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Prediction model for delirium in advanced cancer patients receiving palliative care: development and validation

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Abstract

Background Delirium is a common and distressing mental disorder in palliative care. To date, no delirium prediction model is available for thepalliative care population. The research aimed to develop and validate a nomogram model for predicting the occurrence of delirium in advanced cancer patients admitted to palliative care units.

Methods This was a prospective, multicenter, observational study. Logistic regression was used to identify the independent risk factors for incident delirium among advanced cancer patients in palliative care units. Advanced cancer patients admitted to palliative care units between February 2021 and January 2023 were recruited from four hospitals in Chengdu, Sichuan Province, China. Model performance was evaluated via the area under the receiver operating characteristic curve, calibration plots and decision curve analysis.

Results There were 592 advanced cancer patients receiving palliative care in the development cohort, 196 in the temporal validation cohort and 65 in the external validation cohort. The final nomogram model included 8 variables (age, the Charlson comorbidity index, cognitive function, the Barthel index, bilirubin, sodium, the opioid morphine equivalent dose and the use of anticholinergic drugs). The model revealed good performance in terms of discrimination, calibration, and clinical practicability, with an area under the receiver operating characteristic curve of 0.846 in the training set, 0.838 after bootstrapping, 0.829 in the temporal validation and 0.803 in the external validation set.

Conclusions The model serves as a reliable tool to predict delirium onset for advanced cancer patients in palliative care units, which will facilitate early targeted preventive measures to reduce the burden of delirium.

Keywords Palliative care, Neoplasms, Delirium, Risk factors, Nomogram

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Introduction

With population aging and the increasing incidence of malignant tumors, the palliative care population, which consists mainly of advanced cancer patients, have received increasing attention. Delirium is a common and serious neurocognitive disorder in palliative care units, which is characterized by acute and fluctuating changes in attention, awareness and cognition [1]. A systematic review reported that the prevalence of delirium in adult cancer palliative care inpatients ranged from 13.3 to 42.3% at admission, from 26 to 62% during hospitalization and from 58.8 to 88% 1 week or hours before death [2]. Delirium in palliative care units is related to prolonged hospital stays, increased medical costs and high mortality, resulting in burdens to the patients, their families and the healthcare system [3, 4, 5].

At present, knowledge about delirium in the palliative care population is scarce, and effective therapeutic measures for delirium are still lacking. Thus, it is critical to identify risk factors and construct prediction models for delirium so that optimal strategies can be developed to prevent delirium in palliative care units. Although several risk prediction models for delirium in elderly inpatients, intensive care patients and surgical patients have been published [6, 7, 8], there is no prediction model available for delirium in the palliative care population. To our knowledge, the prevalence and risk of delirium differ across different populations and settings [9]. Patients admitted to palliative care units are mainly terminally ill cancer patients with poor physical condition, who usually need opioids and antipsychotics to relieve pain, dyspnea and other distressing symptoms. Thus, the incidence of delirium in palliative care units is high and current delirium risk prediction models are not applicable to this particular population.

The aims of our study were to develop and validate a model for predicting delirium in advanced cancer patients during their stay in palliative care units. Such a model may help to identify individuals at high risk of delirium and provide an important reference for targeted prevention and control measures, thereby contributing to a decreased incidence of delirium in palliative care units.

Methods

Study design and data sources

This was a multicenter prospective observational study conducted in four hospitals. To develop the prediction model, we performed a prospective cohort study in the palliative care unit at the West China Fourth Hospital of Sichuan University from February 2021 to May 2022. We subsequently conducted a second prospective cohort study in the same hospital for temporal validation of the prediction model from June 2022 to December 2022. We externally validated the delirium prediction model with data from advanced cancer patients admitted to the Department of Palliative Medicine at the Sixth People's Hospital of Chengdu, the Eighth People's Hospital of Chengdu, and the Gleneagles Hospital of Chengdu from June 2022 to January 2023. The study was registered in the National Medical Research Registration Information System (MR-51-21-013129) in China and approved by the Ethics Committee of West China Fourth Hospital, Sichuan University (HXSY-EC-2021002) in January 2021.

Participants

The inclusion criteria for participants were as follows: (1) patients admitted to inpatient palliative care units with advanced cancer at stage III or IV according to the tumor-node-metastasis (TNM) classification of the International Union Against Cancer (UICC), (2) aged more than 18 years old, (3) whose predicted survival time was less than 6 months, and (4) participant informed consent. Written informed consent was obtained from all participants or from designated healthcare surrogates if they were unable to provide it themselves.

The exclusion criteria were as follows: (1) patients with delirium or coma on admission, (2) patients who stayed in palliative care units for less than 24 h, (3) patients with uncorrected severe hearing or visual impairment, and (4) patients unable to speak.

