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Risk factors and prognosis of pulmonary infection in hepatitis B-related acute-on-chronic liver failure: a retrospective cohort study

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Abstract

Objective To identify risk factors for pulmonary infection in patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (ACLF), assess its impact on prognosis, and develop a prognostic prediction model.

Methods We retrospectively analyzed the clinical data of 393 patients with HBV-ACLF. Logistic regression was used to analyze the risk factors for lung infection in ACLF patients, as well as the factors affecting the prognosis of those who were infected. Additionally, a prognostic prediction model was established using the Nomogram method.

Results The incidence of pulmonary infections in patients with ACLF was 38.7%, and patients with ACLF combined with pulmonary infections had a higher short-term mortality rate than those without infections (65.71% vs. 35.02%). Multivariate logistic regression analysis indicated that independent risk factors for pulmonary infection included TBIL, CRP, invasive procedures, peritoneal effusion, and hepatic encephalopathy. Additionally, creatinine, INR, comorbid diabetes mellitus, neutrophil counts, and lymphocyte counts were identified as independent risk factors affecting 30-day mortality in patients with pulmonary infection. Incorporating these risk factors, a new predictive model was established, with an area under the receiver operating characteristic curve of 0.832 (95% CI, 0.765-0.900). This model demonstrated higher discriminatory performance compared to traditional prognostic models such as CTP, MELD, and MELD-Na, with statistically significant differences ($P < 0.05$).

Conclusion HBV-ACLF patients are susceptible to pulmonary infection, with fungal infection posing a significant threat. Pulmonary infection is associated with worse prognosis in HBV-ACLF patients. Early identification of risk factors and prognostic assessment can facilitate timely intervention and improve prognosis.

Keywords Hepatitis B, Acute-on-chronic liver failure, Pulmonary infection, Risk factors, Prediction model

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Introduction

Acute-on-chronic liver failure (ACLF) is a clinical syndrome that occurs on the basis of chronic liver disease and is the most common type of liver failure encountered in clinical practice [1]. Patients with ACLF have a poor clinical prognosis, with a 30-day mortality rate ranging from 30–39.9% [2–4]. The Asia-Pacific region is a high-burden area for hepatitis B virus (HBV) infection, accounting for more than 60% of the global annual deaths related to chronic liver disease, among which HBV-related ACLF (HBV-ACLF) is a common cause of HBV-related mortality [5, 6]. Patients with HBV-ACLF suffer from severe liver dysfunction and immune dysfunction, making them susceptible to various infections, including pulmonary infections, which occur in 18.76–29.17% of cases and significantly impact disease progression and prognosis [7–9].

Early identification of risk factors for pulmonary infection and timely prognostic assessment can guide the implementation of precise prevention and treatment strategies, reducing the incidence of pulmonary infection and improving survival and quality of life. While the risk factors for infection in ACLF patients have been reported, research on specific site infections, particularly pulmonary infection, is relatively limited and often focuses on the overall characteristics and risk factors of bacterial or fungal infections in ACLF patients.

The prognosis of ACLF patients with pulmonary infection is worse compared to those without infection. Infection exacerbates the inflammatory cascade, leading to multi-organ dysfunction and further increasing mortality [10]. In-depth research on the impact of various biochemical indicators on the occurrence and prognosis of pulmonary infection is crucial for guiding the rational selection of antimicrobial agents, individualized treatment plans, and the development of appropriate prognostic assessments.

Based on this, this study aims to investigate the risk factors for pulmonary infection in ACLF patients and establish a prediction model to assess the prognosis of patients with pulmonary infection, providing references for the prevention and intervention of pulmonary infection in ACLF patients.

Materials and methods

Study population

We retrospectively collected clinical data on ACLF patients admitted to the Shanghai Public Health Clinical Center from January 2019 to January 2024. Inclusion Criteria: (1) Complete medical records; (2) Hospital stay of at least 5 days; (3) Age of 18 years or older. Chronic Hepatitis B (HBV) infection is defined as positivity for Hepatitis B Surface Antigen (HBsAg) and/or Hepatitis B Virus DNA for more than 6 months. The diagnostic criteria for Acute-on-Chronic Liver Failure (ACLF) in this study are based on the 2018 Chinese guidelines for the diagnosis and treatment of liver failure [1]: (1) Extreme fatigue accompanied by significant anorexia, abdominal bloating, nausea, and vomiting, among other severe gastrointestinal symptoms; (2) Rapid deepening of jaundice, with serum total bilirubin ≥ 10 times the upper limit of normal or an increase of ≥ 17.1 μmol/L per day; (3) Bleeding manifestations with prothrombin activity ≤ 40% (or INR ≥ 1.5), excluding other causes. Exclusion Criteria: (1) Concurrent liver failure due to other types of hepatitis viruses or other viruses; (2) Liver failure due to drugs, ethanol, poisoning, or other causes; (3) Pregnant women; (4) Hematological diseases; (5) Underlying kidney diseases or renal insufficiency; (6) Underlying pulmonary diseases, tuberculosis, lung cancer, or other malignant tumors with pulmonary metastasis.

The incidence of pulmonary infections after admission is divided into the infected group and the uninfected group. The clinical diagnostic criteria for pulmonary infection are: new or progressive infiltrates or consolidations on chest X-ray or CT, plus two or more of the following three clinical symptoms: (1) Fever, with body temperature > 38 °C; (2) Purulent airway secretions; (3) Peripheral white blood cell count > 10 × 10^9/L or < 4 × 10^9/L [11].

