Original article

Pretreatment viral DNA stratifies mortality risk in patients receiving antiviral therapy for severe acute exacerbation of chronic hepatitis B

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Background: Prognostic factors have not been elucidated for severe acute exacerbation of chronic hepatitis B treated with antiviral therapy. This study aimed to explore the role of baseline viral load in predicting mortality.
Methods: This retrospective cohort study screened consecutive chronic hepatitis B patients (*n*=84) receiving antiviral therapy for severe acute exacerbation, defined as abrupt elevation of serum alanine aminotransferase >10× the upper limit of normal along with hyperbilirubinaemia. Survival pattern was evaluated by the Kaplan–Meier method and predictors for mortality determined by the Cox regression analysis.
Results: A total of 66 patients were eligible and followed-up for a median of 23 months (range 0.1–75.0). Overall, 20 (30.3%) patients died during the study period, with the vast majority (*n*=17) succumbing rapidly within 3 months of severe acute exacerbation. The multivariate Cox model revealed that mortality was associated with baseline viral DNA level (HR 1.49 per log copies/ml, 95% CI 1.13, 1.96), international normalized ratio for prothrombin time (HR 2.68 per unit, 95% CI 1.81, 3.98), platelet count (HR 0.87 per 10^4 cells/μl, 95% CI 0.78, 0.98) and age (HR 1.10 per year, 95% CI 1.05, 1.15). A significant interaction existed between viral DNA and prolonged prothrombin time (*P*=0.005). Stratified analyses further demonstrated that pronounced coagulopathy heralded death irrespective of viral load, whereas serum level of viral DNA stratified mortality risk among those without marked coagulopathy.
Conclusions: Pretreatment viral DNA level stratifies risk of death in patients with severe acute exacerbation of chronic hepatitis B before the manifestation of overt liver failure.

Introduction

Chronic infection with HBV is a major liver disease worldwide, affecting 350 million people globally [1]. Severe acute exacerbation is a unique complication of chronic hepatitis B (CHB), resulting from massive viral reactivation and subsequent immune clearance that leads to extensive hepatic necroinflammation [2–4]. Characterized clinically by abrupt elevation of serum aminotransferases along with jaundice, severe acute exacerbation of CHB is associated with substantial morbidity and mortality [5,6]. Although antiviral treatment with oral nucleoside/nucleotide analogues may improve survival, a number of treated patients still succumb to this devastating complication [7,8].

Outcome determinants for severe acute exacerbation of CHB have not been fully elucidated. It is imperative to identify patients at risk of poor prognosis as early as possible, because acute-on-chronic liver failure (ACLF) may ensue rapidly and result in death in a short period of time without timely liver transplantation [9,10]. Previously identified prognostic factors were parameters that represented severity of hepatic dysfunction such as serum bilirubin, albumin, prothrombin time, Child–Pugh classification and model for end-stage liver disease (MELD) score. Factors that indicate stage of underlying chronic liver disease (for example, cirrhosis and platelet count) might also be prognostic [6,7,11–13].

Nonetheless, not all fatal cases manifest with profound hepatic failure or have pre-existing cirrhosis. It remains unknown how to further stratify risk of death among patients with relatively preserved liver function at initial presentation.

The role of baseline HBV DNA in risk stratification has not been determined in CHB patients developing severe acute exacerbation. Earlier researches did not uncover associations between pretreatment viral DNA and risk of death, but methods of measurement used in prior studies were either qualitative or were insensitive [6,7]. By using PCR methods, Jeng *et al.* [14] were able to show that HBV DNA level predicted development of hepatic decompensation after episodes of acute exacerbation. Furthermore, Garg *et al.* [8] reported in a randomized controlled trial that reduction of viral load after 2 weeks of antiviral therapy correlated with chance of survival in patients with ACLF due to CHB. However, the relationship between pretreatment viraemic burden and risk of mortality in these vulnerable patients remains elusive. We therefore set to investigate the prognostic value of serum viral DNA level in CHB patients with severe acute exacerbation.

