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Original article

Epidemiology of invasive fungal infections after liver transplantation and the risk factors of late-onset invasive aspergillosis

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ABSTRACT

Invasive fungal infection (IFI) in liver transplant recipients is associated with poor outcomes. Targeted antifungal prophylaxis is recommended for high-risk populations; however, the epidemiology of IFI has changed, and the risk criteria remain unclear. In addition, the risk factors for late-onset invasive aspergillosis (IA) have not been fully characterized. We examined 279 recipients over 16 years of age to uncover their IFI epidemiology, clinical characteristics and outcomes. In addition, a case–control study was performed to identify the risk factors of late-onset IA. Of the 279 recipients, 96.1% underwent living donor liver transplantation. Antifungal prophylaxis was administered to 80.6% of the recipients. IFI occurred in 15 patients, among which 8 cases were early-onset (≤90 days after liver transplantation) and 7 cases were late-onset (>90 days after liver transplantation). Five of the late-onset cases were invasive pulmonary aspergillosis, and 2 were fungemia cases. The mortality rate of late-onset IA was 80.0%. According to a multivariate analysis, steroid use before liver transplantation, bloodstream infection within 90 days after liver transplantation and reoperation within 90 days after liver transplantation were significant risk factors for late-onset IA after liver transplantation. The prevalence of IFI was low in our population given that over 80% of liver recipients received antifungal prophylaxis. The prognosis of late-onset IA remains poor, and predictors associated with late-onset IA, such as steroid use before liver transplantation, bloodstream infection and reoperation after liver transplantation, may help clinicians to optimize prevention measures for these devastating infections.

1. Introduction

Invasive fungal infection (IFI) is an important cause of morbidity and mortality among liver transplant recipients [1–7]. Recent studies have revealed that the incidence of IFI after liver transplantation has declined since the mid-1990s; however, the reported incidence of IFI in liver transplant recipients varies, and infections still develop in approximately 5–20% of recipients [4–8]. Previously, we reported that preoperative steroid administration for fulminant hepatitis could predispose patients to develop invasive aspergillosis (IA) in living-donor liver transplant recipients; however, guidelines for the selection of antifungal prophylaxis have changed, and many studies regarding the risk factors for IFI have been published since our earlier report [9].

In addition, because of improvements in surgical techniques and immunosuppression therapy, the liver function prognosis of transplant patients has improved; however, a delayed occurrence of IFI has been observed and still represents a significant burden [10–12]. An understanding of the specific risk factors for IFI, especially for IA is essential for guiding effective empiric and preventive antifungal strategies. However, studies on risk factors for IA have primarily focused on early-onset infection, and few studies have revealed the risk factors for late-onset infection [13–15].

This study was performed to assess the current epidemiology of IFI after liver transplantation during the era of newer antifungal

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agents. In addition, we performed a case–control study to reveal the risk factors for late-onset IA after liver transplantation.

2. Material and methods

2.1. Study population

This study was a retrospective analysis of patients who received liver transplantations at Kyoto University Hospital, Japan, from 2007 to 2013. Follow-up continued until December 2014. All transplant recipients over 16 years of age were included in the analysis, irrespective of whether they had received a graft from a deceased or living donor or if they had undergone a primary transplant or re-transplantation. Only one transplantation event (the most recent) per person was included. All medical records were reviewed to obtain data on demographics, underlying diseases, transplant types, clinical characteristics, microbiological screening results, potential risk factors, types and sites of infections and medical and surgical complications during the study period.

To reveal the risk factors for late-onset IA in our population, we performed a case–control study. The controls included 5 recipients without IA or other fungal infections who had undergone liver transplantation within a month before or after each IA patient so that the surgical techniques and choices of immunosuppressive regimens might not affect the results, because attending doctors periodically rotate through the hospitals affiliated with our institution.

