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Predictors of long-term opioid effectiveness in chronic non-cancer pain patients attending multidisciplinary pain treatment clinics: A Quebec Pain Registry study

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ABSTRACT

Objective: This study aimed at identifying characteristics of individuals who are most likely to benefit from long-term opioid therapy in terms of reduction in pain severity and improved mental health-related quality of life (mQoL) without considering potential risks.

Methods: This was a retrospective cohort study of 116 patients (age=51.3 ±12.5 years, male=42.2%) enrolled in the Quebec Pain Registry between 2008 and 2011 and who initiated opioid therapy after their first appointment in a multidisciplinary pain clinic and persisted with this treatment for at least 12 months. Clinically significant improvement was defined as a 2-point decrease on the PEG 0-10 Scale of pain severity at 12-month follow-up and a 10-point increase on the SF-12v2 Mental Health-Related Quality of Life Summary Scale which corresponds to one standard deviation of the mean in the general population (Mean = 50, SD = 10).

Results: Clinically significant reduction in pain severity was observed in 26.7% of patients while improvement in mQoL was reported by 20.2% of patients on long-term opioid therapy. Older age (OR=1.04 (95% CI: 1.0 – 1.08), p=0.032) and alcohol or drug problems (OR=0.26 (95% CI: 0.07 – 0.96), p=0.044) were weakly associated with pain severity at 12-month follow-up. Baseline higher pain severity (OR=0.62 (95% CI: 0.43 – 0.91), p=0.014) and baseline higher mQoL (OR=0.89 (95% CI: 0.83 – 0.95), p=0.001) were associated with non-improvement in mQoL.

Conclusion: The analysis failed to identify clinically meaningful predictors of opioid therapy effectiveness making it difficult to inform clinicians about which CNCP patients are most likely to benefit from long-term opioid therapy.

INTRODUCTION

Chronic non-cancer pain (CNCP) is a public health burden affecting nearly 20% of the general population in developed countries [1, 2]. CNCP can lead to decreased physical functioning and poor quality of life in addition to being associated with high direct (e.g., treatments) and indirect (e.g., lost work productivity) health care costs [3, 4]. To manage this chronic condition, opioid analgesics have been widely prescribed over the past decades despite the limited evidence of their long-term effectiveness [5-7]. Indeed, most of our knowledge on the efficacy of opioid treatment comes from randomized controlled trials with follow-up periods shorter than 1 year [7]. Results of these studies suggest that opioid use in CNCP patients results in a small reduction in pain intensity compared to placebo, and similar pain relief and physical functional improvement compared to non-opioid medications [8-11]. Furthermore, opioid therapy has been associated with high rates of discontinuation ranging from 10% to 23% due to insufficient pain relief and/or adverse events such as fractures, cardiovascular events, and bowel obstruction to name just a few [9, 12]. Long-term opioid therapy has also been associated with negative long-term consequences such as opioid-induced hyperalgesia, tolerance, misuse, and addiction [8, 13].

Despite these challenges, some studies have shown that a subgroup of CNCP patients may benefit from long-term opioid therapy [14, 15]. The difficulty is to differentiate responders from

non-responders prior to treatment initiation, so that treatments are better tailored and potential harms associated with opioid prescriptions are minimized [16]. The identification of suitable candidates should be grounded in the biopsychosocial model of pain [16]. This model states that in order to fully understand a person's pain experience, the interrelationships among biological changes, psychological status, and the sociocultural context need to be considered [16, 17].

Experimental, clinical, and observational studies identified factors such as age, sex, depression, anxiety, and treatment expectations as playing an important a role in the effectiveness of short-term opioid therapy [15, 18-23]. However, the predictors of the effectiveness of long-term opioid therapy remain unknown and further research is clearly needed to identify characteristics of patients most and least likely to benefit from this type of treatment. In a previous study on long-term opioid effectiveness, a research team showed that more than 20% of CNCP patients experienced a meaningful reduction in pain intensity and interference as well as improvement in mental health-related quality of life (mQoL) at 12-month follow-up [14]. However, the phenotype of this subgroup of patients has yet to be examined. The purpose of opioid therapy is to reduce pain and improve quality of life. As such, identifying the factors that can predict these outcomes could help to optimize opioid prescribing. The aim of the present study was therefore to identify predictors of reduction in pain severity and improvement in mQoL among CNCP patients on long-term opioid therapy.

METHODS

Study design

This was a retrospective cohort study of CNCP patients enrolled in the Quebec Pain Registry (QPR) between 2008 and 2011 and who consented for their QPR data to be used for research purpose.

QPR database

The QPR (https://quebecpainregistry.com/) is a registry of ambulatory patients suffering from CNCP who were admitted for the first time to multidisciplinary treatment in one of three large university-affiliated pain clinics in the province of Quebec, Canada [24]. Patients were enrolled in the QPR if they came for a first visit at one of the pain clinics, were fluent in spoken and written French and/or English, and were aged 18 years or above. Patients were excluded if they presented with cognitive impairment that prevented them from answering questionnaires [24]. Questionnaires were administered for clinical and administrative purposes at baseline (initial visit at the pain clinic) and at 6-month follow-up for all patients, as well as at the 12- and 24-month follow-ups in those patients who had not been discharged from the pain clinic in the meantime.

