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Clinical Study

Predicting outcomes of neuroreflexotherapy in patients with subacute or chronic neck or low back pain

Ana Royuela, MSc[a,b,c,*], Francisco M. Kovacs, MD, PhD[c,d], Carlos Campillo, MD, MPH, PhD[e], Montserrat Casamitjana, MD[f], Alfonso Muriel, MSc[b,c], Víctor Abraira, PhD[a,b,c]

[a]*CIBER Epidemiología y Salud Pública (CIBERESP), C/ Melchor Fernandez Almagro 3-5, 28029 Madrid, Spain*
[b]*Unidad de Bioestadística Clínica, Hospital Ramón y Cajal, IRICYS, C/ Colmenar Viejo, 9, 28031 Madrid, Spain*
[c]*Spanish Back Pain Research Network, Paseo de Mallorca 36, 07012 Palma de Mallorca, Spain*
[d]*Departamento Cientifico, Fundación Kovacs, Paseo de Mallorca 36, 07012 Palma de Mallorca, Spain*
[e]*Servei de Salut de les Illes Balears (Ib-Salut), Calle Reina Esclaramunda 9, 07003 Palma de Majorca, Spain*
[f]*Regió Sanitària de Barcelona | Consorci Sanitari de Barcelona, Servei Català de la Salut (CatSalut), Parc Sanitari Pere Virgili - Edifici Mestral - Esteve Terradas, 30 4ta planta, 08023 Barcelona, Spain*

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Abstract

BACKGROUND CONTEXT: In the context of shared decision-making, a valid estimation of the probability that a given patient will improve after a specific treatment is valuable.

PURPOSE: To develop models that predict the improvement of spinal pain, referred pain, and disability in patients with subacute or chronic neck or low back pain undergoing a conservative treatment.

STUDY DESIGN AND SETTING: Analysis of data from a prospective registry in routine practice.

PATIENT SAMPLE: All patients who had been discharged after receiving a conservative treatment within the Spanish National Health Service (SNHS) (n=8,778).

OUTCOME MEASURES: Spinal pain, referred pain, and disability were assessed before the conservative treatment and at discharge by the use of previously validated methods.

METHODS: Improvement in spinal pain, referred pain, and disability was defined as a reduction in score greater than the minimal clinically important change. A predictive model that included demographic, clinical, and work-related variables was developed for each outcome using multivariate logistic regression. Missing data were addressed using multiple imputation. Discrimination and calibration were assessed for each model. The models were validated by bootstrap, and nomograms were developed.

RESULTS: The following variables showed a predictive value in the three models: baseline scores for pain and disability, pain duration, having undergone X-ray, having undergone spine surgery, and receiving financial assistance for neck or low back pain. Discrimination of the three models ranged from slight to moderate, and calibration was good.

CONCLUSIONS: A registry in routine practice can be used to develop models that estimate the probability of improvement for each individual patient undergoing a specific form of treatment. Generalizing this approach to other treatments can be valuable for shared decision making.

Keywords: Predictive model; Multiple imputation; Calibration; Back pain; Disability; Neuroreflexotherapy

FDA device/drug status: Not applicable.

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* Corresponding author. Clinical Biostatistics Unit, Hospital Ramón y Cajal, Ctra. Colmenar Km 9.1, 28034 Madrid, Spain. Tel.: (34) 913368103.

E-mail address: ana.royuela@hrc.es (A. Royuela)

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Introduction

In industrialized countries, neck and common low back pain (LBP) affect more than 70% of the general population and represent a major health, social, and economic burden [1–8]. Diagnosing common neck pain or LBP implies that the pain is not related to fractures, direct trauma, or systemic conditions such as spondylitis or neoplastic-, infectious-, vascular-, metabolic-, visceral-, or endocrine-related processes. In more than 90% of the patients, it is impossible to identify the exact cause of pain, which is believed to originate in soft tissues [1,9–13]. In routine practice, many treatments are prescribed for patients with neck pain and LBP, although very few are based on solid evidence on efficacy, effectiveness, safety, and cost/effectiveness [9,11,14].

Neuroreflexotherapy (NRT) is an intervention consisting in the temporary (up to 90 days), subcutaneous implantation of surgical devices on trigger points in the back, at the site of dermatomes clinically involved in each case, and on referred tender points located in the ear [15–22]. The intervention is assumed to deactivate neurons involved in the mechanisms that prolong pain, neurogenic inflammation, and muscle dysfunction and contracture [15–18]. The evidence available, including a Cochrane review, shows that it is efficacious, safe, effective, and cost-effective for improving pain and disability in subacute and chronic LBP patients [9,15–18]. A registry that uses test-piloted postimplementation surveillance methods was set up in 2002, when NRT was implemented in the Spanish National Health Service (SNHS) [19–22].

In clinical practice, there is always some uncertainty as to how results from randomized controlled trials will apply to an individual patient. In the context of sharing decision-making, it would be suitable to reduce this uncertainty by informing each patient of the probability that each treatment will trigger a clinically relevant improvement in his/her specific case. This would allow patients to balance this probability against personal preferences and the risk and gravity of adverse events. To this end, it would be valuable to explore the feasibility of using registries in routine practice to develop valid predictive models for the results of each form of treatment.

Registries and other observational studies in routine practice frequently present a high proportion of missing data, which can affect the validity of results. Multiple imputation by chained equations has been considered an appropriate method to address this problem [23–26]. A predictive model requires validation before considering its use in routine clinical practice [27,28]; bootstraping is considered to be the most efficient validation procedure [29,30].

Therefore, the objective of this study was to assess the feasibility of using a registry in routine practice to develop models predicting the probability of improvement following a specific form of conservative treatment, using multiple imputation to manage missing data and bootstrapping for validating the models.

Material and methods

Setting

This study was conducted in the SNHS of the Balearic Islands (“Ib-Salut”), Asturias (“SESPA”), Cataluña (“Cat-Salut”), Murcia (“SMS”), and Madrid (“SERMAS”). The population covered by these Health Services is approximately 17.6 million inhabitants, or approximately 37.5% of the Spanish population [31].

