Heliyon 9 (2023) e18560

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Development of a nomogram for the early prediction of PACU VAS in patients undergoing laparoscopic radical resection of colorectal cancer with fentanyl

Yan Zhou [a,1], Jian Huang [b,1], Lei Cao [c,1], Yaoyi Gao [a], Yihao Li [a], Beili Wang [a], Baishen Pan [a], Wei Guo [a,**], Jing Cang [b,*]

[a] Department of Laboratory Medicine, Zhongshan Hospital, Fudan University, 111 Yi Xue Yuan Road, Shanghai, 200032, PR China
[b] Department of Anesthesiology, Zhongshan Hospital, Fudan University, 111 Yi Xue Yuan Road, Shanghai, 200032, PR China
[c] Department of Pharmacy, Zhongshan Hospital, Fudan University, 111 Yi Xue Yuan Road, Shanghai, 200032, PR China

ARTICLE INFO

Keywords:
Analgesia
Fentanyl
Nomograms
Polymorphism
Precision medicine
Vas deferens

ABSTRACT

Introduction: To make early predictions of PACU VAS before surgery, we created a novel nomogram for the early prediction of PACU VAS in patients having laparoscopic radical excision of colorectal cancer with fentanyl.

Methods: From July 2018 to December 2020, a total of 101 patients in Zhongshan Hospital Affiliated to Fudan University who underwent laparoscopic radical resection of colorectal cancer were enrolled in this study. For feature selection, a stepwise regression model was utilized. Multivariable logistic regression analysis was used to establish a prediction model. We incorporated age, gender, weight, height, fentanyl dosage during operation, operation time, and *OPRM1* genotype, and this was presented with a nomogram. The nomogram's performance was evaluated in terms of discrimination and clinical utility.

Results: The signature, which comprised of seven carefully chosen characteristics, was linked to the PACU VAS for the development dataset. Predictors contained in the individualized prediction nomogram included age, gender, weight, height, fentanyl dosage during operation, operation time, and *OPRM1* genotype. With an area under the ROC curve of 0.877 (95% CI, 0.6874–1.0000), the model showed good discrimination. The nomogram still had good discrimination. Decision curve analysis demonstrated that the nomogram was clinically useful.

Conclusions: The nomogram presented in this study incorporates age, gender, weight, height, fentanyl dosage during operation, operation time, and *OPRM1* genotype and can be conveniently used to facilitate the individualized prediction of PACU VAS in patients undergoing laparoscopic radical resection of colorectal cancer with fentanyl.

1. Introduction

Effective pain control must be provided after surgery, which is very important to accelerate postoperative recovery, shorten the

* Corresponding author.
** Corresponding author.
E-mail addresses: guo.wei@zs-hospital.sh.cn (W. Guo), cang.jing@zs-hospital.sh.cn (J. Cang).
[1] Yan Zhou, Jian Huang, and Lei Cao, contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2023.e18560
Received 14 December 2022; Received in revised form 19 July 2023; Accepted 20 July 2023
Available online 22 July 2023

hospitalization period and improve patient satisfaction [1]. At present, fentanyl is widely used in anesthesia and patient-controlled analgesia (PCA) because of its strong and quick analgesic effect [2]. Its usage and dose are mainly based on the patient's height and weight, as well as the clinical experience of the anesthesiologist. However, the response to fentanyl varies among people. The insufficient or excessive dose is prone to occur during the anesthesia process. The former will lead to incomplete analgesia, while the latter will lead to severe respiratory depression [3,4]. Individualized application of fentanyl is critical to perioperative pain management and clinical treatment.

Many studies have shown that individual differences in fentanyl response are closely related to the human genetics [5,6]. Mu-opioid receptor (MOR) is encoded by human opioid receptor-1 gene (*OPRM1*) and is the main target of fentanyl. One of its SNP A118G, which is common and important in *OPRM1*, leads to a change in the amino acid at the extracellular glycosylation site of MOR cells. *OPRM1* A118G polymorphism can affect the function of MOR.

1.1. Study aims

To effectively predict opioid drug response to opioid drugs and enhance their safety and efficacy, we developed a new multivariate prediction model of the Visual Analogue Score (VAS) in the post-anesthesia care unit (PACU) by combining maternal factors, age, weight, height, the dose of fentanyl, gender, operation time and genotype of *OPRM1*. The prediction model was evaluated using the area under the ROC curve and the clinical decision curve. Our prediction algorithm identifies the object indications during the usual preoperative assessment, therefore no further tests are required. We established a simplified multiparameter risk scoring system for predicting VAS in PACU, which is suitable for clinical practice.

