Gut and Liver
https://doi.org/10.5009/gnl210449
pISSN 1976-2283 eISSN 2005-1212

Original Article

Metabolic Risk Factors Are Associated with the Disease Severity and Prognosis of Hepatitis B Virus-Related Acute on Chronic Liver Failure

Lu Chen[1], Jinjin Dai[2], Qing Xie[1], Xiaolin Wang[1], and Wei Cai[1]

[1]Department of Infectious Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, and [2]Department of Infectious Disease, Suzhou Hospital of Anhui Medical University (Suzhou Municipal Hospital of Anhui Province), Suzhou, China

Article Info

Received October 2, 2021
Revised December 12, 2021
Accepted December 27, 2021
Published online March 24, 2022

Corresponding Author

Wei Cai
ORCID https://orcid.org/0000-0001-9324-5987
E-mail carieyc@hotmail.com

Xiaolin Wang
ORCID https://orcid.org/0000-0001-5286-8758
E-mail visit-12345@hotmail.com

Qing Xie
ORCID https://orcid.org/0000-0003-2889-5670
E-mail xieqingrjh@163.com

Background/Aims: Metabolic risk factors could accelerate hepatitis B virus (HBV)-related mortality; however, their impacts on disease severity in HBV-related acute on chronic liver failure (HBV-ACLF) patients remain unexplored. In this study, we assessed the effects of metabolic risk factors on the outcome of HBV-ACLF patients.

Methods: This study retrospectively enrolled antiviral therapy naïve HBV-ACLF patients from a single center in China. Patients were evaluated according to Child-Turcotte-Pugh score, Model for End-Stage Liver Disease (MELD) score, 30-day, 90-day mortality and survival rate to estimate the prognosis of HBV-ACLF. The impacts of different metabolic risk factors were further analyzed.

Results: A total of 233 patients, including 158 (67.8%) with metabolic risk factors and 75 (32.2%) without metabolic risk factors, were finally analyzed. Patients with metabolic risk factors had significantly higher MELD score (22.6±6.1 vs 19.8±3.8, p<0.001), 90-day mortality rate (56.3% vs 38.7%, p=0.017), and shorter median survival time (58 days vs 75 days: hazard ratio, 1.553; 95% confidence interval, 1.061 to 2.274; p=0.036) than patients without them. Moreover, metabolic risk factors were independently associated with patients' 90-day mortality (hazard ratio, 1.621; 95% confidence interval, 1.016 to 2.585; p=0.043). Prediabetes/diabetes and hypertension were related to higher rates of infection and worse renal function in HBV-ACLF patients.

Conclusions: HBV-ACLF patients with metabolic risk factors, especially prediabetes/diabetes or hypertension, could have more severe disease and lower survival rates. In addition, the existence of metabolic disorder is an independent risk factor for HBV-ACLF patients' 90-day mortality. **(Gut Liver 2022;16:456-464)**

Key Words: Metabolic risk factor; Hepatitis B virus; Acute-on-chronic liver failure; 90-Day mortality

INTRODUCTION

Chronic hepatitis B (CHB) infection remains the leading cause of end-stage liver disease and hepatocellular carcinoma (HCC) in China, with about 90 million people infected with hepatitis B virus (HBV) and around 400,000 people died from CHB-related diseases annually.[1] As the prevalence of metabolic disorders, such as obesity, diabetes and metabolic syndrome dramatically increased in recent years, the co-occurrence of metabolic disorders and CHB is commonly encountered at present.[2,3] Gao *et al.*[4] reported that about 24.1% of CHB patients who received long-term antiviral therapy had concomitant metabolic risk factors in China. In addition, accumulating evidence has suggested the systematic effect of metabolic disorders on the progression and prognosis in CHB patients.[5,6] For example, previous studies have revealed that obesity was strongly associated with the risk of CHB-related fibrosis, cirrhosis and HCC.[7] A 14-year follow-up study in Taiwan yielded that diabetes was independently associated with the incidence of HCC in CHB patients.[8] Moreover, hepatic steatosis, which is closely related with obesity was a promoting factor for liver fibrosis and cirrhosis in CHB patients.[9] These studies suggested that metabolic risk factors were involved

in the outcome and prognosis in CHB patients.

HBV-related acute on chronic liver failure (HBV-ACLF) is characterized by an acute insult on the basis of CHB background. As an end-stage type of CHB, it occurs in approximately 30% of HBV-related cirrhosis patients.[10,11] The short-term mortality of HBV-ACLF is as high as 50%[12,13] and the only alliable treatment is liver transplantation. Several predisposing factors have been demonstrated to affect the outcome of patients with HBV-ACLF, such as HBV genotype,[14] infection,[15] and acute kidney injury.[16] Up till now, the impact of metabolic risk factors on the progression of HBV-ACLF patients remain poorly understood. Given that metabolic disorders can lead to several complications, such as fatty liver,[17] chronic kidney injury,[18] and infectious disease,[19] we suspected that metabolic risk factors may accelerate the progression of HBV-ACLF.

In this study, in order to identify the impact of metabolic risk factors on the disease severity and prognosis of HBV-related ACLF, we enrolled patients with HBV-ACLF and investigated the characteristics of HBV-ACLF patients with or without concomitant metabolic risk factors, including overweight/obesity, dyslipidemia, prediabetes/diabetes, and hypertension and we evaluated the impact of metabolic risk factors on the prognosis of HBV-ACLF patients.

