Invasive fungal infections in kidney and liver transplant recipients in a center in northeast Brazil

Infecções fúngicas invasivas em receptores de transplante renal e hepático em um centro do Nordeste do Brasil

Infecciones fúngicas invasivas em receptores de transplante renal y hepático em um centro del nordeste de Brasil

Pablo Eliack Linhares de Holanda
ORCID: https://orcid.org/0000-0002-4383-2187
Hospital São José de Doenças Infecciosas, Brasil
E-mail: pabloeliack@gmail.com
Claudia Maria Costa de Oliveira
ORCID: https://orcid.org/0000-0002-2795-6681
Universidade Federal do Ceará, Brasil
E-mail: claudiadrl@gmail.com
Terezinha do Menino Jesus Silva Leitão
ORCID: https://orcid.org/0000-0002-3301-3057
Hospital São José de Doenças Infecciosas, Brasil
E-mail: tsilva@ufc.br
José Huygens Parente Garcia
ORCID: https://orcid.org/0000-0003-4401-137X
Universidade Federal do Ceará, Brasil
E-mail: huygensgarcia@hotmail.com
Maria Danielly de Almeida Sousa
ORCID: https://orcid.org/0000-0003-4036-9120
Centro Universitário Unicristos, Brasil
E-mail: mdaniellyalmediasousa@gmail.com
Renata Antunes Bruno da Silva
ORCID: https://orcid.org/0000-0003-0307-9853
Universidade de Fortaleza, Brasil
E-mail: renata.bruno@edu.unifor.br
Sonia Leite da Silva
ORCID: https://orcid.org/0000-0003-2732-8543
Universidade Federal do Ceará, Brasil
E-mail: sonials@unifor.br
Evelyne Santana Girão
ORCID: https://orcid.org/0000-0003-3059-5490
Universidade Federal do Ceará, Brasil
E-mail: egirao@uol.com.br

Abstract
Objective: Describe the main invasive fungal infections (IFIs) after kidney and liver transplantation at a referral center, as well as their evolution, treatment, and clinical features. *Material and Methods:* This was a retrospective, observational, descriptive, case series study involving IFIs diagnosed between January 2012 and December 2019 in kidney and liver transplant recipients. *Results:* Among 769 kidney transplants, only 1 patient received the organ from a living donor and the other transplants were from deceased donors. 15 IFIs were diagnosed (7 histoplasmoses, 4 cryptococcoses, 3 candidemias, and 1 aspergillosis), while in 673 liver transplants, 8 IFIs were diagnosed (6 candidemias, 1 murcomycosis, and 1 cryptococcosis). Of the total 23 patients, 6 (26%) had infection diagnosed within 6 months after transplantation. The primary immunosuppressive regimen used was tacrolimus (82.6%), prednisone (82.6%), and mycophenolate (56.5%). Amphotericin B deoxycholate was the leading antifungal agent used for treatment, with nephrotoxicity in 80% of the cases. In the clinical follow-up, 14 patients progressed to cure (60.9%) and 9 to death (39.1%). A worsening of renal function was observed in most patients in the present study. *Conclusion:* Candidemia, histoplasmosis, and cryptococcosis were the most frequent IFIs, with the majority occurring later, 6 months after transplantation, and associated with high mortality.
Keywords: Invasive fungal infections; Transplant; Immunosuppressive agents.

Resumo

Objetivo: Descrever as principais infecções fúngicas invasivas (IFIs) após transplante renal e hepático em um centro de referência, bem como sua evolução, tratamento e características clínicas. *Material e Métodos:* Trata-se de um estudo retrospectivo, observacional, descritivo, de série de casos envolvendo IFIs diagnosticados entre janeiro de 2012 e dezembro de 2019 em receptores de transplante renal e hepático. *Resultados:* Entre 769 transplantes renais, apenas 1 paciente recebeu o órgão de doador vivo e os demais transplantes foram de doadores falecidos. 15 IFIs foram diagnosticados (7 histoplasmoses, 4 criptococose, 3 candidemias e 1 aspergilose), enquanto em 673 transplantados hepáticos, 8 IFIs foram diagnosticados (6 candidemias, 1 murcomicose e 1 criptococose). Do total de 23 pacientes, 6 (26%) tiveram infecção diagnosticada dentro de 6 meses após o transplante. O esquema imunossupressor primário utilizado foi tacrolimus (82,6%), prednisona (82,6%) e micofenolato (56,5%). A anfotericina B desoxicolato foi o principal antifúngico utilizado no tratamento, com nefrotoxicidade em 80% dos casos. No seguimento clínico, 14 pacientes evoluíram para cura (60,9%) e 9 para óbito (39,1%). Piora da função renal foi observada na maioria dos pacientes do presente estudo. *Conclusão*: Candidemia, histoplasmose e criptococose foram os IFIs mais frequentes, com a maioria ocorrendo mais tarde, 6 meses após o transplante, e associados a alta mortalidade.

Palavras-chave: Infecções fúngicas invasivas; Transplante; Agentes imunossupressores.

Resumen

Objetivo: Describir las principales infecciones fúngicas invasivas (IFI) tras el trasplante renal y hepático en un centro de referencia, así como su evolución, tratamiento y características clínicas. *Material y métodos*: Se trata de un estudio retrospectivo, observacional, descriptivo, de serie de casos que involucró a IFI diagnosticadas entre enero de 2012 y diciembre de 2019 en receptores de trasplante de riñón e hígado. *Resultados*: Entre 769 trasplantes de riñón, solo 1 paciente recibió el órgano de un donante vivo y los otros trasplantes fueron de donantes fallecidos. Se diagnosticaron 15 IFI (7 histoplasmosis, 4 criptococosis, 3 candidemias y 1 aspergilosis), mientras que en 673 receptores de trasplante hepático se diagnosticaron 8 IFI (6 candidemias, 1 murcomicosis y 1 criptococosis). Del total de 23 pacientes, 6 (26%) tenían una infección diagnosticada dentro de los 6 meses posteriores al trasplante. El régimen inmunosupresor primario utilizado fue tacrolimus (82,6%), prednisona (82,6%) y micofenolato (56,5%). El anfotericina B desoxicolato fue el principal antifúngico utilizado en el tratamiento, con nefrotoxicidad en el 80% de los casos. En el seguimiento clínico, 14 pacientes progresaron a curación (60,9%) y 9 a muerte (39,1%). En la mayoría de los pacientes del presente estudio se observó un empeoramiento de la función renal. *Conclusión*: Candidemia, histoplasmosis y criptococosis fueron las IFI más frecuentes, la mayoría ocurrieron más tarde, 6 meses después del trasplante, y se asociaron con alta mortalidad.

