



OPEN Development and validation of a dynamic prognostic nomogram for conditional survival in hepatocellular carcinoma: an analysis from the Korea Liver Cancer Registry

Jae Hyun Kwon^{1✉}, Eun-Kyoung Jwa², Jong Woo Lee¹, Eunyoung Tak^{3,4} & Shin Hwang²

Compared to overall survival, conditional survival is a more relevant measure of prognosis in surviving patients over time. This study developed and validated a nomogram-based dynamic prognostic model to predict the conditional survival estimates of patients with hepatocellular carcinoma (HCC) through an analysis of a nationwide cancer registry. This retrospective cohort study included 2492 patients with HCC registered in the Korea Liver Cancer Registry. Patients underwent hepatic resection (HR) from 2008 to 2017, were followed up until December 2019, and were divided into development and validation cohorts. Univariate and multivariate Cox regression analyses were conducted to determine the risk factors for conditional survival of patients who underwent HR. The patients were scored based on the Cox regression coefficients; the nomogram was predicted by calculating the survival probability with Cox model. Our dynamic prognostic model nomogram for predicting conditional overall survival demonstrated Harrell's C-index of 0.622 and 0.674 in the development and validation sets; for conditional disease-specific survival, it was 0.623 and 0.686 in the development and validation sets. The prediction power of the model is applicable in clinical practice. Factors incorporated in our nomogram included age, albumin, the ADV score, lymph node metastasis, and T stage in American Joint Commission on Cancer staging system. We developed and validated a nomogram to predict conditional survival estimates for overall survival and disease-specific survival. The proposed nomogram incorporating the ADV score presents a more accurate and useful prognostic prediction for patients with HCC who received HR.

Keywords Hepatocellular carcinoma, Hepatectomy, Prognosis

Abbreviations

AFP	Alpha-fetoprotein
AJCC	American Joint Commission on Cancer
ADV score	Alpha-fetoprotein (AFP)–des-gamma-carboxyprothrombin (DCP)–tumor volume (TV) score
AFP	Alpha-fetoprotein
AUC	Area under the receiver operating characteristic curve
CS	Conditional survival
DCP	Des-gamma-carboxyprothrombin
DSS	Disease-specific survival

¹Department of Surgery, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22, Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang-si, Gyeonggi-do 14068, South Korea. ²Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. ³Asan Institute for Life Sciences, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea. ⁴Department of Biochemistry and Molecular Biology, Asan Medical Center, AMIST, University of Ulsan College of Medicine, Seoul, South Korea. ✉email: kwonjh@hallym.or.kr

HCC	Hepatocellular carcinoma
HR	Hepatic resection
KCCR	Korea Central Cancer Registry
KLCR	Korea Liver Cancer Registry
OS	Overall survival
ROC curve	Receiver operating characteristic curve

Primary liver cancer, of which hepatocellular carcinoma (HCC) accounts for 75–85% of cases, is the sixth most diagnosed cancer and the third leading cause of cancer-related death worldwide^{1,2}. Hepatic resection (HR) is the standard and first-line treatment for HCC in patients with preserved hepatic reservoirs. The practice guidelines for HCC recommend liver resection as the treatment of choice for single- or limited-numbered HCC without significant cirrhosis or portal hypertension^{3,4}. However, tumor recurrence occurs frequently and unpredictably after HR. In contrast to other solid-organ tumors, the survival of patients with HCC is affected by other factors beyond the tumor characteristics. HCC usually occurs in patients with chronic liver disease and liver cirrhosis; thus, functional reserve of the liver significantly impacts patient survival, including overall survival (OS) and HCC recurrence.

Treatment modalities for the recurrence of HCC also vary depending on the tumor burden and the functional reserve of the liver. Therefore, patient survival prediction is quite difficult, especially due to the heterogeneity of patients' clinical course. In this situation, conditional survival (CS), survival beyond a pre-defined time interval, can identify and integrate the comorbidities and risk factors related to survival and recurrence for real-world prognostic values in the survivorship setting. The conventionally used OS is a relatively static concept and does not reflect the impact of changing variables. The concept of CS estimates applies this heterogeneous and changeable patient status and determines the probability that a patient who has survived for a designated period will be alive at another fixed interval⁵. Until now, the CS analyses performed in patients with HCC were limited and some studies focused on specific patient types, including a focus on patients with cirrhosis or patients treated with radiofrequency ablation^{6–11}.

We previously demonstrated that the score derived from the multiplication of alpha-fetoprotein (AFP), des-gamma-carboxyprothrombin (DCP) (proteins induced by vitamin K antagonist or absence-II), and tumor volume (TV) (AFP–DCP–TV score or, simply, ADV score) is an integrated surrogate marker of postresection prognosis in solitary HCCs and a quantifiable parameter reflecting tumor aggressiveness¹². It was also proven to be valid in patients with preoperatively treated HCCs¹³. The prognostic role of the ADV score for HCC resection has been validated in single-center and multicenter studies and nationwide HCC databases in various conditions, including small and large solitary HCC, as well as HCC with portal vein tumor thrombus^{12–16}.

No prior studies have described the development of a nomogram specifically to predict CS in patients with HCC. This study aimed to develop and validate a dynamic prognostic model for patients with HCC who received HR and were registered in the Korea Liver Cancer Registry (KLCR) database. The objective was to make a clinical nomogram for CS in these patients by applying the predictive power of the ADV score. The clinical nomogram could be used in clinical settings to provide more accurate prognostic information to patients and their families.

Patients and methods

Patient selection

The Ministry of Health and Welfare of Korea initiated a nationwide cancer registry in 1980 called the Korea Central Cancer Registry (KCCR). In concordance with the KCCR, the Korean Liver Cancer Association, previously known as the Korean Liver Cancer Study Group, established the KLCR as a nationwide HCC cohort.

Clinical data for 13,838 patients with HCC who were registered in the KLCR database from January 2008 to December 2017 and followed up with the KCCR until December 2019 were reviewed. The information of 2648 patients who underwent HR was extracted. We excluded patients with missing data on important clinical or laboratory parameters, including tumor size and number and preoperative AFP and DCP values. We also excluded patients who underwent liver transplantation after HR because transplantation can change the postresection prognosis. Finally, we selected 2,492 patients as the entire study cohort.

