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A prediction model for moderate to severe pain in primary hepatic carcinoma after chemotherapy: a multi-center prospective case–control study

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The incidence of moderate to severe pain after chemotherapy with primary hepatic carcinoma (PHC) patients is high. Although standardized treatment can effectively relieve pain, the control effect is poor. More attention should be paid to the prevention of pain at the beginning of symptoms, so as to reduce the incidence of pain and promote the health of patients. However, there are lack of a prospective design to predict pain before it occurs. The study is a prospective case–control study. Population was PHC patients who received chemotherapy from April to August to 2024 in three grade 3 and first-class hospital. Data were collected in two periods (on the day of admission and within 24 h of chemotherapy). According to the Brief Pain Inventory, the patients were divided into case group and control group. Then the patients were randomly divided into a training group and an internal validation group at a 2:1 ratio. Single-factor logistics regression was used to analyze the risk factors, and the back-propagation artificial neural network (BP-ANN) model was constructed and verified. A total of 467 patients consisting of 312 training samples and 155 validation samples. BP-ANN model showed the AUC, sensitivity, specificity, and accuracy of prediction were 0.808, 70.6%, 81.7%, 93%, respectively. Internal verification also indicated these indicators were 0.783, 78.8%, 70.8%, and 94.2%, respectively. Significant predictors identified were age > 57.5, BMI > 19.9, symptoms of insomnia prior to illness, worker, Renvastinib, Child–Pugh = B, glutamic oxalacetic transaminase, other platinum drugs, cancer staging of IV, ECOG = 2, NRS-2002 = 3, Oxaliplatin, and Donafenib. The BP-ANN model holds high predictive value for the moderate to severe pain of PHC patients after chemotherapy. In the future, the model can be further visualized to facilitate clinical screening and to provide a basis for subsequent intervention.

Keywords Cancer-related pain, Primary hepatic carcinoma, Back-propagation artificial neural networks, Risk factors

Primary hepatic carcinoma (PHC) presents a significant public health challenge worldwide, particularly in China. According to the National Cancer Center of China, PHC ranks fourth in new cancer cases, fifth in incidence, and second in mortality among all cancer types. Notably, 39 to 53.6% of PHC patients are diagnosed at an advanced stage[1].

Pain is a common and feared symptom of cancer, affecting a substantial proportion of cancer patients. Cancer-related pain includes pain caused directly by the tumor, metastatic invasion of surrounding tissues, and pain related to cancer treatments such as surgery, radiotherapy, and chemotherapy[2,3]. Pain prevalence increases in patients with advanced or terminal disease, with studies indicating that 40 to 50% of cancer patients

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experience moderate to severe pain requiring continuous analgesic treatment, and 25 to 30% report unbearable or extreme pain[4]. Despite standardized pain management approaches, surveys reveal that many patients still suffer from inadequate pain control, which could negatively impact survival rates[5]. However, mild pain can be alleviated by non-drug treatment[6]. Unlike many other cancers, PHC is characterized by late diagnosis, treatment difficulties, and poor prognosis. The incidence of pain in patients with advanced PHC ranges from 60 to 80%, and approximately one-third of these patients experience severe pain[7]. The presence of severe pain in advanced cancer patients is associated with significant social and psychological challenges, including an increased risk of suicide. As surgical resection is generally not recommended for advanced PHC, transcatheter arterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) are the primary treatment options[8]. However, approximately 75% of PHC patients experience significant pain within the first day following TACE, with a numerical rating scale score reaching as high as 10[9]. Therefore, patients diagnosed PHC late and serious, and the chemotherapy further aggravated the severe pain. In addition, moderate to severe pain is easier effect of treatment and quality of life of patients in the advanced stage more than mild pain. More attention should be paid to the moderate to severe pain of PHC after chemotherapy, and to develop an authoritative screening and intervention program.

The pathogenesis of pain in PHC is complex, and effective pain relief remains elusive, with approximately 30% of patients continuing to experience severe pain until death[10]. While most studies on PHC-related pain are cross-sectional, they indicate that pain is associated with tumor metastasis location[11], performance Status[12], surgical method[13], chemotherapy regimens[14], inflammatory factors[15] and so on. These studies primarily focus on factors influencing pain after its onset, lacking a prospective design to predict pain before it occurs. To address this, the back-propagation artificial neural network (BP-ANN) has been proposed as a predictive model for pain, leveraging its adaptive, self-organizing, and self-learning capabilities. BP-ANN models have demonstrated superior performance compared to traditional predictive models across various domains, primarily due to their ability to capture complex, non-linear relationships within data. Unlike linear regression or decision trees, which rely on predefined structures and assumptions, neural networks adaptively learn patterns through layers of interconnected neurons, enabling them to model intricate interactions and high-dimensional data effectively. Moreover, BP-ANN models excel in handling large-scale datasets, where traditional models often struggle with scalability and computational efficiency[16]. Early identification of patients at risk for moderate to severe pain could enable timely interventions. For example, studies have shown that using anhydrous alcohol during transarterial chemoembolization in hepatocellular carcinoma patients increases the risk of severe abdominal pain, yet early intervention can mitigate this risk[17].