Methods

Study population

This retrospective cohort study was conducted in a regional teaching hospital in Taiwan (E-Da Hospital, Kaohsiung, Taiwan). By searching the computerized database that recorded all prescribed pharmacotherapy in this hospital, we were able to identify all CHB patients who received nucleoside/nucleotide analogues between November 2004 and February 2010. We then manually reviewed their medical records to screen the eligibility. Those who met all of the following inclusion criteria were enrolled: positive serum hepatitis B surface antigen (HBsAg) or unequivocal history of hepatitis B infection for >6 months, severe acute exacerbation defined as both abrupt elevation of serum alanine aminotransferase (ALT)>10× the upper limit of normal (ULN; 40 IU/l) and hyperbilirubinaemia with serum total bilirubin level >2×ULN (1.3 mg/dl) [15,16], antiviral treatment with any nucleoside/nucleotide analogue, and detectable serum HBV DNA before treatment. Patients meeting any of the following criteria were excluded from analysis: superinfection with other viral hepatitis (A, C, D or E), coinfection with HIV, confirmed or suspected liver diseases from aetiology other than HBV (for example, alcohol, toxin, drug, shock and autoimmune disorder), diagnosis of hepatocellular carcinoma, no data of pretreatment viral DNA and previous exposure to antiviral therapy. Cirrhosis was diagnosed principally on the basis of sonographic assessment [17]. Development of encephalopathy and/or ascites within 4 weeks of presentation defined the condition of ACLF [9]. The institutional review board of E-Da Hospital approved the protocol of this study (protocol identification EMRP-100-028).

Management and follow-up

All enrolled patients received antiviral therapy with nucleoside/nucleotide analogues. Generally the daily dosages were 100 mg for lamivudine, 0.5 mg for entecavir and 600 mg for telbivudine, but occasionally varied according to patients' conditions, such as renal insufficiency. During the enrolment period, tenofovir was unavailable and adefovir was only reimbursed for the indication of rescue therapy in patients developing drug resistance. Some patients might initially receive a short course of combination therapy with two agents at the discretion of treating physicians. Every patient continued antiviral therapy for a minimum of 1 year unless they died, acquired drug resistance, or were lost to follow-up. Add-on adefovir (10 mg per day) was administered to those who later developed drug resistance. All patients were managed with standard supportive care in addition to antiviral medication. This included intravenous fluid, antibiotics, lactulose, albumin, proton pump inhibitor and parenteral nutrition per individual indication. None of the enrolled participants underwent liver transplantation, which was unavailable during the study period in this hospital.

In general, patients were hospitalized until severe flares and hepatic dysfunction subsided. After discharge, they were followed-up on a monthly basis for physical and biochemical examinations to monitor hepatic function. The interval between outpatient visits might have been lengthened to 3–6 months in stabilized patients. The study cohort was followed-up until 1 September 2011.

Laboratory measurement

Serological tests (HBsAg, antibody against HBsAg, hepatitis B e antigen [HBeAg] and antibody against HBeAg) were determined by immunoassays (Abbott GmbH and Co., Wiesbaden, Germany). The upper limit in the semi-quantification of serum HBsAg was 250 IU/ml, as per the manufacturer's protocol. All pretreatment viral loads were measured by the quantitative method of branched DNA assay (Versant 440 Molecular System, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA), because the more sensitive real-time PCR method was not available until 1 May 2010 in E-Da Hospital. The detection range was 2,000–10^8 copies/ml for the branched DNA assay. The expression of viral DNA was logarithmically transformed, and undetectable HBV DNA was defined as 1 copy/ml (0 log copies/ml) and value beyond measurable range as 10^8 copies /ml. Serum HBV was tested for signature mutations

Table 1. Pretreatment characteristics of chronic hepatitis B patients with severe acute exacerbation

