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Original Article

Nucleoside analogues improve short-term prognosis of HBV-related acute-on-chronic liver failure but as not an independent risk factor

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Abstract: Aim: To evaluate the effects of nucleoside analogue (NAs) treatment in improving short-term prognosis of patients with HBV-related acute-on-chronic liver failure (ACLF) and to investigate factors predicting mortality. Methods: In 132 patients hospitalized with HBV-related ACLF, 35 patients were in NAs treatment (NAs group) while 97 patients received NAs after admission (late NAs group). All patients were followed up for 12 months. Child-Turcotte-Pugh (CTP), a model for end-stage liver disease (MELD), and MELD-Na scores with other characteristics and short-term mortality were evaluated. Logisitic regression, COX regression, and Kaplan-Meier analysis were used to determine independent predictors of short-term mortality and overall survival. ROC analysis was used to validate diagnostic power of score systems and their simplification and combination with significant indexes. Results: NAs group showed lower creatinine and higher serum sodium levels, with decreased rates of cirrhosis, gastrointestinal bleeding, and general complications. Mortality in the NAs group was lower at each time point ($P < 0.001$). Logistic regression showed that only NAs treatment was an independent risk factor within 180 days and 1 year. PT was an independent risk factor for overall survival, with only a slight influence. According to ROC analysis, MELD-Na performed better than CTP and MELD scores. Binary transformation of the MELD-Na score in a cut-off value of 26 with combination of NAs treatment showed familiar diagnostic power with MELD-Na scores. Conclusion: NAs improved short-term survival in HBV-related ACLF. NAs treatment might not be an independent factor to predict short-term mortality within 90 days. MELD-Na scores have superior diagnostic power, while binary transformation combination performed closely.

Keywords: Acute-on-chronic liver failure, chronic hepatitis B, nucleoside analogues, prognosis, short-term mortality

Introduction

Hepatitis B virus (HBV) infection is a worldwide health problem, with over 400 million new affected cases and nearly 1 million deaths every year. This infection causes serious diseases, including chronic hepatitis B (CHB), cirrhosis, hepatocellular carcinoma (HCC), and liver failure [1]. Acute-on-chronic liver failure (ACLF) is a clinical syndrome with acute deterioration of chronic liver disease, resulting in jaundice and coagulopathy, with other complications, including hepatic encephalopathy, ascites, and hepatorenal syndromes. ACLF is a leading cause of death for CHB, worldwide, due to various manifestations and high rate of short-term mortality [2-5]. Common antiviral agents, like nucleoside analogues (NAs), prevent further cirrhosis, liver failure, and HCC in addition to recovery of physiological function [6, 7].

HBV-related ACLF is the most prevalent liver failure in China. Unfortunately, available medical treatments are limited. Bioartificial livers and orthotopic liver transplantation are suitable [8-10] with inevitable limitations, including shortages of plasma and donor livers, host versus graft reaction(HVGR) or graft versus host reactions (GVHR), repeated viral infections, and

heavy financial costs [11, 12]. This present study was conducted to understand the potential of NAs in reducing liver-related complications and mortality and to determine significant factors predicting mortality in HBV-related ACLF patients.

Patients and methods

Patients

This study was conducted on a retrospective cohort, from January 2012 to July 2016, enrolling 132 patients (95 males and 37 females) diagnosed with HBV-related ACLF, with an average age of 46.6±12.8 years. All patients were admitted to the Department of Infection and Liver Diseases, the First Affiliated Hospital of Wenzhou Medical University, for an acute liver failure with chronic hepatitis B. Diagnosis of HBV-related CHB and ACLF were performed, according to consensus recommendations from the Asian Pacific Association for the study of liver (APASL) in 2014 [13]. CHB is defined as an HBV carrier with a clinical course of hepatitis B infection for over 6 months, with symptoms of hepatitis and abnormal liver function, with/without histological changes. ACLF in patients with chronic HBV infections is known to have an acute hepatic insult, manifesting with jaundice (bilirubin ≥ 5 mg/dl) and coagulopathy when international normalized ratio (INR) ≥ 1.5, ascites for 4 weeks, and/or hepatic encephalopathy. Patients were excluded from this study if they had suffered or were superinfected with other viruses (hepatitis A, C, D and E), human immunodeficiency virus (HIV), history of alcohol abuse, autoimmune responses, toxic or other causes of chronic liver failure, with coexistent hepatocellular carcinoma (HCC), liver transplantations, and serious diseases in other organ systems.

