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Invasive Fungal Infections With Good Survival Following Liver Transplant: A Single-Center Experience From a Developing Country

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Abstract

Objectives: **Invasive fungal infection following liver transplant is considered as one of the important factors influencing morbidity and mortality among liver transplant recipients. The aim of the present study was to describe the prevalence of invasive fungal infections and their predisposing factors in a single-center cohort of patients who received liver transplant.**

Materials and Methods: **For this study, 250 adult patients undergoing orthotopic liver transplant between March 2010 and March 2015 were enrolled. All patients were followed prospectively for infections.**

Results: **The diagnosis of invasive fungal infection was made in 15 patients (6%). One patient had 2 episodes of fungal infection, and reoperation was performed for 3 patients. Invasive aspergillosis developed in 8 patients (53.3%), followed by *Candida* species infection in 3 patients (20%) and cryptococcosis in 2 patients (13.3%). The main predisposing factors were renal failure (12/15) and positive history of rejection (11/15). Other risk factors for development of invasive fungal infections were choledochojejunostomy in 3 patients (20%), bile leaks in 3 patients (20%), and pretransplant steroid use in 2 patients (11.8%). Two patients (13.3%) died due to invasive fungal infections.**

Conclusions: **In this single-center series of liver transplant recipients, the incidence of invasive fungal infections was relatively low, probably due to the universal prophylaxis with fluconazole and limited use of the broad-spectrum antibiotics. Early diagnosis and treatment of invasive fungal infections could lead to a better prognosis for liver transplant recipients with invasive fungal infections.**

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Introduction

Over the past few decades, major advances have been made in different aspects of the transplant field such as surgical techniques, posttransplant care, immunosuppressive agents, and antimicrobial regimens.[1] However, infectious complications are still considered as major causes of morbidity and mortality in liver transplant recipients. The frequency of infection in liver transplant recipients is higher than in other transplant recipients due to manipulation of the hepatobiliary system. Bacterial infections are the most common type of infections after liver transplant. However, invasive fungal infections (IFI) are also common and are associated with significant morbidity and mortality among liver transplant recipients. Prior to the administration of antifungal prophylaxis, the occurrence of IFIs had been reported in up to 42% of liver transplant recipients.[2-4] Moreover, death with any underlying cause occurred in 25% to 81% of patients diagnosed with IFIs, of which 72% of deaths was attributed to IFIs.[5,6]

Previous studies have suggested several preoperative and postoperative risk factors for IFIs. Prolonged surgical time, high volume of blood transfusion during surgery, early surgical reexploration, and choledochojejunostomy are surgical parameters associated with IFIs.[2,5,7,8] Preoperative factors for IFIs include prolonged intensive care unit stay, antibiotics used for spontaneous bacterial peritonitis, hepatic artery thrombosis, retransplant, and fulminant hepatic failure. *Candida* species colonization early after transplant, bile leaks, significant renal dysfunction, and *Cytomegalovirus* (CMV) reactivation are perioperative risk factors for IFIs, according to previously reported studies.[2-5,7]

Despite the decreased trend in incidence of IFIs since the mid-1990s, fungal infections still pose a significant burden to liver transplant recipients. According to recently published studies, the incidence of IFIs ranges from 5% to 20% of recipients.[9-13] Therefore, the aim of this study is to investigate the current status of IFI in the early period after liver transplant in a medium-volume liver transplant center.

Materials and Methods

Study population

The medical records of 250 patients who received liver transplant at Imam Khomeini Hospital, Tehran, Iran, from March 2010 to March 2015 were retrospectively reviewed. All transplanted livers were from deceased donors who were medical and legally dead. All liver transplant recipients underwent routine follow-up. Data obtained from medical records included demographic features, underlying diseases, transplant type, clinical characteristics, microbiologic screening results, potential risk factors, types and sites of infection, and medical and surgical complications during the study period.

Fifteen patients were diagnosed with IFI according to the criteria proposed by the European Organization on Research and Treatment in Cancer and the Mycoses Study Group.[14] Two episodes of IFI had occurred in one patient. The day of the first microbiologic documentation of infection was considered as the day of diagnosis. For cases with postmortem diagnoses, the day of death was considered as the day of diagnosis.

