EJPMR, 2026, 13(9), 467-476 **Research Article** **Impact Factor: 8.158**

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

ISSN (O): 2394-3211
ISSN (P): 3051-2573
Coden USA: EJPMAG

DEVELOPMENT AND INTERNAL VALİDATİON OF A PREOPERATİVE CLİNİCAL PROGNOSTİC MODEL FOR OVERALL SURVİVAL AND RECURRENCE AFTER CURATİVE RESECTİON OF HEPATOCELLULAR CARCİNOMA

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Inonu University Faculty of Medicine, Department of Biostatistics and Medical Informatics, 44280, Malatya, Turkey. **DOI:** https://doi.org/10.5281/zenodo.22687281

How to cite this Article: Ipek Balikci Cicek*, Zeynep Kucukakcali. (2026). Development And Internal Validation of A Preoperative Clinical Prognostic Model For Overall Survival And Recurrence After Curative Resection of Hepatocellular Carcinoma. European Journal of Pharmaceuticaland Medical Research, 13(9), 467–476.
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Article Received on 14/08/2026 **Article Revised on 05/09/2026** **Article Published on 10/09/2026**

ABSTRACT

Background: Established staging systems for hepatocellular carcinoma (HCC), including the Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), and Tumor-Node-Metastasis (TNM) classifications, were primarily developed to inform treatment allocation and offer comparatively limited discriminative ability for individualized outcome prediction after curative resection. We aimed to develop and internally validate a prognostic model based exclusively on routinely available preoperative variables for overall survival (OS) and time-to-recurrence (TTR) following hepatic resection for HCC. **Methods**: We retrospectively analyzed an openly available cohort of 535 patients who underwent curative resection for histologically confirmed HCC. Multivariable Cox proportional hazards regression was used to construct separate models for OS and TTR from a candidate set of preoperative clinical and laboratory variables. Model performance was benchmarked against the BCLC, CLIP, and TNM staging systems using Harrell's concordance index (C-index), internally validated via 500-repetition bootstrap resampling with optimism correction, and evaluated for calibration and clinical utility using calibration plots and decision curve analysis (DCA). Because death without recurrence constitutes a competing risk for TTR, we additionally compared naive Kaplan-Meier estimates with Aalen-Johansen cumulative incidence functions. **Results**: Over a median follow-up of 42 months, 219 patients (40.9%) died and 245 (45.8%) developed recurrence. The multivariable OS model achieved a C-index of 0.658, and the TTR model achieved a C-index of 0.574; both exceeded the BCLC (0.556/0.539), CLIP (0.511/0.529), and TNM (0.502/0.493) systems. Bootstrap-corrected C-indices were 0.636 (OS) and 0.559 (TTR), indicating limited overfitting. Calibration was satisfactory across risk strata, and DCA demonstrated positive net benefit across a clinically plausible range of risk thresholds (5%-50%). Aalen-Johansen analysis indicated that naive Kaplan-Meier estimation overstated 5-year recurrence risk by approximately 5 percentage points relative to the competing-risk-adjusted estimate. Multiple tumor number was independently associated with lower, rather than higher, mortality risk in the multivariable model (hazard ratio 0.66); sensitivity analyses did not support this being a statistical artifact. **Conclusions**: A prognostic model built exclusively from routinely available preoperative variables demonstrated better discrimination than established staging systems, particularly for overall survival, together with satisfactory calibration and positive clinical net benefit after HCC resection. Discrimination for TTR remained modest despite outperforming the evaluated staging systems. External validation in independent cohorts is required before clinical implementation.

KEYWORDS: hepatocellular carcinoma; hepatectomy; prognostic model; nomogram; competing risks; recurrence; decision curve analysis.

1. INTRODUCTION

Hepatocellular carcinoma (HCC) remains among the most common causes of cancer-related death worldwide, with marked geographic variation in incidence driven largely by the prevalence of chronic viral hepatitis and cirrhosis.[1,2] Curative surgical resection continues to represent a cornerstone of treatment for patients with preserved liver function and localized disease; however,

postoperative recurrence remains frequent, and long-term survival is heterogeneous even among patients who undergo resection with curative intent.[2]

Several staging and prognostic systems are used in routine clinical practice, including the Barcelona Clinic Liver Cancer (BCLC) classification,[3] the American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) practice guidance documents that incorporate it,[4,5] the Cancer of the Liver Italian Program (CLIP) score,[6] and the Tumor-Node-Metastasis (TNM) system. These frameworks were developed principally to guide treatment allocation across the full spectrum of HCC presentations, from early-stage disease amenable to curative therapy to advanced, unresectable disease. Consequently, their ability to discriminate individual-level postoperative prognosis among patients who have already undergone curative resection—a comparatively favorable and biologically distinct subgroup—is often limited, since key variables driving these staging systems (tumor burden, performance status, and hepatic function on a coarse ordinal scale) do not fully capture the finer-grained clinical and laboratory heterogeneity relevant to postoperative outcomes. More objective liver function measures, such as the albumin-bilirubin (ALBI) grade, have therefore been proposed to refine assessment of hepatic functional reserve in patients with HCC.[7]

