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Invasive Fungal Infections After Liver Transplantation: A Retrospective Matched Controlled Risk Analysis

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Background: Invasive fungal infections (IFI) are major risks for mortality after liver transplantation (LT). The aim of this study was to evaluate possible risk factors for the development of IFI after LT.

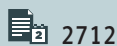
Material/Methods: All adult patients with IFI after LT between January 2012 and December 2016 at Essen University were identified. Pre-, intra-, and postoperative data were reviewed. These were compared to a 1-to-3 matched control group. Multinomial univariate and multivariate regression analyses were performed.

Results: Out of the 579 adults who underwent LT, 33 (5.6%) developed postoperative IFI. Fourteen had invasive aspergillosis with 7 (50%) mortality, and 19 had Candida sepsis with 7 (37%) mortality. The overall mortality due to invasive fungal infections was 42%. Perfusion fluid contamination with yeast was detected in 5 patients (15%). Multivariate regression analyses showed that preoperative dialysis (OR=1.163; CI: 1.038-1.302), Eurotransplant donor risk index (OR=0.04; CI=0.003-0.519), length of hospital stay (OR=25.074; CI: 23.99-26.208), and yeast contamination of the preservation fluid (OR=47.8; CI: 4.77-478, 96) were associated with IFI in the Candida group, whereas duration of surgery (OR=1.013; CI: 1.005-1.022), ventilation hours (OR=0.993; CI=0.986-0.999), and days of postoperative dialysis (OR=1.195; CI: 1.048-1,362) were associated with IFI in the aspergillosis group.

Conclusions: Post-LT IFI had 42% mortality in our cohort. Prophylactic antifungal therapy should be expanded to broader risk groups as defined above.

Keywords: Antifungal Agents • Aspergillosis • Liver Transplantation

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Background

Liver transplantation (LT) is the ultimate treatment for end-stage liver disease [1-3]. Despite improvements in liver transplantation, infections in the early postoperative phase play a significant role in postoperative morbidity and mortality [3-5]. Among those that lead to sepsis, invasive fungal infections (IFI) are detrimental for patient outcomes [5]. Fungal infections are the cause of 12% of all sepsis-related deaths and 2% of all deaths after LT [3]. *Candida* and *Aspergillus* species are the most common pathogens of an IFI after liver transplantation [5,6].

The pathogenesis is different for these 2 types of fungi. Invasive fungal infections caused by *Candida* spp (species pluralis) are primarily endogenous infections, which start from a colonization in the body or from an already existing microbial biofilm [7]. If the milieu conditions are fulfilled, these fungal species can spread superficially or invasively [8]. The most common pathogen of this genus is *Candida albicans*. Risk factors for the development of invasive *Candida* spp infections include existing colonization with *Candida* spp, performance of major intra-abdominal procedures, prolonged hospitalization, central venous catheters, corticosteroid therapy, broad-spectrum antibiotic therapies, or congenital immunodeficiencies [7]. *Aspergillus* spp are aspergilliform, spore-bearing molds. They occur in the environment and are saprophytes. *Aspergillus* spores are found in varying concentrations in the air. Through inhalation, the 2-4 µm small spores enter the alveoli [8]. Predisposing factors, such as lung tissue damage, smoking, and cellular immune dysfunction, favor hematogenous spread to other organs [7]. Organ transplantation is also a risk factor for the development of invasive fungal infection by *Candida* spp as well as *Aspergillus* spp [7]. Therefore, the intra-abdominal surgery, central venous catheters, and disturbances in cellular immune defense due to immunosuppressive therapy are unavoidable risk factors for the development of invasive fungal infection in the LT population. In addition, fungal infection can also be transmitted with the donor organ. Rarely, the preservation fluid is contaminated with fungus [9].

Antimycotic prophylaxis during LT is variable among institutes [10-13]. Various risk factors for IFI after LT are described in the literature [5,13,16-26]. To date, there has been no multinomial multivariate analysis of these known risk factors. Our primary aim was to investigate the incidence and mortality of IFI after LT at our center. Our secondary aim was identification of possible risk factors for the development of IFI, which could potentially help us to select patients with high risk for IFI who would benefit from proper prophylaxis or early treatment.