Thus, this study aimed to identify independent risk factors for moderate to severe pain in PHC patients following chemotherapy, develop a predictive model, and provide a basis for managing this critical aspect of cancer care.

Methods

Study design and participants

This study employed a prospective case–control design. PHC patients who underwent chemotherapy from April to August 2024 were included. Data, including demographic and clinical information, as well as ECOG and NRS-2002 scores, were collected on the day of admission. Pain was assessed using the Brief Pain Inventory (BPI) within 1 to 2 days post-chemotherapy. According to BPI criteria, 101 patients with moderate to severe pain (BPI score ≥ 4) were classified as the case group, and 366 patients with mild or no pain (BPI score < 4) were classified as the control group. Patients were then randomly assigned to a training group (312 cases) and an internal validation group (155 cases) in a 2:1 ratio.

Individuals from three Grade III and Class A hospitals were eligible. The diagnostic criteria were histopathologic diagnosis of PHC. Inclusion criteria were (1) currently receiving adjuvant chemotherapy (at least one cycle of chemotherapy has been completed); (2) age ≥ 18 years old; (3) able to complete the required study questionnaire independently or with the assistance of the investigator; (4) informed of the diagnosis and consented to be interviewed; (5) Grade of ECOG ≤ 2; and (6) Grade of Child–Pugh $\leq$ B. Exclusion criteria were (1) non-initial diagnosis and combined with other site malignancies; (2) secondary hepatic cancer; (3) cognitive impairment and inability to express oneself accurately; (4) mental illness or central nervous system disease; and (5) transferred or dropped out of the study.

Data collection

Data were collected by uniformly trained research staff, who guided patients through the questionnaires at the bedside. Questionnaires with inconsistent or repetitive answers were deemed invalid. According to NCCN guidelines[6], pain should be assessed within 24 h of admission. Data were thus collected on the day of admission and within 24 h after chemotherapy. A total of 467 patients were followed up, with no patient lost to follow-up.

Instruments

General information

(1) Demographic data included sex, age, height, weight, body mass index (BMI), smoking history, education level, work type, monthly family income.
(2) Clinical data included insomnia, clinical staging, chemotherapy regimens, chemotherapy agents, chemotherapy cycle, targeted therapy or immunotherapy, ablation therapy, radiotherapy, surgery, glutamic pyruvic transaminase, glutamic oxalacetic transaminase, total bilirubin, total protein, globulin, albumin, white blood cell count, neutrophil count, hemoglobin, distant metastasis, jaundice, and Child–Pugh classification, et al.

Brief pain inventory (BPI)
The BPI was developed by the Pain Research Group of the World Health Organization Collaborating Centre for Symptom Assessment in Cancer Care and used to assess the degree of pain in patients on a scale of 0–10. A score of 0 points indicated no pain, 1–3 points indicated mild pain, 4–6 points indicated moderate pain, and 7–10 points indicated severe pain[18]. Cronbach's α coefficient for this scale was 0.954–0.958, and the correlation validity is 0.774–0.89[19]. In this study, we used this scale to assess the most serious pain within 24 h. The scores of BPI ≥ 4 was used as the dependent variable for modeling.

Eastern cooperative oncology group (ECOG)
ECOG is widely used to assess activities of daily living and self-care in cancer patients. The scoring system consists of six grades: 0, 1, 2, 3, 4, and 5. A level of 0 indicates completely normal mobility and a level of 5 indicates death[20].

Nutritional risk screening (NRS-2002)
The scale is a preliminary screening tool developed by the European Society for Parenteral and Enteral Nutrition (ESPEN) for nutritional risk in hospitalized patients, which includes three parts: impaired nutritional status, disease severity and age. The total score was 7, ≥ 3 was considered to be at nutritional risk. The reliability kappa was 0.67[21].