Palabras clave: Infecciones fúngicas invasivas; Trasplante; Agentes inmunosupresores.

1. Introduction

Invasive fungal infections (IFIs) are major causes of morbidity and mortality among solid organ transplant (SOT) recipients. Their incidence is lower (approximately 5%) in kidney transplant patients, (Zicker, Colombo, Ferraz-Neto, & Camargo, 2011), (Shekar, et al., 2019) although since the kidney is the most transplanted organ in the world, the proportion of cases of IFIs in these patients is quite significant. Published data from a Brazilian center showed a 4.6% prevalence of IFIs in kidney transplant recipients (Guimarães, et al., 2016). Meanwhile, in liver recipients, the frequency of IFIs before the implementation of antifungal prophylaxis was around 42%. After the implantation of this strategy, a decrease of 5% to 20% was observed (Ebrahimi, Dashti, Mohammadpour, & Ahmadinejad, 2020).

The primary causative agent of IFIs in SOT recipients is Candida spp., followed by Aspergillus spp., the latter being more frequent in lung transplants (18%) (Shoham & Marr, 2012) compared to a prevalence of 1 to 4.5% in liver transplants and 0.5 - 2.2% in kidney transplants (Ergin, et al., 2003). The majority of these infections are acquired from endogenous sources, as is the case of Candida spp., a colonizer of the human intestinal tract, but there is also the possibility of acquisition by inhaling fungi particles from the environment, as occurs in aspergillosis. Reactivation of latent infections is the main form of infection acquisition in cases of cryptococcosis, coccidioidomycosis, and histoplasmosis.5 However, although rare, there is a well-documented report of transmission of Histoplasma capsulatum through organ transplantation (Limaye, et al., 2000).

Some risk factors seem to be associated with the development (even early) of IFIs, such as corticosteroid pulse therapy, anti-lymphocyte antibodies (Guimarães, et al., 2016), rejection, hyperglycemia, leukopenia, advanced age, and multiple organ transplantation (Shekar, et al., 2019). The risk of IFI is lower after the first six months of transplant, unless

there is excessive exposure to the pathogen or an increase in the patient's immunosuppression, as occur in multiple episodes of rejection and anti-rejection therapy (Shekar, et al., 2019). Early diagnosis and treatment are imperative for the reduction in morbidity and mortality (Batista, et al., 2011).

Among the IFIs, cryptococcosis, paracoccidioidomycosis, histoplasmosis, and sporotrichosis are associated with higher mortality rates in SOT, usually 180 days after the procedure, especially with increased doses of immunosuppressive agents in the treatment of chronic rejection (Batista, et al., 2011). Studies have shown a survival rate of 67.5% and 54% after 3 and 12 months of IFI, respectively.[1] Complications such as respiratory failure (55%), intensive care admission (53%), septic shock (50%), the need for mechanical ventilation (44%), and kidney failure (40%) were reported in a cohort study on transplant recipients with IFIs (Bodro, et al., 2012). Difficulties in the diagnosis and early management of these mycoses, particularly in underdeveloped regions, greatly impact survival. Knowledge of local epidemiology could provide valuable contributions to these issues (Batista, et al., 2011).

There are few national publications on this subject, and epidemiological data in our country are scarce. The state of Ceara has one of the highest rates of histoplasmosis in HIV patients in the world, with substantial mortality, although information on other immunosuppressed patients is scarce (Leitão, et al., 2019). The aim of the present study was to describe the main IFIs after kidney and liver transplantation in a reference center, as well as their evolution, treatment, and clinical features, in an attempt to enable better identification of cases and earlier and more appropriate management.

2. Methodology

2.1 Type of Study

This retrospective, descriptive, observational, case series study was carried out between November 2019 and February 2020 (Pereira, Shitsuka, Parreira, & Shitsuka, 2018)

2.2 Study Population

Kidney and liver transplant recipients diagnosed with invasive fungal infection (IFI) in the period from 2012 to 2019 were enrolled in the study, which was carried out at the Hospital Universitário Walter Cantídio da Universidade Federal do Ceará (HUWC-UFC), an important reference center in Northeast Brazil.

2.3 Inclusion Criteria

The inclusion criteria comprised the following: recipients of kidney and liver transplants that presented IFIs, diagnosed in the period from 2012 to 2019, with confirmation of infection through sterile site cultures, biopsies, or bronchoalveolar lavage, evidencing the presence of fungus, according to specifications of the Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (Donnelly, et al., 2019). Probable or possible cases, in which there was no mycological or anatomopathological evidence of infection, were excluded. In cases of infection by Candida spp., only candidemias were considered, with growth of this agent in blood culture.

2.4 Data Collection

The data were obtained from the healthcare infection notification records of the Hospital Infection Control Committee (CCIH) of the HUWC, the microbiological test results from the UFC Mycology Laboratory, the HUWC database of Kidney and Liver Transplant Units, and the patient records.

2.5 Collection Instrument

A semi-structured form was used to extract the following data: clinical and epidemiological characteristics of the recipients; exposure factors; comorbidities (hypertension and diabetes); transplant data (previous transplant, type of donor, duration of cold ischemia, delayed graft function, induction schedule, maintenance immunosuppressive drugs); cytomegalovirus (CMV) infection, and diagnosis and treatment of rejection in the six months prior to IFI. Regarding systemic mycosis, the following information were recorded: post-transplant time of diagnosis of systemic mycosis; duration of hospitalization; main laboratory tests, especially to assess myelo- and nephrotoxicity; antifungal drugs used, and progression of the condition (discharge, death, graft loss).

2.6 Data Analysis

Descriptive statistical measures, such as frequency, percentage, means, and standard deviation, were calculated for quantitative variables. The SPSS 20.0 statistical software, license number 10101131007, was used for data analysis.

2.7 Ethical Aspects

The present study met the requirements of the guidelines and regulatory standards for research involving human beings present in Resolution 466/12 of the National Health Council. The project was referred to the Research Ethics Committee of the Hospital Universitário Walter Cantídio da Universidade Federal do Ceará, and approved under Protocols No. 2.114.570 and 2.174.880.

