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Mimicking Borderline Resectable Population in Solitary Hepatocellular Carcinoma of BCLC Stage A

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Abstract

Background

Early recurrence (≤ 6 months) after curative resection of hepatocellular carcinoma (HCC) carries markedly worse prognosis than late recurrence. While borderline resectable (BR1/BR2) HCC is defined anatomically, a biologically high-risk subgroup with BR-like features may exist within resectable (R) disease; we developed and validated a preoperative score to identify such patients within BCLC Stage A primary HCC.

Methods

We analyzed a single-center discovery cohort of 473 patients with solitary BCLC Stage A primary HCC (2001–2021) and a later validation cohort of 63 patients (2022–2025). An additive 2-factor score (0–2) combined tumor size (≥ 60 mm) and PIVKA-II (≥ 50 mAU/mL); ROC/Youden-index analysis in the same cohort yielded closely similar thresholds. Bootstrap resampling that re-derived cutoffs within each replicate showed a less optimistic, more variable AUC than the fixed-cutoff model.

Results

Early recurrence occurred in 44/473 (9.3%) discovery patients and carried worse 5-year overall survival than late or no recurrence (38.1% vs. 78.4% vs. 94.6%; $p < 0.001$). Tumor size ≥ 60 mm (OR 3.94) and PIVKA-II ≥ 50 mAU/mL (OR 2.27) were independent predictors. The score stratified early-recurrence risk in discovery (score 0/1/2: 4.4%/7.7%/27.9%; AUC 0.694, optimism-corrected 0.662–0.692) and validation cohorts (5.6%/12.2%/50.0%; AUC 0.664, 95% CI 0.421–0.870), and was independently associated with distant recurrence after adjustment for early-recurrence status (adjusted OR 3.01 per point, $p < 0.001$).

Conclusions

A simple 2-factor score combining tumor size and PIVKA-II identifies, within solitary BCLC Stage A HCC, a high-risk subgroup whose recurrence mimics borderline resectable (BR1) disease. Preoperative (neoadjuvant) systemic therapy in this high-risk group warrants prospective evaluation.

Introduction

Hepatocellular carcinoma (HCC) remains one of the most common causes of cancer death worldwide [1], and liver resection remains a cornerstone of curative treatment for patients with preserved liver function and localized disease [2]. Even after curative (R0) resection, however, intrahepatic recurrence is common, and the timing of recurrence carries major prognostic significance: recurrence within the first

several months after surgery is generally attributed to occult microvascular invasion or dissemination already present at surgery, whereas later recurrence more often represents metachronous multicentric carcinogenesis in the remnant, cirrhotic liver and carries a comparatively favorable prognosis [3–5].

Early recurrence, rather than recurrence per se, is therefore the clinically relevant target for risk stratification: patients at high risk could be considered for intensified postoperative surveillance, referral for (neo)adjuvant systemic therapy trials, or reconsideration of surgical strategy [6]. This distinction was reflected in our own cohort's overall survival by recurrence timing (Fig. 1; see Results).

Postoperative pathological features — most notably microvascular invasion and infiltrative/poorly differentiated histology — are well-established risk factors for early recurrence [4, 7], but are available only after resection. Tumor size correlates with microvascular invasion and higher tumor grade [7], and PIVKA-II similarly correlates with microvascular invasion and aggressive tumor biology [8]; both are measured routinely before surgery, making them attractive surrogates for occult aggressive biology. Our group has previously reported similar preoperative recurrence-risk markers in other liver malignancies [9–11].

We hypothesized that a simple, additive score combining preoperative tumor size and PIVKA-II could identify a biologically high-risk subgroup, within resectable (R) BCLC Stage A HCC, whose recurrence mimics borderline resectable (BR1) disease. We derived cutoffs and the score in a discovery cohort, examined discrimination, calibration, and internal validation, and tested it in a chronologically later (temporal) validation cohort, also comparing it against a more complex model given the statistical challenges of multivariable modeling in cohorts with limited events [12].

Patients and Methods

Study design and patients

This retrospective, single-center study was conducted at Osaka International Cancer Institute and included two chronologically distinct cohorts of patients undergoing curative hepatectomy for primary, treatment-naïve HCC of Barcelona Clinic Liver Cancer (BCLC) Stage A [2], restricted to a solitary tumor of any size (without macrovascular invasion or extrahepatic spread), preserved liver function (Child-Pugh A or B7), and ECOG performance status 0–1; the few patients with multiple (up to three, ≤ 3 cm) tumors otherwise meeting BCLC Stage A criteria were excluded to keep the cohort homogeneous. The discovery cohort comprised 477 consecutive eligible patients treated between 2001 and 2021; 4 were excluded for indeterminate 6-month recurrence status, leaving 473. The validation cohort comprised 63 consecutive patients treated at the same institution between 2022 and 2025, with complete 6-month recurrence status.

Outcome definition

The primary outcome was early recurrence, defined as radiologically or pathologically confirmed intrahepatic or extrahepatic recurrence within 6 months of hepatectomy; this threshold was chosen a priori, before outcome analyses, because recurrence within approximately 6 months is attributed in prior literature predominantly to occult microvascular invasion or dissemination already present at surgery, whereas later recurrence more often reflects metachronous carcinogenesis [3–5]. Recurrence beyond 6 months (late vs. none) was recorded separately for the supporting survival analysis (Fig. 1) only.

