

Development of an ALBI and ascites based model to predict survival for BCLC Stage B hepatocellular carcinoma

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Abstract

Background: The outcome of the patients with BCLC stage B hepatocellular carcinoma (HCC) varied. Albumin-Bilirubin (ALBI) grade, as a surrogate of the Child-Pugh (CP) grade, was evaluated to be a simple tool for the assessing of the liver function and prognosis. However, it appears to be arbitrary and crude to eliminate the ascites variable from the ALBI grade. We aimed to develop a predictive model constituted with the ALBI grade, the ascites and tumor burden related parameters in patients with BCLC stage B HCC.

Methods: Patients diagnosed as the BCLC stage B HCC were collected from a retrospective database. Construction and validation of the predictive model were performed based on multivariate Cox regression analysis. Predictive accuracy, discrimination and fitness performance of the model were compared with the other eight models. The decision curve analysis (DCA) was used to evaluate the clinical utility.

Results: A total of 1773 patients diagnosed as BCLC stage B HCC between 2007 to 2016 were included in the present study. As the methods for the assessing of the liver function, the ALBI grade and ascites showed their independent prognostic value, and then the two parameters were combined into one, the ALBI-AS grade. Subsequently, the ALBI-AS grade (hazard ratio (HR)=1.26, p=0.008) along with two tumor burden related parameters (the AFP level and the 8-and-14 grade, p<0.001) were used for the development of a prognostic prediction model after multivariate analysis. The area under the receiver operator characteristic curve (AUROC) for overall survival at 1, 2 and 3 years predicted by the present model were 0.73, 0.69 and 0.67 in the training cohort. The concordance index (c-index) and the Aiken information criterion (AIC) were 0.68 and 6216.3, respectively. In the internal and external validation cohorts, the present model still revealed excellent predictive accuracy, discrimination and fitness performance. Then the ALBI-AS based model was evaluated to be superior to other prognostic models with highest AUROC, c-index and lowest AIC values. Moreover, DCA also demonstrated that the present model was clinical beneficial. Additionally, participants could be classified into three distinct risk groups by the model.

Conclusion: The ALBI-AS grade, as a pragmatic alternative of the ALBI grade, is a novel predictor of survival for patients with BCLC stage B HCC. The ALBI-AS based model was evaluated to be an accurate prognostic tool for individual prognostication, and performed well in terms of discrimination and fitness against other prognostic models. And it is appropriate to validate our findings on a larger prospective cohort.

Introduction

Hepatocellular carcinoma (HCC) is a fatal disease with the fifth leading cause of cancer-related deaths in the world (1-3). The prognosis of HCC remains poor due to the relatively high proportion of unresectable disease at the time of diagnosis. The Barcelona Clinic Liver Cancer (BCLC) staging system, endorsed by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), has been largely used in clinical practice (4). Patients of BCLC stage B are considered unsuitable for curative treatment and their overall survival rate are highly variable (5). The

wide variations of overall survival are mainly due to the heterogeneity of liver function and tumor burdens. Therefore several subclassification system or risk predication models for the BCLC stage B HCC patients were proposed based on the parameters related to the liver function and the tumor burden (6-10).

The Child-Pugh (CP) grade is the most widely used tool for the assessing of liver function, and that has been applied in several prognosis prediction models for BCLC stage B HCC patients, such as the BCLC stage B Subclassification system and the SNACOR model (5, 8). However, there are several limitations for the application of CP grade in HCC patients. The CP grade have five parameters, the bilirubin, albumin, prothrombin time, hepatic encephalopathy and ascites. The selection of cut points for the continuous variables (the bilirubin, albumin and prothrombin time), and the subjectivity in the use of the categorical variables (hepatic encephalopathy and ascites) lead to the decreased discrimination power for the prognosis prediction (11). Recently, the Albumin-Bilirubin (ALBI) grade was reported to be a simple method for evaluating liver function and prognosis in HCC patients. The ALBI grade only contains two objective parameters of the Child-Pugh grade, and that was evaluated to have better performance in terms of prognosis prediction compared with the Child-Pugh grade (12). The ALBI grade has been incorporated into the prognostic models for BCLC stage B HCC patients or patients underwent TACE.

The ascites variable is eliminated in the ALBI grade. The reasons for that are as follows, the grading of ascites was believed to be highly subjective that the distinguishing between mild and moderate ascites was subject to interobserver variability, and the ascites and serum albumin level were interrelated. Actually, the proportion of patients with moderate to large amount of ascites is low in the BLCL stage B HCC population. Therefore the ascites variable could be set as a binary variable (with or without ascites), that reduced the subjectivity of judging on the amount of ascites (11). The production of ascites and its volume mainly depend on the portal vein pressure, though that might be influenced by the albumin level (13). And the ascites always predicted the prognosis more accurately than the albumin level in previous HCC related risk models. Additionally, the ascites have been incorporated into several HCC-related prognostic model (such as HCC with portal vein tumor thrombus, HCC after ablation, HCC after palliative treatments, and BCLC stage C HCC) (14-18). Therefore it appears arbitrary and crude that eliminating the ascites variable from the risk prediction model for BCLC stage B HCC patients. The sum of the size of the largest tumor and the number of the tumors were always used for the evaluation of the tumor burden, for instance, the up-to-seven criteria for patients underwent liver transplantation, and the up-to-11 criteria for patients underwent TACE (9, 19). However, the optimal cutoff point of that parameter in the BCLC stage B HCC patients are still on debate. In the present study, the ALBI, the ascites, the size of the tumor, the number of the tumors and other clinical parameters were all used for the development of a prognostic model for the BCLC stage B HCC patients.

