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Prospective Study

Multivariate Prognostic Modeling of Persistent Pain Following Lumbar Discectomy

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Background: Persistent postsurgical pain (PPSP) affects between 10% and 50% of surgical patients, the development of which is a complex and poorly understood process. To date, most studies on PPSP have focused on specific surgical procedures where individuals do not suffer from chronic pain before the surgical intervention. Individuals who have a chronic nerve injury are likely to have established peripheral and central sensitization which may increase the risk of developing PPSP. Concurrent analyses of the possible factors contributing to the development of PPSP following lumbar discectomy have not been examined.

Objective: The aim of this study is to identify risk and protective factors that predict the course of recovery following lumbar discectomy and to develop an easily applicable preoperative multivariate prognostic model for the occurrence of PPSP in this patient cohort.

Study Design: A prospective study of elective lumbar discectomy with a 3 month follow-up.

Setting: University setting in Ireland

Methods: All ASA I-II patients, (n = 53, 18-65 years old), undergoing elective lumbar discectomy at a single institute were included and followed for a 3 month period postsurgery. Preoperative potential predictors were collected: age, gender, pain intensity (McGill score, visual analog scale [VAS], Present Pain Intensity), degree of dysfunction (Roland-Morris Function score), psychological status (pain catastrophizing, anxiety, and depression scores), health-related quality of life (SF-36), quantitative sensory testing (QST), inflammatory biomarkers, and a genetic pain profile. The proposed primary outcome was significant pain reduction (VAS > 70%) 3 months following surgery compared to the preoperative pain intensity.

Results: A final prediction model was obtained using a multivariate logistic regression in combination with bootstrapping techniques for internal validation. Twenty (37.7%) patients developed PPSP. Independent predictor factors included age (odds ratio [OR] = 1.0 per year), present pain intensity (OR = 0.6), and degree of dysfunction (OR = 1.2). The concordance index C (.658) supports a good monotonic association (where perfect prediction is 1) and the Akaike's information criteria indicated a good fit of the model. Inclusion of additional measured parameters (QST, biomarker, or genotyping) did not improve the model.

Limitations: Before this internally validated model can be integrated into clinical practice, and used for patient counselling and quality assurance purposes, external validation studies are necessary.

Conclusions: We demonstrated that the occurrence of PPSP can be predicted using a small set of variables easily obtained at the preoperative visit. This a prediction rule that could further optimize perioperative pain treatment and reduce attendant complications by allowing the preoperative classification of surgical patients according to their risk of developing PPSP.

Key words: Persistent post surgical pain, predictive modeling, prognostic, lumbar discectomy

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Persistent postsurgical pain (PPSP) affects between 10% and 50% of surgical patients (1). It has been defined by the International Association for the Study of Pain as pain that develops after surgery and has been present for at least 3 months, which is beyond the time for normal healing (2). It is estimated that there are between 41,000 to 103,000 new cases of PPSP in the United Kingdom every year (3,4).

The development of PPSP is a complex and poorly understood process. However, certain surgical, psychological, and physiological factors appear to confer a greater risk of developing PPSP. They include women, severity of preoperative pain, and those of a younger age (5-8). To date, most studies on PPSP focus on specific surgical procedures where individuals do not suffer from chronic pain before the surgical intervention. Individuals who have a chronic nerve injury are likely to have established peripheral and central sensitization (9,10) which may increase the risk of developing PPSP. Concurrent analyses of the possible factors contributing to the development of PPSP following lumbar discectomy have not been examined.

The aim of this study is to identify risk and protective factors that predict the course of recovery following lumbar discectomy and to develop an easily applicable preoperative multivariate prognostic model for the occurrence of PPSP in this patient cohort. If successful, such a prediction rule could further optimize perioperative pain treatment and reduce attendant complications by allowing the preoperative classification of surgical patients according to their risk (11).

Methods

Patient Recruitment

With institutional ethics committee approval, and having obtained informed written consent, a prospective study of all ASA I-II patients, 18-65-years-old undergoing elective lumbar discectomy at a single institute were included. Patients were considered for inclusion if they had an intervertebral disc herniation confirmed on magnetic resonance imaging (MRI), and persistent symptoms despite nonoperative treatment for at least 12 weeks. Specific inclusion criteria were the presence of radicular pain and/or low back pain and evidence of nerve root irritation with a positive nerve root tension sign (straight leg raise positive between 30o and 70o or positive femoral tension sign), or a corresponding neurological deficit (dermatomal distribution of pain, asymmetrical depressed reflex, decreased sensation in a dermatomal distribution, or weakness in a myotomal distribution). Lumbar disc protrusion was confirmed using preoperative MRI as reported by independent radiologists. Patients requiring lumbar discectomy from L1/L2 to L5/S1 were eligible for inclusion provided that only one of the herniations was judged to be symptomatic.

