Pre-admission proteinuria impacts risk of non-recovery after dialysis-requiring acute kidney injury

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Renal recovery after dialysis-requiring acute kidney injury (AKI-D) is an important clinical and patient-centered outcome. Here we examined whether the pre-admission proteinuria level independently influences risk for non-recovery after AKI-D in a community-based population. All adult members of Kaiser Permanente Northern California who experienced AKI-D between January 1, 2009 and September 30, 2015 were included. Pre-admission proteinuria levels were determined by dipstick up to four years before the AKI-D hospitalization and the outcome was renal recovery (survival and dialysis-independence four weeks and more) at 90 days after initiation of renal replacement therapy. We used multivariable logistic regression to adjust for baseline estimated glomerular filtration rate (eGFR), age, sex, ethnicity, short-term predicted risk of death, comorbidities, and medication use. Among 5,347 adults with AKI-D, the mean age was 66 years, 59% were men, and 50% were white. Compared with negative/trace proteinuria, the adjusted odds ratios for non-recovery (continued dialysis-dependence or death) were 1.47 (95% confidence interval 1.19–1.82) for 1+ proteinuria and 1.92 (1.54–2.38) for 2+ or more proteinuria. Among survivors, the crude probability of recovery ranged from 83% for negative/trace proteinuria with baseline eGFR over 60 mL/min/1.73m^2 to 25% for 2+ or more proteinuria with eGFR 15–29 mL/min/1.73m^2. Thus, the pre-AKI-D level of proteinuria is a graded, independent risk factor for non-recovery and helps to improve short-term risk stratification for patients with AKI-D.

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Dialysis-requiring acute kidney injury (AKI-D) is among the most severe acute medical conditions affecting hospitalized patients[1,2] and is independently associated with increased short-term mortality and long-term adverse outcomes.[2–5] Some reports indicate that the incidence of AKI-D has recently increased as much as 10% per year nationally.[6–10] Meanwhile, in-hospital mortality rates among patients with AKI-D have declined,[6,11] suggesting that the overall number of AKI-D survivors is increasing and that outcomes in this vulnerable population deserve more attention. Existing studies among AKI-D survivors have reported that up to one-third remain dialysis-dependent at the time of hospital discharge, of whom 40% to 80% remain dialysis-dependent at 90 days after initiation of renal replacement therapy (RRT) and are typically deemed to have end-stage renal disease (ESRD).[1,12–14]

Renal recovery after AKI-D—defined here as return of sufficient native kidney function to come off dialysis—is a critically important clinical and patient-oriented outcome. Although a majority of patients with normal baseline renal function eventually recover enough to come off dialysis if they survive the AKI-D hospitalization,[15] many cases of AKI-D represent AKI superimposed on chronic kidney disease, and these patients may transition directly to ESRD.[3,15,16]

Predicting the probability of recovery after AKI-D is a common dilemma faced by physicians (including nephrologists, intensivists, and hospitalists), patients, and patients' families. The ability to predict recovery accurately would help guide decisions regarding dialysis access placement (e.g., temporary versus tunneled catheters during the AKI-D hospitalization, earlier fistula or graft placement after hospital discharge). Improved prognostic abilities would also influence the timing of outpatient dialysis-chair placement (which could affect initial hospital length of stay) and guide appropriate counseling for patients and their families.

However, we currently have limited ability to predict renal recovery in an individual AKI-D patient.[12,17] The identification of independent risk factors for non-recovery is the first step toward improving risk stratification after AKI-D. Reduced baseline estimated glomerular filtration rate (eGFR) before an AKI-D episode has been consistently shown to predict non-recovery after AKI-D.[3,16] Other selected risk

factors that have been implicated include older age, diabetes mellitus, heart failure, and greater comorbidity burden.[12,13,18,19]

Recently, there has been increasing recognition of the importance of proteinuria—independent of eGFR—as a risk factor for kidney-related adverse outcomes,[20–23] and these associations are consistent even with proteinuria determined semiquantitatively using urine-dipstick assessment.[24–28] Whether pre-admission proteinuria level is an independent risk factor for and helps predict non-recovery after AKI-D is not known. We examined these questions in a large, diverse, community-based population to fill this key prognostic knowledge gap.

