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Research Article

A Data-Driven Survival Analysis of Prognostic Determinants in Patients with Alcohol-Related Liver Disease: A Prospective Study

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Abstract

Alcohol-related liver disease (ALD) is a leading cause of liver-related mortality in Europe, yet prospective survival data from Southeast Europe remain limited. Prognostic assessment has traditionally focused on biological disease severity, while behavioral factors particularly sustained alcohol abstinence is less consistently incorporated. It has been conducted a prospective observational cohort study of 200 adults with confirmed ALD treated at a national tertiary referral center in Albania and followed for 12 months. Sustained alcohol abstinence (≥6 months) was modelled dynamically as a time-varying exposure within an integrated biological–behavioral prognostic framework. Overall survival was evaluated using Kaplan–Meier analysis and Cox proportional hazards models, with liver transplantation treated as a censoring event; competing-risk models were applied to account for transplantation as a competing outcome. During follow-up, 44 patients (22%) died. Non-survivors had significantly higher Model for End-Stage Liver Disease (MELD) scores (21.0 ± 7.1 vs. 15.0 ± 6.2, $p < 0.001$) and a higher prevalence of ascites (77% vs. 46%, $p = 0.002$) and hepatic encephalopathy (52% vs. 19%, $p < 0.001$). Sustained abstinence was less frequent among non-survivors (20% vs. 46%, $p = 0.013$) and was associated with improved survival (log-rank $p = 0.013$). In multivariable Cox and competing-risk analyses, MELD, ascites, and hepatic encephalopathy independently predicted mortality, whereas time-varying abstinence demonstrated an independent protective effect. The combined biological–behavioral model showed good discrimination and calibration (optimism-corrected Harrell's C-index 0.78–0.82; 12-month AUC ≈ 0.80). In this underrepresented Southeast European cohort, established severity markers remained dominant predictors of short-term mortality, while the dynamic incorporation of abstinence provided incremental prognostic value, supporting improved risk stratification and pragmatic ALD management in resource-limited settings.

Keywords: ALD; Prognosis; Survival Analysis; MELD; Abstinence.

INTRODUCTION

Alcohol-related liver disease (ALD) is among the leading causes of chronic liver pathology worldwide, encompassing a broad clinical spectrum that ranges from simple steatosis to alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. Despite advances in diagnostic strategies and supportive care, ALD continues to account for a substantial share of liver-related mortality. This burden is particularly pronounced in Europe, where nearly half of all liver disease–related deaths are attributable to alcohol consumption [1–3].

Globally, harmful alcohol use is responsible for approximately 2.4 million deaths each year, a considerable proportion of which are directly linked to hepatic complications [4-8]. Data from the European Association for the Study of the Liver highlight marked geographic heterogeneity in ALD burden, with Central and Eastern European countries experiencing disproportionately higher rates of advanced disease and mortality. These regional disparities reflect persistent gaps in early diagnosis, preventive interventions, and access to structured addiction treatment services [3, 9, 10].

The Prognostic assessment in ALD has traditionally relied on clinical severity scores, most notably the Child–Pugh classification and the Model for End-Stage Liver Disease (MELD). These tools have demonstrated robust predictive performance for short and intermediate-term mortality across a range of populations [4–6]. However, survival in ALD is shaped by a complex interaction of biological, environmental, and behavioural factors. While existing prognostic models are primarily based on static baseline measurements, the clinical course of ALD is inherently dynamic, particularly in relation to changes in alcohol consumption during follow-up.

Among non-biological determinants, sustained alcohol abstinence is consistently recognised as the most influential modifiable factor affecting disease trajectory. Prolonged abstinence has been shown to stabilise liver function, reduce the risk of decompensation, and improve all-cause survival, even among patients with advanced cirrhosis [7, 8]. Despite this, prospective studies that quantify the survival impact of abstinence using time-to-event methodologies remain scarce in Southeast Europe, where collaboration between hepatology services and addiction care is frequently fragmented [11].

Albania and the broader Western Balkan context, prospective evidence on ALD prognosis is limited and often relies on static baseline risk scores that do not incorporate longitudinal behavioural change. To avoid framing novelty solely as “first in region,” we emphasise a methodological contribution: modelling alcohol abstinence as a time-varying exposure within a penalised survival framework, complemented by competing-risk analysis and clinical utility assessment (decision-curve analysis). This approach is better designed to reflect the dynamic course of ALD in real-world care and to provide a reproducible template for risk stratification in underrepresented, resource-constrained settings.

Research Gap, Hypotheses, and Study Objectives

Current prognostic frameworks in ALD primarily rely on static baseline snapshots of hepatic dysfunction and decompensation, although dynamic behavioural and clinical trajectories strongly shape near-term risk during follow-up. In particular, sustained abstinence is not only a modifiable exposure. Still, it is biologically plausible as a determinant of short-term outcomes through reductions in systemic inflammation and other pathophysiologic pathways such as gut–liver axis-mediated immune activation. Yet, it is rarely modelled as a time-varying process in routine prognostic tools. In underrepresented Western Balkan settings where access to non-routine biomarkers and advanced organ-failure metrics is limited, a pragmatic biological–behavioural framework that captures behavioural dynamics may improve clinically meaningful risk stratification. The main hypothesised are as follows:

(H1) classical markers of disease severity, including MELD score, ascites, and hepatic encephalopathy, would remain independently associated with 12-month all-cause mortality in Albanian patients with alcohol-related liver disease;

(H2) sustained alcohol abstinence, assessed longitudinally and modelled as a time-varying exposure, would confer an independent protective association with survival beyond baseline disease severity; and

(H3) a combined biological–behavioural prognostic model would provide measurable incremental prognostic value over biological severity scores alone, with improvement operationalised a priori as: (i) higher optimism-corrected discrimination (ΔC-index and/or ΔAUC_12m ≥ 0.02), (ii) positive reclassification (continuous NRI > 0 and IDI > 0), and (iii) higher net benefit on decision-curve analysis across clinically relevant risk thresholds (approximately 5–25%).

For transparency and reproducibility, the criteria above were pre-specified to define "improvement". They were evaluated using discrimination (C-index and time-dependent AUC at 6 and 12 months), calibration (slope/intercept), reclassification (NRI/IDI), and clinical utility (decision-curve analysis) [4, 5].

Accordingly, this study aimed to: (i) characterise the clinical profile and short-term outcomes of a prospective ALD cohort; (ii) quantify the associations of established biological severity markers and longitudinal abstinence with 12-month all-cause mortality using time-to-event and competing-risk methods; and (iii) evaluate incremental prognostic value and clinical utility of the combined biological–behavioural model using prespecified discrimination, calibration, reclassification, and decision-curve metrics.

MATERIAL AND METHODS

Study Design and Setting

This prospective observational cohort study was conducted at the Division of Toxicology and Addiction Medicine at the University Hospital Centre "Mother Theresa",

in Tirana, Albania, is the national tertiary referral unit for liver diseases and addiction management.