The Research Ethics Boards of the Centre hospitalier de l'Université de Montréal, McGill University Health Center, and Centre hospitalier de l'Université de Sherbrooke approved the QPR project.

Participants

In this study, patients were included if they met criteria for long-term opioid use—i.e., they did not report opioid use in the past 6 months before the initial visit to the pain clinic, they started opioid medication within the first 6 months following their initial visit, and they continued taking opioids at 6- and 12-month follow-ups. Patients could have switched opioid prescriptions during the follow-up period and were included as long as they reported taking opioids at each of the follow-ups. Data collected at 24-month follow-up were not considered in the present study due to

too small a sample size at this time point, many patients having been discharged from the pain clinic in the meantime.

Procedures

Data collection and measurement tools

Baseline and follow-up data were collected with a patient self-administered and a nurse-administered questionnaires [24].

Patient self-administered questionnaire

Socio-demographic characteristics

Sociodemographic data included patients' age, sex, education level, and work status.

Pain severity index

Pain severity was computed using the PEG scale which contains three items assessing average pain intensity, emotional functioning, and physical functioning using the pain intensity score on the average in the past 7 days (P), interference with enjoyment of life (E) score, and interference with general activity (G) score provided by the Brief Pain Inventory Scale [25, 26]. The scores on the three items were averaged and varied from 0 (no pain/no interference) to 10 (worst possible pain/pain interferes completely). The PEG is a reliable and valid measure of pain severity in CNCP patients; it has been shown to be sensitive to change and differentiated well between patients with and without pain improvement [25].

SF-12v2® Health Survey

The SF-12v2® Health Survey is a 12-item questionnaire used to assess health-related quality of life [27, 28]. It covers eight domains of health outcomes and generates norm-based scores for each domain as well as two composite scores representing mental health-related quality of life (mQoL) and physical health-related quality of life (pQoL) that have a mean of 50 and a standard deviation of 10. Higher scores indicate better quality of life. This questionnaire demonstrated good internal consistency reliability, construct validity, and responsiveness in patients with pain [29].

Pain Catastrophizing Scale

The Pain Catastrophizing Scale is a 13-item scale assessing the extent to which individuals ruminate, magnify, and feel helpless in the presence of pain [30]. It is one of the most widely used instruments for measuring catastrophic thinking related to pain and is used extensively in clinical practice and research [30]. Each item is scored from 0 (not at all) to 4 (all the time) and the total score is comprised between 0 and 52 [30]. Higher scores indicate a higher level of pain catastrophizing. The PCS has demonstrated good validity and reliability [31].

Beck Depression Inventory-I (BDI)

The Beck Depression Inventory-I (BDI-I) is a 21-item, self-rated scale that assesses depressive symptomatology (both psychological and somatic symptoms) [32-34]. Each item is scored from 0 to 3 and the total summed score was ranged from 0 to 63. Higher scores indicate a higher level of depressive symptoms. The BDI-I was shown to have psychometric proprieties in a variety of medical populations [35].

CAGE alcohol and drugs

The CAGE questionnaire was developed to screen for excessive drinking and alcoholism while the CAGE-AID (CAGE Questionnaire Adapted to Include Drugs) is a version adapted to include drug use [36, 37]. The CAGE-AID comprised 4 questions scored 0 for "no" and 1 for "yes" for a total score ranging from 0 to 4 [36]. A total score of two or more is considered clinically significant for alcohol and drug use disorders [36]. The CAGE-AID exhibited good validity and reliability [36, 37]. In the QPR, questions about alcohol and drug use were assessed separately and not together as in the CAGE-AID to increase precision of the information collected. In our analysis, we merged responses to recreate the CAGE-AID.

Nurse-administered questionnaire

Pain history information and medication

The nurse-administered questionnaire was designed to collect information on patient's pain history (e.g., pain duration and frequency) and type(s) of medication currently used and used in the past 6 months to treat their pain at each time point [24].

Pain diagnosis

Patient pain diagnosis was established by the pain physician at the multidisciplinary clinic using a comprehensive grid of pain diagnoses elaborated by experienced pain physicians specifically for the QPR [24].

Questionnaire

The DN4 (Douleur Neuropathique 4) is a screening diagnostic tool that assesses the presence of neuropathic pain qualities through self-report and physical examination. It consists of 4 questions with a total of 10 items. A score of 1 is given when the answer is "yes" and a score of 0 when the answer is "no". The total score is calculated as the sum of all 10 items, and a total score of 4/10 or more suggests the presence of a neuropathic component [38].

