Development and validation of a prognostic nomogram for incidental gallbladder adenocarcinoma patients without distant metastasis after surgery: a SEER population-based study

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Research Article

Keywords: Incidental gallbladder adenocarcinoma, Nomogram, Overall survival, Cancer-specific survival, SEER

Posted Date: October 27th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2187482/v1

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Abstract

Background

Gallbladder cancer is the most common malignant tumor of the biliary system, most of which is adenocarcinoma. Our study explored developing and validating a nomogram to predict overall and cancer-specific survival probabilities internally and externally for incidental gallbladder adenocarcinoma patients without distant metastasis after surgery.

Methods

Patients screened and filtered in the Surveillance, Epidemiology, and End Results (SEER) database, whose years of diagnosis between 2010 and 2015 were collected as a derivation cohort, while those between 2016 and 2019 were a temporal validation cohort. Overall survival (OS) and cancer-specific survival (CSS) were chosen as our retrospective cohort study's primary and secondary endpoints. Potential clinical variables were selected for a cox regression model analysis by performing both-direction stepwise selection to confirm the final variables. The performance of final nomograms was evaluated by Harrell's C statistic and Brier score, with a graphical receptor operating characteristic (ROC) curve and calibration curve.

Results

6 variables of age, race, tumor size, histologic grade, T stage, and positive regional lymph nodes were finally determined for the OS nomogram; sex had also been added to the CSS nomogram equally. Novel dynamic nomograms were established to predict the prognosis of incidental gallbladder adenocarcinoma patients without distant metastasis after surgery. The ROC curve demonstrated good accuracy in predicting 1-, 3-, and 5-year OS and CSS in both derivation and validation cohorts. Correspondingly, the calibration curve presented perfect reliability between the death or cancer-specific death probability and observed death or cancer-specific death proportion in both derivation and validation cohorts.

Conclusions

Our study established novel dynamic nomograms based on 6 and 7 clinical variables separately to predict OS and CSS of incidental gallbladder adenocarcinoma patients without distant metastasis after surgery, which might assist doctors in advising and guiding therapeutic strategies for intraoperative or postoperative gallbladder adenocarcinoma patients in the future.

Background
Gallbladder cancer is the most common malignant tumor of the biliary system, with the tendency of early lymph node metastasis and distant metastasis\[1, 2\], of which more than 90% are adenocarcinoma\[3−5\]. According to the GLOBOCAN 2020, 115,949 new cases of gallbladder cancer (41,062 males and 74,887 females) and 84,695 deaths (30,265 males and 54,430 females) were reported worldwide, ranking sixth in digestive system tumors, and China is one of the regions with a high incidence\[6\]. Gallbladder cancer confirmed by pathological diagnosis during or after cholecystectomy is considered incidental gallbladder cancer, in which stages T1 and T2 are the most typical\[7\]. Therefore, simple cholecystectomy can achieve long-term survival for patients with Tis and T1a stages\[8\]. In contrast, the T1b stage or above is recommended to re-operate and perform standard or extended radical cholecystectomy according to their stages\[8\]. Fortunately, with the boom of laparoscopy, laparoscopic cholecystectomy (LC) appears to bring about the earlier discovery of gallbladder cancer in some patients, resulting in an increased probability of survival\[9, 10\].

The American Joint Committee on Cancer (AJCC) Tumor Node Metastasis (TNM) staging system is the most commonly applied in clinics for gallbladder cancer\[11\]. However, even if considered in the same TNM stage, the survival probability of gallbladder cancer patients still varies widely, causing poor predicting accuracy. Nomograms are graphical illustrations of clinical prediction models that apply several variables to acquire more accurate and trustworthy diagnostic or prognostic predictions\[12, 13\]. Therefore, they have been considerably adopted in multiple tumors, which were reported to be superior to the traditional staging system, such as TNM, for prognostic predictions\[14, 15\]. Similarly, various studies have investigated the role of prognostic nomograms via the SEER database using standard clinical variables for gallbladder cancer\[16\]. Most recently, Lin Y et al. constructed nomograms that showed better discrimination abilities to predict OS and CSS, assisting in risk stratification to guide gallbladder adenocarcinoma treatment\[17\]. Furthermore, Zhang W et al. established a more accurate and effective nomogram to predict the prognosis of patients with non-metastatic gallbladder cancer after surgical resection\[18\]. Moreover, Zhang Y et al. integrated tumor size with other prognostic factors into a predictive nomogram to predict the CSS of gallbladder cancer patients. Given the above, all these nomogram models utilized the previous version of AJCC TNM classification instead of the latest updated 8th edition. In addition, either the amounts of samples in these studies were relatively limited, or they did not perform external validation yet.

