

ALBI Score for Predicting Acute Liver Failure in Patients with Acute Hepatitis B and D in Mongolia

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Submitted: February 22, 2021

Revised: February 28, 2021

Accepted: March 26, 2021

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Objectives: Mongolia is known as one of the countries with a high prevalence of hepatitis B and D virus infection. Although the number of acute hepatitis D cases is decreasing since the national vaccination program against HBV launched in 1991, it is still a main cause of acute liver failure (ALF) in Mongolia. The aim of this study is to determine the prognostic value of an ALBI score in patients with acute hepatitis B with or without D. **Methods:** A total of 114 patients (58 patients with acute hepatitis B (AHB), five patients with HBV/HDV co-infection, and 51 patients with HBV/HDV superinfection), who were admitted to the National Center for Communicable Diseases between 2017 and 2019 were enrolled into this study. **Results:** We compared the AHB group to the HBV/HDV superinfection group. The mean age was 25.8 ± 6.5 years in the AHB group vs. 28.9 ± 7.4 years in the HBV/HDV superinfection group ($p = 0.019$). Also, a majority of patients live in Ulaanbaatar (87.5% vs. 62.7%, $p = 0.037$). The mean hospitalization days was 23 ± 11 in the AHB, on the other hand it was 28 ± 13 in the HBV/HDV superinfection group ($p = 0.022$). The ALF patients had a higher ALBI score, total bilirubin, transaminase, and INR compared with the non-ALF group. The platelet count was significantly lower in the AHB and HBV/HDV infection group with ALF compared with AHB and HBV/HDV infection without ALF. This study showed that the ALBI score in AHB with ALF patients was significantly higher than in AHB without ALF ($p = 0.001$), and HBV/HDV superinfection with ALF had a higher ALBI score than HBV/HDV superinfection without ALF ($p = 0.041$). The area under the curve (AUC) value was 0.766 for ALBI scores. The cut-off value, sensitivity and specificity of ALBI score values were -1.71, 72.2%, and 75.6%, respectively. **Conclusions:** ALBI score determined on admission indicates the likelihood of survival of patients with AHB and AHD.

Keywords: Acute Hepatitis B, Acute Hepatitis Delta, Acute Liver failure

Introduction

Hepatitis Delta Virus (HDV) is a defective virus, which requires Hepatitis B virus surface antigen (HBsAg) for its lifecycle [1]. Acute HDV infection may occur either simultaneously with hepatitis B virus (HBV) infection (coinfection) or in chronic HBV carrier (superinfection). The clinical course of HBV/HDV coinfection may range from self-limited hepatitis to severe or fulminant hepatitis. The outcome is a complete recovery or in only 2% of cases it may progress to chronicity [2]. In superinfections, pre-existing HBV infection plays a major role, so that most patients developed severe acute hepatitis and further developed chronic liver disease including liver cirrhosis and hepatocellular carcinoma [3]. Fulminant hepatitis occurs more frequently in patients with either acute delta co-infection or acute superinfection, than in patients with acute HBV infection alone [4-6]. The mortality rate for acute delta hepatitis ranges from 2 to 57% compared to less than 1% for acute HBV infection [7, 8]. Acute liver failure (ALF), also known as fulminant hepatic failure, is a life-threatening condition caused by acute insult and sudden loss of hepatic function in a person without evidence of chronic liver disease [9].

Mongolia has one of the highest hepatitis A, C, B and D infection incidences worldwide [10-13]. The HBV infection rate has been declining significantly since the national vaccination program against HBV was introduced in 1991. The WHO supported a series of national serological surveys and found that Mongolia had reached its regional goal, with 96% of children fully vaccinated as of 2009 [14]. Also the Mongolian government has launched the Viral Hepatitis Prevention, Control and Elimination Program to reduce the burden of viral hepatitis related liver cirrhosis and hepatocellular carcinoma. According to this program access to antiviral therapies is now improving in Mongolia. The incidence of acute hepatitis B (AHB) per 10000 populations has decreased from 3.4 in 2000 to 0.7 in 2019 [15,16]. For acute hepatitis D, the incidence per 10000 populations was 0.4 in 2009 and has decreased to 0.2 in 2019 [11].

