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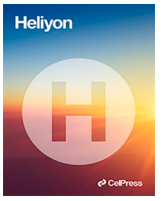

Research article

A prognostic model and novel risk classification system for radical gallbladder cancer surgery: A population-based study and external validation

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ABSTRACT

Background: This research aimed to create a predictive model and an innovative risk classification system for patients with gallbladder cancer who undergo radical surgery.
Methods: A cohort of 1387 patients diagnosed with gallbladder cancer was selected from the SEER database. The researchers devised a prognostic tool known as a nomogram, which was subjected to assessment and fine-tuning using various statistical measures such as the concordance index (C-index), receiver operating characteristic (ROC) curve, and calibration curve, decision curve analysis (DCA), and risk stratification were included in the catalog of comparisons. An external validation set comprising 93 patients from Nanchong Central Hospital was gathered for evaluation purposes.
Results: The nomogram effectively incorporated seven variables and demonstrated satisfactory discriminatory ability, as evidenced by the C-index (training cohort: 0.737, validation cohort: 0.730) and time-dependent AUC (>0.7). Additionally, calibration plots confirmed the excellent alignment between the nomogram and actual observations. Our investigation unveiled NRI scores of 0.79, 0.81, and 0.81 in the training group, while the validation group exhibited NRI values of 0.82, 0.77, and 0.78. Additionally, when evaluating CSS at three-, six-, and nine-year intervals using DCA curves, our established nomograms demonstrated significantly improved performance compared to the old model ($P < 0.05$), showcasing enhanced discriminatory ability. The results of the external validation set proved the above results.
Conclusions: The current investigation has devised a practical prognostic nomogram and risk stratification framework to aid healthcare practitioners in evaluating the postoperative outlook of individuals who have received extensive surgical treatment for gallbladder carcinoma.

1. Introduction

Although gallbladder cancer is relatively rare globally, it remains the predominant type of malignancy affecting the biliary system [1–3]. Gallbladder stones, gallbladder polyps, obesity, primary sclerosing cholangitis, biliary cysts, typhoid fever, bacterial infections,

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smoking, and exposure to certain chemicals have all been identified as risk factors associated with the development of gallbladder malignancy [4,5]. Patients suffering from gallbladder cancer frequently exhibit vague symptoms during the initial phases, resulting in considerably limited rates of early detection. This includes around 2 % of patients who coincidentally stumble upon their gallbladder cancer [6,7]. Gallbladder cancer cells display notable diversity and demonstrate a strong inclination for spreading to distant anatomical locations through the vascular lymphatics, blood vessels, and peritoneum [8–10]. Despite the advanced stage at which most patients are diagnosed with gallbladder cancer, radical surgery still yields significant clinical benefits for many individuals [11–13].

The available studies not only have a limited number of patients with gallbladder cancer but also lack comprehensive follow-up information. Surgery plays a crucial role in the management of radical gallbladder cancer; however, there is a paucity of reports on the postoperative prognosis based on large cohorts [14,15]. The tumor stage serves as the primary determinant of prognosis, while factors such as age and gender that impact patient outcomes are not taken into account. In the field of oncology, clinical prognostic models and risk grading systems based on nomograms have gained increasing acceptance [16,17]. The AJCC staging system is widely utilized for tumor staging, making it the preferred choice among healthcare professionals globally [18,19]. This research introduces the creation of a predictive model and an innovative risk categorization framework for individuals who have received extensive surgical treatment for gallbladder cancer, utilizing a vast collection of patient information from the SEER (Surveillance Epidemiology and End Results) database. We further compared the nomogram and AJCC prediction efficacy.

2. Methods

2.1. Information on research

The SEER*Stat 8.4.1 software, a publicly accessible platform for oncology data that adheres to legal research regulations, was utilized to acquire the clinical information of patients diagnosed with gallbladder cancer from the SEER database. Patient information in the SEER database, including tumor data, is publicly available and does not require informed consent. To detect individuals diagnosed with malignancies in the gallbladder, we employed the ICD-O-3 code C23.9 according to the International Classification of Diseases for Oncology. Inclusion criteria for the study can be summarized as: (a) primary malignant tumor originating in the gallbladder, (b) absence of distant metastases, (c) availability of tumor size data, and (d) completion of radical surgery. Exclusion criteria included: (a) secondary gallbladder cancer, (b) unknown surgical information, (c) unknown age, (d) lack of follow-up data, (e) unknown tumor stage, and (f) missing lymph node information. The process of selecting is depicted in Fig. 1.

