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Original Article

Clinical-pathological characteristics and prognosis of elderly primary liver cancer patients

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Abstract: Primary liver cancer (PLC) is a highly malignant disease, with an increasing incidence among the elderly population. However, there is a lack of systematic evaluation regarding its progression, recurrence, and prognostic factors. This study aims to investigate the clinicopathologic characteristics of elderly patients with PLC and to establish predictive models for overall survival and recurrence risk in this population. A retrospective analysis was conducted on 460 elderly PLC patients admitted to Longyou County People's Hospital from January 2018 to December 2019. According to pathological types, patients were classified into hepatocellular carcinoma group (HCC, n=395), intrahepatic cholangiocarcinoma group (ICC, n=49), and combined hepatocellular-cholangiocarcinoma group (CHC, n=16). Based on clinical outcomes, patients were further grouped as survivors (n=228) and non-survivors (n=232), or recurrence (n=223) and non-recurrence (n=237) groups. To validate the predictive models, 210 elderly patients with PLC from the same hospital, admitted between January 2020 and December 2020, were included as a verification cohort. Demographic and clinical data collected included age, sex, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alpha-fetoprotein (AFP), tumor number, and tumor size. Univariate analysis was performed using the chi-square (χ^2) test. Then, multivariate logistic regression analysis was performed to identify independent risk factors and establish predictive models for mortality and recurrence. A Random Forest model was also constructed for comparison. Model performance was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) for discrimination, and the Hosmer-Lemeshow test for calibration. HCC predominated among male patients ($P<0.05$), with significantly higher AFP expression in males ($P<0.05$). Multivariate analysis identified age ≥80 years, AFP>400 ng/ml, multifocal tumors, tumor size >2 cm as independent predictors of mortality (all $P<0.05$). Additionally, hypertension, smoking, alcohol consumption, AFP>400 ng/ml, and tumor multiplicity were identified as independent predictors of postoperative recurrence ($P<0.05$). The constructed predictive models demonstrated good performance in both the training and validation cohorts. Comparative analysis showed similar predictive efficacy between logistic regression and Random Forest models (AUC for mortality prediction: 0.846/0.852 vs. 0.842/0.858, respectively; AUC for recurrence prediction: 0.756/0.762 vs. 0.761/0.764, respectively). The Hosmer-Lemeshow test suggested adequate model calibration ($P>0.05$). HCC is the most common form of PLC among elderly patients and is closely associated with metabolic and lifestyle factors. Advanced age, elevated AFP, multilocality, and larger tumor size increase mortality risk, while smoking and alcohol consumption further elevate recurrence risk. Early identification of high-risk patients, individualized intervention, and close postoperative follow-up focusing on modifiable risk factors are recommended to improve patient outcomes.

Keywords: Elderly, primary liver cancer, prognosis, recurrence, alpha-fetoprotein, multivariate analysis

Introduction

Primary liver cancer (PLC) is among the most common malignancies worldwide and ranks the 6th most prevalent cancer, accounting for the highest number of cancer-related deaths [1]. Most PLC cases are hepatocellular carcinoma (HCC), comprising approximately 75-85% of cases, followed by intrahepatic cholangiocarcinoma (ICC) and combined hepatocellular-cholangiocarcinoma (CHC) [2]. The 5-year survival rate of HCC remains low, less than 25%, largely due to delayed diagnosis [3]. HCC development is multifactorial, commonly associated with hepatic infections (hepatitis B and C), excessive alcohol consumption, and obesity, which can

lead to hepatic inflammation, fibrosis, cirrhosis, and steatosis [4]. Other risks factors include aflatoxin B1 exposure and viral oncogenesis [5].

With population aging, the number of elderly PLC patients is increasing. Elderly patients often present with multiple comorbidities, including hypertension, diabetes, cardiovascular disease, and may have reduced hepatic reserve, limiting their tolerance to surgical resection or transplantation. Preoperative frailty has been identified as an independent predictor of both short- and long-term outcomes in elderly HCC patients undergoing hepatectomy [6]. Individuals aged 65 years or older account for over 1/3 of all HCC cases [7]. Age-related declines in physiological function and immune responsiveness may contribute to more aggressive tumor behavior and a higher risk of recurrence [8].

Recurrence remains a major determinant of poor 5-year survival in elderly HCC patients, with reported intermediate- and late-phase recurrence rate of 94.7% and 90.7%, respectively [9, 10]. Recent advances in diagnostic techniques and multidisciplinary management have improved early detection and treatment outcomes. Established prognostic indicators encompass alpha-fetoprotein (AFP) levels [11], tumor morphology [12], tumor number [13], and tumor size [14]. However, the predictive value of these factors has not been systematically compared across different PLC subtypes.

To address these gaps, we conducted a retrospective study of 460 elderly PLC patients. Patients were stratified according to pathological subtype (HCC, ICC, CHC), and further classified based on 5-year survival and recurrence status. Demographic information, laboratory data, and tumor characteristics were comprehensively analyzed. Multivariate logistic regression analysis was used to identify independent predictors of survival and disease recurrence. This study aims to provide evidence-based guidance for risk stratification, clinical management, and individualized care of elderly PLC patients.

Materials and methods

Study subjects

This retrospective study included 460 elderly PLC patients who were treated at Longyou County People's Hospital between January 2018 and December 2019, as the training cohort. Patients were classified according to pathological types: HCC group (n=395), ICC group (n=49), and CHC group (n=16). For survival analysis, patients were divided into a survival group (n=228) and a death group (n=232) based on 5-year post-discharge outcomes. For recurrence analysis, patients were grouped into a recurrence group (n=223) and a non-recurrence group (n=237). A separate cohort of 210 elderly patients with PLC admitted between January 2020 and December 2020 were selected as a validation cohort to validate the performance of the mortality and recurrence risk models. Baseline characteristics of the training group and the validation cohorts are summarized in **Table 1**, showing no significant differences between the two groups (all $P>0.05$). This study was approved by the Ethics Committee of Longyou County People's Hospital.

Inclusion criteria: (1) age ≥60 years; (2) diagnosis of PLC based on pathological or clinical indication; (3) complete clinic data available; (4) patients with Child-Pugh class A-C liver function and all Barcelona Clinic Liver Cancer [BCLC] stages (0-D).

Exclusion criteria: (1) concurrent diagnosis of another primary malignant tumor; (2) metastatic or secondary liver cancer; (3) severe heart, lung, or kidney failure, or other end-stage disease, with an expected survival <3 months; (4) participants in other interventional clinical trials.

