A Scoring System For Predicting Hepatocellular Carcinoma Risk In Alcoholic Cirrhosis: A Competing Risk Analysis

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Research Article

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Abstract

Background & Aims: The role of hepatocellular carcinoma (HCC) surveillance is being questioned in alcoholic cirrhosis because of the relative low HCC risk. Comorbid viral hepatitis may synergistically increase the HCC risk in alcoholic cirrhosis. This study aimed to assess the risk and predictors of HCC in patients with alcoholic cirrhosis by using competing risk analysis in an area with intermediate prevalence for hepatitis B virus.

Methods: A total of 965 patients with alcoholic cirrhosis were recruited at a university-affiliated hospital in Korea and randomly assigned to either the derivation (n=643) and validation (n=322) cohort. Subdistribution hazards model of Fine and Gray was used with deaths and liver transplantation treated as competing risks. Death records were confirmed from Korean government databases. A nomogram was developed to calculate the Alcohol-associated Liver Cancer Estimation (ALICE) score.

Results: Markers for viral hepatitis were positive in 21.0 % and 25.8 % of patients in derivation and validation cohort, respectively. The cumulative incidence of HCC was 13.5 and 14.9 % at 10 years for derivation and validation cohort, respectively. Age, positivity for viral hepatitis markers, alpha-fetoprotein level, and platelet count were identified as independent predictors of HCC and incorporated in the ALICE score, which discriminated low, intermediate, and high risk for HCC in alcoholic cirrhosis at the cut-off of 120 and 180.

Conclusions: HCC risk can be stratified by using clinical parameters including viral markers in alcoholic cirrhosis in an area where the prevalence of viral hepatitis is substantial.

Introduction

Alcohol-related liver disease (ALD) poses great global health burden. According to the Global Burden of Disease study 2017, 332,300 people died of ALD annually, which comprises approximately one fourth of mortalities associated with chronic liver disease[1]. Hepatocellular carcinoma (HCC), the most common form of primary liver cancer in ALD, is responsible for one-third of ALD-related mortality, and one-third of all HCC-related deaths are attributed to alcohol use globally[2]. Surveillance for HCC is recommended for high-risk groups in order to facilitate early detection and improve survival[3]. However, alcohol-related HCC is prone to insufficient surveillance and therefore delayed detection compared to viral hepatitis-associated HCC[4]. One of the reasons for under-surveillance may be related to relatively low incidence of HCC in ALD. For example, a recent Swedish cohort study (n = 3,410) reported HCC incidence rate of 6.2 per 1000 person-years and the 10-year cumulative incidence of only 5.0% in alcoholic cirrhosis[5], which was much lower than previously published (annual incidence of 2.6 - 2.9 %)[6–9]. Another recent Danish study showed similar result (cumulative incidence of 6.0% after 10 years)[10]. These findings suggest that HCC screening for all alcoholic cirrhosis may not be cost-effective, and that further risk stratification is warranted to identify ideal candidates for surveillance in alcoholic cirrhosis.

Many prediction models of HCC risk have been proposed and validated for chronic viral hepatitis[11]. In comparison, risk prediction has been less explored for alcoholic cirrhosis. Available data were derived from studies with all etiologies of liver cirrhosis, and relative risk of HCC was lower in alcoholic cirrhosis compared to viral hepatitis-associated cirrhosis[12,13]. Recently, a novel HCC prediction model was developed which was based solely on alcoholic cirrhosis from US Veterans Affairs healthcare system (VAHS)[14]. This US-VA model is an internally validated scoring system with age, sex, BMI, diabetes, platelet count, serum albumin, and serum AST/$\sqrt{}$ALT ratio as predictors[14]. In this model, however, patients with viral hepatitis had been excluded.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) may accelerate disease progression and increase the HCC risk in ALD[15]. Therefore, comorbid viral hepatitis needs to be considered in the generation of prognostic models for ALD. However, the effect of co-morbid viral hepatitis is largely unknown because patients with chronic viral hepatitis were usually excluded in the epidemiologic studies of alcoholic cirrhosis[9,10,14]. The prevalence of HBV infection is decreasing over time in Korea, but still is classified as intermediate, i.e., ≥ 2% of population[16]. For HCV infection, the prevalence in Korea shows regional variation (0.6 – 1.8%)[17,18].

In building a HCC prediction model, deaths and liver transplantations should be considered as competing events because many ALD patients experience hepatic decompensations and deaths before HCC is detected. Conventional Kaplan-Meier and Cox analysis may over-estimate the actual risk of HCC in the presence of competing risks[19]. For competing-risk survival analysis, cause-specific hazards or Fine-Gray model is recommended[20]. The aforementioned alcohol-related HCC prediction models, however, used conventional cox regression without competing risk analysis.

