European Journal of Clinical Microbiology & Infectious Diseases (2020) 39:1543–1550
https://doi.org/10.1007/s10096-020-03871-2

ORIGINAL ARTICLE

Risk factors for development and mortality of invasive pulmonary Aspergillosis in kidney transplantation recipients

Hyeri Seok[1,2] · Kyungmin Huh[1] · Sun Young Cho[1] · Cheol-In Kang[1] · Doo Ryeon Chung[1] · Woo Seong Huh[3] · Jae Berm Park[4] · Kyong Ran Peck[1]

Received: 25 January 2020 / Accepted: 18 March 2020 / Published online: 11 April 2020

Abstract

Invasive pulmonary aspergillosis (IPA) is a high mortality opportunistic infection among kidney transplant recipients. This study assessed the risk factors and outcomes of IPA after KT. A retrospective study was conducted at a tertiary-care referral hospital in Korea. Electronic medical records of patients diagnosed with IPA after KT between February 1995 and March 2015 were reviewed. The control patients comprised two patients who received KT before and after each IPA case. Twenty-six cases were diagnosed with IPA among 1963 recipients at a median of 58 years old. The most common cause of end-stage renal disease was diabetic nephropathy. The median time to diagnosis was 161 days. Delayed graft function was associated with the development of IPA. The overall 12-week mortality rate of IPA was 57.5%. Serum GM level ≥ 2 and BAL GM level ≥ 5 were associated with 12-week mortality in the Kaplan-Meier survival analyses. Approximately half of IPA in KT recipients developed during the late posttransplant period (> 6 months), especially after treatment for acute rejection. Careful monitoring for IPA is required in patients with delayed graft function, DM, and who received rejection therapy. Higher serum and BAL GM were associated with 12-week mortality.

Keywords Invasive pulmonary aspergillosis · Kidney transplantation · Risk factor · Mortality

Introduction

Invasive pulmonary aspergillosis (IPA) is a life-threatening opportunistic infection in immunocompromised patients including solid organ transplant (SOT) recipients [1]. The number of SOT recipients is increasing annually with advances in transplant medicine [2]. The incidence of invasive fungal disease (IFD) after SOT is typically 1–2%, although occasionally as high as 10%, and that of invasive aspergillosis, the second most common IFD after SOT transplantation is 14–65% among all IFDs [3–8]. Kidney transplantation (KT) is the most frequently performed SOT worldwide. The incidence of IFD after KT is 1–10% [1, 3, 7, 8]. Because the incidence of IPA is low in KT recipients compared with that in other types of SOT [9–11], the risk factors for IPA in KT recipients are rarely studied [12–14]. Although epidemiologic data on invasive fungal infections in SOT recipients have shown geographical variations, regional studies have not been published in Asia. Therefore, this study assessed the risk factors for the development of IPA and mortality of patients with IPA after KT.

✉ Kyong Ran Peck
krpeck@skku.edu

[1] Division of Infectious Diseases, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06531, Republic of Korea

[2] Division of Infectious Diseases, Department of Medicine, Korea University Ansan Hospital, Korea University Medicine, Ansan-si, Gyeonggi-do, Republic of Korea

[3] Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

[4] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Materials and methods

Setting and patients

This retrospective case-control study was conducted at the Samsung Medical Center (SMC). SMC, one of the largest tertiary hospitals in Korea, performs approximately 100 KT per year. Data of all patients who underwent renal

transplantation between February 1995 and March 2015 were reviewed. Patients with IPA after kidney transplant were selected by reviewing electronic medical records, laboratory results including cultures, *Aspergillus* galactomannan (GM) antigen tests, radiologic data, and antifungal therapy. The control group comprised patients who underwent KT just before and after each IPA case.

Immunosuppression and prophylactic methods

Intravenous methylprednisolone (500 mg) was administered during the operation and tapered over 7 days. Antithymocyte globulin (ATG) was administered as induction therapy at 1.5 mg/kg for 5–7 days when one of the following conditions was satisfied: re-KT, panel reactive antibody (PRA) > 30%, donor-specific antibody positivity, and creatinine > 2.0 mg/dL in the deceased donor. Basiliximab, an anti-interleukin 2 receptor antibody, replaced the induction agent on the day of operation and on postoperative day (POD) 4 for some recipients since 2004. KT recipients received a triple immunosuppressive regimen including a calcineurin inhibitor (tacrolimus or cyclosporine), antimetabolites, and corticosteroids. Mycophenolate mofetil (MMF) has replaced azathioprine as an antimetabolite since 2001. Every acute rejection after KT was diagnosed according to the results of kidney biopsy. Steroid pulse therapy or ATG was administered in all cases of cellular rejection. Immunoglobulin and plasmapheresis were combined for humoral rejection.