The DN4 has good validity and reliability properties [39]. For this study, we also considered the pain diagnosis made by the treating physician at the pain clinic. Thus, a physician diagnosis of neuropathic pain combined with a DN4 score ≥ 4 was classified as neuropathic type of pain; physician diagnosis of neuropathic pain and DN4 score < 4 or diagnosis of non-neuropathic pain with DN4 score ≥ 4 were classified mixed evidence of neuropathic pain while a diagnosis of non-neuropathic pain with DN4 score < 4 was classified as non-neuropathic pain.

Outcomes

The outcomes of long-term opioid therapy considered in the present study were pain severity and mQoL. As recommended by the IMMPACT Group [40], a statistically significant reduction in pain severity was considered as clinically meaningful if it was at least a 2-point decrease on the PEG 0-10 scale. With regards to mQoL, an improvement was considered as clinically meaningful if the norm-based score on the SF-12v2 Mental Health Summary Scale had increased by at least 1 standard deviation of the mean norm-based score in the general population (Mean = 50, SD = 10) [14, 41]. A clinically significant improvement in physical functioning measured by the SF12v2 Physical Health Summary Scale was observed in only 8% of the participants. As such, this outcome was not considered in the present research.

Statistical analysis

Independent Student's tests, Mann-Whitney test, and Pearson's chi-square tests were employed to compare the baseline characteristics of patients with and without missing data on the outcome measures (PEG pain severity score, SF-12v2 Mental Health Summary Scale). The same tests

were used to compare the baseline characteristics between patients who experienced improvement in pain severity and those who did not.

Multivariable logistic regression analyses were used to identify predictors of long-term opioid effectiveness (model 1- PEG pain severity; model 2 - mQoL) and purposeful selection process proposed by Bursac et al.[42] was used for variable selection. The following baseline biopsychosocial characteristics were considered for inclusion using the purposeful selection process [42]: age, sex, education, work status, pain severity, pain duration, pain frequency, type of pain, pQoL, mQoL, pain catastrophizing, depression level, and alcohol or drug problems. These variables were first screened in univariable analyses and selected for inclusion in the multivariable model if their p-value was < 0.25. Backward elimination using all the variables entered in the multivariable model was then performed to build a more parsimonious model. Variables were removed from the model if they were not statistically significant at the threshold of $p < 0.05$ and if their removal did not change coefficient of any of the remaining variables by more than 20%. Age and sex were maintained in the final model as forced variables. Finally, variables that did not reach the significance level of $p < 0.25$ in univariable analysis were added back one at a time in the multivariable model and retained in the final model if they were significant at $p<0.05$. This step was helpful in identifying variables that, by themselves, are not significantly related to the outcome but make an important contribution in the presence of other variables [42]. Only variables statistically significant at $p < 0.05$ were retained in the final model. Odds ratios (OR) and their 95% confidence intervals (CI) were calculated. The Hosmer–Lemeshow test was run to test the goodness of fit for the final predictive model. Sensitivity, specificity, and the area under curve (AUC) were also calculated. Analyses were performed using Stata 15.1 for Windows, StataCorp LLC, College Station, TX, USA. Finally, statistical power analyses were conducted using G*Power 3.1, Universität Kiel, Germany and revealed that the study was sufficiently powered to detect statistically significant predictors for each of the two outcomes **(see Supplementary file)**.

RESULTS

Participants' characteristics

A total of 160 patients classified as long-term opioid users were included. Forty-four of them were excluded from the analyses because they had missing data on pain severity at baseline or at 12-month follow-up. Comparisons between patients with and without missing data revealed no significant differences regarding all the variables included in the study (all $p > 0.05$).

Table 1 depicts the baseline characteristics of patients on long-term opioid therapy according to whether they reported a clinically significant reduction in pain severity or not (improvers vs non-improvers) and for the total sample (N=116). Median pain duration was 4 (interquartile range: 2 – 10) years, and almost one third of sample (31.1%) suffered from neuropathic pain while 40.6% showed mixed evidence of neuropathic pain. Mean baseline pain severity score on the PEG scale was 6.3 ±1.8 while the norm-based mean scores were 28.8 ±8.2 for pQoL and 38.5 ±12.2 for mQoL. Mean baseline scores of 20.9 ±11.3 and 31.3 ±12.9 were reported for depression levels and on the Pain Catastrophizing Scale respectively**.** As shown in **Table 1**, among the 116 patients included, 31 (26.7%) experienced a clinically meaningful reduction in pain severity at 12-month follow-up. Comparison of baseline characteristics between improvers in pain severity (N = 31, 26.7%) and non-improvers (N = 85, 73.3%) showed that improvers were older than non-improvers (55.2 ±14.0 vs 49.9 ±11.7 years, p-value = 0.045).