Study population

Following the referral protocol which was used in previous studies and current evidence-based Clinical Guidelines [9,19–21], primary care physicians referred patients with indication criteria for NRT to NRT-certified units. Indication criteria were as follows: common neck, thoracic or LBP, pain severity ≥3 points on a 10-point visual analog scale (VAS) [32], and pain lasting ≥14 days despite medication and other treatment. Referral should not be considered for patients with neurogenic claudication caused by lumbar spinal stenosis or those showing criteria for urgent referral to surgery, such as signs suggesting cauda equina syndrome (eg, progressive motor weakness in the legs, sphincter disturbance, saddle anesthesia, or sensory level). (A flowchart containing the referral protocol to NRT is available online [1].) Patients who did not respond to back surgery could be referred to NRT, as well as those with “red flags” in whom the appropriate tests had established that pain was not caused by fractures or systemic diseases [1]. All SNHS patients treated with NRT who were discharged before June 30, 2012, were included in this study.

Intervention

NRT interventions were performed according to the indication criteria and under the application conditions in which it had proven effective, safe, and cost-effective [15,19,20]. Specialists at the NRT units confirmed indication criteria and, once patients had given their written informed consent, performed the interventions. Each SNHS region had its own NRT unit and team of physicians, certified according to specialized professional standards [33], Physicians had been in full-time NRT practice for between 3 and 23 years.

Patients were instructed to contact the NRT unit or their primary care center in the event of experiencing an adverse effect. Twelve weeks after the intervention was performed, the surgical material that had been implanted was removed, adverse events identified by patients or physicians were recorded, and indication criteria for repeating NRT were assessed.

Outcome assessment

Standardized postimplementation surveillance mechanisms were used to gather the data introduced into the registry [19,20]. The clinical condition of each patient upon referral to NRT was assessed by the referring primary care physician, who gathered data on duration of pain (days since the first episode and for the current episode, separately); reason for referral (neck pain, thoracic pain or LBP); existence of referred pain (yes/no); history of spine surgery; diagnosis of failed surgery syndrome; pain caused by symptomatic disc protrusion or herniation (defined as referred pain being more intense than spinal pain and after a distribution that corresponded to the root compressed by a disc protrusion/herniation on magnetic resonance imaging [MRI]); pain caused by symptomatic lumbar spinal stenosis (defined as referred pain corresponding to the root/s compressed by lumbar spinal stenosis on MRI) (yes/no); ''common'' syndrome (defined as no clinical signs of nerve compression on physical examination and MRI); established diagnosis of fibromyalgia; comorbidities; diagnostic tests undertaken (X-rays, MRI, other, eg, electromyogram or scintigraphy); imaging findings (disc degeneration, facet joint degeneration, scoliosis, difference in leg length, spondylolysis, spondylolisthesis, spinal stenosis, disc protrusion, disc herniation, other findings, no findings); treatments received for the current episode (drugs [eg, analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], steroids, muscle relaxants, opioids, codeine, other], physiotherapy/rehabilitation, surgery); and date of referral to the NRT unit.

Patients provided data on gender, age (date of birth), whether they were pregnant, employment status (''passive,'' eg, housewife, student, or retired; ''receiving financial assistance for neck pain or LBP,'' eg, sick leave or workers compensation benefits; or ''working''), involvement in neck pain or LBP-related employment claims (eg, disability pension), and involvement in neck pain or LBP-related litigation (eg, traffic accident). From May 2009 onwards, they were also requested to provide data on their academic level (less than elementary school, elementary school, high school, university).

Primary outcomes were pain and disability [34]. Patients used previously validated instruments to score these variables. Separate 10-cm VAS were used for spinal pain (neck pain or LBP) and referred pain [32]. The Spanish version of the Roland-Morris Questionnaire (RMQ) was used to score LBP-related disability [36]. The Neck Disability Index (NDI) was used to assess neck pain–related disability in patients treated after its Spanish version was validated, in April 2008 [36]. Value ranges from best to worst are 0–10 for VAS, 0–24 for RMQ, and 0–100 for NDI [32,35,36].

The severity of spinal pain, referred pain, and disability were assessed on each visit to the primary care center and specialized NRT unit. All diagnostic and therapeutic procedures undergone after NRT recorded throughout the follow-up period. Twelve weeks after performing the NRT intervention, pain and disability were assessed, and patients without indication criteria for repeating the procedure were discharged.

Analysis

Absolute and relative frequencies were calculated for categorical variables. Values for continuous variables were described using their median and interquartile range. It was hypothesized that different pain episodes in the same subject (either at the same or different locations, eg, neck pain and LBP) could be nonindependent events. Therefore, analyses were restricted to the first episode treated with NRT in each patient.

''Improvement'' in spinal pain, referred pain, and disability was defined as any reduction in the corresponding score being greater than the minimal clinically important change (MCIC) [37–39]. MCICs have been established at 30% of the baseline value, with a minimum value of 1.5 VAS points for spinal pain and referred pain, 7 NDI points for neck pain-related disability, and 2.5 RMQ points for LBP-related disability [37–39]. These definitions made it impossible for patients with a baseline score less than the corresponding cut-off point for a given variable to show a clinically relevant improvement for that variable (eg, referred pain could not improve in patients without referred pain at baseline). Therefore, these patients were excluded from the analysis on that variable.

Three separate multivariate logistic regression models were developed to predict improvement of spinal pain, referred pain, and disability, respectively. Because value ranges are different for the NDI (0–100) and the RMQ (0–24), a standardized score for disability was calculated, ranging from 0 to 100 (from better to worse). For neck pain-related disability, this score corresponded to the NDI score. For LBP-related disability, it corresponded to the percentage of the maximum possible RMQ score (eg, 24 points in the RMQ corresponded to 100 points in the standardized score). Because no instrument for assessing disability derived from thoracic pain has been validated in Spanish, patients with thoracic pain were excluded from the models.

