Supplemental Material

Hospitalization Trajectories and Risks of ESKD and Death in Individuals with CKD

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Supplemental Methods

CRIC Study

Individuals were included if they met specific age-defined criteria for estimated glomerular filtration rate (eGFR) of 20 to 70 ml/min/1.73m^2. Because CKD is more common in minorities, black and Hispanic participants were oversampled. Exclusion criteria included inability to provide consent, institutionalization, enrollment in competing studies, pregnancy, New York Heart Association class III or IV congestive heart failure, human immunodeficiency virus infection, multiple myeloma, polycystic kidney disease, kidney cancer, cirrhosis, recent chemotherapy or immunosuppressive therapy, organ transplantation, or prior dialysis treatment for at least 1 month. The CRIC Study participants were followed up annually by clinic visits and through telephone contact visits every 6 months.

Hospitalization Data

At each annual study visit, we calculated cumulative all-cause hospitalizations as the sum of hospitalizations through that respective study visit. Causes for hospitalization were categorized using the Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software categorization scheme on the basis of the first position International Classification of Diseases, Ninth Revision code (ICD-9).[1] Since a number of infectious disease diagnoses are categorized under other organ systems instead of the 'Infection' category in the AHRQ Clinical Classifications Software, authors AS and RM reviewed all AHRQ categories and re-classified any infectious disease diagnosis to the 'Infection' category to better represent infectious causes for hospitalization.

Covariate Data

We used covariate data obtained at the year 4 study visit, which included sociodemographic characteristics, medical history, lifestyle behaviors, medications, standardized blood pressure measurements, anthropometric measures, and laboratory measurements. We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate eGFR.[2] We used either a 24-hour urine protein excretion or a spot urine protein to creatinine ratio to quantify proteinuria.[3] If both values were present, we used the 24-hour urine protein excretion value.

Missing Data

To account for missing covariate data, we used multiple imputation, for which we used a multiple regression procedure in IVEware 2.0.[4] We generated five imputed datasets and imputed values for missing data on the basis of the observed data with the assumption that the data was missing at random. Imputations were created through a sequence of multiple regression models.[5] We combined the test results across the imputed datasets using the rules of Rubin.[6]

1.   Healthcare Cost and Utilization Project: Clinical Classifications Software (CCS) for ICD-9-CM. Available at: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp
2.   Levey, A, Stevens, L, Schmid, C, Zhang, Y, 3rd, CA, Feldman, H, et al.: A new equation to estimate glomerular filtration rate. *Ann Intern Med,* 150**:** 604-612, 2009.
3.   Ricardo, AC, Yang, W, Sha, D, Appel, LJ, Chen, J, Krousel-Wood, M, et al.: Sex-Related Disparities in CKD Progression. *J Am Soc Nephrol,* 30**:** 137-146, 2019.
4.   Raghunathan, T, Solenberger, P, Van Hoewyk, J: IVEware: Imputation and Variance Estimation Software, Ann Arbor, MI, University of Michigan, Institute for Social Research, Survey Research Center. 2000.

5.   Raghunathan, T, Lepkowski, J, Van Hoewyk, J: A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol,* 27**:** 85-95, 2001.

