

Predictors for Invasive Pulmonary Aspergillosis in Acute-on-Chronic Liver Failure Patients: A Retrospective Study

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Introduction: Acute-on-chronic liver failure (ACLF) is a severe syndrome that manifests as acute liver function deterioration and organ failure. Coinfection with invasive pulmonary aspergillosis (IPA) in ACLF patients is characterized by high mortality and increasing morbidity. The aim of this study was to explore the early warning factors and prognosis of ACLF patients with IPA coinfection.

Methods: In this retrospective study, we collected clinical, biochemical, and microbiological data from patients with ACLF and IPA from May 2019 to May 2023. Univariable and multivariate analyses were used to identify independent risk factors for IPA in ACLF patients. Moreover, the area under the curve (AUC) and decision curve analysis (DCA) were used to evaluate the model performance.

Results: A total of 438 patients with ACLF were enrolled, 408 (93.2%) non-IPA patients and 30 IPA (6.8%) including 29 probable cases and one proven case. The 28-day case fatality rate (56.7% vs 29.4%) was higher in ACLF patients with IPA than in ACLF patients without IPA, but without statistical difference. Multivariate analysis revealed that early warning factors for IPA coinfection in ACLF patients included nausea ($p = 0.010$), expectoration ($p < 0.001$), bacterial and fungal infections ($p < 0.001$), corticosteroid use ($p = 0.037$), surgery ($p = 0.081$), haemoptysis ($p = 0.015$) and increased leukocyte counts ($p = 0.010$). The AUC was 0.934 ($p < 0.001$), and DCA verified the validity and clinical effectiveness of our model.

Conclusion: These findings provide valuable insights for clinicians in the early diagnosis of IPA in ACLF patients and may facilitate timely intervention and treatment.

Keywords: acute-on-chronic liver failure, invasive pulmonary aspergillosis, decision curve analysis

Introduction

Acute-on-chronic liver failure (ACLF), a severe clinical syndrome caused by various factors, including severe disruption of synthesis, detoxification, immune metabolism, and biological transformation, is characterized by acute decompensation, organ failure and high 28-day mortality (32%).^{1–3} It presents as a group of clinical symptoms mainly characterized by hepatic insult, jaundice and coagulopathy, with decreased liver function, severe disruption of the cellular immune system, and increased risk of infection and death.^{1,4–10} A variety of bacterial, parasitic, and fungal infections may affect the liver. The prevalence of fungal coinfection ranges between 2% and 15%, and fungal coinfection has been associated with worsening liver function and increasing mortality.^{11–13}

Aspergillus fumigatus was listed as the critical priority group in the first fungal priority pathogen list issued by the World Health Organization (WHO) in 2022, and relevant research and public health action need to be expanded.¹⁴ Invasive pulmonary aspergillosis (IPA) is a severe opportunistic infection that mainly affects immunocompromised patients, leading to prolonged neutropenia and cancer.¹³ It is difficult to obtain pathologic samples from patients at high

risk of IPA, so it is important to identify early diagnostic warning signs. The 6-week mortality of IPA is 20–30%, especially in critical patients.^{15–18}

IPA seriously affects the prognosis of patients with ACLF and leads to deterioration of their condition. The prevalence of IPA in hepatitis B virus (HBV)-related ACLF patients has been reported to be 5.0–8.3%, with the mortality rate increasing to 80% in patients with IPA.^{2,19} In terms of liver failure with IPA coinfection, patients with hepatic failure without a definite type or mainly individual cases have been studied.^{12,16,17,20,21} So far, there are few studies on the ACLF patients with IPA, and some scholars have analyzed its prognosis model and treatment, but its early warning risk factors are still unknown.^{22–24}

The onset of IPA in the context of liver failure is occult, and early symptoms and imaging features are not typical, making it difficult to diagnose. Few studies have focused on *Aspergillus* infection in ACLF patients, and early warning signs for developing IPA in ACLF patients have not been characterized.

The primary aim of this study was to compare the clinical phenotypes of ACLF patients with IPA and non-IPA patients to identify early warning risk factors. This study developed a model for the early diagnosis of IPA in ACLF patients to facilitate timely intervention and treatment and improve patient survival.