Data collection

Collect demographic information of patients, including gender and age, through the patient management system. The data of uninfected patients is clinical data within 24 h of admission, while the baseline data of infected patients is laboratory test data at the time of infection diagnosis. The data encompassed total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), serum creatinine (Cr), sodium (Na), white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, platelet count, hemoglobin (Hb), Child-Turcotte-Pugh (CTP) score, Model for End-Stage Liver Disease (MELD) score, and MELD-Na score. Clinical characteristics documented included diabetes, hepatic encephalopathy, gastrointestinal bleeding, ascites, steroid use, and invasive surgery. Data collection and entry were performed by two individuals to ensure accuracy.

Statistical analysis

SPSS 26.0 and R 4.3.0 software were used for statistical analysis. Categorical variables were expressed as frequencies and percentages (%), and comparisons between groups were made using the chi-square test (χ^2 test). Measurements that conformed to normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm s$), and comparisons between groups were made using the

independent samples t-test; continuous variables that were not normally distributed were expressed as median (interquartile spacing), and two-by-two comparisons were made using the Mann-Whitney U test. For categorical variables, the chi-square test was used for between-group comparisons. Independent predictors of 30-day mortality for ACLF combined with lung infection were identified by multivariate logistic regression analysis, which included variables with statistically significant differences in univariate analysis. Subsequently, a risk prediction model was constructed. The applicability of the model was assessed using the Hosmer-Lemeshow test, and its predictive performance was evaluated using the subject's work characteristics (ROC) curve and the area under the ROC curve (AUC). p-value < 0.05 was considered statistically significant.

Results

Distribution of pathogenic bacteria in the infected group of patients

A total of 393 patients with HBV-ACLF were collected, of which 138 (35.11%) were combined with pulmonary infection. Out of 138 patients with ACLF combined with lung infection, positive sputum specimens were obtained from 49 patients and 52 strains of pathogenic bacteria were detected. Among them, 12 strains of Gram-negative bacteria accounted for 23.08%. The most detected categories were Klebsiella pneumoniae 4 strains, Stenotrophomonas maltophilia 4 strains and Pseudomonas aeruginosa 1 strain respectively. Gram-positive bacteria 6 strains, accounting for 27.27%. The most detected categories were 3 strains of Staphylococcus aureus, 2 cases of Enterococcus faecalis and 1 strain of Staphylococcus epidermidis, respectively. Fungi were 34 strains, accounting for 65.38%, and the most detected categories were 17 strains of Candida albicans, 5 strains of Aspergillus fumigatus, and 4 strains of Candida tropicalis, respectively. See Table 1 for details.

Comparison of general information between HBV-ACLF-infected and uninfected groups

Comparison of baseline data between HBV-ACLF patients with and without co-infected lungs revealed that neutrophils, lymphocyte count, monocyte count, TBIL, PT, INR, Hb, CRP, Invasive Operations, hepatic encephalopathy, and Ascites were higher in the infected group than in the uninfected group. lymphocyte count, total cholesterol, LDL-C, HDL-C, albumin and blood sodium were lower than those in the infected group, and the difference was statistically significant ($P < 0.05$). The MELD, MELD-Na and CTP prognostic model scores as well as 30-day mortality rates of patients in the pulmonary infection group were also significantly higher than those in the uninfected group ($P < 0.05$), as shown in Table 2.

Analysis of risk factors for the occurrence of pulmonary infections

Univariate analysis identified ALT, TBIL, Cr, albumin, invasive operation, hepatic encephalopathy, ascites, Hb, CRP, Na, neutrophil count, TC, and lymphocyte count as risk factors associated with the development of pulmonary infection. Multivariate analysis revealed that TBIL, CRP, invasive operation, ascites, and hepatic encephalopathy were independent risk factors for the development of pulmonary infection ($P < 0.05$), as shown in Table 3.

Characteristics of the survival and mortality groups of patients with HBV-ACLF combined lung infections

Based on 30-day mortality, 138 ACLF patients with co-infected lungs were categorized into survival and death

Table 1 Distribution of pathogenic bacteria

Pathogen Category	Pathogen Name	Number($n = 52$)	Proportion (%)
Gram-Negative Bacteria	Klebsiella pneumoniae	4	7.69
	Stenotrophomonas maltophilia	4	7.69
	Pseudomonas aeruginosa	1	1.92
	Escherichia coli	1	1.92
	Acinetobacter baumannii	1	1.92
	Burkholderia multivorans	1	1.92
Gram-Positive Bacteria	Staphylococcus aureus	3	5.76
	Enterococcus faecalis	2	3.85
	Staphylococcus epidermidis	1	1.92
Fungi	Candida albicans	17	32.69
	Aspergillus fumigatus	5	9.61
	Candida tropicalis	4	7.69
	Candida glabrata	4	7.69
	Candida glabrata	2	3.85
	Mucor spp.	1	1.92
	Aspergillus niger	1	1.92

Table 2 Baseline characteristics of the lung-infected and uninfected groups of patients with HBV-ACLF