MATERIALS AND METHODS

1. Patients

HBV-ACLF patients admitted to the Department of Infectious Diseases, Ruijin Hospital, between 2015 and 2020, aged 18 to 80 years, were retrospectively recruited in the study. CHB was defined as detection of hepatitis B virus surface antigen on two occasions measured at least 6 months apart.[20] The including criteria of HBV-ACLF were based on both the Chinese Group on the Study of Severe Hepatitis B[21] and Asian Pacific Association for the Study of the Liver criteria:[22] (1) hepatitis B virus surface antigen positive longer than 6 months; (2) serum bilirubin ≥5 mg/dL and coagulopathy (international normalized ratio [INR] ≥1.5 or prothrombin activity <40%); or (3) complicated within 4 weeks by clinical ascites and/or encephalopathy. The excluding criteria were as followed: (1) patients received liver transplantation; (2) accompanied with HCC or other solid organ cancer; or (3) copresence of other hepatitis, such as hepatitis C, hepatitis E or autoimmune hepatitis, drug-induced liver injury. A detailed flowchart for the enrollment of the patients is presented in Fig. 1. The study was approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine (approval number: 2016-111). Informed consent was waived due to the retrospective study design.

2. Study design

Patients included in this study were further classified into three groups: patients with no metabolic risk factor, patients with single metabolic risk factor and patients with ≥2 metabolic risk factors. The diagnosis standards of metabolic risk factors were as followed: (1) overweight/obesity was defined as body mass index ≥23 kg/m^2;[23] (2) dyslipidemia was defined as plasma triglycerides ≥1.7 mmol/L or plasma high-density lipoprotein cholesterol <1.0 mmol/L for men and <1.3 mmol/L for women;[24] (3) prediabetes was diagnosed as fasting glucose levels 5.6 to 6.9 mmol/L, or 2-hour post-load glucose levels 7.8 to 11.0 mmol/L, or hemoglobin A1c 5.7% to 6.4%. Diabetes was diagnosed according to the standard diagnostic criteria;[25] or (4) hypertension was defined as blood pressure ≥130/85 mm Hg or specific drug treatment.[26] Among 233 patients, 75 patients had no metabolic risk factor, 102 patients had one metabolic risk factor (37 with only overweight/obesity, 14 with only dyslipid-

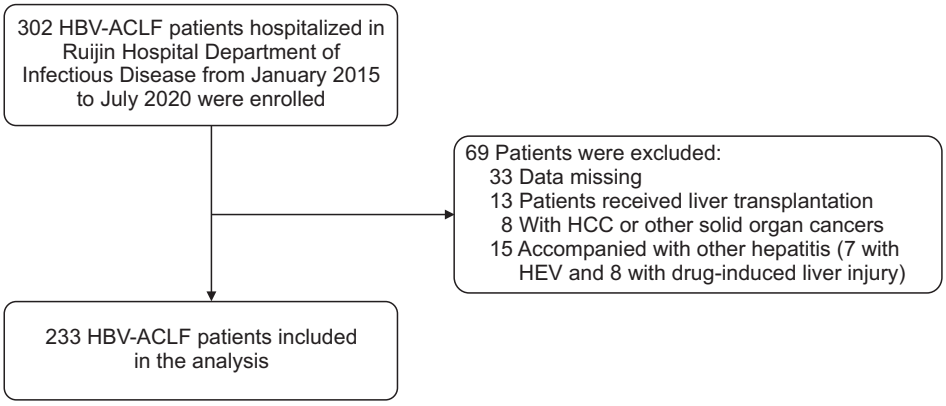

Fig. 1. Flowchart of patients with HBV-ACLF in the study.
HBV-ACLF, hepatitis B virus-related acute on chronic liver failure; HCC, hepatocellular carcinoma; HEV, hepatitis E virus.

emia, 38 with only prediabetes/diabetes, and 13 with only hypertension) and 56 patients had ≥2 risk factors.

3. Laboratory examination

Blood samples were collected at the time of admission to the hospital. Complete the whole blood count, liver function panel, renal function panel, lipid panel (total cholesterol, triglyceride, high-density lipoprotein cholesterol, and lower-density lipoprotein cholesterol), and disseminated intravascular coagulation panel (prothrombin activity and international normalization ratio) were tested. The patients' medical history and blood pressure were also recorded at admission. The Child-Turcotte-Pugh (CTP) score and Model for End-Stage Liver Disease (MELD) score were calculated from the first results of laboratory examination of the patients. Examinations to evaluate the infection were undertaken as needed, including chest computed tomography scan, abdominal paracentesis, urinary test, and blood culture.

4. Statistical analysis

GraphPad Prism v8.0 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis in the study. Mean±standard deviation was used for data expression. Continuous variables were compared with the Student t-test or the Mann-Whitney U test, and three-group continuous variables comparison were analyzed by analysis of variance. The categorical variables were analyzed with the chi-square test. The Cox-regression method was performed by SPSS version 25 (IBM Corp., Armonk, NY, USA), and multivariant including age, CTP score, MELD score, with metabolic risk factors, with infection, with decompensated cirrhosis, total bilirubin, serum creatinine, INR, HBV DNA were analyzed.