In these models, improvement in spinal pain, referred pain and disability were the dependent variables. Independent variables were those considered to be clinically relevant and those that had shown to have a prognostic value [17,19,20,32,34,40–42]: gender, age (in years), baseline score for spinal pain (VAS points), baseline score for referred pain (VAS points), baseline score for disability (standardized disability score), reason for referral (neck pain or LBP), time elapsed since the first pain episode (<1 year, 1 to <5 years, 5 to <10 years, ≥10 years), duration of the current episode (''subacute'' if between 14 and 89 days, ''chronic'' if between 90 and 365 days, and highly chronic if more than 365 days) [22,43,44], employment status (''passive'', ''receiving financial assistance for neck pain or LBP'', or ''working''), type of pain (''radicular pain

Table 1
Baseline characteristics of patients included in the study (N=8,778)

Variables	n Filled	Value
Gender, male*	8,694	2,775 (31.9)
Age, years†	8,774	53 (42; 64)
Region within the Spanish National Health Service*	8,778	
Balearic Islands (Ib Salut)		7,033 (80.1)
Asturias (SESPA)		765 (8.7)
Murcia (SMS)		484 (5.5)
Madrid (SERMAS)		382 (4.4)
Catalonia (Cat Salut)		114 (1.3)
Reason for referral to NRT*	8,666	
Neck pain		2,588 (29.9)
Low back pain		6,078 (70.1)
Type of pain*,‡	8,552	
Nonspecific		8,097 (94.7)
Radicular pain caused by disc protrusion/extrusion or spinal stenosis		455 (5.3)
Employment status*	7,682	
Passive		3,103 (40.4)
Receiving financial assistance for low back pain		806 (10.5)
Working		3,773 (49.1)
Duration of the pain since diagnosis, months†	8,371	73 (24.3; 146)
Duration of the pain since diagnosis categorized, years*		
≤1		1,360 (16.2)
1–5		2,663 (31.8)
5.001–10		2,125 (25.4)
>10		2,223 (26.6)
Duration of the pain episode, days†	8,778	300 (90; 540)
Duration of the pain episode, days, categorized*		
Subacute, ≤90		2,2116 (25.2)
Chronic, 91–365		3,932 (44.8)
Highly chronic, >365		2,635 (30.0)
Pregnancy*	8,778	32 (0.4)
Diagnosis of fibromyalgia*	8,778	305 (3.5)
Other comorbidities*	8,778	3,579 (40.8)
Involved in work-related claims*	8,778	67 (0.8)
Involved in litigation*	8,778	35 (0.4)
Baseline severity of SP (VAS)†	8,674	7.0 (6.0; 8.0)
Baseline severity of RP (VAS)†	8,555	7.0 (5.0; 8.0)
Baseline disability (standardized 0–100 score)†	7,217	54.2 (37.5; 70.8)
Previous lumbar surgery* (yes)	8,778	676 (7.7)
Failed back syndrome* (yes)	8,765	102 (1.2)
Diagnostic procedures during the episode*		
X-ray	8,778	2,196 (25.0)
MRI	8,778	2,701 (30.8)
Other§	8,778	592 (6.7)

MRI, magnetic resonance imaging; NDI, Neck Disability Index; RMQ, Roland-Morris Questionnaire; RP, severity of referred pain (in the 6,649 patients who had it); SP, severity of spinal pain; VAS, visual analog scale (range from better to worse; 0–10).

Note: Baseline disability (in the 6,766 patients who had it; range from better to worse: 0–100; for neck pain–related disability, the score of the NDI was used. For low back pain–related disability, the score reflects the percentage of the maximum possible RMQ score).

* Frequency (%).

† Median (percentile 25; percentile 75).

‡ Type of pain: ''Radicular pain caused by disc protrusion/extrusion or spinal stenosis'' if; (a) severity of referred pain≥spinal pain, (b) corresponding imaging finding on MRI, (c) distribution of pain consistent with the nerve root compressed by the corresponding imaging finding. ''Nonspecific pain,'' if one or more of these criteria were not met.

§ Other diagnostic procedures: electromyography, computed tomography scan, scintigraphy, and other.

caused by symptomatic disc protrusion/herniation or lumbar spinal stenosis'' vs. ''common neck pain or LBP''), diagnosis of fibromyalgia, other comorbidities, involvement in employment claims, involvement in litigation, diagnostic tests undertaken before NRT (X-rays, MRI, other), imaging findings, history of spine surgery, and treatments before referral for NRT. To avoid number instability, variables with a prevalence of <1% were eliminated from the models.

A multiple imputation analysis was performed by creating several plausible imputed datasets and combining results from each of them [23,26]. Imputation of missing values was carried out by means of multiple imputation using chained equations and assuming a missing at random pattern of

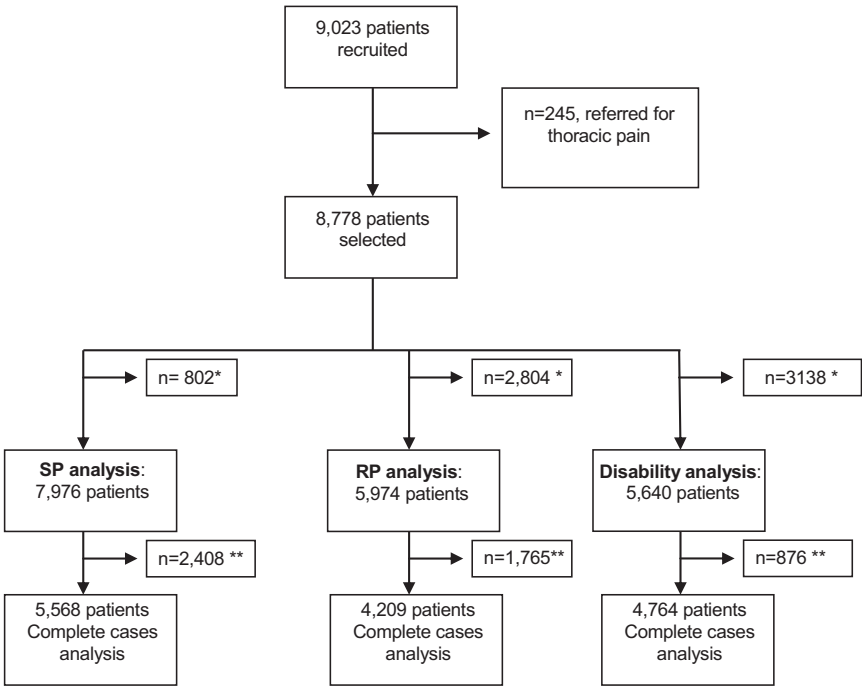

Fig. 1. Flowchart showing the number of patients analyzed. *Patients excluded because their baseline scores were below the cut-off points identifying potential improvement as "clinically relevant." **Patients with at least one missing data in any of the variables included in the corresponding model.

missingness [23,24]. A total of 10 imputed datasets were created [45]. Rubin rules were used to average the regression coefficients and standard errors of the predictors in the final model [46]. *Ice* and *mim* Stata commands were used to perform the multiple imputation and analyze the imputed datasets, respectively [23]. At the design phase of the study, it was established that variables with ≥50% missing data would be excluded from the analyses, because it would be inappropriate to use multiple imputation analysis [23].