Efforts to improve postoperative risk stratification have included biomarker-based and pathology-based prognostic models. Lin and colleagues, using the same open-access cohort analyzed in the present study, demonstrated associations between autophagy-related tissue markers (LC3, Beclin-1, and p62) and overall survival following resection.[8] Because these markers require immunohistochemical analysis of resected tissue, however, they cannot inform preoperative counseling or surgical decision-making, and the original analysis did not address recurrence as a distinct, competing-risk-adjusted outcome. However, important methodological gaps remain in postoperative HCC prognostic modeling, including the exclusive use of preoperative variables, direct quantitative benchmarking against established staging systems, appropriate consideration of competing risks for recurrence, and assessment of calibration and clinical utility alongside discrimination, as recommended by contemporary prediction-model reporting standards.[9,10]

The present study was designed to address these methodological gaps. Our objectives were threefold: first, to develop a prognostic model for overall survival (OS) and time-to-recurrence (TTR) restricted to routinely available preoperative clinical and laboratory variables, in order to maximize clinical applicability at the point of preoperative counseling; second, to benchmark this model's discriminative performance against the BCLC, CLIP, and TNM staging systems and to assess its internal validity, calibration, and clinical utility using bootstrap resampling and decision curve analysis; and third, to model recurrence within an explicit competing-risks framework, given that a substantial proportion of patients die without recurrence.

2. METHODS

2.1 Data Source and Study Population

This study used an openly available dataset (S1 Dataset) published alongside Lin and colleagues in PLoS ONE (2018;13(9):e0202650) under a Creative Commons Attribution license.[8] The cohort comprises 535 consecutive patients with histologically confirmed HCC who underwent curative surgical resection between 2010 and 2014 at two Taiwanese centers (E-Da Hospital, Kaohsiung, and Changhua Christian Hospital). Median follow-up was 42 months (range, 1-84 months). No additional ethical approval was sought for the present secondary analysis, as the dataset is publicly available and fully de-identified.

2.2 Candidate Predictors

Analysis was restricted to variables routinely available before surgery, to maximize the clinical applicability of the resulting model at the point of preoperative counseling. Candidate variables were screened using univariable Cox regression; ten variables reaching a threshold of $p<0.10$ (sex, hypertension, smoking, preoperative aspartate aminotransferase [AST], preoperative platelet count, hepatitis C virus [HCV] status, cirrhosis, tumor number, tumor size ≥5 cm, and macrovascular invasion) were retained as the final predictor set for the OS model. Variables ascertainable only after resection (surgical approach, margin status, tumor differentiation grade, microvascular invasion) and immunohistochemical tissue markers (LC3, Beclin-1, p62) were excluded a priori, as these cannot inform decision-making before surgery.

2.3 Outcome Definitions

Two time-to-event outcomes were defined. Overall survival (OS) was calculated from the date of surgery to death from any cause or last follow-up. Time-to-recurrence (TTR) was calculated from the date of surgery to radiologically or histologically confirmed recurrence; patients who died without documented recurrence (n=64) were censored at the time of death in the primary TTR analysis. Because death without recurrence precludes subsequent recurrence and therefore constitutes a competing event, its impact was additionally evaluated using a competing-risk sensitivity analysis as described below. This definition was chosen deliberately to avoid conflating two biologically distinct processes, and is referred to throughout as TTR rather than the composite endpoint of disease-free or recurrence-free survival, which by convention counts death as an event regardless of recurrence status.

2.4 Statistical Analysis

Candidate variables were evaluated using univariable Cox proportional hazards regression[11], followed by

multivariable modeling of the retained predictor set. The proportional hazards assumption was assessed using Schoenfeld residual tests; macrovascular invasion in the TTR model showed a significant violation (p=0.007) and was therefore incorporated as a stratification variable rather than as a conventional covariate. Preoperative AST in the OS model showed evidence of a modest departure from the proportional hazards assumption (p≈0.03); this was not considered sufficiently pronounced to warrant additional stratification and is acknowledged as a model limitation.[12]