2.2. Clinical definitions

IFI was suspected on the basis of clinical or radiological signs. A diagnosis of proven or probable IFI was based on histopathological findings or blood/tissue cultures according to EORTC/MSG criteria [16]. Early-onset IFI was defined as an infection that occurred within 90 days after transplantation and late onset IFI was defined as an infection that occurred at least 90 days after transplantation. The day of diagnosis was defined as the day of the first microbiological documentation of infection or the day of death in the case of postmortem diagnosis.

2.3. Microbiological monitoring

Screening for IA was performed before and after transplantation using serum samples to test for *Aspergillus* galactomannan (GM) antigen (the Platelia *Aspergillus* test, SRL, Japan) and radiologic evaluations from head to abdomen by computed tomography (CT). The test was performed twice prior to transplantation (generally at 3 months and then within 1 month prior to surgery) and then weekly after surgery until discharge. A GM antigen index over 0.5 was designated as positive according to the manufacturer's recommendations. The beta-(1,3)-D glucan concentration was not determined as a monitoring tool but was instead used as a part of the diagnostic measures for IFI. Treatments for fungal infections were administered at the discretion of the physician if probable or proven IFI was present. Weekly monitoring for cytomegalovirus antigenemia was also performed during the hospital stay.

2.4. Prophylaxis strategy

Perioperative prophylaxis consisted of ampicillin and cefotaxime for 48 h. Trimethoprim and sulfamethoxazole were administered once daily as prophylaxis against *Pneumocystis jirovecii* infection. In addition, either fluconazole 400 mg or micafungin 100 mg was administered as an antifungal prophylaxis. The selection of recipients for antifungal prophylaxis was performed at the doctors' discretion if the recipients had at least one known risk factor for IFI including retransplantation, renal replacement therapy (RRT), repeat intra-abdominal surgery and transplantation for fulminant hepatic failure [7–9]. Enteral tube feeding was administered immediately after liver transplantation if there were no complications with the digestive organs. An antiviral agent for prophylaxis against cytomegalovirus infection was not routinely administered.

2.5. Statistical analysis

Data were compared between patients using the chi-square test for categorical data and the independent samples t-test for continuous data. The two-sided statistical significance was set at $P = 0.05$. Statistically significant variables ($P < 0.1$) in the univariate analysis were introduced within a multivariate model by using a forward stepwise logistic regression. The statistical analyses including an estimate for the c statistic for the logistic regression model were performed with PASW, version 18.0 (SPSS), for Microsoft Windows.

3. Results

3.1. Clinical characteristics of the entire cohort

A total of 279 patients underwent transplantation during the study period (Table 1). The overall incidence of IFI was 5.4%, which comprised 8 cases of early-onset IFI (5 IA cases and 3 cases of fungemia) and 7 cases of late-onset IFI (5 IA cases and 2 cases of fungemia). The most common indication for liver transplantation was cirrhosis from hepatitis B and/or C infection (47.5%), followed by primary biliary cirrhosis (15.1%) and post-Kasai biliary atresia (6.1%). Two hundred and fifty-five recipients (91.4%) underwent living-

Table 1
Patient characteristics, risk factors, and the incidence of invasive fungal infections.

	Total N = 279% (n)
Age, years, median (range)	54 (16–70)
Male gender, % (n)	47.3% (132)
Underlying liver disease, % (n)	
Hepatitis B and or C virus infection	47.3% (132)
Primary biliary cirrhosis	15.1% (42)
Post-Kasai biliary atresia	6.1% (17)
Alcoholic cirrhosis	5.7% (16)
Fulminant hepatitis	5.4% (15)
Primary sclerosing cholangitis	4.3% (12)
Autoimmune hepatitis	2.9% (8)
Nonalcoholic steatohepatitis	2.5% (7)
Others	10.8% (30)
Living donor	96.1% (268)
Deceased donor	3.9% (11)
Retransplantation	6.1% (17)
MELD score, median, (range)	18, (6–46)
MELD score ≧20	43.0% (120)
Steroid use before liver transplantation	9.0% (25)
ABO incompatible	25.1% (70)
Hepatocellular carcinoma	28.7% (80)
GM positive before transplantation	37.2% (90/242)[a]
Choledochojejunostomy	18.6% (52)
Rejection	33.3% (93)
Cytomegalovirus antigenemia	77.1% (168/218)[a]
Antifungal prophylaxis	80.6% (225)
Invasive fungal infection (total)	5.4% (15)
Early-onset invasive fungal infection	2.9% (8)
In-hospital mortality for first admission	20.4%

