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Invasive Fungal Infections in Solid Organ Transplant Recipients: A Case Series from a Tertiary University Hospital

Solid Organ Nakil Alıcılarında İnvazif Mantar Enfeksiyonları: Üçüncü Basamak Üniversite Hastanesinden Bir Olgu Serisi

Çağlayan Merve AYAZ[1], Berire YAVUZ[1], Haydar ADANIR[2], Özlem KOYUNCU ÖZYURT[3], Özge TURHAN[1]

[1]*Akdeniz University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Antalya, Turkey*
[2]*Akdeniz University Faculty of Medicine, Department of Internal Medicine, Clinic of Gastroenterology, Antalya, Turkey*
[3]*Akdeniz University Faculty of Medicine, Department of Medical Microbiology, Antalya, Turkey*

Abstract

In solid organ transplant (SOT) recipients, invasive fungal infections (IFIs) are a significant cause of morbidity and mortality. Thus, the diagnosis, treatment, and management of these infections are of great importance. Eleven different IFIs (five candidemia, three aspergillosis, one cryptococcosis, one intra-abdominal mucormycosis, and one *Magnusiomyces* infection) were followed up in nine SOT recipients (four kidney, four liver, and one heart transplant), aged 35-66 years. The diagnosis of mucormycosis was based on pathology test results; the other fungi were identified via culture. One patient with candidemia (*Candida parapsilosis)* developed resistance to fluconazole while under treatment. The study patients had several risk factors for IFIs, including prolonged hospitalization, immunosuppression, broad-spectrum antibiotic use, renal replacement therapy, in-situ central venous catheter, previous antifungal exposure, and reoperation. Focal control was attempted in all patients by withdrawing the catheter if present. Treatments were administered based on antifungal susceptibility results, if available, or in accordance with guideline recommendations. During the follow-up period, six of the nine study patients (66.7%) died. Despite appropriate antifungal treatment and patient management, the mortality rate of IFIs remains high. Therefore, a multidisciplinary approach, including rapid diagnosis, appropriate treatment and focal control, is essential.
Keywords: Invasive fungal infections, aspergillosis, candidemia, organ transplantation

Öz

Solid organ nakli (SOT) alıcılarında, invazif mantar enfeksiyonları (İFİ) önemli bir morbidite ve mortalite nedenidir. Bu nedenle, bu enfeksiyonların tanı, tedavi ve yönetimi büyük önem taşımaktadır. Bu olgu serisinde, yaşları 35-66 arasında değişen dokuz SOT alıcısında (dört böbrek, dört karaciğer ve bir kalp nakli) on bir farklı İFİ (beş kandidemi, üç aspergilloz, bir kriptokokkoz, bir intraabdominal mukormikoz ve bir *Magnusiomyces* enfeksiyonu) izlendi. Mukormikoz tanısı patoloji test sonucuyla; diğer mantarlar kültür yoluyla tanımlanmıştır. Kandidemisi olan (*Candida parapsilosis*) bir hastada tedavi altındayken flukonazole karşı direnç gelişmiştir. Çalışma hastaları, uzun süreli hastanede yatış, immünsüpresyon, geniş spektrumlu antibiyotik kullanımı, renal replasman tedavisi, santral venöz kateter, önceden antifungal maruziyeti ve reoperasyon dahil olmak üzere İFİ'ler için çeşitli risk faktörlerine sahipti. Tüm hastalarda varsa kateter çekilerek lokal kontrol sağlanmaya çalışılmıştır. Tedaviler, varsa antifungal duyarlılık sonuçlarına göre veya kılavuz önerilerine uygun olarak uygulanmıştır. Takip süresi boyunca, dokuz çalışma hastasından altısı (%66,7) ölmüştür. Uygun antifungal tedavi ve hasta yönetimine rağmen, İFİ'lerin mortalite oranı yüksek kalmaya devam etmektedir. Bu nedenle, hızlı tanı, uygun tedavi ve lokal kontrolü içeren multidisipliner bir yaklaşım esastır.
Anahtar Kelimeler: İnvaziv fungal enfeksiyonlar, aspergillozis, kandidemi, organ transplantasyonu