Candidate predictors and data handling

Candidate preoperative variables included age, sex, Child-Pugh class, albumin, prothrombin time, ICG-R15, platelet count, ALBI score/grade [13], AFP, PIVKA-II (also termed des-gamma-carboxy prothrombin, DCP), CEA, and maximum tumor diameter. Postoperative pathological variables (microvascular invasion, graded per the General Rules of the Liver Cancer Study Group of Japan [14]; macroscopic tumor type) were analyzed for biological context only, not as predictors. Marker values below/above assay limits were imputed at 0.5×/1.5× that limit; AFP, PIVKA-II, and CEA were log2-transformed given skewed distributions. PIVKA-II was unavailable for 9/473 patients (5 missing, 4 excluded for concurrent warfarin therapy, which spuriously elevates PIVKA-II) and tumor size for 1/473; all were scored as factor-negative (0 points) for that component, the default used for values below the assay's lower limit. Tumor number was not tested as a candidate predictor, since the cohort was restricted by design to patients with a solitary tumor (see Study design and patients); eligibility, including tumor number, was confirmed at the time of surgery from multidisciplinary tumor-board imaging review.

Statistical analysis

Continuous variables were summarized as median [IQR] and compared by Mann-Whitney U test; categorical variables by chi-square or Fisher's exact test. Univariable logistic regression screened candidate predictors; ROC/Youden-index analysis derived optimal cutoffs for tumor size, PIVKA-II, and AFP for comparison against the cutoffs used. Multivariable logistic regression (tumor size ≥ 60 mm, PIVKA-II ≥ 50 mAU/mL) tested independence after mutual adjustment; a likelihood-ratio test assessed whether adding AFP ≥ 78 ng/mL improved fit (Model B). Because a laparoscopic approach was associated with early recurrence on univariable analysis, a further sensitivity model additionally adjusted for laparoscopic approach (Model C), to test whether it confounded the two primary predictors. An additive 2-factor score (0–2) was constructed and its discrimination (AUC) assessed; observed recurrence rates by score were examined descriptively (Fig. 3B), but formal calibration (calibration-in-the-large and calibration slope) was not assessed in the discovery cohort.

Internal validation used bootstrap resampling (1,000 replicates) for optimism in the fixed-cutoff model, and a second, more conservative bootstrap (500 replicates) that re-derived cutoffs within each resample. Temporal validation applied the pre-specified score to the 2022–2025 cohort, with AUC and diagnostic performance (sensitivity, specificity, PPV, NPV; Wilson 95% CI) at score ≥ 2. Cumulative incidence of early recurrence by score was estimated by the Kaplan-Meier method, truncated at 6 months (the 0–6-month

cumulative incidence function, not a landmark analysis); deaths before recurrence were not treated as a competing risk. Overall survival by recurrence-timing group was estimated and compared by log-rank test. Recurrence pattern (distant vs. intrahepatic-only) was compared between early and late recurrence, and across score groups, by Fisher's exact test and logistic regression. All tests were two-sided; $p < 0.05$ was significant. Reporting followed TRIPOD guidance where applicable [15].

Results

Early recurrence and overall survival

Among 472 discovery-cohort patients with complete follow-up, 182 (38.6%) had no recurrence, 246 (52.1%) had late recurrence (> 6 months), and 44 (9.3%) had early recurrence (≤ 6 months). Five-year overall survival differed markedly across these groups (log-rank $p < 0.001$; Fig. 1); overall survival could not be assessed in the validation cohort because its observation period was under 5 years for a substantial proportion of patients.

Baseline characteristics

Baseline characteristics are shown in Table 1. The validation cohort was significantly older (median 73 vs. 69 years, $p = 0.002$); sex (84.1% vs. 74.6% male, $p = 0.097$), tumor size, AFP, and PIVKA-II did not differ significantly (all $p > 0.05$). Both cohorts were predominantly male with a low prevalence of Child-Pugh B (4.2% discovery; none validation), consistent with preoperative selection for adequate hepatic reserve.

Table 1
Baseline characteristics of the discovery (2001–2021) and validation (2022–2025) cohorts

Variable	Discovery cohort (n = 473)	Validation cohort (n = 63)	p-value
Age, years, median [IQR]	69 [62–74]	73 [64–79]	0.002
Male sex, n (%)	352 (74.6)	53 (84.1)	0.097
Child-Pugh B, n (%)	20 (4.2)	0 (0)	—
Albumin, g/dL, median [IQR]	4.0 [3.7–4.3]	4.3 [4.1–4.5]	—
Prothrombin time, %, median [IQR]	87 [80–98]	96 [91–106]	—
Tumor size, mm, median [IQR]	30 [23–48]	34 [25–46]	0.512
Tumor size ≥ 60 mm, n (%)	83 (17.5)	9 (14.3)	—
AFP, ng/mL, median [IQR]	10 [5–99]	6 [4–81]	0.196
PIVKA-II, mAU/mL, median [IQR]	71 [20–522]	90 [37–364]	0.513
PIVKA-II ≥ 50 mAU/mL, n (%)	275 (58.1)	40 (63.5)	—
Early recurrence ≤ 6 months, n (%)	44 (9.3)	8 (12.7)	—

IQR, interquartile range. Both cohorts were treated at the same single institution; the validation cohort is a chronologically later (temporal), not geographically external, series. p-values by Mann-Whitney U test (continuous) or chi-square test (categorical); dashes indicate comparisons not performed. The validation cohort was significantly older than the discovery cohort; other tested characteristics (sex, tumor size, AFP, PIVKA-II) did not differ significantly, most likely reflecting a temporal trend at the institution rather than genuine population heterogeneity. Validation-cohort figures reflect an updated data file (n = 63) supplied by the authors.