GM, Aspergillus galactomannan antigen.
MELD, Model for end-stage liver disease.
[a] Number of patients with positive results/number of patients tested.

donor liver transplantation and 24 recipients underwent deceased-donor liver transplantation. Seventeen recipients underwent re-transplantation. Prior to liver transplantation, 37.2% of the patients (90/242 recipients) were positive for the serum GM antigen; however, none of the patients had radiological abnormalities according to their head and chest CTs nor had clinical symptoms that were suggestive of IA; thus those results were regarded as false positives. Only 1 recipient, who was positive for GM antigen before liver transplantation, subsequently developed IA after transplantation. The thirty-day mortality rate after liver transplantation was 6.5%.

3.2. Real-world prescription of antifungal prophylaxis

Eighty percent of recipients underwent antifungal prophylaxis, and the mean duration of total antifungal prophylaxis, including parenteral and oral antifungal agents, was 41 days. In 2007, intravenous fluconazole was given to 16.7% of the recipients, and micafungin was given to 35.7%. However, the number of recipients that received micafungin-based prophylaxis (either micafungin alone or micafungin followed by oral fluconazole) gradually increased each year, and more than 95% of the recipients received micafungin based prophylaxis in 2013. In total, 202 (90.2%) recipients received micafungin-based antifungal prophylaxis, 20 (7.2%) recipients received fluconazole, 1 received liposomal amphotericin B, and the others received no prophylaxis. In our cohort, no patient experienced clinical side effects that required the cessation of micafungin treatment.

3.3. Clinical characteristics of patients with invasive fungal infections

The characteristics of the 15 IFI patients are shown in Table 2. IA developed in 10 cases (5 cases each for early and late-onset infection), and fungemia developed in 5 cases (3 cases for early-onset IFI and 2 cases for late-onset IFI). *Aspergillus fumigatus* was isolated from 3 IA cases and the rest were diagnosed on the basis of either serological or pathological findings. The serum GM antigen tests remained negative until diagnosis of IA. All *Candida albicans* isolates and one *Kodamaea ohmeri* isolate recovered from the fungemia cases were susceptible to fluconazole and micafungin. All IFI cases underwent living-donor liver transplantation and had at least 2 risk factors out of the following list: steroid use before liver transplantation, retransplantation, RRT, reoperation, prolonged ICU admission, a requirement of more than 40 units of

Table 2
Clinical characteristics and risk factors for invasive fungal infections.

