PAIN®

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Abstract

It is still unclear how and why some patients develop painful and others painless polyneuropathy. The aim of this study was to identify multiple factors associated with painful polyneuropathies (NeuP). A total of 1181 patients of the multicenter DOLORISK database with painful (probable or definite NeuP) or painless (unlikely NeuP) probable or confirmed neuropathy were investigated clinically, with questionnaires and quantitative sensory testing. Multivariate logistic regression including all variables (demographics, medical history, psychological symptoms, personality items, pain-related worrying, life-style factors, as well as results from clinical examination and quantitative sensory testing) and machine learning was used for the identification of predictors and final risk prediction of painful neuropathy. Multivariate logistic regression demonstrated that severity and idiopathic etiology of neuropathy, presence of chronic pain in family, Patient-Reported Outcomes Measurement Information System Fatigue and Depression T-Score, as well as Pain Catastrophizing Scale total score are the most important features associated with the presence of pain in neuropathy. Machine learning (random forest) identified the same variables. Multivariate logistic regression archived an accuracy above 78%, random forest of 76%; thus, almost 4 out of 5 subjects can be classified correctly. This multicenter analysis shows that pain-related worrying, emotional well-being, and clinical phenotype are factors associated with painful (vs painless) neuropathy. Results may help in the future to identify patients at risk of developing painful neuropathy and identify consequences of pain in longitudinal studies.

Keywords: Painful neuropathy, Painless neuropathy, Neuropathic pain, Machine learning, Pain prediction, PROMs, QST

1. Introduction

Prevalence of chronic pain with neuropathic characteristics ranges between 7% and 10% in the general population, with polyneuropathy being a common cause.[68] Over 100 different causes of polyneuropathy have been identified, including diabetic neuropathies (estimated prevalence of 11%-30%,[1,4,18]) and multiple nondiabetic conditions (ie, alcoholic, associated with endocrine or immune diseases, hereditary, drug or toxin-associated, malignant etc.[31,45,58]). Painful neuropathies can be grouped into symmetrical polyneuropathies, ie, diseases affecting many nerves simultaneously, typically in a length-related glove-and-stocking distribution, asymmetrical neuropathies with

mono- or multiplex distribution, or processes affecting plexuses or single nerves.[58]

It is still unclear why some patients develop painful and others painless polyneuropathies. Because there is no definitive single or overall composite factor that explains individual pain vulnerability in polyneuropathy, surrogate markers potentially associated with mechanisms for pain can be used. One approach is to assess the individual functioning of the somatosensory nervous system (loss of function/gain of function of nociceptive and non-nociceptive sensory modalities) using quantitative sensory testing (QST). The German Research Network on Neuropathic Pain has developed a standardized QST battery that investigates different afferent

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nerve fiber functions and their central pathways[53] to address the hypothesis that different clinical signs reflect different underlying mechanisms.[5] Hierarchical cluster analysis has shown that these mechanism-related sensory profiles can be classified into 3 groups of neuropathic pain profiles: (1) sensory loss, (2) thermal hyperalgesia, and (3) mechanical hyperalgesia.[6]

However, signs and symptoms of polyneuropathy are not restricted to sensory dysfunction but may also include motor and autonomic disturbances.[12] Although some characteristic symptoms may be indicative of certain etiologies of polyneuropathy especially genetic causes, the clinical phenotype usually varies between patients even with the same etiology.[41,64] There is likely a bidirectional relationship between the initiation and maintenance of pain and factors such as genetic variants,[56,57,78] sociodemographic factors,[8,19] physical activity,[21,50] multiple psychosocial,[37,66] and lifestyle factors,[3,59] including sleep problems, life satisfaction, and adverse childhood events, as well as pain-related worrying[65] and emotional functioning (anxiety or depression[39,65]).

The study aimed to identify the various factors that differentiated patients with painful neuropathy from those with painless neuropathy. Therefore, data from self-reported measures, clinical findings, and QST from the Dolorisk database[46] were analyzed with multiple regression analyses and machine learning (ML) models.

2. Methods

2.1. Standard protocol approvals, registrations, and patient consents

The study was approved by the local ethics committees at each participating center. Informed consent was obtained from all participants according to the Declaration of the World Medical Association. The study was registered at clinicaltrials.gov (NCT04888455).

2.2. Study set-up

The DOLORISK consortium recruited patients with neuropathy >18 years of age from tertiary centers between 2016 and 2019. The DOLORISK study protocol has been described by Pascal et al.[46] In short, patients attending tertiary centers for treatment or further evaluation of symptoms of neuropathy underwent phenotyping by different questionnaires and clinical neurological examination including QST according to the German Research Network on Neuropathic Pain,[53] using a shortened protocol (see below). Questionnaires assessed demographic data, pain characteristics, health status, emotional well-being, personality, and lifestyle. Only data of the cross-sectional measures were used for this analysis.

2.3. Patients sample

Data of 1550 patients of the DOLORISK database were screened, and all records extracted that fulfilled the criterion of presence of probable (presence of a combination of symptoms and signs of neuropathy include any 2 or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflexes) or confirmed (presence of an abnormality of nerve conduction or validated measure of small fiber neuropathy with class 1 evidence with corresponding symptoms) neuropathy according to the Toronto Consensus Panel on Diabetic Neuropathy.[20,63] Patients were then further divided into those with painful and painless neuropathy according to the NeuPSIG

algorithm[23]: Patients with probable or definite neuropathic pain were classified as painful neuropathy, and those with unlikely neuropathic pain and without neuropathic pain classified as painless neuropathy. Note that in those patients with painless neuropathy, patients may still experience pain at other locations (ie, headache or musculoskeletal joint pain). Patients with possible neuropathic pain were excluded from analysis because of lack of certainty for neuropathic pain. Also, patients with skin lesions or dermatological disorders in the areas to be tested upon QST, with any painful or neurological comorbidity that could otherwise influence testing results such as vascular disease, radiculopathy, spinal canal stenosis etc. Inclusion was restricted to patients with distal symmetrical polyneuropathy to make the investigated patient sample as homogenous as possible.

2.4. Questionnaires

2.4.1. Demographic data and lifestyle

Age, sex, body mass index (BMI), ethnicity, years in education, family history of chronic pain (whether a first-degree relative report suffering from pain for more than 3 months), etiology of neuropathy, presence of adverse childhood experiences and hospital admissions, smoking, and alcohol habits were assessed. Harmful alcohol consumption was defined as more than 7 drinks per week of 0.5 to 0.6L beer or 0.25 to 0.3L wine or 25 mL spirits for males and more than 3.5 drinks/week of 0.25 to 0.3 L beer or 0.125 to 0.15L wine or 12.5 mL spirits for females according to >140 g (males) resp. >70 g (females) alcohol per week as limit recommended by the German Society for Nutrition.

2.4.2. Pain characteristics

In the group of patients with pain, pain duration, pain course, and chronic pain grade (CPG) according to Von Korff[71] were assessed. Pain severity was assessed by calculating the average of the 4 pain items from Brief Pain Inventory (BPI[14]): "Pain at its worst in the last 24 hours," "Pain at its least in the last 24 hours," "BPI Pain on the average in the last 24 hours," "Pain right now" upon the BPI.

Severity of neuropathic pain was assessed using the Neuropathic Pain Symptom Inventory.[9]

2.4.3. Emotional well-being

The Patient-Reported Outcomes Measurement Information System (PROMIS[13]) questionnaires were used to assess anxiety (PROMIS Short Form v1.0—Anxiety 4a or 6a[48]), depression (PROMIS Short Form v1.0—Depression 4a or 6a[48]), sleep disturbances (PROMIS Short Form v1.0 Sleep Disturbance 4a or 6a[11]), and fatigue (PROMIS Short Form v1.0—Fatigue 4a, 6a, or 8a[36]). Items of these self-report questionnaires have 5 response options ranging from 1 to 5 (1 = not at all, 5 = very much). Sum scores of each scale are converted into a T-Score, resulting in a standardized score with a mean of 50 and a SD of 10 in a reference population. Values > 60 are considered above average. Higher scores reflect problem severity. For example, a T-score of 60 on the depression scale is indicative of a moderate depressed mood.

2.4.4. Personality

The Ten-Item Personality Inventory (TIPI) evaluates 5 personality dimensions (extraversion, agreeableness, conscientiousness,

emotional stability, and openness to experience) with 2 items each. The TIPI norms are based on data collected at https://gosling.psy.utexas.edu/scales-weve-developed/ten-item-personality-measure-tipi/.[29] Higher values are associated with more extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience, respectively.

