Prognostic Value of a Dynamic AFP–LDH Index for Predicting Recurrence After Curative Resection in Hepatocellular Carcinoma

Ann. Ital. Chir., 2026 97, 9: 1681–1689
https://doi.org/10.62713/aic.4711

Bartu Çetin[1], Emine Bihter Eniseler[2], Atike Pınar Erdoğan[2]

[1]Department of General Surgery, Izmir University of Economics Faculty of Medicine, 35575 Izmir, Türkiye
[2]Department of Medical Oncology, Manisa Celal Bayar University Faculty of Medicine, 45030 Manisa, Türkiye

AIM: Although curative resection remains a cornerstone treatment for hepatocellular carcinoma (HCC), recurrence continues to limit durable disease control in a considerable proportion of patients. Improved postoperative risk assessment may facilitate more individualized surveillance and management strategies. Accordingly, we examined the prognostic performance of a dynamic alpha-fetoprotein–lactate dehydrogenase (AFP–LDH) Index in predicting recurrence after curative resection.

METHODS: Patients who underwent curative resection for HCC between January 2020 and January 2025 were retrospectively analyzed. The AFP–LDH Index was calculated as $\log_{10}$ (postoperative AFP × LDH / preoperative AFP). Survival probabilities were estimated using the Kaplan–Meier method, and the relationship between clinical variables and outcomes was examined with Cox proportional hazards models. Receiver operating characteristic (ROC) analysis was used to identify the optimal cutoff value. Internal validation of the discriminative performance of the AFP–LDH Index was performed using bootstrap resampling (2000 repetitions), and optimism-corrected area under the curve (AUC) estimates with bootstrap-derived 95% confidence intervals were reported.

RESULTS: A total of 50 patients were included, with a median follow-up duration of 27.9 months. Recurrence occurred in 26 patients (52.0%). The median RFS was 23 months (95% confidence interval [CI]: 14.5–31.5). ROC analysis identified an optimal AFP–LDH Index cutoff value of >1.67, demonstrating promising discriminative performance (AUC = 0.960). In multivariable analysis, the AFP–LDH Index remained an independent predictor of recurrence (hazard ratio [HR]: 27.24, 95% CI: 5.41–137.14, $p < 0.001$). ROC analysis demonstrated good discriminative performance for recurrence prediction (AUC = 0.960; 95% CI: 0.863–0.995; $p < 0.001$).

CONCLUSIONS: The dynamic AFP–LDH Index was independently associated with recurrence risk after curative resection for HCC. This exploratory composite biomarker demonstrated promising prognostic performance; however, further multicenter validation is required before routine clinical application.

Keywords: alpha-fetoprotein; composite biomarker; hepatocellular carcinoma; lactate dehydrogenase; liver resection; recurrence

Introduction

Hepatocellular carcinoma (HCC) is an aggressive malignancy characterized by high recurrence rates despite curative surgical resection. Early and late recurrence following resection represent the most important determinants of long-term survival. Therefore, postoperative biological risk stratification has become a critical requirement in clinical management.

Alpha-fetoprotein (AFP) remains a key serum biomarker in hepatocellular carcinoma and has established diagnostic and prognostic significance. Recent evidence indicates that elevated baseline AFP levels are associated with poor prognosis and an increased risk of recurrence [1]. However, assessment based solely on single time-point AFP measurements may not adequately reflect the biological heterogeneity of tumors. Models combining AFP with other laboratory parameters have been shown to demonstrate stronger prognostic performance compared with AFP alone [2].

Efforts to refine recurrence prediction in resectable HCC have led to the development of prognostic approaches that integrate multiple biological and clinical determinants. In particular, nomograms and radiomics-based models incorporating biochemical parameters have demonstrated improved predictive accuracy beyond conventional pathological variables [3,4]. In a radiomics-based model developed by Cui et al. [3], both AFP and lactate dehydrogenase (LDH) were identified as independent prognostic factors contributing significantly to the prediction of recurrence-free survival (RFS). Similarly, AFP-based laboratory scores and prognostic nomograms have enabled more precise estimation of recurrence risk [2,4].

LDH is considered a biochemical marker of tumor cell metabolism and increased proliferative activity. The inclusion of LDH in prognostic models for HCC may reflect the

Submitted: 21 April 2026 Revised: 11 June 2026 Accepted: 22 June 2026 Published: 15 September 2026
Correspondence to: Emine Bihter Eniseler, Department of Medical Oncology, Manisa Celal Bayar University Faculty of Medicine, 45030 Manisa, Türkiye (e-mail: drbihtereniseler@gmail.com).
Editor: Weihua Yu

metabolic aggressiveness of the tumor [3]. In this context, integrating the dynamic changes in AFP, which reflect tumor burden, with LDH, an indicator of metabolic activity, may provide a more comprehensive representation of the biological risk following resection.

Based on this rationale, the AFP–LDH Index ($\log_{10}$ [postoperative AFP × LDH / preoperative AFP]) was defined to integrate postoperative tumor marker kinetics and metabolic proliferative potential into a single composite parameter. Although AFP-based models and LDH-containing prognostic systems have been described in the literature [1,2,3,4], data regarding the independent impact of an index combining dynamic AFP changes with LDH in patients with resectable HCC remain limited.

The present study investigated whether an index combining AFP dynamics and LDH levels could identify patients at increased risk of recurrence following curative resection for HCC.