RESULTS
Cohort assembly and baseline characteristics
We initially identified 13,213 patients who received RRT in the hospital between January 1, 2009 and September 30, 2015. After excluding patients who were on chronic dialysis before the index hospitalization, age <18 years, unknown sex, had <12 consecutive months of membership or drug coverage before the index hospitalization, or had baseline eGFR >150 ml/min per 1.73 m^2, we had a final analytic cohort of 5347 AKI-D patients (Figure 1).

Overall, 3633 of eligible patients (68%) had pre-admission dipstick proteinuria data available within 4 years before the AKI-D hospitalization (median: 128 days, interquartile range: 35 to 390) (Table 1): 876 (24.1%) had negative or trace proteinuria, 930 (25.6%) had 1+ proteinuria, and 1827 (50.3%) had ≥2+ proteinuria. Compared with patients with negative or trace proteinuria, those with greater proteinuria were more likely to be persons of color, to be current smokers, and to have lower baseline kidney function, hypertension, diabetes, and anemia. Those with greater

proteinuria were less likely to have documented mitral or aortic valvular disease, atrial flutter or fibrillation, and cirrhosis.

Outcomes after AKI-D by proteinuria level
In the overall cohort, 3601 (67.3%) were classified as non-recovery at 90 days after initiation of acute RRT. Among those who did not recover, 1542 died while on dialysis or within 28 days of stopping dialysis.

The crude risk for non-recovery was higher with greater pre-admission proteinuria level: 57.8% (95% confidence interval [CI]: 54.5%–61.0%) for negative or trace, 68.8% (95% CI: 65.8%–71.8%) for 1+, and 81.0% (95% CI: 79.2%–82.8%) for ≥2+ (Table 2 shows results further stratified by eGFR). In multivariable analyses, compared with negative or trace proteinuria, higher level of pre-admission proteinuria was associated with a graded, increased adjusted odds of non-recovery, even after accounting for potential differences in demographic characteristics, baseline eGFR, comorbidities, short-term predicted mortality,[29] and pre-admission medication use (Figure 2, Supplementary Table S1). The addition of proteinuria to our multivariable model significantly improved the discrimination of non-recovery after AKI-D, as demonstrated by changes in the C-statistic, net reclassification improvement, and integrated discrimination improvement (Table 3).

In a sensitivity analysis that excluded patients with the highest 20% predicted risk of short-term death, similar findings were observed: adjusted odds ratios were 1.42 (95% CI: 1.12–1.79) for 1+ proteinuria and 2.06 (95% CI: 1.62–2.61) for ≥2+ proteinuria as compared with negative or trace proteinuria. We also performed another sensitivity analysis including only patients who had dipstick proteinuria measured within 1 year of the index hospitalization and
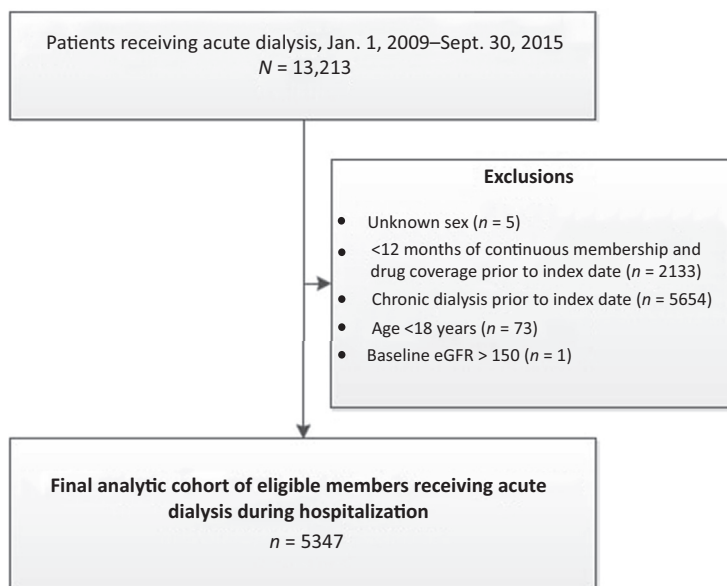

Figure 1 | Identification of study cohort containing adults experiencing dialysis-requiring acute kidney injury. eGFR, estimated glomerular filtration rate.