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Original article

Title page

Complete title: Multinational retrospective case-control study of risk factors for the development of late invasive pulmonary aspergillosis following kidney transplantation.

Running title: Late pulmonary aspergillosis in kidney transplantation

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Abstract (250 words)

Objectives: To assess the risk factors for the development of late-onset invasive pulmonary aspergillosis (IPA) after kidney transplantation (KT).

Methods: We performed a multinational case-control study that retrospectively recruited 112 KT recipients diagnosed with IPA between 2000 and 2013. Controls were matched (1:1 ratio) by center and date of transplantation. Immunosuppression-related events (IREs) included the occurrence of non-ventilator-associated pneumonia, tuberculosis, cytomegalovirus disease and/or *de novo* malignancy.

Results: We identified 61 cases of late (>180 days after transplantation) IPA from 24 participating centers (accounting for 54.5% [61/112] of all cases included in the overall study). Most diagnoses (54.1% [33/61]) were established within the first 36 post-transplant months, although 5 cases occurred more than 10 years after transplantation. Overall mortality among cases was 47.5% (29/61). Compared to controls, cases were significantly older (*P*-value = 0.010) and more likely to have pre-transplant chronic obstructive pulmonary disease (*P*-value = 0.001) and a diagnosis of bloodstream infection (*P*-value = 0.016) and IRE (*P*-value <0.001) within the 6 months prior to the onset of late IPA. After multivariate adjustment, previous occurrence of IRE (odds ratio: 19.26; 95% confidence interval: 2.07 - 179.46; *P*-value = 0.009) was identified as an independent risk factor for late IPA.

Conclusion: More than half of IPA cases after KT occur beyond the sixth month, with some of them presenting very late. Late IPA entails a poor prognosis. We identified some risk factors that could help the clinician to delimit the subgroup of KT recipients at the highest risk for late IPA.

Introduction

Invasive pulmonary aspergillosis (IPA) constitutes one of the most feared complications occurring in patients undergoing solid organ transplantation (SOT) in terms of both patient and graft survival [1-3]. Apart from local susceptibility associated with specific surgical procedures (e.g., ulcerative aspergillus tracheobronchitis at the bronchial anastomosis site after lung transplantation) [4], it is conventionally assumed that the lifelong use of immunosuppression to avoid graft rejection confers the most relevant risk for this event [5].

The intensity of the immunosuppressive therapy is usually higher during the first 6 months following SOT, and therefore this period has been traditionally considered as carrying the maximum risk for opportunistic infection including IPA [6]. Nevertheless, kidney transplant (KT) recipients require potent triple-drug regimens —often containing steroids, calcineurin inhibitors and antiproliferative agents— for indefinite time periods [7]. Although the relative risk of post-transplant IPA after KT is lower compared to other types of grafts [1,3,8], KT recipients suffer from the highest absolute disease burden due to the large number of procedures performed worldwide [9,10]. In addition, recent decades have witnessed a continuous improvement in long-term graft survival [11], thus increasing the population of aged KT recipients chronically exposed to a high degree of immunosuppression.

By using a multicenter case-control design, we have recently analyzed the risk factors for the occurrence of early IPA (i.e., diagnosed within the first 180 days) after KT [12]. Only one previous study has analyzed the predisposing conditions for the late forms of infection, although its results were limited by its single-center nature and by the inclusion of only 26 cases of late IPA [13].

Transplant physicians may benefit from identifying, among the increasing population of long-term KT recipients, that subgroup of patients at increased risk for late IPA in order to implement individualized follow-up and prevention strategies. Unfortunately, such an approach remains an unmet clinical need. To the best of our knowledge, this is the first study specifically aiming to ascertain the predisposing factors for the development of late IPA from a large representative population of KT recipients.