(Table 1)

Baseline predictors of reduction in pain severity among long-term opioid users at 12-month follow-up

Results of the multivariable regression analysis revealed that age and alcohol or drug problems were significant predictors of a clinically meaningful reduction in pain severity at 12-month follow-up **(Table 2)**. Older age was associated with higher likelihood of a reduction in pain severity at 12 months (OR = 1.039 (95% CI: 1.003 – 1.075), p = 0.032). Patients with alcohol and drug problems were less likely to report a reduction in pain severity at follow-up (OR = 0.26

(95% CI: 0.07 – 0.96), p = 0.044). Neither the type of pain nor the baseline pain characteristics (severity, duration, frequency) or psychological factors were identified as significant predictors. **(Table 2)**

(Table 2)

Post-hoc tests were performed to evaluate the quality of the prediction model. The p-value of the Hosmer–Lemeshow test was 0.718 suggesting adequate goodness of fit [43]. The maximum likelihood R^2 of Cox & Snell was 0.083 which means that only 8.3% of the reduction in pain severity was related to our identified predictors. The sensitivity of the model was 19.4% while its specificity was 95.2%. The area under the ROC curve was 0.70 which indicated a low level of accuracy of the prediction model according to Swets guidelines [44].

(Figure 1 & 2)

Baseline predictors of improved mQoL among long-term opioid users at 12-month follow-up

Of the 114 patients without missing data on the SF-12v2 Mental Health-Related Quality of Life Summary Scale at baseline and 12-month follow-up, 23 (20.2%) reported a clinically meaningful

improvement in mQoL at 12-month follow-up. As shown in **Table 3**, results of the multivariable regression analysis revealed that the more severe was the pain at baseline, the less likely the patients were to report improved mQoL at 12-month follow-up (OR = 0.62 (95% CI: 0.43 – 0.91), p = 0.014). Those who reported better mQoL at baseline were also less likely to exhibit improvement on this measure at follow-up (OR = 0.89 (95% CI: 0.83 – 0.95), p = 0.001). The baseline pain severity was correlated with baseline mQoL (*Pearson r = -0.626, p < 0.001*) which explains the high changes in p-values from univariable to multivariable analyses. These two variables were maintained in the final model because they measure two different constructs which are not interchangeable. Furthermore, the test of multicollinearity showed that the variance inflation factor was less than 10 and the tolerance higher than 0.1, which meant there was no evidence of high multicollinearity [45, 46].

Examination of the quality of the final predictive model showed adequate goodness of fit as revealed by the Hosmer-Lemeshow test whose p-value was equal to 0.836 [43]. The maximum likelihood R^2 of Cox & Snell was 0.129 suggesting that only 12.9% of the improvement in mQoL was explained by the multivariable model. Its sensitivity was 13% while its specificity was 97.8%. The area under the ROC curve was 0.765 which indicates a moderate level of accuracy of the prediction model according to Swets guidelines [44]. (**Figure 3 & 4).**

DISCUSSION

This real-life study showed that long-term opioid use is beneficial for a subgroup of patients, but also suggested that opioid effectiveness is difficult to predict from baseline biopsychosocial factors. We found that one-quarter of patients experienced a reduction in pain severity and 20% reported an improvement in mQoL. However, we failed to identify clinically meaningful predictors associated with this improvement, demonstrating the challenge in predicting treatment response to long-term opioid therapy in heterogeneous tertiary care pain population based on self-reports and diagnostic measures.

Our results contribute to the heterogeneous literature on predictors of opioid treatment response. Older age, for example, has been identified as a predictor of opioid treatment response in some studies[47-49] but not in others[21, 22, 49]. These conflicting findings could result from the mixed changes that occur with ageing such as increased pain sensitivity, higher level of opioid active metabolites in plasma, and decrease in μ-opioid receptor densities accompanied by increase in affinity [50-52]. In addition, a history of alcohol or drug problems has been shown to influence treatment response[53] or pain/opioid tolerance[54-56] which could result in decreased efficacy of pain treatment as reported in our study. Indeed, a previous study showed that CNCP patients with a history of a drug use disorder experienced poorer pain-related functioning and poorer pain treatment outcomes [53]. Studies also reported that alcohol use disorder appeared to be associated with greater pain severity [57, 58] which could result from hyperalgesia and dysregulated nociception induced by the excessive use of alcohol [59-61]. Furthermore, alcohol and drug problems were documented as risk factors of opioid abuse and can be a relative contraindication for opioid therapy [8, 62, 63]. Given the mixed results found in the literature regarding the significance of these predictors and the directions of the effects, our lack of clinically meaningful predictors of long-term opioid therapy is not surprising.

Considering the impact of opioid therapy on quality of life, no clinically meaningful predictors were identified. The statistical association between baseline mQoL and changes at 12-month follow-up could result from regression to the mean which occurs when scores on a variable are extreme (very high or very low) at the first measure, it will be closer to the average at the next measure [64, 65]. Thus, patients with low scores at baseline will present with higher scores closer to the average at 12-month follow-up which will artificially look as an improvement. Another

explanation could be a spurious statistical association called the horse-racing effect which occurs if what happened before the baseline visit is not adequately considered [66, 67]. Indeed, the increase in mQoL scores in patients with lower scores might have started before the baseline visit at the pain clinic. In this case, adjusting the baseline scores in the prediction of change scores induces a spurious relation [67]. Furthermore, the baseline pain severity was negatively and strongly correlated with baseline mQoL which may have induced the statistical significance between baseline pain severity and mQoL at 12-month follow-up. In addition, since opioids are prescribed with the goal to decrease pain, increase function, and improve quality of life, these findings do not provide clinically relevant information to enhance opioid prescribing. This difficulty in identifying relevant predictors could be due to the multidimensional aspect of quality of life which is influenced by several factors, of which pain is one [68, 69].