RESULTS

1. Characteristics of enrolled patients

A total of 302 patients were enrolled in this study and

Table 1. The Characteristics of Study Cohort

Characteristic	Total patients (n=233)	With no risk factors (n=75)	With risk factor (n=158)	With 1 risk factor (n=102)	With ≥2 risk factors (n=56)
Age, yr	48.0±13.0	46.0±14.6	48.7±12.3 p=0.191	47.5±13.0 p=0.467	49.4±12.3 p=0.152
Male sex	205 (88.0)	64 (85.3)	141 (89.2) p=0.396	94 (92.2) p=0.218	47 (83.9) p>0.999
Alanine aminotransferase, IU/L	1,163.9±837.1	1,175.7±904.1	1,158.2±806.4 p=0.882	1,185.2±790.7 p=0.941	1,109±839.3 p=0.667
Aspartate aminotransferase, IU/L	911.1±666.1	899.4±671.4	916.6±665.6 p=0.855	959.2±671.5 p=0.559	838.9±653.4 p=0.607
Total bilirubin, μmol/L‡	274.0±121.5	248.9±105.5	286.0±127.0 p=0.029*	277.3±120.3 p=0.105	301.9±138.1 p=0.014*
Serum creatinine, μmol/L‡	78.4±43.6	67.6±19.6	83.5±50.5 p=0.009†	79.4±34.4 p=0.009†	91.0±70.7 p=0.007†
International normalized ratio	2.0±1.7	1.8±0.3	2.1±2.0 p=0.228	2.2±2.5 p=0.241	2.0±0.5 p=0.017*
Albumin, g/L	31.7±20.7	30.2±4.5	32.4±24.9 p=0.369	30.7±4.8 p=0.468	35.7±41.4 p=0.211
Alpha-fetoprotein, ng/mL	202.8±512.3	139.9±239.3	232.8±598.9 p=0.198	234.1±593.2 p=0.176	230.4±614.6 p=0.207
HBV DNA, log IU/mL	6.19±1.46	6.26±1.37	6.16±1.50 p=0.865	6.12±1.56 p=0.603	6.24±1.42 p=0.869
HBeAg positive	91 (39.1)	25 (33.3)	66 (41.8) p=0.251	45 (44.1) p=0.164	21 (37.5) p=0.712
Ascites	210 (90.1)	67 (89.3)	143 (90.5) p=0.816	92 (90.2) p>0.999	51 (91.1) p>0.999
Hepatic encephalopathy	81 (34.8)	24 (32.0)	57 (36.1) p=0.560	39 (38.2) p=0.430	18 (32.1) p>0.999
Cirrhosis	123 (52.8)	39 (52.0)	84 (53.2) p=0.889	55 (53.9) p=0.879	29 (51.8) p>0.999

Data are presented as mean±SD or number (%).
HBV DNA, hepatitis B virus DNA; HBeAg, hepatitis B e antigen.
*p<0.05, †p<0.01 as compared with patients with no risk factors (with Student t-test or Mann-Whitney U test); ‡Analysis of variance (patients with no risk factors vs patients with 1 risk factor vs patients with ≥2 risk factors).

233 patients were finally included in the analysis (Fig. 1). Patients were predominantly male (88%) with a mean age of 48±13 years. Patients were divided into three groups according to the number of co-existing metabolic risk factors. As illustrated in Table 1, 75 patients (32.2%) had no metabolic related risk factor; 102 patients (43.8%) had only one metabolic risk factor (37 with overweight/obesity, 14 with dyslipidemia, 38 with prediabetes/diabetes, 13 with hypertension) and 56 patients (24%) had ≥2 metabolic risk factors. We then compared the biochemical parameters among the three groups. All patients received antiviral treatment when they were admitted to the hospital. There were no statistical differences in age, sex, alanine aminotransferase, aspartate aminotransferase, serum albumin, alpha-fetoprotein, HBV DNA, hepatitis B e antigen positivity, the incidences of ascites and hepatic encephalopathy (HE) and the proportion of underlying cirrhosis among different groups. Notably, analysis of variance test indicated that total bilirubin and serum creatinine were significantly different among the three groups (patients with no risk factors vs patients with one risk factor vs patients with ≥2 risk factors). Further analysis showed that the characteristics including total bilirubin (286.0±127.0 vs 248.9±105.5, p=0.029) and serum creatinine (83.5±50.5 vs 67.6±19.6, p=0.009) were significantly increased in patients with metabolic risk factors compared to patients with no risk factors. Patients with ≥2 metabolic risk factors had significantly higher total bilirubin (301.9±138.1 vs 248.9±105.5, p=0.014), serum creatinine (91.0±70.7 vs 67.6±19.6, p=0.007), and INR (2.0±0.5 vs 1.8±0.3, p=0.017) compared to patients with no risk factors (Table 1). Patients with only one metabolic risk factor had significantly higher serum creatinine than patients with no metabolic risk factor (79.4±34.4 vs 67.6±19.6, p=0.009) (Table 1).

2. Impact of metabolic risk factors on disease severity

The MELD and the CTP scores were valued to evaluate the disease severity. The mean CTP and MELD scores for total patients were 10.2±1.2 and 21.7±5.6, respectively. Significantly higher MELD scores were observed in patients with metabolic risk factor as compared to patients with no metabolic risk factor (22.6±6.1 vs 19.8±3.8, p<0.001). Both patients with only one (22.3±5.9, p=0.001) and with ≥2 metabolic risk factors (23.2±6.5, p<0.001) had significantly higher MELD scores than patients without risk factor. No significant differences in CTP scores were detected (Table 2).