3. Results

A total of 673 liver transplants and 769 kidney transplants were performed during the study period; only 1 patient received the organ from a living donor and the other transplants were from deceased donors. Thirty patients were enrolled, and seven, excluded: one IFI was identified prior to transplantation, and six because their infections were represented by candida in other sites, such as ascitic fluid, urine, and growth in a central venous catheter. The clinical and demographic characteristics of the patients included in the present study are shown in Table 1.

Table 1. Clinical-demographic characteristics of the kidney and liver transplant recipients with invasive fungal infection. Fortaleza, Ceará, Brazil (2012-2019).

Variables	Kidney Transplant		Liver Transplant	
	N (%)	ME±SD	N (%)	ME±SD
Sex of the recipient				
Female	09 (60)		02 (25.0)	
Male	06 (40)		06 (75.0)	
Age at transplant (years)		41.27±14.02		51.62±9.60
12 to 19	02 (13.3)		-	
20-40	04 (26.7)		01 (12.5)	
41-59	07 (46.7)		05 (62.5)	
60-80	02 (13.3)		02 (25.0)	

Age at IFI (years)	47.73±13.45	52.87±10.14
20-40	04 (26.7)	01 (12.5)
41-59	08 (53.3)	05 (62.5)
60-63	03 (20.0)	02 (25.0)
Type of donor		
Deceased	14 (93.3)	08 (100.0)
Alive	01 (6.7)	00 (0.0)
Comorbidities		
DM		
No	13 (86.7)	06 (75.0)
Yes	02 (13.3)	02 (25.0)
SAH		
No	07 (46.7)	06 (75.0)
Yes	08 (53.3)	02 (25.0)
BMI	23.53±3.94	24.61±3.57
Underweight	01 (6.7)	00 (0.0)
Normal	05 (33.3)	05 (62.5)
Overweight	05 (33.3)	01 (12.5)
Obese	00 (0.0)	01 (12.5)
Not evaluated	04 (26.7)	01 (12.5)

ME: Mean; SD: standard deviation; DM: Diabetes mellitus; SAH: Systemic Arterial Hypertension; BMI: Body Mass Index.
Source: The authors themselves.

Overall, 23 patients were included in the final analysis: 15 kidney transplant recipients and 08 liver transplant recipients. Regarding comorbidities, 53% of the kidney transplant recipients were hypertensive, while in the liver transplant group, most had normal blood pressure and were non-diabetic.

The most common underlying disease in the liver transplant recipients was liver cirrhosis due to the Hepatitis C virus (62.5%). In kidney patients, the most prevalent primary renal disease was glomerulonephritis (26.7%).

Table 2. shows the variables related to the patients with IFI. There was no difference regarding cytomegalovirus (CMV) infection and acute rejection per transplanted organ.

Variables	Kidney Transplant		Liver Transplant	
	N (%)	ME ± SD	N (%)	ME ± SD
Previous transplant				
Yes	-		-	
No	15 (100.0)		08 (100.0)	
Duration of hospitalization (days)*		27.86 ± 16.65		32.12 ± 22.96
8-15	03 (20.0)		02 (25.0)	
16-30	08 (53.4)		03 (37.5)	
31-60	04 (26.7)		02 (25.0)	
61-73	-		01 (12.5)	
Induction therapy				
Thymoglobulin	09 (60.0)		-	
antiIL2-R	04 (26.7)		-	
None	02 (13.3)		08 (100.0)	
Post-transplant CMV infection				
Yes	04 (26.7)		05 (62.5)	
No	11 (73.3)		03 (37.5)	
Acute rejection post-transplant				
Yes	01 (6.7%)		03 (37.5)	
No	14 (93.3%)		05 (62.5)	

ME: Mean; SD: Standard Deviation; *Duration of hospitalization during fungal infection; CMV: Cytomegalovirus; IFI: Invasive Fungal Infections.
Source: The authors themselves.

CMV infection was important in liver transplant recipients, with more than half presenting this infection.

Regarding maintenance immunosuppression, tacrolimus was used in 60.9% of the cases, mycophenolate in 60.9%, mTor inhibitors in 8.7%, and prednisone in 56.5%.

Among the IFIs, fever was observed in 22% of the patients with candidemia and 100% of the patients with histoplasmosis. Fever was the most common symptom in these patients, followed by diarrhea (71%) and cough (57%). In cases of cryptococcosis, all patients presented fever, followed by cough (80%), dyspnea (60%), and headache (60% of the cases).

A large portion of the patients was anemic before IFI diagnosis (44%), whereas some developed anemia at the time of diagnosis (32%). Pancytopenia was identified in approximately 24% of the patients upon IFI diagnosis, mainly in the liver transplant recipients.

Table 3 highlights the variables related to IFI in kidney and liver transplantation.

Table 3. Duration, progression, and treatment of invasive fungal infection in kidney and liver transplantation. Fortaleza, Ceará, Brazil (2012-2019).

Characteristics	Kidney Transplant		Liver Transplant	
	N (%)	ME±SD	N (%)	ME±SD
Duration of IFI post-TX (years)		Median: 48 months		Median: 8.5 months
0-1	05 (33.3)		06 (75.0)	
2-5	04 (26.7)		01 (12.5)	
6-10	04 (26.7)		00 (0.0)	
11-19	02 (13.3)		01 (12.5)	
IFI < 6 months post-TX				
Histoplasmosis	-		-	
Cryptococcosis	01 (25.0)		-	
Candidemia	02 (66.7)		02 (33.3)	
Murcomycosis	-		-	
Aspergillosis	01 (100)		-	
Type of mycosis				
Histoplasmosis	07 (46.7)		00 (0.0)	
Cryptococcosis	04 (26.7)		01 (12.5)	
Candidemia	03 (20.0)		06 (75.5)	
Murcomycosis	00 (0.0)		01 (12.5)	
Aspergillosis	01 (6.7)		00 (0.0)	
Duration of hospitalization (days)		36.13±12.92		29.38±25.48
0-6	00 (0.0)		01 (12.5)	
7-15	01 (6.7)		02 (25.0)	
16-30	05 (33.3)		02 (25.0)	
31-60	09 (60.0)		02 (25.0)	
61-78	00 (0.0)		01 (12.5)	
Infection resolution				
Yes	12 (80.0)		03 (37.5)	
No	03 (20.0)		05 (62.5)	

Antifungal Treatment		
Amphotericin B deoxycholate	07 (46.7)	02 (25.0)
Amphotericin B lipid complex	02 (13.3)	01 (12.5)
Amphotericin B deoxycholate + Voriconazole	01 (6.7)	00 (0.0)
Fluconazole	02 (13.3)	03 (37.5)
Micafungin	02 (13.3)	01 (12.5)
Deceased before therapy	01 (6.7)	01 (12.5)

ME: Mean; SD: Standard Deviation; IFI: Invasive Fungal Infection; TX: transplant.
Source: The authors themselves.