Although the incidence of acute hepatitis D is decreasing, morbidity is higher among the 20-44 age groups than other ages, and it is still a main cause of acute liver failure in Mongolia. This is explained by the association between high HBV prevalence among the population that was born before 1991, the existence of HDV in the community, and blood-borne virus transmission

in health and non-health settings over the past decades [11]. Two decades ago, Altankhuu et al. demonstrated the clinical course and outcome of acute viral hepatitis among the adults in this country [17]. They reported that severe acute hepatitis occurred in 30%, 49% and 13.3% of acute hepatitis B, D and C cases respectively. In 1998 Zulkhuu et al. found that severe acute hepatitis occurred in 16% of HBV/HDV superinfected and in 17.9% of co-infected children [18]. Both were observational studies and did not evaluate the predictors for acute liver failure or mortality.

Several prognostic models have been used to predict outcomes in acute on chronic liver failure, including age, serum bilirubin, international normalized ratio (INR), serum creatinine (ABIC), Albumin-Bilirubin (ALBI), King's College Criteria (KCC), Model for End-stage Liver Disease (MELD), and Child-Turcotte-Pugh (CTP) score. The King's College Criteria is widely used for selecting patients for liver transplantation [19], MELD and CTP score have been used for predicting prognosis in end-stage liver diseases such as cirrhosis and hepatocellular carcinoma [20-22]. The ABIC score, which is based on age and parameters indicating liver function, coagulation and renal function test, provides prognostic stratification in patients with alcoholic hepatitis [23]. The albumin-bilirubin (ALBI) score, by combining the serum albumin and bilirubin, is a new model for assessing the severity of liver dysfunction [17]. As mentioned before, morbidity and mortality of acute viral hepatitis remains high in our country, although assessing the early predictors such as ALBI score for acute liver failure is still lacking. We hypothesized that ALBI score is potentially associated with clinical outcomes in acute viral hepatitis B with and without D. The aim of the study is to determine prognostic value of the ALBI score in patients with acute hepatitis B with and without D.

Materials and Methods

Subjects

A total of 114 patients with acute hepatitis B or acute hepatitis Delta, who were admitted to the National Center for Communicable Diseases (NCCD) between 2017 and 2019 were enrolled into this study. The inclusion criteria were patients who presented with acute hepatitis (elevated ALT >400 U/L) and had a positive serological test for HBsAg and/or Immunoglobulin M (IgM) antibody to hepatitis B core antigen (anti-HBc IgM) or

positive for HBsAg, anti Hbc, and anti-HDV IgM.

The diagnosis of AHB was based on symptoms such as fever, loss appetite, fatigue and dark urine, signs such as jaundice, laboratory examinations (elevated serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST)), detection of either anti-Hbc IgM or HBsAg or both, and no detection of HBsAg for 6 months before presentation. Acute HBV/HDV co-infection diagnostic criteria was positive anti-HBc, IgM, and anti-HDV IgM. HBV/HDV superinfection diagnostic criteria was positive tests for HBsAg, Anti-HBc, anti-HDV IgM, and negative for anti-HBc IgM. Acute liver failure was defined as a severe clinical syndrome with encephalopathy (any degree of altered mentation, range 1-4), jaundice (serum bilirubin >5 mg/dL) and coagulation abnormalities (INR>1.5).

Laboratory data

All laboratory tests were performed using standardized laboratory procedures at the Laboratory Department of NCCD. Serum ALT, AST, albumin, total bilirubin, and total protein were detected using an automatic analyzer (COBAS® INTEGRA400 plus, Roche Diagnostics, Germany). All serum samples were analyzed using commercial Enzyme-Linked Immunosorbent Assay kits for detection of HBsAg, anti-HDV, HBeAg, anti-HBe, anti-HBc IgM, anti-HBs, anti-HDV and anti-HDV IgM (Wantai, Beijing) following the manufacturer's instructions.