Underlying liver disease	MELD score	Risk factors stated in the AST/IDSA guidelines	Other risk factors	Types of infection	Days from transplant to IFI	Antifungal agents for prophylaxis	Days after cessation of antifungal prophylaxis	Outcome
Budd-Chiari syndrome	22	None	Blood transfusion, CMV, Choledochojejunostomy	*C. albicans* BSI (proven)	5	MCFG	During prophylaxis	Survived
Post-Kasai biliary atresia	30	Re-transplantation	Blood transfusion, Steroid	Pulmonary IA (probable)	10	L-AMB	During prophylaxis	Survived
AIH	24	None	Blood transfusion, Steroid, CMV	Pulmonary IA (probable)	12	MCFG	During prophylaxis	Died
HCV	16	None	CMV	*C. albicans* BSI (proven)	19	None	15 days	Died
Alcoholic cirrhosis	22	RRT	Blood transfusion	*Kodamaea ohmeri* BSI (proven)	37	MCFG	5 days	Died
PBC	27	None	Blood transfusion, Rejection, CMV	Pulmonary IA (probable)	40	MCFG	During prophylaxis	Died
PSC	11	None	Blood transfusion, Rejection, Steroid, Choledochojejunostomy	Pulmonary IA (probable)	41	MCFG	During prophylaxis	Died
PBC	19	None	Blood transfusion, Rejection, CMV	Pulmonary IA (probable)	42	FLCZ	During prophylaxis	Died
Post-Kasai biliary atresia	29	Re-transplantation	Blood transfusion, Rejection, Steroid, Choledochojejunostomy	*C. albicans* BSI (proven)	105	MCFG	During prophylaxis	Died
HBV	16	None	Blood transfusion, Rejection	Pulmonary IA (probable)	117	MCFG	97 days	Survived
AIH	27	None	Steroid, CMV	*Cryptococcus neoformans* BSI (proven)	117	MCFG	No treatment[a]	Died
PBC	20	None	Steroid, CMV	Pulmonary IA (probable)	176	MCFG	During prophylaxis	Died
PBC	17	None	Blood transfusion, Rejection, Steroid, CMV, Choledochojejunostomy	Pulmonary IA (possible)	210	MCFG	140 days	Died
HCV/HBV	19	Reoperation	CMV	Pulmonary IA (probable)	253	MCFG	180 days	Died
HCV	10	None	Blood transfusion, Rejection, CMV, Choledochojejunostomy	Pulmonary IA (proven)	367	FLCZ	No treatment[a]	Died

IFI, invasive fungal infection.
PBC, primary biliary cirrhosis.
PSC, primary sclerosing cholangitis
AIH, autoimmune hepatitis.
CMV, cytomegalovirus infection.
Blood transfusion, requiring substantial amounts of blood products (>40 μnits).
IA, invasive aspergillosis.
BSI, bloodstream infection.
MCFG, micafungin, 100 mg q24 h.
L-AMB, liposomal amphotericin B, 2 mg/kg q24 h.
FLCZ, fluconazole, 100 mg q24 h.
[a] No treatment, diagnosed after patient deceased.

blood transfusion, cytomegalovirus infection, a high MELD score, and choledochojejunostomy. IA developed at 79.5 days (median, range: 8–367 days) after transplantation, and fungemia developed at 37 days (median, range 5–117 days) after transplantation. IA developed in 3 cases during antifungal prophylaxis (2 cases with micafungin and 1 case with liposomal amphotericin B) and other IFI cases developed after the cessation of antifungal prophylaxis (2 cases with fluconazole and 10 cases with micafungin). Among those patients who developed IFI after the cessation of antifungal prophylaxis, the mean durations after the cessation of antifungal prophylaxis were 10 days for early-onset IFI cases and 139 days for late-onset IFI cases. Liposomal amphotericin B was the most common antifungal agents for IFI (6 cases), followed by VRCZ for 4 cases and micafungin for 3 cases and fluconazole for 1 case. Antifungal agents were not given for 2 cases because they were diagnosed at the time of death. Forty percent (6/15) of cases had organ failures involving at least two organs, 40% (6/15) had concomitant infections and all cases who died during hospitalization had at least one of the complications when IFI was diagnosed. The thirty-day mortality for IFI after diagnosis was 80%.

3.4. Risk factors for late-onset invasive aspergillosis

To reveal the risk factors for late-onset IA, we performed a case control study by using 5 late-onset IA cases and 25 controls (Table 3). A univariate analysis revealed that steroid use for autoimmune disease before liver transplantation, ABO-incompatibility, choledochojejunostomy, high total bilirubin value, bloodstream infection within 90 days after liver transplantation, and reoperation within 90 days after liver transplantation were statistically significant risk factors. Furthermore, a multivariate analysis revealed that the use of steroids to treat an autoimmune disease before transplantation (Odds ratio (OR), 16.1; 95% confidence interval (CI), 1.38–25.6), which reflected an underlying disease in a patient, and bacteremia (OR, 10.3; 95% CI, 1.01–21.1) and reoperation (OR, 7.1; 95% CI, 2.22–11.6), which reflected the post-operative course, were significant risk factors for late-onset IA. The estimate for c statistics for this model was 0.897.