External benchmarking was performed by calculating Harrell's C-index for the BCLC, CLIP, and TNM staging systems using the same cohort and comparing these values directly with the C-index of the multivariable model.[13] Internal validation was performed using 500-repetition bootstrap resampling with optimism correction, following the approach described by Harrell and colleagues[13] and Steyerberg and colleagues.[14,15] Calibration was assessed at the 3-year time point by comparing model-predicted and Kaplan-Meier-observed survival probabilities across risk quartiles.[16]

Clinical utility was assessed using decision curve analysis (DCA) across a risk threshold range of 5%-50%.[17] A nomogram was constructed to translate the multivariable OS model into an accessible point-based scoring tool for clinical use, following established methodology for nomogram construction in oncology.[18]

2.5 Competing Risk Sensitivity Analysis

Because death without recurrence represents a competing risk for TTR, naive Kaplan-Meier estimation—which implicitly treats competing events as non-informative censoring—may overstate the cumulative incidence of recurrence.[19,20] We therefore compared naive Kaplan-Meier estimates of recurrence with Aalen-Johansen cumulative incidence function (CIF) estimates, which explicitly account for the competing risk of death. The Aalen-Johansen analysis was used as a descriptive sensitivity analysis to quantify the impact of competing mortality on cumulative recurrence estimates. Covariate-adjusted competing-risk regression was not performed and is acknowledged as a limitation.[19]

2.6 Sensitivity Analyses

Two additional sensitivity analyses were performed. First, because multiple tumor number was associated with lower, rather than higher, mortality risk in the multivariable OS model, a direction inconsistent with prior clinical literature on multifocal HCC,[21,22] we examined whether this reflected multicollinearity (via variance inflation factors), spurious correlation with other predictors, or instability upon variable removal. Second, because antiviral therapy is recorded only among patients with viral hepatitis (n=423 of 535), this variable was excluded from the primary predictor set to preserve the full analytic cohort. Given the well-established literature linking antiviral therapy after resection to reduced recurrence and improved survival in HBV-related HCC,[23, 24] its association with OS was examined separately in the viral-hepatitis subgroup; consistency was further assessed using multiple imputation (m=20 imputations, iterative imputation algorithm, pooled using Rubin's rules) applied to the full cohort.

All analyses were performed in Python (version 3.12) using the lifelines (version 0.30.3) and statsmodels libraries. Statistical significance was defined as a two-sided $p<0.05$.

3. RESULTS

3.1 Patient Characteristics

The study cohort comprised 535 patients (mean age, 63.1±11.5 years; 73.1% male) (Table 1). Over a median follow-up of 42 months, 219 patients (40.9%) died and 245 (45.8%) developed recurrence; 64 patients died without documented recurrence.

Table 1: Baseline Characteristics of the Study Population (N=535).

Characteristic	Value
Age, years, mean±SD	63.1 ± 11.5
Male sex, n (%)	391 (73.1)
Hypertension, n (%)	101 (18.9)
Diabetes mellitus, n (%)	59 (11.0)
Alcohol use, n (%)	129 (24.1)
Smoking, n (%)	152 (28.4)
Preoperative AST (IU/L), mean±SD	55.0 ± 37.9
Preoperative ALT (IU/L), mean±SD	50.5 ± 38.7
Preoperative platelet count (10^3/μL), mean±SD	175.0 ± 71.1
Preoperative AFP (ng/mL), median (IQR)	9.8 (4.2–141.7)
HBV positive, n (%)	271 (50.7)
HCV positive, n (%)	175 (32.7)
Cirrhosis, n (%)	173 (32.3)
Antiviral therapy (viral hepatitis	238 (56.3)

Characteristic	Value
subgroup, n=423), n (%)	
Multiple tumors, n (%)	97 (18.1)
Tumor size ≥5 cm, n (%)	183 (34.2)
Macrovascular invasion, n (%)	111 (20.7)
BCLC stage B/C, n (%)	193 (36.1)
CLIP score ≥2, n (%)	107 (20.0)
Median follow-up, months	42 (range, 1–84)
Mortality, n (%)	219 (40.9)
Recurrence, n (%)	245 (45.8)
Death without recurrence, n (%)	64 (12.0)

Kaplan-Meier estimates of OS and TTR are presented in Figure 1. One-, three-, and five-year OS were 91.0%, 72.3%, and 58.8%, respectively; corresponding recurrence-free probabilities were 90.3%, 66.1%, and 46.7%.

The cohort was predominantly composed of patients with viral hepatitis-related disease: HBV and HCV positivity were present in 50.7% and 32.7% of patients, respectively, and roughly one-third (32.3%) had established cirrhosis at the time of resection. Tumor characteristics were similarly heterogeneous, with 18.1% of patients presenting with multiple tumors, 34.2% with a dominant lesion ≥5 cm, and 20.7% with macrovascular invasion—together indicating that, despite all patients having undergone resection with curative intent, the cohort spanned a clinically meaningful range of tumor burden and hepatic reserve rather than representing a narrowly selected, uniformly early-stage population. This heterogeneity is reflected in the distribution of BCLC and CLIP categories, with over one-third of patients (36.1%) classified as BCLC stage B or C despite having undergone resection, underscoring that surgical candidacy in this cohort was not restricted to the earliest disease stages.