Material and Methods

Patients who underwent deceased donor liver transplantation at Essen University Hospital between January 2012 and December 2016 were retrospectively reviewed. Pediatric patients and living donor liver transplantations were excluded. Patients who were diagnosed with a systemic IFI after LT and during the hospital stay were identified and included to the study. Diagnosis of IFI after LT was done based on the criteria of the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group [14]. Diagnostic confirmation was done by the microbiology institute. None of the patients received antifungal prophylaxis before or during LT. Patients received antifungal treatment based on their postoperative infectious signs and symptom. None of the patients received empiric treatment. Patients did not have pre-transplant immunosuppressive medication or fungal infection. Pre-, intra-, and postoperative data were retrospectively reported from the electronic database of our hospital, and patient records and the electronic database were made available by Eurotransplant. We created a 1-to-3 matched control group; each patient with an IFI after LT was matched with 3 patients without IFI, as the control group. The primary criteria for selecting the control group were the lab MELD score, age of the recipient, portal vein status (thrombosed or not), BMI, and previous abdominal surgery. The IFI group was separated into 2 groups: an invasive aspergillosis group (AG) and a candida sepsis group (CG). IFI was compared to the control group as a whole. In addition, AG and CG groups were compared to the control group as well. The intra- and postoperative variables were: duration of surgery (DOS), intraoperative blood transfusion, cold and warm ischemia time, Eurotransplant donor risk index (ET-DRI), yeast contamination of the perfusion fluid, length of stay (LOS) in the ICU (LOS-ICU), total LOS, preoperative hemodialysis, severe postoperative complications, and survival. Perioperative mortality was defined as 90-day mortality. Morbidity or severe postoperative complications were defined as Clavien-Dindo Class 3b or above complications [15]. Liver transplantation was performed in standardized technique with cava interposition in all patients. The immunosuppressive therapy was based on calcineurin inhibitors, prednisone, and mycophenolate mofetil. Modifications in dose or compounds were made individually, depending on the clinical course. Early allograft dysfunction was defined as a bilirubin level >10 mg/dL on day 7, an international normalized ratio >1.6 on day 7, and/or an alanine aminotransferase or aspartate-aminotransferase level >2000 IU/L within the first 7 days after transplantation [16].

The data were statistically analyzed and compared to the matched control group. The implementation was carried out in

Table 1. Comparison of the preoperative recipient data.

	AG n=14	CG n=19	Control n=99	p-value
Mean age (SD)	52.5 (12.9)	48 (10.8)	49.9 (12.3)	0.177
Sex (Male/Female)	9/5	10/9	62/37	0.913
BMI (IQR)	23.8 (20.5-29.8)	26.9 (22.9-31.1)	25.2 (22.3-29.4)	0.443
Abdominal surgery (n)	8	9	43	0.586
Portal vein thrombosis (%)	3	0	9	0.108
MELD-score (IQR)	26 (15-34)	18 (13-25)	19 (14-30)	0.456

AG – Aspergillus group; CG – Candida group; BMI – body mass index; MELD – Model for End-Stage Liver Disease; IQR – inter-quartile range; SD – standard deviation.