Predicting treatment outcomes in long-term opioid therapy remains a challenge. Some experimental and clinical studies reported age, sex, depression and catastrophizing as predictors of opioid efficacy, but were focused on short-term therapy [15, 18-23]. Other authors reported studies which failed to identify predictors of reduction in pain severity or improvement in quality of life [15, 70]. Our study identified few predictors and reported odds ratio indicating a small effect size and a weak association for those that were identified [71]. In addition, the predictive model showed a low sensitivity and a low accuracy, highlighting the difficulty in predicting which patients will experience improved pain outcomes. However, a previous study which included the whole cohort of patients enrolled in the Quebec Pain Registry between 2008 and 2011(opioid users as well as non-opioid users) reported several predictors associated with the trajectory of patients who experienced a reduction in pain severity [72]. These predictors included age, type of pain, pain duration, pain intensity, depression scores, pain catastrophizing, sleep disturbances, and physical health-related quality of life [72]. Thus, the difficulty in identifying factors associated with improved pain outcomes appears specific to long-term opioid therapy. This inability in predicting could result from dynamic phenomena such as tolerance and hyperalgesia which occur in long-term therapy and affect opioid analgesia [73, 74]. The lack of identifiable predictors could also mean that biopsychosocial factors have a small effect on opioid effectiveness in long-term therapy. Despite this difficulty in predicting treatment outcomes, opioid therapy may be considered for a subgroup of patients at low risk of misuse when non-opioid therapy failed to relieve pain. Indeed, a non-negligible subgroup of patients may benefit from long-term opioid

therapy and as such it should not be excluded from the realm of therapeutic approaches available to clinicians. At the same time, results demonstrate the importance of not systematically resorting to this approach either since a majority of patients will be non-responders.

This study presents several limitations. First, the findings of this study are not generalizable to all CNCP patients. Indeed, tertiary care patients commonly suffer from severe pain that is often difficult to treat [24, 75] and therefore do not represent all CNCP patients. Thus, long-term improvement rates may be higher in primary care patients than those included in our study. In addition, the difficulty in identifying predictors may be specific to our study population who experiences severe impairment and, thus further research is needed for patients followed in primary or secondary care settings.

Second, the changes in scores of pain severity and mQoL during the follow-up could be the result of factors other than opioid therapy such as non-opioid medications, non-pharmacological treatment, regression to the mean, or a fluctuation of pain over time. In addition, the lack of information on pain medication (type and dosage of the opioid, co-prescription of other analgesics), and non-pharmacological treatment (psychology, acupuncture, physiotherapy, occupational therapy) could introduce confounding bias in the identification of predictors. However, a previous study reported no link between psychological and physical treatment approaches with pain severity at 12-month follow-up[76]. Furthermore, variables such as patients' beliefs, anxiety, and fear of avoidance were not recorded and could be potential predictors of pain outcomes [18, 77].

Finally, this study achieved the statistical power to identify predictor with medium and large effect size, but the sample size was insufficient to identify factors with a small effect size. It is thus possible that such predictors could be missed. However, such predictors would have a little impact on pain outcomes and would be of little importance in the decision to prescribe opioids. Nevertheless, new investigation methods such as artificial intelligence/machine learning or genetic screening are promising research avenues to better characterize the best candidates for long-term opioid therapy or to confirm the difficulties in predicting treatment outcomes. This is of great importance in the context of a patient-centered care approach considering the heterogeneity and complexity of chronic pain populations and for which standard statistical approaches have proven to be unhelpful.

CONCLUSION

In summary, this study showed that it is difficult to predict pain outcomes in long-term opioid therapy. The few variables that were statistically significant showed very small effect sizes. No clinically meaningful predictors of long-term opioid effectiveness were identified, making it difficult to inform clinicians about which CNCP patients are most likely to benefit from long-term opioid therapy. These findings suggest that opioids should not be widely prescribed, nor should they be completely discarded since a relatively modest subgroup of patients benefit from long-term opioid therapy in multidisciplinary, tertiary care settings. Thus, it is important to conduct a good opioid trial in patients without drug use problems and at low risk of developing serious adverse events; treatment expectations should also be discussed, and treatment effectiveness should be evaluated routinely against long-term risks associated with opioid therapy.

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Conflict of interest

The authors have no conflict of interest to declare.

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List of tables

Table 1. Baseline characteristics of patients who did and did not report a clinically significant reduction in pain severity at 12-month follow-up (improvers vs non-improvers)* and for the total sample.