Materials and Methods

Study Design and Participants

A retrospective study was conducted among 438 ACLF patients from May 2019 to May 2023 at the First Affiliated Hospital of Anhui Medical University. The exclusion criteria were as follows: (1) younger than 18 years, (2) immunocompromised due to human immunodeficiency virus infection, and (3) prior to organ transplantation or pregnancy before or during hospitalization. The study protocol adhered to the principles outlined in the Declaration of Helsinki and complied with relevant national laws and policies. Approval for this study was obtained from the Human Ethics Committee of Anhui Medical University (approval no. TJ20240556). Given the retrospective nature of the study, the ethics committee waived the requirement for informed consent. Verbal informed consent was obtained and the ethics committee approved this consent process. We ensure that the data was anonymized or maintained with confidentiality.

Diagnosis

Patients who were diagnosed with ACLF during hospitalization were screened. ACLF diagnosis was defined according to the Asian Pacific Association for the Study of the Liver (APASL) consensus recommendations for ACLF:²⁵ (1) jaundice (serum bilirubin ≥ 5 mg/dL (85 mmol/L)); (2) coagulopathy (international normalized ratio (INR) ≥ 1.5); and (3) complications within 4 weeks due to clinical ascites and/or encephalopathy. Failure to meet one of the above three criteria excluded the diagnosis of ACLF. We classified the ACLF patients with IPA into proven, probable and possible groups based on the European Organization for Research and Treatment of Cancer and Mycoses Study Group Education and Research Consortium (EORTC/MSGERC) consensus definitions of invasive fungal disease.^{26,27} In this study, patients were defined as having probable IPA if they had at least 1 clinical feature and had available mycologic evidence. Clinical features included the presence of 1 of the following patterns on computed tomography (CT): dense, well-circumscribed lesions with or without a halo sign, an air crescent sign, a cavity, or wedge-shaped and segmental or lobar consolidation. Mycological evidence included (1) galactomannan antigen detection in plasma with a cut-off point of 0.5 and (2) microscopic detection of fungal elements in bronchial brushing, bronchoalveolar lavage (BAL) or sputum, indicating the presence of a mould. The proven group was defined as patients who met the criteria for probable IPA and whose blood culture yielded *Aspergillus*. The flow chart for selecting ACLF patients with IPA is shown in Figure 1.

Data Retrieval

We extracted the patients' clinical information from the hospital's electronic medical records database. The following data were collected: demographic data (sex and age), patient clinical characteristics (fever, nausea, expectoration, altered consciousness, acute variceal bleeding, and haemoptysis), diabetes status, presence of comorbidities (hepatorenal syndrome, hepatic encephalopathy, septicaemia, spontaneous peritonitis, hyponatremia, hypoproteinaemia, and

