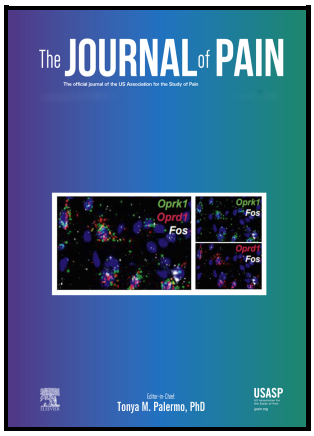

Prognosis of patients with neuropathic low back-related leg pain: An exploratory study using prospective data from UK primary careRunning title: Prognosis of patients with neuropathic low back-related leg pain

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Prognosis of patients with neuropathic low back-related leg pain: An exploratory study using prospective data from UK primary care

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Running title: Prognosis of patients with neuropathic low back-related leg pain

Abstract

This prospective cohort study investigates the prognosis of patients with neuropathic low back-related leg pain (LBLP) consulting in UK primary care. Data from 511 patients were collected using standardised baseline clinical examinations (including MRI scan findings), self-report questionnaires at baseline, 4-months, 12-months and 3-years. Cases of possible neuropathic pain (NP) and persistent-NP were identified using either of two definitions: i) clinical diagnosis of sciatica, ii) self-report version of Leeds Assessment for Neurological Symptoms and Signs (s-LANSS). Mixed-effects models compared pain intensity (highest of mean leg or mean back pain (0-10 NRS)) over 3-years between persistent-NP vs non-persistent NP based on i) clinical diagnosis, ii) s-LANSS. Logistic regression examined associations between potential prognostic factors

and persistent-NP at 4-months based on the two NP definitions. At 4-months, using both definitions: i) approximately 4 out of 10 patients had persistent-NP, ii) mean pain intensity was higher for patients with persistent-NP at all follow-up points compared to those without, iii) only pain self-efficacy was significantly associated with persistent-NP (s-LANSS: OR 0.98, sciatica: 0.98), but it did not predict cases of persistent-NP in either multivariable model. Based on factors routinely collected from self-report and clinical examination, it was not possible to predict persistent-NP in this population.

Perspective

This study provides evidence that neuropathic back-related leg pain in patients consulting in primary care is not always persistent. Patients with persistent neuropathic pain had worse outcomes than those without. Neither leg pain intensity, pain self-efficacy nor MRI scan findings predicted cases of persistent neuropathic pain in this patient population.

Key words

spine-related leg pain; radicular pain; epidemiology; prognostic factor; clinical course

Introduction

Neuropathic pain (NP), defined as pain caused by injury or disease of the somatosensory system[1] is characterised by burning, electric-shock type pain[2] that can be distressing for patients. NP resulting from nerve damage is assumed to be irreversible[3] and the symptoms are often thought to be persistent. There is no gold standard for defining cases of NP, but there is some consensus for a hierarchical grading system to assist researchers and clinicians.[1]

Low back pain is the leading cause of disability globally.[4] Two-thirds of patients with low back pain seeking healthcare in primary and secondary care settings have related leg pain.[5,6] The presence of leg pain related to back pain (LBLP) is associated with increased pain and disability, and poorer

quality of life, compared to those with low back pain alone.[7] LBLP is clinically diagnosed as either sciatica or referred leg pain . Sciatica is defined as leg pain that may radiate to beyond the knee into the foot or toes and may be accompanied by muscle weakness and/or reflex change and/or pins, needles or numbness (paresthesia) in a specific nerve root(s) distribution.[8] The pathophysiological mechanisms underlying sciatica are thought to be neuropathic[9] whereas those with underlying referred leg pain are thought to be nociceptive. Patients with neuropathic LBLP are mostly managed in primary care even when pain is severe.[10] Treatment for people with and without neuropathic LBLP is largely the same, although there are clinical guidelines advocating neuropathic medications for patients with sciatica.[11,12] Recent research highlighted that neuropathic LBLP based on a clinical diagnosis of sciatica was not associated with poor prognosis. [13] However, the presence of self-reported NP signs and symptoms was associated with poor prognosis at 4-months, 12-months and 3-years in patients with LBLP. [13]

In primary care, NP screening tools (for example the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs[14]) are available to try to identify cases of possible NP.[15] A useful proxy indicator for a diagnosis of sciatica can be the presence of pain below the knee.[16, 17] Currently, it is not known whether items based on routine clinical examination and self-report that are important for identifying cases of NP are useful to identify which LBLP patients with NP have a poorer prognosis.[10,18]

There is some evidence that the presence of NP does not change over time in LBLP patients attending a pain clinic.[19] However, these findings may not be generalisable, as it was likely that patients who attended follow-up and provided data were different to those who did not. Prospective cohort studies offer the opportunity for prognostic research in order to address this absence of high-quality data in patients with neuropathic LBLP.

The overall aim of this research was to investigate the prognosis of LBLP patients with NP who consult in primary care. Specific aims were to: i) describe baseline characteristics of patients with

persistent-NP at 4 months; ii) to compare the clinical course, in terms of pain intensity, over a 3 year follow-up period of patients with and without persistent-NP at 4 months. Finally, we utilized the prognosis research strategy guidelines[20] and performed an exploratory analysis that aimed to: iii) to identify potential prognostic factors associated with the outcome of persistent-NP in patients with NP at baseline; iv) to investigate the prognostic value of factors in LBLP patients with NP that may be associated with persistent-NP.

Methods

Study design

This is secondary analysis of people with neuropathic LBLP participating in a prospective, multi-centre cohort study, the Assessment and Treatment of Leg pain Associated with the Spine (ATLAS) study, of LBLP patients consulting and receiving treatment in UK primary care. The South Birmingham Research Ethics Committee granted ethical approval (REC ref 10/H1207/82) in October 2010 for the original study,[21] the longer-term follow-up was approved by the NRES Committee North of Scotland (REC ref 10/NS/0170). Adults aged 18 years and over with LBLP of any duration and severity, who consulted with their family doctor, were invited to take part in the ATLAS study.

Patient recruitment

Participants were recruited to the ATLAS study between April 2011 and March 2013. Potentially eligible patients were identified at consultation with their GP by the use of Read codes.[22] Identified participants were sent information about the study and were invited to telephone the research centre to find out more about the study and to make an appointment at the ATLAS research clinic (a LBLP clinic set in the community). Potential participants were offered an appointment within 10 working days of contacting the research centre; a participant information sheet and a study questionnaire were sent to the participant at this point. At the ATLAS research clinic, all potential participants were screened for potential eligibility by a study nurse and informed consent was gained if they wished to be included in the study. Consent to review the participants' medical

records was also requested. Full eligibility was determined by a full clinical examination by one of the study's physiotherapists.