Materials and Methods

Study design

This is a sub-analysis of a multinational retrospective case-control study performed in 29 hospitals from 10 European (Spain, Switzerland [6 centers included in the Swiss Transplant Cohort Study [14]], Belgium, Portugal, France and United Kingdom) and American institutions (United States, Brazil, Mexico and Argentina). Participating centers included cases of IPA diagnosed in KT recipients between January 1, 2000 and December 31, 2013 [12,15]. In the present *a priori* designed sub-analysis we focused on late episodes of IPA, defined as those diagnosed beyond the first 180 days after transplantation ("IPA cases"). The "control group" was selected (in an 1:1 ratio) among those patients that underwent transplantation at the same center within a 3-month period before or after the calendar date of the corresponding case but without the diagnosis of IPA throughout the post-transplant period. In addition, controls must have survived at least until the time of diagnosis of IPA in the index case. To take into account the effect of post-transplant events on the occurrence of late IPA, controls were assigned a "pseudo-date of diagnosis" to match their cases with the aim of ensuring comparable risk exposure periods in both groups. The criteria used to establish the date of IPA diagnosis is available as **Supplementary Methods**. This research adhered to the STROBE guidelines for observational studies. The study protocol was approved by the local Ethics Committee of the coordinating center and of other participating sites as required.

Study definitions

IPA was defined according to the revised criteria proposed in 2008 by the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group (details provided as **Supplementary Methods**) [16]. It should be noted that we added a modified radiological criterion (beyond the classic dense, well-circumscribed lesions with or without halo sign or cavitation) based on the presence of certain lung patterns that have been specifically associated with post-transplant IPA (peribronchial consolidation or tree-in-bud pattern) [17]. Additional study definitions (including IPA-attributable mortality, cytomegalovirus [CMV] disease, tuberculosis, pneumonia, respiratory tract viral infection, bloodstream infection [BSI] or post-transplant lymphoproliferative disorder [PTLD]) are available in **Supplementary Methods**.

To encompass the different post-transplant complications that may be attributable to over-immunosuppression we constructed a composite variable (termed “immunosuppression-related event” [IRE]) that included the occurrence of any of the following: non-ventilator-associated pneumonia, tuberculosis, CMV disease and/or post-transplant *de novo* malignancy (both PTLD and solid organ tumors). Community-acquired pneumonia has been previously recognized to be more frequent among SOT recipients due to immunosuppression [18] and therefore pneumococcal vaccination is strongly recommended for this population [19]. We did not consider within the definition of IRE certain post-transplant infections (such as BSI or ventilator-associated pneumonia) that may be arguably attributable to invasive procedures, instrumentation (i.e., indwelling catheters) or anatomical abnormalities rather than to the recipient’s immune status.

Statistical analysis

Continuous variables were summarized by the mean ± standard deviation (SD) or the median with interquartile ranges (IQR), while categorical variables were summarized using absolute counts and percentages. Categorical variables were compared using the McNemar test, whereas the Student's t-test for repeated measures or the Wilcoxon signed-ranks test were applied for continuous variables. Conditional logistic regression was used to identify independent risk factors for the development of late IPA. Those variables found to be significant (*P*-value ≤0.1) at the univariate level were included into the multivariable models in a backward stepwise fashion. Collinearity among explanatory variables was assessed by means of the variance inflation factor (VIF), with VIF values over 3 suggesting significant collinearity. Results are given as odds ratios (ORs) with 95% confidence intervals (CIs). As a secondary outcome, we compared patient survival from the date (for cases) or the “pseudodate” (for controls) of IPA diagnosis. Survival curves were plotted by the Kaplan-Meier method and differences between groups were compared with the log-rank test. All the significance tests were two-tailed. Statistical analysis was performed with SPSS version 20.0 (IBM Corp., Armonk, NY) and graphics were generated with Prism v. 6.0 (GraphPad Software Inc., La Jolla, CA).