Exclusion criteria included previous spinal surgery, cauda equina syndrome, known spinal or genetic abnormalities, pregnancy, vertebral fractures, spinal infection or tumor, inflammatory spondyloarthropathy, and preoperative analgesia management that included gabapentin, pregabalin, or opioids in the 2 weeks prior to surgery. Patients with any general pain syndromes (headache, abdominal pain, chest pain, other musculoskeletal pain other than low back pain/radicular pain, or pain not covered by the above) were recorded, and pain occurring weekly or more often, with a Visual Analog Scale (VAS) (0 –10) pain score above 3 was considered as substantial pain and excluded them from the study. Patient refusal/unwillingness to return at 3 months for follow-up excluded them from the study.

All patients presenting for lumbar discectomy to the neurosurgical services at our institute during a 9-month period were screened at the first visit when their demographic details including age, gender, and duration of pain preoperatively were recorded. If, after medical assessment, they were eligible for inclusion, a set of questionnaires regarding the variables of interest were completed on the day before surgery. The progress of each patient was monitored during their hospital admission and a follow-up assessment was arranged 3 months after surgery.

Anesthetic Technique, Analgesia & Surgery

Anesthesia, analgesic, and surgical guidelines were provided to ensure standardization of practice in the study and in accordance with clinical practice at our center. All patients received acetaminophen and diclofenac analgesia postinduction and prior to the commencement of surgery. During surgery each patient received a fentanyl intravenous bolus of 25µg as required if the heart rate increased by 10% compared to the preinduction baseline. Prior to skin closure, the subcutaneous tissue was infiltrated with 10 mL of bupivacaine 2.5mg/mL by the neurosurgeons. Postoperative pain management consisted of a regular combination of oral codeine (30 mg) with acetaminophen (500 mg) and diclofenac (50 mg every 8 hours). This was commenced in the postoperative care unit and continued for 24 hours on the ward as appropriate.

A standardized open microscopic lumbar discectomy surgical technique, with examination of the affected nerve root, was performed by one of 3 consultant neurosurgeons at our institute. The surgical and anesthetic time (from induction to tracheal extubation) was recorded electronically.

Patients were discharged from the postoperative care unit to the ward after approximately 20 minutes and only if they had a visual analog score (VAS) < 2 out of 10 and a sedation score of 1 out of 5 (12) in keeping with local protocol.

Clinical Outcomes

The primary outcome was 3 months of substantial pain relief at the follow-up appointment when they were asked: "Have you experienced persistent pain in your back or leg during the last 2 weeks?" If their pain intensity on movement, standardized as a 5 minute walking test (13,14) using a VAS (0-10) was reduced by > 70% compared to their baseline VAS score, patients were categorized as not having persistent postsurgical pain.

Six preoperative assessments, detailed below, were distributed to the patients for self-completion at their bedside the day before surgery. The researcher explained the instructions for each of the assessments and questionnaires in turn and remained available to the patient until they were completed. Each patient received the assessments in the same order. At the 3-month follow-up appointment, a second set of assessments were again completed by the patients.

Pain Intensity and Functional Assessment

The Short-form McGill Pain Questionnaire (MPQ) (15,16) was used to assess pain quality and the VAS (0-10) was used as a numerical index of the severity of the pain. The Roland-Morris Questionnaire is a health status measure designed to be completed by patients to assess physical disability due to low back pain. Originally designed as a research tool, it is currently the preferred clinical assessment tool for functional recovery after lumbar disc surgery (17,18).

Psychological Assessment

Occurrences of anxiety or depression were investigated by the Hospital and Depression Scale questionnaire (19) and pain coping strategies were investigated by the Pain Catastrophizing Scale (PCS) (20,21). The medical outcomes study Short Form 36 (SF-36) was used as a physical and mental health summary and measured health-related quality of life (HRQoL) in patients with low back pain with and without sciatica (22,23).

Neurophysiological Assessments

Quantitative sensory testing was preformed preoperatively and 3 months postoperatively by a single trained investigator (DH). The pain perception threshold to transcutaneous constant current electrical stimulation was assessed in each patient lying supine in a warm, quiet environment using a Dantec Keypoint Neurodiagnostic stimulator with Dantec disposable surface electrodes (Natas Medical Instruments Inc, San Carlos, CA). Patients were unable to see the monitor, were not distracted during the testing, and were given identical instructions. Sensory, pain perception, and pain tolerance thresholds were recorded 5 minutes apart using a 0.1mA/s ramping rate, and a standardized technique in the forearm (C8-T1 dermatome) contralateral to the nerve root involved, and in the affected dermatome of the affected and contralateral lower limbs. If 2 threshold values differed by > 20% between runs, testing was repeated until 3 consecutive thresholds were recorded, each within 20% of the others.

