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Epidemiology, risk factors and outcomes of invasive aspergillosis in solid organ transplant recipients in the Swiss Transplant Cohort Study

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Abstract

Background. There is lack of recent multicenter epidemiological data on invasive aspergillosis (IA) among solid organ transplant recipient (SOTr) in the mold-acting antifungal era. We describe the epidemiology and outcomes of IA in a contemporary cohort of SOTr using the Swiss Transplant Cohort Study.

Methods. All consecutive SOTr with proven or probable IA between 01.05.2008 and 31.12.2014 were included. A case-control study to identify IA predictors was performed: 1-case was matched with 3-controls based on SOT type, transplant center, and time post-SOT.

Results. Among 2868 SOTr, 70 (2.4%) patients were diagnosed with proven (N: 30/70, 42.9%) or probable (N: 40/70, 57.1%) IA. The incidence of IA was 8.3%, 7.1%, 2.6%, 1.3%, and 1.2% in lung, heart, combined, kidney and liver transplant recipients, respectively Galactomannan immunoassay was positive in 1/3 of patients tested. Only 33/63 (52.4%) of patients presented with typical pulmonary radiographic findings. Predictors of IA included: renal insufficiency, re-operation, and bacterial and viral infections. 12-week mortality was higher in liver (85.7%, 6/7) compared to other (15.9%, 10/63; $P<0.001$) SOTr.

Conclusions. IA remains a rare complication post-SOT, with atypical radiographic presentations and low positivity rates of biomarkers posing significant diagnostic challenges. Whereas overall mortality has decreased in SOTr, it remains high in liver SOTr.

Background

With the exception of lung transplant recipients, invasive aspergillosis (IA) is a relatively rare complication in solid organ transplant recipients (SOTr), albeit associated with poor outcomes (1-13). Multicenter cohorts have provided valuable information in the field, but with several inherent limitations (1, 3). For instance, the Prospective Antifungal Therapy (PATH Alliance®) registry provided data on 515 invasive fungal infections (IFI), including 128 cases of IA, in 429 SOTr from North America between 2004-2007, with relatively detailed clinical information but without denominator data, hence incidence rates were not reported (3). The Transplant Associated Infection Surveillance Network (TRANSNET) reported data on 1208 IFI, including 227 cases of IA, among 1063 SOTr from 15 transplant centers in the United States (US) between 2001-2006, with limited clinical information but providing detailed incidence rate data (1). Since then, newer mold-active antifungals have been introduced into clinical practice, but multicenter contemporary epidemiological data on their impact on the outcomes of IA in SOTr are lacking. We sought to describe the epidemiology and outcomes of IA in a cohort of SOTr using the Swiss Transplant Cohort Study (STCS) between 2008 and 2014.

Methods

Study design and objectives. The STCS is a prospective national cohort, in which all SOTr who sign a written informed consent in Switzerland are registered, representing >95% of SOTr in the country (14). We performed an observational retrospective study to describe the incidence and outcomes of IA in this multicenter cohort of SOTr. All consecutive SOTr with proven or probable IA between 01.05.2008 and 31.12.2014 were included. Patients were censored for death, rejection, or graft loss.

For patients without a censoring event, a minimum 6-month follow-up was required for study inclusion. In addition, a nested case-control study was performed to identify predictors of IA among SOTr. All patients with proven or probable IA were identified as cases and matched with controls at a 1:3 ratio using the entire cohort of SOTr during the study period, based on (a) SOT type within six months of the index case performed at the same center, (b) no diagnosis of IA, and (c) time post-SOT as long as the time between transplantation and IA for the index case. The latter was considered as a "fictitious date of infection" for the controls, with the aim of having comparable exposition times in both groups.

Data collection. Data collection was performed in a two-step approach. All patients were identified using the STCS database and the following data were directly retrieved from the database: (i) demographics (age, gender), (ii) SOT variables: prior transplantation, SOT type, transplant center, type of donor (living vs. cadaveric), induction and maintenance immunosuppression, cytomegalovirus (CMV) donor and recipient serology status, (iii) post-SOT complications: acute organ rejection, renal insufficiency (with and without requirement for hemodialysis), mechanical ventilation, reoperation, and infectious complications with bacterial, viral and other fungal pathogens. Additional data pertaining to IA infection were extracted from hospital charts using a case-report form, including: (i) site of infection, (ii) radiological findings, including computed tomography (CT), (iii) histopathology data, (iv) microbiological findings: direct microscopy, culture, and galactomannan enzyme immunoassay (GM-EIA) in the blood and bronchoalveolar lavage (BAL), and (v) antifungal treatment administered.

Definitions. Proven and probable IA were diagnosed based on revised consensus guidelines (15). Briefly, proven IA required a positive tissue biopsy with concomitant recovery of *Aspergillus* spp. in culture or hyphae resembling *Aspergillus* spp. Probable IA was diagnosed using host, clinical and microbiological criteria, as previously specified (15). Based on prior observations that IA may present with variable chest CT-findings in SOTr, in addition to nodular well-circumscribed pulmonary lesions, the following CT-findings were also included in the modified radiological criteria for the diagnosis of probable IA: ground-glass opacities, pleural effusion, non-specific consolidations or infiltrates (16, 17). In the context of the STCS, a local transplant infectious disease specialist reviews each case of IFI and certainty of diagnosis (proven, probable or possible) is recorded using the STCS and consensus definition guidelines (14, 15). The day the first positive clinical sample for *Aspergillus* spp. or GM-EIA was obtained or, in case of post-mortem diagnosis, the date of death was considered as the day of IA diagnosis. An optical density index of 0.5 and 1.0 were considered for a positive serum and BAL GM-EIA, respectively. Patients with probable IA did not have other pathogens identified in their