Results

We included 61 cases of late IPA (14/61 [23.0%] proven and 47/61 [77.0%] probable) and their corresponding controls from 24 out of 29 participating centers (i.e., 5 centers did not contribute to the present sub-analysis). This figure accounts for 54.5% (61/112) of all the cases enrolled in the overall study. Twenty-nine out of 61 cases (47.5%) were diagnosed between 2010 and 2013. The median time interval between transplantation and diagnosis was 34.4 months (IQR: 11.8 - 78.5). Most diagnoses (54.1% [33/61]) were established within the first 36 months, although this period spanned more than 27 years (with 5 very late-onset cases occurring after the tenth year) (**Figure 1**). The median follow-up from the date (for cases) or the “pseudo-date” of diagnosis (for controls) was 476 days (IQR: 70.0 - 1298.5). Overall and IPA-attributable mortality among IPA cases was 47.5% (29/61) and 21.3% (13/61) and occurred at a median of 53.5 days (IQR: 14.5 - 171.5) and 15 days (IQR: 7.3 - 33.3), respectively, from diagnosis. There were no significant differences in one-year survival rates between cases occurring in months 6 to 36 or >36 months after transplantation (55.0% versus 41.0%, respectively; log-rank test *P*-value = 0.619). Among survivors, 9.4% (3/32) patients experienced definitive graft failure requiring return to permanent dialysis. None of the patients in the control group died during the follow-up. One-year survival was significantly lower among cases than controls (49.0% versus 100.0%; log-rank test *P*-value = 0.021).

The demographics and pre-transplant factors of patients who developed late IPA and their controls are compared in **Table 1**. Cases were significantly older (54.6 ± 14.2 versus 48.6 ± 15.5 years; *P*-value = 0.010) and more likely to have pre-transplant chronic obstructive pulmonary disease (COPD) (18.0% [11/61] versus 0.0% [0/61]; *P*-value = 0.001) than control counterparts. The prevalence of underlying diabetic nephropathy as a reason for end-stage renal disease requiring transplantation was also higher among cases, although not achieving statistical significance (19.7% [12/61] versus 6.6% [4/61]; *P*-value = 0.077).

Donor- and transplant-related and post-transplant variables are compared in **Table 2**. Cases were more likely to have been diagnosed with an IRE during the 6 months prior to the onset of IPA (34.4% [21/61] versus 3.3% [2/61]; *P*-value <0.001), with significant (for non-ventilator-associated pneumonia and CMV disease) or near significant differences (for post-transplant *de novo* malignancy) observed for each of the different individual events included in this composite variable. PTLD was the predominant type of malignancy diagnosed. A prior occurrence of BSI was also more common among cases than controls (11.5% [7/61] versus 0.0% [0/61]; *P*-value = 0.016). No significant differences were observed between the groups regarding the prior occurrence of acute graft rejection or the requirement of steroid boluses. None of these episodes were treated with lymphocyte-depleting agents as anti-rejection therapy, and only one of them (in the control group) received rituximab.

Finally, age at transplantation, pre-transplant COPD, underlying diabetic nephropathy, and the diagnosis of an IRE or BSI within the preceding 6 months were entered into the conditional logistic regression model (**Table 3**). Linear regression analysis showed no significant collinearity among these explanatory variables, with all VIF values <1.5 (data not shown). After multivariate adjustment, prior diagnosis of IRE (OR: 19.26; 95% CI: 2.07 - 179.46; *P*-value = 0.009) was identified as the only independent risk factor associated with late IPA.

Discussion

To our knowledge, our multinational retrospective case-control study represents the largest effort to date to explore the clinical outcome of and risk factors for IPA in the specific population of KT recipients. Our experience highlights the poor prognosis conferred by the late forms of this opportunistic infection, since more than half of the included patients had died at a median time of less than two months from diagnosis. In addition, IPA-attributable mortality was assumed in more than 20% of cases. Notwithstanding such an ominous picture, in our previous study we reported even worse figures for early IPA (first 180 days), with global and attributable mortality of 60.8% and 45.1%, respectively [12]. We hypothesize that this difference may be explained by the relatively more intensive immunosuppression among patients in their first post-transplant months [15].

Remarkably, although most of the episodes of late IPA occurred within the first three years, almost 10% of them were diagnosed across a large time period covering more than a decade after transplantation, including some very late onset episodes occurring more than ten years post-transplantation. In a previous series of IPA among KT recipients [13], 43% of the 41 cases were diagnosed beyond the sixth month, and 6 (14%) beyond the fifth year post-transplantation. These concordant results reinforce the previously stated concept [20] that the period at risk for severe opportunistic infection continues far beyond the classical time scheme proposed for SOT recipients.