Biochemical and genetic profiling

A designated intravenous cannula was placed once the patient was under general anesthesia. After a rest time of 15 minutes, a blood sample was drawn before surgery commenced using a standardized protocol by an experienced phlebotomist to measure the cytokines TNFα, IL-10, and IL-6. These samples were centrifuged and the serum stored at minus 20oC. Plasma TNFα, IL-10, and IL-6 concentrations were measured using commercially available ELISA (Quantikine Human TNFa Immunoassay, R&D systems, Abington, UK) according to the manufacturer's instructions by a single investigator (DH). The ELISA readings were performed by a Microreader instrument MRX (version 1.3), (Dynatech Technologies Microtiter Company, Virginia, USA) using Relevation 4.25 (DLL version 4.25) software and the absorbance measured at 450 nm with the correction wavelength set at 570 nm.

A second blood sample (5 mL) for genetic profiling was also drawn from the designated cannula before surgery commenced and stored at -80oC until commercial genotyping of the following SNP was undertaken; GCH1([G>A]), rs rs8007267); GCH1 ([A>T] rs3783641); GCH1 ([C>G], rs10483639); ORRMu (rs179997); COMT (rs4680); CYP2D6 (rs3892097).

Data Analysis

The primary endpoint was identification of factors that significantly contributed to the development of PPSP 3 months following lumbar discectomy. PPSP was defined as those patients in whom there was not at least a 70% reduction in the VAS pain intensity at 3 months compared to the preoperative VAS pain intensity on movement.

Normality and variance was tested using the Kolmogorov-Smirnov, skew and kurtosis, histograms, and Q-Q plots for each variable. Depending on these results, parametric or nonparametric analysis was undertaken for each variable. Estimating the association between each candidate predictor and the outcome bivariate analysis was performed using Spearman's correlation coefficient. However, since preselection of predictors based on P-values estimated from bivariate analyses may result in unstable prediction models (24,25), all candidate predictors were considered in the multivariable analysis using a logistic backward stepwise regression modeling technique. Predictors were considered using a hierarchical approach where easily obtainable predictors, in combination with the information provided by the bivariate analysis, were included first (26,27).

As it is common in prediction research to use a more liberal *P*-value than 0.05, e.g., 0.15 - 0.25, to keep variables in regressional models (24,25,28), the overall multivariable model was reduced by manually deleting (one by one) predictors with a *P*-value < 0.2 based on the log likelihood ratio test. The backward stepwise method was chosen to limit the suppressor effects, which occur when a predictor has a significant effect but only when another variable is held constant, and to limit the risk of making a type II error and thereby missing an important predictor (29).

The predictive accuracy and fit of the prediction models was estimated using Akaike's information criteria and Schwarz's Bayesian information criterion; the Cox and Snell's measure and Nagelkerke's adjusted value was used to estimate effect sizes; and monotonicity measurement to using the concordance index was used as a measure of the monotonic association in order to predict the strength of the model. Bootstrapping techniques were used to validate the final prediction model, i.e., to adjust the estimated model performance and regression coefficients (odds ratios) for overoptimism or overfitting (25,30). The model's performance obtained after bootstrapping can be considered as the performance that can be expected in similar future patients. Random bootstrap samples were drawn with replacement (100 replications) from the data set consisting of all patients with complete data. The multivariable selection of variables was repeated within each bootstrap sample. All data were coded and stored in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) and analyzed with SPSS 17.0 statistical software (SAS Institute Inc., Chicago, IL).

Results

Patient Demographic Characteristics

Sixty patients were assessed in a 9-month period; 53 were included in the study. Of the 7 excluded, 4 had commenced pregabalin prior to surgery, one suffered from inflammatory spondyloarthropathy, and 2 were unwilling to give consent. In all, 20 patients suffered from persistent postsurgical pain 3 months following lumbar discectomy (37.7% incidence). Table 1 shows the demographic characteristics of both groups. No significant difference was found using Mann-Whitney (U) and Fishers chi square tests where appropriate. Both groups were homogeneous in terms of preoperative pain intensity, opioids and acetaminophen consumption, and duration of pain (Table 1).

PainIintensity and Functionality Assessment

Initial data analysis was undertaken to identify likely predictors of clinical outcome in the 2 groups. Preoperatively, there was no significant difference (2-tailed analysis) in the median pain intensity (VAS), McGill score, or the present pain intensity (PPI) between the 2 groups. While the inter-group median preoperative dysfunctional score did not differ significantly using a 2-tailed analysis, (*P* =.06, with a medium effect size r = 0.25), subsequent one-tailed analysis provided a *P* value = .03, suggesting preoperative dysfunction scores should be considered to significantly influence outcome (Table 2).

Psychological and Quality of life analysis

Psychological Assessment

On average, the PCS ratings were significantly higher preoperatively in the PPSP group compared to non-PPSP group (43.9 [SE 12.6] vs 31. 6[SE 14.9] respectively), t(51)= -3.0, p = .004, which represents a medium sized effect r = 0.38. (43.9 [SE 12.6] vs 31. 6[SE 14.9] respectively), t(51)= -3.0, *P* = .004, which represents a medium sized effect r = 0.38. The subcomponents of the PCS, (helplessness, rumification, and magnification) were also found

Table 1. Demographic details of patients who developed PPSP and those who did not (nPPSP) 3 months following lumbar discectomy. PPSP was defined as a reduction in the VAS score at 3 months compared to pre-operative > 70%. Inter-group analysis showed no significant difference. The Mann-Whitney test (U), z-score, significance value, and effect size is shown except # where Fishers chi-square (Confidence interval [CI]) is used. (SLE = Straight Leg Raising, MRI = Magnetic Resonance Imaging.)