respiratory secretions. Maintenance immunosuppression, acute rejection episodes, renal insufficiency, mechanical ventilation and co-infections were considered within three months prior to IA diagnosis for cases and the "fictitious date of infection" for the controls. Renal insufficiency was defined as serum creatinine ≥1.5mg/dl and/or requirement for hemodialysis. Bacterial infections were diagnosed by a local transplant infectious disease specialist as previously described (14). Briefly, a proven bacterial infection was defined by isolation of a bacterial pathogen, compatible clinical signs and/or symptoms and administration of specific antibiotic treatment. CMV infection and disease were defined based on consensus guidelines (18, 19). Due to the small number of end-organ disease cases, CMV infection included asymptomatic replication, viral syndrome and biopsy-proven CMV disease. Infection with a respiratory virus required the detection of viral replication by polymerase chain reaction (PCR) and relevant clinical syndrome (14).

Statistical analysis. Standard descriptive statistics were used to summarize the study population characteristics. Cumulative incidences of IA among different SOT categories were estimated from first transplantation to IA among all SOTr during the study period, censoring for death and a second SOT. Logistic regression was used to identify: (i) risk factors for IA in the matched case-control patient population, and (ii) mortality predictors among SOTr with IA. Independent variables with $P<0.10$ in the univariate analyses were subsequently entered in a backward stepwise fashion into multivariable logistic regression models with mixed effect. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). The goodness of fit for logistic regression models was assessed by the Hosmer-Lemeshow test. Collinearity among independent variables was assessed using variance inflation factors (VIFs), with VIF values >3 suggesting the presence of significant collinearity. The Pearson correlation coefficient was used to determine the strength of possible correlations between independent variables. The overall 12-week and 5-year mortality were analyzed using Kaplan-Meier survival curves. The log-rank test was used to compare survival distribution between groups. A two sided test was performed and a $P<0.05$ was considered to be statistically significant. Data were analyzed using STATA 14 statistical software.

Results

Among 3035 SOTr during the study period, 2868 (94.5%) signed an informed consent form and were included in the STCS. Seventy of 2868 (2.4%) patients were diagnosed with IA during the study period: 30/2868 (1.0%) with proven and 40/2868 (1.4%) with probable disease. The incidence of IA was 8.3%, 7.1%, 2.6%, 1.3%, and 1.2% in lung, heart, combined, kidney and liver transplant recipients, respectively (**Figure 1a**). Combined SOT included kidney-liver (N=1) and kidney-pancreas (N=3). The patient baseline characteristics are described in **Table 1**.

Invasive aspergillosis diagnosis and treatment. The median time between transplantation and IA was 100 days (interquartile range, IQR: 15-275). This interval was shorter in heart (median 11 days; IQR: 5-103) and liver (median 18.0 days; IQR: 9-122) transplant recipients (**Figure 1b**). Diagnosis of IA was proven in 30 (42.9%) and probable in 40 (57.1%) SOTr (**Table 2**). In the majority of patients, IA presented as an infection involving one site only (N: 57, 81.4%). The most commonly affected site was the lower respiratory tract (N: 64, 91.4%), followed by the central nervous system (N: 7, 10%). Kidney and liver recipients were the most likely to present central nervous system infection (4/20, 20% and 3/7, 42.9%, respectively).

Among 58 patients who underwent a bronchoscopy, a positive microscopy**,** defined as the presence of fungal elements on a sputum or BAL specimen, was observed in 28 (of 57, 49.1%), while a culture was positive for *Aspergillus* spp. in 41 (of 58, 70.7%) cases. A GM-EIA was performed in 50 (of 70, 71.4%) patients: 27 (54%) patients had a GM-EIA performed in blood only, 7 (14%) patients had a GM-EIA in BAL only, and 16 (32%) patients had a GM-EIA in both blood and BAL. Among 43 patients with GM-EIA performed in blood, 15 (34.9%) had a positive GM-EIA result. Among 23 patients with GM-EIA performed in BAL, 9 (39.1%) had a positive GM-EIA result. Among 16 patients with GM-EIA performed in both blood and BAL, 5 (31.25%) had a positive result in both specimens, 1 (6.25%) in blood only, 2 (12.5%) in BAL only, and 8 (50%) negative results in both specimens. Radiographic findings for angio-invasive IA, defined as nodular and/or cavitary or necrotic lesions, among 63 patients with available chest CT were observed in 33 (52.4%) SOTr with IA. Almost half of the patients presented with atypical airway-invasive radiographic findings, including ground-glass opacities (N: 17 of 63, 27%), non-specific lung infiltrates (consolidations, tree-in-bud; N: 23 of 63, 36.5%) and a pleural effusion (N: 33 of 63, 52.3%).

Treatment data were available for 65 patients with IA: 31 (of 65, 47.7%) patients received monotherapy with a single antifungal agent (29/31 voriconazole, 1/31 posaconazole, and 1/31 caspoungin) and 34 (52.3%) patients received treatment with >1 agents. Twelve (of 34, 35.3%) patients received concomitantly administered combination treatment: 7/12 patients were treated with voriconazole-caspofungin, 3/12 with liposomal amphotericin B-caspofungin, 1/12 with itraconazole-casposungin, and 1/12 with posaconazole-caspofungin. A total of 22 (of 34, 64.7%) patients received sequential combination antifungal therapy. Voriconazole was the most frequently used agent (N: 55/65, 84.6%), followed by caspofungin (N: 24, 36.9%), liposomal amphotericin B (N: 14, 21.5%), posaconazole (N: 6, 9.2%) and itraconazole (N: 5, 7.7%).

