A novel nomogram based on machine learning predicting overall survival for hepatocellular carcinoma patients with dynamic α-fetoprotein level changes after local resection

QI WANG[1,2*], LINA SUN[1,2*], GONGMING ZHANG[3*], ZHUANGZHUANG CHEN[3], GUANGMING LI[3] and RONGHUA JIN[1,2]

[1]Beijing Key Laboratory of Emerging Infectious Diseases, Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, P.R. China; [2]Beijing Institute of Hepatology, Beijing You'an Hospital, Capital Medical University, Beijing 100069, P.R. China; [3]Department of General Surgery, Beijing You'an Hospital, Capital Medical University, Beijing 100069, P.R. China

Received August 7, 2024; Accepted March 20, 2025

DOI: 10.3892/ol.2025.15056

Abstract. The principal aim of the present study was to develop and validate a nomogram predicting overall survival (OS) in patients with α-fetoprotein (AFP)-negative hepatocellular carcinoma (AFP-NHCC) who experience dynamic changes in AFP level after hepatectomy. A cohort of 870 patients were enrolled and randomly assigned into a training cohort (n=600) and a validation cohort (n=270) at a 7:3 ratio. The key variables contributing to the nomogram were determined through random survival forest analysis and multivariate Cox regression. The discriminative ability of the nomogram was evaluated using time-dependent receiver operating characteristic curves and the area under the curves. Furthermore, the nomogram was comprehensively assessed using the concordance index (C-index), calibration curves and clinical decision curve analysis (DCA). Kaplan-Meier (KM) curves analysis was employed to discern survival rates across diverse risk strata of patients. Ultimately, the nomogram incorporated critical factors including sex, tumor size, globulin levels, gamma-glutamyl transferase and fibrinogen levels. In the training and validation cohorts, the C-indexes were 0.72 [95% confidence interval (CI): 0.685-0.755) and 0.664 (95% CI: 0.611-0.717], respectively, attesting to its predictive validity. The nomogram demonstrated excellent calibration and DCA further confirmed its clinical usefulness. Additionally, KM curve analysis unveiled statistically significant differences in OS among three distinct risk groups. In conclusion, the present study successfully formulated a nomogram predicting 3-, 5- and 8-year OS in patients with AFP-NHCC with dynamic changes in AFP level post-local resection. This model serves as a valuable tool for clinicians to promptly identify high-risk patients, thereby facilitating timely interventions and potentially enhancing patient survival outcomes.

Correspondence to: Professor Guangming Li, Department of General Surgery, Beijing You'an Hospital, Capital Medical University, 8 Xitoutiao, Youanmenwai Street, Fengtai, Beijing 100069, P.R. China
E-mail: liguangming@ccmu.edu.cn

Professor Ronghua Jin, Beijing Key Laboratory of Emerging Infectious Diseases, Institute of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, 8 Jingshundong Street, Chaoyang, Beijing 10015, P.R. China
E-mail: ronghuajin@ccmu.edu.cn

*Contributed equally

Abbreviations: OS, overall survival; AFP, α-fetoprotein; HCC, hepatocellular carcinoma; AFPN-HCC, AFP-negative HCC; RSF, random survival forest; ROC, receiver operating characteristic; AUC, area under the curves; DCA, decision curve analysis; KM, Kaplan-Meier; GGT, gamma-glutamyl transferase; TACE, transarterial chemoembolization; BCLC, Barcelona Clinic Liver Cancer; SD, standard deviation; C-index, concordance index

Key words: nomogram, α-fetoprotein-negative hepatocellular carcinoma, hepatectomy, overall survival, dynamic α-fetoprotein level changes

Introduction

Primary liver cancer has emerged as a substantial economic burden in global public health, characterized by its high incidence and mortality rates (1). In these cases, hepatocellular carcinoma (HCC) is the predominant form, accounting for 75-80% (2). Notably, China bears a disproportionately high incidence of HCC, contributing to >50% of cases worldwide (3). Currently, there are various treatment options for HCC, including surgical resection, ablation, transarterial chemoembolization (TACE), liver transplantation, systemic therapy and combination therapy (4-6). Among these options, liver resection is the preferred choice for patients with well-functioning livers and localized tumors, offering the potential for cure (7). However, in most Asian centers, overall survival (OS) rates for patients remain unsatisfactory (8). Approximately half of all HCC patients experience recurrence or metastasis within 5 years after curative resection (9,10).

Therefore, it is imperative to identify risk factors that impact OS in HCC patients after liver resection.

α-fetoprotein (AFP), as a pivotal biomarker in the detection of HCC, plays an essential role in accurate diagnosis, early identification, evaluation of treatment effectiveness, recurrence monitoring and prognosis prediction for HCC (11). Nonetheless, it is noteworthy that ~30% of HCC patients do not exhibit elevated serum AFP levels (12). The delayed diagnosis of AFP-negative HCC (AFP-NHCC) often results in treatment postponements, affecting patient prognosis (13). Even during postoperative follow-up, patients with AFP-NHCC continue to undergo regularly AFP level monitoring, given the close correlation between AFP and tumor prognosis (14,15). The findings of the present study indicated that certain patients with AFP-NHCC experience dynamic changes in AFP levels after resection. While current studies have focused on identifying prognostic factors in patients with AFP-NHCC after hepatectomy. A consensus on the prognostic factors for patients experiencing postoperative AFP level elevation remains elusive and research on the risk factors related to OS for this patients cohort is lacking.

The Random Survival Forest (RSF) is a powerful machine-learning algorithm composed of multiple decision trees, demonstrating relatively high accuracy, robustness and strong resistance to over-fitting. Therefore, by combining the RSF with traditional multivariate Cox regression, more reliable prognostic factors related to OS can be identified and a nomogram can be constructed using the aforementioned variables. A nomogram is a common visual representation of clinical prediction models. Constructed from a comprehensive combination of multiple clinical indicators, the nomogram enables physicians to deliver more direct and accurate prognoses for specific patients. This assists in adjusting treatments accordingly, aiming for improved clinical outcomes. Consequently, the present study aimed to predict the OS of HCC patients who initially tested negative for AFP at baseline but exhibited a subsequent change to AFP positivity during follow-up after curative resection. This prediction was based on clinical data and provides improved guidance for patient management.

Materials and methods

Patients. The present study retrospectively analyzed 870 HCC patients who underwent resection at Beijing You'an Hospital, Capital Medical University, China between January 2013 and January 2021. The age of all patients ranged from 22 to 78 years, with a mean age of 56.61±9.08 years, and the male-to-female ratio was 3.58:1. The cohort was randomly divided into a training set and a validation set at a ratio of 7:3. The training set was used for variable selection and model construction, while the validation set was used to confirm the performance of the developed model. Baseline characteristic in the training set and verify set are given in Table I.

The present study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of Beijing You'an Hospital, Capital Medical University, China (approval no. LL-2021-152-K) and followed the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The inclusion criteria for the present study were as follows: i) Pathological diagnosis of HCC, ii) Surgical resection of single or multiple isolated HCC lesions in one liver lobe, iii) Preoperative serum AFP level <20 ng/ml. During follow-up (>2 months after resection), patients exhibited elevation of AFP level and iv) Early-stage HCC patients. Exclusion criteria included: i) Previous receipt of other treatments such as ablation and TACE ii) concomitant other malignancies and iii) missing information.