Of these personality dimension, we aimed to explore the role of emotional stability in more depth, because this personality dimension has been found to be related to the reporting of health complaints and pain.[15,74] For that reason, we also used the 10 item Emotional Stability Scale from the International Personality Item Pool (IPIP[28]). Patients' answer to what extent each item describes themselves using a 5 point scale (1 = "very inaccurate" and 5 = "very accurate"). A sum score is calculated. For the interpretation of individual scores, the mean and SD for a sample of persons (same sex and particular age range) is calculated. Scores within one-half SD of the mean can be interpreted as "average," outside that range as "low" or "high."[33]

Pain-related worrying was recorded through the Pain Catastrophizing Scale (PCS[16,62,75]). It consists of 13 statements describing different thoughts and feelings that may be associated with pain. These statements are to be rated on a 5-point Likert scale (ranging from 0 "not at all" to 4 "all the time"), a total score is obtained by scoring all the items. Higher scores indicate greater pain-related worrying. A total score of 30 is considered a relevant level of pain-related worrying, representing the 75th percentile of PCS scores in clinic samples of patients with chronic pain.

2.5. Clinical examination—severity of neuropathy

During clinical examination, nerve conduction tests and/or skin biopsy were performed to confirm the presence of a length dependent neuropathy using the algorithm of Tesfaye et al.[63] as mentioned above. Upon clinical examination, severity of neuropathy was quantified with the Toronto Clinical Scoring System (TCSS[10]). The TCSS consists of 6 questions for presence of typical symptoms of polyneuropathy and an investigational part that examines muscle tendon reflexes of the lower extremities as well as reaction to different sensory stimuli (pinprick, temperature, vibration, light touch, proprioception) separate on both lower extremities. Two points are awarded for a missing reflex, one point for a weakened reflex, and 0 points for a normal reflex. Abnormal sensory examinations are awarded 1 point, normal ones 0 points. The maximum score is 1 for a simultaneous abnormal sensory sensation on the right and left foot.

Score may range from 0 to 19 (the higher the score, the more symptoms and abnormal findings upon examination). Because the TCSS includes a question for presence of pain that separated the 2 study groups anyway, we excluded this question from the total TCSS score resulting in a possible total score of 18. The TCSS total score was not calculated when one or more items were missing.

2.6. Quantitative sensory testing

All sites underwent strict quality control[69] and an analysis of heterogeneity showed that the database could be analyzed as a homogenous dataset.[70] Quantitative sensory testing was performed unilaterally in the most affected area, and the procedure described by Rolke et al.[53] was followed with some exceptions because of time reasons: First, in case of proven pathological small fiber function, ie, pathological sensory loss detected by warm detection threshold and/or cold detection threshold thermal sensory limen was not be performed

additionally. Second, only 2 repetitions for each stimulus were performed upon stimulus-response function for the assessment of mechanical pain sensitivity and dynamic mechanical allodynia. Before the start of the study, each center was trained for use of the protocol.

For evaluation of individual QST measurements, data were compared to a reference database of healthy controls[40,47,53] and z-scores calculated. Z-Score (mean = 0, SD = 1) values indicate hypo- or hyperfunction of the subject's sensitivity for each parameter as compared with the mean of age- and sex-matched controls. The 95% confidence interval of controls is between −1.96 and +1.96. Z-values above "0" are indicative of hyperfunction, that is, patients are more sensitive to the tested parameter compared to controls (lower thresholds). Z-scores below "0" are indicative of hypofunction and, therefore, a loss of or lower sensitivity of the patient compared to controls (higher thresholds). To determine the sensory phenotype (sensory loss, thermal hyperalgesia, mechanical hyperalgesia) of each patient, we used the algorithm proposed by Baron et al.[6]

2.7. Statistical analysis

2.7.1. Descriptive statistics

The distribution of variables was investigated separately for the 2 subgroups painful/painless neuropathy. Continuous variables are expressed as mean values ± SD. Categorical data are presented by absolute frequencies and/or percentages.

2.7.2. Inferential statistics and predictive modelling

To identify the most powerful variables associated with painful polyneuropathy and to classify patients according to these variables, multivariate logistic regression (MLR) as well as random forest were conducted—for further details, see below.

2.7.3. Multivariate logistic regression

A MLR including all variables (age, sex, BMI, family history of chronic pain, PROMIS anxiety, depression, fatigue and sleep T-Scores, previous traumatic events and hospital stays, TIPI subscores for extraversion, agreeableness, conscientiousness, emotional stability, openness, emotional stability score, PCS total score, TCSS total score, etiology of neuropathy, years of education, QST Cluster, as well as smoking and alcohol habits) was performed to investigate their influence on the pain status (painful or painless neuropathy). Because of missing values, missing imputation was performed by multivariate imputation by chained equations (MICE). Multiple (m = 25) complete data sets were derived by chained equations to account for uncertainty because of the missing information. Multivariate logistic regression models were applied on all complete data sets to determine final results by aggregating individual results according to Rubin rule.[55,67]

To estimate performance of prediction for unseen data, the "Leave-one-out"-method was used. For each participant, the logistic regression model was derived based on the remaining 1180 subjects and the resulting model used to predict the probability of painful neuropathy for the subject, who was left out during the training. If this probability was above 50%, the participant was classified as "painful neuropathy," otherwise as "painless neuropathy." This procedure was repeated for all 1181 subjects. The relative frequency of correct classifications is referred to as the accuracy. To make results comparable to the ML procedure random forest, this and other standard ML-

performance metrics (accuracy, balanced accuracy, F1, and Kappa) were derived. To correct for imbalanced data (painful neuropathy: 843, painless neuropathy: 338), additionally to accuracy, the balanced accuracy and F1 statistics were derived. The balanced accuracy is the mean of the 2 relative frequencies of positive and negative cases identified correctly. The F1 statistics, commonly used in ML in case of imbalanced data, is defined as:

$$F1 = 2 \times (recall \times precision)/(recall + precision)$$

Additionally, the Kappa-coefficient was determined to assess the level of agreement between predictions and true neuropathy status (painful/painless), correcting for random agreement.

2.7.4. Machine learning

As a second method, ML, more specifically random forest, was used for the identification of predictor variables and risk estimation of painful neuropathy. The advantage of random forest compared to MLR with MICE is that random forest also recognizes nonlinear relationships.

A random forest with 500 trees was applied on the data. The 500 random samples of the usual 63.2% of observations were used to fit 500 decision trees. The remaining observations form the out-of-bag set and enable assessing performance on unseen data similar to the leave-one-out technique described above. Additionally, variable importance was assessed to determine how important different variables are for classifying the neuropathy status correctly. As the regular classification and regression trees are biased toward continuous variables and variables with many categories, unbiased conditional inference trees were used to account for the situation of different variable types.[32] The same 4 performance metrics as for logistic regression were assessed for random Forest (ie, accuracy, balanced accuracy, F1, and Kappa).

2.7.5. General

$P < 0.05$ was considered statistically significant; thus, the significance level was not adjusted for multiplicity. The statistical analyses were conducted using the statistical software R.

3. Results

Data from 1181 participants were included in the analysis (**Fig. 1**). Approximately 2 thirds of patients were males. A total of 1061 (89.8%) had a confirmed neuropathy, 120 (10.2%) a probable neuropathy according to Tesfaye et al.[63] A total of 843 (71.4%) of patients had a painful neuropathy (see also **Tables 1–3**), and 338 (28.6%) patients had a painless neuropathy (**Tables 2 and 3**).

The most affected area (99.5% of patients) was the feet. Most of the patients were Caucasian (99.1%) and suffered from diabetic neuropathy (73.8%).

According to the QST, the majority of patients was allocated to the sensory loss phenotype (>50%), followed by the mechanical hyperalgesia phenotype in app. 26% and the thermal hyperalgesia phenotype in app. 19%.

3.1. Painful neuropathy

Pain characteristics of patients with painful neuropathy are shown in **Table 1**. More than 80% had experienced pain for at least 1 year with a high number of patients being only minor impaired according to the CPG (app. 45%, CPG 1 and 2,

Table 1). More than 60% were living with persistent pain with or without paroxysmal attacks (**Table 1**). About 56.1% of patients reported taking pain medication. Of these, 78.2% were treated according to current treatment recommendations for neuropathic pain,[22] ie, had anticonvulsants, antidepressants, topicals, or opioids.

