ABC: A Novel Algorithm to Stratify Decompensation Risk in Patients With Compensated Advanced Chronic Liver Disease: an International, Multicenter Cohort Study

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Research Article

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Abstract

Background: Liver-related death is preceded by clinical decompensation; therefore, the risk stratification of decompensation in compensated advanced chronic liver disease (cACLD) is extraordinary significant.

Methods: The international, multicenter study included three cohorts from January 2009 to August 2021. In training cohort, the unfavorable Baveno VI criteria patients were used to develop the novel CHES criteria to stratify decompensation risk. The **A**lgorithm based on **B**aveno VI criteria plus **C**HES criteria (**ABC** model) was validated in validation cohort, and used to diagnose clinically significant portal hypertension (CSPH) in hepatic venous pressure gradient (HVPG)-performed cohort.

Results: A total of 1377 cACLD patients were enrolled. In training cohort, multivariate analysis revealed that liver stiffness measurement (LSM), platelet count (PLT), albumin, alanine aminotransferase (ALT) and varices were the independent risk factors for hepatic decompensation. The novel CHES criteria was produced, and <-4.4 , -4.4 to -3.1 and >-3.1 indicated the low risk, medium risk, and high risk of decompensation, with a 3 year-time-dependent area under the curve (tAUC) of 0.851 (0.800-0.901). In validation cohort, the 3 year-tAUC of ABC model was 0.843 (0.742-0.943). Notably, in HVPG cohort, the high risk group was used to rule in CSPH with a positive predictive value of 0.930.

Conclusion: The ABC model can stratify the risk of decompensation in cACLD. HVPG evaluation can be waived in both low risk and high risk cACLD patients as they can be managed by Baveno VI criteria and non-selective β -blockers intervention, respectively, and the remaining medium risk patients need further HVPG evaluation.

Introduction

Compensated advanced chronic liver disease (cACLD) commonly indicates severe fibrosis and compensated cirrhosis at risk of developing clinically significant portal hypertension (CSPH) and hepatic decompensation [1–3]. Liver-related mortality is almost unalterably preceded by clinical decompensation [1, 4, 5]. Hence, the prediction of decompensation risk is relevant for the patients with cACLD. The presence of CSPH (defined as hepatic venous pressure gradient [HVPG] ≥ 10 mmHg) is the strongest predictor of hepatic decompensation [1, 6]. However, HVPG measurement is invasive, operator dependent, and not widely available [6–9]. Several non-invasive markers have been proposed to predict the decompensation risk. The existing criteria such as liver stiffness measurement (LSM), platelet count (PLT), albumin, model for end-stage liver disease (MELD), alanine and aspartate aminotransferases (ALT and AST), albumin-bilirubin (ALBI) and fibrosis-4 (FIB-4) indices (ALBI-FIB-4) [1, 6, 10–15] have favorable performances to exclude patients at risk of liver decompensation. Nevertheless, a simple algorithm to cACLD patients at risk of liver decompensation risk remains an unmet need [6].

According to the 2021 updated EASL Clinical Practice Guidelines,[1] cACLD patients who did not meet the Baveno VI criteria but had any of the two variables (LSM > 20 kPa or PLT $< 150 \times 10^9/L$) were suggested to perform screening endoscopy and HVPG measurement. However, the number of cACLD patients with

unfavorable Baveno VI status is heterogeneous and there were no detailed risk stratifications existed at this timepoint. Our study aims to investigate a novel algorithm to stratify decompensation risk in patients with cACLD.

