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Research article

Investigating the risk factors for nonadherence to analgesic medications in cancer patients: Establishing a nomogram model

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A B S T R A C T

Objective: The substantial prevalence of nonadherence to analgesic medication among individuals diagnosed with cancer imposes a significant strain on both patients and healthcare resources. The objective of this study is to develop and authenticate a nomogram model for assessing nonadherence to analgesic medication in cancer patients.

Methods: Clinical information, demographic data, and medication adherence records of cancer pain patients were gathered from the Affiliated Hospital of Chengde Medical University between April 2020 and March 2023. The risk factors associated with analgesic medication nonadherence in cancer patients were analyzed using the least absolute selection operator (LASSO) regression model and multivariate logistic regression. Additionally, a nomogram model was developed. The bootstrap method was employed to internally verify the model. Discrimination and accuracy of the nomogram model were evaluated using the Concordance index (C-index), area under the receiver Operating characteristic (ROC) curve (AUC), and calibration curve. The potential clinical value of the nomogram model was established through decision curve analysis (DCA) and clinical impact curve.

Results: The study included a total of 450 patients, with a nonadherence rate of 43.33%. The model incorporated seven factors: age, address, smoking history, number of comorbidities, use of nonsteroidal antiinflammatory drugs (NSAIDs), use of opioids, and PHQ-8. The C-index of the model was found to be 0.93 (95% CI: 0.907–0.953), and the ROC curve demonstrated an AUC of 0.929. Furthermore, the DCA and clinical impact curves indicate that the built model can accurately predict cancer pain patients' medication adherence performance.

Conclusions: A nomogram model based on 7 risk factors has been successfully developed and validated for long-term analgesic management of cancer patients.

1. Introduction

Cancer has emerged as a prominent public health concern, serving as a primary contributor to mortality rates and posing a substantial impediment to global life expectancy enhancement [1]. The World Health Organization (WHO) conducted an evaluation in 2019, revealing that cancer ranked as the primary or secondary cause of death prior to the age of 70 in 112 out of 183 countries [2]. Alarming trends indicate a continuous rise in global cancer incidences, with projections estimating an escalation from 14 million cases in 2012 to 22 million cases by 2032 [3].

Pain is a prevalent clinical manifestation in individuals diagnosed with cancer, persisting throughout the course of treatment and beyond, encompassing chronic pain resulting from surgical procedures, therapeutic interventions, or pathological fractures. The

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incidence of cancer-related pain is on the rise[[4,5]]. A comprehensive meta-analysis, incorporating studies conducted between 2014 and 2021, revealed an overall prevalence rate of 44% for pain among cancer patients [5]. Notably, approximately 30–50% of patients undergoing curative treatment and 75–90% of those with advanced disease experience pain of sufficient intensity to necessitate opioid therapy[[6,7]]. Currently, the management of cancer pain primarily relies on the administration of various analgesic medications. However, the level of adherence to these drugs among cancer patients is suboptimal, primarily due to variations in the methodologies employed to assess adherence. As a result, adherence rates have been reported to range from 8.9% to 82.0% [8]. The adherence to analgesic drug usage by cancer patients plays a crucial role in the effectiveness of pain management. Medication adherence pertains to the degree to which patients' medication-related behaviors align with the guidelines provided by healthcare professionals [9]. The level of adherence is contingent upon the patient's compliance with the prescribed duration, dosage, and frequency of medication intake. Patients may exhibit nonadherence at various stages of disease therapy [10]. Inadequate drug adherence can be either intentional or unintentional, resulting in patients being unable to derive the desired therapeutic benefits from drug therapy. Consequently, this is more likely to give rise to complications for patients and ultimately lead to a negative prognosis and unnecessary medical expenses.

Previous research on medication adherence among cancer pain patients has primarily concentrated on patient attitudes and gender as barriers[[11,12,13,14]]. However, these studies have not developed predictive models to anticipate medication adherence in cancer pain patients. The implementation of predictive models can enable early identification of high-risk patients who are non-adherent to their medication, aiding healthcare professionals in clinical decision-making and disease management. This approach has the potential to enhance patient outcomes and decrease healthcare expenses [15]. Currently, the utilization of nomograms for the prediction of medication adherence has become prevalent[[16,17,18]]. Consequently, this study endeavors to investigate the determinants influencing patients' medication adherence by analyzing pertinent clinical data of individuals suffering from cancer-related pain. Moreover, a nomogram model is constructed to forecast the likelihood of inadequate medication adherence among patients, thereby facilitating the identification of high-risk individuals. This identification process is crucial in the context of cancer pain patients, as it enables the development of more tailored intervention strategies.

2. Material and methods

2.1. Patients and procedures

The research was carried out at the Affiliated Hospital of Chengde Medical University between April 2020 and March 2023. The participants consisted of cancer patients admitted to the hospital who were experiencing pain. Demographic and clinical characteristics were obtained through a questionnaire and cross-referenced with the hospital information platform. The inclusion criteria encompassed the following: (1) a confirmed cancer diagnosis; (2) the presence of cancer-related pain and utilization of analgesic medication; (3) voluntary participation by the patients. Exclusion criteria included: (1) patients with cognitive, visual, hearing, and language impairments; (2) illiterate patients; (3) incomplete results reports. The study has been approved by the Medical Ethics Committee of participating Hospital (ethics number: LL2020013).

To ensure the consistency of the quality control of the questionnaire, the investigators are required to be familiar with the questionnaire and completed by four members (Ying Wang, Yunwei Liang, ChanChan Hu and Yinhui Yao) who have undergone unified training. Each time, 2 members were randomly selected as a group to participate in a face-to-face questionnaire survey with patients. According to the principle of informed consent, patients voluntarily participate and voluntarily complete the questionnaire. It takes about 15–20 min min for the patient to complete the questionnaire.