This study explored developing and validating prognostic nomograms of overall and cancer-specific survival probabilities internally and externally for incidental gallbladder adenocarcinoma patients without distant metastasis after surgery.

**Methods**

**Study design and data source**

The SEER Program collects cancer incidence data from population-based cancer registries covering approximately 48.0% of the U.S. population. The National Cancer Institute's SEER*Stat software (version
8.4.0.1) was used to collect data. The clinical variables of patients confirmed as gallbladder adenocarcinoma between 2010 and 2019 were retrieved from the SEER database: Incidence - SEER Research Plus Data, 17 Registries, Nov 2021 Sub (2000–2019), using which we undertook a retrospective cohort study. The reference number was 15850-Nov2021. Patients whose years of diagnosis were between 2010 and 2015 were collected as a derivation cohort, while those between 2016 and 2019 were a temporal validation cohort.

The inclusion criteria were: (1) primary site: gallbladder (C23.9), according to the International Classification of Diseases for Oncology, 3rd edition (ICD-O-3); (2) histologic type: adenocarcinoma; (3) only one primary tumor; (4) diagnosis confirmed by positive histology; (5) surgery performed; (6) the main differences between the 7th and 8th editions of AJCC TNM staging systems are T2 stage is subdivided as T2a (on the side of the peritoneum) and T2b (on the side of the liver), and N is staged according to the number of positive regional lymph nodes[19]. T stage classified as T1a, T1b, and T2 in the year 2010–2017, T1a, T1b, T2a, and T2b in the year 2018–2019; complete information on positive regional lymph nodes; M stage classified as M0; (7) no preoperative radiotherapy or chemotherapy. The exclusion criteria included: (1) age < 18 years old; (2) data such as tumor size, histologic grade, and follow-up information missing or incomplete.

Clinical Variables Extracted For Analysis And Transformation

Age, sex, race, tumor size, histologic grade, AJCC T stage, positive regional lymph nodes, and information on radiotherapy or chemotherapy were all selected for subsequent analysis. According to clinical follow-up outcomes, OS and CSS were chosen as the primary and secondary endpoints. Especially the X-tile software (version 3.6.1) was used to determine and visualize the best cut-off values of age and tumor size variables in our study[20, 21]. In addition, T2a and T2b stages were consolidated as the T2 stage, and the number of regional lymph nodes was divided into 0, 1–3, and \( \geq 4 \) positive regional lymph nodes.

Construction And Validation Of The Nomogram For Os And Css

Statistical analysis was conducted by the R software (version 4.1.3). Clinical variables of age, sex, race, tumor size, histologic grade, AJCC T stage, number of positive regional lymph nodes, and information on radiotherapy or chemotherapy were all selected for a cox regression model analysis (survival package version 3.4-0), in which both-direction stepwise selection by AIC method was performed to confirm the final variables (MASS version 7.3–58.1). Based on the analysis results, we used the rms (version 6.3-0) and nomogramEx (version 3.0) packages to formulate the nomogram for OS and CSS and extracted equations for calculating the OS and CSS probability corresponding to the total points. Furthermore, a web calculator of a dynamic nomogram was built by DynNom (version 5.0.2) and rsconnect (version 0.8.27) packages.
Predictive performance was evaluated by Harrell's C statistic and Brier score. Then, the established nomogram was subjected to enhanced-bootstrap internal validation (1,000 bootstrap resamples). Concerning the external validation, the linear predictor of each patient in the validation cohort was calculated based on the nomogram, and performance measures of Harrell's C statistic and Brier score were obtained. Moreover, in both the derivation and validation cohorts, the calibration curve of the nomogram was performed by comparing the predicted 1-, 3-, and 5-year death or cancer-specific death probability with observed death or cancer-specific death proportion (riskRegression package version 2022.03.22). In addition, a ROC curve and the area under the curve (AUC) were calculated to evaluate the accuracy of the nomogram to predict 1-, 3-, and 5-year OS and CSS probability (ggplot2 package version 3.3.6).