Patients And Methods

Study population

This is an international, multicenter cohort study initialed by Chinese Portal Hypertension Alliance (CHESS) and eligible patients were enrolled from China, Japan, Southern Korea, Egypt, Singapore, and India between January 2009 and August 2021 (ClinicalTrials.gov: NCT04975477). The training cohort was originating from China and Japan, and the validation cohort was enrolled from Southern Korea, Egypt, and Singapore. The inclusion criteria were: (1) age above or equal to 18-year-old, (2) fulfilled diagnosis of cACLD based on radiological, histological features of severe fibrosis or cirrhosis according to the Baveno VI consensus [16]. The exclusion criteria were: (1) prior hepatic decompensation, (2) hepatocellular carcinoma, (3) prior liver transplantation, (4) portal vein thrombosis, (5) antiplatelet or anticoagulation, (6) without screening endoscopy within six months of transient elastography, (7) alcoholic cirrhosis with significant ongoing alcohol intake, and (8) incomplete follow-up data. Besides, an external HVPg cohort included cACLD patients from India and China. All patients in HVPg cohort were according with the above inclusion and exclusion criteria. In addition, patients with non-sinusoidal portal hypertension were excluded in the HVPg cohort. All authors had access to the study data and had reviewed and approved the final manuscript.

Study design

In the training cohort, patients were separated into favorable Baveno VI criteria group (Grade 0) and unfavorable Baveno VI criteria group ($\text{LSM} > 20 \text{ kPa}$ or $\text{PLT} < 150 \times 10^9/\text{L}$). The data from unfavorable Baveno VI criteria group was used to develop the CHESS criteria to further predict the risk of hepatic decompensation. Furthermore, the patients in unfavorable Baveno VI criteria group were divided to three subgroups (Grade 1, 2, and 3) according to the CHESS criteria. Grade 1 was assigned to low risk group, and Grade 2 and Grade 3 were defined as medium risk and high risk groups, respectively. The novel **Algorithm based on Baveno VI criteria plus CHESS criteria** were named as **ABC** model. The validation cohort was used to independently evaluate the performance of ABC model for predicting the risk of hepatic decompensation. Finally, we also aim to investigate the diagnostic accuracy of ABC model in diagnosing CSPH (defined as $\text{HVPg} \geq 10\text{mmHg}$).

Measurement of transient elastography, endoscopy and HVPg

Liver stiffness was measured by formally trained operators using Fibroscan® (Echosens, Pairs, France). LSM was performed on a patient with lying supine and right arm elevated to facilitate access to the right liver lobe. Transient elastography was performed as per the manufacturer's instructions. The final result must be in accordance with following criteria: at least 10 valid measurements were obtained, interquartile

range < 30%, and successful rate > 60%. The median value of successful measurements was taken to be the patient's LSM value and was expressed in kPa. Endoscopies were performed by expert endoscopists and HVPG was measured by interventional specialists [17].

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD), median (interquartile range). Categorical variables were expressed in number and percentages (%). The differences of two groups were compared using Student's t-test or Mann-Whitney U test. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify independent predictors of hepatic decompensation. Forward likelihood ratio selection procedures were used for variable selection. Bayes information criterion (BIC) and Akaike information criterion (AIC) was used for selection and final criteria for inclusion of variables in model respectively. We included all the multivariate predictors for hepatic decompensation into a weighted predictive risk score to develop the CHESS criteria. The non-linear relationships between CHESS criteria and risk of hepatic decompensation were visualized using restricted cubic splines by entering the CHESS criteria as a continuous variable into the Cox proportional hazard regression analysis by "rms" packages. Two cutoffs selected from CHESS criteria according to break-point estimation method from "segmented" packages were used to divide restricted cubic splines to three segment which was defined as Grade 1, 2, and 3, respectively. Pairwise comparisons using log-rank test revealed that any two grades had the distinguished incidence of hepatic decompensation. Prognostic accuracy for hepatic decompensation was compared with the models [1, 6, 13, 14] of ALBI-FIB-4, ALBI, LSM > 20 kPa, MELD and $PLT \leq 150 \times 10^9/L$ using time-dependent area under operative characteristic curve (tAUC) at 3 years. The diagnostic accuracy of these models to predict CSPH were compared using the receiver's operating characteristics (ROC). All analyses were conducted using SPSS V.19.0 (IBM, Somers, New York, USA) and R V.4.1.0 (R core team) with the add-on packages rms, segment, time ROC, pROC and cmprsk.

