Clinical Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
0(0) 1–9

DOI: 10.1177/0300060517729907
journals.sagepub.com/home/imr
SAGE

Epidemiology of invasive pulmonary aspergillosis in patients with liver failure: Clinical presentation, risk factors, and outcomes

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Abstract

Objective: Invasive pulmonary aspergillosis (IPA) is a severe and often lethal infection. The possible risk factors, clinical presentation, and treatment of patients with simultaneous liver failure and IPA have received little attention in previous studies. The aim of this study was to investigate the epidemiology of IPA in patients with liver failure in an effort to reduce patient mortality.

Methods: The patients with liver failure (including acute liver failure , sub-acute liver failure , acute-on-chronic liver failure and chronic liver failure) were recruited from 2011 to 2016. The clinical data of these patients were retrieved for the study.

Results: In total, 1077 patients with liver failure were included in this study. Of the 1077 patients, 53 (4.9%) had IPA. Forty-four (83%) patients with IPA died. Independent risk factors for IPA were male sex (hazard ratio [HR] = 2.542), hepatorenal syndrome (HR = 2.463), antibiotic use (HR = 4.631), and steroid exposure (HR = 18.615).

Conclusions: IPA is a fatal complication in patients with liver failure. Male sex, hepatorenal syndrome, antibiotic use, and steroid exposure were independent risk factors for IPA. When patients with liver failure have these risk factors and symptoms of pneumonia such as cough or hemoptysis, clinicians should be cautious about the possibility of IPA.

Keywords

Liver failure, invasive pulmonary aspergillosis, epidemiology, risk factors, clinical presentation, outcomes

Date received: 7 June 2017; accepted: 15 August 2017

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IPA, invasive pulmonary aspergillosis; ACLF, acute-on-chronic liver failure; ALF, acute liver failure; SALF, subacute liver failure; CLF, chronic liver failure; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; INR, international normalized ratio; PTA, prothrombin activity; HIV, human immunodeficiency virus; HR, hazard ratio

Introduction

Invasive pulmonary aspergillosis (IPA) is a severe and often lethal infection[1] that mainly affects immunocompromised patients, such as those with hematologic malignancies and stem cell or solid organ transplants. *Aspergillus* spp. can cause invasive infection in patients with liver failure.[2–5] Although patients with liver failure have a low incidence of invasive aspergillosis, recent data have indicated that this condition should be reconsidered as a devastating infectious disease in this population.[3–5] Wu et al.[5] showed that most patients with acute-on-chronic liver failure (ACLF) died within 7 days after the onset of IPA (25/29 patients).

Achieving a clinical diagnosis of IPA is a huge challenge. Invasive diagnostic procedures such as fiberbronchoscopy are necessary to confirm a diagnosis of aspergillus infection, but such procedures are often not feasible in patients with severe respiratory insufficiency and critical illness who are not undergoing mechanical ventilation.[6–9] Moreover, the European Organization for Research and Treatment of Cancer (EORTC) restricted the scope of the standard diagnostic definitions to receipt of a solid organ transplant, hereditary immunodeficiencies, connective tissue disorders, and receipt of immunosuppressive agents[10]; however, these criteria cannot necessarily be extrapolated to patients with liver failure.

Few studies have been performed to evaluate patients with liver failure who develop IPA, and possible risk factors such as the ABO blood group and use of an artificial liver support system have received little attention. Little is known about the clinical presentation and treatment of IPA in patients with liver failure. Therefore, the aim of this study was to collect data about patients with liver failure to investigate the epidemiology and possible risk factors for IPA in an effort to reduce the mortality in this population.

Methods

Study design

This retrospective study was conducted in the State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Department of Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, China. The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang University, and the need for consent was waived because the study was retrospective and the data were analyzed anonymously.

Study population

Patients with liver failure [including acute liver failure (ALF), subacute liver failure (SALF), ACLF, and chronic liver failure (CLF)] were admitted into the infectious disease wards of the First Affiliated Hospital, College of Medicine, Zhejiang University, China from 2011 to 2016. The clinical data of these patients were retrieved for the study. The follow-up period for the patients with IPA was 3 months after discharge.