Variable	PPSP (n=20)	nPPSP (n=33)	Mann-Whitney (U)	z- score	P value (2-tail)
Age (years) Median (range)	40 (27-50)	39 (22-55)	284	.85	.39
Male : Female ratio	9 :11	19:14			0.54# (CI 95%: 0.34-0.14)
Pain duration pre-operatively (months) Median (range)	9 (3-60)	6 (3-48)	282	.89	.36
Number of days to post-operative follow-up Median (range)	105.5 (59-163)	105 (43-154)	318.5	.21	.83
Anaesthetic duration (minutes) Median (range)	71 (60-120)	80 (50-125)	408.5	-1.44	.15
Surgery duration (minutes) Median (range)	58 (45-100)	55 (34-90)	335	-0.09	.92
Number of patients using analgesia in the 24hrs pre-op	12 (60%)	21 (63%)			1.0# (CI 95%: 0.3-0.2)
Dermatome Effected					
L3/4	1 (5%)	1 (3%)			
L4/5	12 (60%)	22 (57.3%)			
L5/S1	7 (35%)	10 (30.3%)			
Positive SLE (30o-70o)	20	33	-		
MRI evidence of nerve compression	20	33	-		

Table 2. *Pre-operative pain intensity scores (VAS, McGill score and Present Pain Intensity [PP]) and level of dysfunction (Roland-Morris Functional [RM])) with 2-tailed analysis using Mann-Whitney (U) statistic, z-score, and effect size in those who did (PPSP) and did not (nPPSP) develop persistent postsurgical pain (P <.05 level of significance).*

Pre-operative Assessment	Clinical Outcome		Mann-Whitney (U) test	z-score	P value	Effect size
	nPPSP (n=33)	PPSP (n=20)				
VAS Median (range)	6.5 (1-10)	5.7 (0-7)	278	-.95	.34	0.13
McGill score Median (range)	14 (2-44)	17 (4-43)	237	-1.6	.11	0.24
Present Pain Intensity (PPI) Median (range)	2 (0-5)	2 (1-5)	320	-1.8	.85	0.25
Roland-Morris Functional score (RMF) Median (range)	16.5 (3-23)	17.5 (8-23)	230	-1.8	.06	0.25

to differ significantly between the 2 groups (Table 3). Patients who developed PPSP showed significantly higher anxious ratings preoperatively than those who did not develop PPSP (t[51] = -2.4, *P* = .02, r = 0.31). There was no significant difference in the preoperative depression scores between the 2 groups (t[51] = -1.47, *P* = 0.14, r =0.1).

Health Related Quality of Life: SF-36

Preoperatively, both groups were found to have a similar level of health related quality of life scores as assessed by the SF-36 (Table 3).

Neurophysiological and Serum Inflammatory Biomarker Profile

No significant difference was found in either the sensory, pain perception, or pain tolerance threshold between the 2 groups in the Quantitative Sensory Testing (QST) or serum biomarker levels (Table 4).

Pain Genotyping

Fifty-two samples with unambiguous SNP genotyping were successfully sequenced for 4 genes (7 SNP's) as possible candidate genes associated with the development of PPSP following lumbar discectomy (Applied Biosystems,

Table 3. *Psychological and Quality of life assessments*

	PPSP (n = 20)	nPPSP (n = 33)	*P* –value
PCS			
Total score	43.9 (12.6)	31.6 (14.9)	0.004
Helplessness	20.0 (6.6)	14.3 (7.2)	< 0.05
Rumification	9.3 (3.2)	5.6 (3.9)	< 0.001
Magnification	15.3 (4.4)	10.8 (5.2)	<0.05
HADS			
Anxiety	8.5 (3.9)	6.2 (2.9)	0.02
Depression	8.5 (4.6)	6.6 (3.9)	0.14
SF-36			
Physical Component Summary	32.9 (5.9)	30.9 (6.4)	0.1
Mental Component Summary	37.4 (9.9)	43.7 (11.6)	0.1

All data presented as mean (SE: standard error), independent student t-test, P < .05 regarded as significant

Table 4. *Neurological and serum inflammatory biomarkers*

Pre-operative Assessment	Clinical outcome		Mann-Whitney U test	z-score	*P*- value
	PPSP (n=20)	nPPSP (n=33)			
Quantitative Sensory Testing (mAmp)					
St	6.9 (1.2-25.3)	8.7 (0.9-17.2)	277	0.9	0.33
PPt	20.5 (1.5-82.0	18.9 (3.8-62.1)	283	0.8	0.39
PTt	34.1 (3.1-99)	26.6 (7 – 95.8)	277	0.9	0.34
Biomarker analysis					
Il-6 (pg/ml)	5.2 (2.6-12.9)	5.1 (0.3-13.1)	329	0.02	0.9
TNFα (pg/ml)	9.7 (6.3-17.0)	9.0 (5.7-31.1)	373	-0.08	0.4
IL-10 (pg/ml)	3.1 (0.5-17)	3.7 (0.6-14.0)	321	0.16	0.9

