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ORIGINAL ARTICLE

Clinical prediction model for interdisciplinary biopsychosocial rehabilitation in osteoarthritis patients

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ABSTRACT

BACKGROUND: Osteoarthritis (OA) is a heterogenous condition, in which different subgroups are present. Individualized interdisciplinary multimodal pain treatments (IMPT) based on the biopsychosocial model have resulted in positive improvement of pain, health and disability in OA patients. Moreover, predictive factors for treatment success of IMPT in different musculoskeletal pain populations have been examined, but a clinical prediction model which informs whether an OA patient is expected to benefit or not from IMPT is currently lacking.
AIM: The aim was to develop and internally validate a clinical prediction model to inform patient-tailored care based on identified predictors for positive or negative outcomes of IMPT in patients with OA.
DESIGN: Longitudinal prospective cohort study.
SETTING: Center for Integral Rehabilitation at six locations in the Netherlands.
POPULATION: Chronic OA patients.
METHODS: Data in this study were collected during January 2019 until January 2022. Participants underwent a 10-week IMPT program based on the biopsychosocial model. Treatment success was defined by a minimal decrease from baseline of 9 points on the Pain Disability Index (PDI). Candidate predictors were selected by experts in IMPT and literature review. Backward logistic regression analysis was performed to develop the clinical predication model and bootstrap validation was performed for internal validation.
RESULTS: Overall, 599 OA patients were included, of which 324 experienced treatment success. Thirty-four variables were identified as possible predictors for good IMPT outcome. Age, gender, number of pain locations, PDI baseline score, maximal pain severity, use of pain medication and alcohol, work ability, brief illness perceptions questionnaire subscales timeline, consequences, identity and treatment control, pain catastrophizing scale and self-efficacy questionnaire score were found as predictors for treatment success. The internally validated model has an acceptable discriminative power of 0.71.
CONCLUSIONS: This study reports a specific clinical prediction model for good outcome of IMPT in patients with OA. The internally validated model has an acceptable discriminative power of 0.71.
CLINICAL REHABILITATION IMPACT: After external validation, this model could be used to develop a clinically useful decision tool.

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KEY WORDS: Osteoarthritis; Patient care team; Prognosis.

Osteoarthritis (OA) is one of the most common and rising chronic diseases in the elderly[1] and known as a frequent cause of pain, disability and loss of quality of life.[2] It is a heterogeneous condition, in which different subgroups (*i.e.*, phenotypes) are present; several studies identified a subgroup of OA patients experiencing disturbed somatosensory processing with disturbed psychological features, a subgroup with mainly inflammatory features, a subgroup with minimal joint disease, etc.[3, 4] Challenging this condition is highly important, because OA patients still experience more disability days, medication costs and health-care consultations compared to age- and sex-matched people without OA.[5] In recent years, various studies have indicated positive effects of a conservative biopsychosocial oriented approach in OA treatment.[6, 7] Despite the recommendation of this treatment in OA, effect sizes of conservative treatment remain only small or at best moderate.[7] A possible explanation for this relative lack of treatment success could be related to suboptimal patient selection.[8, 9] The European League Against Rheumatism (EULAR) recommends different treatment steps related to a combination of biopsychosocial factors that are present and need attention in each patient, but still holds on to a stepped-care approach (*i.e.*, giving the patient the next treatment only when they do not react sufficiently on the treatment provided in the first or previous step).[10]

However, because of the heterogeneity in OA it is postulated that individuals will benefit more from individualized treatment.[11, 12] Individualized interdisciplinary multimodal pain treatments (IMPT) have resulted in positive improvement of several patient-reported and clinician measured outcomes regarding pain, disability and psychological factors in patients experiencing different chronic primary musculoskeletal pain disorders,[13] but also for self-reported pain, health and clinically observed disability in OA patients specifically.[6] This sort of treatment usually targets different components of the biopsychosocial model that contribute to the maintenance of chronic pain and/ or disability, requires active participation of the patients, and is given by a team of different health professionals (*e.g.* physiotherapist, psychologist, physiatrist, social worker, etc.) who work interdisciplinary.[6, 14] Moreover, predictive factors for IMPT treatment success in different musculoskeletal pain populations (baseline lower levels of negative psychological factors and disability, and higher levels of physical functioning), and some specific in OA populations (younger age, baseline lower BMI and having knee OA) are reported.[15-17] However, a clinical prediction model which informs whether an OA patient is expected to benefit or not from IMPT is currently lacking. This clinical prediction model would fit within the personalized medicine approach and could provide the patient and clinician with a more accurate prediction of treatment success before the start of the IMPT for more optimal use of resources and time and energy. Presenting the patient this specific treatment success percentage could facilitate shared decision- making whether other treatments before IMPT should be started first in order to increase treatment expectancy and hence the chance for a successful IMPT[16] (*e.g.*, integrating motivational interviewing in pain neuroscience education,[18] acceptance and commitment therapy, graded activity, exposure in vivo and emotional awareness and expression therapy).[19] Ultimately, this could lead to a higher efficiency in the healthcare system.

Therefore, the aim of this study was to develop a clinical prediction model for predicting good or negative outcome of IMPT in patients with OA and to internally validate this prediction model.

Materials and methods

The Medical Research Ethics Committee (MREC) Isala Zwolle in the Netherlands has approved this study (reference number: 200510). This prospective cohort study was written according to the Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) guidelines and registered at clinicaltrials.gov (NCT05661760). All participants received and signed informed consent before inclusion.