Microbiologic diagnosis

Pleural and peritoneal fluid, bronchoalveolar lavage, and/or lumbar puncture samples of patients were evaluated for smear and culture for fungi. *Aspergillus galactomannan* antigen was measured in the serum samples. Moreover, pan-fungal polymerase chain reaction assays were performed on some of the samples.

Surgical methods and prophylactic regimens

For transplant procedures, most patients underwent the piggy-back technique; however, in some patients, the standard technique was considered. All liver transplant recipients received antibiotic prophylaxis perioperatively until 48 hours after surgery. The antibiotic regimen included piperacillin tazobactam or ampicillin sulbactam for patients with or without history of recent hospitalization or prolonged antibiotic therapy, respectively. All patients received fluconazole (100 mg twice daily) as antifungal prophylaxis in the early period after transplant, until prednisone dose had been decreased to 15 mg/day. Surveillance for fungal colonization in recipients is not routinely performed in our center. Acyclovir and sulfamethoxazole-trimethoprim are used as universal prophylaxis for herpes simplex virus infection and Pneumocystis jiroveci, respectively, in our center. For prevention of CMV infection, we use preemptive therapy for low-risk to moderate-risk patients. Primary prophylaxis with ganciclovir is used for high-risk recipients (including donor-positive/recipient-negative patients and retransplant patients). The diagnosis of CMV infection was made based on detection of viral antigen (CMV PP65) in peripheral blood leukocytes.

Immunosuppression included administration of 1 g methylprednisone simultaneously when the liver entered the body, with gradual tapering day by day. Mycophenolate mofetil and tacrolimus were initiated on postoperative days 1 and 2, respectively.

Statistical analyses

Continuous variables were examined for normal distribution using the Shapiro-Wilks test. For independent numeric variables, *t* test was used; for independent nominal variables, the Fisher exact test or Mann-Whitney *U* test was used as indicated. Statistical significance was defined as $P < .05$. Data were analyzed using SPSS version 23.0 (SPSS Inc.; Chicago, IL, USA).

Results

Clinical characteristics of patients

The characteristics of the 15 patients are summarized in Table 1. Ten patients were male, and the mean age of the patients was 46.4 years (range, 23-62 y). Patients were followed for 27.1 ± 22.2 months. The most common indication for liver transplant was cryptogenic cirrhosis in 5 patients (33.3%), followed by autoimmune hepatitis in 3 patients (20%), hepatitis C virus infection in 2 patients (13.3%), and hepatitis B virus in 2 patients (13.3%). Hepatocellular carcinoma and nonalcoholic steatohepatitis were diagnosed in 1 patient each. The Model for End-Stage Liver Disease (MELD) score of the patients was 20.7 ± 3.01, ranging from 16 to 25.

Invasive aspergillosis developed in 8 patients (53.3%), followed by *Candida* species infection in 3 patients (20%) and cryptococcosis in 2 patients (13.3%). *Aspergillus fumigatus* was isolated in 1 patient; the remaining cases were diagnosed on the basis of either serologic or pathologic findings. The organism responsible for infection was not identified in 3 patients; diagnoses of IFIs for these patients were made based on radiologic findings and high clinical suspicion.

All patients with IFI underwent deceased-donor liver transplant. The median time of diagnosis was 32 days after transplant (range, 3-588 d). Clinical manifestations, diagnostic criteria, and treatment regimens of patients are shown in Table 1. Liposomal amphotericin B was the most common antifungal

Table 1. Clinical Features, Type of Infection, Diagnostic Criteria, and Risk Factors for Invasive Fungal Infections