2. Materials and methods

2.1. Study design and population characteristics

A total of 101 patients who underwent laparoscopic resection for colon cancer, from July 2018 to December 2020, were enrolled in this study. All included patients were informed and signed informed consent.

Inclusion criteria: patients aged 45–70 years old, and American Society of Anesthesiologists (ASA) class I-II.

Exclusion criteria: morbid obesity or extreme emaciation (BMI$>$30 or $<$20 kg/m^2), liver and kidney dysfunction, chronic pain, patients who have taken enzyme inducers and inhibitors that affect CYP3A4 enzyme activity within 1 month.

Withdrawal criteria: subjects asked to withdraw informed consent, change in operation mode during operation, and the intraoperative blood loss reaching more than 500 ml.

2.2. Data source and research strategy

Data were obtained from patient medical records. The maternal candidate predictor factors selected were trustworthy, quantifiable, frequent, and predictive. Variables considered in our modeling were as follows: age, weight, height, the intraoperative dose of fentanyl, operation time, gender, and genotype of *OPRM1*.

2.3. Analgesia methods and evaluation

No preoperative medication was applied to patients before they entered the operating room. Before induction, the anesthesia mask was used for oxygen and the removal of nitrogen. Fentanyl 3 μg/kg, propofol 2 mg/kg, and CIS atracurium 0.2 mg/kg were used for intravenous induction. No supplementary respiration was performed during the induction. Endotracheal intubation was performed 3 min after all the intravenous induction had been done. Spontaneous respiration was cultivated after peritoneal suture. The dose of fentanyl was adjusted according to the spontaneous respiratory rate. After patients became conscious, the tracheal tube was removed, and they were sent to the postanesthesia care unit (PACU).

Patient-controlled intravenous analgesia (PCIA) was performed with the PCA pump. The pump was attached to the intravenous tube after the tracheal tube was removed. The patient was observed in PACU for 1 h. If the visual analogue scale/score (VAS) $\geq$4, the patient-controlled dose of fentanyl, i.e. 20 μg, was delivered. If necessary, it could be given repeatedly until the VAS score was less than 4. The analgesic effect and adverse reactions were observed at PACU.

2.4. Evaluation indexes and methods

The patient's blood pressure, heart rate, pulse, oxygen saturation, electrocardiogram, and other vital signs were monitored. The following domains were recorded: the fentanyl consumption; the VAS score from the beginning of surgery to 48 h after surgery.

The primary endpoint was that the spontaneous breathing rate of patients was stable at $\leq$ 10 times/minute before the removal of the tracheal tube, and the secondary endpoint was a VAS score of less than 4 when the patient left PACU.

2.5. Detection of genotypes

Main instruments and reagents included Applied Biosystems 7500 Fast Realtime PCR System (Thermo Fisher Scientific (China) Co.,

Ltd.), AB3730 sequencer (ABI, USA), Lab-Aid 820 Midi reagent for nucleic acid extraction (Xiamen Zhishan Biotechnology Co., Ltd.), Permix Taq@Hot Start Version (Bao Bioengineering (Dalian) Co., Ltd.), and sequencing reagent (Thermo Fisher Scientific (China) Co., Ltd.).

Two milliliters of EDTA-K2 anticoagulant were collected before the operation. Lab-Aid 820 Midi reagent was used for DNA extraction in strict accordance with the instructions. The DNA was then stored at −20 °C until detected.

The software Oligo7 was used for PCR primer design. ***OPRM1*** A118G (5′-3′) F-TTGGACTTTAAATATGGCAA; R-CATACATTGGAAATACTTAG.

Reaction conditions: 94 °C for 5 min; 45 cycles (94 °C for 30 s; 56 °C for 30 s; 72 °C for 30 s); 72 °C for 5 min; insulation at 4 °C. After purification, the PCR amplification products were sequenced on ABI 3730 DNA Analyzer, and the results were analyzed by software Chromas.

The present study conformed to the principles of the Declaration of Helsinki. Approval was obtained from the Research Ethics Committee of the Zhongshan Hospital of Fudan University (Approval number: B2018-054R).