The diagnosis of IFI in the total population was conducted mostly six months after the transplant (73.9%), with the vast majority of infections occurring within the first year after the procedure. The percentage of patients with IFI in the first six months following transplantation was 26.7% in the kidney transplant recipients and 25% in the liver transplant group.

After the IFI, most (80%) of the kidney transplant recipients presented favorable outcomes, with resolution of the infectious condition. Meanwhile, in the liver transplant group, only 37.5% of the patients progressed with resolution of infection, preservation of the graft, and discharge, while 62.5% died.

The distribution of IFIs per transplanted organ is shown in Figure 1.

Figure 1. Diagnosed invasive fungal infections in kidney and liver transplant recipients in the study period. Fortaleza, Ceará, Brazil (2012-2019).
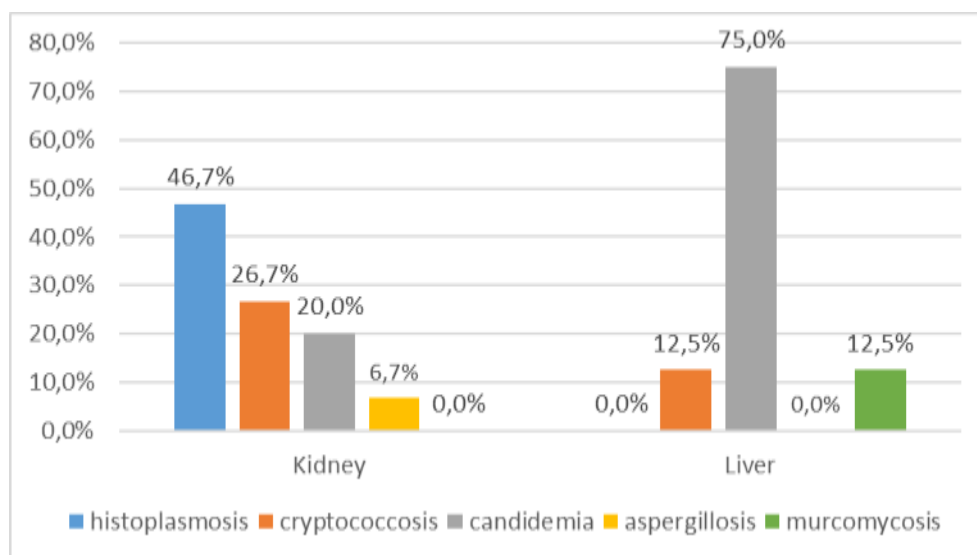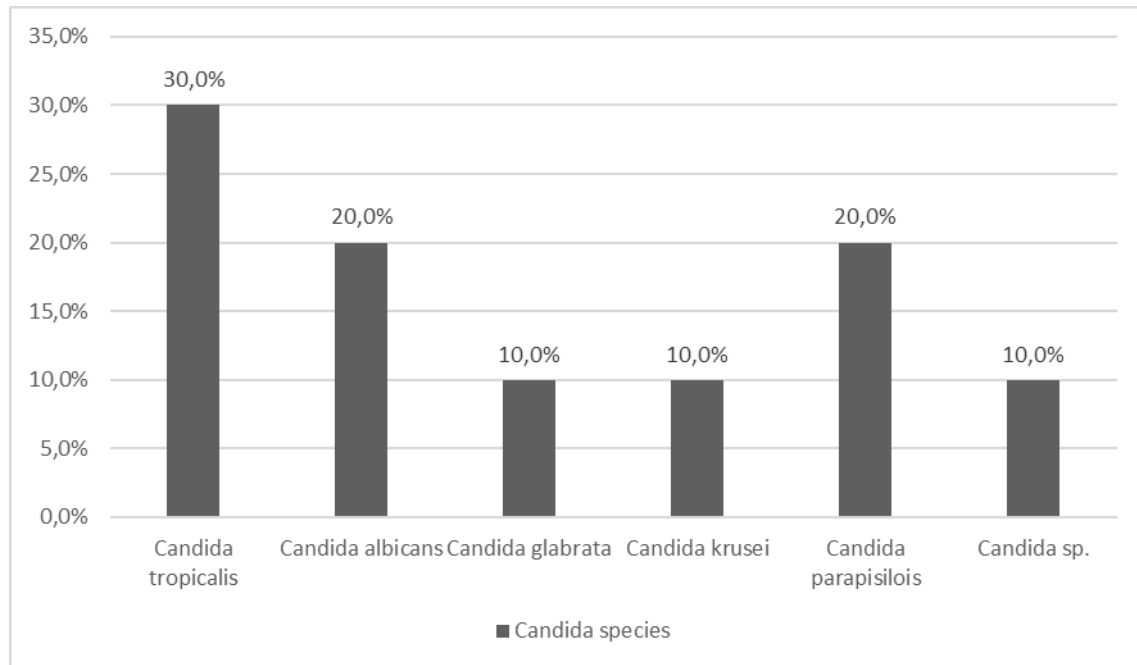

Source: The authors themselves.

The difference in IFI agents is noteworthy when comparing the two types of transplants. Candidemia occurred more frequently in the liver transplant group (66.7%), and all cases of histoplasmosis were diagnosed in kidney transplant recipients.

Among the IFIs whose onset took place earlier (less than six months after transplantation), candidemia was the main condition observed, in 44.4% of the patients (2 from the kidney transplant group and 2 from the liver transplant group). Only

one recipient with cryptococcosis presented infection before six months (20%).

The main species of candida identified in this study are shown in Figure 2.