Methods

Study population

Between January 2007 and December 2016, 2020 consecutive patients with BCLC Stage B HCC were collected from a retrospective database (20). As the description of the databases and the previous studies, 1606 patients from the Sun Yat-sen University Cancer Center were used for the development of training and internal validation cohort. The rest 414 patients from other hospitals were utilized for the external validation. The inclusion criteria were: (1) adult patients diagnosed as HCC according to the AASLD guidelines; (2) patients with liver function of Child-Pugh class A or B; (3) the ECOG performance status were 0; (4) patients with multiple tumors, and no vascular invasion or lymphatic/extrahepatic metastasis; (5) patients had complete follow-up by the magnetic resonance imaging or computed tomography and bio-chemical routine test. The exclusion criteria were: (1) patients with history of malignancies other than HCC; (2) recurrent HCC or HCC with vascular invasion or lymphatic/extrahepatic metastasis; (3) liver function of Child-Pugh class C; (4) patients with hepatic encephalopathy/refractory ascites/gastrointestinal hemorrhage; (5) patients with immunodeficiency or autoimmune disease; (6) the follow-up duration was less than three months.

Development of the prognostic model

The demographics and biochemistry tests of patients were extracted for analysis: the age, gender, virus infection status, the hemoglobin level, white blood cell count, platelet count (PLT), aspartate aminotransferase (AST), albumin, total bilirubin, c-reactive protein (CRP), prothrombin time, ascites, alpha-fetoprotein, tumor number and size, tumor vascular invasion, distant or lymph node metastasis, performance status score. The ALBI score was calculated as the following formula: linear predictor = $(\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, where bilirubin is in mol/L and albumin in g/L (11). We redefined the cutoff value of the ALBI score for grading by the X-tile. The AST to platelet ratio index (APRI) was calculated as the formula: $([\text{AST}/\text{upper limit of normal}]/\text{platelet count } [10^9/\text{L}]) \times 100$ (21). The Child-Pugh grade was evaluated by the laboratory data of AST, albumin and total bilirubin, and clinical data of hepatic encephalopathy and ascites. The ascites were defined as the radiological ascites. The 8-and-14 grade was evaluated by the sum of the size of the largest tumor and the number of the tumors, the cutoff value was defined by the X-tile. The overall survival was the primary outcome, and that was defined as the time span from the HCC diagnosis to the last follow-up. The prognostic value of above laboratory and clinical variables were evaluated respectively. The independent prognostic variables would be put into the model. And the combination variables, not separately, would be used for the development of the model. Such as the ALBI grade, instead of the albumin and total bilirubin, would put into the model if it fulfilled the criteria.

Statistical analysis

The continuous variables were presented as mean with standard deviation or median with interquartile range (IQR). The categorical variables were presented as the number (percent). We used the Kaplan-Meier method to create the cumulative survival curve. Then the survival rate of patients were compared by the method of log-rank test. The cox regression analyses were used to evaluate the prognostic value of the clinical factors for the development of model. By the stepwise backward selection manner, the

multivariable analyses identified the independent prognostic factors, from the variables that achieved statistical significance ($p < 0.05$) in the univariable analyses. A nomogram was generated by the Cox regression coefficients. The discrimination and fitness performance of the prognostic model were evaluated by the concordance index (c-index) and the Aiken information criterion (AIC) separately. And the accuracy for the outcome predicting was evaluated by the area under the receiver operator characteristic curve (AUROC). We compared the present model with other models such as the HAP score, the mHAP II score, the ALBI-TAE model, the up-to-seven system, the four-and-seven system, the six-and-twelve score system, the BCLC-B sub-staging system and the New BCLC B sub-staging system (8-10, 19, 22-25). Then the clinical utilities of the present model were evaluated by the decision curve analysis (DCA). The statistical analyses were done by the using of the R (version 3.5). Statistical significance was set at $p \leq 0.05$.

Results

Patients

After the patients selection, a total of 1773 patients fulfilled the inclusion criteria. There were 903 patients that formed the training cohort, and 527 patients used for internal validation, 343 patients for external validation. The baseline characteristics of the patients from the training cohort were presented in the Table 1, and the baseline characteristics of the internal and external validation cohorts were showed in the Supplementary Table 1. Most of the patients from the training cohort were male (90.9%), and most of them were HBV infected (87.7%). The median follow-up period was 16.6 months in the training cohort, 17.0 months in the internal validation cohorts and 17.5 months in the external validation cohort. More than 80% of patients from the training cohort were Child-Pugh grade B. However, the majority of patients from the internal and external validation cohorts were Child-Pugh grade A. More than 60% of patients had at least 3 lesions in the whole cohorts. The median size of tumors ranged between 63 to 67mm in train, internal and external cohorts, and there were 3% to 5% of the patients with ascites. The mean ALBI score was -2.4 in the training cohort, -2.5 in the internal validation cohort, and -2.4 in the external validation cohort.

Survival analyses and development of the prognostic model

The cut point for the ALBI score in the study of Johnson et al was set as -2.60 and -1.39 (less than -2.60 for grade 1, -2.60 to -1.39 for grade 2, and more than -1.39 for grade 3), and their study was based on the analysis for all stage of HCC (11). The study of Lee et al for BCLC stage B HCC, which used the similar grading method for ALBI as the study of Johnson et al, revealed that there was no significant difference in terms of survival between the patients of ALBI stage 2 and 3 (10). They combined the patients of ALBI grade 2 and 3 as one group for the analyses. The present study also focused on the BCLC stage B HCC, therefore we divided the patients into two groups according to the ALBI score, and we defined the cutoff point by the using of the X-tile. As presented in the Supplementary Figure 1, the cutoff point in the internal cohort (the training and internal validation cohorts) and external cohort were all defined as -2.3. The ALBI

score less than -2.3 was defined as the ALBI grade I, and the other patients was defined as the grade II. As showed in the Figure 1A, there was a significant difference in terms of overall survival between the ALBI grade I and II group ($p < 0.001$).