Results

Characterization of included cases

Based on inclusion and exclusion criteria, 698 patients diagnosed between the years 2010 and 2015 were included in the derivation cohort, then a total of 533 cases diagnosed from the year of 2016 to 2019 were finally selected in the validation cohort (Fig. 1). In general, most of the patients were female (71.5% in derivation vs. 68.7% in validation) and white (75.2% in derivation vs. 69.8% in validation). The rates of T1a, T1b, and T2 were 7.2%, 13.9%, and 78.9% in the derivation population, and 5.1%, 12.9%, and 82.0% in the validation population. Overall, the majority of cases were in AJCC stage II (58.2% in derivation vs. 61.7% in validation), a great number of them have no positive regional lymph nodes (79.7% in derivation vs. 78.6% in validation), and the grade of nearly half of the patients (49.0% in derivation vs. 52.3% in validation) was moderately differentiated. A large scale of patients (83.4% in derivation vs. 87.1% in validation) had not received radiotherapy after surgery. In comparison, many patients (71.9% in derivation vs. 60.6% in validation) had not received chemotherapy after surgery. Among all patients, the mean and median follow-up for the derivation cohort were 41.2 and 34.0 months, 17.4 and 14.0 months in the validation cohort, respectively. Meanwhile, 305 were cancer-specific deaths, 112 died of other causes in the derivation patients, 104 were cancer-specific death, and 25 died of other causes in the validation patients (Table 1). The cut-off points of age and tumor size were decided by X-tile (Fig. 2). Notably, 54.3% and 59.9% were ≤ 72 years old, 32.7% and 26.8% were between 73−84 years old, and 13.0% and 13.3% were ≥ 85 years old separately in derivation and validation groups. 20.3% and 18.9% were ≤ 12 mm, 61.0% and 60.6% were between 13−40 mm, and 18.6% and 20.5% were ≥ 41 mm separately in derivation and validation groups (Table 1).

Selection Of Variables And Establishment Of The Nomogram For Os And Css

The results obtained from stepwise selection analysis of derivation cohort are shown in Fig. 3, which indicated that younger patients had a better OS (age 73−84, ≥ 85 vs. ≤72, HR = 2.09, 3.59, P<0.001) and
CSS (age 73–84, ≥ 85 vs. ≤72, HR = 1.70, 2.35, P< 0.001). Female patients had lower risk of cancer-specific death (vs. male, HR = 0.81, P = 0.109). Black patients showed the lowest OS (race black, others vs. white, HR = 1.32, 0.79, P = 0.07, 0.13) and CSS (race black, others vs. white, HR = 1.07, 0.69, P = 0.72, 0.054). A larger tumor size represented a greater risk of overall death (tumor size 13–40, ≥ 41 vs. ≤12, HR = 1.40, 1.77, P = 0.02, < 0.001) and cancer-specific death (tumor size 13–40, ≥ 41 vs. ≤12, HR = 1.58, 2.00, P = 0.01, < 0.001). Well-differentiated patients had the highest OS (moderately-, poorly- vs. well-differentiated, HR = 1.15, 1.68, P = 0.332, < 0.001) and CSS (moderately-, poorly- vs. well-differentiated, HR = 1.07, 1.69, P = 0.701, 0.002). Regarding the T stage and positive regional lymph nodes, T1a and 0 positive regional lymph node were associated with the highest OS (T1b, T2 vs. T1a, HR = 2.12, 2.80, P = 0.033, 0.002; regional nodes positive 1–3, ≥ 4 vs. 0, HR = 1.41, 3.38, P = 0.005, < 0.001) and CSS (T1b, T2 vs. T1a, HR = 4.82, 6.90, P = 0.01, < 0.001; regional nodes positive 1–3, ≥ 4 vs. 0, HR = 1.39, 3.04, P = 0.019, < 0.001).