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Address for Correspondence/Yazışma Adresi: Özge TURHAN MD, Akdeniz University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Antalya, Turkey
Phone: +90 533 273 73 53 **E-mail:** ozgeturhan@akdeniz.edu.tr **ORCID ID:** orcid.org/0000-0003-1494-9973
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Introduction

Fungal pathogens can cause serious morbidity and mortality in organ recipients[1,2]. The incidence of invasive fungal infections (IFIs) in solid organ transplant (SOT) recipients is 3.1-42%. Furthermore, the distribution of possible agents varies according to the transplanted organ and transplant procedure. IFIs frequently develop within 3-6 months of transplantation and are commonly caused by yeasts. Among the yeasts, *Candida* species are the most common causative agents[2-6]. IFIs may also be caused by *Cryptococcus* species and, less frequently, by rare yeast fungi[5,7,8]. Aspergillosis and zygomycosis are the most commonly reported mold infections[8,9]. Several risk factors have been identified for the different IFIs[10,11]. Early causative agent identification, appropriate antifungal treatment, and source control are vital in SOT recipients. However, diagnosing and treating these infections can be challenging. Empirical treatment options include echinocandins, amphotericin B, or azoles and are based on the transplant type, patient's risk factors, and antifungal susceptibility profile in the region[9].

In this case series, we aimed to present the clinical and microbiological characteristics of nine SOT recipients who developed eleven different IFIs between January 1, 2019, and December 31, 2022.

Nine SOT recipients who were followed up at the Akdeniz University Hospital and developed IFIs between 2019 and 2022 were analyzed. During the study period, 1,104 patients were screened. Patients with isolates obtained from respiratory specimens and that were not considered significant were excluded from the study. One of the most significant risk factors for IFIs in SOT recipients is immunosuppressive therapy. Blood and tracheal culture samples were obtained and inoculated on 5% sheep Blood agar (Becton Dickinson, USA), MacConkey agar (Becton Dickinson, USA), chocolate agar (Becton Dickinson, USA), and Sabouraud Dextrose Agar (SDA; Becton Dickinson, USA). Tracheal samples were inoculated as soon as they arrived at the laboratory, and blood samples were inoculated after the culture bottles signaled. The colonies were identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Daltonics Microflex LT system; Becton Dickinson, Italy). Antifungal susceptibility testing was conducted using disc diffusion tests (Bioanalyse, Turkey) for yeasts and E-tests (Bioanalyse, Turkey) for yeasts and molds. After 24-48 hours, the zone diameters of the disc diffusion tests were evaluated according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) (CLSI Performance Standards for Antifungal Susceptibility Testing of Yeasts M60 1st ed.). The E-test results were evaluated according to the standards of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (EUCAST Antifungal Clinical Breakpoint Table version 9.0 and 10.0). Unsuccessful attempts were made to generate fungal isolates for the identification of minimum inhibitory concentration values.

Case Report

Patient 1

A 35-year-old male with a history of cryptogenic liver cirrhosis underwent liver transplantation from a living donor in September 2019. Postoperatively, the patient developed a surgical site infection (SSI) and was treated empirically with intravenous (IV) meropenem, teicoplanin, and caspofungin. The patient's clinical condition improved, and he was discharged after one month of hospitalization. Approximately one month after discharge, the patient was readmitted to the hospital for a fever. Imaging studies revealed an intra-abdominal abscess. Long-term administration of broad-spectrum antibiotics was initiated due to the multidrug-resistant bacteria isolated in the pus and blood samples obtained from the abscess.

The patient underwent five additional surgeries for the intra-abdominal abscess. In February 2020 (post-transplant day 168), *Candida parapsilosis* was detected in the blood culture. Thus, IV fluconazole treatment was initiated. Although a sterile blood culture result was achieved, the patient remained hospitalized due to the intra-abdominal abscess. He was admitted to the intensive care unit (ICU) because his general condition deteriorated. The patient passed away in May 2020 due to intra-abdominal complications.