Variables	Infected group ($n=136$)	Uninfected group ($n=257$)	Z/χ2	*P* value
Age (years)	53.50(41.25,64.00)	51.00(25,75)	Z=-0.557	0.578
Male n (%)	111 (81.62%)	190 (73.93%)	χ2 = 2.932	0.087
WBC ($\times10^9$/L)	7.31(4.94,10.97)	6.16(4.54,8.64)	Z=-2.804	0.005
Neutrophils ($\times10^9$/L)	5.27(3.62,8.79)	4.04(2.88,6.44)	Z=-3.797	< 0.001
Monocytes($\times10^9$/L)	0.730(0.49,1.10)	0.65(0.45,0.89)	Z=-2.334	0.020
Platelets ($\times10^9$/L)	84.00(57.25,126.00)	92.00(62.00,130.50)	Z=-0.579	0.563
Lymphocytes ($\times10^9$/L)	0.80(0.48,1.14)	1.03(0.71,1.44)	Z=-3.889	< 0.001
TBIL (μmol/L)	417.45(275.88,609.28)	316.10(186.05,451.85)	Z=-4.595	< 0.001
ALT (U/L)	84.50(47.00,209.25)	150.00(52,522.80)	Z=-3.201	0.001
AST(U/L)	122.85(71.00,298.00)	154.00(77.70,361.50)	Z=-1.617	0.106
γ-GT (U/L)	65.50(43.25,127.75)	86.00(49.50,137.00)	Z=-1.233	0.218
Fg(g/L)	1.57(1.07,2.10)	1.61(1.27,2.07)	Z=-0.805	0.421
ALB (g/L)	30.42(27.60,34.44)	32.30(28.67,35.49)	Z=-2.296	0.022
Cr (μmol/L)	71.15(56.33,103.08)	65.80(55.25,83.27)	Z=-2.237	0.025
Hb (g/L)	110(90.00,122.75)	118.00(101.00,135.00)	Z=-3.408	0.001
Na(mmol/L)	134.00(130.00,137.00)	136.00(133.00,138.00)	Z=-4.004	< 0.001
PT(s)	24.75(20.03,29.30)	22.10(18.40,26.35)	Z=-2.761	0.006
INR	2.26(1.69,2.95)	1.94(1.53,2.53)	Z=-2.730	0.006
AFP(ng/mL)	47.85(7.63,65)	65.00(14.24,124.15)	Z=-1.820	0.069
CRP(mg/L)	13.205(6.27,27.32)	7.95(3.69,15.60)	Z=-4.828	< 0.001
TC (mmol/L)	1.740(1.28,2.70)	2.230(1.43,2.89)	Z=-3.708	< 0.001
TG (mmol/L)	1.10(0.86,1.52)	1.23(0.93,1.52)	Z=-1.740	0.082
APOE (mmol/L)	63.00(42.63,75.02)	63.00(48.32,78.25)	Z=-1.301	0.193
LDL-C (mmol/L)	0.93(0.63,1.46)	1.16(0.73,1.64)	Z=-2.694	0.007
HDL-C (mmol/L)	0.14(0.13,0.23)	0.19(0.13,0.30)	Z=-3.232	0.001
Log-HBV	3.54(2.00,5.12)	3.47(2.05,5.52)	Z=-1.060	0.289
HBeAg(+) n (%)	27(19.85%)	61(23.74%)	χ2 = 0.771	0.380
Hepatic encephalopathy n (%)	48(35.29%)	44 (17.12%)	χ2 = 16.383	< 0.001
Ascites n (%)	54(39.71%)	62(24.12%)	χ2 = 10.379	0.001
Diabetes n (%)	19(13.97%)	23(8.95%)	χ2 = 2.349	0.125
Invasive Operations n (%)	88(64.71%)	107(41.63%)	χ2 = 18.937	< 0.001
Using hormones n (%)	13(9.56%)	35(13.62%)	χ2 = 1.367	0.242
Gastrointestinal bleeding n (%)	8(5.88%)	9(3.50%)	χ2 = 1.218	0.270
MELD	21.95(17.76,26.07)	25.73(20.59,31.42)	Z=-4.281	< 0.001
MELD-Na	20.34(13.97,28.72)	27.54(21.34,36.21)	Z=-5.372	< 0.001
CTP	9(8,10)	10(9,12)	Z=-5.058	< 0.001
30-day mortality n (%)	88(64.71%)	90(35.02%)	χ2 = 31.632	< 0.001

Abbreviations: HBV-ACLF, Hepatitis B virus-related acute-on-chronic liver failure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; ALB, Albumin; Hb, Hemoglobin; Cr, Creatinine; WBC, White blood cell count; INR, International normalized ratio; PT, Prothrombin time; Fg, Fibrinogen; CRP: C-reactive protein; AFP, Alpha-fetoprotein; TC, Total cholesterol; TG, Triglyceride; APOE, Apolipoprotein E; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease with Serum Sodium; CTP, Child-Turcotte-Pugh score

groups. There were statistically significant differences in age, leukocyte count, neutrophil count, lymphocyte count, TBIL, AST, Cr, PT, INR, TC, and ApoE levels in the survivor group compared to the mortality group. ($P<0.05$). In addition, CTP scores of patients with end-stage liver disease model, serum sodium end-stage liver disease model, and CTP scores of the lung infection group were significantly higher compared with the survival group ($P<0.05$), Table 4.

Characteristics of survivors and non-survivors of HBV-ACLF patients with pulmonary infection

Univariate analysis identified age, TBIL, AST, Cr, INR, type 2 diabetes, lymphocyte count, and neutrophil count as risk factors for 30-day mortality. ($P<0.05$). Multivariate analysis revealed that Cr, INR, diabetes mellitus, neutrophil count, and lymphocyte count were independent predictors of 30-day mortality. ($P<0.05$). Figure 1; Table 5.