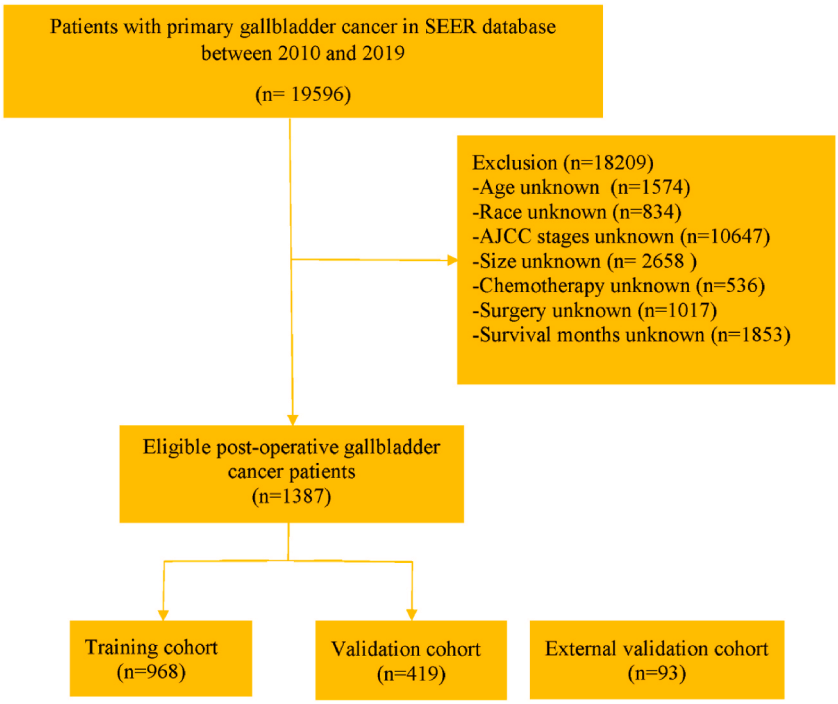

Fig. 1. Flow diagram of the patients after radical surgery for gallbladder cancer.

2.2. Research variables

The tumor patients included in this paper were obtained from the database of patients with tumors, encompassing patient's basic information, tumor characteristics, treatment plan and survival status. Additionally, information regarding time elapsed between diagnosis and treatment initiation, tumor dimensions along with the count of lymph nodes that are positive and tumors were also collected. The AJCC-TNM staging criteria's eighth edition was employed to classify the tumors.

2.3. Construction and validation of the nomogram

A total of 968 patients were randomly assigned to the training group, while 419 patients were allocated to the validation group. The training group was utilized for variable screening and model development purposes, whereas the validation group served as a means for validating the model. To begin with, we conducted univariate and multivariate Cox regression analyses to determine the factors that have a significant impact on the survival specific to gallbladder cancer (CSS). These identified factors were then utilized in the development of a nomogram. We assessed the predictive accuracy of the nomogram by evaluating its concordance index (C-index) and plotted receiver operating characteristic (ROC) curves to demonstrate its sensitivity and specificity. Additionally, we generated calibration curves for intervals of 3, 6, and 9 years along with decision curve analysis (DCA) in order to evaluate the clinical applicability of the nomogram. Finally, we compared the predicted CSS with observed outcomes in our model using a reference line representing actual results.

Table 1
Clinical profile of patients after radical surgery for gallbladder cancer.

Variable	Whole population		Training cohort		Validation cohort		P value	Nanchong Central Hospital
	n	%	n	%	n	%		
	1387		968		419			93
Age								
0–60	380	27.40 %	263	27.17 %	117	27.92 %	0.95	28
60–75	573	41.31 %	404	41.74 %	169	40.33 %		42
75–85	171	12.33 %	120	12.40 %	51	12.17 %		23
>85	263	18.96 %	181	18.70 %	82	19.57 %		0
Race								
Black	149	10.74 %	108	11.16 %	41	9.79 %	0.31	9
White	1047	75.49 %	735	75.93 %	312	74.46 %		65
Other	191	13.77 %	125	12.91 %	66	15.75 %		19
Sex								
F	430	31.48 %	307	31.71 %	123	29.36 %	0.38	23
M	957	68.52 %	661	68.29 %	296	70.64 %		70
Grade								
I	228	16.44 %	166	17.15 %	62	14.80 %	0.24	19
II	624	44.99 %	429	44.32 %	195	46.54 %		37
III	509	36.70 %	351	36.26 %	158	37.71 %		27
IV	26	1.87 %	22	2.27 %	4	0.95 %		10
Size								
0–3	660	47.58 %	473	48.86 %	187	44.63 %	0.10	46
3–6	525	37.85 %	349	36.05 %	176	42.00 %		41
>6	202	14.56 %	146	15.08 %	56	13.37 %		6
Number								
1	1317	94.95 %	922	95.25 %	395	94.27 %	0.44	83
>1	70	5.05 %	46	4.75 %	24	5.73 %		10
Stage T								
T_1	227	16.37 %	161	16.63 %	66	15.75 %	0.63	18
T_2	655	47.22 %	446	46.07 %	209	49.88 %		46
T_3	474	34.17 %	339	35.02 %	135	32.22 %		27
T_4	31	2.24 %	22	2.27 %	9	2.15 %		2
Stage N								
N_0	995	71.74 %	700	72.31 %	295	70.41 %	0.29	65
N_1	356	25.67 %	247	25.52 %	109	26.01 %		23
N_2	36	2.60 %	21	2.17 %	15	3.58 %		5
Chemotherapy								
Yes	532	38.36 %	365	37.71 %	167	39.86 %	0.45	37
No	855	61.64 %	603	62.29 %	252	60.14 %		56
Radiation								
Yes	292	21.05 %	207	21.38 %	85	20.29 %	0.64	18
No	1095	78.95 %	761	78.62 %	334	79.71 %		5