Despite the wide range of time between KT and the onset of late IPA, we were still able to identify some factors associated to this event. Cases were more likely to have been diagnosed with COPD, although such association only showed borderline univariate significance. The presence of pre-transplant COPD may reflect underlying injury to the lung parenchyma [12,21] or act as a surrogate marker for prolonged corticosteroid exposure. BSI during the six preceding months was also more frequent among cases. Comparable associations have been previously reported for the overall SOT population [8] or, specifically, KT recipients [12]. The occurrence of BSI may identify patients commonly suffering from invasive procedures, impaired graft function and antibiotic therapy exposure, which overall reflect increased patient frailty.

Following the example of previous studies [22], we created a composite variable (IRE) that summarized post-transplant complications —such as severe non-device-associated infections, CMV disease or *de novo* cancer— that are consistently assumed to indicate an excess of immunosuppression. In the regression model this condition displayed a significant association with the development of IPA during the following six months. Other authors have also reported the observation of episodes of pneumonia preceding the onset of IPA [23,24]. On the other hand, the deleterious impact exerted by CMV on the risk of IPA has been well established for the SOT recipient [8,25,26]. In accordance with this rationale, the incidence of CMV disease in our experience was ten times higher among cases than controls (16.4% versus 1.6%, respectively). In a similar way, a recent diagnosis of *de novo* cancer (either PTLD or solid organ tumor) had been made in almost one out of every ten cases as compared to none of the controls. In a French nationwide epidemiological study, both hematologic and solid organ malignancies have been described as an important risk factor for invasive aspergillosis [3]. In addition to the direct deleterious effect of the oncologic therapies (B-cell-depleting agents such as rituximab or cytotoxic chemotherapy) on the host's response and infection susceptibility, the function of natural killer cells (which significantly contribute to the protective immunity against fungi [27]) has been shown to be impaired in KT recipients with post-transplant cancer [28].

The design of our study (case-control study) prevents us from estimating the actual incidence of late IPA among KT recipients that develop an episode of IRE. Case-control studies can generate plausible associations rather than demonstrate direct causality. In our opinion, such a circumstance and the heterogeneous distribution of IPA cases over a very long post-transplant period would make it unreasonable to propose the use of antifungal prophylaxis for those recipients fulfilling the characterized risk factors. Nevertheless, our findings do support the recommendation of maintaining a low threshold for suspicion of post-transplant IPA in patients with compatible respiratory symptoms and underlying COPD or recently diagnosed with a serious infection, CMV disease or post-transplant cancer. In addition, this clinical awareness should be maintained even for very long-term KT recipients, as IPA may occur many years after transplantation. In this context, we have previously shown the protean clinical features of IPA among KT recipients and the correlation between the timely initiation of antifungal therapy and the outcome [15].

Strengths of the present collaborative effort include its multicenter nature, the use of uniform diagnostic criteria, and the standardized collection of a large number of variables. However, some limitations must be acknowledged, such as its retrospective design and the relatively low sample size that may have limited statistical power. Therefore, confidence intervals for risk estimates were wide. Most IPA cases were categorized as “probable” rather than “proven” [16]. The protracted inclusion period imposes heterogeneity among participating centers in immunosuppression and standard of care. Nonetheless, the low incidence among KT recipients of late-onset IPA made this approach the only practical method to collect a meaningful number of cases. We lacked detailed data on certain relevant factors (such as the receipt of rituximab or cytotoxic chemotherapy among patients with PTLD). Finally, we were unable to estimate the incidence of late IPA due to the lack of denominator figures (i.e., number of transplant procedures performed at each center or number of at-risk recipients during the study period) since our research was conceived exclusively to ascertain the risk factors for developing such condition. Thus, we chose a case-control design instead than other approaches (i.e., nested case-control study within a multicenter cohort).

In conclusion, late IPA may develop among KT recipients even more than 10 years after transplantation and entails a very poor prognosis. The preceding diagnosis of post-transplant adverse events reflecting an excess of immunosuppression, such as serious or opportunistic infection or *de novo* malignancy, may be useful to identify those patients at the highest risk for this complication.