Overall, 55 patients (23.6%) died in 30 days and 118 patients (50.6%) died in 90 days. The median survival days for patients with or without metabolic risk factors were 58 and 75 days, respectively (hazard ratio [HR], 1.553; 95% confidence interval [CI], 1.061 to 2.274; p=0.036) (Fig. 2). The median survival for patients with only one metabolic risk factor and for patients with ≥2 metabolic risk factors were 65 days and 49 days, respectively. Statistical difference was found between patients with no metabolic risk factor and with ≥2 metabolic risk factors (p=0.029) (Supplementary Fig. 1). Patients with only one metabolic risk factor had significantly higher 90-day mortality than patients without metabolic risk factor (55.9% vs 38.7%, p=0.033). Interestingly, the 90-day mortality of patients with ≥2 metabolic risk factors was not significantly different from patients with no metabolic risk factor. No differences were detected

Table 2. The Disease Severity Evaluations in HBV-ACLF Patients with or without Metabolic Risk Factors

Patients	CTP score	MELD score	30-Day mortality	90-Day mortality
Total (n=233)	10.2±1.2	21.7±5.6	55 (23.6)	118 (50.6)
With no risk factors (n=75, 32.2%)	10.0±1.2	19.8±3.8	13 (17.3)	29 (38.7)
With risk factor (n=158, 67.8%)	10.2±1.2	22.6±6.1	42 (26.6)	89 (56.3)
	p=0.258	p<0.001‡	p=0.139	p=0.017*
With 1 risk factor (n=102)	10.2±1.2	22.3±5.9	24 (23.5)	57 (55.9)
	p=0.476	p=0.001†	p=0.354	p=0.033*
With ≥2 risk factors (n=56)	10.3±1.3	23.2±6.5	18 (32.1)	32 (57.1)
	p=0.367	p<0.001‡	p=0.062	p=0.051
With overweight/obesity (n=84)	10.2±1.3	22.9±5.8	23 (27.4)	46 (54.8)
	p=0.302	p<0.001‡	p=0.184	p=0.056
With dyslipidemia (n=40)	10.1±1.3	21.3±5.3	9 (22.5)	21 (52.5)
	p=0.756	p=0.079	p=0.619	p=0.171
With prediabetes/diabetes (n=81)	10.4±1.2	23.0±5.9	24 (29.6)	49 (60.5)
	p=0.078	p<0.001‡	p=0.090	p=0.010*
With hypertension (n=30)	10.0±1.1	22.4±5.0	12 (40.0)	18 (60.0)
	p=0.978	p=0.005†	p=0.022*	p=0.054

Data are presented as mean±SD or number (%).
HBV-ACLF, hepatitis B virus-related acute on chronic liver failure; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease.
*p<0.05, †p<0.01, ‡p<0.001 as compared with patients with no risk factors.

in 30-day mortality among different groups (Table 2).

3. Metabolic risk factor is independently associated with 90-day mortality

Multivariant analysis by the Cox-regression proportional hazards method was further performed to investigate the association between metabolic risk factors and 30-day or 90-day mortality. The results showed that age, CTP score, MELD score, infection, INR were independent risk factors for 30-day and 90-day mortality. Metabolic risk factor was independently associated with 90-day mortality (HR, 1.621; 95% CI, 1.016 to 2.585; p=0.043) but not 30-day mortality (Table 3).

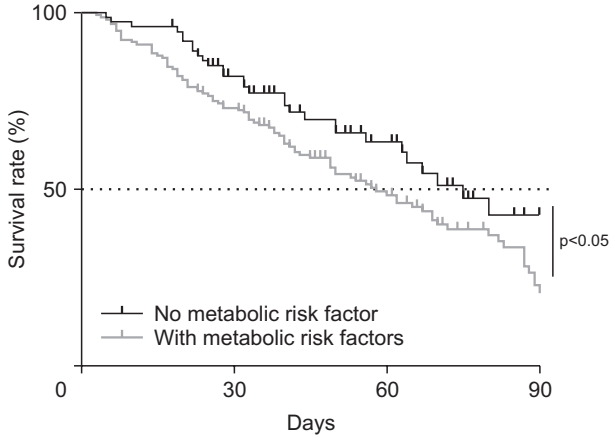

Fig. 2. Comparison of the survival rates of hepatitis B virus-related acute on chronic liver failure (HBV-ACLF) patients with or without metabolic risk factors. The survival curves were generated to compare the overall survival rates between HBV-ACLF patients with metabolic risk factors versus those without metabolic risk factors.

4. The impact of different metabolic risk factors for disease severity

We further analyzed the impact of specific metabolic risk factor on the disease severity and prognosis of HBV-ACLF. As illustrated in Table 2, patients with overweight/obesity, prediabetes/diabetes and hypertension had increased MELD scores. Patients with hypertension had higher 30-day mortality and patients with prediabetes/diabetes had higher 90-day mortality. The survival analysis demonstrated that patients with prediabetes/diabetes (HR, 1.75; 95% CI, 1.123 to 2.728; p=0.015) or hypertension (HR, 1.933; 95% CI, 0.993 to 3.765; p=0.025) had significantly lower survival rate compared to patients with no metabolic risk factor (Fig. 3).