Trimethoprim/sulfamethoxazole was administered as one tablet daily for 6 months after KT. No systemic antifungal agent was used for antifungal prophylaxis. Prophylactic ganciclovir treatment was administered in CMV seronegative recipients from seropositive donors or for ATG induction. The CMV antigenemia titers were checked biweekly within 3 months after KT and thereafter when CMV infection was suspected. Preemptive ganciclovir therapy has been administered since 2000 in cases with CMV antigenemia titers ≥ 50/4×10^5 leukocytes.

Definitions

The definition of IPA was based on that from 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 [15]. Proven IPA was defined as the presence of *Aspergillus* on microscopic findings or positive culture from sterile specimens. Probable IPA was defined on the basis of host factors, clinical criteria, and mycological evidence. Data related to respiratory symptoms and signs, chest radiography, chest computed tomography, and/or sputum fungus culture were obtained in all cases. IPA was reclassified as early IPA (within 6 months after KT) or late IPA (after 6 months). Mycological evidence was supported by positive cultures of respiratory specimens or biomarkers (i.e., serum and bronchoalveolar lavage (BAL) GM test). From July 2006, Aspergillus GM enzyme immunoassays were performed on serum and BAL samples. The peak serum GM titers before antifungal therapy and BAL GM titers when bronchoscopy was performed were checked. GM indexes above 0.5 in any specimens were defined as positive. Possible IPA was excluded in this study.

Data collection and statistical analyses

Medical records were reviewed retrospectively for demographic data, underlying diseases, types of kidney transplant donors, and renal replacement therapy status before KT. Immunologic factors such as total numbers of human leukocyte antigen (HLA) mismatch, ABO incompatibility, CMV serostatus of donors and recipients, and induction and maintenance immunosuppressive regimens were checked. Acute rejection within 3 months before IPA and delayed graft function after KT were checked, and delayed graft function was defined as the use of dialysis within 7 days of the transplant [16]. Microbiological data covered all available cultures and pathologic findings as well as laboratory results. Twelve-week mortality was used as the outcome factor. Graft loss was checked among the surviving cases at 12 weeks after IPA diagnosis. Graft loss was defined as graft nephrectomy or loss of transplanted kidney function requiring renal replacement therapy, without achieving graft function thereafter.

Continuous data were described as means ± standard deviation for normally distributed data and as medians and interquartile range (IQR) for skewed data. Pearson χ^2 and Fisher's exact tests were used for categorical variables and Student's *t*- and Mann–Whitney *U* tests for continuous variables when comparing two groups. Multiple logistic regression analysis was used to identify the risk factors for IPA. Cox proportional hazards regression analysis and Kaplan–Meier curves were used to identify the associations between 12-week mortality and potential confounding factors. We included all variables associated with the dependent variable on bivariable analysis ($p < 0.1$) and pre-defined variables such as the use of lymphocyte-depleting antibody that made clinical sense. All analyses were two-tailed, and p values < 0.05 were considered statistically significant, and Bonferroni correction for multiple testing was done.

Results

Demographic and clinical characteristics

Twenty-six patients were diagnosed with probable IPA among 1963 KT recipients. There were no cases of proven IPA. The

incidence rate was 1.3%. The median age was 58 years old, and half of the patients were male. Eight patients (30.8%) underwent KT for diabetes mellitus (DM)-end-stage renal disease (ESRD), which was the most common cause of ESRD in the case group. Seventeen (65.4%) patients received kidneys from deceased donors. Twelve patients were diagnosed with acute rejection before the development of IPA. The median duration between acute rejection and IPA was 68 days. Other baseline characteristics are shown in Table 1.

The median time to IPA diagnosis was 161 days (IQR, 32–697 days). The onset of IPA after KT could not be specified in a specific period, which was shown in Fig. 1. Five patients were diagnosed with IPA within 1 month, and three patients were diagnosed 5 years after KT. The characteristics of early ($n = 14$) and late IPA ($n = 12$) patients are shown in Table 2. Immunologic factors including donor type, HLA-mismatch, ABO incompatibility, leukopenia, and CMV serostatus did not differ between the two groups. There were more patients with DM and those administered ATG in the early IPA group. Acute rejection events, leukopenia, and those administered basiliximab were more frequent in the late IPA group.

Serum GM levels were measured in 23 patients, with a median value of 0.71 optical densities (IQR, 0.45–4.05). BAL GM levels were measured in 11 patients, with a median value of 5.33 ODs (IQR, 1.59–6.7). The minimum value of BAL GM was 0.42 OD, and 9 patients exceeded 1.0 ODs. The median serum and BAL GM values were higher in the early IPA group than those in the late group; however, the differences were not statistically significant. *Aspergillus* spp. were isolated from respiratory specimens in nine patients; 7 were *A. fumigatus*, and *A. terreus*, *A. niger*, and *A. flavus* were also isolated. *A. fumigatus* and *A. niger* were isolated from one patient.