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- ***Authors´ contribution:*** FLM designed the study; FLM and MFR analyzed data and wrote the manuscript; FLM, MFR, JTS and JMA coordinated the study. FLM, JTS, PLC, CvD, EM, MJPS, MM, JC, MAM, CC, LS, NS, AS, EC, LCV, PLMM, OL, ER, APL, MA, TL, MD, CGR, FHP, JF, MN, OM, JRPP, MM, AV, BSS, AM, JP, JPH, TL, AM, JC, MB, DH, EAHM, MCF and MPC collected data and critically reviewed the final version of the manuscript.
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467 **Tables**

468 **Table 1.** Comparison of demographics and pre-transplant variables between KT recipients with
469 and without late IPA.

Variable	Late IPA group (n = 61)	Control group (n = 61)	*P*-value[a]
Age, years [mean ± SD]	54.6 ± 14.2	48.6 ± 15.5	**0.010**
Gender (male) [n (%)]	33 (54.1)	38 (62.3)	0.458
Pre-transplant conditions [n (%)]			
Diabetes mellitus	18 (29.5)	9 (14.7)	0.093
Chronic obstructive pulmonary disease	11 (18.0)	0 (0.0)	**0.001**
Pre-transplant corticosteroid therapy [n (%)][b]	6 (10.3)	5 (8.8)	0.754
BMI at transplantation, Kg/m^2 [mean ± SD][c]	24.3 ± 3.6	26.7 ± 7.3	0.074
Previous kidney transplantation [n (%)]	7 (11.5)	8 (13.1)	1.000
Underlying end-stage renal disease [n (%)]			
Glomerulonephritis	14 (23.0)	14 (23.0)	1.000
Diabetic nephropathy	12 (19.7)	4 (6.6)	0.077
Nephroangiosclerosis	8 (13.1)	8 (13.1)	1.000
Polycystic kidney disease	8 (13.1)	11 (18.0)	0.824
Chronic interstitial nephropathy	3 (4.9)	3 (4.9)	1.000
Congenital nephropathy	2 (3.3)	3 (4.9)	1.000
Lupus nephropathy	1 (1.6)	1 (1.6)	1.000
Reflux nephropathy	0 (0.0)	1 (1.6)	1.000
Unknown	6 (9.8)	9 (14.8)	0.388
Other	7 (11.5)	7 (11.5)	0.549
Pre-transplant positive serostatus [n (%)]			
Hepatitis C virus	6 (9.8)	1 (1.6)	0.125
Hepatitis B virus (surface antigen)	2 (3.3)	4 (6.6)	0.625
Epstein-Barr virus (anti-EBNA)[d]	49 (87.5)	47 (83.9)	0.754
CMV[e]	45 (73.8)	45 (75.0)	1.000
Pre-transplant maintenance dialysis [n (%)]	55 (90.2)	54 (88.5)	1.000
Duration, months [median (IQR)]	23 (15 - 41)	19.5 (12 - 45.8)	1.000

CMV: cytomegalovirus; EBNA: Epstein-Barr virus nuclear antigen; HBc: hepatitis B core antigen; ICU: intensive care unit; IPA: invasive pulmonary aspergillosis; IQR: interquartile range; SD: standard deviation.

[a] Significant *P*-values (<0.05) are expressed in bold.

[b] Data available for 58 cases and 57 controls.

[c] Data available for 43 cases and 43 controls.

[d] Data available for 56 cases and 56 controls.

[e] Data available for 61 cases and 60 controls.

Table 2. Comparison of donor- and transplant-related factors, post-transplant events and outcomes.