Diagnostic criteria

Liver failure was defined according to the following criteria specified by the 13th Asia-Pacific Congress of Clinical Microbiology and Infection Consensus Guidelines for the diagnosis and treatment of liver failure:[11]

ALF: Abrupt onset accompanied by grade II or higher hepatic encephalopathy (HE)

(according to the I- to IV-grade classification) and appearance of the following symptoms within 2 weeks: a) fatigue with severe gastrointestinal tract symptoms such as anorexia, abdominal distension, nausea, and vomiting; b) progressive aggravation of jaundice; c) hemorrhagic tendency with an international normalized ratio (INR) of $\geq$1.5 or prothrombin activity (PTA) of $\leq$40% and exclusion of other causes; and d) progressive reduction in liver size.

SALF: Slower onset than ALF and appearance of the following symptoms within 2 to 26 weeks: a) fatigue with gastrointestinal tract symptoms, b) rapidly deepening jaundice with a total bilirubin (TBil) level 10 times higher than the upper limit of normality or a daily increase of $\geq$17.1 μmol/L, c) occurrence of HE, and d) hemorrhagic tendency with an INR of $\geq$1.5 or PTA of $\leq$40% and exclusion of other causes.

ACLF: Acute or subacute deterioration of liver function in patients with chronic liver disease, usually accompanied by the following symptoms: a) fatigue with gastrointestinal tract symptoms, b) rapidly deepening jaundice with a TBil level 10 times higher than the upper limit of normality or a daily increase of $\geq$17.1 μmol/L, c) hemorrhagic tendency with an INR of $\geq$1.5 or PTA of $\leq$40% and exclusion of other causes, d) progressive reduction in liver size, and e) occurrence of HE.

CLF: Progressive deterioration and decompensation of liver function in patients with liver cirrhosis, usually accompanied by the following symptoms: a) a significant increase in TBil, b) a significant decrease in albumin, c) a hemorrhagic tendency with an INR of $\geq$1.5 or PTA of $\leq$40% and exclusion of other causes, d) ascites or other symptoms of portal hypertension, and e) occurrence of HE.

We used the EORTC consensus definition of invasive *Aspergillus* infection,[10] which was diagnosed if the following two criteria were fulfilled: one microbiologic criterion (positive sputum culture) and one clinical criterion. In the present study, a diagnosis of IPA was made based on the following: a) positive culture of *Aspergillus* spp. from sputum and b) the presence of one of the following three signs on computed tomography: dense, well-circumscribed lesions(s) with or without a halo sign, air-crescent sign, or cavity.

Risk factors for IPA

In this study, the following variables were assessed as risk factors for the occurrence of IPA: sex, age, ABO blood group, type 2 diabetes mellitus, chronic bronchitis, malignancy, human immunodeficiency virus (HIV) infection, antibiotic use, steroid exposure, use of an artificial liver support system, neutropenia, gastrointestinal bleeding, HE, and hepatorenal syndrome (HRS). The definitions of some of these factors are summarized in Table 1.

Table 1. Risk factors for invasive pulmonary aspergillosis in patients with liver failure.

Risk factors	Remarks (where applicable)
Chronic bronchitis	Defined as the presence of a productive cough or expectoration for >90 days per year (but on separate days) and for >2 consecutive years, provided that a specific disorder responsible for these symptoms is not present.
Malignancy	Solid tumor and hematologic malignancy
HIV infection	Defined as HIV-positive status
Antibiotic use	Antimicrobial agent use for >5 days
Steroid exposure	Steroid treatment for >7 days
Neutropenia	Total neutrophil count of $\leq$500/mm^3

HIV, human immunodeficiency virus.

Statistical analysis

The statistical analysis was performed using SPSS version 18.0 (SPSS, Chicago, IL, USA). Student's t-test was performed for descriptive analysis and comparison of continuous variables. Fisher's exact probability test and the chi-square test were conducted to calculate and compare the percentages for categorical variables. Logistic regression analysis was used to examine the effects of independent variables on IPA. *P* value of <0.05 was considered statistically significant for all analyses.