To assess the accuracy of the final model, both their discrimination and calibration were evaluated. We assessed discrimination by estimating Somer's D rank correlation index, correcting for optimism by using bootstrap sampling (500 replicates). This index reflects the correlation between predicted probabilities and observed responses. Values range between −1 and +1. D_{xy} equals 0 when the model makes random predictions, and it equals 1 when predictions are perfectly discriminating. The *validate* function in the R's *rms* package was used [29,47]. Rubin rules were followed to combine the Somer's D indexes from each of the 10 imputed datasets.

To assess calibration, a calibration plot was developed [47], showing the "Apparent curve" (representing predicted probability using the model against actual probability), the "ideal curve" (representing perfect calibration, ie, predicted probability equals actual probability) [29], and the "bias-corrected curve" (representing the overfitting-corrected calibration curve, obtained by bootstrap resampling).

Bootstrapping makes it possible to estimate the overoptimism in assuming that the final model needs no calibration, that is, that it has overall intercept and slope corrections of 0 and 1, respectively ($\gamma=(\gamma_0, \gamma_1)=(0,1)$). Therefore, γ was calculated to estimate overoptimism [29].

Because 10 imputed datasets had been created for each model (spinal pain, referred pain, and disability), 10 estimated values of $\gamma=(\gamma_0, \gamma_1)$ were averaged to calculate a global calibration curve in each case. Curves were drawn using the *lowess* function of Stata, which provides locally weighted scatterplot smoothing.

Nomograms were drawn to illustrate the results of these models [29]. Stata v11.0 (College Station, TX, USA) and R v2.15 software (available at: http://www.R-project.org) were used for the statistical analysis.

Results

Data from 9,023 patients were available. Two hundred forty-five patients (2.7%) had been referred for thoracic pain and were excluded. Therefore, 8,778 patients were included in this study. Most of these patients were women (68.1%) with chronic (75.0%) LBP (70%). The median baseline value for pain severity (for both spinal pain and referred pain) was 7.0 VAS points, and the median baseline standardized score for disability was 54.2% (Table 1).

Among the 8,778 patients included, 3,003 (34.3%) had been recruited after May 2009. Therefore, data on academic level were missing for 65.7% of the sample, so this variable was excluded from the analyses. Some patients also were excluded from their respective models on spinal pain, referred pain or disability, because their baseline scores were lower than the corresponding minimal clinically relevant change (Fig. 1).

Table 2
Characteristics of patients who showed and did not show clinically relevant improvements in SP, RP, and disability after NRT

Variables	Spinal pain (n=5,568)		Referred pain (n=4,209)		Disability (n=4,764)	
	Showed a clinically relevant improvement (n=4,174)	Did not show a clinically relevant improvement (n=1,394)	Showed a clinically relevant improvement (n=2,996)	Did not show a clinically relevant improvement (n=1,213)	Showed a clinically relevant improvement (n=3,160)	Did not show a clinically relevant improvement (n=1,604)
Gender, male*	1,370 (32.8)	494 (35.4)	970 (32.4)	379 (31.2)	1,088 (34.4)	526 (32.8)
Age, years†	53 (42; 64)	52 (43; 64)	54 (43; 65)	53 (44; 64)	52 (42; 64)	54 (44; 64)
Reason for referral to NRT*						
Neck pain	742 (17.8)	230 (16.5)	529 (17.7)	196 (16.2)	344 (10.9)	234 (14.6)
Low back pain	3,432 (82.2)	1,164 (83.5)	2,467 (82.3)	1,017 (83.8)	2,816 (89.1)	1,370 (85.4)
Type of pain*,‡						
Nonspecific	3,991 (95.6)	1,307 (93.8)	2,794 (93.3)	1,128 (93.0)	3,012 (95.3)	1,501 (93.6)
Radicular pain caused by disc protrusion/extrusion or spinal stenosis	183 (4.4)	87 (6.2)	202 (6.7)	85 (7.0)	148 (4.7)	103 (6.4)
Employment status*						
Passive	1,701 (40.8)	568 (40.7)	1,234 (41.2)	521 (43.0)	1,215 (38.4)	694 (43.3)
Receiving financial assistance for neck pain or low back pain	417 (10.0)	203 (14.6)	296 (9.9)	178 (14.7)	327 (10.3)	215 (13.4)
Working	2,056 (49.3)	623 (44.7)	1,466 (48.9)	514 (42.4)	1,618 (51.3)	695 (43.3)
Duration of the pain since diagnostic categorized, years*						
≤1	687 (16.5)	196 (14.1)	470 (15.7)	168 (13.8)	530 (16.8)	222 (13.8)
1–5	1,313 (31.5)	456 (32.7)	944 (31.5)	396 (32.6)	1,014 (32.1)	504 (31.4)
6–10	1,046 (25.1)	356 (25.5)	773 (25.8)	312 (25.7)	782 (24.7)	407 (25.4)
>10	1,128 (27.0)	386 (27.7)	809 (27.0)	337 (27.8)	834 (26.4)	471 (29.4)
Duration of the pain episode, days, categorized*						
Subacute, ≤90	1,210 (29.0)	266 (19.1)	833 (27.8)	216 (17.8)	947 (30.0)	344 (21.4)
Chronic, 91–365	1,818 (43.6)	674 (48.4)	1,312 (43.8)	593 (48.9)	1,349 (42.7)	763 (47.6)
Highly chronic, >365	1,146 (27.5)	454 (32.6)	851 (28.4)	404 (33.3)	864 (27.3)	497 (31.0)
Diagnosis of fibromyalgia*	135 (3.2)	50 (3.6)	99 (3.3)	51 (4.2)	90 (2.8)	61 (3.8)
Other comorbidities*	1,546 (37.0)	610 (43.8)	1,101 (36.7)	551 (45.4)	1088 (34.4)	697 (43.5)
Involved in work-related claims*	18 (0.4)	20 (1.4)	18 (0.6)	15 (1.2)	17 (0.5)	17 (1.1)
Baseline severity of SP (VAS)†	7 (6; 8)	7 (6; 8)	7 (6; 9)	7 (6; 9)	7 (5; 8)	7 (6; 8)
Baseline severity of RP (VAS)†	7 (5; 8)	7 (5; 8)	7 (5; 8)	7 (5; 8)	7 (5; 8)	7 (5; 8)
Baseline disability (standardized 0–100 score)†	58.3 (41.7; 75.0)	52.0 (37.5; 70.8)	54.2 (38.0; 70.8)	60.0 (44.0; 75.0)	54.2 (37.5; 70.8)	54.2 (37.5; 70.8)
Previous lumbar surgery* (yes)	286 (6.9)	174 (12.5)	231 (7.7)	157 (12.9)	223 (7.1)	190 (11.8)
Failed back syndrome* (yes)	41 (1.0)	26 (1.9)	33 (1.1)	18 (1.5)	28 (0.9)	33 (2.1)
Diagnostic procedures during the episode*						
X-ray	1,164 (27.9)	313 (22.5)	804 (26.8)	275 (22.7)	894 (28.3)	373 (23.3)
MRI	1,403 (33.6)	482 (34.6)	1,012 (33.8)	456 (37.6)	1,120 (35.4)	545 (34.0)
Other§	310 (7.4)	98 (7.0)	240 (8.0)	91 (7.5)	246 (7.8)	111 (6.9)