Then we compared the survival time between the patients with and without ascites, as showed in the Figure 1B, patients without ascites had a significant better overall survival than those with ascites ($p < 0.001$). And the prognostic value of ascites was confirmed in the analyses for the subgroup of ALBI grade I or II patients (Figure 1C and 1D). Therefore we used the ALBI grade and the information of ascites for the assessment of the liver function. We explored the method for the combination of the ALBI grade and the ascites next. We found out that patients with low ALBI score and no ascites had the best prognosis (those patients would be defined as the low risk grade), and the patients with high ALBI score and ascites had the worst prognosis (high risk grade). There was no significant difference in terms of the overall survival for patients with high ALBI score but no ascites and low ALBI score but ascites, therefore we defined those patients as the middle grade (Figure 2).

As presented in the Table 2, we combined the ALBI grade and the ascites to a new variable, the ALBI-AS grade (the grade A represented for the low risk grade, grade B for the middle risk and grade C for the high risk). The ALBI-AS grade was simpler than the Child-Pugh grade, and a little more complicated than the ALBI grade but more comprehensive and accuracy, in terms of assessment for the liver function. The Figure 3 showed the prognostic value of ALBI-AS grade in the training, internal validation and external validation cohorts. Observed survival rates at 1 and 3 years were 69.1% and 42.9% for the ALBI grade I patients, 61.2% and 29.4% for the ALBI grade II patients. And the observed survival rates at 1 and 3 years were 69.9% and 42.4% for the ALBI-AS grade A patients, 61.4% and 9.1% for the ALBI-AS grade C patients. Similar as the up-to-7 criteria or up-to-11 criteria in the previous studies, the sum of the size of the largest tumor and the number of tumors, were used for the assessment of the tumor characteristics. With 8 and 14 as the cutoff point that defined by the X-tile (the Supplementary Figure 2), we used the 8-and-14 grade for the development of the predictive model.

As showed in the Figure 4, the univariate analysis revealed that nine variables including the baseline serum PLT level, the baseline CRP level, the baseline AFP level, the tumor size, the tumor number, the 8-and-14 grade, ascites, the ALBI grade, and the ALBI-AS grade were evaluated to be associated with overall survival. Then the baseline PLT, CRP, AFP level and the 8-and-14 grade, the ALBI-AS grade were put into the multivariable analyses. After the multivariable cox survival analyses, the AFP level, the 8-and-14 grade and the ALBI-AS grade were finally selected out for the development of the model. The Supplementary Figure 3 showed the prognostic value of the AFP level, the 8-and-14 grade and the ALBI-AS grade separable.

Then we formulated a nomogram with the three selected prognostic factors, as showed in the Figure 5. The associated c-index was 0.68 (95% Confidence Interval (CI), 0.66-0.70), that showed the nomogram model could predict 68% of the individual death probability. The calibration curves showed a high consistency in the prediction of the 5 and 8 year overall survival.

Validation of the model and comparison with other models

We validated the efficacy of the present model in the internal and external validation cohort. As showed in the Table 3, the c-index and AIC in the present model were 0.68 and 6216.3. And the 1 to 3 year AUROC ranged from 0.67 to 0.73. The c-index and AIC in the internal validation cohort were 0.70 and 2306.2, and that in the external validation cohort were 0.67 and 2056.6. And the AUROC of three years in the internal and external validation cohort presented a relatively high accuracy for the outcome predicting. Then we compared the present model with other eight models in the training, internal validation and external validation cohort. The present model showed a higher discrimination ability and fitness performance than all other models, and the 1 to 3 year AUROC of the present model were all higher than other models separately. We compared the clinical usefulness of each model by the decision curve analysis. As showed in the Figure 6, the present model we developed provided a larger net benefit compared with other models in the train, internal validation and external validation cohorts.

Performance of the model in stratifying risk of patients

We assigned a corresponding score for each selected prognostic factor of the model, based on its value. Then we calculated the total score for each individual according the sum of the score that obtained from each risk factor. As showed in the Table 4, patients were divided into three risk strata based the score. The survival curve in the Figure 7 revealed that patients in the Stratum 1 had a better overall survival than the Stratum 2, and the overall survival time of patients from the Stratum 2 were better than that of Stratum 3 ($p < 0.001$). Then we compared the prognosis of patients from different strata in different subgroups based on the age, the AST level, and the Child-Pugh class. As showed in the Figure 7, the performance of the model in risk stratifying was still good in the subgroups.

Conclusions

Patients with BCLC stage B HCC had a varied survival, hence several risk models or systems have been developed for the prediction of the outcome for those patients. The ALBI grade, as a surrogate of the CP grade, was evaluated to be a simple tool for the assessing of the liver function (10, 11). However, it appears to be arbitrary and crude that the ascites variable which contained in the CP grade, was eliminated from the ALBI grade. The present study revealed the prognostic value of ascites and combined that with the ALBI grade to get a new variable, the ALBI-AS grade. The ALBI-AS grade provided a well discriminatory ability, the three-year overall survival rate for patients of ALBI-AS grade C was 9.1% which was far below that of the ALBI grade II patients. Subsequently, the ALBI-AS grade along with the AFP level and the 8-and-14 grade were used for the development of a prognostic prediction model for patients with BCLC stage B HCC. The discrimination and fitness performance were investigated in the training cohort and verified in the internal and external validation cohorts, and then compared with the other eight models. The present ALBI-AS grade based model provided an accurate prognostication and performed well against other prognostic models.