The mechanisms underlying the impact of a specific metabolic risk factor on HBV-ACLF might be different. Thus, we assessed the 102 patients with only one risk factor and divided them into four different groups according to their specific metabolic risk factor. Among the 102 patients, 37 (36.3%) had only overweight/obesity, 14 (13.7%) had only dyslipidemia, 38 (37.3%) had only prediabetes/diabetes, and 13 (12.7%) had only hypertension. As illustrated in Table 4, patients with only overweight/obesity had significantly higher serum creatinine levels (0.90±0.37 vs 0.77±0.22, p=0.022) and MELD scores (21.9±4.5 vs 19.8±3.8, p=0.010). Patients with only dyslipidemia had significantly higher previous hospitalization number (42.9% vs 16.0%, p=0.032). Patients with only prediabetes/diabetes had significantly higher rates of bacterial infection (81.6% vs 57.3%, p=0.012) and higher levels of total bilirubin (17.5±7.9 vs 14.6±6.2, p=0.030), INR (2.0±0.3 vs 1.8±0.3, p=0.042), serum creatinine (0.91±0.42 vs 0.77±0.22, p=0.020) and MELD scores (22.6±4.9 vs 19.8±3.8, p=0.001). Patients with only hypertension had significantly higher serum creatinine levels (0.97±0.39

Table 3. Multivariate Analysis of 30-Day and 90-Day Mortality by Using the Cox Proportional Hazards Regression Model

Mortality	Wald	df	Exp (B)	95% CI	p-value
30-Day mortality					
Age	12.118	1	1.037	(1.016–1.058)	0.000
CTP score	21.040	1	1.891	(1.441–2.483)	0.000
MELD score	5.017	1	1.051	(1.006–1.097)	0.025
Infection	5.109	1	2.416	(1.124–5.192)	0.024
INR	4.356	1	1.155	(1.007–1.325)	0.039
90-Day mortality					
Age	11.076	1	1.026	(1.011–1.041)	0.001
CTP score	21.466	1	1.573	(1.299–1.905)	0.000
MELD score	4.036	1	1.036	(1.001–1.072)	0.045
Infection	18.294	1	3.771	(2.052–6.927)	0.000
Metabolic risk factor	4.112	1	1.621	(1.016–2.585)	0.043
INR	5.974	1	1.177	(1.033–1.342)	0.015

CI, confidence interval; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio.