Data collection. Prior to patients undergoing HCC resection, baseline data and tumor characteristics of all patients were obtained from the medical records system, including age, sex, medical history, family history, presence of cirrhosis, Barcelona Clinic Liver Cancer (BCLC) staging, Child-Pugh classification (16), tumor number and size, AFP levels, as well as routine blood test parameters, liver function indices and coagulation indicators. The outcome of resection was primarily obtained through telephone follow-up. The postoperative AFP levels were mainly retrieved from the electronic medical records when patients are readmitted to the hospital.

Follow-up and endpoint. All patients underwent curative liver resection after completing preoperative evaluations. Postoperatively, patients were regularly followed up with various assessments, including physical examinations and monitoring of serum AFP levels. The clinical endpoint was OS, with follow-up data collected until January 2023. OS was defined as the time between the first liver cancer resection and either death or the last follow-up date.

Statistical analysis. Data analysis used IBM SPSS Statistics 27 (IBM Corp.) and R version 4.1.2 (17). Normally distributed data were presented as mean ± standard deviation, while skewed data was represented using quartiles. The Mann-Whitney U test or Student's t-test was employed to compare numerical variables between the derivation set and internal validation set, while Fisher's exact test or χ^2 test was used for assessing categorical variables. Significant predictive factors were identified using RSF and multivariate Cox regression. These variables were subsequently incorporated into a nomogram model. Based on a total score of 130, patients were assigned to the low, medium and high-risk groups using cutoff values of 43 and 86. Kaplan-Meier (KM) analysis and log-rank tests were used to compare differences in OS among the three different risk groups. The areas under the curves (AUCs) of the time-dependent receiver operating characteristic (ROCs) curves were employed to evaluate model accuracy. Additionally, the concordance index (C-index) was used to assess model discrimination, while calibration curves were employed to evaluate consistency between training and validation sets. Clinical utility assessment was conducted through decision curve analysis (DCA), quantifying net benefits at different probability thresholds.

Results

Baseline characteristics and survival outcomes of patients. The final analysis involved 870 eligible patients with AFP-NHCC, divided into the model development group

Table I. Baseline characteristic in the training set and validation set.

Variable	Group	Training set (n=600)	Validation set (n=270)	P-value
Age, n (%)	≤60 years	373 (62.17)	168 (62.22)	0.988
	>60 years	227 (37.83)	102 (37.78)	
Sex, n (%)	Male	469 (78.17)	211 (78.15)	0.995
	Female	131(21.83)	59 (21.85)	
Hypertension, n (%)	Yes	162 (27.00)	72 (26.67)	0.918
	No	438 (73.00)	198 (73.33)	
Diabetes, n (%)	Yes	140 (23.33)	52 (19.26)	0.180
	No	460 (76.67)	218 (80.74)	
Smoking, n (%)	Yes	251 (41.82)	119 (44.07)	0.536
	No	349 (58.17)	151 (55.93)	
Drinking, n (%)	Yes	189 (31.50)	94 (34.81)	0.334
	No	411 (68.50)	176 (65.19)	
Cirrhosis, n (%)	Yes	514 (85.67)	238 (88.15)	0.323
	No	86 (14.33)	32 (11.85)	
Child-Pugh, n (%)	A	462 (77.00)	196 (72.59)	0.161
	B	138 (23.00)	74 (27.41)	
BCLC, n (%)	0	233 (38.83)	95 (35.19)	0.304
	A	367 (61.17)	175 (64.81)	
Tumor number, n (%)	Single	498 (83.00)	210 (77.78)	0.067
	Multiple	102 (17%)	60 (22.22)	
Tumor size, n (%)	≤3 cm	443 (73.83)	198 (73.33)	0.877
	>3 cm	157 (26.17)	72 (26.67)	
RBC (mean ± SD), 10^{12}/l	-	4.18±0.63	4.14±0.60	0.376
HB (mean ± SD), g/l	-	131.51±19.73	129.97±18.77	0.280
WBC (mean ± SD), 10^9/l	-	5.12±2.16	4.88±1.98	0.113
AST (mean ± SD), IU/l	-	31.38±15.00	33.07±16.54	0.136
ALT (mean ± SD), IU/l	-	30.57±18.82	33.29±22.17	0.063
TBIL (mean ± SD), μmol/l	-	19.45±10.06	19.42±10.28	0.975
DBIL (mean ± SD), μmol/l	-	6.66±4.66	6.69±4.97	0.910
Total Protein (mean ± SD), g/l	-	65.37±6.80	65.21±8.23	0.774
GGT (mean ± SD), U/l	-	63.97±57.50	68.64±54.33	0.260
ALP (mean ± SD), IU/l	-	86.98±35.86	87.95±34.59	0.711
Glob (mean ± SD), g/l	-	28.08±5.37	28.25±5.05	0.657
PT (mean ± SD), s	-	12.60±1.57	12.53±1.44	0.526
PTA (mean ± SD), %	-	85.94±15.12	86.68±14.60	0.502
INR (mean ± SD)	-	1.12±0.14	1.11±0.13	0.359
Fibrinogen (mean ± SD), mg/dl	-	2.78±0.92	2.76±0.91	0.827

Continuous variables were presented as mean ± standard deviation. Categorical variables were described as frequency and percentage. BCLC stages, Barcelona Clinic Liver Cancer stages; RBC, red blood cell; HB, Hemoglobin; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; TBIL, direct bilirubin; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; Glob, globulin; PT, prothrombin time; PTA, prothrombin activity; INR, international normalized ratio.

(n=600) and the validation group (n=270). Baseline data comprised 26 items. In the entire cohort, 62.18% of patients were <60 years old and 78.16% were male. Additionally, 86.44% of patients had a background of cirrhosis, with the majority falling into Child-Pugh A (75.63%) and 62.30% of patients were in BCLC stage A. No statistical differences were observed between the model development and validation groups (all P>0.05), indicating consistency between the two groups. Detailed demographic and clinical characteristics between the model development group and the validation group are presented in Table I.

The 3-, 5- and 8-year overall survival rates for all patients were 90.3, 76.7 and 60.5%, respectively. The KM curve of overall survival for the patients is shown in Fig. S1.

Identification of predictors and development of the nomogram. The variables in the model-building group were analyzed, tested and adjusted. Finally, RSF identified the top five prognostic

Table II. Multivariate Cox regression analysis of risk factors for OS in the training cohort.

Variable	P-value	HR	95%CI
Sex	0.004	0.653	0.491-0.869
Tumor size	0.018	1.919	1.659-3.282
Glob	0.015	1.431	1.073-1.729
GGT	0.032	1.671	1.098-1.983
Fibrinogen	0.035	1.114	1.095-1.306

Glob, Globulin; GGT, gamma-glutamyl transferase; HR, hazard ratio; CI, confidence interval.

factors, including sex, tumor size, globulin, gamma-glutamyl transferase (GGT) and fibrinogen (Fig. 1). The reliability of the aforementioned variables was also confirmed by the multifactorial COX regression (Table II). The present study incorporated the aforementioned parameters to combine into a new model and visualized the model with nomogram (Fig. 2). By calculating the total scores, surgeons can easily obtain the probability of OS as predicted by the nomogram.

Evaluation of the nomogram. The predictive performance of the nomogram was assessed using the C-index, revealing a C-index of 0.72 (95% CI: 0.685-0.755) for the model-development group. ROC curve analysis demonstrated area AUCs of 0.731, 0.748 and 0.775 at 3, 5 and 8 years, respectively (Fig. 3A). Calibration curves illustrated good consistency between predicted and actual values for the 3-, 5- and 8-year OS rates (Fig. 4A-C). DCA further indicated the nomogram as a valuable predictive tool (Fig. 5A-C). Moreover, stratifying patients into high-risk, intermediate-risk and low-risk groups showed significant statistical differences in survival rates in the training set ($P<0.001$; Fig. 6A).