Patients were considered to have LBLP if they presented with leg pain of any duration that spread from the lower back beyond the gluteal fold to anywhere in the leg. Pain was considered to include unpleasant sensations such as pins and needles or numbness. Patients were excluded if there was suspected serious spinal pathology, previous spinal surgery, pregnancy, they were already receiving physiotherapy treatment (or osteopathy, chiropractic) or were under the care of a specialist consultant in secondary care for the same condition. Patients were also excluded if they were unable to attend the research clinic, or undergo the study's procedures because of the presence of serious physical or mental co-morbidity, or if they were unable to read and speak English.

All patients participating in the study were invited for a magnetic resonance imaging (MRI) scan within ten days of attending their assessment at the ATLAS research clinic. Exceptions to having an MRI scan were made where the imaging was contraindicated, or when the patient did not wish to have a scan, or when an MRI scan was already available in the previous 6 months for the same clinical presentation. A summary report on the MRI scan was provided by a Consultant Radiologist in the participating NHS Hospital. The assessor was blinded to any clinical information relating to the patient's symptoms other than the clinical presentation (LBLP), the painful leg(s) were not disclosed.

Full details of the recruitment procedure and the MRI protocol is documented in the ATLAS study protocol[21] and the flow of patients in the study is summarised in figure 1.

Clinical examination

All patients in this study were assessed by physiotherapists, and a neurological examination was carried out as part of a clinical examination as recommended in clinical guidelines[24] and specialist books.[25] At the time of clinical examination, a clinical diagnosis of either sciatica or referred leg pain was made by the physiotherapist. For the purpose of the research in this study, the term sciatica is indicative of radicular pain with or without neurological deficits. Physiotherapists in the study were

given training in the ATLAS study's procedures. When making a diagnosis of sciatica in the ATLAS study, there was fair agreement (72%, kappa co-efficient 0.35) between physiotherapists, confidence in diagnosis ranged from 50-100% (median confidence 85%).[26] The full details of the agreement and reliability amongst the clinicians in the ATLAS study when diagnosing low back-related leg pain are provided elsewhere.[26]

Patients participating in the study were treated according to current best clinical evidence and practice guidelines. Treatment plans were agreed between the treating physiotherapist and the patient. Where physiotherapy management was indicated, up to an average of 6 treatment sessions (of 30 min) were delivered over 6 to 8 weeks. Pathways were in place in order that referrals to specialists for an opinion about further treatment (which could include injections and, or surgery) could be made should a patient's symptoms fail to improve, or worsen.

Characteristics of interest

The characteristics chosen to describe LBLP patients with persistent-NP and available in the dataset were based on sociodemographic information (sex, age, socio-economic status based on grouping patients by job title [27] using the Standard Occupational Classification system[28]), pain characteristics (pain intensity using an average of three 0 to 10 numerical rating scales for least, current and usual pain over the previous two weeks for back pain and separately for leg pain intensity,[29] the presence or absence of pain below the knee, and whether or not leg pain was worse than back pain, duration of leg pain symptoms and duration of back pain symptoms in the current episode), limitations in activities (LBLP-related disability using Roland and Morris Disability Questionnaire (RMDQ)[30] leg version,[31] 0 to 23 scale with higher scores indicating higher disability), psychological variables (Hospital Anxiety and Depression Scale (HADS) for symptoms of depression,[32] 0 to 21 scale, where scores ≥11 are probable moderate or severe cases, pain self-efficacy using the Pain Self-Efficacy Questionnaire (PSEQ),[33] 0 to 60 scale where higher scores reflect stronger self-efficacy beliefs), neurological examination findings (presence of muscle weakness in relation to specific lower limb

myotomes, presence of either reduced or absent lower limb reflex, reduction or loss of sensation to pin-prick, presence of allodynia or hyperalgesia in the leg(s), whether or not a straight leg raise, femoral stretch or slump test, reproduced the patient's leg pain were recorded and presented as a positive neural tension test), findings from neuroimaging (any evidence of nerve root compression on MRI in line with clinical presentation) and the number of pain medicines taken (based on the patients self-reported history of medicines prescribed and the number of pain medicines used those bought over the counter).

Definitions of neuropathic pain

Given that there is no clear standard definition of NP in this patient population, the analysis in of the data in this report were based on LBLP patients with either of two definitions of possible NP: using the screening tool s-LANSS score ≥ 12 [12] or a clinical diagnosis of sciatica. Both definitions are thought to identify possible cases of NP[1,34,35]; when completed by self-report, sensitivity of s-LANSS was 74% and specificity was 76%.[14] S-LANSS data were collected at baseline and at 4 months. A proxy for sciatica (the presence of pain below the knee)[16,17] was collected at 4 months.

Cases of persistent-NP were defined based on the two definitions of NP. Firstly, for those cases based on s-LANSS, persistent-NP was defined as s-LANSS score ≥ 12 at baseline and ≥ 12 at 4 months. Patients with s-LANSS score ≥ 12 at baseline but <12 at 4-months were defined as having non-persistent NP. Secondly, for the definition of persistent-NP based on a clinical diagnosis of sciatica, persistent-NP was defined as a clinical diagnosis of sciatica at baseline and pain below the knee at 4 months; those with a clinical diagnosis of sciatica at baseline and an absence of pain below the knee at 4 months were defined as having non-persistent-NP.

Data analysis

Data used in this analysis were collected at baseline and at three follow-up points: 4 months, 12 months and 3 years, using postal self-complete questionnaires.

Descriptive analysis (mean and SD for continuous variables and frequency and percentage for categorical variables), based on complete cases, was used to report the baseline characteristics of patients with neuropathic LBLP with and without persistent-NP (based on 2 NP definitions.

To describe clinical course of LBLP patients with and without persistent-NP, pain intensity scores at baseline, 4 months, 12 months, and 3 years were used. Pain intensity was determined as the highest of mean leg pain intensity or mean back pain intensity in the previous 2 weeks, where leg pain intensity was determined as the mean of three 0 to 10 NRS for current, usual and least leg pain over the previous 2 weeks, and back pain intensity as the mean of current, usual and least back pain over the previous 2 weeks.[29] Linear mixed models, with a NP indicator variable by time interaction, were used to estimate mean and 95% confidence intervals (CI) of pain intensity at all three follow-up time-points. Considering the missingness of the outcome variable (pain intensity), CIs take into account the potential impact of missing data on the estimates.[34] Margins plots were used to graphically summarise the information on the clinical course.