In this study, we sought to perform a competing-risk analysis for predicting the risk and predictors of HCC in alcoholic cirrhosis patients in Korea where the prevalence of viral hepatitis is intermediate. For this aim, we linked the Korean national death registry data to hospital-based cohort data.

Methods

Study population and design

In this retrospective cohort study, an e-cohort was generated by using the clinical data warehouse of Seoul National University Bundang Hospital, a university-affiliated hospital in Korea[21–23]. The inclusion criteria were: 1) ALD based on ICD-10 code K70 AND presence of cirrhosis (see below), 2) >20 years of age, 3) enrolled for HCC screening by liver ultrasonography (US) with or without serum alpha-fetoprotein (AFP). The diagnosis of alcoholic cirrhosis was based on histology, endoscopic confirmation of varices or radiologic demonstration of cirrhosis. The exclusion criteria were 1) patients with short follow-up duration < 6 months, 2) patients with development of primary and secondary outcomes (see below) or other malignancies before or within 6 months from initial screening US, 3) Child-Pugh class C patients at

presentation. Child Pugh class C was excluded because HCC surveillance was generally not recommended unless they are on the transplant waiting list[3,24,25].

The primary outcome was development of HCC. Secondary outcomes were liver transplantation and death which were assessed as competing risks. The death records were confirmed by using the Korean government database of vital statistics generated by Statistics Korea and Ministry of the Interior and Safety.

HCC surveillance

HCC surveillance was performed by liver US with or without serum AFP at 6 - 12 months of interval at the discretion of the attending hepatologists. Multiphase CT or MRI were subsequently performed if liver US exam showed nodule(s) with a diameter ≥10mm, or portal vein thrombosis, or increased AFP level. The diagnosis of hepatocellular carcinoma (HCC) was confirmed based on LiRAD 5 criteria[26]. Liver biopsy was performed to make a definitive diagnosis if imaging studies showed atypical findings[24].

This study was approved by Seoul National University Bundang Hospital Institutional Review Board (IRB No: B-1907-553-105). All clinical investigations have been conducted according to the principles expressed in the Declaration of Helsinki. The requirement of informed consent was waived by Seoul National University Bundang Hospital Institutional Review Board due to the retrospective nature of this study and anonymous analysis of data.

Statistical analysis

Enrolled patients were randomly assigned to one of two cohorts in a 2:1 ratio: the derivation and validation cohorts. Competing risk regression models were used with deaths and liver transplantation being treated as competing risks to assess the absolute risk of HCC and to identify the predictors of alcohol-related HCC from the derivation cohort. For competing risk analysis, the cause-specific cumulative incidences were plotted by non-parametric cumulative incidence function using STATA's stcurve cif, and the subdistribution hazards model of Fine and Gray was built by using STATA's stcrreg competing-risks regression[27,28]. Complete case analysis method was chosen for handling missing data. A nomogram was developed for calculating the HCC scoring system by using R rms package. The calibration of the scoring system was evaluated by using calibration curves (R riskRegression package). The predictive power and discriminative performance of the scoring system was compared with US-VA model by using area under time-dependent ROC analysis with R timeROC package.

Continuous variables were expressed as their median values and interquartile range (IQR), and compared using Wilcoxon rank sum test. Categorical variables were expressed as percentages, and compared using chi-square test. All statistical analyses were performed using STATA for windows ver. 14 (STATA corp., Texas, USA) and R statistical package ver. 3.6.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://R-project.org).

Results

Baseline characteristics of study cohorts

We identified 4,980 patients with ALD who visited our institution and received screening US between April 1, 2004 and December 31, 2017. Among them, 965 patients with alcoholic cirrhosis were finally included in this study and randomly allocated to either derivation (n=643) or validation cohort (n=322). The baseline characteristics of the two cohorts were balanced without significant differences except for baseline AFP levels (Table 1). The markers for viral hepatitis were positive in 21.0 and 25.8% of patients in derivation and validation cohort, respectively (p = 0.106).

Table 1
Baseline characteristics of patients with alcoholic cirrhosis.