Table 3 Unifactorial and multifactorial analysis of lung infections occurring in patients with HBV-ACLF

Variables	Univariate analysis		multivariate analysis	
	OR (95%CI)	*P* value	OR (95CI%)	*P* value
ALT (U/L)	0.999 (0.999-1.000)	0.008		
TBIL (μmol/L)	1.003 (1.002–1.004)	0.000	1.002(1.000-1.003)	0.025
Cr (μmol/L)	1.006 (1.002–1.010)	0.000		
ALB (g/L)	0.955 (0.915–0.998)	0.040		
INR	1.057 (0.927–1.205)	0.407		
Invasive Operations n (%)	2.570 (1.671–3.952)	0.000	1.695(1.025–2.803)	0.040
Hepatic encephalopathy n (%)	2.640 (1.636–4.261)	0.000	2.162(1.225–3.817)	0.008
Ascites n (%)	2.071 (1.325–3.238)	0.001	1.767(1.067–2.924)	0.027
Hb (g/L)	0.985 (0.977–0.993)	0.000		
Na(mmol/L)	0.906 (0.866–0.949)	0.000		
Neutrophils($\times10^9$/L)	1.117 (1.052–1.186)	0.000		
TC (mmol/L)	1.003 (1.002–1.004)	0.000		
CRP(mg/L)	1.029(1.016–1.043)	0.000	1.025(1.010–1.040)	0.001
Lymphocytes($\times10^9$/L)	0.526 (0.361–0.766)	0.001		

Abbreviations: HBV-ACLF, hepatitis B virus-related acute-on-chronic liver failure; ALT, Alanine aminotransferase; ALB, Albumin; Hb, Hemoglobin; Cr, Creatinine; INR, international normalized ratio; CRP, C-reactive protein; TC: Total cholesterol

Construction and predictive performance of the 30-Day mortality prediction model for HBV-ACLF patients with pulmonary infection

From the results of logistic regression analysis, the equation [logistic(p) = 0.8773 + 0.5451* Neutrophils − 0.6371* Lymphocytes + 0.6681 * INR + 1.165* Cr + 0.555 * Diabetes] was obtained, and the variables were assigned values using the variables' The coefficients were assigned to the variables as the assignment criteria, and the Hosmer-Lemeshow test of the established model was used to test the goodness-of-fit of the Logistic(p) model, and the results showed that the goodness-of-fit, $\chi2 = 9.580$, $P = 0.025$, indicated that the column chart prediction model had a good fit. The calibration curves showed good agreement between the predicted probabilities obtained based on the logistic(p) model and the actual probabilities, as shown in Fig. 2.AUC was used to assess the accuracy of the present model versus the conventional prediction models MELD, MELD-Na, and CTP for the prediction of the 30-day mortality rate of patients with infections Table 6. The ROC curves showed that the area under the curve of the logistic(p) model was 0.832 (95% CI, 0.741–0.946) was higher than that of MELD, MELD-Na, CTP ($P < 0.05$). Evaluating the efficacy of logistic(p) versus other models for clinical applications using decision curves showed that the logistic(p) model had a high clinical benefit when the threshold probability was in the range of 0.44–0.99. In addition, the clinical impact curve is a further algorithm of the decision curve, and the clinical impact curves of the line graph of the column gradually overlap when the prediction probability is 0.6, indicating that the predicted values obtained can represent the actual values better. Refer to Fig. 2 for details.

Discussion

The liver, as the largest detoxification organ in the human body, is particularly susceptible to various organic lesions in patients with severe liver failure graded as C, exacerbating the loss of liver immune function. Moreover, the long-term use of steroids and broad-spectrum antibiotics further increases the risk of infection in these patients [12]. Furthermore, ACLF patients experience extensive damage or death of Kupffer cells, leading to the suppression of immune-related regulation and resulting in immunosuppression, making them more susceptible to infections [13]. Pulmonary infection is the most common type of secondary infection in ACLF patients. Previous studies have shown that ACLF patients with pulmonary infection have higher 28-day and 90-day mortality rates compared to patients with other types of infections. Our study revealed that among 393 ACLF patients, 136 cases developed pulmonary infection, with an incidence rate of 34.6%. This incidence rate is higher than those reported in domestic studies [7, 9], which may be attributed to the fact that more than half of our study population comprised late-stage ACLF patients. Late-stage ACLF patients have poor liver function and severe immune impairment, increasing their susceptibility to infections.

Infections are commonly associated with a high short-term mortality rate in patients with ACLF, highlighting the importance of identifying risk factors for the occurrence of infections for early diagnosis and treatment. This study found that the incidence of pulmonary infection was correlated with TBIL, CRP, invasive procedures, concurrent ascites, and hepatic encephalopathy, in line with previous research [14, 15]. Invasive procedures disrupt the normal tissue barriers and structures, diminishing the body's defense against environmental pathogens and increasing the risk of infection in patients. Ascites

Table 4 Characteristics of HBV-ACLF patients with combined lung infections in the mortality and survival groups

