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ORIGINAL ARTICLE

Association between acute graft pyelonephritis and kidney graft survival: A single-center observational study

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The association between acute graft pyelonephritis (AGPN) and graft failure in kidney transplant recipients (KTR) remains controversial. In this single-center observational study, we aimed to assess the incidence of AGPN as a time-dependent posttransplantation event. We also examined the association between the diagnosis of AGPN and graft outcomes. In total, we evaluated 1480 patients who underwent kidney transplantation between January 2007 and December 2017. During a median follow-up of 5.04 years, we observed 297 AGPN episodes that occurred in 158 KTR. To evaluate the association between AGPN and clinical outcomes, we performed Cox proportional hazards regression analyses in which AGPN was entered as a time-dependent covariate. AGPN was independently associated with an increased risk of graft loss (hazard ratio = 1.66; 95% confidence interval [CI]: 1.05–2.64, $p < .03$) and a persistently decreased eGFR (fixed effect on intercept: -2.29 ml/min/1.73 m²; 95% CI: from -3.23 to -1.35 , $p < .01$). However, neither mortality nor biopsy-proven acute rejection was found to correlate with AGPN. Moreover, recurrent AGPN episodes did not appear to have an additive detrimental impact on graft loss. These data represent a promising step in understanding whether AGPN prevention may decrease the risk of graft loss in KTR.

KEYWORDS

clinical research/practice, graft survival, infection and infectious agents—bacterial, infectious disease, kidney transplantation/nephrology

1 | INTRODUCTION

Kidney transplantation has been widely demonstrated to outperform dialysis in terms of life expectancy, quality of life, and cost-effectiveness in patients with end-stage kidney disease (ESKD).¹ Unfortunately,

transplant-related complications can give rise to long-term deleterious effects on allograft outcomes. Infections—which are among the most feared events in kidney transplant recipients (KTR)—account for approximately 15% of all posttransplantation deaths and are responsible for 8% of all death-censored graft failures.² Urinary tract infections

Abbreviations: AGPN, acute graft pyelonephritis; AKI, acute kidney injury; BMI, body mass index; BPAR, biopsy-proven acute rejection; CIs, confidence intervals; CMV, cytomegalovirus; DBD, donation after brainstem death; DCD, donation after circulatory death; ESKD, end-stage kidney disease; HPM, hypothermic perfusion machine; HRs, hazard ratios; KDIGO, Kidney Disease: Improving Global Outcomes; KTR, kidney transplant recipients; UTI, urinary tract infections; VUR, vesicoureteric reflux.

Mehdi Maanaoui and Dulciane Baes contributed equally to this work.

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(UTI) and acute graft pyelonephritis (AGPN) are the most prevalent infectious complications occurring in KTR. Specifically, UTI represent >50% of all infections and are one of the largest contributors to sepsis cases in this patient population.² However, the exact incidence of UTI following kidney transplantation remains difficult to establish and has been reported to range widely between 7% and 80%, depending on various factors such as the study design and the definition of UTI.^{3,4}

While current estimates show the rate of AGPN in KTR to be between 10% and 20%,⁴⁻⁶ its prognostic value on kidney transplantation outcomes remains a matter of debate. Theoretically, AGPN can elicit immune system activation—which may in turn lead to an increased risk of acute or chronic rejection.⁷ However, several large-scale studies that evaluated AGPN as a prognostic factor for graft loss in KTR failed to demonstrate a significant adverse effect.^{5,6,8} Nevertheless, the few studies that have focused on the prognostic significance of early AGPN⁴ or recurrent UTI⁶ have reported a detrimental impact on graft survival. A potential explanation for these discrepancies is that all of the previous investigations in the field relied on a one-time assessment of AGPN (i.e., its presence at baseline). However, AGPN may also develop during the posttransplantation period—thereby being a time-dependent event whose incidence depends on the length of follow-up. The reliance on the AGPN baseline status is unable to capture its potential occurrence over time and may lead to spurious hazard ratio estimates.⁹ Starting from these premises, we aimed to assess the incidence of AGPN in KTR as a time-dependent posttransplantation event. We also examined the association between the diagnosis of AGPN and graft outcomes in this patient group.

2 | METHODS

2.1 | Data source and ethical statement

This single-center observational study conforms to the tenets of the Istanbul Declaration and the ethical guidelines set forth by the Helsinki Declaration. The use of organs obtained from prisoners was banned. The study data were obtained from the *Agence de la Biomédecine*—a state agency that coordinates and administers organ procurement in France—and completed with the patient clinical records. The French legislation stipulates that registry-based research is an integral part of outcome assessment for solid organ transplantation and is exempt from Institutional Review Board approval. All participants provided written informed consent after receiving a detailed explanation of the study procedures. Once fully pseudonymized, the dataset was processed under French and EU data protection laws and regulations (reference: #DEC19-054).