This study was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (IRB No. 2021-07-019) and complied with the tenets of the Declaration of Helsinki. The same review board waived the requirement for informed consent because of the retrospective nature of the analyses.

Study design/cohort definition and variable recode

To analyze conditional survival, we evaluated 2-year and 3-year overall survival (OS) and disease-specific survival (DSS) probabilities among patients who survived at least 1 year after hepatic resection. The patients were divided into the development and validation cohorts according to the year of diagnosis: 2008–2015 (development cohort) and 2016–2017 (validation cohort). The development cohort was used to extract the significant variables for survival outcomes and establish the nomogram model. The validation cohort was used to validate the performance of the developed model. The following variables from the KCCR database were included: age at diagnosis, sex, body mass index, smoking history, primary liver disease, performance status, albumin, total bilirubin, prothrombin time, creatinine, alanine aminotransferase, AFP, DCP, fasting glucose, cholesterol, tumor size and number, Child–Turcotte–Pugh score, model for end-stage liver disease score, indocyanine green retention rate at 15 min, TNM stage, Barcelona Clinic Liver Cancer stage, microvascular invasion, and presence of major hepatic vessel invasion and bile duct invasion. We incorporated the ADV score (calculated as $\text{AFP [ng/mL]} \times \text{DCP [mAU/mL]} \times \text{TV [mL]}$ and expressed in \log_{10}) into the prediction model.

The ADV score was calculated from the existing data. TV was calculated from the maximal tumor diameter under the assumption that the tumor is spherical.

Prediction models and nomograms

We conducted univariate and multivariate Cox analyses to determine the risk factors for CS of patients with HCC, scored based on the Cox regression coefficients. We predicted the nomogram by calculating the survival probability with the Cox model.

Statistical analysis

Descriptive statistics for numerical variables were recorded as mean \pm standard deviation or median with interquartile range, and categorical variables were presented as relative frequencies (percentages). Missing data were handled with multiple imputation using Markov chain Monte Carlo methods. In the development set, univariate and multivariable Cox proportional hazards models were used to predict the overall survival (OS) and disease-specific survival (DSS) of patients who survived for more than 1 year after surgery. Variables in the multivariable model were selected from all variables through 1000-fold bootstrapping, retaining those included in over 50% of the bootstrap models with backward elimination. The multivariable model was presented as a nomogram. The discrimination ability of the nomogram was assessed using the Harrell C-index and time-dependent area under the receiver operating characteristic curve (AUC) at 2 and 3 years. The calibration ability of the nomogram was assessed using a calibration curve by comparing the predicted and observed Kaplan–Meier estimates of OS at 2 and 3 years. Furthermore, to evaluate calibration of the nomogram, we stratified patients into ten risk groups based on predicted survival probabilities. The mean predicted survival within each group was compared to the actual observed survival, which was estimated through Kaplan–Meier method. The discrimination and calibration of the nomogram were evaluated in the validation set using the same method described above. Patient survival (including OS and DSS) was estimated using the Kaplan–Meier method. $P < 0.05$ indicated statistical significance. All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC) and R (version 4.2.2; <https://www.R-project.org>).

Results

Patient demographics and clinical characteristics

A total of 2492 patients were included in this study and divided into the development cohort ($n = 2107$, from 2008 to 2015) and validation cohort ($n = 385$, from 2016 to 2017 as temporal validation). Table 1 summarizes the patients' demographic and clinical characteristics. The mean age was 57.6 ± 10.5 years, with a predominance of male patients (80.5%). The average body mass index was 24.2 ± 3.1 kg/m². Nearly half of the patients had a history of smoking (44.8%), whereas 21.5% had diabetes mellitus, and 35.3% had hypertension. The primary liver disease was predominantly hepatitis B virus infection (69.8%), followed by alcohol-related liver disease (10.0%) and hepatitis C virus infection (5.9%). Performance status, measured using the Eastern Cooperative Oncology Group (ECOG) scale, was 0 in 87.6% of patients¹⁷. The mean Child–Turcotte–Pugh score was 5.2 ± 0.6 , and the Model for End-Stage Liver Disease score was 8.0 ± 2.5 .

The tumor characteristics and ADV scores of the patients are detailed in Table 2. Laboratory results revealed a median AFP level of 20.5 ng/mL (interquartile range: 4.6–232.0) and a median DCP level of 69.5 mAU/mL (interquartile range: 26.0–439.0). The mean maximal tumor size was 4.4 ± 3.1 cm, with an average tumor number of 1.2 ± 0.7 . Most patients had a single tumor (84.8%), and 15.2% had multiple tumors. The mean tumor volume was 210.3 ± 913.9 mL. The mean ADV score, expressed in log₁₀, was 5.11 ± 2.13 .

Survival outcomes of the entire study population

The OS rates of the development and validation cohorts at 2 and 3 years were 91.5 and 93.2% and 84.0 and 86.9%, respectively (Fig. 1). The DSS rates of the development and validation cohorts at 2 and 3 years were 92.4 and 94.3% and 85.6 and 88.4%, respectively. There were no significant differences in OS and DSS between the development and validation cohorts ($P = 0.060$ and $P = 0.071$, respectively; Fig. 1).

Nomogram variable screening and nomogram construction

The prognostic nomogram for conditional OS and DSS was developed based on univariate and multivariate Cox regression results (Supplementary Tables 1 and Table 3). The prognostic nomogram of 2-year and 3-year survival probability consists of the following independent prognostic factors: age, albumin, N stage, T stage, and ADV score (Fig. 2). Each level of these variables was assigned a specific point on the scale. The total score was obtained by adding the scores of each prognostic factor to estimate the CS probability of patients at 2 and 3 years.

Performance and validation of the nomogram

The constructed CS nomogram for OS demonstrated a Harrell's C-index of 0.622 (95% CI: 0.592–0.652) in the development set and 0.674 (95% CI: 0.601–0.747) in the validation set. For conditional DSS, the Harrell's C-index was 0.623 (95% CI: 0.591–0.655) in the development set and 0.686 (95% CI: 0.606–0.765) in the validation set.