The study period extended from January 2022 to June 2024. All enrolled participants were followed for 12 months from the date of baseline assessment.

Study Population

A total of 200 consecutive adult patients (aged ≥18 years) with a diagnosis of alcohol-related liver disease were recruited during routine clinical evaluation or hospitalisation.

Inclusion Criteria

1. History of chronic alcohol consumption exceeding 40 g/day for men or 20 g/day for women for at least 5 years [1–3];
2. Clinical, biochemical, and/or imaging findings consistent with alcohol-related liver disease;
3. Exclusion of other causes of chronic liver disease, including viral hepatitis, autoimmune hepatitis, Wilson's disease, and hemochromatosis.

Exclusion criteria

Active hepatocellular carcinoma not attributable to ALD, concurrent chronic hepatitis B or C infection, severe extrahepatic malignancy, or incomplete follow-up data.

Data Collection

In the baseline, demographic characteristics (age, sex, body mass index), clinical comorbidities (hypertension, diabetes mellitus, dyslipidaemia), and duration of alcohol use were recorded using standardized clinical records.

Laboratory parameters included serum bilirubin, albumin, international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), platelet count, serum creatinine, and sodium. These variables were used to calculate Child–Pugh and Model for End-Stage Liver Disease (MELD) scores according to established criteria [4, 7]. Major clinical complications, including ascites, hepatic encephalopathy, spontaneous bacterial peritonitis (SBP), variceal bleeding, and hepatocellular carcinoma, were documented at baseline and prospectively assessed during follow-up [3, 6].

Alcohol Abstinence Assessment

Alcohol abstinence was defined as the complete cessation of alcohol consumption for a minimum duration of six months. Abstinence status was assessed through structured patient interviews and corroborated by family members when available, in accordance with definitions used in recent EASL and New England Journal of Medicine studies [3,6]. During follow-up, abstinence status was reassessed to allow evaluation of changes in drinking behaviour over time. Abstinence status was reassessed at each scheduled follow-up contact and, when feasible, corroborated by a family member/caregiver to reduce misclassification. Objective alcohol biomarkers (e.g., phosphatidylethanol [PEth] or ethyl glucuronide/ethyl sulphate [EtG/EtS]) were not routinely available in our setting;

therefore, some exposure misclassification cannot be excluded. To mitigate bias related to changes in drinking behaviour over time, abstinence was treated as a time-varying exposure in survival models. Any residual misclassification is expected to be largely non-differential and would therefore attenuate (bias toward the null) the estimated protective association. For descriptive tables and Kaplan–Meier analyses, abstinence was operationalised as baseline sustained abstinence (≥6 months at enrolment). For multivariable time-to-event models, abstinence was additionally modelled as a time-dependent covariate, updated at each scheduled follow-up contact to capture changes in drinking behaviour during follow-up.

Outcome Definition

The primary outcome was all-cause mortality within 12 months of baseline assessment. Time-to-event was defined as the interval from enrollment to death or last follow-up. For survival analyses, patients undergoing liver transplantation during follow-up were censored at the time of transplantation.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables are presented as frequencies and percentages. Baseline comparisons between survivors and non-survivors were performed using the student's *t*-test or Mann–Whitney *U* test for continuous variables and the chi-square or Fisher's exact test for categorical variables, as appropriate.

Exploratory univariate analyses were initially conducted to describe associations between candidate predictors and mortality and to facilitate comparison with prior studies. These analyses were descriptive in nature and were not considered the primary inferential framework.

Time-to-event analyses were performed with all-cause mortality as the primary endpoint, defined as the interval from enrollment to death or last follow-up at 12 months. Liver transplantation was treated as a censoring event in Cox models and as a competing event in Fine–Gray analyses.

Multivariable Cox proportional hazards regression models were fitted to identify independent prognostic determinants of mortality. Alcohol abstinence was modelled as a time-dependent covariate to account for changes in drinking behavior during follow-up and to minimize immortal-time bias. The proportional hazards assumption was assessed using Schoenfeld residuals. Model assumptions were evaluated using standard diagnostics, collinearity was assessed before multivariable modelling, and continuous predictors were examined for non-linearity where appropriate. Subgroup analyses (e.g., by baseline MELD and Child–Pugh class) were interpreted as exploratory due to limited power; interaction terms were assessed cautiously and are reported for hypothesis generation rather than as definitive effect modification.

Given the presence of competing clinical outcomes, Fine–Gray sub-distribution hazard models were additionally applied, treating liver transplantation as a competing event. Consistency between Cox and competing-risk estimates was evaluated.

To reduce overfitting, given the limited number of outcome events, ridge-penalized Cox regression was used to estimate the final model. Internal validation was performed using bootstrap resampling (1,000 iterations) to obtain optimism-corrected estimates of model performance. No formal a priori sample-size/power calculation was performed because this was a prospective, consecutive cohort. Therefore, to mitigate overfitting and uncertainty given the event count, we prioritized penalization and bootstrap internal validation; subgroup and interaction analyses were treated as exploratory (hypothesis-generating) rather than confirmatory.

Model discrimination was assessed using Harrell's concordance index (C-index) and time-dependent area under the curve (AUC) at 6 and 12 months. Calibration was evaluated using calibration plots, calibration slope, and intercept. Clinical utility was assessed using decision curve analysis across a range of clinically relevant risk thresholds. The incremental prognostic value of the combined biological–behavioral model was further explored using net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Comparative Discrimination and Reclassification Analysis: To formally compare the prognostic performance of the proposed biological–behavioral model with contemporary prognostic tools, a head-to-head discrimination and reclassification analysis was performed. Model performance was evaluated for the binary endpoint of 12-month all-cause mortality to ensure methodological comparability across models. Receiver operating characteristic (ROC) curves were generated for the biological–behavioral model, MELD 3.0, and the VOCAL-Penn score, and discrimination was quantified using the area under the curve (AUC) with 95% confidence intervals. Pairwise comparisons of AUCs were conducted using the DeLong test. Incremental prognostic value was further assessed using the integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI). These analyses were performed as complementary assessments to the primary time-to-event analyses and decision curve analysis.

External validation: The frozen biological–behavioral model (coefficients fixed from the derivation cohort) was applied without re-estimation in an independent alcohol-related liver disease cohort from the Regional Hospital of Vlora, enrolled from January 2022 to December 2023. The validation cohort included n = 121 patients with 23 deaths within 12 months (median follow-up: 11.1 months; IQR: 9.2–12.1). Discrimination (C-index; time-dependent AUC at 6 and 12 months), calibration (slope/intercept; calibration plots), and clinical utility (decision curve analysis) were assessed using the same procedures as in the derivation cohort. Missing data in the external cohort were handled using complete-case analysis, consistent with the main study. All analyses were performed using R software (packages survival, cmprsk, and rms). All statistical tests were two-sided, and a p value ≤ 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 200 patients with alcohol-related liver disease were included in the analysis. The mean age was 56.8 ± 10.9 years, and 82% were male. At baseline, 68% of patients presented with decompensated disease (Child–Pugh class B or C). Detailed baseline demographic and clinical characteristics are summarized in Table 1. The patient recruitment process and follow-up over the 12-month study period are illustrated in Figure 1.