All values median (range) where St = sensory threshold; PPt = pain perception threshold; PTt = pain tolerance threshold; IL-6 = Interleulkin-6; TNFα = Tumor Necrosis Factor-alpha; IL-10 = Interleukin 10

Foster City, California, USA). There was 100% concordance between the sequencing results and those determined by TagMan SNP genotyping for both common and uncommon alleles (Applied Biosystems, Life technologies Corporation, California, USA). One sample was resequenced to resolve ambiguous results; however, due to insufficient/ poor DNA quality, this sample was removed from further data analysis. Data from 5′ nuclease assay reactions were analysed on the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Life technologies Corporation, California, USA). The SNP genotype and allele frequency for each polymorphism sequenced is presented in Table 5 categorised on the outcome phenotype – the presence or absence of PPSP. Pearsons' Chi-square testing was preformed and P-values reported where $P < .05$ was regarded as significant. In summary;

The frequency distribution pattern of each of the 7 genotypes or their respective alleles was similar to pre-

Table 5. *Inter-group genotyping*

Genotype	PPSP (n=20)	nPPSP (n=32)	Pearson's X2	*P* value
	Number (frequency)	Number (frequency)		
GCH1 Rs3783641				
T	29 (0.72)	48 (0.75)	0.07	0.77
A	11 (0.28)	16 (0.25)		
Genotype (TT/AT/AA)	10/9/1 (0.50/0.45/0.05)	17/14/1 (0.53/0.43/0.03)	0.14	0.93
GCH1 Rs8007267				
C	31 (0.78)	30 (0.56)	4.86	0.02
T	9 (0.22)	24 (0.44)		
Genotype (CC/CT/TT)	12/7/1 (0.60/0.35/0.05)	10/20/2 (0.31/0.62/0.06)	4.23	0.12
GCH1 Rs10483639				
G	29 (0.73)	41 (0.64)	0.8	0.37
C	11 (0.77)	23 (0.36)		
Genotype (GG/CG/CC)	10/9/1 (0.50/0.45/0.05)	12/17/3 (0.37/0.53/0.09)	0.92	0.63
OPRMu Rs1799971				
A	33 (0.82)	50 (0.78)	0.29	0.58
G	7 (0.18)	14 (0.22)		
Genotype (AA/AG/GG)	15/3/2 (0.75/0.15/0.10)	22/6/4 (0.68/0.18/0.12)	0.23	0.88
COMT Rs4680				
A	29 (0.72)	38 (0.57)	1.85	0.17
G	11 (0.28)	26 (0.43)		
Genotype (AG/GG/AA)	11/7/2 (0.55/0.35/0.10)	16/6/10 (0.50/0.18/0.31)	3.7	0.15
CYP2D6 RS				
C	35 (0.87)	48 (0.77)	1.63	0.2
T	5 (0.13)	14 (0.23)		
Genotype (CC/CT/TT)	15/5/0 (0.75/0.25/0)	20/8/3 (0.62/0.25/0.09)	2.13	0.34

The number of patients and their corresponding frequencies (in brackets) are presented for each allele and single nucleotide peptide (SNP) examined. Pearson's X2 analysis was preformed to establish significance (p value .05).

viously published data and did not significantly differ between the PPSP and nPPSP group.

No significant difference was observed in the distribution pattern of OPRMu, COMT, and 2D6 SNP genotype or allele frequency between the PPSP and nPPSP groups.

No association was identified with the prevention of persistent pain following lumbar discectomy and the presence of 3 SNP's in the GCH1genotype, either individually or in combination.

The Multivariable Predictive Model

All 53 patients included in the study were followed up successfully for the full duration of the study. The initial multivariable model included 9 predictors, all of which were deemed to be easily documented in a preoperative setting (Table 6); a second model included 4 additional possible predictors that required additional investigational resources. Using this approach only 3 predictors (age, present pain intensity [PPI], and Roland-Morris Functional [RMF] score), independently contributed to the prediction of outcome and were included in the final model. Likelihood ratio testing identified that patient age (X2 [1] = 1.9, *P* =0.16), present pain intensity (X2[1] = 2.8, *P* = 0.09) and, RMF score (X2 [1] = 5.9, *P* = 0.015), where a *P* value < .20 is accepted as significant, enabled the prediction of PPSP. The regression coefficient analysis of the final model with the odds ratio is shown in Table 7.

