

# A Novel Nomogram to Predict Prognosis in Elderly Early-Stage Hepatocellular Carcinoma Patients After Ablation Therapy

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**Purpose:** Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer. Early diagnosis is crucial for improving prognosis. Elderly HCC patients often have underlying liver diseases such as chronic hepatitis and cirrhosis, leading to impaired liver function and suboptimal liver reserve. Radiofrequency ablation (RFA) has rapidly become one of the most important methods for treating early-stage hepatocellular carcinoma (EHCC) due to its advantages, including minimal trauma, short operation time, less intraoperative bleeding, quick postoperative recovery, cost-effectiveness, and few postoperative complications. However, the prognostic model for early recurrence after local ablation in elderly EHCC patients has not been widely evaluated. We have developed a prognostic model for the recurrence of local RFA in elderly EHCC patients. This is expected to provide a new early warning system for preventing early recurrence in elderly EHCC patients, prolonging patient's life, and improving overall quality of life.

**Methods:** In this study, we included 661 EHCC patients who underwent local ablation, dividing them into a Primary cohort and a Validation cohort in a 7:3 ratio. We characterized the cohorts and utilized the primary cohort to develop a prognostic nomogram model for recurrence after local ablation in elderly EHCC patients. Additionally, the validation cohort was used to assess the potential of the nomogram as a non-invasive biomarker for post-ablation recurrence in EHCC.

**Results:** The user-friendly nomogram incorporates common clinical variables including gender, BCLC stage, tumor number, tumor size, red blood cell (RBC), gamma-glutamyl transferase (GGT), and prothrombin time activity (PTA). The nomogram constructed using the identified seven variables exhibits robust discriminatory capabilities, favorable predictive performance, and noteworthy clinical utility.

**Conclusion:** We developed a user-friendly nomogram based on the BCLC stage classification, which may provide prognostic assessments for elderly EHCC patients at 1, 3, and 5 years post-RFA.

**Keywords:** hepatocellular carcinoma, elderly, radiofrequency ablation, EHCC, relapse, prognostic model

## Introduction

Hepatocellular carcinoma (HCC) is the predominant form of primary liver cancer, representing over 90% of cases and frequently occurring in approximately 85% of patients diagnosed with cirrhosis.<sup>1</sup> The five-year survival rate for HCC is less than 20% in China.<sup>2</sup> The prognosis for patients with HCC is intricately tied to the tumor stage at the time of diagnosis.<sup>3</sup> Owing to the absence of clear clinical symptoms and signs in the early stages, most cases are diagnosed in advanced stages, resulting in a less favorable prognosis. Therefore, a key strategy to improve the prognosis of HCC is to conduct early tumor diagnosis when feasible in treatment, that is, to detect early hepatocellular carcinoma (EHCC) and intervene early. Over the past three decades, various methods have been developed for treating HCC.<sup>4,5</sup> Liver resection is

one of the most classical methods, with a mortality rate of less than 3%.<sup>6,7</sup> However, it remains a complex procedure with a postoperative complication rate as high as 20–40%.<sup>8</sup> Besides liver resection and liver transplantation, radiofrequency ablation (RFA) is generally considered a viable therapeutic option for HCC.<sup>9</sup>

With improvements in medication and healthcare, human life expectancy is continually increasing. The definition of “elderly” is typically considered to be individuals aged 65 and older.<sup>10,11</sup> The elderly population can be roughly categorized into three groups: “young old”, aged 65 and older but under 75; “intermediate old”, aged 75 and older but under 85; and “the oldest old”, aged 85 and older.<sup>12</sup> Most elderly HCC patients have had underlying liver conditions such as chronic hepatitis and cirrhosis for many years. The majority among them have already been diagnosed with varying degrees of liver function impairment, and their liver function reserve is suboptimal.<sup>13,14</sup> In elderly patients, there is typically a higher incidence of associated comorbidities related to liver resection.<sup>15–17</sup> Therefore, minimally invasive surgery has been widely used due to its advantages, with ultrasound-guided percutaneous RFA and laparoscopic hepatectomy (LH) widely recognized in the clinical treatment of primary small liver cancer.

The principle of RFA involves the generation of physical heat, leading to the coagulative necrosis of tumor tissue. The coagulated and necrotic cells are broken down, eliminated, or organized by the body, eliminating the need for their surgical removal.<sup>18,19</sup> With the continuous advancement of radiofrequency electrodes and auxiliary positioning technology, the treatment has become more precise, and the range of tissue inactivation has expanded. RFA surgery has rapidly become one of the crucial methods for treating small HCC in recent years due to its advantages, including minimal trauma, shorter surgical duration, reduced intraoperative bleeding, faster postoperative recovery, lower hospitalization costs, and fewer postoperative complications.<sup>20,21</sup> It is particularly suitable for elderly patients with poor overall health, impaired liver function, and those requiring multiple surgeries due to liver cancer recurrence after LH.

However, the prognostic model for recurrence after local ablation in elderly patients with EHCC has not yet been universally evaluated. In this study, we included 661 patients with EHCC who underwent local ablation, randomly dividing them into a primary cohort and a validation cohort in a 7:3 ratio. We characterized the cohorts and utilized the Primary cohort to develop a prognostic model for recurrence after local ablation in elderly EHCC patients. Additionally, the Validation cohort was used to assess the potential of the nomogram as a non-invasive biomarker for post-ablation recurrence in EHCC. In anticipation of early recurrence in elderly patients with EHCC, providing a novel approach aims to serve as an early warning system, extending patient lifespans, and improving overall quality of life.

## Materials and Methods

### Patients

661 elderly patients diagnosed with early-stage HCC at Beijing You’an Hospital, affiliated with Capital Medical University, between January 2014 and December 2019, and subsequently undergoing local ablation surgery were included in the study.