Univariable predictors and multivariable score construction

On univariable analysis (Table 2), tumor size (OR 1.017/mm, p < 0.001), AFP (log2, OR 1.154, p < 0.001), and PIVKA-II (log2, OR 1.193, p < 0.001) were significantly associated with early recurrence; age, sex, albumin, prothrombin time, ICG-R15, platelet count, Child-Pugh class, and ALBI score were not. ROC-derived optimal cutoffs (60.0 mm, AUC 0.616; 49 mAU/mL, AUC 0.672) closely matched the 60 mm/50 mAU/mL cutoffs used. Two postoperative features were also associated with early recurrence — infiltrative tumor type (OR 6.76, p = 0.039) and microscopic portal vein invasion (OR 3.48, p = 0.038) — consistent with occult microvascular invasion already present at surgery, but these cannot inform preoperative decisions. A laparoscopic approach was associated with lower odds of early recurrence (OR 0.25, p = 0.024); because this could reflect confounding by indication (preferential selection of smaller, favorable tumors) rather than an effect independent of tumor size and PIVKA-II, we tested a sensitivity model adjusting for it (below, Table 3 Model C).

Table 2
Univariable logistic regression for early recurrence within 6 months (discovery cohort)

Variable	n	OR (95% CI)	p-value
Age, per 1-year increase	473	1.007 (0.974–1.042)	0.683
Male sex	472	0.705 (0.361–1.380)	0.308
Albumin, per 1 g/dL	473	0.593 (0.284–1.238)	0.164
Prothrombin time, per 1%	472	1.019 (0.994–1.045)	0.135
ICG-R15, per 1%	462	0.984 (0.948–1.022)	0.409
Platelet count, per 10^4/μL	472	1.038 (0.999–1.078)	0.056
Child-Pugh B	473	0.502 (0.066–3.841)	0.507
ALBI score	473	1.708 (0.720–4.053)	0.224
Tumor size, per 1 mm	472	1.017 (1.009–1.025)	< 0.001
AFP (log2-transformed)	473	1.154 (1.071–1.242)	< 0.001
PIVKA-II (log2-transformed)	464	1.193 (1.092–1.303)	< 0.001
CEA (log2-transformed)	199	0.516 (0.218–1.218)	0.131
Infiltrative macroscopic type	473	6.762 (1.099–41.612)	0.039
Microscopic portal vein invasion (Vp)	473	3.475 (1.071–11.277)	0.038
Laparoscopic approach	473	0.254 (0.077–0.838)	0.024

ROC/Youden-derived optimal cutoffs closely matched the cutoffs used in the score: tumor size 60.0 mm (AUC 0.616) vs. 60 mm used; PIVKA-II 49 mAU/mL (AUC 0.672) vs. 50 mAU/mL used; AFP 79 ng/mL (AUC 0.605) vs. 78 ng/mL used. Pathological (postoperative) variables, shown for biological context only — not usable as preoperative predictors. Surgical-approach variable, likely confounded by tumor size/location; not a candidate predictor.

Table 3
Multivariable logistic regression for early recurrence (discovery cohort)

Variable	Model A: OR (95% CI), p	Model B (+ AFP): OR (95% CI), p	Model C (+ Lap): OR (95% CI), p
Tumor size ≥ 60 mm	4.00 (2.05–7.81), p < 0.001	3.73 (1.89–7.35), p < 0.001	3.67 (1.86–7.21), p < 0.001
PIVKA-II ≥ 50 mAU/mL	2.27 (1.04–4.98), p = 0.040	2.02 (0.91–4.49), p = 0.084	2.32 (1.06–5.11), p = 0.036
AFP ≥ 78 ng/mL	—	1.94 (1.00–3.78), p = 0.052	—
Laparoscopic approach	—	—	0.29 (0.09–0.98), p = 0.046
Likelihood-ratio test for adding AFP to Model A	—	χ^2=3.68, df = 1, p = 0.055	—
Likelihood-ratio test for adding laparoscopic approach to Model A	—	—	χ^2=5.39, df = 1, p = 0.020

 *Model C tests whether the univariable association between a laparoscopic approach and lower early-recurrence odds (*Table 2*) reflects confounding by tumor size/PIVKA-II. Tumor size and PIVKA-II ORs are essentially unchanged from Model A, and laparoscopic approach remains independently associated with early recurrence after adjustment — i.e., the association is not explained away by these two predictors.*

On multivariable analysis (Table 3, Model A), tumor size ≥ 60 mm (OR 4.00, 95% CI 2.05–7.81, p < 0.001) and PIVKA-II ≥ 50 mAU/mL (OR 2.27, 95% CI 1.04–4.98, p = 0.040) were both independently associated with early recurrence, each closely paralleling its univariable estimate. Adding AFP ≥ 78 ng/mL (Model B) gave only borderline improvement (likelihood-ratio χ^2=3.68, p = 0.055) and was not included in the primary score. Because laparoscopic approach was itself associated with early recurrence (Table 2), we tested a sensitivity model additionally adjusting for it (Table 3, Model C): tumor size ≥ 60 mm (OR 3.67, 95% CI 1.86–7.21, p < 0.001) and PIVKA-II ≥ 50 mAU/mL (OR 2.32, 95% CI 1.06–5.11, p = 0.036) remained materially unchanged, while laparoscopic approach remained independently associated with lower early-recurrence odds after adjustment (OR 0.29, 95% CI 0.09–0.98, p = 0.046; likelihood-ratio χ^2=5.39, p = 0.020) — indicating these two predictors are not confounded by surgical approach. The additive 2-factor score showed a clear, monotonic gradient: 4.4% (8/183), 7.7% (17/222), and 27.9% (19/68) for scores 0, 1, and 2 (AUC 0.694, 95% CI 0.612–0.775; Table 4, Figs. 2, 3A–B); cumulative incidence truncated at 6 months confirmed clear separation (log-rank p < 0.001; Fig. 2).