Variables	survivors (*n* = 48)	non-survivors (*n* = 88)	Z/χ2	*P* value
Age (years)	47(38.25,62.50)	55.50(46.25,65.00)	Z=-2.177	0.029
Male n (%)	41 (85.42%)	70(79.55%)	χ2 = 0.714	0.398
WBC ($\times10^9$/L)	5.97(4.47,8.07)	8.14(5.23,11.57)	Z=-3.092	0.002
Neutrophils ($\times10^9$/L)	4.06(2.94,5.45)	6.43(4.19,9.80)	Z=-3.707	< 0.001
Monocytes($\times10^9$/L)	0.70(0.46,0.91)	0.80(0.52,1.22)	Z=-1.681	0.093
Lymphocytes ($\times10^9$/L)	1.06(0.72,1.51)	0.69(0.47,1.05)	Z=-2.999	0.003
Platelets (×109/L)	93.00(59.25,125.50)	82.00(57.00,126.75)	Z=-0.009	0.993
TBIL (μmol/L)	321.65(164.70,489.80)	459.49(319.68,645.68)	Z=-3.101	0.002
ALT (U/L)	70(34.50,209.25)	103.85(58.25,210.68)	Z=-1.460	0.144
AST (U/L)	102.35(60.50,175.50)	143.00(93.75,319.00)	Z=-2.411	0.016
γ-GT (U/L)	62.15(44.10,118.50)	79.50(41.00,137.00)	z=-0.740	0.459
Fg(g/L)	1.67(1.26,2.24)	1.45(1.01,1.97)	Z=-1.829	0.067
ALB (g/L)	30.29(27.73,34.225)	30.42(27.53,34.70)	Z=-0.323	0.746
Cr (μmol/L)	64.08(51.18,79.43)	75.95(60.14, 117.65)	Z=-2.969	0.003
Hb (g/L)	110.50(90.25,124.50)	109.50(90,121.75)	Z=-0.335	0.738
Na(mmol/L)	134(130.00,138.85)	133.90(130.00,137.00)	Z=-0.930	0.352
PT (s)	21.60(17.80,26.75)	25.25(21.775,30.13)	Z=-3.279	0.001
INR	1.87(1.44,2.52)	2.46(1.87,3.23)	Z=-3.308	0.001
AFP(ng/mL)	62.35(10.43,70.48)	39.75(6.44,65)	Z=-0.706	0.480
CRP(mg/L)	10.09(6.27,20.02)	15.38(6.15,34.95)	Z=-1.364	0.173
TC (mmol/L)	2.09(1.45,2.74)	1.57(1.10,2.41)	Z=-2.180	0.029
TG (mmol/L)	1.20(0.91,1.52)	1.07(0.82,1.47)	Z=-1.093	0.274
APOE (mmol/L)	59.98(42.63,79.98)	63.00(42.25,74.87)	Z=-0.410	0.682
LDL-C (mmol/L)	1.165(0.68,146)	0.88(0.58,1.46)	Z=-1.494	0.135
HDL-C (mmol/L)	0.17(0.13,0.30)	0.13(0.13,0.23)	Z=-1.639	0.101
Log-HBV	3.32(2.00,4.86)	3.81(2.00,5.58)	Z=-0.186	0.852
HBeAg(+) n (%)	13(27.08%)	14(15.91%)	χ2 = 2.437	0.118
Hepatic encephalopathy n (%)	9(18.75%)	39(44.32%)	χ2 = 8.891	0.003
Ascites n (%)	17(35.42%)	37(42.05%)	χ2 = 0.570	0.450
Diabetes n (%)	2(4.17%)	17(19.32%)	χ2 = 5.932	0.015
Gastrointestinal bleeding n (%)	3(6.25%)	5(5.68%)	χ2 = 0.018	0.898
MELD	21.43(16.04,26.36)	28.33(22.47,33.59)	Z=-4.913	< 0.001
MELD-Na	22.93(14.31,30.97)	28.88(25.19,41.53)	Z=-3.693	< 0.001
CTP	9.50(9.00,11.00)	11.00(9.00,12.00)	Z=-3.191	0.001

Abbreviations: HBV-ACLF, Hepatitis B virus-related acute-on-chronic liver failure; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; TBIL, Total bilirubin; ALB, Albumin; Hb, Hemoglobin; Cr, Creatinine; WBC, White blood cell count; INR, International normalized ratio; PT, Prothrombin time; Fg, Fibrinogen; CRP: C-reactive protein; AFP, Alpha-fetoprotein; TC, Total cholesterol; TG, Triglyceride; APOE, Apolipoprotein E; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease with Serum Sodium; CTP, Child-Turcotte-Pugh score

provides a conducive environment for bacterial growth and spread, and due to the compression of lung volume by ascites, which impairs lung expansion, the body's ability to clear pathogenic microorganisms is weakened, thereby reducing the capacity to fight against infections. TBIL is a reliable indicator of changes in the liver's detoxification and excretory functions, and a decline in these functions is a significant cause of infection [16]. Studies have identified TBIL as an independent risk factor for bacterial infection in patients with decompensated cirrhosis [17, 18]. This study suggests that an increase in CRP may indicate the possibility of infection in HBV-ACLF patients. CRP is an important non-specific acute-phase protein synthesized by the liver and released into the bloodstream. The reactive oxygen species produced by its metabolism can induce intracellular oxidative stress, thereby activating NF-κB; it also binds to complement C1q and activates the complement system through the classical pathway, stimulating the release of inflammatory mediators and exacerbating the inflammatory response [19, 20]. Consequently, CRP measurement is frequently used to monitor the therapeutic efficacy in chronic inflammatory diseases and serves as a sensitive indicator for clinical assessment of inflammation [21, 22]. Hepatic encephalopathy is a syndrome characterized by functional derangement of the central nervous system due to metabolic disorders, occurring as a complication of severe liver disease [23]. The results of this study indicate that HBV-ACLF patients with concurrent hepatic encephalopathy are more susceptible to bacterial