Study outcomes

The primary outcome of this study was the time to the first hepatic decompensation (ascites, variceal bleeding, or hepatic encephalopathy) [4, 18]. Ascites was defined by compatible signs on examination and was confirmed by ultrasonography or paracentesis. Variceal bleeding was diagnosed according to the Baveno VI criteria.[16] Hepatic encephalopathy was defined as West-Haven grade 3-4 determined by specialist or requiring admission [19]. CSPH was defined as HVPG ≥ 10 mmHg.

Results

Baseline characteristics

A total of 1377 cACLD patients were enrolled in the study from China, Japan, Southern Korea, Egypt, Singapore, and India between January 2009 and August 2021. The training cohort consisted of 586 patients who were consecutively included from China and Japan; the validation cohort consisted of 532

patients consecutively included from Singapore, South Korea, and Egypt; and the cross-sectional HVPG cohort comprised 259 patients from India and China. The mean ages were 55.1 ($\pm$ 12.9), 53.2 ($\pm$ 10.7), and 53.0 ($\pm$ 10.4) years in the training, validation, and HVPG cohorts, respectively. The median follow-up time was 38.2 (26.4-45.3) and 44.6 (25.7-68.1) months in training and validation cohorts, respectively. The mean HVPG was 12.0 (3.5) mmHg in HVPG cohort. Baseline characteristics of three cohorts were summarized (Table 1, **Supplementary Table 1**).

Table 1
Baseline characteristics in training and validation cohorts

Parameters	Training cohort (n = 586)	Validation cohort (n = 532)
Age, years	55.1 (12.9)	53.2 (10.7)
Male	327 (55.8)	400 (75.2)
Creatinine, $\mu\text{mol/L}$	64.4 (40.6)	95.3 (91.0)
INR	1.1 (0.1)	1.1 (0.1)
LSM, kPa	20.2 (13.9)	19.0 (13.0)
Albumin, g/L	41.1 (5.6)	41.3 (4.2)
Total bilirubin, $\mu\text{mol/L}$	20.0 (12.2)	17.9 (14.9)
ALT, U/L	57.3 (60.1)	59.4 (48.8)
AST, U/L	57.2 (58.2)	55.4 (35.6)
PLT, $\times 10^9/\text{L}$	126.7 (52.2)	157.8 (71.0)
Varices	264 (45.1)	130 (24.4)
MELD	8.7 (2.7)	8.6 (2.9)
Etiology		
Viral hepatitis	402 (68.6)	434 (81.6)
NASH	66 (11.2)	39 (7.3)
Alcohol	41 (7.0)	23 (4.3)
AIH	12 (2.0)	4 (0.7)
PBC	11(1.8)	5 (0.9)
Other	54 (9.2)	27 (5.1)
Follow-up, months	38.2 (26.4-45.3)	44.6 (25.7-68.1)
Data are presented as the means (standard deviations), median (IQR), or n (%). Abbreviations: AIH, Autoimmune Hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HVPg, hepatic venous pressure gradient; INR, international normalized ratio; IQR, interquartile range; LSM, liver stiffness measurement; NASH, non-alcoholic steatohepatitis; MELD, model of end-stage liver disease; PBC Primary Biliary Cholangitis; PLT, platelet count.		

Univariate and multivariate Cox proportional hazard regression analyses

In the training cohort, 74.6% (437/586) of cACLD patients had unfavorable Baveno VI criteria (LSM > 20 kPa or PLT < $150 \times 10^9/\text{L}$). We performed Cox proportional hazard regression analyses to investigate the

independent factors of developing into hepatic decompensation. In the univariate analyses, 13 variables were involved for the analysis (Table 2), and age, international normalized ratio (INR), MELD, LSM, albumin, total bilirubin, ALT, PLT, and varices presented the statistical significances ($p < 0.05$). In the multivariate analyses with forward likelihood ratio method, LSM, PLT, albumin, ALT, and varices were eventually presented the significant differences ($p < 0.05$), which indicated that these 5 variables were independent factors for hepatic decompensation.