The patients were randomly allocated into a primary cohort and a validation set in a 7:3 ratio. Inclusion criteria for this study were as follows: (1) age  $\geq 65$  years; (2) confirmed diagnosis of primary HCC through pathological examination and evaluation at the BCLC 0/A stage; (3) treatment with ablation; (4) availability of complete clinical data. Exclusion criteria included: (1) patients with advanced HCC; (2) secondary liver cancer; (3) history of other malignancies; (4) prior radiotherapy, chemotherapy, or surgical resection before ablation treatment; (5) presence of other hematological diseases, autoimmune disorders, systemic infection or inflammation. We then excluded 110 cases where ablation therapy was not the initial treatment, 144 cases with a history of other malignancies, other hematological diseases, autoimmune disorders, systemic infection or inflammation, and 153 cases lacking clinical or follow-up data. Ultimately, 661 cases were included based on the inclusion criteria. Moreover, the diagnosis of HCC was confirmed by histological findings and/or in accordance with the criteria of the American Association for the Study of Liver Diseases.<sup>22</sup>

The study protocol received approval from the Ethics Committee of Beijing You’an Hospital and adhered to the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study, the necessity for written informed consent from patients was waived.

## Data Collection

The baseline clinicopathological characteristics of patients were collected, including age, gender, demographic indicators (smoking, drinking, hypertension, alcohol-related liver disease [ALD], diabetes and liver cirrhosis), laboratory parameters (blood routine examination, liver function, and coagulation function), tumor burden (tumor number and tumor size), tumor markers (alpha-fetoprotein [AFP]), and records of ablation treatments. Additionally, liver function indicators such as Child-Pugh classification and the Barcelona Clinic Liver Cancer (BCLC) stage were included.

## Follow-Up

The primary endpoint in this study is recurrence-free survival (RFS), defined as the duration from treatment initiation to the first recurrence or the last follow-up. Recurrence is characterized by the identification of new intrahepatic or extrahepatic masses, verified by at least two imaging examinations. Within one-month post-ablation treatment, all patients are mandated to undergo follow-up and re-examination at our hospital's outpatient clinic. The last follow-up date is July 1, 2023, with a median follow-up duration of 1.65 years.

During these sessions, patients undergo evaluations of liver function, as well as imaging tests, including ultrasound, CT, and MRI. Follow-up assessments occur every 3 months in the period from 2 months to 1 year after ablation treatment, and subsequently every six months. In case recurrence or distant metastasis is suspected, confirmatory imaging examinations such as ultrasound, CT, and MRI are conducted.

## Statistical Analysis

In the statistical analysis, R software (version 4.1.3) was employed. Continuous variables are reported as mean  $\pm$  standard deviation and categorical variables are presented as frequency and percentage. Non-parametric tests are employed for comparing differences between variable groups. Lasso regression, an effective method for high-dimensional data regression, is applied in this study to identify potential risk variables. Variables showing statistical significance ( $p < 0.05$ ) are then selected. Random survival forest, employing an integrated method of decision trees, constructs multiple decision trees by randomly selecting samples and features. Variable importance is ranked using the VIMP method to further confirm the risk factors associated with HCC recurrence. A nomogram is generated by combining the results of Lasso regression and random survival forest. The discrimination of the nomogram is evaluated using the C index and ROC curve, with further assessment of its consistency through Calibration plots. Then, Decision Curve Analysis (DCA) is employed to assess the net benefit of the nomogram, demonstrating its clinical practicality and predictive accuracy for recurrence rates. Finally, survival curves were generated using the Kaplan–Meier method.

## Results

### The Demographic and Clinical Characteristics of Patients in the Primary Cohort and Validation Cohort

A total of 661 patients with early-stage HCC who received locoregional ablation at Beijing You'an Hospital affiliated with Capital Medical University from January 2014 to December 2019, were enrolled, including 476 (72.0%) males and 185 (28.0%) females. Out of a total of 661 patients, 208 (31.5%) individuals were diagnosed with hypertension and 158 (23.9%) with diabetes. Among the 661 patients, 277 (41.9%) had a history of smoking, and 199 (30.1%) had a history of drinking. There were 136 (20.6%) patients with ALD and 580 (87.7%) patients with cirrhosis. 471 (71.3%) were Child-Pugh class A, and 190 (28.7%) were Child-Pugh class B. 439 (66.4%) were BCLC stage A. Among the cohort of 661 patients, a total of 199 (30.1%) individuals presented with multiple tumors, and 226 (34.2%) patients had tumors  $\geq 3$ cm in size.

The patients were randomly divided into a primary cohort and a validation set in a 7:3 ratio. The primary cohort was utilized for model establishment, while the validation set was employed to assess the performance of the established model. The baseline characteristics of patients in both cohorts are detailed in [Table 1](#). The included variables exhibited no statistically significant differences between the two groups ( $p > 0.05$ ), affirming the randomness and authenticity of the data grouping ([Table 1](#)).

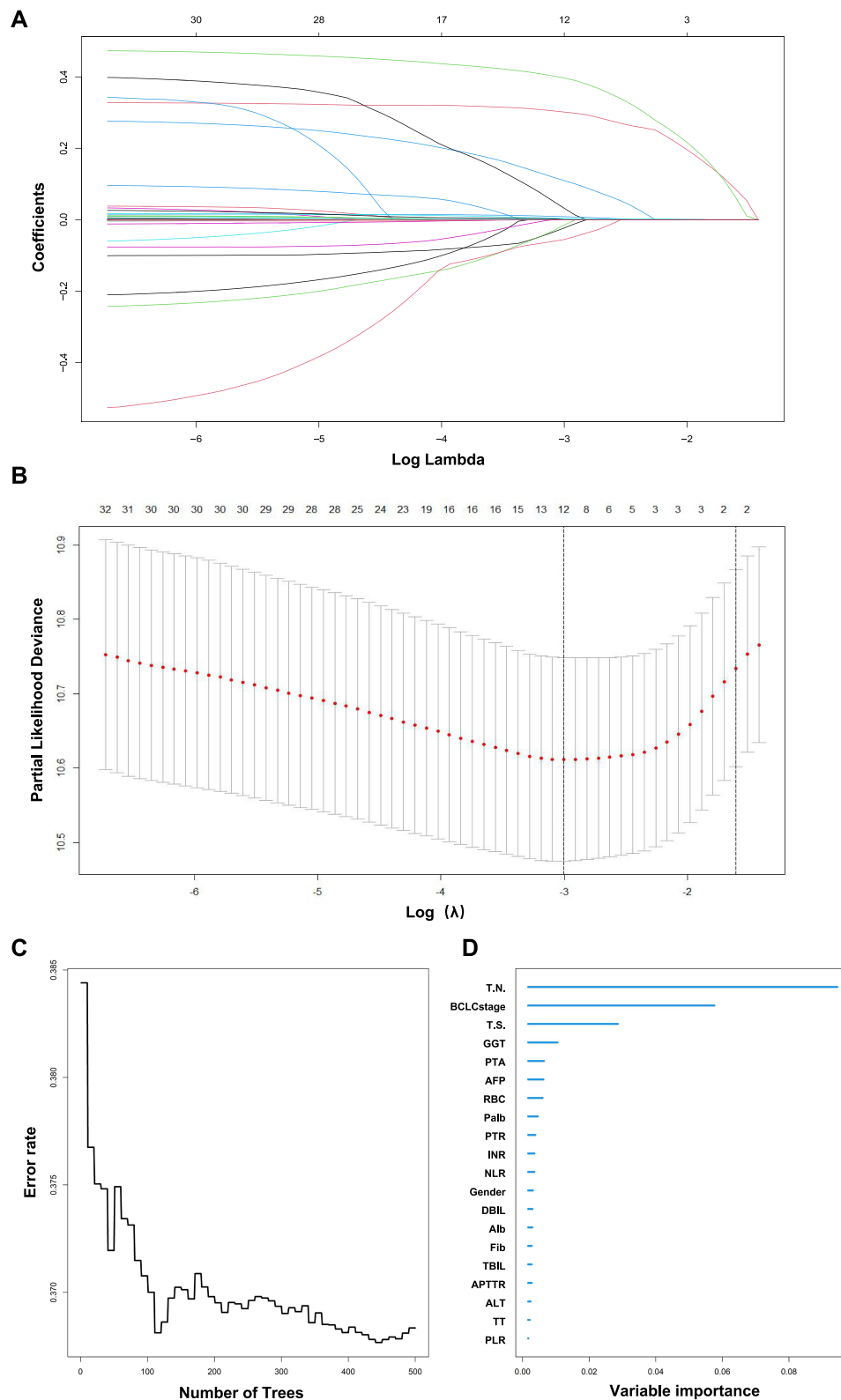
**Table I** Demographic and Clinical Characteristics of the Patients in Two Cohorts