	Derivation cohort (n=643)	Validation cohort (n=322)	P value
Age (year)	55 (15)	55 (12)	0.364
Male sex (%)	80	77	0.266
Decompensated cirrhosis (%)	37	33	0.137
Diabetes (%)	31	30	0.832
Hypertension (%)	21	23	0.589
Dyslipidemia (%)	33	32	0.796
BMI (kg/m^2)	25.3 (4.8)	25.2 (5.9)	0.745
Alcohol use (g/day)	54 (89)	54 (85)	0.972
Duration of alcohol use (y)	30 (15)	30 (20)	0.598
HBsAg positivity (%)	19	21	0.464
Anti-HCV positivity (%)	3.4	5.0	0.242
AFP (ng/mL)	3.7 (3.2)	4.1 (3.6)	0.015
AST (IU/L)	45 (51)	46 (48)	0. 671
ALT (IU/L)	38 (42)	36 (40)	0.703
Prothrombin time (INR)	1.08 (0.17)	1.08 (0.18)	0.955
Platelet count ($x10^3/mm^3$)	173 (107)	173 (107)	0.822
Total bilirubin (mg/dL)	1.0 (0.7)	1.0 (0.8)	0.154
Albumin (mg/dL)	4.2 (0.7)	4.1 (0.7)	0.369
GGT (U/L)	97 (117)	101 (280)	0.176
ALP (U/L)	90 (57)	91 (57)	0.801

Continuous variables were expressed as their median values (interquartile range), and p-value was calculated using Wilcoxon rank-sum test. Categorical variables were expressed as absolute numbers (percentages), and p-value was calculated using chi-square test.

FIB-4 index[39] = age (yr)× AST (U/L)/Platelet count (10^9/L)× (ALT(U/L))$^{0.5}$

APRI score = AST(U/L)/platelet counts (10^9/L)*0.4

BMI, body mass index; HbsAg, hepatitis B surface antigen; Anti-HCV, antibody against hepatitis C virus; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase

	Derivation cohort (n=643)	Validation cohort (n=322)	P value
Child-Pugh class A / B (%)	70/30	72/30	0.439
FIB-4 index*	2.56 (3.40)	2.44 (4.63)	0.872
APRI score			
Liver stiffness value, kPa	7.9 (8.7)	8.7 (8.4)	0.732
Continuous variables were expressed as their median values (interquartile range), and p-value was calculated using Wilcoxon rank-sum test. Categorical variables were expressed as absolute numbers (percentages), and p-value was calculated using chi-square test.			
FIB-4 index[39] = age (yr)× AST (U/L)/Platelet count (10^9/L)× (ALT(U/L))$^{0.5}$			
APRI score = AST(U/L)/platelet counts (10^9/L)*0.4			
BMI, body mass index; HbsAg, hepatitis B surface antigen; Anti-HCV, antibody against hepatitis C virus; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; GGT, gamma-glutamyltransferase; ALP, alkaline phosphatase			

Incidence of HCC in alcoholic cirrhosis

During the median follow-up period of 63 months (range 6 – 197), 102 patients developed HCC, 8 received liver transplantation, and 224 patients died without HCC. The cumulative HCC incidence was 7.1 % and 7.8 % at 5 years, and 13.5 and 14.9 % at 10 years for derivation and validation cohort, respectively (Fig. 1). If patients with positive viral hepatitis markers were excluded, the cumulative HCC incidence decreased to 5.5 % and 5.1 % at 5 years, and 10.3 % and 9.6 % at 10 years for derivation and validation cohort, respectively.

Predictors of HCC in alcoholic cirrhosis

Univariate subdistribution hazards model analysis of the derivation cohort demonstrated that older age, male sex, chronic viral hepatitis, higher AFP level, and lower platelet counts were significantly associated with increased risk of HCC. Among them, four predictors were independently identified through multivariate analysis: age, positive for viral hepatitis markers, AFP level, and platelet count (Table 2). APRI and FIB-4 did not predict the HCC risks.

Table 2
Predictors for HCC development by Fine and Gray's proportional subhazards model in derivation cohort (n = 643)

Variables	**Univariate**		**Multivariate**	
	Subhazard ratio **(95% CI)**	P value	Subhazard ratio **(95% CI)**	P value
Age (y)	1.02 (1.00-1.04)	**0.03**	1.03 (1.01-1.05)	**< 0.01**
Male sex	2.58 (1.03-6.44)	**0.04**	2.48 (0.99-6.22)	0.05
Diabetes	0.83 (0.40-1.72)	0.62		
Hypertension	1.35 (0.81-2.26)	0.25		
Dyslipidemia	1.20 (0.73-1.97)	0.47		
BMI (kg/m^2)	1.03 (0.98-1.09)	0.22		
Alcohol use (g/day)	1.00 (1.00-1.00)	0.86		
Duration of alcohol use (y)	1.01 (0.98-1.03)	0.61		
HBV/HCV positive[a]	1.71 (1.02-2.85)	**0.04**	1.80 (1.03-3.12)	**0.04**
AFP (ng/mL, log10)	2.30 (1.48-3.57)	**< 0.01**	1.76 (1.10-2.82)	**0.02**
AST (IU/L)	1.00 (1.00-1.00)	0.19		
ALT (IU/L)	1.00 (1.00-1.00)	0.53		
Prothrombin time (INR)	1.70 (0.93-3.13)	0.08		
Platelet count ($x10^3/mm^3$)	0.99 (0.99-1.00)	**< 0.01**	0.99 (0.99-1.00)	**0.02**
Total bilirubin (mg/dL)	0.99 (0.90-1.10)	0.90		
Albumin (mg/dL)	0.66 (0.44-1.00)	0.05		
GGT (U/L)	1.00 (1.00-1.00)	0.14		
ALP (U/L)	1.00 (1.00-1.00)	0.99		
APRI score	0.99 (0.96-1.02)	0.36		
FIB-4	1.01 (0.99-1.03)	0.29		