To assess the discriminatory performance of the nomogram, we conducted time-dependent receiver operating characteristic (ROC) curve analysis and calculated the time-dependent AUC for 2-year and 3-year conditional survival, presented in Fig. 3. For 2-year conditional OS, the time-dependent AUC was 0.642 (95% CI: 0.601–0.683) in the development set and 0.665 (95% CI: 0.566–0.764) in the validation set. For 3-year conditional OS, the AUC was 0.636 (95% CI: 0.604–0.669) and 0.681 (95% CI: 0.601–0.760) in the development and validation sets, respectively. Similarly, for 2-year conditional DSS, the time-dependent AUC was 0.651 (95% CI: 0.608–0.695) in the development set and 0.684 (95% CI: 0.574–0.794) in the validation set. The 3-year

	<i>n</i> = 2492
Age (years)	57.6 ± 10.5
Sex (male)	2005 (80.5)
BMI (kg/m ²)	24.2 ± 3.1
Smoking history	1117 (44.8)
Diabetes mellitus	536 (21.5)
Hypertension	880 (35.3)
Primary liver disease	
HBV	1740 (69.8)
HCV	148 (5.9)
HBV HCV	21 (0.8)
Alcohol	248 (10.0)
Others/unknown	335 (13.4)
Performance status*	
0	2181 (87.6)
1	283 (11.4)
≥ 2	27 (1.1)
CTP score	5.2 ± 0.6
MELD	8.0 ± 2.5
MELD-Na	8.8 ± 3.0
Laboratory results	
Albumin (g/dL)	4.2 ± 0.5
Total bilirubin (mg/dL)	0.92 ± 0.96
PT (%)	91.4 ± 13.6
PT (INR)	1.07 ± 0.12
Creatinine (mg/dL)	0.94 ± 0.65
Sodium (mmol/L)	140.0 ± 2.8
ALT (IU/L)	45.1 ± 59.8
Platelet (×10 ³ /uL)	173.5 ± 70.1
ICG R15 (%)	12.2 ± 8.7
Fasting glucose (mg/dL)	120.1 ± 43.9
Total cholesterol (mg/dL)	165.3 ± 37.4

Table 1. Demographics and clinical characteristics of patients. *Performance status (PS) according to the Eastern Cooperative Oncology Group (ECOG) scale. *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein, *BMI* body mass index, *CCC* cholangiocarcinoma, *CTP* Child-Turcotte-Pugh score, *DCP* des-gamma-carboxyprothrombin, *HBV* hepatitis B virus, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *ICG R15* indocyanine green retention rate at 15 min, *INR* international normalized ratio, *MELD* model for end-stage liver disease, *MELD-Na* MELD-Sodium (MELD which including serum sodium), *PT* prothrombin time.

conditional DSS AUC was 0.638 (95% CI: 0.603–0.672) in the development set and 0.691 (95% CI: 0.605–0.778) in the validation set.

We constructed calibration plots to compare the nomograms with ideal reference curves. The calibration curves demonstrated good agreement between the observed and predicted survival probabilities of 2- and 3-year OS and DSS in the development and validation cohorts (Fig. 4).

The risk-stratified calibration table, demonstrating the agreement between predicted and observed survival probabilities for conditional OS, is presented in Table 4, and for conditional DSS in Table 5.

Discussion

This retrospective study included nationwide consecutive patients with HCC who underwent HR to develop a dynamic nomogram to predict the conditional OS and HCC-specific survival. The prognosis of patients with HCC is associated with the intrinsic tumor biology and the functional reserve of the liver. Various additional factors not accounted for in traditional staging systems, including background etiology of liver disease, tumor markers, pathological subtypes, microvascular invasion, and invasion of vessels or bile ducts, can significantly impact the prognosis of patients with HCC^{18–20}. Unlike other solid organ malignancies, which are typically classified using the AJCC TNM staging system for prognostic predictions, the optimal staging system encompassing the factors mentioned above has yet to be established. Consequently, staging systems for HCC are both diverse and complex^{21–23}. The diversity of staging systems highlights the challenge of achieving optimal prognostication, underscoring the need for continued investigation of various approaches.

	<i>n</i> = 2492
Laboratory results	
AFP (ng/mL)	20.5 (4.6–232.0)
DCP (mAU/mL)	69.5 (26.0–439.0)
Pathologic results	
Maximal tumor size (cm)	4.4 ± 3.1
Number of tumor	1.2 ± 0.7
Number of tumor	
Single	2113 (84.8)
Multiple	379 (15.2)
Tumor volume (mL)	210.3 ± 913.9
ADV score (log ₁₀)	5.11 ± 2.13
Microvascular invasion	388 (15.6)
Histology	
HCC	2476 (99.4)
HCC-CCC	16 (0.6)
PV invasion	153 (6.1)
HV invasion	37 (1.5)
Bile duct invasion	56 (2.3)
HA invasion	7 (0.3)
LN metastasis	12 (0.5)
Distant metastasis	11 (0.4)
Preoperative treatment	200 (8.0)
T stage	
1	364 (14.6)
2	1685 (67.6)
3	400 (16.1)
4	43 (1.7)
TNM stage	
I	364 (14.6)
II	1675 (67.2)
III	391 (15.7)
IV-A	62 (2.5)
BCLC stage	
0	150 (6.0)
A	1621 (65.1)
B	332 (13.3)
C	381 (15.3)
D	5 (0.2)

Table 2. Tumor characteristics of patients. *BCLC* Barcelona Clinic Liver Cancer, *HA* hepatic artery, *HV* hepatic vein, *LN* lymph node, *PV* portal vein.

The complexity of prognostication in HCC is further compounded by the interplay of tumor biology, liver functional reserve, and tumor location, all of which influence treatment selection. Each of these factors, including the choice of treatment, acts as a variable that impacts prognosis. Furthermore, treatment modalities for HCC are highly variable, influenced by tumor characteristics and the patient's functional liver reserve, ranging from surgical resection and transplantation to local therapies, such as radiofrequency ablation, transarterial chemoembolization, systemic chemotherapy, and radiation therapy. Each of these treatment options carries distinct prognostic outcomes, further contributing to the dynamic nature of HCC prognosis. As a result, predicting outcomes in HCC becomes a multifaceted and intricate process that extends beyond the capabilities of traditional staging systems. Accurately predicting recurrence following hepatectomy remains a significant clinical challenge. Attributed to advancements in early detection and surgical and interventional techniques with the development of antiviral agents, the OS and DSS of patients with HCC have improved over time in the past decades^{18,24}. Traditional staging systems, which provide prognosis based on diagnostic staging, are inherently static. However, patient outcomes are dynamic, evolving in response to treatment. This dynamic nature of prognosis reveals the limitations of conventional staging methods. The concept of CS addresses these needs by offering a more refined and precise understanding of patient prognosis over time.