Characteristic	Primary Cohort (N=463)	Validation Cohort (N=198)	P value
Gender, male (%)	334 (72.1)	142 (71.7)	0.912
Smoking, n (%)	188 (40.6)	89 (44.9)	0.300
Drinking, n (%)	137 (29.6)	62 (31.3)	0.658
ALD, n (%)	86 (18.6)	50 (25.3)	0.052
Cirrhosis, n (%)	405 (87.5)	175 (88.4)	0.744
Hypertension, n (%)	140 (30.2)	68 (34.3)	0.298
Diabetes, n (%)	107 (23.1)	51 (25.8)	0.465
RBC (10 <sup>6</sup> /L)	4.06±0.61	4.12±0.61	0.152
Hb (g/L)	127.90±18.76	129.28±20.04	0.223
NLR	3.05±1.85	2.98±1.45	0.342
PLR	112.28±60.95	110.25±56.18	0.679
MLR	0.38±0.21	0.36±0.20	0.446
ALT (U/L)	29.99±19.65	29.90±17.89	0.620
AST (U/L)	31.89±15.24	32.04±16.08	0.966
TBIL (umol/L)	19.76±10.38	18.62±9.10	0.342
DBIL (umol/L)	6.96±4.83	6.43±4.89	0.206
Alb (g/L)	36.78±4.73	37.16±4.35	0.228
Globulin (g/L)	28.72±5.77	28.47±5.11	0.860
GGT (U/L)	64.65±59.72	66.24±52.15	0.264
ALP (U/L)	89.55±37.20	87.99±31.87	0.926
Palb (mg/L)	129.07±52.53	137.38±59.31	0.118
TT (s)	15.96±2.20	15.83±2.24	0.383
APTT (s)	33.52±4.39	33.72±4.71	0.777
APTTR	1.12±0.16	1.13±0.17	0.644
PTA (%)	85.82±14.96	85.95±14.30	0.942
PTR	1.12±0.14	1.12±0.12	0.953
INR	1.12±0.14	1.11±0.12	0.993
Fib (mg/dL)	2.81±0.91	2.93±0.99	0.163
AFP (ng/mL)	231.77±182.14	196.16±97.78	0.197
Tumor number, Single/multiple (%)	325 (70.2)/138 (29.8)	137 (69.2)/61 (30.8)	0.797
Tumor size, <3cm/≥3cm (%)	302 (65.2)/161 (34.8)	133 (67.2)/65 (32.8)	0.629
Child-Pugh class, class(A/B) (%)	325 (70.2)/138 (29.8)	146 (73.7)/52 (26.3)	0.357
BCLC stage, (0/A) (%)	154 (33.3)/309 (66.7)	68 (34.3)/130 (65.7)	0.787

**Abbreviations:** ALD, alcohol related liver disease; RBC, red blood cell; Hb, hemoglobin; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL: total bilirubin; DBIL, direct bilirubin; Alb, albumin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; Palb, prealbumin; TT, thrombin time; APTT, activated partial thromboplastin time; APTTR, activated partial thromboplastin time ratio; PTA, prothrombin time activity; PTR, Prothrombin Time Ratio; INR, international normalized ratio; Fib, fibrous protein; AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer.

## Prediction Model Built Based on LassoCox Regression and Random Survival Forest

Lasso regression was employed to meticulously sift through parameters, and the nuanced shifts in the coefficients of these variables are vividly illustrated in [Figure 1A](#). The iterative analysis utilized a 10-fold cross-validation method, revealing that a model exhibiting outstanding performance while minimizing the number of variables was achieved when the parameter  $\lambda$  was set to 0.045 ( $\text{Log } \lambda = -3$ ), as depicted in [Figure 1B](#). The screened variables include gender, diabetes, BCLC stage, tumor number, tumor size, monocyte-to-lymphocyte ratio (MLR), red blood cell (RBC), globulin, Gamma-glutamyl transferase (GGT), prothrombin time activity (PTA), and activated partial thromboplastin time (APTT). Subsequently, a Random Survival Forest (RSF) was re-established, as illustrated in [Figure 1C](#). Through punctiliously parameter tuning, the model's error rate exhibited a stabilizing trend when the number of trees was set to 500. As



**Figure 1** Screening of variables using Lasso regression and Random Survival Forest **(A)** The variation characteristics of variable coefficients in Lasso regression; **(B)** The process of selecting the optimal value for the parameter  $\lambda$  in the Lasso regression model was conducted through a cross-validation method. **(C)** Error rate of the Random Survival Forest; **(D)** Out-of-bag variable importance ranking of the Random Survival Forest.