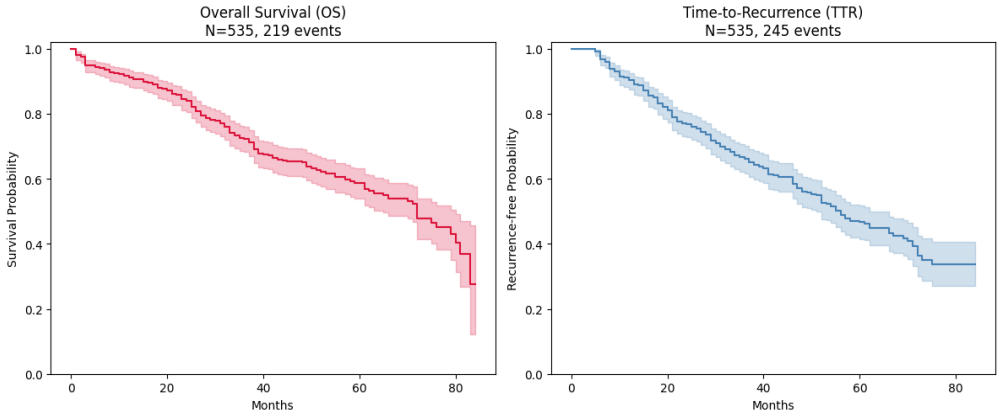

Figure 1. Kaplan-Meier Curves for Overall Survival (OS) and Time-to-Recurrence (TTR).
Shaded bands represent 95% confidence intervals.

3.2 Univariable and Multivariable Cox Regression

On univariable analysis, hypertension, antiviral therapy, HCV status, smoking, and macrovascular invasion were among the variables most strongly associated with OS (Table 2).

Table 2. Univariable Cox Regression for Overall Survival (Variables With p<0.10).

Variable	N	HR	95% CI	p
Hypertension	535	1.850	1.364–2.508	<0.001
Antiviral therapy	423	0.557	0.410–0.759	<0.001
HCV	535	0.604	0.446–0.817	0.001
Smoking	535	0.640	0.469–0.873	0.005
Macrovascular invasion	535	1.529	1.128–2.072	0.006
Preoperative platelet count	535	1.002	1.000–1.004	0.011
Tumor size ≥5 cm	535	1.418	1.081–1.860	0.012
Sex	535	0.694	0.521–0.922	0.012

Variable	N	HR	95% CI	p
Preoperative AST	535	1.004	1.001–1.008	0.012
Cirrhosis	535	0.742	0.550–1.000	0.050
Tumor number (multiple)	535	0.719	0.492–1.052	0.089

A parallel univariable screen was performed for TTR (Table 3).

Table 3: Univariable Cox Regression for Time-to-Recurrence (Variables With p<0.10).

Variable	N	HR	95% CI	p
Antiviral therapy	423	0.616	0.464–0.818	<0.001
Macrovascular invasion	535	1.504	1.126–2.010	0.006
Sex	535	0.716	0.545–0.941	0.017
Age	535	1.012	1.001–1.023	0.038
Cirrhosis	535	0.750	0.568–0.991	0.043
HCV	535	0.765	0.584–1.003	0.052
Preoperative platelet count	535	1.002	1.000–1.003	0.070

Comparison of Tables 2 and 3 indicates only partial overlap between the univariable predictors of OS and TTR. Macrovascular invasion, sex, and cirrhosis were associated with both outcomes in a broadly consistent direction, whereas hypertension, smoking, and preoperative AST reached significance only for OS, and age reached significance only for TTR. This divergence, evident even at the univariable stage, motivated our decision to model OS and TTR as separate, outcome-specific endpoints rather than assuming a shared predictor set, and is revisited in the Discussion.

In the multivariable OS model (N=535, C-index=0.658), hypertension (HR=1.59, 95% CI 1.15-2.19, p=0.005), preoperative AST (HR=1.004, p=0.029), HCV status (HR=0.68, p=0.014), tumor number (HR=0.66, p=0.044), and macrovascular invasion (HR=1.48, p=0.046) were independently associated with OS (Table 4A). In the multivariable TTR model (stratified by macrovascular invasion, C-index=0.574), sex was independently associated with recurrence (HR=0.72, p=0.020; Table 4B).