Risk factors for IA. Using demographics, transplant variables and post-transplant complications as independent variables, we performed risk factor analysis to identify predictors for IA in the case-control population (**Table 3**). Considering possible interactions between viral infections and CMV infection (Pearson correlation coefficient: r=0.76, *P*<0.001) or respiratory viral infections (Pearson correlation coefficient: r=0.41, *P*<0.001), two different models were constructed. In the first model, all viral infections were included, with the following variables found as significant predictors of IA: CMV donor positive/recipient negative serostatus (OR: 3.1, 95%CI: 1.3, 7.0, *P*=0.009), renal insufficiency (OR: 3.7, 95%CI 1.5, 8.6, *P*=0.003), reoperation (OR: 5.4, 95%CI 2.1, 13.9, *P*=0.001), bacterial infection (OR: 2.6, 95%CI 1.2, 5.9, *P*: 0.02), and any viral infection (OR: 5.7, 95%CI 2.7, 11.9, *P*<0.001; Hosmer-Lemeshow test *P*=0.15). When viral infections were replaced by CMV and respiratory viral infections, results were comparable. Moreover, administration of mycophenolate mofetil appeared to be protective for IA (OR: 0.33, 95%CI 0.1, 0.8, *P*=0.02) and respiratory viral infections were a significant predictor of IA (OR: 15.0, 95%CI: 4.2, 53.5, *P*<0.001). The Hosmer-Lemeshow test showed a good fit for this model as well (*P*= 0.476). There was no significant collinearity between any of the independent variables included in either of the models, with all VIF values <1.5 (data not shown).

Mortality and mortality predictors. Sixteen (22.9%) SOTr with IA were dead by 12 weeks post IA diagnosis: 4 (of 15, 26.7%) in heart, 5 (of 20, 25%) in kidney, 6 (of 7, 85.7%) in liver and 1 (of 24, 4.2%) in lung transplant recipients (liver vs. other SOTr, *P*<0.001, chi-square test) (**Figure 2a**). Logistic regression to identify 12-week mortality predictors among SOTr with IA suggested that older patients (OR: 1.2, 95%CI 1.03, 1.47, *P*=0.02) and patients with disseminated IA (OR: 36.05, 95%CI 1.6, 827, *P*=0.02) were more likely to die by 12 weeks (**Table 4**). The Hosmer-Lemeshow test showed a poor fit for this model (*P*<0.001), likely due to low power. A moderate association between SOT type and disseminated IA was identified (Pearson correlation coefficient: r=0.33, *P*=0.005). After removing disseminated IA, the Hosmer-Lemeshow test showed a good fit for the model (*P*=0.960), without significant collinearity between independent variables (all VIF values <1.5; data not shown). In this model, only age remained a significant mortality predictor (OR: 1.2, 95%CI 1.02, 1.39, *P*=0.02). Although liver transplantation appeared to be a strong mortality predictor in univariate analyses (OR: 31.8, 95%CI 3.4, 293, *P*=0.002), it did not retain its significance in multivariable analyses perhaps due to the small number of patients included. Among 280 SOTr included in the nested case-control study, 58 (20.7%) patients had died by 5-years post-transplant: 29 (of 70, 41.4%) among patients with IA (cases) and 29 (of 210, 13.8%) among patients without IA (controls; *P*<0.001, chi-square test; **Figure 2b**).

Discussion

This multicenter observational study represents one of the largest contemporary series of IA in SOTr. Our data suggest that since the early 2000s significant progress has been attained in clinical outcomes among all SOTr with IA, except for liver transplant recipients. Moreover, we report that diagnostic challenges continue to exist in the context of IA among SOTr, mainly due to poor performance of GM EIA and the predominance of atypical chest CT findings, while bacterial and viral coinfections and host-related variables, such as renal insufficiency and surgical complications are important predictors of IA among SOTr.

Mortality appears to have significantly improved among kidney and lung transplant recipients with IA. In contrast to mortality rates as high as 40-60%, reported among kidney transplant recipients with IA since the early 2000s, our data suggest that mortality may be as low as 25% in this contemporary cohort of kidney transplant recipients with IA (8, 17, 20-22). This is consistent with outcomes recently reported from a multicenter multinational study showing improved survival rates among kidney transplant recipients with IA between 2007-2013, as compared to those between 2000-2006 (22). It was hypothesized that this could be partly associated with the effect of voriconazole administration, as demonstrated in other transplant patient populations (11, 23). Although voriconazole was used in 75% patients with IA in this cohort, it was not found to be a significant survival predictor in multivariate analyses, likely due to the low power of this study. Similarly, mortality was notably low among lung transplant recipients with IA (4.1%), as previously described (1). Frequent post-transplant bronchoscopies with early identification of *Aspergillus* spp. and early treatment initiation or the mere absence of invasive disease and airway colonization with *Aspergillus* conidia may, in part, explain the high incidence and low mortality rates reported in this patient population. Furthermore, post-transplant anatomical and functional changes of the transplanted lungs may lead to radiographic changes, at times difficult to distinguish from an infectious process. More efforts should be made to harmonize and refine the diagnosis of IA in lung transplant recipients.