Characteristic	All patients (*n*=66)	Survivors (*n*=46)	Death (*n*=20)
Age, years	47.5 (37–57)	45 (35–53)	56.5 (50–69.5)[a]
Male gender, *n* (%)	54 (81.8)	40 (87.0)	14 (70)
HBeAg-positive, *n* (%)	22 (33.3)	17 (37.0)	5 (25)
HBV DNA, log copies/ml	7.12 (5.28–8.0)	6.76 (4.91–8.0)	7.71 (6.65–8.0)
HBsAg>250 IU/ml, *n* (%)	48 (72.7)	31 (67.4)	17 (85)
AST, IU/l	882 (462–1,436)	869 (459–1,280)	1,041.5 (494.5–1,773.5)
ALT, IU/l	1,066.5 (760–1,747)	1,081 (820–1,750)	968.5 (611.5–1,649.5)
Bilirubin, mg/dl	6.0 (3.2–12.7)	4.6 (2.8–10.8)	11.7 (6.3–15.6)[a]
INR	1.44 (1.19–1.76)	1.26 (1.13–1.47)	2.07 (1.63–3.39)[a]
Creatinine, mg/dl	1 (0.9–1.2)	1 (0.9–1.1)	1 (0.9–1.4)
Platelet count, 10^4 cells/μl	14.0 (11.4–18.1)	15.3 (12.2–19.1)	11.8 (10.7–15.8)[a]
Haemoglobin, g/dl	14.0 (12.8–15.3)	14.5 (13.4–15.4)	13.0 (10.6–15.1)[a]
Leukocyte count, cells/μl	6,160 (4,710–8,385)	5,900 (4,880–8,195)	6,685 (3,855–8,670)
Triggering event, *n* (%)	7 (10.6)	4 (8.7)	3 (15.0)
Non-HCC cancer, *n* (%)	5 (7.6)	2 (4.4)	3 (15.0)
Diabetes mellitus, *n* (%)	5 (7.6)	4 (8.7)	1 (5.0)
Cirrhosis, *n* (%)	13 (19.7)	6 (13.0)	7 (35)[a]
Ascites, *n* (%)	13 (19.7)	8 (17.4)	5 (25)
MELD score	18.1 (13.8–23.1)	14.8 (13.2–19.0)	23.5 (18.6–32.1)[a]
Antiviral agent			
Lamivudine, *n* (%)	38 (57.6)	25 (54.4)	13 (65)
Entecavir, *n* (%)	21 (31.8)	15 (32.6)	6 (30)
Combination, *n* (%)[b]	7 (10.6)	6 (13.0)	1 (5)

Data are expressed as median (IQR) unless indicated otherwise. [a]*P*-value <0.05 between the survivors and those who died. [b]Use of >1 oral antiviral agent. ALT, alanine aminotransferase; AST aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease.

related to drug resistance for the administered drug in patients with confirmed virological breakthrough, which was defined as viral load >10-fold above nadir.

Data analyses

The primary outcome of this study was survival rate during the follow-up period. We expressed continuous variables with median and IQR, and categorical variables with proportion. Survival curves were estimated by the Kaplan–Meier method and compared between groups by the log-rank test. The influence of pretreatment viral load on survival was further examined in the stratified analysis according to baseline international normalized ratio (INR). Cox proportional hazard model was developed to identify predictors associated with mortality. With all probable pretreatment covariates examined, we performed the multivariate analysis using forward and backward stepwise methods and assessed goodness-of-fit of the models. The results were reported as HR with 95% CI. The concordance rate between predictions and outcomes in all usable subjects was estimated by calculating the Harrell's C index [18]. Statistical analyses were conducted using commercially available software (Stata version 9.1; Stata Corp., College Station, TX, USA). All tests were two-sided with significance set at *P*-value <0.05.

Results

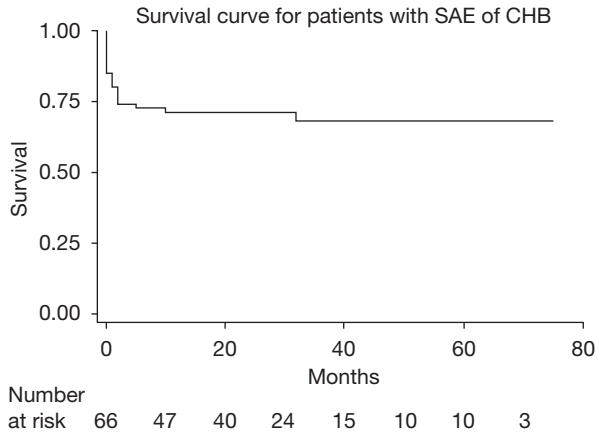
Baseline characteristics of enrolled patients

