Infection in advanced chronic kidney disease leads to increased risk of cardiovascular events, end-stage kidney disease and mortality

Hicham I. Cheikh Hassan[1], Mila Tang[2], Ognjenka Djurdjev[2,4], David Langsford[1], Manish M. Sood[3] and Adeera Levin[1,2,4]

[1]Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; [2]British Columbia Provincial Renal Agency, Vancouver, British Columbia, Canada; and [3]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

The risk of infection in advanced chronic kidney disease (CKD) and its subsequent impact on adverse outcomes are not well established. Therefore, we determined the association of an infectious episode with the subsequent risk of cardiovascular ischemia, congestive heart failure, end-stage kidney disease or mortality in a Canadian prospective cohort (CanPREDDICT) of patients with advanced CKD (eGFR: 15–45 ml/min/1.73m^2) followed by nephrologists for up to 5 years. Infectious episodes were classified by anatomic location and identified by positive culture, hospital admission, or use of antibiotics. Competing risk models were used to examine the time-varying risk of infection and the risk of cardiovascular ischemia, congestive heart failure, or end-stage kidney disease accounting for the competing risk of mortality. All outcomes were independently adjudicated. Of 2370 patients (mean age, 68 years; mean baseline eGFR, 28.2 mL/min/1.73m^2), 575 patients (24.3%) had recorded infections; 378 had 1 infection episode, whereas 197 had 2 or more episodes, the most common being urinary and respiratory. An infectious episode was independently associated with an increased risk of cardiovascular ischemia (hazard ratio 1.80, 95% confidence interval 1.24–2.60), congestive heart failure (hazard ratio, 3.2; confidence interval, 2.25–4.61), end-stage kidney disease (hazard ratio, 1.58; confidence interval, 1.22–2.05) or mortality (hazard ratio, 3.39; confidence interval, 2.65–4.33). Thus, there is a high risk of infection in advanced CKD being associated with subsequent adverse outcomes.

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Correspondence: *Adeera Levin, 1081 Burrard Street, Rm 60101A, Vancouver, BC, V6Z1Y8 Canada. E-mail: alevin@providencehealth.bc.ca or msood99@gmail.com*

[4]OD and AL are CanPREDDICT Investigators.

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Chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) ≤ 60 ml/min per 1.73 m^2 for >3 months and/or a urine albumin-to-creatinine ratio (ACR) of ≥30 mg/mmol.[1] It is common, affecting 10% to 15% of adults in North America, Europe, Australia, and China.[2–7] Patients with CKD experience increased morbidity and mortality compared with the non-CKD population,[5,8–10] primarily from cardiovascular disease.

Increased risk of infection is well recognized in the end-stage kidney disease population (ESKD). The US Renal Data System reports a doubling of infection-related hospitalizations in ESKD patients, whereas those for cardiovascular and other causes are in decline.[8] In patients undergoing renal replacement therapy, infection is one of the most common causes of death, including cardiovascular events and withdrawal.[9] Half of newly diagnosed ESKD patients die or rehospitalized within 30 days of an infection-related admission.

Existing information on infection in the nondialysis CKD population and its contribution to adverse events remains unclear. Evidence of an association between reduced kidney function and increasing infectious risk exists.[8,11–13] Patients with CKD appear to be at a higher risk of acute community-acquired infections,[14] septicemia,[13] and pneumonia.[12] There is sparse evidence that infection causes a faster decline in kidney function,[15] precipitates initiation of dialysis, and increases mortality.[16] However, these studies were limited to examining specific causative organisms or anatomic infection sites such as *Staphylococcus aureus*,[17] pneumonia,[12,15,18] and septicemia.[13] Existing studies were also performed primarily using administrative databases with questionable data quality and validity. Furthermore, recent evidence in the general population demonstrates a strong association between infection and cardiovascular events, the most common complications in CKD patients.[19,20]

We set out to describe the rate of infection in advanced CKD and its subsequent impact on cardiovascular ischemia, congestive heart failure (CHF), ESKD, and mortality in a prospective national pan-Canadian cohort (CanPREDDICT [Canadian Study of Prediction of Risk and Evolution to Dialysis, Death and Interim Cardiovascular Events Over Time]).[21] We hypothesize that an infectious episode will be associated with an increased risk of adverse outcomes.

RESULTS

Figure 1 depicts the analytic cohort derivation: 2370 patients were included in this analysis. The study population was predominantly elderly (68 years of age), male (62%), white (89%) with a high prevalence of diabetes (48%) and cardiovascular disease (44.5%) (Table 1). The most common cause of CKD was diabetes (28%) and hypertensive nephrosclerosis (26%). The mean eGFR at recruitment was 28.2 ± 9 ml/min per 1.73 m^2.[9] The median follow-up time was 3.5 years (interquartile range [IQR], 2.3–4.0) with a total of 7279.9 patient-years of follow-up. Infection episodes were recorded in 575 patients (24.3%).

There were no infections in 1795 patients (75.7%), 1 infection in 378 patients (15.9%), and ≥2 infections in 197 patients (8.3%). The most common infections were respiratory (11.6%) and urinary (10.6%). In 30 reported infections, no location was indicated. The total infection count over 6100.41 infection exposure-years was 868 infections, yielding an infection rate of 14.3 infections/100 patient-years. The median time from cohort entry to first infectious episode was 1.3 years (IQR, 0.44–1.90). When examined by eGFR, there were lower infection rates in those with a baseline eGFR > 30 (12.2/100 patient-years) versus those with an eGFR < 30 ml/min per 1.73 m^2 (16.1 in the eGFR 20–30 group and 15.4 in the eGFR <20 group).