Risk factors for the development of IPA

Older age (odds ratio 1.07, 95% confidence interval 1.02–1.13, $P = 0.006$), DM (OR 4.03, 95% CI 1.37–11.91, $P = 0.012$), delayed graft function (OR 12.14, 95% CI 1.34–110.29, $P = 0.027$), and acute rejection (OR 1.98, 95% CI 1.13–3.51, $P = 0.020$) were associated with the development of IPA in univariate analysis (Table 3). ATG use, RRT before KT, duration of RRT, donor type, seropositive donor or recipient, and HLA mismatch were not related to the incidence of IPA. In multivariate analysis, delayed graft function (OR 10.60, 95% CI 1.05–106.84, $P = 0.045$) was associated with the development of IPA. In subgroup analyses according to the time to IPA diagnosis, DM (OR 6.57, 95% CI 1.26–34.26, $P = 0.026$) was associated with the development of early IPA. In contrast, acute rejection (OR 15.00, 95% CI 2.77–81.38, $P = 0.002$) was associated with late IPA.

The development of IPA among DM patients was significantly higher than that of non-DM patients in overall KT recipients (3.0% vs. 0.8%, $P = 0.003$). The incidence of IPA was higher in patients with delayed graft function than that in patients without delayed graft function (3.5% vs. 1.0%, $P = 0.021$).

Outcomes of IPA after KT

Fifteen of the 26 patients died within 12 weeks after IPA diagnosis. Eleven deaths were attributed to the infection, followed by malignancy and cardiac death. The 12-week mortality rates of

Table 1 Demographic data and patient characteristics of invasive pulmonary aspergillosis (IPA) case, control groups, and all KT recipients

	Cases ($n = 26$)	Controls ($n = 52$)	All KT recipients ($n = 1963$)
Age, years	58 (54–62)	50 (38–56)	43 (33–51)
Male	13 (50%)	32 (61.5%)	1130 (57.6%)
RRT	22 (84.6%)	44 (84.6%)	1735 (88.4%)
Duration of RRT (days)	1366 (443–2268)	459 (34–1849)	752 (202–1907)
DDKT	17 (65.4%)	26 (50%)	726 (37.0%)
HLA-I mismatch	2.5 (1–3)	3 (2–3)	2 (1–3)
ABO incompatibility	6 (23.1%)	18 (34.6%)	409 (20.8%)
Diabetes mellitus	11 (42.3%)	8 (15.4%)	334 (17.0%)
CMV-seropositive recipient	26 (100%)	50 (96.2%)	1827 (93.1%)
CMV-seropositive donor	23 (88.5%)	51 (98.1%)	1801 (91.7%)
Delayed graft function	5 (19.2%)	1 (1.9%)	141 (7.2%)
Induction therapy	22 (84.6%)	44 (84.6%)	1220 (62.1%)
Antithymocyte globulin	11 (42.3%)	16 (30.8%)	540 (27.5%)
Any-lymphocyte depleting antibodies	22 (84.6%)	44 (84.6%)	834 (42.5%)
Acute rejection	12 (46.2%)	16 (30.8%)	618 (31.5%)

Data are expressed as number (%) of patients and as median (IQR)

HLA, human leukocyte antigen; *CMV*, cytomegalovirus; *DDKT*, deceased donor kidney transplants; *RRT*: renal replacement therapy

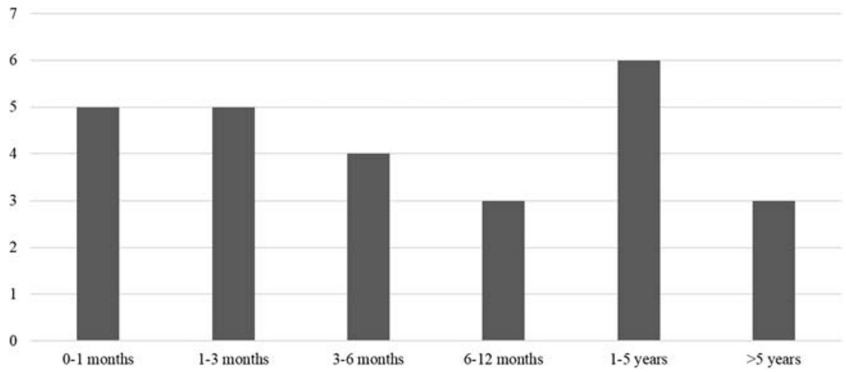

Fig. 1 Distribution of the time interval between kidney transplantation and diagnosis of invasive aspergillosis

early IPA were higher than those of late IPA (79% and 33%, $P > 0.05$). The median follow-up of surviving patients was 1893 days (IQR 590–2047 days). In Cox regression analysis, the only factor associated with 12-week mortality was the level of serum GM (HR 1.27, 95% CI 1.05–1.54, $P = 0.013$). Kaplan–Meier survival analyses were performed according to the variables including early or late IPA, serum, and BAL GM titer (Fig. 2). Serum GM ≥ 2 and BAL GM ≥ 5 were significantly associated with 12-week mortality. Three IPA patients had graft loss on days 10, 152, and 1135 after IPA diagnosis, respectively.