Table 2
Risk factors for hepatic decompensation in training cohort

Parameters	Univariate analyses		Multivariate analyses	
	HR	p value	HR	p value
Age	1.028 (1.009 - 1.048)	0.005	-	-
BMI	0.996 (0.953 - 1.040)	0.847	-	-
Creatinine	0.998 (0.987 - 1.009)	0.715	-	-
INR	67.239 (15.348 - 294.578)	< 0.001	-	-
MELD	1.150 (1.081 - 1.224)	< 0.001	-	-
Male	1.087 (0.708 - 1.669)	0.704	-	-
LSM	1.046 (1.035 - 1.057)	< 0.001	1.036 (1.023 - 1.050)	< 0.001
Albumin	0.878 (0.843 - 0.914)	< 0.001	0.934 (0.893 - 0.976)	0.003
Total bilirubin	1.025 (1.013 - 1.038)	< 0.001	-	-
ALT	0.987 (0.979 - 0.995)	0.001	0.984 (0.976 - 0.992)	< 0.001
AST	0.995 (0.990 - 1.001)	0.083	-	-
PLT	0.985 (0.979 - 0.993)	< 0.001	0.987 (0.981 - 0.994)	< 0.001
Varices	4.161 (2.444 - 7.083)	< 0.001	1.918 (1.904 - 3.363)	0.023
Data are presented with 95% confidence interval. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; LSM, liver stiffness measurement; MELD, model of end-stage liver disease; PLT, platelet count.				

Establishment and performances of CHESS criteria and ABC model in training cohort

These independent factors for the prediction of hepatic decompensation were included to develop the CHESS criteria as following formula: $(0.036 \times \text{LSM [kPa]}) + (-0.013 \times \text{PLT [10}^9/\text{L]}) + (-0.068 \times \text{Albumin [g/L]}) + (-0.016 \times \text{ALT [U/L]}) + (0.651 \times \text{Varices [present: 1, absent: 0]})$. This model showed the lower information criterion (AIC 827 and BIC 840, **Supplementary Table 2**), which indicated that the model was parsimonious and not over fitted. Two cutoff values were determined from the CHESS criteria according

to the break-point of regression models estimation method, i.e., -4.4 and -3.1 (Figure 1). The < -4.4, -4.4 to -3.1 and > -3.1 indicated the low risk, medium risk, and high risk of developing into hepatic decompensation, with a 3 year-tAUC of 0.851 (0.800-0.901), (**Supplementary Table 3**). In training cohort, the risks of hepatic decompensation in low risk, medium risk, and high risk groups were 1.4%, 8.7% and 47.6%, respectively.

Taking the cACLD patients with Grade 0 as the reference, Grade 2 and Grade 3 groups presented significant higher rates of cumulative incidences of hepatic decompensation, excepting Grade 1 (Grade 0 vs Grade 1, HR = 3.1 [0.3-29.2], p = 0.311, Grade 0 vs Grade 2, HR=11.3 [1.5-86.8], p = 0.019; Grade 0 vs Grade 3, HR= 74.5 [10.3-536.6] p < 0.001; Figure 2A). Pairwise comparisons in four grades also showed significant difference in rates of hepatic decompensation (all p adjust < 0.05), except for comparison of Grade 0 and Grade 1 (p adjust = 0.294). Meanwhile, when taking the cACLD patients who met the Baveno VI criteria (Grade 0) and Grade 1 together as the reference (low risk), Grade 2 (medium risk) and Grade 3 (high risk) groups still presented significant higher rates of cumulative incidences of decompensation (low risk vs medium risk, HR = 5.6 [1.8-17.2], p = 0.003; low risk vs high risk, HR = 36.8 [13.4-101.0], p < 0.001; Figure 2B).

Additionally, ALBI-FIB-4, ALBI, LSM > 20 kPa, MELD, and PLT < 150 × 10⁹/L had the 3-year tAUCs of 0.754 (0.688-0.820), 0.702 (0.629-0.775), 0.687 (0.626-0.745), 0.645 (0.570-0.720), 0.632 (0.594-0.671), respectively. Comparing the ABC model with above-mentioned 5 models, all the differences were statistically significant (**Supplementary Table 3**, Figure 3A).