Statistical analysis
All data were double-entered and verified by two independent researchers. The analysis was performed in SPSS 26.0. Continuous variables were described by means and standard deviation or median and interquartile range, and categorical variables were described by frequency and percentage. Single-factor logistics regression analysis was used to screen risk factors. $P < 0.1$ (two tailed) was considered statistically significant. Significant variables from the univariate analysis were included in a multilayer sensing module for the construction of the BP-ANN. The hyperbolic tangent function was used as the activation function in the hidden layer, while the SoftMax function was used in the output layer. The Hosmer-Lemeshow test (H–L test), the area under the receiver operating characteristic curve (AUC), specificity, sensitivity, positive predictive value (PPV) and overall accuracy (OA) were used to evaluate the model of discrimination, calibration and predictive ability. The H–L test is used to verify the fitting degree of the model. AUC is recognized as the best indicator to evaluate the accuracy of screening tools. Generally, a P value of the H–L test > 0.05 and AUC > 0.7 indicate a good fit and discriminative ability[22].

Results
General information on PHC after chemotherapy
A total of 467 PHC patients were followed in the cohort at first, and no patient was lost to follow-up. The final sample comprised 312 patients in the training group and 155 in the validation group, with no statistically significant differences in clinical variables between the two groups ($P > 0.05$). Among all patients, 175 (37.5%) experienced pain (BPI score > 0). Of these, 74 (15.8%) had mild pain, while 101 (21.7%) experienced moderate to severe pain. (Table 1).

Screening risk factors for moderate to severe pain in PHC after chemotherapy
The single-factor logistics regression analysis results of moderate to severe pain factors were from the training group. The categorical variables were assigned, the first option was used as the reference category for analysis, and the original value of continuous variables was used. There were statistically significant differences in thirteen factors, including age, BMI, work type, cancer staging, Oxaliplatin, other platinum drugs, Donafenib, Renvastinib, symptoms of insomnia prior to illness, glutamic oxalacetic transaminase, Child–Pugh grade, ECOG, and NRS-2002 ($P < 0.1$) (Table 2).

Construction of BP-ANN prediction model
Continuous variables were categorized based on cut-off values determined by ROC curves and the Youden index. The cut-off values for age and BMI were 57.5 and 19.9, respectively. Thirteen factors identified in the single-factor logistics analysis were included in the BP-ANN model. The model comprised 13 input units, 5 hidden units, and 2 output units. Based on the independent variable importance analysis, the variables were ranked as follows: age (100%), BMI (88.1%), symptoms of insomnia prior to illness (51.5%), occupation (51.4%), Renvastinib (44.8%), Child–Pugh (44.1%), glutamic oxalacetic transaminase (42.6%), other platinum drugs (40.6%), cancer staging (32.1%), NRS-2002 (28.6%), ECOG (23.0%), Oxaliplatin (19.6%), and Donafenib (13.5%) (Table 3 and Fig. 1). Based on the maximum Youden index, the probability threshold was 0.50. Applying this threshold, the model had a sensitivity of 70.6% and a specificity of 81.7%, and the AUC was 0.808 ($P < 0.01$, 95% CI = [0.749, 0.867]0) (Fig. 2). In addition, H–L test was > 0.05, the PPV was 93.0%, and the OA was 83.0%.

Verification of BP-ANN prediction model
The data from the internal validation group were used to assess the performance of the BP-ANN model. the results showed that the AUC was 0.783 ($P < 0.05$, 95% CI = [0.687,0.879]) (Fig. 3). The maximum Youden index was 0.496, in which the sensitivity, specificity, PPV and OA were 78.8%, 70.8%, 94.2% and 80.0%, respectively.