Outcome definition

The main outcome was the development of delirium during patients' stay in palliative care units. We used the 3-minute diagnostic confusion assessment (3D-CAM) to assess delirium three times daily (morning, midday, and evening). Delirium was defined as a minimum of one positive 3D-CAM screening. The 3D-CAM derived from the confusion assessment method (CAM) provides a brief and structured assessment algorithm to accelerate and simplify the diagnostic process of delirium [10], which has demonstrated high sensitivity and specificity compared with the Diagnostic and Statistical Manual of Mental Disorders Version 5 (DSM-5) [11, 12, 13]. The outcome assessment was standardized but not blinded. The diagnosis of delirium was determined by a consensus between two investigators. If their opinions differed, a neurologist was consulted.

Predictor variables

A total of 21 potential predictor variables were included for initial consideration. Among these variables, thirteen variables including age, sex, brain tumors, jaundice, renal failure, dehydration, the use of opioids, the use of anticholinergic drugs, impaired performance status, frailty, malnutrition, sleep disorders, and dyspnea were independent risk factors confirmed by our previously published systematic review [14]. The other eight risk factors,

including comorbidity, infection, decreased ability to perform activities of daily living, cognitive impairment, hypoproteinemia, hyponatremia, hypercalcemia, and pain were considered important and suggested for inclusion in the study by experts in geriatrics and palliative medicine.

We collected data on patients within the first 24 h of admission to palliative care units, including the following aspects. (1) The demographic characteristics were age and gender. (2) The disease information included primary and metastatic tumor sites, comorbidities, and infection status. (3) The library examination results included the levels of albumin, total bilirubin, serum sodium, blood urea nitrogen and serum creatinine. Dehydration was assessed by the blood urea nitrogen-to-creatinine ratio, and renal function was examined by the estimated glomerular filtration rate (eGFR) via the Modification of Diet in Chronic Renal Disease (MDRD) formula [15, 16]. (4) Data on the use of opioids and anticholinergic drugs within the first 24 h of admission to palliative care units were collected. Given that opioids differ in their potency, formulation and administration routes, we converted the doses of various types of opioid to oral morphine equivalent (OME) doses on the basis of the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Adult Cancer Pain [17]. Anticholinergic drugs were defined by the Anticholinergic Risk Scale (ARS) [18]. (5) Performance status, activities of daily living, frailty, nutrition, sleep, cognitive function, and pain were assessed via scales [19, 20, 21, 22, 23, 24, 25, 26]. Specific scales and assessment thresholds are provided in the supplementary Table 1.

Sample size

The model contained 21 candidate predictors. We calculated the sample size on the basis of the need for 10 delirious patients per candidate predictor plus 10% dropout. According to a previous study, the median incidence of delirium in inpatient palliative care units was 40.2% when patients were screened daily or more often [27]. We use this value as the anticipated delirium incidence. Thus, the required sample size for the development of the model was 580((21 × 10/0.402)/ (1-0.1)).

Currently, there are no generally accepted approaches for sample size estimation in the temporal validation studies of risk prediction models [28]. We estimated the sample size according to the random split sample method with a ratio of 3:1 between the training set and the temporal verification set. Thus, the sample size of the temporal verification set was 193.

For the external validation, we applied Riley's recommendations for calculating the minimum sample size [29]. The following formula was used: $N=(1-\phi)/\phi\ (SE(\ln(O/E)))^2$. The ϕ variable represents the anticipated delirium incidence of 40.2%[27]. The O/E ratio is the ratio of observed to expected delirium. We assumed an O/E ratio of 1.0 with a 95% confidence interval of 0.7–1.3 and then estimated the value of SE via the Wald method. Finally, we determined that at least 63 patients were needed for the external validation.

Quality control and missing data

To ensure the quality of data collection, we randomly checked the completed data and regularly monitored the performance of the 3D-CAM screening. We assessed the extent and type of missing data. Mean interpolation was used to process the missing laboratory data. Hot deck imputation was used to impute missing values for the other variables. In the overall cohort, data were missing for total bilirubin (0.94%), albumin (0.94%), sodium (1.8%), calcium (1.8%), oral morphine equivalent (2.8%) and anticholinergic use (3.5%). The other variables had complete data.

Statistical analysis

We used univariate logistic regression to assess the associations between each potential risk factor and the presence or absence of delirium. We excluded factors with a *P* value above 0.10 in the univariate analysis. With respect to the remaining risk factors, we used multivariate logistic regression analysis with backward and forward stepwise regression to evaluate the independent associations with the occurrence of delirium. All the independent risk factors ($p < 0.05$) were included in the final delirium prediction model.