Figure 2. Main species of candida found in the study. Fortaleza, Ceará, Brazil (2012-2019).
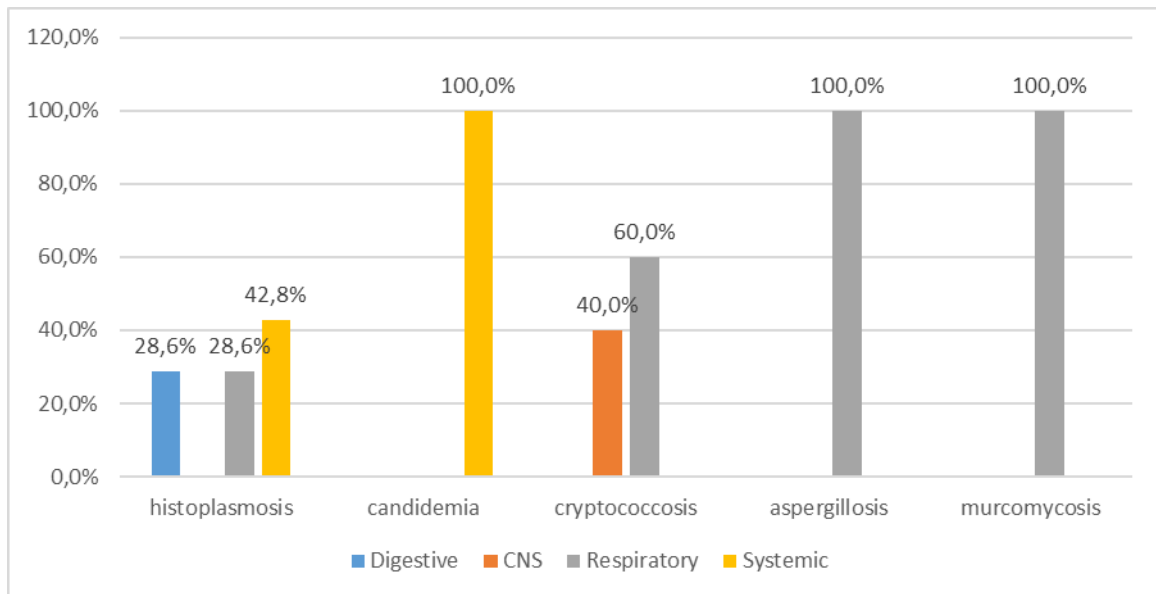

Source: The authors themselves.

Among the species of Candida spp., the most prevalent was Candida tropicalis (30%), with one patient showing positive blood culture for Candida krusei and Candida glabrata, and another who lacked species identification using the same diagnostic method.

Meanwhile, Figure 3 shows the main organs affected in the studied population, according to each type of IFI.

Figure 3. Main affected organs according to the type of invasive fungal infection in the study population. Fortaleza, Ceará, Brazil (2012-2019).

Source: The authors themselves.

Histoplasmosis compromised the digestive tract in two patients (one in the colon and cecum, and the other, in the duodenum). In two other cases, the respiratory tract was affected, while another three patients exhibited systemic involvement.

The primary symptoms observed, according to the type of invasive fungal infection, are shown in Table 4.

Table 4. Main observed symptoms according to the type of invasive fungal infection in the study population. Fortaleza, Ceará, Brazil.

	Candidemia	Histoplasmosis	Cryptococcosis	Aspergillosis	Murcomycosis
Headache	0	42.8%	60%	0	100%
Alteration of consciousness	11.1%	14.3%	0	0	0
Seizure	0	0	20%	0	0
Cough	0	57.1%	80%	100%	100%
Dyspnea	0	42.9%	60%	100%	0
Vomiting	11.1%	42.9%	20%	0	0
Diarrhea	0	71.4%	20%	0	0
Fever	22.2%	100%	100%	100%	0

Source: The authors themselves.

Fever was the most frequent symptom in cases of candidemia, histoplasmosis and cryptococcus.

The IFIs were diagnosed by histopathology in 7 cases, by culture in 13, and by direct examination in 3.

Among the eight kidney transplant patients who used amphotericin B deoxycholate, six (75%) presented worsening of renal function, as did the two who used the drug in the liver transplant group (100%). All patients in the study who took micafungin (n=3) also progressed with worsening of kidney function. Only one individual exhibited worsening of renal function using fluconazole, while the patient on voriconazole therapy did not, despite the use of associated amphotericin B deoxycholate.

The impact of the most frequent IFIs on kidney function, assessed by mean creatinine analysis, is shown in Table 5.

Table 5. Progression of kidney function according to the type of invasive fungal infection in the study population. Fortaleza, Ceará, Brazil, 2020.

Mycosis	Creat. Pre-IFI (mg/dL)	Creat. during IFI (mg/dL)	Creat. after 1 month (mg/dL)	Current Creat. (mg/dL)
Histoplasmosis	2.3 (Max: 5.4)	3.2 (Max: 5.8)	1.9 (Max: 4.8)	2.5 (Max: 8.6)
Candidemia	1.6 (Max:2.8)	2.0 (Max: 6.0)	1.0 (Max: 3.6)	1.5 (Max:3.3)
Cryptococcosis	3.8 (Max: 13.5)	3.5 (Max: 12.3)	2.5 (Max: 5.8)	1.3 (Max: 2.0)

IFI: Invasive Fungal Infection; Creat: Creatinine
Source: The authors themselves.

The IFI that had the greatest impact on renal function was histoplasmosis, causing a greater increase in creatinine.

Most of the patients already presented at least stage-3 chronic kidney disease upon the onset of the IFI. Prior to infection, only 34.8% of the recipients had an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73m2, according to the CKPD-EPI equation. Among these patients, only one of those who used amphotericin B deoxycholate did not exhibit a worsening of renal function. Of the 65.2% who had eGFRs below 60 mL/min/1.73m2, fifteen (60%) used amphotericin B deoxycholate, among which 66.7% showed worsening of kidney function.

The mean duration of treatment with amphotericin B deoxycholate was around 14 days, followed by therapies with imidazoles, mainly itraconazole and fluconazole (maintenance treatment), lasting one year in cases of cryptococcus and histoplasma.

Considering the outcomes after IFI, in the kidney transplant recipients, the majority (80%) of the patients exhibited favorable results, with resolution of the infectious condition, whereas, in the liver transplant group, only 37.5% of the cases presented infection resolution, while 62.5% died.

4. Discussion

The present study is one of the first to describe the epidemiology of IFIs in kidney and liver transplant recipients in the Northeast region of Brazil, namely in Ceará. The Kidney and Liver Transplant Services of the Walter Cantídio University Hospital, of the Federal University of Ceará, is a national reference center that performs an average of 96 kidney and 84 liver transplants per year.

Most patients in the study population developed IFI in the less intensive phase of immunosuppression therapy, corroborating the findings reported by Guimarães et al. (2016), who found 67% of IFI six months after kidney transplantation.