Accordingly, these remaining variables were selected to establish the nomogram for 1-, 3-, and 5-year OS and CSS (Fig. 4). As shown, ages 73–84 and ≥ 85 years old scored 57.6 and 100 in the OS nomogram, 27.4 and 44.4 in the CSS nomogram respectively. White and black patients scored 18.9, 40.9 in the OS nomogram and 19.1, 22.7 in the CSS nomogram. The points of tumor size 13–40 and ≥ 41 mm were 26.5 and 44.8 in the OS nomogram, while 23.8 and 35.9 in the CSS nomogram. Grades moderately- and poorly- differentiated got 10.8 and 40.8 in the OS nomogram, 3.4 and 27.3 in the CSS nomogram. T1b and T2 were marked as 58.4 and 80 in the OS nomogram, separately 81.4 and 100 in the CSS nomogram. Finally, the scores of 1–3 and ≥ 4 positive regional lymph nodes were 27.1 and 95.4 in the OS nomogram, each of which was 17.1 and 57.7 in the CSS nomogram. Remarkably, the male patients scored 10.6 in the CSS nomogram. By accumulating points of each variable, we could reveal the individual non-metastatic postoperative gallbladder adenocarcinoma patients’ probability of OS and CSS using the following formulas in Table 2.

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<th>Table 2</th>
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<td>The formulas for calculating the OS and CSS probability corresponding to the total points.</td>
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<th>Overall Survival Probability</th>
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<th>Cancer-Specific Survival Probability</th>
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Finally, we built a web calculator of the dynamic nomogram for clinicians to use conveniently online at https://jackycome.shinyapps.io/osgba/ and https://jackycome.shinyapps.io/cssgba/. For example, if a white female, aged greater than or equal to 85, with a tumor size between 13 and 40 mm, grade moderately differentiated, on T2 stage, and 0 positive regional lymph node, her 3-year OS and CSS probabilities were 0.248 and 0.440 (Fig. 5).

**Model Performance And Model Validation**

The internal and external assessment of nomogram performance was measured by Harrell's C statistic and Brier score. Harrell's C statistic of OS and CSS nomogram was 0.680 (95% confidence interval (95%CI): 0.655–0.706) and 0.671 (95%CI: 0.641–0.702) in derivation cohort while 0.660 (95%CI: 0.612–0.708) and 0.710 (95%CI: 0.660–0.761) in validation cohort. Furthermore, the ROC curve demonstrated a moderate accuracy in predicting 1-, 3-, and 5-year OS and CSS in derivation cohort, with an AUC of 0.716 (95%CI: 0.656–0.777), 0.739 (95%CI: 0.696–0.782), 0.777 (95%CI: 0.735–0.820) in OS, and 0.695 (95%CI: 0.625–0.765), 0.732 (95%CI: 0.684–0.780), 0.769 (95%CI: 0.722–0.817) in CSS (Fig. 6A, 6C). Meanwhile, the ROC curve also showed a good discrimination of 1-, and 3-year OS and CSS prediction in validation cohort, with an AUC of 0.682 (95%CI: 0.619–0.746), 0.692 (95%CI: 0.605–0.780) in OS, and 0.724 (95%CI: 0.654–0.795), 0.741 (95%CI: 0.653–0.829) in CSS (Fig. 6B, 6D).

In addition, the calibration curve displayed a perfect reliability between the death or cancer-specific death probability with observed death or cancer-specific death proportion in the derivation cohort, with the Brier score of 1-, 3-, and 5-year were 0.164 (95%CI: 0.118–0.210), 0.207 (95%CI: 0.186–0.229), 0.187 (95%CI: 0.170–0.204) in OS, and 0.141 (95%CI: 0.091–0.190), 0.202 (95%CI: 0.177–0.227), 0.196(0.177–0.216) in CSS (Fig. 7A, 7C). While in validation cohort the Brier score of 1-, and 3-year were 0.147 (95%CI: 0.126–0.168), 0.223 (95%CI: 0.194–0.251) in OS, and 0.121 (95%CI: 0.101–0.141), 0.191 (95%CI: 0.169–0.212) in CSS (Fig. 7B, 7D).