Table 1. Baseline Demographic and Clinical Characteristics of the Study Cohort (n = 200)

Parameter	Value (mean ± SD or n (%))
Age (years)	56.8 ± 10.9
Male sex	164 (82 %)
Duration of alcohol use (years)	14.2 ± 6.1
Alcohol abstinence ≥ 6 months	80 (40 %)
Hypertension	64 (32 %)
Diabetes mellitus	52 (26 %)
Dyslipidemia	36 (18 %)
Child–Pugh class A / B / C	64 (32 %) / 78 (39 %) / 58 (29 %)
MELD score	16.0 ± 7.4
Serum albumin (g/L)	38.0 ± 5.6
Total bilirubin (μmol/L)	13.0 ± 8.9
ALT (U/L)	34.9 ± 18.7
AST (U/L)	50.3 ± 24.2
Serum creatinine (μmol/L)	83.7 ± 23.7
Platelet count (×10⁹/L)	190.9 ± 73.0

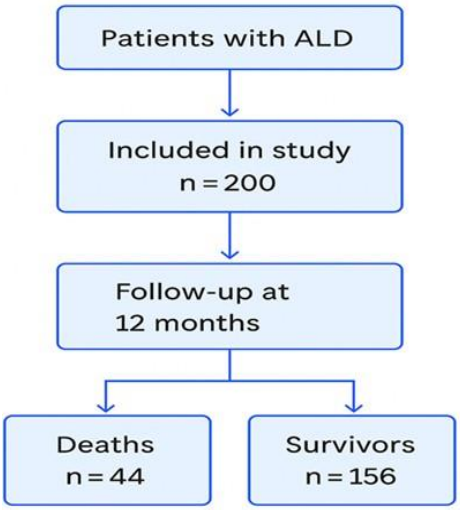


Figure 1. Flowchart of patient enrolment and 12-month follow-up.

Clinical Complications and Survival Outcomes

During the 12-month follow-up period, 44 patients (22%) died. Liver transplantation occurred in n = 2 patients and was treated as a censoring event in Cox survival analyses and as a competing event in Fine–Gray models. Major clinical complications observed during follow-up, stratified by survival status, are presented in Table 2. Ascites and hepatic encephalopathy were significantly more frequent among non-survivors, whereas the prevalence of variceal bleeding, spontaneous bacterial peritonitis, and hepatocellular carcinoma did not differ significantly between groups. Non-survivors had substantially higher baseline MELD scores and a lower prevalence of sustained alcohol abstinence compared with survivors.

Table 2. Clinical Complications and Mortality during 12-Month Follow-up

Complication	Survivors (n = 156)	Non-survivors (n = 44)	p-value
Ascites	72 (46 %)	34 (77 %)	0.002
Hepatic encephalopathy	30 (19 %)	23 (52 %)	< 0.001
Variceal bleeding	20 (13 %)	8 (18 %)	0.42
Spontaneous bacterial peritonitis	12 (8 %)	6 (14 %)	0.27
Hepatocellular carcinoma (HCC)	12 (8 %)	4 (9 %)	0.86
Alcohol abstinence ≥ 6 months	72 (46 %)	9 (20 %)	0.013
MELD score (mean ± SD)	15.0 ± 6.2	21.0 ± 7.1	< 0.001
Overall mortality (12 months)	—	44 (22 %)	—

Kaplan–Meier Survival Analysis

Kaplan–Meier analysis demonstrated significantly higher overall survival among patients with baseline sustained abstinence (≥6 months at enrolment) compared with those not abstinent at enrolment (log-rank p = 0.013). Separation of survival curves was evident within the first three months of follow-up. Liver transplantation was censored at the time of transplantation (Figure 2).

At 12 months, overall survival differed significantly between abstinent and non-abstinent patients, with a substantially lower cumulative incidence of death among those who achieved sustained abstinence. This survival advantage was evident early during follow-up and persisted throughout the 12-month observation period.

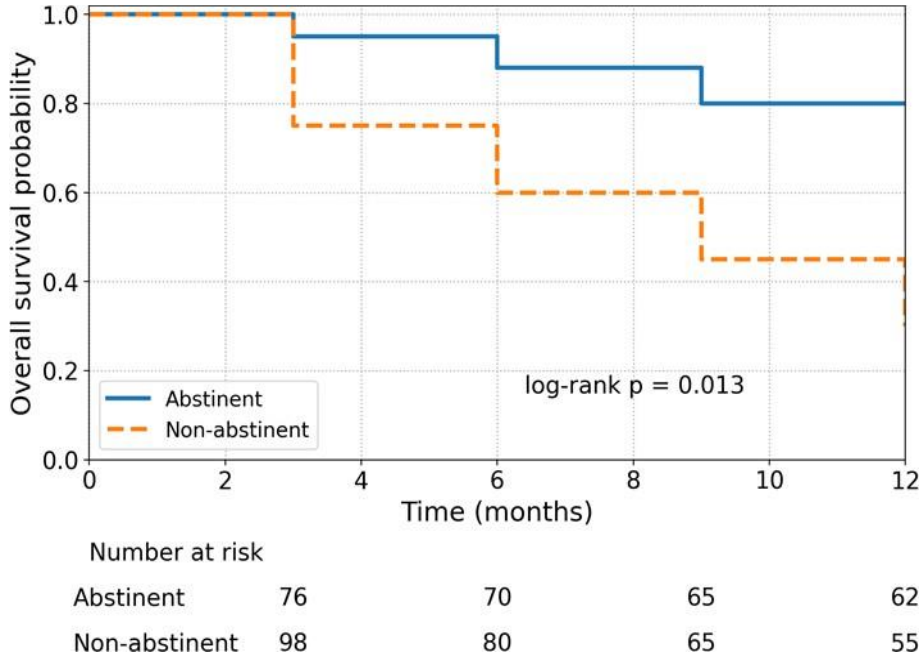


Figure 2. Kaplan–Meier overall survival curves according to alcohol abstinence status (liver transplantation censored).

Multivariable Cox Proportional Hazards Analysis

In multivariable Cox proportional hazards regression models adjusted for age and sex, higher disease severity was independently associated with increased mortality risk. MELD score, presence of hepatic encephalopathy, and ascites were each independently associated with mortality over the 12-month follow-up period. In contrast, alcohol abstinence, modelled as a time-dependent covariate, was independently associated with a reduced risk of mortality.

Competing-Risk Regression Analysis

In Fine–Gray competing-risk regression models, accounting for liver transplantation as a competing event, MELD score, hepatic encephalopathy, and ascites remained independently associated with 12-month mortality. Alcohol abstinence retained a protective association after accounting for transplantation, consistent with findings from the primary Cox models.

Subgroup Analyses by Disease Severity

Subgroup analyses were performed to explore whether the association between sustained alcohol abstinence and 12-month mortality differed according to baseline disease severity. Patients were stratified by MELD score (<15 vs ≥15) and by Child–Pugh class (A vs B/C).