Setting and treatment

Data in this study were collected during routine clinical practice of Center for Integral Rehabilitation (CIR), which is an independent secondary care treatment center specialized in chronic musculoskeletal pain interdisciplinary rehabilitation and provides outpatient IMPT at six locations across the Netherlands (*i.e.*, Alkmaar, Amsterdam, Arnhem, Eindhoven, Zeist, and Zwolle). Data were collected in the electronic patient file developed by Asterisque during a three-year period (January 2019 - January 2022). All participants underwent an average 10-week IMPT program including a combination of physical and psychosocial treatment: emotional awareness and expression therapy, pain neuroscience education, acceptance and commitment therapy, graded activity, exposure in vivo and experiential learning through physical training. An individual program based on an extensive screening of completed self-reported questionnaires by a psychologist, a physical medicine

and rehabilitation physician, and physiotherapist at the start of the treatment was developed. The treatment was divided over three phases: a start- (week 1), an education- (week 2-3) and a skills learning phase (week 4-10). Both individual (physical and mental coaching) and group sessions (education, movement and behavior therapy) were organized. Participants were treated twice a week during two to four sessions (three to four hours) per treatment day by physiotherapists, psychologists and a physiatrist. Detailed information about the IMPT treatment program can be found in a previous publication.[19] The Template for Intervention Description and Replication (TIDieR) Checklist[20] was compiled, with a column based on current study and the study containing the detailed information about the IMPT.[19]

Participants

Participants were included if they were aged ≥18 years, experienced chronic musculoskeletal pain (>3 months) and were diagnosed with and referred because of OA based on clinical and/or radiological examination by a medical doctor.

This study was part of a greater prospective longitudinal study including all people who underwent IMPT, but it was planned to also develop a clinical prediction model solely for OA-patients. Given that the primary referral diagnosis for IMPT was readily available in the electronic patient file, it was decided to examine inclusion criteria related to OA-diagnosis after the ending of the data collection of the study. Therefore, the electronic patient file was searched after data collection ended based on OA-related key terms (Supplementary Digital Material 1 (Supplementary Text File 1). Participants were eligible if the diagnosis 'OA' was reported in either the referral letter of the general practitioner, medical specialist or occupation doctor. In case no diagnosis was present, participants were still included if OA was mentioned as a diagnosis contributing to the pain problem by the physiatrist who was involved in the screening for eligibility for the IMPT program. In addition, participants had to experience personal and social participation problems with an interplay of biological, social and psychological factors maintaining pain and/or disability. Participants were excluded if they were unable to actively participate in treatment (insufficient motivation based on the estimate of the treatment team, limited Dutch language skills, environmental factors, or other pending treatments), if they had severe personality or other psychiatric disorders, if a disagreement was present between patient and care providers on content of treatment, or if pending legal procedures hindered full cooperation.

Outcome variable

The outcome variable was treatment success measured by the evolution of the Pain Disability Index (PDI) over time (from baseline to right after the 10-week IMPT program). The PDI is a patient reported questionnaire to measure the influence of average pain complaints on their daily life activities. It consists of seven subitems: 1) family/home responsibilities; 2) recreation; 3) social activity; 4) occupation; 5) sexual behavior; 6) self-care; and 7) life support activity. Each subitem is scored with a numeric rating scale from 0 ("no disability") to 10 ("maximum disability"), with a maximum score of 70 where higher scores indicate higher degrees of disability. The PDI was dichotomized based on the minimal clinically important change (MCIC): a change from baseline smaller than the MCIC (decrease of ≤8 points, 'no change' or increase in points) was interpreted as no treatment success (non-response), whereas a change equal to or larger than the MCIC (decrease of ≥9 points) was interpreted as treatment success (response).[21] The baseline PDI baseline score was also added as predictor in the model to correct for PDI baseline scores.[22]

Construct validity of the Dutch language version of the PDI is confirmed and test-retest reliability is good in patients with chronic pain.[21, 23] The PDI was chosen based on generalizability and implementation of the model that was developed, because this outcome is included as the primary outcome in the coreset Dutch Dataset Pain Rehabilitation (DDPR) and internationally used.[24]

Candidate predictors

Candidate predictors were carefully selected by opinions of experts in the field (six medical researchers, physiatrist, physiotherapist/IMPT trajectory coordinator and two patients with chronic musculoskeletal pain and OA), in combination with an explorative literature review of individual papers and meta-analyses on predictive factors of IMPT.[16, 25-28] A digital consensus meeting was set up to decide which predictors should be included in the model. All experts were allowed to brainstorm about which factors they assumed important for treatment success of IMPT based on their experience. Again, to ensure generalizability and implementation of the model that was developed, all predictors needed to be quantitative variables and part of the DDPR (both the compulsory and optional part) as standard measured at intake at CIR of each participant. This means that results of both the brainstorm session and the explorative literature review were compared to the list of measured variables of the DDPR. In Supplemen-

tary Digital Material 2 (Supplementary Table I) detailed information is shown about the variables quoted in the brainstorm session and the list of measured variables of the DDPR, including the measurement scales.

Sample size

The required sample size was dependent on the number of candidate predictors and the number of patients who underwent treatment and who provided data at start and end of treatment. Since the candidate predictors were established during this project, the final sample size could not be determined beforehand. However, knowing that roughly 300-400 chronic pain patients with OA are admitted to the IMPT within CIR per year and accounting for an event rate of about 50% responders,[29] even 60-80 predictors could be used in the model using the rule of thumb of at least five events-per-variable as a criterion for enough power in a logistic regression model with binary outcome.[30]

Statistical analysis

Statistical analysis was performed in the IBM Statistical Package for Social Sciences Version v. 25 (SPSS, IBM Corporation, Armonk, NY, USA) and R v. 4.0.2.

Data preprocessing

Multiple imputation with fully conditional specification (N.=5 imputations) was used to impute incomplete records (predictor variables as well as outcome variable). Predictive mean matching was used for the imputation model for the continuous variables.