2.4. Compare the improved performance of the new model compared to the old

The patients were divided into three categories: low-risk, moderate-risk, and high-risk groups. The X-Tile software was employed to identify the most suitable threshold for the overall score. The C-index, net reclassification index (NRI), decision curve analysis (DCA), and integrated discrimination improvement (IDI) were employed to evaluate the benefits and risk stratification of the nomogram. Cancer-specific survival (CSS) was compared among various patient groups using Kaplan-Meier curves and log-rank tests.

2.5. External validation

To improve the versatility of our model, we gathered 93 suitable patient records from a separate medical facility for an external validation process. The reliability of the model was reaffirmed using widely accepted metrics. By analyzing the validation outcomes across various datasets, a thorough evaluation can be conducted to assess the overall effectiveness of the model.

2.6. Statistical analysis

The presentation of cases in the study did not involve the utilization of percentages. To assess and compare the differences between the training and validation cohorts, a chi-square test was conducted. All statistical analyses were conducted using R software version 4.1.2 (http://www.r-project.org/). A significance level below $P < 0.05$, with a two-sided test, was considered statistically significant.

Table 2
Screening of factors affecting survival of patients after radical cholecystectomy for gallbladder cancer based on univariate and multivariate methods.

Factors	Univariate		P value	Multivariate		P value
	HR	95%CI		HR	95%CI	
Age						
0–60	Reference			Reference		
60–75	1.38	1.12–1.71	<0.05	1.28	1.03–1.60	<0.05
75–85	1.82	1.38–2.40	<0.05	2.08	1.55–2.78	<0.05
>85	2.53	1.99–3.22	<0.05	2.43	1.88–3.14	<0.05
Race						
Black	Reference			Reference		
White	1.01	0.78–1.30	0.92	0.89	0.69–1.16	0.41
Other	0.76	0.54–1.06	0.11	0.92	0.72–1.26	0.35
Sex						
F						
M	1.09	0.92–1.29	0.28	1.11	0.93–1.32	0.23
Grade						
I	Reference			Reference		
II	1.95	1.48–2.58	<0.05	1.50	1.12–2.00	<0.05
III	3.35	2.54–4.43	<0.05	2.13	1.59–2.86	<0.05
IV	2.51	1.42–4.21	<0.05	1.85	1.04–3.39	<0.05
Size						
0–3	Reference			Reference		
3–6	1.51	1.26–1.80	<0.05	1.07	0.93–1.29	0.47
>6	2.02	1.61–2.53	<0.05	1.32	1.03–1.68	<0.05
Number						
1.00	Reference			Reference		
>1	0.46	0.29–0.72	<0.05	0.39	0.24–0.63	
Stage_T						
T_1	Reference			Reference		
T_2	3.04	2.15–4.29	<0.05	2.75	1.93–3.92	<0.05
T_3	7.57	5.36–10.69	<0.05	7.08	4.90–10.25	<0.05
T_4	10.18	5.89–17.59	<0.05	10.14	5.65–18.19	<0.05
Stage_N						
N_0	Reference			Reference		
N_1	1.75	1.47–2.08	<0.05	1.34	1.10–1.70	<0.05
N_2	2.17	1.35–3.49	<0.05	1.26	0.76–1.70	0.36
Chemotherapy						
Yes	Reference			Reference		
No	0.90	0.76–1.05	0.20	1.37	1.10–1.70	<0.05
Radiation						
Yes	Reference			Reference		
No	0.94	0.78–1.14	0.56	1.26	0.95–1.57	0.10

3. Results

3.1. Information for gallbladder cancer patients

The study involved a cohort of 1387 participants were included in the study, and they were randomly assigned to either the training or validation groups at a ratio of 7:3. The age group of 60–75 years accounted for the highest proportion of participants (41.31 %). The male-to-female ratio was approximately 2:1, with males accounting for 68.52 % and females for 31.48 %. There were variations in racial composition among the participants; specifically, white individuals constituted 75.49 % while black individuals accounted for only 10.74 %. A small proportion of patients exhibited severe differentiation issues (Grade IV, 1.87 %). Most patients had a single primary lesion (94.95 %), whereas only a few had multiple primary lesions (5.05 %). Tumor size was predominantly less than 6 cm (85.44 %). A significant portion of patients did not undergo chemotherapy (61.64 %) or radiotherapy treatment (78.95 %). The training and validation groups exhibited similar demographic and clinical characteristics, as presented in Table 1, with no statistically significant differences observed ($P > 0.05$).

3.2. Analyzing independent variables affecting patient prognosis

Cox regression analysis was conducted on a range of variables (Table 2), including age, degree of differentiation, size, number, T stage, N stage and chemotherapy.