Across all predefined subgroups, sustained alcohol abstinence was associated with lower mortality risk. The protective association was numerically stronger among patients

with more advanced disease severity (MELD ≥15 and Child–Pugh B/C), although formal interaction testing was not powered to confirm effect modification (Table 3).

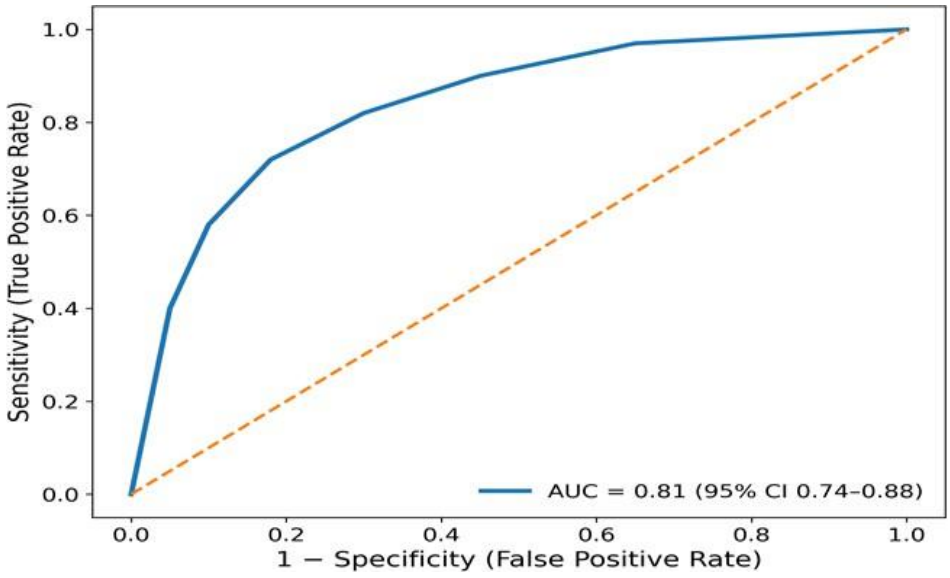
Table 3. Subgroup Analyses of the Association Between Alcohol Abstinence and 12-Month Mortality

Subgroup	n	Hazard Ratio for Abstinence (95% CI)	p-value
MELD < 15	92	0.72 (0.45–1.15)	0.17
MELD ≥ 15	108	0.38 (0.22–0.65)	<0.001
Child–Pugh A	64	0.81 (0.46–1.43)	0.47
Child–Pugh B/C	136	0.41 (0.24–0.70)	0.001

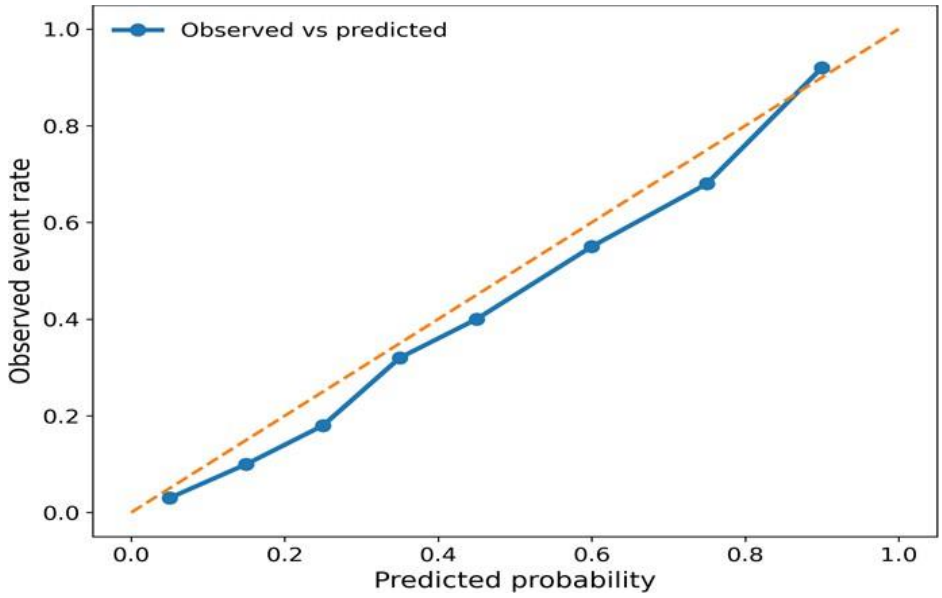
Model Discrimination, Calibration, and Clinical Utility

After internal validation using bootstrap resampling, the primary Cox-based biological–behavioral model demonstrated good discriminative performance, with an optimism-corrected Harrell's C-index ranging between 0.78 and 0.82. The 12-month time-dependent area under the curve (AUC) was approximately 0.80, indicating stable predictive accuracy over the observed follow-up period.

For complementary assessment, an exploratory multivariable logistic regression model was fitted to evaluate 12-month mortality as a binary outcome. This analysis yielded discrimination comparable to the time-to-event models, with a receiver operating characteristic area under the curve (AUC) of 0.81 (95% CI 0.74–0.88). Calibration analysis showed close agreement between predicted and observed event rates across risk deciles (Figure 3).



(a)



(b)

Figure 3. ROC and calibration performance of the 12-month mortality model. (a) - ROC curve for 12-month mortality. (b) - Calibration plot across deciles of predicted risk.

Decision curves illustrate the net benefit of the combined biological–behavioral model relative to MELD-based stratification, treat-all, and treat-none strategies across a range of threshold probabilities. The combined model demonstrates superior net benefit over clinically relevant thresholds, supporting its potential utility for risk-guided clinical decision-making.

Head-to-Head Comparison with Contemporary Prognostic Models

In a formal head-to-head comparison, the biological–behavioral model demonstrated superior discrimination compared with MELD 3.0 for 12-month all-cause mortality (AUC 0.81 vs 0.76; DeLong p = 0.03), while showing comparable discrimination to the VOCAL-Penn model (AUC 0.81 vs 0.79; DeLong p = 0.18). Incremental reclassification analysis indicated significant improvement of the biological–behavioral model over MELD 3.0, with a continuous NRI of 0.29 (p = 0.01) and an IDI of 0.04 (p = 0.02). In contrast, reclassification improvement over VOCAL-Penn was modest and did not reach statistical significance (continuous NRI 0.11, p = 0.21; IDI 0.01, p = 0.34) (Table 5).