Table 4
Calibration and diagnostic performance of the 2-factor score in the discovery and validation cohorts

Score	Discovery: events/n (rate, 95% CI)	Validation: events/n (rate, 95% CI)
0 (both factors negative)	8/183 (4.4%, 2.2–8.4%)	1/18 (5.6%, 1.0–25.8%)
1 (either factor positive)	17/222 (7.7%, 4.8–11.9%)	5/41 (12.2%, 5.3–25.5%)
2 (both factors positive)	19/68 (27.9%, 18.7–39.6%)	2/4 (50.0%, 15.0–85.0%)
AUC of score (ordinal 0–2)	0.694 (0.612–0.775)	0.664 (0.421–0.870)
Sensitivity / Specificity at score ≥ 2	—	25.0% / 96.4%
PPV / NPV at score ≥ 2	—	50.0% / 89.8%
Bootstrap-corrected AUC (internal validation, fixed cutoffs)	0.692	—
Bootstrap-corrected AUC (full pipeline incl. cutoff re-selection)	0.662	—

*Overall survival by recurrence timing (*Fig. 1*) and the association of the score with distant (extrahepatic) recurrence (*Fig. 3C–D*) are reported in the corresponding figure legends (in the manuscript file) rather than in tabular form here. Validation AUC 95% CI is from 2,000 bootstrap resamples (percentile method), given the small validation event count.*

Internal and temporal validation

Bootstrap resampling (1,000 replicates) of the fixed-cutoff model yielded a mean optimism of 0.002 (optimism-corrected AUC 0.692), indicating minimal overfitting. A more conservative bootstrap that re-derived cutoffs within each of 500 resamples showed greater variability, particularly for PIVKA-II (median re-derived cutoff 64 mAU/mL, IQR 49–121), and greater optimism (corrected AUC 0.662), reflecting known instability of data-driven cutoffs for continuous biomarkers rather than a model failure (Table 4).

In the temporally distinct validation cohort (n = 63, 8 early recurrences [12.7%]), the score showed a directionally similar gradient: 5.6% (1/18), 12.2% (5/41), and 50.0% (2/4) for scores 0, 1, and 2 (AUC 0.664, 95% CI 0.421–0.870, a bootstrap interval that still includes 0.5; Table 4, Fig. 3B). Applying discovery-cohort score-specific rates to the validation case-mix gave an expected 5.0 versus 8 observed early recurrences (observed/expected ≈ 1.6), indicating under-prediction at the aggregate level (calibration-in-the-large); a calibration slope/plot could not be computed from available summary data. At score ≥ 2, sensitivity was 25.0% (95% CI 7.1–59.1%), specificity 96.4%, PPV 50.0%, NPV 89.8%; only 4 patients scored 2 points (vs. 68/473, 14.4%, in discovery), so these estimates remain exploratory.

Pattern of recurrence and biological specificity

Among 441 discovery-cohort patients with recurrence-pattern data, early recurrence was more often extrahepatic (distant) than true late recurrence, when the comparison is correctly restricted to patients with confirmed recurrence: 30.2% (13/43) for early recurrence versus 9.8% (24/246) for late recurrence (> 6 months), excluding the 151 non-recurrent patients (Fisher's exact $p < 0.001$; Fig. 3C).

The 2-factor score was itself associated with distant recurrence — rates rose from 3.5% (score 0) to 6.7% (score 1) to 29.0% (score 2) (OR 3.77/point, 95% CI 2.23–6.36, $p < 0.0001$; Fig. 3D) — persisting when restricted to the 246 patients with confirmed true late recurrence (OR 3.86, 95% CI 1.98–7.53, $p < 0.0001$), and after adjustment for early-recurrence status among all 441 patients with pattern data (adjusted OR 3.01, 95% CI 1.76–5.16, $p < 0.001$). By contrast, the score did not discriminate recurrence overall (AUC 0.526, OR 1.17/point, $p = 0.25$) or stratify overall survival directly (3-group log-rank $p = 0.60$), a pattern we interpret cautiously as suggestive of a metastasis-prone phenotype rather than a generic prognostic marker (see Discussion).

Discussion

In this study, a simple additive score combining tumor size and PIVKA-II stratified BCLC Stage A HCC patients by early (≤ 6-month) recurrence risk, an event carrying markedly worse overall survival than later or no recurrence. Both components were independently associated with early recurrence, and the cutoffs used (60 mm, 50 mAU/mL) closely matched data-driven, ROC/Youden-optimal cutoffs derived in the same cohort; because the latter were derived from the same data, this agreement does not constitute external validation of the cutoffs (see Methods). Consistent with prior work distinguishing early from late recurrence after HCC resection [3–5], we selected these two variables because each has an established mechanistic link to microvascular invasion, the presumed substrate of early, biologically aggressive recurrence [7, 8]. Compared with more complex nomograms [12], our approach prioritizes simplicity: adding routine liver-function variables modestly worsened bootstrap-corrected discrimination versus the 2-factor model. This matches our group's prior experience with simple risk scores in hepatectomy for liver malignancy [16]; with only 44 events, estimable predictors are limited [17]. ERASL-pre (combining sex, ALBI grade, AFP, tumor size, and tumor number), the most established preoperative HCC recurrence-risk score, reports an external C-statistic of ~ 0.69 including in a Japanese cohort [18, 19], comparable to our bootstrap-corrected AUC (0.662–0.692); a formal head-to-head comparison remains important.