Variable	Total	Improvers	Non-improvers	P-value
N (%)	116 (100)	31 (26.7)	85 (73.3)	-
Age				
Mean ±SD	51.3 ±12.5	55.2 ±14.0	49.9 ±11.7	0.045
Sex				
N (%) male	49 (42.2)	14 (45.2)	35 (41.2)	0.701
Education				
N (%) ≥ high school	55 (47.4)	16 (51.6)	39 (45.9)	0.584
Work status				
N (%) on temporary or permanent disability	49 (42.2)	12 (38.7)	37 (43.5)	0.642
Pain severity (PEG)				
Mean ±SD	6.3 ±1.8	6.4 ±1.9	6.2 ±1.8	0.685
Pain duration (years)				
Median (IQR)	4 (2 – 10)	6 (3 – 15)	3 (1 – 9)	0.061
Pain frequency				
N (%) with persistent pain	105 (90.5)	28 (90.3)	77 (90.6)	0.966
Type of pain (N (%))				
Non-neuropathic	30 (28.3)	9 (34.6)	21 (26.3)	
Mixed	43 (40.6)	10 (38.5)	33 (41.3)	0.698
Neuropathic	33 (31.1)	7 (26.9)	26 (32.5)	
Physical health-related QoL				
Mean ±SD	28.8 ±8.2	30.4 ±9.8	28.2 ±7.5	0.201
Mental health-related QoL				
Mean ±SD	38.5 ±12.2	38.5 ±11.7	38.5 ±12.5	0.994
Pain catastrophizing				
Mean ±SD	31.3 ±12.9	30.3 ±13.3	31.7 ±12.8	0.606
Depression level				
Mean ±SD	20.9 ±11.3	19.0 ±11.6	21.6 ±11.1	0.282

Alcohol or drug problems				
N (%) yes	26 (22.6)	4 (12.9)	22 (26.2)	0.131

Abbreviations: SD = Standard deviation; IQR = Interquartile range; QoL = quality of life.

** Improvers were those who showed ≥ 20% decrease in the PEG pain severity score (2 units on the 0-10 scale) between baseline and 12-month follow-up.*

Table 2. Results of the univariable and multivariable logistic regression analyses to identify predictors of a clinically meaningful reduction in pain severity at 12-month follow-up* (N = 116).

Variable	**Univariable logistic regression analysis**		**Multivariable logistic regression analysis**	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age**				
Years	1.04 (1.0 – 1.07)	0.048	1.04 (1.0 – 1.08)**	0.032
Sex				
Male vs Female	1.18 (0.51 – 2.69)	0.701	1.56 (0.61 – 3.98)	0.354
Education				
≥ High school vs lower	1.26 (0.55 – 2.87)	0.585	-	-
Work status				
Disability vs no disability	0.82 (0.35 – 1.90)	0.642	-	-
Pain severity				
Score	1.05 (0.83 – 1.32)	0.682	-	-
Pain duration				
Years	1.02 (0.98 – 1.07)	0.369	-	-

Pain frequency				
Persistent vs intermittent	0.97 (0.24 – 3.92)	0.966	-	-
Type of pain				
Non-neuropathic	reference			
Mixed	0.71 (0.25 – 2.03)	0.519	-	-
Neuropathic	0.63 (0.20 – 1.97)	0.425	-	-
Physical health-related QoL* **				
Score	1.03 (0.98 – 1.09)	0.202	1.05 (0.99 – 1.11)	0.075
Mental health-related QoL				
Score	1.0 (0.97 – 103)	0.994	-	-
Pain catastrophizing				
Score	0.99 (0.96 – 1.02)	0.602	-	-
Depression level				
Score	0.98 (0.94 – 1.02)	0.281	-	-
Alcohol or drug problems				
Yes vs No	0.42 (0.13 – 1.33)	0.139	0.26 (0.07 – 0.96)	0.044

Abbreviations: OR = Odds ratio; 95% CI = 95% Confidence interval; QoL = Quality of life;

** A statistically significant reduction in pain severity was considered as clinically meaningful if the score on PEG scale decreased by at least 20% (2 units or more on the 0-10 scale) between baseline and 12-month follow-up.*

*** Odds ratio and confidence interval for the variable age rounded to 3 decimal points: OR = 1.039 (95% CI: 1.003 – 1.075)*

**** The variable "Physical health-related QoL" was maintained in the multivariable model despite it was not statistically significant (p >0.05) because its backward elimination led to a change > 20% in the coefficient of the variable "alcohol or drug problems".*

Backward elimination was performed to build a more parsimonious model and only variables with p<0.05 were maintained in the final model with age and sex as forced variables.

Table 3. Results of the univariable and multivariable logistic regression analyses to identify predictors of a clinically meaningful improvement in mQoL at 12-month follow-up* (N = 114).