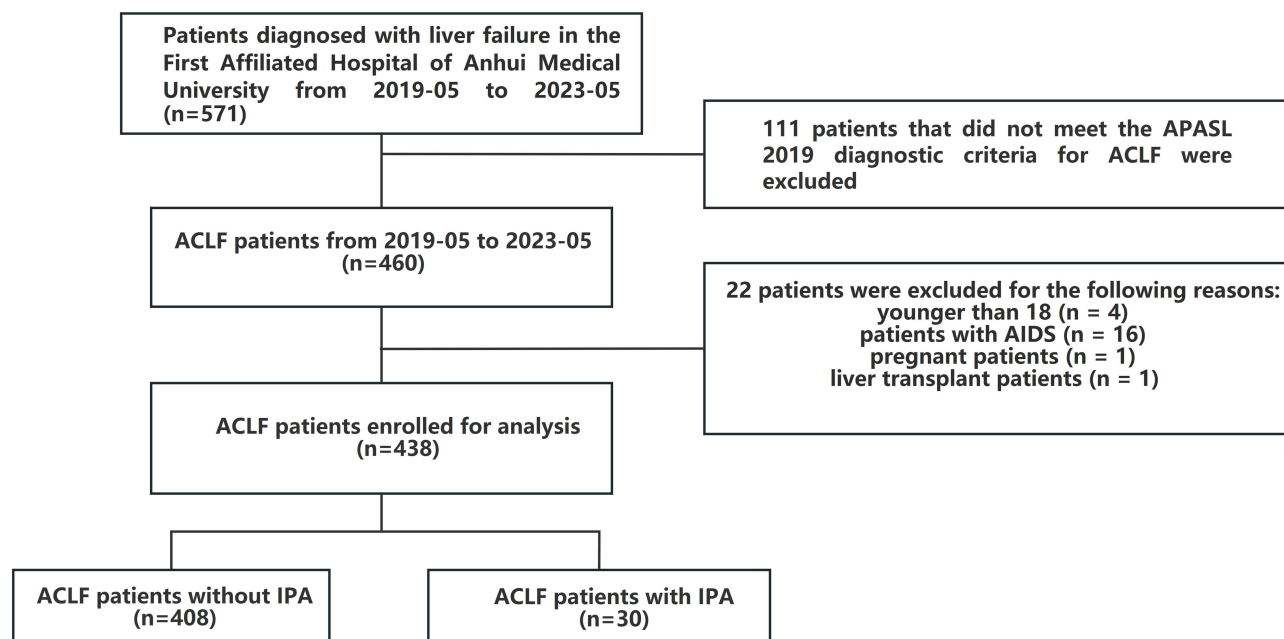


Figure 1 Flow diagram of patient selection.

gastrointestinal bleeding), liver aetiology (hepatitis B virus, drug use, alcohol use, autoimmune disease, and hepatolenticular degeneration), invasive operation including puncture and intubation, surgery, mechanical ventilation, transjugular intrahepatic portosystemic shunt (TIPS) placement, albumin infusion, artificial liver support system use, baseline full blood count, biochemistry results, liver and renal function, corticosteroid use, antimicrobial exposure (carbapenems and cephalosporins), length of hospital stay, ICU admission, 28-day fatality rate and documentation of bacterial and fungal infections. In our study, bacterial and fungal infections specifically referred to bacterial and fungal infections in addition to IPA coinfection in ACLF patients.

Statistical Analysis

IBM SPSS 24.0 and R software (version 4.3.2) were used for analysis. Normally distributed data are presented as the mean $\pm$ standard deviation (SD). The independent sample *t* test was used for comparisons between two groups. Nonnormally distributed data are expressed as medians (Q1–Q3), and the Mann–Whitney *U*-test was used for comparisons between two groups. Categorical variables are expressed as the sample size (*n*) and percentage (%). The chi-squared test or Fisher's exact test was used for categorical variables. We considered a *P* value < 0.05 to indicate statistical significance. Variables found to be significantly different ($P < 0.05$) in group comparisons were included in binary logistic regression (LR) to identify risk factors for ACLF in patients with IPA. Binary logistic regression (LR) can apply the minimum number of factors to construct the model, not all of which are statistically significant factors. Therefore, "surgery" is included in the model construction. The results are reported as β , standard error, odds ratio (OR), and *P* values. To make the results of the predictive model more obvious, factors included in the model were considered to indicate statistical significance, were used as visual indicators on a graph. In addition, the corresponding area under the curve (AUC) was calculated to assess the discrimination ability. Moreover, decision curve analysis (DCA) was used to evaluate the model performance.

Results

Clinical Phenotype of ACLF Patients With IPA

The hospital records of 571 patients with liver failure who were hospitalized between May 2019 and May 2023 were screened; 133 individuals were excluded, 438 patients with ACLF were ultimately enrolled in the study, and 30 patients

were diagnosed with IPA - 29 probable cases and one proven case (Figure 1). As shown in Table 1, the median age was 53 years (Q1-Q3: 46–61 years), and 335 (76%) of the 438 patients were male. The main aetiologies of ACLF among patients with known causes were HBV and alcohol use. The most frequent symptoms were expectoration (66.7% vs 11.0%), nausea (16.7% vs 4.2%) and acute variceal bleeding (13.3% vs 10.5%) in the IPA group and non-IPA group. The occurrence rates of other symptoms, such as haemoptysis, altered consciousness, and fever, were greater in the ACLF with IPA group.