2.2. Adherence assessment

The study utilized the Morisky Medication Adherence Scale (MMAS-8) [19] to assess the adherence of patients to their analgesic medication [20]. The MMAS-8 questionnaire comprised eight questions, with questions 1–7 being answered in a dichotomous manner (yes/no) to determine the reasons behind the patients' adherence or nonadherence behavior. Question 8 offered five possible responses (corresponding to scores of 1, 0.75, 0.5, 0.25, and 0) to indicate the frequency of patients not taking their medication on time. Subsequently, the scores from the aforementioned questions were summed, with a score of 6 indicating nonadherence and a score of $\geq$6 indicating adherence [18].

2.3. Pain assessment

The assessment of pain was conducted utilizing The Brief Pain Inventory (BPI), which was initially developed for the purpose of evaluating cancer-related pain [21]. This questionnaire encompasses several components, including pain mapping, four items pertaining to pain intensity (maximum pain, minimum pain, average pain, and immediate pain), two items regarding pain relief therapy or medication, one item concerning pain interference, and seven sub-items encompassing general activity, mood, walking ability, normal walking, relationship with others, sleep, and enjoyment of life.

2.4. Psychological state

Patients with cancer pain were assessed using the eight-item Patient Health Questionnaire depression scale (PHQ-8) [22]. Among

Table 1
Demographic and clinical characteristics in patients with cancer pain.

Variables	Total (n = 450)	adherence (n = 195)	nonadherence (n = 255)	p
Gender, n (%)				0.707
female	179 (39.78)	80 (41.03)	99 (38.82)	
male	271 (60.22)	115 (58.97)	156 (61.18)	
Age, Median (Q1,Q3)	61 (53.25, 67)	54 (48, 59)	64 (60, 69)	<0.001
Diagnosis, n (%)				0.549
lung cancer	138 (30.67)	62 (31.79)	76 (29.8)	
breast cancer	36 (8)	21 (10.77)	15 (5.88)	
hepatobiliary system cancer	33 (7.33)	13 (6.67)	20 (7.84)	
digestive system cancer (Stomach, intestine, pancreas, esophagus)	133 (29.56)	50 (25.64)	83 (32.55)	
head and neck carcinoma	27 (6)	13 (6.67)	14 (5.49)	
genitourinary Cancer	27 (6)	10 (5.13)	17 (6.67)	
gynecological oncology	26 (5.78)	12 (6.15)	14 (5.49)	
osteosarcoma	15 (3.33)	8 (4.1)	7 (2.75)	
others	15 (3.33)	6 (3.08)	9 (3.53)	
Operation, n (%)				1
no	242 (53.78)	105 (53.85)	137 (53.73)	
yes	208 (46.22)	90 (46.15)	118 (46.27)	
Disease course (month), Median (Q1,Q3)	14 (5, 31.75)	12 (5, 31.5)	14 (4.5, 32)	0.807
Occupation, n (%)				<0.001
farmer	283 (62.89)	95 (48.72)	188 (73.73)	
others have regular jobs	56 (12.44)	45 (23.08)	11 (4.31)	
retirement	88 (19.56)	39 (20)	49 (19.22)	
unemployed	10 (2.22)	6 (3.08)	4 (1.57)	
student	3 (0.67)	1 (0.51)	2 (0.78)	
freelance	10 (2.22)	9 (4.62)	1 (0.39)	
Address, n (%)				<0.001
rural	263 (58.44)	79 (40.51)	184 (72.16)	
urban	187 (41.56)	116 (59.49)	71 (27.84)	
Payment, n (%)				<0.001
medical insurance for urban residents	31 (6.89)	21 (10.77)	10 (3.92)	
medical insurance for urban employees	126 (28)	74 (37.95)	52 (20.39)	
self-supporting	11 (2.44)	5 (2.56)	6 (2.35)	
rural cooperative medical care	276 (61.33)	92 (47.18)	184 (72.16)	
others	6 (1.33)	3 (1.54)	3 (1.18)	
Marital history, n (%)				0.086
divorce	5 (1.11)	4 (2.05)	1 (0.39)	
widowed	4 (0.89)	2 (1.03)	2 (0.78)	
unmarried	8 (1.78)	6 (3.08)	2 (0.78)	
married	433 (96.22)	183 (93.85)	250 (98.04)	
Drinking history, n (%)				0.79
no	295 (65.56)	126 (64.62)	169 (66.27)	
yes	155 (34.44)	69 (35.38)	86 (33.73)	
Smoking history, n (%)				0.752
no	268 (59.56)	114 (58.46)	154 (60.39)	
yes	182 (40.44)	81 (41.54)	101 (39.61)	
Bone metastases, n (%)				0.221
no	249 (55.33)	101 (51.79)	148 (58.04)	
yes	201 (44.67)	94 (48.21)	107 (41.96)	
Background pain NRS, n (%)				<0.001
0	1 (0.22)	1 (0.51)	0 (0)	
1	1 (0.22)	0 (0)	1 (0.39)	
2	115 (25.56)	51 (26.15)	64 (25.1)	
3	163 (36.22)	87 (44.62)	76 (29.8)	
4	126 (28)	35 (17.95)	91 (35.69)	
5	30 (6.67)	13 (6.67)	17 (6.67)	
6	13 (2.89)	8 (4.1)	5 (1.96)	
7	1 (0.22)	0 (0)	1 (0.39)	
Breakthrough cancer pain (BTCP), n (%)				0.349
no	347 (77.11)	155 (79.49)	192 (75.29)	
yes	103 (22.89)	40 (20.51)	63 (24.71)	
BTCP frequency per day, n (%)				0.756
0	347 (77.11)	155 (79.49)	192 (75.29)	
1	46 (10.22)	19 (9.74)	27 (10.59)	
2	36 (8)	15 (7.69)	21 (8.24)	
3	12 (2.67)	3 (1.54)	9 (3.53)	
4	6 (1.33)	2 (1.03)	4 (1.57)	
5	1 (0.22)	0 (0)	1 (0.39)	
6	1 (0.22)	1 (0.51)	0 (0)	