Variable	**Univariable logistic regression analysis**		**Multivariable logistic regression analysis**	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age				
Years	1.0 (0.96 – 1.03)	0.872	1.01 (0.97 – 1.05)	0.562
Sex				
Male vs Female	0.53 (0.20 – 1.42)	0.209	0.56 (0.20 – 1.61)	0.284
Education				
≥ High school vs lower	0.63 (0.25 – 1.60)	0.330	-	-
Work status				
Disability vs no disability	0.86 (0.34 – 2.18)	0.747	-	-
Pain severity**				
Score	1.0 (0.77 – 1.28)	0.974	0.62 (0.43 – 0.91)	0.014
Pain duration				
Years	1.01 (0.97 – 1.06)	0.554	-	-
Pain frequency				
Persistent vs intermittent	1.01 (0.20 – 5.12)	0.988	-	-
Type of pain				
Non-neuropathic	reference			
Mixed	1.30 (0.34 – 4.91)	0.699	-	-
Neuropathic	2.95 (0.81 – 10.74)	0.100	-	-
Physical QOL				
Score	1.02 (0.97 – 1.08)	0.455	-	-
Mental QOL				
Score	0.94 (0.89 – 0.99)	0.010	0.89 (0.83 – 0.95)	0.001
Pain catastrophizing				
Score	1.01 (0.98 – 1.05)	0.473	-	-

Depression level				
Score	1.0 (0.96 – 1.05)	0.841	-	-
Alcohol or drug problems				
Yes vs No	0.65 (0.20 – 2.12)	0.476	-	-

Abbreviations: OR = Odds ratio; 95% CI = 95% Confidence interval; Physical QOL = Physical quality of life; mQoL = Mental health-related quality of life.

** A statistically significant improvement in mQoL was considered as clinically meaningful if the score on SV12v2 scale increased by at least one standard deviation of the mean norm-based scores in general population (10 units or more on the 0-100 scale) between baseline and 12-month follow-up.*

***Pain severity were included in multivariable model despite it did not reach significant level in univariable analysis ($p<0.25$) because according to the purposeful selection non-selected variables were added back one at a time in the multivariable model and retained in the final model if variable was significant at $p<0.05$.*

Backward elimination was performed to build a more parsimonious model and only variables with $p<0.05$ were maintained in the final model with age and sex as forced variables.

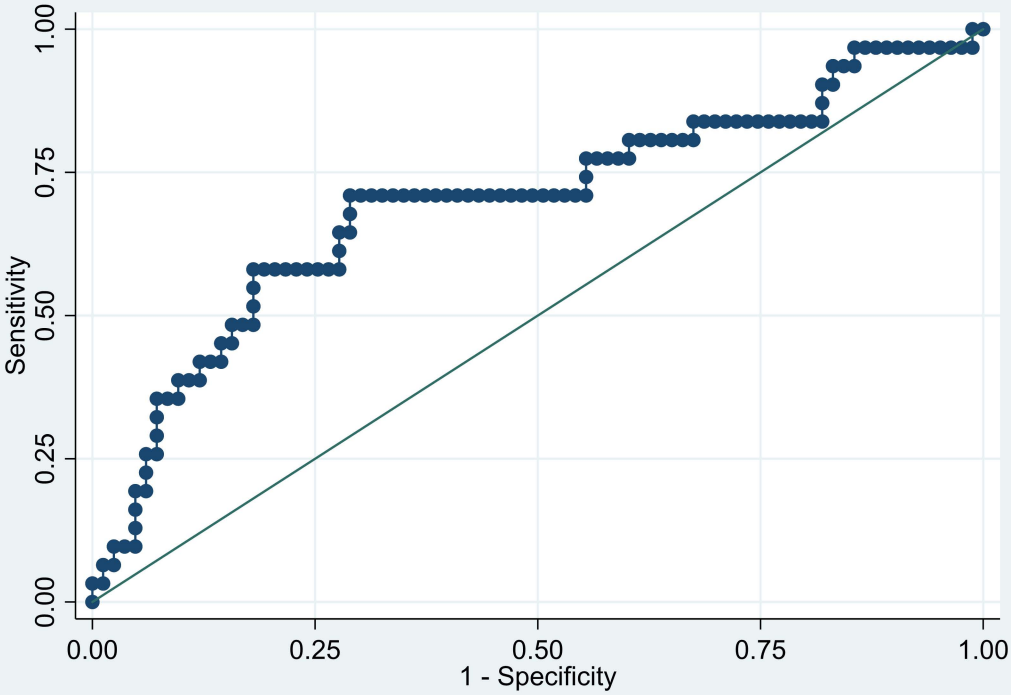
Figure legends

Figure 1. Area under ROC curve for the model predicting reduction in pain severity at 12-month follow-up.

Figure 2. Graph sensitivity and specificity versus probability cutoff for the model predicting reduction in pain severity at 12-month follow-up.

Figure 3. Area under ROC curve for the model predicting improvement in mental health-related quality of life at 12-month follow-up.