Diagnostic criteria

The diagnosis of PLC in patients with HBV or HCV infection and cirrhosis follows three scenarios:

1. Nodule ≤2 cm: Regular surveillance with ultrasound and AFP every six months is recommended. A nodule is considered clinically significant if at least two of the following four imaging modalities - dynamic contrast-enhanced MRI, dynamic contrast-enhanced CT, contrast-enhanced ultrasound, or Gd-EOB-DTPA-enhanced MRI - demonstrate the typical HCC "wash-in/wash-out" pattern (arterial phase hyperenhancement with portal venous and delayed phase washout). If only one modality shows

Table 1. Comparison of baseline data between training group and validation group [n (%)]

Indicator	Training set (n=460)	Validation set (n=210)	t/χ^2	*P*
Age			0.123	0.729
<80	361 (78.48)	161 (76.67)		
≥80	99 (21.52)	49 (23.33)		
Sex			0.074	0.791
Male	332 (72.17)	148 (70.48)		
Female	128 (27.83)	62 (29.52)		
Hypertension	71 (15.43)	28 (13.33)	0.341	0.558
Diabetes	72 (15.65)	36 (17.14)	0.226	0.637
Smoking	369 (80.22)	172 (81.90)	0.352	0.583
Alcohol consumption	169 (36.74)	82 (39.05)	0.288	0.598
ALT			1.753	0.186
≤40 U/L	165 (35.87)	68 (32.38)		
>40 U/L	295 (64.13)	142 (67.62)		
AST			0.897	0.346
≤40 U/L	148 (32.17)	62 (29.52)		
>40 U/L	312 (67.83)	148 (70.48)		
AFP			1.122	0.293
≤400 ng/mL	336 (73.04)	161 (76.67)		
>400 ng/mL	124 (26.96)	49 (23.33)		
Tumor number			0.003	0.985
Single	337 (73.26)	154 (73.33)		
Multiple	123 (26.74)	56 (26.67)		
Tumor size			0.045	0.835
≤2 cm	129 (28.04)	59 (28.10)		
>2 cm	331 (71.96)	151 (71.90)		

Notes: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; AFP, Alpha-fetoprotein.

typical features, ultrasound-guided liver biopsy or close imaging follow-up every 2-3 months is advised.

2. Nodule >2 cm: A single imaging modality demonstrating typical HCC features is sufficient for clinical diagnosis. If the nodule lacks typical imaging characteristics, histological confirmation via ultrasound-guided liver biopsy is required.

3. Elevated AFP without visible lesion: In patients with rising AFP levels, after excluding other causes such as pregnancy, active liver disease, germ cell tumor, or gastrointestinal cancer, close monitoring with AFP trends and repeated imaging every 2-3 months is recommended for early detection of HCC.

This approach ensures early detection and accurate diagnosis, particularly in high-risk elderly patients.

Observation indicators

(1) Demographic and clinical information: age, sex, history of hypotension, diabetes mellitus (DM), smoking, and alcohol consumption.

(2) Laboratory parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alpha-fetoprotein (AFP).

(3) Tumor characteristics: numbers of tumors and maximum tumor diameter.

Statistical analysis

All statistical analyses were performed using SPSS 26.0 and R 4.3.0. Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD) and compared using independent-sample t-test. Non normally distributed continuous variables were expressed as median (IQR) [M (P25, P75)] and

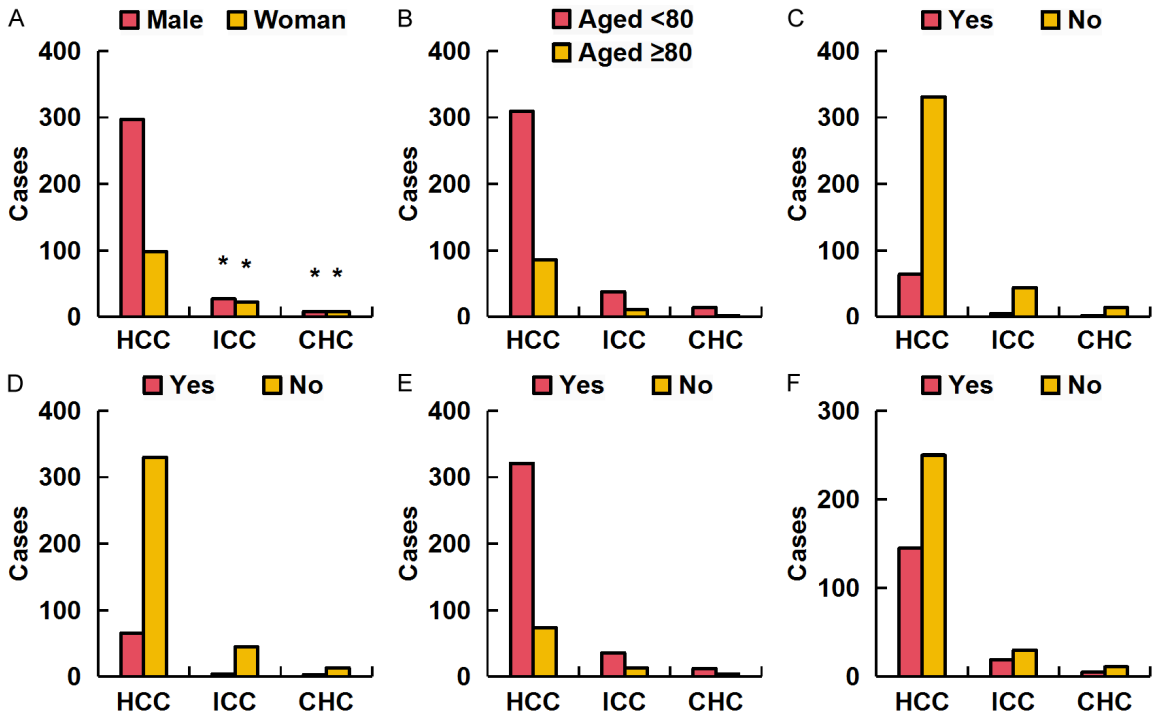

Figure 1. Comparison of demographic data between patients with different pathological subtypes. A: Sex; B: Age; C: Hypertension; D: Diabetes mellitus; E: Smoking; F: Alcohol consumption. Notes: HCC, hepatocellular carcinoma (n=395); ICC, intrahepatic cholangiocarcinoma (n=49); CHC, combined hepatocellular-cholangiocarcinoma (n=16). *P<0.05 compared to HCC group.

compared using the Mann-Whitney U test. Categorical variables were expressed as n (%) and analyzed using the χ^2 test.