2.2 | Study patients

The study included all of the consecutive adult recipients who had undergone kidney transplantation between January 2007

and December 2017 at the Lille University hospital (Lille, France). Patients with a history of multi-organ transplantation and retransplantation were deemed eligible. Pediatric patients were excluded. Follow-up was terminated on December 31, 2018.

2.3 | Exposure

AGPN was diagnosed according to the following *American Society of Transplantation Infectious Diseases Community of Practice*¹⁰ criteria: concomitant presence of suggestive clinical symptoms (i.e., fever with flank/allograft pain and/or symptoms of lower UTI including frequency, urgency, dysuria, and/or suprapubic pain) and typical laboratory findings (i.e., urinalysis showing leukocyte counts >10 per mm³ or >10⁴ colony-forming units of bacteria per milliliter of urine; leukocytosis either with or without bacteria isolated from blood cultures). All of the AGPN episodes were identified and adjudicated by two authors (MM and DB) through a retrospective review of hospital records. AGPN episodes that required hospitalization in different centers were retrieved from the annual report issued by the National Biomedicine Agency—a French health authority which is in charge of allocating patients to organ transplantation and maintaining a nationwide registry of recipients. All disagreements that occurred during the adjudication process were jointly discussed and resolved by consensus.

2.4 | Posttransplantation management

All patients received an immunosuppressive regimen consisting of an induction therapy (basiliximab or thymoglobulin) and a maintenance triple-drug regimen (tacrolimus, mycophenolate mofetil, and steroids). Tacrolimus was started at 0.15 mg/kg/day and subsequently adapted to its trough level (Tac-T0) with a target of 10–15 ng/ml up to day 15 and of 6–8 ng/ml thereafter. Mycophenolate mofetil dosing was 750 mg twice a day. Steroids were withdrawn on day 7 in first-transplant nonsensitized recipients, while being gradually tapered off (0.1 mg/kg/day) in all other participants. Cytomegalovirus (CMV)-seronegative patients who received a kidney from a CMV-seropositive donor were given valganciclovir during the first six posttransplantation months. Additionally, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis was administered during the first three posttransplantation months. According to institutional guidelines, ureteral catheters were removed between the third and fourth posttransplantation week.

2.5 | Data collection

The following donor variables were collected from clinical records: age, sex, body mass index (BMI), blood type, living donor, donation after brainstem death (DBD) (vs. after circulatory death [DCD]), cause of death, cold ischemia time, and preservation modality (hypothermic perfusion machine [HPM] vs. static cold storage). Baseline variables

collected from recipients were age, sex, BMI, blood type, cause of ESKD, time on dialysis, type of dialysis, time on waiting list, history of previous transplantation, number of HLA mismatches, HLA sensitization, induction therapy, serum creatinine values, time of graft failure (defined as return to dialysis or need of pre-emptive retransplantation), cause of graft failure, date of death, and date of biopsy-proven acute rejection (BPAR). Data on the following variables were collected: occurrence and timing of AGPN, causative agent, clinical symptoms, leukocytosis, urinalysis, presence of bacteremia, need for ICU admission, use of vasopressors, and acute kidney injury (AKI). AKI was defined according to the 2012–Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, as follows: stage I, increase of serum creatinine of 50% or 0.3 mg/dl; stage II, increase of serum creatinine of 100%; stage III, increase of serum creatinine of 200% or >4.0 mg/dl.

2.6 | Outcomes

In this study, the effect of AGPN on death-censored graft survival rates was the primary endpoint. Secondary endpoints included the identification of risk factors for AGPN and the impact of AGPN on (1) patient survival rates, (2) time course of estimated glomerular filtration rate (eGFR, estimated with the CKD-EPI formula), and (3) BPAR. We also evaluated the impact of recurrent AGPN on death-censored graft survival rates. BPAR was diagnosed using the Banff classification system at the time of kidney biopsy. To exclude surgery-related cases of AGPN, we performed a sensitivity analysis after the exclusion of all AGPN cases occurring within the first posttransplantation month. We subsequently compared death-censored graft survival rates between KTR with and without AGPN.