3.2. Painless neuropathy

Thirty-seven (app. 11%) of the patients classified as painless reported to suffer from pain of other origin. Of these, 81% reported that they had not suffered from pain within the last 24 hours (BPI), and 77.7% reported that they had not suffered from pain within the last 7 days (BPI) or 4 weeks (BPI). Mean pain intensities were 0.54 ± 1.2, range 0 to 5 NRS (numeric rating scale with zero meaning "no pain" and 10 meaning "the worst pain imaginable") for pain within the last 24 hours; 0.6 ± 1.6, range 0 to 6 NRS for pain intensity within the last 7 days; and 0.75 ± 1.7, range 0 to 9 NRS for pain intensity with the last 4 weeks in the group with painless neuropathy.

3.3. Comparison of patients with painful and painless neuropathy

Compared with painless patients, those reporting painful neuropathy were younger, had a higher BMI, a more severe neuropathy, and were less likely to have diabetic neuropathy and more likely to have idiopathic neuropathy. They also had a higher frequency of pain in their family, higher depression and anxiety scores, more sleep problems and fatigue, were less extraverted and emotional stable, and showed higher levels of pain-related worrying. Finally, they also reported less current or previous misuse of alcohol and a higher number of packyears of smoking compared to patients with painless neuropathy (**Tables 2 and 3**). The frequency of the different sensory clusters (loss, mechanical and thermal hyperalgesia) was similar in both groups (**Table 2**).

3.4. Risk estimation for painful neuropathy using multivariate logistic regression

Multivariate logistic regression with MICE demonstrated that neuropathy severity (TCSS total score, $P < 0.0001$), etiology of neuropathy (presence of idiopathic neuropathy including patients with only small-fiber neuropathy, $P < 0.0001$), presence of chronic pain in family ($P < 0.0001$), PROMIS Depression ($P = 0.0383$), Fatigue T-Score ($P = 0.005$), and PCS total score ($P = 0.0003$) were the most important parameters associated with the presence of pain in neuropathy (**Table 4**).

The results for the 4 performance metrics, accuracy, balanced accuracy, F1, and Kappa, are illustrated in **Table 5**. Using the logistic regression for predicting painful or painless neuropathy, an accuracy of 78% is achieved, which means that almost 4 out of 5 patients will be classified correctly.

3.5. Risk estimation for painful neuropathy using machine learning

Random forest revealed almost the same variables accounting for the presence of painful neuropathy compared to MLR suggesting that results of this analysis are robust (**Fig. 2**).

Using random forest with 500 trees for predicting painful or painless neuropathy, an accuracy of 76% is achieved; thus, more than 3 out of 4 patients will be classified correctly (**Table 5**). The
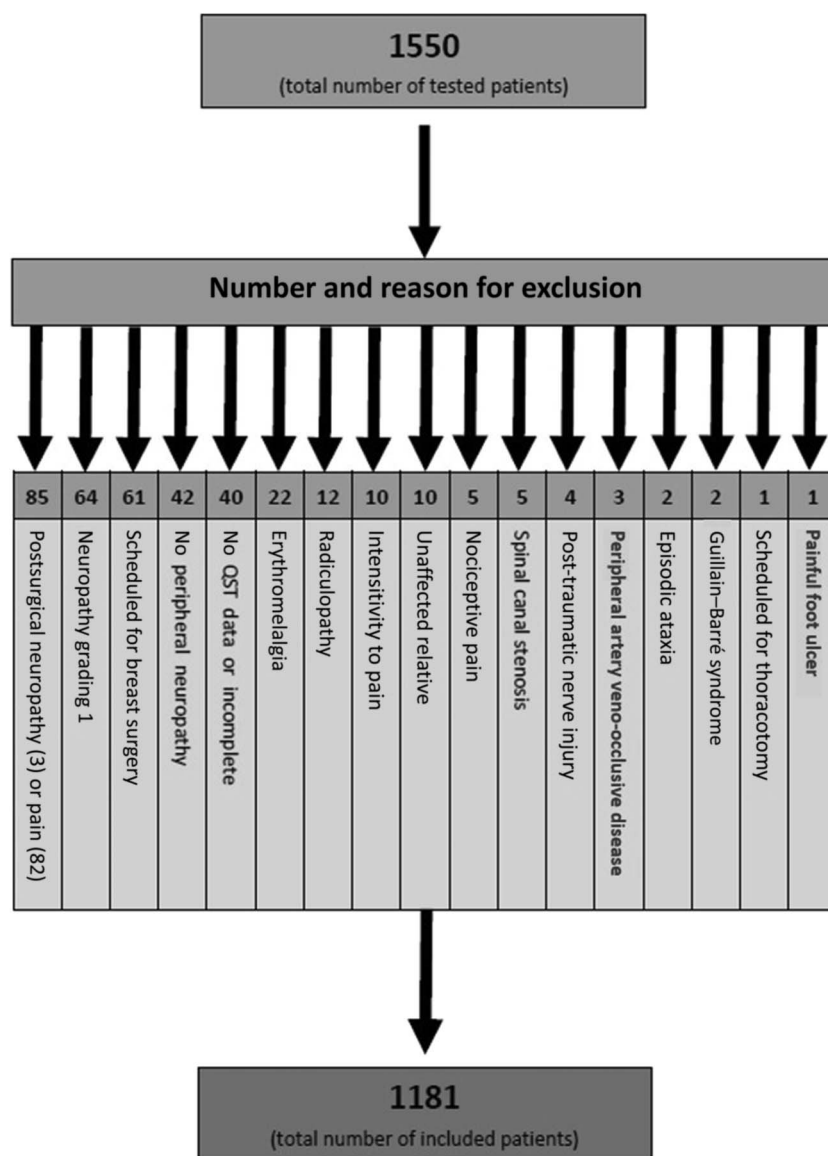
Figure 1. STROBE flowchart of included patients from the DOLORISK database. GBS, Guillan–Barré syndrome; PAVK, Peripheral artery disease; STROBE, Strengthening the Reporting of Observational studies in Epidemiology.

analysis on variable importance also determined the PCS total score, etiology of neuropathy, TCSS total score, presence of chronic pain in family, PROMIS Depression, and PROMIS Fatigue T-Scores as the most relevant.

3.6. Goals and meaning of the different statistical prediction models

Among a vast variety of different candidates, the most meaningful variables for predicting painful or painless neuropathy were identified as mentioned above. Subsequently, the identified variables were combined to actually classify neuropathy (painful/painless). For these purposes, 2 different statistical models were applied for robustness.

Logistic regression models the probability of painful neuropathy in a linear fashion, allowing to express the relationship between predictors and outcome in a closed (ie, direct and explicit) form. For our reduced model, the following formula results for the probability (P) of a painful neuropathy:

$$P = \frac{\exp{(Z)}}{\exp(1 + Z)}, \text{with}$$

$$\begin{aligned} Z = {} & -4.81 + 1.25 \, PainFamily + 0.03 \times PROMISDepression \\ & + 0.045 \times PROMISFatigue + 0.033 \, PCS + 0.109 \, TTS \\ & - 0.076 \times Etiology\ of\ neuropathy : Chemotherapy \\ & - induced + 1.50 \times Etiology\ of\ neuropathy : idiopathic \\ & + 0.82 \times Etiology\ of\ neuropathy : other \end{aligned}$$

History of chronic pain in family are coded No = 0, Yes = 1. Etiology of neuropathy is dummy-coded; thus, if neither chemotherapy-induced, idiopathic or other is true, a 0 has to be inserted for all 3 variables. For example, a subject with presence of chronic pain in the family (PainFamily = 1), a PROMIS Depression and Fatigue score of 55 and 51, respectively, a PCS total score of 20, a TCSS of 11, and a chemotherapy-induced neuropathy (thus the other dummy-variables 0) has an estimated probability of a painful neuropathy of 91.1%.

Table 1

Pain characteristics of patients with painful neuropathy (n = 843).

BPI Pain Severity (mean ± SD [range]), n = 685	4.1 ± 2.4 (0-10)
NPSI total score (mean ± SD [range]), n = 762	29.6 ± 20.9 (0-95)
Pain course (n = 769), n (%)	
Persistent pain with slight fluctuations	198 (23.5%)
Persistent pain with pain attacks	316 (37.4%)
Pain attacks without pain between them	255 (30.2%)
Duration of pain (n = 792), n (%)	
Less than 1 month	9 (1.1%)
1-3 months	8 (0.9%)
3-12 months	64 (7.6%)
1-5 years	371 (44.0%)
More than 5 years	340 (40.3%)
Chronic pain grade (n = 509), n (%)	
Low disability—low intensity	220 (26.1%)
Low disability—high intensity	158 (18.7%)
High disability—moderately limiting	58 (6.9%)
High disability—severely limiting	73 (8.7%)

Note that both, BPI and NPSI, ask for a rating of pain within the last 24 hours; thus, it is possible to have a sum score of "0" (in case of presence of only intermittent pain that has not been present within the last 24 hours). BPI, Brief Pain Inventory; NPSI, Neuropathic Pain Symptom Inventory.