Patient 2

A 57-year-old woman with cryptogenic liver cirrhosis underwent cadaveric liver transplantation in May 2019. She was monitored in the hospital for an extended period due to the development of an SSI. During the hospitalization, an intra-abdominal abscess was discovered. Cultures revealed the presence of a multidrug-resistant bacteria. Thus, long-term administration of broad-spectrum antibiotics and empirical caspofungin was initiated. In June 2019 (post-transplant day 21 day), *C. parapsilosis* and *Candida albicans* were identified in the peripheral and central venous catheter blood cultures. Fluconazole was initiated, and the infected catheter was removed. During the follow-up, the blood cultures yielded negative result. However, *C. parapsilosis* continued to grow in the peripheral blood cultures obtained on the 17th day of treatment. Furthermore, fluconazole resistance was detected in the new isolates. Thus, fluconazole was discontinued, and IV caspofungin was initiated. Although the subsequent blood culture yielded a negative result, the patient developed a peptic ulcer, which perforated during follow-up. The patient underwent five intra-abdominal surgeries. However, the patient died three months after transplantation.

Patient 3

A 56-year-old male with diabetes mellitus-induced chronic renal failure underwent cadaveric kidney transplantation in September 2019. The patient was hospitalized for a prolonged period due to a postoperative SSI, for which he was administered IV broad-spectrum antibiotics and empirical echinocandin. Abdominal computed tomography revealed stomach wall edema. Thus, an endoscopic biopsy was performed, and a sample was obtained from the stomach wall. However, the histopathological examination of the sample was inconclusive regarding malignancy and other pathologies. Because the patient developed gastrointestinal bleeding, a diagnostic laparotomy was performed. Intraoperatively, an ischemic mass was found in the middle of the stomach that was invading the transverse colon. Thus, a gastrectomy was performed. In November 2019 (post-transplant day 61), liposomal amphotericin B (LAmB) treatment was initiated after histopathological findings of the gastrectomy sample were found to be consistent with mucormycosis.

Magnusiomyces clavata was detected in the patient's blood and urine cultures obtained after laparotomy (post-transplant day 65). Thus, the patient's catheter was removed, and LAmB administration was continued. After four weeks of IV LAmB, the patient's blood culture was sterile, and their general condition improved. LAmB was discontinued and oral posaconazole was initiated for mucormycosis treatment. However, anastomotic leakage was observed during follow-up, and the patient underwent resurgery. Together with organ transplantation, the patient underwent a total of four operations. He was admitted to the ICU due to deterioration of his general condition, and he died in December 2019.

Patient 4

A 58-year-old male with heart failure underwent heart transplantation in October 2021. Postoperatively, the patient developed fever and discharge from the surgical incision. Thus, empiric treatment with meropenem and vancomycin was initiated. Because *Candida tropicalis* was isolated in the patient's pus and blood cultures (post-transplant day two), caspofungin was added to the treatment regimen. He was discharged on treatment completion. One month after discharge, the patient was admitted to the ICU for Coronavirus disease-2019 pneumonia. He died in January 2022.

Patient 5

A 50-year-old man with Budd-Chiari syndrome and secondary cirrhosis underwent liver transplantation from a living donor in June 2020. Postoperatively, the patient developed an intra-abdominal abscess and was hospitalized for six months. During this period, he was administered numerous IV antibiotics for multidrug-resistant organisms. Furthermore, fluconazole was administered as an empirical antifungal. The patient underwent seven additional surgeries for the intra-abdominal abscess, and total parenteral nutrition (TPN) was administered via a central line. In December 2020 (post-transplant day 168), *Cryptococcus neoformans* was detected in peripheral blood and catheter blood cultures. Although no pathology was detected on cranial imaging, multiple infectious nodules in clusters were observed on lung imaging. A lumbar puncture could not be performed due to hemodynamic instability, and a cryptococcal antigen test was not performed. The catheter was withdrawn after treatment with LAmB was initiated. Nonetheless, the patient's general condition deteriorated, and he was transferred to the ICU. He died in January 2021.

Patient 6

A 44-year-old woman with antibiotic-induced renal failure underwent a cadaveric kidney transplantation in January 2020. Because *Klebsiella pneumoniae* was detected in the fluid in which the donor organ was transported, the patient was started on relevant antibiotics. *Candida kefyr* was detected in the patient's peripheral and central venous catheter blood cultures obtained on post-transplant day seven. Thus, fluconazole was added to the treatment. The catheter was removed, and the patient improved. The control catheter culture yielded sterile results.