Consistent with prior reports, the incidence of IA among liver transplant recipients was below 1.5% (6, 24-27). However, and although a rare event, our data suggest that IA remains a relatively early post-transplant complication associated with high mortality in liver transplant recipients (1-3, 5, 6, 8-10). High mortality rates may be associated with the late diagnosis of the infection and the overall immune dysfunction in this patient population, due to the devastating effects of impaired liver function prior to transplant. In the last twenty years, a large number of studies have identified risk factors for IA among liver transplant recipients, in order to optimize the type, timing and duration of

antifungal prophylaxis in this patient group (5, 6, 28-30). However, a recent prospective randomized clinical trial for antifungal prophylaxis of liver transplant recipients based on prior identified risk factors for IA failed to show any significant benefit, mainly due to the low number of patients diagnosed with IA (31). In fact, recent data suggest that the pre-transplant overall patient status (e.g. MELD score) and genetic factors (e.g. pentraxin 3 single nucleotide polymorphisms) may be more important predictors of IA among liver transplant recipients (11, 32, 33). Continued efforts should be undertaken to more effectively identify liver transplant recipients at higher risk for IA, who will benefit most from antifungal prophylaxis and high clinical suspicion at the bedside in the early post-transplant period.

The incidence of IA in heart transplant recipients was around 7%, as previously reported (34, 35). Notably, IA was a rather early post-heart transplant complication. The observed mortality rate of 25% was consistent with what was recently reported in a cohort of heart transplant recipients from Spain, in which mortality was 26% in patients with early (<3 months post-transplant) IA diagnosis vs. 63% in patients with late IA (34). Our observations need to be further studied in order to potentially identify IA predictors that may allow us to stratify heart transplant recipients to receive or not post-transplant antifungal prophylaxis.

Airway-invasive radiographic patterns on chest CT of IA in SOTr have been previously reported (16, 17, 36, 37). Angio-invasive patterns, including nodular or necrotic lesions were observed in only half of the patients with an available CT in this series. In contrast, we observed that almost half of the patients with IA in this study had less specific chest CT findings, including pleural effusions and ground-glass opacities. Consistent with prior reports, we observed a poor performance of GM-EIA in this series, both in blood and BAL specimens with a sensitivity of <40% (38, 39). The b-d-glucan test was not used for this diagnosis of IFI in this series and serum or BAL GM was not performed in all patients, hence definitive conclusions about the performance of fungal biomarkers cannot be drawn. The traditional fungal culture on BAL retained the highest positivity rate for the diagnosis of IA. The non-specific radiographic presentation and lack of reliable biomarkers underscore the existing challenges in the diagnosis of IA among SOTr. The above hinder our ability to make an accurate and timely diagnosis of this infection and may, in part, explain the relatively high incidence of disseminated disease and central nervous system involvement of IA in kidney and liver transplant recipients in this series. The (i) atypical clinical and radiographic presentation of IA in SOTr, (ii) variable timing post-SOT, and (iii) poor performance of the available diagnostic modalities contribute to the persistently observed poor clinical outcomes among liver transplant recipients with IA over the last several decades. Clearly, more data are required to effectively and timely diagnose this

infection in the setting of SOT. However, its low incidence urgently calls for multicenter multinational well-orchestrated efforts in order to improve our understanding and diagnostic approaches for IA in SOTr (17, 22).

Similar to previous observations, we identified host-related variables, such as renal insufficiency and surgical complications, and post-transplant complications, such as bacterial and CMV infections, as significant predictors for IA (5-7, 17, 40, 41). In addition, we also identified respiratory virus infections as strong predictor of IA in SOTr. Although respiratory viral infections, including influenza, respiratory-syncytial virus (RSV) and parainfluenza, have been identified as risk factors for IA in allogeneic hematopoietic cell transplant recipients, there have been no prior reports to implicate these infections in the pathogenesis of IA in SOTr (7, 40, 42-44). More recently, an association between IA and infections due to influenza H1N1 virus, adenovirus and RSV was reported in a cohort of variable immunocompromised hosts, including SOTr, with the vast majority being patients with hematologic malignancies (45). In contrast, another recent study failed to identify any possible association between respiratory viral infections and IA in a cohort of asymptomatic lung transplant recipients with positive nasopharyngeal swabs for a respiratory virus (46). The direct bronchial wall epithelial damage induced by respiratory viral pathogens and indirect effect on the local defense mechanisms may predispose patients to superinfection with other pathogens, such as *Aspergillus* spp. (47, 48). More recently, an association between IA and infections due to influenza H1N1 virus, adenovirus and RSV was reported in a cohort of variable immunocompromised hosts, including SOTr, with the vast majority being patients with hematologic malignancies (45). In contrast, another recent study failed to identify any possible association between respiratory viral infections and IA in a cohort of asymptomatic lung transplant recipients with positive nasopharyngeal swabs for a respiratory virus We also found administration of mycophenolate mofetil to be protective against IA. Earlier data have suggested that administration of mycophenolate mofetil could be protective against *Pneumocystis jirovecii* infections (49-51). However, such an association has not been described for IA to our knowledge (51). We postulate that this could be, in part, due to lower rejection rates and associated complications in patients receiving mycophenolate mofetil (52, 53). Additional studies are required to further investigate the validity of this observation and possible mechanisms of action.