Oncologic outcomes were traditionally estimated as 5-year OS or DSS from the time of initial diagnosis or curative treatment. These survival data are valuable for counseling patients during their initial visits and

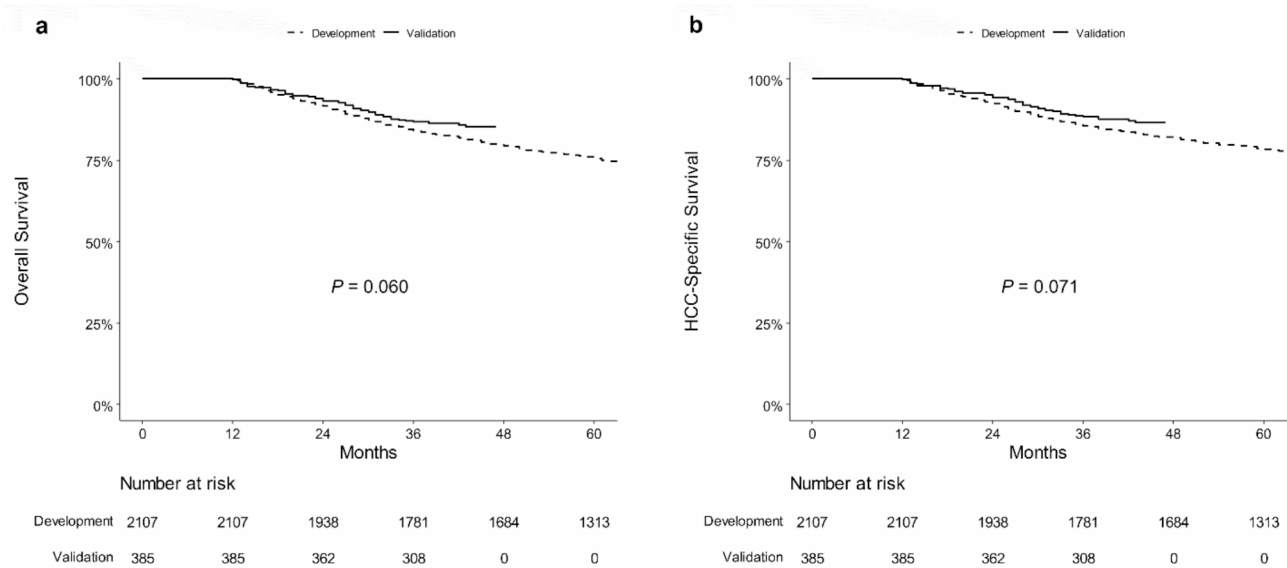


Fig. 1. (a) Overall survival (OS) of the development and validation cohorts. (b) Disease-specific survival (DSS) of the development and validation cohorts.

	Overall survival		Disease-specific survival	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (years)	1.003 (0.993–1.014)	0.528	1.003 (0.992–1.014)	0.562
Albumin	0.708 (0.577–0.869)	0.001	0.744 (0.598–0.925)	0.008
ADV score	1.109 (1.053–1.168)	<0.001	1.113 (1.054–1.176)	<0.001
LN metastasis	3.246 (1.425–7.392)	0.005	3.627 (1.589–8.279)	0.002
T stage				
1	1	0.015	1	0.016
2	0.979 (0.671–1.427)	0.911	1.101 (0.726–1.668)	0.651
3	1.525 (0.991–2.348)	0.055	1.680 (1.048–2.693)	0.031
4	1.141 (0.509–2.555)	0.749	1.389 (0.607–3.176)	0.437

Table 3. Multivariate Cox analyses for patient 1-year conditional overall survival (OS) and disease-specific survival (DSS).

comparing outcomes across various therapeutic modalities. However, they provide limited information about how risk changes over time. For cancers with notably high early recurrence rates, conventional recurrence-free survival estimates are only relevant at initial presentation and lose their accuracy and significance over time. With these conventional survival estimates, even patients who remained recurrence-free for a certain period were still considered at high risk for tumor recurrence or mortality if they were initially classified as high-risk. Recurrence-free CS outcomes were improved with each additional year of recurrence-free survival in patients with HCC who underwent HR⁶.

In recent years, the nomogram has become a widely utilized predictive tool in the field of oncology. Several studies have demonstrated the utility of nomograms across various cancer types^{25–28}. These nomograms provide clinicians with an efficient and reliable tool for predicting patient prognosis. Several studies on nomograms for prognosis and CS estimates in HCC are available; however, to our knowledge, this is the first analysis to develop a nomogram specifically designed to predict CS in patients with HCC. The nomogram developed in the present study was designed to predict CS, offering a robust tool for estimating the dynamic prognosis of patients with HCC following HR. This nomogram demonstrates significant clinical utility by integrating multiple prognostic factors to provide individualized survival estimates, thereby aiding in the optimization of treatment strategies and improving patient outcomes.

Prognostic factors included in the nomogram of our study included age, albumin, ADV score, T stage and node metastasis. Albumin, a key indicator of liver function, demonstrates that tumor factors and liver function significantly impact conditional OS and DSS. The ADV score has demonstrated robust prognostic utility across diverse clinical scenarios in HCC^{12–16,29,30}. This metric provides complementary prognostic information to the AJCC staging system, as each captures distinct aspects of disease burden: the ADV score quantifies tumor biology through tumor markers and volumetric assessment, while AJCC staging evaluates invasion patterns and conventional size metrics. The observed independent prognostic significance of both T stage and ADV