Imaging findings*						
Disc degeneration	1,893 (45.4)	681 (48.9)	1,332 (44.5)	641 (52.8)	1,319 (41.7)	826 (51.5)
Facet joint degeneration	445 (10.7)	158 (11.3)	314 (10.5)	146 (12.0)	309 (9.8)	205 (12.8)
Scoliosis	238 (5.7)	69 (4.9)	153 (5.1)	62 (5.1)	167 (5.3)	93 (5.8)
Spondylolysis	23 (0.6)	9 (0.6)	13 (0.4)	7 (0.6)	17 (0.5)	12 (0.7)
Spondylolisthesis	162 (3.9)	60 (4.3)	109 (3.6)	57 (4.7)	106 (3.4)	75 (4.7)
Spinal stenosis	212 (5.1)	100 (7.2)	171 (5.7)	100 (8.2)	144 (4.6)	115 (7.2)
Disc protrusion	211 (5.1)	90 (6.5)	150 (5.0)	81 (6.7)	134 (4.2)	82 (5.1)
Disc herniation (extrusion)	1,105 (26.5)	452 (32.4)	842 (28.1)	413 (34.0)	857 (27.1)	503 (31.4)
Unspecific syndrome	573 (13.7)	200 (14.3)	402 (13.4)	184 (15.2)	341 (10.8)	227 (14.2)
Other findings‖	365 (8.7)	120 (8.6)	233 (7.8)	100 (8.2)	262 (8.3)	131 (8.2)
No findings	1,692 (40.5)	514 (36.9)	1242 (41.5)	426 (35.1)	1,390 (44.0)	558 (34.8)
Treatments						
Drugs*						
Analgesics	2,797 (67.0)	935 (67.1)	2,035 (67.9)	841 (69.3)	2,121 (67.1)	1,105 (68.9)
Nonsteroidal anti-inflammatory drugs	2,725 (65.3)	871 (62.5)	1,978 (66.0)	768 (63.3)	2,098 (66.4)	1,049 (65.4)
Steroids	391 (9.4)	123 (8.8)	315 (10.5)	123 (10.1)	319 (10.1)	145 (9.0)
Muscle relaxants	1,019 (24.4)	311 (22.3)	770 (25.7)	281 (23.2)	829 (26.2)	354 (22.1)
Opioids	132 (3.2)	66 (4.7)	96 (3.2)	54 (4.5)	99 (3.1)	86 (5.4)
Other	986 (23.6)	365 (26.2)	675 (22.5)	334 (27.5)	744 (23.5)	446 (27.8)
Nonpharmacological treatments*						
Physical therapy/ rehabilitation	580 (13.9)	201 (14.4)	454 (15.2)	172 (14.2)	441 (14.0)	226 (14.1)

MRI, magnetic resonance imaging; NDI, Neck Disability Index; NRT, neuroreflexotherapy; RP, severity of referred pain (in the 6,649 patients who had it); SP, severity of spinal pain; VAS, visual analog scale (range from better to worse; 0–10).

* Frequency (%).

† Median (percentile 25; percentile 75).

‡ Type of pain: ''Radicular pain caused by disc protrusion/extrusion or spinal stenosis'' if (a) severity of referred pain≥spinal pain, (b) corresponding imaging finding on MRI, (c) distribution of pain consistent with the nerve root compressed by the corresponding imaging finding. ''Nonspecific pain'' if one or more of these criteria were not met.

§ Other diagnostic procedures: electromyography, computed tomography scan, and other.

‖ Other imaging findings: annular tear, loss of cervical lordosis, loss of thoracic cifosis, loss of lumbar lordosis, horizontalization of the sacrum, lumbarization of S1, sacralization of L5.