Random forest generates 500 decision trees based on the described random samples of observations. Future subjects follow the branches of all 500 trees according to their individual patient characteristics. For example, a decision node of a tree might check whether "PCS total score <15." If this is true, the subject follows the left branch; if false, the right branch and continue to the next decision node in that tree. Each subject thus ends up in 500, potentially different, final nodes, so-called "leafs." Each leaf represents a classification for painless or painful

neuropathy. The overall final classification is made by a majority vote. Variables meaningful for the prediction are identified by their importance regarding all 500 trees.

Thus, both procedures fulfil both goals of identifying meaningful variables and allowing to predict the outcome, ie, painful or painless neuropathy, based on the identified variables.

4. Discussion

We conducted a multicenter, cross-sectional analysis integrating and investigating clinical and sensory phenotype as well as extensive and detailed demographic and family data, personality, individual differences, emotional well-being, and life-style variables for the prediction of painful neuropathy. Both analyses, MLR and ML, revealed that neuropathy severity and idiopathic etiology as well as family history of pain, pain-related worrying, depressed mood, and fatigue are associated with painful neuropathy.

While logistic regression models the probability of painful neuropathy in a linear fashion, allowing to express the relationship between predictors and outcome in a closed (ie, direct and explicit) form, random forest generates 500 decision trees based on the described random samples of observations. Future subjects follow the branches of all 500 trees according to their individual patient characteristics. For example, a decision node of a tree might check whether "PCS total score <15." If this is true, the subject follows the left branch; if false, the right branch and continue to the next decision node in that tree. Each subject thus ends up in 500, potentially different, final nodes, so-called "leafs." Each leaf represents a classification for painless or painful neuropathy. The overall final classification is made by a majority vote. Variables meaningful for the prediction are identified by their importance regarding all 500 trees. Thus, both procedures fulfil

Table 2

Clinical and demographic characteristics of patients with painful and painless neuropathy.

	All (n = 1181)	Painful neuropathy (n = 843)	Painless neuropathy (n = 338)	*P*
Age (y; mean ± SD [range])	65.8 ± 12.0 (19-92)	64.9 ± 12.4 (19-92)	68.1 ± 10.6 (19-87)	**<0.0001**
Sex, n (%)				
Males	776 (65.7%)	558 (66.2%)	218 (64.5%)	0.63
Females	405 (34.3%)	285 (33.8%)	120 (35.5%)	
BMI (mean ± SD [range]	29.1 ± 5.8 (14.9-67.9)	29.3 ± 5.9 (14.9-67.9)	28.6 ± 5.6 (18.8-58.1)	**0.049**
Ethnicity, n (%)	1001 (84.8%)	697 (82.7%)	304 (89.9%)	0.26
Asian	55 (4.7%)	41 (4.9%)	14 (4.1%)	
Black	33 (2.8%)	27 (3.2%)	6 (1.8%)	
White	992 (76.4%)	620 (73.6%)	282 (83.4%)	
Other	11 (0.9)	9 (1.1%)	2 (0.6%)	
Etiology of polyneuropathy, n (%)	1170 (99.1%)	839 (99.5%)	331 (97.9%)	**<0.0001**
Diabetic	872 (73.8%)	585 (69.4%)	287 (84.9%)	
Chemotherapy induced	55 (4.7%)	33 (3.9%)	22 (6.5%)	
Idiopathic	196 (16.6%)	179 (21.2%)	17 (5.0%)	
Other*	47 (4.0%)	42 (5.0%)	5 (1.5%)	
Toronto Total Score, n (%)†	1175 (99.5%)	839 (99.5%)	336 (99.4%)	**<0.001**
Mean ± SD (range)	9.36 ± 4.22 (0-18)	9.89 ± 4.19 (0-18)	8.03 ± 3.82 (1-18)	
QST cluster, n (%)	1173 (99.3%)	840 (99.6%)	333 (98.5%)	0.98
Mechanical hyperalgesia	303 (25.7%)	218 (25.9%)	85 (25.1%)	
Sensory loss	651 (55.1%)	466 (55.3%)	185 (54.7%)	
Thermal hyperalgesia	219 (18.5%)	156 (18.5%)	63 (18.6%)	

* Etiologies of other neuropathies include alcoholic neuropathy, Vit. B12-deficiency, hereditary neuropathy.
† For the Toronto Total Score, the question for presence of pain was excluded from the total score resulting in a maximum score of 18 instead of 19.[43]
QST, quantitative sensory testing.
P (significance) refers to painful vs painless neuropathy.

Table 3

Questionnaire results of patients.

	All (n = 1181)	Painful neuropathy (n = 843)	Painless neuropathy (n = 338)	P
Years in education, n (%)	723 (61.2%)	522 (61.9%)	201 (59.5%)	0.14
Mean ± SD (range)	13.4 ± 4.7 (3-74)	13.3 ± 5.0 (3-74)	13.8 ± 3.7 (3-28)	
Current or previous alcohol misuse, n (%)*	758 (64.2%)	550 (65.2%)	208 (61.1%)	**0.0022**
No	663 (56.1%)	494 (58.6%)	169 (50%)	
Yes	95 (8.0%)	56 (6.6%)	39 (11.5%)	
Smoking yes/no, n (%)	756 (64.1%)	550 (65.2%)	206 (76.9%)	0.164
Packyears; (mean ± SD [range])	11.2 ± 24.8 (0-247.5)	12.2 ± 26.4 (0-247.5)	8.5 ± 19.9 (0-171.5)	**0.0395**
Family history of chronic pain, n (%)	1069 (90.5%)	748 (88.7%)	321 (95%)	**<0.001**
No	819 (76.6%)	531 (71.0%)	288 (89.7%)	
Yes	250 (23.4%)	217 (29.0%)	33 (10.3%)	
Previous traumatic events, n (%)	739 (62.6%)	534 (63.3%)	205 (60.7%)	0.36
None	514 (69.6%)	363 (68.0%)	151 (73.7%)	
Yes, 1	137 (18.5%)	105 (19.6%)	32 (15.6%)	
Yes, 2	40 (5.4%)	32 (6.0%)	8 (3.9%)	
Yes, more than 2	48 (6.5%)	34 (6.4%)	14 (6.8%)	
Long hospital periods before the age of 18, n (%)	738 (62.5%)	532 (63.1%)	206 (61%)	0.48
No	636 (86.2%)	455 (85.5%)	181 (87.9%)	
Yes	102 (13.8%)	77 (14.5%)	25 (12.1%)	
PROMIS depression, n (%)	77 (48.9%)	408 (48.4%)	169 (50%)	
T-score (mean ± SD [range])	50.0 ± 9.7 (38.2-81.3)	52.0 ± 9.7 (38.2-81.3)	45.3 ± 7.9 (38.2-68.7)	**<0.001**
Abnormal result, n, (%)	89 (15.4%)	82 (20.1%)	7 (4.1%)	**<0.001**
PROMIS anxiety, n (%)	520 (44%)	357 (42.3%)	163 (48.2%)	
T-score (mean ± SD [range])	49.4 ± 10.6 (37.1-83.1)	51.1 ± 11.0 (37.1-83.1)	45.6 ± 8.6 (37.1-70.8)	**<0.001**
Abnormal result, n (%)	79 (15.2%)	71 (19.9%)	8 (4.9%)	**<0.001**
PROMIS sleep, n (%)	571 (48.3%)	404 (47.9%)	167 (49.4%)	
T-score (mean ± SD, [range])	50.9 ± 9.7 (28.9-76.5)	52.3 ± 9.7 (28.9-76.5)	47.4 ± 8.6 (28,9-76.5)	**<0.001**
Abnormal result, n (%)	91 (15.9%)	79 (19.6%)	12 (7.2%)	**<0.001**
PROMIS fatigue, n (%)	439 (37.2%)	342 (40.6%)	97 (28.7%)	
T-score (mean ± SD, [range])	55.81 ± 10.9 (40.7-78.3)	57.8 ± 10.4 (40.7-78.3)	49.0 ± 9.6 (40.7-77.0)	**<0.001**
Abnormal result, n (%)	174 (39.6%)	159 (46.5%)	15 (15.5%)	**<0.001**
TIPI extraversion, n (%)	688 (58.3%)	495 (58.7%)	193 (57.1%)	
Mean ± SD (range)	4.1 ± 1.5 (1-7)	4.0 ± 1.5 (1-7)	4.2 ± 1.6 (1-7)	**0.041**
Highly extraverted, n (%)	102 (14.8%)	64 (12.9%)	38 (19.7%)	**0.025**
TIPI agreeableness, n (%)	686 (58.1%)	491 (58.2%)	195 (57.7%)	
Mean ± SD (range)	5.1 ± 1.3 (1-7)	5.0 ± 1.3 (1-7)	5.2 ± 1.2 (1.5-7)	0.20
High agreeableness, n, (%)	83 (12.1%)	66 (13.4%)	17 (8.7%)	0.09
TIPI conscientiousness, n (%)	692 (58.6%)	497 (59%)	195 (57.7%)	
Mean ± SD (range)	5.6 ± 1.3 (1-7)	5.6 ± 1.3 (1-7)	5.7 ± 1.2 (2-7)	0.28
High conscientiousness, n (%)	166 (24.0%)	118 (23.7%)	48 (24.6%)	0.81
TIPI emotional stability, n (%)	694 (58.8%)	498 (59%)	196 (58%)	
Mean ± SD (range)	5.0 ± 1.5 (1-7)	4.9 ± 1.5 (1-7)	5.2 ± 1.5 (1-7)	**0.009**
High emotional stability, n (%)	188 (27.1%)	128 (25.7%)	60 (30.6%)	0.19
TIPI openness, n (%)	693 (58.7%)	498 (59%)	195 (57.7%)	
Mean ± SD (range)	4.9 ± 1.4 (1-7)	4.9 ± 1.4 (1-7)	4.9 ± 1.2 (1-7)	0.50
High openness, n (%)	55 (7.9%)	44 (8.8%)	11 (5.6%)	0.16
IPIP emotional stability, n (%)	695 (58.8%)	499 (59.2%)	196 (58%)	
Mean ± SD (range)	34.1 ± 8.9 (10-50)	33.1 ± 8.9 (10-50)	36.7 ± 8.2 (14-50)	**<0.001**
PCS, n (%) (mean ± SD, [range])	1061 (89.8%)	716 (84.9%)	300 (88.8%)	
Total	14.9 ± 13.2 (0-52)	17.7 ± 13.5 (0-52)	8.2 ± 9.7 (0-39)	**<0.001**
PCS rumination	5.4 ± 4.9 (0-16)	6.3 ± 4.9 (0-16)	3.4 ± 4.1 (0-16)	**<0.001**
PCS magnification	3.2 ± 3.0 (0-12)	3.8 ± 3.1 (0-12)	1.8 ± 2.2 (0-11)	**<0.001**
PCS helplessness	6.4 ± 6.3 (0-24)	7.7 ± 6.5 (0-24)	3.0 ± 4.2 (0-19)	**<0.001**