2.6. Statistical analysis

Statistical analysis was performed using R version 3.4.1 (R Foundation for Statistical Computing) and the software IBM SPSS (version 21.0). Bivariate analysis was examined using the Mann–Whitney *U* test for continuous and ordinally distributed variables and the chi-squared test for categorical variables. For further analysis, a nomogram was formulated based on a multivariate logistic regression analysis. The forward-backward stepwise selection was applied by using the likelihood ratio test with Akaike's information criterion as the stopping rule [7]. The discrimination was quantified with the area under the receiver operating characteristic (ROC) curve. The 'rms' package was used for the nomogram and calibration curve. Individual predictions were either calculated from nomograms or obtained from the original data for the scoring system. Decision curve analysis was conducted to determine the clinical usefulness of the nomogram by quantifying the net benefits at different threshold probabilities in the validation dataset [8,9]. All statistical tests were two-sided, and P-values of <0.05 were considered significant.

3. Results

3.1. Clinical characteristics

Fig. 1 contains the flow chart of the participants. The clinical and outcome data for subjects were obtained from clinical records. All patient characteristics, including age, gender, weight, height, the dosage of fentanyl, operation time, and genotype of *OPRM1* A118G are described in Table 1.

There was no significant difference in age (59.53 ± 5.87 vs 61.67 ± 4.00), gender, weight (62.23 ± 9.17 vs 64.22 ± 7.60 kg), height (164.80 ± 7.77 vs 162.89 ± 6.53 cm), the dosage of fentanyl (8.95 ± 2.02 vs 10.21 ± 2.28 μg/kg) or operation time (2.33 ± 0.54 vs 2.26 ± 0.33 h) between VAS<4 and VAS≥4.

3.2. Feature selection

Factors with significant differences in the univariate analysis were included in the regression analysis or useful parameters in

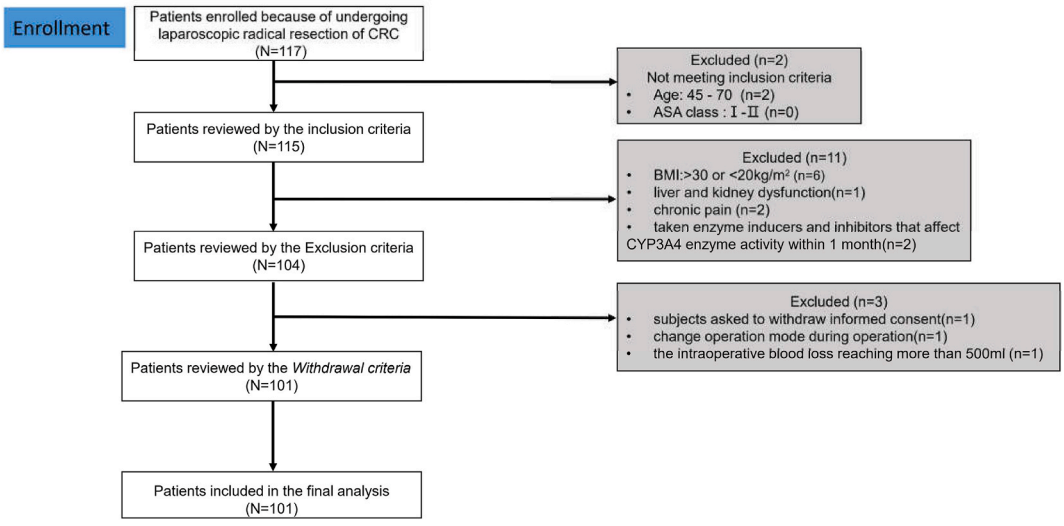

Fig. 1. Flowchart of participants.

Table 1
Characteristics of subjects with VAS<4 and VAS≥4.