[a]Patients with HbsAg or anti-HCV positivity.

Development and validation of alcohol-associated liver cancer estimation (ALICE) scoring system

A parsimonious HCC prediction model, the alcohol-associated liver cancer estimation (ALICE) scoring system, was developed from the result of multivariate cumulative incidence function. Nomogram was constructed with four predictors to calculate the ALICE score (Fig. 2). The calibration plots of the nomogram showed good agreement between the observed and predicted HCC risks (Supplementary Fig. 1). When patients were stratified by ALICE score, HCC risk was minimal with a cut-off ≤ 120, whereas patients with a cut-off of >120 and <180 showed the cumulative incidence exceeding 15% per 10 years, and patients with ≥180 had highest risk for HCC (Fig. 3 and Table 3).

Table 3
Estimated cumulative incidence of HCC according to ALICE score

ALICE score	Derivation cohort	Validation cohort
	5-year HCC risk	
<= 120	0.9	1.8
>120 and <=180	7.2	7.0
>180	31.5	33.8
	10-year HCC risk	
<= 120	1.3	2.8
>120 and <=180	17.0	16.6
>180	37.2	39.9

Finally, we compared the predictive performance of ALICE score with that of the US-VA model. Time-dependent ROC curve analysis revealed that the performance of ALICE score had comparable or higher AUC values than UA-VA score in the validation cohort (Fig. 4).

Discussion

In this study, we assessed the HCC risk in Korean patients with alcoholic liver cirrhosis from a hospital-based cohort. The estimated cumulative HCC risk in our cohort was ~1.5 % per year for overall patients (Fig. 1), and approximately 1.0 % for patients without markers of viral hepatis. The latter figure fell in the range between the two recent European studies (0.7 % and 1.8 %) which excluded patients with chronic viral hepatitis[9,10]. Comorbid viral hepatitis is of special interest in geographic areas where chronic hepatitis virus infection is prevalent. Interestingly, our cohort showed higher prevalence of chronic viral hepatitis compared to Korean general population: 2.9 % for HBV [16] and ~1.8 % for HCV[18]. This high

prevalence may be explained by the synergistic effect of comorbid viral hepatitis on the accelerated progression of alcoholic fatty liver to alcoholic cirrhosis.[29] In line with this hypothesis, the prevalence of positive viral markers was similar to general population in alcoholic fatty liver patients without cirrhosis in our hospital (data not shown).

We also developed and internally validated a risk stratification model for HCC (*i.e.*, ALICE score). Compared to the recently developed prediction models[13,14], we employed competing-risk analysis by incorporating mortality data from causes other than HCC. Liver cirrhosis is typically a multistate disease complicated by discrete outcomes[30]. If patients with competing outcomes such as non-HCC deaths are simply treated as right-censored cases, Kaplan Meier method may overestimate the real cumulative risks[30,31]. Moreover, the predicted risk of HCC does not necessarily correlate with the predicted rate by Cox model of HCC prediction[31]. Indeed, our cohort patients showed that censored cases due to non-HCC deaths were twice more than those censored due to HCC.

The role of HCC surveillance in alcoholic liver disease is still under debate. Practice guidelines recommend HCC surveillance in patients with cirrhosis due to alcohol and other etiologies on the ground that threshold HCC incidence of > 1.5 %/year may justify cost-effectiveness of surveillance[3,24,32]. However, the “1.5 %/year” cut-off itself has been doubted.[33] Since the risk of HCC in alcoholic cirrhosis may not be high enough to ensure cost-effectiveness[5,10], risk stratification may be thus necessary to enhance the effectiveness of HCC surveillance in alcoholic cirrhosis.