Patient 7

A 48-year-old male with chronic renal failure on hemodialysis underwent a cadaveric kidney transplantation in June 2019. In September 2022, he was admitted to the ICU for multiple large fractures, a pulmonary contusion, and minimal pneumothorax following a car accident. The patient was treated with multiple broad-spectrum antibiotics for a prolonged period. Due to the development of sepsis, empirical IV caspofungin was initiated. Subsequently, caspofungin was discontinued and IV LAmB was initiated due to the detection of a fungal morphology in the tracheal aspirate smear. Furthermore, *Aspergillus fumigatus* isolated in the tracheal aspirate culture obtained on post-transplant day 1199. However, serum galactomannan antigen was not detected. Chest computed tomography revealed irregular densities in the basal lower lobe and posterior upper lobe of the right lung. In November 2022, the patient's general condition deteriorated in the ICU, and he died.

Patient 8

A 66-year-old man with a medical history of diabetes, hypertension, gout, chronic hepatitis B virus (HBV) infection, coronary artery disease, and bypass surgery underwent liver transplantation from a living donor for HBV-associated cirrhosis in November 2021. One week after surgery, he developed an

intra-abdominal abscess. Thus, empirical treatment with IV imipenem, teicoplanin, and fluconazole was initiated. Subsequently, the patient's general condition deteriorated. He developed cardiac arrest and was admitted to the ICU. LAmB was initiated empirically due to the presence of a fungus resembling mold in the tracheal aspirate smear. Subsequently, *A. fumigatus* was identified in the aspirate culture (post-transplant day seven). The serum galactomannan antigen level was 5.3. Chest computed tomography was not performed because the patient was clinically unstable. The patient died in December 2021 while being followed up in the ICU.

Patient 9

A 58-year-old man with a history of hypertension, coronary artery disease, and chronic renal failure underwent kidney transplantation from a living donor in January 2018. Approximately five months after surgery, he was hospitalized for seizures. Brain magnetic resonance imaging revealed a cranial abscess. Thus, meropenem, vancomycin, and metronidazole were initiated, and the abscess was drained. *A. fumigatus* was detected in the intraoperative pus culture (post-transplant day 151). Thus, IV voriconazole treatment was initiated. Serum galactomannan antigen was not detected. After eight weeks of IV therapy, oral antifungal therapy was administered for six months. The patient died in September 2021 in another city. The cause of death is unknown because there was no hospitalization record during this period.

The characteristics of all nine patients and the fungal pathogens are shown in Tables 1 and 2, respectively.

Discussion

Invasive fungal infections are an important cause of mortality and morbidity in SOT recipients. *Candida* infections are the most common type of IFIs, except in lung transplant recipients. However, invasive mold infections can also be encountered in SOT recipients. Difficulty in diagnosing mold infections, challenges in treatment, and the need for invasive procedures lead to infections going unrecognized[5,12]. During the study period, 1,104 patients were screened, and the IFI rate was 1%. One of the most significant risk factors for IFIs in SOT recipients is immunosuppressive therapy. In all our patients, except patient 7, IFIs occurred within the first six months of intensive immunosuppressive therapy. In patient 7, his long-term ICU stay was also a risk factor for IFI development.

C. albicans is most commonly observed in *Candida* infections. However, the incidence of infections due to non-albicans species, especially *Candida glabrata* and *C. kefyr*, are also increasing[7]. Patients in this case series had several common risk factors for *Candida* infections, including immunosuppression, abdominal organ transplant surgery, advanced age, use of broad-spectrum IV antibiotics, presence of central catheter, TPN, ICU admission, renal replacement therapy, and reoperation[5]. Patients with *C. parapsilosis* had a history of previous echinocandin use.

Table 1. Demographic, clinical and treatment characteristics and the outcomes of the study patients