Second, multicollinearity of predictor variables was assessed using collinearity diagnostics (variance inflation factor >4 was seen as evidence of multicollinearity).[31] Third, the assumption of linearity between predictor variables and the log odds of the outcome variable (PDI) was explored by using the Box-Tidwell test and visual inspection. In case the linearity assumption was violated for a variable, quadratic (and cubic) terms of this variable were added to the regression model to examine the best fit.

Final model development

Logistic regression analysis was performed to estimate model coefficients. In order to reduce the number of predictors with the goal of building a model that is simple enough to be used in clinical practice, a backwards selection method was used on the imputed datasets based on the significance levels of the likelihood-ratio criterion (cut-off for removal P=0.2 according to regression and prediction modelling guidelines).[32] Variables that were part of at least two out of five final step models were included in a final model through the forced entry method, and the results over imputations were combined using Rubin's rules.[33] The discriminative ability, which is most relevant at the group level, was visualized by a receiver operating characteristic curve (ROC) and estimated by the area under the curve (AUC). The latter was interpreted as acceptable if the AUC≥0.7, and as excellent if the AUC≥0.8.[34] Probability distributions were displayed in a histogram, using three different cut-off points (Youden Index,[35] 0.2, 0.3 and 0.5) to show the prediction quality (sensitivity analysis) and to see when specificity and sensitivity was the highest. In addition, the Hosmer and Lemeshow Goodness-of-fit was applied to test the goodness of fit of the model (P>0.05). Calibration was visualized by a calibration plot of the predicted probabilities versus observed frequencies.

Internal validation

Finally, the internal validity of all five imputed models was evaluated using bootstrap validation (package rms in R with 1000 iterations) to estimate a shrinkage factor to penalize model coefficients, and to estimate optimism-corrected performance (AUC and Nagelkerke R2). The results of all imputed models were again combined using Rubin's rules.[33] The regression coefficients of the original model were multiplied by the shrinkage factor, and the model intercept was subsequently re-estimated.

The logistic regression equation is presented as follows: first, the 'linear predictor' (LP of treatment success) part was computed as "$B0 + B1 \times X1 + B2 \times X2 + \cdots + Bn \times Xn$" based on the regression coefficients from the model. Then, the predicted probability was calculated as: $1 / (1 + EXP - [LP\{\text{treatment success}\}])$.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Participants and descriptive data

Data of 599 chronic pain patients with referral diagnosis of OA that underwent IMPT could be retrospectively retrieved out of the patient's file. Demographics and baseline values of participants are presented in Table I. Of the 599

TABLE I.—*Demographics and baseline values of 599 included participants (possible predictors).*

Variables	Mean±SD	N. missing (%)
Numerical variables		
Age (years)	52.63±10.40	0 (0.00%)
BMI (kg/m²)	28.80±5.57	38 (4.67%)
Number of pain locations	4.79±2.50	23 (4.84%)
PDI at baseline (0-70)	38.68±11.82	22 (3.67%)
Pain severity (average, 0-10)	6.63±1.74	23 (3.84%)
Pain severity (worst, 0-10)	7.74±1.61	23 (3.84%)
CIS (7-140)	52.14±12.73	19 (3.17%)
Self-rated work capacity (0-10)	3.09±2.65	24 (4.01%)
HADS subscale anxiety (0-21)	8.68±4.16	25 (4.17%)
HADS subscale depression (0-21)	8.21±4.23	25 (4.17%)
IPQK subscale consequences (0-10)	8.01±1.85	26 (4.34%)
IPQK subscale timeline (0-10)	8.33±2.05	26 (4.34%)
IPQK subscale personal control (0-10)	3.35±2.47	26 (4.34%)
IPQK subscale treatment control (0-10)	6.40±2.12	26 (4.34%)
IPQK subscale identity (0-10)	7.75±1.62	26 (4.34%)
IPQK subscale illness concern (0-10)	7.33±2.43	26 (4.34%)
IPQK subscale coherence (0-10)	5.35±2.76	26 (4.34%)
IPQK subscale emotional representation (0-10)	7.29±2.25	26 (4.34%)
PCS (0-56)	21.58±10.89	27 (4.34%)
PIPS subscale avoidance (10-70)	34.74±8.73	82 (13.69%)
PIPS subscale cognitive fusion (6-42)	22.73±3.50	21 (3.51%)
PSEQ (0-60)	30.56±11.47	23 (3.84%)
SCL90 subscale hostility (0-30)	8.85±2.89	22 (3.67%)
SF12 mental component (0-50)	38.34±9.95	29 (4.84%)
SF12 physical component (0-50)	29.80±6.41	29 (4.84%)
Categorical variables	N. (%)	N. (%)
Sex		0 (0.00%)
Male	174 (29%)	
Female	425 (71%)	
Pain duration		23 (3.80%)
0-2 years ago	156 (27%)	
2-5 years ago	153 (27%)	
>5 years ago	267 (46%)	
Pain medication		24 (4.00%)
No	168 (29%)	
Yes	407 (71%)	
Education level		24 (4.00%)
Low	126 (22%)	
Medium	334 (58%)	
High	115 (20%)	
Alcohol use		24 (4.00%)
No	304 (53%)	
Yes	271 (47%)	
Smoking		24 (4.00%)
No	454 (79%)	
Yes	121 (21%)	
Drugs		24 (4.00%)
No	561 (98%)	
Yes	14 (2%)	

PDI: Pain Disability Index; CIS: checklist individual strength; HADS: Hospital Anxiety and Depression Scale; IPQK: Illness Perceptions Questionnaire - Short Version; PCS: Pain Catastrophizing Scale; PIPS: Psychological Inflexibility Pain Scale; PSEQ: Pain Self-Efficacy Questionnaire; SCL90: Symptom Checklist – 90 items; SF12: short-form 12.

participants, 553 completed the IMPT program (92.4%). The primary outcome variable had 12.9% missing values because patients either stopped treatment prematurely (N.=46) or did not complete the questionnaires pre- (N.=6) or posttreatment (N.=25). Reasons to stop treatment were too large time investment (N.=5), going into a new medical diagnostic or interventional trajectory (N.=8), insufficient fit between patient and CIR team regarding treatment goals (N.=11), or other (N.=22). However, all missing data was imputed and as such, data of every participant was described and analyzed. The IMPT treatment was a success (≥9 points decrease of PDI) in 324 participants and no success in 275 participants.