A nomogram based on the final model was constructed from the overall data of the training cohort. We estimated the discrimination of the prediction model by the area under the receiver operating characteristic curve (AUROC) and the calibration of the model by the calibration curve and Hosmer-Lemeshow goodness-of-fit test. Decision curve analysis (DCA) was used to evaluate the clinical effectiveness of the prediction model.

In the internal validations based on the training cohort, the model stability was verified after 1,000 bootstraps to adjust the overfitting deviation. In the temporal and external validation datasets, the discrimination, calibration, and clinical effectiveness of the prediction model were validated. All the statistical analyses were performed via R statistics version 4.2.1 and SPSS 26.0. Statistical significance was set at a two-sided p value < 0.05.

Results

Development of the prediction model

In the training cohort, 592 consecutive patients were included, 188 of whom (31.8%) developed delirium during hospitalization. The median hospital stay for all the patients was 12 days (interquartile range, 6-21days).

Table 2 shows the 21 potential risk factors and the univariate logistic regression analysis results for delirium in advanced cancer patients receiving palliative care. Among the 21 potential risk factors, we excluded male sex, brain tumors, renal failure, and frailty because the *P*value was greater than 0.1 in the univariate logistic regression analysis (Table 2). After multivariate logistic regression analysis of the remaining risk factors, eight independent risk factors for delirium were identified (Table 1). The formula of the delirium risk model was as follows: risk of delirium = 1/ (1 + exp- (0.05 × age + 0.15 × Charlson comorbidity index + 0.96×cognitive dysfunction + 0.66 × Barthel Index (41–60) + 1.60× Barthel Index (≤ 40) + 0.30×sodium (125–136mmol/L) + 1.22 × sodium (< 125mmol/L) + 0.76 × bilirubin (34.2–171umol/L) + 1.70 × bilirubin (≥ 171umol/L) + 1.56 × Oral Morphine Equivalent (≤ 30 mg/d) + 1.83 × Oral Morphine Equivalent (30–90 mg/d) + 2.33 × Oral Morphine Equivalent (> 90 mg/d) + 0.74 × Anticholinergic use. A nomogram was constructed on the basis of the results of final multivariable model (Fig. 1A).

Evaluation of the prediction model

In the training set, the AUROC of the nomogram was 0.846 (95% confidence interval 0.813 to 0.878) (Fig. 1B), which did not change noticeably after bootstrapping (AUROC 0.838). The Hosmer-Lemeshow test yieled a chi-square value of 2.96 ($P = 0.228$), indicating good calibration (Fig. 1C). The DCA curve indicated that the corresponding net benefit was 0–33% with the threshold probability value of 5–90% (Fig. 1D).

Temporal validation of the prediction model

In the temporal validation cohort, 196 patients were included, 69 of whom (35.2%) developed delirium during hospitalization. Table 3 shows the characteristics of the training, temporal validation, and external validation cohorts. The AUROC of the nomogram was 0.829 (95% confidence interval 0.773 to 0.886) (Fig. 2A). The calibration curves of the temporal validation set did not significantly deviate from the 45-degree diagonal line (Fig. 2C). The DCA curve indicated that the corresponding net benefit was 0–35% with a threshold probability value of 0–95% (Fig. 2E).

External validation of the prediction model

In the temporal validation cohort, 65 patients were included, 28 of whom (43.1%) developed delirium during hospitalization (Table 3). The AUROC of the nomogram was 0.803 (95% confidence interval 0.689 to 0.917) (Fig. 2B). The calibration curves of the external validation set did not significantly deviate from the 45-degree diagonal line (Fig. 2D). The DCA curve indicated that the corresponding net benefit was 0–45% with a threshold probability value of 0–80% (Fig. 2F).

Table 1 Multiple logistic regression analysis results of Delirium in Advanced Cancer patients receiving Palliative Care

Variables	Regression coefficient	OR(95%CI)	*P*Value
Age (years)	0.05	1.05(1.03–1.07)	< 0.001
Charlson comorbidity index	0.15	1.16(1.01–1.34)	0.04
TBIL			
TBIL ≤ 34.2umol/L	Reference	Reference	Reference
34.2umol/L < TBIL ≤ 171umol/L	0.76	2.13(1.17–3.89)	0.014
TBIL > 171umol/L	1.70	5.45(2.17–14.23)	< 0.001
Sodium			
Sodium ≥ 136mmol/L	Reference	Reference	Reference
125mmol/L ≤ Sodium < 136mmol/L	0.30	1.35(0.84–2.19)	0.219
Sodium < 125 mmol/L	1.22	3.38(1.67–6.98)	0.001
OME			
OME = 0	Reference	Reference	Reference
OME ≤ 30 mg/d	1.56	4.75(2.23–10.88)	< 0.001
30 mg/d < OME ≤ 90 mg/d	1.83	6.22(2.66–15.49)	< 0.001
OME > 90 mg/L	2.33	10.25(4.32–25.95)	< 0.001
Anticholinergic use	0.74	2.09(1.26–3.51)	0.005
Barthel Index			
Independent or mild dependence	Reference	Reference	Reference
Moderate dependence	0.66	1.93(1.00-3.75)	0.050
Severe dependence	1.60	4.94(2.86–8.80)	< 0.001
Cognitive dysfunction	0.96	2.61(1.31–5.38)	0.008