Results

Characteristics of the study cohort

In total, 1077 patients with liver failure were included in this study. Of these 1077 patients, 826 (76.7%) were male and the mean age was 49.22 ± 13.45 years. The characteristics of the patients are shown in Table 2 and Table 3. The most common reason for hospital admission was SCLF (543/50.4%), and the main cause of liver failure was hepatitis B (799/74.2%). A total of 511 (47.4%) patients received artificial liver support therapy, 710 (65.9%) received antibacterial treatment for >5 days, and 84 (7.8%) were exposed to corticosteroids for >7 days. The antibacterial treatments were administered for both prophylaxis and treatment (pneumonia, spontaneous bacterial peritonitis, and septicemia). Steroids were used to decrease persistent hyperbilirubinemia and treat autoimmune diseases. Eight (0.7%) patients developed neutropenia.

Among all 1077 patients, 53 (4.9%) were diagnosed with IPA. The characteristics of the patients with IPA are shown in Table 3. Twenty-five (47.2%) of these patients had blood group O, 30 (56.6%) had received artificial liver support therapy, and 46 (86.8%) and 26 (49.1%) received antibacterial drugs and corticosteroids, respectively.

Table 2. Characteristics of 1077 patients with liver failure.

Characteristic	Number of patients (%)
Disease onset	
ALF	71 (6.6)
SALF	51 (4.7)
SCLF	543 (50.4)
CLF	412 (38.3)
Etiology of liver failure	
Hepatitis B	799 (74.2)
Hepatitis E	5 (0.5)
Alcohol	32 (3.0)
Drug	59 (5.5)
Autoimmunity	23 (2.1)
Hepatolenticular degeneration	3 (0.3)
Schistosome	5 (0.5)
Malignancy	7 (0.6)
Two or more factors	69 (6.4)
Unknown	72 (6.7)

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; SALF, subacute liver failure; CLF, chronic liver failure.

Risk factors

Logistic regression analysis showed that male sex [hazard ratio (HR) = 2.542, p = 0.035], HRS (HR = 2.463, p = 0.014), antibiotic use (HR = 4.631, p = 0.001), and steroid exposure (HR = 18.615, $p < 0.001$) were independent risk factors associated with the occurrence of IPA (Table 4).

Clinical characteristics of patients with IPA

The symptoms and laboratory data of the 53 patients with IPA are shown in Table 5. Among all patients with IPA 44 (83%) died. After IPA diagnosis, three patients were admitted to the intensive care unit where mechanical ventilation and continuous renal replacement therapy were applied. Moreover, nine (17%) patients did not receive antifungal treatment. Twenty-four (45.3%) patients received voriconazole as antifungal treatment, 16 (30.2%) received

Table 3. Demographic features of 1077 patients with liver failure and differences between those with and without IPA.

	All patients with liver failure	Patients with IPA	Patients without IPA	p value
Patients	1077	53	1024	–
Male	826 (76.7)	46 (86.8)	780 (76.2)	0.075
Age (years)	49.18 ± 13.48	48.64 ± 12.07	49.25 ± 13.52	0.748
ABO blood group				
A	343 (31.8)	13 (24.5)	331 (32.3)	0.235
B	271 (25.2)	9 (17.0)	262 (25.6)	0.159
AB	86 (8.0)	6 (11.3)	80 (7.8)	0.358
O	377 (35.0)	25 (47.2)	351 (34.3)	0.055
Morbidities				
Type 2 diabetes mellitus	102 (9.5)	3 (5.7)	99 (9.7)	0.465
Chronic bronchitis	50 (4.6)	2 (3.8)	49 (4.8)	0.995
Malignancy	88 (8.2)	3 (5.7)	85 (8.3)	0.669
HIV infection	12 (1.1)	0 (0.0)	12 (1.2)	0.903
Complications				
Gastrointestinal bleeding	116 (10.8)	7 (13.2)	109 (10.6)	0.557
HE	484 (44.9)	26 (49.1)	458 (44.7)	0.537
HRS	141 (13.1)	14 (26.4)	127 (12.4)	0.003
Antibiotic use	710 (65.9)	46 (88.5)	663 (64.7)	0.001
Steroid exposure	84 (7.8)	26 (49.1)	58 (5.7)	<0.001
Artificial liver support system	511 (47.4)	30 (56.6)	481 (47.0)	0.171
Neutropenia	8 (0.7)	1 (1.9)	7 (0.7)	0.862

Data are presented as mean ± standard deviation or n (%). IPA, invasive pulmonary aspergillosis; HIV, human immunodeficiency virus; HE, hepatic encephalopathy; HRS, hepatorenal syndrome

Table 4. Logistic regression analysis of risk factors associated with invasive pulmonary aspergillosis development in patients with liver failure.

