Albuminuria and posttransplant chronic kidney disease stage predict transplant outcomes

Ngan N. Lam[1], Marcello Tonelli[2], Krista L. Lentine[3], Brenda Hemmelgarn[2], Feng Ye[1], Kevin Wen[1] and Scott Klarenbach[1]

[1]Department of Medicine, Division of Nephrology, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Medicine, Division of Nephrology, University of Calgary, Calgary, Alberta, Canada; and [3]Center for Abdominal Transplantation, Saint Louis University School of Medicine, St. Louis, Missouri, USA

In 2012, the KDIGO guidelines updated the classification system for chronic kidney disease to include albuminuria. Whether this classification system predicts adverse clinical outcomes among kidney transplant recipients is unclear. To evaluate this, we conducted a retrospective study using linked databases in Alberta, Canada to follow kidney transplant recipients from 2002-2011. We examined the association between an estimated glomerular filtration rate (eGFR of 60 or more, 45-59, 30-44, 15-29 mL/min/1.73 m^2) and albuminuria (normal, mild, heavy) at one year post-transplant and subsequent mortality and graft loss. There were 900 recipients with a functioning graft and at least one outpatient serum creatinine and urine protein measurement at one year post-transplant. The median age was 51.2 years, 38.7% were female, and 52% had an eGFR of 60 mL/min/1.73 m^2 or more. The risk of all-cause mortality and death-censored graft loss was increased in recipients with reduced eGFR or heavier albuminuria. The adjusted incidence rate per 1000 person-years of all-cause mortality for recipients with an eGFR of 15-29 mL/min/1.73 m^2 and heavy albuminuria vs. an eGFR 60 mL/min/1.73 m^2 or more and normal protein excretion was 117 (95% confidence interval 38-371) vs. 15 (9-23) (rate ratio 8). Corresponding rates for death-censored graft loss were 273 (88-1203) vs. 6 (3-9) (rate ratio 49). Reduced eGFR and heavier albuminuria in kidney transplant recipients are associated with an increased risk of mortality and graft loss. Thus, eGFR and albuminuria may be used together to identify, evaluate, and manage transplant recipients who are at higher risk of adverse clinical outcomes.

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Correspondence: *Ngan N. Lam, 11-113 Clinical Sciences Building, 11350-83 Avenue NW, University of Alberta, Edmonton, Alberta, Canada T6G 2G3. E-mail: nlam@ualberta.ca*

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In 2012, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines updated the former classification system for chronic kidney disease (CKD) to include albuminuria.[1,2] The purpose of this classification system was to improve patient care by using evidence-based recommendations to guide health care providers in the identification, evaluation, and management of patients with CKD. For the general population, the risk of adverse outcomes (mortality, progression to end-stage renal disease [ESRD]) at a given level of estimated glomerular filtration rate (eGFR) increases with higher levels of albuminuria.[3–6]

Although previous studies have shown the independent association between lower eGFR or higher albuminuria and adverse clinical outcomes in kidney transplant recipients,[7–10] only a few studies have assessed the combined effects. One single-center longitudinal study of 990 deceased-donor kidney transplant recipients assessed clinical outcomes based on graft function and albuminuria at 3 months post-transplantation.[11] Compared with recipients with an eGFR >60 ml/min per 1.73 m^2 and albuminuria <100 mg/d at 3 months, recipients with an eGFR <60 ml/min per 1.73 m^2 and albuminuria >100 mg/d had a 2-fold higher risk of mortality (adjusted hazard ratio: 1.7, 95% confidence interval [CI] 1.0–2.8; $P = 0.042$) and death-censored graft failure (adjusted hazard ratio: 2.2, 95% CI 1.3-3.7; $P = 0.003$). This study dichotomized early posttransplantation eGFR and albuminuria levels and did not assess the graded levels suggested in the KDIGO guidelines. The investigators also excluded recipients with a lower eGFR (≤30 ml/min per 1.73 m^2) or significant albuminuria (>1 g/d). Another single-center prospective study of 231 kidney transplant recipients suggested that stratification according to the KDIGO risk classes using eGFR and albuminuria was predictive of graft outcomes.[12] Both studies measured albuminuria with 24-hour urinary protein excretion rather than tests more commonly used in clinical practice, such as albumin-creatinine ratio (ACR), protein-creatinine ratio (PCR), or urine dipstick. Recently, White *et al.*[13] reported a single-center study of 269 kidney transplant recipients that found that there was a graded increase in outcomes (doubling of serum creatinine, graft failure, death) with decreasing eGFR and increasing ACR. This study used only 1 set of serum creatinine and albuminuria measurements for their analyses taken at a mean duration of 7 years posttransplantation. Also, the

relatively small cohort resulted in infrequent events and the inability to present adjusted analyses. In the current study, we examined the associations of eGFR and albuminuria with all-cause mortality and graft failure among a large cohort of kidney transplant recipients in 1 Canadian province.

RESULTS

Of 1154 adult kidney-only transplant recipients in Alberta between 2002 and 2011, 900 had a functioning graft and at least 1 outpatient serum creatinine and urine protein measurement at the 1-year posttransplantation date (Supplementary Figure S1). Baseline characteristics of the recipients at their index date by level of eGFR and albuminuria are shown in Table 1. The average number of serum creatinine values was 6.9 (SD 5.3) with a median value of 56.8 ml/min per 1.73 m^2 (interquartile range, 41.9–71.8). At 1 year posttransplantation, 52.0% of the recipients had an eGFR ≥60 ml/min per 1.73 m^2 and 5.9% had an eGFR <30 ml/min per 1.73 m^2. The median age of the recipients was 51.2 years (interquartile range, 40.0–61.2) and 17.6% were 65 years of age or older. The median age increased across the declining levels of eGFR (48.5 years for eGFR ≥60 ml/min per 1.73 m^2 vs. 58.8 years for eGFR <30 ml/min per 1.73 m^2). Less than half of the recipients were female (38.7%).