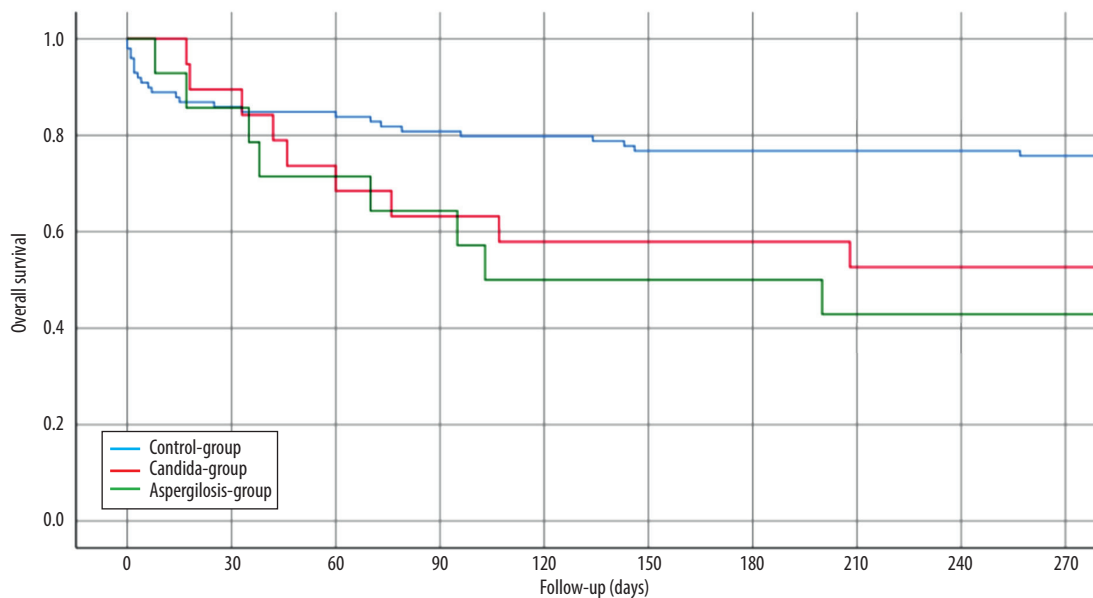


Figure 1. Kaplan-Meier Survival analysis.

accordance with the principles of the World Medical Association laid down in the Helsinki declaration and the national regulations for the conduct of clinical trials. Institutional review board approval was obtained.

Statistical Analysis

According to distribution, values are reported either as median and interquartile range (IQR) or as mean and standard deviation. Continuous variables were compared using the Mann-Whitney test. Comparisons of proportions were performed using Fisher's exact test or chi-square test. The survival rates were presented by Kaplan-Meier analysis and compared by log-rank test. At first, a univariate multinomial logistic regression

analysis, ie, a logistic regression with more than 2 characteristics (Aspergillus, Candida, no IFI), was performed. In order to minimize presumed relevance, the significant variables were then included in a conditional logistic multinomial multivariate analysis with a stepwise forward selection. The level of significance was defined with a p-value <0.05. All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp. Released 2017. Armonk, NY: IBM Corp).

Results

Out of the 579 adults who underwent LT in 2012-2016, 33 patients (5.6%) developed postoperative IFI. Of these, 14 patients

Table 2. Comparison of the peri and postoperative recipient data.

	AG n=14	CG n=19	Control n=99	p-value
DOS minutes (median IQR)	313 (267-372.5)	267 (239-353)	245 (209-288)	0.002
CIT minutes (median IQR)	501 (400-565)	505 (420-570)	450 (277-542)	0.323
WIT minutes (median IQR)	32 (29.5-35)	30 (27-35)	30 (26-34)	0.346
Hospital stay (days IQR)	46 (29-106)	38 (18-60)	21 (15-29)	<0.005
ICU-stay (days IQR)	39 (20-61)	16 (7-32)	5 (3-11)	<0.005
Ventilation hours (IQR)	334 (79.2-983.2)	104 (17-368)	25 (7-51)	<0.005
Dialysis preoperatively n (%)	2 (14.0)	10 (53.0)	33 (33.0)	0.001
Dialysis days (median IQR)	45 (13-70)	1 (0-39)	0 (0-2)	<0.005
Re-listing (%)	3 (21.0)	0 (0.0)	7 (7.0)	0.068
Re-operation (%)	11 (78.6)	12 (63.0)	25 (25.0)	<0.005

AG – Aspergillus group; CG – Candida group; DOS – duration of surgery; CIT – cold ischemic time; WIT – warm ischemic time; ICU – Intensive Care Unit; IQR – interquartile range.

Table 3. Comparison of the donor data.