We have built our risk stratification model based on four independent predictors of HCC risk: age, chronic viral hepatitis, AFP level, and platelet count. AFP level was a significant predictor in addition to other well-established markers[13,14], and this finding is in concordance with the French cohort study[9]. These four factors are readily available in routine practice, and nomogram-based ALICE score was able to discriminate the low, high, and super high-HCC risk groups in alcoholic cirrhosis. Patients with ALICE score ≤ 120 carries minimal risk for HCC and may not be indicated for routine HCC surveillance, whereas those with ≥180 show highest risk for HCC and regular surveillance may be justified. In other word, the ALICE score may serve dual purposes: (1) to exclude ALD patients with low risk from HCC surveillance, and (2) to identify patients with very high risk for HCC in need of enhanced surveillance. Further studies will be necessary to assess whether risk-based surveillance is cost-effective in alcoholic cirrhosis.

As mentioned earlier, competing risks were not considered in the US-VA model building. Moreover, the US-VA model may underestimate the HCC risk of alcoholic cirrhosis patients with viral markers in real-world practice. Time-dependent ROC analysis showed that the ALICE score had comparable or higher AUC values compared with the US-VA score (Fig. 4). Compared to the US-VA model, our score is more parsimonious with using only 4 readily available parameters. However, further validation would be warranted for the clinical utility of ALICE score by prospective studies.

It is of note that APRI and FIB-4 were not significant predictors of HCC in our data, because these non-invasive markers of hepatic fibrosis typically predict HCC risk in CHB[34] and CHC[35]. This finding may be

explained by the fact that the risk of HCC may be less dependent on the transaminase levels in alcoholic cirrhosis compared to viral hepatitis (Table 2). The pathogenetic mechanisms responsible for this observation needs to be further investigated in future studies.

There are potential limitations in our study. First, the study population is confined to Koreans. The performance of our model may be affected by the prevalence of HBV and HCV and need to be validated in other countries with different prevalence for viral hepatitis. Second, the nature of retrospective design suffers potential liability for bias. We tried to minimize selection bias by using our pre-defined EMR system[21,36] and validated the model in an internal validation cohort; however, further external validation is needed by prospective studies. Further cost-effectiveness analysis may also be needed for the clinical utility of ALICE score-guided surveillance strategy. Finally, the diagnosis of cirrhosis was mostly made clinically, and there was a possibility that liver cirrhosis was underdiagnosed and not included in our cohort[37,38]. Since liver biopsy is not generally required for the management of compensated alcoholic liver disease, however, we believe that our model can be applicable to real-world practice of clinically diagnosed alcoholic liver cirrhosis.

In conclusion, the risk of HCC can be stratified by using readily available clinical parameters (age, viral hepatitis markers, AFP level, and platelet counts) in patients with alcoholic cirrhosis in areas where the prevalence of viral hepatitis is substantial.

Abbreviations

AFP, alpha-fetoprotein; ALICE, alcohol-associated liver cancer estimation; ALD, Alcohol-related liver disease; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; BCLC, Barcelona Clinic Liver Cancer; GGT, gamma-glutamyl transferase; HBV; BMI, body mass index; hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Disease; IQR, interquartile range; ROC, receiver operating characteristic; INR, international normalized ratio; NAFLD, non-alcoholic fatty liver disease; US, ultrasonography;

Declarations

Conflicts of interest

Kyunghan Lee, Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong, and Jin-Wook Kim declare that they have no conflict of interest.

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Ethics approval

The IRB approved the study protocol (IRB No: B-1907-553-105).

Consent to participate

Written consents were waived by the IRB due to the retrospective nature of study.

Consent for publication

All authors agree to *publication* if the paper is accepted.

Availability of data and material

Data will be shared on request to the corresponding author with permission of our IRB.

Code availability

Not applicable

Animal research

Not applicable

Clinical trials registration

Not applicable

Gels and Blots/ Image Manipulation

Not applicable

Author contributions:

Jin-Wook Kim: designed the research study, collected and analyzed the data and wrote the paper; Kyunghan Lee: collected and analyzed the data and wrote the paper; Gwang Hyeon Choi, Eun Sun Jang, Sook-Hyang Jeong: analyzed the data and wrote the paper.