Factors	Training group (n = 312)		Internal validation group(n = 155)	
	BPI ≥ 4 (n = 68)	BPI < 4(n = 244)	BPI ≥ 4 (n = 33)	BPI < 4 (n = 122)
Demography factors				
Age	52.74 ± 10.22	57.61 ± 10.94	51.97 ± 10.80	57.46 ± 11.33
Gender				
Male	62(91.2%)	211(86.5%)	32(97.0%)	101(82.8%)
Female	6(8.8%)	33(13.5%)	1(3.0%)	21(17.2%)
Height	167.25 ± 7.08	167.15 ± 7.13	167.97 ± 7.35	166.14 ± 7.26
Weight	61.43 ± 9.69	63.69 ± 9.73	62.95 ± 11.06	62.18 ± 9.55
BMI	21.89 ± 2.74	22.74 ± 2.74	22.23 ± 3.10	22.49 ± 2.79
Smoking of previous				
Yes	26(38.2%)	80(32.8%)	19(57.6%)	59(48.4%)
No	42(61.8%)	164(67.2%)	14(42.4%)	63(51.6%)
Smoking of present				
Yes	0 (0%)	13 (5.3%)	0(0%)	10(8.2%)
No	68 (100%)	231 (94.7%)	33(100%)	112()
Degree of education				
Junior high school and below	49(72.1%)	181(74.2%)	26(78.8%)	93(76.2%)
High school or technical secondary school	12(17.6%)	43(17.6%)	5(15.2%)	18(14.8%)
Junior college	4(5.9%)	10(4.1%)	1(3.0%)	5(4.1%)
College school	3(4.4%)	8(3.3%)	1(3.0%)	4(3.3%)
Master degree or above	0(0.0%)	2(0.8%)	0(0.0%)	2(1.6%)
Work type				
Unemployed	6(8.8%)	51(20.9%)	2(6.1%)	19(15.6%)
Worker	20(29.4%)	47(19.3%)	10(30.3%)	16(13.1%)
Farmer	13(19.1%)	55(22.5%)	5(15.2%)	44(36.1%)
Teacher	1(1.5%)	13(5.3%)	1(3.0%)	7(5.7%)
Government functionary	2(2.9%)	5(2.0%)	1(3.0%)	2(1.6%)
Individual management	9(13.2%)	25(2.0%)	5(15.2%)	14(11.5%)
Other	17(25.0%)	48(19.6%)	9(27.3%)	20(16.4%)
Family monthly income				
≤¥3000	21(30.9%)	73(29.9%)	13(39.4%)	47(38.5%)
¥3000–¥4500	22(32.4%)	53(21.7%)	10(30.3%)	24(19.7%)
¥4500–¥8500	19(27.9%)	57(23.4%)	9(27.3%)	35(28.7%)
¥8500–¥350,000	6(8.8%)	54(22.1%)	1(3.0%)	12(9.8%)
≥¥350,000	0(0.0%)	7(2.9%)	0(0.0%)	4(3.3%)
Clinicopathologic factors				
Cancer staging				
I	2(2.9%)	35(14.3%)	1(3.0%)	16(13.1%)
II	12(17.7%)	45(18.5%)	5(15.2%)	27(22.1%)
III	47(69.1%)	123(50.4%)	22(66.6%)	59(48.4%)
IV	7(10.3%)	41(16.8%)	5(15.2%)	20(16.4%)
Chemotherapy type				
Intravenous chemotherapy	15(22.1%)	90(36.9%)	2(6.1%)	23(18.9%)
Interventional or arterial infusion chemotherapy	3(4.4%)	142(58.2%)	28(84.8%)	95(77.9%)
Oral chemotherapy	4(5.9%)	11(4.5%)	3(9.1%)	4(3.3%)
Peritoneal perfusion	46(67.6%)	1(0.4%)	0(0.0%)	0(0.0%)
Cycles of chemotherapies	3(2)	2(3)	3(2)	2(3)
Oxaliplatin				
Yes	42(61.8%)	189(77.5%)	23(69.7%)	87(71.3%)
No	26(38.2%)	55(22.5%)	10(30.3%)	35(28.7%)
Raltitrexed				
Yes	28(41.2%)	135(55.3%)	16(48.5%)	74(60.7%)
No	40(58.8%)	109(44.7%)	17(51.5%)	48(39.3%)
Idarubicin				
Yes	4(5.9%)	5(2.0%)	0(0.0%)	1(0.8%)
Continued				