Characteristic	VAS<4	VAS≥4	*P*
N	92	9	
Age	59.53 ± 5.87	61.67 ± 4.00	0.293
Gender			1.000
Male	53 (57.61%)	5 (55.56%)	
Female	39 (42.39%)	4 (44.44%)	
Weight	62.23 ± 9.17	64.22 ± 7.60	0.417
Height	164.80 ± 7.77	162.89 ± 6.53	0.440
Dosage of fentanyl	8.95 ± 2.02	10.21 ± 2.28	0.079
Operation time	2.33 ± 0.54	2.26 ± 0.33	0.812
OPRM1 A118G			0.005
GG	81 (88.04%)	4 (44.44%)	
GA + AA	11 (11.96%)	5 (55.56%)	

clinical application. Based on univariate results, multifactorial logistic regression analysis of each operation was carried out. Among texture features, 15 were reduced to 7 potential predictors based on 101 patients in the research with the stepwise multivariable logistic model. The seven features that we screened were age, gender, weight, height, dosage of fentanyl, operation time, and genotype of *OPRM1*, as shown in Table 2.

3.3. Development of an individualized prediction model

A logistic regression analysis identified the 7 features as independent predictors. The model that incorporated the above independent predictors was developed and is presented as the nomogram (Table 2 and Fig. 2).

3.4. Apparent performance of the nomogram in the subjects

Using a nomogram, the value of a single subject is located on each variable axis, and a line is drawn upward to determine the number of points for each variable value. The sum of these figures is on the total and sub-axis, and a line is drawn down to determine the risk of the vas.

The area under the ROC curve for the prediction nomogram was 0.877 (95% CI, 0.6874–1.0000) for the subjects' dataset (Fig. 3).

3.5. Clinical use

The decision curve analysis for the preeclampsia nomogram is presented in Fig. 4. The decision curve showed that if the threshold probability of a patient was between 10 and 95%, the use of the nomogram to predict PACU VAS in patients undergoing laparoscopic radical resection of colorectal cancer with fentanyl added more benefit than either using traditional methods scheme.

The y-axis measures the net benefit. The nomogram is shown by the dotted line. The assumption shown by the solid black line is that all patients with PACU VAS≥4. The solid gray line represents the assumption that no patients with PACU VAS≥4. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion who are true positive [10].

4. Discussion

We propose a new scoring system based on individual factors, the dose of fentanyl, operation time, and the gene polymorphism of pharmacodynamics and pharmacokinetics of fentanyl. The scoring system predicts PACU VAS in patients undergoing radical resection

Table 2
Risk factors of VAS.

Intercept and variable	Odds ratio	95% CI of OR	*P*
Age	1.07	0.94–1.22	0.290
Gender			
Male	Reference		
Female	1.09	0.27–4.31	0.905
Weight	1.02	0.95–1.11	0.528
Height	0.97	0.88–1.06	0.474
Dosage of fentanyl	1.30	0.96–1.76	0.088
Operation time	0.76	0.19–3.02	0.696
OPRM1 A118G			
GG	Reference		
GA + AA	14.73	3.21–67.49	0.001
Area under ROC curve	0.877		

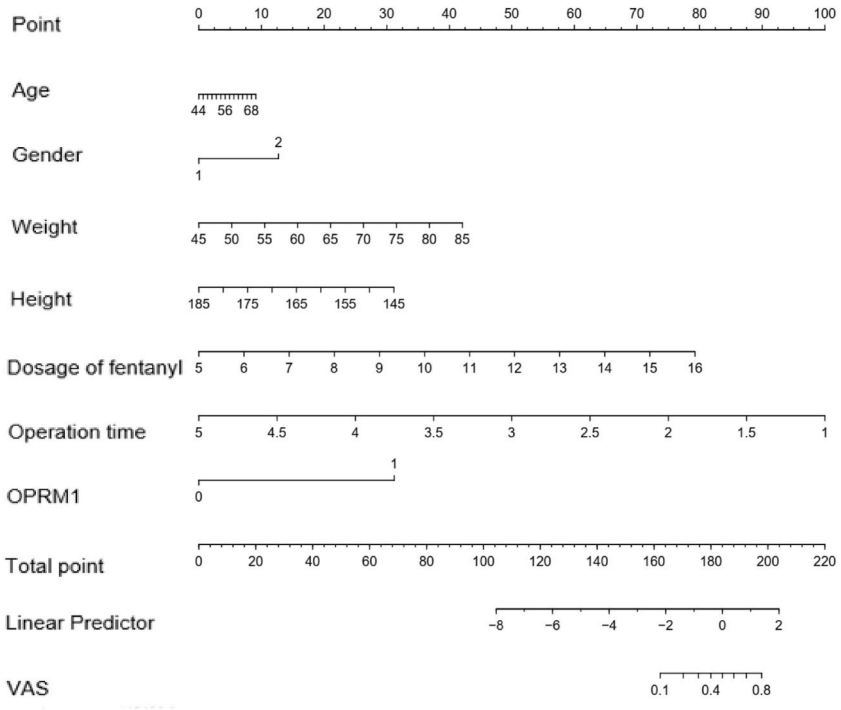

Fig. 2. Nomogram for predicting VAS.