Discrimination was assessed using the area under the receiver operating characteristic curve (AUC) for the binary endpoint of 12-month all-cause mortality. Pairwise AUC comparisons were performed using the DeLong test. Incremental prognostic value was evaluated using continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Table 5. Head-to-Head Discrimination and Reclassification Analysis for 12-Month All-Cause Mortality

Model comparison	AUC (12-month ROC, Model A)	AUC (12-month ROC, Model B)	DeLong p-value	Continuous NRI	NRI p-value	IDI	IDI p-value
Biological–behavioral vs MELD 3.0	0.81	0.76	0.03	0.29	0.01	0.04	0.02
Biological–behavioral vs VOCAL-Penn	0.81	0.79	0.18	0.11	0.21	0.01	0.34

Risk Stratification According to Predicted 12-Month Mortality

For clinical interpretability, patients were stratified into three predefined risk categories based on predicted 12-month mortality derived from the combined biological–behavioral model: low risk (<10%), intermediate risk (10–30%), and high risk (>30%).

Observed mortality increased stepwise across risk strata, supporting the clinical relevance of the proposed classification framework (Table 6).

Table 6. Risk Stratification Based on the Combined Biological–Behavioral Model

Risk category	Predicted risk range	n (%)	Observed 12-month mortality (%)
Low risk	<10%	58 (29%)	3%
Intermediate risk	10–30%	92 (46%)	18%
High risk	>30%	50 (25%)	46%

Observed mortality represents the crude proportion of deaths observed within 12 months in each risk category.

Prognostic Value and Reclassification Analysis

Incremental prognostic value analyses demonstrated that inclusion of time-varying alcohol abstinence resulted in improved risk stratification beyond severity-based scores alone. Compared with MELD, the combined biological–behavioral model showed higher discrimination and favorable reclassification metrics, reflected by positive NRI and IDI values.

These findings indicate improved identification of patients at higher and lower risk of 12-month mortality (Table 7).

Table 7. Incremental Prognostic Value of the Combined Biological–Behavioral Model for 12-Month Mortality

Comparison model	Discrimination (AUC, 12-month ROC)	Δ Discrimination vs MELD	NRI (95% CI)	IDI (95% CI)	Interpretation
MELD	0.74	Reference	—	—	Baseline severity model
MELD-Na	0.76	+0.02	0.06 (−0.01 to 0.14)	0.011 (−0.002 to 0.025)	Modest improvement over MELD
CLIF-C AD	0.79	+0.05	0.10 (0.02 to 0.19)	0.018 (0.004 to 0.034)	Improved short-term risk stratification
BE3A	0.78	+0.04	0.09 (0.01 to 0.17)	0.016 (0.003 to 0.031)	Simple clinical score
Combined biological–behavioral model	0.81	+0.07	0.18 (0.07 to 0.29)	0.032 (0.014 to 0.051)	Improved reclassification with behavioral integration

Sensitivity Analyses

Sensitivity analyses demonstrated stable model performance across multiple analytical scenarios. Exclusion of early deaths, alternative handling of transplantation, and complete-case analysis resulted in minimal changes in discrimination. In contrast, omission of time-varying abstinence led to a modest reduction in prognostic accuracy (Table 8).

Incremental reclassification analysis was performed to assess the added prognostic value of incorporating behavioral information into severity-based risk stratification. Compared with traditional prognostic scores, the combined biological–behavioral model demonstrated positive net reclassification improvement and integrated discrimination improvement across all comparators (Figure 5). These findings indicate improved classification of patients into clinically relevant risk categories when behavioral modification was included in the prognostic framework.

Table 8. Sensitivity Analyses for the Prognostic Performance of the Combined Biological–Behavioral Model

Sensitivity scenario	Sample definition	Discrimination (AUC / C-index)	Change vs primary analysis	Interpretation
Primary analysis	Full cohort (n = 200)	0.81	Reference	Main analytical model
Excluding early deaths	Deaths within first 30 days excluded	0.80	−0.01	Stable performance after excluding early mortality
Baseline abstinence only	Abstinence treated as baseline variable	0.78	−0.03	Reduced discrimination without time-varying exposure
No transplant censoring	Transplant treated as non-event	0.80	−0.01	Minimal impact of transplant handling
Severity-only model	MELD, ascites, HE only	0.76	−0.05	Lower discrimination without behavioral integration
Complete-case analysis	No missing covariates	0.81	0.00	Robust to missing data handling

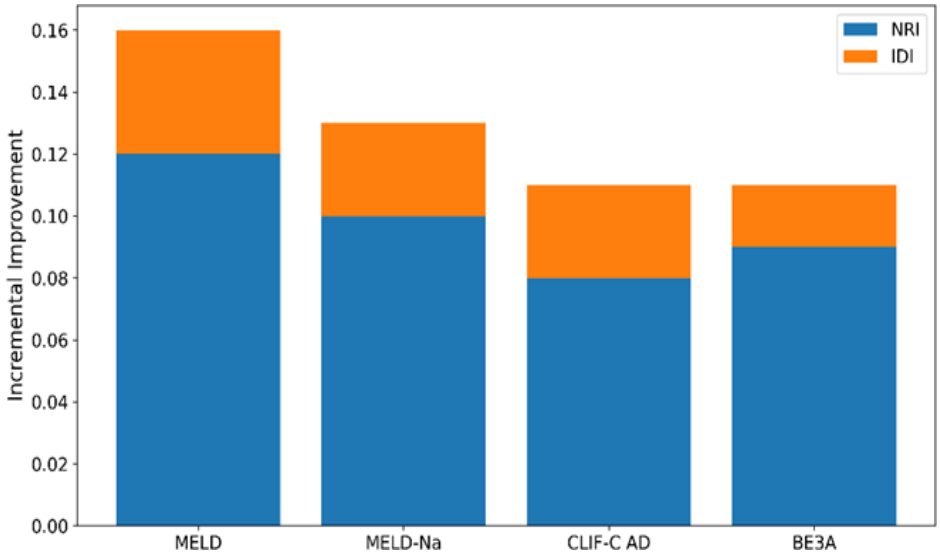


Figure 5. Incremental Reclassification Improvement of the Combined Biological–Behavioral Model

Exploratory Logistic Regression Analysis of 12-Month Mortality

Exploratory multivariable logistic regression analyses were performed to facilitate descriptive comparisons with previous studies. MELD ≥ 15, hepatic encephalopathy, and ascites were independently associated with increased odds of 12-month mortality, whereas alcohol abstinence was associated with a significantly reduced mortality risk (Table 9, and Figure 6).