Our 60 mm cutoff exceeds the 50 mm (5 cm) Milan transplant-eligibility threshold (solitary tumor ≤ 5 cm, or ≤ 3 tumors each ≤ 3 cm) [6]; we retained 60 mm as the ROC/Youden-optimal cutoff for early recurrence here (AUC 0.616), since Milan's threshold targets post-transplant survival rather than post-resection recurrence. PIVKA-II is likewise the sole biomarker in Japanese transplant-selection criteria — Kyoto (< 400 mAU/mL) and Kyushu University (< 300 mAU/mL) [31] — at thresholds 6- to 8-fold higher than ours, reflecting a different goal (excluding disseminated disease pre-transplant) rather than post-resection recurrence risk; these criteria are not comparable to ours.

Gadoxetic acid-enhanced MRI, where specific imaging features predict microvascular invasion with good discrimination [20], offers a complementary approach, but requires infrastructure our score does not. The association between a laparoscopic approach and lower odds of early recurrence (Table 2) persisted, essentially unchanged, after adjustment for tumor size and PIVKA-II (Table 3, Model C: OR 0.29, 95% CI 0.09–0.98, p = 0.046), indicating it is not simply explained by surgeons preferentially selecting smaller, lower-marker tumors for a laparoscopic approach. Residual confounding cannot be excluded, though meta-analyses report comparable oncological outcomes between approaches after adjustment [21]; we did not include surgical approach as a candidate predictor, as it reflects a perioperative decision rather than a fixed preoperative characteristic.

This study has several limitations. Both cohorts were treated at a single institution; validation was temporal, not geographically external (2022–2025 vs. 2001–2021) and was significantly older at baseline (median 73 vs. 69 years), so external generalizability remains unconfirmed. Validation events were still limited (8/63, only 4 scoring 2 points) — below the ~ 100 events recommended for reliable temporal validation — so the validation AUC's bootstrap 95% CI (0.421–0.870) includes 0.5 and discrimination was not formally established there; estimates remain exploratory. Formal calibration (calibration-in-the-large, slope, plot) was not assessed; an aggregate comparison suggested under-prediction in validation (observed/expected ≈ 1.6) that should be confirmed with patient-level analysis. A more conservative bootstrap re-deriving cutoffs within each resample showed the PIVKA-II cutoff is not highly stable under resampling (optimism-corrected AUC 0.662 vs. apparent 0.694). AFP showed only borderline significance (p = 0.056–0.059) and was omitted from the primary score for parsimony. We also lacked complete data on etiology, blood loss, and margin width, and did not perform central radiological review; whether the score performs comparably across etiologies, amid the shift toward metabolic- and alcohol-related HCC [22, 23], awaits study, as does validation beyond a single team. Finally, although associated with distant recurrence, the score did not stratify recurrence overall or survival; at score = 2, roughly 72% of patients did not recur within 6 months (PPV 27.9%), so using the score alone to select patients for systemic therapy would over-treat many, a point we address below.

As a post hoc check, we repeated the analysis using a 1-year rather than 6-month definition. Discrimination fell substantially (discovery AUC 0.604 vs. 0.694), PIVKA-II lost independent significance, and ALBI score emerged as an additional predictor — consistent with a shift from occult metastatic disease toward background liver function. This followed, rather than justified, the a priori 6-month definition and is best read as descriptive context.

Early recurrence is thought to arise from occult microvascular invasion or micrometastatic cells already present at surgery [4, 7]; our data support this, as early recurrence was roughly three times more likely to present as distant disease than true late recurrence (30.2% vs. 9.8%; p < 0.001), and the score remained associated with distant recurrence among patients with confirmed late recurrence, while not predicting recurrence overall or survival directly — consistent with, though not proof of, occult systemic disease at surgery (see Limitations). Systemic therapy has demonstrated survival benefit across the HCC spectrum since sorafenib [24] and atezolizumab plus bevacizumab for unresectable disease [25]; adjuvant

atezolizumab plus bevacizumab after resection of high-risk HCC improved recurrence-free survival in IMbrave050 [26]. Early-phase neoadjuvant immunotherapy experience is encouraging: neoadjuvant cemiplimab was delivered safely before hepatectomy without delaying surgery in a phase 2 trial [27], and pathological response after neoadjuvant ICI was associated with improved relapse-free survival in a cross-trial analysis [28]. These studies generally selected candidates by tumor size, number, or stage rather than a validated biomarker; our score = 2 group's RFS (median 21.2 months; 1-year recurrence 41.6%; 5-year RFS 30.9%) resembles reported BR1 RFS outcomes in Supplementary Table S1 [29] — illustrative only, given differing cohorts. The 1-year figure matches Haruki et al.'s BR1 rate (40%) [29], while our 5-year RFS is lower than Hamada et al.'s (39.3%); the match is therefore partial, not uniform. Given heterogeneous cohorts and BR-classification criteria, this is rough concordance rather than equivalence, confirmable only with a direct, prospectively comparable cohort. Given the score's modest PPV (27.9% at score = 2) and lack of survival stratification, we regard it as a candidate enrichment criterion for future neoadjuvant trials rather than a basis for selecting patients for systemic therapy in routine practice.