Identification of potential prognostic factors

To identify prognostic factors in LBLP with NP, the start point was identified as those patients with NP at baseline and the end-point was those with persistent-NP at 4 months. This approach was applied to cases of persistent-NP based on s-LANSS and separately to cases with a clinical diagnosis of sciatica.

Potential prognostic factors, all of which were available in the dataset were identified a-priori. Where prognostic factors were thought to be closely related, correlation coefficients were estimated and if correlation was present ($r > 0.7$) one of the two potential prognostic factors was dropped to limit the effects of collinearity. Priority was given to the prognostic factor known to be associated with NP in this patient population (leg pain intensity, pain self-efficacy, reduction or loss in sensation to pin-prick, presence of pain below the knee).[13] Factors were selected on the condition that they are used to identify cases of neuropathic pain in LBLP (evidence of clear or possible nerve root

compression on MRI, reduction or loss in sensation to pin-prick, presence of pain below the knee) [13, 18, 35-6] and/or are factors known to be associated with poor outcomes in broader low back pain populations (pain self-efficacy, leg pain intensity, leg pain duration in the current episode).[37,38] A s-LANSS score of 12 or greater, or a clinical diagnosis of sciatica were factors chosen and entered into one but not both multivariable models. Age, sex and socioeconomic status were also selected as factors because of their broad clinical relevance. In preparation for analysis, selected prognostic factors that were continuous in the dataset were retained as continuous variables, all other factors were categorical and dummy variables were created for prognostic factors with more than two categories.

Binary logistic regression was used to examine the associations between any potential prognostic factor and the end-point, persistent-NP (based on the two definitions). Factors were considered for multivariable logistic regression based on the strength of association with either definition of persistent NP ($p<0.25$). It has been suggested that the number of events of the outcome per predictor parameter should not be less than one factor per ten events.[39] Given the size of the smallest sample in the analyses was 164 with 44% (n=72) having persistent-NP, a multivariable model with seven prognostic factors was considered adequate. Age, female sex, leg pain intensity, evidence of clear or possible nerve root compression on MRI accounted for four factors, leg pain duration (< 6 weeks, 6 to 12 weeks, > 3 months) accounted for two factors, allowing us to investigate the prognostic value for a maximum of one further potential prognostic factor. Odds ratios with 95% confidence intervals were reported for all chosen prognostic factors.

Missing data

For the analysis of prognostic factors, data from all 609 patients in the ATLAS study were used to impute missing values on the outcome (neuropathic pain based on s-LANSS with missing data). Characteristics that were associated with missingness at each of the follow-up points were included in the imputation model, as well as characteristics that were consistently associated with

neuropathic pain at baseline[13] and all characteristics that were included in any multivariable models. At three-years, 341 out of 609 observations for s-LANSS were either completely or partially missing (56.0%) therefore 60 imputed sets of data were created. The 60 multiply-imputed sets were combined to give a single mean estimate according to Rubin's rules.[40] Please see supplementary content for a description of the assumptions of multiple imputation and for the details of the imputation model used for the analysis.

Statistical analysis was performed using STATA version 14.0.[41] The Reporting recommendations for tumour MARKer prognostic studies (REMARK)[42] advocated for prognostic factor studies of low back pain patients[43] was used alongside the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)[44] checklist for cohort studies was used when writing the report.

Results

Study population

Out of the 609 eligible patients who participated in the ATLAS study, 511 patients met the criteria for either definition of NP and were included in this analysis; 450 had a clinical diagnosis of sciatica and 293 had an s-LANSS score of 12 or greater. Two-thirds of patients (336 out of 511, 65.8%) provided data at 4 month follow-up and 314 (61.4%) had complete data for s-LANSS. There was one missing observation for the presence of pain below the knee at 4 months. Out of 293 patients with an s-LANSS score of 12 or greater at baseline, 164 patients provided complete data for s-LANSS at 4 month follow-up; 305 out of 450 patients with a clinical diagnosis of sciatica at baseline provided data for the presence of pain below the knee at 4 months. Nearly seven out of ten patients (67.9%, 374 out of 511) provided data at 12 month follow-up and 48.1% provided data at 3 years.

Patients who responded to follow-up at 4 months were older than non-responders (mean 54 years compared with 42 years), fewer scored 12 or greater on s-LANSS (54% compared with 65%), a higher proportion had a clinical diagnosis of sciatica (91% compared with 83%) and they had slightly lower

LBLP-related disability (mean RMDQ score 12.4 compared with 13.9) at baseline. This was consistent at 12 months and 3 years.

Nearly 9 of 10 (88%) patients received a course of physiotherapy treatment as part of the ATLAS cohort study. Those with persistent-NP based on s-LANSS more frequently received a course of physiotherapy than those patients with persistent-NP based on a clinical diagnosis of sciatica (85% compared with 72%). Patients with persistent-NP based on a clinical diagnosis of sciatica were more often referred for an opinion about further treatment than those with persistent-NP based on s-LANSS (28% compared with 15%).

Baseline characteristics

At 4 months, 44% (72 out of 164) of patients with NP at baseline had persistent-NP (based on s-LANSS) and 40% (123 out of 305) of patients with a clinical diagnosis of sciatica had persistent-NP. Based on the analysis of complete cases, Table 1 summarises the baseline characteristics of LBLP patients with persistent-NP and those without (based on the two definitions).

Leg pain intensity (4.9 vs 3.7 for cases with persistent-NP vs cases without persistent-NP based on s-LANSS , 5.0 vs 3.3 for cases with persistent-NP vs cases without based on a clinical diagnosis of sciatica) and back pain intensity (4.8 vs 2.6 for cases with and without persistent-NP based on s-LANSS, 4.5 vs 2.6 for cases with and without persistent-NP based on a clinical diagnosis of sciatica) were consistently worse for patients with persistent-NP compared to patients with non-persistent NP based on either of two NP definitions. Patients with persistent-NP often reported duration of back pain symptoms longer than 3-months (48.6% vs 37.4% for cases with persistent-NP based on s-LANSS compared to those without, 43.4% vs 35.7% based on a clinical diagnosis of sciatica) and for leg pain symptoms (48.5% vs 34.8% for cases with persistent-NP based on s-LANSS, 42.0% vs 28.6% based on a clinical diagnosis of sciatica). LBLP-related disability (13.9 vs 7.0 for cases based on s-LANSS and 12.9 vs 6.4 for cases with and without persistent-NP based on sciatica) was worse for patients with persistent-NP compared to those without.

The mean score for depressive symptoms was highest in patient with persistent-NP based on an s-LANSS score of 12 or greater (7.9) compared to all other groups of patients with or without persistent NP, this may be clinically important because scores of 8 or greater are likely to be clinically diagnosed with depression.