	Sex	Age, y	Underlying Liver Disease	MELD Score	Risk Factor	Comorbidity	Type of Disease	Type of Organism	Diagnostic Method	Definition of IFD	Therapeutic Regimen	Days From Transplant to IFDs	Outcome
1	M	54	Cryptogenic	19	Renal failure, rejection	Diabetes	Meningitis	*Cryptococcus* sp.	CSF	Proven	First: amphotericin Second: fluconazole	130	Alive
2	M	61	Cryptogenic	22	Renal failure, CMV viremia, rejection, biliary complication	Wound infection, cholelithiasis, cholangitis	Liver abscess	*Candida albicans*	Liver biopsy culture	Proven	First: amphotericin Second: fluconazole	32	Dead (sepsis)
3	F	23	Fulminant hepatitis	NA	Renal failure, rejection, CCJ	Surgical wound infection, lesser sac abscess, pneumonia	Pneumonia	*Aspergillus* sp.	BAL culture/ halo sign in chest CT scan	Probable	First: voriconazole Second: itraconazole	19	Alive
4	M	53	Cryptogenic	21	Renal failure, prolonged ICU admission, CMV viremia, rejection, retransplant	None	Liver abscess	*Candida albicans*	Liver biopsy culture/ drainage liver abscess	Proven	First: amphotericin Second: itraconazole	167	Alive
5	M	37	Autoimmune	23	HAT	None	Liver abscess	*Aspergillus* sp.	Drainage liver abscess	Proven	First: amphotericin Second: itraconazole	60	Alive
6	F	24	AIH	16	Renal failure, CMV viremia, Rejection, steroid use, biliary complication	None	Peritonitis	*Aspergillus* sp.	TAP ascites	Proven	First: amphotericin Second: fluconazole	14	Alive
7	M	51	NASH	24	Renal failure, CMV viremia, rejection	Surgical site abscess, PTLD	Pneumonia	*Aspergillus* sp.	BAL culture/ nodular lesions in chest CT	Probable	First: amphotericin, Second: itraconazole	32	Dead (PTLD)
8	M	49	HCC	22	Renal failure, prolonged ICU admission (15 days)	None	Pneumonia	*Aspergillus* sp.	BAL culture/ nodular lesions in chest CT	Probable	First: amphotericin Second: itraconazole	22	Dead (PTLD)
9	M	59	HBV	23	Renal failure, CMV viremia, rejection, CCJ	None	Pneumonia	*Aspergillus* sp.	BAL culture/ nodular lesions in chest CT	Probable	First: amphotericin Second: voriconazole	588	Alive
10	F	58	Cryptogenic	25	Renal failure, CMV viremia, rejection	SBP, umbilical hernia, pyelonephritis	Sinusitis	None	Pansinusitis in paranasal CT/ surgical evidence of necro-inflammation suggestive of mucor mycosis				
11	F	56	HCV	16	Renal failure, rejection	None	Pneumonia	Unknown	Halo sign in chest CT	Possible	First: amphotericin	151	Alive
12	M	53	HCV	23	Renal failure, rejection	Sepsis	Abdominal abscess	*Aspergillus* sp	CT/surgical evidence of necro-inflammation	Proven	Amphotericin	15	Dead (renal failure)
13	F	23	AIH	21	Renal failure, steroid use	PCP	Pneumonia	*Candida albicans*	BAL culture/ nodular lesions in chest CT	Probable	Amphotericin	3	Alive
14	M	62	Cryptogenic	16	CMV viremia	None	Pneumonia and meningitis	*Cryptococcus*	CSF and BAL culture	Proven	First: amphotericin Second: fluconazole	17	Alive
15	M	33	HBV	20	CMV viremia, rejection, biliary complication, CCJ	None	Pneumonia	*Aspergillus* sp.	BAL culture/ nodular lesions in chest CT	Probable	Voriconazole	28	Alive

Abbreviations: AIH, autoimmune hepatitis; BAL, bronchoalveolar lavage; CCJ, choledochojejunostomy; CMV, *Cytomegalovirus*; CSF, cerebrospinal fluid; CT, computed tomography; F, female; HAT, hepatic artery thrombosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; IFD, invasive fungal disease; M, male; MELD, Model for End-Stage Liver Disease; NA, not available; NASH, nonalcoholic steatohepatitis; PCP, *Pneumocystis jiroveci* pneumonia; PTLD, posttransplant lymphoproliferative disease; SBP, spontaneous bacterial peritonitis

agent administered for IFIs (13 patients), followed by fluconazole (4 patients) and voriconazole (4 patients). The main predisposing factors were renal failure (12/15) and positive history of rejection (11/15). Other risk factors for development of IFIs were choledochojejunostomy in 3 patients (20%), bile leaks in 3 patients (20%), and pretransplant steroid use in 2 patients (11.8%). Two patients (13.3%) died due to IFIs.