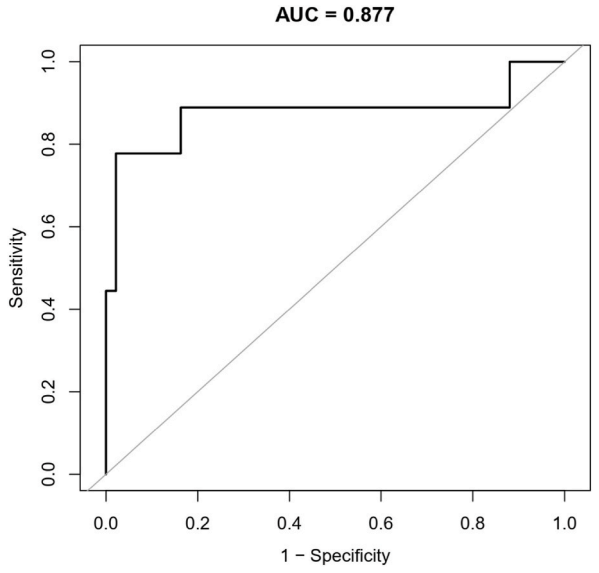

Fig. 3. ROC of the nomogram.

of colorectal cancer with fentanyl.

Our research has several advantages. First, the indicators included in our research model are routine preoperative examinations, which do not require additional tests for patients. Second, our research has strict rules for subjects enrollment and avoid selection bias. Third, we have drawn a concise nomodiagram to facilitate the application to clinical practice. Fourth, we evaluated the net benefit of our model through the clinical decision curve.

In our prediction model, logistic regression analysis identified age, gender, weight, height, fentanyl dosage during operation, operation time, and *OPRM1* genotype for PACU VAS [11]. In our study, the areas under the ROC curve for the prediction PACU VAS were 0.877 (95% CI, 0.6874–1.0000) for the dataset, which shows that our prediction model has good clinical applicability. Combining

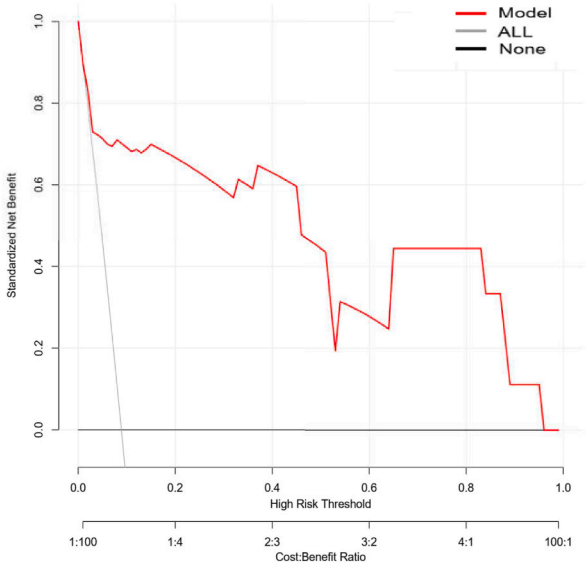

Fig. 4. Decision curve analysis for the nomogram.

the basic characteristics of patients with the genes related to the pharmacodynamics and pharmacokinetics of fentanyl to develop the prediction model is helpful in comprehensively evaluating and predicting the effect of anesthesia and improving the safety of anesthesia.

4.1. Genes factors

Many studies have reported that single nucleotide polymorphisms of pharmacodynamics and pharmacokinetics are related to drug efficacy and adverse reactions [12,13]. Detecting the SNPs and analyzing the metabolic characteristics according to different genotypes may guide clinics to choose appropriate anesthetic drugs before surgery, to improve the efficacy, reduce toxicity and adverse reactions, and provide accurate individualized medication guidance for the use of anesthetic drugs in surgical patients.