Candidate predictors

Pooling possible predictors from the consensus meeting and literature review yielded a definite list of 34 possible predictor variables (32 variables, of which two were categorical with three categories and therefore counted as two extra) before the start of the backward selection logistic regression analysis, which are presented in Supplementary Digital Material 3 (Supplementary Table II). A mix of demographic (age and sex), pain-related (number of pain locations, duration, severity-average, severity-worst, and use of pain medication), social (education and work capacity), psychological (anxiety, depression, pain catastrophizing, avoidance, cognitive fusion, self-efficacy, hostility, mental health, fatigue and illness perceptions), functional (disability/physical function, and physical health), and other (body mass index, alcohol use, smoking, and drugs) variables were included.

Missing value analysis showed that 30 out of 32 predictor variables had missing values (all <6.3%). The avoidance scale of the Psychological Inflexibility Pain Scale (PIPS) had 13.7% missing values. One question of the PIPS appeared to not have been included by the software developer in Asterisque, and was added halfway through the study period. Patients who completed the first version of the scale were given a missing value allocated to that question, in order to ensure recorded values were comparable.

Multicollinearity and assumption testing

Collinearity diagnostics revealed no evidence for multicollinearity (range variance inflation factor: 1.06-3.18), as such all possible predictor variables were used for model development. Regarding the linearity assumption, the Box-Tidwell Test indicated non-linearity for the relationship between the log odds of the outcome on the one hand, and the

PDI score at baseline (P=0.013) and number of pain locations (P=0.005) on the other hand. After visually inspecting the relationship between the log odds of the outcome and the frequency of successful outcome for deciles of these two variables, the quadratic and cubic terms were added to the regression model. The Wald test indicated that cubic terms of the two variables did not improve the model significantly and were therefore not implemented in the final model.

Model development

The backward selection method reduced the number of predictors to 21. Five out of these 21 variables were withheld in only one of the five final step models. The removal of this block of five variables did not lead to a significant decrease in log-likelihood for all imputed sets, and therefore these variables were removed from the model. Our remaining model thus resulted in 16 predictors and an intercept (including variables of at least two of five final step models). The (pooled) results from this model can be found in Table II. Performance measures for the model for five imputed datasets can be found in Supplementary Digital Material 4 (Supplementary Table III).

Calibration

The Hosmer and Lemeshow goodness-of-fit test implied no evidence that the model was not well calibrated (P value varied from 0.13 to 0.68 for the five imputed datasets). The calibration plot can be seen in Figure 1. The model seems to predict well over the whole range of probabilities, meaning all points in the calibration plot are positioned close to the 45° midline and no obvious under- or overestimation in part of the range.

Discrimination

The ROC-curve for the pooled model of all imputed datasets can be found in Figure 2. The AUC for this pooled model was 'acceptable' (0.74 with 95% confidence interval [CI] 0.70-0.77).

Figure 3 shows a histogram of the predicted probabilities for the treatment responders (PDI score = 1) and non-

TABLE II.—*Estimated parameters of final model and internally validated model.*

Variables	Exp(B) (95% CI)	B	Shrunk B*
Constant (B_0)	NA	-4.413	-3.659
Age (years)	0.98 (0.96-1.00)	-0.017	-0.014
Sex	1.35 (0.85-2.14)	0.300	0.252
N. of pain locations	0.55 (0.39-0.77)	-0.598	-0.502
N. of pain locations (quadratic term)	1.06 (1.02-1.09)	0.053	0.045
PDI baseline	1.28 (1.15-1.42)	0.246	0.207
PDI baseline (quadratic term)	1.00 (1.00-1.00)	-0.002	-0.002
Pain severity (worst)	0.93 (0.80-1.08)	-0.078	-0.066
Use of pain medication	0.56 (0.35-0.91)	-0.574	-0.482
Self-rated work capacity	1.12 (1.02-1.24)	0.118	0.099
Alcohol use	1.36 (0.90-2.07)	0.308	0.259
IPQK consequences	1.09 (0.93-1.27)	0.084	0.071
IPQK timeline	0.94 (0.85-1.03)	-0.064	-0.054
IPQK treatment control	1.12 (1.01-1.23)	0.109	0.092
IPQK identity	0.88 (0.73-1.06)	-0.128	-0.108
PCS	1.03 (1.01-1.05)	0.026	0.022
PSEQ	1.02 (1.00-1.05)	0.023	0.019

B: regression coefficient; SE: standard error; Exp(B): odds ratio; CI: confidence interval; PDI: Pain Disability Index; HADS: Hospital Anxiety and Depression Scale; IPQK: Illness Perceptions Questionnaire-Short Version; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire.
*Intercept estimated again (not multiplied by shrunk factor).