Performances of the ABC model in validation cohort

In validation cohort, when taking the cACLD patients with Grade 0 as the reference, Grade 2 and Grade 3 groups presented significant higher rates of cumulative incidences of hepatic decompensation, excepting Grade 1 (Grade 0 vs Grade 1, HR = 1.1 [0.2-7.7], p = 0.935; Grade 0 vs Grade 2, HR = 7.8 [1.7-36.7], p < 0.009; Grade 0 vs Grade 3, HR = 27.9 [6.4-121.3], p < 0.001; Figure 2C). Meanwhile, when taking the cACLD patients who met the Baveno VI criteria (Grade 0) and Grade 1 together as the reference (low risk), Grade 2 (medium risk) and Grade 3 (high risk) groups still presented significant higher rates of cumulative incidences of hepatic decompensation (low risk vs medium risk, HR = 7.5 [2.3-24.9], p = 0.001; low risk vs high risk, HR = 26.8 [9.0-80.2], p < 0.001; Figure 2D).

Additionally, the 3-year tAUCs of ABC model for the prediction of hepatic decompensation was 0.843 (0.742-0.943). Comparing with ALBI-FIB-4, ALBI, LSM > 20 kPa, MELD, and PLT < 150 × 10⁹/L that had the 3-year tAUCs of 0.720 (0.586-0.854), 0.710 (0.578-0.842), 0.718 (0.618-0.819), 0.537 (0.385-0.688), 0.665 (0.576-0.753), respectively. The tAUCs of ABC model was significantly higher than all the above-mentioned 5 models (**Supplementary Table 3**, Figure 3B).

Performance of the ABC model to predict CSPH in HVPG cohort

In HVPg cohort, the ABC model can be used to diagnose the CSPH with an AUC of 0.818 (Figure 4A). The AUC of ABC model was higher than above-mentioned 5 models to diagnose CSPH (Figure 4A). The ideal cut-off of ABC model to diagnose CSPH was -4.1. Notably, the positive predictive value of high risk group to diagnose CSPH was 0.930. Accordingly, the median values of HVPg in low risk, medium risk, and high risk groups was 10.0 (IQR: 4.0), 12.0 (IQR: 4.0) and 13.0 (IQR: 4.0) mmHg, respectively (Figure 4B).

Discussion

Given the difficulty in distinguishing between severe fibrosis and compensated cirrhosis in clinic, the Baveno-VI consensus has proposed the terminology of cACLD to identify advanced liver disease patients at risk of liver decompensation [1, 6]. Cirrhosis can be divided into compensated and decompensated types, the former is commonly asymptomatic, and the latter is symptomatic with the presence of one or more complications of portal hypertension, including ascites, variceal bleeding, hepatic encephalopathy [6]. The development of hepatic decompensation is the main determinant of survival in patients with cACLD. Therefore, discriminating the probability of hepatic decompensation is an important unmet need in cACLD patients. In this international, multicenter cohort study, we found that the ABC model can stratify the decompensation risk in cACLD patients.

While several non-invasive models have been proposed to predict hepatic decompensation [15], however, only few of them have been widely validated in cACLD patients [1]. LSM is a useful non-invasive predictor of liver decompensation in cACLD patients [1, 13], with the accuracy similar to that of HVPg for predicting decompensation in previous studies [10, 20]. Compared with the parameter like LSM [1], controlled attenuation parameter [11, 21], PLT [22], albumin [8], and parameters combinations and models were also employed to predict hepatic decompensation, such as ALBI and FIB-4 [14]. More importantly, the existing non-invasive criteria has not been validated to identify cACLD patients. It was also unclear if these criteria correlate well with HVPg measurement among cACLD patients.

Currently, LSM at diagnosis was recommended as a non-invasive tool to stratify the risk of hepatic decompensation in patients with cACLD by the 2021 updated EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis [1]. However, how to apply LSM to predict hepatic decompensation has not been explained thoroughly. The proposed usage indicates that cACLD patients who had either the $LSM > 20 \text{ kPa}$ or $PLT < 150 \times 10^9/L$ should perform screening endoscopy as well as HVPg measurement. Our finding suggests both the CHESS criteria and HVPg has complementary role in risk stratification of cACLD patients.