Using these regression coefficients of the final prediction model, one can estimate for each patient the probability of developing PPSP using the formula given in Fig. 1. As an example a 30-year-old, with PPI = 4 (high pain score), and a RMF = 16 (high level of dysfunction) corresponds to a probability of PPSP = 0.9.

The Pearson and Deviance testing of this model indicates that the model is a good fit for the data (P= 0.09) and suggests that overdispersion of the data is of no concern. The Akaike's information criteria (AIC) and the Schwarz's Bayesian information criterion (BIC) are

Table 6. *Bivariate association between each candidate predictor and the clinical outcome.*

Predictor (n=53)	Spearman's (rho) correlation coefficient	*P* value (2-tailed)
Gender (male or female)	.08	.56
Age	.11	.41
VAS pre-op	.006	.96
PPI pre-op	-.11	.43
McGill Word pre-op	.16	.26
RMF pre-op	.24	.08
PCS pre-op	.26	.06
Anxiety score pre-op	.18	.19
Depression score pre-op	.17	.22

pre-op = preoperative assessment; VAS = visual analogue score; PPI = present pain intensity; McGill Word = McGill Pain score; RMF= Roland Morris function score; PCS = Pain catastrophizing score; Anxiety score and depression score from the Hospital Anxiety and Depression score

Table 7. *Reduced model to predict preoperatively the development of persistent post surgical pain*

Predictor	b (SE)	Wald statistic	P value*	Odds ratio
Intercept	-5.1 (2.3)	4.6	.03	-
Age	.05 (.04)	1.8	.16	1.0
PPI	-.53 (.34)	2.6	.17	.6
RMF	.22 (.11)	4.5	.03	1.2

PPI = present pain intensity; RMF = Roland-Morris function score

Predictive Model
Probability of PPSP = 1/(1+exp(-(-5.1 + [0.05 x Age] - [0.53 x PPI] + [0.22 x RMF])

Fig.1. *Multivariate Predictive model for the development of persistent post surgical pain (PPSP) where Age is in years, PPI = present pain intensity, and RMF = Roland Morris function score. Example: 30 year old, with PPI = 4 (high pain score), and a RMF = 16 (high level of dysfunction) corresponds to a probability of PPSP = 0.9.*

both low values which also indicate a good fit for the model. The Cox and Snell's measure (.13) and Nagelkerke's adjusted value (.17) are similar and represent reasonable sized effects. The concordance index C (.658) supports a good monotonic association (where perfect prediction is 1). Bootstrapping techniques were used to validate the final prediction model, i.e., to adjust the estimated model performance and regression coefficients (odds ratios) for overoptimism or overfitting. The inclusion of the additional measured parameters (QST, biomarkers, and genotyping profiles) or the inclusion of the SF36 predictors (when added to the model as a separate domain score or as a summary score) did not improve the model.

Discussion

This study confirmed and extends the existing evidence of the association between surgery and PPSP. The incidence of PPSP is in agreement with those estimates in the literature ranging between 10-60%. We demonstrated that PPSP following lumbar discectomy can be predicted using a limited set of simple preoperative patient characteristics (age, pre-operative pain, and functional status) and devised a clinically relevant multivariable predictive model to describe this association.

We regard the incidence of PPSP reported in this study to be at the higher end of normal and that, in general, the incidence is in agreement with those estimates of the literature varying for pain between 25% and 60% and for sensory disturbances between 20% and 80%. Some of the reasons acknowledged for such a difference in persistent pain estimations is (1) a variety of definitions for persistent postsurgical pain; 2) the retrospective nature of the data collection; and 3) the combination of different procedural groups (8). Our study proposed that a 70% reduction in pain intensity within 3 months following lumbar discectomy surgery only was both practical and relevant to clinical practise. This was based on evidence that 2 months following lumbar discectomy median VAS scores were reduced by 80% and this early assessment point was a reliable predictor of outcome at least in 1-year follow up.

In this demographically homogenous cohort of patients with chronic lumbar radicular pain the multivariable predictive model was based on a combination of 1) prior knowledge of the predictors identified in different patient populations (5,7,11,20,31) and 2) with judicious and informed use of statistical methods (28,32). Uniquely, our model focuses on predicting PPSP in individuals who were known to suffer chronic pain prior to any surgical intervention. Although the presented prognostic model contains 3 different covariates that are partially dependent on each other, the analysis suggests that each individual factor has statistical significance. The addition of extensive preoperative measurements, including SF-36 questionnaires, QST, and genetic or biomarker profiling did not have any added predictive value on the final model.

Patients' Age

An age-related pattern of pain prevalence is mixed and has been reported in many types of pain, including persistent pain (33), recurrent body pains (34) and acute postsurgical pain (28) that peaks in middle age (3,35,36). In some situations younger age is a predictor of persistent pain (3). Several physiological processes have be proposed to explain this increase in age-related pain that our study identifies and include 1) the a degeneration of peripheral neuronal structure (37) that slows transduction and transmission involved in signalling pain (38); 2) a lowering of the density of descending inhibitory circuits (39) and an impaired ability to recover from hyperalgesic or allodynic states (40); and 3) a decline in function of the endogenous antinociceptive mechanisms as well as the capacity to reverse spinal and supraspinal sensitization (41) places older patients at greater risk for developing persistent pain following an illness, surgery, or trauma (42).

