

Risk Factors and Prevalence for Candidemia in Liver Transplant Recipients without Antifungal Prophylaxis, 10-Year Follow-Up

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Abstract

Objective: Candidemia rates in liver transplant recipients (LTRs) differs from center to center, geographic locations and type of solid organ transplantation. We aimed to investigate the risk factors and prevalence of candidemia in adult LTRs in our center.

Methods: Between January 2003 and December 2012, microbiological and clinical data of adult (>18 years) LTRs were searched from mycology laboratory and patients' records retrospectively. The presence of candidemia was defined by determining at least one positive blood culture. Cases were followed at least 150 days after transplantation (150 days-10 years). The risk factors were investigated in preoperative, intraoperative and postoperative periods. None of the patients received antifungal prophylaxis.

Result: In the study period, 388 of 472 patients undergoing liver transplantation were included. Candidemia was detected in 10 (2.6%) patients. Among the important risk factors albumin level below 2.8 mg/dl, the use of vascular graft, the presence of biliary complication, hospitalization in intensive care unit(>6 days), re-operation, the presence of surgical site infection and postoperative length of stay were detected as significant risk factors. The most common pathogen was *C. albicans*. Five (50%) patients with candidemia died and *C. albicans* was responsible for candidemia. Attributable mortality of candidemia was 60%. The presence of candidemia increases the mortality rate significantly (p-value=0.023)

Conclusion: Candidemia should be diagnosed as early as possible. In the population without antifungal prophylaxis,

candidemia ratio is not higher than the other studies reported formerly. The lower rate of candidemia can be achieved through good patient preparation in pre-transplant period, meticulous surgical technique, use of biological rather than synthetic vascular graft and early discharge after transplantation.

Introduction

Candida infections are among the causes of mortality during early postoperative period in liver transplant recipients (LTRs). The types of these infections can vary from colonization to candidemia or invasive candidiasis (IC). Candidemia can be defined as a subgroup of IC. Candidemia rates in LTRs differ from center to center, geographic locations and type of solid organ transplantation (SOT). Among SOT recipients, candidemia occurs most frequently in liver and pancreatic transplant patients (1%-32%) [1]. In many SOT centers, antifungal prophylaxis is recommended to decrease incidence and mortality attributable to *Candida* infections, especially for high-risk patients [2]. In our transplantation center, the incidence of fungal infection was detected to be 3.2% between January 2003 and December 2006 in LTRs. During this period, in two patients *Candida* species were isolated from blood cultures [3]. Antifungal prophylaxis is not routinely performed in LTRs. Therefore; we aimed to investigate the risk factors and prevalence of candidemia in adult LTRs without antifungal prophylaxis until December 2012.

Methods

Between January 2003 and December 2012, microbiological and clinical data of adult (>18 years) LTRs were searched from mycology laboratory and patients' records retrospectively. The

study was approved by Dokuz Eylul University faculty of medicine ethical committee for noninvasive research. The candidemia was defined by determining at least one of the species of genus *Candida* in one peripheral or central line blood culture. Cases were followed at least 150 days after transplantation (150 days-10 years). Risk factors were investigated in preoperative, intraoperative and postoperative periods. Collected data included; age, gender, body mass index, primary etiology, model for end-stage liver disease (MELD) score, preoperative albumin (<2.8 g/dl) and creatinine levels (≥ 1.3 mg/dl), diabetes mellitus, the presence of ascites and encephalopathy, intraoperative glucose levels (≥ 180 mg/dl), operation and cold ischemia time, type of donor, the number of red blood cell (>6 units), fresh frozen plasma (>12 Units), the use of vascular graft, the level of intraoperative blood loss (≥ 1000 cc), the type of biliary anastomosis, duration of antibiotic prophylaxis (>3 days), biliary complication, hospitalization in intensive care unit (>6 days), reoperation, the presence of bacterial infection (the infections of surgical site, blood stream and pulmonary) and preoperative and postoperative length of stay. Immunosuppression protocol consisted of Cyclosporine A/tacrolimus, Mycophenolate mofetil and corticosteroid [4]. None of the patients received antifungal prophylaxis. statistical package for the social sciences (SPSS) version 15.0 was used for statistical analysis. Multivariate, forward stepwise, logistic

regression analyses were used for the identification of independent risk factors for candidemia.

Results

In the study period, 388 of 472 patients who underwent liver transplantation were included. Candidemia was detected in 10 (2.6%) patients. Of these, catheter cultures were also positive in 3 (30%) patients. The median time to candidemia was 29.0 ± 100.84 days (7-309 days) after liver transplantation. In 7 (70%) of patients, candidemia was detected within the first 3 months after transplantation. Demographic and microbiological characteristics and risk factors of the patients were presented at **Tables 1 and 2**, respectively. Cytomegalovirus (CMV) infection (all patients were CMV IgG positive) and renal failure were not observed in any of the patients with candidemia. Preoperative albumin level below 2.8 mg/dl was determined as the most important risk factor for candidemia. ($p=0.022$). For the intraoperative period, the use of vascular graft was found to be significant ($p=0.025$). In postoperative period, presence of biliary complication, hospitalization in intensive care unit (>6 days), re-operation, presence of surgical site infection and length of stay were also detected as significant risk factors ($p=0.000$, $p=0.002$, $p=0.026$, $p=0.011$, $p=0.000$, respectively) (**Table 1**).