The starting date of the follow-up period was the date of diagnosis of HBV-related ACLF. All patients were followed up for at least 1 year to assess short-term mortality. Informed consent was obtained from each patient enrolled in this study and all procedures were approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University. This study was performed according to the Declaration of Helsinki, ethical principles regarding human experimentation.

General management in patients

A total of 132 patients were given standard medical treatment, including absolute bed rest, energy and vitamin supplements, intravenous infusions of albumin, antibiotics, or plasma, maintenance of water, electrolytes, and acid-base equilibrium, along with preventive medication and treatment of complications. Due to an extreme shortage of plasma and lack of available donors, the artificial liver support system was not carried out regularly for this study, neither was orthotopic liver transplantation.

Antiviral treatment in patients

All 132 patients associated with HBV-related acute-on-chronic liver failure were admitted to the hospital. All included patients met antivirus therapy standards, according to APASL guidelines. Of the 132 patients, 35 patients received persistent NAs treatment, including lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LDT), and tenofovir disoproxil fumarate (TDF), at least one year before they suffered ACLF. The other 97 patients did not choose NAs therapy, due to poor compliance, ignorance of the disease, or other personal reasons. Patients that did not take NAs therapy were mandatorily given NAs after admission into the hospital. Patients with NAs treatment were still given the same standard medical treatment as the others and were switched to NAs combination therapy if they met the HBV virological breakthrough. Of these 35 patients, there were 28 males and 7 females, with an average age of 46.6±13.7 years. Patients administrated pegylated interferons or receiving antiviral therapy after hospital admission were not included in this study. No one discontinued the nucleoside analogue treatment during hospitalization.

Baseline assessment of patients

Retrospectively collected data included physical examination, clinical, laboratory tests, and abdominal ultrasound scanning. Data collection was performed within the first 24 hours after admission.

Laboratory parameters, including serum total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), γ-glutamyl transferase (γ-GT), alkaline phosphatase (AKP), albumin

Table 1. Demographic data and baseline characteristics among HBV-related ACLF patients at admission

Variables	NAs treatment (n = 35)	Late NAs treatment (n = 97)	P
Age (years)	46.6±13.9	46.6±12.5	0.984[b]
Age ≥ 50 (%)	15/35 (42.9%)	41/97 (42.3%)	0.952[a]
Gender (male/female)	28/7	67/30	0.217[a]
Cirrhosis (%)	9/35 (25.7%)	48/97 (49.0%)	0.015[a]
Ascites (%)	14/35 (40%)	51/97 (52.6%)	0.072[a]
Encephalopathy (%)	3/35 (8.6%)	18/97 (18.6%)	0.166[a]
Gastrointestinal bleed (%)	0/35 (0%)	17/97 (17.5%)	0.018[e]
Spontaneous peritonitis (%)	1/35 (2.9%)	12/97 (12.4%)	0.198[e]
Hepatorenal syndrome (%)	0/35 (0%)	4/97 (4.1%)	0.573[f]
General complications (%)	15/35 (42.9%)	70/97 (72.2%)	0.002[a]
HBsAg (%)	33/35 (94.3%)	87/97 (89.7%)	0.640[e]
ALT (U/L)	308.1 (36-1474)	291.1 (13-2060)	0.459[d]
AST (U/L)	295.1 (56-1472)	247.1 (31-1580)	0.475[d]
TBiL (μmol/L)	256.8±141.4	302.5±192.3	0.201[b]
γ-GT	97.3 (19-295)	99.9 (15-514)	0.608[d]
AKP (U/L)	138.1 (46-389)	131.8 (8-461)	0.661[d]
ALB (g/L)	29.5±5.6	30.0±6.1	0.705[b]
BUN (mmol/L)	4.5 (1.2-11.8)	7.0 (0.8-113)	0.122[d]
Creatinine (μmol/L)	59.5 (33-142)	71.5 (22-294)	0.017[d]
WBC (10^9/L)	7.6 (2.8-29)	8.3 (1.9-42)	0.426[d]
N# (10^9/L)	4.7 (0.8-23.8)	5.4 (0.7-16.2)	0.246[d]
PLT (10^9/L)	113.5 (32-206)	107.1 (17-340)	0.115[d]
Hb (g/L)	118.8±17.8	114.1±24.4	0.298[b]
PT (s)	26.5 (15.8-44.9)	30.7 (13.1-72.7)	0.152[d]
PTA (%)	34.2±10.4	31.2±11.3	0.167[b]
INR	2.4 (1.36-4.00)	2.9 (1.08-6.93)	0.112[d]
AFP (μg/L)	264.4 (0.7-2176.4)	183.3 (1.8-1623.9)	0.118[d]
Serum sodium (mmol/L)	138.0 (128-145)	134.4 (113-149)	< 0.001[d]
HBV-DNA(log) (s * (Log10 IU/mL))	5.37±2.02	5.44±2.25	0.868[b]
28 d Mortality (%)	0/35 (0%)	19/97 (19.6%)	0.005[a]
90 d Mortality (%)	2/35 (5.7%)	27/97 (27.8%)	0.007[a]
180 d Mortality (%)	2/35 (5.7%)	28/97 (28.9%)	0.005[a]
1 year Mortality (%)	2/35 (5.7%)	32/97 (33.0%)	0.002[a]
MELD scores	21.18±4.49	24.52±7.00	0.002[c]
MELD-Na scores	21.8 (14.09-37.18)	28.54 (2.66-60.71)	< 0.001[d]
Child scores	9.86 (7-13)	10.4 (7-14)	0.020[d]

