




RESEARCH ARTICLE

Finding predictors for successful opioid response in cancer patients: An analysis of data from four randomized controlled trials

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Abstract

Context: There is no consensus on which “strong” (or step 3 WHO analgesic ladder) opioid to prescribe to a particular patient with cancer-related pain. A better understanding of opioid and patient characteristics on treatment response will contribute to a more personalized opioid treatment.

Objectives: Assessment of potential predictors for successful opioid treatment response in patients with cancer pain.

Methods: An international partnership between four cancer pain research groups resulted in a combined individual-level database from four relevant randomized controlled trials (RCTs; $n=881$). Together, these RCTs investigated the short-term (1 week) and medium-term (4 or 5 weeks) treatment responses for morphine, buprenorphine, methadone, oxycodone, and fentanyl. Candidate predictors for treatment response were sex, age, pain type, pain duration, depression, anxiety, Karnofsky performance score, opioid type, and use of anti-neuropathic drug.

Results: Opioid type and pain type were found statistically significant predictors of short-term treatment success. Sex, age, pain type, anxiety, and opioid type were statistically, significantly associated with medium-term treatment success. However, these models showed low discriminative power.

Conclusion: Fentanyl and methadone, and mixed pain were found to be statistically significant predictors of treatment success in patients with cancer-related pain. With the predictors currently assessed our data did not allow for the creation of a clinical prediction model with good discriminative power. Additional–unrevealed–predictors are necessary to develop a future prediction model.

KEYWORDS

cancer, opioid analgesics, pain

INTRODUCTION

“Strong” opioids are the cornerstone of cancer-related pain management.¹ Although several opioid types are available in most European countries, no differences are found in their analgesic effect. Therefore, no consensus can be reached on the choice of which opioid to start with

when necessary.² Nevertheless, in clinical practice, it is observed that while one patient may respond well to a particular opioid, another might not.³ Therefore, a prediction model for treatment success for the individual patient may improve pain management in patients with cancer.

Available opioids differ in their receptor affinity, solubility in water and lipids, metabolites, distribution

volume, drug interactions, and routes of administration.⁴ Patients differ in pain characteristics, pharmacogenetics, organ function, and as a consequence pharmacodynamics and pharmacokinetics of opioids administered. A better understanding of opioid and patient's characteristics on treatment response is likely to contribute to a more personalized opioid treatment.⁵ Previous studies have found associations between treatment response and, among others, the presence of liver metastases, breakthrough pain, genetic markers, duration of pain, neuropathic pain, age, and opioid type.^{3,6} However, these studies have investigated only a limited selection of opioids. Therefore, the rationale of this study is that by combining the data of multiple randomized controlled trials (RCT's), the number of opioids in mutual comparison can be increased.

In this study, we aim to detect predictors for a successful treatment response to treatment with strong opioids in patients with cancer-related pain. An international partnership was established between four cancer pain research groups to share individual patient-level data of relevant RCTs included in the analysis.

METHODS

Patients

A literature search was conducted in PubMed from January 1, 1985, up to December 31, 2020, to identify RCTs on the efficacy of “strong” opioids in cancer pain (see Appendix S1 for search string). An additional search via reference tracking was performed (see flowchart in Figure 1). The authors of the selected publications were approached to share individual-level data to compose an aggregated database for the assessment of predictors for opioid response. This resulted in an international partnership between four cancer pain research groups to share data from five RCTs and to cooperate in the current study.

Patients with cancer pain from four RCTs were included in the present study.^{3,6-9} These studies were conducted between 2006 and 2015 in Italy, Poland, and the Netherlands. Details of each study design, recruitment of participants, treatment protocol, ethics committee approval, and treatment are provided in Appendix S2. Baseline characteristics of each study population are depicted in Table 1.

Outcomes and predictors

The opioid response was evaluated at 1 week (short-term) and at 4 or 5 weeks (medium-term) by means of a pain intensity assessed by the numeric rating scale (NRS). A successful response was defined by $\geq 50\%$ NRS reduction in pain intensity compared to baseline.