Among 84 CHB patients who received nucleoside/nucleotide analogues for severe acute exacerbation during the enrolment period, 18 patients were excluded because of hepatocellular carcinoma (*n*=10), no data of viral load prior to treatment (*n*=5), or immediate transferral to another hospital within 3 days of admission (*n*=3). A total of 66 patients (age range 18–81 years) were eligible and enrolled into analysis (Table 1). These study subjects were predominantly male (*n*=54, 81.8%) with a median serum ALT>1,000 IU/ml and MELD scores >18 points. Severe acute exacerbation was spontaneous in most subjects but was preceded by triggers in seven patients (chemotherapy for malignancy in three, immunosuppressives for rheumatic diseases in two, hypovolemic and septic shock each in one). Further details on the five patients who received cytotoxic chemotherapy for cancers or immunosuppressant for autoimmune disorders can be found in Additional file 1. Lamivudine was the most common antiviral therapy (*n*=38, 57.6%), while >1 antiviral agent was administered in seven patients: lamivudine plus entecavir in six and entecavir plus telbivudine in one patient.

Survival pattern of patients with severe acute exacerbation of chronic hepatitis B

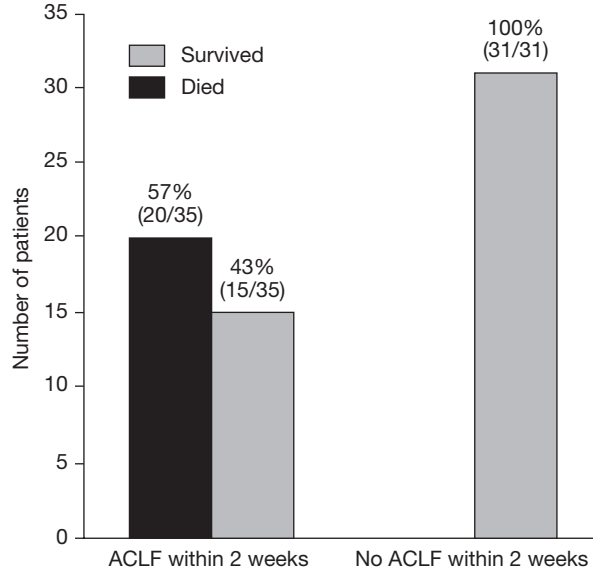
A total of 20 patients died during a median follow-up of 23 months (range 3 days to 75 months). Among the patients who died, the median time to death was 17 days (range 3 days to 32 months). The survival curve was characterized by an early mortality pattern with one-half (n=10) of the deceased succumbing within 1 month, 85% (n=17) within 3 months, and 90% (n=18) within 6 months of presentation (Figure 1). Both of the two late (>6 months) mortality cases were cirrhotic at baseline. Progression to ACLF within 2 weeks preceded all deaths, illustrating the potentially fulminant course of severe acute exacerbation in patients with CHB (Figure 2).

Figure 1. Survival curve for patients with severe acute exacerbation of chronic hepatitis B



The survival pattern was characterized by early mortality within 3 months of presentation.

Figure 2. Progression to acute-on-chronic liver failure precedes mortality



All deaths occurred in patients developing acute-on-chronic liver failure (ACLF) within 2 weeks.

Baseline prognostic factors for mortality

Older age, high serum level of aspartate aminotransferase, severe hyperbilirubinaemia, pronounced coagulopathy, low platelet count, low haemoglobin concentration and high MELD score were prognostic of death in the unadjusted analyses (Table 2).

After considering all variables listed in the Table 2 as potential covariates in developing the multivariate Cox proportional hazard model, we uncovered that mortality was independently associated with older age (adjusted HR 1.10 per increment of year, 95% CI 1.05, 1.15; P<0.001), higher baseline HBV DNA level (adjusted HR 1.49 per log copies/ml, 95% CI 1.13, 1.96; P=0.005), more severe coagulopathy denoted by higher INR (adjusted HR 2.68 per increment of unit, 95% CI 1.81, 3.98; P<0.001) and lower platelet count (adjusted HR 0.87 per 10^4 cells/μl higher, 95% CI 0.78, 0.98; P=0.020). The Harrell's C index for this model was 0.932.

Since variables contributing in a multivariate model may have interrelationships unforeseen in the univariate evaluation, interactions among these cofactors were examined to address the discrepancy between univariate and multivariate analyses. We discovered that serum HBV DNA interacted with coagulopathy on the association of mortality (interaction term with both treated as continuous variables, P=0.005).