**Abbreviations:** T.N, Tumor number; T.S, Tumor size; GGT, gamma-glutamyl transpeptidase; PTA, prothrombin time activity; AFP, alpha fetoprotein; RBC, red blood cell; Palb, prealbumin; PTR, Prothrombin Time Ratio; INR, international normalized ratio; NLR, neutrophil to lymphocyte ratio; DBIL, direct bilirubin; Alb, albumin; Fib, fibrous protein; TBIL: total bilirubin; APTTR, activated partial thromboplastin time ratio; ALT, alanine aminotransferase; TT, thrombin time; PLR, platelet to lymphocyte ratio.

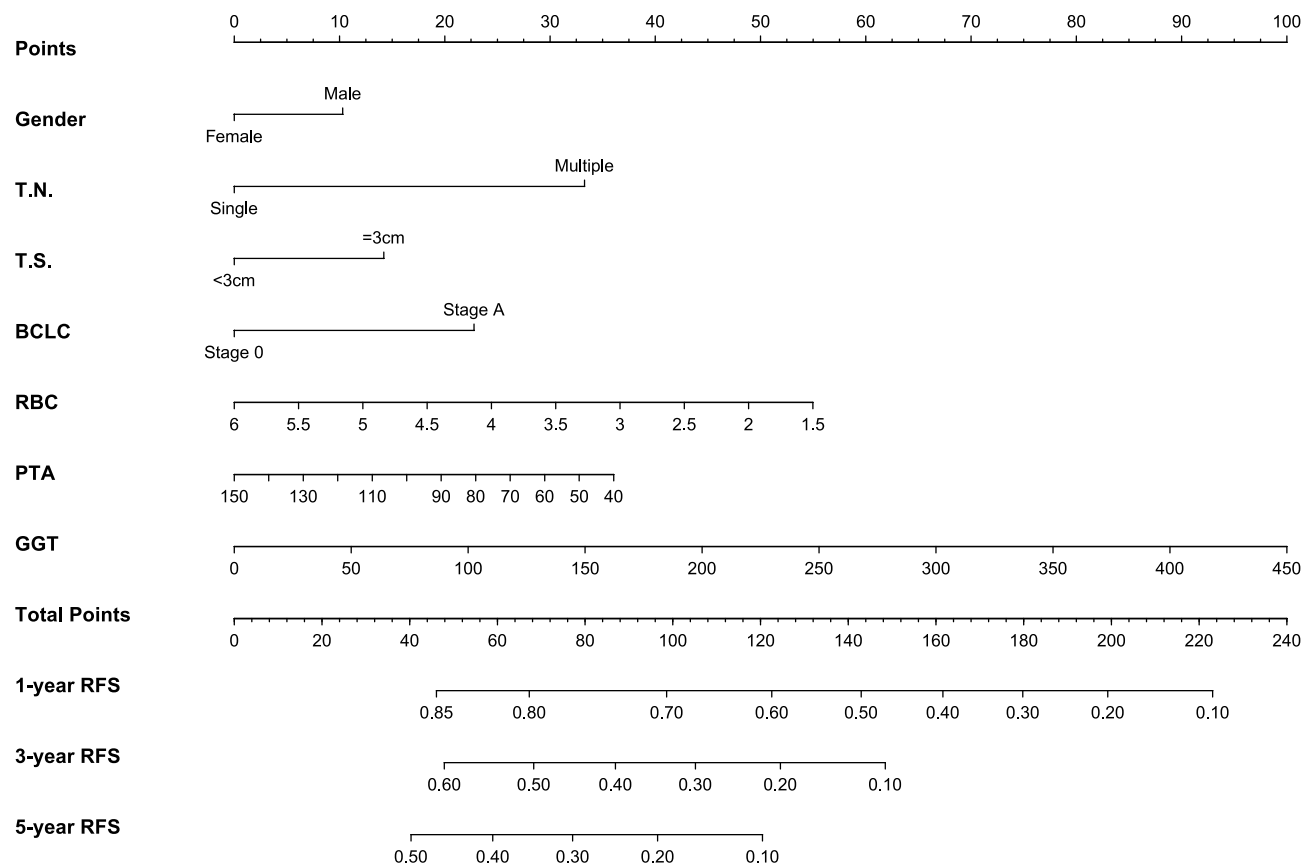
depicted in Figure 1D, variable importance was meticulously ranked using the VIMP method. Ultimately, through the integration of findings from the two models, a meticulous selection process has identified the following seven variables—Gender, BCLC, T.N., T.S., RBC, GGT, and PTA—to be incorporated into the nomogram model.

## Nomogram as a Tool for Visualization

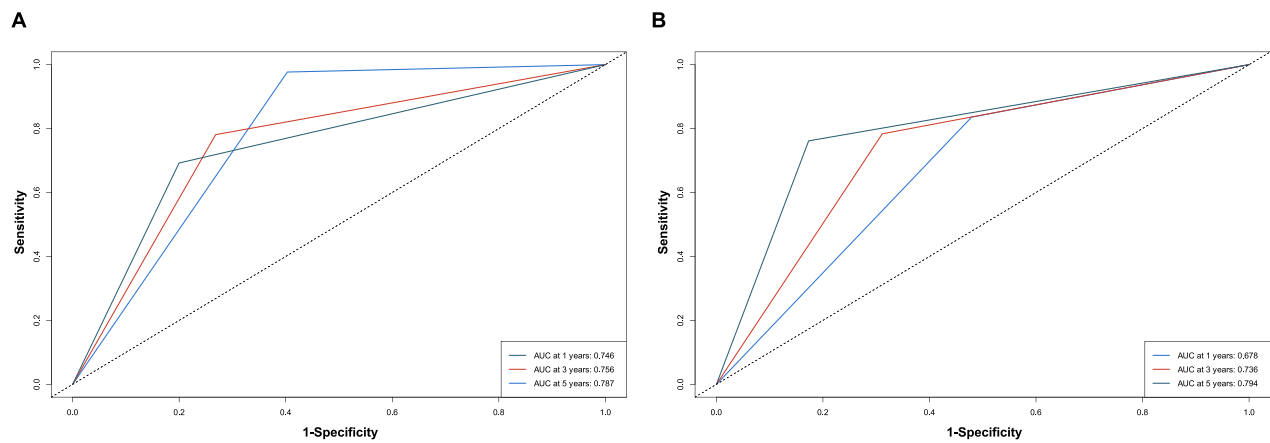
From the above, we ultimately integrated the Lasso model and the Random Survival Forest model, selecting 7 variables for the nomogram model to predict the recurrence risk in elderly early-stage HCC patients after ablation therapy (Figure 2). The aggregation of scores from the included variables was essential. A vertical line was drawn at the total points, intersecting with the three lines representing the predicted RFS. The values at the point of intersection represented the predicted 1-, 3-, and 5-year RFS for individuals. For instance, a 75-year-old male patient with a solitary tumor measuring <3cm in diameter, categorized as BCLC stage A, a red blood cell count of  $3.5 \times 10^6/L$ , GGT of 50 U/L, and PTA of 90%, accumulated a total score of approximately 97. According to the model, the anticipated 1-year RFS was about 72%, 3-year RFS stood at around 34%, and 5-year RFS was about 20%. It can be observed that the nomogram is more user-friendly in clinical practice compared to mathematical formulas.