* Defined as more than 7 drinks per week of 0.5 to 0.6 L beer or 0.25 to 0.3 L wine or 25 mL spirits for males and more than 3.5 drinks/week of 0.25 to 0.3 L beer or 0.125 to 0.15 L wine or 12.5 mL spirits for females.
IPIP, The 10-item International Personality Item Pool's; PCS, Pain Catastrophizing Scale; PROMIS, Patient-Reported Outcomes Measurement Information System; TIPI, Ten-Item Personality Inventory.
P (significance) refers to painful vs painless neuropathy.

Table 4

Final results of the multivariate logistic regression with multivariate imputation by chained equations.

	Coefficient	P
Presence of chronic pain in family	1.2464	<0.0001
PROMIS depression T score	0.0304	**0.0383**
PROMIS fatigue T score	**0.0454**	**0.0051**
PCS total score	**0.0334**	0.0003
Toronto total score	**0.109**	**<0.0001**
Diagnosis of neuropathy: chemotherapy induced	−0.0755	0.8254
Diagnosis of neuropathy: idiopathic	**1.4973**	**<0.0001**
Diagnosis of neuropathy: other*	0.8155	0.1326

This table show the regression coefficients and their respective P-values of all variables included in the multivariate logistic regression model investigating their influence on pain status (painful or painless neuropathy). A positive coefficient represents an increased probability of painful neuropathy with increasing value of the respective variable.
Note that chemotherapy-induced neuropathy has a negative algebraic sign, meaning that this is not a risk factor for painful neuropathy but rather induced painless neuropathy in our sample.
* Diagnosis of neuropathy "other" includes alcoholic neuropathy, Vit. B12-deficiency, hereditary.
IPIP, International Personality Item Pool's; MICE, multivariate imputation by chained equations; PROMIS, Patient-Reported Outcomes Measurement Information System; PCS, Pain Catastrophizing Scale; TIPI, Ten-Item Personality Inventory.

both goals of identifying meaningful variables and allowing to predict the outcome, ie, painful or painless neuropathy, based on the identified variables.

In the present study, polyneuropathy was defined using the criteria according to the Toronto Consensus Panel on Diabetic Neuropathy,[63] neuropathic pain according to the NeuPSIG definitions,[23] and the TCSS[10] for severity of neuropathy. As various clinician-rated measures that incorporate neuropathy signs exist, it is not clear which of these measures performs best for various polyneuropathy phenotypes.[24] Results might have been different if other classifications would have been used.

Some of the factors associated with painful neuropathy have already been shown to be risk factors associated with chronic pain or are well known to modulate pain perception such as pain-related worrying and emotional well-being,[27,44,54,61] larger areas of hypoesthesia after surgery,[2] family history of body pain,[76] or obesity.[60,61] A unique feature of this study, however, is the integration of sensory phenotype as well as extensive and detailed demographic and family data, personality, emotional well-being, and life-style variables. Our analysis identified some unique factors associated with painful neuropathy. Although the use of a cross-sectional design does not allow cause–effect inferences, our findings may provide input to research specifically focusing upon causal inference.[17] These results may then help to identifying patients at risk for the development of painful

Table 5

Final results of the logistic regression and random forest analysis by comparison.

	Logistic regression	Random forest
Accuracy	0.7772	0.7612
Kappa	0.4094	0.4082
Balanced accuracy	0.6891	0.7016
F1	0.5536	0.5740

This tables demonstrates and compares the performance of the 2 statistical analyses applied to classify pain status (painless or painful neuropathy). Because of imbalance of the classes in addition to the accuracy (overall relative frequency of correct classifications) and Kappa-statistics, the balanced accuracy (arithmetic mean of relative frequencies of correct classifications of both classes) and F1 statistics are shown (see Methods section for details). Higher values indicate better performance, max. value is 1 (100%).

neuropathy in clinical practice. Our findings are promising in this regard: our final algorithms allow to classify patients with painful neuropathy in almost 4 out of 5 cases.

Supporting our findings, a recent study testing ML approaches including random forest applied to questionnaire data only in people with diabetic neuropathy also found that depression and personality traits were of value in classifying painful (vs painless) diabetic neuropathy in addition to the metabolic factors HBA1C and BMI.[7]

In this study, factors from each dimension of the biopsychosocial model of pain were associated with neuropathic pain: biological factors (severity of neuropathy, etiology), psychological factors (depression, fatigue, anxiety, pain-related worrying), as well as social factors (pain in family). This strengthens the importance to not only focus on one of these 3 factors in the risk evaluation for chronic pain, ie, to consider the patient not only in terms of the biological causes of pain, but also in terms of his or her emotional state and social environment. This might be useful not only for diagnostic settings but also for therapy evaluation.[26,49]

Comparison of patients with painful and painless neuropathy revealed that patients with painful neuropathy were slightly younger and not as extraverted and emotional stable than patients with painless neuropathy. Often older age is thought to be associated with a risk for the development of chronic pain such as in postherpetic neuralgia,[30,38,73] but there are also several prospective and retrospective studies that have demonstrated that younger age is associated with the presence of chronic pain.[35,52,72] The exact mechanisms how age influences pain are still unclear. While a reduced immune system in the elderly and age-related changes of the nociceptive system because of, for example, a diminished supply of neurotrophic factors and thus a higher susceptibility to neuropathy-inducing insults might add to the risk for postherpetic neuralgia in older people,[51] other factors, ie, psychological or social might be more important than biological reasons for the risk of chronic pain in younger patients. This again strengthens the importance to regard pain in a biopsychosocial context. However, it is noteworthy that age did not turn out to be an important predictor in the final multivariate model.