Validation of the nomogram. To ascertain the reliability of the nomogram, internal validation process was undertaken. The C-index for the validation cohort was 0.664 (95% CI: 0.611-0.717), indicating that the predicted results of the nomogram were consistent with the actual observed outcomes, confirming the good discriminative ability of the model. The corresponding AUCs for 3-, 5- and 8-year ROC curves were 0.664, 0.708 and 0.753, respectively, attesting to its strong classification capability (Fig. 3B). The calibration curves also exhibited good alignment between predicted and observed values (Fig. 4D-F). DCA curves validated good clinical utility as well as a fine balance between benefits and risks (Fig. 5D-F). Lastly, the OS rates stratified by risk groups were consistent with those in the model development group, also showing notable disparities ($P<0.01$; Fig. 6B).

Discussion

Approximately 30% of HCC cases are AFP-NHCC, representing a clinically distinct subgroup that is frequently underdiagnosed owing to nonspecific clinical manifestations. Consequently, the delayed diagnosis and treatment poses threat to their survival (12,18). Among these patients, some exhibit dynamic changes from AFP negativity to AFP positivity indicating a unique population within patients with AFP-NHCC. AFP levels have been associated with the pathological grading, progression and prognosis of the patients, suggesting that this subgroup of patients differ from AFP-negative patients (14,15). After surgical resection for HCC, patients may sustain varying degrees of damage to both the tumor and its surrounding tissues, leading to inflammation. Additionally, the liver initiates a regenerative process to repair the damaged areas following the resection (19,20). These responses can both stimulate hepatocyte proliferation and the secretion of AFP, ultimately resulting in a temporary elevation of AFP levels post-surgery. However, this is not indicative of a poor prognosis. Furthermore, guidelines indicate that for AFP-positive liver cancer patients, AFP levels typically return to normal within two months after hepatic resection (21). To ensure that fluctuations in AFP levels in AFP-negative HCC patients after hepatic resection were not transient increases, the present study established a two-month observation period as a basis for assessing AFP level fluctuations. AFP levels, to a certain extent, reflect the size of the tumor and their dynamic changes are related to the disease status, serving as a sensitive indicator for assessing treatment efficacy and prognosis (21-24). Additionally, early-stage liver cancer or liver cancer confined to a single lobe, with small lesions and no metastasis, generally responds well to treatment. By contrast, advanced liver cancer, characterized by larger lesions often accompanied by metastasis, presents markedly greater treatment challenges. Despite various treatment options such as immunotherapy and targeted therapy, overall treatment outcomes remain limited and patient survival rates are unsatisfactory (25-28). Survival predictions for early-stage liver cancer can help doctors devise more reasonable treatment plans and improve treatment outcomes. However, for patients with advanced liver cancer, even with survival predictions, the rapid progression of the disease and poor treatment efficacy may lead to significant discrepancies between predicted and actual survival outcomes. Furthermore, clinical practice focusses more on early detection of disease changes, enhancing treatment efficacy and improving patient prognosis. Therefore, research on survival predictions for early-stage liver cancer confined to a single lobe aligns more closely with the needs of clinical practice. Therefore, the present study aimed to focus on this special patient cohort and develop a nomogram to predict their OS. Moreover, for these patients, treatments such as liver transplantation and extended resection should be considered and follow-up frequency should be increased (29,30).

The nomogram developed in the present study incorporated sex, tumor size, globulin, GGT and fibrinogen. It assigned scores to each level of these key factors based on their contribution to the outcome variable within the model. By aggregating these scores, the total score was then translated into the predicted OS probability using a function transformation relationship. The model demonstrated robust predictive capability through multidimensional validation. As evidenced by the calibration curve and ROC analysis, the model displayed robust diagnostic performance. DCA analysis also indicated

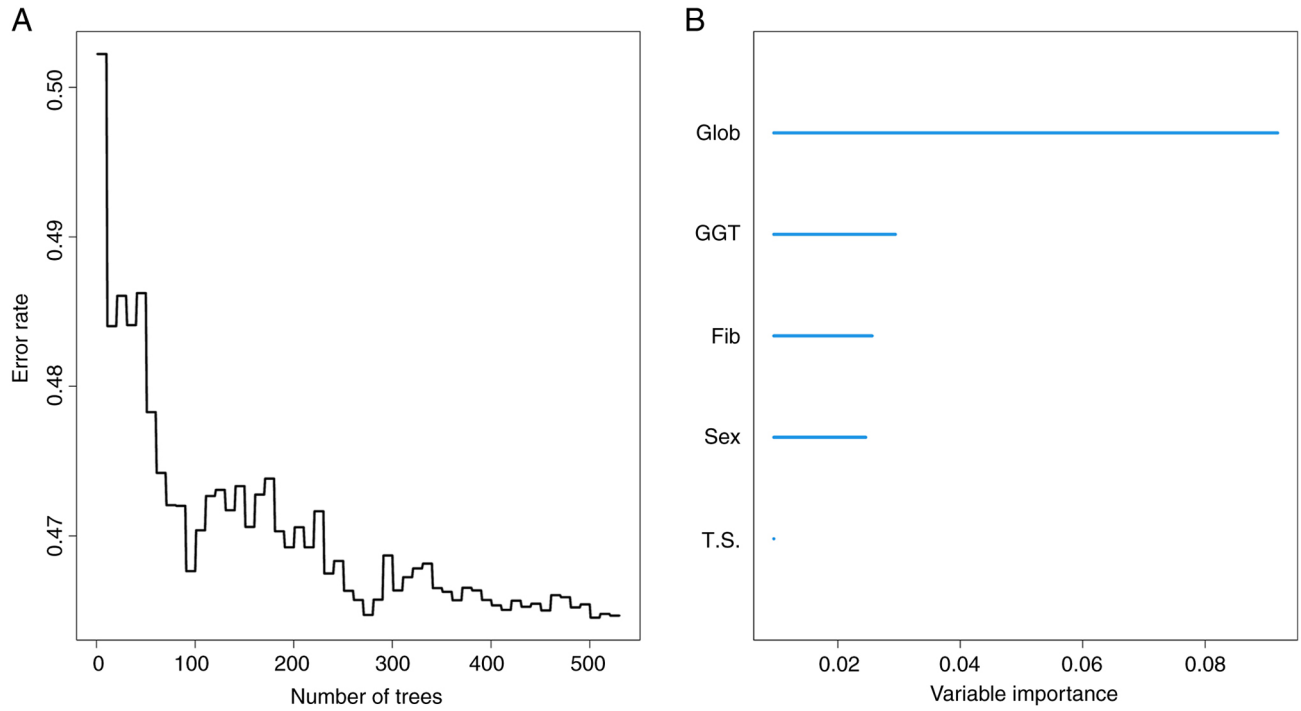

Figure 1. The RFS model for variables. (A) Error rate when number of trees=530. (B) Variable importance for each variable. RSF, random survival forest; Glob, globulin; GGT, gamma-glutamyl transferase; Fib, fibrinogen; T.S., tumor size.