Figure 4. Graph sensitivity and specificity versus probability cutoff for the model predicting improvement in mental health-related quality of life at 12-month follow-up.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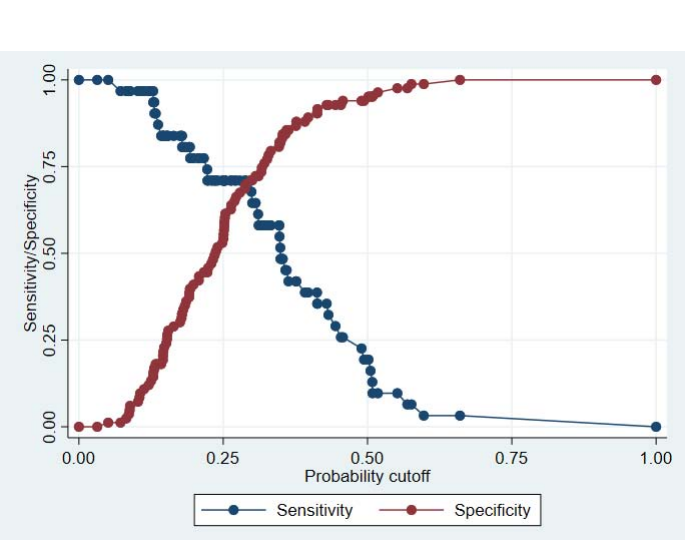
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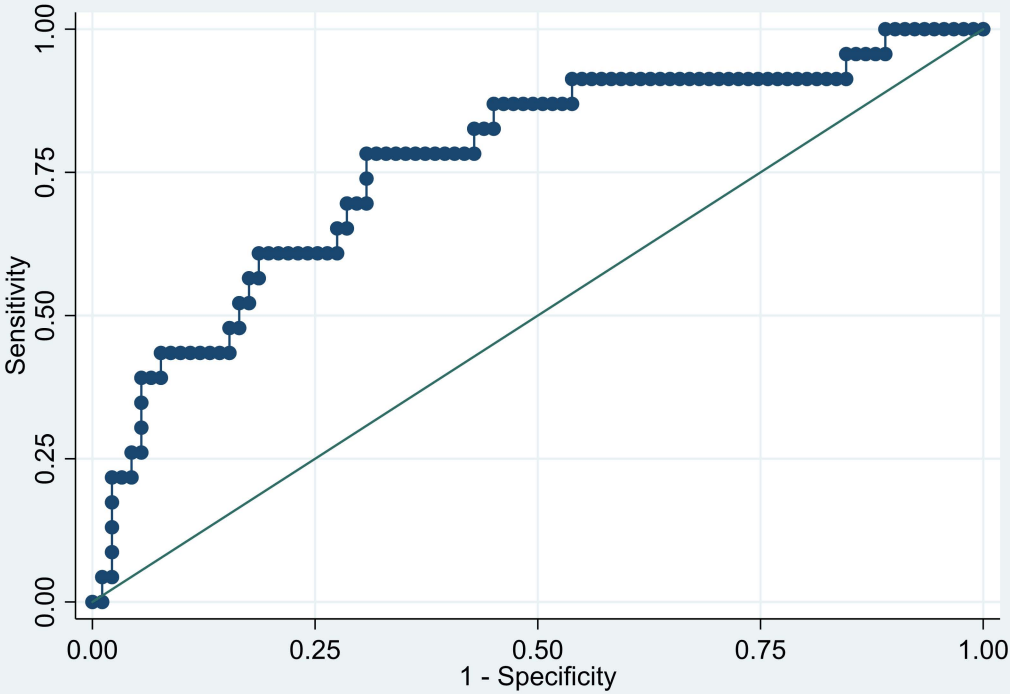
Probability cutoff
Sensitivity
Specificity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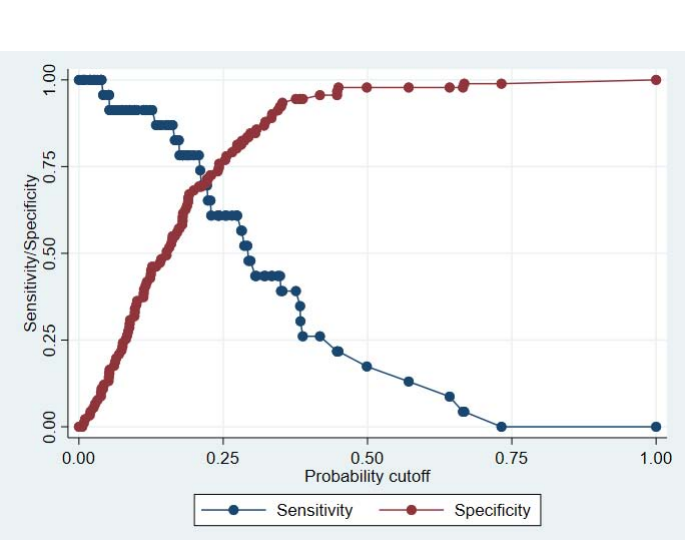
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