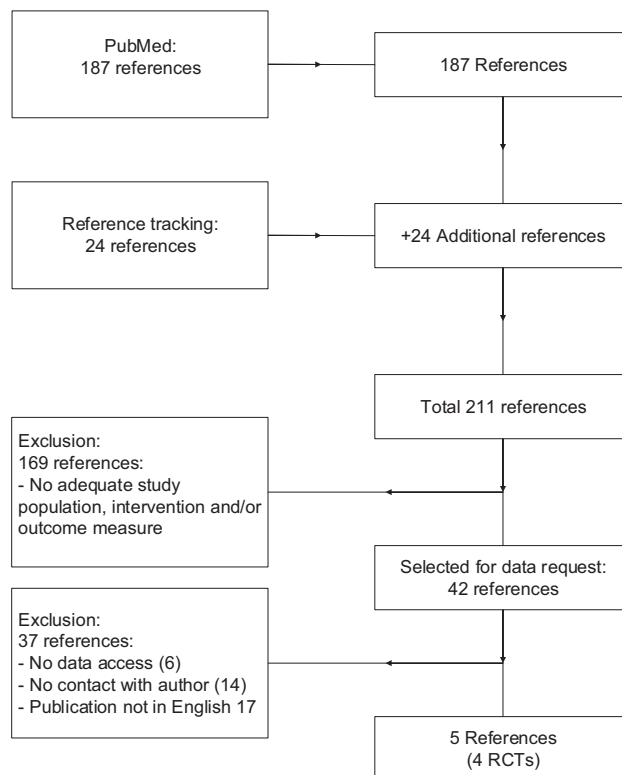


FIGURE 1 Flowchart of literature search.

The following candidate predictors for opioid response were available: sex (male/female), age (years), pain type (nociceptive/nociceptive and neuropathic), pain duration (months), depression (yes/no, measured with Hospital Anxiety and Depression Score (HADS), using a cut-off >10 to represent depression, or a single item question on a four-point Likert scale (0 = not at all, 1 = to some extent, 2 = rather much, 3 = very much) using a cut-off >0 , anxiety (yes/no, measured with HADS, using a cut-off >10 to represent anxiety, or a single item question on a four-point Likert scale: 0 = not at all, 1 = to some extent, 2 = rather much, 3 = very much) using a cut-off >0 , functional impairment: yes/no, measured with Karnofsky performance score (KPS) using a cut-off ≤ 70 to indicate functional impairment, or measured with the sum of the first three items of the EQ5D >3 (yes/no), opioid treatment (morphine/fentanyl/oxycodone/methadone/buprenorphine), and use of anti-neuropathic adjuvant analgesics at baseline (yes/no). Concerning the type of pain, in the studies of Corli et al. and Haumann et al., the DN4 was used to establish the presence of neuropathic pain, Nosek and Leppert divided patients into two subgroups: patients with predominant nociceptive pain component (bone and/or visceral), and those with predominant neuropathic pain component, while the study of Zecca et al. included patients with cancer pain and did not further specify the type of pain.

TABLE 1 Baseline characteristics of patients from four randomized controlled trials. [Correction added on 9 September 2023 after first online publication: Table 1 headings for the last 4 columns were corrected in this version]

Characteristics	All patients (n=881)	Corli et al. (n=498)	Haumann et al. (n=134)	Nosek et al. & Leppert et al. (n=62)	Zecca et al. (n=187)
Gender (male)	507 (57.5%)	277 (55.6%)	85 (63.4%)	29 (46.8%)	116 (62.0%)
Age (years)	65.6 (11.8)	66.9 (11.8)	64.2 (9.6)	69.2 (13.0)	62.0 (12.0)
Chemotherapy ^a	416/713 (58.3%)	302/393 (77.0%)	39 (29.1%)	–	–
Radiotherapy ^a	273/526 (51.9%)	165/392 (42.1%)	208 (80.6%)	–	–
Surgery ^a	252/526 (47.9%)	230/392 (58.7%)	22 (16.4%)	–	–
Pain duration (months)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–5.0)	–	–
Depression	445/694 (64.1%)	370 (74.3%)	32 (23.9%)	43 (69.4%)	–
Anxiety	458/693 (66.1%)	375 (75.3%)	62 (46.3%)	21/61 (34.4%)	–
KPS (≤70)	566/877 (64.5%)	330 (66.3%)	94 (70.1%)	60 (96.8%)	82/183 (44.8%)
Morphine	231 (26.2%)	122 (24.5%)	–	14 (22.6%)	95 (50.8%)
Fentanyl	205 (23.3%)	124 (24.9%)	66 (49.3%)	15 (24.2%)	–
Oxycodone	233 (26.4%)	125 (25.1%)	–	16 (25.8%)	92 (49.2%)
Methadone	68 (7.7%)	–	68 (50.7%)	–	–
Buprenorphine	144 (16.3%)	127 (25.5%)	–	17 (27.4%)	–
Opioid increase ratio (baseline to last follow-up)	1.5 (1.0–2.0)	1.3 (1.0–2.0)	1.5 (1.0–3.0)	1.8 (1.8–3.2)	–
Use of anti-neuropathic medication at baseline	117/857 (13.7%)	70/487 (14.4%)	16/127 (12.6%)	3/56 (5.4%)	28 (15.0%)