Patient	Age/ sex	Comorbidities/ type of transplantation	TPN	CVC	RRT	Number of operation	Prior AB use	Prior antifungal use	ICU stay	Neutropenia	Treatment	30-day outcome
1	38/M	Cryptogenic cirrhosis/liver	+	+	+	5 times	+	+ (Caspofungin)	+	-	Fluconazole	Death
2	57/F	Cryptogenic cirrhosis, DM/liver	+	+	-	5 times	+	+ (Caspofungin)	+	-	Fluconazole, caspofungin	Death
3	60/M	DM/renal	+	+	+	4 times	+	+ (Caspofungin)	+	-	LAmB	Death
4	59/M	Cardiac failure/ heart	-	+	+	-	+	+ (Caspofungin)	-	-	Caspofungin	Discharge
5	53/M	Budd-Chiari syndrome/liver	+	+	-	7 times	+	+ (Caspofungin)	+	-	LAmB	Death
6	44/F	Chronic renal failure/renal	-	+	+	-	+	-	-	-	Fluconazole	Discharge
7	49/M	Chronic renal failure/renal	+	+	+	-	+	+ (Caspofungin)	+	-	LAmB	Death
8	67/M	DM, hypertension, gout, HBV infection, CAD/liver	-	+	-	-	+	+ (Fluconazole)	+	-	LAmB	Death
9	58/M	Chronic renal failure, CAD, hypertension/renal	-	-	-	-	-	-	-		Voriconazole	Discharge

M: Male, F: Female, TPN: Total parenteral nutrition, CVC: Central venous catheter, RRT: Renal replacement therapy, AB: Antibiotics, ICU: Intensive care unit, LamB: Liposomal amphotericin B, DM: Diabetes mellitus, HBV: Hepatitis B virus, CAD: Coronary artery disease

Table 2. Antifungal susceptibility and minimum inhibitory concentration results of the isolated fungal pathogens

Patient	Etiology	Antifungal susceptibility
1	*Candida parapsilosis*	NA
2	*Candida albicans* + *Candida parapsilosis*	Fluconazole and voriconazole S Fluconazole and voriconazole S Latter culture results voriconazole S (MIC 0.38 mg/l), fluconazole R (MIC 32 mg/l)
3	*Magnusiomyces clavata*	AmB S (MIC 0.25 mg/l), micafungin (MIC 0.25 mg/l), fluconazole (MIC >64 mg/l), and all other azoles (MIC >4 mg/l)
4	*Candida tropicalis*	Fluconazole, voriconazole and caspofungin S
5	*Cryptococcus neoformans*	Fluconazole (MIC 1.5 mg/l), AmB (MIC 0.125 mg/l)
6	*Candida kefyr*	Fluconazole and voriconazole S
7	*Aspergillus fumigatus*	NA
8	*Aspergillus fumigatus*	NA
9	*Aspergillus fumigatus*	NA

NA: Not applicable, S: Sensitive, R: Resistant, MIC: Minimum inhibitory concentration, AmB: Amphotericin B

All the identified isolates were sensitive to fluconazole. However, in patient 2 with a concurrent *C. albicans* infection, the *C. parapsilosis* from the second blood culture was resistant to fluconazole. The central venous catheters were removed in all the patients to achieve focal control. In general, previous exposure to any antifungal drugs, site of infection, *Candida* species isolated and drug interactions should be considered when treating patients with *Candida* infections[5,13].

Aspergillus is a ubiquitous fungus in the form of mold that frequently causes invasive lung infections due to the inhalation of its spores. It can even be fatal[12]. The most common *Aspergillus* species causing infections is *A. fumigatus* (73%)[8,12]. All the IFIs in our study were caused by this species. The risk factors for *Aspergillus* infections include the first three months after transplantation, use of vasoactive agents, prolonged ICU stay, development of renal failure after transplantation, concomitant *Cytomegalovirus* infection, previous bacterial infection, advanced age, graft rejection, and presence of immunosuppression-related malignancies[12,14]. Voriconazole is the preferred treatment for invasive aspergillosis (IA), while isavuconazole and LAmB are considered its alternatives. Both American and European guidelines endorse this recommendation[12,15]. Difficulty in obtaining tissue samples, clinically unstable patients, associated bleeding disorders, *Aspergillus* colonization of the respiratory tract, false-negative or false-positive galactomannan antigen tests, and inadequate use of imaging techniques make the diagnosis of IA difficult. Thus, IA is most likely underdiagnosed[14]. Of our three patients with IA, one had intracranial aspergillosis and two had pulmonary aspergillosis.