This study has several limitations, including the retrospective review of prospectively collected data and consequently a relatively limited documentation of IA clinical presentation and combination treatment. Detailed information on antifungal prophylaxis protocols was not included in this study due to, in part, different antifungal prophylactic strategies across different transplant centers,

protocol changes during the study period within each center, and case-specific prophylaxis adjustments. In conclusion, we report a low incidence of IA in a contemporary cohort of SOT with -in comparison to older reviews- an improved survival among non-liver SOTr. This study illustrates the persistent challenges in the diagnosis of IA in the context of SOT, due to the poor performance of available biomarkers and the predominance of non-specific chest CT findings. The identification of significant risk factors for IA may enable us to be more successful with targeted antifungal prophylactic approaches in the future, particularly among liver SOTr. Well-organized, multi-center, multinational research projects and collaboration among Transplant Infectious Disease specialists may facilitate and further enhance the optimization of the care of these patients.

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Disclosures

All authors report no conflicts of interest associated with this manuscript.

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Figure Legends

Figure 1. (1a) Cumulative incidence of invasive aspergillosis among solid organ transplant recipients. (1b) Time to invasive aspergillosis post-transplant by different solid organ transplant categories.

Figure 2. (2a) 12-week survival among solid organ transplant recipients with invasive aspergillosis. (2b) 5-year survival between cases (70 solid organ transplant recipients with invasive aspergillosis) and controls (210 solid organ transplant recipients without invasive aspergillosis).

Table 1: Baseline patient characteristics

Patient Characteristic	All patients N: 70 (%)	Heart N: 15 (%)	Kidney N: 20 (20%)	Liver N: 7 (%)	Lung N: 24 (%)	Combined N: 4 (%)[1]
Demographics						
Gender, Female	33 (47.1)	3 (20)	6 (30)	4 (57.1)	18 (75)	2 (50)
Age, mean years (range ± SD)	54.7 (14, 73±13.5)	60.7 (48, 69±6.8)	59.4 (22, 73±12.5)	54 (39, 69±10.4)	48.8 (14, 65±15.9)	45.1 (32, 56±9.7)
SOT Characteristics						
Transplant Center						
Center 1	2 (2.9)	0	2 (10)	0	0	0
Center 2	9 (12.9)	3 (20)	6 (30)	0	0	0
Center 3	2 (2.9)	0	0	0	0	2 (50)
Center 4	24 (34.2)	4 (26.7)	1 (5)	0	19 (79.2)	0
Center 5	1 (1.4)	0	1 (5)	0	0	0
Center 6	32 (45.7)	8 (53.3)	10 (50)	7 (100)	5 (20.8)	2 (50)
Donor Type						
Cadaveric	64 (91.4)	15 (100)	14 (70)	7 (100)	24 (100)	4 (100)
Living	6 (8.6)	0	6 (30)	0	0	0
Prior SOT	6 (8.6)	0	4 (20)	1 (14.3)	1 (4.2)	0
Induction IS	44 (62.9)	11 (73.3)	10 (50)	4 (57.1)	16 (66.7)	3 (75)
Thymoglobuline	13 (29.5)	9 (60)	1 (5)	0	1 (4.2)	2 (50)
Basiliximab	31 (70.5)	3 (20)	8 (40)	4 (57.1)	15 (62.5)	1 (25)
Maintenance IS[2]						
Cyclosporine	20 (28.6)	8 (53.3)	5 (25)	1 (14.3)	5 (20.8)	1 (25)
Tacrolimus	46 (65.7)	5 (33.3)	14 (70)	5 (71.4)	20 (83.3)	2 (50)
MMF	50 (71.4)	11 (73.3)	15 (75)	1 (14.3)	21 (87.5)	2 (50)
Steroids	68 (97.1)	14 (93.3)	19 (95)	7 (100)	24 (100)	4 (100)
Other[3]	6 (8.6)	1 (6.7)	2 (10)	1 (14.3)	2 (8.3)	0
CMV Serostatus						
D-/R-	10 (14.3)	1 (6.7)	2 (10)	0	7 (29.2)	0
R+	40 (57.1)	5 (33.3)	13 (65)	7 (100)	13 (54.2)	2 (50)
D+/R-	20 (28.6)	9 (60)	5 (25)	0	4 (16.6)	2 (50)

N : Number, SD : Standard Deviation, SOT : Solid Organ Transplant, IS : Immunosuppression, MMF : Mycophenolate Mofetil, CMV : Cytomegalovirus, D : Donor, R : Recipient

[1] Combined transplants included: kidney-liver (N : 1) and kidney-pancreas (N : 3).
[2] Patients could have received more than one agent for maintenance immunosuppression (agents were not mutually exclusive).
[3] Other maintenance immunosuppression included : everolimus (N : 1) and azathioprine (N : 5).

Table 2. Characteristics of invasive aspergillosis infections.