Compared with the non-IPA group, the IPA group had more leukocytes [$6.2 (4.4\text{--}8.9) \times 10^9/\text{L}$ vs $9.0 (6.2\text{--}13.0) \times 10^9/\text{L}$], a lower lymphocyte percentage [$17.5 (10.6\text{--}23.4)$ vs $14.0 (7.5\text{--}25.2)$] and a lower monocyte percentage [$8.7 (6.7\text{--}11.0)$ vs $7.4 (5.7\text{--}9.3)$]. The total protein, globulin, total bilirubin, platelet, prothrombin time, INR, and thrombin time were greater in the non-IPA group, while the serum urea and haemoglobin levels were lower than those in the IPA group, as shown in Table 2.

Hepatic encephalopathy and gastrointestinal bleeding occurred more frequently in patients with ACLF and IPA, while hepatorenal syndrome, septicaemia, spontaneous peritonitis, hypoproteinaemia and multiple comorbidities were less frequent in patients with ACLF and IPA.

The mean model for end-stage liver disease score (25.0 vs 23.1, $p = 0.211$) was greater in the ACLF patients than in the ACLF patients with IPA. Nevertheless, the ICU admission rate (23.3% vs 2.7%, $p < 0.001$) and bacterial and fungal infection rate (63.3% vs 15.0%, $p < 0.001$) were greater in ACLF patients with IPA. Patients with IPA coinfection

Table 1 | Baseline Characteristics of the Study Participants (n=438)

	ACLF Patients without IPA (n=408)	ACLF Patients with IPA (n=30)	χ^2/Z	P-value
Clinical characteristics, symptoms or signs				
Age (years)	53 (46–61)	56 (43–68)	−0.189	0.850
Male, N (%)	309 (75.7%)	26 (86.7%)	1.857	0.173
Fever, N (%)	5 (1.2%)	2 (6.7%)	NA	0.077
Nausea, N (%)	17 (4.2%)	5 (16.7%)	NA	0.002
Expectoration, N (%)	45 (11.0%)	20 (66.7%)	NA	<0.001
Altered consciousness, N (%)	10 (2.5%)	2 (6.7%)	NA	0.172
Acute variceal bleeding, N (%)	43 (10.5%)	4 (13.3%)	NA	0.633
Haemoptysis, N (%)	2 (0.5%)	3 (10.0%)	NA	0.003
Liver aetiology, N (%)			NA	0.725
Unexplained	156 (38.2%)	11 (36.7%)		
Hepatitis B virus	184 (45.1%)	12 (40.0%)		
Drug use	16 (3.9%)	2 (6.7%)		
Alcohol use	23 (5.6%)	2 (6.7%)		
Autoimmune diseases	4 (1.0%)	1 (3.3%)		
Hepatolenticular degeneration	4 (1.0%)	1 (3.3%)		
Two or more factors	21 (5.1%)	1 (3.3%)		
Comorbidities, N (%)			NA	0.590
No comorbidities	96 (23.5%)	7 (23.3%)		
Hepatic encephalopathy	28 (6.9%)	4 (13.3%)		
Hepatorenal syndrome	2 (0.5%)	0 (0.0%)		
Septicaemia	11 (2.7%)	0 (0.0%)		
Spontaneous peritonitis	42 (10.3%)	2 (6.7%)		
Hypoproteinaemia	55 (13.5%)	4 (13.3%)		
Gastrointestinal bleeding	4 (1.0%)	1 (3.3%)		
Two factors	95 (23.3%)	4 (13.3%)		
Three or more factors	75 (18.4%)	8 (26.7%)		

Notes: The data are expressed as the means $\pm$ SDs/medians (Q1–Q3)/percentages (number of patients). The fact that the numbers do not add up to 100% is attributable to missing data.

Abbreviations: ACLF, Acute-on-chronic liver failure; IPA, Invasive pulmonary aspergillosis; MELD, Model for end-stage liver disease; NA, Not available.