Methods

Study Setting and Patient Selection

A retrospective review was conducted in patients with HCC treated between January 2020 and January 2025. Decisions regarding surgical resection were made following multidisciplinary tumor board assessment. During the study period, a total of 82 patients assessed for surgical resection were retrospectively reviewed. Patients who did not undergo curative resection, those with incomplete clinical or laboratory data, and those with insufficient follow-up duration were excluded from the study. A total of 50 patients who met the inclusion criteria and underwent curative resection were included in the final analysis.

Clinical and Pathological Evaluation

Demographic and clinicopathological data were retrospectively extracted from electronic medical records. Liver function reserve was assessed according to the Child–Pugh classification [5]. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) performance score [6].

Pathological evaluation included the maximum tumor diameter, tumor number, presence of microvascular invasion, tumor differentiation grade, and tumor necrosis percentage. Tumor necrosis percentage was recorded directly from the original pathology reports, as estimated by the reporting pathologist during routine histopathological evaluation. No retrospective re-evaluation or independent quantitative measurement of tumor necrosis was performed for the present study. Tumor capsule presence was defined according to the pathological examination report as the presence of a histologically identifiable fibrous capsule partially or completely surrounding the tumor. Resection margins were reported as negative (R0) in all cases.

Laboratory Parameters and AFP–LDH Index

Serum AFP levels, measured in ng/mL, were evaluated in both the preoperative and postoperative periods. Preoperative AFP and LDH values were defined as serum measurements obtained within 7 days prior to surgery. The postoperative AFP value was defined as a stable measurement obtained at least 4 weeks after surgery, before the initiation of any adjuvant therapy, in order to minimize early biochemical changes related to surgical intervention. The AFP–LDH Index was designed to integrate baseline tumor burden, postoperative tumor marker kinetics, and tumor metabolic activity into a single composite parameter. Accordingly, preoperative AFP was used as a reference measure of baseline tumor burden, postoperative AFP was intended to reflect residual biological activity following resection, and preoperative LDH was incorporated as a surrogate marker of tumor metabolic activity.

The AFP–LDH Index was calculated using the following formula:

AFP–LDH Index = $\log_{10}$ (postoperative AFP × LDH / preoperative AFP).

AFP and LDH levels may vary widely in clinical practice and typically exhibit a right-skewed distribution. In particular, multiplication of postoperative AFP and LDH values may increase variance and amplify the influence of extreme values on statistical analyses. This may reduce the stability of regression estimates and violate the assumption of linearity for continuous variables. Therefore, logarithmic ($\log_{10}$) transformation was applied during index calculation. LDH was entered as its numerical value measured in U/L and was not standardized or transformed into a dimensionless variable before index calculation. Accordingly, the AFP–LDH Index should be interpreted as an empirically derived statistical index rather than a dimensionless biochemical quantity.

Log transformation contributes to stabilizing variance by producing a more symmetric distribution and reducing the impact of outliers on model estimates. This approach improves model fit and reliability in Cox regression analyses. In addition, logarithmic transformation enables proportional scaling of biomarker kinetics, allowing more reliable comparisons among patients with widely variable baseline AFP levels.

Follow-up and Endpoints

Patients were followed at regular intervals according to the institutional follow-up protocol, including clinical evaluation, serum AFP measurement, and contrast-enhanced computed tomography or magnetic resonance imaging.

The primary endpoint was defined as RFS. RFS was defined as the time from the date of surgery to the date of the first radiological or clinical recurrence. Patients without recurrence during follow-up were censored at the date of their last clinical assessment.

The secondary endpoint was defined as overall survival (OS). OS was calculated as the time from the date of surgery to the date of death. Patients who were alive at the time of analysis were censored at the date of their last follow-up.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range [IQR]), as appropriate according to data distribution, while categorical variables were summarized as frequencies and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Group comparisons for continuous variables were performed using Student's *t*-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate according to expected cell frequencies.

RFS and OS were analyzed using the Kaplan–Meier method, and differences between groups were evaluated using the log-rank test. RFS was analyzed using Kaplan–Meier and Cox proportional hazards methods. Conventional ROC analysis was performed separately as an exploratory analysis to assess discrimination between patients with and without recurrence during the observed follow-up period and was not used to evaluate time-to-event RFS.

To identify factors associated with recurrence, univariate Cox proportional hazards regression analysis was performed. The proportional hazards assumption was assessed using Schoenfeld residuals and was not violated. Variables considered clinically relevant and those with $p < 0.10$ in univariate analysis were included in the multivariate Cox regression model. Given the limited number of events, a parsimonious model was constructed by including a restricted number of clinically relevant variables that met the $p < 0.10$ threshold in univariate analysis, in order to reduce the risk of overfitting. The AFP–LDH Index was entered into the Cox regression models as a continuous variable.

The discriminative performance of the AFP–LDH Index for distinguishing patients with versus without recurrence during follow-up was evaluated using conventional receiver operating characteristic (ROC) curve analysis, and the area under the curve (AUC) was calculated. The optimal cutoff value was determined using the Youden index. Internal validation of the discriminative performance of the AFP–LDH Index was performed using bootstrap resampling (2000 repetitions). Since the primary objective was to assess discrimination, optimism-corrected area under the curve (AUC) estimates with bootstrap-derived 95% confidence intervals were reported.

Multicollinearity among variables included in the multivariate model was assessed using variance inflation factor (VIF) analysis, and no significant collinearity was detected. Statistical analyses were performed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA), and a two-sided p value < 0.05 was considered statistically significant.