The analgesic efficacy and adverse reactions of opioids mainly act on three opioid receptors, named δ, κ, and μ. Among them, μ opioid receptors is the key targets of endogenous and exogenous opioid analgesia, tolerance, dependence, and other effects, which are coded by μ Receptor gene (*OPRM1*). *OPRM1* A118G mutation is the most common and reported functional gene. Studies have shown that its gene mutation reduces the efficacy of various opioids, and patients with GG need more opioids to relieve pain [14–17]. Other studies have shown that *OPRM1* A118G mutation can enhance the analgesic effect of patients [18–21].

Our results show that patients with A genotype are more likely to have PACU VAS≥4. Simultaneously, in the prediction model, compared with wild-type homozygous (AA) and heterozygous (AG) individuals, mutant homozygous (GG) means to have a protective factor of VAS<4 and may obtain the more significant analgesic effect.

4.2. The dose of fentanyl

Fentanyl is a potent synthetic analgesic [22]. The analgesic mechanism of fentanyl is similar to that of morphine. As an opioid receptor agonist, the effect of fentanyl is 60–80 times more powerful than morphine. Compared with morphine and pethidine, it takes effect in a shorter time, does not release histamine, has little impact on cardiovascular function, and can inhibit the stress response during endotracheal intubation.

According to the experience of clinical application, we have included the fentanyl dose in the prediction model. The results show that the fentanyl dose is a protective factor of PACU VSA less than 4. Increasing the fentanyl dose during the perioperative period can enable patients to obtain better analgesic effects.

4.3. Individual factors

The prediction model includes some individual factors, such as age, gender, weight, and height. Among these characteristics, weight and height are crucial factors in determining the fentanyl dosage in clinical settings. According to our nomogram, female, aged, shorter, and heavier are protective factors for PACU VAS below 4. According to studies, men need to take more opioids than women do in order to have the same analgesic effect. The mechanism may be caused by gender differences in the endogenous regulation of opioid receptors on pain [23]. At the same time, the dosage of anesthetic drugs gradually decreases with age. Our prediction model indicates that the outcomes are in line with the provided data.

Therefore, to justify the clinical usefulness, we assessed whether VAS of PACU nomogram-assisted decisions would provide an early warning of VAS of PACU≥4. In this study, decision curve analysis was used. Base on threshold likelihood, this innovative approach provides insight into clinical repercussions from which the net benefit may be deduced. The net benefit is defined as the proportion of true positives minus the proportion of false positives, weighted by the relative harm of false-positive and false-negative results [7,24]. The decision curve showed that if the threshold probability of a patient or doctor is between 10 and 95%, using the nomogram in the current study to early predict VAS of PACU in patients undergoing laparoscopic radical resection of colorectal cancer with fentanyl adds more benefit.

At present, the best prediction algorithm or prediction factor is not clear. The rarity of systematic model validation and calibration demonstrates the current lack of a coordinated effort to implement VAS prediction in clinical practice.

The limitations of the study include the fact that the genes markers currently included in the study are not comprehensive enough. In recent years, to predict the effect of gene polymorphism on anesthesia safety, other studies have reported that gene polymorphism such as *CYP3A4**1G and *ABCB1* C3435T is related to the dose of fentanyl and anesthesia tolerance [25]. On the other hand, due to the small size of the study cohort, we couldn't establish an independent validation set to evaluate the performance of the nomogram in the development dataset. Our predictive model is based on retrospective clinical data, and the characteristics of subjects are clinical basic data and routine examination results; thus, other novel markers are not included.

5. Conclusion

In conclusion, this study presents a nomogram that incorporates both clinical and polymorphism parameters, which can be used to easily predict PACU VAS in patients undergoing laparoscopic radical resection of colorectal cancer with fentanyl.

Author contribution statement

Yan Zhou: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Jian Huang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Lei Cao: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Yaoyi Gao; Yihao Li: Analyzed and interpreted the data.

Beili Wang; Baishen Pan: Conceived and designed the experiments.

Jing Cang; Wei Guo: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

All authors read and approved the final manuscript.

Funding statement

The National Natural Science Foundation of China, China (81972000, 82172348, 81902139), the constructing project of clinical key disciplines in Shanghai (shslczdzk03302).

Data availability statement

Data associated with this study has been deposited at The datasets generated and/or analyzed during the current study are available in the Genome Variation Map (GVM) repository, [https://bigd.big.ac.cn/gvm/getProjectDetail?Project=GVM000503].

