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Research Article

Risk Factors of Invasive Pulmonary Fungal Infections in Patients with Hepatitis B Virus Related Acute-on-Chronic Liver Failure

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To analyze the risk factors of invasive pulmonary fungal infections in patients with HBV-ACL, the clinical data and risk factors of 60 patients with HBV-ACLF complicated IPFI were analyzed retrospectively including clinical parameters, broad-spectrum antibiotics usage, neutropenia, invasive medical manipulations, serum total bilirubin, international normalized ratio (INR), and MELD scores were compared with non-IPFI. Risk factors were analyzed using mathematical tools. Candida species and Aspergillus were detected as the most prominent fungal strains (61.11% and 33.33%, respectively). The risk factors included prolong broad-spectrum antibiotic usage (OR = 4.362, $P = 0.008$), neutropenia (OR = 3.288, $P = 0.007$), invasive procedures (OR = 3.263, $P = 0.010$), serum total bilirubin (OR = 1.006, $P = 0.011$), INR (OR = 2.101, $P = 0.007$), and MELD scores (OR = 1.074, $P = 0.008$). Candida is the main IPFI strains in patients with HBV-ACLF. Broad-spectrum antibiotics usage, neutropenia, invasive manipulations, and the severity of ACLF might be risk factors for IPFI in patients with HBV-ACLF.

1. Introduction

Acute-on-chronic liver failure (ACLF) is a common medical liver disease syndrome with a high risk of short-term death and demonstrated immune dysfunction [1–3]. Damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) can lead to unbalance between systemic inflammatory response and anti-inflammatory response and are highly predisposed to develop various infections [1–4]. Frequent bacterial infections and reactivation of hepatitis B virus (HBV) infection contributed to the progression of ACLF in the Asian region. Although the introduction and the expanded access to antiviral treatment have significantly improved the outcome of patients with hepatitis B virus-related acute-on-chronic liver failure (HBV-ACLF) [3, 5–8], infections displayed a significant public health problem, contributed to increase prolonged hospitalization and additional healthcare costs, and made a deterioration in the morbidity and mortality.

Invasive pulmonary fungal infections (IPFI) play an important role in stimulating and aggravating liver failure [9, 10]. However, it remained extremely challenging to be timely and accurately diagnosed, since the onset of invasive pulmonary fungal infections (IPFI) is occult, and the early clinical manifestations such as fever, tachycardia, and cough are not specific and overlap with symptoms of bacterial infections. Furthermore, fungal conventional culture methods are poor sensitivity, requiring invasive tissue sampling. At the same time, low index of alertness for clinicians, lack of normalized diagnostic standard, and tests also attributed to the difficulty. Recent studies have revealed that (1,3)-β-D-glucan (BDG) and galactomannan (GM) in blood or respiratory samples

showed a promising diagnostic performance for IPFI. However, the interpretation in patients with HBV-ACLF is still debated.

In order to improve the recognition, diagnosis, and treatment of IPFI in patients with HBV-ACLF, the clinical data of patients with HBV-ACLF and invasive pulmonary fungal infection in our hospital were retrospectively analyzed.

2. Materials and Methods

2.1. Study Design and Patients. A total of 143 patients with HBV-ACLF from November 2013 to March 2021 were retrospectively analyzed, including 60 patients with invasive pulmonary mycosis (fungal infection group) and 83 patients without fungal infection (control group). The inclusion criteria were as follows: (1) age over 18 years; hepatitis B surface antigen-positive ≥6 months; (2) ACLF was diagnosed according to the diagnostic and treatment guidelines recommended by the Asian Pacific Association for the Study of the Liver (APASL) [1], excluding patients with any of the following conditions: (1) superinfection with hepatitis A, C, D, and E viruses; (2) malignancies, such as hepatocellular carcinoma; and (3) with one or more additional known primary or secondary causes of liver disease, other than hepatitis B. Patients with ACLF and IPFIs were assigned to the IPFI group, and patients with ACLF without IPFIs were assigned to the control group. All patients were well informed of the study, and written consent was obtained from the study subjects before enrolment. The study protocol was approved by the Ethics Committee of the Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University).