Preoperative Pain Intensity

As the presence of pain preoperatively is associated with the development of postoperative pain (5), the emergence of preoperative pain intensity as a significant prognostic covariant in the model was not surprising. It is perceived that chronic noxious afferent input related to the chronic radicular pain, produces neuroplastic changes in the spinal cord (central sensitisation by upregulation of receptor subsystems) that may manifest as a relatively hyperpathic state in the postoperative period. A specific intensity of preoperative radicular or back pain was not required for inclusion because 1) we expected that there would be a large variation in the duration of pain symptoms (Table 2) (43); and 2) we accepted the individuality of each patient's pain.

Nociceptive inputs trigger a prolonged increase in the excitability and synaptic efficacy of neurons in the central nociceptive pathway and results in the phenomenon of central sensitization (10). Studies in a variety of clinical cohorts reveal that changes in pain sensitivity may reflect the development of central sensitization and contribute to the pain phenotype (10). In our study all patients report increased pain prior to their lumbar discectomy suggesting that the signaling in the pain pathway has being altered. The important question that needs to be addressed is whether there are individuals at higher propensity for developing central sensitization than others, and whether this contributes to the development of PPSP.

If the only statistical analysis preformed to estimate the association between each candidate predictor (i.e. preoperative pain) and the clinical outcome was bivariate analysis and Spearman's correlation coefficient, we have wrongly concluded that as there was no significant difference between the 2 groups and the presence of preoperative pain played no role in the development of PPSP. Instead by applying a recognized statistical methodology, such as a multivariable analysis using a logistic backward stepwise regression modeling technique, we identified that the presence of chronic pain preoperatively in the study contributes to the development of PPSP reported in this cohort.

Preoperative Functional Score

The degree of dysfunction pre-operatively is a significant prognostic covariant in the predication model following lumbar discectomy. However, functional status is a patient-referenced concept and differs for each individual, with some patients making higher demands than others (44). In this way the patient is presumed to "calibrate" the instrument (45,46). The RMF questionnaire is a short scientifically validated questionnaire that is best suited to settings in which patients have mild to moderate disability compared to persistent severe disability (4,17). The questionnaire focuses on a limited range of problems that a patient with "back pain" may experience and does not address psychological or social problems. This focused assessment of functionality makes the scores easy to understand and interpret (17), thereby reinforcing the importance in the final predictive model.

Other Co-variants

Despite previous evidence for gender, psychological status, the degree of neurophysiological impairment, and the role of "pain-genes" as possible independent predictors in other pain models, they did not have any added predictive value on the final model. Although the bivariate analysis identified some of these covariants as possible "predictors," this information was the used to position these covariants in a hierarchical approach as part of the logistic backward stepwise regression modeling technique where their ultimate influence on the final model was reduced (24-27).

The Multivariate Predictive Model

The development of a predictive model enables identification of variables that are influential in predicting patient outcome and can be used by clinicians to direct patient treatment and predict patient outcome. Ideally a predictive model is developed based on a combination of prior knowledge of the disease with appropriate statistical methodology. However, many of the multiple steps involved to develop a prognostic model can lead to flawed or biased models if used without good statistical understanding. The aim of the study was to develop a new prognostic model using a combination of 2 or more independent risk factors to predict patient outcome. We focused on study design, definition of outcomes, identifying covariants, and statistical validation methods to develop a robust model.

The simplicity of our prognostic rule represents a fundamental strength because time considerations and potential unavailability of prediction variables represent important reasons for the lack of clinical implementation of more complex tools. Our prognostic rule is devoid of these limitations as it rests on predictors that are invariably available without any additional investigations.

Limitations

The model is designed on a small cohort of patients aged between 18 and 56 years p;d who, apart from suffering chronic pain, were otherwise in good health. Although we were able to quantify the robustness of our scoring rule using bootstrapping techniques, external validation studies in new patients in various clinical settings, with and without underlying co-morbities, are necessary before this preoperative prediction rule can be applied clinically.

There is no clear definition of PPSP in the literature (3). Our study proposed that a 70% reduction in pain intensity within 3 months following surgery was practical and clinically relevant. This was based on evidence that 2 months following lumbar discectomy median VAS scores were reduced by 80% and this early assessment point was a reliable predictor of outcome at least one-year follow-up (43). Extension of the follow-up period was beyond the scope of the present study and could be considered in the future.

We reported a predictive model that can directly be applied to preoperatively classify patients according to their absolute risk of postoperative pain. However, if the overall pain incidence is different from ours (37.7%), the intercept may require adjustments using standard techniques (47).

The apparent lack of influence of genotyping on the final model is most likely due to the small sample size. In an effort to maximize the return from our data pool, we specifically targeted high priority pain genes; however, we recognize that a larger study population will be required to clearly identify the role genotyping has on clinical outcome in the future.