Table 2 Laboratory Parameters and Clinical Outcomes of the Study Participants (n=438)

	ACLF Patients without IPA (n=408)	ACLF patients with IPA (n=30)	χ^2/Z	P-value
Laboratory parameters				
Total protein (g/L)	56.9 (51.7–62.5)	50.8 (47.3–63.1)	−2.025	0.043
Serum albumin (g/L)	30.8 (27.9–34.3)	31.9 (26.9–35.0)	−0.025	0.980
Globulin (g/L)	26.2 ± 8.2	22.6 ± 7.2	−2.433	0.019
Total bilirubin (umol/L)	255.2 (158.6–364.8)	226.6 (124.7–350.8)	−1.313	0.189
Serum urea (umol/L)	4.8 (3.1–7.7)	7.0 (4.7–11.3)	−2.691	0.007
Serum creatinine (umol/L)	62.0 (49.5–83.0)	64.2 (51.0–82.9)	−0.009	0.993
Estimated Glomerular Filtration Rate (L/min)	111.0 (90.0–126.0)	112.5 (93.2–127.2)	−0.323	0.747
Leukocytes (10 ⁹ /L)	6.2 (4.4–8.9)	9.0 (6.2–13.0)	−2.928	0.003
Lymphocyte percentage (%)	17.5 (10.6–23.4)	14.0 (7.5–25.2)	−0.806	0.420
Monocyte percentage (%)	8.7 (6.7–11.0)	7.4 (5.7–9.3)	−2.227	0.026
Neutrophils (10 ⁹ /L)	4.3 (2.9–6.8)	6.5 (4.0–8.8)	−2.711	0.007
Haemoglobin (g/L)	115.0 (94.0–133.0)	114.5 (98.2–135.5)	−0.149	0.881
Platelets (g/L)	89.0 (57.0–129.0)	80.0 (55.8–110.8)	−0.442	0.658
Prothrombin time (S)	23.9 (19.8–30.4)	21.8 (17.4–28.2)	−1.326	0.185
INR	2.1 (1.6–2.9)	1.9 (1.5–2.7)	0.212	0.212
Thrombin time (S)	20.6 (19.0–22.5)	18.9 (17.8–20.9)	−3.528	<0.001
MELD score	25 ± 8	23 ± 8	1.281	0.211
Clinical measures				
Surgery, N (%)	8 (2.0%)	4 (13.3%)	NA	<0.001
Mechanical ventilation, N (%)	8 (2.0%)	5 (16.7%)	NA	<0.001
Invasive operation, N (%)	281 (68.9%)	25 (83.3%)	2.776	0.096
Albumin infusion, N (%)	349 (85.5%)	26 (86.7%)	NA	0.865
Artificial liver support system use, N (%)	183 (44.9%)	21 (70.0%)	7.102	0.008
Carbapenem application, N (%)	178 (43.6%)	20 (66.7%)	5.988	0.014
Corticosteroid use, N (%)	46 (11.3%)	13 (43.3%)	NA	<0.001
Length of hospital stay(days)	22 (9–39)	24 (15–47)	−1.644	0.100
Bacterial and fungal infections, N (%)	61 (15.0%)	19 (63.3%)	43.818	<0.001
ICU admission, N (%)	11 (2.7%)	7 (23.3%)	NA	<0.001
Diabetes, N (%)	62 (15.2%)	4 (13.3%)	NA	0.783
28-day fatality rate, N (%)	120 (29.4%)	17 (56.7%)	9.657	0.223

Notes: The data are expressed as the means ± SDs/medians (Q1–Q3)/percentages (number of patients). The fact that the numbers do not add up to 100% is attributable to missing data.

Abbreviations: ACLF, Acute-on-chronic liver failure; IPA, Invasive pulmonary aspergillosis; MELD, Model for end-stage liver disease; NA, Not available. MELD, Model for end-stage liver disease.

received more clinical interventions than patients without IPA coinfection, including surgery (13.3% vs 2.0%, $p < 0.001$), mechanical ventilation (16.7% vs 2.0%, $p < 0.001$), invasive operations (83.3% vs 68.9%), albumin infusion (86.7% vs 85.5%), artificial liver support system use (70.0% vs 44.9%, $p = 0.008$), carbapenem application (66.7% vs 43.6%, $p = 0.014$), and corticosteroid use (43.3% vs 11.3%, $p < 0.001$).