		95% CI for HR		
Risk factors	HR	Lower	Upper	p value
Hepatorenal syndrome	2.463	1.199	5.061	0.014
Male sex	2.542	1.065	6.063	0.035
Antibiotic use	4.631	1.866	11.496	0.001
Steroid exposure	18.615	9.819	35.048	<0.001

HR, hazard ratio; CI, confidence interval.

caspofungin, and 4 (7.5%) received micafungin. There were no differences in the survival rate among patients treated with different antifungal agents (Table 6).

Discussion

Invasive aspergillosis has been traditionally regarded as an infection mainly occurring in immunocompromised or immunodeficient patients, such as those with neutropenia, hematologic malignancies, organ transplantation, or HIV.[12] Although invasive aspergillosis has been reported in patients with liver cirrhosis and liver transplantation,[13,14,15] IPA has rarely been observed in patients with liver failure.

A previous study[16] confirmed invasive aspergillosis as a frequent undiagnosed complication of patients with ALF or end-stage liver disease, with a mortality rate exceeding 70%. In the present study, the mortality rate among patients with liver failure who developed IPA was 83%. The reason for the high

Table 5. Characteristics of 53 patients with liver failure who developed invasive pulmonary aspergillosis (IPA).

Characteristics	Number of patients (%)
Symptoms	
Fever	53 (100.0)
Cough	50 (94.3)
Hemoptysis	23 (43.4)
Dyspnea	20 (37.7)
Chest pain	2 (3.8)
Laboratory data	
Leukocyte count ($\times 10^9$/L)	11.31 ± 5.71
Neutrophil count ($\times 10^9$/L)	9.29 ± 5.26
Total bilirubin (μmol/L)	489.12 ± 135.15
INR	3.08 ± 1.37
Imaging findings (X-ray or CT)	
Changes in bilateral lung fields	43 (81.1)
Right unilateral lung	8 (15.1)
Left unilateral lung	2 (3.8)
Cavity	13 (24.5)
Air-crescent sign	10 (18.9)
Pleural effusion	19 (35.8)
Antibiotic use (before IPA diagnosis)	46 (86.8)
One antibiotic	44 (95.7)
Two antibiotics	2 (4.3)
Carbapenems	13 (28.3)
Penicillins	18 (39.1)
Third-generation cephalosporins	11 (23.9)
Fourth-generation cephalosporins	2 (4.3)
Glycopeptides	2 (4.3)
Quinolones	2 (4.3)

IPA, invasive pulmonary aspergillosis; INR, international normalized ratio; CT, computed tomography

Table 6. Effect of antifungal agents in the treatment of invasive pulmonary aspergillosis.

	Death	Recovery	p value
Patients	44 (83%)	9 (17%)	–
Antifungal agent			
Voriconazole	19	5	0.755
Caspofungin	13	3	0.822
Micafungin	3	1	0.536
Untreated	9	0	0.329

mortality was not only the difficulty in diagnosis and treatment of IPA but also a lack of enough recognition of IPA and the heavy economic burden, which led patients to give up treatments.

Diagnosis of IPA in patients with liver failure is challenging. Patients with liver failure often have a high bleeding tendency, which is a contraindication for invasive examinations such as pulmonary puncture biopsy or bronchoscope. Thus, only one patient in our study had tissue evidence of *Aspergillus fumigatus* infection that was acquired after the recovery of liver failure. Moreover, liver failure is not a host factor of invasive fungal disease in the EORTC consensus; thus, the diagnosis of invasive *Aspergillus* infection in patients with liver failure is quite difficult according to the EORTC consensus definition. Because of delayed diagnosis and patients' financial constraints, 17% of patients did not receive antifungal treatment. One study[16] showed that a high percentage (52.8%) of patients with acute or advanced liver disease were diagnosed with invasive aspergillosis postmortem. Therefore, further research of the epidemiology, risk factors, and clinical manifestations of IPA in patients with liver failure may improve the diagnosis rate.