Table 2 Demographic data and patient characteristics of early and late invasive pulmonary aspergillosis

	Early IPA ($n = 14$)	Late IPA ($n = 12$)	P value
Age	58 (56–62)	58 (49–60)	0.391
Male	7 (50.0%)	6 (50.0%)	1.000
Deceased donor kidney transplant	10 (71.4%)	7 (58.3%)	0.683
History of KT	1 (7.1%)	0	1.000
Duration of RRT	1366 (373–2472)	1348 (436–2233)	1.000
HLA-I mismatch	3 (1.75–3.00)	2 (0.25–3.00)	0.739
HLA-II mismatch	1 (1.00–1.50)	1 (0.25–1.75)	0.163
ABO incompatibility	3 (21.4%)	3 (25.0%)	1.000
Leukopenia (ANC < 3000)	0	5 (41.7%)	0.012
Diabetes mellitus	9 (64.3%)	2 (16.7%)	0.014
CMV-seropositive recipient	14 (100.0%)	11 (91.7%)	0.462
CMV-seropositive donor	13 (92.9%)	9 (81.8%)	0.565
CMV D+/R-	0	1	
Induction			
Antithymocyte globulin	10 (71.4%)	1 (8.3%)	0.001
Basiliximab	2 (14.3%)	8 (66.7%)	0.014
Any lymphocyte-depleting antibody	13 (92.9%)	9 (75.0%)	0.230
Maintenance			
Mycophenolate	12 (85.7%)	10 (83.3%)	1.000
Cyclosporine	1 (7.1%)	3 (25.0%)	0.306
Tacrolimus	11 (78.6%)	7 (58.3%)	0.401
Delayed graft function	4 (28.6%)	1 (8.3%)	0.330
Acute rejection	3 (21.4%)	9 (75.0%)	0.006
CMV antigenemia	2 (14.3%)	4 (33.3%)	0.365
Concomitant bacterial infection	13 (92.9%)	11 (91.7%)	1.000
Serum GM, peak before diagnosis	1.03 (0.49–7.17)	0.59 (0.20–2.75)	0.295
BAL GM	6.42 (4.74–6.84)	2.69 (1.01–4.72)	0.052
12-week mortality	11 (78.6%)	4 (33.3%)	0.020

Data are expressed as number (%) of patients and as median (IQR)

KT, kidney transplant; *RRT*, renal replacement therapy; *HLA*, human leukocyte antigen; *ANC*, absolute neutrophil count; *CMV*, cytomegalovirus; *GM*, galactomannan; *BAL*, bronchoalveolar lavage

Table 3 Risk factors for invasive pulmonary aspergillosis after kidney transplantation: overall, early, and late IPA (univariate analysis)

Variables	Overall IPA		Early IPA		Late IPA	
	OR	*P* value	OR	*P* value	OR	*P* value
Age	1.07 (1.02–1.13)	0.006	1.09 (1.01–1.18)	0.028	1.07 (0.99–1.15)	0.091
Male	0.63 (0.24–1.62)	0.332	0.56 (0.15–2.04)	0.376	0.71 (0.18–2.88)	0.636
Diabetes mellitus	4.03 (1.37–11.91)	0.012	10.80 (2.35–49.46)	0.002	1.00 (0.16–6.42)	1.000
DDKT	1.89 (0.71–5.00)	0.201	2.89 (0.73–11.43)	0.132	1.19 (0.29–4.81)	0.813
RRT	1.00 (0.27–3.69)	1.000	1.64 (0.29–9.40)	0.581	0.46 (0.06–3.70)	0.461
Duration of RRT	1.00 (1.00–1.01)	0.155	1.00 (1.00–1.01)	0.083	1.00 (1.00–1.01)	0.865
Re-transplantation	1.62 (0.31–8.36)	0.567	2.43 (0.34–17.52)	0.378		1.000
ABO incompatibility	0.57 (0.19–1.66)	0.301	0.42 (0.10–1.86)	0.254	0.79 (0.49–1.27)	0.326
Delayed graft function	12.14 (1.34–110.29)	0.027		0.999	2.09 (0.12–36.64)	0.614
Acute rejection	1.98 (1.13–3.51)	0.020	0.36 (0.08–1.60)	0.180	15.00 (2.77–81.38)	0.002
Any-lymphocyte depleting antibody	1.00 (0.27–3.69)	1.000	0.41 (0.03–8.32)	0.615	1.24 (0.24–5.97)	0.793
Antithymocyte globulin	1.65 (0.62–4.38)	0.314	3.33 (0.84–13.25)	0.087	0.46 (0.05–4.59)	0.504
Basiliximab	0.68 (0.26–1.76)	0.422	0.17 (0.03–0.89)	0.036	2.36 (0.56–10.02)	0.243
Alemtuzumab	0.65 (0.07–6.61)	0.718	2.08 (0.12–35.89)	0.615		0.999