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Figures

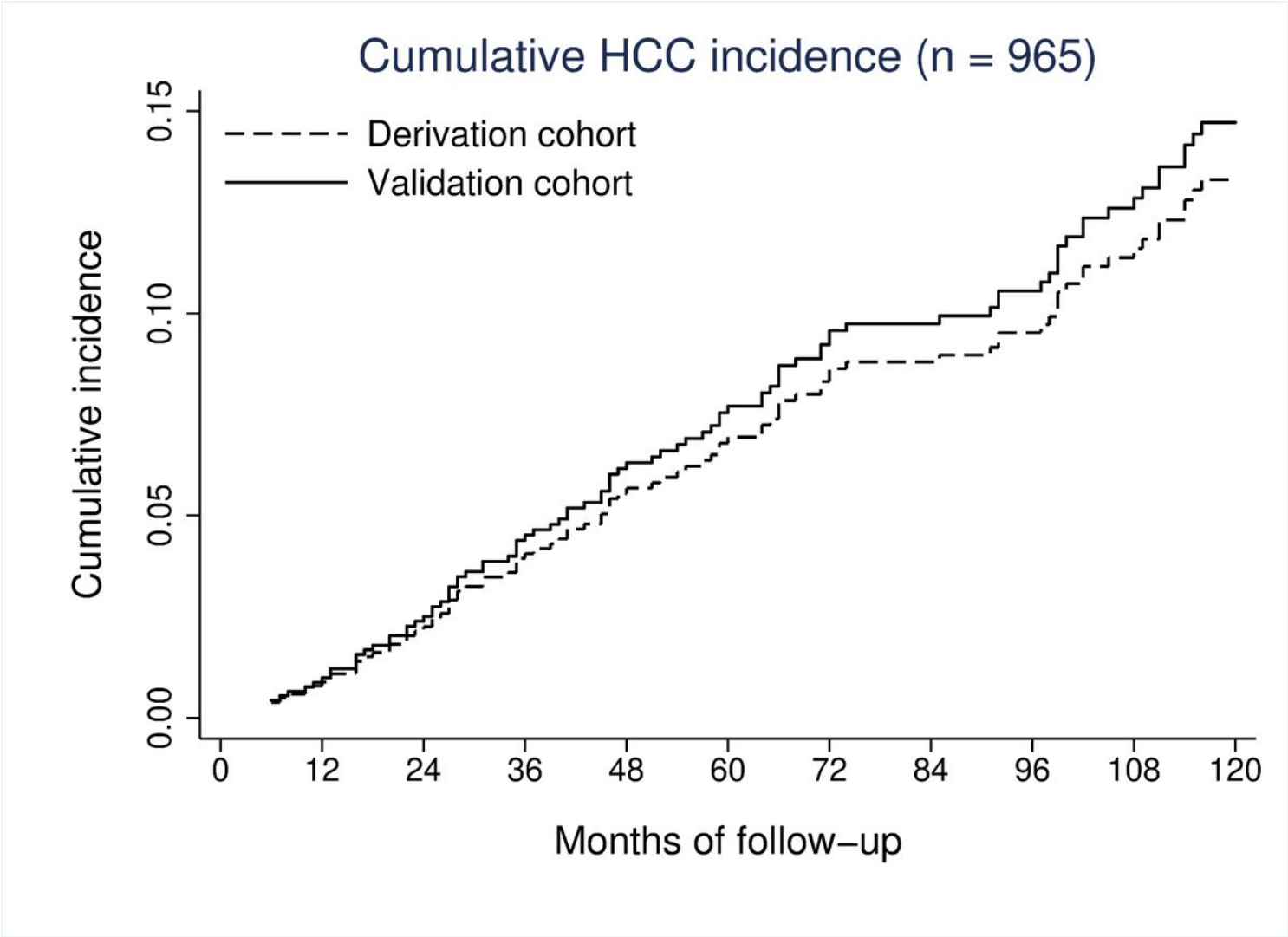

Figure 1

Cumulative incidence functions for HCC in the derivation and validation cohorts.