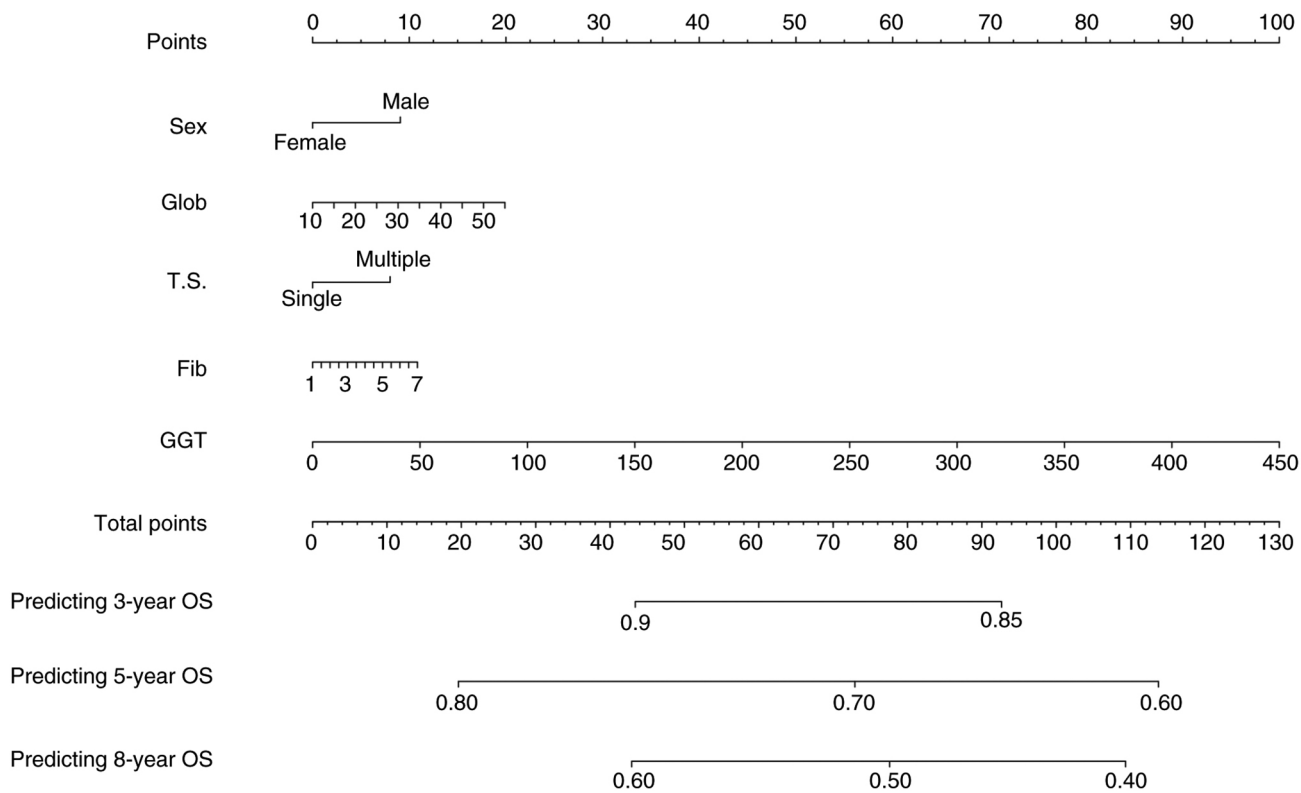

Figure 2. Nomogram, including sex, Glob, T.S., Fib and GGT for 3-, 5- and 8-years OS in patients with AFP-NHCC with dynamic AFP level changes. Glob, globulin; GGT, gamma-glutamyl transferase; AFPN-HCC, α-fetoprotein-negative hepatocellular carcinoma; Fib, fibrinogen; T.S., tumor size; OS, overall survival.

satisfactory predictive ability, while the variable availability made this model user-friendly for practical clinical applications. KM analysis further confirmed the ability of this model in clinical practice. Stratifying patients based on total scores into low, intermediate and high-risk groups revealed markedly distinct OS rates.

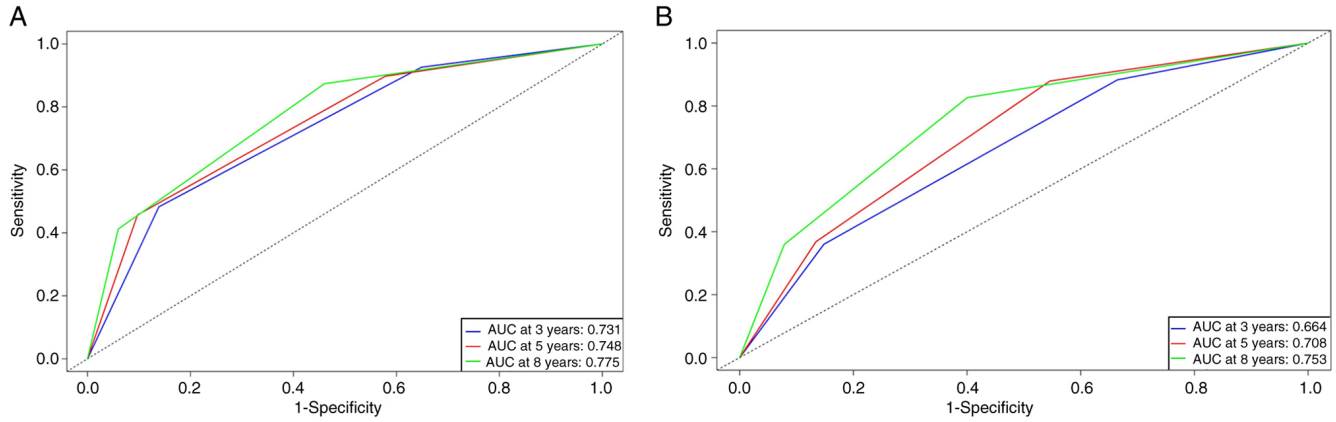

Figure 3. Time-dependent ROC curves for the nomograms in the test and proof cohorts. (A) The AUCs for OS at 3, 5 and 8 years in the test cohort. (B) The AUCs for OS at 3, 5 and 8 years in the proof cohort. ROC, receiver operating characteristics; AUC, area under the curve; OS, overall survival.