Table 1 highlights the baseline characteristics, comparing patients with any infection with those with no infections. Patients in whom an infection developed were more likely, compared with those with no infection, to have diabetes (52% vs. 46%, $P = 0.012$) and cardiovascular disease (52% vs. 42%, $P < 0.001$) and less likely to be male (52% vs. 66%, $P < 0.001$) or have glomerulonephritis as a cause of kidney disease (8% vs. 13%, $P = 0.001$). Patients with infections also had, at baseline, a lower albumin (40 vs. 41 g/l, $P < 0.001$) and hemoglobin (121 vs. 124 g/l, $P < 0.01$) level and a higher C-reactive protein (CRP) (3.5 vs. 2.6 mg/l, $P < 0.001$) level. Urine protein excretion (urine ACR or urine protein-to-creatinine ratio [PCR]) was not statistically different between those with and without infections ($P = 0.41$ and $P = 0.86$, respectively). This remained the case even for patients with higher levels of proteinuria (ACR > 250 mg/mmol vs. ACR < 250 mg/mmol = 24.3% vs. 24.3%, $P = 0.97$).

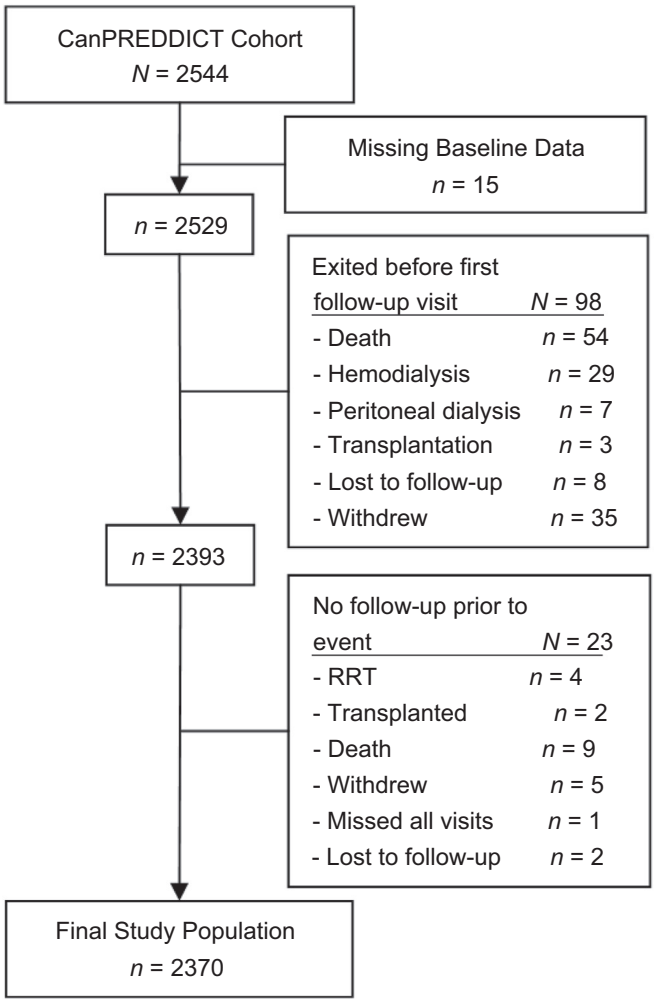

Figure 1 | Final study population after exclusions. RRT, renal replacement therapy.

Association of infection with cardiovascular ischemia, CHF, ESKD, and mortality

Over the study period, the crude rates per 100 patient-years for cardiovascular ischemia, CHF, ESKD, and mortality were 3.06, 2.46, 5.43, and 4.50 patients, respectively (Table 2). The median time in years from an infectious episode to cardiovascular ischemia, CHF, ESKD, and mortality were 2.09 (IQR, 0.86–2.99), 2.12 (IQR, 0.99–3.00), 2.53 (IQR, 1.35–3.00), and 2.53 (IQR, 1.35–3.00), respectively. The risk of all adverse outcomes was higher after infection. Infection was independently associated with cardiovascular ischemia (hazard ratio [HR] 1.80, 95% confidence interval [CI] 1.24–2.60), CHF (HR 3.22, 95% CI 2.25–4.61), ESKD (HR 1.58, 95% CI 1.22–2.05), and mortality (HR 3.39, 95% CI 2.65–4.33) (Table 3). In models excluding patients with a history of cardiovascular ischemia and CHF, the adjusted HRs for cardiovascular ischemia, CKF, ESKD, and mortality were 1.14 (95% CI 0.57–2.31), 2.47 (95% CI 1.15–5.32), 1.47 (95% CI 1.05–2.07), and 4.23 (95% CI 2.66–6.73). Additional models including the number of comorbidities resulted in slight attenuation of the effect estimate; however, all outcomes remained statistically significant (results not shown). Men had a stronger association with infection and ischemia (interaction $P = 0.052$) or CHF (interaction $P = 0.004$) (Figure 2). The association of ischemia and infection was higher in those with higher serum albumin levels (interaction $P = 0.01$) and a higher ACR (interaction $P = 0.04$). ACR was an effect modifier for the association of infection and ESKD (interaction $P = 0.01$), and no statistically significant effect modifiers were observed between infection and mortality (Figure 3). CHF was associated with pneumonia (HR 2.54, 95% CI 1.04–6.16) and bacteremia (HR 3.13, 95% CI 1.16–8.44) (Supplementary Table S1). Bacteremia was also associated with an increased risk of ESKD (HR 3.15, 95% CI