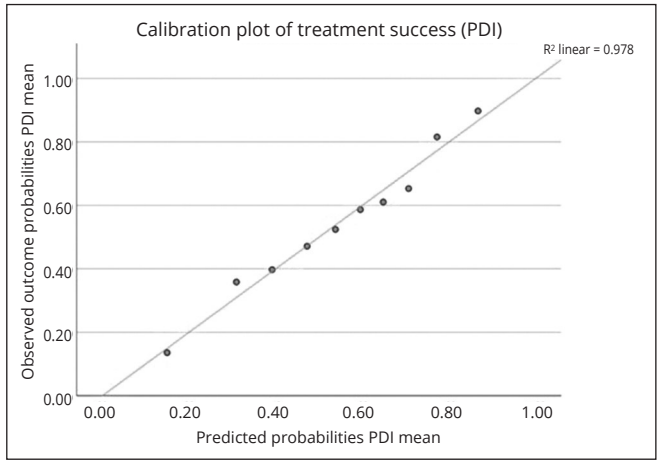

Figure 1.—Calibration plot.
PDI: Pain Disability Index.

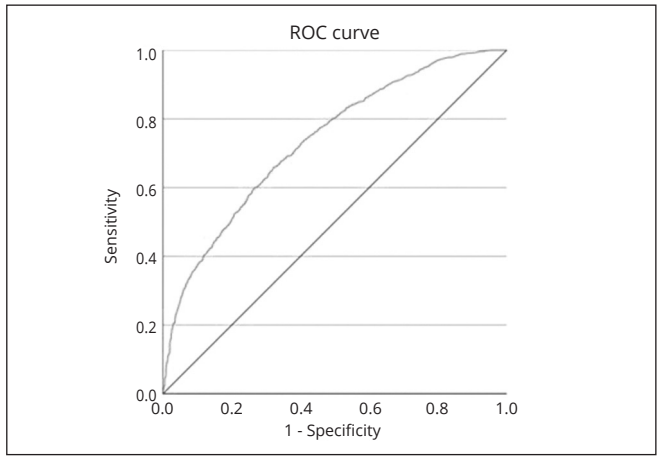

Figure 2.—Receiver operating characteristics curve.
ROC: receiver operating characteristics.

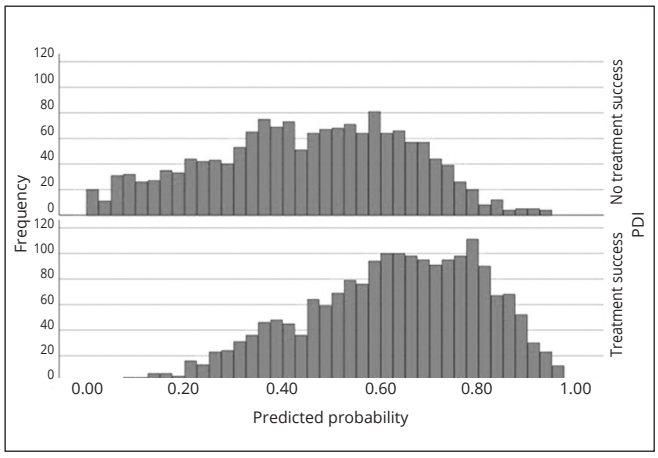

Figure 3.—Histogram of predicted probabilities stratified by event status.

responders (PDI score = 0). There is a large amount of overlap between the probability distributions, indicating that there is no clear separation of the two groups. Taking a cut-off point of 0.568 for the model, resulted in the highest sensitivity (65%) and specificity (70%), *i.e*. Youden's Index value.[35] Also other cut-off points (0.2, 0.3 and 0.5) of the model are tabulated, together with their sensitivity, specificity, positive and negative predictive value in Table III.

Internal validation

The bootstrap and shrinkage technique resulted in a pooled optimism-corrected AUC value of 0.71 and a pooled optimism-corrected Nagelkerke R^2 value of 0.18. The pooled shrinkage factor was 0.84. The internally validated model with adjusted intercept (B0) and regression coefficients (B) can be found in Table II. In order to acquire a clear idea of the actual chance of treatment success based on these results, the logistic regression equation is presented according to an example, which can be found in Table IV.

Discussion

This prospective cohort study intended to develop a clinical prediction model based on different predictors for good or negative outcome of IMPT to facilitate patient-tailored interdisciplinary care in patients with OA and to internally validate this model. A clinical prediction model is report-

TABLE IV.—*Example for treatment success calculation.*

Data of patient (example)	Formulas
• 58 years old	LP for treatment success = -3.659 –
• Man	(0.014*58) + (0.252*1) –
• 4 pain locations	(0.502*4) + (0.045*4^2) +
• PDI score: 41	(0.207*41) – (0.002*41^2) –
• Pain severity (worst): 8	(0.066*8) – (0.482*1) +
• Use of pain medication	(0.099*4) + (0.259*0) +
• Ability to work: 4/10	(0.071*4) – (0.054*7) +
• No alcohol use	(0.092*6) – (0.108*5) +
• IPQK consequences score: 4	(0.022*38) + (0.019*32) = 0.366
• IPQK timeline score: 7	Chance for treatment success:
• IPQK treatment control score: 6	$1/(1 + e^{-(-0.366)}) = 0.24 = 24\%$
• IPQK identity: 5	
• PCS score: 38	
• PSEQ score: 32	

PDI: Pain Disability Index; HADS: Hospital Anxiety and Depression Scale; IPQK: Illness Perceptions Questionnaire-Short Version; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire; LP: linear predictor.