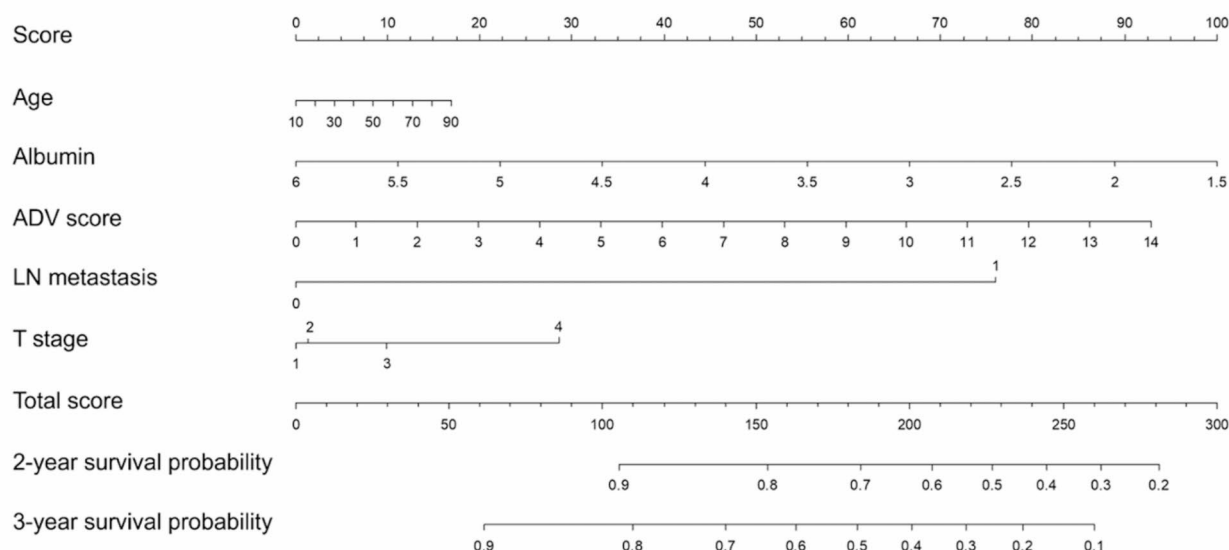
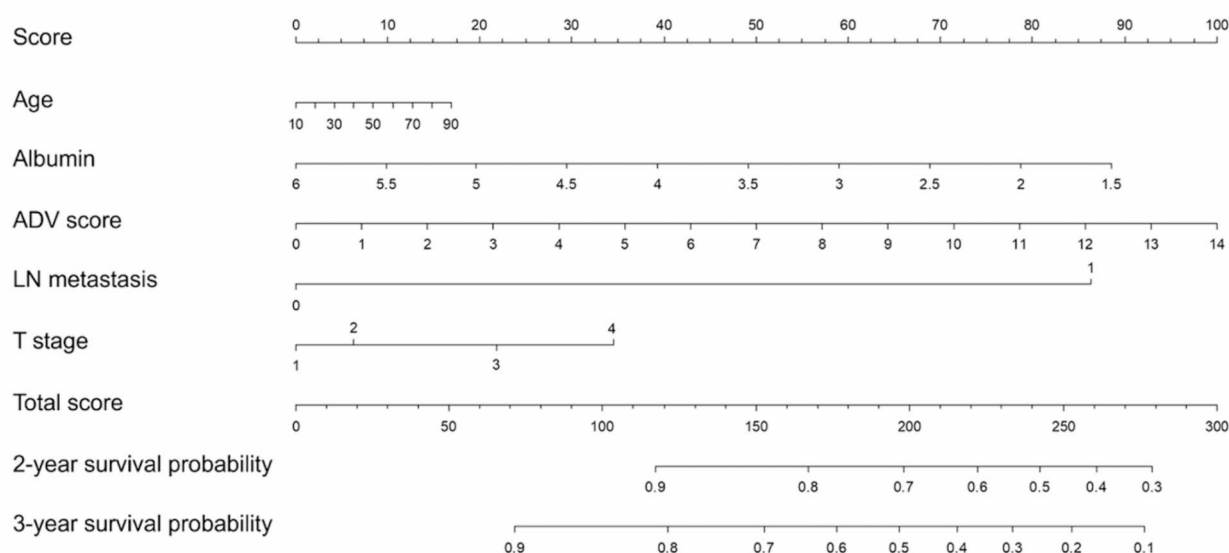
a**b**

Fig. 2. (a) Nomogram for calculating overall 2-year and 3-year conditional survival predictions conditional after 1 year of survival. (b) Nomogram for calculating disease-specific 2-year and 3-year conditional survival predictions conditional after 1 year of survival.

score in our multivariate analysis, despite their shared incorporation of tumor size metrics, validates their non-redundant contributions to outcome prediction. This finding, combined with the demonstrated importance of age and hepatic functional parameters in CS, supports our nomogram's comprehensive approach to dynamic risk stratification in post-resection HCC patients.

Despite the significant contributions of our study, several limitations should be acknowledged. First, our analysis was based on public data from the KLCR. Although this database provides a comprehensive and valuable resource for research, it is subject to inherent limitations of public datasets, including potential inaccuracies in data entry and variations in data collection methods across different institutions. Additionally, public datasets often lack detailed information on certain clinical variables that could be relevant to the study outcomes. Second, the presence of missing values in the dataset could introduce bias, and the imputation methods used may not fully replicate the missing information. Third, the exclusive inclusion of the study population with Korean patients may limit the generalizability of our findings to other ethnic and racial groups.

In conclusion, in this study, we developed and validated the nomogram to predict CS estimates for OS and DSS. The proposed nomogram incorporating the ADV score presents a more accurate and useful prognostic prediction that can be applied in real-world clinical practice for patients with HCC who undergo HR. Additional