This score could also guide preoperative counseling and surveillance intensity: a score of 2 might prompt closer postoperative surveillance [30], while a score of 0 should not alter baseline surveillance. Prospective, multi-institutional validation — ideally including more non-viral HCC — remains the logical next step.

In conclusion, a simple, preoperatively available score combining tumor size (≥ 60 mm) and PIVKA-II (≥ 50 mAU/mL) identifies a biologically high-risk subgroup (score = 2) within solitary BCLC Stage A HCC whose early, often distant, recurrence mimics borderline resectable (BR1) disease, with a directionally consistent, though imprecise and uncalibrated, gradient in a small, temporally distinct validation cohort. The score did not stratify overall survival or recurrence overall, and its PPV at score = 2 (27.9%) is modest; we therefore view it chiefly as a candidate enrichment tool for future prospective trials of preoperative systemic therapy, informed by emerging neoadjuvant immunotherapy evidence, rather than a basis for selecting patients in current practice.

Declarations

Conflict of interest:

The authors declare that they have no competing interests.

Ethics approval:

This retrospective study was approved by the institutional ethical committee (No. 26137), in accordance with institutional and national policy governing retrospective studies that use existing clinical data; informed consent was obtained by an opt-out method, as permitted for retrospective studies using

existing clinical data under Japanese ethical guidelines [please confirm this is the method actually used at your institution].

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Author contributions:

[YS] designed the study, collected and analyzed the data, and drafted the manuscript. [YY], [YF], [HK], [KF], [KA], [KY], [MK], [YK], [NM], [YU], [KM], [TH], [YY], [TK], [TS], [YK], [KY], and [HM] contributed to data collection and interpretation of the results. [KG] and [SK] performed the operations and critically revised the manuscript. [SK] supervised the study and critically revised the manuscript. All authors read and approved the final manuscript.

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None.

Data availability:

The data supporting the findings of this study are available from the corresponding author upon reasonable request, subject to institutional ethical approval and patient privacy considerations.

Supplementary Material

Supplementary Table S1 (reported RFS [recurrence-free survival] outcomes in borderline resectable [BR1/BR2] HCC across the published literature, compared with the present study's score = 2 group) is provided in the accompanying tables file, consistent with the journal's preference that figures be submitted as files separate from the manuscript text; tables may likewise be provided separately, as done here at the authors' request.