Prognostic value of pretreatment viral DNA according to severity of coagulopathy

In order to illustrate the interrelationship between baseline viral load and coagulopathy in predicting mortality, enrolled subjects were divided into having high (n=35) or low (n=31) viral load by the closest integer to the median of baseline HBV DNA levels (7 log copies/ml). Consistent with the result of univariate analysis (Table 2), the survival probability was numerically but insignificantly (P=0.076) worse in the high viral load group.

The association between pretreatment viral DNA and mortality was further explored after accounting for the strong influence of INR. Based on the receiver operating characteristic curve of INR for mortality (Additional file 2), INR of 1.7 was chosen as the optimal point to distinguish outcomes. In

Table 2. Pretreatment factors predictive of mortality by univariate and multivariate Cox regression analyses

Variable	Univariate analysis			Multivariate analysis		
	Crude HR	95% CI	*P*-value	Adjusted HR	95% CI	*P*-value
Age, per year	1.07	1.03, 1.10	<0.001	1.10	1.05, 1.15	<0.001
Male gender	2.36	0.90, 6.18	0.079	–	–	–
HBsAg>250 IU/ml	2.46	0.72, 8.41	0.151	–	–	–
HBeAg-positive	0.63	0.23, 1.74	0.373	–	–	–
HBV DNA, per log copy/ml	1.16	0.88, 1.52	0.291	1.49	1.13, 1.96	0.005
AST, per 100 U/l	1.05	1.01, 1.09	0.024	–	–	–
ALT, per 100 U/l	0.99	0.93, 1.05	0.717	–	–	–
Bilirubin, per mg/dl	1.06	1.01, 1.11	0.014	–	–	–
INR, per unit	1.55	1.27, 1.89	<0.001	2.68	1.81, 3.98	<0.001
Creatinine, per mg/dl	1.04	0.88, 1.23	0.673	–	–	–
Platelet count, per 10^4 cells/μl	0.91	0.84, 0.99	0.038	0.87	0.78, 0.98	0.020
Haemoglobin, per g/dl	0.75	0.60, 0.94	0.011	–	–	–
Leukocyte count, per cell/μl	0.98	0.91, 1.06	0.638	–	–	–
Preceding trigger	1.47	0.43, 5.04	0.535	–	–	–
Non-HCC cancer	2.45	0.71, 8.42	0.156	–	–	–
Diabetes mellitus	0.65	0.088, 4.89	0.680	–	–	–
Cirrhosis	2.39	0.95, 6.01	0.064	–	–	–
Ascites	1.37	0.50, 3.78	0.541	–	–	–
MELD score, per point	1.06	1.03, 1.10	<0.001	–	–	–
Initial antiviral therapy						
Lamivudine monotherapy	1	–	–	–	–	–
Entecavir monotherapy	0.81	0.31, 2.13	0.668	–	–	–
Combination therapy[a]	0.40	0.52, 3.06	0.378	–	–	–

[a]Use of >1 oral antiviral agents. ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; INR, international normalized ratio; MELD, model for end-stage liver disease.

patients manifesting with pronounced coagulopathy (INR≥1.7), the prognosis was dismal with a mortality rate of 70% (*n*=14/20) regardless of their viral loads (Figure 3A). However, pretreatment HBV DNA level significantly stratified risk of mortality in those with initial INR<1.7 (Figure 3B). The *c* statistic for baseline viral DNA in predicting mortality was 0.78 (95% CI 0.62, 0.93) among these patients without markedly prolonged prothrombin time at baseline.