In the present study, the incidence of IPA in patients with liver failure was 4.9%. Bone marrow transplantation, prolonged neutropenia, and solid organ transplantation have been identified as high-risk factors for invasive aspergillosis.[17–21] Invasive aspergillosis occurs in 1% to 9% of liver transplant recipients[14]; this is similar to the morbidity rate of the patients with liver failure in the present study. As a result of a depression of both humoral and cell-mediated immunity, liver disease alone predisposes to bacterial and fungal infections.[22] Patients with liver failure patients are

immunosuppressed and should be considered an at-risk population for IPA.

An expert consensus[23] recommended that the main risk factors for IPA should include neutropenia, malignancy, and prolonged steroid treatment. In the present study, HRS ($p = 0.014$), steroid exposure ($p < 0.001$), and antibiotic use ($p = 0.001$) were independent risk factors associated with the occurrence of IPA in patients with liver failure. These findings are consistent with those of previous research.[3,4,22]

In this study, 26 (49.1%) patients had steroid exposure before IPA diagnosis. Surprisingly, patients with liver failure who took corticosteroids for >7 days had an 18-fold (HR = 18.615) higher risk of developing IPA than those who did not use corticosteroids or used them for <7 days. Corticosteroids predispose patients to opportunistic infections through functional impairment of macrophages and neutrophil function.[24] Thus, corticosteroids should be used with caution in patients with liver failure.

HRS may be precipitated by infection.[25] Additionally, renal failure has been associated with defective cell-mediated immunity and impaired granulocyte–macrophage function, which are the predominant host defenses against fungal pathogens.[26]

Moreover, male sex ($p = 0.035$) was also a risk factor for IPA; this has not been found in previous studies. A possible reason for this result is that immune system damage in male patients with liver failure is more severe than in female patients. However, this needs further research.

In patients with liver failure, both the clinical diagnosis and treatment of IPA are challenging. The guidelines of the Infectious Diseases Society of America[27] recommended voriconazole as the primary therapy for IPA. However, this drug is metabolized in the liver and potentially hepatotoxic.[27] Thus, it should be used with caution in patients with liver failure patients. In the present study, 24 (45.3%) patients received voriconazole as an antifungal agent, and the dose of voriconazole was not adjusted. No skin rashes or transient visual disturbances were observed. Moreover, it is difficult to estimate whether liver injury has been induced by voriconazole in patients with liver failure. Because such patients' liver function is severely damaged, infection could lead to impaired liver function and ultimately higher mortality.[28] However, liver function did not worsen after using voriconazole in our recovered patients.

Our study has some limitations. First, the small numbers of patients with some host factors of invasive fungal disease development in the EORTC consensus, such as HIV or neutropenia, may have led to statistical error. Second, liver failure is not a host factor of invasive fungal disease development in the EORTC consensus; therefore, the patients in our study did not fulfill the definition of proven IPA according to the EORTC consensus. Moreover, invasive diagnostic procedures were not feasible in our patients with liver failure, which may have resulted in missing patients with suspected disease based on radiologic imaging. Third, we did not collect data on the daily corticosteroid dose and could not fully explore the impact of dose or duration on mortality. Finally, male sex as a risk factor for IPA was not thoroughly researched.

In conclusion, IPA is a potentially fatal complication in patients with liver failure, and delayed diagnosis and treatment may contribute to high mortality. Steroid exposure, antibiotic use, male sex, and HRS were independent risk factors associated with the occurrence of IPA. When patients with liver failure have these risk factors and symptoms of pneumonia such as cough or hemoptysis, clinicians should be aware of the possibility of IPA. Early and appropriate antifungal treatment may improve the survival rate in patients with liver failure.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This study was supported by the Medical and Health Science and Technology Project of Zhejiang province (2015KYA102).

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