Table 1: Demographic and Microbiological characteristics.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age	46	52	28	50	64	38	47	59	31	57
Gender (Male/Female)	K	E	E	E	E	E	E	E	K	E
Donor (Deceased/Living)	L	L	L	L	D	L	L	D	D	L
MELD score	14	12	41	11	12	22	16	8	22	18
Etiology	HBV	HCC	Fulminant hepatitis	HBV	HBV+HDV	HBV	HBV	HBV+HCC	HBV+HDV	HCV
Timing of candidemia (day)	67	12	33	205	7	21	25	309	16	103
<i>Candida</i> species	<i>C. guilliermondii</i>	<i>C. lusitaniae</i>	<i>C. albicans</i>	<i>C. albicans</i>	<i>C. albicans</i>	<i>C. albicans</i> + <i>C. parapsilosis</i>	<i>C. albicans</i>	<i>C. albicans</i>	<i>C. albicans</i> + <i>C. glabrata</i>	<i>C. albicans</i>
Mortality	Live	Live	Live	EX	Live	EX	EX	EX	Live	EX

The most common pathogen was *C. albicans* (6 patients) followed by *C. guilliermondii* (1 patient) and *C. lusitaniae* (1 patient). In the remaining 2 patients both albicans and non-albicans strains were detected (**Table 2**). Antifungal therapy was started in all patients except one with candidemia because of delayed diagnosis. Five (50%) patients with candidemia have died. Attributable mortality of candidemia was 60.0% (3/5 patients). In all these 5 cases, *C. albicans* was responsible for candidemia. Post-transplant mortality rate was significantly higher in patients with candidemia ($p=0.023$).

Conclusion

In this study, the candidemia rate of LTRs without antifungal prophylaxis was 2.6%. In the literature, candidemia rate is evaluated in either invasive fungal infections of LTRs or candidemia of solid organ transplantation recipients. It had been informed that the candidemia rate was 2.2% in Australian SOT recipients (455 of patients were LTRs) who have received antifungal prophylaxis in the article which investigated the incidence of candidemia [5]. On the other hand, the incidence

of invasive fungal infections has been reported as 7%-42% in LTRs [6]. Hussain et al. [7], reported that the candidemia has been diagnosed in 40% of invasive candidiasis, median time of infection was 13.5 days and 78% of the infections were detected in first 3 months after transplantation. In our study, the candidemia was determined in 70% of LTRs within the first 3 months with a median of 29 days. These findings showed that first 3 months was crucial era for candidemia development regardless of antifungal prophylaxis treatment after liver transplantation.

Diagnosis of candidemia is the easiest one among the fungal infections. The important point is to estimate which risk factors have contribution in candidemia development, obtaining blood culture from the patient and starting the treatment at the earliest. In fact, risk factors have been handled for invasive candidiasis of LTRs in many studies [7-11]. In these studies risk factors associated with candidemia have been reported as re-transplantation, preoperative creatinine level (≥ 2.0 mg/dl), need for renal replacement therapy within the first 30 days after transplantation, re-operation, choledochojunostomy, the use of intraoperative blood products to more than 40 units, prolonged intraoperative time (≥ 11 hours), fulminant hepatic failure, candidemia and CMV co-infection and *candida* colonization in pre-transplantation period. However, there are few studies which detect risk factors for especially candidemia [5,12]. These studies emphasized that the risk factors were similar with candidemia risk factors for non-SOT recipients; but specific candidemia risk factors only for SOT recipients were immunosuppression, candidemia and CMV co-infection, hyperglycemia treated with insulin over two weeks before candidemia and previous pre-exposure to more than three different intravenous antibiotics. In our study, CMV infection, high creatinine level and renal replacement therapy requirements were determined in none of the cases of candidiasis. Only three patients had MELD score greater than 20 and all patients were at relatively low risk for CMV infection (Table 2). CMV seronegativity is 4.7 for LTRs in our center [13]. Besides, the usage of three different types of antibiotics has been detected in 70% of patients (Table 3).

Our study revealed that the most important risk factor for candidemia is the low albumin level (<2.8 mg/dl) in pre-operative period for our LTRs. It is clear that hypoalbuminemia delays wound healing after the surgical intervention.