2.7 | Statistical analysis

The median and first-third quartile were used for continuous data, whereas categorical variables were summarized as counts and proportions. As for intergroup comparisons, variables were analyzed with the chi-square test (categorical data) or the Student's *t*-test (continuous data). The Aalen-Johansen estimator was used to estimate the cumulative incidence of AGPN; to this aim, graft failure and death were considered as competing events. Survival curves were plotted with the Kaplan–Meier method. To evaluate risk factors of AGPN or the association between AGPN and the outcomes of interest, we performed Cox proportional hazards regression analysis. We expressed the results as hazard ratios (HRs) with their 95% confidence intervals (CIs). A multivariable backward selection procedure was implemented, with a univariate threshold $p < .20$ for inclusion and a $p < .05$ being defined as statistically significant in the final model. AGPN—which was considered as a time-dependent variable—was forced into the Cox model when it did not meet the inclusion threshold ($p < .20$). Albeit not significant in univariate analysis, cold-ischemia time was retained as a covariate in the final multivariable model because of its known impact on graft survival. Log linearity

and proportional hazards assumptions were tested both graphically (log-minus-log method and Schoenfeld residuals, respectively) and numerically tested (by comparing a linear model and a model with splines and by using a score test, respectively). We used linear mixed model estimated by restricted maximum likelihood to assess longitudinal changes in eGFR starting from the first posttransplantation month. AGPN was treated as (1) a time-dependent covariate and (2) a fixed effect associated with two random effects for baseline and slope values, respectively. We subsequently selected the optimal fitting model for eGFR changes over time using Bayesian information criterion values. We built univariate models by using two effects for each variable, that is, (1) baseline values and (2) slope (interaction with time). Nonsignificant variables with a $p > .20$ were removed. When a statistically significant association was evident on the slope, the corresponding association with baseline values was also assessed. Finally, significant variables were entered into a multivariable linear mixed model to identify independent predictors for the outcomes of interest (backward selection procedure, $p < .05$). AGPN was systematically included as a covariate in multivariate models. The normal distribution of random effects on intercept, random effects on slope, and the residuals and homoscedasticity assumptions was tested using a graphical method. Calculations were performed in R, version 3.6.3, using the survival and “mice” packages. All tests were two-sided, and statistical significance was set as a p value $< .05$.

3 | RESULTS

3.1 | Study patients

In total, we evaluated 1480 patients who underwent kidney transplantation between January 2007 and December 2017. A study flowchart is provided in Figure S1. At the end of follow-up, there were 1101 recipients who were alive with a functional graft, 131 KTR who had died with a functioning graft, and 236 graft losses. A total of 12 KTR in our cohort were lost to follow-up (median follow-up time: 3.98 years; first to third quartile: 3.01–4.78 years). Donor and recipient characteristics are shown in Table 1. Overall, the median follow-up was 5.04 years (first to third quartile: 3.01–8.02 years). A total of 297 AGPN events were identified in 158 KTR. The median number of AGPN episodes in the study participants was 1.0 (first to third quartile: 1.0–2.0). The probability of experiencing at least one AGPN episode at 6 months, 1 year, and 2 years of follow-up were 6.2% (95% CI: 5.1%–7.6%), 7.6% (95% CI: 6.4%–9.1%), and 8.8% (95% CI: 7.5%–10.4%), respectively (Figure 1). During the first AGPN episode, *Escherichia coli* was the most common isolate ($n = 93/158$), followed by *Pseudomonas aeruginosa* ($n = 15/158$) and *Klebsiella pneumoniae* ($n = 14/158$). *Escherichia coli* accounted for 52.2% ($n = 165/297$) of all AGPN episodes, followed by *Klebsiella pneumoniae* ($n = 37/297$) and *Pseudomonas aeruginosa* ($n = 21/297$; Table S1). The median time elapsed between kidney transplantation and the first AGPN episode was 142 days (first to third quartile: 38–516 days). We observed 66 events (22.22%) of concomitant AGPN and bacteremia, whereas a