Results

During the study period, a total of 82 patients diagnosed with HCC who were evaluated for surgical resection by the multidisciplinary tumor board were retrospectively reviewed. Of these, 14 patients who did not undergo curative resection, 8 patients with incomplete clinical or laboratory data, and 10 patients with insufficient follow-up duration were excluded. A total of 50 patients who met the inclusion criteria and underwent curative resection were included in the final analysis.

The median follow-up duration was 27.9 months (range: 3–59 months). During follow-up, recurrence occurred in 26 patients (52.0%), while 24 patients (48.0%) remained recurrence-free. At the end of follow-up, 33 patients (66.0%) were alive and 17 patients (34.0%) had died. Mortality was significantly higher among patients who developed recurrence ($p < 0.001$).

Baseline clinicopathological characteristics of the patients are presented in Table 1. The mean age was 62.2 ± 7.5 years, and 70.0% of the patients were male. There were no significant differences between recurrence groups in terms of age and sex distribution ($p = 0.744$ and $p = 0.902$, respectively). No significant differences were observed regarding etiology, Child–Pugh class, or Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (all $p > 0.05$).

Tumor size was significantly associated with recurrence ($p = 0.024$), with tumors >5 cm being more frequent in the recurrence group. Microvascular invasion was markedly more common in patients who developed recurrence compared with those without recurrence (69.2% vs. 16.7%, $p < 0.001$). Tumor necrosis percentage was also significantly higher in the recurrence group ($p = 0.023$). No significant differences were observed in terms of tumor number or tumor capsule presence.

Preoperative AFP levels did not differ significantly between recurrence groups ($p = 0.162$). In contrast, postoperative AFP levels were significantly higher among patients who developed recurrence ($p < 0.001$). The composite analysis was primarily conducted based on the AFP–LDH Index in accordance with the main study hypothesis. The AFP–LDH Index was significantly higher in patients who developed recurrence ($p < 0.001$) (Table 1).

In Kaplan–Meier survival analysis, the median RFS for the overall cohort was 23 months (95% CI: 14.5–31.5). The estimated RFS probabilities were 67.2% at 1 year, 45.7% at 2 years, and 43.0% at 3 years. Patients with an AFP–LDH Index >1.67 demonstrated significantly shorter RFS compared with those with an index ≤1.67 (log-rank $p < 0.001$) (Fig. 1).

In univariate Cox regression analysis, tumor size >5 cm (hazard ratio [HR]: 3.49; 95% CI: 1.16–10.47; $p = 0.026$), presence of microvascular invasion (HR: 3.76; 95% CI:

Table 1. Baseline clinicopathological characteristics according to recurrence status.

Variable		Total (n = 50)	No recurrence (n = 24)	Recurrence (n = 26)	*p* value
Age, years (mean ± SD)		62.2 ± 7.5	61.9 ± 6.6	62.6 ± 8.4	0.744
Male, n (%)		35 (70.0)	17 (70.8)	18 (69.2)	0.902
Etiology, n (%)	HBV	19 (38.0)	10 (41.7)	9 (34.6)	0.642
	HCV	13 (26.0)	6 (25.0)	7 (26.9)	
	HBV+HCV	3 (6.0)	0 (0.0)	3 (11.5)	
	NASH	10 (20.0)	6 (25.0)	4 (15.4)	
	Alcohol	2 (4.0)	1 (4.2)	1 (3.8)	
	Idiopathic	3 (6.0)	1 (4.2)	2 (7.7)	
Child–Pugh class, n (%)	A	44 (88.0)	20 (83.3)	24 (92.3)	0.409
	B	6 (12.0)	4 (16.7)	2 (7.7)	
ECOG-PS, n (%)	0	35 (70.0)	15 (62.5)	20 (76.9)	0.266
	1	15 (30.0)	9 (37.5)	6 (23.1)	
Tumor size, n (%)	<3 cm	17 (34.0)	12 (50.0)	5 (19.2)	0.024
	3–5 cm	22 (44.0)	10 (41.7)	12 (46.2)	
	>5 cm	11 (22.0)	2 (8.3)	9 (34.6)	
Tumor number, n (%)	1	33 (66.0)	17 (70.8)	16 (61.5)	0.558
	2	12 (24.0)	4 (16.7)	8 (30.8)	
	3	5 (10.0)	3 (12.5)	2 (7.7)	
Tumor capsule presence, n (%)		40 (80.0)	19 (79.2)	21 (80.8)	0.887
Microvascular invasion, n (%)		22 (44.0)	4 (16.7)	18 (69.2)	<0.001
Tumor necrosis (%), mean±SD		24.3±13.1	19.9±11.8	28.3±13.3	0.023
Preoperative AFP (ng/mL), median (IQR)		43.0 (28.25–100.63)	36.6 (26.5–80.2)	57.95 (31.5–135.75)	0.162
Postoperative AFP (ng/mL), median (IQR)		10.55 (4.10–24.55)	4.20 (3.10–7.93)	18.55 (13.35–37.43)	<0.001
LDH (U/L), mean±SD		213.0±58.0	200.0±51.0	226.0±62.0	0.116
AFP–LDH Index, mean±SD		1.60±0.31	1.36±0.23	1.83±0.17	<0.001

HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; AFP, alpha-fetoprotein; LDH, lactate dehydrogenase; AFP–LDH Index, $\log_{10}$ (postoperative AFP × LDH / preoperative AFP), SD, standard deviation; IQR, interquartile range. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate according to expected cell frequencies.

1.62–8.70; $p = 0.002$), tumor necrosis percentage (HR: 1.03; 95% CI: 1.00–1.06; $p = 0.033$), and the AFP–LDH Index (HR: 35.72; 95% CI: 8.13–157.00; $p < 0.001$) were significantly associated with RFS (Table 2).