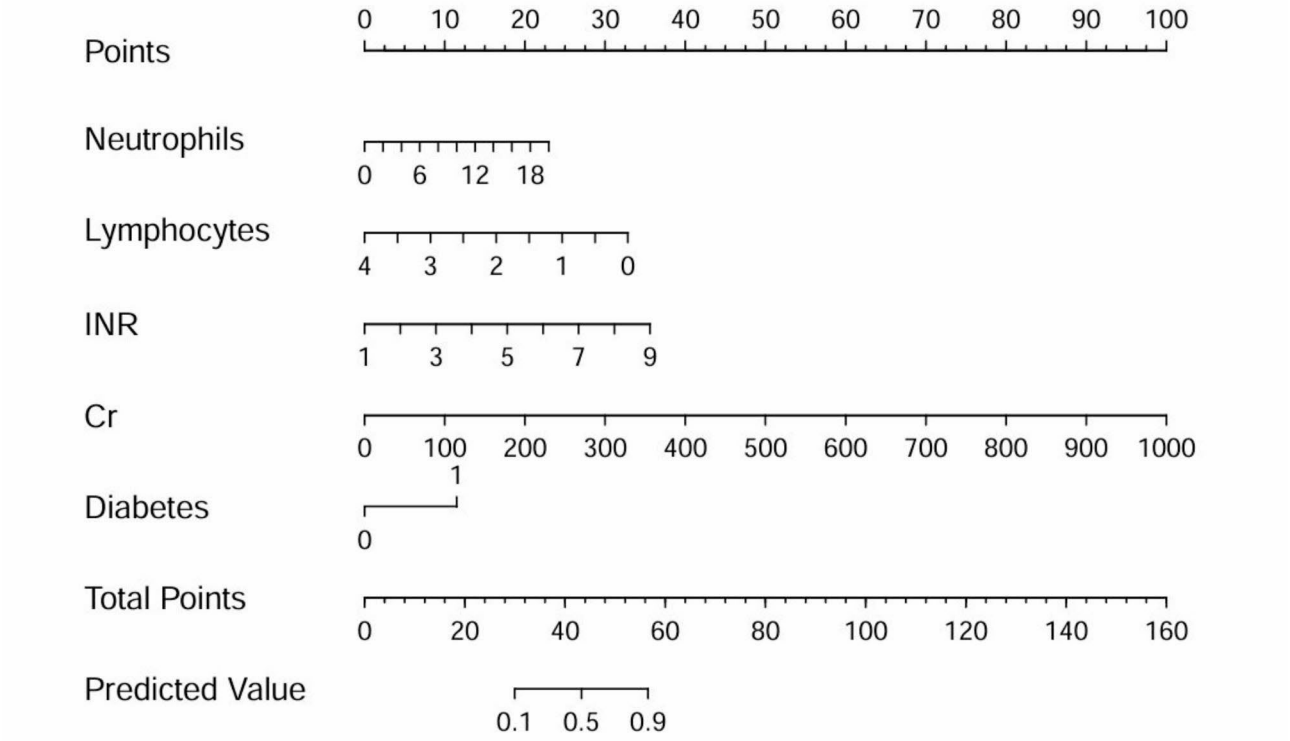

Fig. 1 Nomogram for predicting 30-day mortality in HBV-ACLF patients with pulmonary infection

Table 5 Univariate and multivariate regression analysis of 30-d morbidity and mortality in patients with HBV-ACLF combined with lung infection

Variables	Univariate analysis		Multivariate analysis	
	OR(95%CI)	*P* value	OR(95%CI)	*P* value
Age (years)	1.026(1.001–1.052)	0.043		
TBIL (μmol/L)	1.003 (1.001–1.005)	0.002		
AST (U/L)	1.000 (0.999–1.001)	0.781		
Cr (μmol/L)	1.018 (1.006–1.030)	0.004	1.016(1.004–1.028)	0.01
INR	1.082 (1.022–1.146)	0.006	1.951(1.169–3.254)	0.01
Diabetes n (%)	5.507 (1.215–24.964)	0.027	6.608(1.191–36.67)	0.031
Lymphocytes ($\times 10^9$/L)	0.448 (0.239–0.842)	0.013	0.287(0.123–0.666)	0.004
Neutrophils ($\times 10^9$/L)	1.235 (1.089–1.401)	0.001	1.203(1.037–1.394)	0.015
TC (mmol/L)	0.633(0.425–0.943)	0.025		
Hepatic encephalopathy n (%)	3.449 (1.492–7.973)	0.004		

Abbreviations: HBV-ACLF, Hepatitis B virus-related acute-on-chronic liver failure; AST, Aspartate aminotransferase; TBIL, Total bilirubin; ALB, Albumin; Hb, Hemoglobin; Cr, Creatinine; INR, International normalized ratio; PT, Prothrombin time; TC, Total cholesterol

infections than those without hepatic encephalopathy. Zang et al. [24] found that hepatic encephalopathy is a risk factor for inducing infections in ACLF patients, with those suffering from hepatic encephalopathy having a 2.083-fold increased risk of infection. For patients with hepatic encephalopathy, consciousness disorders can lead to aspiration and reflux, which are risk factors for pulmonary infection. In addition, In previous studies, hormones