Table 4: Multivariable Cox Regression Analysis.

4A. Overall Survival (OS)

Variable	HR	95% CI	p
Sex	0.806	0.588–1.106	0.182
Hypertension	1.589	1.154–2.189	0.005
Smoking	0.808	0.573–1.140	0.224
Preoperative AST	1.004	1.000–1.007	0.029
Preoperative platelet count	1.001	0.999–1.003	0.282
HCV	0.677	0.495–0.925	0.014
Cirrhosis	0.766	0.547–1.072	0.120
Tumor number (multiple)	0.662	0.444–0.988	0.044
Tumor size ≥5 cm	0.951	0.669–1.352	0.780
Macrovascular invasion	1.482	1.007–2.181	0.046

4B. Time-to-Recurrence (TTR, stratified by macrovascular invasion).

Variable	HR	95% CI	p
Sex	0.722	0.549–0.951	0.020
Age	1.009	0.998–1.020	0.116
Preoperative platelet count	1.001	0.999–1.002	0.517
HCV	0.781	0.594–1.027	0.077
Cirrhosis	0.828	0.615–1.115	0.214

Macrovascular invasion was used as a stratification variable owing to violation of the proportional hazards assumption; no hazard ratio is reported for this variable.

Several variables retained after univariable screening did not retain independent associations in the multivariable models. In the OS model, smoking and preoperative platelet count were no longer independently associated with OS after multivariable adjustment. Conversely, tumor number remained independently associated with OS despite its relatively modest univariable association; the unexpected direction of this association is further examined in the sensitivity analyses (Section 3.6). In the TTR model, sex remained independently associated with recurrence (HR=0.72, 95% CI 0.55–0.95, p=0.020), whereas age, preoperative platelet count, HCV status,

and cirrhosis were not independently associated with TTR.

3.3 Comparison With Established Staging Systems

The multivariable preoperative model demonstrated higher C-indices than the BCLC, CLIP, and TNM staging systems for both OS and TTR (Table 5). The difference was more pronounced for OS than for TTR.

Table 5: C-index Comparison With Established Staging Systems.

Model	OS C-index	TTR C-index
Preoperative model (this study)	0.658	0.574
BCLC staging	0.556	0.539
CLIP score	0.511	0.529
TNM staging	0.502	0.493

For OS, the preoperative model achieved a C-index of 0.658, compared with 0.556 for BCLC, 0.511 for CLIP, and 0.502 for TNM. For TTR, the corresponding C-indices were 0.574, 0.539, 0.529, and 0.493, respectively. The difference between the preoperative model and BCLC was approximately 0.10 for OS and 0.04 for TTR.

3.4 Internal Validation, Calibration, Nomogram, and Clinical Utility

Bootstrap internal validation yielded optimism-corrected C-indices of 0.636 for OS and 0.559 for TTR (Table 6), corresponding to optimism estimates of 0.023 and 0.016, respectively.

Table 6: Bootstrap Internal Validation (500 Resamples).

Outcome	Apparent C-index	Optimism	Corrected C-index
OS	0.658	0.023	0.636
TTR	0.574	0.016	0.559

After optimism correction, the OS model retained a higher C-index than BCLC (0.636 versus 0.556), while the corresponding values for the TTR model and BCLC were 0.559 and 0.539, respectively.

A nomogram translating the multivariable OS model into a point-based scoring system is presented in Figure 2. For a patient with the mean covariate profile, predicted 1-, 3-, and 5-year survival probabilities were 91.9%, 73.9%, and 59.9%, respectively.