## Validation of the Original Scoring System in Both the Primary Cohort and Validation Cohort

The C-statistic in the primary cohort yielded a value of 0.722 (95% confidence interval [CI]: 0.698–0.745), while in the validation cohort, it recorded 0.678 (95% CI: 0.635–0.721). The area under the time-dependent ROC curve demonstrated AUCs of 0.746, 0.756, and 0.787 for 1-, 3-, and 5-year RFS in the primary cohort (Figure 3A). Moreover, in the validation cohort, the AUCs at 1, 3, and 5 years were 0.678, 0.736, and 0.794, respectively (Figure 3B). These findings collectively indicate a robust discriminatory capability of the original scoring system for RFS in both cohorts.



**Figure 2** Nomogram for predicting time-related recurrence in elderly patients with early-stage HCC after ablation therapy.



**Figure 3** Comparison of ROC curves for the original scoring system at various time points in both the primary (A) and validation (B) cohorts.  
**Abbreviations:** ROC, receiver operating characteristics; AUC, the area under the curve.

## Calibrating the Model Jointly Constructed by Lasso Regression and Random Survival Forest

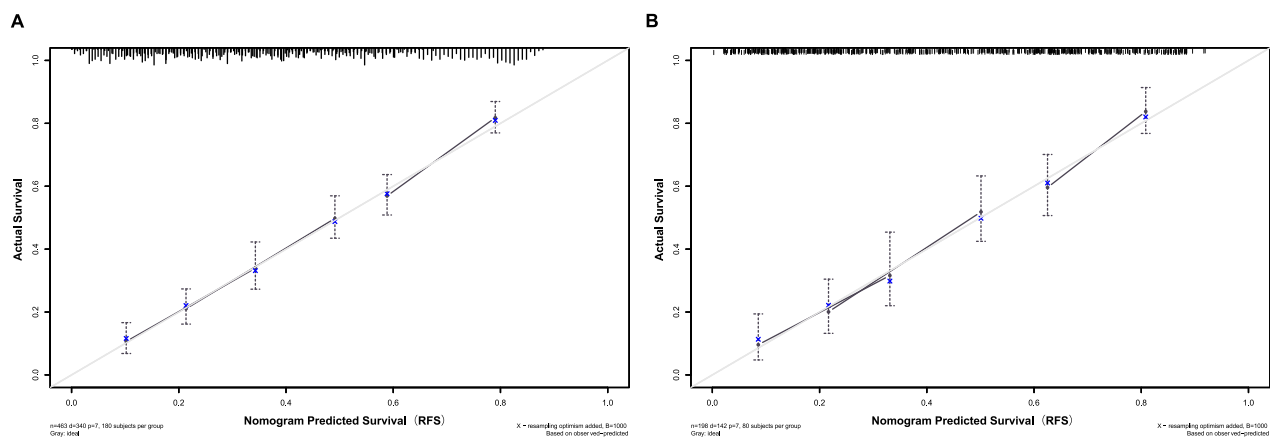
The calibration curves for the model, predicting recurrence at 1, 3, and 5 years, demonstrated strong alignment between predicted and observed outcomes in both the primary and validation cohorts (Figure 4). This suggests that the model exhibits no departure from a perfect fit.

## Discrimination Ability of the Nomogram

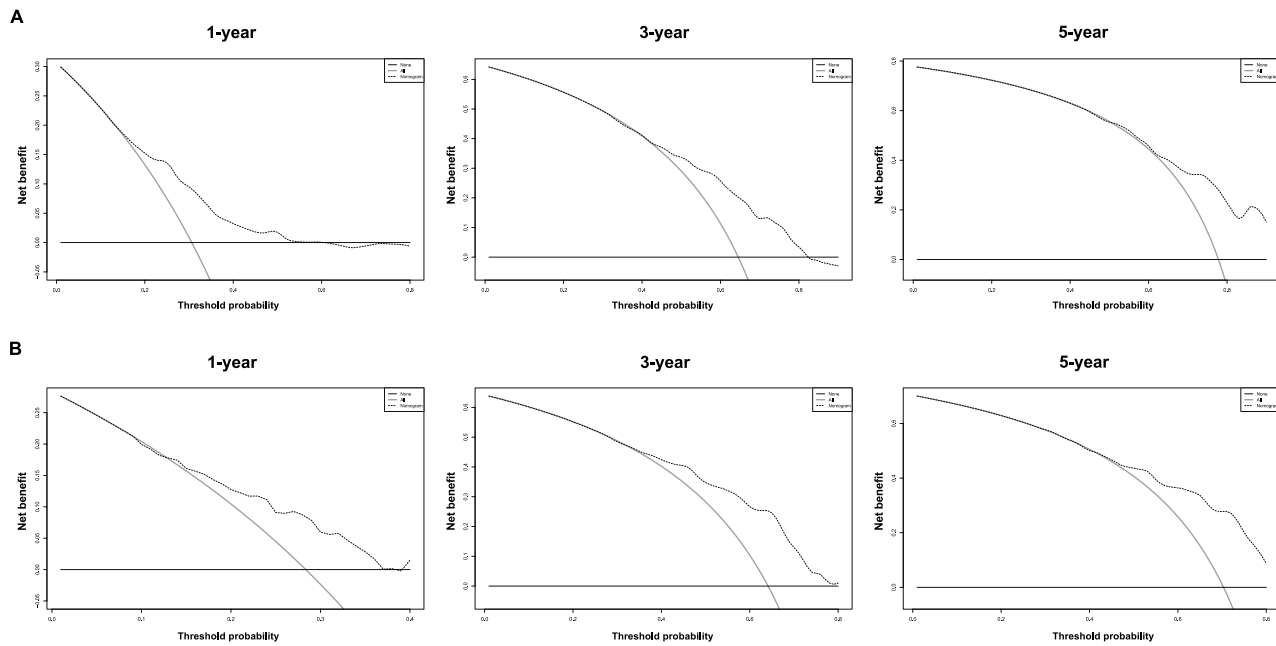
As illustrated in Figure 5, the DCA curves for 1, 3, and 5-year RFS in both the primary and validation cohorts indicate that, across most reasonable threshold probability ranges, employing the nomogram provides greater benefits compared to traditional staging systems.