Survival outcome was defined as death (yes/no), and recurrence outcome was defined as postoperative recurrence (yes/no). Variables with P<0.05 in univariate analysis, together with clinically relevant covariates, were included in multivariate analysis. Binary logistic regression and Random Forest algorithms were used to identify independent risk factors. Stepwise regression was applied, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Based on the multivariate analysis, two predictive models were developed: one for mortality and one for recurrence in elderly PLC patients. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and model calibration was evaluated by the Hosmer-Lemeshow goodness-of-fit test. All tests were two-sided, with P<0.05 considered statistically significant.

Results

Demographic characteristics by histopathological types

Baseline demographic and clinical characteristics of the training cohort (n=460), including 395 HCC, 49 ICC, and 16 CHC patients, are summarized in **Figure 1**. A male predominance was observed in the HCC group (P=0.033). No remarkable differences were observed among groups regarding age, history of smoking or alcohol consumption, or prevalence of hypertension or diabetes (*all P>0.05*).

Laboratory indices by histopathological types

Laboratory markers (ALT, AST, and AFP) stratified by PLC subtype are presented in **Figure 2**. A higher proportion of HCC patients exhibited ALT and AST levels >40 U/L compared with levels ≤40 U/L. AFP≤400 ng/mL were predominant in HCC patients, whereas the proportion of patients with AFP>400 ng/mL was minimal in the ICC and CHC groups (P=0.026), indicating greater specificity of elevated AFP for HCC.

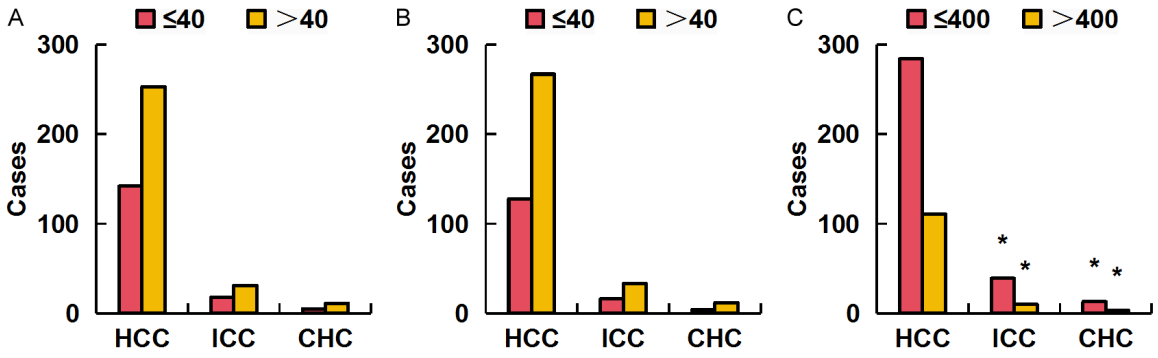

Figure 2. Comparison of laboratory indices among patients with different pathological subtypes. A: ALT; B: AST; C: AFP. Note: HCC, hepatocellular carcinoma (n=395); ICC, intrahepatic cholangiocarcinoma (n=49); CHC, combined hepatocellular-cholangiocarcinoma (n=16). *P<0.05 compared to HCC group.

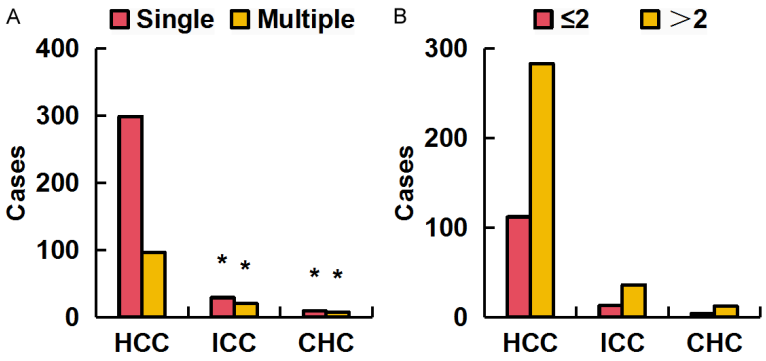

Figure 3. Comparison of tumor characteristics among patients with different pathological subtypes. A: Tumor number; B: Tumor size. Note: HCC, hepatocellular carcinoma (n=395); ICC, intrahepatic cholangiocarcinoma (n=49); CHC, combined hepatocellular-cholangiocarcinoma (n=16). *P<0.05 compared to HCC group.

Tumor characteristics by histopathological types

Tumor characteristics, including lesion number and maximum tumor size, are summarized in **Figure 3**. Tumor multiplicity differed significantly among the pathological subtypes (P=0.011), with HCC patients more frequently presenting with a single lesion. Tumor size distribution did not differ obviously across HCC, ICC, and CHC groups (P=0.092).

Demographic characteristics by different survival and recurrence status

The general clinical characteristics of patients stratified by survival and recurrence outcomes are presented in **Figure 4**. Male patients constituted the majority in both the survival and deceased groups, with no significant difference in gender distribution (P=0.082). Age distribution, however, differed significantly (P=0.029): patients aged <80 years predominated in the survival group, whereas those aged ≥80 years was more prevalent in the deceased group. The prevalence of comorbidities, including hypertension, diabetes, smoking, and alcohol consumption, was similarly distributed between survival and death groups (P=0.068).

In the recurrence analysis, no remarkable differences were noted in gender (P=0.073) or age distribution (P=0.082) between patients with and without tumor recurrence. However, hypertension was more prevalent in patients with recurrence compared to those in the non-recurrence group (P=0.037). Both smoking history and alcohol consumption were reported more frequently among patients with recurrence (P=0.035), whereas the prevalence of DM was balanced between the two subgroups (P=0.058).