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] R. Chou, D.B. Gordon, O.A. de Leon-Casasola, J.M. Rosenberg, S. Bickler, T. Brennan, T. Carter, C.L. Cassidy, E.H. Chittenden, E. Degenhardt, S. Griffith, R. Manworren, B. McCarberg, R. Montgomery, J. Murphy, M.F. Perkal, S. Suresh, K. Sluka, S. Strassels, R. Thirlby, E. Viscusi, G.A. Walco, L. Warner, S. J. Weisman, C.L. Wu, Management of postoperative pain: a clinical practice guideline from the American pain society, the American society of regional anesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anesthesia, executive committee, and administrative council, J. Pain 17 (2) (2016 Feb) 131–157.

[2] J. Luo, S. Min, Postoperative pain management in the postanesthesia care unit: an update, J. Pain Res. 10 (2017 Nov 16) 2687–2698, https://doi.org/10.2147/JPR.S142889.

[3] E.D. McNicol, M.C. Ferguson, J. Hudcova, Patient controlled opioid analgesia versus non-patient controlled opioid analgesia for postoperative pain, Cochrane Database Syst. Rev. 2015 (6) (2015 Jun 2) CD003348, https://doi.org/10.1002/14651858.CD003348.pub3.

[4] D. Viderman, K. Tapinova, F. Nabidollayeva, R. Tankacheev, Y.G. Abdildin, Intravenous versus epidural routes of patient-controlled analgesia in abdominal surgery: systematic review with meta-analysis, J. Clin. Med. 11 (9) (2022 May 5) 2579, https://doi.org/10.3390/jcm11092579.
[5] Y.J. Lee, C.S. Oh, J.M. Choi, S. Park, S.H. Kim, Mu-opioid receptor polymorphisms and breast cancer recurrence in adult Korean women undergoing breast cancer surgery: a retrospective study, Int. J. Med. Sci. 17 (18) (2020 Oct 18) 2941–2946.
[6] K. Fukuda, M. Hayashida, S. Ide, N. Saita, Y. Kokita, S. Kasai, D. Nishizawa, Y. Ogai, J. Hasegawa, M. Nagashima, M. Tagami, H. Komatsu, I. Sora, H. Koga, Y. Kaneko, K. Ikeda, Association between OPRM1 gene polymorphisms and fentanyl sensitivity in patients undergoing painful cosmetic surgery, Pain 147 (1–3) (2009 Dec 15) 194–201, https://doi.org/10.1016/j.pain.2009.09.004.
[7] G.S. Collins, J.B. Reitsma, D.G. Altman, Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement, Eur. J. Clin. Invest. 45 (2) (2015) 204–214.
[8] A.J. Vickers, A.M. Cronin, E.B. Elkin, M. Gonen, Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers, BMC Med. Inf. Decis. Making 8 (2008 Nov 26) 53, https://doi.org/10.1186/1472-6947-8-53.
[9] A.J. Vickers, B. Van Calster, E.W. Steyerberg, Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests, BMJ (2016 Jan 25) 352.
[10] T.P. Debray, J.A. Damen, K.I. Snell, J. Ensor, L. Hooft, J.B. Reitsma, R.D. Riley, K.G. Moons, A guide to systematic review and meta-analysis of prediction model performance, BMJ 356 (2017 Jan 5) i6460, https://doi.org/10.1136/bmj.i6460.
[11] M. Saiz-Rodríguez, D. Ochoa, C. Herrador, C. Belmonte, M. Román, E. Alday, D. Koller, P. Zubiaur, G. Mejía, M. Hernández-Martínez, F. Abad-Santos, Polymorphisms associated with fentanyl pharmacokinetics, pharmacodynamics and adverse effects, Basic Clin. Pharmacol. Toxicol. 124 (3) (2019 Mar) 321–329, https://doi.org/10.1111/bcpt.13141.
[12] K.N. Grimsrud, X. Ivanova, C.M. Sherwin, T.L. Palmieri, N.K. Tran, Identification of cytochrome P450 polymorphisms in burn patients and impact on fentanyl pharmacokinetics: a pilot study, J. Burn Care Res. 40 (1) (2019 Jan 1) 91–96.