The liver function is a key parameter that would have influence on the survival of the patients with BCLC stage B HCC. The BCLC-B subclassification system and the new BCLC-B subclassification system adopted Child-Pugh score or class as the surrogate of the liver function (8, 9). The ascites could be incorporated into the predictive model as a part of the CP score or class. And the patients of Child-Pugh B had a dismal prognosis compared with the patients of Child-Pugh A, owing to the high percent of patients with ascites and clinical jaundice (26). Recently, as the ALBI grade was proposed and incorporated into several HCC related prognostic models, the ALBI grade has been regarded as a simple and pragmatic tool for assessing of liver function rather than the CP grade. Therefore the ascites variable was abandoned for not being part of the ALBI grade. And the prognostic value of the ascites was seldom evaluated in the studies on the ALBI related prognostic model, and there were even no studies on the survival analysis for the ascites when the ALBI grade was applied in the populations with BCLC stage B HCC. One of the reasons for that was, most published studies of on BCLC stage B or TACE, either exclude or have limited inclusion of patients with decompensated cirrhosis, usually corresponding to presence of ascites, and definitive conclusions regarding these patients cannot be made from the literature (26).

In fact, in western countries, 90% of liver cancer occur in the background of cirrhosis, which itself is a progressive disease that affects the survival of patients (26). The most serious complication of cirrhosis is portal hypertension. Ascites are the most common first symptom of liver decompensation, which seriously affects the prognosis of patients with cirrhosis (13). The ascites were evaluated to be independent risk factor for the survival of HCC patients, and has been incorporated into several HCC-related risk models (13, 14, 16, 18). Therefore there might be an over-simplification in the ALBI grade, and the ascites could be retained as the parameters for the assessing of the liver function. In the present study, both the ALBI grade and the ascites were used for the assessment of the liver function, and the predictive value of the ALBI-AS grade was acceptable. According to the models performance comparison results, we could find out that the present ALBI-AS based model was a reasonable simplification of the Child-Pugh based models, and an improvement compared with the ALBI based models.

We included the patients with decompensated cirrhosis to develop a comprehensive prognosis model for patients with BCLC stage B HCC. TACE has been established as the standard of care for patients of BCLC stage B, and applied as the first-line treatment in our study (27, 28). The decompensated cirrhosis was not considered to be an absolute contraindication to TACE. The study of Kim et al revealed that, decompensated patients with Child-Pugh class B (Child score 8 or 9) can benefit from TACE treatment if they have limited tumor burden (9). The HCC complicated with refractory ascites was believed to be a contraindication for the treatment of the TACE (29). About 60% of cirrhotic patients develop ascites within 10 years, only ten percent of patients have refractory ascites. And there was a low percent of patients with refractory ascites, which part of patients were not included in the present study, in the BCLC stage B populations. TACE can be used for patients with marginal hepatic reserve (i.e., hyperbilirubinemia, ascites) (30). Our study included patients with little amount of ascites and no encephalopathy, that could be deemed as a marginal hepatic reserve. Hence there was no heterogeneity in terms of primary treatment due to the inclusion of patients with decompensated cirrhosis. The TACE was not recommended for patients with HCC and ascites due to a more vulnerable chance of the ischemic injury

after TACE (31). However, the ascites variable was only one of the parameters that would have influence on the survival. Patients of ALBI-AS grade B had a better prognosis than patients of ALBI-AS grade C, and patients of ALBI-AS grade C could also get a treatment benefit if they have a low AFP level or a better 8- and-14 grade. Through the prediction of the whole model, the prognosis of patients could be better evaluated, and the patients suitable for TACE treatment can be screened out.

There were several limitations in the present study. First, the inherent limitations of the retrospective study; Second, although the study was validated with multi-center data, all participants were from the Asian centers. Our findings should be further validated in the western populations; Third, despite the included patients received the TACE as their first-line treatment, the additional treatments, such as radioembolization, targeted therapy or ablation therapy, during the follow-up period could have influence on survival but not be controlled; Fourth, the radiological ascites variable was used for the development of the present model. However, different radiological techniques (computed tomography or ultrasonography) and observers might have influence on the results; Fifth, the conventional regression methods were utilized in the present model, and the machine learning methods, which were believed to be flexible prediction algorithms, that may be more accurate than the conventional regression and could be applied in the future studies on BCLC stage B HCC.

Conclusion

In summary, the ALBI-AS grade, as a pragmatic alternative of the ALBI grade, is a novel predictor of survival for patients with BCLC stage B HCC. The ALBI-AS based model was evaluated to be a useful prognostic tool for individual prognostication, and performed well in terms of discrimination and fitness against other prognostic models. The present model could be applied to identity patients with BCLC stage B HCC that need aggressive treatment. However it is appropriate to validate our findings on a larger prospective cohort.

Declarations

Ethics approval and consent to participate

Ethical approval was not required due to that all the participants of the present study were from a public clinical database of the DRYAD.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in this study are available from the corresponding author upon reasonable request.

Authors' contributions

YZ, HPL: protocol/project development; YZ, HPL, ZJ, JY: data collection or management; HPL, WH: data analysis; YZ, HPL, WH: manuscript writing/editing. All authors read and approved the final manuscript.

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Conflict of Interest

We declare that we have no conflict of interest.