Compared to patients with persistent-NP based on s-LANSS and based on a clinical diagnosis of sciatica, a higher proportion of patients with persistent-NP were female (71.4% vs 62.5%), reported pain below the knee (96.0% vs 83.3%) but a smaller proportion reported leg pain was worse than back pain (40.0% vs 51.4%). Similarly, a higher proportion of patients with persistent-NP based on sciatica had evidence of nerve root compression on MRI (67.0% vs 60.9%) compared to those with either of two NP definitions.

Compared to patients with persistent-NP based on a clinical course of sciatica and of the six items from the neurological examination, a higher proportion of patients with persistent-NP based on s-LANSS reported having pins and needles (76.4 vs 61.8) but a smaller proportion were found to have a positive neural tension test (55.4% vs 62.6); the four remaining items were similar for patients with persistent-NP compared to baseline across either definition of NP.

Clinical course

The mean pain intensity of patients with persistent-NP based on s-LANSS was significantly higher at baseline, 4 months (6.4 v 3.2), 12 months (5.0 v 3.0) and at 3 years (4.8 v 2.9), compared to those without persistent-NP (Figure 2). Similarly, for patients with persistent-NP based on a clinical diagnosis of sciatica, mean pain intensity was higher at 4 months (5.4 v 2.8), 12 months (4.2 v 2.9) and at 3 years (4.2 v 2.8), compared to those with non- persistent NP (Figure 3).

Identification of potential prognostic factors

Table 2 reports univariable associations between each of the factors identified as having potential prognostic value in persistent-NP based on either s-LANSS or a clinical diagnosis of sciatica. Based on the analysis of imputed data, only pain self-efficacy was statistically significantly associated with

persistent-NP (based on s-LANSS); for every one-unit reduction in pain self-efficacy score (using PSEQ; indicating reduced self-efficacy), the odds of having persistent-NP defined in this way increased by 2%.

Based on a clinical diagnosis of sciatica, four potential factors were significantly associated with persistent-NP. These potential factors were female sex (OR 1.95); leg pain duration greater than three months (OR 1.91); leg pain intensity (for every one-unit increase in leg pain intensity score, the odds of having persistent-NP increased by 21%); pain self-efficacy (for every one-unit reduction in PSEQ score, the odds of having persistent-NP increased by 2%).

Prediction of persistent neuropathic pain

In multivariable analysis of potential factors based on imputed datasets, pain self-efficacy was not associated with persistent-NP across the two definitions of NP (table 3). Female sex and leg pain intensity were associated with persistent-NP based on one definition (clinical diagnosis of sciatica); for every one-unit increase in leg pain intensity, the odds of having persistent-NP increased by 13%.

Discussion

To our knowledge, this is the first time the persistence of NP as we defined it and prognostic factors have been investigated and reported in patients consulting in primary care. The majority of LBLP patients with NP at baseline (approximately 6 out of 10) did not have NP at 4-months, irrespective of the definition of persistent-NP. This is a novel finding at odds with the commonly held assumption that NP is persistent by nature.[3] Across both definitions, patients with persistent-NP presented with more severe leg pain intensity, leg and back pain-related disability at baseline. It was surprising that all items from the neurological examination were similar for patients with and without persistent-NP across both definitions. This suggests that items from the neurological examination may be indicative of mechanisms underlying NP at baseline, but the same mechanisms may not explain NP persistence.

The clinical course in patients with persistent-NP was characterised by a gradual improvement of pain intensity over short-term (4-months), intermediate (12-months) and long-term (3-years) follow up. Consistent at all time points and for both definitions of NP, mean pain intensity could have been described as moderate or severe[45] at all time points for patients with persistent-NP, and mild for those without. Clinical course of patients with persistent-NP is distinct to the broader group of patients with non-persistent-NP whose course rapidly improved by 4-months,[13] which corresponds to the time in which normal tissue healing takes place. The clinical course of patients with persistent-NP remained worse even though some patients in both groups with persistent-NP received more care compared to those without persistent-NP, suggesting this patient population is difficult to treat in current clinical practice.

Understanding factors that predict which patients with NP are likely to have persistent-NP is important, since their likely future course will be worse than those patients without persistent symptoms. In this cohort, there was no evidence that potential prognostic factors from neurological examination (such as presence of pins and needles in the leg(s), reduction or loss of pin-prick sensation in the painful leg), or evidence of nerve root compression on MRI, were associated with persistent-NP at 4-months follow-up. Items from neurological examination deemed important for defining cases of NP at baseline did not explain the presence of persistent-NP at 4-months.

The finding, that evidence of MRI findings does not predict poor outcome is consistent with previous research in patients with low back pain.[46] Only one potential factor, pain self-efficacy (measured using the PSEQ), was significantly associated with persistent-NP in univariable regression models across both NP definitions but was no longer significantly associated when entered into a multivariable model with other potential factors considered to be clinically important in this population. In the multivariable model, female sex and higher leg pain intensity remained significantly associated with persistent-NP. However, this finding was observed using one (sciatica), not both definitions of the outcome.

The finding that higher leg pain intensity was associated with one definition of persistent-NP was consistent with other NP conditions[47]. In non-surgically treated sciatica patients[48] higher leg pain intensity has been shown to be associated with poorer outcomes, and in broader back pain[49] populations in primary care, pain severity has been found to be associated with poorer outcomes. In our analysis and comparable to previous research[50], female sex was associated with persistent-NP (sciatica diagnosis). However, it was unexpected that none of the potential prognostic factors selected, were significantly associated with persistent-NP based on the definition using s-LANSS. This study highlights the challenge of developing prognostic models in this population[51] and in predicting which LBLP patients with NP will go on to have persistent symptoms.

Factors considered clinically important for LBLP patients with or without NP (pain duration, pain self-efficacy and pain intensity) were statistically associated with persistent-NP (based on sciatica). In the multivariable model, higher leg pain intensity predicted cases of persistent-NP (but only based on one definition). This may lend support to an argument that persistent-NP in LBLP patients may be explained more by factors common to the broader group of low back pain and LBLP patients, with and without NP, than those factors thought to be signs and symptoms of underlying pathophysiological NP mechanisms. It is therefore possible that persistent-NP in this patient population may also respond to treatments recommended for broader back pain and LBLP patient populations, irrespective of neuropathic status, but this would require confirmatory research.

Strengths and limitations

The main strength of this research is the prospective cohort design that allowed for investigation of the temporal relationship of neuropathic LBLP at baseline and at 4-months, and outcomes in terms of pain intensity. This approach addresses the limitations of previous research with this patient population (for example, Hüllemann et al. 2017[19]). This cohort of neuropathic LBLP patients consulting and receiving treatment at stages of their condition best reflects real clinical practice in

primary care settings. We questioned the impact of treatment and neuroimaging; in primary analysis of the ATLAS study[52] treatment did not confound the results. Furthermore, the clinical course for patients with persistent-NP remained consistently worse compared to those without which supported our findings.