Note: Values represent mean (standard deviation), median (interquartile range), or number (%).

Abbreviation: KPS, Karnofsky performance score.

^aTreatment at baseline.

Statistical analysis

Baseline characteristics of patients stratified by study were described as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and count and percentage for nominal variables.

Missing data were imputed using Multiple Multivariate Imputation by Chained Equations.^{10–13} Theoretically, it is best to use a high number of imputations that is at least equal to the percentage of missingness. In practice, the maximum number can be set taking the computational power into account. We therefore created 53 imputed datasets using predictive mean. All candidate predictors and the outcome successful response were included in the imputation model.

A logistic regression analysis was performed to estimate regression coefficients of the short-term and medium-term association between predictors and successful response. First, an univariable logistic regression model was computed for each candidate predictor in each of the imputed datasets. Candidate predictors that were statistically significant in ≥50% of the imputed datasets were included in a multivariable logistic regression model. A backward stepwise elimination across all imputed datasets was used to determine the definitive set of predictors, using a liberal *p*-value of 0.3 according to current guidelines for developing prediction models.¹⁴ Because convenience sampling was used, at most one

predictive variable was included for every 10 events to keep the risk of overfitting the model low. In addition to the multivariable analysis, an interaction between pain type and opioid type was assessed for both the short-term and medium-term model. To decrease the complexity of the models examining the interaction effect, the following opioid groups based on the receptor activity were created: (1) Morphine, Fentanyl, and Oxycodone (μ -agonist); (2) Methadone (μ -agonist and *N*-Methyl-D-Aspartate (NMDA)-antagonist); and (3) Buprenorphine (μ -agonist and κ -antagonist).

Internal validation of the regression models was performed to evaluate the predictive performance, using the Area Under the Receiver Operating Characteristic Curve (AUC). The AUC reflects how well the model discriminates between those with a successful and unsuccessful response and has a range from 0.5 (i.e., no discriminative ability) to 1.0 (perfect discriminative ability). Calibration of the models, i.e., the correspondence of the predicted and observed probabilities, was evaluated visually by using calibration plots. The goodness of fit for the models was assessed using the Hosmer–Lemeshow test (where a non-significant *p*-value represents a good fit) and the accuracy of the predicted probabilities by a scaled Brier score (where a score of 0 represents accurate predicted probabilities and a score of 1 inaccurate). To assess the degree of overfitting, bootstrapping techniques for internal validation with 1000 bootstrap samples in each of the imputed datasets was used. The

estimated shrinkage factor was applied to the regression coefficients to arrive at the final models. Sensitivity analysis of the model was performed using a more liberal outcome of $\geq 33\%$ NRS reduction in pain intensity.

All analyses were performed with the R software version 4.1.2. in RStudio 2021.09.1+372 (RStudio Inc.) using the following packages: *mice*, *rms*, *auctestr*, *pROC*, and *psfmi*.

RESULTS

In total, 881 patients were available for the predictor analysis. All included patients were strong opioid-naïve at study entrance. Baseline characteristics stratified by study are summarized in Table 1. Chemotherapy, radiotherapy, surgery, and pain duration were not available from all studies. As different studies compared different opioids, not all opioid types were administered in all studies.

A successful short-term response was reported by 440/861 patients (51.1%) and 406/645 patients (62.9%) reported a successful medium-term treatment response.