a: X^2 test; b: T test; c: adjusted T test; d: M-W-U test; e: adjusted X^2 test; f: Fisher's exact test.

(ALB) levels, renal function tests with blood urea nitrogen (BUN), and serum creatinine were collected. Routine blood tests with white blood cell counts, neutrophilic granulocyte counts (N#), and platelet counts (PLT), hemoglobin levels (Hb), coagulation profiles, including prothrombin time (PT), prothrombin activity (PTA), and INR, along with α-fetoprotein (AFP) levels and serum electrolyte levels, such as serum sodium and HBV serologic markers, were collected from each patient (AXSYM; Abbott, Abbott Park, IL). Serum HBV DNA was measured by quantitative polymerase chain reaction assay (Roche Amplicor, limit of detectability of 100 IU/mL; Roche Diagnostics, Basel, Switzerland) after admission. Encephalopathy, gastrointestinal bleeding, spontaneous peritonitis, hepatorenal syndrome, and general complications were recorded before treatment.

Table 2. Univariate analysis of baseline predictors of survival of patients with HBV-related ACLF

Variables	28 days survival (n = 19:113)	90 days survival (n = 29:103)	180 days survival (n = 30:102)	1 year survival (n = 34:98)
Age	0.064	0.129	0.113	0.074
Gender	0.467	0.598	0.516	0.499
TBiL (μmol/L)	0.023	0.027	0.028	0.017
ALT (U/L)	0.750	0.876	0.965	0.705
AST (U/L)	0.815	0.129	0.155	0.297
AKP (U/L)	0.999	0.901	0.935	0.689
γ-GT	0.718	0.993	0.860	0.652
ALB	0.290	0.160	0.224	0.273
BUN (mmol/L)	0.752	0.906	0.939	0.168
Cr (μmol/L)	0.369	0.536	0.546	0.333
AFP	0.564	0.557	0.487	0.310
INR (%)	0.254	0.108	0.138	0.032
PT (s)	0.237	0.092	0.120	0.040
PTA (%)	0.615	0.368	0.411	0.171
Serum sodium (mmol/L)	0.005	0.003	0.002	< 0.001
WBC (10^9/L)	0.818	0.440	0.598	0.562
N# (10^9/L)	0.337	0.068	0.105	0.061
PLT (10^9/L)	0.882	0.909	0.958	0.698
Hb (g/L)	0.133	0.251	0.185	0.038
HBV-DNA(log)	0.794	0.961	0.921	0.761
HBsAg (%)	0.814	0.643	0.602	0.456
NAs treatment	0.998	0.015	0.013	0.006
Cirrhosis	0.021	0.023	0.013	0.013
Spontaneous peritonitis	0.355	0.140	0.163	0.004
Gastrointestinal bleed	0.685	0.868	0.933	0.712
Ascites	0.021	0.007	0.005	0.007
Encephalopathy	0.493	0.725	0.661	0.824
Hepatorenal syndrome	0.547	0.197	0.213	0.056
General complications	0.161	0.063	0.048	0.038
MELD scores	0.064	0.022	0.024	0.003
MELD-Na scores	0.005	0.002	0.002	< 0.001
Child Pugh scores	0.924	0.719	0.923	0.909