In this study, steps were taken to address selection bias (in particular, non-response bias) and loss of power due to loss to follow-up; mixed-effect models for repeated measures took into account missingness of the outcome data (pain intensity) using likelihood methods and multiple imputation to replace missing observations with plausible estimates creating a predefined number of imputed datasets.[53] A further strength of this analysis is the approach to selecting potential prognostic factors from the available dataset, chosen as they were thought to be potentially important factors for poor prognosis in NP conditions and separately in broader LBP populations. This approach of factor selection was chosen over variable selection based on univariable statistical significance, and it is thought to reduce potential bias and over-optimism of potential prognostic effects.[54]

In the current research, two definitions of persistent-NP based on either s-LANSS or clinical diagnosis of sciatica were used. Our definitions of NP were synonymous with recommendations for identifying cases in this population published since the completion of this research.[55] Given the novelty of this research and the absence of a gold standard for defining cases of NP, the use of two definitions of persistent-NP allowed for comparisons to be made and conclusions to be drawn. Our proxy indicator for a diagnosis of sciatica at 4-months (the presence of pain below the knee) may over-identify cases[17] and may have led to an over-estimation of persistent-NP at short-term follow-up.

One key limitation is the small number of participants who were identified as having persistent-NP. This was an important consideration when interpreting differences and similarities in baseline characteristics, resulted in wide confidence intervals around point estimates of pain intensity when comparing clinical course, and in few prognostic factors being able to be selected for the exploratory prognostic factor analysis. The number of factors selected for the multivariable model was thought

to be conservative based on the smallest group of patients with either of end-point (n=72 patients with persistent-NP based on s-LANSS). A maximum of seven factors were selected but this may not have been conservative enough.[54] It is also possible that there is prognostic value in other factors not yet identified.

Implications for clinical practice and research

These new data provide evidence of the likely prognosis of patients with neuropathic LBLP consulting in primary care. Patients with persistent-NP reported higher mean pain intensity at 4-months, the implication being that patients in this subgroup may benefit from more timely, targeted treatment and/or support to adjust to living with pain.

It is plausible that prognostic factors thought to predict persistent-NP based on s-LANSS may not explain cases of persistent-NP based on clinical diagnosis of sciatica. The findings of the current research exploring the potential prognostic value of factors is important to inform future research (for example, to estimate sample size of future observational cohorts and to support the development of prognostic models).[50, 53] Given the small numbers of patients with persistent-NP the findings from this study should be interpreted with some caution. Future studies of prognostic factors in this patient population could consider i) using broader factors related to social and psychological constructs not available within this dataset; ii) whether there are factors common and/or unique to distinct definitions of persistent-NP in this population.

Conclusions

Despite the expectation of persistence, NP once present does resolve over time for most patients with LBLP. In this study, persistent-NP was experienced by approximately 4 out of 10 LBLP patients with NP who consulted in this UK primary care setting. Baseline leg pain intensity and LBLP-related disability in patients with persistent-NP were worse compared to those without, otherwise patients with persistent-NP were broadly similar and were difficult to distinguish from patients without

persistent-NP based on their profiles at baseline. However, the clinical course of patients with persistent-NP was consistently worse compared to those without. Using the baseline data available in this study, it was not possible to predict which patients might have persistent neuropathic pain. This research highlights the challenge of identifying factors that predict who will develop persistent-NP.

Disclosures

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Figure legend

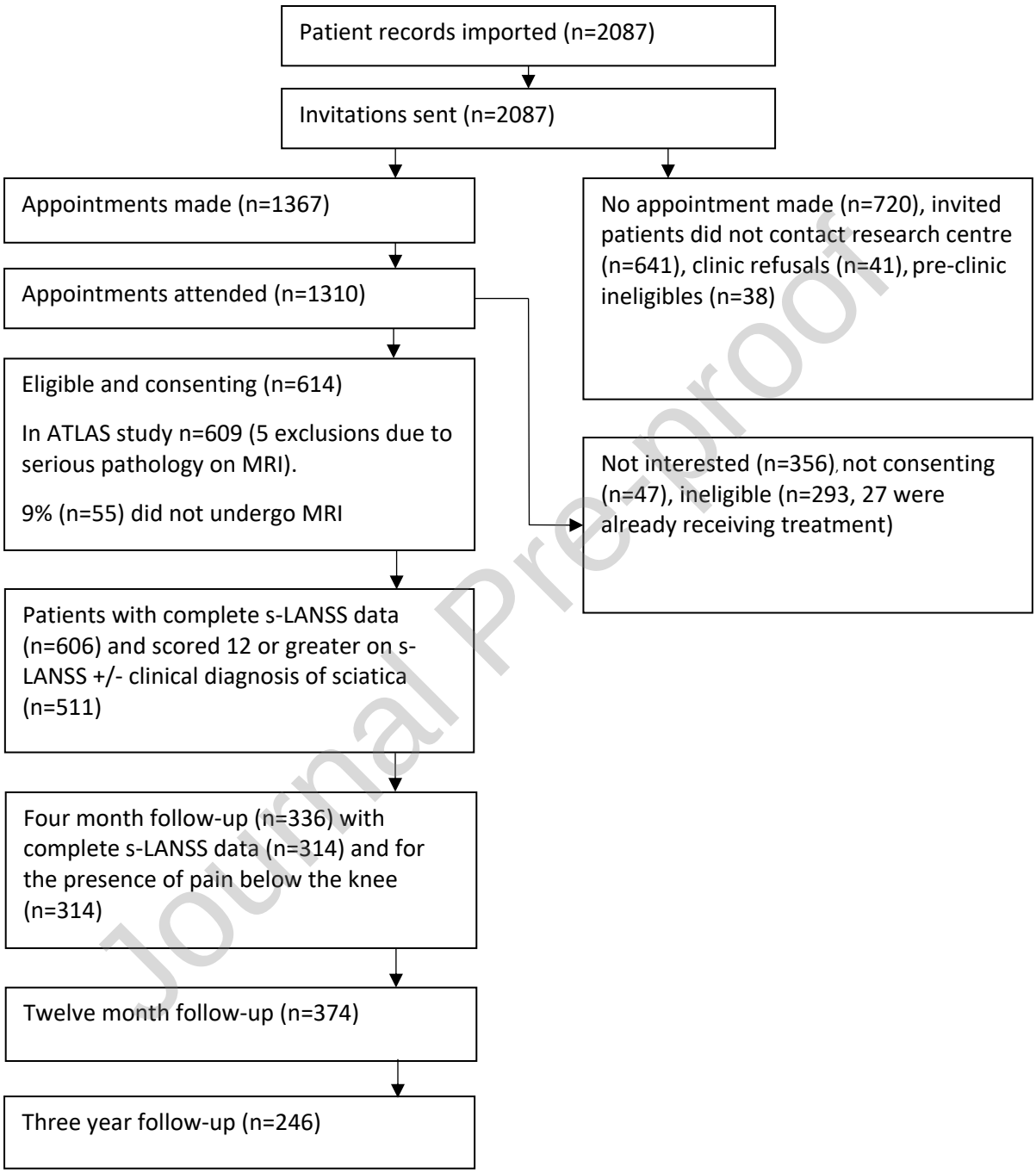
Figure 1. Study flow diagram (adapted from Konstantinou et al 2015 [23])