Variable	**Late IPA group** (n = 61)	**Control group** (n = 61)	*P*-value[a]
Age of donor, years [mean ± SD]	49.8 ± 16.3	46.8 ± 13.5	0.283
Living donor [n (%)]	12 (19.7)	12 (19.7)	1.000
Double kidney transplantation [n (%)]	3 (4.9)	0 (0.0)	0.250
Induction therapy [n (%)][b]			
None	22 (36.7)	20 (33.9)	1.000
Anti-CD25 (basiliximab or daclizumab)	22 (36.7)	20 (33.9)	0.815
Anti-thymocyte globulin	16 (26.7)	19 (32.2)	0.648
Primary immunosuppression regimen including [n (%)][b]			
Steroids	54 (88.5)	57 (93.4)	0.375
Tacrolimus	29 (48.3)	30 (50.8)	1.000
Cyclosporine	19 (31.7)	20 (33.9)	1.000
MMF / MPA	47 (78.3)	50 (84.7)	0.375
Azathioprine	5 (8.5)	7 (11.9)	0.375
mTOR inhibitor	6 (10.0)	2 (3.4)	0.219
Length of hospital admission for transplantation, days [median (IQR)]	12 (8 - 18.8)	11 (6.3 - 18.8)	0.314
Delayed graft function [n (%)]	13 (21.3)	8 (13.1)	0.388
Surgical reintervention [n (%)][c]	6 (10.2)	2 (3.7)	0.687
eGFR at month 3 after transplantation, mL/min/1.72 m^2 [mean ± SD][d]	23.8 ± 3.2	25.6 ± 3.4	0.873
eGFR at month 6 after transplantation, mL/min/1.72 m^2 [mean ± SD][e]	22.9 ± 3.1	20.5 ± 2.8	0.159
Leukopenia (<3.0 x 10^9 cells/L) [n (%)][f,g]	10 (16.9)	6 (10.2)	0.388
Neutropenia (<1.5 x 10^9 cells/L) [n (%)][f,h]	6 (12.2)	3 (6.2)	0.687
Serum IgG levels, mg/dL [mean ± SD][i]	879 ± 627	763 ± 571	0.750
Post-transplant events within the previous 6 months [n (%)][j]			
IRE[k,l]	21 (34.4)	2 (3.3)	**0.000**
CMV disease	10 (16.4)	1 (1.6)	**0.004**
Non ventilator-associated pneumonia	9 (14.8)	1 (1.6)	**0.021**
De novo malignancy[m]	5 (8.2)	0 (0.0)	0.063
Laboratory-confirmed respiratory tract viral infection[n]	5 (8.2)	0 (0.0)	0.063
Bloodstream infection[o]	7 (11.5)	0 (0.0)	**0.016**
ICU admission for ≥72 hours	2 (3.3)	0 (0.0)	0.500
Acute graft rejection	4 (6.6)	5 (8.2)	1.000
Episode treated with steroid boluses	4 (4.9)	5 (8.2)	0.687
Overall mortality [n (%)]	29 (47.5)	0 (0.0)	0.001

IPA-attributable mortality [n (%)]	13 (21.3)	-	NA

CMV: cytomegalovirus; eGFR: estimated glomerular filtration rate; ICU: intensive care unit; IgG: immunoglobulin G; IPA: invasive pulmonary aspergillosis; IQR: interquartile range; IRE: immunosuppression-related event; MMF / MPA: mofetil mycophenolate / mycophenolate acid; mTOR: mammalian target of rapamycin; NA: not applicable; SD: standard deviation.

[a] Significant *P*-values (<0.05) are expressed in bold.

[b] Data available for 60 cases and 59 controls.

[c] Data available for 59 cases and 54 controls.

[d] Data available for 56 cases and 56 controls.

[e] Data available for 54 cases and 54 controls.

[f] At any point during the first 6 months after transplantation.

[g] Data available for 59 cases and 59 controls.

[h] Data available for 49 cases and 48 controls.

[i] Serum IgG levels measured within the 6-month period prior to or following the date of diagnosis of IPA (for cases) or the analogous "pseudo-date" of diagnosis (for controls). Data available for 10 cases and 4 controls.

[j] Events occurring within the 6-month period prior to the date or the "pseudo-date" of diagnosis of IPA.

[k] The total number of IREs may be less than the sum of each conditions since more than one event was consecutively present in some patients.

[l] There were 3 cases of post-transplant tuberculosis, although none of them occurred within the 6-month period prior to the date or the "pseudo-date" of diagnosis of IPA.

[m] Includes PTLD (3 cases), colorectal adenocarcinoma and metastatic adenocarcinoma of unknown primary origin (one case each).

[n] Includes influenza virus infection (4 cases).

[o] Includes BSI due Enterobacteriaceae (3 cases), *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *S. aureus* and *Candida albicans* (one case each).