Additionally, it is reported that four weeks are required for returning to normal nutritional metabolism after transplantation [14]. In this case, low albumin level during the preoperative stage and catabolic process which can be expected within the first 2-4 weeks after transplantation may delay the healing process of surgical wound. The delay in the healing of surgical wound is a predisposing factor for bacterial infection. The presence of bacterial infection also can require the use of more than one antibiotic for a long time. In our study, 80% of patients with candidemia have also been diagnosed with bacterial SSI. The deep tissue or aspiration culture positivity and the usage of three different groups of antibiotics before candidemia in the post-operative period have been detected in more than 60% of study patients (Table 2). This data explain that hypoalbuminemia is a risk factor for secondary candidemia derived from gut. Additional risk factors (the use of vascular graft, presence of biliary complication, reoperation) associated with following intraoperative technique, multiple use of antibiotics in the post-operative period and longer duration of intensive care unit and hospital stay can increase the risk of infection. Assessment of all risk factors has led to simplification in management of patients with candidemia.

As determined in this study, *C. albicans* was determined as the most common species in the literature [8,9,15,16]. It was shown that especially the use of broad-spectrum antibiotics changed the intestinal flora and increased concentration of *candida* species in the gut [12]. In our study, 70% of patients with candidemia have used three different types of antibiotics. Antifungal prophylaxis is not routinely performed in our center. It is determined that all patients have some problems related to surgical technique (re-operation, vascular graft usage, biliary complication etc.) In the view of this information, it can be concluded that detection of *C. albicans* as most common species and high mortality rate were expected in the LTRs. Additionally, *C. albicans* is still the most common species which has the highest mortality rate in surgical ICU of patients with candidemia in our center. Crude mortality rate at 30th day was 43.9% and mortality rate of candidemia associated with *C. albicans* was significantly higher than with non-*albicans candida* strains. The attributable mortality in LTRs is rising up to 60% in the study presented here.

Table 2: Risk factors for the patients with candidemia. *-SSI: Surgical site infection, **-The usage of three different groups antibiotics before candidemia, ***-Hyperglycemia treated with insulin up to 2 weeks before candidemia.

Risk Factors	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Preoperative albumin levels (g/dl)	2.8	4	2.7	1.6	2.5	2.4	2.5	2.2	2.1	2.3
Operation time (min)	570	660	230	480	180	730	580	460	300	590
Vascular graft usage	No	Cadaveric	No	Gorotex	No	Cadaveric	No	Gorotex	No	No
Choledochojunostomy	No	Yes	Yes	No	No	Yes	No	No	Yes	Yes

Biliary complication	Yes	No	No	No	Yes	No	Yes	No	No	No
Reoperation	Yes	Yes	Retrans	No	No	Yes	No	Yes	Yes	Yes
Intraoperative blood loss (ml)	3900	4000	2000	5900	5250	5400	9000	3500	4000	4500
The number of red blood cell / fresh frozen plasma (U)	9/7 (16)	8/12 (20)	4/22 (26)	4/13 (17)	3/5 (8)	19/44 (63)	8/12 (20)	11/19 (30)	25/23 (48)	18/23 (41)
The presence of SSI*	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes
The presence of blood stream and/or pulmonary infection	Yes/No	Yes/No	Yes/No	Yes/No	No / No	Yes / No	Yes / No	No / No	Yes / No	No / No
Antibiotic usage **	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes
Hyperglisemia***	No	No	No	No	Yes	No	No	Yes	No	No
Postoperation ICU stay (day)	10	10	7	1	2	26	7	1	27	52
Postoperation LOS (day)	123	41	27	26	19	26	42	21	31	170

Table 3: Significant risk factors for Candidemia.

	OR	95 % CI	P<0.05
Preoperative risk factors			
Preoperative albumin levels	11.331	1.421-90.340	0.022
Intraoperative risk factors			
The use of vascular graft	4.849	1.221-19.258	0.025
Postoperative risk factors			
The presence of biliary complication	0.04	0.012-0.132	0
The presence of surgical site infection	0.183	0.005-0.673	0.011
Postoperative length of hospital stay (> 21 day)	1.054	1.035-1.073	0
Postoperative ICU stay (> 6 day)	0.138	0.039-0.494	0.002
Reoperation	0.26	0.079-0.853	0.026

There are some limitations of this study. One of the limitations is that the study is a retrospective single-center study, another one is the ignorance of the donor related candidemia and finally *Candida* colonization has not followed for each recipient through the preoperative period. Despite these limitations, this study has contribution to literature. In this study, risk factors and mortality for only candidemia on the basis of LTRs' characteristics were separately presented. The prognosis of these patients depends on patients' characteristics, technical problems and developing postoperative care complications.

In conclusion, candidemia should be diagnosed as early as possible. In our study population without antifungal prophylaxis, candidemia ratio is not higher than the other studies reported formerly. But mortality of infections especially due to *C. albicans* was high. A lower rate of candidemia can be achieved through good patient preparation in pre-transplant period, meticulous surgical technique, use of

biological rather than synthetic vascular graft and early discharge after transplantation.

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