In the current study, this fact was observed mainly with histoplasmosis, in which all of the cases developed IFI six months after the surgery (on average, 3 years later), except for one patient who presented the mycosis after 10 months. This data is consistent with the literature, which considers this IFI to appear later, usually 1 to 2 years after transplantation (Abdala, et al., 2018).

A considerable difference was observed regarding the time of IFI onset in the two transplant groups, occurring predominantly after the first year in kidney recipients and within the first year in the liver transplant group. This fact may be related to the late occurrence of histoplasmosis in kidney transplant patients (Abdala, et al., 2018) and early-onset candidemia in liver transplant recipients (Bodro, et al., 2012).

A greater number of IFIs occurred in the kidney recipients (15 patients) compared with the liver recipients (8 patients). The vast majority of kidney transplant patients already showed an elevation in creatinine levels before the onset of IFI, a fact that could predispose to a higher risk of IFIs than the others. Studies show that, although there is no understanding of the cause, these patients exhibited impaired humoral immunity due to persistent uremia, which could cause humoral and metabolic abnormalities (Gandhi, Bahadur, Dodeja, Aggrwal, & A Thamba, 2005).

Our findings corroborate international data, in which candidemia is the most common IFI in solid organ transplants (SOT) (Gavalda, et al., 2014). Chronic liver disease has already been identified as an important and independent risk factor for candidemia in transplant recipients, a fact that may justify the high frequency of this infection in liver transplant patients in the present study (Leitheiser, et al., 2019). Among the eight liver recipients, six developed candidemia, and of the 15 kidney recipients, only three acquired this condition. The vast majority of patients who developed candidemia presented infection within the first year (66.7%, n=6), 4 of which (44,4%) occurred in less than six months after transplantation, corroborating other studies that address this issue (Bodro, et al., 2012).

The clinical manifestations of candidiasis are nonspecific and can vary from asymptomatic, presenting only laboratory findings, such as leukocytosis, to signs of septic shock, including fever, chills, oliguria, and multiple organ dysfunction (Aslam & Rotstein, 2019). Of the nine patients with candidemia, only one exhibited symptoms of altered states of consciousness and evolved to shock, thus requiring ICU, in addition to significant neutropenia, which probably occurred due to some underlying, unidentified pathology. Only two patients developed leukocytosis.

According to the literature, the mortality rate from invasive candidiasis in the first year was 34% (Gavalda, et al., 2014). In the current study, five of the patients with candidemia (55.6%) died in the first year. However, they presented other severe pathologies, such as metastatic breast cancer and septic shock by multi-resistant bacteria. Therefore, according to the attending physician, their death was not IFI-related. Among the liver transplant recipients, four (66.7%) died, two of which exhibited graft loss, one due to Hepatitis C virus persistence and the other to poor adherence to immunosuppressive medication, a fact that may have contributed to this unfavorable outcome.

In our institution, antifungal prophylaxis is not routinely performed in kidney transplant recipients. In liver transplant recipients, however, fluconazole is indicated for patients at high risk for candidemia, i.e., re-transplant patients, fulminant hepatitis, or those presenting at least two of the following risk factors: kidney failure, choledochojejunostomy, previous use of broad-spectrum antibiotics, prolonged hospitalization, pre-transplant fungal colonization, and large-volume blood transfusions. In these cases, the protocol recommends 200 to 400 mg of fluconazole for 14 days, starting on the day of liver transplantation.

An increase in the frequency of filamentous fungi is observed in SOTs. Among these fungi, invasive aspergillosis is the second most frequent IFI, being only less prevalent than Candida spp (Lemonovich, 2018). The incidence of aspergillosis in the present study was considerably low, with only one case identified, a fact that may be related to the difficulty in diagnosis, due to the unavailability of antigen or PCR detection tests and the lack of routine necropsy tests, which enable post-mortem diagnosis. The mortality of this IFI is 50 to 100%, depending on the type of transplant (Öner-Eyüboglu, et al., 2003),

generally occurring in the immediate post-transplant period, and its form of presentation is mainly pulmonary (Gavalda, et al., 2014). Early diagnosis and aggressive antifungal therapy is essential for successful treatment (Tepeoğlu, Atılgan, Özdemir, & Haberal, 2015). Here, the only patient with this IFI had pulmonary presentation, and the progression to death was related to the mycosis.

According to the literature, histoplasmosis occurs in less than 1% in SOT, varying based on each center's epidemiology (Nieto-Ríos, et al., 2014). In transplant recipients, the most commonly found form of the disease is disseminated, mostly diagnosed after the first or second year of transplant (Abdala, et al., 2018). In the present study, this condition was the second most frequent IFI after candidemia, with 7 cases (30.4%). All cases of this disease were diagnosed in kidney transplant patients, with the majority (42.8%) in disseminated form. This high frequency differs from other studies that claim that histoplasmosis is a rare infection, even in endemic areas (Abdala, et al., 2018).

There were no cases of histoplasmosis in the liver transplant recipients, although a high incidence of the disease was observed in the kidney transplant group. This fact probably reflects the setting's diagnostic difficulty, in which only poorly sensitive or time-consuming tests, including leukocyte buffy coat, culture, biopsy, or spinal aspirate, are available, often requiring severe disseminated cases for greater diagnostic accuracy. Due to the high prevalence of this mycosis in the State of Ceará, and the absence of more sensitive and specific tests for its diagnosis, it is possible that there are more cases of this disease, many of which are treated empirically on account of diagnostic difficulty (Ramos, et al., 2018). The use of mycophenolate by kidney transplant recipients may contribute to the emergence of more cases since this drug is associated with the greater severity of this IFI (Assi, et al., 2013).

Studies indicate a 10% mortality rate for histoplasmosis when the disease occurs in SOT recipients. A large portion of these patients (around 72% in some studies) progresses to death near the time of IFI diagnosis, usually within the first month (Assi, et al., 2013). In the current study, only one patient with histoplasmosis died (14.2%); disease progression was fast, occurring in the first month after diagnosis.

The general incidence of cryptococcosis in the literature varies from 0 to 1.5%, being the third most common fungal infection, occurring mainly in kidney and heart transplant recipients (Gavalda, et al., 2014). It usually occurs 16 to 21 months post-transplant, and may present earlier, in the first year, in liver and lung recipients (Atılgan, et al., 2014). At least more than half of SOT patients exhibit disseminated symptoms or involvement of the Central Nervous System (CNS), with 33% of these individuals presenting fungemia (Gavalda, et al., 2014). This infection occurred in 21.7% of our patients, comparatively being the third IFI in frequency, with two individuals exhibiting neurological involvement and three, pulmonary involvement.