(*continued on next page*)

Table 1 (*continued*)

Variables	Total (n = 450)	adherence (n = 195)	nonadherence (n = 255)	p
7	1 (0.22)	0 (0)	1 (0.39)	
Comorbidity, n (%)				<0.001
no	182 (40.44)	101 (51.79)	81 (31.76)	
yes	268 (59.56)	94 (48.21)	174 (68.24)	
Comorbidity types, n (%)				<0.001
0	182 (40.44)	101 (51.79)	81 (31.76)	
1	131 (29.11)	51 (26.15)	80 (31.37)	
2	84 (18.67)	24 (12.31)	60 (23.53)	
3	37 (8.22)	14 (7.18)	23 (9.02)	
4	11 (2.44)	5 (2.56)	6 (2.35)	
5	2 (0.44)	0 (0)	2 (0.78)	
6	2 (0.44)	0 (0)	2 (0.78)	
8	1 (0.22)	0 (0)	1 (0.39)	
Analgesic types, n (%)				0.443
1	377 (83.78)	161 (82.56)	216 (84.71)	
2	53 (11.78)	22 (11.28)	31 (12.16)	
3	18 (4)	11 (5.64)	7 (2.75)	
4	2 (0.44)	1 (0.51)	1 (0.39)	
Analgesic oral, Median (Q1,Q3)	4 (2, 6)	4 (2, 6)	4 (2, 6)	0.562
NSAIDs, n (%)				0.756
no	355 (78.89)	152 (77.95)	203 (79.61)	
yes	95 (21.11)	43 (22.05)	52 (20.39)	
Opioids, n (%)				0.164
no	59 (13.11)	31 (15.9)	28 (10.98)	
yes	391 (86.89)	164 (84.1)	227 (89.02)	
Morphine sulfate sustained release tablets (MST), n (%)				0.747
no	330 (73.33)	145 (74.36)	185 (72.55)	
yes	120 (26.67)	50 (25.64)	70 (27.45)	
Oxycodone hydrochloride sustained-release tablet (OST), n (%)				0.607
no	228 (50.67)	102 (52.31)	126 (49.41)	
yes	222 (49.33)	93 (47.69)	129 (50.59)	
Quick release preparation, n (%)				1
no	401 (89.11)	174 (89.23)	227 (89.02)	
yes	49 (10.89)	21 (10.77)	28 (10.98)	
Total quick release preparation per day, n (%)				0.974
0	400 (88.89)	173 (88.72)	227 (89.02)	
2	1 (0.22)	0 (0)	1 (0.39)	
3	26 (5.78)	13 (6.67)	13 (5.1)	
4	2 (0.44)	1 (0.51)	1 (0.39)	
5	1 (0.22)	0 (0)	1 (0.39)	
6	15 (3.33)	6 (3.08)	9 (3.53)	
8	1 (0.22)	0 (0)	1 (0.39)	
9	3 (0.67)	1 (0.51)	2 (0.78)	
12	1 (0.22)	1 (0.51)	0 (0)	
Total MST, n (%)				0.122
0	330 (73.33)	145 (74.36)	185 (72.55)	
2	60 (13.33)	25 (12.82)	35 (13.73)	
4	35 (7.78)	13 (6.67)	22 (8.63)	
6	11 (2.44)	7 (3.59)	4 (1.57)	
8	7 (1.56)	1 (0.51)	6 (2.35)	
10	3 (0.67)	3 (1.54)	0 (0)	
12	2 (0.44)	0 (0)	2 (0.78)	
28	1 (0.22)	0 (0)	1 (0.39)	
30	1 (0.22)	1 (0.51)	0 (0)	
Total OST, n (%)				0.92
0	228 (50.67)	102 (52.31)	126 (49.41)	
2	90 (20)	37 (18.97)	53 (20.78)	
4	78 (17.33)	37 (18.97)	41 (16.08)	
6	31 (6.89)	12 (6.15)	19 (7.45)	
8	14 (3.11)	5 (2.56)	9 (3.53)	
10	5 (1.11)	2 (1.03)	3 (1.18)	
12	2 (0.44)	0 (0)	2 (0.78)	
14	1 (0.22)	0 (0)	1 (0.39)	
24	1 (0.22)	0 (0)	1 (0.39)	
Total Opioids, Median (Q1,Q3)	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.284
Other oral, n (%)				0.505
no	414 (92)	177 (90.77)	237 (92.94)	
yes	36 (8)	18 (9.23)	18 (7.06)	
PHQ-8, n (%)				<0.001

(*continued on next page*)

Table 1 (*continued*)

Variables	Total (n = 450)	adherence (n = 195)	nonadherence (n = 255)	p
0-4	19 (4.22)	14 (7.18)	5 (1.96)	
5-9	128 (28.44)	91 (46.67)	37 (14.51)	
10-14	109 (24.22)	70 (35.9)	39 (15.29)	
15-19	145 (32.22)	16 (8.21)	129 (50.59)	
20-24	49 (10.89)	4 (2.05)	45 (17.65)	

the most widely used depression screening and severity assessments in the world, the PHQ-8 is reliable and cross-nationally comparable, making it one of the most used depression questionnaires around the world [23]. The PHQ-8 is a self-reported measure for assessing depression symptoms, utilizing eight Likert-type items with response options ranging from "not at all" (0–1 day) to "nearly every day" (12–14 days). Each item is assigned a score of 0, 1, 2, or 3. The cumulative score, ranging from 0 to 24, is obtained by summing the scores of all items. A higher score indicates a greater severity of depression. Scores are divided into five parts: low (0–4), moderate (5–9), high (10–14), moderately severe (15–19), and severe (20–24), which represent low depression scores and mild depression scores, moderate depression scores, moderate depression scores, and severe depression scores [22].