## Clinical Application of the Nomogram

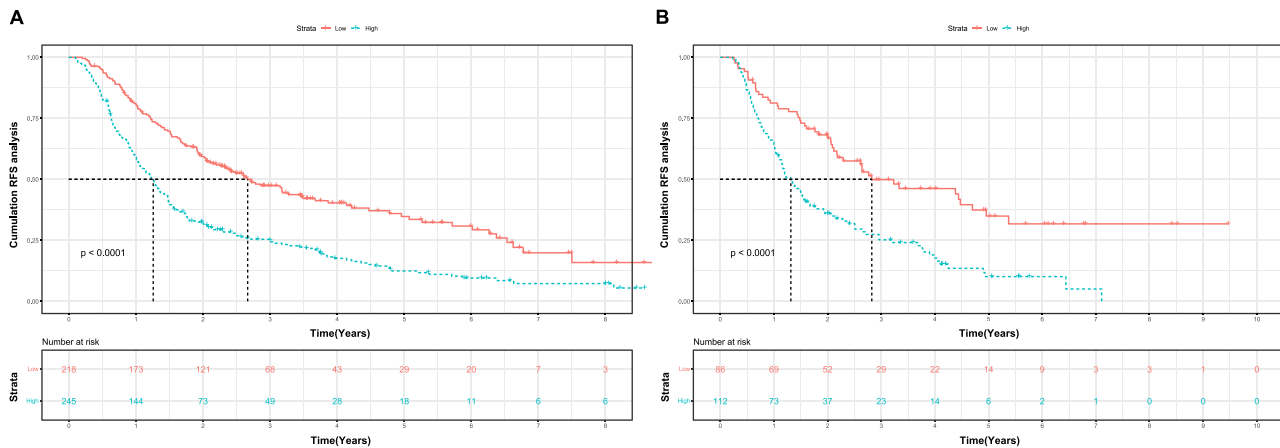
Utilizing the cumulative scores generated by the nomogram, we have devised a comprehensive risk stratification system, categorizing patients into two distinct risk groups: low-risk and high-risk. Kaplan-Meier analysis unveiled the profound implications of our stratification system, demonstrating a notable contrast in recurrence-free probabilities between these risk categories. In both the primary and validation cohorts, individuals in the low-risk group exhibited significantly



**Figure 4** Calibration plots of predicted 1-, 3-, and 5-year RFS based on Cox regression modeling in the primary and validation cohorts. (A) primary cohort; (B) validation cohort.  
**Abbreviation:** RFS, recurrence-free survival.



**Figure 5** The DCA curves of the original scoring system in 1, 3, and 5 years of RFS in the primary (A) and validation (B) cohorts.  
**Abbreviations:** RFS, recurrence-free survival; DCA, decision curve analysis.



**Figure 6** The risk stratification for RFS is based on the nomogram risk scores in the primary (A) and validation (B) cohorts.  
**Abbreviation:** RFS, recurrence-free survival.

higher recurrence-free rates, whereas those in the high-risk group faced a more ominous prognosis (Figure 6A and B). This divergence underscores the effectiveness of the nomogram in accurately identifying patients at a heightened risk of adverse outcomes.

## Discussion

With improvements in healthcare, socioeconomic development, and increased life expectancy, the incidence of HCC has surged, making the prognosis for elderly patients a global challenge.<sup>23</sup> Firstly, elderly individuals diagnosed with HCC undergo the natural aging process, experiencing a decline in various bodily functions and reduced resilience to risks. Secondly, elderly patients often have comorbidities such as hypertension, diabetes, cirrhosis, and related portal hypertension, as well as liver fibrosis, leading to a worsened prognosis.<sup>24</sup> Additionally, factors related to cancer-associated wasting conditions in elderly patients, such as muscle atrophy,<sup>25</sup> cachexia,<sup>26</sup> and malnutrition,<sup>27</sup> contribute to a lower



surgical tolerance, thereby diminishing the safety of surgeries and overall survival rates to some extent.<sup>28</sup> Considering the factors mentioned above, elderly patients exhibit poor tolerance to open surgeries, resulting in lower safety levels of the procedures and relatively reduced survival rates among elderly patients. In comparison to traditional open surgeries, radiofrequency ablation boasts characteristics like minimally invasive procedures, safety, broad applicability, good patient tolerance, confirmed efficacy, fewer complications, and the ability for repeat treatments.<sup>29,30</sup> More significantly, it effectively enhances the quality of life and extends the lifespan of elderly liver cancer patients. Consequently, radiofrequency ablation is considered a more suitable option for curative treatment in elderly patients.

In this article, we have developed an evaluative nomogram tailored for a cohort of elderly patients undergoing radiofrequency ablation treatment for EHCC. This nomogram is proficient in generating personalized estimates for the risk of RFS following radiofrequency ablation. The user-friendly nomogram incorporates common clinical variables such as “Gender”, “BCLC”, “T.N”, “T.S”, “RBC”, “GGT”, and “PTA”. This intuitive graphical tool is designed for ease of use and is grounded in pre-treatment clinical variables. With this nomogram, patients can quickly determine their future survival rate based on the levels of various influencing factors, which facilitates patient evaluation and helps them to pay more attention to their health status. In addition, This can effectively improve communication and decision-making between patients and doctors. On the one hand, using these visual nomograms before treatment can help doctors explain possible risks to patients. This may further improve patient selection for clinical trials and treatment decisions. On the other hand, identifying risk factors based on the nomogram can help doctors in preoperative planning. It can be used to guide the development of individualized treatment plans for specific patients.