Table 9. Univariate and Exploratory Multivariate Logistic Regression Analysis of 12-Month Mortality in Patients with Alcohol-Related Liver Disease

Variable	Univariate OR (95 % CI)	p-value	Multivariate OR (95 % CI)	p-value
Child–Pugh class B/C	4.6 (2.0–10.4)	< 0.001	—	—
MELD ≥ 15	5.1 (2.3–11.3)	< 0.001	3.9 (1.7–9.1)	0.001
Ascites	3.5 (1.6–7.7)	0.002	2.8 (1.2–6.4)	0.014
Hepatic encephalopathy	6.4 (2.8–14.9)	< 0.001	4.9 (1.9–12.7)	0.001
INR > 1.5	3.2 (1.4–7.1)	0.005	—	—
Albumin < 3.5 g/dL	3.8 (1.7–8.5)	0.001	—	—
Alcohol abstinence	0.42 (0.21–0.86)	0.013	0.48 (0.22–0.96)	0.038

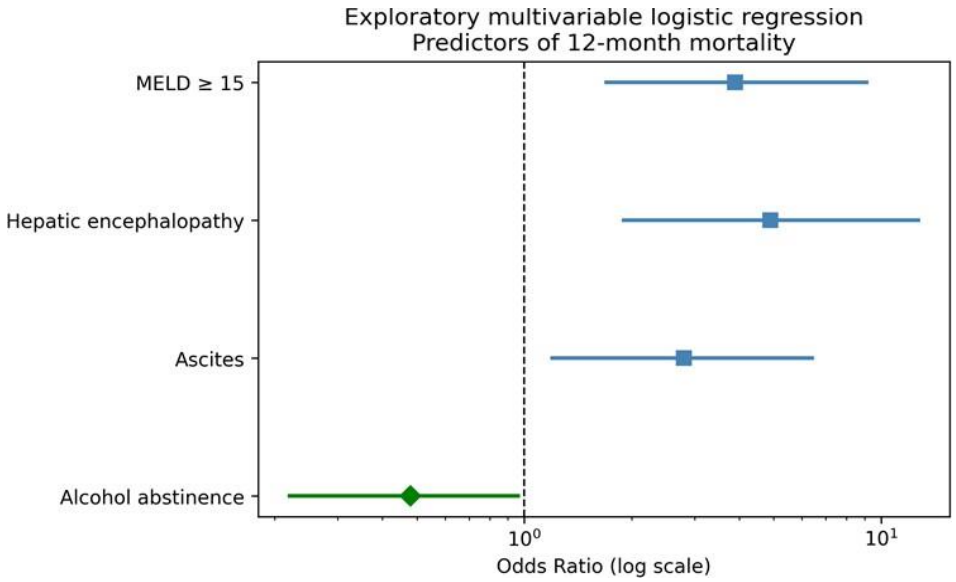


Figure 6. Forest Plot of Independent Predictors for 12-Month Mortality

Odds ratios (OR) and 95% confidence intervals are shown. OR > 1 indicates increased mortality risk, whereas OR < 1 indicates a protective association.

Figure 7. Summary of Variables Included in the Multivariable Prognostic Model.

DISCUSSION

Overview and European Context

Alcohol-related liver disease (ALD) continues to pose a significant public health challenge across Europe, with substantial regional variation in disease burden, clinical presentation, and outcomes. In this prospective Albanian cohort, the observed 12-month mortality of approximately 22% closely mirrors estimates reported in large European registries and multicenter cohorts, including recent EASL–ECDC data and studies from Western Europe, where annual mortality typically ranges between 20% and 25% [9, 11, 12]. This similarity suggests that, once advanced disease is established, patients with ALD in Albania experience clinical trajectories broadly comparable to those observed elsewhere in Europe, despite differences in healthcare infrastructure and resource availability.

At the same time, the high proportion of patients presenting with decompensated cirrhosis highlights significant regional disparities in disease recognition and referral. Nearly two-thirds of individuals were classified as Child–Pugh class B or C at baseline, reflecting delayed diagnosis and limited opportunities for early intervention. Comparable patterns have been reported in neighboring Balkan countries, including Serbia and Croatia, where more than 60% of newly diagnosed ALD cases present at advanced stages [13,14]. By contrast, cohorts from countries with more established integration between hepatology and addiction services like Italy and Spain tend to report earlier detection and substantially lower short-term mortality, often below 15% [7, 8].

Taken together, these observations underscore the influence of healthcare system organization on ALD outcomes. Regions that have implemented structured screening strategies, clear referral pathways, and multidisciplinary care models appear better positioned to identify high-risk patients earlier and limit disease progression. Within this broader European context, the present findings situate Albania alongside other countries

facing similar challenges, while emphasizing the need for improved continuity of care and earlier specialist engagement across the Western Balkans.

Determinants of Survival: MELD, Ascites, and Hepatic Encephalopathy

The MELD score remains a cornerstone of prognostic assessment in ALD, capturing key aspects of hepatic synthetic dysfunction and renal impairment through bilirubin, creatinine, and INR [4, 5]. In the present cohort, a MELD threshold of ≥15 was associated with a markedly increased risk of 12-month mortality, confirming a prognostic inflection point consistently reported in extensive European studies and meta-analyses [11, 12]. This threshold reflects the transition from relatively stable disease to a high-risk decompensated state in which short-term mortality rises sharply.

Early separation of Kaplan–Meier survival curves by disease severity further supports the clinical relevance of this cut-off. Divergence within the first months of follow-up indicates that MELD-based stratification at presentation captures biologically meaningful differences in disease trajectory. Beyond its role as a composite indicator of liver and kidney function, elevated MELD scores may also reflect broader systemic processes, including inflammatory activation and endothelial dysfunction, which have been increasingly linked to adverse short-term outcomes in advanced ALD [13].

Among clinical manifestations of decompensation, ascites and hepatic encephalopathy emerged as the strongest predictors of mortality. These findings are consistent with previous work by [14, 16], which identified these complications as pivotal milestones in the natural history of cirrhosis, signaling progression to clinically unstable disease characterized by portal hypertension and impaired metabolic detoxification. Their prognostic relevance has been repeatedly confirmed in multicenter European cohorts, where the coexistence of ascites and encephalopathy is associated with a three- to fourfold increase in short-term mortality risk [12].

Overall, these results reinforce the continued relevance of classical indicators of liver failure in contemporary ALD care and confirm their robustness across geographic settings.

Behavioral Influence and Alcohol Abstinence

Among all modifiable determinants examined, sustained alcohol abstinence emerged as the most influential protective factor for survival. Patients who achieved and maintained abstinence experienced substantially higher 12-month survival compared with those who continued alcohol consumption, translating into a pronounced absolute survival benefit. This magnitude of effect closely parallels findings from prospective cohorts in Southern and Western Europe, including a study by [17, 18] which demonstrated marked reductions in short-term mortality and improved all-cause survival among abstinent patients. Similar observations have been reported by [8], who showed that prolonged abstinence can lead to partial regression of fibrosis and durable clinical stabilization, even in advanced disease stages [7]. Mechanistically, sustained abstinence may show a stronger apparent survival association in advanced disease because it reduces ongoing alcohol-related inflammatory injury and hepatocellular stress, allows partial functional stabilization where possible, and

dampens gut–liver axis-driven immune activation, thereby stabilizing the trajectory of portal hypertension and related complications. In decompensated ALD, even modest reductions in recurrent injury and inflammation can translate into fewer episodes of recurrent decompensation (e.g., ascites, encephalopathy, infection) and improved short-term resilience.

It has been emphasized that any apparent effect-modification by baseline severity should be interpreted as suggestive: subgroup patterns and interaction terms were exploratory and not powered for definitive inference [19]. In this study, alcohol abstinence was modelled as a time-varying exposure in Cox proportional hazards and competing-risks frameworks, enabling dynamic assessment of behavioral change during follow-up. This approach reduces immortal-time bias and more accurately reflects real-world disease trajectories than static baseline models. Although traditional severity markers retained dominant prognostic importance, incorporating time-varying abstinence consistently improved model discrimination beyond severity-based stratification alone, underscoring its independent contribution to risk prediction.