2.2. Definitions of IPFIs. Diagnoses of IPFIs [11] were based on the diagnostic criteria developed by the European Organization for Research and Treatment of Cancer and the Mycoses Study Group. The criteria were divided into host, clinical, mycological, and histopathological criteria. However, patients with ACLF often cannot tolerate lung biopsy due to coagulation dysfunction and poor basic conditions, and thus, the IPFIs in this study were probable IPFIs.

2.3. Data Collection

(1) The general condition, vital signs, number of neutrophils in peripheral blood, total bilirubin (TBIL), international normalized ratio (INR), BDG test and GM test, the type and cumulative time of antibiotics used during hospitalization, and the number of invasive operations (including abdominal puncture and/or central venous catheterization) of the HBV-ACLF patients from admission to the day of diagnosis of probable IPFIs

(2) The number of neutrophils in peripheral blood, TBIL, INR, serum creatinine, BDG test, and GM test was routinely measured in the central laboratory of our hospital

(3) The prolonged using antibiotics referred to the use of third-generation cephalosporins or carbapenems for more than 2 weeks; neutropenia in peripheral blood means that the number of neutrophils was less than 1.5×10^9/L for 10 consecutive days. The Model for End-Stage Liver Disease (MELD) scores is based on the objective parameters of serum bilirubin, serum creatinine, and the international normalized ratio of prothrombin time, and MELD scores was calculated using the following formula: MELD scores = $3.78 \times \ln$ [serum bilirubin (mg/dL)] $+ 11.2 \times \ln$ [INR] $+ 9.57 \times \ln$ [serum creatinine (mg /dL)] $+ 6.4 \times$ Etiology (etiology: biliary or alcoholic is 0; others is 1).

2.4. Statistical Analysis. ANOVA was used for analysis with the Chi-squared test. Continuous variables were described as means ± SD, and categorical variables were presented as counts (percentage). Binomial logistic regression analysis was performed. P value < 0.05 was considered statistically significant for all comparisons. Analysis was performed using the statistical software SPSS (version 23.0).

3. Results

3.1. The Clinical Data and General Information. We enrolled 60 patients (41 males and 19 females) in the IPFI group and 83 patients (65 males and 18 females) in the no-IFPI group, respectively. The baseline characteristics were comparable. The patients with IPFI had more prolonged antibiotics use [54 (90.00%) versus 51 (61.45%); $P \leq 0.001$], and invasive operation [46 (76.67%) versus 39 (46.98%); $P \leq 0.001$]; the number of patients with neutropenia, total bilirubin, INR, and MELD scores are larger for IPFI groups [41 (68.33%) versus 27 (32.53%); $P \leq 0.001$], [389.22 ± 103.41 versus 326.15 ± 102.01; $P \leq 0.001$], [3.16 ± 0.84 versus 2.67 ± 0.78; $P \leq 0.001$], and [34.87 ± 8.39 versus 30.03 ± 8.24; $P \leq 0.001$], respectively (Table 1).

3.2. Clinical Characteristics of IPFI in Patients with HBV-ACLF. Cough and fever were the most frequent clinical signs reported ($n = 53$, 88.3% and $n = 51$, 85.0%, respectively), followed by dyspnea ($n = 16$, 26.7%), hemoptysis ($n = 5$, 8.3%), and chest pain ($n = 3$, 5.0%). The positive rates of BDG and GM test were 73.3% (44/60) and 38.3% (23/60), respectively (Table 2).

3.3. Species and Constituent Ratio of IPFI in HBV-ACLF Patients. Candida species had the highest frequency 22 (61.11%) followed by Aspergillus species 12 (33.33%). Table 3 presents the fungi data for 36 infection episodes.