TABLE 1 Donor and recipient characteristics

	Entire cohort (n = 1480), median (IQR) or n (%)	Missing values, n (%)
Donors		
Age (years)	53.00 (41.00–62.00)	0 (0)
Male donor	859 (58.04)	0 (0)
BMI (kg/m ²)	25.51 (22.68–28.77)	0 (0)
Living donor	111 (7.50)	0 (0)
DBD	1281 (96.7)	0 (0)
Death from vascular causes	704 (47.57)	0 (0)
Hypothermic perfusion machine	302 (20.41)	13 (0.88)
Recipients		
Age (years)	52.56 (40.15–60.69)	0 (0)
Male recipient	939 (63.45)	0 (0)
First kidney transplantation	1211 (81.82)	0 (0)
Combined transplantation with another organ	34 (2.30)	0 (0)
History of organ transplantation different from KT	30 (2.03)	0 (0)
Dialysis type		0 (0)
Hemodialysis	1157 (78.18)	
Peritoneal dialysis	160 (10.81)	
Pre-emptive transplantation	163 (11.01)	
Waiting time on dialysis	2.12 (1.06–3.75)	0 (0)
Cause of ESKD		0 (0)
Glomerulonephritis	416 (28.11)	
Vascular nephropathy	116 (7.84)	
Undetermined	183 (12.36)	
Diabetes	95 (6.42)	
ADPKD	277 (18.72)	
Tubulo-interstitial nephritis	171 (11.55)	
Others	222 (15.00)	
HLA sensitization class I	283 (19.12)	1 (0.07)
HLA sensitization class II	308 (20.81)	20 (1.35)
Transplantation		
Cold ischemia time (h)	16.07 (11.93–20.96)	0 (0)
ABDR mismatches (>4)	382 (26.2)	2 (0.14)
Induction therapy		13 (0.88)
Thymoglobulin	947 (63.99)	

(Continues)

TABLE 1 (Continued)

	Entire cohort (n = 1480), median (IQR) or n (%)	Missing values, n (%)
Anti-IL2 receptor	520 (35.14)	

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; BMI, body mass index; DBD, donation after brainstem death; ESKD, end-stage kidney disease; HLA, human leukocyte antigen; IQR, interquartile range; KT, kidney transplantation.

total of 207 events (69.70%) of concomitant AGPN and AKI were identified (Table 2). At the time of the first AGPN episode, AGPN was found to occur concomitantly with bacteremia and AKI in 42 (26.58%) and 115 events (72.78%), respectively. Multivariable Cox regression model revealed that recipient sex (HR for male recipients: 0.34 [0.24–0.47], $p < .01$) and retransplantation (HR: 0.42 [0.25–0.72], $p < .01$) were independently associated with a lower risk of AGPN. Conversely, cold ischemia time (HR: 1.04 [1.01–1.06], $p < .01$) was identified as a significant independent risk factor (Table S2). We found no independent effect of donor and recipient age, induction therapy (thymoglobulin), and rejection episodes on the risk of AGPN.

3.2 | Association between AGPN and death-censored graft survival

A total of 236 graft losses occurred in the 1480 patients, of whom 22 presented with at least one AGPN episode. Five- and 10-year death-censored graft survival rates were 85.3% (95% CI: 83.0%–87.7%) and 75.6% (95% CI: 71.1%–80.1%), respectively (Figure 2). Multivariable Cox regression model revealed that AGPN (as a time-dependent exposure) was independently associated with an increased risk of graft loss (HR = 1.66; 95% CI: 1.05–2.64, $p < .03$). The concomitant presence of AGPN and bacteremia showed a trend towards an increased risk of graft loss (HR = 2.07, 95% CI: 0.96–4.46, $p = .06$). Notably, the concomitant presence of AGPN and AKI was significantly associated with an increased risk of graft loss (HR = 1.69, 95% CI: 1.01–2.85, $p = .05$). Other independent predictors of graft loss included retransplantation, recipient sex, waiting time on dialysis, donor age, and donor type (Table 3). To avoid cases with surgery-related infections, we performed a sensitivity analysis after the exclusion of patients who developed AGPN within the first posttransplantation month. We identified 119 episodes among 1441 KTR. AGPN remained independently associated with an increased risk of graft loss (HR = 2.00; 95% CI: 1.19–3.35, $p = .01$). Other independent predictors of graft loss did not appreciably change in sensitivity analysis (Table S3).

3.3 | Association between AGPN and patient survival

Of 1480 patients, 159 died during follow-up. Twelve deaths occurred after at least one AGPN episode. In multivariable analysis,