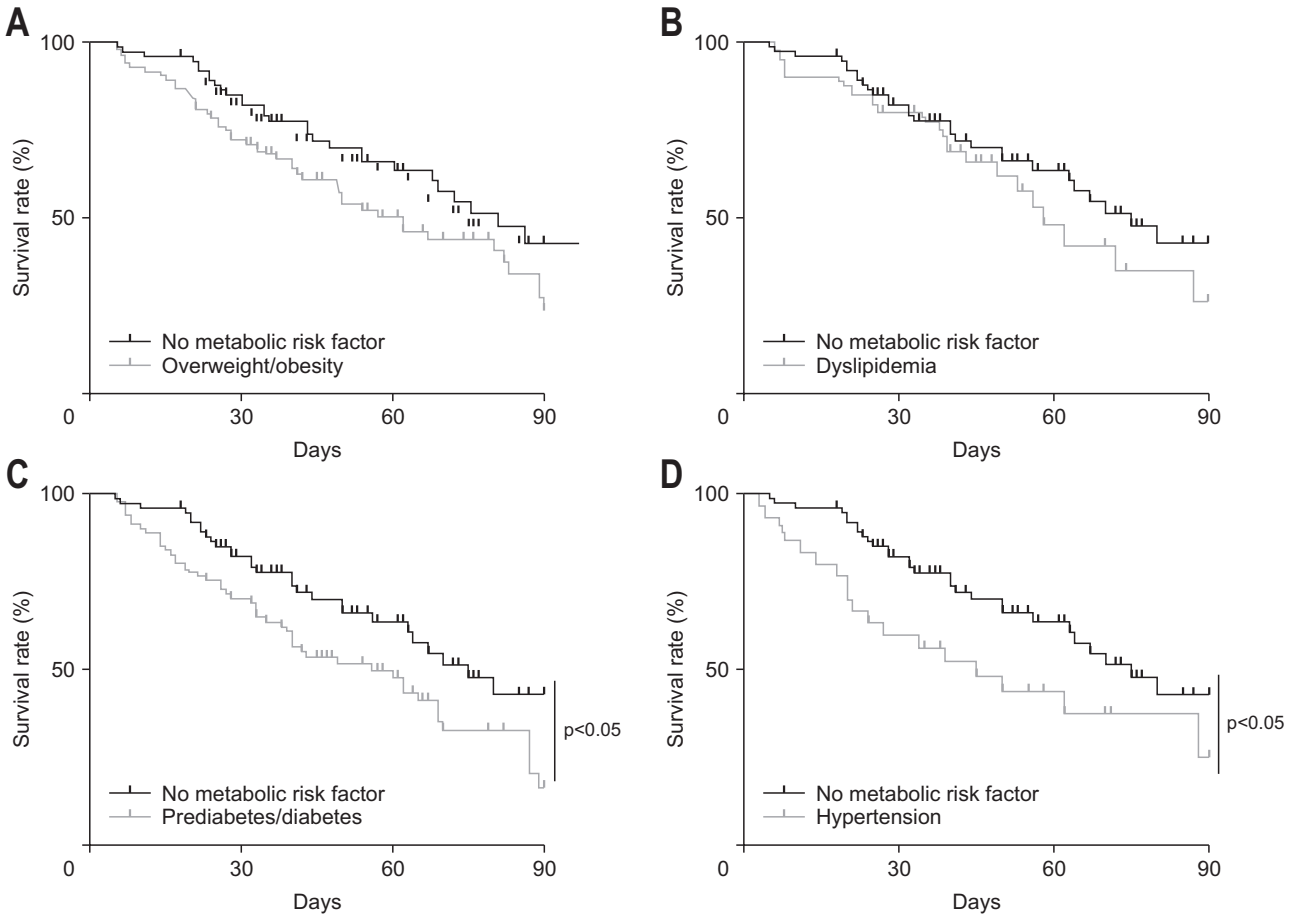

Fig. 3. Comparison of the survival rates in hepatitis B virus-related acute on chronic liver failure (HBV-ACLF) patients with different metabolic risk factors. The survival curves were drawn to compare survival rates among HBV-ACLF patients with concomitant overweight/obesity (A), dyslipidemia (B), prediabetes/diabetes, (C) or hypertension (D).

vs 0.77±0.22, p=0.009) and MELD scores (25.0±10.9 vs 19.8±3.8, p=0.002) (Table 4). These results suggested that the lower survival rates in patients with prediabetes/diabetes might be due to increased infection rates and worse liver and renal function. And the impact of hypertension on HBV-ACLF might be largely due to the impaired renal function.

DISCUSSION

Accumulating studies have reported that the hepatic steatosis, metabolic syndrome or metabolic risk factors are associated with CHB disease progression and outcome;[27-29] however, the impact of metabolic risk factors on the progression of HBV-ACLF remain unknown. Our results lend further credence that metabolic risk factors are associated with the disease severity and progression of HBV-ACLF. Patients with prediabetes/diabetes or hypertension could have more severe disease and a lower survival rate. Furthermore, the metabolic factor was an independent risk factor for HBV-ACLF patients' 90-day mortality.

Previous studies regarding the impact of metabolic risk factors on ACLF were mainly focused on alcohol-related ACLF.[30] To the best of our knowledge, the current study is the first study to explore the impact of the metabolic related risk factors in HBV-ACLF patients in China. Our study suggested that HBV-ACLF patients with metabolic risk factors tended to have poor outcomes compared with patients without metabolic risk factors. The higher total bilirubin and serum creatinine levels in patients with metabolic risk factors suggested that their liver and kidney were more vulnerable during the progression of HBV-ACLF. Notably, MELD scores were significantly increased in patients with metabolic risk factors; however, no differences were detected in CTP scores. CTP scores included variables of HE and ascites, which were common in patients in our study because of the cirrhosis background (45.1% patients had HE and 90.1% patients had ascites in total). Thus, we speculated that the comparable CTP scores between groups of patients with or without metabolic disorders might be due to the similar prevalence of HE and

Table 4. Characteristics of HBV-ACLF Patients with a Single Metabolic Risk Factor

Characteristics	With no risk factor (n=75)	With only overweight/obesity (n=37)	With only dyslipidemia (n=14)	With only prediabetes/diabetes (n=38)	With only hypertension (n=13)
Age, yr	46.5 ±14.3	45.8±13.3 p=0.937	49.3±11.1 p=0.430	47.7±12.4 p=0.550	52.8±13.3 p=0.122
Decompensation	67 (89.3)	32 (86.5) p=0.937	13 (92.9) p>0.999	36 (94.7) p=0.491	11 (84.6) p=0.638
Any previous hospitalization	12 (16.0)	6 (16.2) p>0.999	6 (42.9) p=0.032*	6 (15.8) p>0.999	3 (23.1) p=0.689
Bacterial infection	43 (57.3)	22 (46.8) p=0.270	9 (64.3) p=0.771	31 (81.6) p=0.012*	10 (76.9) p=0.230
Gastrointestinal hemorrhage	3 (4.0)	0 p=0.550	0 p>0.999	2 (5.3) p>0.999	1 (7.7) p=0.479
Ascites	67 (89.3)	32 (86.5) p=0.756	13 (92.9) p>0.999	36 (94.7) p=0.491	11 (84.6) p=0.638
Hepatic encephalopathy	24 (32.0)	16 (43.2) p=0.296	3 (21.4) p=0.538	16 (42.1) p=0.305	4 (30.8) p>0.999
Total bilirubin, mg/dL	14.6±6.2	15.2±6.8 p=0.605	16.5±5.5 p=0.281	17.5±7.9 p=0.030*	14.9±6.6 p=0.845
International normalization ratio	1.8±0.3	1.9±0.6 p=0.147	1.7±0.2 p=0.315	2.0±0.3 p=0.042*	2.0 ±0.3 p=0.084
Alanine aminotransferase, U/L	1,175.7±904.1	1,195.7±746.8 p=0.908	1,166.2±965.7 p=0.972	1,095.7±779.4 p=0.643	1,437.8 ±781.3 p=0.329
Aspartate aminotransferase, U/L	899.4±671.4	954.9±689.8 p=0.684	967.1±697.6 p=0.732	914.2±721.7 p=0.914	1,094.9 ±455.9 p=0.316
Serum creatinine, mg/dL	0.77±0.22	0.90±0.37 p=0.022*	0.82±0.4 p=0.476	0.91±0.42 p=0.020*	0.97±0.39 p=0.009†
Serum sodium, mmol/L	135.7±4.6	133.6±20.5 p=0.408	136.3±4.0 p=0.643	134.3±5.4 p=0.171	133.4±3.8 p=0.091
MELD	19.8±3.8	21.9±4.5 p=0.010*	20.2±4.5 p=0.693	22.6±4.9 p=0.001†	25.0±10.9 p=0.002†