Risk Factors for IPA in ACLF Patients

In this study, univariable analysis revealed statistically significant differences in 17 factors, including total protein, globulin, serum urea, leukocyte count, neutrophil count, monocyte percentage, thrombin time, surgery, mechanical ventilation, corticosteroid use, artificial liver support system use, nausea, expectoration, haemoptysis, ICU admission, carbapenem use, and bacterial and fungal infections, between the IPA group and the non-IPA group. As shown in Table 3, 7 variables, including leukocyte count, corticosteroid use, nausea, expectoration, haemoptysis, surgery and bacterial and fungal infections, were identified as early warning signs for IPA occurrence in ACLF patients. Based on independent predictors identified through binary logistic regression, we developed a risk prediction model for the early detection of IPA in ACLF

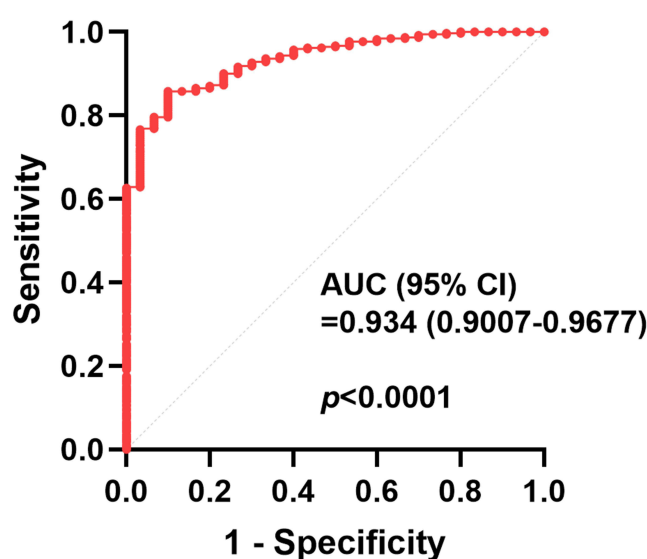
Table 3 | Multivariable Logistic Regression for Exploring Risk Factor of ACLF With IPA Patients

Effect	Wald	p-value	OR (95% CI)
Leukocytes ($10^9/L$)	6.585	0.010	1.117 (1.026–1.215)
Nausea	6.623	0.010	6.778 (1.578–29.11)
Expectoration	20.387	<0.001	9.262 (3.524–24.342)
Bacterial and fungal infections	15.557	<0.001	7.542 (2.763–20.582)
Surgery	3.043	0.081	4.200 (0.838–21.06)
Corticosteroid use	4.370	0.037	3.009 (1.071–8.453)
Haemoptysis	5.946	0.015	20.863 (1.815–239.835)

patients, aiming to guide clinical interventions (Figure 1). To make the results of the predictive model more obvious, we converted the indicators into a nomogram. The validity of our model was determined using multiple indicators, including the AUC (0.934, $p < 0.001$), Youden's index (0.758), sensitivity (0.900), specificity (0.858), cut-off value (0.064), Hosmer–Lemeshow test ($\chi^2 = 6.974$, $p = 0.539$) and DCA (Figure 2). The DCA revealed that using this model provides additional benefits for the entire cohort, as shown in Figure 3.

Clinical Outcomes

We found that the 28-day case fatality rate did not significantly differ between the groups; however, there was a clear trend towards a higher 28-day case fatality rate in the IPA group, as shown in Figure 3. The 28-day case fatality rate (56.7% vs 29.4%) was greater in ACLF patients with IPA, and the length of hospital stay was longer (24 days [Q1–Q3: 15–47 days] vs 22 days [Q1–Q3: 9–39 days], $p = 0.1$), as shown in Table 2. The 28-day mortality rate among patients was 31.3% (137 of 438 patients). No significant difference in the 28-day case fatality rate was observed between female and male patients. Infections were considered a significant contributing factor to death for ACLF patients. As shown in sTable 1, there was a significant difference between the incidence of bacterial and fungal infections and the 28-day case fatality rate of IPA among the ACLF patients (26.3% vs 14.6%, $p = 0.003$). The sTable 2 shown the infection sites and cases for “Bacterial and fungal infections” in ACLF patients.