Of note, almost half of the patients with painful neuropathy reported low levels of pain-related disability measured with CPG. This fits well with the observation that the influence on daily life does not result from CPG or pain intensity.[25]

Interestingly, in this study, diabetes did not turn out as a risk factor for painful neuropathy—the frequency of diabetic neuropathy was even lower than in patients with painful neuropathy. Unfortunately, we did not ask for previous pain conditions during the course of diabetes. It might be possible that painful neuropathy in some patients moved to painless neuropathy in the course of disease. However, this can only be investigated in prospective longitudinal studies and not in a cross-sectional study like the one performed here. So far, few longitudinal studies are available; one recently published study interestingly showed an increased number of patients with pain in diabetic neuropathy upon 5-year follow-up.[77] Thus, it seems also necessary for future studies to investigate stability of clinical phenotypes over the years.

5. Limitations

Our aim was to investigate the factors that are associated with painful neuropathy and not for the occurrence of pain overall. Our categorization of painful and painless neuropathy (see methods)
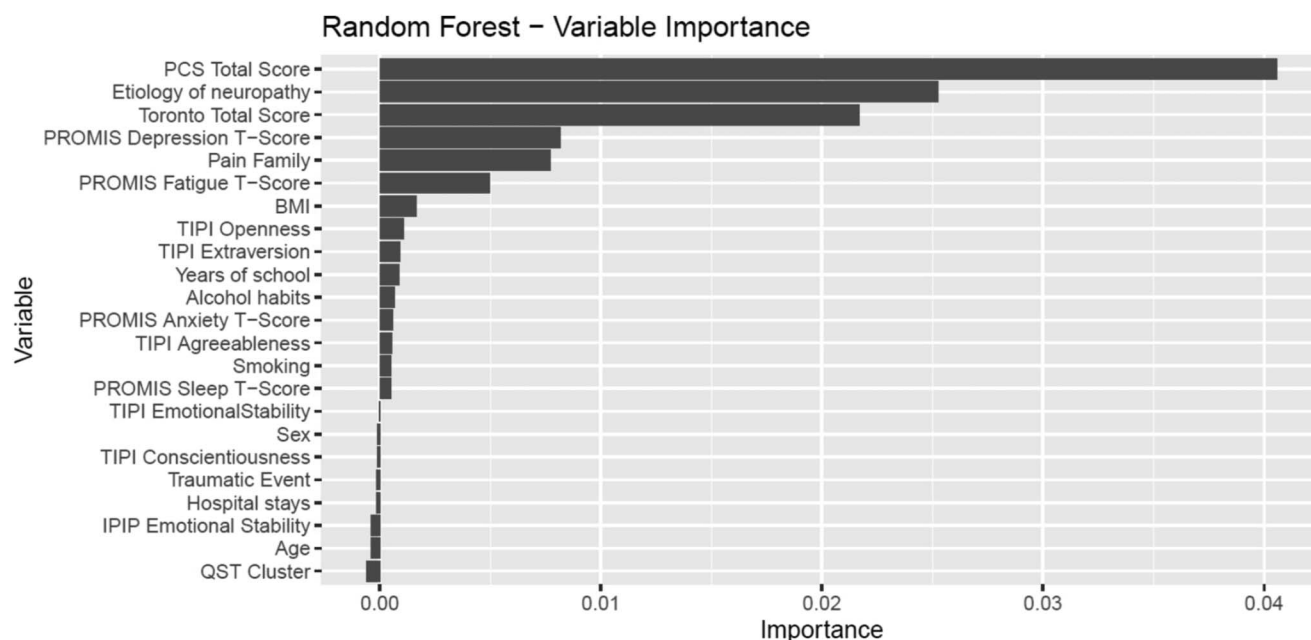
Figure 2. Importance of variables for the presence of painful neuropathy. This figure illustrates the variable importance (VI) of variables included in the random forest analysis to classify pain status (painless or painful neuropathy), ranked from highest importance to lowest. Higher VI demonstrates a stronger contribution to the accuracy (relative frequency of correct classifications) and thus a higher relevance for classifying pain status compared to variables with a lower VI.

did not take into account other forms of pain. It may well be that these other forms of pain may have impacted our results. Pain, regardless of whether it is neuropathic or not,[43] has an impact of mood and quality of life. Nevertheless, we attempted to minimize that bias by excluding patients with other pain conditions in the area of neuropathy. Also, all included patients were instructed to fill out the questionnaires with regard to the symptoms of neuropathy.

Our study design was cross-sectional, and it may well be that some factors may be consequences rather than antecedents of chronic pain, eg, depressed mood and pain-related worrying. Results should be interpreted with care and confirmed in an independent prospective longitudinal study, taking into account possible biases. This, however, is difficult in polyneuropathy because with the exception of chemotherapy-induced neuropathy, where a possible trigger of neuropathy allows for prospective investigation, the onset of neuropathy is often insidious and no starting point can be determined. Additionally, even in chemotherapy-induced neuropathy, prior existing risk factors for a manifestation of neuropathy have been demonstrated such as obesity, smoking, alcohol, nutritional deficiencies, and a poorly controlled diabetes,[34,42] ie, here too there are individual differences present before an identical possible trigger of a neuropathy, which makes a comparison of patients difficult.

Furthermore, the participating centers in this study are specialized in pain treatment, and since about 2 thirds of the patients in this study had a painful neuropathy, there is a potential recruitment bias.

Regarding family history of chronic pain, we accept that there may be a reporting bias as we did not have the capacity to independently corroborate with the affected family member unless they had been independently recruited to DOLORisk.

Additionally, some etiologies of neuropathy, eg, diabetes, might be more severely affected in health status because of the numerous body systems affected by diabetes, which might distort the results. Furthermore, we cannot exclude an influence of medication on questionnaire results such as, for example, treatment with antidepressants.

6. Conclusion

The knowledge of associated factors for chronic neuropathic pain is important. Neuropathic pain is likely to arise from a complex interaction of biopsychosocial factors. We have made a first step to predict the probability of painful neuropathy classification through multiple statistical analyses. Knowing individual risk might help in the future to prevent the onset of pain by early interventions.

Further multicenter and longitudinal prospective studies are necessary to confirm our results and understand the causal relationships between the factors that we have identified in this cross-sectional cohort and neuropathic pain development and progression.

Conflict of interest statement

A.S.C.R. reports the following interests occurring in last 24 months: A.S.C.R. undertakes consultancy and advisory board work for Imperial College Consultants—A.S.C.R. undertakes consultancy and advisory board work for Imperial College Consultants—in the last 36 months, this has included remunerated work for Abide, Confo, Vertex, Pharmanovo, Lateral, Novartis, Mundipharma, Orion, Shanghai SIMR BiotechAsahi Kasei, Toray & Theranexis. A.S.C.R. was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015. The final payment was made in 2019. A.S.C.R. is named as an inventor on patents: A.S.C.R., Vandevoorde S., and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain. WO 2005/079771. Okuse K et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/

Acknowledgement

References

[1] Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care 2011;34:2220–4.

[2] Andersen KG, Duriaud HM, Kehlet H, Aasvang EK. The relationship between sensory loss and persistent pain 1 year after breast cancer surgery. J Pain 2017;18:1129–38.

[3] Anke A, Damsgard E, Røe C. Life satisfaction in subjects with long-term musculoskeletal pain in relation to pain intensity, pain distribution and coping. J Rehabil Med 2013;45:277–85.

[4] Argoff CE, Cole BE, Fishbain DA, Irving GA. Diabetic peripheral neuropathic pain: clinical and quality-of-life issues. Mayo Clin Proc 2006;81(4 Suppl):S3–11.

[5] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. Lancet Neurol 2010;9:807–19.

[6] Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, Finnerup NB, Haanpaa M, Hansson P, Hullemann P, Jensen TS, Freynhagen R, Kennedy JD, Magerl W, Mainka T, Reimer M, Rice ASC, Segerdahl M, Serra J, Sindrup S, Sommer C, Tolle T, Vollert J, Treede RD; German Neuropathic Pain Research Network DFNS and the EUROPAIN and NEUROPAIN consortia. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. PAIN 2017;158:261–72.

[7] Baskozos G, Themistocleous AC, Hebert HL, Pascal MMV, John J, Callaghan BC, Laycock H, Granovsky Y, Crombez G, Yarnitsky D, Rice ASC, Smith BH, Bennett DLH. Classification of painful or painless diabetic peripheral neuropathy and identification of the most powerful predictors using machine learning models in large cross-sectional cohorts. BMC Med Inform Decis Mak 2022;22:144.

[8] Blanco-Hungria A, Rodriguez-Torronteras A, Blanco-Aguilera A, Biedma-Velazquez L, Serrano-Del-Rosal R, Segura-Saint-Gerons R, de la Torre-de la Torre J, Esparza-Diaz F. Influence of sociodemographic factors upon pain intensity in patients with temporomandibular joint disorders seen in the primary care setting. Med Oral Patol Oral Cir Bucal 2012;17:e1034–1041.