4. Discussion

Although recent studies have reported that the IFI incidence has been declining, our analysis of all the liver transplantation

Table 3
Univariate and multivariate analyses of risk factors for late-onset invasive aspergillosis among liver transplant recipients.

	Univariate analysis					Multivariate analysis		
	Case (n = 5)	Percentage of total cases (%)	Control (n = 25)	Percentage of total controls (%)	*P*	OR	95% CI	*P*
Age, Mean ± SD	51.8 ± 8.8		53.5 ± 10.8		0.644			
Sex (male)	4	80.0%	14	56.0%	0.318			
MELD score, Mean ± SD	18.8 ± 6.53		21.3 ± 8.12		0.413			
MELD ≧20	2	40.0%	11	44.0%	0.633			
Diabetes mellitus	1	20.0%	2	8.0%	0.433			
Malignancy	2	40.0%	11	44.0%	0.633			
RRT before transplantation	0	0.0%	1	4.0%	0.833			
Retransplantation	1	20.0%	3	12.0%	0.538			
Steroid use before transplantation	3	60.0%	1	4.0%	0.009	16.1	1.38–25.6	0.041
Underwent surgery before transplantation	1	20.0%	0	0.0%	0.167			
ABO-incompatible	3	60.0%	2	8.0%	0.022			0.328
Viral hepatitis	3	60.0%	19	76.0%	0.404			
Duration of intubation Mean ± SD (days)	6.13 ± 10.4		4.19 ± 5.11		0.583			
Duration of ICU stay Mean ± SD (days)	10.4 ± 13.9		7.57 ± 6.98		0.323			
Duration of intravenous antifungal prophylaxis Mean ± SD (days)	27.0 ± 37.7		13.2 ± 18.4		0.471			
Duration of total antifungal prophylaxis Mean ± SD (days)	42.2 ± 22.2		21.9 ± 6.76		0.421			
Choledochojejunostomy	2	40.0%	1	4.0%	0.064			0.426
Rejection	3	60.0%	6	24.0%	0.143			
Clinical course at day 90								
Hospitalized	3	60.0%	9	36.0%	0.304			
Total bilirubin value Mean ± SD	12.1 ± 8.5		1.32 ± 0.86		0.005			0.498
INR value, Mean ± SD	1.82 ± 0.54		1.30 ± 0.08		0.093			
History of documented microbiological infection	4	80.0%	15	60.0%				
History of bacteremia	4	80.0%	3	12.0%	0.006	10.3	1.01–21.1	0.038
History of fungal colonization	2	40.0%	4	16.0%	0.254			
History of pathological diagnosis of rejection	2	40.0%	3	12.0%	0.183			
Steroid pulse	1	20.0%	8	32.0%	0.521			
History of reoperation	4	80.0%	4	16.0%	0.011	7.1	2.22–11.6	0.044
History of CMV viremia	1	20.0%	9	36.0%	0.449			
History of RRT	3	60.0%	4	16.0%	0.068			

OR, odds ratio.
CI, confidence interval.
MELD, model for end-stage liver disease.
CMV, cytomegalovirus.
RRT, renal replacement therapy.

performed in our institution revealed that the overall incidence of IFI was 5.4% and the mortality rate among patients with IFI was 80%. This finding suggests that IFI remains an important predictor of morbidity after liver transplantation and that effective preventive strategies are needed.

A recent study reported that liver failure was one of the predisposing risk factors for IA [17]. GM antigen has been reported to be useful for the surveillance of IA after transplantation; however, its utility in screening for IA prior to liver transplantation has not been clarified [18]. In our cohort, although one antigen-positive recipient who underwent retransplantation eventually developed IA, it might be reasonable to regard GM antigen positivity for the rest of the recipients as a false-positive result. After this study, we decided to stop routine screening for GM antigen *before* liver transplantation unless the candidate was receiving immunosuppression therapy. However, an effort has been made to use GM antigen detection after liver transplantation as a monitoring technique.