Predicting the sample size calculation to examine a possible correlation between any of the pain-related polymorphisms and clinical outcome is hugely challenging because 1) the allelic frequency has not being settled and 2) the definition of outcome has not being adequately addressed. For example, 168 caucasians undergoing lumbar discectomy were screened for 15 polymorphisms of the GCH1 gene. Stepwise analysis identified a single halpotype with an allelic frequency of 15.4% that was highly associated with low pain scores (P = 0.0009) (48). Published population frequencies for the opioid receptor (OPRMu) of the C17T polymorphism range from 1.5% to 22%, and for the A118G polymorphism, 10–16% (49).

While genetic tests can be bought cheaply, one needs large increases in sample size to detect smaller increases in relative risk (RR) (50). The key question, which will only be answered by multiple studies, is the magnitude of RR conferred by pain-related candidate polymorphisms. If the chronic pain phenotype proves analogous to Crohns' disease or late-onset Alzheimer disease, where single copies of the NOD2 or ApoE4 allele impart an RR of approximately 3, then the collection of several hundred patients will allow thousands of genes to be tested. However, most replicated common variant/common disease associations show RRs between 1.2 and 2.0. RR values of 1.5 or less will require thousands of patients to sensitively search the genome. However, pain researchers should not be discouraged by the latter estimate because RR imparted by a polymorphism can be increased by thoughtful definition of the phenotype. Characterisation of the phenotype similar to the methods used in our study will help deepen our understanding of PPSP.

The study design sought to be as clear as possible with regard to the anaesthesia and analgesic protocols used. A standardized protocol was used to 1) secure ethical committee approval with the delivery of adequate perioperative anesthesia and analgesia; 2) to guide each anaesthetists in order reduce individual viability of practice within the study; and 3) to represent what is likely to occur in clinical practice. We believe that this clarity contributed to the quality of the dataset as there were no breaches of protocol recorded which resulted in loss of recruited patients in the study population.

We accept that it may appear as if a pre-emptive analgesic plan was undertaken. The concept of pre-emptive analgesia to reduce postoperative pain was founded on a series of successful animal experimental studies that demonstrated central nervous system plasticity and sensitization after nociception. Pre-emptive analgesia is defined as an antinociceptive treatment that prevents the establishment of altered central processing of afferent input, which amplifies postoperative pain (51). By decreasing the altered central sensory processing, pre-emptive analgesia is thought to consequently decrease the incidence of hyperalgesia and allodynia after surgery. Whether pre-emptive analgesic interventions are more effective than conventional regimens in managing acute postoperative pain is debated, but what is clear is that the provision of analgesia for a surgical procedure is a fundamental right for each patient. The use of a standardized protocol ensured the delivery of adequate perioperative analgesia, reduced individual viability of practice within the study, and would be expected to represent what is likely to occur in clinical practice. We provide supplementary data

to support this observation. We understand that there will be patient variability in their individual response to the analgesia/pain which is at the centre of the study. This may represent the same variability in the response to chronic pain and the development of PPSP.

With regard to the integration of anticonvulsants etc. as part of the analgesic package, this study was designed and undertaken prior to the availability of this knowledge. Indeed, our group has published on the use of pregabalin in the perioperative period (52,53). The objective of the present study was not focused on confirming the presence or absence of sensitisation but to characterize the parameters related to the development of PPSP.

The influence of surgery is recognized as playing an important role in the possible generation of PPSP. The response of each individual to a surgical insult is variable. In the study surgical time, anesthetic duration, postoperative recovery, and complications were similar in both groups. Some of these data sets were presented in Fig. 1. Post-hoc analysis of the anti-inflammatory response to the surgical insult, as indicated by the rise and fall of serum interleukin-6 (IL-6) levels in the immediate 24 hours following surgery, reflected the "normal" response patterns expected for surgery of this duration and intragroup analysis showed that there was no significant difference in the patterns between the PPSP and nPPSP groups. The results suggest that all patients who underwent a lumbar discectomy in our study were exposed to a similar degree of surgical insult; therefore, the clinical outcome represents the response of each patient.

Conclusion

In this contemporary, prospective study, a number of predictive factors for PPSP were identified and we demonstrated that the occurrence of significant postoperative pain following lumbar discectomy can be predicted with a multivariate prediction equation. Although we were able to quantify the robustness of our prediction model using bootstrapping techniques, external validation studies in new patients in various clinical settings are necessary before this preoperative prediction rule can be integrated into clinical practice. Diagnostic criteria to assist in the phenotyping of patients will identify the best clinical management pathways for patients. We conclude that this predictive model may be useful for patient counseling and for quality assurance, purposes in the modern era of evidence based clinical practice.

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Research Ethics Committee

Approval was granted by the local Research Ethics committee of the Cork University Teaching hospitals for this research project to be undertaken. Everyone in this study signed an informed consent form prior to commencement of the research.

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