In the present study, none of the patients with cryptococcosis progressed to death, a fact that may be related to the low incidence of central nervous system involvement (2 cases) (Shoham & Marr, 2012).

According to the literature, murcomycosis occurs at a frequency of less than 3% in SOT recipients (Gavalda, et al., 2014). Our study revealed only one case of this IFI, located in the sinuses, in a liver transplant recipient with significant risk factors, such as diabetes and kidney dysfunction.

The primary sites of murcomycosis infection include the rhino-orbital-cerebral region, the lungs, the gastrointestinal tract, or the skin (Nucci, Engelhardt, & Hamed, 2019). In a systematic review of this IFI, the main form of presentation was rhino-orbital-cerebral. However, when evaluated in TOS, the predominant form was pulmonary, with neutropenia being an important manifestation mainly because neutrophils play a crucial role in the defense against this infection (Kurşun, et al., 2015), (Jeong, et al., 2018). Our patient developed sinus infection diagnosed by biopsy, with neutropenia. Murcomycosis usually occurs one year after transplantation and presents a high lethality rate (around 50% to 60%). Among the leading risk factors, the use of corticosteroids, diabetes, renal dysfunction, and neutropenia have been described (Lemonovich, 2018). In our study, the patient diagnosed with murcomycosis was diabetic, as well as neutropenic, and evolved to death.

Among the risk factors for IFI, CMV infection is considered an independent factor, being especially relevant in liver transplant recipients (Yong, Slavin, & Kontoyiannis, 2018). A high frequency of CMV infection was observed herein (50%), six months before IFI diagnosis, in 5 liver and 4 kidney transplant recipients.

Another significant risk factor for IFI is the use of anti-lymphocytic antibodies, which cause an impact on infection within six months of organ transplantation (Guimarães, et al., 2016). Among the analyzed patients who used thymoglobulin (n=9), 33.3% presented IFI up to six months after the procedure. However, in this case, two were due to candidemia and one, to aspergillosis, both of which are already expected to have an early onset (Anesi & Baddley, 2016).

A significant worsening of renal function was observed in kidney transplant recipients, especially those infected with histoplasmosis, in which 71.4% presented an increase in creatinine levels during infection. Meanwhile, in cases of cryptococcosis, the worsening of kidney function was more evident in the first month after infection (50%). Such worsening of function may have been due to the nephrotoxicity of amphotericin B deoxycholate, used due to the difficulty of accessing lipid formulations in the public sector on account of their higher costs. A marked worsening of renal function was noted in the patients who used this formulation, a fact that is consistent with the literature (Aguirre & Hamid, 2015).

The present study had some limitations, such as the fact that it was a retrospective study and that the necropsy cases at the center were not evaluated, considering that many IFI cases are diagnosed post-mortem. We also highlight that the candidemias may have been underdiagnosed, given that only cases with positive blood cultures were considered. No scores, such as the Candida Score, which could provide additional data, including abdominal surgery and multifocal candida colonization, were used. This scoring method could lead to information regarding the possibility of candidemia in a given patient (León, et al., 2006).

In the case of invasive aspergillosis, underdiagnosis was also likely, since possible and probable cases were not included, due to the limited availability of galactomannan in our transplant center, which can be a promising tool for diagnosis in patients at high risk for IFIs (Ergin, et al., 2003), as well as in candidemia, where beta-2 glucan was not available. It was difficult to correlate demographic data, such as profession, housing, and place of birth, among others, due to lack of information in the medical records.

Further prospective studies are necessary to better define risk factors for IFI in order to adequately prevent the onset of these conditions and reduce morbidity and mortality, as well as to identify the best prophylactic and therapeutic regimen for the optimal follow-up of these patients.

5. Conclusion

Candidemia was the most prevalent IFI in SOT, especially in the liver transplant recipients.

The mortality rate of the IFIs was high and similar to that described in the literature in transplant recipients, namely in the cases of histoplasma, candida, and cryptococcus, which represented the majority of cases.

The worsening of kidney function was attributed to the treatment, since patients who used amphotericin B deoxycholate showed a decrease in glomerular filtration rates.

Comparative case-control studies are needed for a better assessment of the main risk factors for IFIs so that we can guarantee an earlier treatment for these patients in an attempt to reduce the morbidity and mortality caused by them.

References

Abdala, E., Miller, R., Pasqualotto, A. C., Muñoz, P., Colombo, A. L., & Cuenca-Estrella, M. (2018). Endemic Fungal Infection Recommendations for Solid-Organ Transplant Recipients and Donors. Transplantation, 102(2S-2), S52 - S59.

Aguirre, B., & Hamid, R. (2015). Amphotericin B deoxycholate versus liposomal amphotericin B: effects on kidney function (Review). Cochrane Database of Systematic Reviews, 1 - 60.

Anesi, J. A., & Baddley, J. W. (2016). Approach to the Solid Organ Transplant Patient with Suspected Fungal Infection. Infectious Disease Clinics of North America, 30(1), 277 - 296.

Aslam, S., & Rotstein, C. (2019). Candida infections in solid organ transplantation: Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clinical Transplantation, 1 - 11.

Assi, M., Martin, S., Wheat, L. J., Hage, C., Freifeld, A., Avery, R., & Kaul, D. R. (2013). Histoplasmosis After Solid Organ Transplant. Clinical Infectious Diseases, 57(11), 1542 - 1549.

Atılgan, A. O., Özdemir, B. H., Kırnap, M., Akdur, A., Akçay, E. Y., Özkan, E. A., & Haberal, M. (2014). Invasive Fungal Infections in Liver Transplant Recipients. Experimental and Clinical Transplantation, 110 - 116.

Batista, M. V., Pierrotti, L. C., Abdala, E., Clemente, W. T., Girão, E. S., Rosa, D. R., & Shikanai-Yasuda, M. A. (2011). Endemic and opportunistic infections in Brazilian solid organ transplant recipients. Tropical Medicine and International Health, 16(9), 1134 - 1142.

Bodro, M., Sabé, N., Gomila, A., Ayats, J., Baliellas, C., Roca, J., & Carratalà, J. (2012). Risk Factors, Clinical Characteristics, and Outcomes of Invasive Fungal Infections in Solid Organ Transplant Recipients. Transplantation Proceedings, 44, 2682 - 2685.