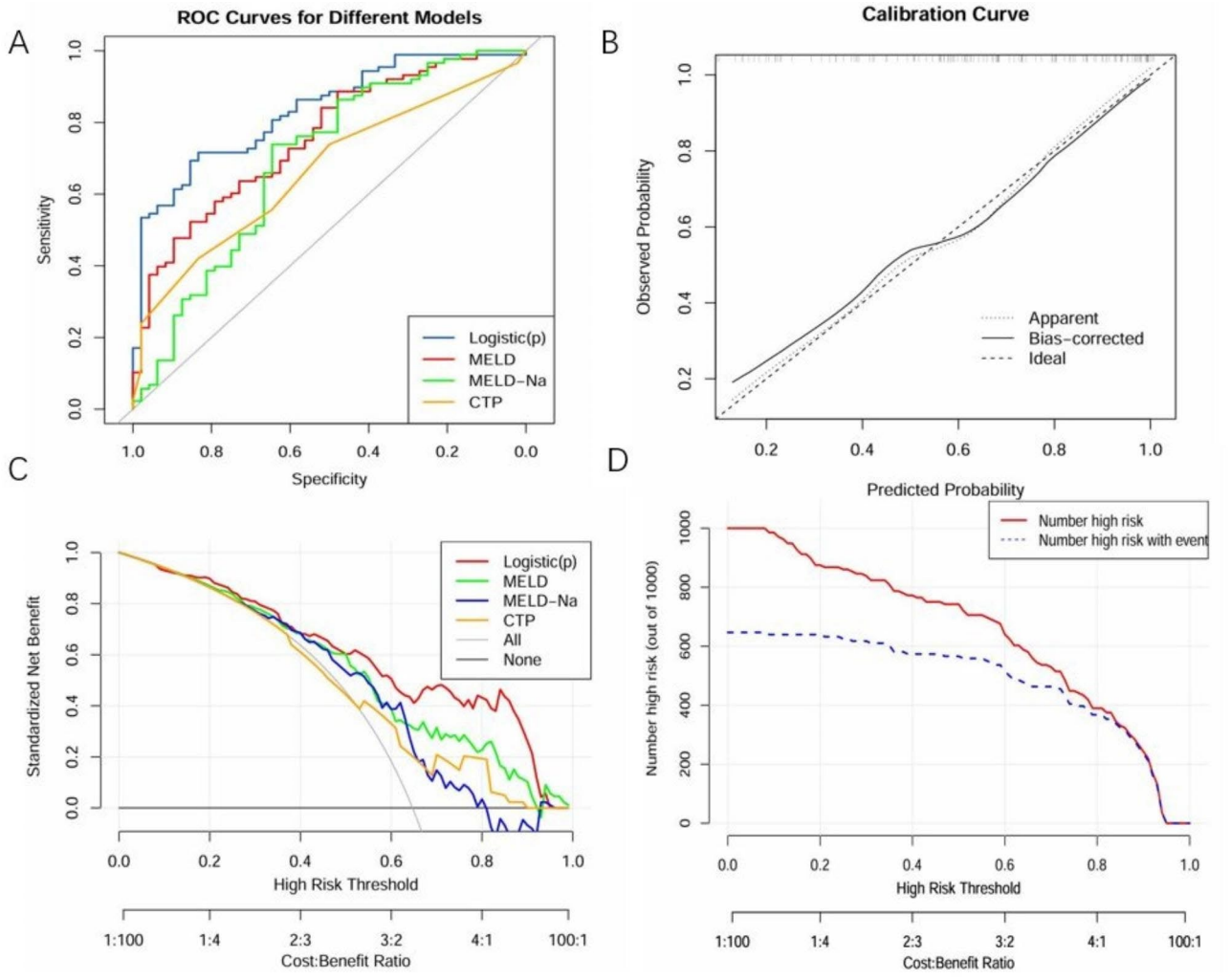

Fig. 2 Prediction performance and clinical applicability of the Logistic (p) model. (**A**) Comparison of ROC Curves for Logistic (p) and Other Prognostic Models (**B**) Calibration Curve for the Logistic (p) Prediction Model (**C**) Comparison of Decision Curves for Logistic (p) and Other Prognostic Prediction Models (**D**) Clinical Impact Curve for the Logistic (p) Prediction Model

Table 6 Comparison of the predictive value of different prediction models for 30-day prognosis of HBV-ACLF lung infection

Indicators	Youden index	Cut-off	Sensitivity	Specificity	AUC	95%CI	*P* value
MELD	0.377	27.720	0.523	0.854	0.755	0.673–0.838	< 0.001
MELD-Na	0.385	25.459	0.739	0.646	0.692	0.594–0.790	< 0.001
CTP	0.253	11.500	0.420	0.833	0.664	0.573–0.755	< 0.001
Logistic(p)	0.549	0.660	0.716	0.833	0.832	0.765-0.900	< 0.001

Abbreviations: MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease with Serum Sodium; CTP, Child-Turcotte-Pugh score

were the main cause of hospital-acquired infections [25, 26]. However, in our study, no statistically significant difference was seen in hormone use between the infected and uninfected groups. This may be related to the different courses of hormone use in different patients and the shorter duration of hormone therapy in some patients. In addition, due to the current controversy over the indications for hormone use in slow plus acute liver failure, there are no standardized criteria for hormone dosage, route of administration, and discontinuation [15, 27, 28]. Therefore, further studies are needed to address the effect of hormones between the occurrence of pulmonary infections in ACLF.