2.5. Statistical analysis

Initially, a univariate analysis was conducted to examine the factors influencing medication adherence in cancer pain patients. The analysis employed the least absolute shrinkage and selection operator (LASSO) regression technique to identify the most effective predictors. Subsequently, the outcomes of the LASSO regression analysis were integrated with multiple logistic regression analysis to derive distinct predictors [24]. Additionally, a nomogram model was developed to forecast drug noncompliance in patients suffering from cancer pain [25].

Next, we proceed to assess the established nomogram prediction model by employing the Concordance index (C-index) as a metric to gauge the consistency, reliability, and accuracy of the data. Additionally, we generate a receiver operating characteristic (ROC) curve and utilize the area under the ROC curve (AUC) to evaluate the predictive efficacy of the nomogram model specifically in patients experiencing cancer pain [4]. Furthermore, calibration curves are employed to visually depict the discriminative capabilities of the nomogram model. Clinical significance of the nomogram model was determined by decision curve analysis (DCA) and clinical impact analysis.

The statistical significance was $P < 0.05$. All analyses were performed using R 4.2.1 software. The packages used are "glmnet", "rms", "nortest", "CBCgrps", "ROCR", "Hmisc", and "rmda".

3. Results

3.1. Demographic characteristics

Between April 2020 and March 2023, a cohort of 502 patients diagnosed with cancer pain at the Affiliated Hospital of Chengde Medical University were administered questionnaires. Subsequently, the hospital information platform was utilized to ascertain the disease characteristics and treatment modalities employed for these patients. Ultimately, a total of 450 patients successfully completed all questionnaires, yielding an effective response rate of 89.64%. Among these respondents, 271 were male and 179 were female, with a mean age of 61 years (range: 53.25 to 67). Notably, 43.33% (195 patients) demonstrated medication adherence. The average duration of the disease was 14 months. Data on 450 cancer pain patients are presented in Table 1, which includes demographics, clinical features of the disease, medication status, adherence to medications, and PHQ-8. Comparing the two groups, it is found that

Table 2
Comparison of adverse drug reaction between medication adherence and medication nonadherence groups.

Adverse drug reaction	Total (n = 450)	0 (n = 195)	1 (n = 255)	p
Constipation, n (%)				0.043
no	282 (63)	133 (68)	149 (58)	
yes	168 (37)	62 (32)	106 (42)	
Cough sputum, n (%)				0.378
no	376 (84)	159 (82)	217 (85)	
yes	74 (16)	36 (18)	38 (15)	
Diarrhea, n (%)				0.52
no	437 (97)	191 (98)	246 (96)	
yes	13 (3)	4 (2)	9 (4)	
Abdominal distension, n (%)				0.378
no	376 (84)	159 (82)	217 (85)	
yes	74 (16)	36 (18)	38 (15)	
Dysuria, n (%)				0.378
no	376 (84)	159 (82)	217 (85)	
yes	74 (16)	36 (18)	38 (15)	

there are differences between the two groups: age, occupation, address, payment, background pain numerical rating scale (NRS), comorbidity, comorbidity types, PHQ-8.

During the investigation, it was found that every patient had adverse reactions, but the severity and types of individuals were different. In this study, we only recorded five common adverse reactions. The specific comparison of patients in compliance and non-compliance groups is shown in Table 2. Only Constipation has statistical difference ($p = 0.043$).

3.2. Factors screening and developed for nomogram model

This study encompassed a cohort of 450 patients suffering from cancer pain, wherein a comprehensive examination of 30 potential factors encompassing demography, medication adherence, therapeutic drug characteristics, and psychological characteristics was conducted. To identify significant predictors linked to medication nonadherence, univariate LASSO regression analysis was employed, as depicted in Fig. 1A and **B**.

From the results of LASSO regression, 17 factors are closely related to the prediction of medication nonadherence of cancer patients. These 17 factors are shown in red font in Fig. 1A.

A multivariate logistic regression analysis was performed utilizing the aforementioned characteristics, and the findings were presented in Table 3. A total of seven potential risk factors, namely age, address, smoking history, number of comorbidities, use of NSAIDs, use of opioids, and PHQ-8, were identified ($p < 0.05$). These seven predictive factors were subsequently integrated into the model, leading to the development of a nomogram model for predicting medication nonadherence among patients experiencing cancer pain (Fig. 2). On the left side of the figure, the names of variables (that is, different forecasting indicators) are marked with scales on the lines corresponding to each variable, representing the desirable range of the variable. The length of the line segment reflects the contribution of this factor to clinical outcome events. Score: including the single score (that is the 'Point' in the figure), indicating the single score corresponding to each variable under different values; Total score (that is 'Total Point') means the total score of the corresponding individual scores after all variables are valued. Prediction probability: the Risk in the figure represents the risk of medication nonadherence. Therefore, a simple prediction tool of medication nonadherence is made.

3.3. Evaluation of the nomogram

The calibration curves for the nomogram were validated using the bootstrap self-sampling technique, which was repeated 1000 times. The X-axis denotes the predicted probability by the nomogram, while the Y-axis represents the actual probability of drug noncompliance in patients suffering from cancer pain. An exemplary prediction aligns with the "Ideal" label on a dotted line. The dashed line in question represents the entirety of the queue, and this line is adjusted for deviation through the process of Bootstrapping, which involves 1000 repetitions. This adjustment indicates that the observed performance of the normogram aligns well with expectations. The C-index is calculated to be 0.93 (with a confidence interval of 0.907–0.953), and the ROC curve has an AUC of 0.929 (Fig. 3). These findings demonstrate that the monogram effectively discriminates and accurately identifies the predicted outcomes.