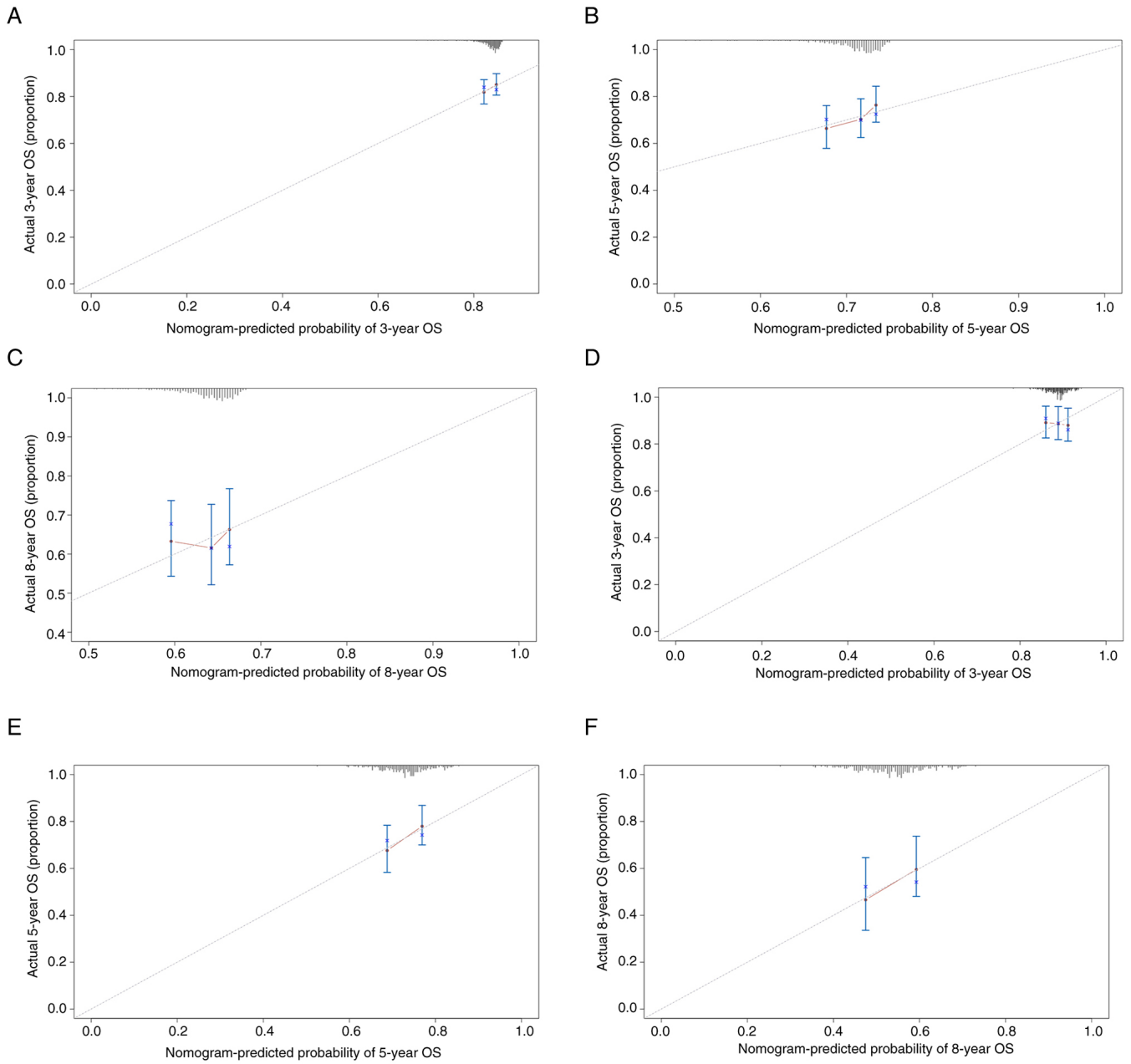

Figure 4. Calibration curve of the nomogram in the training and validation cohort. (A) 3-year OS in the test cohort. (B) 5-year OS in the test cohort. (C) 8-year OS in the test cohort. (D) 3-year OS in the proof cohort. (E) 5-year OS in the proof cohort. (F) 8-year OS in the proof cohort. OS, overall survival.

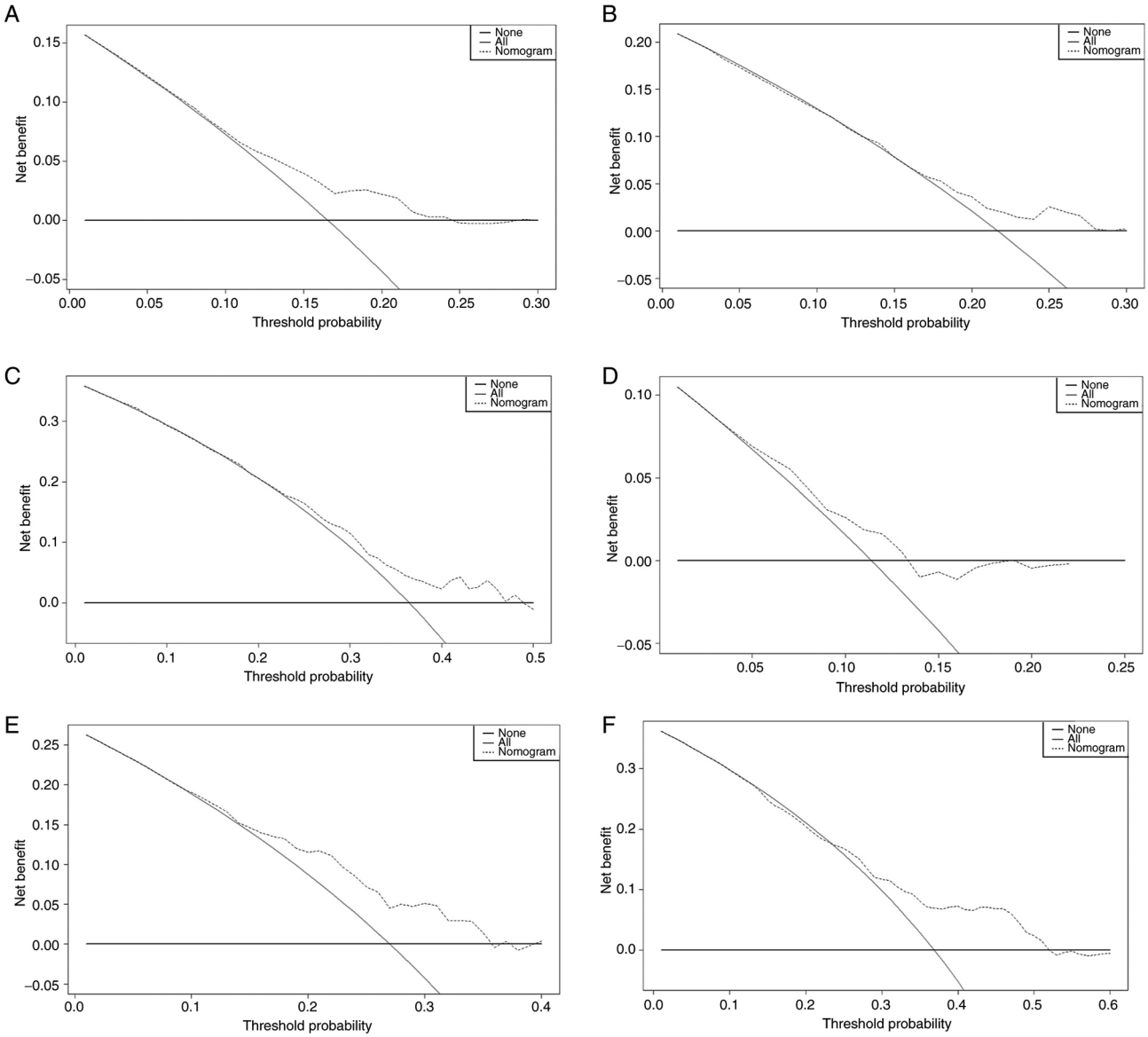

Figure 5. DCA for nomogram depicts the clinical net benefit. (A) 3-year DCA in the test cohort. (B) 5-year DCA in the test cohort. (C) 8-year DCA in the test cohort. (D) 3-year DCA in the proof cohort. (E) 5-year DCA in the proof cohort. (F) 8-year DCA in the proof cohort. DCA, decision curve analysis.