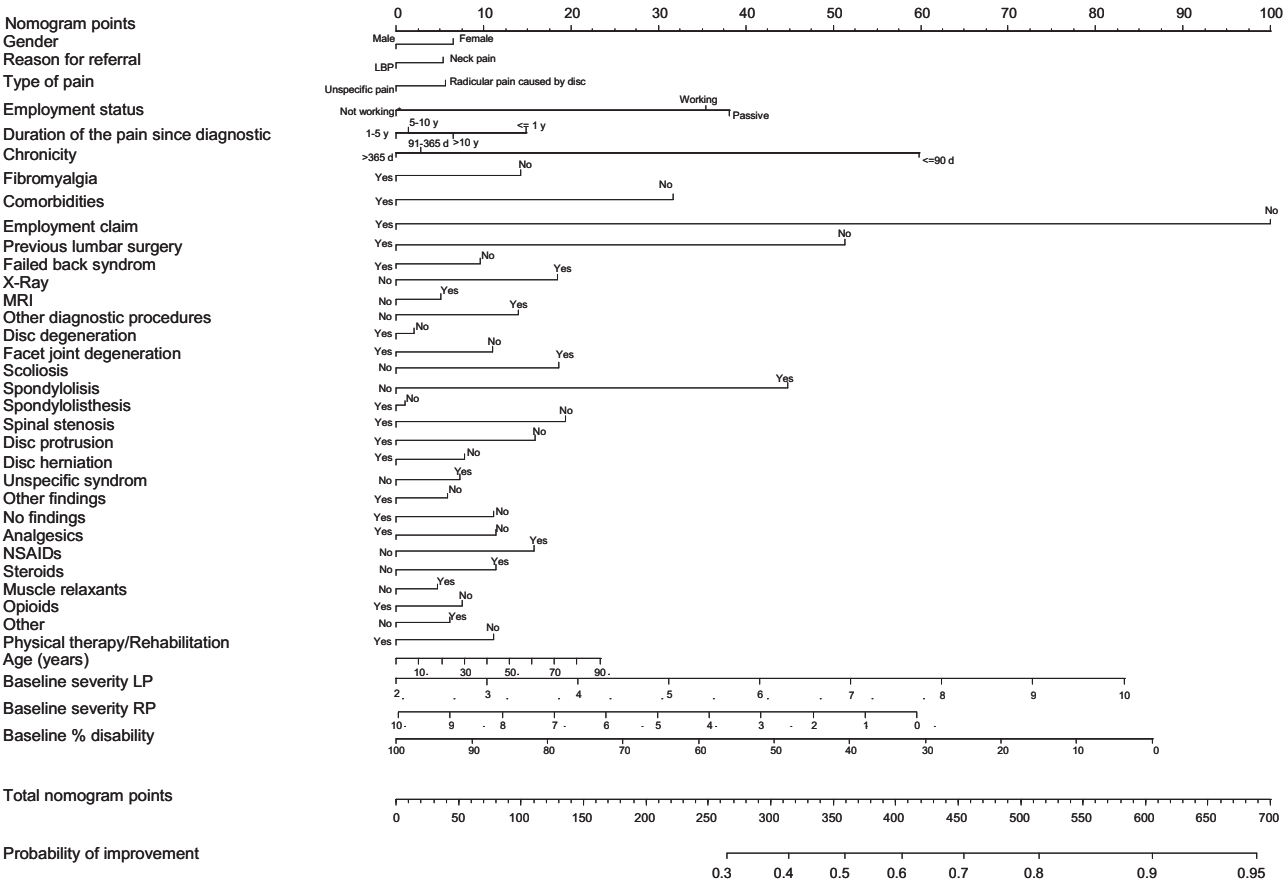

Fig. 2. Nomogram for improvement of spinal pain.

As a result, the ''complete cases'' analysis included 5,568 subjects for spinal pain, 4,209 for referred pain, and 4,764 for disability (Fig. 1). At discharge, a clinically relevant improvement was experienced by 4,174 (75%) patients for spinal pain, 2,996 patients (71.1%) for referred pain, and 3,160 (66.3%) for disability (Table 2).

Among the 2,588 patients treated for neck pain, 1,397 (54%) underwent NRT after the Spanish version of the NDI had become available. The volume of missing data ranged from 4 (0.04%) for age, to 1,096 (12.5%) for employment status, and 2,762 (31.5%) of the 8,778 patients showed one or more missing data.

Once multiple imputation was performed, the analysis included 7,976 patients for spinal pain, 5,974 for referred pain, and 5,640 for disability. The same variables were included in the multiple imputation analysis and in the regression models, except for the variables, which were eliminated from the models because a prevalence of <1% (being involved in litigation, having a difference in leg length and using codeine).

The tables showing the coefficients of the final models for spinal pain, referred pain and disability, for both the complete cases and the imputation analyses, are available online. Results from both analyses identified the same variables as those which have the greatest predictive value. Their coefficients were also very similar, although limits of the 95% confidence interval were generally narrower in the imputation analysis and coefficients for variables with smaller predictive value showed larger variations across analyses.

Figures 2–4 show the nomograms corresponding to the models on improvement of spinal pain, referred pain and disability, respectively. The variables contributing the most to predicting a clinically relevant improvement in all outcomes (spinal pain, referred pain and disability) are: pain being subacute (as opposed to chronic or highly chronic), not having previously undergone spine surgery, not receiving financial assistance for neck pain or LBP (vs. having a ''passive'' employment status), and having undergone X-ray. In addition, a lower baseline severity of spinal pain is associated with a worse prognosis for improvement of spinal pain and a better one for referred pain; a lower baseline severity of referred pain is associated with a worse prognosis for referred pain and a better one for spinal pain and disability, and a lower degree of disability is associated with a worse prognosis for disability and a better one for spinal pain and referred pain. Not having comorbidities is associated with a better prognosis for spinal pain and referred pain, but not for disability.

Additional variables contributing significantly to predicting a clinically relevant improvement in spinal pain are ''not being involved in an employment claim'' and ''using NSAIDs''; for improvement in referred pain, ''not