DDKT, deceased donor kidney transplants; *RRT*, renal replacement therapy; *OR*, odds ratio

Discussion

IPA occurs commonly in patients with hematologic malignancies or those who undergo hematopoietic stem cell transplantations; however, few studies have assessed IPA among KT recipients [17]. With the development of transplant medicine, the number of SOT recipients is increasing, and KT is the most common among SOTs [18]. In Korea, the rate of KT is rising, reaching 50% among all SOT recipients in the Korean Network for Organ Sharing (KONOS) [2]. Of the various types of opportunistic infections, IPA contributes to high mortality rates [19, 20]. Recently, epidemiologic data on IPA following KT have been published in European and South American countries [12, 13]. To our knowledge, the present study is the first to evaluate the risk factors and clinical outcomes of IPA among KT recipients in Asia.

In this study, the incidence rate of IPA after KT was 1.3%, which was not different from previously reported rates [9, 11]. The median time to the diagnosis of IPA after KT was 161 days, which was also similar to previous data, ranging from 93 to 141 days [9, 11, 14]. IPA occurs most frequently 1–6 months after SOT, when immunosuppression levels are high [21]. However, studies have shown late IPA to be as common as early IPA in KT recipients [12]. This suggests that IPA can occur in any period after KT, although the risk factors may differ according to the periods, and these risk factors should be evaluated.

Delayed graft function was associated with an increased incidence of IPA among KT recipients in this study. In the case of delayed graft function, a previous study reported that the association between early IPA and delayed graft function may be the result of clinical surrogate [12]. To date, delayed graft function has been assessed with a focus on its pathophysiology and long-term graft outcome [22]. The proposed treatment and prevention of delayed graft function include the use of antilymphocyte-depleting antibodies such as antithymocyte globulin [23]. In the present study, anti-lymphocyte-depleting antibody use did not differ significantly between the case and control groups, and there was no significant difference in the development of IPA. However, delayed graft function may be a clinical surrogate reflecting over-immunosuppression.

DM was significantly associated with the development of early IPA in this study. In previous studies, the relationship between diabetes and development of IPA has been discussed. Diabetes may be a risk factor for IPA in non-immunocompromised hosts [24]. DM may be associated with chronic necrotizing pulmonary aspergillosis and invasive aspergillosis in critically ill patients [25–27]. In KT patients with DM, difficulties with glucose control due to the use of immunosuppressive agents might contribute to increased susceptibility to invasive aspergillosis. Because KT cases may increase and DM is the most common cause of KT, we should be aware of DM as a risk factor for IPA. Preceding acute rejection was associated with late IPA. Intense immunosuppressive therapy to treat acute rejection could be attributed to the development of IPA. Treatment of acute rejection warrants cautious monitoring for the development of invasive aspergillosis.

The 12-week mortality was also high similar to those of previous studies, ranging from 39% to 70% [11, 14, 28]. The rate was significantly higher in the early IPA group compared with that in the late IPA group. This might be associated with