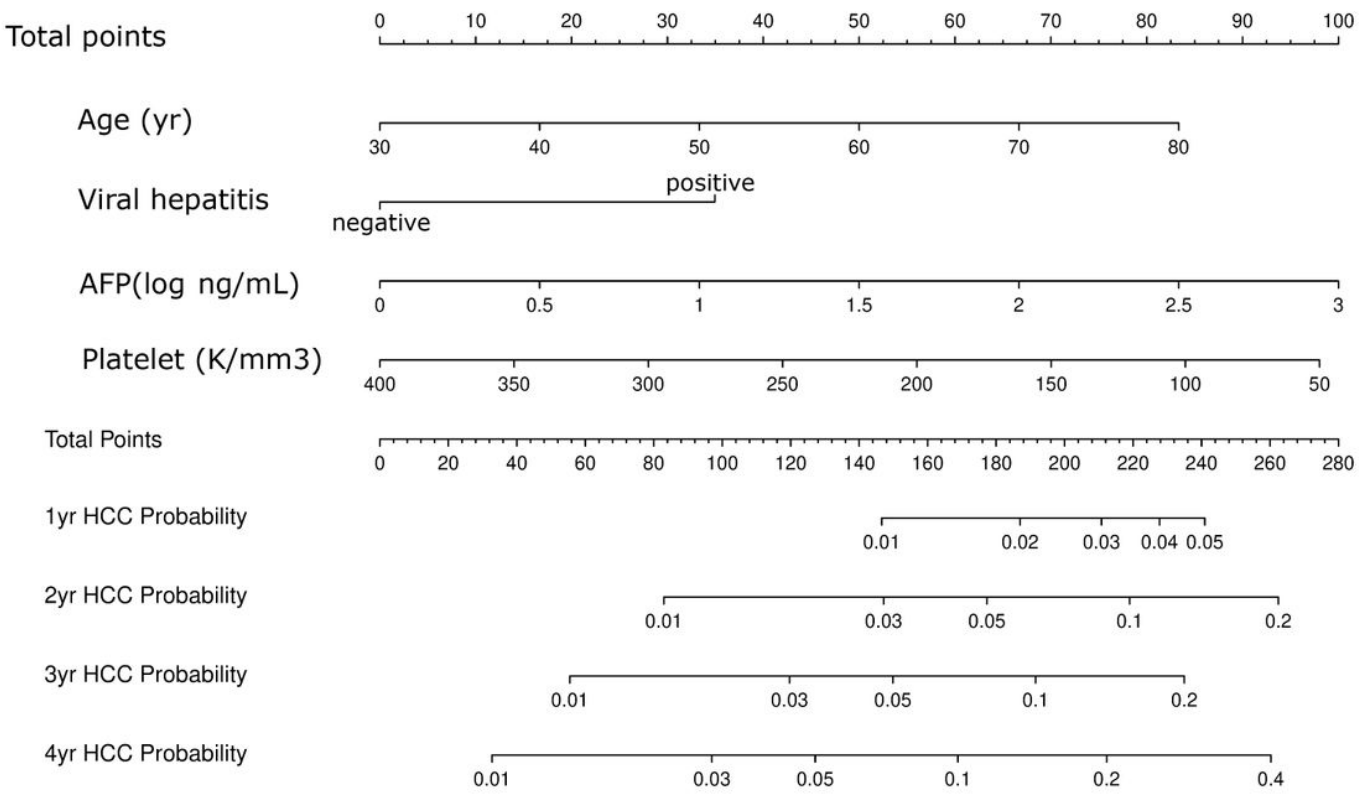

Figure 2

A nomogram for the alcohol-associated liver cancer estimation (ALICE) score.

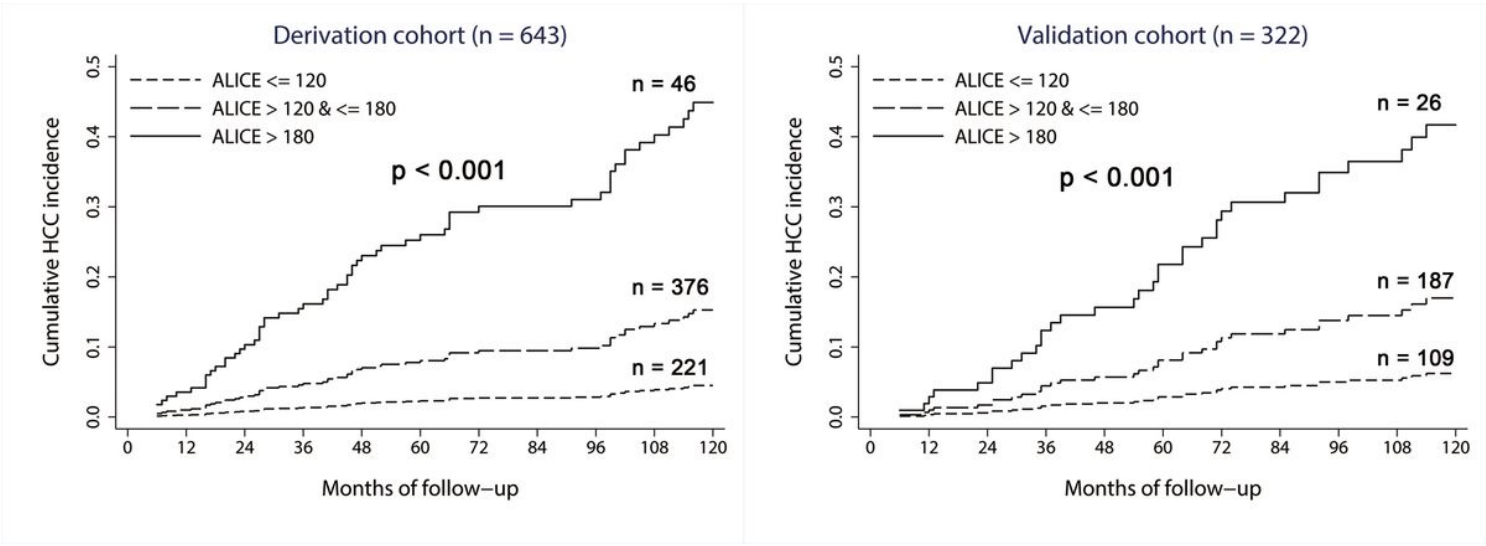

Figure 3

Cumulative incidence curves of HCC in the derivation and validation cohorts according to Alcohol-associated Liver Cancer Estimation (ALICE) score.