Table 3. Uni- and multivariable analyses (conditional logistic regression) of risk factors predicting the occurrence of late IPA.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age at transplantation, years[a]	1.04	1.01 - 1.08	0.017	-	-	-
Diabetic nephropathy	3.00	0.97 - 9.30	0.057	-	-	-
Pre-transplant COPD	65.29	0.51 - 8324.28	0.091	-	-	-
Prior IRE[b,c]	20.00	2.68 - 149.02	0.003	19.26	2.07 - 179.46	0.009
Prior BSI[b]	7.00	0.86 - 56.89	0.069	-	-	-

BSI: bloodstream infection; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IPA: invasive pulmonary aspergillosis; IRE: immunosuppression-related event; OR: odds ratio.

[a] OR per unitary increment.

[b] Events occurring within the 6 months previous to the date of diagnosis of IPA for cases or the analogous “pseudo-date of diagnosis” for corresponding controls.

[c] Includes non-ventilator-associated pneumonia, CMV disease and post-transplant *de novo* malignancy.

Figure legend

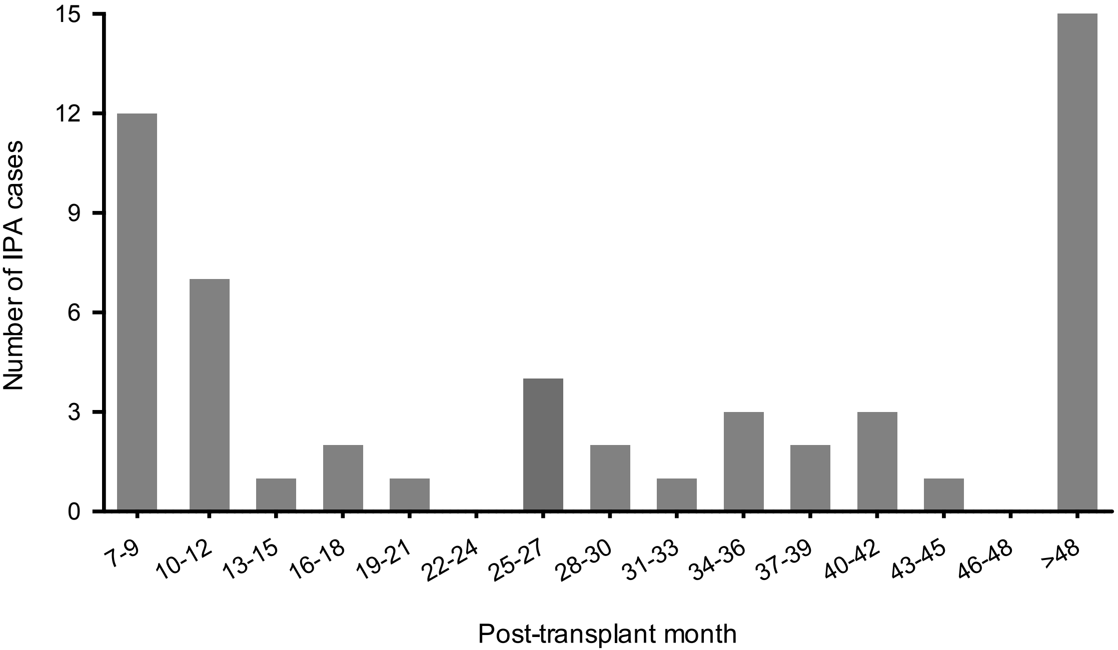
- **Figure 1.** Temporal distribution of cases of late invasive pulmonary aspergillosis occurring according to post-transplant month of diagnosis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

- **Supplementary Materials and Methods:** Definitions used for date of IPA diagnosis, IPA-attributable diagnosis, CMV disease, tuberculosis, pneumonia, respiratory tract viral infection, BSI, PTLD, delayed graft function, acute graft rejection and eGFR.

Figure 1.


15
12
9
6
3
0
Number of IPA cases
7-9
10-12
13-15
16-18
19-21
22-24
25-27
28-30
31-33
34-36
37-39
40-42
43-45
46-48
>48
Post-transplant month