Laboratory indices by different survival and recurrence status

Laboratory parameters (ALT, AST, AFP) stratified by survival and recurrence outcomes are shown in **Figure 5**. No significant differences were observed in ALT or AST levels between survival and death groups (P=0.062) or between recurrence and non-recurrence groups (P=0.082). In contrast, AFP levels differed sig-

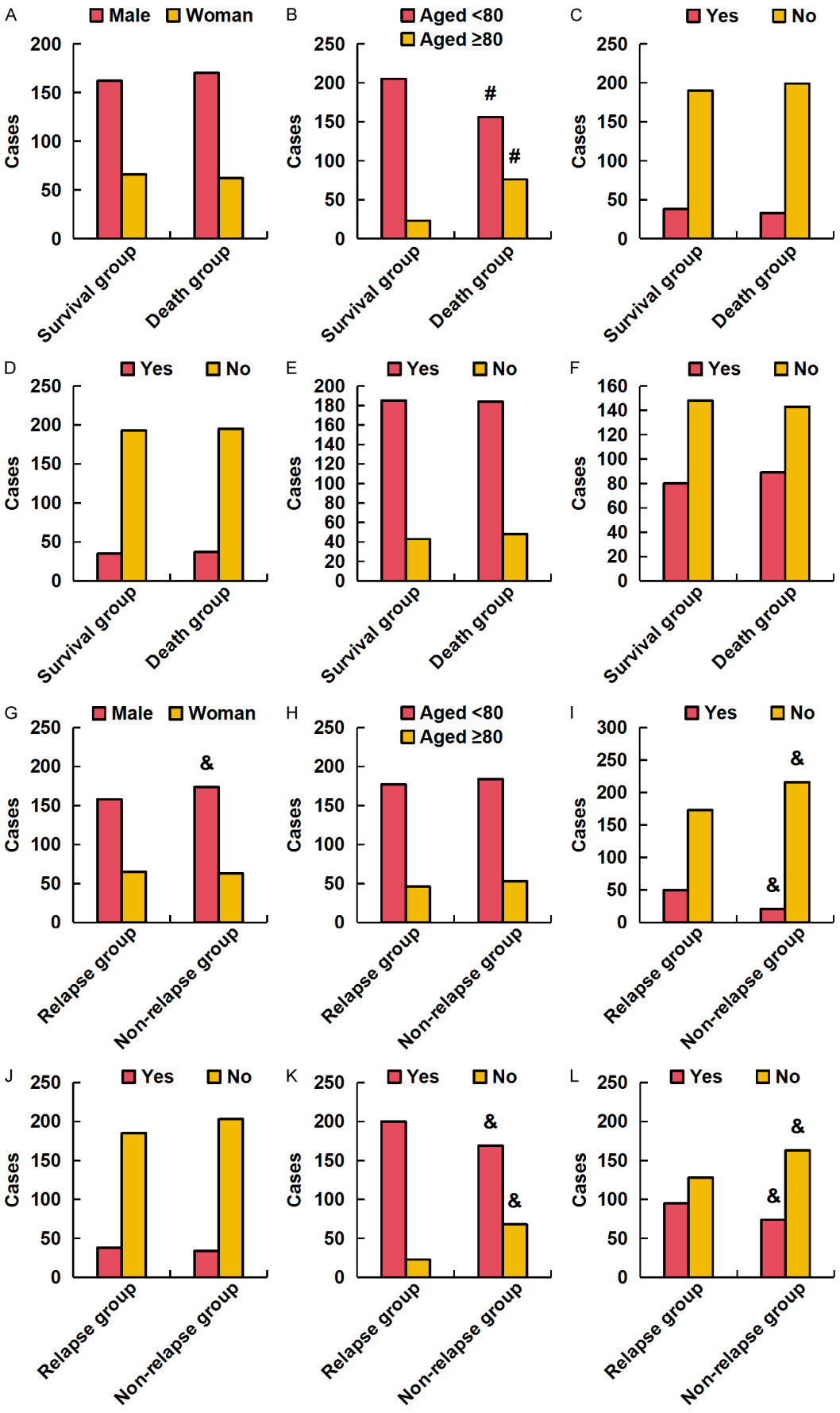
A
Male
Woman
Cases
Survival group
Death group
B
Aged <80
Aged ≥80
#
C
Yes
No
D
E
F
G
&
Relapse group
Non-relapse group
H
I
J
K
L

Figure 4. Comparison of demographic characteristics of patients stratified by survival status and recurrence status. (A-F) Comparison of gender (A), age (B), hypertension (C), diabetes mellitus (D), smoking (E), and alcohol consumption (F) for patients with different survival outcomes; (G-L) Comparison of gender (G), age (H), hypertension (I), diabetes mellitus (J), smoking (K), and alcohol consumption (L) for patients with different recurrence outcomes. Note: *P<0.05, compared to the survival group; &P<0.05, compared to the recurrence group.