6.   Rubin, D: *Multiple Imputation for Nonresponse in Surveys,* New York, John Wiley and Sons, 2004.
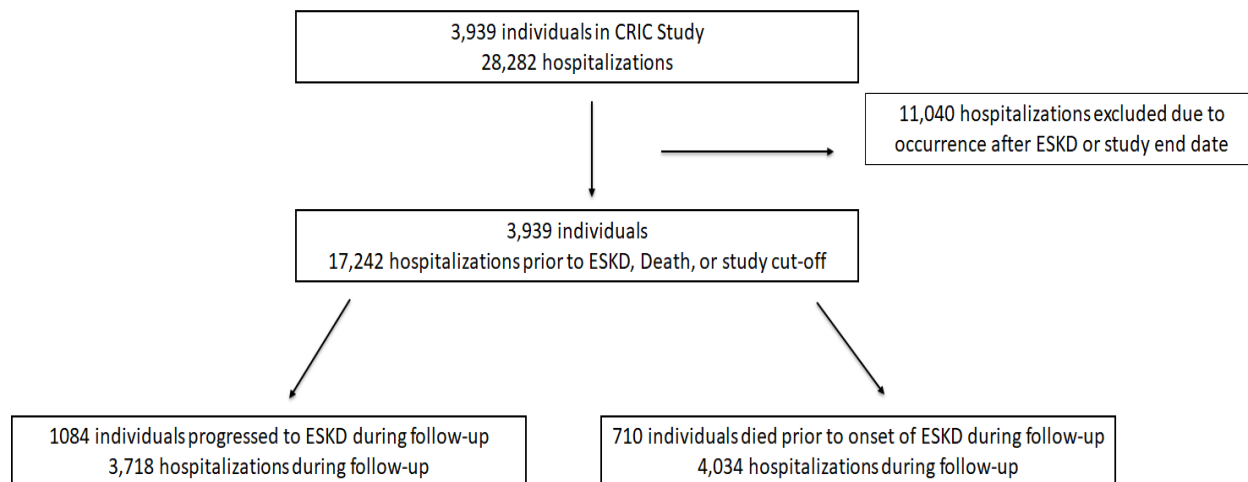
Supplemental Figure 1. Flowchart describing participants