	AG n=14	CG n=19	Control n=99	p-value
Age (median IQR)	48.1 (17.9)	51.4 (20.3)	56.4 (16.27)	0.175
Sex (Male/Female)	6/8	8/11	38/61	0.919
BMI (kg/m ²) (median IQR)	25 (22.6-26.4)	26.7 (4.7-27.8)	26.0 (23-28)	0.475
LOS-ICU (median IQR)	6 (2-7)	3 (2-4)	4 (2-7)	0.387
AST (U/l) (median IQR)	77 (38-133)	49 (30-117)	53 (27-108)	0.598
ALT (U/l) (median IQR)	57 (30-94)	37 (21-60)	30 (17-74)	0.135
γGT (U/l) (median IQR)	52 (24-167)	54 (23-118)	34 (16-101)	0.339
Bilirubin(mg/dl) (median IQR)	0.5 (0.3/0.85)	0.4 (0.22/0.82)	0.5 (0.3/0.8)	0.888
Fungal contamination of preservation fluid n (%)	1 (7.0%)	4 (21.0%)	2 (2%)	0.007
ET-DRI (median IQR)	1.6 (1.4-2.1)	1.7 (1.5-2.0)	1.9 (1.7-2.2)	0.053

AG – Aspergillus-group; CG – Candida-group; BMI – body mass index; ICU – Intensive Care Unit; AST – aspartate-aminotransferase; ALT – alanine-aminotransferase, γGT – glutamat-pyruvat-transaminase; ET-DRI – Eurotransplant Donor-Risk-Index; IQR – interquartile range.

(42.4%) had invasive aspergillosis (AG) and 19 patients (57.6%) had Candida sepsis (CG). There were 19 male (58%) and 14 female (42%) patients. The mean age was 48 years (SD11.89) and the mean lab MELD score was 22 (SD 9.4). The etiology of the liver cirrhosis was primary sclerosing cholangitis in 9 patients (27%), hepatitis B or C virus infection in 7 patients (21%), alcoholic liver disease in 8 patients (24%), hepatocellular tumor in 2 patients (6%), 1 acute liver failure (3%), and other reasons in 6 patients (18%). Twenty-two (66.7%) patients

required hemodialysis preoperatively. The median ET-DRI of the IFI study group was 1.74. There was no statistically significant difference between IFI and matched control group in recipient characteristics, such as age of the recipient, gender distribution, diagnoses leading to liver transplantation, BMI, pre-transplant abdominal surgery, portal vein status, and lab MELD score (**Table 1**).

Table 4. Multivariate multinominal analysis of the Aspergillus group.

	p-value	Odds ratio	95% CI
DOS	0.003	1.013	1.005-1.022
ICU LOS	0.12	1.323	0.93-1.883
Total LOS	0.906	0.983	0.738-1.309
Ventilation hours	0.032	0.993	0.986-0.999
Preoperative dialysis	0.194	0.139	0.007-2.725
Dialysis days	0.008	1.195	1.048-1.362
EAD	0.26	3.769	1.168-12.162
Re-operation	0.391	0.689	0.294-1.615

DOS – duration of surgery; ICU – Intensive Care Unit; LT – liver transplantation; EAD – early allograft dysfunction.

Table 5. Multivariate multinominal analysis of the Candida group.

	p-value	Odds ratio	95% CI
Fungal contamination of preservation fluid	0.001	47.8	4.77-478,96
ET-DRI	0.013	0.042	0.003-0,519
DOS	0.231	1.006	0.996-1,015
ICU -stay	0.987	0.628	0.01-1.08
Hospital stay	<0.0005	25.074	23.990-26.208
Ventilation hours	0.256	0.997	0.991-1.002
Dialysis days	0.009	1.163	1.038-1.302
Re-Operation	0.443	1.295	0.669-2.509

ET-DRI – Eurotransplant Donor Risk Index; DOS – duration of surgery; ICU – Intensive Care Unit; LT – liver transplantation.