TABLE III.—*Cross-tabulated predicted versus observed 'cases' for Youden's index, and cut-off points 0.2, 0.3 and 0.5 accompanied with sensitivity, specificity, positive predictive and negative predictive values.*

Parameters	0/1	PDI		Total	Metrics	Sig.
Youden Cut-off point 0.568		0	1		Sensitivity	0.65
	0	190	117	307	Specificity	0.70
	1	85	207	292	Positive predictive value	0.71
Total		275	324	599	Negative predictive value	0.62
Cut-off point 0.5		0	1		Sensitivity	0.75
	0	158	80	238	Specificity	0.57
	1	118	243	361	Positive predictive value	0.67
Total		275	324	599	Negative predictive value	0.66
Cut-off point 0.3		0	1		Sensitivity	0.95
	0	67	17	83	Specificity	0.24
	1	209	307	516	Positive predictive value	0.59
Total		275	324	599	Negative predictive value	0.81
Cut-off point 0.2		0	1		Sensitivity	0.99
	0	37	4	41	Specificity	0.13
	1	238	320	558	Positive predictive value	0.57
Total		275	324	599	Negative predictive value	0.90

PDI: Pain Disability Index; 0: no treatment responder; 1: treatment responder.

ed, including a specific regression equation (with lower age, being female, fewer number of pain locations, higher disability, lower pain severity at worst, no use of pain medication, higher self-rated work capacity, alcohol use, lower negative illness perceptions regarding timeline and identity and higher regarding consequences of condition, higher positive illness perceptions regarding treatment control, higher pain catastrophizing and higher pain self-efficacy as predictors) for good outcome of IMPT. The internally validated model has an acceptable discriminative power (AUC=0.71), which is only a small decrease compared to the value of 0.74 of the original model.

Interpretation of findings and relation to previous studies

Our goal was to develop a clinical prediction model based on current available data standard measured at intake at CIR, which can be directly used in clinical practice (after external validation). Different cut-off points for treatment success are presented (Youden's Index, 20-50%), because we advise not to use any cut-off scores as the 'gold standard' to in- or exclude the patient in the IMPT program. Each cut-off point has his own specific performance values, which helps the treatment team decide whether higher sensitivity (higher value means lower chance for an incorrect fault negative prediction of 'treatment success') or specificity (higher value means lower chance for an incorrect fault positive prediction of 'treatment success') is the most important element for in- or exclusion in the IMPT program. In other words, this calculated chance for treatment success should be used to start and facilitate the discussion between the treatment team and patient whether to join the IMPT program or not, whether other treatment goals (not improving disability as measured with PDI, but improving other relevant factors for the patient) for the patient are relevant, or whether other treatment modalities should be started first (*e.g*., to improve certain predictive factors for treatment success of IMPT). Another option could be to start with a short try-out treatment and evaluate with the patient after a few weeks whether the treatment is suitable and changes on modifiable predictive factors have been achieved. Besides, presenting patients a certain percentage for treatment success can increase their motivation and as such improve their active involvement in the therapy.[36] This in turn can lead to higher treatment and healthcare system efficiency.

The findings of the current study are in line with some findings of previous studies in different musculoskeletal populations, which also indicated lower pain severity levels,[37] lower number of pain location,[26] lower age,[15, 16, 37] high levels of protective cognitive behavioral factors (*e.g*., high self-efficacy, positive illness perceptions regarding treatment control), and low levels of cognitive behavioral risk factors (*e.g*., avoidance and pain catastrophizing, negative illness perceptions regarding timeline and identity)[16, 26, 27, 37, 38] as important predictive factors for good outcome after IMPT while pain duration[26, 37] and education level[37] were not. Remarkably, a recent meta-analysis in OA patients found that higher pain severity was a moderator for better function post-treatment,[39] contrasting our and another IMPT study's findings.[37] This difference may arise because this meta-analysis' solely focused on exercise therapy, and not IMPT. Moreover, it focused on other disability measures (*e.g*., Western Ontario and McMaster Universities Osteoarthritis Index *vs.* PDI in our study).[39]

Higher scores on the subscale consequences of the IPQ-K and pain catastrophizing can be seen as 'cognitive behavioral risk factors', but according to our model, a higher score predicted better chance of treatment success. This is in contrast with a previous meta-analysis, which included 4068 patients but pooled various cognitive and behavioral factors together (did not only focus on illness perception).[16] Also, our study found that higher levels of disability predicted good treatment outcome, while others showed the opposite.[16, 38] In addition, other studies indicated that lower BMI,[15] lower emotional stress,[16, 37] lower pain acceptance, higher psychological inflexibility[40] were relevant predictive factors for good treatment outcome, and that higher pain severity[16, 37] and sex[15, 37] were not. In this study, we also investigated whether emotional stress (anxiety and depression), BMI and psychological inflexibility were important factors to set-up our regression equation to predict treatment success, but these did not add significantly to the prediction of treatment success when other predictors are taken into account. On the other hand, pain severity at worst and sex were found to be relevant to include in our final regression equation model.

The main reason for above mentioned differences might be explained by the use of a different P value cut-off for predictor exclusion in the model (P=0.2 in our study *versus* P=0.05 in the other studies).[26, 27, 37, 38, 40] However, the best model is postulated to be the most complete model, in which choosing a P value of 0.05 would be too strict to define whether a variable is a predictor or not.[32] Moreover, the model of current study was created to easily use in clinical practice in a later phase; and all chosen variables are part of the DDPR, which is standardly measured at intake at CIR and other (Dutch) pain rehabilitation centers for every participant. As such, it would be a waste not to

use all the (relevant) information that is available. Other possible reasons for differences in findings compared to other studies are the development of a clinical prediction model in this study instead of just looking at possible influencing factors for treatment outcome in other studies,[15, 40] the different multidisciplinary treatment content in another study (*e.g.*, treatment team did not include a psychiatrist, education had a biomedical approach instead of a pain neuroscience-directed approach, or a dietician was involved in the treatment),[15] the different outcome measurements to calculate treatment success, or the focus on other chronic pain populations, not specifically diagnosed with OA.[16, 37, 38, 40]

Interestingly, also the use of pain medication and alcohol, and work capacity appeared important for calculating treatment success, but were not examined as possible predictive factors in the previous studies.[15, 16, 37, 38] However, as this is the first study to explicitly present a clinical prediction model for IMPT in OA patients, direct comparison with other studies is not possible.