included to characterize longitudinal evolution of hospital utilization
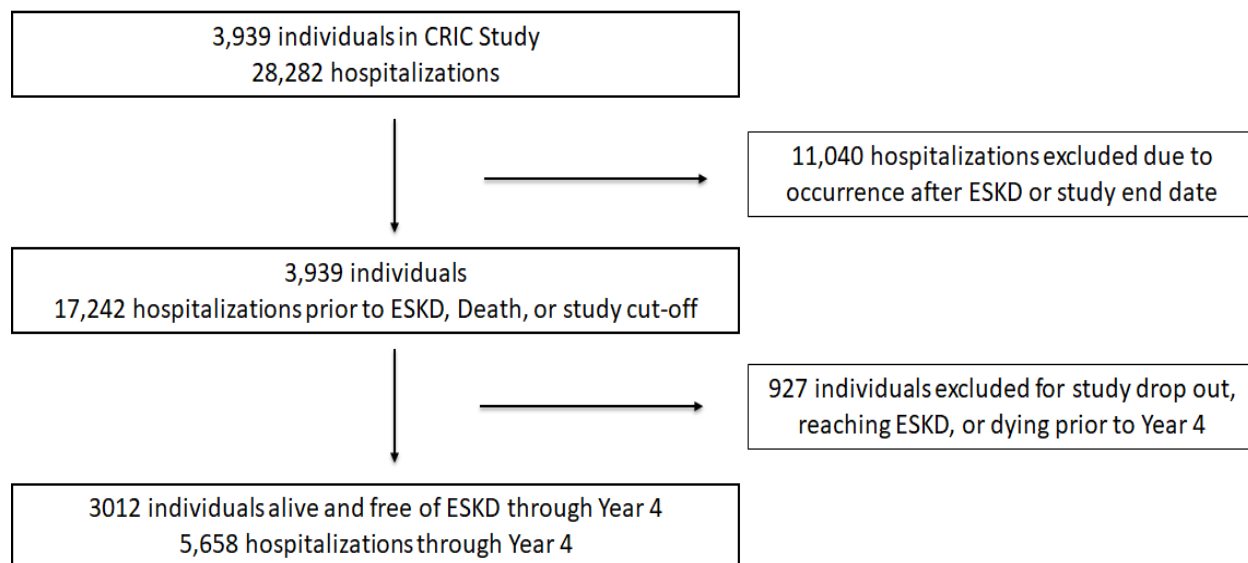
Supplemental Figure 2. Flowchart describing study cohort to derive hospitalization trajectories