Data are presented as mean±SD or number (%).
HBV-ACLF, hepatitis B virus-related acute on chronic liver failure; MELD, Model for End-Stage Liver Disease.
*p<0.05, †p<0.01 as compared with patients with no risk factors.

ascites in different groups.

We noticed that patients with ≥2 metabolic risk factors did not show significant differences in 30-day and 90-day mortality compared to those without metabolic risk factors; however, their 30-day mortality rates (32.1%) and 90-day mortality rates (57.1%) were higher than patients with one risk factor (23.5% and 55.9%, respectively) and even higher than patients without risk factors (17.3% and 38.7%, respectively). Since the number of patients with two risk factors was relatively small (n=56), we speculated that the small number of patients we studied could be the possible reason for the results. A larger amount of data should be analyzed in the future.

A previous study studied the impact of metabolic risk factors on the alcoholic-related ACLF patients. It has been reported that that overweight/obesity and dyslipidemia could affect the disease severity and 30-day mortality.[30] Intriguingly, our results showed that overweight/obesity or dyslipidemia had no impact on 30-day or 90-day mortality and survival rate, but prediabetes/diabetes or hypertension had significant effect on survival rate. It has been proven that diabetes could pose a higher mortality in CHB patients,[31] and was independently associated with an increased risk of fungal infection and worse 30-day mortality in alcoholic-related ACLF patients.[32] Our results revealed that patients with prediabetes/diabetes had higher risk of bacterial infection and worse renal function. The higher total bilirubin and INR levels in those patients suggested that their livers are more susceptible to acute insult happened in ACLF. Since diabetes is associated with increased risk of infection,[19] chronic kidney disease,[18] and fatty liver,[17] we speculated that the higher MELD scores and lower survival rates in patients with prediabetes/diabetes might be due to increased infection rates and worse liver and renal function.

In recent years, nonalcoholic fatty liver disease (NAFLD) has emerged as the predominant cause for liver transplantation and HCC.[33,34] Evidence has suggested that NAFLD is closely related with metabolic disorders. Based on a meta-analysis results, 42% of NAFLD patients had metabolic

syndrome, 69% had hyperlipidemia, 51% had obesity, 39% had hypertension and 22% had diabetes globally.[33] Our results provided evidence that metabolic risk factors are associated with HBV-ACLF patients' prognosis and outcomes. Since patients with metabolic risk factors were most likely to have NAFLD,[35] we speculated that NAFLD was also a risk factor for the mortality of patients with HBV-ACLF. Unfortunately, we did not include the prevalence of NAFLD in our study. It will be interesting to explore the impact of NAFLD in the mortality of HBV-ACLF patients in the future.

Taken together, our study suggested that metabolic risk factors, especially prediabetes/diabetes and hypertension were associated with higher mortality in HBV-ACLF patients. The mechanisms underlying the interplay between metabolic related risk factors and HBV-ACLF are poorly understood, which need to be further explored. With the increased prevalence of metabolic diseases, patients with concomitant HBV-ACLF and metabolic disorders are increasingly encountered in clinical practice. Thus, the influence of metabolic disorders should be carefully considered and managed in patients with HBV-ACLF. It will be interesting to evaluate the benefits of strict glucose and blood pressure control in patients with HBV-ACLF. Clinical studies with large-sample cohort are advocated to reveal more comprehensive characteristics of the clinical features and provide more evidence for the management of patients with coincidental HBV-ACLF and metabolic disorders.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (grant number: 81770578), the National Natural Science Foundation of Shanghai (grant number: 20ZR1433500), the Major Project of National Thirteenth Five-year Plan (grant number: 2017ZX09304016), project of Shanghai Municipal Health and Family Planning (grant number: 20184Y0091).

AUTHOR CONTRIBUTIONS

Study concept and design: W.C., X.W. Data acquisition: J.D., L.C. Data analysis and interpretation: L.C., X.W. Drafting of the manuscript; critical revision of the manuscript for important intellectual content: L.C., X.W. Statistical analysis: L.C. Obtained funding: W.C., X.W., L.C. Administrative, technical, or material support; study supervision: Q.X.

ORCID

Lu Chen https://orcid.org/0000-0003-1845-1320
Jinjin Dai https://orcid.org/0000-0003-1365-2625
Qing Xie https://orcid.org/0000-0003-2889-5670
Xiaolin Wang https://orcid.org/0000-0001-5286-8758
Wei Cai https://orcid.org/0000-0001-9324-5987

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl210449.