Factors	Training group (n = 312)		Internal validation group(n = 155)	
	BPI ≥ 4 (n = 68)	BPI < 4(n = 244)	BPI ≥ 4 (n = 33)	BPI < 4 (n = 122)
No	64(94.1%)	239(98.0%)	33(100.0%)	121(99.2%)
Other platinum drugs				
Yes	19(27.9%)	1(9.8%)	8(24.2%)	17(13.9%)
No	49(72.1%)	220(90.2%)	25(75.8%)	105(86.1%)
Immune-targeted therapy				
Yes	42(61.8%)	148(60.7%)	19(57.6%)	60(49.2%)
No	26(38.2%)	96(39.3%)	14(42.4%)	62(50.8%)
Cycles of Immune-targeted therapy	2(3)	1(3)	1(3)	0(2)
Sintilimab				
Yes	18(26.5%)	39(16.0%)	9(27.3%)	20(16.4%)
No	50(73.5%)	205(84.0%)	24(72.7%)	102(83.6%)
Pembrolizumab				
Yes	2(2.9%)	1(0.4%)	0(0.0%)	0(0.0%)
No	66(97.1%)	243(99.6%)	33(100%)	122(100%)
Renvastinib				
Yes	5(7.4%)	44(18.0%)	3(9.1%)	14(11.5%)
No	63(92.6%)	200(82.0%)	30(90.9%)	108(88.5%)
Donafini				
Yes	8(11.8%)	5(2.0%)	6(18.2%)	0(100%)
No	60(88.2%)	239(98.0%)	27(81.8%)	122(100%)
Anlotinib				
Yes	2(2.9%)	1(0.4%)	0(0.0%)	1(0.8%)
No	66(97.1%)	243(99.6%)	33(100%)	121(99.2%)
Ablation therapy				
Yes	58(85.3%)	203(83.2%)	29(87.9%)	93(76.2%)
No	10(14.7%)	41(16.8%)	4(12.1%)	29(23.8%)
Radiotherapy				
Yes	6(8.8%)	26(10.7%)	3(9.1%)	18(14.8%)
No	62(91.2%)	218(89.3%)	30(90.9%)	104(85.2%)
Surgery				
Yes	14(20.6%)	54(22.1%)	7(21.2%)	27(22.1%)
No	54(79.4%)	190(77.9%)	26(78.8%)	95(77.9%)
Distant metastasis				
Yes	25(36.8%)	69(28.3%)	13(39.4%)	34(27.9%)
No	43(63.2%)	175(71.7%)	20(60.6%)	88(72.1%)
The severity of jaundice				
None	60(88.2%)	219(89.9%)	28(84.8%)	106(86.9%)
Mild	8(11.8%)	15(6.1%)	5(15.2%)	11(9.0%)
Moderate	0(0.0%)	7(2.9%)	0(0.0%)	4(3.3%)
Severe	0(0.0%)	3(1.2%)	0(0.0%)	1(0.8%)
Glutamic-pyruvic transaminase				
Normal	47(69.1%)	179(73.4%)	20(60.6%)	95(77.9%)
Abnormal	21(30.9%)	65(26.6%)	13(39.4%)	27(22.1%)
Glutamic oxalacetic transaminase				
Normal	13(19.1%)	114(46.7%)	8(24.2%)	65(53.3%)
Abnormal	55(80.9%)	130(53.3%)	25(75.8%)	57(46.7%)
Total bilirubin				
Normal	42(61.8%)	180(73.8%)	18(54.5%)	88(72.1%)
Abnormal	26(38.2%)	64(26.2%)	15(45.5%)	34(27.9%)
Total protein				
Normal	52(76.5%)	181(74.2%)	29(87.9%)	97(79.5%)
Abnormal	16(23.5%)	63(25.8%)	4(12.1%)	25(20.5%)
Globulin				
Normal	52(76.5%)	206(84.4%)	26(78.8%)	99(81.1%)
Continued				

Factors	Training group (n = 312)		Internal validation group(n = 155)	
	BPI ≥ 4 (n = 68)	BPI < 4(n = 244)	BPI ≥ 4 (n = 33)	BPI < 4 (n = 122)
Abnormal	16(23.5%)	38(15.6%)	7(21.2%)	23(18.9%)
Albumin				
Normal	20(29.4%)	89(36.5%)	16(48.5%)	61(50.0%)
Abnormal	48(70.6%)	155(63.5%)	17(51.5%)	61(50.0%)
White blood cell count($\times 10^9$/L)	7.45 ± 4.80	6.86 ± 8.24	7.19 ± 4.89	6.5 ± 4.21
Neutrophil count($\times 10^9$/L)	5.67 ± 4.79	5.20 ± 8.16	5.21 ± 4.50	4.22 ± 4.08
Hemoglobin(g/L)	124.18 ± 25.48	122.17 ± 26.29	128.64 ± 23.57	124.19 ± 24.26
Child–Pugh classification				
A	38(55.9%)	183(75%)	20(60.6%)	89(73.0%)
B	30(44.1%)	61(25.0%)	13(39.4%)	33(27.1%)
Symptoms of insomnia prior to illness				
None	32(47.1%)	146(59.8%)	14(42.4%)	75(61.5%)
Difficulty falling asleep	3(4.4%)	4(1.6%)	3(9.1%)	3(2.5%)
Early awakening	15(22.1%)	65(26.6%)	6(18.2%)	24(19.7%)
Poor sleep quality	18(26.5%)	26(10.7%)	10(30.3%)	18(14.8%)
Grades of ECOG				
0	21(30.9%)	99(40.6%)	9(27.3%)	45(36.9%)
1	46(67.6%)	121(49.6%)	23(69.7%)	64(52.5%)
2	1(1.5%)	24(9.8%)	1(3.0%)	13(10.6%)
Grades of NRS-2002				
1	48(70.6%)	164(67.2%)	21(63.6%)	92(75.4%)
2	5(7.4%)	46(18.9%)	3(9.1%)	16(13.1%)
3	15(22.0%)	34(13.9%)	9(27.3%)	14(11.5%)

Table 1. General information of 467 PHC samples.