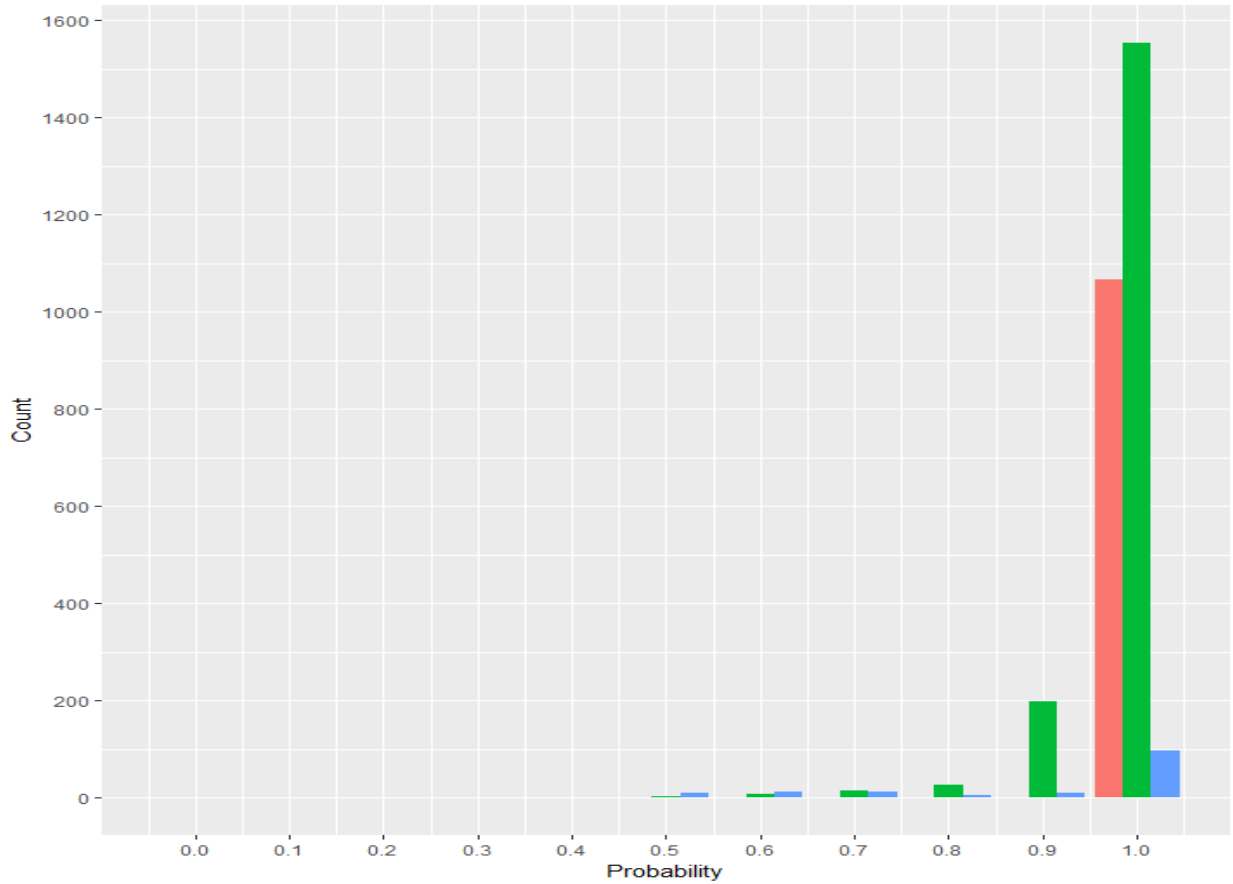
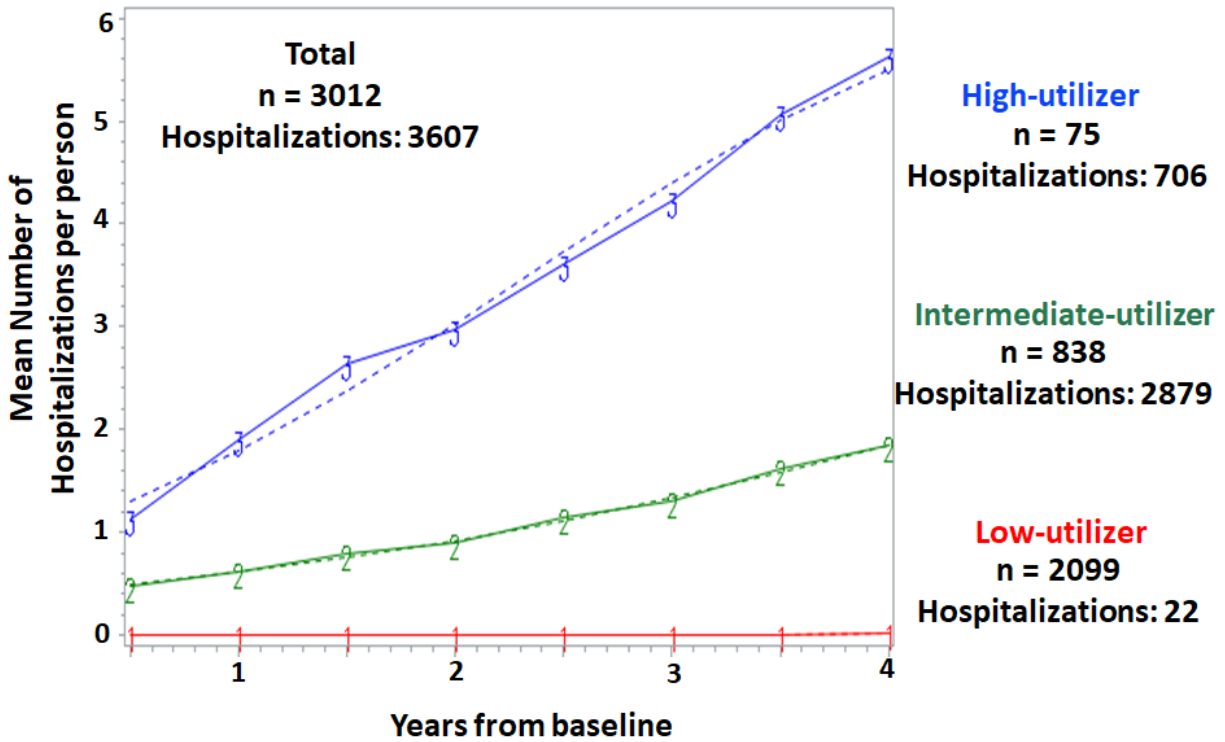**Supplemental Figure 3. Posterior probability of membership to each hospitalization trajectory group**