Due to the limited number of events, clinically relevant variables were included in the multivariate model. After adjustment for tumor size, microvascular invasion, and tumor necrosis, the AFP–LDH Index remained an independent prognostic factor for RFS (HR: 27.24; 95% CI: 5.41–137.14; $p < 0.001$) (Table 2).

The original ROC curve analysis demonstrated that the AFP–LDH Index had good discriminative performance for distinguishing patients with versus without recurrence during follow-up (AUC = 0.960; 95% CI: 0.863–0.995; $p < 0.001$). The optimal cutoff value determined using the Youden index was >1.67, yielding a sensitivity of 84.62% and a specificity of 95.83%. Internal validation of the discriminative performance using bootstrap resampling (2000 repetitions) yielded an optimism-corrected AUC of 0.961 (95% CI: 0.901–0.997). However, given the limited sample size and the absence of external validation, the observed performance should be interpreted with caution. The ROC curve is presented in Fig. 2.

In Kaplan–Meier analysis, the median OS was not reached during the follow-up period. The estimated OS probabilities were 89.7% at 1 year, 70.3% at 2 years, and 62.0% at 3 years (Fig. 3).

In univariate Cox regression analysis, microvascular invasion (HR: 4.54; 95% CI: 1.47–13.98; $p = 0.008$) and the AFP–LDH Index (HR: 20.89; 95% CI: 3.51–124.24; $p < 0.001$) were significantly associated with OS. In multivariate analysis, after adjustment for tumor size and microvascular invasion, the AFP–LDH Index remained an independent prognostic factor for OS (HR: 17.20; 95% CI: 2.04–144.98; $p = 0.009$) (Table 3).

Discussion

In this retrospective study, we evaluated the prognostic value of the dynamic AFP–LDH Index for recurrence-free survival in patients with HCC undergoing curative resection. Our findings demonstrated that the AFP–LDH Index was independently associated with recurrence risk in multi-

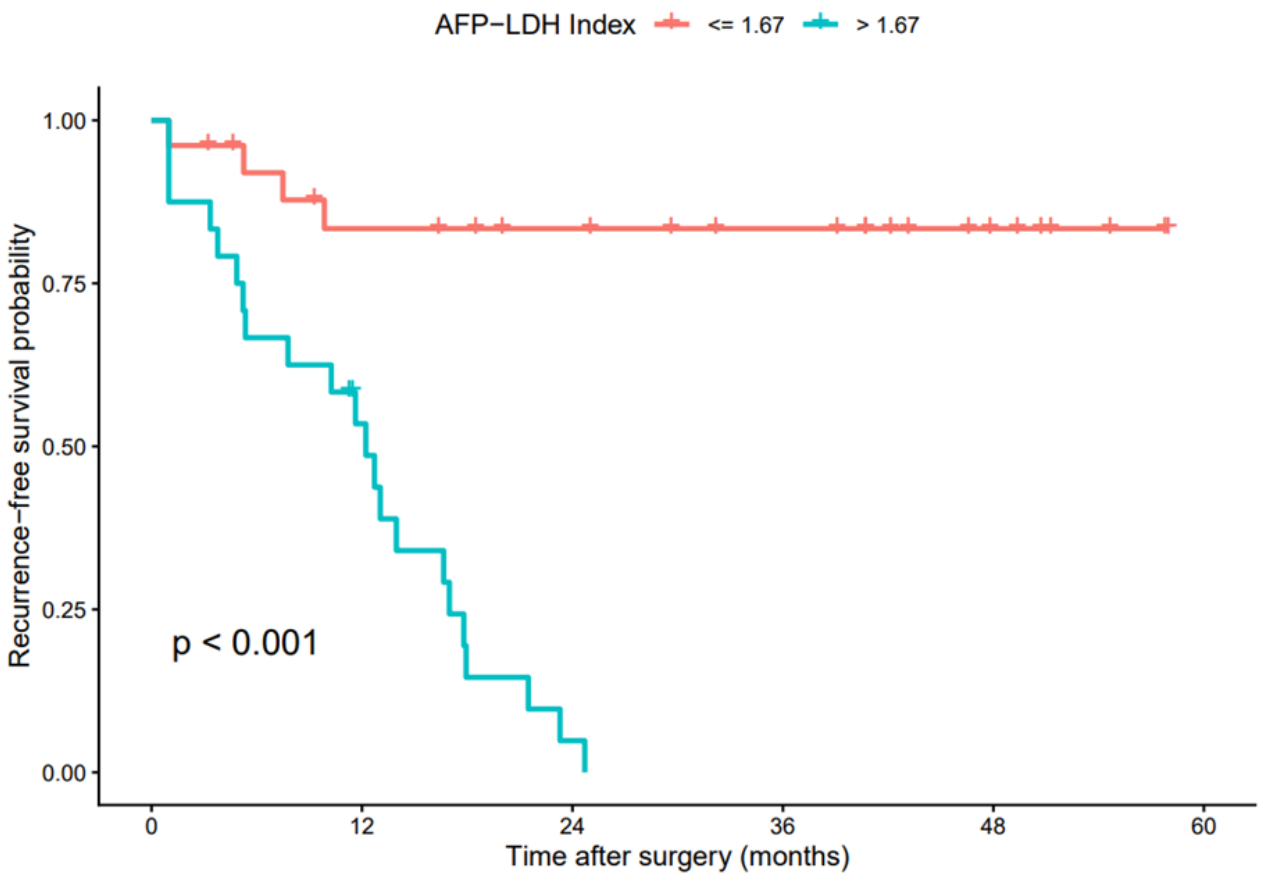

Fig. 1. Kaplan–Meier curve showing recurrence-free survival according to AFP–LDH Index cutoff values (≤1.67 vs >1.67).