Discussion

Invasive fungal infections are major problems in organ transplant recipients. The highest incidence and the greatest mortality from fungal infection occur in liver transplant recipients.[15] Our study revealed that, in our institution, the overall incidence of IFIs was 6% and the mortality rate due to IFI was 0.8%.

In a study from Raghuram and associates that assessed the occurrence of IFIs and their associated factors in 502 liver transplant recipients, 12% of liver transplant recipients were diagnosed with IFIs.[16] In another study of the epidemiology of IFI after liver transplant in Japanese liver transplant recipients, the overall rate of IFI was 5.4% and the mortality rate among patients with IFIs was 80%.[17] According to previous studies, the most common IFI diagnosed in solid-organ transplant recipients is candidiasis, accounting for 53% of infections.[11] However, the rate of diagnosed candidiasis was 20% in our patients with IFIs. Low prevalence of candidiasis in our patients could be explained by universal fungal prophylaxis with high dose of fluconazole in liver transplant recipients in our center and the lower incidence of fluconazole-resistant *Candida* species infections.

Almost all of our patients had at least one of the risk factors associated with IFIs highlighted in previous studies. According to the American Society of Transplantation Infectious Diseases Community of Practice and the Infectious Diseases Society of America clinical practice guidelines, retransplant, reoperation, and renal failure are among the major risk factors for IFIs following liver transplant.[18] In our cohort of patients diagnosed with IFIs, renal failure occurred in the majority of them and 1 patient underwent retransplant. Other recently suggested risk factors for IFIs in the posttransplant period include pretransplant fungal colonization,[16] high MELD score,[16] low dose of daily prophylactic fluconazole (< 200 mg),[16] steroid use before liver transplant,[17] blood stream infection within 90 days after liver transplant,[17] reoperation within 90 days after liver transplant,[17] and living-donor liver transplant.[17] History of rejection, CMV infection, and choledochojejunostomy were the 3 major risk factors of IFIs in the liver transplant recipients in our study; these factors compare to those mentioned in previous studies.[2,7,19] Our results are in concordance with previously defined risk factors for IFIs such as bile leaks and choledochojejunostomy.[2]

Interestingly, our survival rate following IFIs was significantly lower than that shown in previous studies. In a study from Nagao and associates,[17] only 20% of patients diagnosed with IFIs survived; however, only 2 patients in our series died due to IFIs. All of our patients underwent deceased-donor liver transplant, which is in contrast to 90% living donors in the Japanese center study. Therefore, we hypothesized that living-donor transplant could result in a significant difference in mortality rate. In another study, conducted in the United States, in which medical records of 502 patients who underwent deceased-donor liver transplant were retrospectively reviewed, the 1-year patient survival rate was 41% in patients with IFI.[16] In another study, Singh and associates prospectively followed 40 transplant recipients diagnosed with invasive aspergillosis. Of these, 50% of the infections were late-onset. The investigators found that mortality rate attributable to invasive aspergillosis was 15% in patients with early-onset infection and 35% in those with late onset infection.[20] In a study from Husain and colleagues, the mortality rate was 36.1% in 35 liver transplant recipients with invasive candidiasis.[5] Lower MELD score and early onset of antifungal treatment after the onset of symptoms are other reasons for our low rate of mortality in this study. In addition, we may have underestimated the incidence and mortality of IFIs due to the retrospective design of this study and some episodes of IFIs could have been missed, especially among deceased recipients with undiagnosed causes of death.

Our results were significantly limited by several important factors. Similar to other retrospective studies, it is difficult to establish a precise cause-effect relationship between risk factors and occurrence of IFIs. Furthermore, our criteria for diagnosis of IFIs were radiologic findings in a few patients, and we

were not able to make a definite diagnosis based on serologic findings or tissue sampling.

Conclusions

Our study revealed that the incidence of IFIs in Iranian liver transplant recipients is relatively low and is comparable with other centers. Moreover, our mortality rate was significantly lower than that shown in previous studies. Early diagnosis and treatment of IFIs could lead to a better prognosis of liver transplant recipients with IFIs. However, larger prospective studies are recommended to strengthen the current evidence.

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