[9] Bouhassira D, Attal N, Fermanian J, Alchaar H, Gautron M, Masquelier E, Rostaing S, Lanteri-Minet M, Collin E, Grisart J, Boureau F. Development and validation of the Neuropathic Pain Symptom Inventory. PAIN 2004;108:248–57.

[10] Bril V, Perkins BA. Validation of the Toronto Clinical Scoring System for diabetic polyneuropathy. Diabetes Care 2002;25:2048–52.

[11] Buysse DJ, Yu L, Moul DE, Germain A, Stover A, Dodds NE, Johnston KL, Shablesky-Cade MA, Pilkonis PA. Development and validation of patient-reported outcome measures for sleep disturbance and sleep-related impairments. Sleep 2010;33:781–92.

[12] Callaghan BC, Price RS, Feldman EL. Distal symmetric polyneuropathy: a review. JAMA 2015;314:2172–81.

[13] Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, Devellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai JS, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays R; PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. J Clin Epidemiol 2010;63:1179–94.

[14] Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singap 1994;23:129–38.

[15] Crombez G, Beirens K, Van Damme S, Eccleston C, Fontaine J. The unbearable lightness of somatisation: a systematic review of the concept of somatisation in empirical studies of pain. PAIN 2009;145:31–5.

[16] Crombez G, De Paepe AL, Veirman E, Eccleston C, Verleysen G, Van Ryckeghem DML. Let's talk about pain catastrophizing measures: an item content analysis. PeerJ 2020;8:e8643.

[17] Crombez G, Veirman E, Van Ryckeghem D, Scott W, De Paepe A. The effect of psychological factors on pain outcomes: lessons learned for the next generation of research. Pain Rep 2023;8:e1112.

[18] Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006;29:1518–22.

[19] Dorner TE, Muckenhuber J, Stronegger WJ, Rasky E, Gustorff B, Freidl W. The impact of socio-economic status on pain and the perception of disability due to pain. Eur J Pain 2011;15:103–9.

[20] Dyck PJ, Albers JW, Andersen H, Arezzo JC, Biessels GJ, Bril V, Feldman EL, Litchy WJ, O'Brien PC, Russell JW; Toronto Expert Panel on Diabetic Neuropathy. Diabetic polyneuropathies: update on research definition, diagnostic criteria and estimation of severity. Diabetes Metab Res Rev 2011;27:620–8.

[21] Ellingson LD, Colbert LH, Cook DB. Physical activity is related to pain sensitivity in healthy women. Med Sci Sports Exerc 2012;44:1401–06.

[22] Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaa M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.

[23] Finnerup NB, Haroutounian S, Kamerman P, Baron R, Bennett DL, Bouhassira D, Cruccu G, Freeman R, Hansson P, Nurmikko T, Raja SN, Rice AS, Serra J, Smith BH, Treede RD, Jensen TS. Neuropathic pain: an updated grading system for research and clinical practice. PAIN 2016;157:1599–606.

[24] Gewandter JS, Gibbons CH, Campagnolo M, Lee J, Chaudari J, Ward N, Burke L, Cavaletti G, Herrmann DN, McArthur JC, Russell JW, Smith AG, Smith SM, Turk DC, Dworkin RH, Freeman R. Clinician-rated measures for distal symmetrical axonal polyneuropathy: ACTTION systematic review. Neurology 2019;93:346–60.

[25] Gierthmuhlen J, Greinacher J, Hoper J, Oberlojer V, Lankes M, Traulsen F, Hullemann P, Borzikowsky C, Reimer M, Baron R. Sensory symptoms in low back pain-how do they matter? Curr Med Res Opin 2018;34:657–67.

[26] Gierthmuhlen J, Bohmer J, Attal N, Bouhassira D, Freynhagen R, Haanpaa M, Hansson P, Jensen TS, Kennedy J, Maier C, Rice ASC, Sachau J, Segerdahl M, Sindrup S, Tolle T, Treede RD, Ventzel L, Vollert J, Baron R. Association of sensory phenotype with quality of life, functionality, and emotional well-being in patients suffering from neuropathic pain. PAIN 2022;163:1378–87.

[27] Giusti EM, Lacerenza M, Gabrielli S, Manzoni GM, Manna C, D'Amario F, Marcacci M, Castelnuovo G. Psychological factors and trajectories of post-surgical pain: a longitudinal prospective study. Pain Pract 2022;22:159–70.

[28] Goldberg, L. R. (1999). A Broad-bandwidth, public domain personality inventory measuring the lower-level facets of several five-factor models. In: Mervielde I, Deary I, De Fruyt F, Ostendorf F, editors. Personality Psychology in Europe, Vol. 7: Tilburg, The Netherlands: Tilburg University Press, 1999. p. 7–28.

[29] Gosling SD, Rentfrow PJ, Potter J. Norms for the Ten Item Personality Inventory, 2014. Unpublished Data. Available at https://gosling.psy.utexas.edu/scales-weve-developed/ten-item-personality-measure-tipi/

[30] Gruver C, Guthmiller KB. Postherpetic neuralgia. Treasure Island: StatPearls, 2021.

[31] Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol 2016;31:5–20.

[32] Hothorn T, Hornik K, Zeileis A. Unbiased recursive partitioning: a conditional inference framework. J Comput Graph Stat 2006;15:651–74.

[33] Interpreting Individual IPIP Scale Scores. n.d. Available at: https://ipip.ori.org/InterpretingIndividualIPIPScaleScores.htm. Accessed November 11, 2020.

[34] Kawakami K, Tunoda T, Takiguchi T, Shibata K, Ohtani T, Kizu J, Nishio M, Horai T, Hama T, Taguchi K. Factors exacerbating peripheral neuropathy induced by paclitaxel plus carboplatin in non-small cell lung cancer. Oncol Res 2012;20:179–185.

[35] Keene DJ, Knight R, Bruce J, Dutton SJ, Tutton E, Achten J, Costa ML. Chronic pain with neuropathic characteristics after surgery for major trauma to the lower limb: prevalence, predictors, and association with pain severity, disability, and quality of life in the UK WHiST trial. Bone Joint J 2021;103-B:1047–54.

[36] Lai JS, Cella D, Choi S, Junghaenel DU, Christodoulou C, Gershon R, Stone A. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS fatigue item bank example. Arch Phys Med Rehabil 2011;92(10 Suppl):S20–27.

[37] Lee PW, Chow SP, Lieh-Mak F, Chan KC, Wong S. Psychosocial factors influencing outcome in patients with low-back pain. Spine (Phila Pa 1976) 1989;14:838–43.

[38] Li T, Wang J, Xie H, Hao P, Qing C, Zhang Y, Liao X, Liang T. Study on the related factors of post-herpetic neuralgia in hospitalized patients with herpes zoster in Sichuan Hospital of Traditional Chinese Medicine based on big data analysis. Dermatol Ther 2020;33:e14410.

[39] Linton SJ, Nicholas MK, MacDonald S, Boersma K, Bergbom S, Maher C, Refshauge K. The role of depression and catastrophizing in musculoskeletal pain. Eur J Pain 2011;15:416–22.

[40] Magerl W, Krumova EK, Baron R, Tolle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. PAIN 2010;151:598–605.

[41] Maier C, Baron R, Tolle TR, Binder A, Birbaumer N, Birklein F, Gierthmuhlen J, Flor H, Geber C, Huge V, Krumova EK, Landwehrmeyer GB, Magerl W, Maihofner C, Richter H, Rolke R, Scherens A, Schwarz A, Sommer C, Tronnier V, Uceyler N, Valet M, Wasner G, Treede DR. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): somatosensory abnormalities in 1236 patients with different neuropathic pain syndromes. PAIN 2010;150:439–50.

[42] Majithia N, Loprinzi CL, Smith TJ. New practical approaches to chemotherapy-induced neuropathic pain: prevention, assessment, and treatment. Oncology (Williston Park) 2016;30:1020–9.

[43] Mork H, Motte J, Fisse AL, Gruter T, Brunger J, Stoykova Z, Bulut Y, Athanasopoulos D, Sturm D, Tegenthoff M, Gold R, Enax-Krumova E, Pitarokoili K. Prevalence and determinants of pain in chronic inflammatory demyelinating polyneuropathy: results from the German INHIBIT registry. Eur J Neurol 2022;29:2109–20.

[44] Moshirfar M, Bhavsar UM, Durnford KM, McCabe SE, Ronquillo YC, Lewis AL, Hoopes PC. Neuropathic corneal pain following LASIK surgery: a retrospective case series. Ophthalmol Ther 2021;10:677–89.