Of the 900 recipients, 57 (6.3%) had ACR measurements, 561 (62.3%) had PCR measurements, and 899 (99.9%) had urine dipstick measurements. For the recipients with ACR measurements, the average number of tests included was 5.0 (SD 7.0) with a median value 2.7 mg/g (interquartile range, 0.9–21.8). At 1 year, 62.1% of recipients had normal protein excretion when measured by ACR, PCR, or urine dipstick. Compared with these recipients, for the 576 in the sensitivity analyses whose albuminuria was measured by ACR or PCR only, there was a higher proportion of recipients who had mild (44.3% vs. 33.1%) or heavy (5.6% vs. 4.8%) albuminuria ($P < 0.01$) (Table 1).

Adjusted likelihood of clinical outcomes by level of eGFR and albuminuria

After a median follow-up of 61 months (range, 3–119 months), 12.9% ($n = 116$) recipients died and 7.3% ($n = 66$) initiated dialysis. The rate of all-cause mortality increased as kidney function declined, such that the adjusted incidence rate per 1000 person-years for the eGFR ≥60, 45 to 59, 30 to 44, and 15 to 29 ml/min per 1.73 m^2 was 18.1, 20.5, 36.8, and 42.0, respectively ($P < 0.01$) (Table 2). For the lower levels of eGFR (30–44 and 15–29 ml/min per 1.73 m^2), the adjusted incidence rates also increased with worsening albuminuria ($P < 0.01$). The risk of all-cause mortality was 8-fold higher for kidney transplant recipients with an eGFR of 15 to 29 ml/min per 1.73 m^2 and heavy albuminuria compared with recipients with an eGFR ≥60 ml/min per 1.73 m^2 and normal protein excretion (rate ratio: 7.9, 95% CI 3.3–18.8) (Figure 1a). Even recipients with relatively preserved renal function (eGFR 45–59 and 30–44 ml/min per 1.73 m^2) but mild albuminuria had a 2-fold increased risk of all-cause mortality compared with recipients with an eGFR ≥60 ml/min per 1.73 m^2 and normal protein excretion (rate ratio: 2.2 and 2.7, respectively).

The rates of death-censored graft loss also increased with lower levels of kidney function (adjusted incidence rate per 1000 person-years: 8.6, 10.3, 22.7, and 63.5 for eGFR ≥60, 45 to 59, 30 to 44, and 15 to 29 ml/min per 1.73 m^2, respectively, $P < 0.01$) (Table 2). Within each category of the eGFR, the adjusted rates increased with heavier albuminuria (all $P < 0.05$). The risk of death-censored graft loss was 49-fold higher for kidney transplant recipients with an eGFR of 15 to 29 ml/min per 1.73 m^2 and heavy albuminuria compared with recipients with an eGFR ≥60 ml/min per 1.73 m^2 and normal protein excretion (rate ratio: 49.4, 95% CI 17.4–140.6) (Figure 1b). Recipients with relatively preserved renal function (eGFR of 45–59 and 30–44 ml/min per 1.73 m^2) but heavy albuminuria had a 10-fold and 34-fold, respectively, increased risk of death-censored graft loss compared with recipients with an eGFR ≥60 ml/min per 1.73 m^2 and normal protein excretion.

Similar results were observed for death with a functioning graft and all-cause graft loss (Table 3, Figure 1c and d). We repeated the analyses for the subgroup of recipients ($n = 576$) whose albuminuria was measured by ACR or PCR alone (not by urine dipstick) and found similar results; however, given the smaller number of events, the CIs were wider (Supplementary Table S1).

DISCUSSION

In this population-based study of adults with a first kidney transplant, we found that the risk of all-cause mortality and graft loss significantly increased with worsening eGFR. Generally, in each category of eGFR, the risk was also more pronounced with worsening albuminuria. Comparing an eGFR of 15 to 29 ml/min per 1.73 m^2 and heavy albuminuria with an eGFR ≥60 ml/min per 1.73 m^2 with normal albuminuria, the risks of all-cause mortality and death with a functioning graft were 8-fold and 5-fold higher, respectively. Similarly, the risks of death-censored graft loss and all-cause graft failure were 49-fold and 15-fold higher, respectively, for the recipients with reduced graft function and significant albuminuria. We also found an increased risk among recipients with relatively preserved renal function (eGFR 45–59 and 30–44 ml/min per 1.73 m^2) and mild to heavy albuminuria. These results were consistent among the subgroup of recipients whose albuminuria was measured by ACR or PCR alone.

In the nontransplant population, the interactive effects of reduced renal function and albuminuria on outcomes, such as mortality and progression to ESRD, have been reported.[3,5,6,14,15] In a retrospective study of almost 1 million participants from 2002 to 2007 with a median follow-up of 35 months, Hemmelgarn *et al.*[3] reported that the risk of all-cause mortality, myocardial infarction, and progression to kidney failure was higher in those with a lower eGFR or heavier albuminuria. For example, the adjusted mortality rate was

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