Perfusion fluid contamination with yeast was detected in 5 patients (15%): 1 in the AG group and 4 in the CG group. None of the patients received prophylactic antifungal therapy based on the fluid culture result but rather based on active infection signs or symptoms after LT. The mean duration of surgery was 327 minutes (SD 140). Intraoperative blood transfusion occurred in 22 patients (66.7%). There were no intraoperative complications. The mean LOS-ICU was 29.9 days (SD 23.2). The mean hospital LOS was 54.6 days (SD 43.8). Major postoperative complications were observed in 13 patients (39.4%). Perioperative death within 90 days after LT occurred in 4 patients (12.1%). Of the patients with AG, 7 (50.0%) died within 102 days (mean) after LT and of the patients with CG, 7 (37%) died within 98 days (mean) after LT. The 1- and 3-year overall survival rates of IFI group were 48.5% and 24%, whereas the control group had 75.5% 1-year survival ($p < 0.003$) (Figure 1). In the univariate analysis, the duration of surgery (DOS), LOS-ICU, postoperative ventilation time, the need for preoperative dialysis, as well as the duration of dialysis, transaminase peak, re-operation rate and the total LOS, were significantly higher in patients who developed invasive aspergillosis or Candida sepsis (Tables 2, 3). In the Candida group, regarding donor-related factors, only the incidence of perfusion fluid contamination

was significantly higher in the study group compared to the control group ($p < 0.001$; OR=47.8; CI: 4.77-478) and remained significant for Candida in multivariate multinominal analysis but not for aspergillosis. Multivariate regression analyses showed that preoperative dialysis (OR=1.163; CI: 1.038-1.302), Eurotransplant donor risk index (OR=0.04; CI=0.003-0.519), length of hospital stay (OR=25.074; CI: 23.99-26.208), and yeast contamination of the preservation fluid (OR=47.8; CI: 4.77-478, 96) were associated with IFI in the Candida group, whereas duration of surgery (OR=1.013; CI: 1.005-1.022), ventilation hours (OR=0.993; CI=0.986-0.999), and days of postoperative dialysis (OR=1.195; CI: 1.048-1,362) were associated with IFI in the aspergillosis group (Tables 4,5).

Discussion

Systemic fungal infection after LT is one of the important causes of perioperative death within the first month after LT [17]. Consequently, the identification of significant risk factors and evaluation of the role of prophylactic antifungal treatment is essential. The incidence of IFI after organ transplantation is reported to be 5-20% in the literature [18,19]. Our IFI

incidence was 5.6% among 579 adult patients following LT. The ratio of aspergillosis to *Candida* septicemia was rather atypical (42.4% to 57.5%). In international comparison, the rate of *Candida* species as the cause of IFI is described in the literature is up to 90% [20]. One-year mortality after an IFI is up to 62.5% [21,22]. One-year survival of patients with IFI in our series was 48.5%, which is significantly lower than that of the control group. Levesque et al described a significant correlation between the contamination of the preservative fluid and the development of invasive mycosis [21]. Of all the possible risk factors analyzed, the presence of fungi in the preservation fluid was the greatest risk factor for a fungal infection by *Candida* spp after liver transplantation in our analysis but not for *Aspergillus* infection. Existing donor invasive fungal infections can contaminate the donor organ and can be detected as a “contamination” of the preservative liquid. Yeast contamination of the preservation fluid was identified as an independent risk factors to develop IFI after LT in our study. In our practice, donor cultures are reviewed regularly at the time of accepting the donor and we do not accept donors with active fungal infection; however, the donor culture data and fungal infection data of the donors were not available at the time of this study. Preservation fluid culture is also a routine practice in our center following findings in this report. After the findings in our study, we changed our practice so that any patient with preservation fluid contamination with yeast is now receiving empiric antifungal treatment independent from clinical signs and symptoms.

The DRI is used as a predictive value to determine the probable survival of the transplant recipient after LT; however, the influence of DRI on the incidence of postoperative infections is still unclear. Rosenberger et al analyzed the relation between DRI and post-transplant infections, concluding that infections depend more heavily on recipient factors [23]. There were 673 infectious complications in 378 patients, including 53 cases with *Candida glabrata*. *Candida glabrata* was isolated more frequently in the high-DRI score group compared to the low-DRI score group [38 (9%) vs 15 (5%) $p=0.01$] (23). However, no further fungal infections were mentioned. In the present study, multivariate analysis showed a significant correlation between the ET-DRI and postoperative invasive fungal infection by *Candida* species, but not aspergillosis, which is similar to the aforementioned report. The possible association between DRI and aspergillosis or fungi other than *Candida* should be investigated further in larger series.