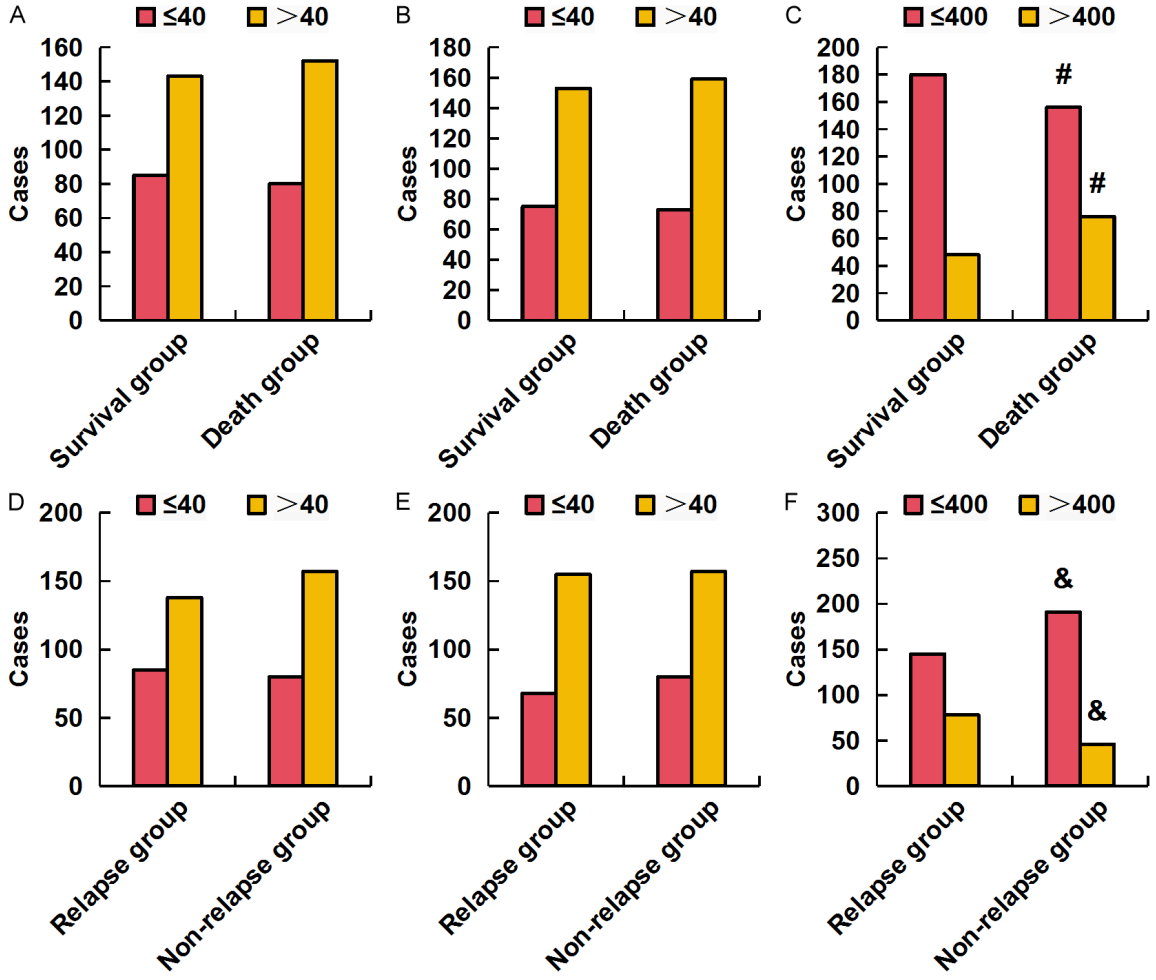

Figure 5. Comparison of laboratory indicators of patients stratified by survival and recurrence status. (A-C) Comparison of the levels of alanine aminotransferase (ALT) (A), aspartate aminotransferase (AST) (B), and alpha-fetoprotein (AFP) (C) between patients with different survival outcomes. (D-F) Comparison of the levels of ALT (D), AST (E), and AFP (F) between patients with different recurrence outcomes. Notes: *P<0.05, compared to the survival group; &P<0.05, compared to the recurrence group.

nificantly: the majority of patients in the survival and non-recurrence groups had AFP≤400 ng/mL, whereas patients in the death and recurrence groups had a higher proportion with AFP>400 ng/mL (survival vs. death: P=0.018; recurrence vs. non-recurrence: P=0.015).

Tumor characteristics by different survival and recurrence status

Figure 6 illustrates the distribution of tumor characteristics, including tumor number and size, in patients with different survival and recurrence outcomes. Patients with a solitary lesion predominated in the survival group, while multifocal lesions were more common in the survival group (P=0.028). Tumors ≤2 cm predominated in the survival group, whereas the death group had a considerably greater proportion of patients with tumors >2 cm (P=0.018).

Regarding recurrence, multifocal lesions were more frequent in the recurrence group, while

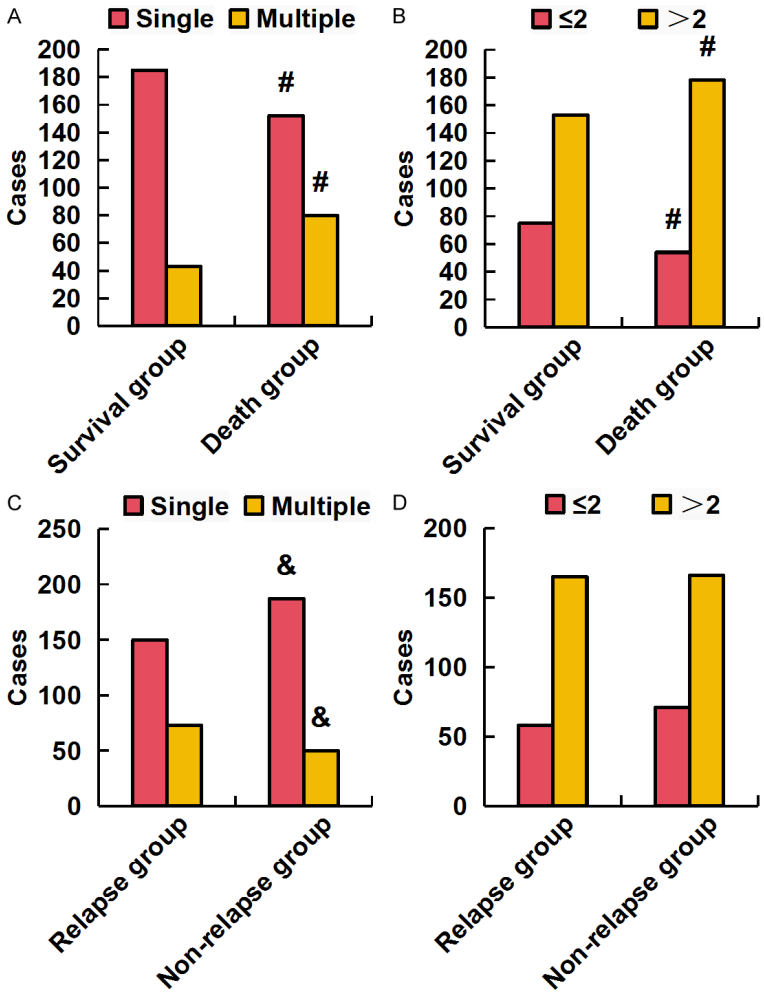

Figure 6. Comparison of tumor characteristics of patients stratified by survival and recurrence status. (A, B) Tumor number (A) and tumor size (B) of patients with different survival outcomes; (C, D) Tumor number (C) and tumor size (D) of patients with different recurrence outcomes. Notes: *P<0.05, compared to the survival group; &P<0.05, compared to the recurrence group.

solitary tumors predominated in the non-recurrence group (P=0.023). Tumor size did not differ significantly between recurrence and non-recurrence groups (P=0.082).

Multivariate logistic analysis of factors influencing prognosis

Multivariate logistic regression analysis identified age (OR=1.918; 95% CI: 1.582-2.501; P=0.001), AFP level >400 ng/mL (OR=1.776; 95% CI: 1.132-2.558; P=0.003), multiple tumors (OR=1.812; 95% CI: 1.338-2.456; P=0.002), and tumor size (OR=1.559; 95% CI: 1.201-2.028; P=0.003) as independent predictors of mortality (**Tables 2**, **3**).