Demographic and clinical characteristics were displayed by using CTP, MELD and MELD-Na scores (with high scores indicating more severe illness) to evaluate the prognosis of recruited patients. CTP scores were assessed according to standard criteria published previously [14]. MELD scores were calculated according to the Malinchoc formula: MELD score = 3.78 * ln [total bilirubin (mg/dl)] + 11.2 * ln INR + 9.57 *ln [creatinine (mg/dl)] + 6.43 * (constant for liver disease etiology: 0 if cholestatic or alcoholic, 1 otherwise) [15]. MELD-Na scores [16] were calculated using MELD + 1.59 * [135-Na (mmol/L)], with the maximum and minimum Na values of 135 and 120 mmol/L, respectively.

Statistical analysis

All continuous variables are expressed by mean ± standard deviation (SD) or medians or interquartile ranges. Categorical values are described by counts and proportions. In univariate analysis, categorical variables were analyzed using the Chi-square test or Fisher's exact test, depending on minimum expected values. Comparison of continuous variables was analyzed using Student's *t*-test or nonparametric Mann-Whitney U-test. Variables statistically different between the groups in univariate analysis were subjected to multivariate analysis if *p* values achieved in univariate analysis were ≤ 0.05. Logistic regression was applied to determine independent predictors associated with short-term mortality. Kaplan-Meier test with Breslow method and COX regression were performed to evaluate risk factors for overall survival. ROC curve was performed to compare the diagnostic power of relevant variables. All data analyses were performed using SPSS 21 (Chicago, IL) and *p* values < 0.05 are considered significant.

Results

Comparison between NAs group and late NAs group

In this study, a total of 132 patients with HBV-related ACLF were included. A total of 35 pa-

Table 3. Multivariate analysis of baseline predictors of survival of patients with HBV-related ACLF

Variables	28 days survival (n = 19:113)	90 days survival (n = 29:103)	180 days survival (n = 30:102)	1 year survival (n = 34:98)
TBiL (μmol/L)	0.059	0.118	0.057	0.091
INR (%)	N/A	N/A	N/A	0.956
PT (s)	N/A	N/A	N/A	0.742
Serum sodium (mmol/L)	0.186	0.249	0.293	0.168
Hb (g/L)	N/A	N/A	N/A	0.465
NAs treatment	N/A	0.081	0.046	0.046
Cirrhosis	0.354	0.777	0.647	0.965
Spontaneous peritonitis	N/A	N/A	N/A	0.083
Ascites	0.251	0.130	0.056	0.099
General complications	N/A	N/A	0.147	0.157

N/A: not available.

Table 4. COX regression and Kaplan-Meier analysis of baseline predictors for survival of patients with HBV-related ACLF

Variables	COX-Uni	COX-Multi	Kaplan-Meier
Age >50	0.252		0.257
Gender	0.553		0.529
HBV-DNA	0.273		0.751
HBsAg	0.497		0.661
NAs treatment	0.001	0.060	< 0.001
Cirrhosis	< 0.001	0.483	0.001
Spontaneous peritonitis	0.012	0.351	0.018
Gastrointestinal bleed	0.010	0.362	0.149
Ascites	0.002	0.814	0.001
Encephalopathy	0.177		0.687
Hepatorenal syndrome	0.010	0.064	0.030
General complications	< 0.001	0.386	0.002
Age	0.003	0.192	
HBV-DNA(log)	0.806		
ALT	0.547		
AST	0.290		
ALB	0.141		
ALP	0.867		
GGT	0.681		
AFP	0.324		
WBC	0.717		
N#	0.197		
HB	0.031	0.422	
PLT	0.105		
PT	< 0.001	0.022	
PTA	< 0.001	0.500	
INR	< 0.001	0.081	
TB	0.044	0.443	
BUN	0.057		
SCR	0.230		
Serum sodium	0.002	0.575	

tients used nucleoside analogues treatment before hospital admission (26.5%). **Table 1** shows the basic characteristics of patients with or without nucleoside analogue antiviral therapy. Patients in the NAs group had lower levels of serum creatinine and higher levels of serum sodium, compared to the late NAs group (**Table 1**). There were no significant differences in the baseline characteristics of age, gender, serum TBiL, ALT, AST, γ-GT, AKP, ALB, BUN, WBC, N#, PLT, Hb, PT, PTA, INR, AFP, HBV-DNA levels, and HBsAg proportion between these two groups. Patients suffering from ACLF receiving NAs treatment showed decreased rates of cirrhosis, gastrointestinal bleeding, and general complications, compared to the late NAs group. No significant differences in complications such as ascites, encephalopathy, spontaneous peritonitis, and hepatorenal syndrome were shown between the groups (**Table 1**).