3.3. Construction of the nomogram and establishment of risk stratification systems

The variables that underwent screening were used to create a nomogram, which aimed to develop a model for predicting the likelihood of CSS in patients diagnosed with gallbladder cancer. Initially, each included variable was assigned risk scores based on individual patient conditions. The cumulative score was obtained by aggregating the risk scores. By plotting a straight line in the last 3 rows, we calculated the likelihoods of CSS occurring within 3, 6, and 9 years among individuals diagnosed with gallbladder cancer. The nomogram allowed for risk stratification using total points. Using this algorithm, gallbladder cancer patients with scores below 245 were classified as low-risk, those with scores ranging from 245 to 298 were considered middle-risk, and individuals with total scores exceeding 298 were identified as high-risk (Fig. 2) (Supplementary Material).

3.4. Multiple dimension results showed that the new model outperformed the old

Different statistical measures, such as C-index, ROC, NRI, and IDI were employed to assess the efficacy of both the nomogram and AJCC staging system. In the training cohort, a C-index value of 0.737 (95 % CI: 0.725–0.746) was achieved (Fig. 3A), while in the validation cohort it was slightly lower at 0.730 (95 % CI: 0.723–0.745) (Fig. 3B). Notably, the nomogram exhibited a higher C-index

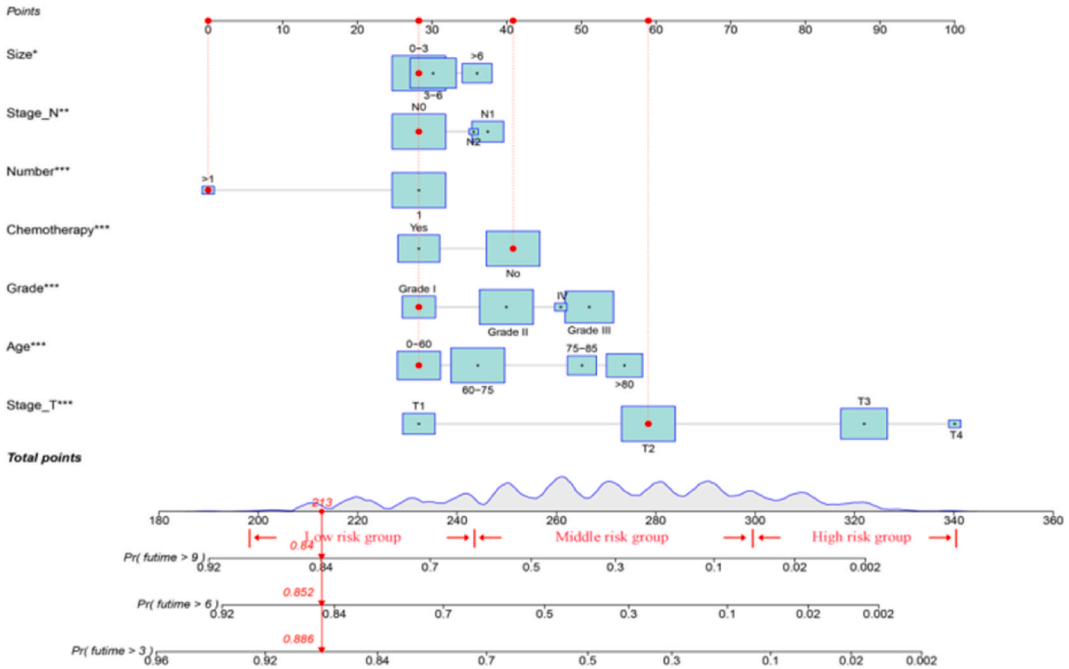

Fig. 2. Building the nomogram for patients after radical surgery.

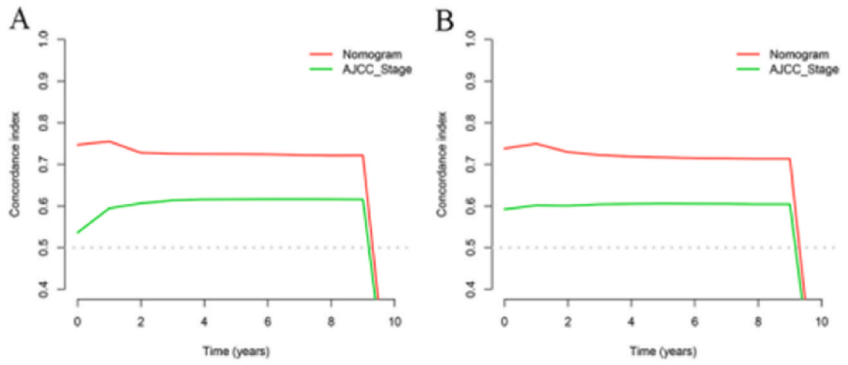

Fig. 3. C-index results (A) Training cohort analysis results. (B) Validation cohort analysis results.