Table 2. Univariable and multivariable Cox regression analysis for recurrence.

Variable	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Tumor size >5 cm	3.49 (1.16–10.47)	0.026	2.11 (0.61–7.28)	0.236
Microvascular invasion	3.76 (1.62–8.70)	0.002	2.94 (1.01–8.52)	0.048
Tumor necrosis (%)	1.03 (1.00–1.06)	0.033	1.02 (0.99–1.05)	0.141
AFP–LDH Index	35.72 (8.13–157.00)	<0.001	27.24 (5.41–137.14)	<0.001

HR, hazard ratio.

Table 3. Univariate and multivariable Cox regression analysis for overall survival.

Variable	Univariable HR (95% CI)	*p* value	Multivariable HR (95% CI)	*p* value
Tumor size >5 cm	2.55 (0.94–6.91)	0.066	1.62 (0.58–4.50)	0.354
Microvascular invasion	4.54 (1.47–13.98)	0.008	2.32 (0.73–7.39)	0.154
AFP–LDH Index	20.89 (3.51–124.24)	<0.001	17.20 (2.04–144.98)	0.009

variable analysis and showed favorable discriminative performance in ROC analysis. Internal validation using bootstrap resampling supported the stability of the discriminative performance of the AFP–LDH Index. Taken together, these findings suggest that integrating postoperative AFP dynamics with LDH may provide complementary biological information for postoperative recurrence risk assessment in HCC. However, given the limited sample size and absence of external validation, the findings should be interpreted cautiously.

It is well established that recurrence rates remain high after curative resection for HCC, and early risk stratification plays a critical role in postoperative clinical management [2,3,4,7]. AFP has long been used as a prognostic biomarker in HCC; however, its discriminative capacity may be limited, particularly in patients with early-stage disease or low AFP levels [1,2]. Therefore, in recent years, several models integrating AFP with additional laboratory parameters have been developed. An et al. [8] demonstrated that nomograms incorporating PIVKA-II and mul-