According to Child Pugh, MELD, and MELD-Na scoring systems, the NAs group had lower Child Pugh, MELD, and MELD-Na scores than the late NAs group (P = 0.020, P = 0.002 and P < 0.001) (**Table 1**).

Follow up studies of more than 1 year showed that a total of 19, 29, 30, and 34 patients died in 28 days, 90 days, 180 days, and 1 year. In the NAs group, no patients died within 28 days and 2 patients died within 90 days, while no additional patients died after one year. In contrast, 19, 27, 28, and 32 patients died in 28 days, 90 days, 180 days and 1 year (**Table 1**).

Table 5. Comparison of score systems as prognostic predictors for patients with HBV-related ACLF

Variables/AUC	28 days survival	90 days survival	180 days survival	1 year survival
Child Pugh scores	.484	.477	.495	.507
MELD scores	.617	.639	.638	.670
MELD-Na scores	0.691	0.683	0.684	0.713
M26†	0.639	0.623	0.623	0.651
M26† with NAs treatment	0.661	0.647	0.658	0.676
M26† with Cirrhosis	0.670	0.615	0.628	0.619
M26† with both	0.670	0.615	0.628	0.619

†: Binary transformation of MELD-Na scores with cut-off value of 26.

Prognostic predictors associated with short-term mortality

Several baseline clinical and laboratory variables were analyzed and used to determine possible predictor criteria associated with 28-day, 90-day, 180-day and 1-year mortality. Univariate logistic regression analysis demonstrated that patients with cirrhosis base, ascites, higher TBil levels, and lower serum sodium had significantly greater death hazards at all time points. Late NAs treatment had significant differences in all time points, except for 28-day. Including all complications together, general complications only had significant differences in the latter two time points. Higher INR and PT with lower Hb levels and more spontaneous peritonitis only had a significantly greater death hazard in 1-year (**Table 2**). As the score systems are a combination of other indexes, these were not included in multivariate logistic regression analysis. Other indexes were included in the univariate logistic regression, showed that only NAs treatment was an independent factor at 180-day and 1-year time points. None of the indexes had significant differences at the other two time points (**Table 3**).

Risk factors of overall survival of patients with HBV-related ACLF

Familiar with prognostic predictor exploration, all relevant indexes were brought into survival analysis. Kaplan-Meier analysis showed that NAs treatment, cirrhosis, SBP, ascites, HRS, and general complications had significant differences. While running univariate COX regression, gastrointestinal bleeding, age, Hb, PT, PTA, INR, TBil, and serum sodium also had significant differences, besides the index above, which had already been screened out from Kaplan-Meier analysis. All indexes, with significant differences in univariate COX regression, were placed into multivariate COX regression, finding that PT was the only independent risk factor. However, the HR of PT was 1.084 (1.012~1.161), a very low value, indicating that higher PT only slightly influenced overall survival (**Table 4**).

ROC analysis

This study validated the diagnostic power of 3 common scoring systems in clinical practice, Child-Pugh scores, MELD scores, and MELD-Na scores. All 4 time points were assessed. Results showed that the AUC of Child-Pugh scores was from 0.484 to 0.507, AUC of MELD scores was from 0.617 to 0.670, and AUC of MELD-Na scores was from 0.691 to 0.713. MELD-Na scores were generally superior to the other 2 scoring systems (**Table 5**). Next, this study explored the cut-off value of MELD-Na scores at each time point, finding that most of the cut-off values were very close to 26, which is easy to calculate. Next, the feasibility of cut-off values in clinical practice was explored. Meld-Na in 26, also was called M26, got the AUC from 0.623 to 0.639 at each time point. This was attenuated more than the original one (**Table 5**; **Figure 1**). This study then analyzed significant risk factors, with multivariate analysis, that had not been included in MELD-Na scores. Results showed that NAs treatment and the base of cirrhosis had relatively the most diagnostic power (**Table 6**). Afterward, attempts were made to find a way to put this factor together with the M26. Data indicated that adding NA treatment with M26 could promote specificity without reduction of sensitivity. Adding cirrhosis with M26 could promote specificity significantly more than NA treatment, but with significant reduction in sensitivity. Putting these 3 factors together was generally familiar with sensitivity and specificity as with cirrhosis alone (**Table 7**; **Figure 1**).