compared to the AJCC staging system. The ROC curves demonstrated that for predicting CSS at 3, 6, and 9 years, the AUC values were respectively calculated as follows: nomogram - 0.808, 0.822, and 0.807; AJCC staging system - 0.802, 0.789, and 0.839 (Fig. 4A and B). These findings indicate that our developed nomogram displayed favorable predictive accuracy in comparison with traditional AJCC staging system. DCA curve depicted a comparative analysis of net benefits between our proposed nomogram and AJCC staging system across different time points (3, 6, and 9 years) (Fig. 5A, B, 5C, 5D, 5E, 5F). Our nomogram consistently outperformed other methods in predicting CSS, as demonstrated by our results in both the training and validation groups. This suggests that our model has great potential for practical use in clinical settings. We have included calibration curves to visually represent these findings (Fig. 6A and B). Our analysis indicates that the model is highly accurate and consistent, as shown in Fig. 7A, B, and 7C.

In the training group, the NRIs for individuals with 3, 6, and 9 years of experience were found to be within the range of 0.79 (95 % confidence interval [CI] = 0.68–0.92), 0.81 (95 % CI = 0.71–0.95), and (95 % CI = 0.66–0.98) respectively, indicating significant improvement over time ($P < 0.05$). Similarly, in the validation group, NRIs at different time points showed a positive trend with values ranging from 0.73 to 0.94 (95 % CI = 0.82), 0.64–096 (95 % CI = 0.77), and finally reaching a range of 0.60–0.98 (95 % CI = 0.78) at year intervals of three, six and nine years respectively ($P < 0.05$). The IDIs also demonstrated statistically significant improvements over time in both groups. The results mentioned above suggested that the nomogram developed in this study exhibited notable benefits when compared to the AJCC staging system. (Table 3).

3.5. *New systematic risk rating system demonstrating stronger differentiation capabilities*

The patients were once again categorized into three groups based on their risk level: low risk (total score <245), moderate risk (245≤total score <298), and high risk (total score ≥298). The Kaplan–Meier curves illustrated that the newly suggested method for assessing risk showed improved discriminatory ability among distinct patient risk categories when compared to the traditional staging

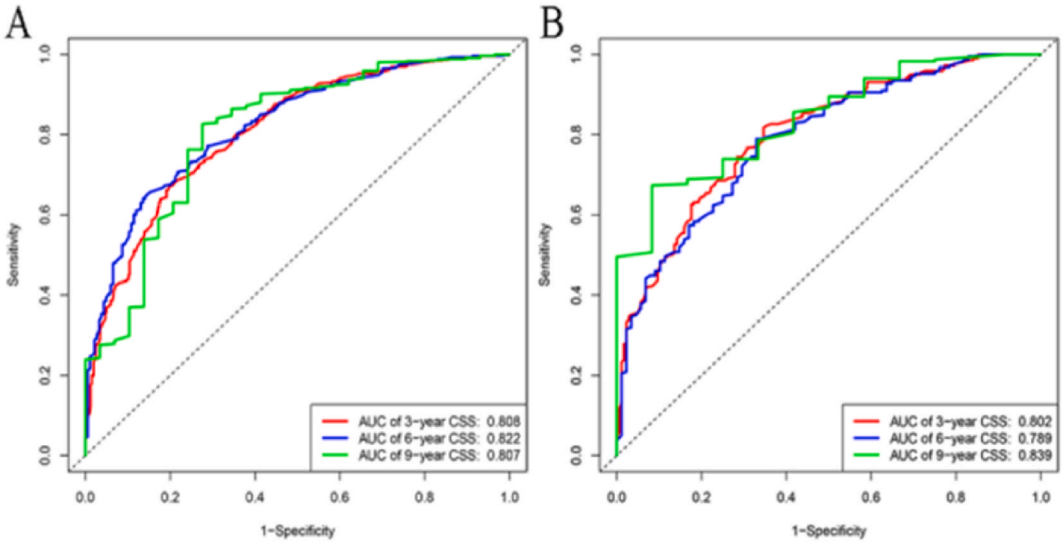

Fig. 4. Assessing the effectiveness of novel models by utilizing time-varying receiver operating characteristic (ROC) curve. (A) Training cohorts. (B) Validation cohorts.