TBIL: Total Bilirubin; ALB: Albumin; BUN: Blood Urea Nitrogen; OME: Oral Morphine Equivalent; BI: Barthel Index

Table 2 Univariate Logistic Regression Analysis Results of Delirium in Advanced Cancer patients receiving Palliative Care

Variables	Total ($n=592$)	Delirium ($n=188$)	No delirium ($n=404$)	OR (95%CI)	*P* Value
Age (years)	61.8 ± 14.2	65.5 ± 13.2	60.1 ± 14.2	1.23 (1.02–1.04)	< 0.001
Male sex, *n* (%)	281 (47.5)	96 (51.0)	185 (45.8)	1.22 (0.86–1.72)	0.270
Brain tumor, *n* (%)	51 (8.6)	14 (7.4)	37 (9.2)	0.78 (0.40–1.52)	0.469
Infection, *n* (%)	364 (61.5)	138 (73.4)	226 (55.9)	2.17 (1.50–3.19)	< 0.001
Renal failure, *n* (%)	11 (1.9)	4 (2.1)	7 (1.7)	1.23 (0.32–4.13)	0.741
Charlson comorbidity index	6.8 ± 1.6	7.2 ± 1.7	6.6 ± 1.5	1.30 (1.16–1.46)	< 0.001
TBIL					
TBIL ≤ 34.2umol/L	474 (80.1)	133 (70.7)	341 (84.4)	Reference	Reference
34.2umol/L < TBIL ≤ 171umol/L	84 (14.2)	34 (18.1)	50 (12.4)	1.74 (1.07–2.81)	0.023
TBIL > 171umol/L	34 (5.7)	21 (11.2)	13 (3.2)	4.14 (2.04–8.72)	< 0.001
Hypoproteinemia(ALB < 35 g/L)	388 (65.5)	147 (78.2)	241 (59.7)	2.42 (1.64–3.65)	< 0.001
Sodium, *n* (%)					
Sodium ≥ 136mmol/L	216 (36.5)	51 (27.1)	165 (40.8)	Reference	Reference
125mmol/L ≤ Sodium < 136mmol/L	314 (53.0)	100 (53.2)	214 (53.0)	1.51 (1.02–2.25)	0.039
Sodium < 125 mmol/L	62 (10.5)	37 (19.7)	25 (6.2)	4.78 (2.65–8.79)	< 0.001
Hypercalcemia(Calcium > 2.75umol/L)	16 (2.7)	9 (4.8)	7 (1.7)	1.69 (1.02–2.79)	0.041
Dehydration(BUN/creatinine > 20)	436 (73.6)	150 (79.8)	286 (70.8)	1.63 (1.08–2.47)	0.021
OME, *n* (%)					
OME = 0	143 (24.2)	11 (5.9)	132 (32.7)	Reference	Reference
OME ≤ 30 mg/d	256 (43.2)	95 (50.5)	161 (39.9)	7.08 (3.79–14.50)	< 0.001
30 mg/d < OME ≤ 90 mg/d	102 (17.2)	37 (19.7)	65 (16.1)	6.83 (3.71–14.86)	< 0.001
OME > 90 mg/L	91 (15.4)	45 (23.9)	46 (11.4)	11.74 (5.78–25.67)	< 0.001
Anticholinergic use, *n* (%)	365 (61.7)	148 (78.7)	217 (53.7)	3.19 (2.15–4.81)	< 0.001
ECOG-PS, *n* (%)					
2	68 (11.5)	6 (3.2)	62 (15.3)	Reference	Reference
3	263 (44.4)	57 (30.3)	206 (51.0)	2.859 (1.18–6.95)	< 0.001
4	261 (44.1)	125 (66.5)	136 (33.7)	9.498 (3.97–22.75)	< 0.001
Barthel Index, *n* (%)					
Independent or mild dependence	197 (33.3)	23 (12.2)	174 (43.1)	Reference	Reference
Moderate dependence	130 (22.0)	33 (17.6)	97 (24.0)	2.57 (1.44–4.68)	0.002
Severe dependence	265 (44.8)	132 (70.2)	133 (32.9)	7.51 (4.64–12.60)	< 0.001
Frailty, *n* (%)					
Non-frail	5 (0.8)	1 (0.5)	4 (1.0)	Reference	Reference
Pre-frail	79 (13.3)	7 (3.7)	72 (17.8)	0.39 (0.05–8.16)	0.426
Frail	508 (85.8)	180 (95.7)	328 (81.2)	2.18 (0.32–42.75)	0.488
Nutrition status (MNA-SF), *n* (%)					
Normal nutrition status	21 (3.5)	1 (0.5)	20 (5.0%)	Reference	Reference
Risk of malnutrition	159 (26.9)	30 (16.0)	129 (31.9)	4.65 (0.91–85.09)	0.141
Malnutrition	412 (69.6)	157 (83.5)	255 (63.1)	12.31 (2.53-222.06)	0.015
Quality of sleep (PSQI), *n* (%)					
No sleep disorder	89 (15.0)	17 (9.0)	72 (17.8)	Reference	Reference
Mild sleep disorder	121 (20.4)	34 (18.1)	87 (21.5)	1.66 (0.86–3.26)	0.135
Moderate sleep disorder	219 (37.0)	74 (39.4)	145 (35.9)	2.16 (1.21–4.03)	0.012
Severe sleep disorder	163 (27.5)	63 (33.5)	100 (24.8)	2.67 (1.47–5.05)	0.002
Cognitive dysfunction, *n* (%)	58 (9.8)	40 (21.3)	18 (4.5)	5.80 (3.27–10.66)	< 0.001
Pain (NRS), *n* (%)					
No pain	77 (13.0)	15 (8.0)	62 (15.3)	Reference	Reference
Mild pain	103 (17.4)	21 (11.2)	82 (20.3)	1.06 (0.51–2.25)	0.880
Moderate pain	79 (13.3)	15 (8.0)	64 (15.8)	0.97 (0.43–2.16)	0.938
Severe pain	333 (56.3)	137 (72.9)	196 (48.5)	2.89 (1.62–5.46)	< 0.001
Dyspnea, *n* (%)	116 (19.6)	46 (24.5)	70 (17.3)	1.56 (1.02–2.37)	0.038