Previous studies (31-35) have primarily focused on the prognosis of AFP-NHCC patients after hepatectomy, neglecting the dynamic changes in AFP levels. To address this gap, the present study developed a more accurate predictive model for this subgroup to improve their prognosis. The cohort was not only massive in scale but also had a long follow-up period, lending greater credibility to the conclusions. In addition, published reports (36-40) have shown the trustworthiness of the aforementioned five indicators in predicting OS for patients with HCC. Generally, male patients have poorer prognoses. Beyond liver cancer, they are more prone to non-reproductive system tumors and worse prognoses, possibly due to factors related to Y chromosome genes and testosterone (28,41,42). Studies suggest that testosterone promotes CD8+ T cell exhaustion, leading to faster tumor cell growth (43,44). Additionally, another study indicates a correlation between higher levels of Inc-FTX, a regulator transcribed from the X chromosome inactivation center XIST, and longer prognosis in HCC patients. Inc-FTX acts as a tumor suppressor, with higher expression levels observed in the female liver (45). Tumor size is a critical determinant of the 2-year postoperative recurrence rate in isolated HCC. Specially, patients with a tumor diameter >5 cm and AFP ≥20 ng/ml have a 4.5 times higher mortality rate than those with a tumor diameter <5 cm (46,47). Retrospective analysis of patients surviving postoperative HCC for over 10 years found that isolated and small tumors are critical factors for long-term postoperative survival (48). The globulin levels in HCC patients are markedly elevated compared with healthy individuals. As HCC continues to progress, it can activate the body's immune mechanism, leading to the production of a large number of inflammatory factors, further burdening the liver and affecting its normal physiological functions. This leads to a further increase in globulin levels, which in turn affects the patient's liver function, thereby exacerbating HCC. GGT, a key enzyme associated with liver metabolism,

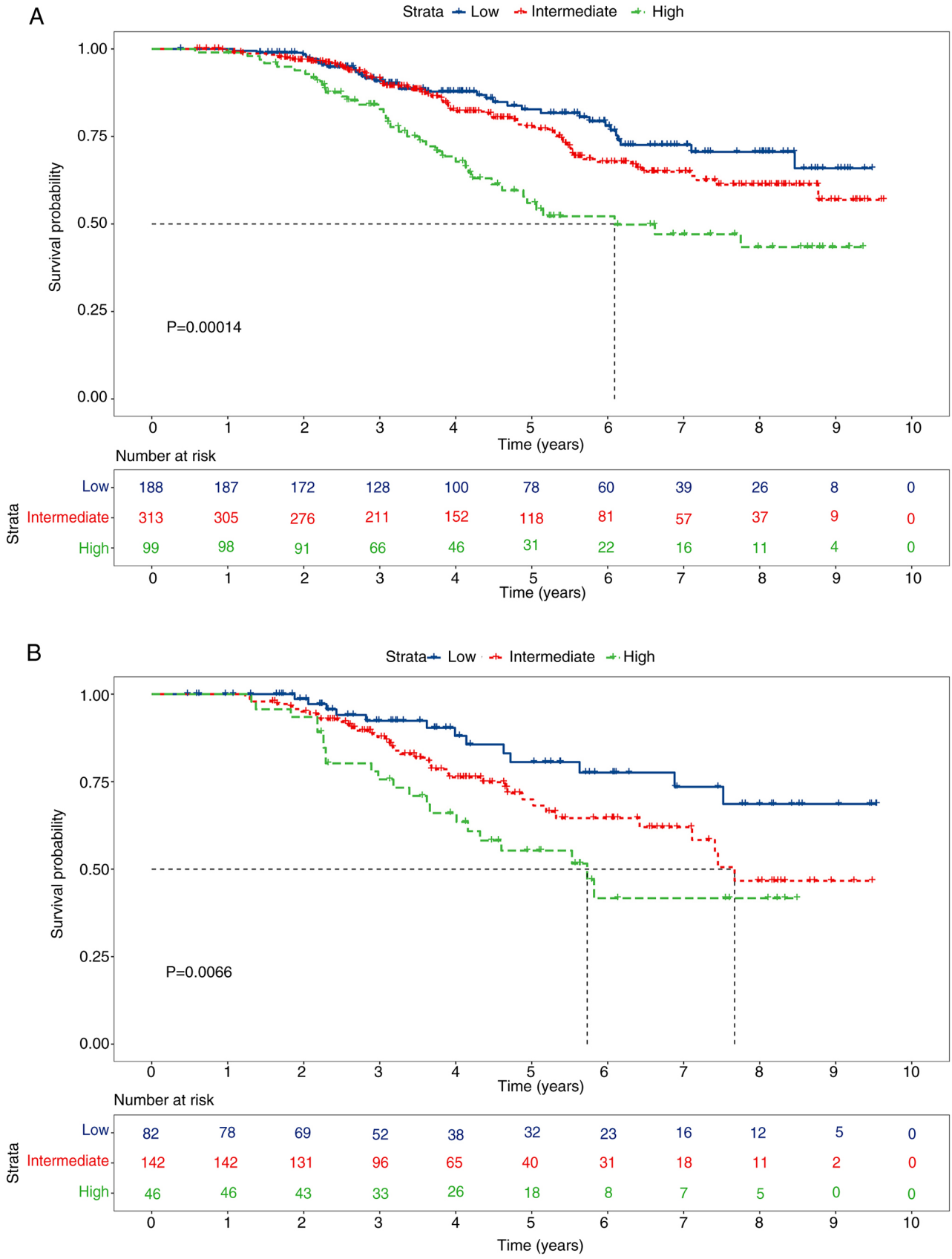

Figure 6. Kaplan-Meier survival curves for patients with high-, intermediate- and low-risk by the nomogram score. (A) Test cohort. (B) Proof cohort.

has recently been implicated in oxidative stress, extracellular inflammation and tumor progression (49). Inflammation stimuli within or surrounding HCC may induce abundant GGT production in hepatocytes and the cancer cells themselves also synthesize GGT, further increasing serum GGT levels. Moreira *et al* (50) demonstrated that serum GGT levels

increase with the progression of liver cancer and promote tumor advancement in the male Wistar rat HCC animal model. Moreover, GGT levels are closely linked to the prognosis of patients with AFP-NHCC (51-53). AFP-low-level HCC patients, those with high GGT levels, are more likely to experience lower survival rates (54), in accordance with the findings of the present study. Fibrinogen, a common coagulation-related protein, apart from participating in blood clotting, is closely associated with tumors (55). Studies (56-60) reveal a significant increase in preoperative plasma fibrinogen in various malignant tumors, closely correlating with tumor progression, metastasis and prognosis. Elevated fibrinogen usually implies a hypercoagulable and inflammatory state, which inevitably affects the patient's postoperative recovery and prognosis, prolongs the postoperative hospital stay and affects the OS of the patient.

Limitations existed in the present study. First, retrospective studies inevitably introduce selection bias, mitigated to some extent by the ample sample size of the present study. Second, although the model exhibited good internal performance during validation, external validation in additional cohorts is necessary to enhance the credibility and persuasiveness of the model, as well as to validate its generalization ability. Third, the present study did not include recurrence patterns or surgery-related indicators, such as the extent of operation, surgical margin, need of blood transfusion and tumor pathology. More comprehensive indicators should be encompassed in any future study. Nevertheless, the model still provided more timely treatment guidance for patients with AFP-NHCC who exhibit dynamic AFP changes due to the identification of high-risk patients in this subgroup.

Acknowledgements

Not applicable.