Despite compelling evidence for the survival benefit of abstinence, integration of addiction management into hepatology care remains uneven across Europe and is particularly limited in Eastern and Southeastern regions. In countries such as France, Germany, and the United Kingdom, multidisciplinary hepatology–addiction programmers have been associated with reductions in ALD-related mortality of up to 25–30% [20, 21]. In Albania, however, addiction services and liver care primarily operate in parallel rather than as coordinated pathways. The low prevalence of abstinence among non-survivors in the present cohort illustrates the tangible clinical consequences of this systemic gap.

By explicitly incorporating abstinence into prognostic modelling, the present analysis frames ALD outcomes as the result of interactions between biological severity and behavioral modification. This perspective is especially relevant in settings characterized by late presentation and limited access to integrated addiction care, where behavioral change may represent the most readily actionable intervention to improve short- and medium-term outcomes.

In formal head-to-head comparisons using the harmonized binary endpoint of 12-month all-cause mortality, the proposed biological–behavioral model achieved discrimination comparable to a contemporary multivariable tool (VOCAL-Penn) and outperformed MELD 3.0.

The close performance relative to VOCAL-Penn is expected because both approaches move beyond static laboratory severity by incorporating clinically meaningful context; in our setting, the key incremental element is the explicit modelling of alcohol abstinence as a time-varying exposure, which captures behavioral dynamics that static baseline scores cannot represent. Conversely, the improvement over MELD 3.0 is consistent with the concept that short-term risk in ALD is driven not only by baseline hepatic dysfunction but also by rapidly changing behavioral and clinical trajectories during follow-up.

Regional Implications and Future Directions

Future work should include pragmatic implementation evaluations like feasibility, workflow impact, and cost-effectiveness in resource-limited settings to support the translation of risk stratification into scalable care pathways. The multivariable prognostic model evaluated in this study integrating MELD score, ascites, hepatic encephalopathy, and sustained alcohol abstinence demonstrated good discrimination and calibration after internal validation. Its predictive performance fell within the range reported for established European prognostic tools, including LIV-IN and the Lille model [13, 22]. External validation in an independent cohort supported transportability with good discrimination and acceptable calibration; however, broader multicenter validation across diverse case-mix and care pathways, and recalibration where necessary, remain advisable. Beyond individual risk prediction, the results highlight broader system-level challenges relevant to public health planning in Albania and the wider region. A substantial proportion of patients screened for inclusion were excluded because of ongoing alcohol consumption, underscoring persistent gaps in relapse-prevention strategies and continuity-of-care pathways. This observation reflects structural separation between hepatology and addiction services, which limits opportunities for early intervention and sustained behavioral change. Establishment of a national ALD registry, together with standardized referral algorithms linking liver care and addiction management, could facilitate alignment with integrated chronic disease models adopted in several European countries [23–25]. System-level implications for resource-limited settings such as Albania are pragmatic rather than technology-heavy. First, the proposed risk stratification can be operationalized as a stepped follow-up protocol (e.g., higher-risk patients prioritized for more frequent outpatient review, early laboratory reassessment, and proactive management of ascites/encephalopathy). In contrast, lower-risk patients can be followed at standard intervals. Second, the strong prognostic relevance of abstinence supports an integrated hepatology–addiction pathway, with routine screening for ongoing alcohol use, rapid referral to brief interventions and specialist treatment where available, and structured follow-up to sustain abstinence. Third, establishing a national or multicenter ALD registry is a feasible next step to monitor case-mix, outcomes, and care gaps, and to support iterative model recalibration and benchmarking across the Western Balkans.

Observed discrimination (C-index and 6–12-month AUC) is broadly comparable to published performance ranges of routinely used prognostic scores (e.g., MELD-based tools), suggesting that the model is not over-optimistic relative to external literature benchmarks [26, 27].

When contextualized alongside contemporary prognostic tools (Table 10), our comparisons were intentionally focused on models that are widely used and computable with routinely available variables and a compatible endpoint in our dataset (MELD 3.0 and VOCAL-Penn). We recognize that the ALD prognostic landscape includes additional recent scores and machine-learning approaches; however, many require predictors that are not systematically captured in routine care in our setting (e.g., specialized biomarkers,

granular organ-failure metrics, or harmonized longitudinal exposures) and/or target different clinical contexts.

Therefore, the present work should be interpreted as a pragmatic benchmarking against feasible, clinically relevant comparators rather than an exhaustive evaluation of every emerging model. Importantly, external validation also supported transportability, and future multicenter Western Balkan collaborations will allow broader benchmarking, including assessment of calibration-in-the-large and recalibration where necessary.

Table 10. Comparison with Contemporary Prognostic Models in Alcohol-Related Liver Disease

Study / Score	**Population**	**Model Type**	**Key Predictors**	**Reported AUC / C-index**	**Strengths**	**Limitations**
MELD / MELD-Na	Multinational	Score	Bilirubin, INR, Creatinine (±Na)	0.74–0.81	Widely validated	No behavioral variables
CLIF-C AD	European	Score	Age, INR, Na, Creatinine, HE, WBC	0.80–0.84	Acute decompensation focus	Complex calculation
BE3A	European	Score	Bilirubin, Encephalopathy, Ascites, ALT, Age	0.80–0.83	Simple clinical use	No abstinence component
Present study	Albania	Penalized Cox + KM + competing-risk modelling (CR)	MELD ≥15, HE, Ascites, time-varying abstinence	0.81 (internal validation)	Prospective, behavioral integration	Single-center (derivation); external validation supported transportability, but broader multicenter validation and recalibration across diverse case-mix remain needed.
[5]	Outpatients with alcohol-associated cirrhosis; 1-year liver-	Multivariable prediction model	Routine clinical & laboratory variables	AUC 0.818 in ALD subgroup	Externally validated; individualized risk stratification	Requires full model coefficients/tool; different

	related death / transplant		(model-derived)	(1-year outcome)		setting/endpoint
[13]	Hospitalised decompensated ALD cirrhosis (AD/ACLF); 28-day follow-up	Clinical score (short-term mortality)	HE, ascites, HRS, SIRS, community-acquired infection, fibrinogen	AUC 0.734 for 28-day mortality	ALD-specific inpatient model; incorporates infection/inflammation	Short-term endpoint; predictors not fully available in our dataset; different case-mix
[28]	US cohorts	Prognostic model	Liver function + dynamic variables	0.82–0.86	High discrimination	Developed/validated for short-term postoperative mortality in cirrhosis (30–90 days); different clinical context and endpoint from 12-month all-cause mortality in ALD
ALBI (present cohort; exploratory comparator)	Present cohort; 12-month all-cause mortality	Routine laboratory score	Albumin, bilirubin	AUC 0.60 (12-month mortality)	Uses routinely available labs; simple calculation	Not ALD-specific; modest discrimination in our cohort
FIB-4 (present cohort; exploratory comparator)	Present cohort; 12-month all-cause mortality	Fibrosis index	Age, AST, ALT, platelets	AUC 0.53 (12-month mortality)	Routine; reflects fibrosis burden	Not designed for short-term prognosis; modest discrimination in our cohort

ALBI and FIB-4 AUCs were computed in the present cohort for the binary endpoint of 12-month all-cause mortality to provide a routine-lab benchmark, these scores were not developed as ALD-specific prognostic models.