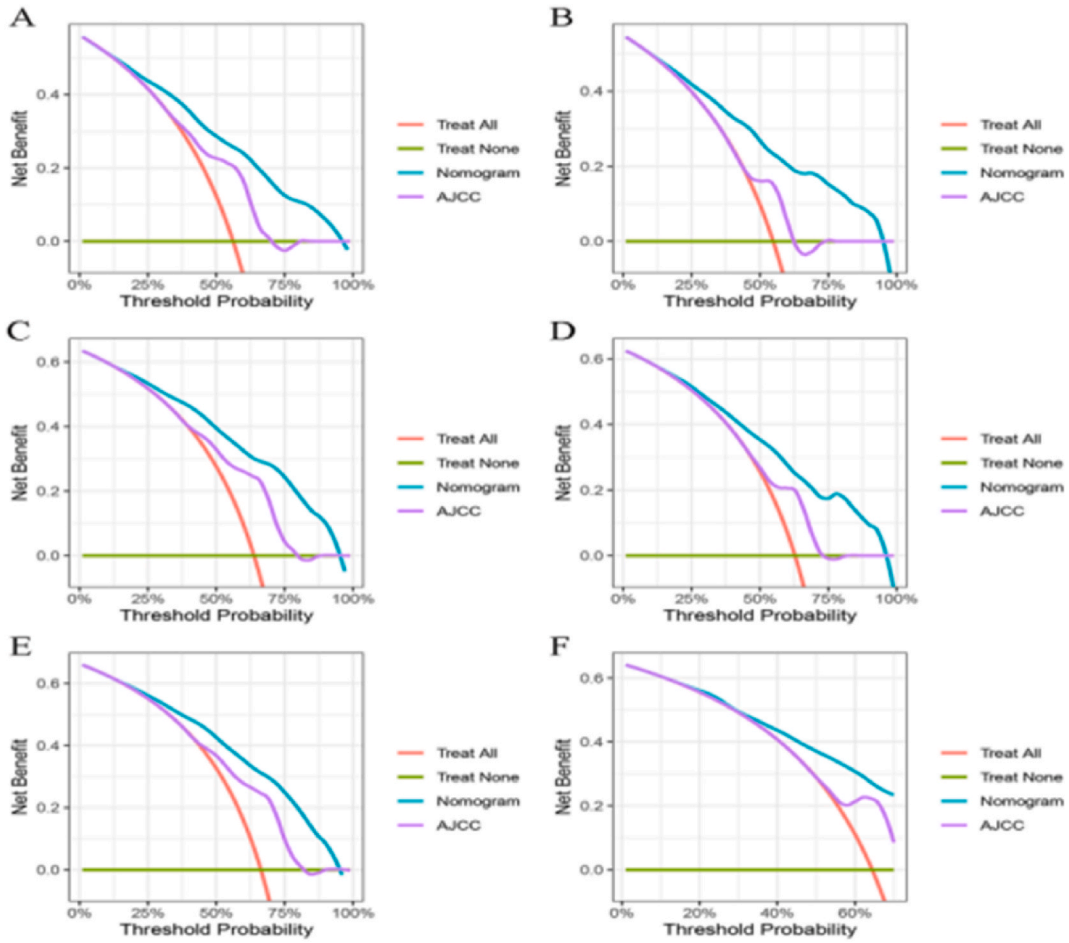

Fig. 5. DCA curves of 3 year, 6 year, and 9 year CSS in the training cohort (A, C, E) and in the validation cohort (B, D, F).

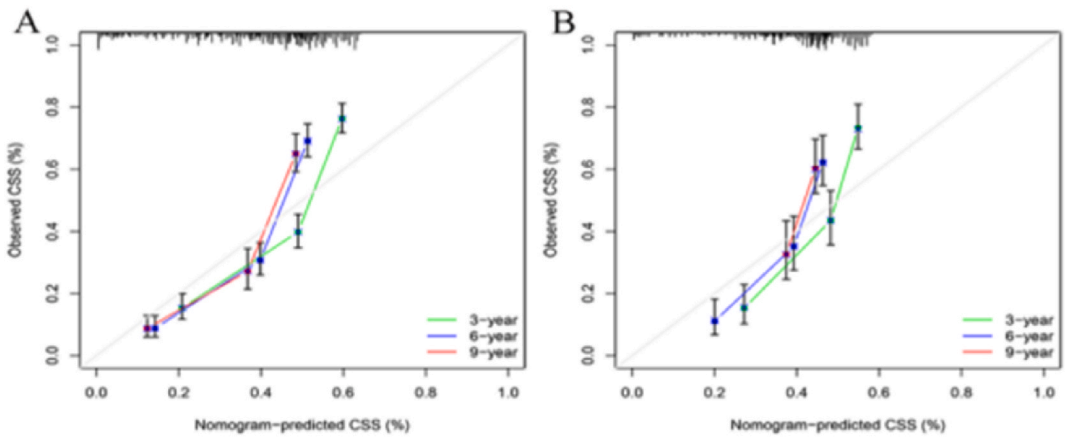

Fig. 6. Calibration curves (A) observed in the training cohorts. (B) obtained from the validation cohorts.

system (Fig. 8A, B, 8C, 8D).

4. Discussion

Gallbladder carcinoma is a commonly encountered malignant tumor that impacts the biliary system, posing considerable