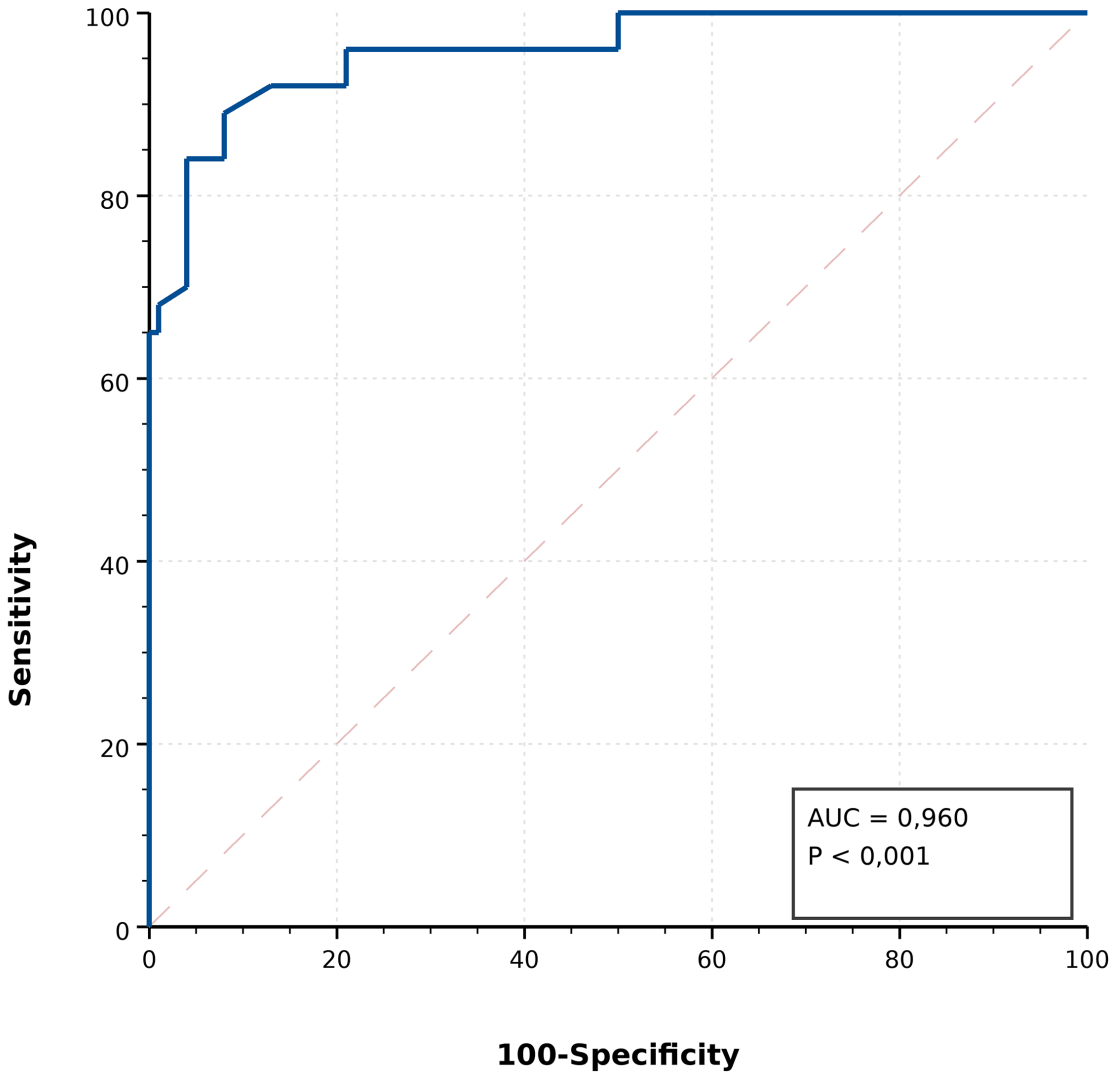

Fig. 2. Receiver operating characteristic (ROC) curve of the AFP–LDH Index for recurrence prediction. The displayed curve represents the original ROC analysis. AUC, area under the curve.

tiple serum biomarkers could improve prognostic accuracy in HCC. Similarly, Wang et al. [9] reported that prognostic nomograms developed for AFP-negative HCC patients provided superior predictive performance compared with AFP alone. These findings support the concept that combined biomarker approaches may offer superior prognostic performance compared with single-parameter models.

LDH is an important indicator of tumor metabolism and is associated with increased glycolysis and a hypoxic tumor microenvironment. Previous studies have suggested that LDH may reflect tumor aggressiveness and adverse oncological outcomes in patients with HCC [10,11,12]. The ability of LDH to reflect the metabolic dimension of tumor biology suggests that it represents more than a simple enzymatic parameter and may serve as an indirect indicator of tumor aggressiveness. AFP, in contrast, is an established prognostic biomarker in HCC, with elevated serum AFP levels being associated with an increased risk of recurrence and poorer survival [13]. Therefore, the combined evaluation of AFP and LDH allows integrated assessment of tumor burden and metabolic activity. The rationale for the AFP–LDH Index was to integrate complementary biological information from routinely available laboratory parameters. Preoperative AFP was used as a reference measure of baseline tumor burden, postoperative AFP reflected residual biological activity following resection, and preoperative LDH served as a surrogate marker of tumor metabolic activity. By combining these parameters, the AFP–LDH Index was designed to capture both tumor marker dynamics and metabolic aggressiveness within a single composite measure.

The AFP–LDH Index may also be biologically associated with microvascular invasion and tumor size. However, these potential biological associations should be further explored and validated in prospective studies.

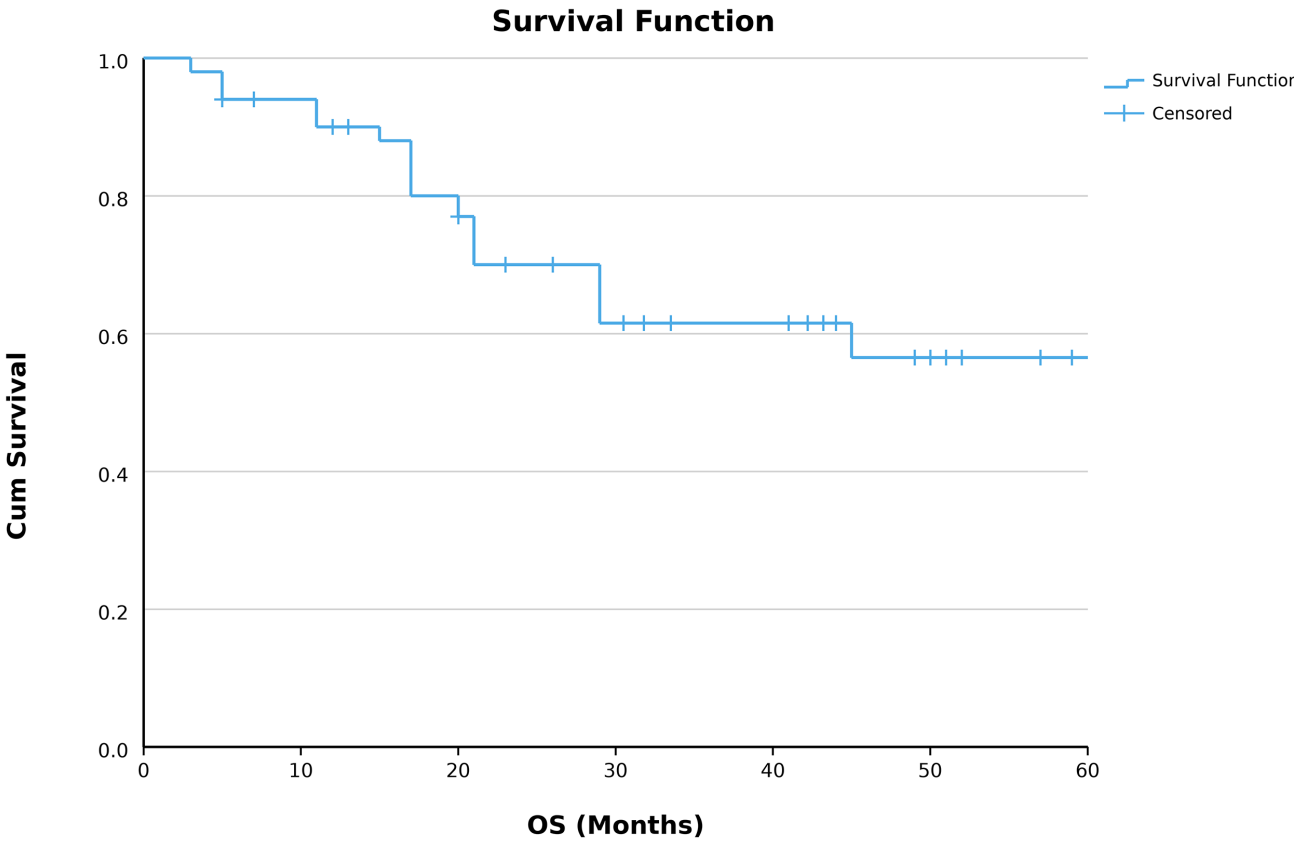

Fig. 3. Kaplan–Meier curve for overall survival in the study cohort.