Patient Characteristic	All patients N: 70 (%)	Heart N: 15 (%)	Kidney N: 20 (20%)	Liver N: 7 (%)	Lung N: 24 (%)	Combined N: 4 (%)[1]
Time to IA, Mean Days (Range; SD)	**203 (0-1502; 296)**	**75 (4-544; 141)**	**225 (24-799; 218)**	**174 (5-887; 303)**	**274 (0-1502; 391)**	**254 (20-618; 254)**
Certainty of diagnosis						
Proven	30 (42.9)	8 (53.3)	11 (55)	4 (57.1)	6 (25)	1 (25)
Probable	40 (57.1)	7 (46.7)	9 (45)	3 (42.9)	18 (75)	3 (75)
Site of infection						
1 Site only	57 (81.4)	12 (80)	17 (85)	3 (42.9)	22 (91.7)	3 (75)
>1 Sites	13 (18.6)	3 (20)	3 (15)	4 (57.1)	2 (8.3)	1 (25)
LRT Infection	64 (91.4)	15 (100)	17 (85)	6 (100)	22 (91.7)	4 (100)
CNS Infection	7 (10)	0	4 (20)	3 (42.9)	0	0
Other[2]	15 (21.4)	3 (20)	4 (20)	4 (57.1)	3 (12.5)	1 (25)
Histopathology, Performed	46 (65.7)	10 (66.7)	16 (80)	5 (57.1)	13 (54.2)	2 (50)
Positive[3]	30 (65.2)	8 (80)	11 (68.7))	4 (80)	6 (46.2)	1 (50)
Culture, Any						
Positive	59 (84.3)	10 (66.7)	18 (90)	7 (100)	21 (87.5)	3 (75)
Negative	11 (15.7)	5 (33.3)	2 (10)	0	3 (12.5)	1 (25)
Culture, BAL, Performed	58 (82.9)	10 (66.7)	18 (90)	5 (57.1)	22 (91.7)	3 (75)
Positive[3]	41 (70.7)	7 (70)	12 (66.7)	4 (80)	17 (77.3)	1 (33.3)
Microscopy, BAL, Performed	57 (81.4)	10 (66.7)	18 (90)	5 (57.1)	21 (87.5)	3 (75)
Positive[3]	28 (49.1)	5 (50)	8 (44.4)	4 (80)	10 (47.6)	2 (66.7)
GM-EIA, Blood, Performed	43 (61.4)	10 (66.7)	17 (85)	6 (85.7)	7 (29.2)	3 (75)
Positive, Blood[3]	15 (34.9)	3 (30)	7 (41.2)	2 (33.3)	2 (28.6)	1 (33.3)
GM-EIA, BAL, Performed	23 (32.9)	2 (13.3)	7 (35)	1 (14.3)	11 (45.8)	2 (50)
Positive, BAL[3]	9 (39.1)	2 (100)	1 (16.7)	1 (100)	4 (66.7)	1 (100)
Radiology						
Chest CT, Performed[4]	63 (90)	13 (86.7)	19 (95)	7 (100)	20 (83.3)	4 (100)
Nodular Lesions[3]	26 (41.3)	6 (46.1)	8 (42.1)	1 (14.3)	10 (50)	1 (25)
Halo Sign[3]	5 (7.9)	1 (7.7)	2 (10.5)	0	2 (10)	0
Cavitary / Necrotic Lesion[3]	14 (22.2)	1 (7.7)	7 (36.8)	1 (14.3)	4 (20)	1 (25)
Ground Glass Opacities[3]	17 (27)	1 (7.7)	8 (42.1)	0	7 (35)	1 (25)
Non-Specific Infiltrates[3]	23 (36.5)	4 (30.8)	11 (57.9)	2 (28.6)	4 (20)	2 (50)
Pleural Effusion[3]	33 (52.3)	9 (69.2)	9 (47.4)	4 (57.1)	11 (55)	0
Sinusitis[3]	7 (11.1)	1 (7.7)	1 (5.3)	2 (28.6)	3 (15)	0

N : Number, IA : Invasive Aspergillosis, SD : Standard Deviation, LRT : Lower Respiratory Tract, CNS : Central Nervous System, BAL : Bronchoalveolar lavage, GM-EIA : Galactomannan Enzyme Immunoassay, CT : Computed Tomography

[1] Combined transplants included: kidney-liver (N : 1) and kidney-pancreas (N : 3).

[2] Other included : bone and joint (N : 4), heart (N : 3), surgical site (N : 2), urinary tract (N : 2), gastro-intestinal tract (N : 2), Eye (N : 1) and Other (N : 1).

[3] Proportions of positive results were estimated using as a denominator the number of tests performed.

[4] Patients could have more than one radiographic finding.

Table 3. Risk factor analysis for invasive aspergillosis.

Variable	Univariate Analysis			Multivariable Analysis-I*			Multivariable Analysis-II*		
	OR	95%CI	*P*-Value	OR	95%CI	P	OR	95%CI	*P*-Value
Demographics									
Gender, Female	0.7	0.4, 1.2	0.23						
Age, mean years (range ± SD)	1.0	1.0, 1.05	0.006	1.0	0.9, 1.0	0.50	1.0	0.9, 1.0	0.29
Transplant Characteristics									
Donor type, Cadaveric vs. Living	0.8	0.3, 2.1	0.65						
Prior SOT	1.64	0.8, 3.5	0.21						
Induction IS	1.06	0.6, 1.8	0.83						
Cyclosporine	0.8	0.4, 1.4	0.42						
Tacrolimus	1.4	0.8, 2.4	0.26						
MMF	0.32	0.2, 0.6	0.001	0.43	0.2, 1.1	0.08	0.33	0.1, 0.8	0.02
Steroids	4.2	0.9, 18.2	0.06	3.3	0.5, 22.5	0.22	3.7	0.5, 24	0.18
Other maintenance IS[2]	3.3	1.2, 8.7	0.02	2.4	0.6, 8.9	0.20	1.5	0.4, 5.7	0.57
CMV Serostatus, D+R- vs. other	2.1	1.1, 4.1	0.02	3.1	1.3, 7.0	0.009	2.8	1.2, 6.4	0.01
Post-Transplant Complications									
Renal Insufficiency, Any	5.3	2.7, 10.3	<0.001	3.7	1.5, 8.6	0.003	2.9	1.2, 7.0	0.01
Mechanical Ventilation	NA								
Reoperation	10.0	4.6, 21.9	<0.001	5.4	2.1, 13.9	0.001	6.0	2.4, 15.2	<0.001
Rejection	2.8	1.6, 5.1	<0.001	1.4	0.6, 3.2	0.37	1.9	0.9, 4.2	0.009
Bacterial Infections, Any	4.5	2.4, 8.4	<0.001	2.6	1.2, 5.9	0.02	3.2	1.4, 7.1	0.005
Viral Infections, Any	5.8	3.2, 10.5	<0.001	5.7	2.7, 11.9	<0.001	ND		
CMV Infection	3.6	1.8, 6.9	<0.001	ND			2.1	0.9, 4.9	0.09
Respiratory Viral Infections	6.8	2.2, 20.8	0.001	ND			15.0	4.2, 53.5	<0.001