Anxiety and depression showed a statistically significant association with short-term treatment success in univariable analyses ($\beta=0.318$, $p=0.038$; $\beta=0.433$, $p=0.003$; Table 2). The presence of mixed pain, and the use of fentanyl, methadone, or buprenorphine (versus morphine) showed a statistically significant (inverse) association

with treatment response ($\beta=-0.527$, $p=0.007$; $\beta=-0.755$, $p<0.001$; $\beta=-1.026$, $p<0.001$; $\beta=-0.395$, $p=0.044$). In multivariable analysis, two predictors, i.e., pain type and opioid type, showed a statistically significant (inverse) association with short-term treatment outcome ($\beta=-0.366$, $p=0.028$; fentanyl versus morphine: $\beta=-0.735$, $p<0.001$, methadone vs. morphine: $\beta=-0.944$, $p<0.001$, buprenorphine versus morphine: $\beta=-0.400$, $p=0.039$).

For medium-term treatment success, only fentanyl (vs. morphine) showed a statistically significant (inverse) association in univariable analysis ($\beta=-0.412$, $p=0.008$; Table 3). In multivariable analysis, male gender, anxiety, and fentanyl (versus morphine) showed a statistically significant (inverse) association with medium-term treatment response ($\beta=-0.266$, $p=0.025$; $\beta=-0.375$, $p=0.004$; $\beta=-0.484$, $p=0.003$).

Internal validation of the prediction models using bootstrapping across 53 imputed datasets showed poor discriminative ability for predicting short-term treatment success (AUC 0.615, IQR 0.575–0.654) and for predicting medium-term treatment success (AUC 0.600, IQR 0.558–0.641). Both prediction models showed moderate accuracy of predicted probabilities (mean Brier score 0.240 for short-term prediction, and 0.251 for medium-term prediction).

Good calibration was observed for short-term prediction (Hosmer–Lemeshow test, $p>0.999$), while poor calibration was found for medium-term prediction ($p<0.001$; Figures 2 and 3). Predicted probabilities for

TABLE 2 Univariable and multivariable regression coefficients of predictors for short-term treatment success.

Predictor	Univariable			Multivariable		
	B	OR (95% CI)	p-Value	B	OR (95% CI)	p-Value
Gender (male)	-0.008	0.992 (0.745–1.321)	0.738			
Age (years)	0.000	1.000 (0.891–1.122)	0.372			
Pain type (mixed)	-0.527	0.590 (0.371–0.938)	0.007*	-0.366	0.694 (0.476–1.011)	0.028*
Pain duration (months)	0.010	1.011 (0.919–1.111)	0.409			
Depression	0.433	1.542 (0.686–3.465)	0.003*			
Anxiety	0.318	1.374 (0.690–2.738)	0.038*			
KPS (≤ 70)	-0.354	0.702 (0.167–2.956)	0.115			
Opioid						
Morphine	(Reference)			(Reference)		
Fentanyl	-0.755	0.470 (0.319–0.694)	<0.001*	-0.735	0.480 (0.325–0.708)	<0.001*
Oxycodone	-0.154	0.857 (0.589–1.246)	0.387	-0.153	0.858 (0.589–1.251)	0.393
Methadone	-1.026	0.360 (0.201–0.644)	<0.001*	-0.944	0.390 (0.217–0.700)	<0.001*
Buprenorphine	-0.395	0.674 (0.441–1.029)	0.044*	-0.400	0.671 (0.439–1.026)	0.039*
Use of anti-neuropathic medication at baseline	0.047	1.048 (0.647–1.698)	0.591			
Intercept ^a				0.464		

Note: Significance level: 0.05.

Abbreviations: 95% CI, 95% confidence interval; KPS, Karnofsky performance score; OR, odds ratio.

*Significant result.

^a The intercept is given for the multivariable model to allow for the computation of the probability of short-term treatment success for an individual patient based on their predictor variable values.

treatment success in both models were centered between 20%–30% and 50%–70% probabilities, i.e., low and high probabilities were rarely predicted.

Sensitivity analysis using a more liberal definition of treatment success did not improve the models (data not shown).