**Discussion**

As a common malignant biliary system tumor, the clinical manifestations of gallbladder cancer were obscure, most patients are clinically advanced with early metastasis, and the prognosis is unsatisfactory [1, 2]. So high-quality research is urgently needed to break through the bottleneck of early diagnosis and following treatment. Along with the continuous development of medical science and technology, early diagnosis and radical surgical resection are still possible means to cure gallbladder cancer[22]. In recent years, morbidity and mortality have shown a slow upward trend, with more than 90% adenocarcinoma[3–6]. Age standard incidence rate of gallbladder cancer is 2.3 per 100,000 people on average globally, with the highest in East Asia and South America, accompanying the incidence in men and young people has increased as well[6, 23, 24]. Since the spring-up of laparoscopic surgery, gallbladder cancers have been spotted earlier in some patients, contributing to a higher chance of survival[25]. Altiok M et al. observed a phenomenal growth in the number of incidental gallbladder cancers after cholecystectomy operations
over the past 20 years, of whom 90% were T1a, T1b, and T2, and 92.5% were adenocarcinoma[26]. Furthermore, surgery is the only potential way for gallbladder cancer to be cured and survive for a long time[8, 27]. Hence, it is very meaningful to predict the prognosis of incidental gallbladder adenocarcinoma patients diagnosed after open or laparoscopic cholecystectomy without distant metastasis.

The therapeutic regimen for incidental gallbladder adenocarcinoma differs from its stage. For stage T1a, simple cholecystectomy is adequate in over 90% of patients, and extended cholecystectomy, including lymphatic dissection, should be considered for T1b or more advanced stages [8]. Wang Z et al. reported no positive lymph nodes observed in T1b gallbladder adenocarcinoma with tumor size < 1 cm, indicating that simple cholecystectomy is curative for these patients, minimalizing the re-operation need[28]. Notably, 6 variables of age, race, tumor size, histologic grade, T stage, and positive regional lymph nodes were finally determined to establish the OS prediction nomogram. Similarly, sex had also been added to the CSS nomogram, in which female was recognized as a protective factor. Additionally, the nomograms demonstrated a moderate accuracy of Harrell's C statistic and induced a well-behaved calibration plot for OS and CSS prediction in both deviation and validation cohorts. Nevertheless, our nomograms overestimated 3-year overall death and cancer-specific death risks. This might be because the upper limit of follow-up in the temporal validation cohort is 47 months, and the median and mean follow-up time are 14.0 and 17.4 months, respectively, leading to excessive censored data. Due to short follow-up time, many cases have not yet observed death events until the last correspondence for the survival calculation. Other than that, overall and cancer-specific baseline survival probability is higher in the validation cohort. With the increasing medical technologies and living standards improvements, the average age is steadily rising globally, bringing about the elderly's healthier and longer life[29]. Thus, we need to wait for the SEER database to be updated before re-evaluating and re-verifying our nomogram model.

The TNM staging system only considers the depth of tumor invasion but not the tumor size[19]. Various researchers have found that tumor size could influence the prognosis of gallbladder cancer patients. However, the best cut-off points of tumor size to forecast the survival outcome remains arbitrary. Zhang Y et al. advocated that larger tumor size significantly contributed to the development of more advanced T stage, more frequent distant metastasis, and more positive regional lymph nodes, which was a confounding variable to predict the CSS of postoperative gallbladder cancer patients[30]. Zhang W et al. developed a CSS model setting tumor size > 3 cm as an essential prognostic predictor in gallbladder cancer patients without distant metastasis after surgical operation[18]. In contrast, Yadav S et al. created a clinically based predictive scoring nomogram for gallbladder cancer patients in which tumor size ≥ 5 cm and worse OS went hand in hand[31]. Generally, increased gallbladder cancer mortality might be associated with age increases[1]. However, a thorough investigation of the association between age and overall or gallbladder cancer-specific death risk remains unexplored without highlighting the predictive capacity of age until now. To facilitate clinical application, X-tile software that illustrates a graphical construction of a two-dimensional projection of every possible subpopulation was used to optimize outcome-based cut-point optimization of consecutive age and tumor size variables[20, 21]. Our work implied that age played a more crucial role in OS than the CSS nomogram, with ≥ 85 years old scoring
100 in OS but 44.4 points in CSS. Our study's best cut-off values of tumor size were 13 and 40 mm, showing that larger tumor size was in line with a higher overall or gallbladder adenocarcinoma-specific death probability. Tumor size 13–40 mm, ≥ 41 mm were 1.40, 1.77 times higher overall death risk, and 1.58, 2.00 times higher gallbladder adenocarcinoma-specific death risk than tumor size ≤ 12 mm. Given the above, our nomograms attributed to age and tumor size are essential determinants in OS or CSS prediction models for incidental gallbladder adenocarcinoma without distant metastasis patients who underwent surgery.