Strengths and limitations of the study

The main strength of this article is the state of the art and detailed statistical analysis (multiple imputation for missing data, large enough sample for the number of predictors, calibration testing, etc.) and the fact that this is the first study to actually present and internally validate a clinical prediction model (with an example) to facilitate shared decision making for implementing IMPT in patients with chronic musculoskeletal pain and OA. Other strengths of this article include the way of selecting potential predictor variables for treatment success (literature review and consensus meeting); and the inclusion of predictor variables that are part of the DDPR (both the compulsory and optional part) as standard measured at intake at CIR of each participant.[24] This requires no need for extra measurements (which take extra time and resources) to predict an acceptable realistic chance for treatment success after IMPT. A first limitation of the study could be the fact that the OA diagnosis was retrospectively searched in existing medical patient files without knowing that the OA complaint is the main responsible factor for their chronic pain (despite it was the referral diagnosis of the medical doctor for IMPT). A second limitation can be the choice of using the MCIC in PDI to calculate treatment success. Previous research in other patient reported outcomes found that OA patients with only mild symptoms require less improvement than the provided MCIC to experience treatment success.[22] However, because >76.5% of the included participants reported a relatively high baseline PDI score of 30 or higher (max score = 70), we believe this limitation is kept to a minimum in our study. Another remark is that this MCIC calculation was based on chronic low back pain patients. However, a MCIC for PDI change for OA patients specifically is not yet available, and that is why in our opinion using a value in another chronic musculoskeletal population was the best option.

Clinical and research implications

First, we recommend to externally validate the model as developed in this study before it can be used as a clinically useful decision tool in clinical practice.[41] After external validation, this model can be used as a guideline for clinical practitioners next to the inclusion criteria mentioned in the method section. By developing a prediction model, we aimed to facilitate shared decision-making about inclusion in the IMPT program, and the focus of the content of the IMPT program (based on scores of the identified predictors), and whether other treatment goals (not improving disability as measured with PDI, but improving other relevant factors for the patient) are relevant, or whether other treatments before IMPT should be started first in order to increase expectance and hence the chance for a successful IMPT. The predictive profile could be of help for choosing the right treatments in clinical rehabilitation settings based on the identified predictor scores, which could include motivational interviewing,[18] pain medication withdrawal,[42] etc.[43-50]

Conclusions

This study reports a specific clinical prediction model including lower age, being female, fewer number of pain locations, higher disability, lower pain severity at the worst, no use of pain medication, higher ability to work, alcohol use, lower negative illness perceptions regarding timeline and identity and higher regarding consequences of condition, higher positive illness perceptions regarding treatment control, higher pain catastrophizing and higher pain self-efficacy as predictors for good outcome of IMPT in patients with OA. The internally validated model has an acceptable discriminative power of 0.71. We recommend to externally validate this model before using it as a useful decision tool in daily clinical practice.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Rob J. Smeets and Laura Beckers were responsible for earning the funding of the project and Rob J. Smeets was one of the clinicians providing the IMPT program. Lissa Breugelmans, Laura Beckers, Rob J. Smeets, Sander M. Van Kuijk, Bjorn Winkens, and Miranda Van Hooff attended the consensus meeting about the predictors. Lissa Breugelmans performed the statistical analyses together with the help of Sander M. Van Kuijk and Bjorn Winkens. Sander M. Van Kuijk designed the tables and wrote the manuscript; and all authors contributed to reviewing the manuscript.

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SUPPLEMENTARY DIGITAL MATERIAL 1

Osteoarthritis related key words

All Dutch & English Key-terms: artrose, arthrose, arthrosis, coxarthrose, coxarthrosis, coxartrose, coxartrosis, degeneratie, discogeen, discogene, facetartrose, facetarthrose, facetartrosis, failed back, FBSS, foramen vernauwing, foramen, gonarthrose, gonarthrosis, heupprothese, kanaalstenose, knieprothese, modic, omoartrose, prothese, recessus vernauwing, slijtage, total hip prosthesis, total knee arthroplasy, total knee prosthesis, tussenwervelschijf versmalling

SUPPLEMENTARY DIGITAL MATERIAL 2

Supplementary Table I.—Possible predictors found in the expert-brainstorm session, literature review and Dutch Dataset Pain Rehabilitation.

Brainstorm experts in the field	Literature review	Dutch Dataset Pain Rehabilitation (compulsory and optional part)
• Depression • To take responsibility for the treatment • Level of limitation • Avoidance • Pain intensity • Pain duration • Pain experience • Absence of work • Motivation • Communication with treatment team • Openness and hostility • To be motivated to participate in the treatment • Having confidence in the treatment team to make decisions about the rehabilitation procedure	• Emotional factors • Cognitive and behaviour factors • Self-reported physical function/physical limitations • Number of pain locations • Pain intensity • Pain duration • Age • Work level • Educational level	• General amnestic questionnaire (age, sex, body mass index, other chronic diseases, alcohol, smoking, drugs, use of medication, living situation, having children, highest education level) • Pain location • Pain duration • Pain intensity (mean) • Pain intensity (peak) • Level of cognitive problems • Work status • Working capacity • Receiving payment benefits • Help request • Adverse effects • Physical activity • Influence of pain on mood • Help needed for daily activities • Adjustments at home • Use of help devices • Experienced drastic events • Activities during a normal day • Pain Catastrophizing Scale • Hospital Anxiety and Depression Scale • Douleur Neuropathique- questionnaire • Pain Disability Index

	• Short-form 12 physical component • Short-form 12 mental component • Psychological stress • Sleep problems (Checklist individual strength) • Global perceived effect • Psychological inflexibility pain scale • Pain self-efficacy questionnaire • llness perceptions questionnaire-short version • Fear avoidance beliefs questionnaire

PDI: Pain Disability Index; HADS: Hospital Anxiety and Depression Scale; PCS: Pain Catastrophizing Scale; PIPS: Psychological Inflexibility Pain Scale; SF12: short-form 12; PSEQ: pain self-efficacy questionnaire; CIS: Checklist Individual Strength; IPQK: Illness Perceptions Questionnaire-Short Version.