[45] Murphy D, Lester D, Clay Smither F, Balakhanlou E. Peripheral neuropathic pain. NeuroRehabilitation 2020;47:265–83.

[46] Pascal MMV, Themistocleous AC, Baron R, Binder A, Bouhassira D, Crombez G, Finnerup NB, Gierthmühlen J, Granovsky Y, Groop L, Hebert HL, Jensen TS, Johnsen K, McCarthy MI, Meng W, Palmer CNA, Rice ASC, Serra J, Sola R, Yarnitsky D, Smith BH, Attal N, Bennett DLH. DOLORisk: study protocol for a multi-centre observational study to understand the risk factors and determinants of neuropathic pain. Wellcome Open Res 2018;3:63.

[47] Pfau DB, Krumova EK, Treede RD, Baron R, Toelle T, Birklein F, Eich W, Geber C, Gerhardt A, Weiss T, Magerl W, Maier C. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): reference data for the trunk and application in patients with chronic postherpetic neuralgia. PAIN 2014;155:1002–15.

[48] Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D; PROMIS Cooperative Group. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS®): depression, anxiety, and anger. Assessment 2011;18: 263–83.

[49] Reimer M, Hullemann P, Hukauf M, Keller T, Binder A, Gierthmühlen J, Baron R. Prediction of response to tapentadol in chronic low back pain. Eur J Pain 2017;21:322–33.

[50] Rice D, Nijs J, Kosek E, Wideman T, Hasenbring MI, Koltyn K, Graven-Nielsen T, Polli A. Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. J Pain 2019;20: 1249–66.

[51] Ringkamp M, Raja SN, Campbell JN, Meyer RA. Neurobiology of pain. In: McMahon SB, Koltzenburg M, Tracey DJ, Turk DC, editors. Wall and Melzack's textbook of pain. Philadelphia: Elsevier Saunders, 2013. p. 1–30.

[52] Rodriguez Roca MC, Brogly N, Gredilla Diaz E, Pinedo Gil P, Diez Sebastian J, Guasch Arévalo E, Gilsanz Rodriguez F. Neuropathic component of postoperative pain for predicting post-caesarean chronic pain at three months: a prospective observational study. Minerva Anestesiol 2021;87:1290–99.

[53] Rolke R, Baron R, Maier C, Tolle TR, Treede DR, Beyer A, Binder A, Birbaumer N, Birklein F, Botefur IC, Braune S, Flor H, Huge V, Klug R, Landwehrmeyer GB, Magerl W, Maihofner C, Rolko C, Schaub C, Scherens A, Sprenger T, Valet M, Wasserka B. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. PAIN 2006;123:231–43.

[54] Ross JDW, Cole CMW, Lo W, Ura M. Postoperative pain in thoracic surgical patients: an analysis of factors associated with acute and chronic pain. Heart Lung Circ 2021;30:1244–50.

[55] Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons, 1987.

[56] Sachau J, Bruckmueller H, Gierthmühlen J, Magerl W, Kaehler M, Haenisch S, Binder A, Caliebe A, Maier C, Treede RD, Tolle T, Cascorbi I, Baron R. SIGMA-1 receptor gene variants affect the somatosensory phenotype in neuropathic pain patients. J Pain 2019;20:201–14.

[57] Sachau J, Bruckmueller H, Gierthmühlen J, Magerl W, May D, Binder A, Forstenpointner J, Koetting J, Maier C, Tolle TR, Treede RD, Berthele A, Caliebe A, Diesch C, Flor H, Huge V, Maihofner C, Rehm S, Kersebaum D, Fabig SC, Vollert J, Rolke R, Stemmler S, Sommer C, Westermann A, Cascorbi I, Baron R. The serotonin receptor 2A (HTR2A) rs6313 variant is associated with higher ongoing pain and signs of central sensitization in neuropathic pain patients. Eur J Pain 2021;25:595–611.

[58] Scadding JW, Koltzenburg M. Painful peripheral neuropathies. In: McMahon SB, Koltzenburg M, Tracey I, Turk DC, editors. Wall and Melzack's textbook of pain. Philadelphia: Saunders, an Imprint of Elsevier Ltd, 2013. p. 926–51.

[59] Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, Treede RD. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. PAIN 2013;154:1613–21.

[60] Song SJ, Min J, Suh SY, Jung SH, Hahn HJ, Im SA, Lee JY. Incidence of taxane-induced peripheral neuropathy receiving treatment and prescription patterns in patients with breast cancer. Support Care Cancer 2017;25:2241–48.

[61] Spivey TL, Gutowski ED, Zinboonyahgoon N, King TA, Dominici L, Edwards RR, Golshan M, Schreiber KL. Chronic pain after breast surgery: a prospective, observational study. Ann Surg Oncol 2018;25:2917–24.

[62] Sullivan M, Bishop SR, Pivik J. The pain catastrophizing scale: development and validation. Psychol Assess 1995;7:524–32.

[63] Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P; Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285–93.

[64] Themistocleous AC, Ramirez JD, Shillo PR, Lees JG, Selvarajah D, Orengo C, Tesfaye S, Rice AS, Bennett DL. The Pain in Neuropathy Study (PiNS): a cross-sectional observational study determining the somatosensory phenotype of painful and painless diabetic neuropathy. PAIN 2016;157:1132–45.

[65] Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012;28:819–41.

[66] Tietjen GE, Brandes JL, Peterlin BL, Eloff A, Dafer RM, Stein MR, Drexler E, Martin VT, Hutchinson S, Aurora SK, Recober A, Herial NA, Utley C, White L, Khuder SA. Childhood maltreatment and migraine. Part II: emotional abuse as a risk factor for headache chronification. Headache 2010;50:32–41.

[67] van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. J Stat Softw 2011;45:1–67.

[68] van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. PAIN 2014;155:654–62.

[69] Vollert J, Mainka T, Baron R, Enax-Krumova EK, Hullemann P, Maier C, Pfau DB, Tolle T, Treede RD. Quality assurance for Quantitative Sensory Testing laboratories: development and validation of an automated evaluation tool for the analysis of declared healthy samples. PAIN 2015; 156:2423–30.

[70] Vollert J, Attal N, Baron R, Freynhagen R, Haanpaa M, Hansson P, Jensen TS, Rice AS, Segerdahl M, Serra J, Sindrup SH, Tolle TR, Treede RD, Maier C. Quantitative sensory testing using DFNS protocol in Europe: an evaluation of heterogeneity across multiple centers in patients with peripheral neuropathic pain and healthy subjects. PAIN 2016;157:750–8.

[71] Von Korff M, Ormel J, Keefe FJ, Dworkin SF. Grading the severity of chronic pain. PAIN 1992;50:133–49.

[72] von Sperling ML, Hoimyr H, Finnerup K, Jensen TS, Finnerup NB. Persistent pain and sensory changes following cosmetic breast augmentation. Eur J Pain 2011;15:328–32.

[73] Wang XX, Zhang Y, Fan BF. Predicting postherpetic neuralgia in patients with herpes zoster by machine learning: a retrospective study. Pain Ther 2020;9:627–35.

[74] Watson D, Pennebaker JW. Health complaints, stress, and distress: exploring the central role of negative affectivity. Psychol Rev 1989;96: 234–54.

[75] Webster F, Connoy L, Longo R, Ahuja D, Amtmann D, Anderson A, Ashton-James CE, Boyd H, Chambers CT, Cook KF, Cowan P, Crombez G, Feinstein AB, Fuqua A, Gilam G, Jordan I, Mackey SC, Martins E, Martire LM, O'Sullivan P, Richards DP, Turner JA, Veasley C, Wurtzen H, Yang SY, You DS, Ziadni M, Darnall BD. Patient responses to the term pain catastrophizing: thematic analysis of cross-sectional international data. J Pain 2023;24:356–67.

[76] Wong CK, Mak RY, Kwok TS, Tsang JS, Leung MY, Funabashi M, Macedo LG, Dennett L, Wong AY. Prevalence, incidence, and factors associated with non-specific chronic low back pain in community-dwelling older adults aged 60 Years and older: a systematic review and meta-analysis. J Pain 2022;23:509–34.

[77] Ziegler D, Bonhof GJ, Strom A, Strassburger K, Karusheva Y, Szendroedi J, Roden M. Progression and regression of nerve fibre pathology and dysfunction early in diabetes over 5 years. Brain 2021; 144:3251–63.

[78] Zorina-Lichtenwalter K, Parisien M, Diatchenko L. Genetic studies of human neuropathic pain conditions: a review. PAIN 2018;159:583–94.