Funding

The present study was funded by the National Science and Technology Major Project (grant nos. 2023ZD0502405 and 2023ZD0502402) and 2023 Young and middle-aged Talents Incubation Project (Youth Innovation) of Beijing You'an Hospital, Capital Medical University (grant no. BJYAYY-YN2023-13).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

Conceptualization and design were performed by RJ and GL. Data collection was performed by QW, LS, GZ and ZC. Data analysis and interpretation were conducted by QW, LS and GZ. The manuscript was drafted by QW, ZC and LS. Critical review and editing were carried out by RJ and GL. GL obtained funding. Supervision was provided by RJ and GL. GL and RJ confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of Beijing You'an Hospital, Capital Medical University, China (approval no. LL-2021-152-K) and followed the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Institutional Review Board of Beijing You'an Hospital, Capital Medical University, China waived informed consent because of the retrospective nature of our study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

References

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, *et al*: Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 29 cancer groups, 1990 to 2017: A systematic analysis for the global burden of disease study. JAMA Oncol 5: 1749-1768, 2019.
2. Marquardt JU, Andersen JB and Thorgeirsson SS: Functional and genetic deconstruction of the cellular origin in liver cancer. Nat Rev Cancer 15: 653-667, 2015.
3. Gordon AC: Ectopic anus in the adult. Br J Surg 74: 654, 1987.
4. Vitale A, Cabibbo G, Iavarone M, Viganò L, Pinato DJ, Ponziani FR, Lai Q, Casadei-Gardini A, Celsa C, Galati G, *et al*: Personalised management of patients with hepatocellular carcinoma: A multiparametric therapeutic hierarchy concept. Lancet Oncol 24: e312-e322, 2023.
5. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, Lencioni R, Koike K, Zucman-Rossi J and Finn RS: Hepatocellular carcinoma. Nat Rev Dis Primers 7: 6, 2021.
6. Couri T and Pillai A: Goals and targets for personalized therapy for HCC. Hepatol Int 13: 125-137, 2019.
7. European Association for the Study of the Liver: EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 69: 182-236, 2018.
8. Deng W, Chen F, Li Y and Xu L: Development of a clinical scoring model to predict the overall and relapse-free survival of patients with hepatocellular carcinoma following a hepatectomy. Mol Clin Oncol 19: 87, 2023.
9. Bruix J, Gores GJ and Mazzaferro V: Hepatocellular carcinoma: Clinical frontiers and perspectives. Gut 63: 844-855, 2014.
10. Roayaie S, Obeidat K, Sposito C, Mariani L, Bhoori S, Pellegrinelli A, Labow D, Llovet JM, Schwartz M and Mazzaferro V: Resection of hepatocellular cancer ≤2 cm: Results from two Western centers. Hepatology 57: 1426-1435, 2013.
11. Song P, Tobe RG, Inagaki Y, Kokudo N, Hasegawa K, Sugawara Y and Tang W: The management of hepatocellular carcinoma around the world: A comparison of guidelines from 2001 to 2011. Liver Int 32: 1053-1063, 2012.
12. She S, Xiang Y, Yang M, Ding X, Liu X, Ma L, Liu Q, Liu B, Lu Z, Li S, *et al*: C-reactive protein is a biomarker of AFP-negative HBV-related hepatocellular carcinoma. Int J Oncol 47: 543-554, 2015.
13. Farinati F, Marino D, De Giorgio M, Baldan A, Cantarini M, Cursaro C, Rapaccini G, Del Poggio P, Di Nolfo MA, Benvegnù L, *et al*: Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: Both or neither? Am J Gastroenterol 101: 524-532, 2006.
14. Cucchetti A, Piscaglia F, Grigioni AD, Ravaioli M, Cescon M, Zanello M, Grazi GL, Golfieri R, Grigioni WF and Pinna AD: Preoperative prediction of hepatocellular carcinoma tumour grade and micro-vascular invasion by means of artificial neural network: A pilot study. J Hepatol 52: 880-888, 2010.