3.4. The clinical use of the nomogram

The DCA was used to evaluate the benefit rate of the established nomogram model (Fig. 4A), and the results showed that the nomogram was more favorable than the whole-patient intervention or no-intervention protocol in this study, with a threshold probability of 0.01–0.99. As depicted in Fig. 4A, the red curve represents the projected benefit according to the model, the gray curve

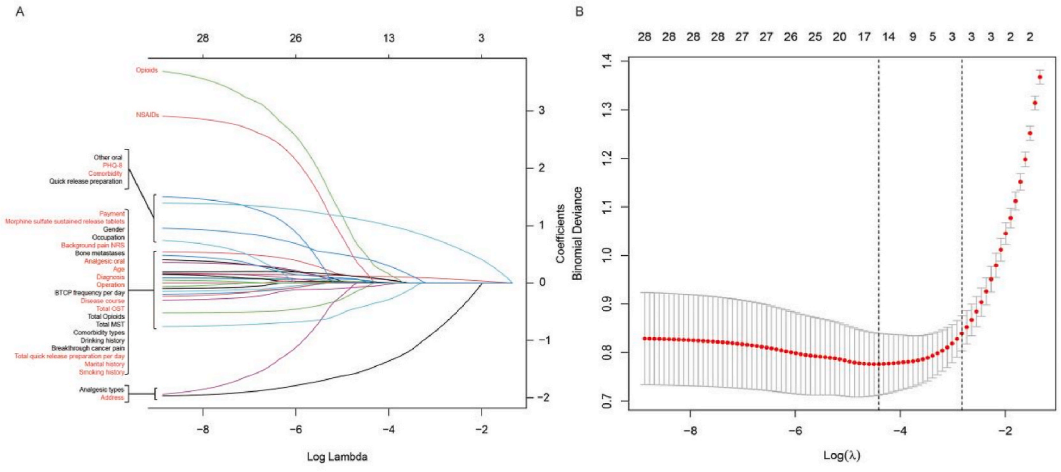

Fig. 1. Prediction factors for analgesic medication nonadherence in cancer patients. (A, B) Least absolute shrinkage and selection operator (LASSO) coefficient profiles of the prediction factors.

Table 3
Multiple logistic regression of the factors for the risk of medication nonadherence in cancer patients.

Variables	prediction model		
	β	OR (95% CI)	*P* value
(Intercept)	−13.66	$1.16e^{-6}$ ($9.19e^{-9}$, $1.04e^{-4}$)	<0.0001
Age	0.15	1.16 (1.12, 1.21)	<0.0001
Diagnosis	0.051	1.05(0.92, 1.21)	0.465
Operation	0.14	1.15 (0.58, 2.29)	0.681
Disease course	0.0033	1.003 (0.99, 1.01)	0.526
Address	−1.89	0.15 (0.049,0.42)	0.0004
Payment	0.24	1.27 (0.77, 2.08)	0.329
Marital history	−0.53	0.58 (0.27, 1.28)	0.165
Smoking history	−0.66	0.52 (0.27, 0.97)	0.0419
Background pain NRS	0.20	1.22 (0.93, 1.61)	0.145
Comorbiditiy	0.65	1.91 (1.02, 3.60)	0.0431
Analgesic oral	−0.0012	0.99 (0.87, 1.14)	0.987
NSAIDs	1.48	4.41(1.21, 17.19)	0.0281
Opioids	1.84	6.31 (1.27, 32.73)	0.0257
Morphine sulfate sustained release tablets	0.32	1.38 (0.47, 4.14)	0.556
Total quick release preparation per day	−0.11	0.89 (0.67, 1.18)	0.457
Total OST	0.055	1.05(0.86, 1.31)	0.614
PHQ-8	1.33	3.77 (2.76, 5.33)	<0.0001

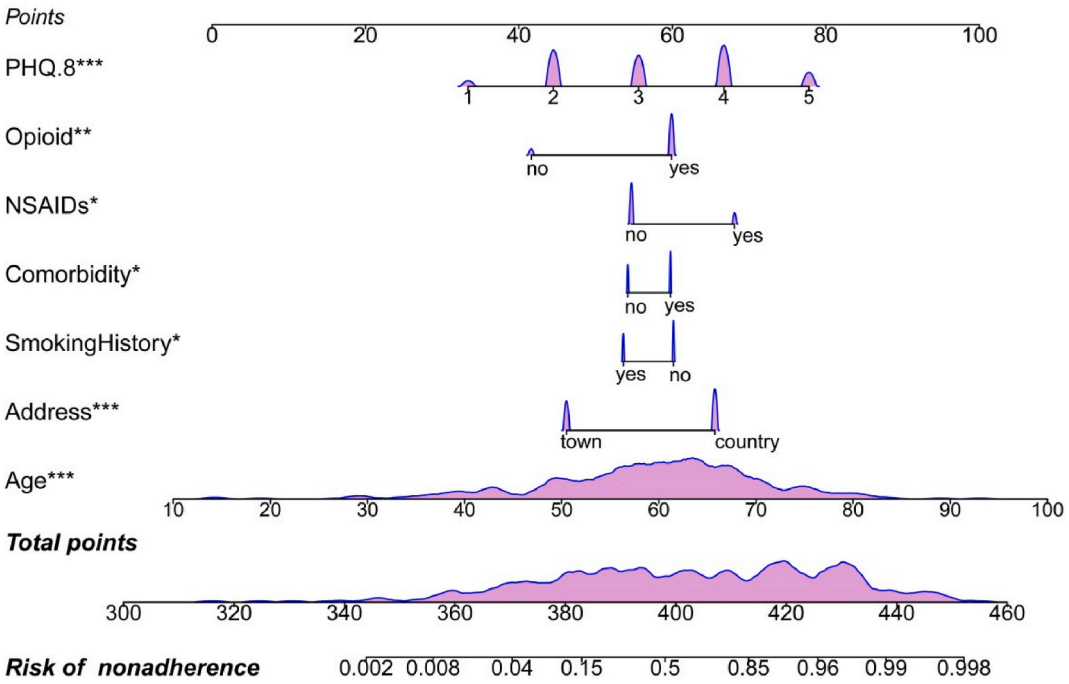

Fig. 2. Nomogram for analgesic medication nonadherence in cancer patients.

represents the benefit rate observed among all patients who underwent intervention, and the horizontal line represents the benefit rate among all patients who received no intervention. The point at which the red curve intersects with "All" is considered the initiation point, while the point of intersection with "None" is regarded as the termination point. Patients falling within this range are eligible for additional benefits.