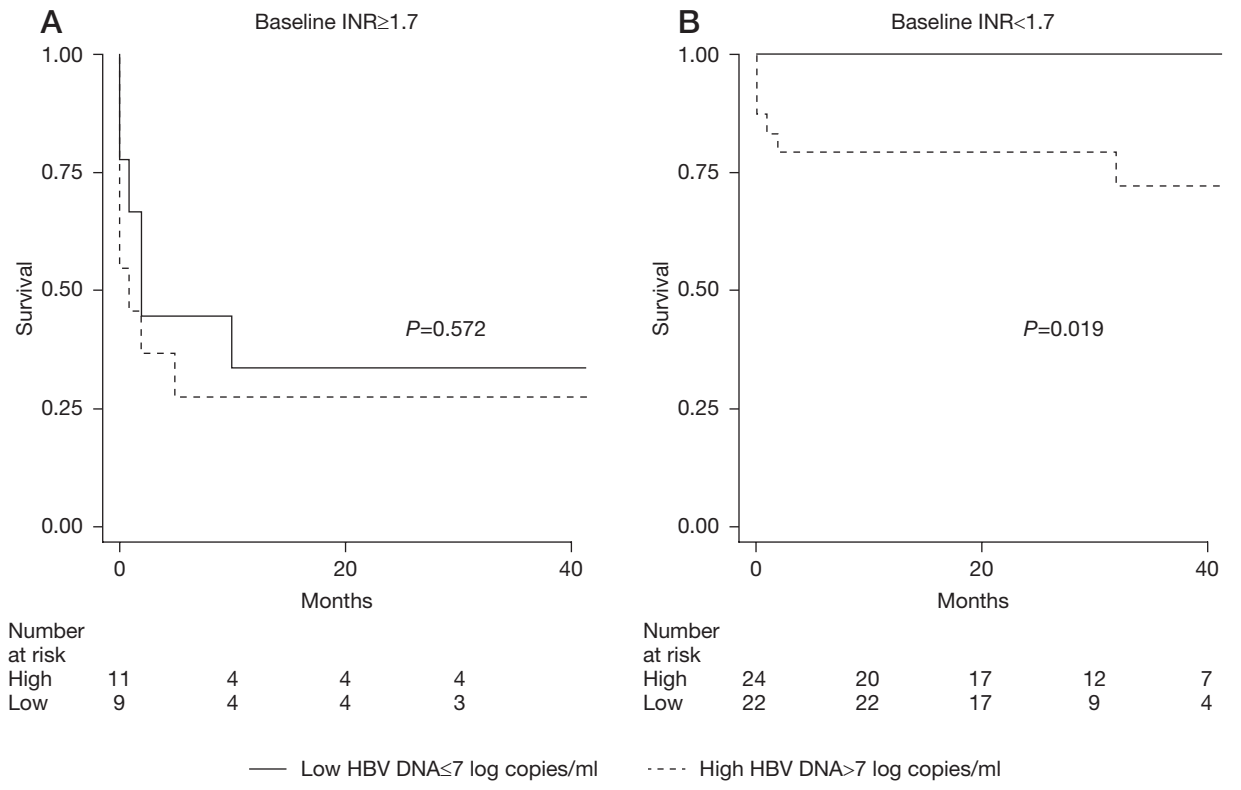
Discussion

This study demonstrates for the first time that baseline HBV DNA level is prognostic for mortality in patients with severe acute exacerbation of CHB. The value of viral load is modified by the severity of coagulopathy, because markedly prolonged INR (≥1.7) strongly foretells death by itself. In patients without initial manifestation of profound coagulopathy, serum level of HBV DNA significantly correlates with risk of mortality. These novel findings identify baseline HBV DNA level as a prognostic factor before the disease deteriorates to overt liver failure. Our research implicated that high viraemic burden may warrant more aggressive antiviral therapy among CHB patients suffering from severe acute exacerbation.

The prominent role of HBV DNA in assessing risk of long-term complications such as cirrhosis, hepatocellular carcinoma and liver-related mortality has been well-established [19–21]. Nonetheless, less has been elucidated about its prognostic value for adverse outcomes in the short term. Since acute exacerbation results pathogenically from extensive hepatic necrosis as a result of vigorous immune reactions trying to clear infected hepatocytes [2], the amount of virus may correlate with the magnitude of inflammatory responses and thus liver injury. Accordingly, higher viral load may stimulate more severe liver injury and hence poorer clinical outcomes. It has been shown that HBV DNA >1.55×10^9 copies/ml was independently associated with the development of hepatic decompensation (defined as hyperbilirubinaemia plus coagulopathy) following episodes of exacerbation (defined as serum ALT>5×ULN) [14]. In addition, rapid reduction in HBV DNA>2 logs at 2 weeks has been reported as crucial to improving survival of CHB-related ACLF [8]. These lines of evidence along with our results point out that viral load plays a central role in driving the pathogenic mechanism toward morbidity and mortality caused by acute HBV reactivation.