15. Chan AWH, Zhong J, Berhane S, Toyoda H, Cucchetti A, Shi K, Tada T, Chong CCN, Xiang BD, Li LQ, *et al*: Development of pre and post-operative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 69: 1284-1293, 2018.
16. Moazzam Z, Alaimo L, Endo Y, Lima HA, Shaikh CF, Ratti F, Marques HP, Cauchy F, Lam V, Poultsides GA, *et al*: Variations in textbook oncologic outcomes after curative-intent resection: Early versus intermediate hepatocellular carcinoma based on barcelona clinic liver cancer criteria and child-pugh classification. Ann Surg Oncol 30: 750-759, 2023.
17. R Core Team R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, 2021. URL http://www.R-project.org/.
18. Wang M, Devarajan K, Singal AG, Marrero JA, Dai J, Feng Z, Rinaudo JA, Srivastava S, Evans A, Hann HW, *et al*: The doylestown algorithm: A test to improve the performance of AFP in the detection of hepatocellular carcinoma. Cancer Prev Res (Phila) 9: 172-179, 2016.
19. Schwartz M: A biomathematical approach to clinical tumor growth. Cancer 14: 1272-1294, 1961.
20. Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, Yoshida H, Akamatsu M, Kawabe T and Omata M: Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. Hepatology 44: 1518-1527, 2006.
21. Wen T, Jin C, Facciorusso A, Donadon M, Han HS, Mao Y, Dai C, Cheng S, Zhang B, Peng B, *et al*: Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: An international expert consensus. Hepatobiliary Surg Nutr 7: 353-371, 2018.
22. Peterson ML, Ma C and Spear BT: Zhx2 and Zbtb20: Novel regulators of postnatal alpha-fetoprotein repression and their potential role in gene reactivation during liver cancer. Semin Cancer Biol 21: 21-27, 2011.
23. Rebouissou S and Nault JC: Advances in molecular classification and precision oncology in hepatocellular carcinoma. J Hepatol 72: 215-229, 2020.
24. Wang W and Wei C: Advances in the early diagnosis of hepatocellular carcinoma. Genes Dis 7: 308-319, 2020.
25. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M and Gores G: Hepatocellular carcinoma. Nat Rev Dis Primers 2: 16018, 2016.
26. Singal AG, Kanwal F and Llovet JM: Global trends in hepatocellular carcinoma epidemiology: Implications for screening, prevention and therapy. Nat Rev Clin Oncol 20: 864-884, 2023.
27. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, Roberts LR and Heimbach JK: Diagnosis, staging, and management of hepatocellular carcinoma: 2018 Practice guidance by the American association for the study of liver diseases. Hepatology 68: 723-750, 2018.
28. Yu X, Li S, Xu Y, Zhang Y, Ma W, Liang C, Lu H, Ji Y, Liu C, Chen D and Li J: Androgen maintains intestinal homeostasis by inhibiting BMP signaling via intestinal stromal cells. Stem Cell Reports 18: 410, 2023.
29. Ferrer-Fàbrega J, Forner A, Liccioni A, Miquel R, Molina V, Navasa M, Fondevila C, García-Valdecasas JC, Bruix J and Fuster J: Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology 63: 839-849, 2016.
30. Tsilimigras DI, Sahara K, Moris D, Hyer JM, Paredes AZ, Bagante F, Merath K, Farooq AS, Ratti F, Marques HP, *et al*: Effect of surgical margin width on patterns of recurrence among patients undergoing R0 hepatectomy for T1 hepatocellular carcinoma: An international multi-institutional analysis. J Gastrointest Surg 24: 1552-1560, 2020.
31. Li W, Han L, Xiao B, Li X and Ye Z: A predictive nomogram of early recurrence for patients with AFP-negative hepatocellular carcinoma underwent curative resection. Diagnostics (Basel) 12: 1073, 2022.
32. Yan X, Li Y, Qin W, Liao J, Fan J, Xie Y, Wang Z, Li S and Liao W: Radiomics model based on contrast-enhanced computed tomography imaging for early recurrence monitoring after radical resection of AFP-negative hepatocellular carcinoma. BMC Cancer 24: 700, 2024.
33. Gan W, Huang JL, Zhang MX, Fu YP, Yi Y, Jing CY, Fan J, Zhou J and Qiu SJ: New nomogram predicts the recurrence of hepatocellular carcinoma in patients with negative preoperative serum AFP subjected to curative resection. J Surg Oncol 117: 1540-1547, 2018.
34. Mao S, Yu X, Shan Y, Fan R, Wu S and Lu C: Albumin-bilirubin (ALBI) and monocyte to lymphocyte ratio (MLR)-based nomogram model to predict tumor recurrence of AFP-negative hepatocellular carcinoma. J Hepatocell Carcinoma 8: 1355-1365, 2021.
35. Huang J, Liu FC, Li L, Zhou WP, Jiang BG and Pan ZY: Nomograms to predict the long-time prognosis in patients with alpha-fetoprotein negative hepatocellular carcinoma following radical resection. Cancer Med 9: 2791-2802, 2020.
36. Yang D, Hanna DL, Usher J, LoCoco J, Chaudhari P, Lenz HJ, Setiawan VW and El-Khoueiry A: Impact of sex on the survival of patients with hepatocellular carcinoma: A Surveillance, Epidemiology, and End Results analysis. Cancer 120: 3707-3716, 2014.
37. Goh BK, Teo JY, Chan CY, Lee SY, Jeyaraj P, Cheow PC, Chow PK, Ooi LL and Chung AY: Importance of tumor size as a prognostic factor after partial liver resection for solitary hepatocellular carcinoma: Implications on the current AJCC staging system. J Surg Oncol 113: 89-93, 2016.
38. Hwang S, Lee YJ, Kim KH, Ahn CS, Moon DB, Ha TY, Song GW, Jung DH and Lee SG: The impact of tumor size on long-term survival outcomes after resection of solitary hepatocellular carcinoma: Single-institution experience with 2558 patients. J Gastrointest Surg 19: 1281-1290, 2015.
39. Li J, Li Z, Hao S, Wang J, Chen W, Dai S, Hou Z, Chen B, Zhang Y and Liu D: Inversed albumin-to-globulin ratio and underlying liver disease severity as a prognostic factor for survival in hepatocellular carcinoma patients undergoing transarterial chemoembolization. Diagn Interv Radiol 29: 520-528, 2023.
40. Yan H, Chen S, Qiong Y and Cai L: Preoperative prealbumin-to-fibrinogen ratio to predict survival outcomes in hepatocellular carcinoma patients after hepatic resection. J Med Biochem 41: 290-298, 2022.
41. Li J, Lan Z, Liao W, Horner JW, Xu X, Liu J, Yoshihama Y, Jiang S, Shim HS, Slotnik M, *et al*: Histone demethylase KDM5D upregulation drives sex differences in colon cancer. Nature 619: 632-639, 2023.
42. Abdel-Hafiz HA, Schafer JM, Chen X, Xiao T, Gauntner TD, Li Z and Theodorescu D: Y chromosome loss in cancer drives growth by evasion of adaptive immunity. Nature 619: 624-631, 2023.
43. Kwon H, Schafer JM, Song NJ, Kaneko S, Li A, Xiao T, Ma A, Allen C, Das K, Zhou L, *et al*: Androgen conspires with the $CD8^+$ T cell exhaustion program and contributes to sex bias in cancer. Sci Immunol 7: eabq2630, 2022.
44. Zhang X, Cheng L, Gao C, Chen J, Liao S, Zheng Y, Xu L, He J, Wang D, Fang Z, *et al*: Androgen signaling contributes to sex differences in cancer by inhibiting NF-κB activation in T cells and suppressing antitumor immunity. Cancer Res 83: 906-921, 2023.
45. Liu F, Yuan JH, Huang JF, Yang F, Wang TT, Ma JZ, Zhang L, Zhou CC, Wang F, Yu J, *et al*: Long noncoding RNA FTX inhibits hepatocellular carcinoma proliferation and metastasis by binding MCM2 and miR-374a. Oncogene 35: 5422-5434, 2016.
46. Shinkawa H, Tanaka S, Takemura S, Ishihara T, Yamamoto K and Kubo S: Tumor size drives the prognosis after hepatic resection of solitary hepatocellular carcinoma without vascular invasion. J Gastrointest Surg 24: 1040-1048, 2020.
47. Dai CY, Lin CY, Tsai PC, Lin PY, Yeh ML, Huang CF, Chang WT, Huang JF, Yu ML and Chen YL: Impact of tumor size on the prognosis of hepatocellular carcinoma in patients who underwent liver resection. J Chin Med Assoc 81: 155-163, 2018.
48. Shimada S, Kamiyama T, Orimo T, Nagatsu A, Asahi Y, Sakamoto Y, Kamachi H and Taketomi A: Long-term prognostic factors of patients with hepatocellular carcinoma who survive over 10 years after hepatectomy. J Surg Oncol 121: 1209-1217, 2020.
49. Brennan PN, Dillon JF and Tapper EB: Gamma-glutamyl transferase (γ-GT)-an old dog with new tricks? Liver Int 42: 9-15, 2022.
50. Moreira AJ, Rodrigues GR, Bona S, Fratta LX, Weber GR, Picada JN, Dos Santos JL, Cerski CT, Marroni CA and Marroni NP: Ductular reaction, cytokeratin 7 positivity, and gamma-glutamyl transferase in multistage hepatocarcinogenesis in rats. Protoplasma 254: 911-920, 2017.
51. McCaffrey P, Gilmore DH and Beringer TR: Relief care and risk of death in psychogeriatric patients. BMJ 298: 1522, 1989.
52. Wang Z, Song P, Xia J, Inagaki Y, Tang W and Kokudo N: Can gamma-glutamyl transferase levels contribute to a better prognosis for patients with hepatocellular carcinoma? Drug Discov Ther 8: 134-138, 2014.

53. Huang L, Mo Z, Hu Z, Zhang L, Qin S, Qin X and Li S: Diagnostic value of fibrinogen to prealbumin ratio and gamma-glutamyl transpeptidase to platelet ratio in the progression of AFP-negative hepatocellular carcinoma. Cancer Cell Int 20: 77, 2020.
54. Carr BI, Guerra V, Giannini EG, Farinati F, Ciccarese F, Rapaccini GL, Di Marco M, Benvegnù L, Zoli M, Borzio F, *et al*: Low alpha-fetoprotein HCC and the role of GGTP. Int J Biol Markers 29: e395-e402, 2014.
55. Palumbo JS, Kombrinck KW, Drew AF, Grimes TS, Kiser JH, Degen JL and Bugge TH: Fibrinogen is an important determinant of the metastatic potential of circulating tumor cells. Blood 96: 3302-3309, 2000.
56. Son HJ, Park JW, Chang HJ, Kim DY, Kim BC, Kim SY, Park SC, Choi HS and Oh JH: Preoperative plasma hyperfibrinogenemia is predictive of poor prognosis in patients with nonmetastatic colon cancer. Ann Surg Oncol 20: 2908-2913, 2013.
57. Jiang HG, Li J, Shi SB, Chen P, Ge LP, Jiang Q and Tang XP: Value of fibrinogen and D-dimer in predicting recurrence and metastasis after radical surgery for non-small cell lung cancer. Med Oncol 31: 22, 2014.
58. Hefler-Frischmuth K, Lafleur J, Hefler L, Polterauer S, Seebacher V, Reinthaller A and Grimm C: Plasma fibrinogen levels in patients with benign and malignant ovarian tumors. Gynecol Oncol 136: 567-570, 2015.
59. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, Fushiya N, Koike K, Nishino H, Matsushima M and Tajiri H: Elevated plasma fibrinogen levels are associated with a poor prognosis in patients with hepatocellular carcinoma. Oncology 85: 269-277, 2013.
60. Tanaka N, Kikuchi E, Matsumoto K, Hayakawa N, Ide H, Miyajima A, Nakamura S and Oya M: Prognostic value of plasma fibrinogen levels in patients with localized upper tract urothelial carcinoma. BJU Int 111: 857-864, 2013.