Composite biomarker approaches integrating multiple biological dimensions have increasingly been investigated as prognostic tools in oncology, and previous studies suggest that combining laboratory and biological parameters may improve prognostic stratification compared with single biomarkers alone [14,15,16,17].

In the present study, the AFP–LDH Index yielded a high AUC value for predicting recurrence (AUC = 0.960). However, this finding should be interpreted with caution given the limited sample size and the absence of external validation. In the literature, most models developed to predict early recurrence after curative resection demonstrate moderate to high discriminative performance. In a systematic review and meta-analysis evaluating MRI-based models for preoperative prediction of early recurrence (<2 years) following curative surgery in HCC, Lu et al. [18] reported a pooled summary ROC AUC of 0.89 (95% CI: 0.86–0.91) for radiomics-based models and 0.83 (95% CI: 0.80–0.86) for clinical and non-radiomics models. Notably, significant heterogeneity and potential publication bias were also identified among radiomics studies in that analysis. However, direct comparison with our findings should be interpreted cautiously, as Lu et al. [18] evaluated preoperative MRI-based prediction of early recurrence (<2 years), whereas the present study assessed a postoperative blood-based index for recurrence during the overall follow-up period; therefore, differences in predictor modality, timing, and outcome definition limit direct comparability between the reported AUC values.

In this context, the observed discriminative performance of the AFP–LDH Index using simple, widely available, and cost-effective laboratory parameters is noteworthy. Nevertheless, this finding should be interpreted cautiously, and external validation in independent cohorts remains necessary. Furthermore, the high AUC observed in our study may partly reflect optimistic estimation due to the single-center design and limited sample size. Therefore, the potential clinical utility of the AFP–LDH Index requires further validation in larger multicenter prospective studies before routine clinical application can be considered.

A substantial proportion of HCC recurrences occur within the first years following surgery and are associated with more aggressive tumor biology [19,20]. In a large series, Du et al. [19] reported that a considerable proportion of recurrences developed during the early postoperative period. Similarly, Yao et al. [20] demonstrated that recurrence timing after surgery was closely associated with long-term outcomes. These findings suggest that the AFP–LDH Index may have potential utility for identifying patients at higher risk of early recurrence, although further validation is required.

This study has several limitations that should be acknowledged. First, this was a retrospective single-center study with a relatively limited sample size and number of recurrence events, which may have reduced the generalizability of the findings and increased the risk of overfitting in the multivariable model. Therefore, the high HR and AUC values observed in the present study should be interpreted cautiously. Second, although internal validation using bootstrap resampling was performed, external validation in an independent cohort was not available. In addition, the optimal cutoff value was derived from the same dataset used for model development, which may have resulted in optimistic estimation of predictive performance. Finally, LDH levels may be influenced by hepatic function and inflammatory processes, and therefore the extent to which the AFP–LDH Index specifically reflects tumor biology requires further investigation in larger prospective studies.

Taken together, these findings suggest that the AFP–LDH Index may represent a practical and readily available approach for postoperative recurrence risk stratification in HCC. If externally validated in larger multicenter cohorts, this index may contribute to individualized surveillance strategies and postoperative patient monitoring following curative resection.

Conclusions

In patients with HCC undergoing curative resection, the dynamic AFP–LDH Index emerged as an independent prognostic marker associated with recurrence risk. Although the index demonstrated favorable discriminative performance in this exploratory single-center study, the findings should be interpreted cautiously given the limited sample size and potential risk of overfitting. Further multicenter prospective studies are required to validate its prognostic value across different patient populations before routine clinical application can be considered.

Availability of Data and Materials

The data used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

BÇ and EBE designed the research study. BÇ and APE performed the research and contributed to the data collection and curation. EBE analyzed and interpreted the data. BÇ and EBE drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Clinical Research Ethics Committee of Izmir University of Economics (Approval No: E-97429853-050.04-118680) and was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments. Due to the retrospective and anonymized design of the study, the requirement for informed consent was waived in accordance with institutional policies.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Mazza S, Frigerio C, Alfieri D, Mauro A, Torello Viera F, Scalvini D, et al. Prognostic Role of Basal Serum Alpha-Fetoprotein in Patients with Hepatocellular Carcinoma Suitable for Curative Treatment. Medicina (Kaunas, Lithuania). 2024; 60: 692. https://doi.org/10.3390/medicina60050692

[2] Xu J, An S, Lu Y, Li L, Wu ZQ, Xu HG. Preoperative alpha fetoprotein, total bilirubin, fibrinogen, albumin, and lymphocytes predict postoperative survival in hepatocellular carcinoma. Cancer Medicine. 2023; 12: 13319–13328. https://doi.org/10.1002/cam4.6030