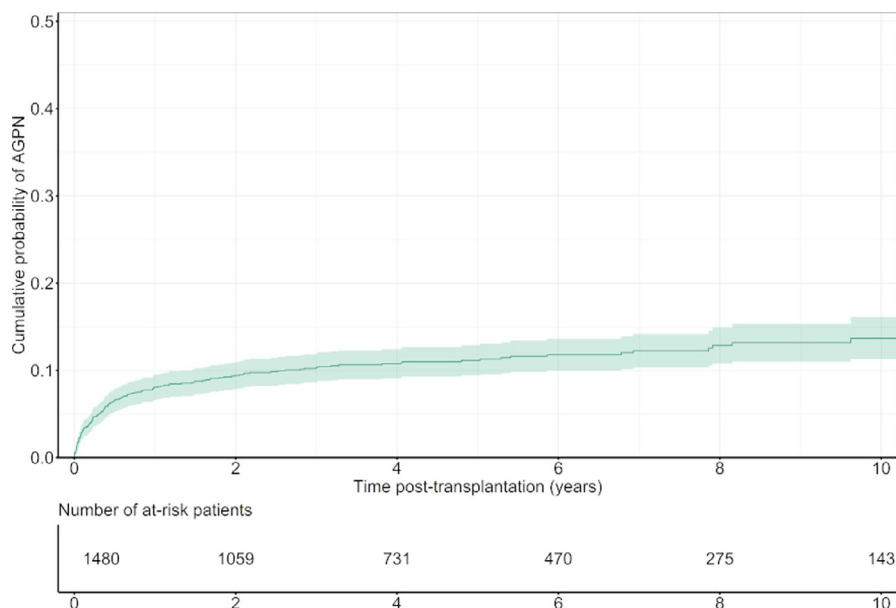


FIGURE 1 Cumulative probability of acute graft pyelonephritis over time in the entire cohort. AGPN, acute graft pyelonephritis [Color figure can be viewed at wileyonlinelibrary.com]

retransplantation, a history of previous nonkidney transplantation, and recipient age were independently associated with an increased mortality risk, whereas AGPN was not (HR = 0.89; 95% CI: 0.49–1.62, $p = .71$; Table S4).

3.4 | Association between AGPN and eGFR

A median of 22 (first to third quartile: 17–31) serum creatinine measurements was obtained for each KTR—resulting in 35 877 available values of eGFR for 1403 patients who had at least one assessment. eGFR values (CKD-EPI estimation) showed a normal distribution. The Bayesian information criterion revealed that the linear model provided the most suitable description for the relationship between eGFR and time. Using a linear mixed model (Figure S2), longitudinal changes of eGFR (CKD-EPI estimation) over time were investigated with respect to the occurrence of the first AGPN episode (as a time-dependent covariate). After adjustment for variables identified as significant in univariate analysis (i.e., recipient and donor age, recipient and donor sex, donor type, cold ischemia time, and recipient BMI), the first AGPN episode was found to be significantly associated with a persistently decreased eGFR (fixed effect on intercept: -2.29 ml/min/ 1.73 m²; 95% CI: from -3.23 to -1.35 , $p < .01$). However, no significant impact on the eGFR slope was observed (fixed effect: -0.20 ml/min/ 1.73 m² per year; 95% CI: from -0.53 to 0.13 , $p = .23$; Table 4).

3.5 | Association between AGPN and BPAR

Multivariable Cox regression was used to investigate the impact of AGPN on the risk of developing BPAR. A total of 218 BPAR occurred in the 1480 patients, of whom 22 presented with at least one AGPN episode. In multivariable analysis, a history of previous nonkidney transplantation, HLA class II sensitization, and donor sex

were independently associated with BPAR, whereas AGPN was not (HR = 1.19; 95% CI: 0.68–2.11, $p = .54$; Table S5).

3.6 | Impact of recurrent AGPN

Finally, we examined the impact of recurrent AGPN episodes on graft-censored death survival rates. Of 158 KTR who presented at least one AGPN episode, recurrences (i.e., a second AGPN within 6 months after the first) were observed in 45 patients. The median time of recurrence was 49 days (first to third quartile: 33–109.8 days). Compared with recipients who had a single AGPN episode, those with recurrent AGPN did not show an increased risk of graft loss in multivariable analysis (HR = 1.09; 95% CI: 0.39–3.04, $p = .86$; Table S6). However, men were characterized by a higher risk of graft loss after a first AGPN episode (HR for male recipients = 9.74; 95% CI: 2.61–36.36, $p = .01$). To explore this association further, we compared the baseline characteristics of men and women at the time of first AGPN episode. Compared with women, men were significantly older (61 years [53.9–68.2] vs. 52 years [36.8–60.2], $p < .01$), and their AGPN episodes occurred earlier (84 days [21–262] vs. 176 days [48–588], $p = .01$). Furthermore, men had lower baseline eGFR values (40.5 ml/min/ 1.73 m² [25.1–50.7] vs. 58.6 ml/min/ 1.73 m² [45.7–76.5], $p < .01$) and more frequently presented with stage III AKI at the time of AGPN (28.8% vs. 9.1%, $p = .01$; Table S7).