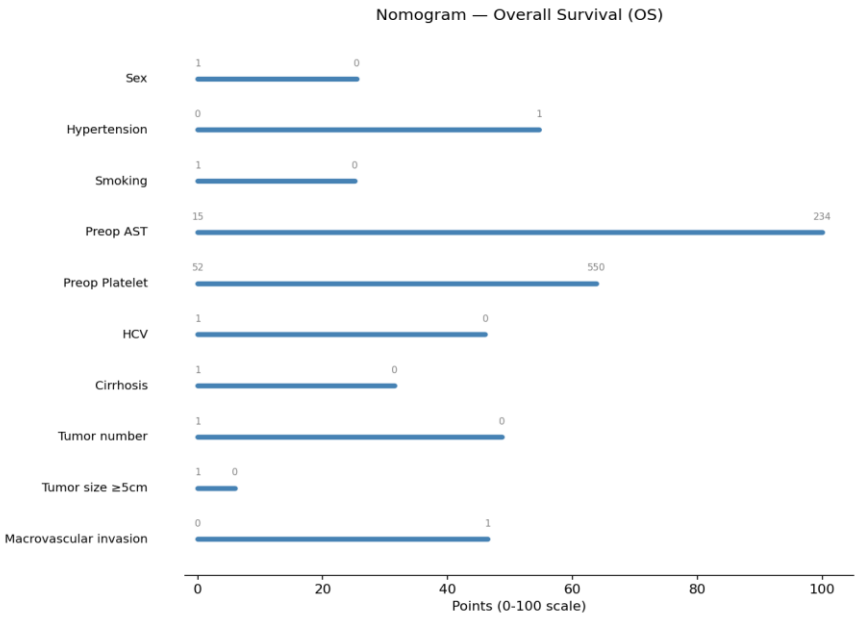

Figure 2. Nomogram for Overall Survival (OS).

Points assigned to each variable are summed to yield 1-, 3-, and 5-year survival probability estimates.

Three-year calibration analysis showed close agreement between predicted and observed survival probabilities across risk quartiles (Figure 3).

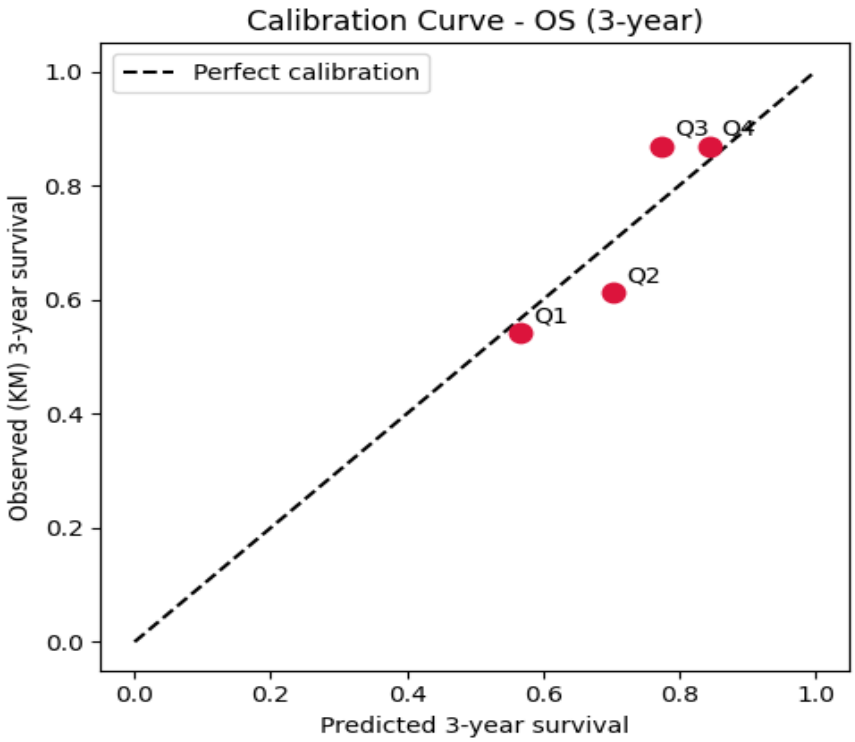

Figure 3. Calibration Curve for OS (3-Year).

Decision curve analysis demonstrated positive net benefit for the model relative to both "treat all" and "treat none" strategies across the entire 5%–50% risk threshold range (Figure 4).

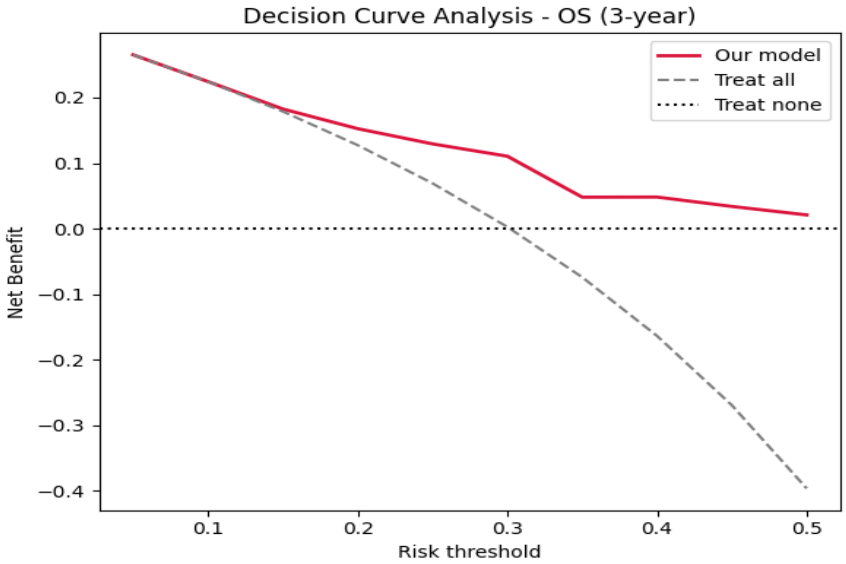

Figure 4. Decision Curve Analysis for OS (3-Year).