Additionally, multivariate logistic analysis identified hypertension (OR=1.342; 95% CI: 0.925-1.947; P=0.038), smoking history (OR=1.823; 95% CI: 1.372-2.127; P=0.009), AFP>400 ng/mL (OR=1.766; 95% CI: 1.268-2.747; P=0.012), alcohol consumption (OR=1.328; 95% CI: 0.985-2.071; P=0.038), and the presence of multiple tumors (OR=1.538; 95% CI: 1.021-3.142; P=0.023) as independent predictors for recurrence (**Tables 4**, **5**).

Nomogram construction and validation

Two nomogram models were developed based on independent risk factors for mortality and recurrence. The mortality model was: logit(P) = -3.215 + 2.541 × Age + 1.681 × AFP + 2.193 × TumorNum + 1.445 × TumorSize (**Figure 7A**), and the recurrence model was: logit(P) = -2.874 + 1.194 × Hypertension + 1.612 × Smoking + 1.176 × Alcohol consumption + 1.424 × AFP + 1.212 × TumorNum (**Figure 7B**). The scoring system was established based on regression coefficients (β). A point-based scoring system was derived from the regression coefficients (β) by dividing each coefficient by a scaling factor (approximately 1.27) and rounding to the nearest integer, enabling practical clinical application.

Calibration curves showed good agreement between predicted and observed outcomes in both training (mortality: χ^2=3.892, P=0.369; recurrence: χ^2=3.589, P=0.386; **Figure 8A**, **8B**) and validation cohorts (mortality: χ^2=5.124, P=0.447; recurrence: χ^2=4.231, P=0.417; **Figure 8C**, **8D**), closely following the ideal 45° line.

As shown in **Figure 9**, the ROC analysis demonstrated satisfactory discriminative ability. For

Table 2. Multivariate logistic analysis on factors influencing the prognosis of elderly PLC patients

Indicator	*B*	*SE*	*OR*	*Wald* χ^2	*P*	*95% CI*
Age	2.541	0.203	1.918	17.216	0.001	1.582-2.501
AFP	1.681	0.165	1.776	9.156	0.003	1.132-2.558
Number of tumors	2.193	0.182	1.812	10.123	0.002	1.338-2.456
Tumor size	1.445	0.151	1.559	8.654	0.003	1.201-2.028

Notes: PLC, Primary Liver Cancer; AFP, Alpha-fetoprotein; B, Regression Coefficient; SE, Standard Error; OR, Odds Ratio.

Table 3. Assignment of prognosis model for elderly patients with primary liver cancer

Risk factor	Category definition	Assigned score	Rationale
Age≥80 years	Yes/No	2	Strong independent predictors of mortality
AFP>400 ng/mL	Yes/No	1	High tumor burden marker
Number of tumors (≥2)	Yes/No	2	Significantly associated with poor survival
Tumor size >2 cm	Yes/No	1	A larger size indicates aggressive disease

Notes: PLC, Primary Liver Cancer; AFP, Alpha-fetoprotein.

Table 4. Multivariate logistic analysis on factors influencing recurrence in elderly PLC patients

Indicator	*B*	*SE*	*OR*	*Wald* χ^2	*P*	*95% CI*
Hypertension	1.194	0.198	1.342	2.203	0.038	0.925-1.947
Smoking	1.612	0.176	1.823	9.467	0.009	1.372-2.127
Alcohol consumption	1.176	0.189	1.328	3.542	0.038	0.985-2.071
AFP	1.424	0.201	1.766	5.635	0.012	1.268-2.747
Number of tumors	1.212	0.228	1.538	2.764	0.023	1.021-3.142

Notes: PLC, Primary Liver Cancer; AFP, Alpha-fetoprotein; B, Regression Coefficient; SE, Standard Error; OR, Odds Ratio.

Table 5. Assignment of recurrence model for elderly patients with primary liver cancer

Risk factor	Category definition	Assigned Score	Rationale
Hypertension	Yes/No	1	Modest but statistically significant (P=0.038); modifiable
Smoking history	Yes/No	2	Strong lifestyle-related risk factor
Alcohol consumption	Yes/No	1	Clinically relevant despite borderline significance
AFP>400 ng/mL	Yes/No	2	Robust predictor of early recurrence
Number of tumors (≥2)	Yes/No	1	Reflects multifocal disease and residual risk

mortality, the AUCs of the logistic regression model were 0.846 (95% CI: 0.748-0.963) in the training set and 0.852 (95% CI: 0.753-0.972) in the validation set; while the Random Forest model showed similar performance (0.842 and 0.858, respectively) (**Figure 9A**, **9B**). For recurrence, the logistic regression model AUCs were 0.756 (95% CI: 0.673-0.847) and 0.762 (95% CI: 0.681-0.858), with the Random Forest model performing comparably (0.761 and 0.764) (**Figure 9C**, **9D**).

DCA indicated that the nomogram provided a higher net benefit than treating all or none across a wide range of threshold probabilities (mortality: 0.03-0.85; recurrence: 0.04-0.78) in both training and validation cohorts (**Figure 10A-D**), supporting the potential clinical utility of the models.

Discussion

In this study, we comprehensively analyzed the clinical data of 460 elderly PLC patients, comparing demographic data, laboratory indices, tumor biological behavior of different pathological types (HCC, ICC, CHC), survival status, and recurrence status. Multivariate Logistic regres-

Figure 7. Nomogram models for mortality (A) and recurrence (B) in elderly patients with primary liver cancer.

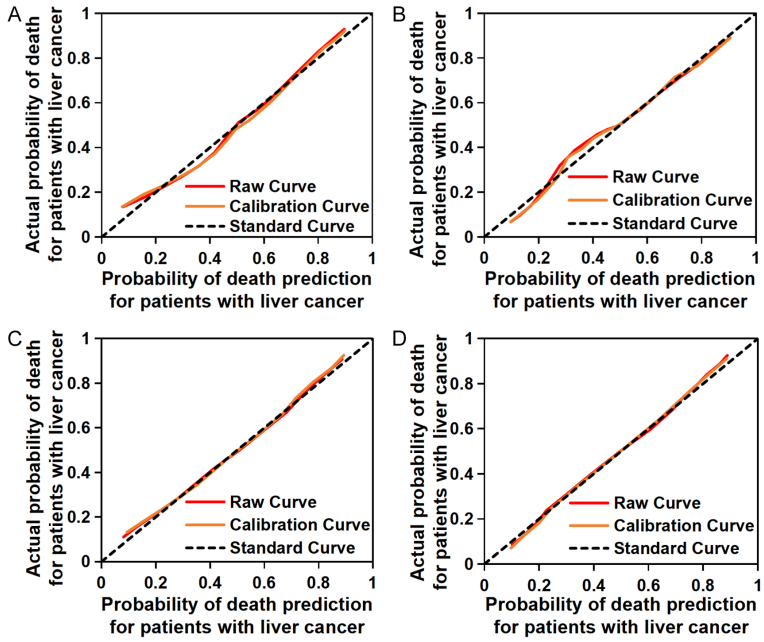

Figure 8. Calibration curves of the predictive nomograms for mortality and recurrence in both training and validation set. A: Mortality training set; B: Mortality validation set; C: Recurrence training set; D: Recurrence validation set.

sion analyses identified independent risk factors of overall survival (advanced age, AFP>400 ng/mL, multiple lesions, and larger tumor size) and recurrence (hypertension, smoking history, alcohol consumption, AFP>400 ng/ml, and multifocality). Based on these findings, two nomogram models for mortality and recurrence risk were constructed and validated, demonstrating good discrimination (AUC>0.75) and calibration (Hosmer-Lemeshow P> 0.05) in the training and validation cohorts.