OR : Odds Ratio, CI : Confidence Intervals, SOT : Solid Organ Transplant, IS : Immunosuppression, MMF : Mycophenolate Mofetil, CMV : Cytomegalovirus, D : Donor, R : Recipient, NA: Not Applicable, ND : Not Done

* In multivariable analyses-I, CMV and respiratory viral infections were not included, due to potential interactions with the "viral infections, any" variable. Similarly, in multivariable analyses-II, the "viral infections, any" variable was replaced by CMV and respiratory viral infections.

[1] Combined transplants included: kidney-liver (N : 1) and kidney-pancreas (N : 3).

[2] Other IS included : everolimus (N : 1) and azathioprine (N : 5) in cases and everolimus (N : 9) and azathioprine (N : 3) in controls.

[3] Post-transplant complications were assessed within 3 months prior to the diagnosis of invasive aspergillosis for cases and the "fictitious date of infection" for the controls.

Table 4. Mortality predictor analysis among solid organ transplant recipients with invasive aspergillosis.

Variable	Univariate Analysis			Multivariable Analysis*		
	OR	95%CI	*P*-Value	OR	95%CI	*P*-Value
Demographics						
Gender, Female	1.7	0.5, 5.2	0.30			
Age, mean years (range ± SD)	1.07	1.0, 1.15	0.03	1.2	1.0, 1.5	0.02
Transplant Characteristics						
SOT Type, Liver vs. Other	31.8	3.4, 293	0.002	12.7	0.2, 743	0.22
Donor Type, Cadaveric vs. Living	1.8	0.3, 10.8	0.53			
Prior SOT	1.3	0.4, 4.5	0.63			
Induction IS	0.7	0.2, 2.2	0.54			
Cyclosporine	1.7	0.5, 5.6	0.37			
Tacrolimus	0.6	0.2, 1.8	0.37			
MMF	0.2	0.06, 0.6	0.008	0.3	0.3, 2.8	0.30
Steroids	ND					
Other[2]	1.8	0.4, 8.4	0.43			
CMV Serostatus, D+/R- vs. other	0.5	0.1, 2.0	0.34			
Post-Transplant Complications						
Renal Insufficiency, Any	4.3	1.3, 14.0	0.01	2.3	0.3, 18.4	0.43
Mechanical Ventilation	3.6	0.93, 14.1	0.06	7.6	0.6, 103	0.13
Reoperation	4.3	1.3, 14.0	0.01	1.5	0.2, 11.8	0.69
Rejection	4.4	1.3, 14.6	0.01	2.1	0.2, 23	0.54
Bacterial Infections, Any	2.4	0.7, 7.4	0.14			
Viral Infections, Any	3.5	0.9, 12.2	0.05	4.8	0.3, 75	0.27
CMV Infection	4.0	1.3, 13.0	0.02	ND		
Invasive Aspergillosis	NA					
Time to Diagnosis, Early vs. Late[4]	2.9	0.3, 31.8	0.38			
Site of Infection, >1 vs. 1	9.8	2.5, 37.6	0.001	36.1	1.6, 827	0.02
Certainty of Diagnosis, Proven vs. Probable	2.8	0.9, 8.9	0.08	0.4	0.06, 3.7	0.46
Galactomannan, Positive vs. Negative	2.4	0.7, 8.8	0.18			
Treatment, 1 vs. >1 Antifungal Agent	2.6	0.8, 8.0	0.10	3.7	0.3, 44	0.30
Surgical Intervention	0.6	0.1, 3.2	0.58			

OR : Odds Ratio, CI : Confidence Intervals, SOT : Solid Organ Transplant, IS : Immunosuppression, MMF : Mycophenolate Mofetil, ND : Not Donne , CMV : Cytomegalovirus, D : Donor, R : Recipient, NA : Not Applicable, ND: Not Done