Discussion

Chronic hepatitis B (CHB) and severe acute exacerbation are major leading causes associated to ACLF in China [17]. HBV replication causes severe liver damage. High virus load-

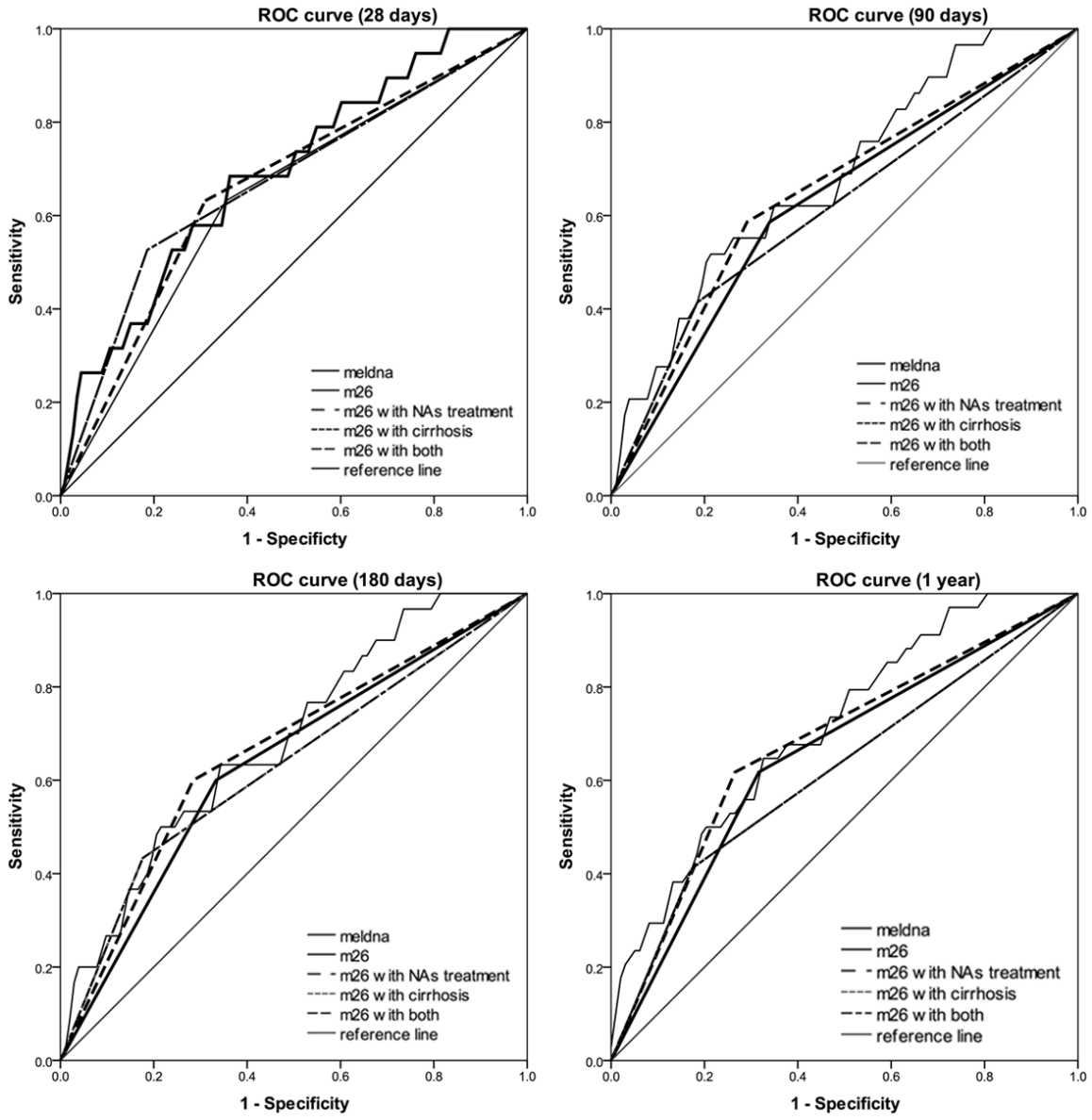

Figure 1. Comparison of AUC between MELD-Na scores, binary transformation of MELD-Na scores with cut-off value of 26 (M26), and combinations of M26 with other key indexes in the four time points.

ing is, therefore, linked to rapid progression and higher risk of HCC development [18]. Early antiviral therapy for CHB patients shortens the symptomatic phase of infection and allows for clinical and biochemical improvement [19, 20].