Simultaneously, the Clinical Impact Curve (Fig. 4B) was constructed, wherein the horizontal axis denotes the probability threshold, while the vertical axis represents the count of individuals. The blue line signifies the count of individuals identified as high-risk by the model across various probability thresholds, whereas the red lines indicate the count of individuals identified as high-risk by the model and subsequently experiencing an outcome event, also across different probability thresholds. Additionally, the Cost: Benefit Ratio, illustrating the relationship between cost and benefit across various probability thresholds, is presented at the bottom. The findings consistently demonstrate that the projected count of patients at high risk for nonadherence to analgesic medication exceeds the actual count, while maintaining a satisfactory cost: benefit ratio. Collectively, these outcomes strongly suggest that the nomogram exhibits

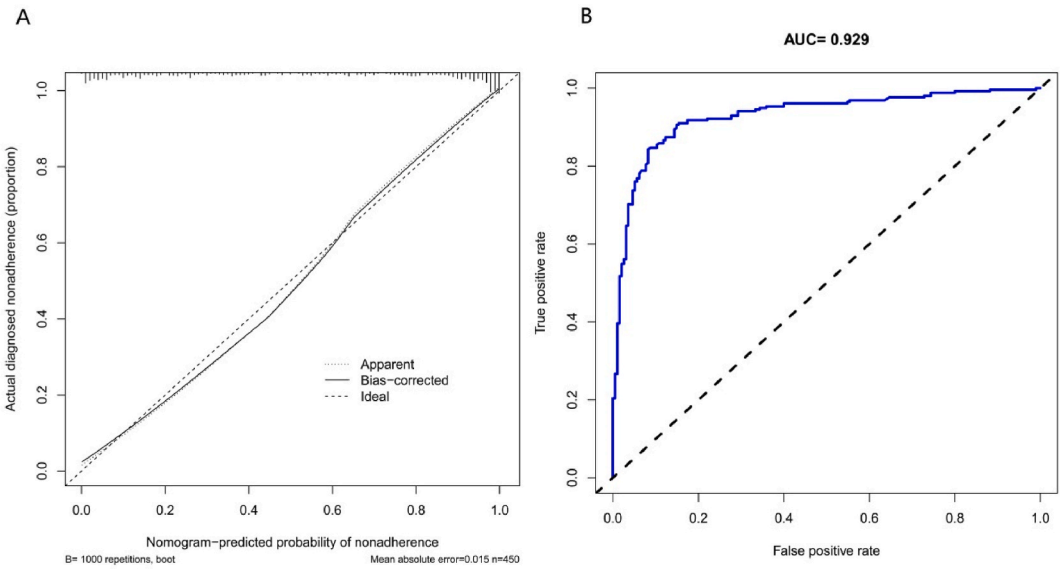

Fig. 3. Evaluation of the nomogram to predict analgesic medication nonadherence in cancer patients. (A) Calibration plots for nomogram. (B) ROC curve with AUC = 0.929 based on the predictive nomogram for analgesic medication nonadherence in cancer patients.

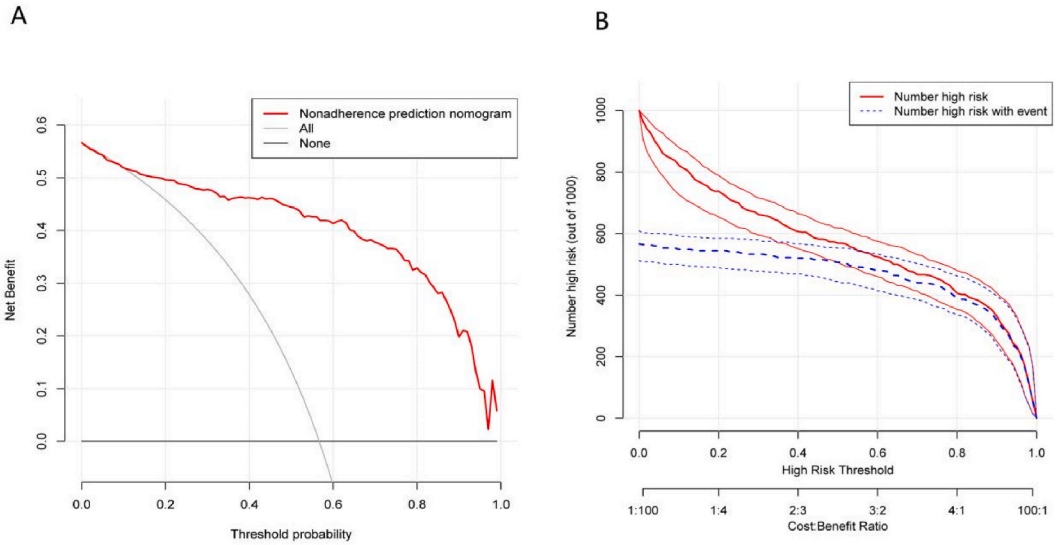

Fig. 4. Medication nonadherence of nomogram evaluation and clinical use in cancer patients. (A) Decision curve analysis for the nonadherence nomogram in cancer patients. (B) Clinical impact plot for predicting patient medication nonadherence.

considerable promise for the clinical prediction of analgesic medication nonadherence in individuals suffering from cancer-related pain.