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Figures

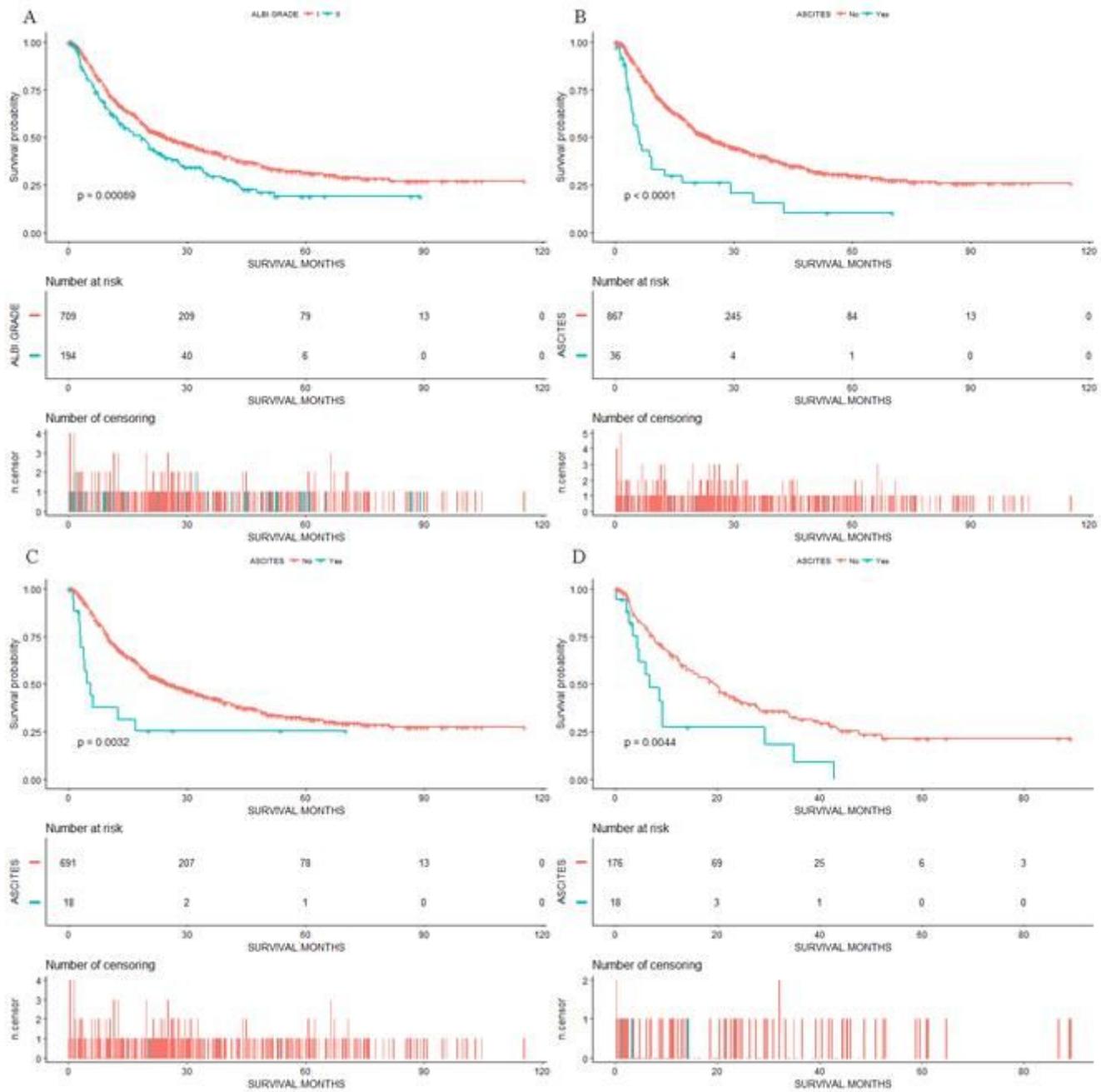


Figure 1

Kaplan-Meier curves of overall survival in patients with BCLC stage B HCC stratified by A) the ALBI grade and B) the ascites. And the Kaplan-Meier curves of overall survival in patients of C) ALBI grade I subgroup and D) ALBI grade II subgroup, stratified by the ascites.