[13] K. Thota, K. Prasad, M.V. Basaveswara Rao, Detection of cytochrome P450 polymorphisms in breast cancer patients may impact on tamoxifen therapy, Asian Pac. J. Cancer Prev. APJCP 19 (2) (2018 Feb 26) 343–350.
[14] A. Suzuki, T. Shirata, K. Noto, Y. Matsumoto, H. Muraosa, M. Abe, K. Goto, K. Otani, Associations of the A118G OPRM1 polymorphism with sociotropy and interpersonal sensitivity, Brain Behav 12 (7) (2022 Jul), e2674, https://doi.org/10.1002/brb3.2674.
[15] M. Peciña, T. Love, C.S. Stohler, D. Goldman, J.K. Zubieta, Effects of the Mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures, Neuropsychopharmacology 40 (4) (2015 Mar) 957–965.
[16] G.H. Xu, M. Gao, Q.Y. Sheng, X.S. Liu, E.W. Gu, Opioid receptor A118G polymorphism does not affect the consumption of sufentanil and ropivacaine by patient-controlled epidural analgesia after cesarean section, Ther. Drug Monit. 37 (1) (2015 Feb) 53–57.
[17] S.W. Choi, D.M.H. Lam, S.S.C. Wong, H.H.C. Shiu, A.X.M. Wang, C.W. Cheung, Effects of single nucleotide polymorphisms on surgical and postsurgical opioid requirements: a systematic review and meta-analysis, Clin. J. Pain 33 (12) (2017 Dec) 1117–1130.
[18] X. Zhang, Y. Liang, N. Zhang, Y. Yan, S. Liu, H. Fengxi, D. Zhao, H. Chu, The relevance of the OPRM1 118A>G genetic variant for opioid requirement in pain treatment: a meta-analysis, Pain Physician 22 (4) (2019 Jul) 331–340, https://doi.org/10.36076/ppj/2019.22.331.
[19] Z. Yu, L. Wen, X. Shen, H. Zhang, Effects of the OPRM1 A118G polymorphism (rs1799971) on opioid analgesia in cancer pain: a systematic review and meta-analysis, Clin. J. Pain 35 (1) (2019 Jan) 77–86, https://doi.org/10.1097/AJP.0000000000000636.
[20] X. Kong, H. Deng, S. Gong, T. Alston, Y. Kong, J. Wang, Lack of associations of the opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) with alcohol dependence: review and meta-analysis of retrospective controlled studies, BMC Med. Genet. 18 (1) (2017 Oct 26) 120, https://doi.org/10.1186/s12881-017-0478-4.
[21] X. Kong, H. Deng, T. Alston, Y. Kong, J. Wang, Association of opioid receptor mu 1 (OPRM1) A118G polymorphism (rs1799971) with nicotine dependence, Oncotarget 8 (48) (2017 Sep 15) 84329–84337, https://doi.org/10.18632/oncotarget.20939.
[22] E. Treillet, S. Laurent, Y. Hadjiat, Practical management of opioid rotation and equianalgesia, J. Pain Res. 11 (2018 Oct 29) 2587–2601, https://doi.org/10.2147/JPR.S170269.
[23] H. Zhong, H.N. Ladenhauf, L.A. Wilson, J. Liu, K.R. DelPizzo, J. Poeran, S.G. Memtsoudis, Persistent opioid use after surgical treatment of paediatric fracture, Br. J. Anaesth. 126 (6) (2021 Jun) 1192–1199, https://doi.org/10.1016/j.bja.2020.12.044.
[24] V.P. Balachandran, M. Gonen, J.J. Smith, R.P. DeMatteo, Nomograms in oncology: more than meets the eye, Lancet Oncol. 16 (4) (2015 Apr) e173–e180, https://doi.org/10.1016/S1470-2045(14)71116-7.
[25] C. Belmonte, D. Ochoa, M. Román, M. Saiz-Rodríguez, A. Wojnicz, C.I. Gómez-Sánchez, S. Martín-Vílchez, F. Abad-Santos, Influence of CYP2D6, CYP3A4, CYP3A5 and ABCB1 polymorphisms on pharmacokinetics and safety of aripiprazole in healthy volunteers, Basic Clin. Pharmacol. Toxicol. 122 (6) (2018 Jun) 596–605, https://doi.org/10.1111/bcpt.12960.