Evaluation of prognostic score

ALBI score was calculated for each patient based on the results of a biochemical test on admission. The detailed formula that was used was as follows: $ALBI = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times 0.085)$.

Statistical analysis

All statistical analyses were performed using a standard software package (Stata, version 12.0; StataCorp). Continuous variables were summarized as mean and standard deviation, and categorical data was expressed as percentage. Differences in variables were analyzed using Student's t test. Categorical data was evaluated by the Chi-squared test or Fisher's exact test. Some biochemical tests such as ALT, AST, and total bilirubin

levels that measured too high, we expressed as multiples of upper limits of normal (ULN). The diagnostic accuracy of ALBI score was examined by receiver operating characteristic (ROC) analysis. A two-tailed $p < 0.05$ was considered statistically significant.

Ethical statement

The Ethical Review Committee of Mongolian National University of Medical Sciences approved the current study protocol and the written consent forms were obtained from all subjects' prior blood sampling (No2017/3-201702).

Results

Baseline characteristics

Out of 114 hospitalized patients aged between 17-52 years, 60.5% were males, 56.1% were married and 93%.

Table 1. Demographics of patients.

Variables	All patients n=114
	Mean ± SD
Age	27.3±6.9
	N (%)
Gender: male	69 (60.5)
Married	646 (56.1)
Residence: Ulaanbaatar	93 (81.6)
Disease	
Acute hepatitis B	58 (50.9)
HBV/HDV co-infection	5 (4.4)
HBV/HDV superinfection	51 (44.7)

A total of 58 patients were diagnosed with acute hepatitis B, five patients were diagnosed with HBV/HDV co-infection, and 51 patients were diagnosed with acute HDV superinfection on chronic hepatitis B. Then we compared the AHB group to the HBV/HDV superinfection group (Table 2). The Mean age was 25.8 ± 6.5 years in the AHB group vs. 28.9 ± 7.4 years in the HBV/HDV superinfection group ($p = 0.019$). Also, the majority of patients live in Ulaanbaatar (87.5% vs. 62.7%, $p = 0.037$). 41.4% of patients with AHB were married vs. 70.6% of the HBV/HDV superinfection group ($p = 0.004$).

Table 2. Clinical and laboratory characteristics of AHB and HBV/HDV superinfection group.

Variables	Acute hepatitis B n=58	HBV/HDV superinfection n=51	p-value
	Mean ± SD	Mean ± SD	
Age	25.8±6.5	28.9±7.4	0.019
Duration of hospitalization (days)	23±11	28±13	0.022
	N (%)	N (%)	
Gender: Male	33 (56.9)	32 (62.7)	0.336
Residence of Ulaanbaatar	51 (87.9)	32 (62.7)	0.037
Married	24 (41.4)	36 (70.6)	0.004
Alcohol intake: no	13 (22.7)	15 (29.4)	0.269
Smoking: yes	22 (37.9)	16 (31.7)	0.266
Death	10 (17.2)	8 (15.7)	0.518

Mean hospitalization days was 23±11 in AHB, on the other hand it was 28±13 in the HBV/HDV superinfection group (p = 0.022).

No significant differences in alcohol intake or smoking habits was detected in the number of patient deaths.

Table 3. Comparison of clinical symptoms between AHB and HBV/HDV superinfection group.

Variables	Acute hepatitis B n=58	HBV/HDV superinfection n=51	p-value
	N (%)	N (%)	
Jaundice	58 (100)	50 (98)	0.468*
Fatigue	48 (82.8)	51 (90.2)	0.283
Drowsiness	15 (25.9)	7 (13.7)	0.091
Insomnia	12 (20.7)	10 (19.6)	0.540
Loss appetite	50 (86.2)	41 (80.4)	0.288
Vomiting	44 (75.9)	37 (72.5)	0.430
Abdominal pain	46 (79.3)	41 (80.4)	0.540
Fever	14 (24.1)	16 (31.1)	0.264
Arthralgia	2 (3.4)	4 (7.8)	0.426*
Loss weight	6 (10.3)	1 (2.0)	0.079*
Headache	23 (39.7)	14 (27.5)	0.225
Itching	5 (8.6)	6 (11.8)	0.752
Bloating	13 (22.4)	11 (21.6)	0.551

*Fisher's exact test

Clinical symptoms including jaundice, fatigue, drowsiness, insomnia, loss appetite, vomiting, abdominal pain, fever, arthralgia, loss weight, headache, itching and bloating did not differ between groups (Table 3). Laboratory test results were compared in Table 4. HBeAg was positive in 22 (37.9%) of patients in AHB group vs. 10 (19.6%) of patients in the HBV/

HDV superinfection group (p = 0.022). Also baseline platelet count was significantly lower in HBV/HDV superinfection group (165±47 * 10⁹/L vs. 208±67* 10⁹/L; p < 0.001). However, there were no significant differences in bilirubin, AST, ALT and albumin levels between the two groups.

Table 4. Comparison of laboratory tests in study groups.

Variables	Acute hepatitis B n=58	HBV/HDV superinfection n=51	p-value
	Mean ± SD	Mean ± SD	
Total bilirubin X ULN	8.5±3.5	9.4±4.7	0.234
ALT X ULN	72.9±40.1	84.3± 62.2	0.256
Total Proptein (g/L)	65.5±5.9	65.1±8.8	0.790
Albumin (g/L)	35.5±5.3	40.2±4.7	0.891
AST/ALT ratio	0.61±0.27	0.67±0.27	0.215
Platelet 10 ⁹ /L	208±67	165±47	0.001
INR	2.1±2.3	1.9±1.7	0.710
	N (%)	N (%)	
HBeAg postivie	22 (37.9)	10 (19.6)	0.029

Comparing laboratory tests in AHB and HBV/HDV superinfection with/out ALF subgroups

Finally, each study group was divided into two subgroups such as ALF and without ALF. The comparisons of mean values of laboratory tests of subgroups are shown in Table 5 and 6. Although mean bilirubin levels did not differ between groups, the AHB with ALF subgroup had a significantly higher mean ALT level (107.6±52.0xULN vs. 65.7±33xULN; p = 0.002) compared with subgroups of AHB without ALF. Serum mean AST level was also

significantly higher in AHB with ALF patients (129.1±64.2xULN vs. 0.9±32.6xULN; p = 0.001). Compared with the AHB without ALF, the AHB patients with ALF subgroup had significantly lower serum total protein (60.7±9.6g/L vs. 66.5± 4.5g/L; p = 0.006) and albumin (34.7±6.3g/L vs 41.3±3.4g/L; p < 0.001) level. While INR level is significantly higher in AHB with ALF patients than the AHB without ALF (6.1±4.3 vs. 1.4±0.7; p < 0.001), the platelet count is significantly lower in AHB with ALF patients (66.2±68.9x10⁹/L vs. 217.5±63.8x10⁹/L; p = 0.026).

Table 5. Liver function and coagulation test compared AHB patients with ALF and non-ALF subgroups.

Variables	Acute hepatitis B		p-value
	with ALF n=10	without ALF n=48	
	Mean ± SD	Mean ± SD	
Total bilirubin X ULN	6.5±2.2	8.8±3.6	0.103
ALT X ULN	107.6±52.0	65.7±33	0.002
AST XULN	129.1±64.2	40.9±32.6	0.001
Total Proptein (g/L)	60.7±9.6	66.5± 4.5	0.006
Albumin (g/L)	34.7±6.3	41.3±3.4	0.001
Platelet 10 ⁹ /L	66.2±68.9	217.5±63.8	0.026
INR	6.1±4.3	1.4±0.7	0.001

When we compared HBV/HDV superinfected patients with ALF to the without ALF subgroup serum total bilirubin, total protein and albumin levels did not differ (Table 6). On the other hand mean ALT and AST level were significantly higher in HBV/HDV superinfected patients with ALF (123.7±77.2 x ULN 76.9±57.1xULN; p = 0.050 and 100.7±66.0 x ULN vs.

48.3±41.3xULN; p = 0.004). Although serum platelet level was significantly lower in HBV/HDV superinfected patients with ALF than those without ALF (126.6±63.3 10⁹/L vs. 172.3±41.3 10⁹/L; p= 0.011), INR level is significantly higher in HBV/HDV superinfected patients with ALF than the without ALF (4.5±3.1 vs. 1.3±0.4; p < 0.001).

Table 6. Liver function and coagulation test compared HBV/HDV superinfected patient with ALF and without ALF.

Variables	HBV/HDV superinfection		p-value
	with ALF	without ALF	
	n=8	n=43	
	Mean ± SD	Mean ± SD	
Total bilirubin X ULN	9.2±4.8	8.9±4.1	0.403
ALT X ULN	123.7±77.2	76.9±57.1	0.050
AST XULN	100.7±66.0	48.3±41.3	0.004
Total Proptein (g/L)	60.5±7.8	66.0±8.8	0.107
Albumin (g/L)	35.1±4.5	39.1±5.7	0.074
Platelet 10 ⁹ /L	126.6±63.3	172.3±41.3	0.011
INR	4.5±3.1	1.3±0.4	0.001

Comparing ALBI score in AHB and HBV/HDV superinfection with/out ALF subgroups

Comparison of ALBI scores in 4 subgroups are shown in Table 7. The mean ALBI score is significantly different between AHB with and without ALF subgroups (-1.6±0.32 vs. -2.09±0.32; p= 0.001). Also ALBI score is also significantly different

between HBV/HDV superinfected patients with and without ALF subgroups (-1.51±0.49 vs. -1.95±0.55; p = 0.041).

The area under the ROC curve value for predicting acute liver failure was 0.766 for ALBI score (Figure 1). The best cut-off value of ALBI score was -1.71 with sensitivity of 72.2%, and specificity of 75.6%.

Table 7. Comparison of ALBI score in study subgroups.

Variable	with ALF	without ALF	p-value
	Mean ± SD	Mean ± SD	
Acute hepatitis B	-1.60±0.45	-2.09±0.32	0.001
HBV/HDV superinfection	-1.51±0.49	-1.95±0.55	0.004

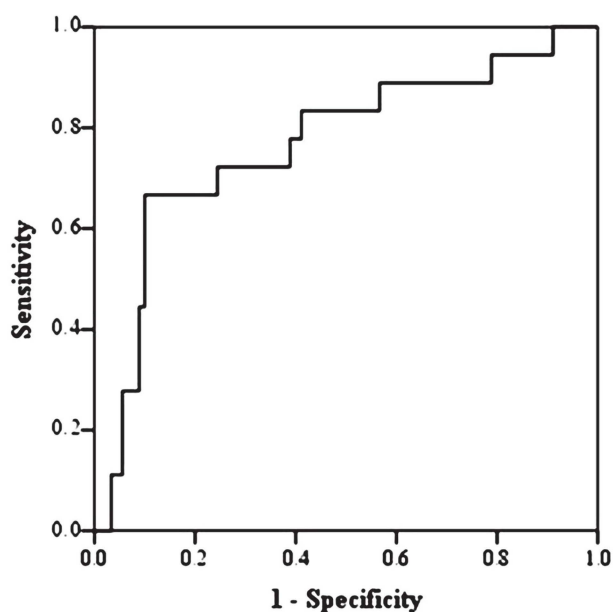


Figure 1. Receiver operating characteristic curve indicating the relative efficiencies for predicting 1-month mortality by the ALBI score at admission.

Discussion

The common cause of ALF is acute viral hepatitis B and D in Mongolia [23]. Since the national immunization program against HBV launched in 1991, the morbidity and mortality rate of acute viral hepatitis had decreased dramatically. A totally of 45-60 mortalities due to acute liver failure caused by acute viral hepatitis were registered every year from 1996 to 2000, and since 2015 this has decreased steadily. 2-6 cases have been registered annually during the last 5 years [20]. Three decades ago, Altankhuu et al. reported that acute hepatitis B, HBV/HDV co-infection and HBV/HDV superinfection rates were 36.3%, 16.8% and 17.1%. The mortality rate was 2.3% in AHB vs. 19.6% in acute Delta hepatitis [17]. Baatarkhuu et al. reported that acute hepatitis B and D were diagnosed in 40.7% and 14.7% of patients with acute viral hepatitis. Also 21% of the patients had a dual infection [11]. In our study HBV/HDV co-

infection occurred less frequently compared with HBV/HDV superinfection (4.4% vs. 44.7%), which is explained by the National Immunization Program that led to decreased incidences of HBV/HDV con-infection. In contrast, mortality rates for acute hepatitis B increased in our study compared to the previous study (17.2% in 2021 vs. 2.3% in 1993) [17].

Mele et al. reported a male predominance and 92% was icteric. Mean hospitalization day was 21.3 ± 13.3 in retrospective studies among the patients with acute hepatitis Delta [23]. Our study demonstrated similar finding. However, the mortality rate was quite high in our study (15.8% vs. 0.9%). All patients with ALF in our study died. Patients with ALF of both AHB and HBV/HDV superinfection have a severe degree of liver dysfunction such as high levels of bilirubin, transaminase, INR and lower levels of albumin and platelet count compare with non-ALF groups.

It is well known that there are several scoring systems available to evaluate the severity of liver dysfunction and predict the prognosis of patients with liver disease, such as ABIC, ALBI, KCC, the MELD and Child–Pugh scores in patients with acute on chronic liver disease. The ALBI score, the simplest and easiest score to calculate using serum albumin and bilirubin level, has been already used in patients with HCC and acute in chronic liver failure for assessing the severity of liver dysfunction [17, 18]. Here we assessed ALBI score as a predictor for survival in patients with AHB and HBV/HDV superinfection. The prognostic ALBI scores were significantly increased in both ALF due to both AHB and HBV/HDV superinfection. Chen et al. found that the cut-off values for sensitivity and specificity of the ALBI score in patients with acute on chronic liver failure were 0.95, 65.9%, and 81.4%, respectively. Our results showed that higher cut-off values of ALBI score were cut off; -1.71, sensitivity 72.2%, and specificity 75.6% in acute hepatitis B and Delta patients.

This is the first study evaluating prediction score for ALF in acute B and Delta hepatitis among patients who were admitted to the tertiary hospital in Mongolia.

Our study has several limitations. First of all, HBV and HDV viral loads in patients were not included in this study due to insufficient data. Since 2017, only HBV and HCV viral loads were reimbursed by National Health Insurance. So the patients were divided into study groups of AHB, HBV/HDV co-infection, and superinfection only by the immunology test results. Second, we could not calculate KCC, ABIC and MELD scores between the

patients with ALF and without ALF because the serum levels of creatinine, ammonia, sodium, lactate were not measured in the majority of patients in without ALF.

Further studies are needed to validate the dynamic of ALBI score by comparing other prognostic models including KCC, MELD, ABIC, acute liver failure early dynamic model predicting for ALF in patients with acute viral hepatitis and severe alcoholic hepatitis.

Conclusion

ALBI score determined on admission indicates the likelihood of survival of patients with AHB and AHD. The early identification and prognostic evaluation of ALF can provide a guiding basis for active and effective treatment.

Conflict of Interest

The authors state no conflict of interest.

Acknowledgements

The authors thank the patients who participated in this study, Dr. Sarangua Ganbold, Dr. Ariunbileg Jamiyan, Dr. Gansaikhan Badarch and nurse Urantugs Tumen-Od for data handling and laboratory work.

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