At present, prophylaxis against fungi is not routinely recommended in liver transplant recipients, and targeted prophylaxis in liver transplant recipients is employed most frequently during the initial hospital stay or for the first month post-transplant. According to AST/IDSA guidelines, high risk factors include renal dysfunction, retransplantation and reoperation, however, recent studies have revealed that high MELD scores, choledochojejunostomy, bile leaks and living-donor liver transplantation are also risk factors for IFI [12–16]. In fact, all recipients had at least one risk factor that was reported in previous studies for our population, and as many as 80% of the recipients received antifungal prophylaxis. In general, candidiasis is reported to be the most common IFI in solid organ transplantation recipients and accounts for 50–60% of infections, but invasive candidiasis occurred in 26.7% of IFI cases in our study [2–8]. Universal prophylaxis using micafungin and the early administration of enteral feeding might have affected the prevalence rate of invasive candidiasis in our cohort. Furthermore, the incidence of IA was lower than it was in previous studies (1.8%) possibly because of micafungin-based antifungal prophylaxis. In 2013, 408 liver transplantations were performed in Japan, and as many as 90% of the cases were living-donor liver transplantations, which contrasts with the United States, where 96% of cases were deceased-donor liver transplantations [19]. Given that a high mortality rate for IFI was observed in our population, the donor type should be taken into account before applying the criteria for high-risk IFI recipients. We need to reconsider the definition of a high-risk population under circumstances in which living-donor liver transplantation is common.

As Singh et al. reported in 2003, IA in solid organ transplant recipients occurs later in the post-transplantation period [10,13,14,20,21]. A trend towards a later onset *Aspergillus* infection has also been noted among patients undergoing hematopoietic stem cell transplantation; longer survival and the delayed occurrence of graft-versus-host disease are proposed to account for this phenomenon [21]. Although recent studies reported that the prognosis for IA has been improving, late-onset IA was associated with high mortality after transplantation in our series [22]. In this study, appropriate antifungal agents were given for most cases soon after diagnosis; however, as many as 73% had severe underlying conditions and 2 IFI cases could not be diagnosed before death. Thus, those factors may explain the poor prognosis of IA cases in our cohort and diagnostic strategies as well as the fact that preventive measures would be the key to better prognoses. A multivariate analysis revealed that receiving steroids for autoimmune diseases before transplantation, which reflects the presence of underlying diseases, and a history of bloodstream infection within 90 days and a history of reoperation, which is indicative of post-operative complications, were significant risk factors for late-onset IA. Surveillance monitoring for IA or even antifungal prophylaxis might be a choice for those who have these risk factors.

This study has several important limitations. The retrospective and single center design of this study could result in the underestimation of the IFI incidence. In addition, the absence of an autopsy in deceased patients is another limitation because some episodes of IFI could have been missed, as suggested by the postmortem diagnosis of one unsuspected infection. The relatively small sample size also limited the multivariate analysis, and we were unable to evaluate the risk factors for *Cryptococcus* bloodstream infection and candidemia.

Here, we report the current epidemiology of IFI after liver transplantations in which all recipients had at least one reported risk factor. We found that the prevalence rate of IFI was low in our population, which is likely because more than 80% of the recipients received antifungal prophylaxis. The predictors for late-onset IA identified in this study, such as steroids for autoimmune diseases before liver transplantation, bloodstream infection and reoperation within 90 days after liver transplantation, may help clinicians to optimize the prevention of this infection. Although further prospective studies are needed, we may need to consider close monitoring and antifungal prophylaxis for those who have these risk factors.

Conflict of interest

None of the authors of this manuscript have any conflicts of interest to disclose.

Authors' contributions

MN and YF contributed to the study design, analyzed the data and wrote the first draft of the manuscript. All authors contributed to the study procedures and data collection, provided comments on the manuscript, and approved the final version of the manuscript.

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