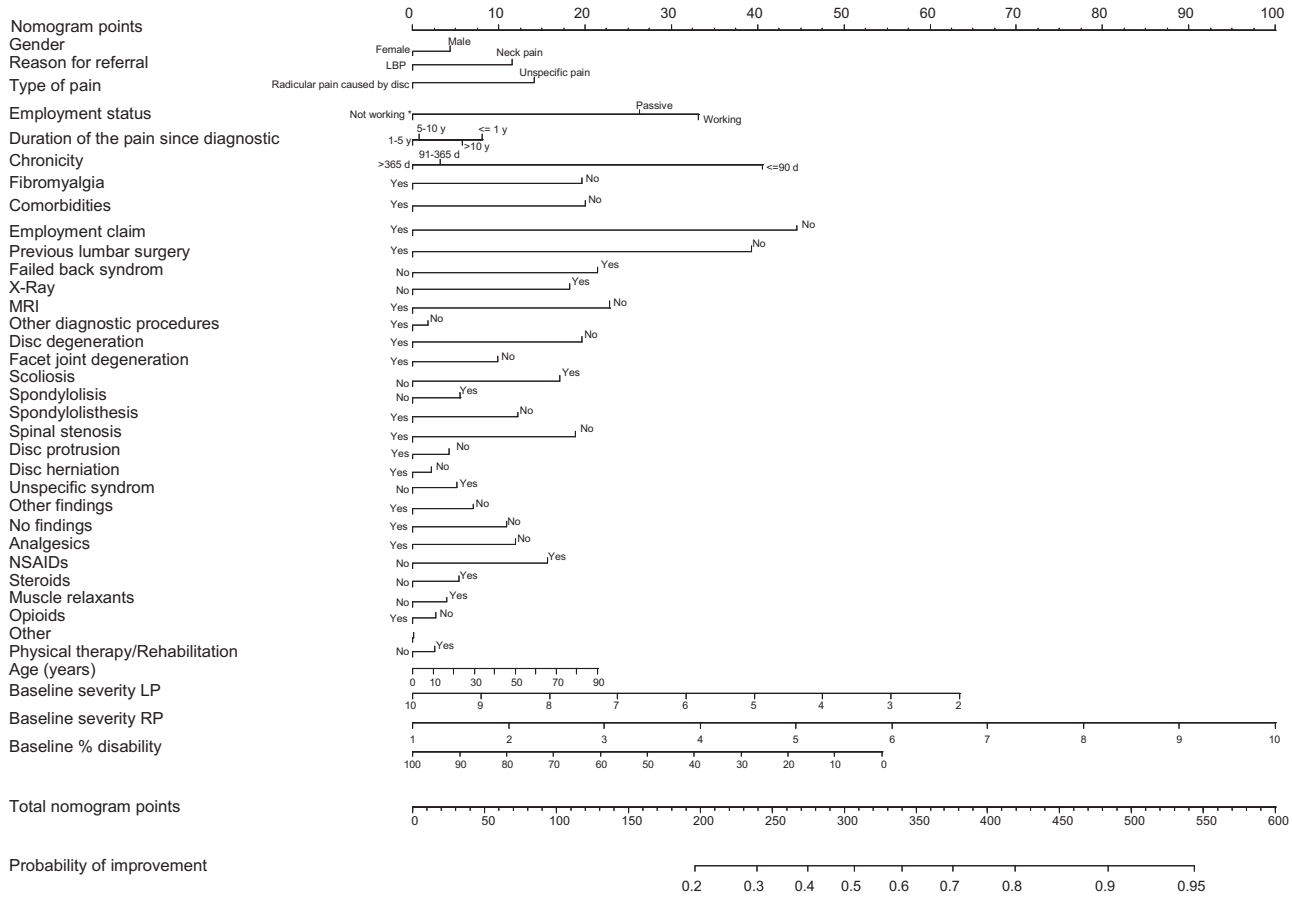

Fig. 3. Nomogram for improvement of referred pain.

showing disc degeneration'' and ''using NSAIDs''; and for improvement in disability, ''having been treated for LBP (vs. for neck pain)'' and ''using muscle relaxants.''

Discrimination of the three models was slight to moderate [48], with a corrected D_{xy} index of 0.241 for spinal pain, 0.278 for referred pain, and 0.215 for disability. Calibration of the models was good, as shown in the three calibration plots available online. These plots show that the models accurately predict the actual likelihood of improvement in spinal pain, referred pain and disability, especially in the range of probabilities predicted by a greater number of actual observations.

Discussion

These results show that it is feasible to use registries and postimplementation surveillance mechanisms in routine practice to identify factors predicting the clinical response to treatments. The models developed in this study are valid for predicting a clinically relevant improvement in spinal pain, referred pain, and disability after undergoing a minimally invasive, nonpharmacological treatment. The nomograms based on these models make it possible to quantify the likelihood that a given patient will experience a clinically relevant improvement in routine practice if undergoing this procedure (Figs. 2–4). For instance, according to these nomograms, the probability of experiencing a clinically relevant improvement in spinal pain after NRT is 87% for a 40-year old housewife who presents a lumbar disc herniation and no other findings on MRI, has been symptomatic for the first time in her life during the last 6 weeks, with scores of 8 VAS points for both spinal and referred pain, and 19 Roland-Morris points for disability, has no other comorbidities, has not undergone other diagnostic procedures or rehabilitation, and is using opioids, NSAIDs, and steroids. However, the probability would have been 72% if pain had lasted for more than 1 year and she had been receiving compensation benefits. The use of these methods to produce nomograms for all neck pain and LBP treatments would provide patients and clinicians with valuable tools in the context of informed shared decision making.

Registries compiled in routine practice, which include large numbers of variables and subjects, often present missing data [23,49]. Under the assumption of a missing at random pattern, performing multiple imputation analysis by chained equations is more efficient than restricting the analysis to complete cases [25,49,50]. Moreover, the former could address the potential risk of bias implied by the latter