TBIL: Total Bilirubin; ALB: Albumin; BUN: Blood Urea Nitrogen; OME: Oral Morphine Equivalent; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; BI: Barthel Index; MNA-SF: Mini Nutritional Assessment Short Form; PSQI: Pittsburgh Sleep Quality Index; NRS: Numerical Rating Scale

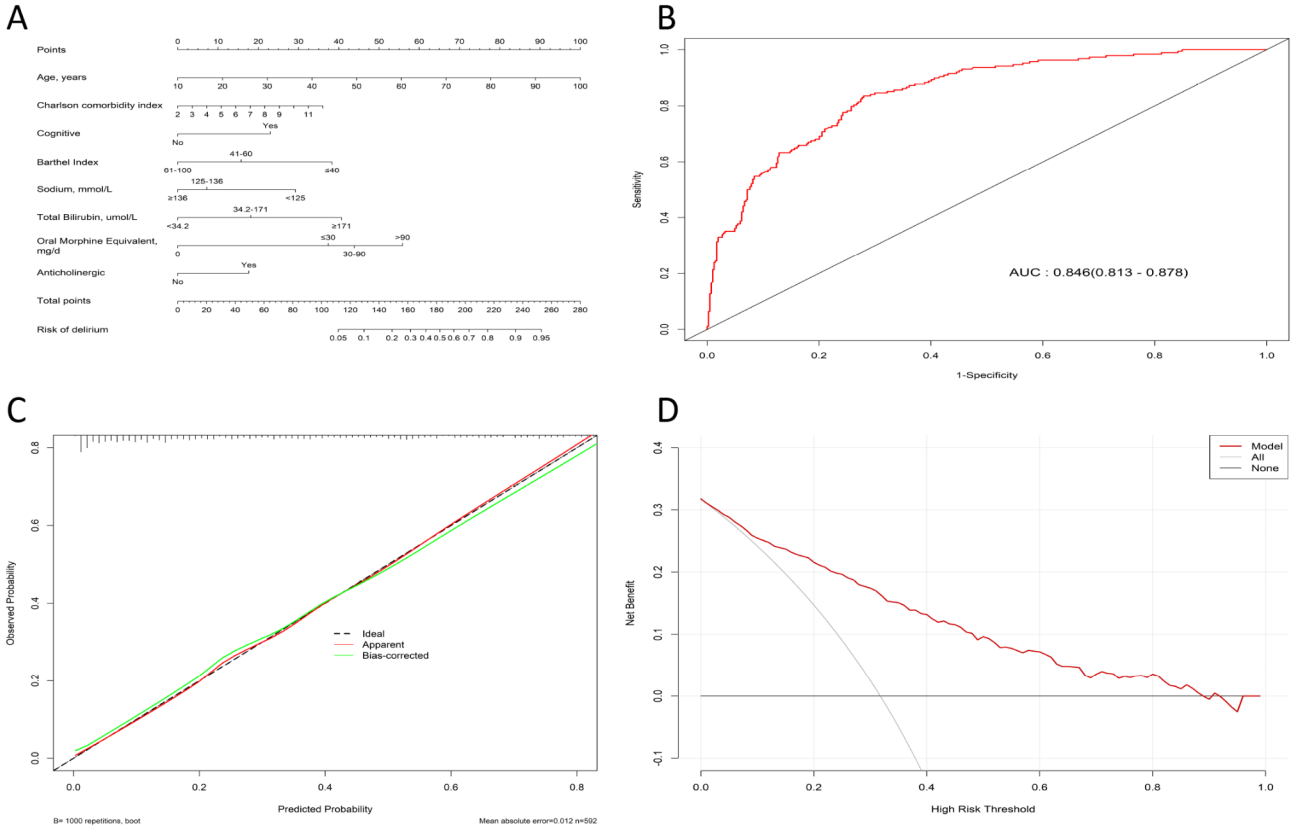

Fig. 1 Nomogram for predicting risk of delirium in advanced cancer patients receiving palliative care and its predictive performance in training Set. Nomogram (**A**). Receiver operating characteristic curve of the nomogram in training set (**B**). Calibration curve of the nomogram in training set (**C**). Decision curve analysis of the nomogram in training set (**D**)

Discussion

Main findings

In this multicenter prospective cohort study, we first developed and validated a model for predicting delirium in advanced cancer patients during their stay in palliative care units, which revealed excellent discrimination, calibration, and clinical practicability. All 8 risk factors included in the model are readily available clinical or laboratory data within 24 h of admission to palliative care units. The model does not require additional complex procedures or specialized tests and all the necessary clinical data can be gathered through routine monitoring processes. Therefore, we believed that the model could be a convenient and effective tool for clinicians to predict delirium in palliative care units.

Interpretation

Among the eight predictors of our model, seven predictors including old age, cognitive impairment, comorbidities, decreased ability to perform activities of daily living, hyponatremia, opioids, and hyperbilirubinemia have been identified as independent risk factors for delirium in hospitalized elderly patients, intensive care patients and postoperative patients, with the exception of the use of anticholinergic drugs [30, 31, 32, 33]. Anticholinergic drugs are widely used in palliative care patients to reduce glandular secretion and relieve gastrointestinal spasm. However, the use of anticholinergic drugs may induce cholinergic deficiency, which has been postulated to cause