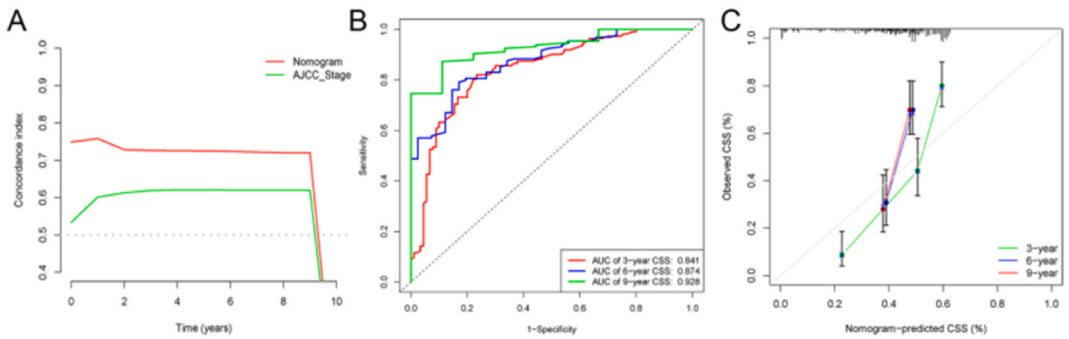

Fig. 7. The validation outcomes of the patient were acquired from our establishment, covering (A) analysis of C-index. (B) examination of ROC curve, and (C) assessment of calibration curve.

Table 3
The new model demonstrated superior capabilities.

Index	Training cohort		P value	Internal validation		P value
	Value	95 % CI		Value	95 % CI	
NRI value						
3 year	0.79	0.68–0.92		0.82	0.73–0.94	
6 year	0.81	0.71–0.95		0.77	0.64–0.96	
9 year	0.81	0.66–0.98		0.78	0.60–0.98	
IDI value						
3 year	0.18	0.13–0.22	<0.001	0.22	0.16–0.27	<0.001
6 year	0.18	0.14–0.22	<0.001	0.18	0.13–0.23	<0.001
9 year	0.19	0.11–0.26	<0.001	0.23	0.14–0.37	<0.001

difficulties for healthcare professionals due to its remarkably aggressive characteristics [20,21]. Majority of individuals diagnosed with gallbladder cancer do not exhibit distinct symptoms, and the detection of such cases often occurs during investigations for gallbladder stones, cholecystitis, or gallbladder polyps [22,23]. The rising popularity of laparoscopic cholecystectomy, due to its enhanced safety and convenience, has led to a surge in the number of patients opting for minimally invasive gallbladder removal. Consequently, this has resulted in an increased chance of incidentally detecting cases of gallbladder cancer [24]. While the majority of individuals with gallbladder cancer are typically beyond surgical intervention upon diagnosis, the identification of incidental gallbladder cancer can potentially enhance early detection rates [25,26]. Although bioinformatics has shown the potential of genes and noncoding RNAs in improving the prognosis of individuals diagnosed with gallbladder cancer, their practical clinical implementation remains significantly restricted. Clinical variables are currently favored for managing patient prognosis [27–29].

Effectively managing patients diagnosed with gallbladder cancer presents significant challenges in clinical practice [30]. Experienced physicians have accumulated extensive expertise in handling such cases through numerous encounters [31]. However, inexperienced doctors still find it overwhelming to handle these specific individuals [32]. Hence, it is crucial to create novel solutions that can ease the load on young doctors while handling individuals diagnosed with gallbladder cancer. The outcomes of this investigation effectively fill this research void. The prognosis of patients can be affected by various factors, such as age, level of differentiation, tumor size, number of tumors, T-stage and N-stage classifications, as well as the use of chemotherapy. COX regression analysis has confirmed the significance of these variables in relation to patient prognosis. By incorporating these seven variables into a prognostic model that considers individual differences among patients, it is possible to enhance the accuracy of predicting survivability. The performance evaluation of this model involved assessing its C-index and AUC values, both of which yielded satisfactory results. Furthermore, the calibration curves for both the training and validation groups were modified appropriately to ensure consistency between the observed and predicted results obtained from the model. In contrast to the AJCC staging system where survival curves for patients in stage I and II intersected each other, our newly developed risk stratification system successfully categorized patients into high-risk, middle-risk, and low-risk groups with distinct non-overlapping survival curves. This revolutionary system provides a useful instrument for tailoring clinical management, as it allows the identification of patients with diverse risk profiles.

Numerous scholars have developed gallbladder-related models. Wang [33] applied binary logistic regression analysis based on 800 patients to build a model for predicting the risk probability of gallbladder cancer. Han [34] predicted the probability model of malignancy of gallbladder polyps by the clinical and imaging features of the patients. Yin [35] modeled the survival probability of the gallbladder cancer population by deep learning. Unlike the aforementioned research, our main emphasis lies in the prediction of patient outcomes following surgical removal of gallbladder cancer.