The interaction effects between opioid type and pain type for short-term treatment success were assessed (Table 4), showing a statistically significant interaction between methadone and pain type ($\beta=1.511$, $p=0.002$). However, model performances did not improve by adding this interaction effect. For medium-term treatment success, no statistically significant associations were found for the interaction between pain type and opioid (Table 5).

DISCUSSION

Fentanyl and methadone, and mixed pain were found statistically significant predictors of short-term treatment success. Sex, age, pain type, anxiety, and opioid type were statistically significant associated with medium-term treatment success.

In the present study, an attempt was made to assess predictors of short-term and medium-term treatment response, with five different opioids considered in four RCTs. Nine candidate predictors were considered, which included the opioids themselves but also a series of

clinical parameters that were collected in all the examined studies. Of these, only a small number of predictors resulted to be statistically, significantly associated with short-term or medium-term opioid response.

Among the factors statistically significant associated with short-term treatment response, some aspects emerged. In particular, the presence of “mixed” pain – nociceptive and neuropathic at the same time – was, in comparison to nociceptive pain only, negatively associated with successful treatment response (independent from other predictor variables). This is not surprising as the two types of pain have different pathophysiology mechanisms and usually benefit from different pharmacological treatments. In six clinical practice guidelines adjuvant analgesics, such as anticonvulsants, especially gabapentin and pregabalin, and antidepressants, namely SNRI (duloxetine and venlafaxine) and tricyclics (amitriptyline), are mentioned as possible first-line treatment.^{15–19} The use of strong opioids was mentioned mostly as third-line treatment in non-cancer patients, whereas in cancer patients with severe pain they are used more frequently as a first- or second-line treatment, in the absence of other alternatives. Although the majority of the guideline development groups extrapolated their results from non-cancer publications to formulate their recommendations in cancer patients, it is plausible that the presence of the neuropathic component of pain decreases the analgesic possibilities of opioids.

TABLE 3 Univariable and multivariable regression coefficients of predictors of long-term treatment success.

Predictor	Univariable			Multivariable		
	<i>B</i>	OR (95% CI)	<i>p</i> -Value	<i>B</i>	OR (95% CI)	<i>p</i> -Value
Gender (male)	−0.397	0.672 (0.372–1.215)	0.053	−0.266	0.766 (0.558–1.053)	0.025*
Age (years)	−0.071	0.932 (0.294–2.948)	0.110	0.010	1.010 (0.997–1.023)	0.052
Pain type (mixed)	−0.102	0.903 (0.165–4.948)	0.179	−0.244	0.783 (0.535–1.47)	0.084
Pain duration (months)	0.008	1.008 (0.931–1.092)	0.218			
Depression	−0.097	0.908 (0.477–1.726)	0.362			
Anxiety	−0.443	0.642 (0.332–1.242)	0.017	−0.375	0.687 (0.485–0.974)	0.004*
KPS (≤ 70)	0.257	1.294 (0.504–3.323)	0.200			
Opioid						
<i>Morphine</i>	<i>(Reference)</i>			<i>(Reference)</i>		
Fentanyl	−0.412	0.662 (0.420–1.043)	0.008*	−0.484	0.617 (0.398–0.956)	0.003*
Oxycodone	−0.150	0.861 (0.557–1.330)	0.363	−0.146	0.864 (0.558–1.340)	0.415
Methadone	−0.241	0.786 (0.421–1.469)	0.283	−0.275	0.760 (0.406–1.423)	0.272
Buprenorphine	−0.102	0.903 (0.566–1.443)	0.565	−0.141	0.869 (0.542–1.394)	0.436
Use of anti-neuropathic medication at baseline	−0.080	0.923 (0.523–1.629)	0.608			
Intercept ^a				−0.085		

Note: Significance level: 0.05.

Abbreviation: KPS, Karnofsky performance score.

*Significant result.

^aThe intercept is given for the multivariable model to allow for the computation of the probability of long-term treatment success for an individual patient based on their predictor variable values.