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Figures

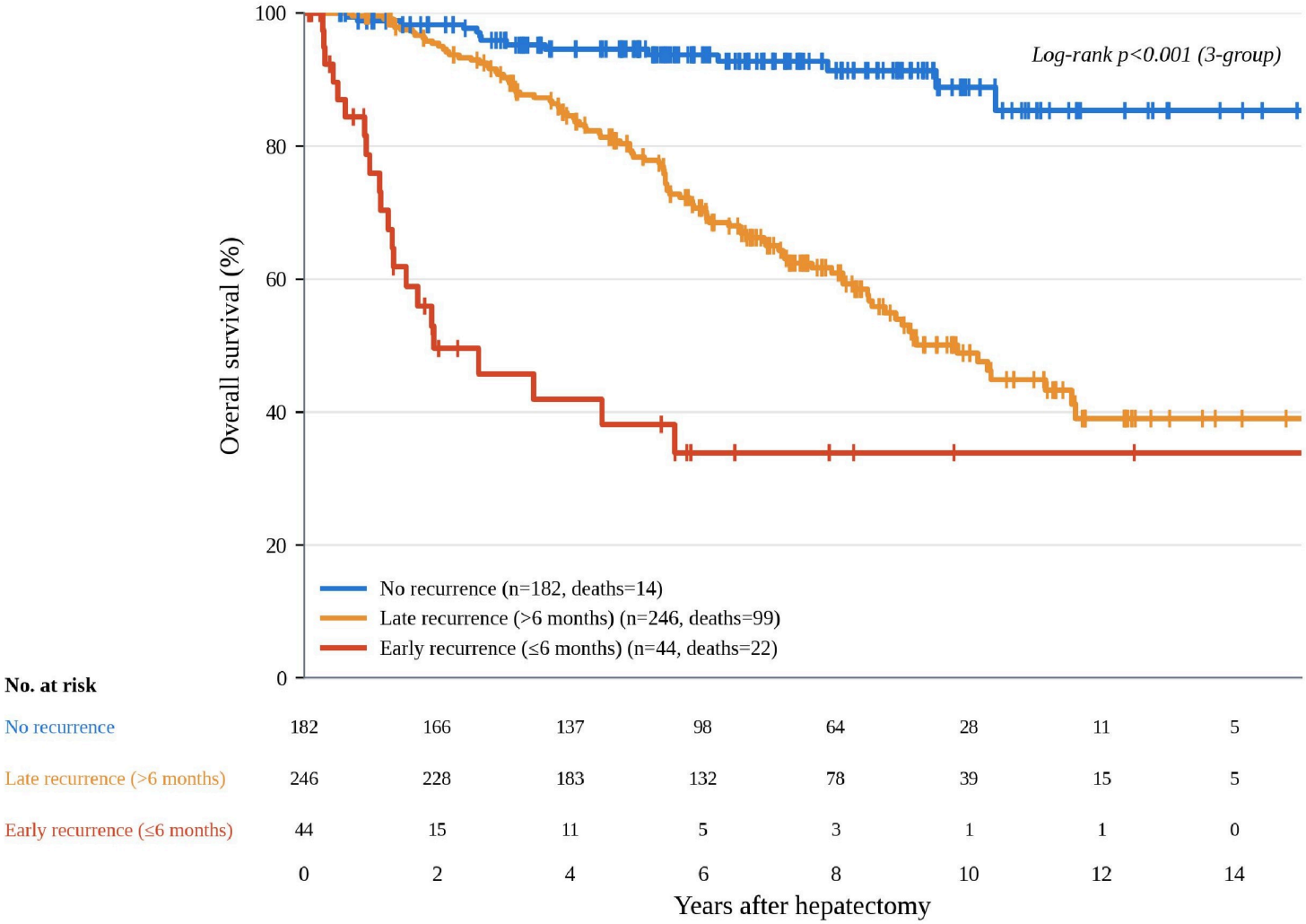


Figure 1

Overall survival according to recurrence timing (discovery cohort, n=472). Kaplan-Meier estimates of overall survival for patients with no recurrence (n=182, 14 deaths, 5-year overall survival [OS] 94.6%, median not reached), late recurrence (>6 months; n=246, 99 deaths, 5-year OS 78.4%, median 9.8 years), and early recurrence (≤6 months; n=44, 22 deaths, 5-year OS 38.1%, median 1.95 years). Three-group log-rank p<0.001; early vs. late recurrence alone, log-rank p<0.001. Tick marks indicate censored observations; numbers at risk are shown below the x-axis.

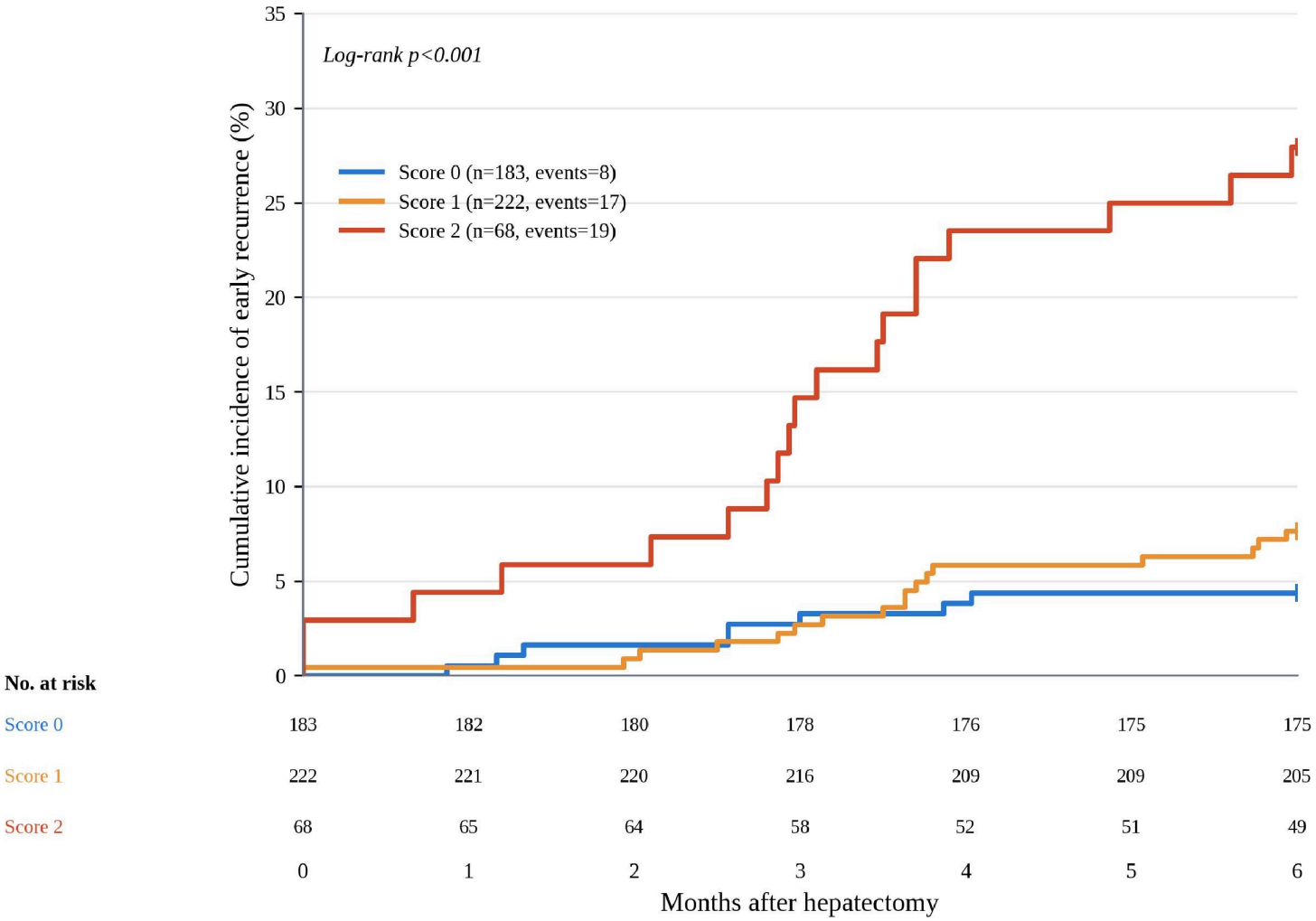


Figure 2

Cumulative incidence of early recurrence by 2-factor score, truncated at 6 months (discovery cohort). Kaplan-Meier cumulative incidence curves for early recurrence, stratified by score (0, 1, or 2 positive factors among tumor size ≥60 mm and PIVKA-II ≥50 mAU/mL). Log-rank p<0.001. Tick marks indicate censored observations; numbers at risk are shown below the x-axis.