HCC was the predominant subtype, accounting for 85.9% of the cohort, with a higher prevalence in males, consistent with the epidemiological pattern of HBV-related HCC in China. For instance, Guo et al. [15] a male-to-female ratio of 1.67:1 among 497 PLC patients, with 64.39% HBV positivity. AFP expression was significantly higher in HCC compared to ICC and CHC, reaffirming its clinical utility as a biomarker for HCC. Notably, genetic studies suggest distinct molecular profiles between AFP-positive and AFP-negative HCC, with AFP-negative HCC exhibiting enhanced amino acid metabolism [16]. Histological and immuno-histological analyses also indicate that AFP-producing neuroendocrine tumors harbor FGFR2 and TP53 gene mutation [17], highlighting molecular heterogeneity. HCC lesions were predominantly large and solitary, whereas ICC/CHC were more frequently multifocal. CHC tumors display biphenotypic characteristics, while ICC and HCC maintain subtype-specific phenotypes [18, 19], which may influence treatment strategies

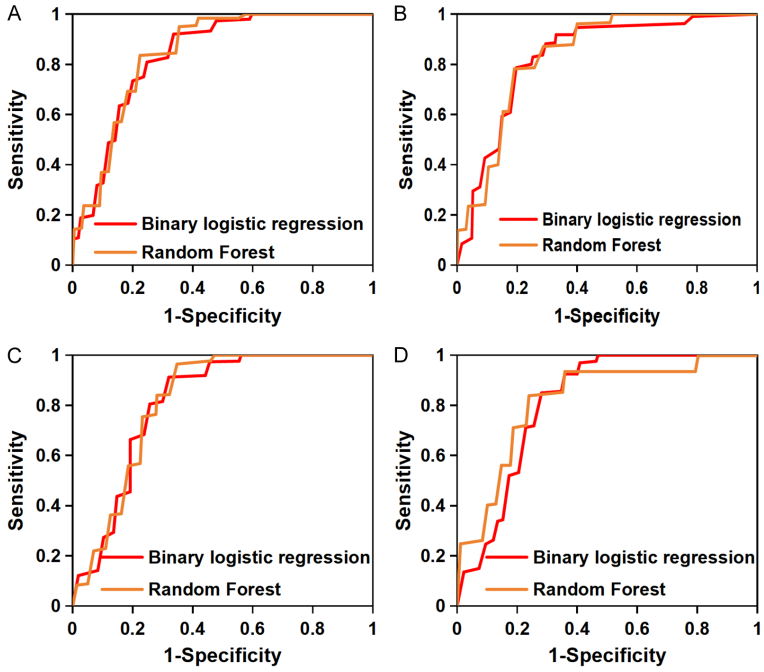

Figure 9. Predictive performance of mortality and recurrence risk models in the training and validation sets. A: Mortality training set; B: Mortality validation set; C: Recurrence training set; D: Recurrence validation set.

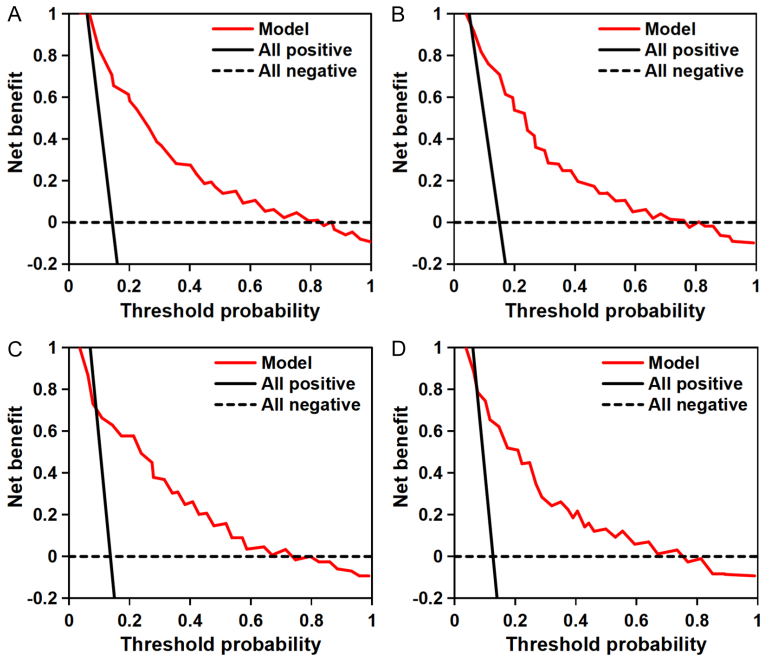

Figure 10. Decision curve analysis of the predictive nomogram for mortality and recurrence in both the training and validation cohorts. A: Mortality training set; B: Mortality validation set; C: Recurrence training set; D: Recurrence validation set.

and impact patient quality of life. Beaufrère [20] used a weakly supervised learning method for automated classification of PLC on routine biopsy specimens, showing promise in differentiating HCC and ICC based on histological features, potentially aiding in precision diagnosis and management.