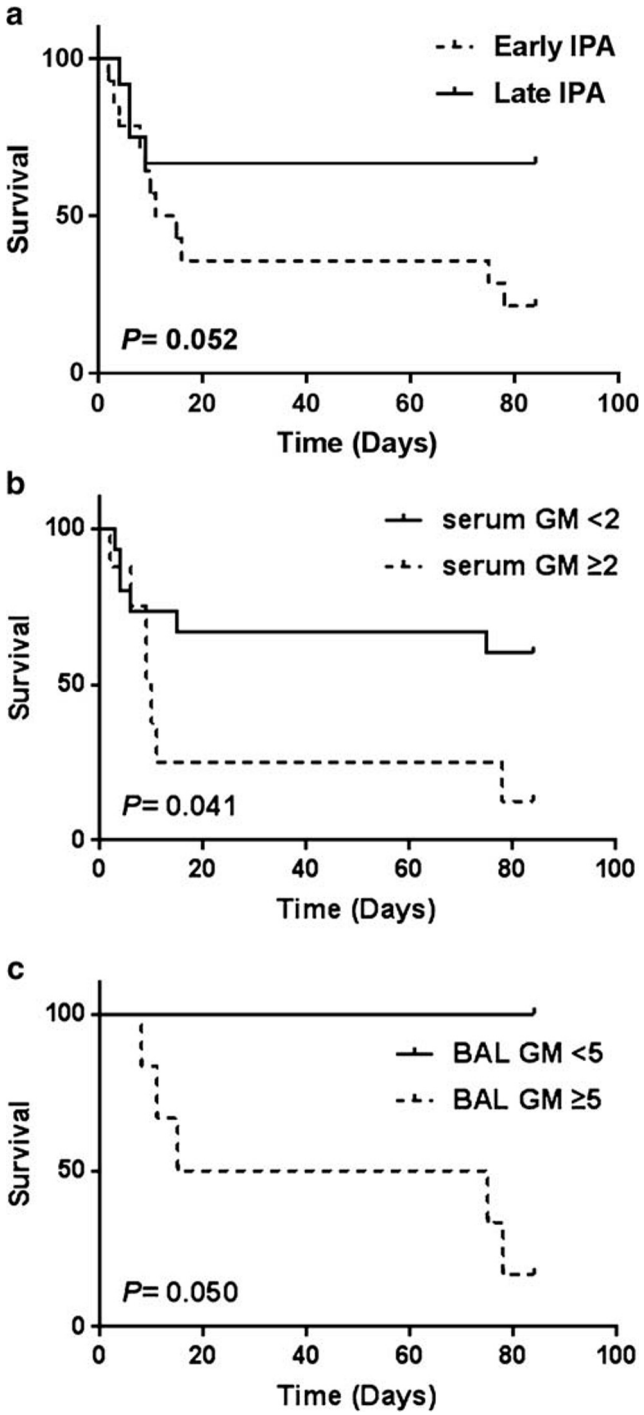

Fig. 2 Kaplan–Meier curves for 12-week survival according to **a** early or late invasive pulmonary aspergillosis (IPA), **b** serum galactomannan (GM) < 2 or ≥ 2, and **c** bronchoalveolar lavage galactomannan (BAL) < 5 or ≥ 5

immunosuppressive agents for induction therapy, intensive rather than maintenance therapy, and even acute rejection rescue. The development of IPA may be devastating during the early periods. Multivariate analyses showed a tendency for early IPA to be associated with 12-week mortality without statistical significance. A previous study also reported early IPA to be associated with 6-week mortality [12].

In this study, high serum and BAL GM levels were independent variables related to 12-week mortality. In prior studies, serum GM levels may predict mortality in patients with hematopoietic stem cell transplant recipients and hematologic malignancies [29, 30], but not in KT recipients. This study suggests that serum GM level may be useful as a predictor of prognosis as well as diagnostic utility of IPA patients after KT. The BAL GM has been shown to be of diagnostic value in non-hematologic immunocompromised patients [31]. Although this study could not demonstrate the usefulness of BAL GM in diagnosis, it has been shown to be associated with poor outcome in IPA patients after KT.

The limitations of the present study include temporal heterogeneity because of the long study periods and relatively small number of included cases due to low incidence rates of IPA. However, the heterogeneity could also have been minimal because the cases were collected from a single center. In addition, the risk factors could have been evaluated by comparison with control patients. To our knowledge, this is the first study to be conducted outside of Europe and South America to demonstrate that DM was a risk factor for IPA development in KT recipients.

In conclusion, IPA may occur at any period after KT. Delayed graft function may increase the risk of IPA. Older age and DM tended to increase the development of early IPA, while acute rejection was associated late IPA. More cautious diagnostic approach may be needed for the early diagnosis of IPA in these high-risk patients. Despite the low incidence rate of IPA following KT, the mortality rate remained high. Higher serum and BAL galactomannan levels were associated with 12-week mortality and show potential value for prognostic predictors in addition to diagnostic utility in patients with IPA after KT.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For this type of study, formal consent is not required.

Informed consent This study protocol was approved by the institutional review board of the Samsung Medical Center (no. 2018-01-150) and informed consent was waived.

References

1. Pappas PG, Alexander BD, Andes DR, Hadley S, Kauffman CA, Freifeld A, Anaissie EJ, Brumble LM, Herwaldt L, Ito J, Kontoyiannis DP, Lyon GM, Marr KA, Morrison VA, Park BJ, Patterson TF, Perl TM, Oster RA, Schuster MG, Walker R, Walsh TJ, Wannemuehler KA, Chiller TM (2010) Invasive fungal

