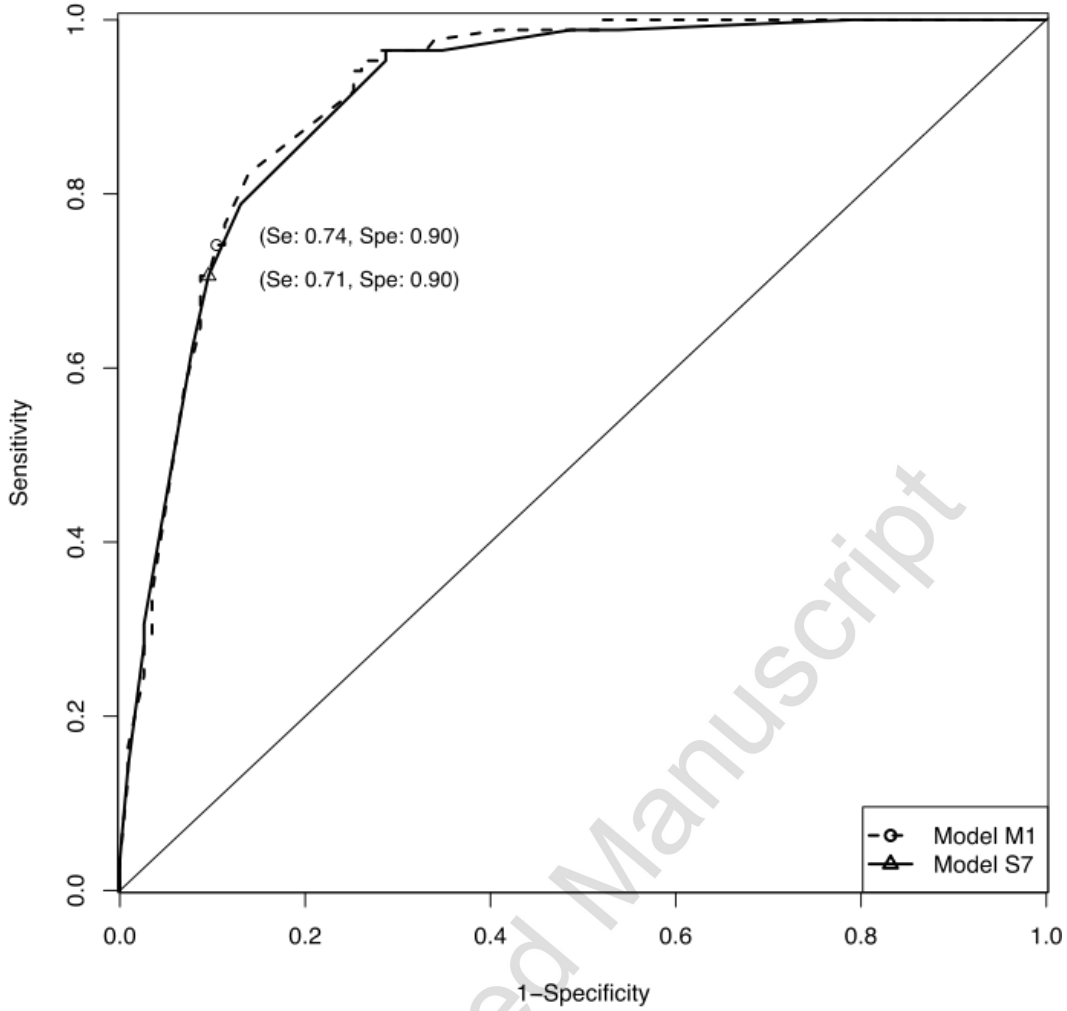
Table 5: RAPIDH (RAdicular PaIn caused by Disc Herniation) score (simplified weighted score).

ITEM	POINTS
Monoradicular leg pain	6
SLR $\leq 60°$ or positive femoral stretch test	4
Unilateral ankle reflex decrease	4
Unilateral muscle weakness	3
Unilateral patient-reported pain in legs	3

SLR: straight leg raise test

The patient is classified as having radicular pain caused by disc herniation if the total score is 11 (range 0 to 20) or more (specificity 90.4%, sensitivity 70.6%).

1 Figure 1



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3