[3] Cui J, Lin Z, Huang X, Wang S, Guo J, Song J, et al. Predictive Radiomics-Based Model for Recurrence-Free Survival After Curative Resection in Patients with Hepatocellular Carcinoma. Journal of Hepatocellular Carcinoma. 2025; 12: 1755–1766. https://doi.org/10.2147/JHC.S535492

[4] Li J, Wang Q, Yan Y, Sun L, Zhang G, Li G, et al. Development and validation of a prognostic nomogram to predict the recurrence of AFP-negative and DCP-positive hepatocellular carcinoma after curative resection. Frontiers in Oncology. 2024; 14: 1414083. https://doi.org/10.3389/fonc.2024.1414083

[5] Peng Y, Qi X, Guo X. Child-Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis: A Systematic Review and Meta-Analysis of Observational Studies. Medicine. 2016; 95: e2877. https://doi.org/10.1097/MD.0000000000002877

[6] Sok M, Zavrl M, Greif B, Srpčič M. Objective assessment of WHO/ECOG performance status. Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer. 2019; 27: 3793–3798. https://doi.org/10.1007/s00520-018-4597-z

[7] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018; 69: 182–236. https://doi.org/10.1016/j.jhep.2018.03.019

[8] An S, Zhan X, Liu M, Li L, Wu J. Diagnostic and Prognostic Nomograms for Hepatocellular Carcinoma Based on PIVKA-II and Serum Biomarkers. Diagnostics (Basel, Switzerland). 2023; 13: 1442. https://doi.org/10.3390/diagnostics13081442

[9] Wang X, Mao M, He Z, Zhang L, Li H, Lin J, et al. Development and Validation of a Prognostic Nomogram in AFP-negative hepatocellular carcinoma. International Journal of Biological Sciences. 2019; 15: 221–228. https://doi.org/10.7150/ijbs.28720

[10] Zhang JP, Wang HB, Lin YH, Xu J, Wang J, Wang K, et al. Lactate Dehydrogenase Is an Important Prognostic Indicator for Hepatocellular Carcinoma after Partial Hepatectomy. Translational Oncology. 2015; 8: 497–503. https://doi.org/10.1016/j.tranon.2015.11.006

[11] Yada M, Miyazaki M, Motomura K, Masumoto A, Nakamuta M, Kohjima M, et al. The prognostic role of lactate dehydrogenase serum levels in patients with hepatocellular carcinoma who are treated with sorafenib: the influence of liver fibrosis. Journal of Gastrointestinal Oncology. 2016; 7: 615–623. https://doi.org/10.21037/jgo.2016.03.10

[12] Petrelli F, Cabiddu M, Coinu A, Borgonovo K, Ghilardi M, Lonati V, et al. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. Acta Oncologica (Stockholm, Sweden). 2015; 54: 961–970. https://doi.org/10.3109/0284186X.2015.1043026

[13] Chen HL, Chen YH, Du L, Song YP, Zhu B. Elevated serum alpha-fetoprotein levels are associated with poor prognosis of hepatocellular carcinoma after surgical resection: A systematic review and meta-analysis. Arab Journal of Gastroenterology: the Official Publication of the Pan-Arab Association of Gastroenterology. 2021; 22: 12–22. https://doi.org/10.1016/j.ajg.2020.09.004

[14] Wang F, Jiang C, He W, Li H, Guo GF, Xu L. Assessing the Prognostic Value of 13 Inflammation-Based Scores in Patients with Unresectable or Advanced Biliary Tract Carcinoma After Immunotherapy. ImmunoTargets and Therapy. 2024; 13: 541–557. https://doi.org/10.2147/ITT.S471502

[15] Argalácsová S, Dytrych P, Wágnerová M, Černý V, Špaček J, Hloušek S, et al. Prognostic Value of Hematologic Indices and Composite Models in Anal Squamous Cell Carcinoma Treated with Image-Guided Chemoradiotherapy. Cancers. 2025; 17: 3838. https://doi.org/10.3390/cancers17233838

[16] Frühling P, Urdzik J, Strömberg C, Isaksson B. Composite Score: prognostic tool to predict survival in patients undergoing surgery for colorectal liver metastases. BJS Open. 2021; 5: zrab104. https://doi.org/10.1093/bjsopen/zrab104

[17] Sohda M, Sakai M, Yamaguchi A, Watanabe T, Nakazawa N, Ubukata Y, et al. Pre-treatment CRP and Albumin Determines Prognosis for Unresectable Advanced Oesophageal Cancer. In Vivo (Athens, Greece). 2022; 36: 1930–1936. https://doi.org/10.21873/invivo.12914

[18] Lu M, Wang C, Zhuo Y, Gou J, Li Y, Li J, et al. Preoperative prediction power of radiomics and non-radiomics methods based on MRI for early recurrence in hepatocellular carcinoma: a systemic review and meta-analysis. Abdominal Radiology (New York). 2024; 49: 3397–3411. https://doi.org/10.1007/s00261-024-04356-y

[19] Du ZG, Wei YG, Chen KF, Li B. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution's experience with 398 consecutive patients. Hepatobiliary & Pancreatic Diseases International : HBPD INT. 2014; 13: 153–161. https://doi.org/10.1016/s1499-3872(14)60025-4

[20] Yao LQ, Chen ZL, Feng ZH, Diao YK, Li C, Sun HY, et al. Clinical Features of Recurrence After Hepatic Resection for Early-Stage Hepatocellular Carcinoma and Long-Term Survival Outcomes of Patients with Recurrence: A Multi-institutional Analysis. Annals of Surgical Oncology. 2022; 29: 4291–4303. https://doi.org/10.1245/s10434-022-11454-y