infections among organ transplant recipients: results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 50(8):1101–1111
2. Ahn C, Koo TY, Jeong JC, Kim M, Yang J, Lee J, Min SI, Lee JE, Kim MS, Kwon OJ, Kim SJ, Kim YH, Kim YH, Choi BS, Choi SJ, Lee DH, Chung SY, Cho WH, Kim YS (2014) Initial report of the Korean Organ Transplant Registry: the first report of national kidney transplantation data. Transplant Proc 46(2):425–430
3. Einollahi B, Lessan-Pezeshki M, Pourfarziani V, Nemati E, Nafar M, Pour-Reza-Gholi F, Hassan Ghadyani M, Samadian F, Ahmadpoor P, Aslani J (2008) Invasive fungal infections following renal transplantation: a review of 2410 recipients. Ann Transplant 13(4):55–58
4. Grossi P, Farina C, Fiocchi R, Dalla Gasperina D (2000) Prevalence and outcome of invasive fungal infections in 1,963 thoracic organ transplant recipients: a multicenter retrospective study. Italian Study Group of Fungal Infections in Thoracic Organ Transplant Recipients. Transplantation 70(1):112–116
5. Badiee P, Kordbacheh P, Alborzi A, Zeini F, Mirhendy H, Mahmoody M (2005) Fungal infections in solid organ recipients. Exp Clin Transplant 3(2):385–389
6. Bodro M, Sabe N, Gomila A, Ayats J, Baliellas C, Roca J, Melilli E, Carratala J (2012) Risk factors, clinical characteristics, and outcomes of invasive fungal infections in solid organ transplant recipients. Transplant Proc 44(9):2682–2685
7. Sahin SZ, Akalin H, Ersoy A, Yildiz A, Ocakoglu G, Cetinoglu ED, Dizdar OS, Kazak E, Ener B (2015) Invasive fungal infections in renal transplant recipients: epidemiology and risk factors. Mycopathologia 180(1–2):43–50
8. Ezzatzadegan S, Chen S, Chapman JR (2012) Invasive fungal infections after renal transplantation. Int J Organ Transplant Med 3(1):18–25
9. Perez-Saez MJ, Mir M, Montero MM, Crespo M, Montero N, Gomez J, Horcajada JP, Pascual J (2014) Invasive aspergillosis in kidney transplant recipients: a cohort study. Exp Clin Transplant 12(2):101–105
10. Ju MK, Joo DJ, Kim SJ, Chang HK, Kim MS, Kim SI, Kim YS (2009) Invasive pulmonary aspergillosis after solid organ transplantation: diagnosis and treatment based on 28 years of transplantation experience. Transplant Proc 41(1):375–378
11. Hoyo I, Sanclemente G, de la Bellacasa JP, Cofan F, Ricart MJ, Cardona M, Colmenero J, Fernandez J, Escorsell A, Navasa M, Moreno A, Cervera C (2014) Epidemiology, clinical characteristics, and outcome of invasive aspergillosis in renal transplant patients. Transpl Infect Dis 16(6):951–957
12. Lopez-Medrano F, Silva JT, Fernandez-Ruiz M, Carver PL, van Delden C, Merino E, Perez-Saez MJ, Montero M, Coussement J, de Abreu MM, Cervera C, Santos L, Sabe N, Scemla A, Cordero E, Cruzado-Vega L, Martin-Moreno PL, Len O, Rudas E, de Leon AP, Arriola M, Lauzurica R, David M, Gonzalez-Rico C, Henriquez-Palop F, Fortun J, Nucci M, Manuel O, Pano-Pardo JR, Montejo M, Munoz P, Sanchez-Sobrino B, Mazuecos A, Pascual J, Horcajada JP, Lecompte T, Lumbreras C, Moreno A, Carratala J, Blanes M, Hernandez D, Hernandez-Mendez EA, Farinas MC, Perello-Carrascosa M, Morales JM, Andres A, Aguado JM (2016) Risk factors associated with early invasive pulmonary aspergillosis in kidney transplant recipients: results from a multinational matched case-control study. Am J Transplant 16(7):2148–2157
13. Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, Carver PL, van Delden C, Merino E, Perez-Saez MJ, Montero M, Coussement J, de Abreu MM, Cervera C, Santos L, Sabe N, Scemla A, Cordero E, Cruzado-Vega L, Martin-Moreno PL, Len O, Rudas E, Ponce de Leon A, Arriola M, Lauzurica R, David MD, Gonzalez-Rico C, Henriquez-Palop F, Fortun J, Nucci M, Manuel O, Pano-Pardo JR, Montejo M, Vena A, Sanchez-Sobrino B, Mazuecos A, Pascual J, Horcajada JP, Lecompte T, Moreno A, Carratala J, Blanes M, Hernandez D, Hernandez-Mendez EA, Farinas MC, Perello-Carrascosa M, Munoz P, Andres A, Aguado JM (2018) Multinational case-control study of risk factors for the development of late invasive pulmonary aspergillosis following kidney transplantation. Clin Microbiol Infect 24(2):192–198
14. Heylen L, Maertens J, Naesens M, Van Wijngaerden E, Lagrou K, Bammens B, Claes K, Evenepoel P, Meijers B, Kuypers D, Sprangers B (2015) Invasive aspergillosis after kidney transplant: case-control study. Clin Infect Dis 60(10):1505–1511
15. Segal BH, Herbrecht R, Stevens DA, Ostrosky-Zeichner L, Sobel J, Viscoli C, Walsh TJ, Maertens J, Patterson TF, Perfect JR, Dupont B, Wingard JR, Calandra T, Kauffman CA, Graybill JR, Baden LR, Pappas PG, Bennett JE, Kontoyiannis DP, Cordonnier C, Viviani MA, Bille J, Almyroudis NG, Wheat LJ, Graninger W, Bow EJ, Holland SM, Kullberg BJ, Dismukes WE, De Pauw BE (2008) Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis 47(5):674–683
16. Yarlagadda SG, Coca SG, Garg AX, Doshi M, Poggio E, Marcus RJ, Parikh CR (2008) Marked variation in the definition and diagnosis of delayed graft function: a systematic review. Nephrol Dial Transplant 23(9):2995–3003
17. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE (2016) Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 63(4): e1–e60
18. Global Observatory on Donation and Transplantation (GODT). Global Data. http://www.transplant-observatory.org/data-charts-and-tables/. Accessed 5 Aug 2019
19. Baddley JW, Andes DR, Marr KA, Kontoyiannis DP, Alexander BD, Kauffman CA, Oster RA, Anaissie EJ, Walsh TJ, Schuster MG, Wingard JR, Patterson TF, Ito JI, Williams OD, Chiller T, Pappas PG (2010) Factors associated with mortality in transplant patients with invasive aspergillosis. Clin Infect Dis 50(12):1559–1567
20. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Ame S, Fohrer C, Lioure B, Bilger K, Lutun P, Marcellin L, Launoy A, Freys G, Bergerat JP, Herbrecht R (2008) Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis 47(9):1176–1184
21. Fishman JA (2017) Infection in organ transplantation. Am J Transplant 17(4):856–879
22. Siedlecki A, Irish W, Brennan DC (2011) Delayed graft function in the kidney transplant. Am J Transplant 11(11):2279–2296
23. Chen G, Gu J, Qiu J, Wang C, Fei J, Deng S, Li J, Huang G, Fu Q, Chen L (2013) Efficacy and safety of thymoglobulin and basiliximab in kidney transplant patients at high risk for acute rejection and delayed graft function. Exp Clin Transplant 11(4):310–314
24. Ghanaat F, Tayek JA (2017) Weight loss and diabetes are new risk factors for the development of invasive aspergillosis infection in non-immunocompromized humans. Clin Pract (Lond) 14(5 spec Iss):296–301
25. Nam HS, Jeon K, Um SW, Suh GY, Chung MP, Kim H, Kwon OJ, Koh WJ (2010) Clinical characteristics and treatment outcomes of chronic necrotizing pulmonary aspergillosis: a review of 43 cases. Int J Infect Dis 14(6):e479–e482
26. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, Dimopoulos G, Paiva JA, Misset B, Rello J, Vandewoude K, Vogelaers D (2012) A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 186(1):56–64