cognitive decline [34]. Currently, the relationship between anticholinergic burden and delirium has rarely been investigated, and the existing results are conflicting [18]. The variation could partially stem from the use of diverse anticholinergic rating scales, which include various anticholinergic drugs and assign distinct levels of anticholinergic severity to these medications. According to our study and a recent systematic review by Egberts, the ARS is a potential tool for identifying the risk of delirium in patients [18]. Notably, we confirmed the use of anticholinergic drugs only as an independent predictor of delirium in advanced cancer patients receiving palliative care. Further research is still needed to determine whether the cumulative anticholinergic burden is associated with increased delirium risk.

Opioids, as the mainstay of cancer pain management, are well-recognized precipitating factors of delirium [35]. Several studies have reported that high-dose opioids increase the risk of delirium more significantly than

Table 3 The characteristics of the training, temporal validation and external validation cohorts

Variables	Training cohort (*n* = 592)	Temporal validation cohort (*n* = 196)	External validation cohort (*n* = 65)
Age(years)	61.84 ± 14.16	61.58 ± 13.42	67.02 ± 16.89
Male sex, *n*(%)	281(47.5)	102(52.0)	31(47.7)
Charlson comorbidity index	6.81 ± 1.58	7.21 ± 1.47	7.17 ± 1.86
Cognitive dysfunction, *n*(%)	58(9.8)	11(5.6)	7(10.8)
Barthel Index, *n*(%)			
61–100	197(33.3)	39(19.9)	10(15.4)
41–60	130(22.0)	49(25.0)	17(26.1)
≤ 40	265(44.7)	108(55.1)	38(58.5)
Sodium, *n*(%)			
≥ 136 mmol/L	474(80.1)	153(78.1)	25(38.5)
125–136 mmol/L	84(14.2)	27(13.8)	36(55.4)
< 125 mmol/L	34(5.7)	16(8.1)	4(6.1)
TBIL, *n*(%)			
< 34.2 umol/L	216(36.5)	87(44.4)	56(86.2)
34.2–171 umol/L	314(53.0)	93(47.4)	6(9.2)
≥ 171 umol/L	62(10.5)	16(8.2)	3(4.6)
OME, *n*(%)			
0	143(24.2)	49(25.0)	19(29.2)
≤ 30 mg/d	256(43.2)	84(42.9)	29(44.6)
30–90 mg/d	102(17.2)	30(15.3)	10(15.4)
> 90 mg/d	91(15.4)	33(16.8)	7(10.8)
Anticholinergic use, *n*(%)	365(61.7)	113(57.7)	45(69.2)
Delirium, *n*(%)	188(31.8)	69(35.2)	28(43.1)