4 | DISCUSSION

In this single-center study comprising a large number of KTR, the results of a time-dependent proportional hazards ratio regression model revealed an independent association between AGPN and the risk of graft loss. While AGPN was also independently associated

TABLE 2 Acute graft pyelonephritis demographics and characteristics

		Missing values, n (%)
At least one AGPN during follow-up	158	
Total number of AGPN	297	
Time between KT and the first AGPN, days (IQR)	142 (38–516)	
Characteristics of the total number of AGPN, n (%)		
Allograft pain	79 (26.60)	0 (0)
Symptoms of low UTI	160 (53.87)	0 (0)
Fever	271 (91.25)	0 (0)
Leukocytosis	187 (63.00)	0 (0)
Urinalysis with leukocyte counts >10 ³ /ml	281 (94.61)	0 (0)
Urinalysis with CFU of bacteria >10 ⁴ /ml	274 (92.26)	0 (0)
Bacteremia	66 (22.22)	1 (0.6)
Transfer in the ICU	10 (3.37)	0 (0)
Use of vasopressors	5 (1.68)	0 (0)
AKI	207 (69.70)	0 (0)
Stage I	149 (50.17)	
Stage II	23 (7.74)	
Stage III	35 (11.78)	
Length of stay in hospital, days (IQR)	6 (4–8)	0 (0)
Characteristics of the first episode of AGPN, n (%)		
Allograft pain	37 (23.41)	0 (0)
Symptoms of low UTI	81 (51.27)	0 (0)
Fever	140 (88.60)	0 (0)
Leukocytosis	102 (64.56)	0 (0)
Urinalysis with leukocyte counts >10 ³ /ml	149 (94.30)	0 (0)
Urinalysis with CFU of bacteria >10 ⁴ /ml	146 (92.41)	0 (0)
Bacteremia	42 (26.58)	1 (0.3)
Transfer in the ICU	7 (4.43)	0 (0)
Use of amines	3 (1.90)	0 (0)
AKI	115 (72.78)	0 (0)
Stage I	73 (46.20)	
Stage II	13 (8.23)	
Stage III	26 (16.46)	
Length of stay in hospital, days (IQR)	6 (4–11)	0 (0)

Abbreviations: AGPN, acute graft pyelonephritis; IQR, interquartile range; KT, kidney transplantation.

with a persistently decreased eGFR, neither mortality nor BPAR was found to correlate with this condition. In addition, recurrent AGPN

episodes did not appear to have an additive detrimental impact on the risk of graft loss.

Estimates derived from previous studies show that AGPN is a relative common complication occurring in KTR, especially between 3 and 6 posttransplantation months.² The incidence of AGPN in the current study was 10.7%—a finding in line with previous observations.^{4,11,12} In a study involving 1387 consecutive KTR (DIVAT cohort), Giral et al.⁴ reported that at least one AGPN episode occurred in 180 patients. They found that AGPN had no significant detrimental impact on graft survival, the only exception being early episodes occurring within the first three posttransplantation months. Other studies confirmed that being diagnosed with AGPN did not increase the risk of graft loss.^{6,8,11} Several potential explanations for these discrepancies can be offered—including differences in study designs and AGPN definitions. UTI in general (i.e., not limited to AGPN alone) seem to portend an increased risk of graft loss. Accordingly, a 10-year study conducted using data from the USRDS registry in Medicare-insured KTR¹³ found that UTI occurring during the first posttransplantation year was a risk factor for graft loss and mortality. In a research involving 2494 KTR, Britt et al.⁶ analyzed the occurrence and recurrence of UTI after transplantation (i.e., no UTI; nonrecurrent UTI, and recurrent UTI). They found that, compared with no UTI, both nonrecurrent and recurrent UTI were independently associated with an increased risk of graft loss. To our knowledge, all of the studies that have investigated the prognostic value of AGPN for graft loss in KTR analyzed this parameter as a baseline variable. However, these investigations were prone to a time-dependent bias as they used a future event (i.e., the development of AGPN) to classify patients at baseline.⁹ In this scenario, our study has two main strengths. First, we used an objective, standardized definition of AGPN. Second, on analyzing the impact of AGPN on clinical outcomes in KTR, this parameter was modeled as a time-dependent variable, and we were then able to demonstrate its adverse prognostic significance both in terms of graft loss and declining eGFR. The latter finding is consistent with published results showing an association between AGPN or UTI with reduced eGFRs.^{14–16} However, Fiorante et al.¹⁷ reported no differences in renal function in KTR who developed AGPN compared with those who did not. Ariza-Heredia et al.¹⁸ evaluated the impact of UTI/AGPN on renal function in KTR, and they concluded that at least one UTI was associated with a decreased GFR, whereas serum creatinine and eGFR were unaffected. In our study, the occurrence of at least one AGPN was independently associated with a fixed effect on eGFR intercept but not on slope. Consistent with previous animal findings,⁷ this observation suggests that AGPN may induce renal scarring—ultimately resulting in an incomplete functional recovery.