In the current study, we employed three screening endoscopy-performed cohorts to demonstrate the above-mentioned hypothesis. In training cohort, the cACLD patients unfavorable Baveno VI criteria were used to develop the CHESS criteria, which categorized cACLD patients into low risk (< -4.4), medium risk (-4.4 to -3.1), and high risk (> -3.1) of developing hepatic decompensation. During the median follow-up period of 38.2 (26.4-45.3) months in training cohort, we found that low risk group indeed has low risk of hepatic decompensation. Meanwhile, high risk group had significant higher incidence of hepatic

decompensation during follow-up (Figure 2). Additionally, these findings were demonstrated in the independent validation cohort (Figure 2). Notably, ABC model has significantly better performance over other models (ALBI-FIB-4, ALBI, LSM > 20 kPa, MELD or PLT < $150 \times 10^9/L$) in predicting the 3-year hepatic decompensation in both training and validation cohorts (**Supplementary Table 3**, Figure 3). Most importantly, after using the ABC model to diagnose CSPH in the HVPG cohort, it was found that the diagnostic performance was also better than that of existing models and parameters (Figure 4). Besides, the high risk group with positive predictive value of 0.930 could be used to rule in CSPH.

For clinical usage of the ABC model, in detail, after screening by Baveno VI criteria and endoscopy, cACLD patients who had the CHESS criteria < -4.4 can be regarded and managed as those of who met the Baveno VI criteria (**Supplementary Figure 1**). The CHESS criteria > -3.1 can be regarded and managed as those of CSPH patients and entered into non-selective β -blockers intervention directly according the PREDESCI study [23]. In other words, the HVPG measurement can be waived for both low risk and high risk groups of cACLD, and the remaining medium risk patients should be further evaluated by the HVPG measurement (**Supplementary Figure 2**).

We acknowledged that there are limitations in our study. First, this study is retrospective, and the long time period of inclusion of this study might influence the results. Second, cACLD patients had different etiologies, mostly focusing on viruses, non-alcoholic steatohepatitis, and alcohol, and the three cohorts did not have the equal proportion of the corresponding etiologies. However, on the other hand, these limitations exactly reflect various real-life scenarios to some extent, and on the contrary, may strengthen its applicability and validity in real-life practice.

In conclusion, this multicenter cohort study demonstrates the ABC model to stratify decompensation risk in patients with cACLD. HVPG evaluation can be waived in both low risk and high risk cACLD patients as they can be directly managed by Baveno VI criteria and non-selective β -blockers intervention, respectively, and the remaining medium risk patients need further HVPG evaluation.

Declarations

Conflict of Interest (Col) statements

All the authors declare that they have no conflict of interest.

Informed Consent in Studies with Human Subjects

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Conflict of interest

None.

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Supplementary Figure

Supplementary Figure 2 is not available with this version.

Figures

Figure 1

Association of CHESS criteria with hepatic decompensation in cACLD patients unfavorable Baveno VI criteria.

Figure 2

Cumulative incidence of hepatic decompensation in training and validation cohorts.

A and C: Grade 0 group included the patients who met the Baveno VI criteria. B and D: Low risk group included patients in the subgroups of Grade 0 and Grade 1.

Figure 3

Comparisons of different models for predicting hepatic decompensation in training (A) and validation (B) cohorts.

ABC, Algorithm based on Baveno VI criteria plus CHESS criteria; ALBI-FIB-4, albumin-bilirubin (ALBI) and fibrosis-4 (FIB-4); LSM, liver stiffness measurement; MELD, model of end-stage liver disease; PLT, platelet count.

Figure 4

Area under the curve of different models for prediction of clinically significant portal hypertension (A) and comparisons of HVP levels throughout the different risk groups in HVP cohort (B).

HVP, hepatic venous pressure gradient; ABC, Algorithm based on Baveno VI criteria plus CHES criteria; ALBI-FIB-4, albumin-bilirubin (ALBI) and fibrosis-4 (FIB-4); LSM, liver stiffness measurement; MELD, model of end-stage liver disease; PLT, platelet count.

Supplementary Files

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