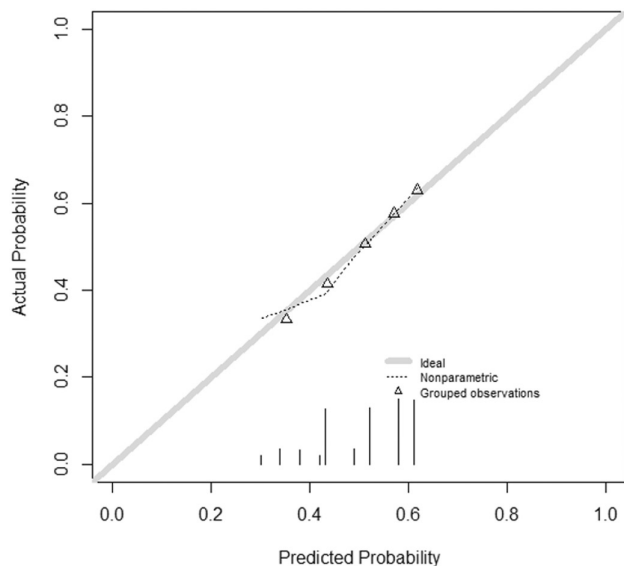


FIGURE 2 Calibration plot of short-term prediction of treatment success. Calibration plot visualizing the mean predicted treatment success probability by the model against observed frequencies per decile of treatment success. Hosmer–Lemeshow test: $p > 0.999$.

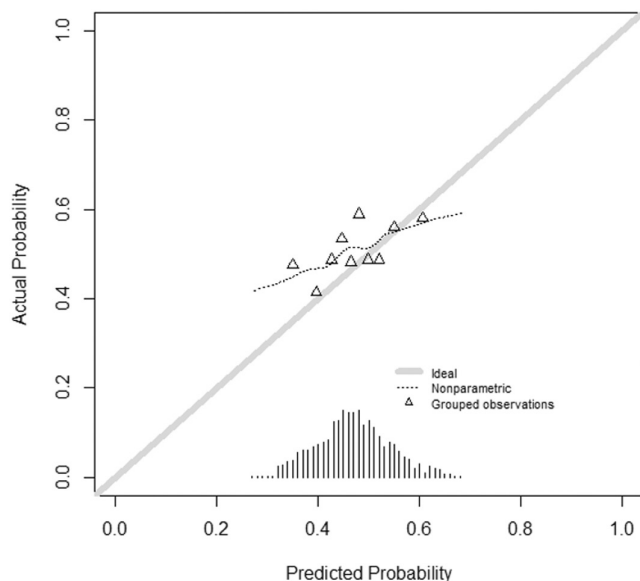


FIGURE 3 Calibration plot of medium-term prediction of treatment success. Calibration plot visualizing the mean predicted treatment success probability by the model against observed frequencies per decile of treatment success. Hosmer–Lemeshow test: $p < 0.001$.

Furthermore, this study showed that the type of opioid used had a statistically significant association with short-term treatment response (independent from other predictor variables), indicating that fentanyl, methadone, and buprenorphine are negatively associated with treatment response in comparison to morphine. Oxycodone did not show a statistically significant association with treatment

TABLE 4 Interaction effects between the opioid type and pain type (short term).

Predictor	<i>B</i>	OR (95% CI)	<i>p</i> -Value
<i>Morphine, fentanyl, and oxycodone</i>	(Reference)		
Buprenorphine	−0.084	0.919 (0.615–1.373)	0.641
Methadone	−1.223	0.294 (0.136– 0.635)	<0.001*
Mixed pain	−0.488	0.614 (0.394–0.958)	0.006*
Buprenorphine* Mixed pain	−0.228	0.796 (0.288–2.202)	0.587
Methadone* Mixed pain	1.511	4.53 (1.412–14.544)	0.002*
Intercept	0.007		

Note: Significance level: 0.05.

*Significant result.

TABLE 5 Interaction effects between opioid type and pain type (long-term).

Predictor	<i>B</i>	OR (95% CI)	<i>p</i> -Value
<i>Morphine, fentanyl, and oxycodone</i>	(Reference)		
Buprenorphine	0.053	1.055 (0.691–1.610)	0.577
Methadone	−0.048	0.953 (0.492–1.847)	0.709
Mixed pain	−0.104	0.901 (0.594–1.368)	0.243
Buprenorphine* Mixed pain	−0.059	0.943 (0.354–2.516)	0.741
Methadone* Mixed pain	0.085	1.088 (0.362–3.276)	0.696
Intercept	0.324		

Note: Significance level: 0.05.