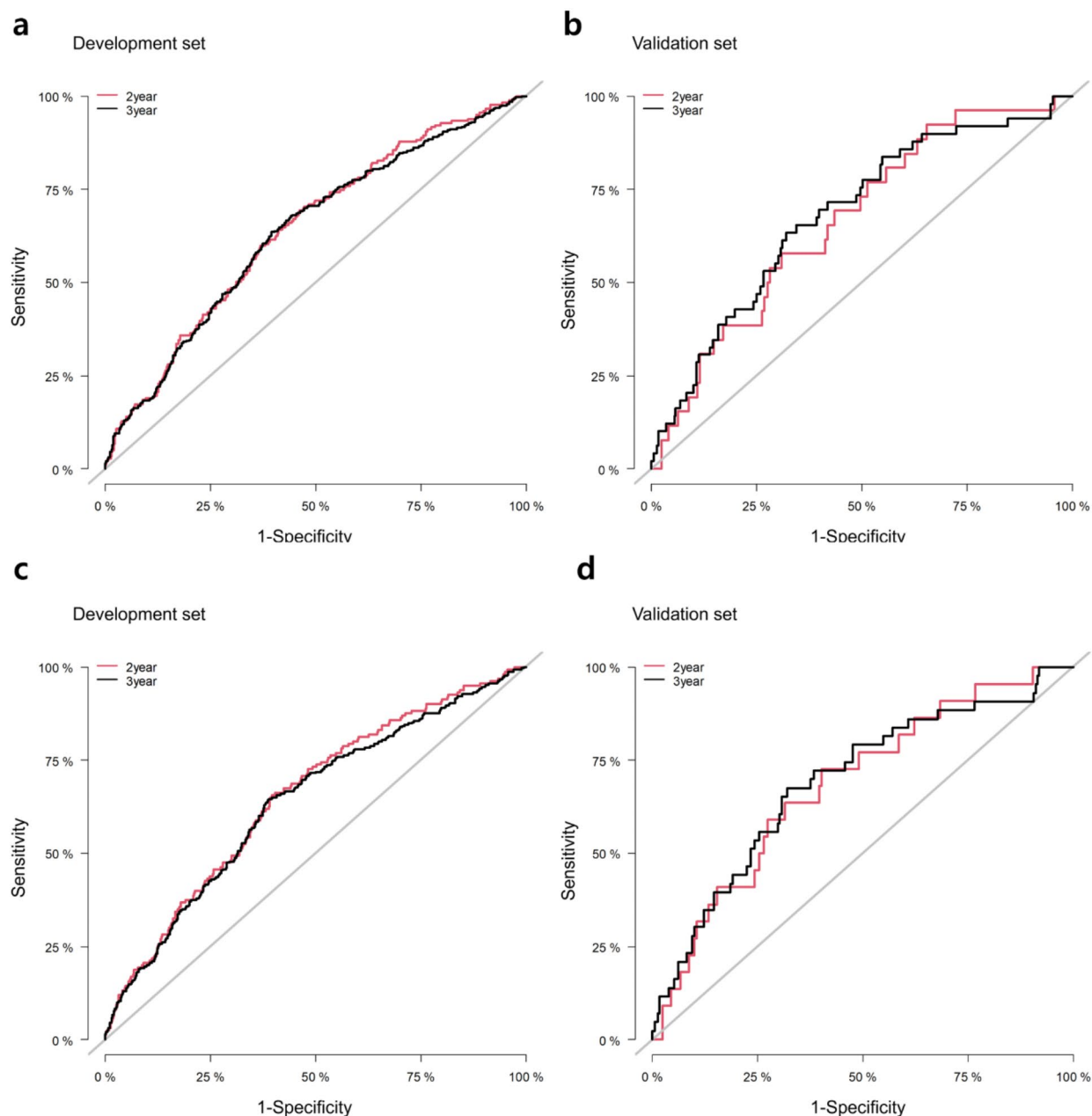


Fig. 3. Time-dependent AUC for conditional overall survival (OS) in the (a) development set and (b) validation set. Time-dependent AUC for conditional disease-specific survival (DSS) in the (c) development set and (d) validation set.

studies are required to evaluate the potential generalizability of the nomogram to patients with HCC from other countries and regions.