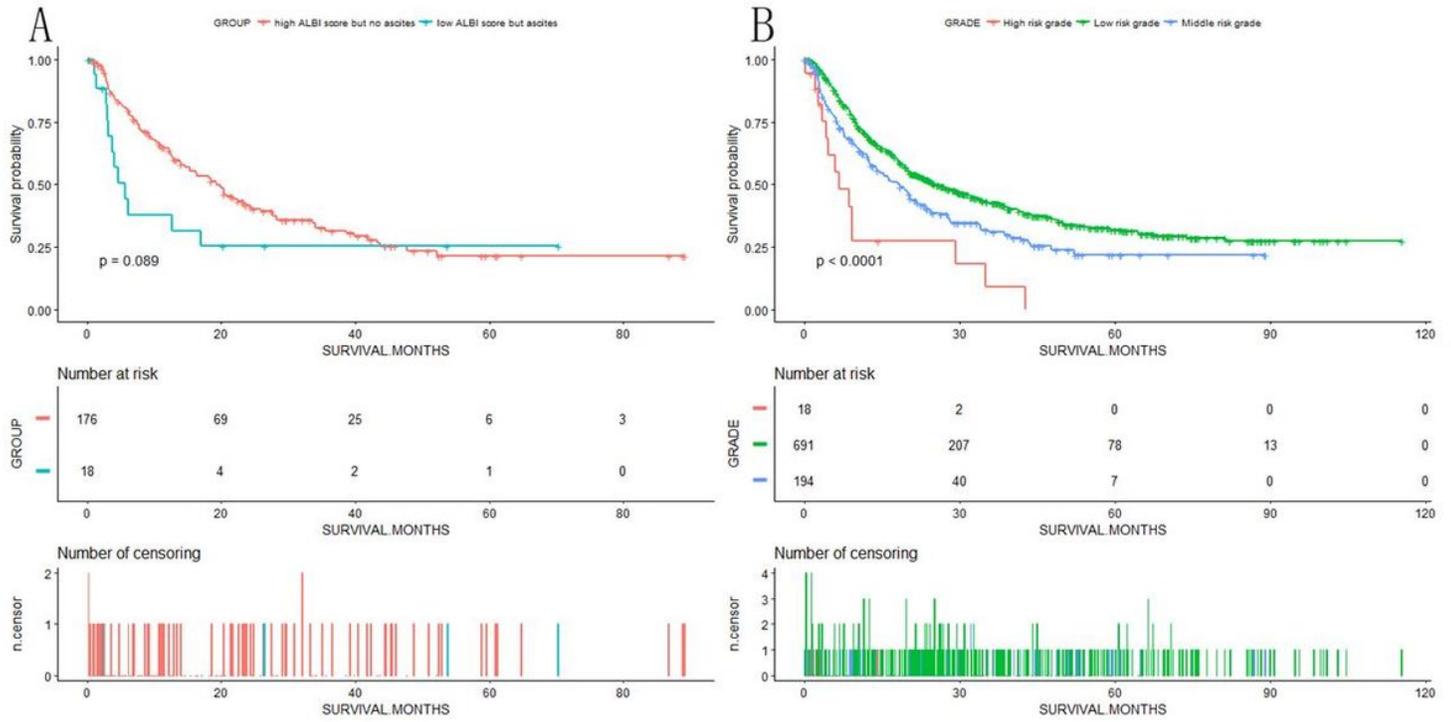


Figure 2

A) Kaplan-Meier curve of overall survival in patients from the group of high ALBI score and no ascites and group of low ALBI score and ascites. Kaplan-Meier curve of overall survival in patients from the low risk (low ALBI score and no ascites), high risk (high ALBI score and ascites) and the rest patients (the middle risk).

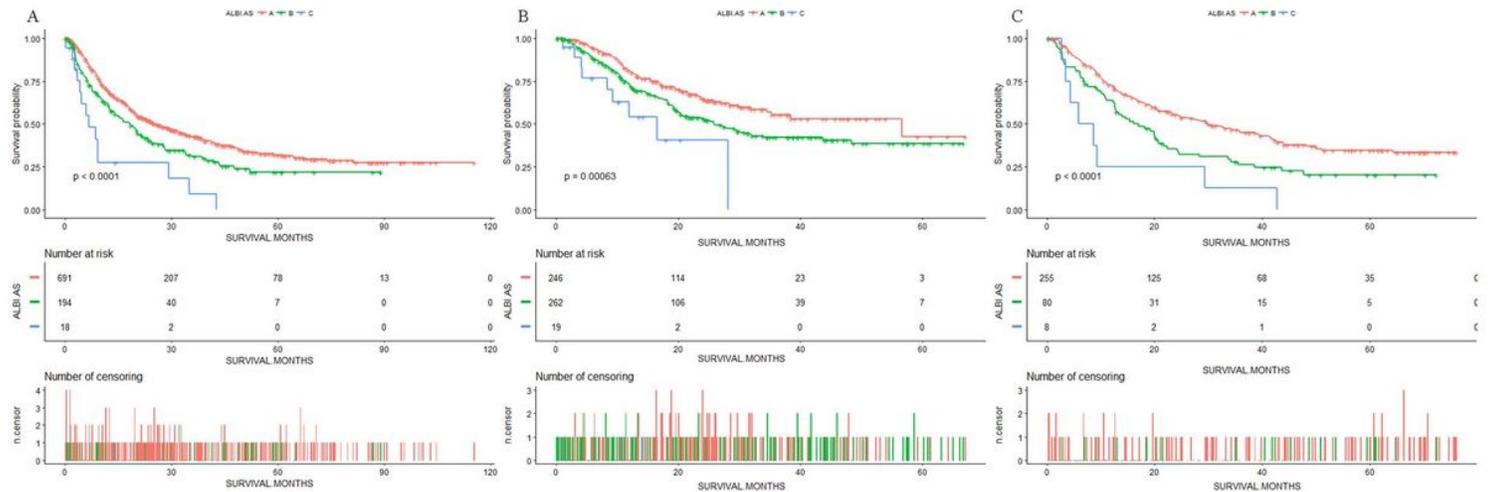


Figure 3

Kaplan-Meier curves of overall survival in patients stratified by the ALBI-AS grade in the A) training, B) internal validation and C) external validation cohorts.