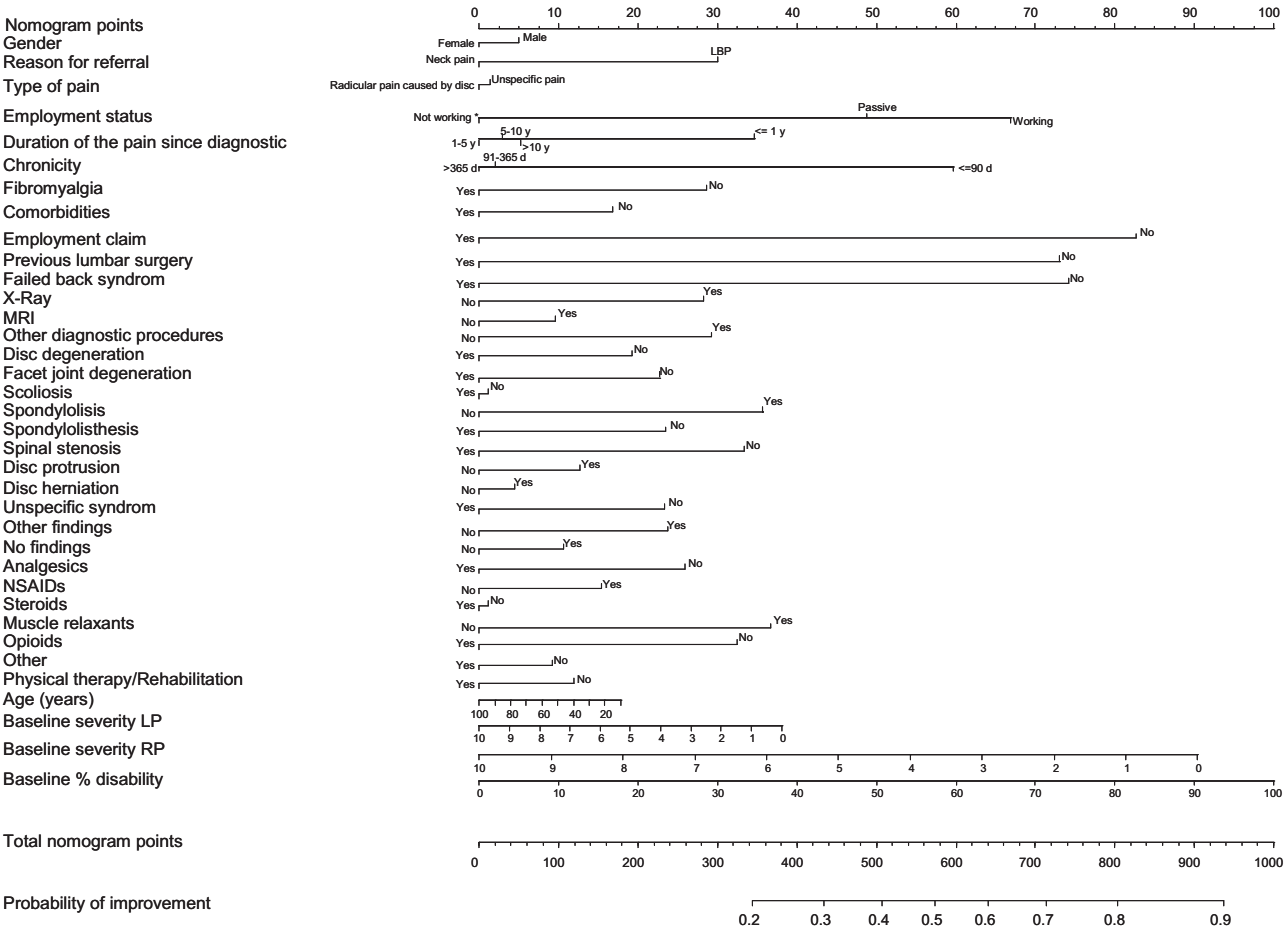

Fig. 4. Nomogram for improvement of disability.

[26,30]. The current study had approximately 30% of missing data, and multiple imputation led to a rise of between 20% and 40% in the number of cases analyzed in each model. This increased statistical power and made it possible to identify variables with a relevant prognostic value. Nevertheless, the coefficients of the variables with the greatest predictive value were very similar in both analyses, which supports their validity.

This registry included all SNHS patients who underwent a specific form of conservative treatment during a period of over 7 years across five different geographic regions. It gathered data on clinically relevant variables through previously validated methods [17,19,20,32,34,40]. The calibration and discrimination of the three predictive models were assessed using complex statistical and computational techniques, which provide bias-corrected indexes (resampling by bootstrap) [29,47], and take into account the multiple datasets derived from multiple imputation. These models had only slight-to-moderate discrimination capacity but showed good calibration, so the nomograms based on these models are applicable in routine practice.

However, a registry analysis is an observational study, and ''association'' does not necessarily imply ''causation.'' Therefore, results showing the association between a given variable and a better or worse prognosis should be interpreted cautiously, taking clinical plausibility into account. For instance, prescribing X-rays has shown to increase patients' satisfaction, but to be clinically superfluous in patients with neck pain or LBP who do not show ''red flags'' for potential systemic diseases [10,14,51]. Therefore, it is unlikely that undergoing X-rays ''improves'' patients' prognosis; it is more likely that, when patients insist on having imaging, clinicians prescribe X-rays (as opposed to other more complex imaging procedures, such as magnetic resonance) to those in whom there is no reason to suspect any serious condition (ie, those for whom they expect a better prognosis). Similarly, taking into account evidence on the effectiveness of muscle relaxants [9,14,52], it is likely the association between using these drugs and a slightly better prognosis for disability reflects that clinicians prescribe them to patients who they perceive are less severely impaired.

Nevertheless, most associations found in this study are plausible, consistent with the existing evidence, and make clinical sense; NSAIDs are effective for treating SP [9,14,52]; receiving financial benefits for neck pain or LBP is associated with delayed recovery [53–57]; and the prognosis of LBP and neck pain is worse for patients

who have been in pain for longer, which also implies that previous treatments have failed [1,2,22,53]. Moreover, a greater baseline value for a given variable (spinal pain, referred pain, or disability) leaves more room for its improvement [58], either because of treatment or regression to the mean, whereas recovery is more difficult among patients who are more severely affected (in terms of the other variables). It also makes clinical sense that the prognosis of pain is worse for patients involved in employment claims [53–57], and among those with comorbidities (Figs. 2–4), suggesting poorer general health, less physically active lifestyles and potential additional psychological distress.

This study has some weaknesses. Academic level has been reported to influence LBP prognosis [53,59,60], but data on education level could not be included in this study because they were available only for a minority of patients. However, from May 2009 onwards these data have been systematically registered and will be analyzed in future reports. This registry does not include any psychological variables, whereas pain is a sensory and emotional experience which is influenced by psychological factors [53,59–68]. However, the psychological variables influencing the prognosis of patients with LBP specifically in the Spanish cultural setting are yet to be identified; to date, only the influence of fear avoidance beliefs and catastrophizing have been assessed, and shown to be clinically irrelevant or null [40,44,69–72]. Once psychological variables with a prognostic influence in this setting are identified, they will be added to this registry. The definition of the degree of improvement that is clinically important may vary across procedures and settings. However, the definitions used in this study are those which have shown to be valid in the setting where the study took place [37,38], and are in line with those determined in other settings [39]. Moreover, most patients were severely impaired and few had baseline scores below the value established as an MCIC (Table 1). Therefore, it is unlikely that using other definitions would have a major impact on results from this study.

In conclusion, this study developed three models that predict the evolution of spinal pain, referred pain, and disability in subacute and chronic patients treated with NRT for neck pain and LBP. Good calibration of these models suggests that they are applicable in routine practice, and nomograms allow clinicians and patients to quantify the likelihood of improvement for a given patient. Generalizing this approach to all forms of neck pain and LBP treatment could be valuable in the context of informed shared decision-making.

Appendix

Supplementary material

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.spinee.2013.09.039.

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