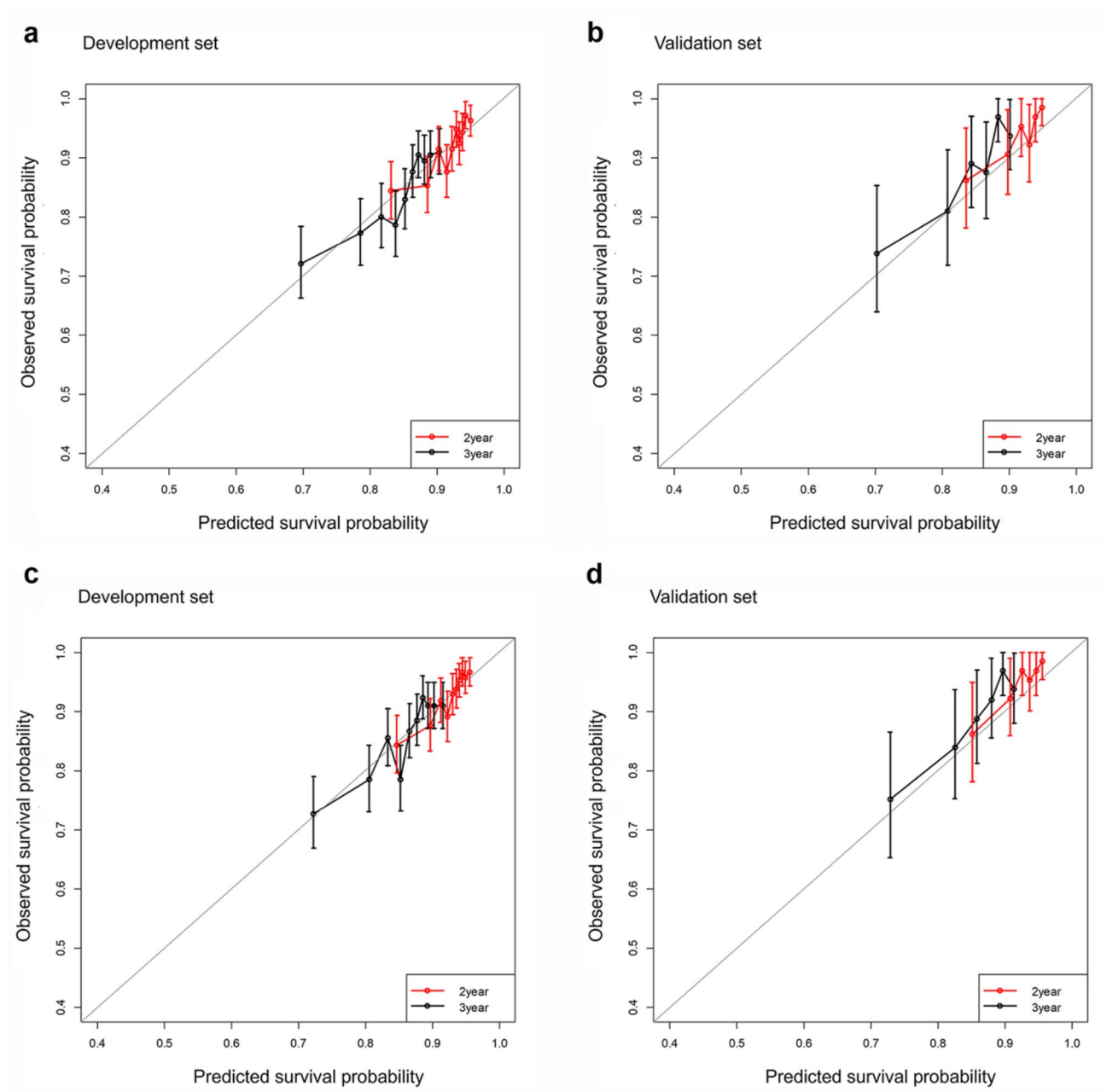


Fig. 4. Calibration curve for conditional OS prediction in the (a) development set and (b) validation set. Calibration curve for conditional DSS prediction in the (c) development set and (d) validation set.

Risk group	n	Events	Predicted survival		Observed survival	
			2-year	3-year	2-year (95% CI)	3-year (95% CI)
1	211	59	0.832	0.697	0.844 (0.796–0.894)	0.720 (0.662–0.784)
2	211	48	0.886	0.786	0.853 (0.807–0.902)	0.773 (0.718–0.831)
3	210	42	0.903	0.817	0.914 (0.877–0.953)	0.800 (0.748–0.856)
4	211	45	0.915	0.839	0.877 (0.834–0.922)	0.787 (0.733–0.844)
5	211	36	0.923	0.852	0.915 (0.878–0.953)	0.829 (0.780–0.882)
6	210	26	0.929	0.864	0.948 (0.918–0.978)	0.876 (0.833–0.922)
7	211	20	0.934	0.873	0.924 (0.889–0.961)	0.905 (0.867–0.946)
8	210	22	0.938	0.882	0.943 (0.912–0.975)	0.895 (0.855–0.938)
9	211	20	0.943	0.891	0.972 (0.949–0.994)	0.905 (0.867–0.946)
10	211	19	0.950	0.904	0.962 (0.937–0.988)	0.910 (0.872–0.949)

Table 4. Risk-stratified calibration table for conditional overall survival (OS) prediction.

Risk group	n	Events	Predicted survival		Observed survival	
			2-year	3-year	2-year (95% CI)	3-year (95% CI)
1	211	57	0.847	0.723	0.843 (0.796–0.894)	0.728 (0.670–0.791)
2	211	45	0.897	0.805	0.876 (0.833–0.922)	0.785 (0.731–0.843)
3	210	30	0.913	0.834	0.918 (0.882–0.956)	0.855 (0.808–0.904)
4	211	45	0.923	0.853	0.891 (0.849–0.934)	0.786 (0.732–0.843)
5	211	28	0.930	0.866	0.929 (0.895–0.964)	0.866 (0.822–0.914)
6	210	24	0.936	0.877	0.938 (0.906–0.971)	0.885 (0.843–0.929)
7	211	16	0.941	0.885	0.952 (0.924–0.982)	0.923 (0.888–0.960)
8	210	19	0.945	0.894	0.967 (0.943–0.991)	0.909 (0.871–0.949)
9	211	19	0.950	0.903	0.957 (0.930–0.985)	0.909 (0.871–0.949)
10	211	19	0.957	0.915	0.967 (0.943–0.991)	0.910 (0.872–0.949)

Table 5. Risk-stratified calibration table for conditional disease-specific survival (DSS) prediction.

Data availability

The data that support the findings of this study are available from the Korean Liver Cancer Association (KLCA) but restrictions apply to the availability of these data, which were used under license for the current study. Data are available from the corresponding author, Jae Hyun Kwon, MD (ponakwon@gmail.com; kwonjh@hallym.or.kr), upon reasonable request and with permission from the KLCA. Data requests may also be submitted to the KLCA directly (klca@livercancer.or.kr).

Received: 8 December 2024; Accepted: 27 February 2025

Published online: 13 March 2025

References

1. Ferlay, J. et al. Global cancer observatory: Cancer today. *Int. Agency Res. Cancer* (2024). <https://gco.iarc.who.int/today>
2. Rumgay, H. et al. Global, regional and National burden of primary liver cancer by subtype. *Eur. J. Cancer*. **161**, 108–118. <https://doi.org/10.1016/j.ejca.2021.11.023> (2022).
3. Marrero, J. A. et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American association for the study of liver diseases. *Hepatology* **68**, 723–750. <https://doi.org/10.1002/hep.29913> (2018).
4. Kudo, M. et al. Management of hepatocellular carcinoma in Japan: JSH consensus statements and recommendations 2021 update. *Liver Cancer*. **10**, 181–223. <https://doi.org/10.1159/000514174> (2021).
5. Hieke, S., Kleber, M., König, C., Engelhardt, M. & Schumacher, M. Conditional survival: A useful concept to provide information on how prognosis evolves over time. *Clin. Cancer Res.* **21**, 1530–1536. <https://doi.org/10.1158/1078-0432.Ccr-14-2154> (2015).
6. Park, Y. K. et al. Conditional survival analysis demonstrates that recurrence risk of surgically treated hepatocellular carcinoma evolves with time. *J. Gastrointest. Surg.* **21**, 1237–1244. <https://doi.org/10.1007/s11605-017-3437-7> (2017).
7. Shah, M. M. et al. Conditional survival analysis of hepatocellular carcinoma. *J. Surg. Oncol.* **122**, 684–690. <https://doi.org/10.1002/jso.26049> (2020).
8. Lee, J. S. et al. Conditional survival estimates improve over time for patients with hepatocellular carcinoma: An analysis for nationwide Korea cancer registry database. *Cancer Res. Treat.* **51**, 1347–1356. <https://doi.org/10.4143/crt.2018.477> (2019).
9. Zhang, G., Li, R., Deng, Y. & Zhao, L. Conditional survival of patients with hepatocellular carcinoma: Results from the surveillance, epidemiology, and end results registry. *Expert Rev. Gastroenterol. Hepatol.* **12**, 515–523. <https://doi.org/10.1080/17474124.2018.1453806> (2018).
10. Cucchetti, A. et al. Conditional survival after hepatic resection for hepatocellular carcinoma in cirrhotic patients. *Clin. Cancer Res.* **18**, 4397–4405. <https://doi.org/10.1158/1078-0432.Ccr-11-2663> (2012).