3.4. Analysis of Risk Factors for IPFI in Patients with HBV-ACLF. The risk factors included prolong broad-spectrum antibiotic use (OR = 4.362, $P = 0.008$), invasive procedures (OR = 3.263, $P = 0.010$), neutropenia (OR = 3.288, $P = 0.007$), serum total bilirubin (OR = 1.006, P = 0.011), INR (OR = 2.101, $P = 0.007$), and MELD scores (OR = 1.074, $P = 0.008$). The risk factors for IPFI in patients with HBV-

Table 1: Basic data for IPFI and non-IPFI with HBV-ACLF at risk for fungal infections.

Risk factors	IPFI ($n = 60$)	No IPFI ($n = 83$)	Statistical value	P value
Age	54 ± 15.56	53 ± 14.90	$\chi^2 = 0.219$	0.6401
Gender (man)	41 (68.33%)	65 (78.31%)	$\chi^2 = 1.808$	0.1788
Prolong antibiotics use	54 (90.00%)	51 (61.45%)	$\chi^2 = 14.55$	≤0.001
Invasive operation	46 (76.67%)	39 (46.99%)	$\chi^2 = 12.72$	≤0.001
Neutropenia	41 (68.33%)	27 (32.53%)	$\chi^2 = 17.90$	≤0.001
TBIL (μmol/L)	389.22 ± 103.41	326.15 ± 102.01	$F = 13.15$	≤0.001
INR	3.16 ± 0.84	2.67 ± 0.78	$F = 13.28$	≤0.001
MELD scores	34.87 ± 8.39	30.03 ± 8.24	$F = 11.85$	≤0.001

IPFI: invasive pulmonary fungal infections; TBIL: total bilirubin; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease.

Table 2: Clinical signs, BDG, and GM results.

	N	%
Signs and symptoms		
Cough	53	88.3
Fever	51	85.0
Dyspnea	16	26.7
Hemoptysis	5	8.3
Chest pain	3	5.0
Investigation		
BDG test positive	44	73.3
GM test positive	23	38.3

BDG: 1,3-β-D-glucan; GM: galactomannan.

Table 3: The fungi data for 36 infection episodes.

Causative microorganism	Frequency	Constituent ratio (%)
Candida albicans	16	44.44
Aspergillus spp.	12	33.33
Candida glabrata	4	11.11
Candida krusei	2	5.56
Unclassified yeast-like fungi	2	5.56
Total	36	100

ACLF (bivariate logistic regression analysis) are described in Table 4.

Table 4: Independent risk factors for IPFI (bivariate logistic regression analysis).

	OR	95% CI	P
Prolong antibiotics use	4.362	1.458-13.050	0.008
Invasive procedures	3.263	1.317-7.949	0.010
Neutropenia	3.288	1.375-7.861	0.007
TBIL (μmol/L)	1.006	1.001-1.010	0.011
INR	2.101	1.221-3.612	0.007
MELD scores	1.074	1.019-1.133	0.008

IPFI: invasive pulmonary fungal infections; OR: odds ratio; CI: confidence interval; TBIL: total bilirubin; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease.

4. Discussion

Due to immune dysfunction, ACLF patients are more susceptible to infection. One-third of ACLF patients can be detected infections, and the remaining patients approximately half would develop bacterial infections in a short time [4]. The incidence of ACLF complicated with invasive fungal infection is increasing gradually, with high mortality and poor prognosis. Verma et al. [12] reported 14.7% ACLF patients with IFI, and Lin et al. [13] reported 47.6% HBV-ACLF patients with IFI. Both of them reported that one of the commonest target sites was respiratory (approximately 34%, 25%, respectively), but their clinical manifestations were not specific and the same as bacterial pneumonia, such as cough, fever, dyspnea, hemoptysis, and chest pain. The human defense system against fungi included both the naive and acquired immune systems, including neutrophil, natural killer cells, and dendritic cells. Neutropenia typically involved in candidemia with a poor prognosis [13]. When HBV-ACLF patients were complicated with bacterial infections, it was critical to administrate antibiotics to kill them. Sometimes, frequent unreasonable and overuse antibiotics can be seen to ideally improve the outcome of ACLT patients and unfortunately lead to suppress the normal bacterial flora and fungi proliferated rapidly. These organisms can migrate across the intestinal wall to disseminate. In our study patients, it was found that the long-term use of broad-spectrum antibiotics and neutropenia was independently related to fungal infection, which was consistent with recent studies [9, 12, 14, 15].