Figure 2. Three-year clinical course of LBLP patients with and without persistent neuropathic pain based on s-LANSS

Figure 3. Three-year clinical course of LBLP patients with and without persistent neuropathic pain based on a clinical diagnosis of sciatica

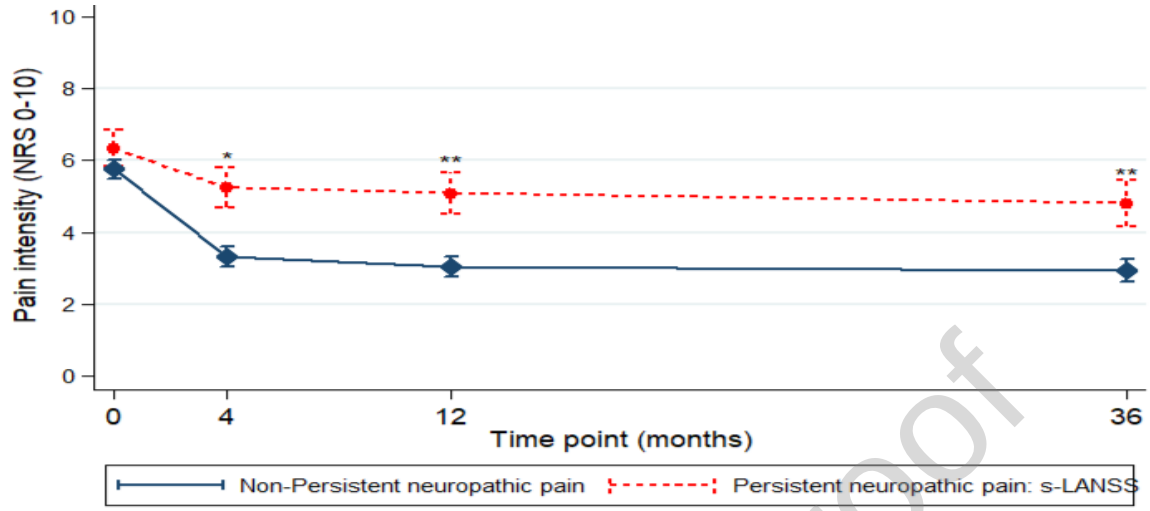
Figures

Figure 1.



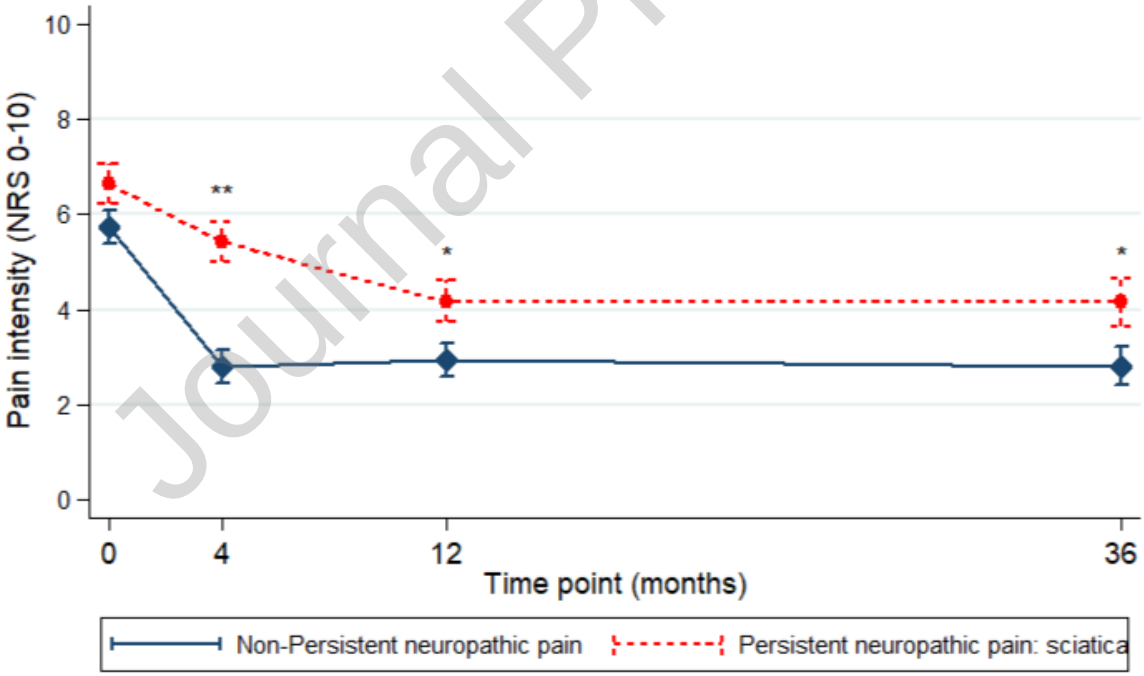
Abbreviations: ATLAS, Assessment and Treatment of Leg pain Associated with the Spine. MRI, magnetic resonance imaging. S-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs scale.

Figure 2.



Margin plots derived from analysis using linear mixed models, based on data completed by 511 LBLP patients with neuropathic pain (either a clinical diagnosis of sciatica, or s-LANSS ≥ 12) who responded to questionnaires at baseline; 336 at 4-months; 374 at 12-months; 246 at 3-years. Bars indicate 95% confidence intervals. *p<0.05. **p<0.001

Figure 3.