4. Discussion

Pain emerges as a prevalent clinical symptom among individuals diagnosed with cancer, often prompting their admission to medical facilities. Although pain per se does not pose an immediate threat to life, it remains a frequently encountered and incapacitating manifestation of cancer. Psychological distress, such as fatigue and depression, as well as diminished quality of life resulting from impaired functioning, invariably accompany pain [16]. Certain investigations have even suggested that inadequate pain management may adversely impact the survival rates of cancer patients[[26,27]]. Cancer pain is currently treated largely with analgesic drugs, but cancer patients are not adhering to analgesic medications effectively [28]. It is essential to improve adherence with the use of analgesics in cancer patients, as only 43.33% of patients in this study adhered to their medication. Therefore, we established

nomogram in predicting analgesic medication nonadherence in cancer pain.

Compared with previous studies[[4,10]], the nomogram constructed in this study has better performance in the following aspects. (1) Logistic regression analysis were used in previous studies to analyze the factors of medication adherence in cancer pain patients, and the results did not intuitively reflect the predicted results of each patient. But the nomogram assigns scores to each value level of each influencing factor, and then adds all scores to get a total score. Then the prediction probability of the outcome event for the individual is calculated by transforming the relationship between the total score and the probability of the outcome event. the utilization of nomogram in predicting medication nonadherence among patients has proven to be valuable in transforming intricate regression equations into easily interpretable visual graphs. This approach enhances the readability of prediction model outcomes, enabling researchers to accurately identify influential factors, evaluate the study object, and ultimately increase its practicality[[15,17,18,29]]. (2) We did not only consider the effects of opioid use or psychology on medication adherence in patients with cancer pain, as in previous studies. Instead, we developed a nomogram model combining demographic, clinical, pain medication, and psychological state. We developed a cost-effective nomogram model utilizing seven readily available variables, which demonstrated good discrimination and accuracy with a C-index of 0.93 (95% CI: 0.907–0.953) and an AUC of 0.929. Furthermore, the Decision Curve Analysis (DCA) and Clinical Impact Curve analysis provided evidence of the nomogram's considerable potential for clinical application in predicting nonadherence to analgesic medication among cancer patients. (3) Easy access to indicators and low economic cost make nomogram more practical. This will help develop an online nomogram to quantify the probability of patients with medication nonadherence.

Previous studies have reported that cancer patients themselves are complicated with other symptoms, which are easily decompensated during anti-cancer treatment. Multi-drug therapy for patients requires not only comprehensive drug review, but also psychological management of patients. Therefore, the collaborative practice of pharmacists can prove to be valuable when compliance is difficult or supplementary drugs are used [30]. Tateai Y et al. investigated the compliance of lovatinib in patients with thyroid cancer and hepatocellular carcinoma. It was reported that hypertension was the main reason for nonadherence, followed by skin reaction of hands and feet and diarrhea [31]. However, the sample size of this study is small, and the clinical characteristics of patients are not as comprehensive as this paper. The compliance survey of breast cancer patients focuses on socio-economic factors and treatment-related factors. However, the sample size of this study is small, and the clinical characteristics of patients are not as comprehensive as this paper. The compliance survey of breast cancer patients focuses on socio-economic factors and treatment-related factors. The results of the study emphasize that patients' education and monitoring or strategies to promote cost control and side effect management can optimize adherence and gain potential benefits. For young patients in British Columbia, Hungary, the evaluation of shame, physical shame and self-sympathy and the improvement of the availability of evidence-based psychological intervention may improve their adherence [32]. This is similar to the economic and psychological factors that this study focuses on patients. Although this paper focuses on the adherence of patients with cancer pain, the psychological relationship of each disease is not as detailed as that of a specific single disease. In this paper, the psychological investigation only started with PHQ-8, but ignored the influence of psychological investigation of Stigma Scale for Clinical Illnesses (SSCI-8), Experience of Shame Scale (ESS) and Self-Compassion Scale (SCS) on patients' medication adherence. In addition to the patient's own influence on medication adherence, the surrounding environment also affects the patient's medication behavior. Dang TH et al. pointed out that cancer patients need all kinds of support and hope to be respected and encouraged, so that a positive attitude can develop high adherence [33]. However, this paper lacks the research content of the relationship between patients and the surrounding environment during the investigation, which is also the focus of our follow-up research.

According to the results of this study, opioids and NSAIDs may be the main influencing factors in cancer patients' nonadherence to their analgesic medications. Presently, analgesic drugs are mostly prescribed in accordance with the WHO's three-step analgesic ladder [34]. This principle serves as the initial step in guiding clinicians to approach drug analgesia treatment in a systematic manner, with the selection of drug analgesia treatment being contingent upon the severity of pain. For cases of mild pain, the recommended first step involves the utilization of non-opioids, specifically non-steroidal anti-inflammatory drugs and other over-the-counter analgesics. Strong opioids, on the other hand, remain a fundamental component in the management of moderate to severe cancer pain. In our study, it was observed that patients who utilized opioids exhibited a higher risk of nonadherence, with a substantial proportion (86.89% or 391 patients) primarily relying on sustained release formulations of opioids, OST, and MST. Similar to previous research[[14,8]], patients exhibited nonadherence as a result of apprehension regarding addiction and tolerance. Concurrently, adverse effects pose a significant challenge, with constipation and gastrointestinal reactions being the most prevalent in this study. Individuals utilizing NSAIDs face an elevated likelihood of nonadherence to analgesic medication, potentially attributable to the occurrence of gastrointestinal events as an adverse reaction to NSAID usage.