Donnelly, J. P., Chen, S. C., Kauffman, C. A., Steinbach, W. J., Baddley, J. W., Verweij, P. E., & Pappas, P. G. (2019). Revision and Update of the Consensus Definitions of Invasive Fungal Disease From the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clinical Infectious Diseases, 1 - 10.

Ebrahimi, A., Dashti, H., Mohammadpour, Z., & Ahmadinejad, Z. (2020). Invasive Fungal Infections With Good Survival Following Liver Transplant: A Single-Center Experience From a Developing Country. Experimental and Clinical Transplantation, 2, 196 - 200.

Ergin, F., Arslan, H., Azap, A., Demirhan, B., Karakayali, H., & Haberal, M. (2003). Invasive aspergillosis in solid-organ transplantation: report of eight cases and review of the literature. Transplant International, 16, 280 - 286.

Gandhi, B., Bahadur, M., Dodeja, H., Aggrwal, V., & A Thamba, M. M. (2005). Systemic fungal infections in renal diseases. Journal of Postgraduate Medicine, 51(5), 30 - 36.

Gavalda, J., Meije, Y., Fortún, J., Roilides, E., Saliba, F., Lortholary, O., & Cuenca-Estrella, M. (2014). Invasive fungal infections in solid organ transplant recipients. Clinical Microbiology and Infection, 20(7), 27 - 48.

Guimarães, L., Halpern, M., Lemos, A. d., Gouvêa, E., Gonçalves, R., Santos, M. D., & Santoro-Lopes, G. (2016). Invasive Fungal Disease in Renal Transplant Recipients at a Brazilian Center: Local Epidemiology Matters. Transplantation Proceedings, 48, 2306-2309.

Jeong, W., Keighley, C., Wolfe, R., Lee, W., Slavin, M., Kong, D., & Chen, S.-A. (2018). The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clinical Microbiology and Infection, 25(1), 26 - 34.

Kurşun, E., Turunç, T., Demiroğlu, Y. Z., Yabanoğlu, H., Demir, Ş., Çalışkan, K., & Haberal, M. (2015). Mucormycosis with Orbital Apex Syndrome in a Renal Transplant Recipient. Cukurova Medical Journal, 40(2), 384 - 389.

Leitão, T. M., Filho, A. M., Filho, J. E., Tavares, B. M., Mesquita, J. R., Farias, L. A., & Damasceno, L. S. (2019). Accuracy of Buffy Coat in the Diagnosis of Disseminated Histoplasmosis in AIDS-Patients in an Endemic Area of Brazil. Journal of Fungi, 47(5), 1 - 8.

Leitheiser, S., Harner, A., Waller, J. L., Turrentine, J., Baer, S., Kheda, M., & Colombo, R. E. (2019). Risk Factors Associated With Invasive Fungal Infections in Kidney Transplant Patients. American Journal of the Medical Sciences, 1 - 9.

Lemonovich, T. L. (2018). Mold Infections in Solid Organ Transplant Recipients. Infectious Disease Clinics of North America, 32, 687 - 701.

León, C., Ruiz-Santana, S., Saavedra, P., Almirante, B., Nolla-Salas, J., Álvarez-Lerma, F., & León, M. Á. (2006). A bedside scoring system ("Candida score") for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. Critical Care Medicine, 34(3), 730 - 737.

Limaye, A. P., Connolly, P. A., Sagar, M., Fritsche, T. R., Cookson, B. T., Wheat, L. J., & Stamm, W. E. (2000). Transmission Of Histoplasma Capsulatum By Organ Transplantation. The New England Journal of Medicine, 343(16), 1163 - 1166.

Nieto-Ríos, J., Serna-Higuita, L., Guzman-Luna, C., Ocampo-Kohn, C., Aristizabal-Alzate, A., Ramírez, I., & Zuluaga-Valencia, G. (2014). Histoplasmosis in Renal Transplant Patients in an Endemic Area at a Reference Hospital in Medellin, Colombia. Transplantation Proceedings, 46, 3004 - 3009.

Nucci, M., Engelhardt, M., & Hamed, K. (2019). Mucormycosis in South America: A review of 143 reported cases. Mycoses, 62(9), 730 - 738.

Öner-Eyüboglu, F., Karacan, Ö., Akçay, S., Arslan, H., Demirhan, B., & Haberal, M. (2003). Invasive Pulmonary Fungal Infections in Solid Organ Transplant Recipients: A Four-Year Review. Transplantation Proceedings, 35, 2689 - 2691.

Pereira, A. S., Shitsuka, D. M., Parreira, F. J., & Shitsuka, R. (2018). Metodologia da Pesquisa Científica [e-book grátis]. Santa Maria: UAB / NTE / UFSM. Fonte: https://repositorio.ufsm.br/bitstream/handle/1/15824/Lic_Computacao_Metodologia-Pesquisa-Cientifica.pdf?sequence=1

Ramos, I. C., Soares, Y. C., Damasceno, L. S., Libório, M. P., Farias, L. A., Heukelbach, J., & Leitão, T. d. (2018). Predictive factors for disseminated histoplasmosis in AIDS patients with fever admitted to a reference hospital in Brazil. Revista da Sociedade Brasileira de Medicina Tropical, 51(4), 479 - 484.

Shekar, M., Elumalai, R., Elayaperumal, I., Yelahanka, R. P., Anandkumar, D. G., Bandi, V. K., & Matcha, J. (2019). Prevalence and Outcome of Systemic Fungal Infections in Renal Transplant Recipients - A Tertiary Care Experience. Saudi Journal of Kidney Disease and Transplantation, 30(5), 1137 - 1143.

Shoham, S., & Marr, K. A. (2012). Invasive fungal infections in solid organ transplant recipients. Future Microbiology, 7(5), 639 - 655.

Tepeoğlu, M., Atılgan, A. O., Özdemir, B. H., & Haberal, M. (2015). Role of Bronchoalveolar Lavage in Diagnosis of Fungal Infections in Liver Transplant Recipients. Experimental and Clinical Transplantation, 331 - 334.

Yong, M. K., Slavin, M., & Kontoyiannis, D. P. (2018). Invasive fungal disease and cytomegalovirus infection: is there an association? Current Opinion in Infectious Diseases, 31(6), 481 - 489.

Zicker, M., Colombo, A. L., Ferraz-Neto, B.-H., & Camargo, L. F. (2011). Epidemiology of fungal infections in liver transplant recipients: a six-year study of a large Brazilian liver transplantation centre. Memorias do Instituto Oswaldo Cruz, 106(3), 339-345.