Margin plots derived from analysis using linear mixed models, based on data completed by 511 LBLP patients with neuropathic pain (either a clinical diagnosis of sciatica, or s-LANSS ≥ 12) who responded to questionnaires at baseline; 336 at 4-months; 374 at 12-months; 246 at 3-years. Bars indicate 95% confidence intervals. *p<0.05. **p<0.001

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Tables

Table 1. Baseline characteristics of patients with neuropathic pain and persistent neuropathic pain (based on the analysis of complete cases)

Baseline characteristics*	**Patients with neuropathic pain[†] (either s-LANSS ≥12 or on a clinical diagnosis of sciatica)**	**Persistent neuropathic pain (s-LANSS ≥12, n=164) [‡]**		**Persistent neuropathic pain (Clinical diagnosis of sciatica, n=305)[§]**	
	n=511	*Yes (n=72)*	*No (n=92)*	*Yes (n=123)*	*No (n= 182)*
Sociodemographic characteristics					
Female	321 (62.8)	45 (62.5)	62 (67.4)	88 (71.4)	100 (54.6)

Baseline characteristics*		Patients with neuropathic pain† (either s-LANSS ≥12 or on a clinical diagnosis of sciatica)	Persistent neuropathic pain (s-LANSS ≥12, n=164) ‡		Persistent neuropathic pain (Clinical diagnosis of sciatica, n=305)§	
		n=511	*Yes (n=72)*	*No (n=92)*	*Yes (n=123)*	*No (n= 182)*
Age, mean (SD)		50.2 (13.8)	53.7 (13.0)	53.3 (12.3)	55.9 (13.6)	54.2 (12.5)
Socio-economic status (n=496)	Higher managerial, administrative and professional occupations	102 (20.6)	15 (16.7)	9 (13.4)	25 (21.4)	39 (21.9)
	Intermediate occupations	132 (26.6)	24 (26.7)	17 (25.4)	30 (25.6)	49 (27.5)
	Routine and manual occupations, never worked and long-term unemployed	262 (51.2)	51 (56.7)	41 (61.2)	62 (53.0)	90 (50.6)
Pain characteristics						
Leg pain intensity (0-10), mean (SD) (n=489)		4.3 (2.6)	4.9 (3.7)	3.7 (2.4)	5.0 (2.6)	3.3 (2.4)
Back pain intensity (0-10), mean (SD) (n=505)		3.4 (2.6)	4.8 (2.5)	2.6 (2.2)	4.5 (2.6)	2.6 (2.3)
Pain below the knee		403 (78.9)	60 (83.3)	72 (78.3)	118 (96.0)	143 (48.6)
Leg pain worse than back pain (n=509)		260 (51.1)	37 (51.4)	50 (55.0)	50 (40.7)	105 (58.0)
Duration of back pain symptoms in current episode (n=509)	< 6 weeks	191 (37.5)	24 (33.3)	35 (38.5)	44 (36.1)	77 (42.3)
	6 to 12 weeks	107 (21.0)	13 (18.1)	22 (24.2)	25 (20.5)	40 (22.0)
	> 3 months	211 (41.5)	35 (48.6)	34 (37.4)	53 (43.4)	65 (35.7)
Duration of leg pain symptoms in current episode (n=491)	< 6 weeks	212 (43.2)	23 (33.8)	35 (39.3)	41 (34.5)	84 (48.0)
	6 to 12 weeks	107 (21.8)	12 (17.7)	23 (25.8)	28 (23.5)	41 (23.4)
	> 3 months	172 (35.0)	33 (48.5)	31 (34.8)	50 (42.0)	50 (28.6)

Baseline characteristics*		Patients with neuropathic pain† (either s-LANSS ≥12 or on a clinical diagnosis of sciatica)	Persistent neuropathic pain (s-LANSS ≥12, n=164) ‡		Persistent neuropathic pain (Clinical diagnosis of sciatica, n=305)§	
		n=511	*Yes (n=72)*	*No (n=92)*	*Yes (n=123)*	*No (n= 182)*
Limitations in activities						
RMDQ (0-23), mean (SD)		9.1 (7.6)	13.9 (7.6)	7.0 (6.8)	12.9 (7.5)	6.4 (6.5)
Psychological variables						
HADS (depression) (0-21), mean (SD)		6.5 (4.1)	7.9 (4.3)	5.9 (3.5)	6.4 (4.0)	5.9 (3.9)
PSEQ ‖ (0-60), mean (SD) (n=496)		33.2 (14.6)	29.4 (15.0)	34.3 (14.2)	32.2 (14.9)	36.7 (14.4)
Neurological examination findings						
Presence of muscle weakness **	5/5	406 (79.5)	68 (73.9)	59 (81.9)	88 (71.5)	143 (78.6)
	4/5	92 (18.0)	22 (23.9)	12 (16.7)	27 (22.0)	36 (19.8)
	0 to 3/5	13 (2.5)	2 (2.2)	1 (1.4)	8 (6.5)	3 (1.7)
Presence of either reduced or absent lower limb reflex	None	399 (78.1)	70 (76.1)	50 (69.4)	98 (79.7)	134 (73.6)
	Slightly reduced	30 (5.9)	4 (4.4)	9 (12.5)	11 (8.9)	9 (5.0)
	Significantly reduced or absent	82 (16.0)	18 (19.6)	13 (18.1)	14 (11.4)	39 (21.4)
Reduction or loss of sensation to pin-prick		240 (47.0)	34 (47.2)	39 (42.4)	63 (51.2)	82 (45.1)
Presence of pins and needles		286 (56.0)	55 (76.4)	67 (72.8)	76 (61.8)	99 (54.4)
Presence of allodynia or hyperalgesia in the leg(s) **		55 (10.8)	9 (9.8)	10 (14.0)	10 (8.1)	14 (7.7)
Neural tension test ‡‡ (any positive test)		327 (64.0)	51 (55.4)	41 (56.9)	77 (62.6)	128 (70.3)
Neuroimaging						
Evidence of nerve root compression on MRI (n=462)		265 (57.4)	39 (60.9)	43 (50.6)	77 (67.0)	104 (60.8)
Pain medicines use						

Baseline characteristics*		Patients with neuropathic pain† (either s-LANSS ≥12 or on a clinical diagnosis of sciatica)	Persistent neuropathic pain (s-LANSS ≥12, n=164) ‡		Persistent neuropathic pain (Clinical diagnosis of sciatica, n=305)§	
		n=511	*Yes (n=72)*	*No (n=92)*	*Yes (n=123)*	*No (n= 182)*
Number of pain medicines §§	None	68 (13.3)	8 (11.1)	12 (13.0)	14 (11.4)	30 (16.5)
	One	199 (38.9)	28 (38.9)	31 (33.7)	50 (40.7)	73 (40.1)
	Two or more	244 (46.0)	36 (50.0)	49 (53.3)	59 (48.0)	79 (43.4)

Abbreviations: CI, confidence intervals. HADS, Hospital Anxiety and Depression scale. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire. RMDQ, Roland Morris Disability Questionnaire leg version. S-LANSS, self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs scale. SD, standard deviation.