Variable	β	SE	Wald χ^2	*P*	OR(95% CI)
Age	0.044	0.016	7.691	*0.006*	0.938(0.928–0.987)
BMI	− 0.185	0.068	7.365	*0.007*	0.913(0.727–0.950)
Work type					
Worker	1.452	0.563	6.661	*0.010*	0.698(0.078–0.705)
Cancer staging					
IV	1.222	0.543	5.073	*0.024*	2.149(1.172–9.837)
Oxaliplatin	1.181	0.350	11.391	*0.001*	2.239(1.641–6.468)
Other platinum drugs	1.628	0.429	14.401	*0.000*	0.431(0.085–0.455)
Donafenib	1.589	0.694	5.252	*0.022*	0.214(0.052–0.794)
Renvastinib	1.090	0.502	4.720	*0.030*	1.417(1.112–7.947)
Symptoms of insomnia					
Difficulty falling asleep	1.186	0.404	8.603	*0.003*	0.423(0.138–0.675)
Glutamic oxalacetic transaminase	0.880	0.366	5.796	*0.016*	0.475(0.203–0.849)
Grade of ECOG					
2	2.516	1.060	5.634	*0.018*	3.338(1.551–8.911)
Grade of NRS-2002					
3	1.488	0.570	6.820	*0.009*	0.317(0.074–0.690)
Grade of Child–Pugh					
B	0.795	0.362	4.826	*0.028*	0.485(0.222–0.918)

Table 2. The single factor logistics regression analysis of moderate to severe pain factors. β: the standardized beta; OR: odd ratio; CI: confidence interval. Significant values are in [italics].

Variable	Importance	The importance of normalization (%)
Age	0.172	100
BMI	0.153	88.7
Symptoms of insomnia	0.089	51.5
Work type	0.089	51.4
Renvastinib	0.077	44.8
Child–Pugh	0.076	44.1
Glutamic oxalacetic transaminase	0.073	42.6
Other platinum drugs	0.070	40.6
Cancer staging	0.055	32.1
NRS-2002	0.049	28.6
ECOG	0.040	23.0
Oxaliplatin	0.034	19.6
Donafenib	0.023	13.5

Table 3. The importance of individual variables in neural network analysis.

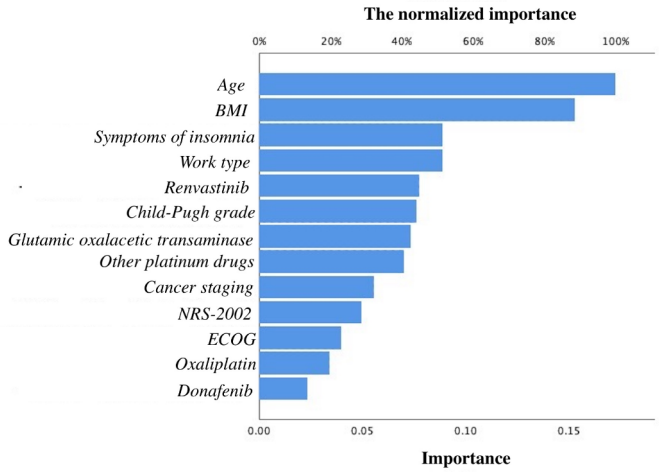

Fig. 1. The normalized importance rank of variables in the BP-ANN model.

Discussion

Cancer-related pain is often considered the fifth vital sign, alongside blood pressure, pulse, heart rate, and respiration. In our study, the overall prevalence of pain in PHC patients was 37.5%, with 21.7% of patients experiencing moderate to severe pain. This rate is somewhat lower compared to previous studies[4], potentially due to improved pain management practices in hospitals.

The use of machine learning, specifically the BP-ANN model, to build an effective predictive model holds great significance for screening high-risk groups and enabling early diagnosis. The BP-ANN model can overcome issues of multicollinearity between variables, which cannot be easily handled by traditional logistic regression models[23]. In this study, the AUC was > 80% and H–L test > 0.05, indicating that the BP-ANN model provides a good fit for predicting moderate to severe pain in PHC patients post-chemotherapy. The sensitivity, specificity, and PPV were all above 70%, demonstrating the model's strong ability to identify patients at risk for moderate to severe pain. Furthermore, the PPV in the internal validation was > 80%, confirming its reliability as a clinical screening tool with potential for wider implementation.