SUPPLEMENTARY DIGITAL MATERIAL 3

Supplementary Table II.—Potential predictor variables included in model development.

Potential predictor (all measured at baseline)	Measurement method
Age	-General questionnaire DDPR
Sex	-General questionnaire DDPR -1= male, 2= female
Number of pain locations	-A list with 10 body regions -Scored from 1 to maximum 10 body regions
Body Mass Index (kg/m^2)	-Calculated with body weight and height assessed by physiotherapist
Disability/physical function	-Total score PDI [23] -0 (no limitations) to 10 (completely limited)
Pain duration	-General questionnaire DDPR -Time since symptoms started: 0= 0-2 years ago, 1= 2-5 years ago, 2= more than 5 years ago
Pain severity (average)	-Average pain during the last week- general questionnaire DDPR -Numeric rating scale -0 (no pain) to 10 (worst imaginable pain)
Pain severity (worst)	-Worst pain during the last week- general questionnaire DDPR -Numeric rating scale -0 (no pain) to 10 (worst imaginable pain)
Use of pain medication	-General questionnaire DDPR, -0= no, 1= yes
Highest education level	-General questionnaire DDPR -1= low (no education, primary school or pre-vocational secondary education), 2= medium (secondary vocational or senior general secondary education, or higher professional education or university not completed), 3= high (higher professional education, university or postdoctoral education)
Self-rated work capacity	-Numeric rating scale -0=not able to work at all, 10= able to work as in my best period
Alcohol use	-General questionnaire DDPR -0= no, 1= yes
Smoking	-General questionnaire DDPR -0= no, 1= yes
Drugs (not medication)	-General questionnaire DDPR -0= no, 1= yes
Fatigue	-Measures subjective tiredness -Total score CIS [43] -1 (no fatigue) to 7 (extreme fatigue)
Anxiety	-Measures feelings of anxiety -HADS subscale anxiety [44] -0 to 3 (variable meaning per item)
Depression	-Measures feelings of depression -HADS subscale depression [44] -0 to 3 (variable meaning per item)
Consequences	-Measures illness perceptions about consequences of disease -IPQK subscale consequences [45]

	-0 (no influence) to 10 (many influence)
Timeline	-Measures illness perceptions about timeline of disease -IPQK subscale timeline [45] -0 (very short) to 10 (my whole life)
Personal control	-Measures illness perceptions about personal control of disease -IPQK subscale personal control [45] -0 (no control) to 10 (many control)
Treatment control	-Measures illness perceptions about treatment control of disease -IPQK subscale treatment control [45] -0 (not at all) to 10 (very much)
Identity	-Measures illness perceptions about identity of disease -IPQK subscale identity [45] -0 (no complaints) to 10 (very serious complaints)
Illness concern	-Measures illness perceptions about concerns about disease -IPQK subscale illness concern [45] -0 (not worried) to 10 (very much worried)
Coherence	-Measures illness perceptions about coherence of disease -IPQK subscale coherence [45] -0 (no understanding) to 10 (very much understanding)
Emotional representation	-Measures illness perceptions about emotional representation -IPQK subscale emotional representation [45] -0 (no influence) to 10 (many influence)
Pain catastrophizing	-Measures to what degree patient experiences catastrophizing -Total score PCS [46] -0 (not at all) to 4 (all the time)
Avoidance	-Measures aspects of psychological inflexibility (avoidance) -PIPS subscale avoidance [47] -0 (never true) to 7 (always true)
Cognitive fusion	-Measures aspects of psychological inflexibility (cognitive fusion) -PIPS subscale cognitive fusion [47] -0 (never true) to 7 (always true)
Self-efficacy	-Measures confidence of being able to perform daily tasks despite the pain -Total score PSEQ [48] -0 (not at all confident) to 6 (completely confident)
Hostility	-Measures to what degree patient was bothered by 90 psychological and physical symptoms -SCL90 subscale hostility [49] -1 (completely not) to 5 (really bad)
Mental health	-Measures general mental health status -Mental Component Summary SF12 [50] -Likert scale is item dependent, scored from 0-50 (higher scores is better mental health)
Physical health	-Measures general physical health status -Physical Component Summary SF12 [50] -Likert scale is item dependent, scored from 0-50 (higher scores is better physical health)

PDI: Pain Disability Index; CIS: Checklist individual strength; HADS: Hospital Anxiety and Depression Scale; IPQK: Illness Perceptions Questionnaire-Short Version; PCS: Pain Catastrophizing Scale; PIPS: Psychological Inflexibility Pain Scale; PSEQ: Pain Self-Efficacy Questionnaire; SCL90: Symptom Checklist – 90 items; SF12: short-form 12; DDPR: Dutch Dataset Pain Rehabilitation.

SUPPLEMENTARY DIGITAL MATERIAL 4

Supplementary Table III.—Performance measures of the final model for 5 imputed datasets.

Imputed number	**-2 log likelihood**	**Cox & Snell R Square**	**Nagelkerke R^2**
Original data	586.555	0.20	0.27
1	694.495	0.19	0.26
2	727.278	0.16	0.21
3	718.625	0.17	0.22
4	721.570	0.16	0.22
5	703.251	0.19	0.25