In this study, constipation was identified as the most common adverse reaction in 168 patients. As the results of this study show, every patient has adverse reactions. There are many kinds of adverse reactions in each patient in this investigation, but the shortcoming of this study is the incompleteness of the records, only five common types of adverse reactions were recorded. Therefore, considering the complexity of adverse reactions, it is not included as a factor that affects medication adherence again. At the same time, it has been reported that constipation management is a key part of nursing care for elderly patients with chronic diseases. The study also shows that risk assessment and appropriate drug treatment should mean that constipation can be minimized, preventing additional drug burden and reducing the risk of nonadherence [33]. Opioid drugs have become an integral part of the treatment of moderate to severe chronic non-cancerous pain. They may cause unpleasant side effects such as nausea, vomiting and constipation. Good compliance of pain treatment for cancer patients is inseparable from opioids. Therefore, long-acting opioids can continuously relieve pain within 24 h, and the side effects are easy to control [35]. For the same reason, cancer patients can also effectively learn how to avoid or reduce constipation.

Nonadherence in analgesic treatment is often linked to aging. In this study, the median age of participants was 54, and the median age of nonadherence was 64. The study results support previous findings that the higher one's age, the greater the likelihood of noncompliance[[19,36,37]]. Comorbidity emerges as a significant determinant of nonadherence to analgesic medication in cancer patients. In contrast to prior investigations [38], our study findings reveal that non-smoking individuals exhibit a greater propensity for nonadherence to analgesic medications compared to their smoking counterparts. Furthermore, residing in rural locales amplifies the risk of nonadherence to analgesic drugs among cancer pain patients, surpassing that of their urban-dwelling counterparts.

The findings of our study indicate a significant correlation between the severity of depression and nonadherence to analgesic medication. It is worth noting that depression is a prevalent psychological symptom among individuals experiencing cancer-related pain, as supported by previous research[[39,40,41]]. Furthermore, insufficient pain control not only exacerbates the prevalence and intensity of these symptoms but also complicates the management of pain. Therefore, achieving effective relief from cancer pain necessitates a comprehensive understanding of the detrimental impact of pain on the patient's psychological well-being. In a study conducted by Li et al. in China, it was demonstrated that individuals suffering from cancer pain exhibited notably elevated levels of state anxiety and depression, while no significant difference was observed in trait anxiety when compared to patients without pain. Furthermore, patients experiencing pain also displayed significantly higher rates of depression [42]. Our own investigation revealed a positive correlation between the patient's PHQ-8 score and the likelihood of nonadherence.

This study aimed to develop a nomogram for the prediction of nonadherence to analgesic medication in cancer pain patients, thereby facilitating the prompt identification of high-risk patients by healthcare professionals and enabling early intervention for their benefit. The related factors of drug treatment non-compliance caused by cancer pain can be divided into variable factors and modifiable factors. First of all, for patients with unchangeable factors such as old age and living in rural areas. Follow-up should be paid attention to in drug treatment of these patients to improve their cognitive level of drug education. Health care professionals are advised to be patient with these patients and provide constructive solutions to their problems. Secondly, among the modifiable factors, the concept of drug use and the acceptance of various diseases can be changed through education on the effectiveness and safety of drug treatment. In addition, the intervention plan guided by the psychological self-regulation theory of patients and their families can be considered as improving patients' motivation and self-confidence, thus improving compliance and quality of life.

It cannot be ignored that there are some limitations in this study. First of all, despite the one-on-one and face-to-face survey methods, some surveys have met with the reluctance of patients, which may bring slight deviation to our research results. Secondly, the report bias in the self-report questionnaire exists because patients tend to provide answers that meet social expectations. The main factors that lead to biases in self-report are so-called memory-experience gap and recalled affective state [43]. The retrospective overestimation of symptoms, compared to the average transient assessment, occurred immediately after symptom onset [44]. In addition, positive and negative emotional effects are often retrospectively exaggerated [43], which can lead to the illusion of positive change when comparing retrospective measures of pre-treatment pain with actual pain assessment [45]. Therefore, end-of-day diaries and day reconstruction method are very important to reduce biases in self-report[[46,47,48]]. Patients can be encouraged to keep a journal at the end of each day or to do a day reconstruction. Patients can also be encouraged to record symptoms as they occur. In this way, medical workers can grasp the dynamic changes of patients' symptoms and contribute to the accuracy of disease assessment. Finally, including only one hospital in this study may produce different results from those observed in other geographical areas. Therefore, it is necessary to replicate and verify the results of this study through additional comprehensive research to investigate patient-related variables that may further affect pain management and enhance the existing framework. Nevertheless, this study provides significant advantages. These results provide valuable insights for health care professionals to implement tailor-made educational interventions for patients, thus promoting standardized management of cancer pain and ultimately improving its curative effect.

5. Conclusions

It was found that cancer patients were less likely to adhere to their analgesic medications. The development and validation of a 7-factor nomogram model for the management of pain caused by cancer has been successful.

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Data availability statement

Data supporting the results of this study can be obtained from the corresponding authors.

CRediT authorship contribution statement

Ying Wang: Writing – original draft, Methodology, Investigation, Funding acquisition. **ChanChan Hu:** Conceptualization. **Junhui Hu:** Writing – review & editing, Software. **Yunwei Liang:** Methodology, Investigation, Conceptualization. **Yanwu Zhao:** Funding acquisition. **Yinhui Yao:** Writing – review & editing, Software, Formal analysis. **Xin Meng:** Data curation. **Jing Xing:** Data curation. **Lingdi Wang:** Validation. **Yanping Jiang:** Validation. **Xu Xiao:** Investigation, Formal analysis.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, there is no professional or other personal interest of any nature or kind in any product, service and/or compaby that could be constued as influencing the position presented in, or the review of, the manuscript entitled.

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