The BCLC staging system, proposed by the American and European Associations for the Study of Liver Diseases,<sup>31</sup> serves as the basis for the treatment and prognosis assessment of HCC patients. Treatment selection is guided by the BCLC staging system, with surgical therapies primarily recommended for early-stage disease. In our study, we constructed a nomogram based on BCLC stage classification, which can be used for personalized assessment of the RFS in elderly patients with early-stage HCC undergoing RFA. Additionally, in our research, gender, tumor factors (such as tumor size and multiplicity), and poor liver functional reserve (ie, lower red blood cell count, decreased prothrombin activity, and elevated gamma-glutamyl transpeptidase) were found to be significantly correlated with higher RFS after RFA. Gender emerged as an independent prognostic factor for HCC, with a noticeably higher incidence in males, constituting approximately 74.6% of patients in our cohort. Sex hormones play a role in modulating the risk of developing HCC and influencing its invasiveness, response to treatment, and prognosis.<sup>32</sup> The liver functional reserve is also an independent risk factor for HCC prognosis, with a worsening prognosis as liver function declines.<sup>33</sup>

There are many crucial factors to consider in constructing a medical prognostic nomogram. Firstly, it is essential to precisely define the target variable for prediction, which, in our study, is RFS. This predictive nomogram aids in determining the RFS of elderly patients with early-stage HCC undergoing RFA, facilitating better detection and intervention in the progression of the disease and extending the expected lifespan. Secondly, based on domain expertise, clinical variables used for prediction were selected, comprising common and easily accessible clinical factors. The sample size is sufficiently large to ensure statistical robustness. The data is divided into primary and validation sets in a 7:3 ratio for internal validation. Subsequently, calibration of the nomogram is performed to ensure consistency between predictions and observed outcomes. We evaluated the performance of the nomogram, including sensitivity, specificity, and AUC. The area under the time-dependent ROC curve demonstrated AUCs of 0.746, 0.756, and 0.787 for 1-, 3-, and 5-year RFS in the primary cohort. In the validation cohort, the AUCs were 0.678, 0.736, and 0.794 respectively. We further corrected the model jointly constructed by Lasso regression and Random Survival Forest, indicating that the model did not deviate from perfect fitting. Finally, to validate its discriminative ability and clinical application prospects, we employed DCA curves and Kaplan-Meier analysis techniques, confirming its high discriminative ability and clinical application prospects. In conclusion, we have constructed a reliable, practical, and effective prognostic nomogram for the RFS of elderly patients with early-stage HCC undergoing RFA.

As a frontline treatment for EHCC, RFA is highly valuable for elderly patients with early-stage HCC. The 1, 3, and 5-year survival rates of patients' post-radiofrequency ablation are progressively rising each year, highlighting a promising and increasing benefit for the patients. We have developed a user-friendly nomogram based on the BCLC stage classification, which may provide prognostic assessments for individual patients at 1, 3, and 5 years post-RFA.

Certainly, this study also has limitations. First, this study is retrospective, which may introduce inevitable selection bias in the samples studied. Second, when considering the early recurrence prognosis of elderly patients with HCC, it should be noted that there are other potential risk factors at play. Adverse living habits, specific treatment interventions implemented, the medical history of the patient, and the presence of tumor markers should be considered, all of which might significantly influence the study's results. Therefore, future studies must broaden their scope and consider these variables to more comprehensively evaluate the risk factors for early recurrence prognosis in elderly patients with HCC. We hope that our study findings can better guide clinical treatment and early predictions, benefiting elderly patients with early-stage HCC.

## Conclusions

We developed a user-friendly nomogram based on the BCLC stage classification, which may provide prognostic assessments for elderly early-stage HCC patients at 1, 3, and 5 years post-RFA.

## Data Sharing Statement

For further inquiries regarding all relevant data, please feel free to contact the corresponding author, Caixia Hu, at hucaixia1217@126.com.

## Ethics Statement

The study protocol was approved by the Ethics Committee of Beijing You'an Hospital and conducted following the ethical principles outlined in the Helsinki Declaration of 1964 and its subsequent amendments, or other ethical standards with equivalent requirements. As a retrospective study as well as to ensure patient confidentiality, the identities of the individuals included in this study were anonymized using computer-generated ID numbers, and thus, patient consent was waived.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was funded by the Beijing Bethune Charitable Foundation (QZHX-21-ZQN-014) and Beijing You'an Hospital Affiliated to Capital Medical University Incubation Program for Young and Middle-aged Talents (BJYAYY-YN2022-25).

## Disclosure

The authors declare no competing interests in this work.

## References

- Ioannou GN, Splan MF, Weiss NS, McDonald GB, Beretta L, Lee SP. Incidence and predictors of hepatocellular carcinoma in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2007;5(8):938–45. doi:10.1016/j.cgh.2007.02.039
- Zeng H, Chen W, Zheng R, et al. Changing cancer survival in China during 2003–2015: a pooled analysis of 17 population-based cancer registries. *Lancet Glob Health*. 2018;6(5):e555–e567. doi:10.1016/S2214-109X(18)30127-X
- Ayuso C, Rimola J, Vilana R, et al. Diagnosis and staging of hepatocellular carcinoma (HCC): current guidelines. *Eur J Radiol*. 2018;101:72–81. doi:10.1016/j.ejrad.2018.01.025
- Cheng AL, Amarapurkar D, Chao Y, et al. Re-evaluating transarterial chemoembolization for the treatment of hepatocellular carcinoma: consensus recommendations and review by an International Expert Panel. *Liver Int*. 2014;34(2):174–183. doi:10.1111/liv.12314
- Wu CC. Progress of liver resection for hepatocellular carcinoma in Taiwan. *Japan J Clin Oncol*. 2017;47(5):375–380. doi:10.1093/jcco/hyx007
- Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. *J Am Coll Surg*. 2000;191(1):38–46. doi:10.1016/S1072-7515(00)00261-1
- Jarnagin WR, Gonen M, Fong Y, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1803 consecutive cases over the past decade. *Ann Surg*. 2002;236(4):397–406; discussion 406–7. doi:10.1097/0000658-200210000-00001