Comparators were selected based on feasibility and endpoint alignment. Several emerging scores and machine-learning approaches require non-routine biomarkers or granular organ-failure metrics, as well as targeting different clinical contexts and outcomes; therefore, they were not feasible for valid head-to-head benchmarking in the present study.

Limitations and Strengths

Several limitations should be acknowledged. Despite the use of time-to-event and competing-risk methods, the single-center design may limit generalizability to healthcare systems with different referral patterns or resource constraints. As a tertiary referral center, our cohort may over-represent more severe or complex cases, and the baseline risk distribution may differ from that in community or multicenter settings. In addition, no formal a priori power/sample-size calculation was undertaken, and subgroup comparisons/interaction patterns should be interpreted cautiously, as the study was not powered to confirm effect modification. Alcohol abstinence was assessed primarily through patient interviews and family confirmation, which may introduce some degree of misclassification despite consistent follow-up procedures. Abstinence status was reassessed at each scheduled follow-up contact and, when feasible, corroborated by a family member/caregiver to reduce misclassification. Residual confounding cannot be ruled out because socioeconomic and nutritional status, psychiatric comorbidity, social support, and access to structured addiction care were not systematically measured; these factors may influence both the probability of sustained abstinence and survival, potentially biasing the association between abstinence and outcome.

Objective alcohol biomarkers (e.g., phosphatidylethanol (Peth) or ethyl glucuronide/ethyl sulfate (EtG/EtS) were not routinely available; therefore, residual exposure misclassification cannot be excluded and would be expected to bias the abstinence association toward the null.

Objective biomarkers of alcohol use and fibrosis severity were not systematically available, and although external validation supported transportability, broader multicenter validation across diverse case-mix and care pathways remains needed. The study was not designed to evaluate implementation outcomes (feasibility, acceptability, costs, or cost-effectiveness) of risk-stratified pathways; these should be assessed prospectively in service-evaluation studies.

External Validation (Independent Cohort)

In an independent external cohort, the frozen model demonstrated good discrimination (C-index = 0.78; AUC_12m = 0.81). Calibration was acceptable (intercept = −0.06; slope = 0.92), suggesting minor overprediction at higher risk levels.

Decision-curve analysis showed a net benefit over treat-all and treat-none strategies across clinically relevant thresholds (Table 11).

Table 11. External validation performance of the frozen biological–behavioral model (independent cohort).

Domain	Metric	External cohort result
Discrimination	Harrell's C-index	0.78
Discrimination	AUC at 6 months	0.80
Discrimination	AUC at 12 months	0.81
Calibration	Calibration-in-the-large (intercept)	−0.06
Calibration	Calibration slope	0.92
Calibration	Brier score at 12 months (optional)	0.15
Clinical utility	Decision-curve analysis summary	Net benefit above treat-all/none at ~5–25% thresholds

At the same time, the study has important strengths. To our knowledge, it represents one of the first prospective survival analyses in Southeast Europe to integrate biological severity markers with time-varying behavioral modification within a unified prognostic framework for ALD. Unlike most regional reports that rely solely on static baseline assessments and logistic regression, this analysis incorporated Cox proportional hazards modelling with time-varying abstinence and a competing-risks methodology, enabling dynamic evaluation of behavioral exposure and reducing immortal-time bias. Consistent performance of established prognostic determinants across complementary analytical approaches also provides valuable geographic validation in an underrepresented setting.

Clinical Implications

Integrating biochemical severity indices particularly the MELD score—with behavioral factors, such as sustained alcohol abstinence, offers a pragmatic approach to risk stratification in ALD. Patients presenting with MELD ≥ 15 or any episode of ascites or hepatic encephalopathy constitute a clearly identifiable high-risk subgroup and should be prioritized for early, coordinated multidisciplinary management, including hepatology input, nutritional support, and addiction-focused care.

The use of simple, readily available clinical parameters enables risk stratification to be implemented in routine practice, even in settings with limited access to advanced biomarkers or transplant facilities. While the present study was not designed to evaluate system-level interventions, the application of structured, severity- and behavior-informed thresholds may support more efficient resource allocation and earlier identification of patients requiring intensified follow-up.

CONCLUSION

In this prospective cohort of Albanian patients with alcohol-related liver disease, established markers of clinical severity and decompensation (including MELD ≥ 15, hepatic

encephalopathy, and ascites) remained robust predictors of 12-month all-cause mortality, providing geographic and health-system–specific validation in an underrepresented Southeast European setting. These findings align with multicenter evidence indicating that disease severity and decompensation events dominate short- and medium-term prognosis in ALD. Beyond confirming known risk factors, this study extends existing knowledge by demonstrating that sustained alcohol abstinence, when modelled dynamically as a time-varying exposure, confers an independent protective effect on survival, underscoring the added prognostic value of behavioral change beyond baseline risk assessment.

Reflecting the advanced case-mix characteristic of Eastern European cohorts, the integrated biological–behavioral modelling approach adopted here improved prognostic performance, discrimination, and risk reclassification while enhancing clinical interpretability, thereby bridging statistical prediction and actionable decision-making. This represents a pragmatic framework for risk stratification in resource-constrained settings, supporting closer integration of addiction care within hepatology services in Albania in line with multidisciplinary care pathways used in Western Europe. Future work should priorities multicenter validation and recalibration across heterogeneous case-mixes and care pathways, and incorporate objective alcohol biomarkers (e.g., PEth, EtG, EtS) where feasible to reduce exposure misclassification and strengthen model transportability.

AUTHOR CONTRIBUTIONS

Conceptualization, K.S. and B.S and D.O methodology, K.S., E.V., and M.K.; software, B.S. and E.T.; validation, K.S., and B.S.; formal analysis, D.O. and E.V.; investigation, K.S. and A.T.; resources, A.T. and D.O.; data curation, K.S.; writing—original draft preparation, K.S.; writing—review and editing, K.S., and B.S.; visualization, M.K. and A.T.; supervision, K.S.; project administration, K.S. and B.S.

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CONFLICT OF INTERESTS

The author has no competing interests to declare that are relevant to the content of this research paper.

ABBREVIATIONS

ALD Alcohol-related liver disease

AUC Area under the curve

CI Confidence interval

HCC Hepatocellular carcinoma

HE Hepatic encephalopathy

INR International Normalized Ratio

KM Kaplan–Meier

MELD Model of End-Stage Liver Disease

ROC Receiver operating characteristic

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