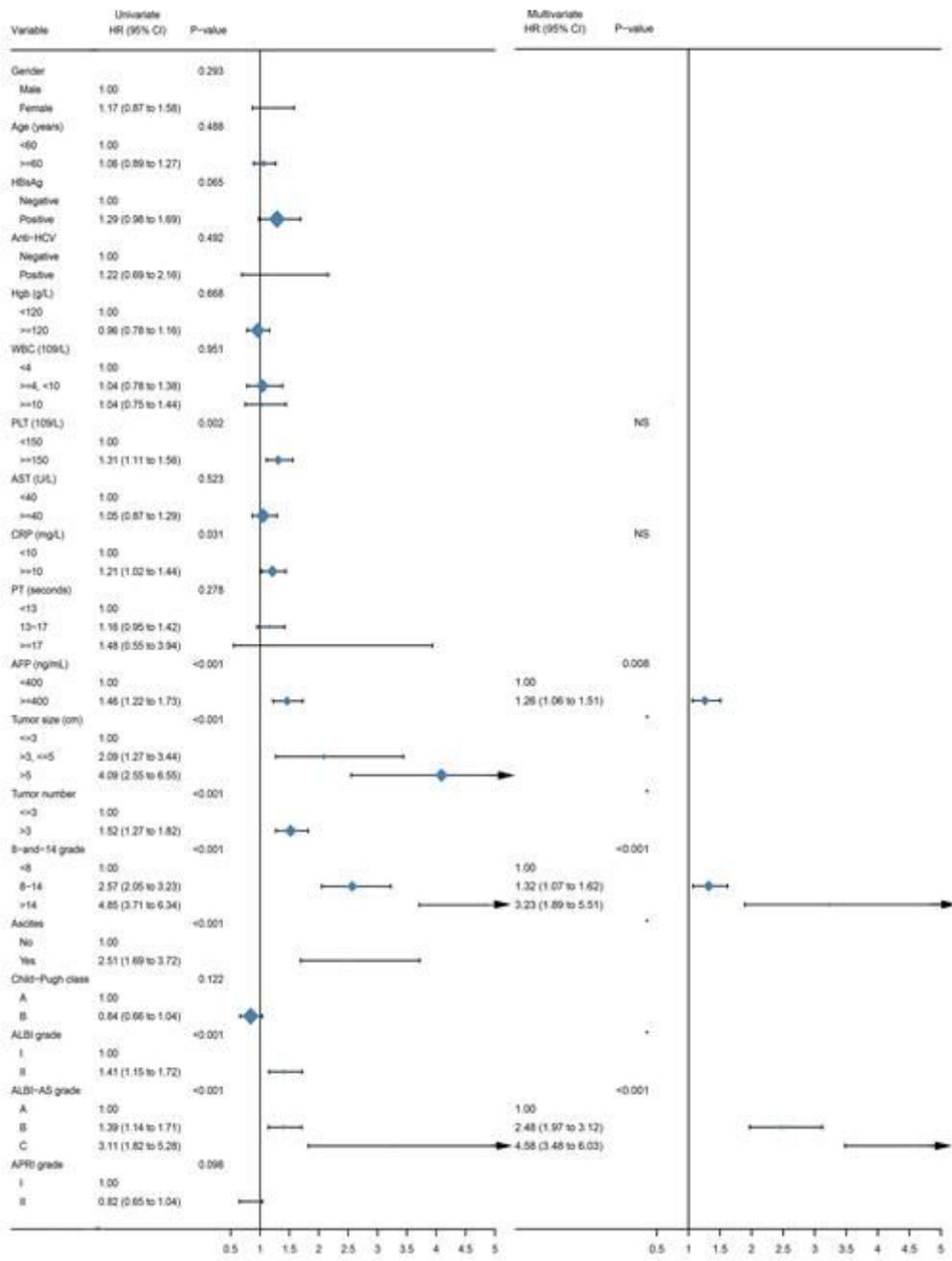


Figure 4

The univariate (left panel) and multivariable (right panel) survival analyses. * represents significance in the univariate analyses but not included in the multivariable analyses.

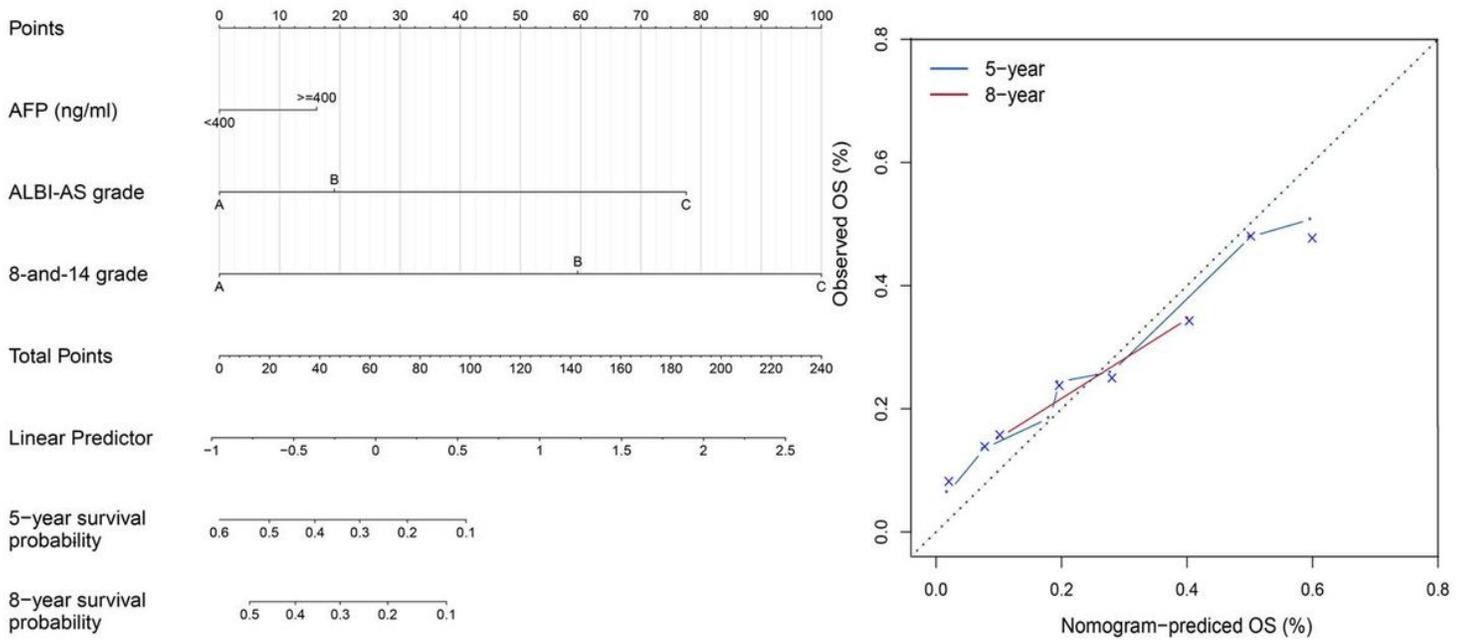


Figure 5

Nomogram (left panel) to predict 5-year and 8-year overall survival. Calibration plot (right panel) at 5 and 8 years for the final model.