Further clarification of the mechanisms by which AGPN may increase the risk of kidney graft loss is necessary. Two main pathways have been hypothesized to account for the detrimental effect of AGPN, including an increased rejection risk¹⁹ and a direct impact of recurrent infections. However, consistent with previous findings obtained in a large cohort,⁴ we found no association between AGPN and BPAR. In this scenario, it can be contended that a histological

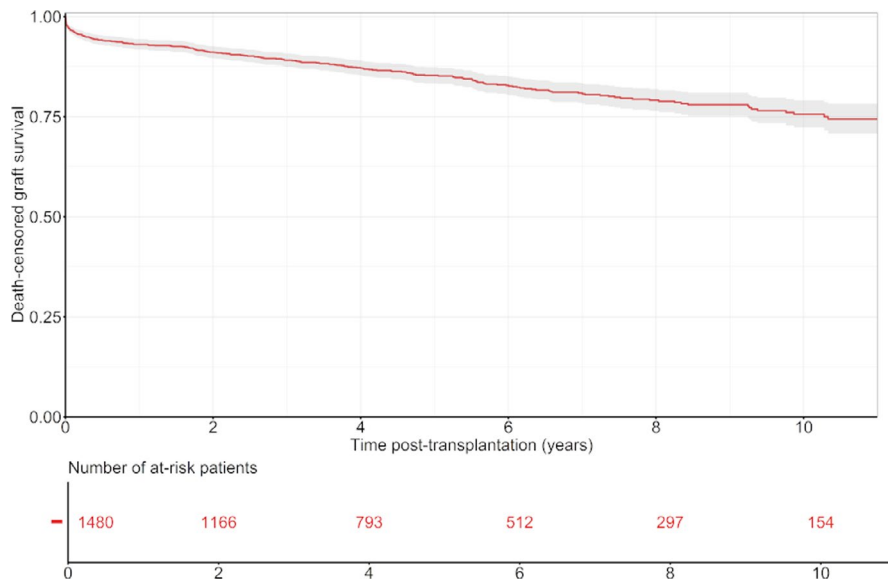


FIGURE 2 Kaplan–Meier estimates for death-censored graft survival in the entire cohort [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Multivariable Cox regression model for death-censored graft survival

	Death-censored graft survival	
	Multivariable HR [95% CI]	<i>p</i> -value
AGPN (first episode), overall effect	1.66 [1.05–2.64]	.03
AGPN without bacteremia	1.43 [0.81–2.54]	.22
AGPN with bacteremia	2.07 [0.96–4.46]	.06
AGPN without AKI	1.57 [0.64–3.86]	.32
AGPN with AKI	1.69 [1.01–2.85]	.05
Male recipient	1.47 [1.11–1.96]	.01
Retransplantation	1.50 [1.09–2.08]	.01
Recipient age (per year)	0.99 [0.98–1.01]	.24
Waiting time on dialysis	1.07 [1.04–1.10]	<.01
Donor age (per year)	1.02 [1.01–1.03]	<.01
Donor vital status		
Living donor	Ref.	
DBD from vascular cause	2.12 [1.01–4.48]	.05
DBD from nonvascular cause	1.30 [0.61–2.78]	.49
DCD	3.27 [1.32–8.10]	.01
Cold ischemia time (per hour)	1.00 [0.98–1.02]	.99
Recipient BMI (per kg/m ²)	1.03 [1.00–1.06]	.07

Abbreviations: AGPN, acute graft pyelonephritis; BMI, body mass index; DBD, donation after brainstem death; DCD, donation after circulatory death.

distinction between AGPN and acute cellular rejection is challenging and represents a potential source of confounding. While a predominant neutrophil infiltration in a renal graft points to an AGPN diagnosis, a clear distinction between cellular rejection—diagnosed according to the Banff criteria^{20–22}—and recurrent infections is

difficult to make when nonspecific mononuclear cells infiltration is observed in the tubule-interstitial compartment. A line of research that holds promise for differential diagnosis is the study of gene expression patterns.²³