3.5 Competing Risk Analysis

Naive Kaplan-Meier estimation yielded a higher 5-year cumulative recurrence risk than the Aalen-Johansen cumulative incidence estimate (53.3% versus 48.2%), corresponding to a difference of approximately 5 percentage points (Figure 5). The corresponding differences at 1 and 3 years were approximately 0.6 and 2.5 percentage points, respectively.

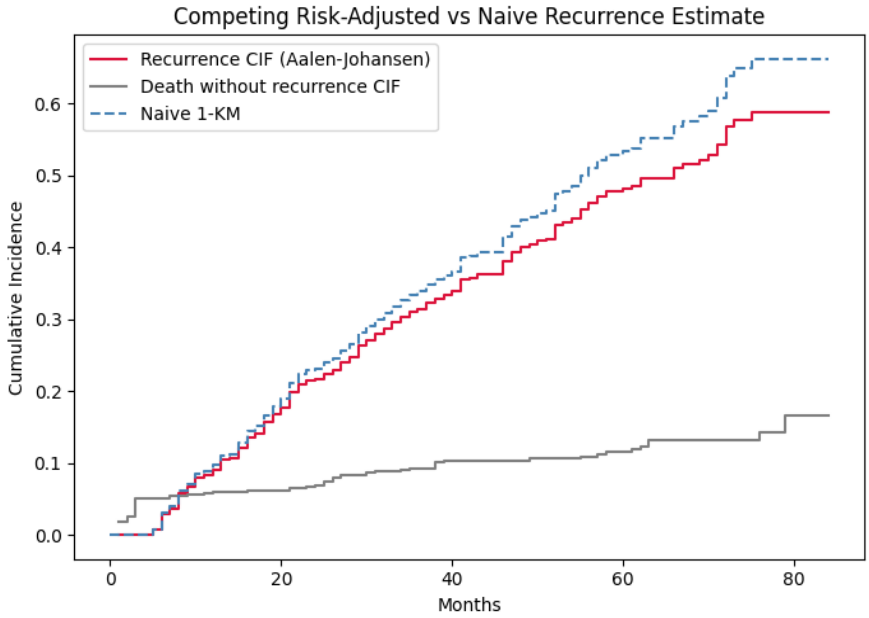

Figure 5. Competing Risk Analysis: Aalen-Johansen Cumulative Incidence Versus Naive Kaplan-Meier Estimation.

3.6 Sensitivity Analyses

Tumor number: The inverse association between multiple tumor number and mortality risk observed in the multivariable OS model (HR=0.66) was further examined in sensitivity analyses. No substantial multicollinearity was identified (VIF=1.27; all model variables VIF <5), and the maximum pairwise correlation with other covariates was r=0.15. The direction of association was consistent with the univariable estimate (HR=0.72, p=0.089) and with the unadjusted mortality rates (single tumor: 188/438 [42.9%]; multiple tumors: 31/97 [32.0%]). Removal of tumor number resulted in only a small change in model discrimination (C-index: 0.652 versus 0.658 for the full model).

Table 7: Antiviral Therapy Among the Viral Hepatitis Subgroup (n=423).

Variable	HR	95% CI	p
Sex	0.612	0.419–0.894	0.011
Hypertension	1.287	0.875–1.893	0.200
Smoking	0.894	0.588–1.358	0.599
Preoperative AST	1.005	1.001–1.009	0.009
Preoperative platelet count	1.001	0.999–1.004	0.311
HCV	0.542	0.379–0.773	0.001
Cirrhosis	1.140	0.783–1.659	0.494
Tumor number (multiple)	0.675	0.434–1.051	0.082
Tumor size ≥5 cm	1.238	0.832–1.841	0.292
Macrovascular invasion	1.445	0.917–2.275	0.112
Antiviral therapy	0.520	0.377–0.715	<0.001

4. DISCUSSION

In this analysis of 535 patients undergoing curative resection for HCC, a prognostic model restricted to routinely available preoperative clinical and laboratory variables demonstrated higher discrimination than the BCLC, CLIP, and TNM staging systems for both OS and TTR, with a more pronounced improvement for OS. This finding is consistent with the conceptual distinction between staging systems designed primarily to guide treatment allocation across the spectrum of HCC and prognostic models developed specifically to stratify risk within an already-selected surgical population. The latter can incorporate more detailed preoperative clinical and laboratory information that may not be fully captured by conventional staging categories.[3,4,6]