In the survival analysis, advanced age (≥80 years), AFP >400 ng/ml, multifocal lesions, and tumor diameter >2 cm were identified as independent predictors of mortality in elderly PLC patients. Advanced age not only reflects diminished physiological reserves but is also associated with multiple comorbidities and reduced treatment tolerance, negatively influencing both treatment selection and outcomes. AFP serves as both a diagnostic marker and an indicator of tumor burden. High AFP levels have been linked to microvasculature invasion, satellite nodules, and early tumor spread [21-24]. Notably, AFP>400 ng/mL has been reported as an independent predictor of recurrence (HR 4.0, 95% CI 1.8-9.0) and poor overall prognosis [25]. For small tumors (2-3 cm), patients with elevated postoperative AFP may have better outcomes after hepatic resection compared to radiofrequency ablation (RFA), suggesting that AFP levels could inform treatment selection [26]. Additionally, Takaura et al. [27] reported that RFA may be a viable option for patients ≥80 years with tumors ≤3 cm. Ndow et al. [28] observed a median survival of 1.5 months among patients with multifocal disease (64% of cases, median size 7.5 cm). The mortality risk prediction model developed in this study demonstrated strong discriminative ability in both the training and validation cohorts, indicating

robust generalizability and minimal sensitivity to temporal or sample variations. The traditional logistic regression model performed comparably to the Random Forest algorithm, with minimal differences in AUC (<0.01) and extensive overlap of 95% CIs, indicating that the inclusion of complex machine learning methods did not yield significant improvements. This suggests that the logistic regression model constructed in this study adequately captured both linear and interactive relationships among key clinical variables. The advantages of the logistic regression model include its simplicity, transparency, and clinical interpretability. It provides clear OR and can be translated into a nomogram for intuitive risk assessment, facilitating individualized prognosis estimation and clinical decision-making. Calibration test demonstrated good agreement between predicted and observed outcomes, confirming the model's reliability and low risk of overfitting. In summary, age ≥80 years, AFP>400 ng/ml, multiple lesions, and tumor diameter >2 cm validated as core predictors of mortality with robust predictability. The model offers a practical tool for individualized treatment planning, adjustment of follow-up frequency, and early treatment.

In the analysis of recurrence risk, smoking was recognized as the most prominent independent predictor in the elderly PLC patients. Tobacco exposure introduces carcinogenic compounds that can induce DNA damage, impair immune surveillance, and contribute to microenvironments conducive to tumor recurrence. This highlights the importance of smoking cessation in post-operative management to reduce recurrence risk. Additionally, elevated AFP over 400/ng/ml and multifocal tumors were also confirmed as predictors of recurrence, consistent with the survival analysis. These factors are strongly associated with both biological aggressiveness and the potential for early recurrence. Yang et al. have demonstrated that AFP trajectories, rather than single baseline factor, provide valuable prognostic information for HCC recurrence, including in AFP-negative patients [29, 30]. Tumor size and multifocality are further associated with portal vein invasion and more aggressive tumor growth patterns [31]. Notably, age alone does not notably influence recurrence risk in elderly patients when adequate perioperative management is implemented [32]. Other reported factors, including COPD, poor prognostic nutritional index, satellite nodules, tumor encapsulation, and microvascular invasion [33, 34], also contribute to recurrence risk in this population. Beyond AFP, circulating tumor cells (CTCs) and composite biochemical indices (e.g., alkaline phosphatase + γ-glutamyl transferase/leukocyte ratio) have also been associated with tumor progression [35]. Although hypertension was identified as a weak independent risk factor in the model (OR=1.342), its high prevalence and modifiability confer public health significance. From a pathophysiological perspective, chronic hypertension may promote tumor recurrence by inducing vascular endothelial damage, enhancing angiogenesis via vascular endothelial growth factor (VEGF), creating a pro-inflammatory microenvironment, and altering hemodynamics to facilitate tumor cell extravasation and colonization. Therefore, for high-risk patients, strict systolic blood pressure control (below 130 mmHg) is recommended to mitigate these pro-recurrence mechanisms while reducing cardiovascular complications.

The recurrence risk prediction model developed in this study demonstrated stable and strong predictive performance in both the training and validation cohorts (AUCs>0.75). Though the discriminative ability was slightly lower than the mortality model, the model reliably identified elderly patients at high risk for postoperative recurrence. Calibration assessed by the Hosmer-Lemeshow test confirmed good agreement between predicted and observed recurrence events. Importantly, the model incorporated modifiable lifestyle and metabolic factors such as hypertension and smoking, which enhance its clinical utility. It facilitates individualized recurrence risk stratification and guides follow-up strategies. For high-risk patients, the model supports targeted interventions, such as smoking cessation with professional counseling and pharmacologic support (e.g., varenicline) and alcohol restriction (e.g., naltrexone), as well as intensified monitoring, including imaging every three months and monthly liver function tests.

Several limitations should be acknowledged in this study. First, it was a single-center retrospective study, with all subjects recruited from a single institution. This design inevitably introduces potential geographic bias and limits the

external generalizability of the predictive model, as patient demographics, surgical techniques, and perioperative management protocols may vary across regions and institutions. The absence of an independent external multicenter cohort for validation further constrains the robustness of the findings. Second, although the multivariate models were adjusted for clinically meaningful covariates, residual confounding cannot be fully excluded. Important factors such as Child-Pugh grade, BCLC stage, and treatment modality were not fully incorporated. The retrospective real-world cohort design inherently introduces indication bias, as treatment allocation was driven by disease severity and liver function. Stratified analyses based on specific treatment modalities or detailed Child-Pugh subclasses were not conducted to avoid sample fragmentation and selection bias. Third, the follow-up duration was relatively short, potentially leading to an underestimation of recurrence events. Long-term outcomes and late recurrences may therefore not have been fully captured. Future research should focus on large, multicenter prospective cohorts that integrate multidimensional data, including radiomics, genomics, and other molecular markers, to improve predictive accuracy and facilitate individualized risk stratification. Additionally, exploring molecular and mechanistic heterogeneity among disease subtypes could provide insights into tailored therapeutic strategies for elderly PLC patients.

Conclusion

This study comprehensively analyzed the clinicopathological data from elderly PLC patients and identified key differences in several characteristics among HCC, ICC, and CHC. Multivariate analysis showed that advanced older (≥80 years), AFP>400 ng/ml, multiple lesions, and tumor diameter >2 cm were independent predictors of patients survival. Additionally, hypertension, smoking, alcohol use, AFP>400 ng/mL, and multifocality were identified as independent risk factor for recurrence.

These findings underscore the need for early detection, accurate tumor staging, and rigorous postoperative follow-up in elderly PLC patients. More importantly, lifestyle modification, particularly smoking cession, are important to reduce the risk of recurrence. Moreover, routine evaluation of AFP levels, tumor number, and tumor size can help identify high-risk patients, guide individualized treatment strategies, and ultimately improve long-term survival and quality of life in this vulnerable population.

Disclosure of conflict of interest

None.

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