* All figures are for frequency (percentage) unless stated as mean (SD) and the denominator varies for some characteristics varies due to missing or not-applicable cases in which case the denominator is reported in parentheses.

† Based on data completed by LBLP patients with neuropathic pain (either a clinical diagnosis of sciatica, or s-LANSS ≥ 12) who responded to questionnaires at baseline.

‡ Based on data completed by LBLP patients who responded to questionnaires at baseline and at 4 months with and without persistent neuropathic pain based on s-LANSS (s-LANSS ≥ 12 at baseline and ≥ 12 at 4 months).

§ Based on data completed by LBLP patients who responded to questionnaires at baseline and at 4 months with and without persistent neuropathic pain based on a clinical diagnosis of sciatica (clinical diagnosis of sciatica at baseline and pain below the knee at four months).

|| Higher scores on PSEQ reflect stronger self-efficacy beliefs.

** Muscle strength was tested according to a 6-point grading scale where; 0 No visible flicker of movement or contraction, 1 Flicker of movement, 2 Full active movement with gravity counterbalanced, 3 Full active movement against gravity but not applied resistance, 4 Full active movement against gravity and some applied resistance, 5 Full active movement against gravity and strong resistance.

†† Hyperalgesia is an increased pain response to painful stimuli. Allodynia is pain response to non-painful stimuli (for example, brush strokes).

‡‡ Neural tension tests; straight leg raise, femoral stretch and slump test.

§§ Pain medicines include self-reported history of prescribed pain medicines and those purchased over the counter.

Table 2. Univariable associations (and 95% confidence intervals) between potential prognostic factors and persistent neuropathic pain based on two definitions of neuropathic pain (based on the analysis of 60 imputed datasets)

Prognostic factor		**Persistent neuropathic pain, odds ratio (95% CI) based on**	
		s-LANSS*	**Clinical diagnosis of sciatica†**
Age		1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
Female sex		0.85 (0.47, 1.52)	1.95 (1.20, 3.16)
Socio-economic status	Higher managerial, administrative and professional occupations	1	1
	Intermediate occupations	0.99 (0.39, 2.49)	0.96 (0.49, 1.87)
	Routine and manual occupations, -never worked and long-term unemployed	1.12 (0.48, 2.60)	1.05 (0.58, 1.89)
Leg pain intensity (0-10)		1.10 (0.97, 1.25)	1.21 (1.09, 1.35)
Pain below the knee		1.22 (0.60, 2.50)	1
Duration of leg pain symptoms in	< 6 weeks	1	-
	6 to 12 weeks	0.82 (0.39, 1.74)	1.38 (0.76, 2.52)
	> 3 months	1.21 (0.65, 2.28)	1.91 (1.12, 3.26)

current episode		
Pain self-efficacy using PSEQ‡ (0-60)	0.98 (0.96, 0.998)	0.98 (0.96, 0.99)
Reduction or loss of sensation to pin-prick	1.06 (0.61, 1.83)	1.28 (0.81, 2.02)
Presence of pins and needles	1.26 (0.68, 2.33)	1.34 (0.85, 2.13)
Clinical diagnosis of sciatica§	0.75 (0.38, 1.49)	-
s-LANSS ≥ 12‖	-	1.45 (0.92, 2.30)
Evidence of nerve root compression on MRI	1.40 (0.80, 2.45)	1.27 (0.78, 2.08)

Abbreviations: CI, confidence intervals. MRI, magnetic resonance imaging. PSEQ, pain self-efficacy questionnaire.
Results underlined highlight significance level p<0.05
Showing results for 60 multiply-imputed datasets.
· LBLP patients with persistent neuropathic pain: s-LANSS ≥ 12 at baseline and ≥ 12 at four months. Non-persistent neuropathic pain: s-LANSS ≥ 12 at baseline and < 12 at four months.
† LBLP patients with persistent neuropathic pain based on sciatica: clinical diagnosis of sciatica at baseline and pain below the knee at four months. Non-persistent neuropathic pain: clinical diagnosis of sciatica at baseline with no pain below the knee at four months.
‡ Higher scores on PSEQ reflect stronger self-efficacy beliefs
§ LBLP patients with a clinical diagnosis of sciatica are described as having "possible" neuropathic pain
‖ LBLP patients with s-LANSS ≥ 12 are described as having "possible" neuropathic pain

Table 3. Multivariable associations (and 95% confidence intervals) between potential prognostic factors and persistent neuropathic pain based on two definitions of neuropathic pain (based on the analysis of 60 imputed datasets)

Prognostic factor	**Persistent neuropathic pain, odds ratio (95% CI) based on**

		s-LANSS*	Clinical diagnosis of sciatica†
Age		1.01 (0.98, 1.03)	1.01 (0.99, 1.03)
Female sex		0.94 (0.50, 1.76)	2.09 (1.24, 3.53)
Leg pain intensity (0-10)		1.02 (0.88, 1.19)	1.13 (1.01, 1.28)
Duration of leg pain symptoms in current episode	< 6 weeks	1	1
	6 to 12 weeks	0.82 (0.37, 1.78)	1.47 (0.77, 2.78)
	> 3 months	1.12 (0.58, 2.18)	1.59 (0.91, 2.79)
Pain self-efficacy using PSEQ‡ (0-60)		0.98 (0.96, 1.00)	0.98 (0.97, 1.00)
Evidence of nerve root compression on MRI		0.80 (0.15, 4.35)	1.26 (0.74, 2.15)

Abbreviations: CI, confidence intervals. PSEQ, pain self-efficacy questionnaire.
Results underlined highlight significance level p<0.05
Showing results for 60 multiply-imputed datasets.
* LBLP patients with persistent neuropathic pain: s-LANSS ≥ 12 at baseline and ≥ 12 at four months. Non-persistent neuropathic pain: s-LANSS ≥ 12 at baseline and < 12 at four months.
† LBLP patients with persistent neuropathic pain based on sciatica: clinical diagnosis of sciatica at baseline and pain below the knee at four months. Non-persistent neuropathic pain: clinical diagnosis of sciatica at baseline with no pain below the knee at four months.
‡Higher scores on PSEQ reflect stronger self-efficacy beliefs

Highlights

- Prospective primary care cohort of patients consulting with neuropathic low back-related leg pain
- Neuropathic pain was persistent in only 4 out of 10 patients four months after baseline

- For those with persistent neuropathic LBLP, clinical course was worse three years after baseline
- Neurological examination items were not associated with persistent neuropathic LBLP
- Findings highlight the challenges of prognostic research in patients with neuropathic pain