The impact after radical surgery in patients with gallbladder cancer is primarily influenced by variables such as age, degree of differentiation, size, number, T-stage, N-stage, and chemotherapy. These findings align with the majority of studies conducted on this subject. The surgical approach is significantly determined by the tumor stage. Patients with incidental stage I gallbladder cancer who

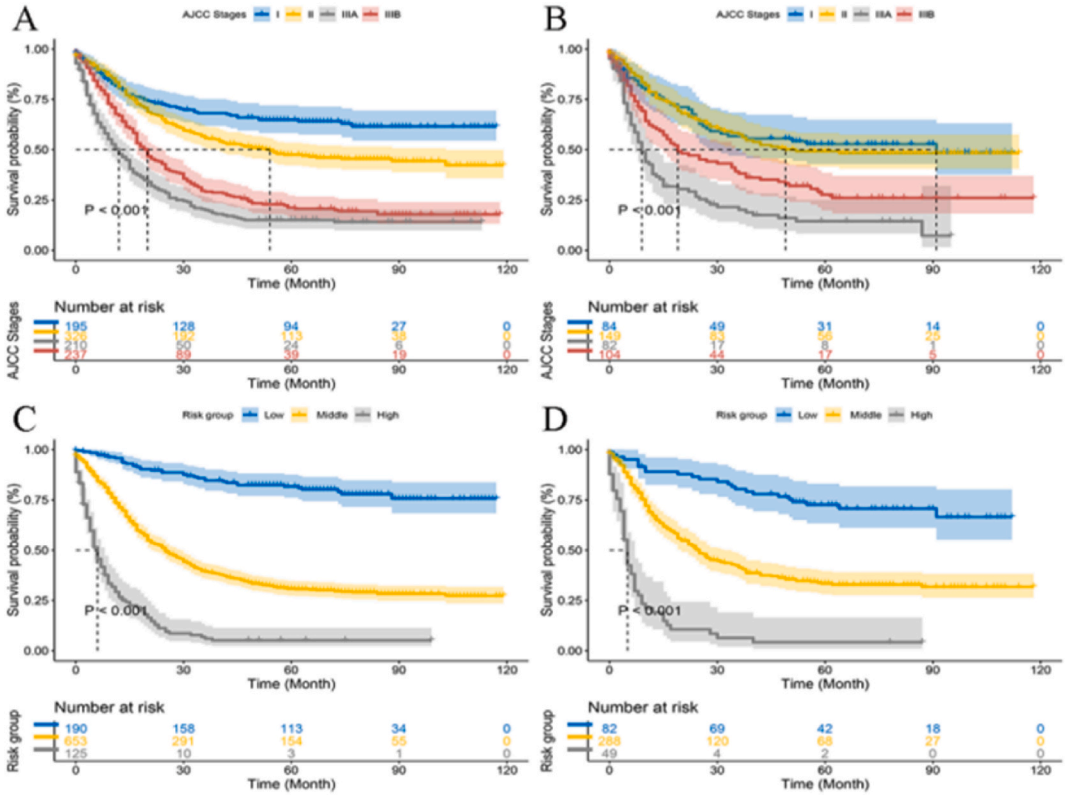

Fig. 8. Survival curves were used to compare differences in population prognosis between subgroups. (A, B) Prognostic differences in comparative populations based on AJCC staging. (C, D) The newly established stratification system better differentiates patients with different prognoses.

undergo cholecystectomy alone show comparable tumor-specific survival rates to those who opt for secondary radical surgery again [36,37]. However, it is crucial to perform extensive surgical removal for patients diagnosed with stage II and III gallbladder cancer [38,39]. Chen [40] et al. found that most patients gained a survival benefit from radical surgery by performing radical surgery in 112 patients with stage II and III gallbladder cancer at long-term follow-up. Gallbladder cancer exhibits a high degree of infiltration, and while certain patients may not exhibit lymph node infiltration during preoperative examination, intraoperative assessment revealed the presence of lymph node infiltration in some cases [41]. Extended surgical resection in lymph node-positive patients prolongs tumor-specific survival [42]. Preoperative identification of tumor pathological grading is challenging for the majority of gallbladder cancer patients, and a lower grade classification is indicative of an unfavorable prognosis [43]. Gallbladder polyps pose a significant risk for the development of gallbladder cancer, particularly those that exceed 2 cm in size which are classified as potentially malignant polyps [44]. Furthermore, the majority of cases of gallbladder cancer are diagnosed in elderly individuals [45].

Certain limitations are still associated with this study. The SEER database lacks data on tumor markers as recorded indicators in patients. Furthermore, patient etiology, such as stones or polyps, is not documented within the database. Additionally, the prognosis of patients may be influenced by various sites of morbidity; however, this information is not captured in the database.

5. Conclusion

The nomogram demonstrates encouraging prospects in effectively forecasting the prognosis of patients who have undergone radical surgery for gallbladder cancer, as opposed to the existing AJCC staging system. It demonstrates considerable practicality and reliability when applied in clinical settings. Nevertheless, additional research is necessary to authenticate its effectiveness.

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Informed consent statement

The Ethics Committee of Nanchong Central Hospital granted approval for this study. A statement from the Institutional Review Board confirms this.

Data availability statement

Publicly available datasets were analyzed in this study (https://seer.cancer.gov/). Scientific studies can contact the corresponding author for access to the codes and data analyzed in the manuscript.

CRediT authorship contribution statement

Yuan Feng: Writing – original draft. **Junjun Yang:** Data curation, Conceptualization. **Ankang Wang:** Resources, Project administration. **Xiaohong Liu:** Supervision, Software. **Yong Peng:** Resources, Project administration. **Yu Cai:** Writing – review & editing.

Declaration of competing interest

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

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e35551.

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