The inverse association between multiple tumor number and mortality risk warrants careful interpretation. Sensitivity analyses showed no substantial multicollinearity, only weak correlation with other model covariates, a consistent direction of association in univariable and multivariable analyses, and minimal change in model discrimination after removal of tumor number. One possible clinical explanation relates to the distinction between intrahepatic metastasis and multicentric carcinogenesis as mechanisms underlying

multifocal HCC. Previous studies have reported more favorable outcomes for multicentric occurrence than for intrahepatic metastatic spread, potentially reflecting differences in underlying tumor biology.[21,22] However, given the relatively small number of patients with multiple tumors in our cohort (n=97), the unexpected direction of the association, and the absence of pathological information regarding clonal origin, this finding should be considered hypothesis-generating and requires confirmation in independent cohorts.

Our competing-risk analysis showed that Kaplan-Meier estimation yielded a higher cumulative recurrence estimate than the Aalen-Johansen approach, with a difference of approximately 5 percentage points at 5 years. This finding is consistent with the established principle that Kaplan-Meier estimates may overestimate the cumulative incidence of an event when competing events are treated as non-informative censoring.[19,20] Given that 12% of patients in this cohort died without documented recurrence, the observed difference highlights the importance of considering competing mortality when estimating recurrence after HCC resection.

In the viral hepatitis subgroup, antiviral therapy was independently associated with improved postoperative survival, and the direction of this association was maintained in the multiple-imputation analysis. This finding is consistent with previous evidence demonstrating favorable postoperative outcomes associated with antiviral therapy in viral hepatitis-related HCC.[23,24] Although antiviral therapy was not included in the primary model because of its structural missingness outside the viral hepatitis subgroup, these findings support its clinical relevance in the perioperative management of affected patients.

Beyond discrimination, calibration and decision curve analysis provided complementary information on model performance. The agreement between predicted and observed 3-year survival probabilities across risk quartiles supports the calibration of the OS model within the study cohort. Decision curve analysis also demonstrated positive net benefit relative to the “treat all” and “treat none” strategies across the evaluated 5%–50% threshold range. These findings suggest potential clinical utility, but should not be interpreted as establishing specific treatment or surveillance thresholds. Prospective evaluation would be required before the model could be incorporated into clinical decision-making.

These findings should also be considered in the context of existing prognostic models for HCC.[18] Many published models incorporate postoperative pathological variables, such as microvascular invasion, tumor differentiation grade, or margin status, which may improve prognostic performance but are unavailable at the time of preoperative counseling. By restricting the candidate predictor set to routinely available preoperative variables, the present model prioritizes applicability before surgery, although potentially at the expense of some discriminative performance. The original analysis of the same cohort by Lin and colleagues[8] incorporated immunohistochemical tissue markers obtained after resection. The present approach therefore addresses a different clinical time point by focusing on information available before surgery.

5. LIMITATIONS

Several limitations warrant consideration. First, this retrospective analysis was based on 535 patients without an external validation cohort; therefore, the generalizability of the model performance and the unexpected association between multiple tumor number and OS remains to be established in independent populations. Second, our TTR endpoint differs from the conventional composite endpoint of disease-free or recurrence-free survival, which counts death as an event regardless of recurrence status; this distinction should be considered when comparing our estimates with those of previous studies. Third, preoperative AST showed evidence of a modest departure from the proportional hazards assumption in the OS model ($p \approx 0.03$); no additional stratification was applied, and this should be considered when interpreting the corresponding effect estimate. Fourth, the competing-risk analysis was limited to descriptive comparison of Kaplan-Meier and Aalen-Johansen estimates, and covariate-adjusted competing-risk regression was not performed. Fifth, antiviral therapy was recorded only among patients with viral hepatitis and therefore could not be incorporated into the primary model for the full cohort. Finally, the inverse association between multiple tumor number and mortality remains unexplained, and the proposed distinction between multicentric carcinogenesis and intrahepatic metastasis cannot be evaluated without pathological or molecular information on clonal origin. This finding should therefore be regarded as hypothesis-generating pending confirmation in independent cohorts.

6. CONCLUSIONS

A prognostic model developed exclusively from routinely available preoperative clinical variables demonstrated higher discrimination than established staging systems, particularly for overall survival, together with satisfactory calibration and positive clinical net benefit after curative resection for hepatocellular carcinoma. Competing-risk analysis showed that accounting for death without recurrence meaningfully affected cumulative recurrence estimates compared with conventional Kaplan-Meier analysis. Pending external validation in independent cohorts, this model may provide a practical tool to support individualized risk stratification and preoperative counseling in patients being evaluated for curative resection of hepatocellular carcinoma.

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