On analyzing the impact of recurrent AGPN, we found that recurrences were not independently associated with an increased risk of graft loss. This finding is consistent with the results reported by Britt et al.,⁶ who showed that the presence of recurrent UTI did not increase the risk of graft loss compared with isolated episodes. However, further research is needed to replicate these findings in a larger sample. Interestingly, men were found to have a significantly higher risk of graft loss after a first AGPN episode. Although male sex was identified as a protective factor against the development of AGPN both in our study and in the published literature,^{4,6,24} the clinical sequelae of AGPN (as shown by the higher occurrence of stage III AKI) may be more severe in men than in women. Our findings need to be interpreted in the context of some caveats. First, the retrospective nature of the study could be associated with information bias. Another limitation pertains to the lack of information on urological complications (e.g., ureteral obstruction and stenting) which may act as potential confounders; however, as mentioned above, patients who developed AGPN during the first posttransplantation month were excluded in the sensitivity analysis to mitigate this issue.

Despite these limitations, our data suggest that active AGPN prevention may be clinically useful for kidney transplant recipients. While effective strategies for tackling the onset of UTI and urological complications following kidney transplantation still remain an unmet medical need, various modifiable risk factors—including, among others, the duration of catheterization and the presence of vesicoureteric reflux (VUR)¹⁰—can serve as potential prevention targets. Although late removal (i.e., >6 weeks) of ureteral catheters after kidney transplantation is associated with an increased risk of symptomatic UTI,^{25–27} early catheter withdrawal may result in ureteral leakage or stenosis. In this scenario, current guidelines maintain that catheters and stents should remain positioned for a total of four weeks following kidney

TABLE 4 Multivariable linear mixed model analysis analysis for longitudinal estimated glomerular filtration rate changes

	Association with GFR (baseline effect)			Association with GFR evolution (slope effect)		
	Coefficient	95% CI	p-value	Coefficient	95% CI	p-value
Intercept	108.94	[103.5; 114.37]	<.01			
Time (per year)				-1.84	[-3.76; 0.08]	.06
AGPN (first episode)	-2.29	[-3.23; -1.35]	<.01	-0.20	[-0.53; 0.13]	.23
Recipient age (per year)	-0.10	[-0.19; -0.02]	.02	0.03	[-0.01; 0.06]	.11
Donor age (per year)	-0.57	[-0.65; -0.49]	<.01	-0.05	[-0.08; -0.02]	<.01
Retransplantation	1.57	[-0.45; 3.59]	.13	-1.44	[-2.2; -0.67]	<.01
Male donor	2.41	[0.82; 3.99]	<.01	-1.10	[-1.69; -0.51]	<.01
Male recipient	-0.49	[-2.08; 1.09]	.54	0.93	[0.33; 1.53]	<.01
Donor vital status						
Living donor	Ref.	—	—	Ref.	—	—
DBD from vascular cause	-6.70	[-10.18; -3.23]	<.01	ns	ns	ns
DBD from nonvascular cause	-3.23	[-6.65; 0.2]	.06	ns	ns	ns
DCD	-19.61	[-24.98; -14.25]	<.01	ns	ns	ns
Cold ischemia time (per hour)	-0.14	[-0.26; -0.03]	.02	ns	ns	ns
Recipient BMI (per kg/m ²)	-0.71	[-0.89; -0.53]	<.01	0.11	[0.04; 0.18]	<.01

Abbreviations: AGPN, acute graft pyelonephritis; BMI, body mass index; DBD, donation after brainstem death; DCD, donation after circulatory death; ns, nonsignificant.

transplantation.¹⁰ The potential usefulness of systemic or temporary (i.e., when urinary catheters are inserted and removed) antibiotic prophylaxis is a matter of ongoing debate.^{28,29} Interestingly, a recent randomized clinical trial demonstrated that the perioperative use of fosfomycin was safe and effective in reducing the incidence of symptomatic UTI.³⁰ The routine search for VUR and/or lower tract complications is not currently recommended—the only exception being patients with recurrent UTI.² Owing to the increasing age of KTR, numerous predisposing factors for UTI—including prostatic hyperplasia³¹ in men and pelvic floor dysfunction in women³²—are becoming increasingly common. In this scenario, patients who develop low UTI may be candidates for cystourethrography and/or early assessment of postvoid residual volumes and VUR—with the ultimate goal of preventing the onset of AGPN.

5 | CONCLUSION

In our study, APGN was independently associated with an increased risk of graft loss and a persistently decreased eGFR. However, neither mortality nor BPAR was found to correlate with this condition.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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