TBIL: Total Bilirubin; ALB: Albumin; BUN: Blood Urea Nitrogen; OME: Oral Morphine Equivalent; BI: Barthel Index

low-dose opioids do [36]. However, there is no clear definition of high-dose opioids associated with delirium. To confirm the impact of opioid dose on delirium, we converted the doses of various types of opioids to the oral morphine equivalent (OME) doses and divided OME into four categories:0, ≤ 30 mg/d (low dose), 30–90 mg/d (medium dose) and > 90 mg/d (high dose). We demonstrated that increased opioid consumption increased the risk of delirium in patients, and the high-dose group (OME > 90 mg/d) had the highest incidence of delirium. The Disease Control and Prevention (CDC) guidelines also suggest that high-dose opioids (OMEs > 90 mg/d) should be used with great caution due to increased overdose risk. Although previous studies reported a positive association of pain with delirium in univariate analysis, this correlation was not confirmed in our multivariate analysis [37, 38, 39, 40]. We speculated that pain may not be an independent risk factor for delirium but rather may be associated with the use of opioids. To reduce the incidence of delirium in palliative care units, we should ensure the rational use of opioids by starting opioids at the lowest effective dosage, cautiously increasing the opioid dosage and avoiding high-dose opioids [41].

Implications

Our prediction model has important implications for clinical practice. The probability of developing delirium in each advanced cancer patient admitted to palliative care units can be calculated on the basis of the nomogram, which may help palliative care staff to identify patients at high risk of delirium and pay increased attention to these patients. According to our study, hyponatremia, opioid use, and anticholinergic use are modifiable risk factors for delirium. Vigilant monitoring of serum electrolytes, appropriate treatment of hyponatremia, and prudent use of opioids and anticholinergic drugs may be effective for reducing the incidence of delirium in palliative care units. Non-modifiable risk factors, including advanced age, cognitive impairment, comorbidities, and decreased ability to perform daily living, are useful for delirium prediction and can also suggest possible directions for delirium prevention. For example, strategies to improve patients' ability for daily living and cognitive function seem feasible and potential for delirium prevention, which include minimizing tethers and physical restraint, assisting in physical activity, and encouraging patients to reminisce and talk, seem feasible and potentially useful for preventing delirium [42]. However, their effectiveness still needs further investigation.

Strengths and limitations

Our study is the first to develop and validate a risk prediction model for incident delirium in palliative care units. The main strengths of this study are the prospective cohort design and multicenter validation. Moreover, we performed internal, temporal and external validation