**Figure 2** ROC curves of the model for the risk of ACLF with IPA.

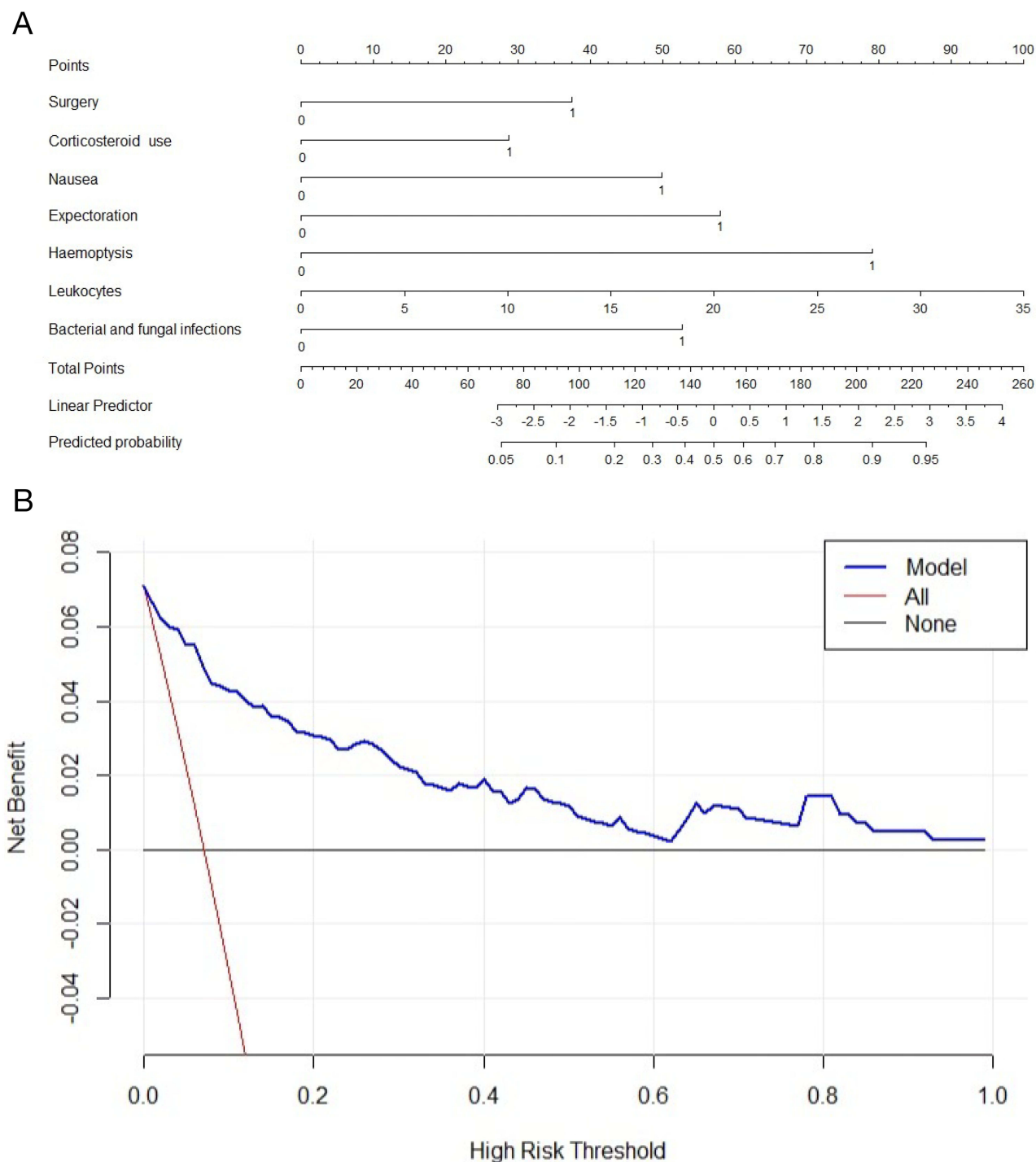


Figure 3 Nomogram and DCA curves of the model for the risk of ACLF with IPA. **(A)** Nomogram and **(B)** decision curve analysis of the model for the risk of ACLF with IPA.

Discussion

Identifying the early warning risk factors for IPA in ACLF patients is critical for administering early antifungal prophylaxis and empiric treatment. This study is the first to describe the early warning signs of ACLF patients with IPA. The incidence of IPA coinfection in ACLF patients was 6.8% in this study. Leukocyte count, corticosteroid use, nausea, expectoration, haemoptysis, surgery, and bacterial and fungal infections were identified as early warning signs for

IPA occurrence in ACLF patients. This retrospective study established an early prediction model for ACLF patients with IPA to guide clinicians in achieving an early IPA diagnosis in these patients.