response. Furthermore, it should be underlined that these findings do not imply that morphine is the best clinical choice. To be able to compare efficiency between opioids an RCT, cohort, or network meta-analysis including all opioids is necessary. Based on the opioid characteristics, differences could be expected between opioids with μ -opioid receptor agonism (morphine, fentanyl, and oxycodone), opioids with both μ -agonism and NMDA receptor antagonism receptor affinity (methadone), and opioids with μ -agonism and κ -receptor antagonist activity (buprenorphine). There is some evidence that methadone and buprenorphine might be effective in patients with neuropathic pain.^{20–22} In this study, we explored this and found a statistically significant interaction effect between methadone and mixed pain. Patients with mixed pain responded better to methadone. Incorporation of this effect into the predictor analysis however did not improve the

predictive capacity. In addition, it should be underlined that our findings concerning methadone are based on one RCT only. We did not find an association between mixed pain and buprenorphine.

When evaluating medium-term treatment response, female sex and presence of anxiety were predictors of a reduced analgesic response. An earlier systematic review and meta-analysis suggested that men and women may differ in the response to opioids for pain relief, although the evidence was of low quality.²³ Only fentanyl had a statistically significant association versus morphine indicating an inverse association with therapeutic success.

The strength of this study is that individual patient-level data of 881 patients were available for analyses. This allowed for a more detailed analysis when compared to regular meta-analyses using published data only. Nonetheless, we were confronted with several limitations. The most important limitation of our study is the low discriminative power of the predictors we found. Using a more liberal outcome measure (33% pain reduction instead of a 50% reduction) in the sensitivity analyses did not improve predictive performance. Therefore, the findings are not ready to be applied in clinical practice. Another important limitation is the heterogeneity between the studies with regard to the titration schedules and plans for dose increase. These differences may have influenced the results since it cannot be excluded that part of the effects is caused by the titration schedule rather than the opioid as a substance. However, the differences in opioid increase ratios from baseline to last follow-up were relatively small, with median values between 1.3 and 1.8. In addition, although the treatment protocols concerning the use of rescue medication for breakthrough pain are summarized in the supplemental information, its use is not incorporated in the analyses. This implies a risk of bias and might be a cause for the low discriminate power as previously mentioned. Also, the use of anti-neuropathic adjuvant analgesics during follow-up is not incorporated; however, baseline use did not reveal as a significant predictor in the univariate analyses. Another limitation is that the type of cancer, cancer stage, and the use of non-opioid analgesics were not included in the analyses. Furthermore, it is important to highlight that this study was a search for associations, but cannot be used to make statements about causal relations. The authors must admit that the results of the internal validation of the prediction model that was built using these predictors did not function as hoped. It is impossible to predict the effect of opioids on an individual using the predictors examined in this study. In order to build a prediction model with good discriminative power, other predictors are necessary, such as genetic markers, that were not incorporated in our data sets. The genetic markers that most research has been focused on (but not limited to) are the CYP2D6 pathway and genes involved in the μ -receptor.^{24–26} The

research done on these genes does show some promising results; however, they do not provide meaningful directions in clinical practice yet. We hope that in the future incorporation of genetic markers in predictor analyses may result in a good prediction model which can guide clinicians in treating patients with cancer-related pain.

In conclusion, the analyses highlighted that patient's characteristics (mixed pain) and opioid characteristics (fentanyl and methadone) significantly influence treatment outcome, although not clinically significant. Therefore, additional – unrevealed – predictors are necessary for the development of a well performing prediction model. Therefore, our study should be considered to be a forerunner towards a future prediction model and a conscious choice of opioid drug use in cancer patients. New studies, collaborations, and a greater number of parameters and indicators appear necessary to better substantiate in advance the possibilities of therapeutic success.

AUTHOR CONTRIBUTIONS

Conception and design: MI, MT, SK, MBE. Data acquisition: MT, JH, OC, CB, WL, CB, EZ. Data analysis: MI, SK. Data interpretation: MI, MT, SK, MBE, JH. Discussion of results: all authors. Drafting the work or revising it critically for important intellectual content: all authors. Final approval: all authors.

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CONFLICT OF INTEREST STATEMENT

Nothing to disclose.

DATA AVAILABILITY STATEMENT

Study data are available on request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1.

Appendix S2.

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