The independent variable importance analysis helped to identify the most influential predictors in the model. Age was the strongest predictor, contributing 100% to the model. The average age of the 467 patients in the study was 57 ± 11.31 years, consistent with the epidemiological trend that liver cancer typically affects individuals aged 40–60 years[1]. However, recent lifestyle changes have led to a younger onset of the disease, with the youngest patient in this study being just 26 years old. Advanced cancer stage (stage IV) was also a significant demographic risk factor, as these patients often experience severe pain due to tumor metastasis to the nervous system, bones, and other tissues[11].

BMI was the second most important predictor. Research has suggested that low BMI may result in lower concentrations of opioids in the blood, reducing the effectiveness of pain relief [24]. Additionally, the NRS-2002 score of 3 or higher was associated with an increased risk of pain, indicating the close correlation between nutritional status and cancer-related pain. Malnutrition can exacerbate inflammation and metabolic stress,

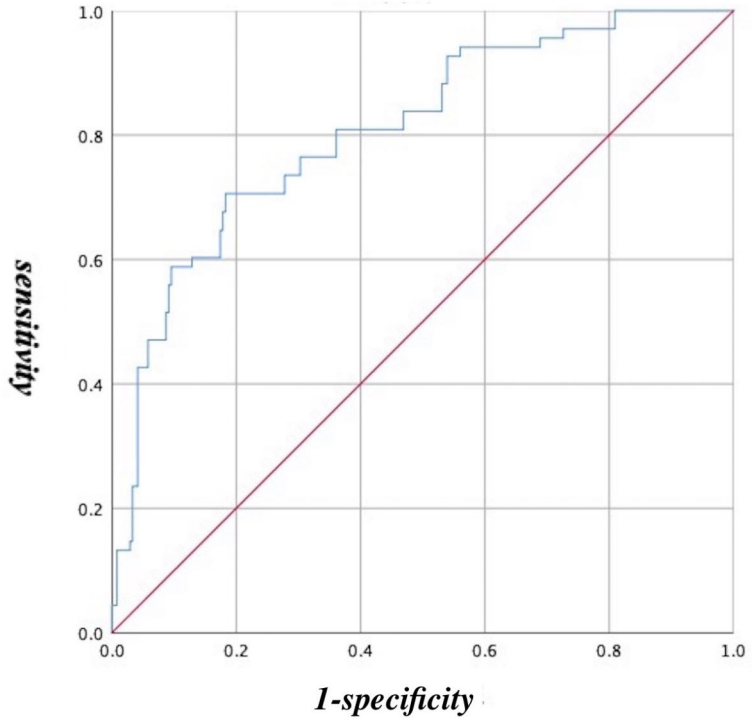

Fig. 2. ROC curves of BP-ANN model.

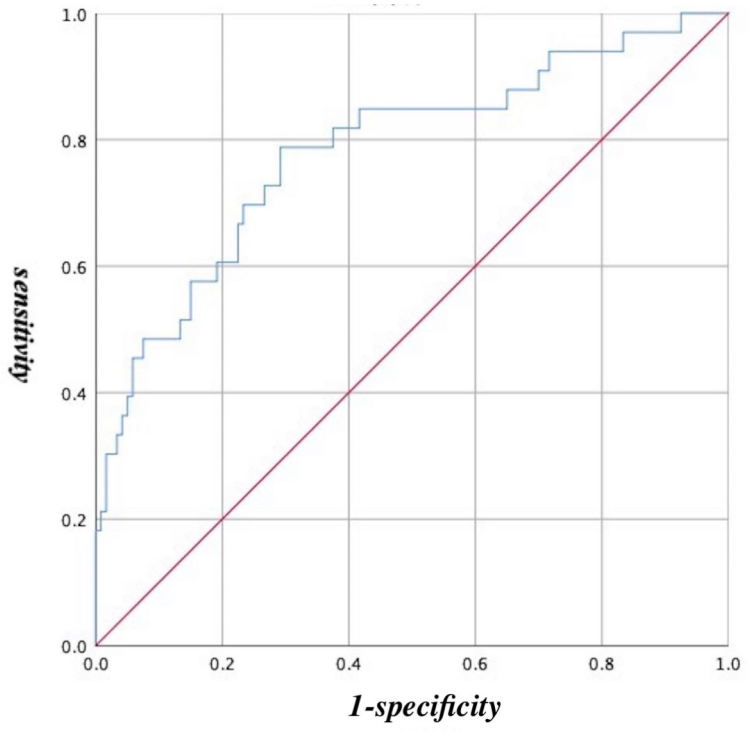

Fig. 3. ROC curves of the internal validation result.

further aggravating pain[25]. Therefore, timely and comprehensive assessment of nutritional status is critical for managing pain in these patients.