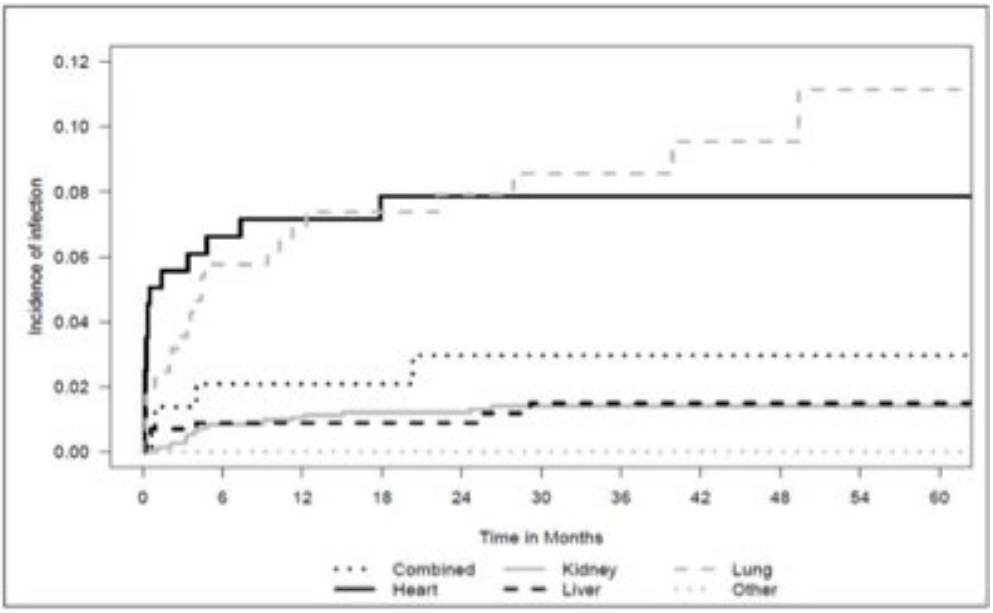
[1] Combined transplants included: kidney-liver (N:1) and kidney-pancreas (N:3).

[2] Other included : everolimus (N : 1) and azathioprine (N : 5) in cases and everolimus (N : 9) and azathioprine (N : 3) in controls.

[3] Post-transplant complications were assessed within 3 months prior to the diagnosis of invasive aspergillosis for cases and the "fictitious date of infection" for the controls.

[4] Early and late invasive aspergillosis were defined based on the time of diagnosis: <180 days – early, >180 days – late.

1a.



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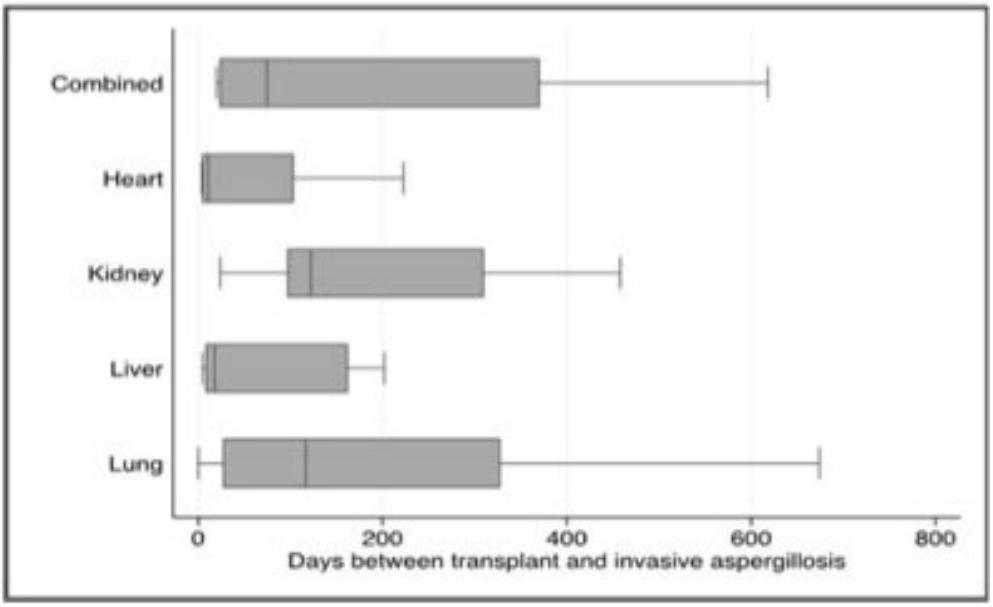

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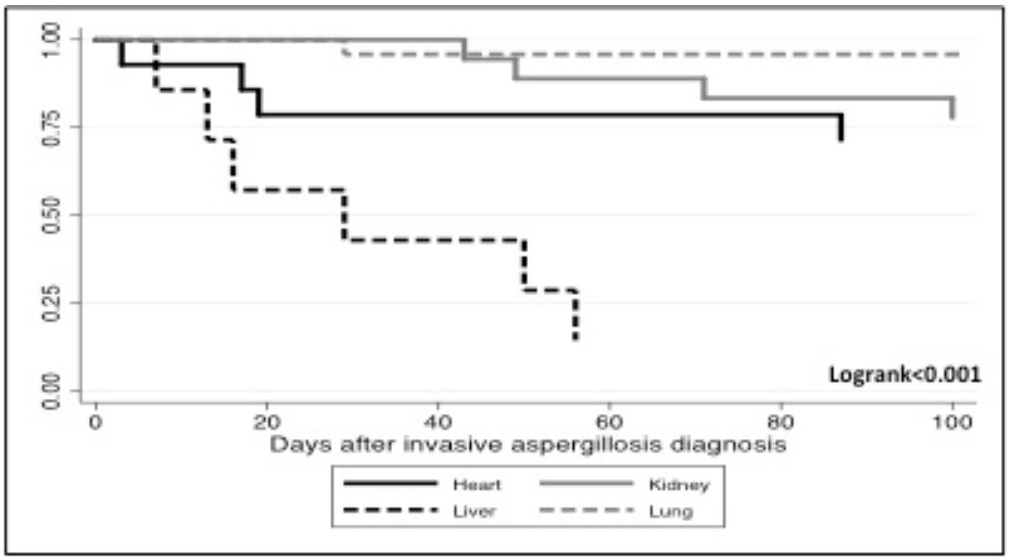

2b.