Of the 36 confirmed IPFI cases, Candida albicans infection was the most frequent pathogens in HBV-ACLF patients, accounting for 44.44% (16/36), followed by Aspergillus 33.33% (12/36), and Candida glabrata 11.11% (4/36). These findings are also consistent with previous studies on patients with acute liver failure [12, 13, 16, 17]. And other types of severe liver diseases patients also have been reported the same spectrum of fungal infections [9, 13, 14, 18]. This may be due to the disorder of fungal flora and dysfunction of the intestinal mucosal barrier in patients with advanced

liver cirrhosis, as well as the displacement of symbiotic candida or overlapping infection with Aspergillus species.

Patients with ACLF suffered from a large number of damaged hepatocytes with a high level of jaundice and coagulation abnormalities, which led to prolonged hospital stay to be recovered and repeatedly performed all kinds of invasive procedures such as central venous catheters, artificial liver support system, and abdominal paracentesis, thus increased probability of nosocomial infection accordingly. We also showed the higher prevalence of higher undergoing invasive operations, total bilirubin, INR, and MELD scores in patients with IPFI as compared with non-IPFI. These invasive operations for developing of IPFI were similar to those previously reported [15, 19]. It is difficult to explain whether the poor liver function is the cause or result of fungal infection in the HBV-ACLF area. On the one hand, the worsening of immune paralysis and fungal ecological imbalance, coupled with the increasingly serious ACLF, is the trend of IPFI. On the other hand, the occurrence of IPFI disease triggers higher cytokine release, which leads to higher liver failure damage, and finally presents a vicious circle, which worsens the ongoing damage and immune dysfunction.

BDG is present in the cell wall of many fungi and a diagnostic value test when combined with epidemiologic risk factors, clinical manifestations, and imaging. At the same time, GM is produced by all kinds of fungal strains and becomes another mark which is routinely used in the diagnosis of invasive aspergillosis in immunosuppressed critically ill patients [20]; however, the BDG test needs further evaluation in patients with ACLF. Our study revealed that the positive rates of BDG and GM tests were 73.3% (44/60) and 38.3% (23/60), respectively. A recent meta-analysis shows that BDG has a good predictive ability in the diagnosis of IFI, with a sensitivity of 97%, a specificity of 60%, and an AUROC of 0.770 [12]. Another detection of GM in BAL samples is 56-73% sensitive and 89-94% specific for the diagnosis of invasive aspergillosis [17, 21, 22]. The above data can be used for future clinical studies, such as meta-analysis [23–25] and many other statistical tools [26, 27]. Clinical studies are suggested to be analyzed with math tools for comprehensive and scientific findings.

5. Conclusions

In conclusion, to improve the outcome in IPFI patients with HBV-ACLF, clinicians should pay more attention to this unusual and lethal condition so that it can be diagnosed early and timely, and empiric antifungal treatment should be started, until reasonable treatment can be applied. Candida species and Aspergillus were detected as the most prominent fungal strains (61.11% and 33.33%, respectively). The risk factors included prolong broad-spectrum antibiotic usage ($OR = 4.362, P = 0.008$), neutropenia ($OR = 3.288, P = 0.007$), invasive procedures ($OR = 3.263, P = 0.010$), serum total bilirubin ($OR = 1.006, P = 0.011$), INR ($OR = 2.101, P = 0.007$), and MELD scores ($OR = 1.074, P = 0.008$). Candida is the main IPFI strains in patients with HBV-ACLF. Broad-spectrum antibiotics usage, neutropenia, invasive manipulations, and the severity of ACLF might be risk factors for IPFI in patients with HBV-ACLF.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

The medical ethics approval form. *(Supplementary Materials)*

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