Cryptococcosis represents the third most frequent IFI among SOT recipients, with a reported incidence of 0.2% to 8%. The mortality rates of SOT recipients with cryptococcosis is reportedly 5% to 20%[7]. Immunosuppression, steroid therapy, T-cell depleting antibodies, advanced age, the presence of concomitant diabetes, and the type of transplanted organ are risk factors for the development of cryptococcosis[7,16]. Although cryptococcosis is frequently a late-onset infection[7,17], it developed within the first 6 months of transplantation in patient 5. Determining the location and severity of the disease is crucial in guiding the choice of antifungal and treatment duration for SOT recipients with cryptococcosis[7]. A complete evaluation of extrapulmonary sites of infection, via lumbar puncture and cultures of blood, urine, or other tissues, should be performed in all SOT recipients with a suspected or confirmed diagnosis of cryptococcosis[7,18]. Fluconazole is recommended for patients with pulmonary cryptococcosis who are otherwise asymptomatic or have a mild-to-moderate disease[18]. Because the patient's clinical condition was severe, he was treated with LAmB according to established guidelines[7,18].

Magnusiomyces clavatus, previously classified as *Geotrichum clavatum* and *Saprochaete clavata,* is an ascomycetous filamentous yeast. It can cause life-threatening invasive infections in immunocompromised patients, particularly those with hematological malignancies[19]. Infections with these species have been reported in SOT recipients[20-22] and are associated with a high mortality rate (range, 60-80%). Furthermore, there has been a recent increase in the number of published studies on its emergence as a pathogen[23]. The most commonly reported risk factors of *Magnusiomyces* infection include echinocandin use, immunosuppression, hematological malignancies, high-dose steroid therapy, prolonged neutropenia, broad-spectrum antibiotic use, presence of a central catheter, and gastrointestinal colonization[23-25]. Although no clinical breakpoint has been established, these species appear to be intrinsically resistant to echinocandins and highly resistant to

fluconazole. Therefore, LAmB and azoles are frequently used for the treatment of *Magnusiomyces* infections[24-26]. Despite the numerous risk factors, our patient responded well to LAmB treatment. He was subsequently switched to oral posaconazole for maintenance.

Mucormycosis, is a fungal infection caused by species within the order *Mucorales* of the class *Zygomycetes*. Typically, human infections are caused by species within the *Rhizopus*, *Mucor*, *Rhizomucor*, *Absidia*, and *Cunninghamella* genera are associated with a high mortality rate[8,27,28]. The incidence of mucormycosis among SOT recipients varies between 0.4% and 16% and depends on the transplanted organ. In renal transplant recipients, the incidence is between 0.2% and 1.2%[8,29]. Mucormycosis can occur within 3-6 months or even years after transplantation[30]. In our study, patient 3 developed early post-transplant mucormycosis. The risk factors for mucormycosis include immunosuppression, hematological malignancies, diabetes mellitus, steroid use, neutropenia, trauma, burns, metabolic acidosis, and disruption of the gastrointestinal mucosal barrier by peptic acid disease, iron overload, or deferoxamine treatment[8,28,29]. Mucormycosis typically manifests as a sinus-rhino-cerebral disease in SOT recipients. In cases of gastrointestinal mucormycosis, the stomach is the most frequently affected site, followed by the colon and small bowel[8,29]. In patient 3, both the stomach and colon were affected simultaneously, which is an extremely rare presentation. Amphotericin B, isavuconazole, and posaconazole are the drugs commonly used in mucormycosis treatment[28]. In our case series, one of the three patients with IA had an intracranial abscess; the other two patients had invasive pulmonary aspergillosis. Based on the host, clinical, and mycological criteria, these patients were considered to have probable invasive pulmonary aspergillosis. Thus, they were treated accordingly.

Conclusion

In conclusion, IFIs are an important cause of morbidity and mortality in high-risk patients, such as SOT recipients. Furthermore, these patients require a multidisciplinary approach for their management. Although *Candida* infections are common in SOT recipients, rarer fungi with multiple risk factors are now being identified. Further studies are needed to bridge the knowledge gap and identify early diagnostic and effective treatment methods for IFIs in SOT recipients.

Ethics

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ç.M.A., B.Y., H.A., Ö.K.Ö., Ö.T., Concept: Ç.M.A., Ö.T., Design: Ç.M.A., Ö.T., Data Collection or Processing: Ç.M.A., B.Y., Ö.K.Ö., Analysis or Interpretation: Ç.M.A., B.Y., Ö.K.Ö., Ö.T., Literature Search: Ç.M.A., B.Y., Ö.K.Ö., Writing: Ç.M.A., B.Y., H.A., Ö.K.Ö., Ö.T.

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