8. Yasunaga H, Horiguchi H, Matsuda S, et al. Relationship between hospital volume and operative mortality for liver resection: data from the Japanese Diagnosis Procedure Combination database. *Hepatol Res.* 2012;42(11):1073–1080. doi:10.1111/j.1872-034X.2012.01022.x
9. Wicks JS, Dale BS, Ruffolo L, et al. Comparable and complimentary modalities for treatment of small-sized HCC: surgical resection, radio-frequency ablation, and microwave ablation. *J Clin Med.* 2023;12(15):5006. doi:10.3390/jcm12155006
10. Singh S, Bajorek B. Defining ‘elderly’ in clinical practice guidelines for pharmacotherapy. *Pharm Pract.* 2014;12(4):489 doi:10.4321/s1886-36552014000400007.
11. Rea F, Corrao G, Mancina G. Risk of Dementia during antihypertensive drug therapy in the elderly. *J Am Coll Cardiol.* 2024;83(13):1194–1203. doi:10.1016/j.jacc.2024.01.030
12. Morita T, Yamamoto K, Ozaki A, Tsuda K, Tanimoto T. The oldest-old in China. *Lancet.* 2017;390(10097):846–847. doi:10.1016/S0140-6736(17)31830-5
13. Wang CM, Chen ZX, Ma PC, et al. Oncological prognosis and morbidity of hepatectomy in elderly patients with hepatocellular carcinoma: a propensity score matching and multicentre study. *BMC Surg.* 2023;23(1):323. doi:10.1186/s12893-023-02230-0
14. Zhou H, Chen J, Liu K, Xu H. Prognostic factors and predictive nomogram models for early death in elderly patients with hepatocellular carcinoma: a population-based study. *Front Mol Biosci.* 2023;10:1275791. doi:10.3389/fmolb.2023.1275791
15. Wu FH, Shen CH, Luo SC, et al. Liver resection for hepatocellular carcinoma in oldest old patients. *World J Surg Oncol.* 2019;17(1):1. doi:10.1186/s12957-018-1541-0
16. Nozawa A, Kubo S, Takemura S, et al. Hepatic resection for hepatocellular carcinoma in super-elderly patients aged 80 years and older in the first decade of the 21st century. *Surg Today.* 2015;45(7):851–857. doi:10.1007/s00595-014-0994-1
17. Inoue Y, Tanaka R, Fujii K, et al. Surgical outcome and hepatic regeneration after hepatic resection for hepatocellular carcinoma in elderly patients. *Digest Surg.* 2019;36(4):289–301. doi:10.1159/000488327
18. Minami Y, Aoki T, Hagiwara S, Kudo M. Tips for Preparing and practicing thermal ablation therapy of hepatocellular carcinoma. *Cancers.* 2023;15(19):4763. doi:10.3390/cancers15194763
19. Zou YW, Ren ZG, Sun Y, et al. The latest research progress on minimally invasive treatments for hepatocellular carcinoma. *Hepatobiliary Pancreatic Dis Int.* 2023;22(1):54–63. doi:10.1016/j.hbpd.2022.08.004
20. Curley SA, Izzo F, Ellis LM, Nicolas Vauthey J, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann Surg.* 2000;232(3):381–391. doi:10.1097/0000658-200009000-00010
21. Ceppa EP, Collings AT, Abdalla M, et al. SAGES/AHPBA guidelines for the use of microwave and radiofrequency liver ablation for the surgical treatment of hepatocellular carcinoma or colorectal liver metastases less than 5 cm. *Surg Endosc.* 2023;37(12):8991–9000. doi:10.1007/s00464-023-10468-1
22. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology.* 2018;67(1):358–380. doi:10.1002/hep.29086
23. Carreca I, Balducci L, Extermann M. Cancer in the older person. *Cancer Treat Rev.* 2005;31(5):380–402. doi:10.1016/j.ctrv.2005.04.012
24. Osawa M, Akuta N, Suzuki F, et al. Prognosis and predictors of hepatocellular carcinoma in elderly patients infected with hepatitis B virus. *J med Virol.* 2017;89(12):2144–2148. doi:10.1002/jmv.24890
25. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet. Oncology.* 2008;9(7):629–635. doi:10.1016/S1470-2045(08)70153-0
26. Poisson J, Martinez-Tapia C, Heitz D, et al. Prevalence and prognostic impact of cachexia among older patients with cancer: a nationwide cross-sectional survey (NutriAgeCancer). *J Cachexia Sarcop Musc.* 2021;12(6):1477–1488. doi:10.1002/jcsm.12776
27. Zhang X, Pang L, Sharma SV, Li R, Nyitray AG, Edwards BJ. Malnutrition and overall survival in older patients with cancer. *Clin Nutr.* 2021;40(3):966–977. doi:10.1016/j.clnu.2020.06.026
28. Guo H, Wu T, Lu Q, et al. Hepatocellular carcinoma in elderly: clinical characteristics, treatments and outcomes compared with younger adults. *PLoS One.* 2017;12(9):e0184160. doi:10.1371/journal.pone.0184160
29. Ding W, Yu J, Liu F, et al. Percutaneous microwave ablation versus robot-assisted hepatectomy for early hepatocellular carcinoma: a real-world single-center study. *Digestive Liver Dis.* 2022;54(2):243–250. doi:10.1016/j.dld.2021.04.008
30. Koza A, Bhogal RH, Fotiadis N, Mavroeidis VK. The role of ablative techniques in the management of hepatocellular carcinoma: indications and outcomes. *Biomedicine.* 2023;11(4). doi:10.3390/biomedicine11041062
31. Galle PR, Tovoli F, Foerster F, Wörns MA, Cucchetti A, Bolondi L. The treatment of intermediate stage tumours beyond TACE: from surgery to systemic therapy. *J Hepatol.* 2017;67(1):173–183. doi:10.1016/j.jhep.2017.03.007
32. Nevola R, Tortorella G, Rosato V, et al. Gender differences in the pathogenesis and risk factors of hepatocellular carcinoma. *Biology.* 2023;12(7):984. doi:10.3390/biology12070984
33. Greten TF, Villanueva A, Korangy F, et al. Biomarkers for immunotherapy of hepatocellular carcinoma. *Nature reviews. Clin Oncol.* 2023;20(11):780–798. doi:10.1038/s41571-023-00816-4

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