27. Rees JR, Pinner RW, Hajjeh RA, Brandt ME, Reingold AL (1998) The epidemiological features of invasive mycotic infections in the San Francisco Bay area, 1992-1993: results of population-based laboratory active surveillance. Clin Infect Dis 27(5):1138–1147
28. Lopez-Medrano F, Fernandez-Ruiz M, Silva JT, Carver PL, van Delden C, Merino E, Perez-Saez MJ, Montero M, Coussement J, de Abreu MM, Cervera C, Santos L, Sabe N, Scemla A, Cordero E, Cruzado-Vega L, Martin-Moreno PL, Len O, Rudas E, de Leon AP, Arriola M, Lauzurica R, David M, Gonzalez-Rico C, Henriquez-Palop F, Fortun J, Nucci M, Manuel O, Pano-Pardo JR, Montejo M, Munoz P, Sanchez-Sobrino B, Mazuecos A, Pascual J, Horcajada JP, Lecompte T, Moreno A, Carratala J, Blanes M, Hernandez D, Farinas MC, Andres A, Aguado JM (2016) Clinical presentation and determinants of mortality of invasive pulmonary aspergillosis in kidney transplant recipients: a multinational cohort study. Am J Transplant 16(11):3220–3234
29. Upton A, Kirby KA, Carpenter P, Boeckh M, Marr KA (2007) Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors associated with mortality. Clin Infect Dis 44(4):531–540
30. Miceli MH, Grazziutti ML, Woods G, Zhao W, Kocoglu MH, Barlogie B, Anaissie E (2008) Strong correlation between serum aspergillus galactomannan index and outcome of aspergillosis in patients with hematological cancer: clinical and research implications. Clin Infect Dis 46(9):1412–1422
31. Fortun J, Martin-Davila P, Gomez Garcia de la Pedrosa E, Silva JT, Garcia-Rodriguez J, Benito D, Venanzi E, Castano F, Fernandez-Ruiz M, Lazaro F, Garcia-Lujan R, Quiles I, Cabanillas JJ, Moreno S, Aguado JM (2016) Galactomannan in bronchoalveolar lavage fluid for diagnosis of invasive aspergillosis in non-hematological patients. J Inf Secur 72(6):738–744