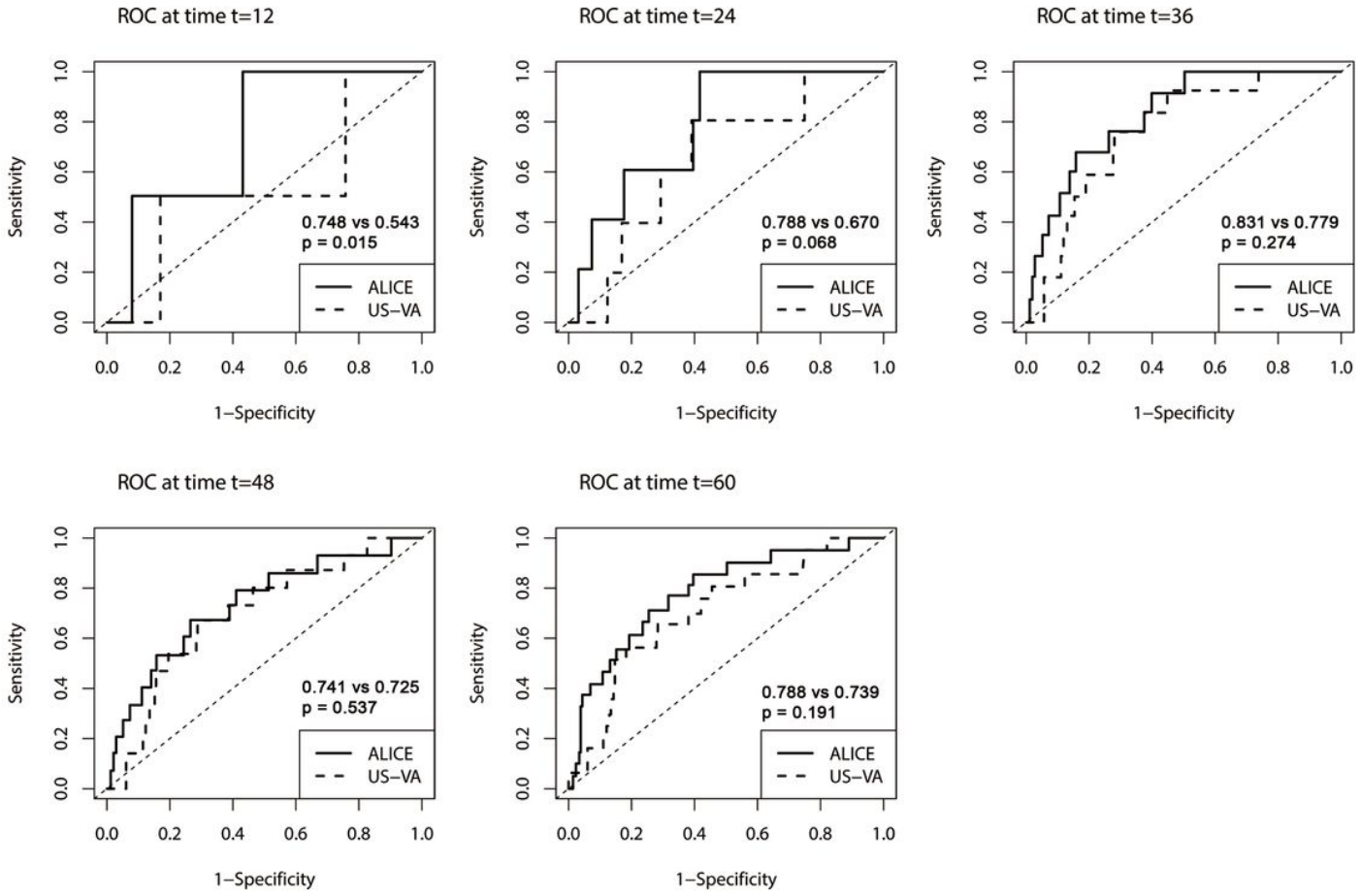

Figure 4

Comparison of time-dependent receiver operating characteristic curves between the ALICE score and US-VA score.

Supplementary Files

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- FigS1calibration.pdf