Insomnia, identified as the third major predictor, is common in cancer patients and has been linked to central sensitization, a condition where the central nervous system becomes hyper-responsive to pain stimuli [26]. Addressing sleep disturbances early could potentially reduce pain perception in these patients.

Occupation was another significant predictor, with workers showing higher pain risk. Most workers class in China are manual laborers. Some scholars have studied the relationship between occupational stratification and tumor-related characteristics and found that manual laborers are more likely to be accompanied by severe tumor comorbidities, leading to pain and other symptoms, which has a chain effect on prognosis[27].

Both Renvastinib and Donafenib, two targeted therapies, were also identified as risk factors. The contribution of variables of Renvastinib was greater than that of Donafenib which suggests that the use of Renvastinib is more likely to cause pain than the use of Donafenib. The drugs of targeted therapy have the dual anti-tumor effect of inhibiting the growth and proliferation of tumor cells and anti-angiogenesis. But oral cavity is a common site of adverse reactions caused by targeted drugs, often leading to oral ulcers, resulting in severe pain that cannot eating. Among them, neutropenia caused by immunosuppression may be one of the causes of oral ulcers[28,29]. In this study, the chemotherapy drug of Oxaliplatin and other platinum drugs were one of the risk factors. Although chemotherapy drugs can kill cancer cells, their side effects can not be underestimated. For example, 50–90% of patients using oxaliplatin have chemotherapy-induced peripheral neuropathy (CIPN), the main pathogenesis of which is the damage of the neuron damage and the change of the activity of the ionizing channel[30]. Also commonly used are paclitaxel and other platinum drugs that are toxic to peripheral sensory neurons in the dorsal root ganglia and spinal cord[31]. Therefore, regular monitoring of changes in clinical adverse reactions after medication is conducive to early detection of pain risk. If the patient is detected in time and the appropriate intervention is carried out, the pain can be relieved.

The Child–Pugh score and glutamic oxalacetic transaminase levels were significant predictors of pain. The higher the Child–Pugh grade is, the worse the liver function of patients with primary liver cancer is, and the body metabolism is disturbed. It has been pointed out that the decompensated stage of cirrhosis will produce a variety of interrelated symptoms, including pain, abdominal distension, fatigue, sleep disorders, etc., forming a symptom cluster and aggravating the damage to patients' quality of life and functional status[32]. Hence, through regular monitoring of child–Pugh and glutamic oxalacetic transaminase to evaluate liver function indicators, it is found that abnormal disease symptoms can be predicted and treated in advance, which may avoid a series of symptoms. Finally, the ECOG was another important predictor, specifically a score of 2. The score of ECOG reflects a patient's overall health and treatment tolerance, with higher scores indicating poorer functional status and a greater likelihood of experiencing pain.

Strengths and limitations

This study has several strengths. First, the use of a prospective case–control study design allows for a clearer understanding of the causal relationship between variables, reducing the likelihood of recall bias. Second, the study's sample size, drawn from three centers, was sufficiently large to support reliable conclusions. However, some limitations of this study are also unavoidable. No psychological and social predictors were collected in this study and variables were mostly self-reported. Therefore, we should further include social psychology and more objective indicators in future studies. Second, the model was only internally validated to evaluate the predictive power of the model. In the future studies, external validation should be examined to prove the extrapolation ability of the model.

Conclusion

The BP-ANN model has high predictive ability for the moderate to severe pain of PHC patients after chemotherapy. In this study, we finally included thirteen significant predictors: age > 57.5, BMI < 19.9, symptoms of insomnia prior to illness, worker, Renvastinib, Child–Pugh = B, glutamic oxalacetic transaminase, other platinum drugs, cancer staging of IV, ECOG = 2, NRS-2002 = 3, Oxaliplatin, and Donafenib. Clinical nursing should pay more attention to patients with those risk factors and make patients aware of the necessity of early intervention. In the future, the model can be further visualized to facilitate clinical screening and to provide a basis for subsequent intervention.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

Siting Huang: Conceptualization, Software, Writing-original draft. Aiqin Liu: Project administration, Writing-reviewing and editing. Hui Lin: Investigation, Methodology, Validation. Xi Ke: Supervision, Resources. Xiaoruo Yu; Zhifeng Qiu; Guizhen Weng; Dun Liu; Yan Wang; Zhuo Yan; Liuqing Yao and Mei Yang: Investigation, Data curation.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Hospital (K2023-408-1). All methods adhered to relevant ethical guidelines and regulations, and no participant could be identified from the data. The studies were conducted in accordance with the local legislation and institutional requirements. Informed consent was obtained from all subjects and/or their legal guardians.

Additional information

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