11. Facciorusso, A. et al. Conditional survival analysis of hepatocellular carcinoma patients treated with radiofrequency ablation. *Hepatol. Res.* **45**, E62–72. <https://doi.org/10.1111/hepr.12458> (2015).
12. Hwang, S. et al. Multiplication of tumor volume by two tumor markers is a post-resection prognostic predictor for solitary hepatocellular carcinoma. *J. Gastrointest. Surg.* **20**, 1807–1820. <https://doi.org/10.1007/s11605-016-3187-y> (2016).
13. Jung, D. H. et al. Small hepatocellular carcinoma with low tumor marker expression benefits more from anatomical resection than tumors with aggressive biology. *Ann. Surg.* **269**, 511–519. <https://doi.org/10.1097/sla.0000000000002486> (2019).
14. Hwang, S. et al. Prognostic accuracy of the ADV score following resection of hepatocellular carcinoma with portal vein tumor thrombosis. *J. Gastrointest. Surg.* **25**, 1745–1759. <https://doi.org/10.1007/s11605-020-04800-6> (2021).
15. Hwang, S. et al. Prognostic prediction models for resection of large hepatocellular carcinoma: A Korean multicenter study. *World J. Surg.* **42**, 2579–2591. <https://doi.org/10.1007/s00268-018-4468-2> (2018).
16. Park, G. C., Hwang, S., Park, Y. H. & Choi, J. U. Validation of prognostic impact of ADV score for resection of hepatocellular carcinoma: Analysis using Korea Liver Cancer Registry database. *Ann. Surg. Treat. Res.* **98**, 235–246. <https://doi.org/10.4174/astr.2020.98.5.235> (2020).
17. Oken, M. M. et al. Toxicity and response criteria of the Eastern cooperative oncology group. *Am. J. Clin. Oncol.* **5**, 649–655 (1982).
18. Zhang, X., El-Serag, H. B. & Thrift, A. P. Predictors of five-year survival among patients with hepatocellular carcinoma in the United States: An analysis of SEER-Medicare. *Cancer Causes Control.* **32**, 317–325. <https://doi.org/10.1007/s10552-020-01386-x> (2021).
19. Nevala, R. et al. Predictors of early and late hepatocellular carcinoma recurrence. *World J. Gastroenterol.* **29**, 1243–1260. <https://doi.org/10.3748/wjg.v29.i8.1243> (2023).
20. Nagasue, N. Liver resection for hepatocellular carcinoma: Indications, techniques, complications, and prognostic factors. *J. Hepatobiliary Pancreat. Surg.* **5**, 7–13. <https://doi.org/10.1007/pl00009954> (1998).
21. Tellapuri, S., Sutphin, P. D., Beg, M. S., Singal, A. G. & Kalva, S. P. Staging systems of hepatocellular carcinoma: A review. *Indian J. Gastroenterol.* **37**, 481–491. <https://doi.org/10.1007/s12664-018-0915-0> (2018).
22. Chavez-Villa, M. & Domínguez-Rosado, I. Overview of current hepatocellular carcinoma staging systems: Is there an optimal system? *Surg. Oncol. Clin. N. Am.* **33**, 29–41. <https://doi.org/10.1016/j.soc.2023.06.010> (2024).
23. Liu, P. H. et al. Prognosis of hepatocellular carcinoma: Assessment of eleven staging systems. *J. Hepatol.* **64**, 601–608. <https://doi.org/10.1016/j.jhep.2015.10.029> (2016).
24. Ding, J. & Wen, Z. Survival improvement and prognosis for hepatocellular carcinoma: Analysis of the SEER database. *BMC Cancer.* **21**, 1157. <https://doi.org/10.1186/s12885-021-08904-3> (2021).
25. Wang, J. et al. A nomogram for predicting cancer-specific survival of osteosarcoma and Ewing's sarcoma in children: A SEER database analysis. *Front. Public Health.* **10**, 837506. <https://doi.org/10.3389/fpubh.2022.837506> (2022).
26. Wu, J. et al. A nomogram for predicting overall survival in patients with low-grade endometrial stromal sarcoma: A population-based analysis. *Cancer Commun. (Lond.)* **40**, 301–312. <https://doi.org/10.1002/cac2.12067> (2020).
27. Lv, J. et al. A nomogram model for predicting prognosis of obstructive colorectal cancer. *World J. Surg. Oncol.* **19**, 337. <https://doi.org/10.1186/s12957-021-02445-6> (2021).
28. Zhang, W. et al. Nomogram predicts risk and prognostic factors for bone metastasis of pancreatic cancer: A population-based analysis. *Front. Endocrinol. (Lausanne)* **12**, 752176. <https://doi.org/10.3389/fendo.2021.752176> (2021).
29. Hwang, S. et al. Salvage living donor liver transplantation for hepatocellular carcinoma recurrence after hepatectomy: Quantitative prediction using ADV score. *J. Hepatobiliary Pancreat. Sci.* **28**, 1000–1013. <https://doi.org/10.1002/jhbp.863> (2021).
30. Hwang, S. et al. Quantitative prognostic prediction using ADV score for hepatocellular carcinoma following living donor liver transplantation. *J. Gastrointest. Surg.* **25**, 2503–2515. <https://doi.org/10.1007/s11605-021-04939-w> (2021).

Acknowledgements

The database used in this study was provided by the Korean Liver Cancer Association and the Korea Central CancerRegistry, Ministry of Health and Welfare, Korea.

Author contributions

Jae Hyun Kwon and Shin Hwang made substantial contributions to conception and design, and acquisition of data. Eun-Kyoung Jwa, Eunyoung Tak, and Jong Woo Lee made substantial contributions to the analysis and interpretation of data and drafting of the article. Jae Hyun Kwon and Shin Hwang made substantial contributions to the collection of data, analysis of the results, revising the article critically for important intellectual content, and reviewing the article.

Funding

This research was supported by Hallym University Research Fund 2022 through grant HURF-2022-19 awarded to Jae Hyun Kwon.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-92500-z>.

Correspondence and requests for materials should be addressed to J.H.K.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025, corrected publication 2025