Findings of the present research are consistent with previous studies that have identified severity of hepatic

Figure 3. Pretreatment viral DNA stratifies mortality risk according to severity of coagulopathy



(A) Profound coagulopathy foretells death regardless of pretreatment viral load. **(B)** Serum level of HBV DNA distinguishes risk of mortality in patients without initial presentation of profound coagulopathy. INR, international normalized ratio (for prothrombin time).

dysfunction as the major determinant of outcome in acute exacerbation of CHB [6,7,11–13,22]. We found that indicators of the remaining liver reserve including serum bilirubin concentration, INR and MELD score were all associated with mortality in the univariate analyses, and that INR was the strongest and most independent predictor. INR was preferred to signify coagulopathy because measurement of prothrombin time should be calibrated by control [23,24]. The Child–Pugh score, which required subjective judgement for scoring, was not incorporated into our study because the inter-observer variability could be considerable, especially in the absence of prospectively standardized appraisal [25]. By showing the independent association between thrombocytopaenia and death, our findings concur with prior observations reporting status of underlying chronic liver disease as another essential determinant of outcome [11,16,26]. It has been demonstrated that thrombocytopaenia in chronic liver disease was pathogenically attributed to hepatic fibrosis [27]. Furthermore, the validity of platelet count in reflecting stage of hepatic fibrosis has been replicated in CHB patients [28,29].

The survival curve of our enrolled subjects, which is characterized by early mortality pattern, illustrates the importance of identifying at-risk individuals as early as possible. Our data also supports the consensus of using encephalopathy and/or ascites to define a devastating clinical entity, that is, ACLF [9]. The rapidly progressive course to ACLF and subsequent fatality despite antiviral treatment implies that the condition has deteriorated irreversibly beyond viral inhibition in these vulnerable patients [7]. Therefore, the presence of serious hepatic insufficiency, such as INR≥1.7, manifestation of encephalopathy or development of ascites should prompt the evaluation of liver transplantation. By contrast, identification of at-risk individuals before they develop overt liver failure allows greater opportunity to halt the progression toward irreversibility. Based on our results, further investigation is now warranted to explore whether more intense antiviral regimen will improve survival in highly viraemic CHB patients suffering from severe acute exacerbation.

Several limitations of this study are discussed. First, patients were not managed on the basis of a

standardized protocol in this retrospective analysis of 'real-world' data. However, they all received potent antiviral agents and whether the choice of pharmacotherapy influenced clinical outcomes was rigorously analysed. Fatal lactate acidosis has been reported in association with entecavir among patients with severely decompensated liver diseases [30], but this safety concern was not confirmed in clinical trials that prospectively monitored serum lactate [31,32]. It was unlikely that any specific antiviral agent was associated with particularly serious side effects in the study. Apart from antiviral therapy, the supportive care was similarly unstandardized. Second, serum concentration of HBsAg was semi-quantified and its value in assessing the outcomes of severe acute exacerbation could not be fully appreciated. Emerging evidence has established the utility of HBsAg quantification in predicting long-term prognosis [33,34], but its usefulness in evaluating outcomes of short-term complications requires more investigation. Third, although the sample size of our research is relatively large among studies focusing on severe acute exacerbation, the statistical power might be inadequate to explore the association for certain factors with lower prevalence, such as triggering event or combination therapy. Nonetheless, influence of any unaccounted variable could hardly be crucial in view of the high Harrell's C index achieved by the multivariate model. Finally, liver transplantation was unavailable to this study cohort. Whether our findings may be extrapolated to countries where liver transplantation is routinely available warrants further research.

In summary, this research uncovers the prognostic value of pretreatment HBV DNA in patients treated with antiviral therapy for severe acute exacerbation of CHB. High serum level of HBV DNA correlates with risk of death among patients who have not progressed to overt liver failure. Our findings not only contribute to a more accurate prognostication but also shed light on how to improve survival in these vulnerable patients.

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Both J-TL and L-RM supervised and contributed equally in this study. The listed authors acknowledge contribution from all staff in the Division of Gastroenterology in E-Da Hospital. We are grateful to Jing-Ju Lee for her efficient assistance.

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Disclosure statement

The authors declare no competing interests.

Additional files

Additional file 1: A supplementary table displaying characteristics of patients with triggering events for severe acute exacerbation of CHB can be found at http://www.intmedpress.com/uploads/documents/AVT-12-OA-2624_Hsu_Add_file_1.pdf

Additional file 2: A supplementary figure illustrating the receiver-operating characteristic curve of INR to predict mortality can be found at http://www.intmedpress.com/uploads/documents/AVT-12-OA-2624_Hsu_Add_file_2.pdf

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