An association between a prolonged duration of surgery and increased rate of infection after LT is described in many studies [24-26]. The duration of surgery is also one of the significant predictive factors for invasive fungal infection and is associated with postoperative complications as shown previously [27]. We also report that duration of surgery was significantly longer in

the study group compared to the control group and was identified as a significant predictive factor for development of IFI by *Aspergillus* species; therefore, transplant teams may consider this risk factor for antifungal prophylaxis.

The total LOS among patients in the mycosis groups was significantly longer than that of the patients in the control group ($p<0.0005$) These results are concordant with the study by Levesque et al in which a prolonged LOS was also demonstrated for postoperative invasive mycoses ($p=0.002$) [17]. Biological plausibility has a key role in assessing the association between variables considered as risk factors and outcomes. In that sense, the length of hospitalization, as well as the duration of ventilation, might be the consequence of the fungal infection rather than the cause.

The Infectious Diseases Society of America (IDSA) Treatment of Candidiasis guidelines stated patients who undergo liver transplantation with at least 2 key risk factors, including re-transplantation, creatinine level 12.0 mg/dL, choledochojejunostomy, intraoperative use of >40U of blood products, prolonged intraoperative time (defined as >11 h), and fungal colonization detected at least 2 days before and 3 days after transplantation, are at higher risk of invasive candidiasis and are recommended to receive prophylaxis treatment [28]. In our study, median duration of surgery was 5.2 h in AG, 4.45 h in CG, and 4.08 h in the control group ($p<0.05$). So, we can argue that DOS could still be considered prolonged when approaching 6 h, which is a much shorter cut off as defined by IDSA. Considering it is common that LT takes longer than 6 h, surgeons could consider antifungal prophylaxis more often if there are other risk factors as well.

According to the Guidelines of the American Society of Transplantation, Infectious Diseases Community of Practice, Singh et al reported *Candida* has been isolated in about 4% of the preservation fluids from liver transplant recipients [29]. They also stated cultures of blood, urine, and drainage fluids should be performed prior to initiating empiric therapy when *Candida* is identified in preservation fluid cultures or following organ procurement complicated by intestinal contamination [29]. The authors concluded liver transplant recipients in whom *Candida* species are identified in the preservation fluid cultures or in patients with surgeries complicated by intestinal contamination during organ recovery should receive empiric antifungal therapy for 2 weeks [29]. As stated above, we now imply empiric antifungal treatment independent from clinical signs and symptoms when contamination is detected.

Renal replacement or chronic kidney disease have been reported as risk factor for post-liver transplant yeast infection [30,31]. Eschenauer et al also commented that dialysis and re-transplantation patients should be considered for

fungal prophylaxis [32]. The IFI group in our study had higher incidence of hemodialysis and the duration of dialysis was significantly longer compared to the control group. Although we had a small number of patients and we performed a retrospective review, we agree that liver transplant patients who have been on hemodialysis prior to transplant should be considered for antifungal prophylaxis.

The limitations of our study include its retrospective nature and small sample size. Given that only patients with systemic fungal infections were included in the analysis, a selection bias is inevitable. Furthermore, due to the multimodal analysis, an over-interpretation of the collected data is possible as well. Lastly, the control group was not fully randomized with the IFI group, which is suboptimal, thus we cannot make firm conclusions.

Conclusions

Based on the results of the study, duration of surgery, hours of mechanical ventilation, and preoperative dialysis days were significant factors for the development of postoperative invasive aspergillosis. Yeast contamination of the preservation fluid, ET-DRI, dialyses days, and hospital stay were identified as significant factors for the development postoperative Candida sepsis. Despite the small cohort and retrospective nature of the study, we believe patients with these risk factors may benefit from prophylactic antifungal treatment. Larger cohorts and prospective analyses are necessary to improve the power of these findings.

Conflict of interest

None.

Declaration of Figure Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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