Previous studies have demonstrated that NAs treatment confers beneficial effects for biochemical, virological, and serological improvement in CHB patients [7, 21], as well as preventing cirrhosis, liver failure, and HCC, even for patients with decompensated liver diseases [6]. Recent studies have reported that NAs has effects that improve the status of patients with severe decompensated chronic liver disease and HBV-related ACLF [22-26]. However, there are studies showing that NAs treatment does not produce significant biochemical changes nor slow down progression of liver failure and acute exacerbation in CHB patients [27-29]. These inconsistent clinical results suggest that more studies are warranted.

The current study compared two groups of HBV-related ACLF patients with/without receiving

Table 6. AUC of risk factors out of the MELD-Na scores for patients with HBV-related ACLF

Variants	28 days	90 days	180 days	1 year
PT	0.525	0.570	0.561	0.587
HB	0.570	0.540	0.553	0.602
NAs treatment	0.655	0.626	0.628	0.639
Cirrhosis	0.647	0.621	0.630	0.625
Spontaneous peritonitis	0.535	0.547	0.544	0.592
Hepatorenal syndrome	0.513	0.525	0.524	0.539
Gastrointestinal bleed	0.517	0.506	0.503	0.512
General complications	0.585	0.596	0.601	0.601

NAs. Results showed that patients with CHB receiving NAs treatment had no significant differences in demographics (age, gender) and most laboratory parameters, compared to patients receiving NA therapy. However, the NAs group had decreased levels of creatinine and relatively higher levels of serum sodium, compared to the late NAs group, indicating that CHB patients receiving NAs treatment may have an improved liver and renal function when they suffer from severe acute exacerbation.

The NAs group displayed a smaller/lower proportion of symptoms and complications than the late NAs group, although few of them (cirrhosis, gastrointestinal bleeding, and general complications) were statistically significant. Importantly, this follow-up retrospective study showed that a total of 34 patients passed away within one year, making the mortality rate in NAs group (2/35 5.7%) significantly lower than the late NAs group (32/97 33%). This situation was also analogous to the remaining time points. The mortality rate was significantly higher in the late NAs group, compared to the NAs group, and most deaths happened within 90 days ($P = 0.005$, $P = 0.007$, $0 = 0.005$, $P = 0.002$ in each time point) (**Table 1**). Although mild changes in laboratory parameters and HBV virological breakthroughs were seen, patients with CHB accepting NAs therapy earlier may still prevent the short-term mortality and occurrence of complications effectively. HBV-DNA between the NAs group and late NAs group had no statistic differences, showing that most ACLF patients in the NAs group met the virological breakthrough (33/35). This indicates that HBV virological breakthroughs may be the main cause of ACLF in the NAs group. For patients diagnosed with severe liver disease associated with CHB, measurements of baseline serum bilirubin and creatinine levels and assessment of disease severity at the time of initiating antiviral treatment may be useful determinants of short-term mortality, even better than virological responses [30]. This may be explained by the observation that patients in the late NAs group, hospitalized and receiving NA therapy at a later stage, still encountered a higher mortality rate. Failure of HBV eradication at the early stages is likely another reason associated to high mortality in the late NAs group, as HBV continuously stimulates the body's immune system to recruit pro-inflammatory factors. Furthermore, elevated HBV-DNA loads continuously activate liver NK-T cells, thereby impairing liver regeneration capability [31].

Poor survival rates of HBV-related ACLF patients makes predicting disease severity and prognosis important. Classically, the CTP score has been used to stratify patients with cirrhosis based on biochemical and clinical evidence of decompensation [14, 32]. On the other hand, MELD scores, which reflect international normalized ratio (INR), bilirubin, and creatinine, have been reported to be closely associated with prognosis of patients with ACLF [33]. Nevertheless, MELD scores have been found inferior to CTP scores in predicting 3-month survival among CHB patients that developed liver related complications [34]. Addition of serum sodium scores (MELD-Na score) has been shown to improve MELD score performance [35, 36], initially developed and broadly used to predict survival after transjugular intrahepatic portosystemic shunts and subsequently validated in patients with decompensated liver cirrhosis. However, over the past decade, MELD scores have served as the method most widely to determine priority on the liver transplant waiting list for patients with end-stage liver disease [37-39]. The present study revealed that, although most of the index has no differences between patients in NAs and late NAs group, CTP, MELD and MELD-Na scores still had significant differences between these two groups. CHB patients that received NA treatment had lower MELD-Na scores, which may imply a priority on the liver transplant waiting list. While exploring the simplifica-

Table 7. Sensitivity and specificity of score system combinations as prognostic predictors for patients with HBV-related ACLF

Variables/AUC	Sensitivity				Specificity			
	28 days	90 days	180 days	1 year	28 days	90 days	180 days	1 year
MELD-Na	0.684	0.517	0.633	0.647	0.646	0.796	0.667	0.684
M26†	0.632	0.586	0.600	0.618	0.646	0.660	0.667	0.684
M26† with NAs treatment	0.632	0.586	0.600	0.618	0.690	0.709	0.716	0.735
M26† with cirrhosis	0.562	0.414	0.433	0.412	0.814	0.816	0.824	0.827
M26† with both	0.562	0.414	0.433	0.412	0.814	0.814	0.824	0.827

†: Binary transformation of MELD-Na scores with cut-off value of 26.

tion of MEL-Na scores, it was found that the attempt of transforming MELD-Na to a binary variable would cause the alleviation of diagnostic power. With the combination of other key indexes, especially NAs treatment, the AUC and Youden's index would restore to a familiar level (**Figure 1**). However, trying other indexes failed to act better than the original binary transformed MELD-Na scores. Thus, modification of MELD-Na scores may serve well for some specific clinical practice, but the MELD-Na score itself is still convincing and universally acknowledged with definite diagnostic power.

There were several findings debating the etiology of antiviral treatment with NAs for effectiveness in improving the prognosis of patients with HBV-related ACLF. Cui et al. found that NA therapy did not improve short-term prognosis of HBV-associated ACLF, although it was efficacious and safe in the management of HBV-DNA levels [40]. In contrast, Chen et al. reported, in 2012, that NA therapy may improve both short-term and the long-term prognosis of HBV-related ACLF patients [31]. Evidently, many studies have demonstrated that continuous antiviral treatment may prevent these patients from further recurrence and progression to HCC, which may benefit long-term survival [27, 41]. The current study found that early use of NAs can improve short-term prognosis of patients with HBV-related ACLF, significantly, from 28 days to 1 year. Although several indexes showed significant differences in univariate analysis, only NAs treatment had significant differences in multivariate analysis in 180-day and 1-year time slots, in agreement with other similar findings reported [40, 42]. However, it was found that, in shorter time points like 28-days and 90-days, in which most deaths happened, no indexes included in the multivariate analysis could be an independent risk factor. Also, in overall survival analysis, only PT filtered out as an independent risk factor, with only a slight influence in COX regression. This may indicate that, for short-term survival, all factors take part in the process of ACLF and influence each other. It must be noted that with or without NAs treatment, as a determinant of short-term mortality, is ambiguous. It is still necessary to beware of occurrence of ACLF and death among patients suffering from CHB with higher MELD-Na scores, with cirrhosis, and more complications without NAs treatment. Early commencement of antiviral treatment, preferably before the onset of jaundice, may prevent the dreadful complication of liver failure [29]. Antiviral treatment is still recommended for decompensated patients with possible liver transplantation as viral prophylaxis.

In conclusion, HBV-related ACLF is a serious disease, leading to high mortality. Patients with CHB that receive an early NA treatment may have lower MELD-Na scores, less complications, and improved short-term prognosis. Late NAs treatment, more complications, and high MELD-Na scores were associated with poor outcomes. However, NAs treatment may not be an independent risk factor for short-term mortality for patients with HBV-related ACLF, especially within 90 days.

The present study had several limitations, as it was a retrospective review of a single-center research on a small number of samples, with an inability to compare different groups of NA drugs due to a small number of patients. Compliance of patients in follow-ups was not collected, which may have influenced bias to some extent. Patients without NA therapy may not visit the hospital as regularly as those with NAs, which may lead them to a later diagnosis. However, as all patients with or without NAs

therapy have similar symptoms, differences between the groups were not to a considerable extent. In future investigations, larger sample sizes are necessary to validate the beneficial effects of early use of NA treatment in improving the prognosis of patients with HBV-related ACLF.

Disclosure of conflict of interest

None.

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