Nonetheless, SEER, one of the largest tumor databases, was applied to develop and validate a prognostic nomogram for incidental gallbladder adenocarcinoma patients without distant metastasis after surgery; the drawback of this framework was its retrospective nature, which is associated with inevitable selection bias and information bias[32]. Furthermore, the follow-up time of the temporal validation cohort is not long enough. Also, due to this study’s small retrospective cohort size, more large-scale prospective studies or an updated SEER database are needed to re-validate our conclusions. The AUC of our developed nomogram was between 0.682 and 0.777 from the derivation and validation cohort, which only offers a moderate accuracy in predicting prognosis for incidental gallbladder adenocarcinoma patients without distant metastasis after surgery. Counseling of potential parents on prognosis prediction, clinicians should take complete account of these drawbacks when using these prognostic nomograms. According to the latest 8th version of the AJCC TNM classification system, the T2 category is separated into T2a and T2b based on tumor location on the gallbladder's peritoneal or hepatic side. Our next step updating the model by adding a subdivided T2 stage, might improve the accuracy of the nomogram.

Conclusions

Our study established novel dynamic nomograms based on 6 and 7 clinical variables separately to predict OS and CSS of incidental gallbladder adenocarcinoma patients without distant metastasis after surgery. The internal and external validation of the nomogram showed a moderate accuracy performance. Notwithstanding some limitations, these nomograms will assist doctors in advising and guiding therapeutic strategies for intraoperative or postoperative gallbladder adenocarcinoma patients conveniently. In the future, more randomized controlled trials are needed to update these nomograms.

Abbreviations

SEER: the Surveillance, Epidemiology, and End Results; AJCC: the American Joint Committee on Cancer; TNM: Tumor Node Metastasis; ICD-O-3: the International Classification of Diseases for Oncology, 3rd edition; OS: Overall survival; CSS: Cancer-specific survival; ROC: Receptor operating characteristic; AUC: Area under the curve.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

This study analyzed data from the publicly available SEER database under license (ID: 15850-Nov2021). Data are available from the authors upon reasonable request and with permission of the SEER database.

Competing interests

The authors declare that the research was conducted without any commercial or financial relationships construed as a potential conflict of interest.

Funding

This work was supported by the Chinese Medicine Research Program of Zhejiang Province (2020ZB030).

Authors' contributions

J.C. and Y.H. conceived and designed the experiments. J.C. performed data analysis and drafted the manuscript. S.H. did the literature research and edited the manuscript. All authors read and approved the final manuscript.

Acknowledgments

Not applicable.

References


Table 1

Table 1 is available in Supplementary Files section.

Figures
Figure 1

The flowchart of patient selection in the SEER database.
Figure 2

The optimal cut-off values of age and tumor size by X-tile software analysis. A the X-tile plot of age in the derivation cohort; B the optimal cut-off value of age highlighted by a histogram; C the Kaplan-Meier plot of prognosis determined by the optimal cut-off value of age; D the X-tile plot of tumor size in the derivation cohort; E the optimal cut-off value of tumor size highlighted by a histogram; F the Kaplan-Meier plot of prognosis determined by the optimal cut-off value of tumor size.
Figure 3

The forest plot for the hazard ratio of selected nomogram variables to predict OS and CSS. **A** selected nomogram variables to predict OS; **B** selected nomogram variables to predict CSS.
Figure 4

The nomogram to predict OS and CSS probability. **A** prognostic nomogram of OS; **B** prognostic nomogram of CSS.

Note: 1-, 3-, and 5-year baseline OS probability: 0.9943277, 0.9914994, 0.9871056; 1-, 3-, and 5-year baseline CSS probability: 0.9983498, 0.9973744, 0.9953482.
Figure 5

Web dynamic nomogram calculator with a clinical example. A web dynamic nomogram calculator of OS with a clinical example; B web dynamic nomogram calculator of CSS with a clinical example.
Figure 6

ROC curves of the nomogram model. **A** ROC curve of OS in the derivation cohort; **B** ROC curve of OS in the validation cohort; **C** ROC curve of CSS in the derivation cohort; **D** ROC curve of CSS in the validation cohort.
Figure 7

Calibration curves of the nomogram model. **A** calibration curve of OS in the derivation cohort; **B** calibration curve of OS in the validation cohort; **C** calibration curve of CSS in the derivation cohort; **D** calibration curve of CSS in the validation cohort.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf