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Original Research

RISK FACTORS ASSOCIATED WITH PROGRESSION TO ACUTE-ON-CHRONIC LIVER FAILURE IN SEVERE ACUTE EXACERBATION OF CHRONIC HEPATITIS B

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ABSTRACT: Hepatitis B virus (HBV) infection is a prevalent and serious infectious disease. Severe acute exacerbation of chronic hepatitis B occurs in 40-50% of patients with chronic hepatitis B, which can progress to acute-on-chronic liver failure (ACLF) when their liver damage worsens. Early diagnosis and treatment play an important role in the survival of patients with ACLF. To investigate risk factors associated with the progression of ACLF in severe acute exacerbation of chronic hepatitis B. A retrospective, cross-sectional study with longitudinal follow-up was conducted on 69 patients with severe acute exacerbation of chronic hepatitis B, conducted at the Department of Gastroenterology, The University of Medicine Center of Ho Chi Minh City from January 2022 to December 2023. Of the 69 patients, 30 (43.5%) progressed to ACLF. Univariate analysis identified a history of compensated cirrhosis (OR = 9.04; 95% CI: 3.0–27.2), spider angiomas (OR = 4.43; 95% CI: 1.54–12.75), palmar erythema (OR = 5.07; 95% CI: 1.75–14.64), lower serum sodium (OR = 1.18; 95% CI: 1.02–1.37), higher total bilirubin (OR = 1.06; 95% CI: 1.01–1.12), and lower serum albumin (OR = 1.29; 95% CI: 1.13–1.47) as significant risk factors for ACLF progression in severe acute exacerbation of chronic HBV. Risk factors associated with the progression of ACLF in severe acute exacerbation of chronic hepatitis B are a history of compensated cirrhosis, spider angiomas, palmar erythema, serum sodium, total bilirubin, and serum albumin. Serum albumin is an independent risk factor.

Keywords: acute-on-chronic liver failure; severe acute exacerbation of chronic hepatitis B; chronic hepatitis B.

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1. INTRODUCTION

Hepatitis B virus (HBV) infection is a prevalent and dangerous infectious disease, representing a serious global health issue. Vietnam is a country within a region of high HBV prevalence worldwide. Epidemiological studies in Vietnam have recorded that the HBV infection rate remains high among individuals undergoing general health assessments (9%), and even in the under-30 age group (7%) [1]. Acute exacerbations occur in 40-50% of HBeAg-positive patients with chronic hepatitis B (CHB) and in 15-30% of HBeAg-negative patients [2]. A severe acute exacerbation can progress to acute-on-chronic liver failure (ACLF) as the patient's liver damage worsens. Despite improvements in clinical management, the mortality rate for ACLF patients ranges from 50% to 80% in the absence of liver transplantation. Early diagnosis and treatment play a critical role in the survival of patients with ACLF. In the early stages, aggressive therapy can be effective in halting the progression of the disease. Therefore, we conducted this study, "Risk Factors Associated with Progression to Acute-on-Chronic Liver Failure in Severe Acute Exacerbation of Chronic Hepatitis B," with the objective of investigating the risk factors associated with progression to ACLF in patients with a severe acute exacerbation of CHB.

2. METHODS

2.1. Study Design and Participants

The study population comprised patients aged 18 years and older with a severe acute exacerbation of chronic hepatitis B (CHB), who were admitted to the Department of Gastroenterology at the University of Medicine and Pharmacy Center of Ho Chi Minh City. The patient data were collected over a two-year period, from January 2022 to December 2023.

2.2. Inclusion Criteria

Patients were included if they met the diagnostic criteria for a severe acute exacerbation of CHB [2]:

- HBsAg and/or HBV DNA positivity for more than 6 months.
- Alanine aminotransferase (ALT) level >10 times the upper limit of normal (ULN) (>410 U/L for males and >310 U/L for females) and
- Total bilirubin level ≥3 times the ULN (≥51 μmol/L or ≥3 mg/dL) and
- Prothrombin activity (PT%) between 40% and 60%.

2.3. Exclusion Criteria

- Patients were excluded from the study if they had any of the following conditions:
- Co-infection with hepatitis A, C, or E viruses; alcoholic liver disease; drug-induced liver injury; hepatocellular carcinoma; hyperthyroidism; or pregnancy.
- The presence of severe extrahepatic comorbidities or active infections.
- Prior chemotherapy or immunosuppressive therapy.
- A history of decompensated cirrhosis.
- Refusal to participate in the study.

2.4. Definitions and Data Collection

The diagnosis of ACLF was based on the 2019 consensus recommendations from the Asia-Pacific Association for the Study of the Liver (APASL). These criteria define ACLF as an acute hepatic insult manifesting as jaundice (serum bilirubin >5 mg/dL or >85.5 μmol/L) and coagulopathy (International Normalized Ratio >1.5 or PT% <40%), complicated by the development of ascites and/or hepatic encephalopathy within a four-week period [3].

Data were systematically extracted from patient medical records using a standardized data collection form. Patients were assessed for a range of variables, including demographic data (age, sex), personal and family history of chronic hepatitis B (CHB), and the presence of cirrhosis or hepatocellular carcinoma. Potential precipitating factors and comorbidities were also documented, such as co-infection with other hepatitis viruses (HAV, HCV); use of immunosuppressants, chemotherapy, or hepatotoxic drugs; history of organ transplantation; discontinuation of antiviral therapy; chronic alcohol consumption; hyperthyroidism; pregnancy; and

autoimmune or metabolic diseases (e.g., Wilson's disease, hemochromatosis). Laboratory parameters obtained within 24 hours of admission included aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, serum albumin, INR, white blood cell (WBC) count, platelet (PLT) count, serum sodium, blood urea, creatinine, and HBV DNA. Subsequently, patients were monitored for progression to acute-on-chronic liver failure during their hospitalization.

2.5. Statistical Analysis

Data were entered using EpiData software (version 3.3) and analyzed using R Studio (version 3.6.0). Continuous variables were assessed for normality; normally distributed data were presented as mean ± standard deviation (SD), while non-normally distributed data were presented as median and interquartile range (IQR, 25th–75th percentile). Categorical variables were described using frequencies and percentages. For comparative analysis between groups, the Student's t-test was used for normally distributed continuous variables, and the Mann-Whitney U test was used for non-normally distributed continuous variables. The Chi-square ($\chi 2$) test or Fisher's exact test was used for categorical variables. A p-value of < 0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline Characteristics of the Study Cohort

Our study enrolled 69 patients with severe acute exacerbation of chronic hepatitis B (CHB) who met the inclusion criteria. Within the study population, males accounted for 78.3%, with a male-to-female ratio of 3.6:1. The mean age of the cohort was 51.6 ± 1.7 years. The incidence of acute-on-chronic liver failure (ACLF) in this setting was 43.48%.

3.2. Comparative Analysis of Clinical and Laboratory Parameters between the ACLF and non-ACLF groups in severe acute exacerbation of CHB

Table 1. Comparison of clinical characteristics between the ACLF and non-ACLF groups in severe acute exacerbation of CHB.

Characteristic	ACLF Group (n=30)	Non-ACLF Group (n=39)	p-value
Male gender, n (%)	21 (70.0)	33 (84.6)	0.145
Age (years), median (IQR)	60 (50 – 69)	47 (40 – 52.5)	<0.001[b]
Compensated cirrhosis, n (%)	21 (70.0)	8 (20.5)	<0.001[a]
Fever, n (%)	8 (26.7)	6 (15.4)	0.248[a]
Splenomegaly, n (%)	7 (23.3)	3 (7.7)	0.067[a]
Spider angiomas, n (%)	16 (53.5)	8 (20.5)	0.005[a]
Palmar erythema, n (%)	17 (56.7)	8 (20.5)	0.002[a]

[a]Chi-square test; [b]Mann-Whitney U test.

Table 2. Comparison of laboratory characteristics between the ACLF and non-ACLF groups in severe acute exacerbation of CHB.

Characteristic	ACLF Group (n=30)	Non-ACLF Group (n=39)	p-value
HBeAg positive, n (%)	8 (26.7)	12 (30.7)	0.710[a]
log HBV DNA (copies/mL), median (IQR)	5.4 (4.1 – 7.5)	6.3 (4.7 – 7.1)	0.937[b]
Sodium (mmol/L), median (IQR)	134 (132 – 136)	136 (134.5 – 138)	0.025[b]
ALT (IU/L), median (IQR)	846.5 (550 – 1549)	1846 (1047 – 2432.5)	0.006[b]
AST (IU/L), median (IQR)	986 (462 – 1514)	1363 (963.5 – 1837.5)	0.017[b]
GGT (IU/L), median (IQR)	182 (127 – 291)	266 (139.5 – 385)	0.387[b]
Total Bilirubin (μmol/L), median (IQR)	17.2 (10.6 – 24.2)	12.9 (5.7 – 19.4)	0.028[b]

Albumin (g/L), median (IQR)	30.0 (26.6 – 33.6)	36.9 (32.5 – 38.8)	<0.001[b]
Urea (mmol/L), median (IQR)	25.8 (20.4 – 38.4)	22.8 (19.8 – 28.2)	0.221[b]
Creatinine (mg/dL), median (IQR)	0.89 (0.75 – 0.96)	0.90 (0.82 – 0.99)	0.467[b]
INR, median (IQR)	1.68 (1.59 – 1.90)	1.59 (1.46 – 1.78)	0.067[b]
WBC (K/mL), median (IQR)	7.8 (6.1 – 10.7)	7.1 (5.5 – 8.4)	0.175[b]
Platelets (K/mL), median (IQR)	133.5 (93.6 – 202.0)	165.0 (134.5 – 198.5)	0.197[b]

[a]Chi-square test; [b]Mann-Whitney U test. HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; INR, international normalized ratio; WBC, white blood cell.

3.3. Risk Factor Analysis for ACLF Progression in severe acute exacerbation of CHB

The plot displays the Odds Ratios (OR), 95% confidence intervals (horizontal bars), and p-values for risk factors. In the univariate analysis (blue), all investigated factors were statistically significant risks, with their confidence intervals located entirely to the right of the no-effect line (OR = 1).

Table 3. Univariate and multivariate logistic regression analysis of risk factors for ACLF progression in severe acute exacerbation of CHB.

Risk Factor	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Compensated cirrhosis	9.04 (3.0 – 27.2)	<0.001	4.27 (0.75 – 24.34)	0.102
Spider angiomas	4.43 (1.54 – 12.75)	0.006	3.27 (0.29 – 37.28)	0.339
Palmar erythema	5.07 (1.75 – 14.64)	0.003	0.78 (0.06 – 37.28)	0.847
Sodium	1.18 (1.02 – 1.37)	0.028	1.06 (0.84 – 1.34)	0.607
ALT	1.00 (0.99 – 1.01)	0.064		
AST	1.00 (0.99 – 1.01)	0.054		
Total Bilirubin	1.06 (1.01 – 1.12)	0.026	0.93 (0.86 – 1.00)	0.060
Albumin	1.29 (1.13 – 1.47)	<0.001	1.31 (1.08 – 1.58)	0.005

OR, odds ratio; CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

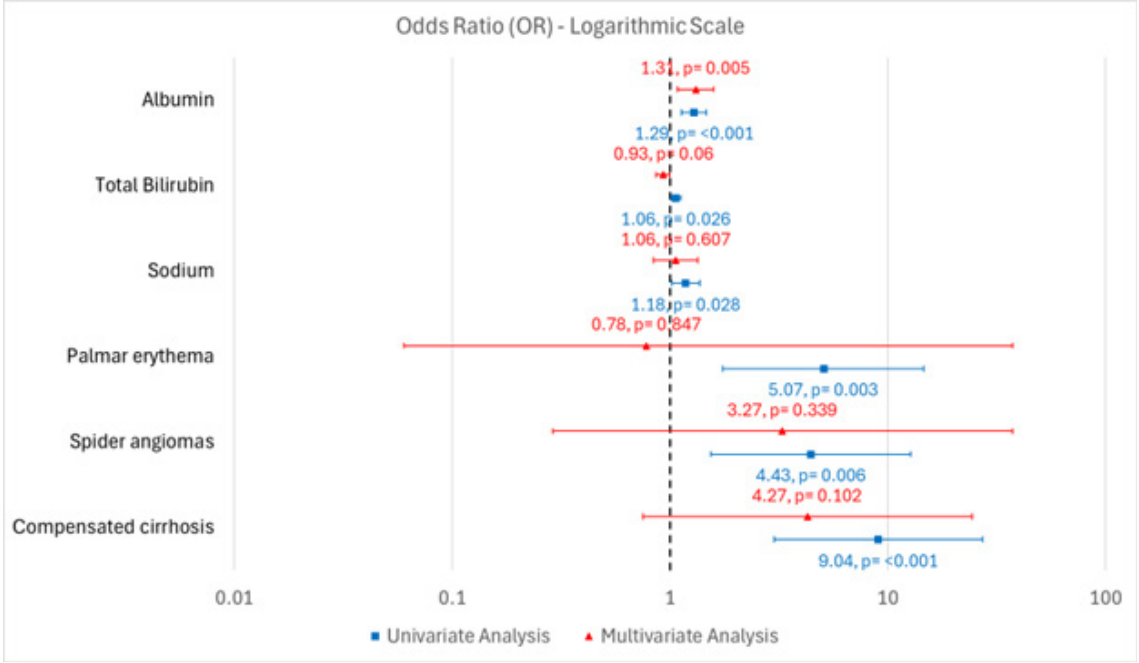

Figure 1. Forest Plot showing Odds Ratios, 95% Confidence Intervals, and p-values (from Table 3)

However, when these factors were adjusted for each other in the multivariate model (red), only Albumin remained a statistically significant independent risk factor (p=0.005). Other factors, including "Compensated Cirrhosis" which initially had a very high OR, lost their statistical significance, suggesting their effects were explained by other variables in the model.

4. DISCUSSION

4.1. Baseline Characteristics of the Study Cohort

In our study, there was a male predominance with a male-to-female ratio of 3.6:1, and the mean age was 51.6 ± 1.7 years. These findings are consistent with the study by Jiaqi Li et al. , which reported a male prevalence of 83.7% and a mean age of 49 ± 12 years [4]. The higher prevalence in males may be attributed to a greater tendency for exposure to risk factors for Hepatitis B virus infection, such as unsafe sexual practices and the sharing of intravenous drug paraphernalia. The age characteristic is likely due to the fact that the majority of chronic hepatitis B patients in Vietnam are infected in early childhood; therefore, the disease typically progresses to active hepatitis only after passing the immune-tolerant phase (usually after 30 years of age).

4.2. Comparative Analysis of Clinical and Laboratory Parameters between the ACLF and non-ACLF groups in severe acute exacerbation of CHB

The proportion of males did not differ statistically between the two groups. The group that progressed to ACLF had a higher median age than the non-ACLF group (60 vs. 47 years, p<0.001). Similar results were also reported in the study by Barosa et al. [5].

When comparing clinical characteristics, we noted that the group that progressed to ACLF had a significantly higher rate of compensated cirrhosis than the non-ACLF group (70.0% vs. 20.5%, p<0.001). This finding is consistent with the study by Ling Yuan et al. [6]. Our study recorded a higher prevalence of spider angiomas and palmar erythema in the ACLF group compared to the non-ACLF group. The symptoms of fever and splenomegaly showed no statistically significant difference between the two groups. Differences in clinical presentations between the groups vary across studies. In the study by Jiaqi Li et al., the ACLF group had a higher incidence of ascites (56.9%) compared to the non-ACLF group (54.6%) [4].

Regarding the specific markers for hepatitis B, HBeAg positivity and log HBV DNA levels showed no statistically significant difference between the two groups in our study. Similarly, the study by Jiaqi Li et al. reported no difference in the rates of HBeAg positivity and log HBV DNA levels between their groups [4]. In the study by Ling Yuan et al., however, while the rate of HBeAg positivity did not differ, the log HBV DNA level was higher in the group that progressed to ACLF compared to the non-ACLF group [6].

Biochemical and hematological tests for GGT, urea, creatinine, INR, white blood cell count, and platelet count also yielded no statistically significant differences between the two groups. Serum sodium levels in the ACLF group were lower than in the non-ACLF group, with a median of 134 (132–136) versus 136 (134.5–138). Levels of the liver enzymes ALT and AST were lower in the group that progressed to ACLF than in the non-ACLF group. Conversely, total bilirubin levels were higher in the ACLF group (median 17.2 [10.6–24.2] µmol/L) compared to the non-ACLF group (median 12.9 [5.7–19.4] µmol/L). Serum albumin levels were lower in the ACLF group, with a median of 30.0 (26.6–33.6) g/L, compared to 36.9 (32.5–38.8) g/L in the non-ACLF group. In the study by Jiaqi Li et al. , the ACLF group had higher levels of ALT, AST, total bilirubin, INR, white blood cells, and platelets, but lower values for GGT and urea [4]. In the study by Ling Yuan et al. , AST, GGT, and total bilirubin were higher in the ACLF group, while INR and PT were lower [6]. The study by Barosa et al. found that INR, total bilirubin, and creatinine were higher in the ACLF group, whereas serum sodium was lower [5]. Differences in biochemical and hematological test results among studies may be attributable to variations in anthropometric characteristics across study populations.

4.3. Risk Factor Analysis for ACLF Progression in severe acute exacerbation of CHB

This study utilized univariate logistic regression analysis to identify risk factors for progression to ACLF in patients with a severe acute exacerbation of CHB. Regarding clinical factors, patients with compensated cirrhosis had a 9-fold higher risk of developing ACLF than those without cirrhosis; patients with spider angiomas had a 4.4-fold higher risk, and those with palmar erythema had a 5-fold higher risk compared to patients without these signs. In terms of laboratory parameters, each 1-unit decrease in serum sodium was associated with a 1.18-fold increase in the risk of ACLF progression. Furthermore, each 1-unit increase in total bilirubin increased the risk by 1.06-fold, while each 1-unit decrease in serum albumin increased the risk by 1.29-fold. In a study by Ling Yuan et al. , univariate logistic regression analysis identified the following risk factors for ACLF progression: a history of cirrhosis (OR=3.091, 95% CI=1.280–7.465, p=0.012), HBV DNA (OR=1.463, 95% CI=1.018–2.101, p=0.04), AST (OR=1.001, 95% CI=1.000–1.002, p=0.013), and PT (OR=0.777, 95% CI=0.704–0.858, p<0.001) [6]. Similarly, Yi Ren et al. identified several statistically significant risk factors in their univariate analysis, including: age (OR=1.052, 95% CI=1.010–1.096, p=0.015), log HBV DNA (OR=1.761, 95% CI=1.202–2.579, p=0.004), total bilirubin (OR=1.004, 95% CI=1.001–1.008, p=0.013), serum sodium (OR=0.832, 95% CI=0.718–0.965, p=0.015), PT (OR=0.938, 95% CI=0.904–0.973, p=0.001), and INR (OR=64.82, 95% CI=12.7–329.6, p=0.005) [7].

Multivariate logistic regression analysis revealed that serum albumin was an independent risk factor for the progression to ACLF in severe acute exacerbation of CHB. In the study by Ling Yuan et al. , the statistically significant independent risk factors for ACLF progression included a history of compensated cirrhosis (OR=8.369, 95% CI=2.389–8.369, p=0.001), AST (OR=1.001, 95% CI=1.000–1.002, p=0.021), and PT (OR=0.758, 95% CI=0.672–0.855, p<0.001) [6]. Yi Ren et al. conducted a multivariate logistic regression analysis and identified independent risk factors significantly associated with the progression of ACLF, including age (OR = 1.054, 95% CI = 1.004–1.107, p = 0.034), log HBV DNA (OR = 1.705, 95% CI = 1.105–2.631, p = 0.016), and INR (OR = 37.74, 95% CI = 6.70–211.20, p < 0.001) [7].

It is noteworthy that while spider angiomas (OR = 4.43; p = 0.006), and palmar erythema (OR = 5.07; p = 0.003) were all significant risk factors in the univariate analysis, they lost their statistical significance in the multivariate model (p > 0.05 for all). This can be attributed to multicollinearity, as spider angiomas and palmar erythema are common clinical manifestations of underlying cirrhosis. Consequently, in the multivariate analysis, the predictive effect of these signs was likely subsumed by the more foundational variable of compensated cirrhosis, rendering them independently non-significant.

Interestingly, compensated cirrhosis, which was the most potent predictor in the univariate analysis (OR = 9.04, p < 0.001), also lost its statistical significance in the final multivariate model (p = 0.102). This is likely because the clinical diagnosis of cirrhosis is strongly correlated with a decline in hepatic synthetic function, which is more accurately and quantitatively captured by serum albumin levels. The fact that serum albumin remained a robust independent predictor (OR = 1.31, p = 0.005) suggests that its value as a direct biochemical marker of liver failure subsumed the more general clinical effect of a cirrhosis history in the model.

5. CONCLUSION

The risk factors associated with progression to acute-on-chronic liver failure (ACLF) in severe acute exacerbation of chronic hepatitis B (CHB) found in this study were a history of compensated cirrhosis, spider angiomas, palmar erythema, serum sodium, total bilirubin concentration, and serum albumin. Among these, serum albumin was an independent risk factor for the progression to ACLF in severe acute exacerbation of CHB. Therefore, close monitoring of serum albumin levels in patients with severe acute exacerbation of chronic hepatitis B is crucial for clinicians to early predict the risk of progression to ACLF and implement timely interventions.

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