ACLF patients with IPA group had an increased leukocytes count, especially neutrophil count, while had a decreased lymphocyte percentage as compared to the ACLF patients without IPA group. These findings suggest that the innate immune system plays an important role in the development of ACLF, which is consistent with previous findings.³ Our findings first indicated that nausea was significantly associated with early warning risk factors of IPA, possibly because inflammation, septicaemia and Invasive Aspergillosis can also affect the gastrointestinal tract in patients with cirrhosis and portal hypertension.

Underlying pulmonary disease is more likely to occur in the upper airway, bronchi, lung parenchyma, and contiguous structures.^{28,29} It has the potential to cause extensive and diffuse damage to the respiratory mucosa, disrupting normal ciliary clearance. Moreover, underlying pulmonary disease can create conditions conducive to fungal invasion by impairing alveolar macrophages, hindering local phagocytic activity, delaying immune response initiation, and suppressing anti-inflammatory mechanisms.³⁰ Thus, these phenomena explain why expectoration and haemoptysis were identified as independent factors influencing IPA development.³¹ When encountering patients with these symptoms clinically, clinicians need to be aware that they may be at high risk of IPA and initiate targeted early prevention and treatment.

This study also indicated that bacterial and fungal infections were independent risk factors for IPA in ACLF patients, consistent with previous results.^{28,32} Infection promotes a highly inflammatory state in ACLF patients.^{33,34} Recently, it has been shown that the immune response to sepsis is biphasic, ie, the initial hyperinflammatory phase may be followed by an anti-inflammatory response, leading to a hyperinflammatory condition.^{33,35,36} This process is known as compensatory anti-inflammatory response syndrome or immune paralysis and can be viewed as a form of acquired immunodeficiency.^{4,34} The existence of a constant and persistent hyperinflammatory milieu contributes to immunosuppression by inhibiting innate immune defensive responses and regulating immune cell expansion.^{37,38} The clinical consequence of this inhibition is increased susceptibility to IPA infection, a serious opportunistic infection that mainly affects immunocompromised patients.³⁹ Steroid exposure is a well-known risk factor for IPA coinfection. Several studies have demonstrated that corticosteroids have immunosuppressive effects and impair phagocytosis, oxidative bursts, cytokine and chemokine production, and the antifungal activity of monocytes/macrophages, which may increase the risk of IPA coinfection.

Our study had several limitations. First, due to the low incidence of fungal coinfection in ACLF patients and the retrospective nature of this study, the sample sizes of the two groups were unbalanced. Second, due to the retrospective nature of the study, some data, such as the dosage, specific timing, and duration of antibiotic and glucocorticoid treatment before admission, were missing. As our analysis revealed inconsistent predictive effects of different antibiotics and hormones on patient outcomes, further prospective studies are needed to confirm the effect of antibiotic and glucocorticoid use on IPA.

Conclusions

Compared with ACLF patients without IPA, ACLF patients with IPA had a higher 28-day case fatality rate, but without statistical difference. Leukocyte count, corticosteroid use, nausea, expectoration, haemoptysis, bacterial and fungal infections, and surgery were significantly more common in ACLF patients with IPA. This study can help clinicians effectively identify high-risk patients and initiate targeted early prevention and treatment.

Data Sharing Statement

The data that support the findings of this study are included and will be available from the corresponding author(s) upon reasonable request.

Ethics/Ethical Approval

The study protocol adhered to the principles outlined in the Declaration of Helsinki and complied with relevant national laws and policies. Approval for this study was obtained from the Human Ethics Committee of Anhui Medical University (approval no. TJ20240556). Given the retrospective nature of the study, the ethics committee waived the requirement for informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors participated in the development, review and approval of the manuscript. All authors have read and approved the final manuscript. We confirm that the manuscript has not been submitted (or simultaneously) elsewhere, is not under consideration by another journal at the time of submission and that no portion of the data has been or will be published elsewhere. The authors declare that they have no conflicts of interest to disclose and have approved the manuscript. Chenxi Yuan, Rongqing Zhu, Jiabin Li and Lifen Hu declare that they have no competing interests.

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