REFERENCES

1. Wang H, Men P, Xiao Y, et al. Hepatitis B infection in the general population of China: a systematic review and meta-analysis. BMC Infect Dis 2019;19:811.
2. Machado MV, Oliveira AG, Cortez-Pinto H. Hepatic steatosis in hepatitis B virus infected patients: meta-analysis of risk factors and comparison with hepatitis C infected patients. J Gastroenterol Hepatol 2011;26:1361-1367.
3. Lim CT, Goh GB, Li H, et al. Presence of hepatic steatosis does not increase the risk of hepatocellular carcinoma in patients with chronic hepatitis B over long follow-up. Microbiol Insights 2020;13:1178636120918878.
4. Gao H, Kuang Z, Zhong CX, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in patients with chronic hepatitis B receiving antiviral therapy. Zhonghua Gan Zang Bing Za Zhi 2019;27:347-351.
5. Peleg N, Issachar A, Sneh Arbib O, et al. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. JHEP Rep 2019;1:9-16.
6. Lee YB, Ha Y, Chon YE, et al. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. Clin Mol Hepatol 2019;25:52-64.
7. Choi HS, Brouwer WP, Zanjir WM, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2020;71:539-548.
8. Chen CL, Yang HI, Yang WS, et al. Metabolic factors and

risk of hepatocellular carcinoma by chronic hepatitis B/C infection: a follow-up study in Taiwan. Gastroenterology 2008;135:111-121.
9. Karacaer Z, Okur G, Cermik H, Altun D. Is there an influence of hepatic steatosis on fibrosis and necroinflammation in young patients with chronic viral hepatitis B? Postgrad Med 2016;128:697-700.
10. Arroyo V, Moreau R, Jalan R, Ginès P; EASL-CLIF Consortium CANONIC Study. Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol 2015;62(1 Suppl):S131-S143.
11. Sarin SK, Choudhury A, Sharma MK, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL): an update. Hepatol Int 2019;13:353-390.
12. Shi Y, Yang Y, Hu Y, et al. Acute-on-chronic liver failure precipitated by hepatic injury is distinct from that precipitated by extrahepatic insults. Hepatology 2015;62:232-242.
13. Li H, Chen LY, Zhang NN, et al. Characteristics, diagnosis and prognosis of acute-on-chronic liver failure in cirrhosis associated to hepatitis B. Sci Rep 2016;6:25487.
14. Ren X, Xu Z, Liu Y, et al. Hepatitis B virus genotype and basal core promoter/precore mutations are associated with hepatitis B-related acute-on-chronic liver failure without pre-existing liver cirrhosis. J Viral Hepat 2010;17:887-895.
15. Zhai XR, Tong JJ, Wang HM, et al. Infection deteriorating hepatitis B virus related acute-on-chronic liver failure: a retrospective cohort study. BMC Gastroenterol 2020;20:320.
16. Yuan W, Zhang YY, Zhang ZG, Zou Y, Lu HZ, Qian ZP. Risk factors and outcomes of acute kidney injury in patients with hepatitis B virus-related acute-on-chronic liver failure. Am J Med Sci 2017;353:452-458.
17. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism 2016;65:1096-1108.
18. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis 2018;25:121-132.
19. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. Indian J Endocrinol Metab 2012;16(Suppl1):S27-S36.
20. Tang LS, Covert E, Wilson E, Kottilil S. Chronic hepatitis B infection: a review. JAMA 2018;319:1802-1813.
21. Wu T, Li J, Shao L, et al. Development of diagnostic criteria and a prognostic score for hepatitis B virus-related acute-on-chronic liver failure. Gut 2018;67:2181-2191.
22. Sarin SK, Kedarisetty CK, Abbas Z, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. Hepatol Int 2014;8:453-471.
23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-163.
24. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-2752.
25. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 Suppl 1:S81-S90.
26. Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension 2020;75:1334-1357.
27. Seto WK, Hui RW, Mak LY, et al. Association between hepatic steatosis, measured by controlled attenuation parameter, and fibrosis burden in chronic hepatitis B. Clin Gastroenterol Hepatol 2018;16:575-583.
28. Yu MW, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of metabolic risk factors on risk of hepatocellular carcinoma and liver-related death in men with chronic hepatitis B: a large cohort study. Gastroenterology 2017;153:1006-1017.
29. Lee YB, Moon H, Lee JH, et al. Association of metabolic risk factors with risks of cancer and all-cause mortality in patients with chronic hepatitis B. Hepatology 2021;73:2266-2277.
30. Duseja A, De A, Taneja S, et al. Impact of metabolic risk factors on the severity and outcome of patients with alcohol-associated acute-on-chronic liver failure. Liver Int 2021;41:150-157.
31. Shyu YC, Huang TS, Chien CH, Yeh CT, Lin CL, Chien RN. Diabetes poses a higher risk of hepatocellular carcinoma and mortality in patients with chronic hepatitis B: a population-based cohort study. J Viral Hepat 2019;26:718-726.
32. Bajaj JS, Reddy RK, Tandon P, et al. Prediction of fungal infection development and their impact on survival using the NACSELD cohort. Am J Gastroenterol 2018;113:556-563.
33. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease: meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73-84.
34. Sundaram V, Jalan R, Shah P, et al. Acute on chronic liver failure from nonalcoholic fatty liver disease: a growing and aging cohort with rising mortality. Hepatology 2021;73:1932-1944.
35. Kanwal S, Ghaffar T, Aamir AH, Usman K. Frequency of non-alcoholic fatty liver disease in patients with type-2 diabetes mellitus and its associated risk factors. Pak J Med Sci 2021;37:1335-1341.