Our study identified creatinine, INR, neutrophil count, and lymphocyte count as independent predictors of 30-day mortality risk in ACLF patients with pulmonary infection. Creatinine and INR have been established as independent risk factors for mortality in ACLF and are widely used as parameters in ACLF prognostic scoring systems [29, 30]. Neutrophils and lymphocytes are the

primary immune cells of the body, with neutrophils playing roles in chemotaxis, phagocytosis, and bactericidal activities, reflecting the body's response to inflammation [31]. The occurrence of extensive hepatocyte necrosis in HBV-ACLF patients activates the immune response, leading to an increase in the proportion of monocytes and neutrophils in peripheral blood [32]. Under the influence of infection, the cascade of inflammation is exacerbated, with neutrophils releasing a series of inflammatory cytokines (IL-1 and IL-8) and a large number of granules (such as myeloperoxidase, protease, and collagenase) that cause inflammation and oxidative stress injury to hepatocytes, as well as degradation of cellular structures [32]. During the progression of HBV-ACLF, lymphocytes may be damaged due to the need to regulate the excessive inflammatory response caused by immune system activation, leading to lymphopenia and eventually lymphocyte exhaustion in peripheral blood [33, 34]. Thus, the imbalance between these two cell types reflects the disruption of the dynamic equilibrium between the body's immune status and inflammation. It is noteworthy that our study results suggest that diabetes mellitus is not a high-risk factor for ACLF patients with pulmonary infection. However, in the prognostic analysis, diabetes mellitus was identified as a key factor determining the 30-day mortality rate in ACLF patients with pulmonary infection. Elevated blood glucose levels lead to a decline in the phagocytic function of white blood cells, which may facilitate the progression of infection and may be an important cause of death in ACLF patients. This is consistent with previous studies [35, 36]. This highlights the need to pay sufficient attention to the metabolic status of glucose in the management of HBV-ACLF patients and to take appropriate interventions to reduce the progression of infection and the risk of mortality.

Analysis of the etiology of positive patients in our study revealed a high proportion of fungal infections at 65.38%, including Candida and Aspergillus species, with Candida being the most prevalent (32.69%). Although Candida albicans is often considered a commensal organism in the airway, its pathogenic potential should not be overlooked in patients with immunosuppression, such as those with liver failure. Patients with liver failure have severe disease conditions and compromised immune function, coupled with the extensive use of broad-spectrum antibiotics and immunosuppressive agents, leading to a high incidence of fungal infections in this population. In recent years, with the continuous development of fungal detection techniques, the detection and diagnostic rates of fungal infections have gradually increased [37]. A study in 2013 found that the incidence of invasive fungal infections in ACLF patients reached 47.6% [38]. Pulmonary fungal infections are often overlooked, leading to delayed treatment, which is related to various factors. Firstly, the onset of pulmonary fungal infections is insidious, with early clinical symptoms being inconspicuous or even absent. Secondly, the pathogens of pulmonary infections are often viruses and bacteria, and empirical treatment is primarily targeted at viruses and bacteria, with insufficient emphasis on fungal infections. Our study suggests that pulmonary fungal infections are highly prevalent in patients with liver failure, differing significantly from those in the general population. This indicates that when routine empirical antimicrobial therapy is ineffective and the condition of liver failure patients progressively worsens, consideration should be given to empirical treatment against fungi, especially Candida and Aspergillus. Given the high detection rate of fungal infections, future research should also focus on optimizing antifungal treatment strategies and on how to better balance antimicrobial therapy with immune function protection.

This study analyzed the risk factors for pulmonary infection in patients with HBV-ACLF and the factors influencing adverse prognosis in HBV-ACLF patients. Based on these analyses, a predictive model for 30-day mortality in HBV-ACLF patients was constructed. Through the analysis of the model's ROC curve and clinical decision curve, the study demonstrated that the model has good predictive efficacy for the 30-day prognosis of HBV-ACLF patients with pulmonary infection. However, this study also has some limitations. The sample size was relatively small, and the data were retrospective. Therefore, the conclusions of this study need to be confirmed by more prospective studies. It is worth noting that, given the background of HBV infection in China, our model focuses on HBV-ACLF patients, and since different criteria affect patient stratification and prognostic outcomes, exploring whether the application of Western criteria (e.g., the CLIF-ACLF score) would yield similar or different predictive efficacy deserves further investigation.

In summary, HBV-ACLF patients are prone to pulmonary infection, with fungi being the predominant pathogens. The clinical manifestations are diverse, and it is essential to use antibiotics judiciously based on the etiological results. Furthermore, the prognosis of HBV-ACLF patients with pulmonary infection is poorer, and early identification of risk factors and prognostic assessment can facilitate early intervention and improve prognosis.

Abbreviations

HBV-ACLF	Hepatitis B virus-related acute-on-chronic liver failure.
ALT	Alanine aminotransferase.
AST	Aspartate aminotransferase.
TBIL	Total bilirubin.
ALB	Albumin.
Hb	Hemoglobin.
Cr	Creatinine.
WBC	White blood cell count.
INR	International normalized ratio.
PT	Prothrombin time.

Fg	Fibrinogen.
CRP	C-reactive protein
AFP	Alpha-fetoprotein.
TC	Total cholesterol.
TG	Triglyceride.
APOE	Apolipoprotein E.
MELD	Model for end-stage liver disease.
MELD-Na	Model for end-stage liver disease with serum sodium.
CTP	Child-turcotte-pugh score.

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Author contributions
NW and YZ: screening, data extraction, and writing. NW, YZ and ST: analysis. NW and ST: manuscript revision. LC: manuscript finalization. All authors contributed to the article and approved the submitted version.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Shanghai Public Health Clinical Center. Owing to the retrospective nature of the research, the Ethics Committee of the Shanghai Public Health Clinical Center waived the requirement for written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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