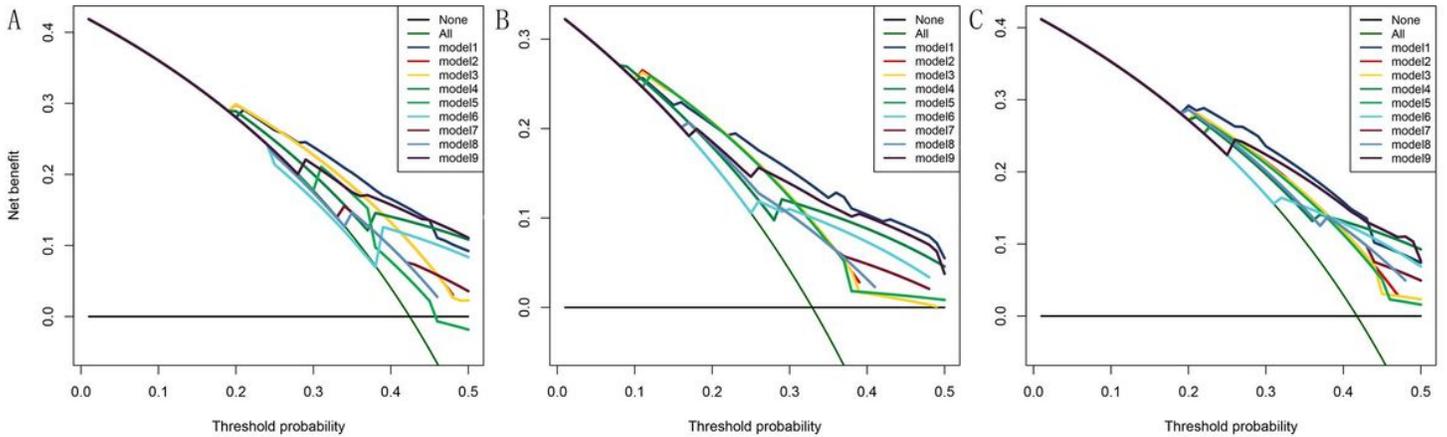


Figure 6

The Decision Curves Analysis curve in the A) training, B) internal validation and C) external validation cohorts. Model 1: the present model; model 2: Up-to-seven; model 3: Four-and-seven; model 4: Six-and-twelve; model 5: BCLC-B sub-staging system; model 6: New BCLC B sub-staging system; model 7: HAP; model 8: mHAP II; model 9: ALBI-TAE model.

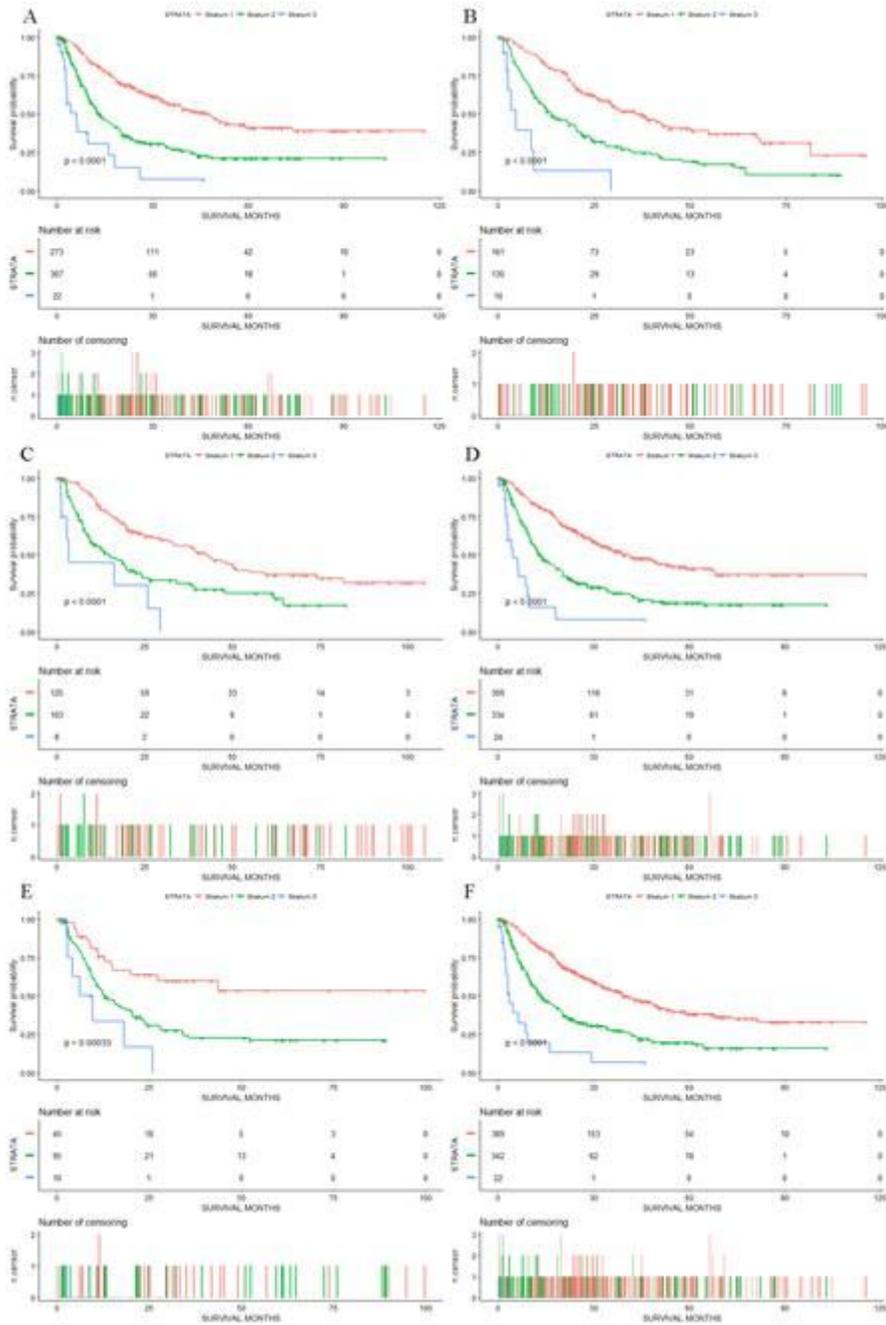


Figure 7

Kaplan-Meier curves of overall survival in patients from the subgroup of A) ≤ 60 years old, B) ≥ 60 years old, C) AST level ≤ 40 U/L, D) AST level ≥ 40 U/L, E) Child-Pugh A and F) Child-Pugh B, stratified by the risk strata. AST, Aspartate aminotransferase.