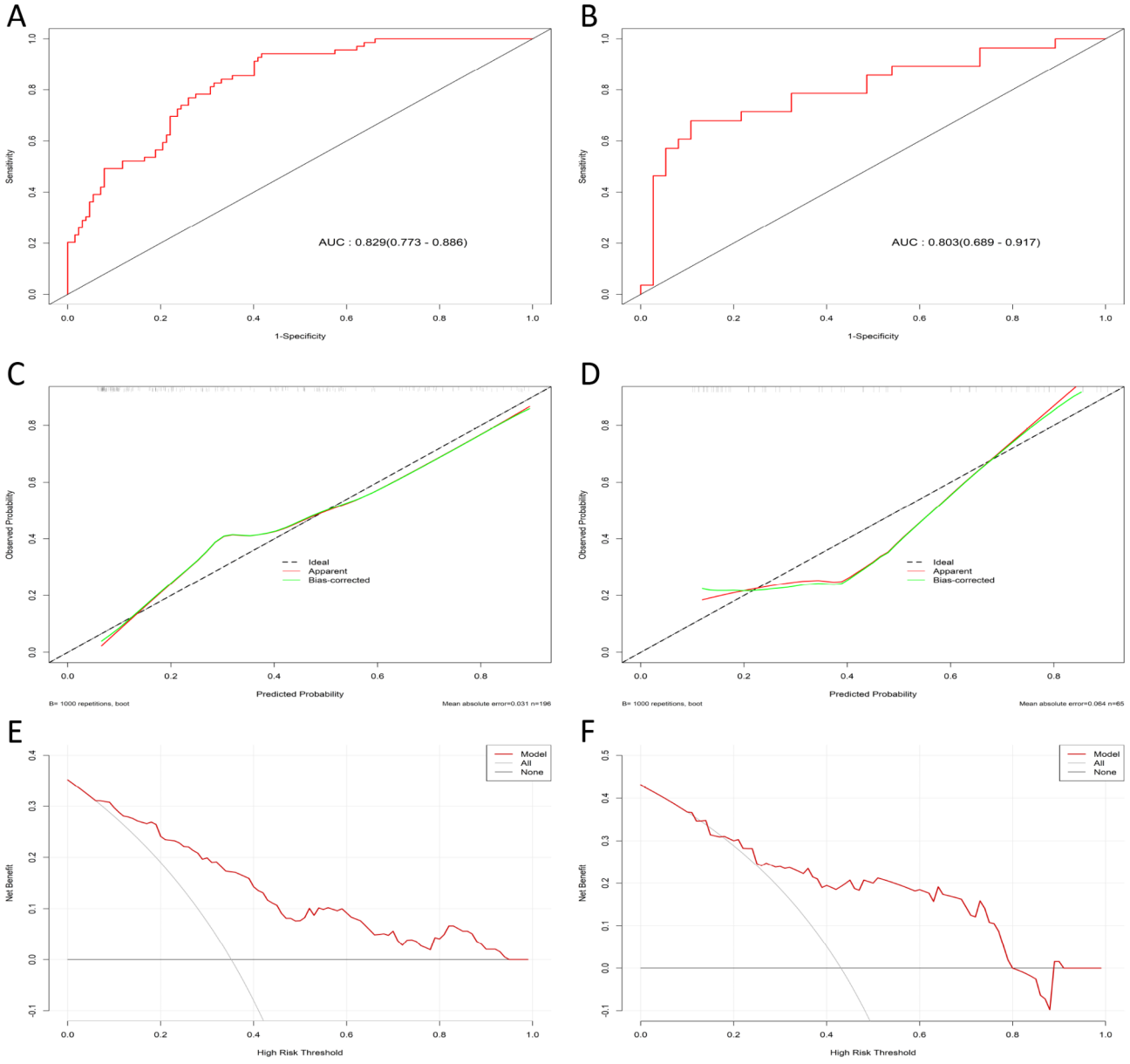

Fig. 2 Temporal and external validation. Receiver operating characteristic curve of the nomogram in temporal validation set (**A**), and external validation set (**B**). Calibration curve of the nomogram in the temporal validation set (**C**), and external validation set (**D**). Decision curve analysis of the nomogram in temporal validation set (**E**), and external validation set (**F**)

to ensure the reliability of the model, which has rarely been conducted at the same time in previous studies. Certainly, there are still some limitations in our study. First, the delirium model is a static model that predicts the incidence of delirium during palliative care units by using eight variables available within 24 h of admission. As the physical health of advanced cancer patients can deteriorate over time, the probability of developing delirium may also change However, our model does not consider such a change. Given that the interquartile range of hospital stays in the training cohort was 6–21 days, our prediction model could be more applicable to patients with hospital stays within this range. Therefore, it will be necessary in the future to develop a dynamic prediction model or a version that predicts delirium risk within a defined time period for palliative care patients. Second, some potential risk factors, including hearing impairment and visual impairment, were not included in our analysis because the prevalence rate of hearing and visual impairment in palliative care patients is low, and severe hearing and visual impairment may affect the accurate assessment of delirium. Finally, the outcome assessment was not blinded, thus, assessment bias could be present.

To minimize bias, delirium assessment was performed by two separate investigators.

Conclusion

The model incorporating eight predictors can predict delirium in advanced cancer patients during their stay in palliative care units. The application of the prediction model will help palliative care staff to identify patients at high risk of delirium and facilitate targeted initiation of preventive measures.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12904-025-01683-9.

Supplementary Material 1

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Author contributions

DG, JY and NG contributed to the conception and design of the study. DG, CZ, CL, YW, LC and HZ collected the data. JY and NG contributed to quality control of the data. DG and YF performed the statistical analysis. DG and CZ drafted the manuscript. All the authors contributed to data interpretation and manuscript revision and approved the submitted version.

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Data availability

The datasets used and analyzed in this study are not publicly available due to protection of participant's statements and identities but are partially available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China Fourth Hospital, Sichuan University (HXSY-EC-2021002) in January 2021. All participants provided written informed consent.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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