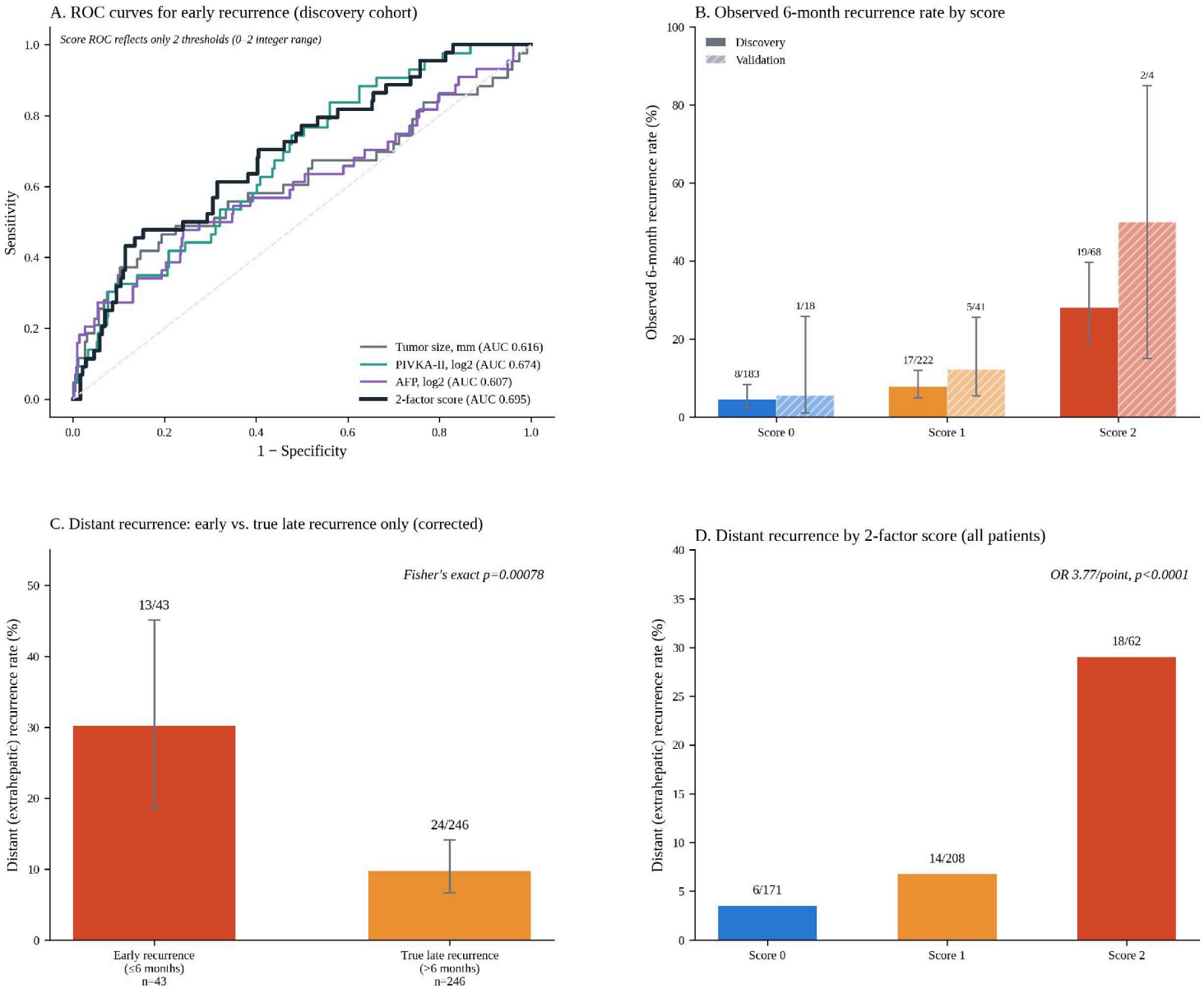


Figure 3

Discrimination, observed recurrence rates, and association with distant recurrence of the 2-factor score (discovery cohort, n=473, unless stated). (A) ROC curves for tumor size, PIVKA-II (log2), AFP (log2), and the 2-factor score, for prediction of early recurrence; the score's ROC curve reflects only two possible thresholds, given its 0–2 integer range, and should be interpreted accordingly. (B) Observed 6-month recurrence rate by score, discovery (n=473) and validation (n=63) cohorts side by side, with number of

events/patients and Wilson 95% CI per bar; this is a descriptive comparison of observed rates, not a formal calibration assessment (see Methods/Limitations), and the validation score = 2 bar (2/4) is especially imprecise. (C) Distant (extrahepatic) recurrence rate, early recurrence (n=43) versus true late recurrence only (n=246, non-recurrent patients excluded; Fisher's exact p<0.001). (D) Distant recurrence rate by 2-factor score (all 473 patients; OR 3.77/point, 95% CI 2.23–6.36, p<0.0001); this persisted when restricted to the 246 patients with confirmed true late recurrence (OR 3.86, 95% CI 1.98–7.53, p<0.0001) and after adjustment for early-recurrence status among all 441 patients with recurrence-pattern data (adjusted OR 3.01, 95% CI 1.76–5.16, p<0.001). The score did not discriminate recurrence overall irrespective of timing (AUC 0.526; OR 1.17/point, 95% CI 0.90–1.54, p=0.25) and did not stratify overall survival directly across all patients (3-group log-rank p=0.60).

Supplementary Files

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- SupplementaryTableS1.docx