The mean posterior probabilities and 95% confidence intervals were 1.0 (1.0 – 1.0), 0.98 (0.97 – 0.98), and 0.89 (0.87 – 0.92) for the low- (red), intermediate- (green), and high-utilizer (blue) groups, respectively.

Supplemental Figure 4. Cumulative all-cause hospitalization trajectories for hospitalizations with length of stay greater than 1 day

There were 3607 hospitalizations that had a length of stay greater than 1 day among 3012 participants who did not progress to ESKD and survived to their year 4 study visit. The low-utilizer group had 2099 participants with 22 hospitalizations, the intermediate-utilizer group had 838 participants with 2879 hospitalizations, and the high-utilizer group had 75 individuals with 706 hospitalizations.
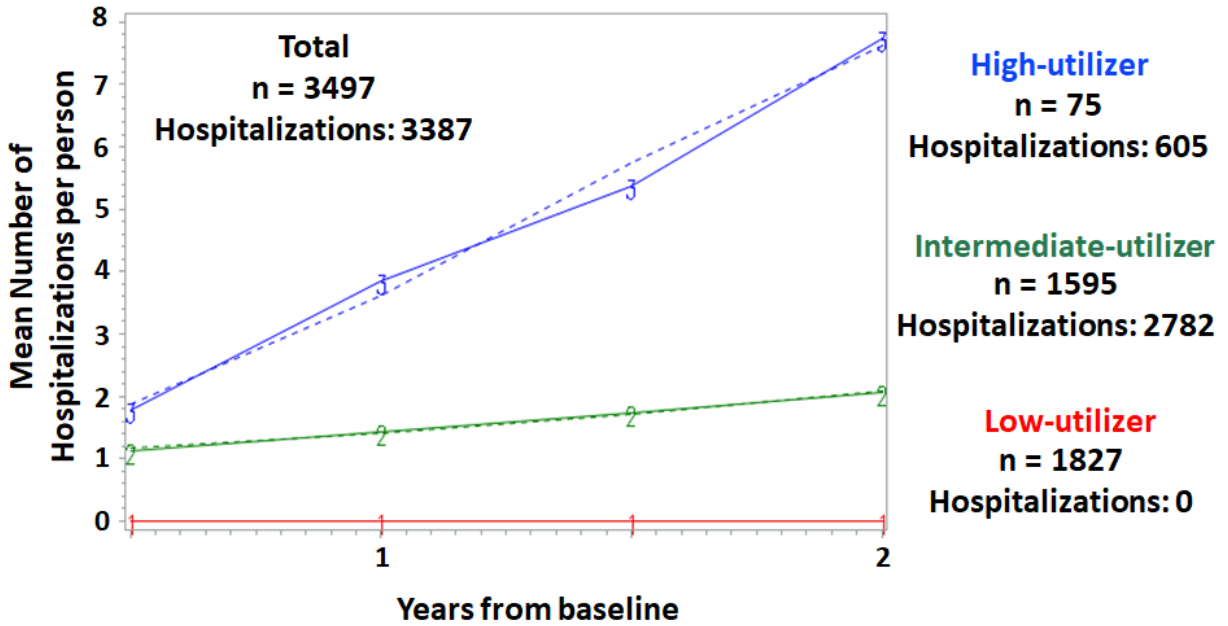
Supplemental Figure 5. Cumulative all-cause hospitalization trajectories for hospitalizations through the year 2 visit

There were 3387 hospitalizations among 3497 participants who did not progress to ESKD and survived to their year 2 study visit. The low-utilizer group was comprised of 1827 participants who were not hospitalized through their year 2 study visit. The intermediate-utilizer group had 1595 participants with 2782 hospitalizations, and the high-utilizer group had 75 participants with 605 hospitalizations.

Supplemental Table 1. Risks of ESKD and death by hospitalization trajectory for hospitalizations with length of stay greater than 1 day

Trajectory Groups (N = 3012)		ESKD					
	N	No. Events	Events per 1000 person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Low-utilizer	2099	324	28.9	Reference	Reference	Reference	Reference
Intermediate-utilizer	838	200	52.9	1.80 (1.51 – 2.14)	1.79 (1.49 – 2.15)	1.61 (1.34 – 1.94)	1.33 (1.10 – 1.61)
High-utilizer	75	20	70.8	2.36 (1.50 – 3.71)	2.39 (1.51 – 3.78)	2.14 (1.34 – 3.40)	1.66 (1.03 – 2.66)
		ESKD-censored death					
	N	No. Events	Events per 1000 person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Low-utilizer	2099	220	19.6	Reference	Reference	Reference	Reference
Intermediate-utilizer	838	193	51.1	2.62 (2.16 – 3.18)	2.14 (1.76 – 2.61)	1.92 (1.57 – 2.35)	1.83 (1.50 – 2.25)
High-utilizer	75	24	84.9	4.39 (2.88 – 6.69)	4.17 (2.70 – 6.43)	3.74 (2.41 – 5.82)	3.46 (2.22 – 5.40)

Model 1 is unadjusted
Model 2 is stratified by center and adjusts for age, sex, race, ethnicity, income level, education level, health insurance
Model 3 is Model 2 with further adjustment for systolic blood pressure, body mass index, smoking status, diabetes mellitus, any cardiovascular disease, ACEi/ARB, beta-blockers, statins, anti-platelet drugs
Model 4 is Model 3 with further adjustment for hemoglobin, serum albumin, natural log transformed proteinuria, and eGFR

Supplemental Table 2. Risks of ESKD and death by hospitalization trajectory after introduction of 1-year lag period

Trajectory Groups (N = 2774)	ESKD						
	N	No. Events	Events per 1000 person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Low-utilizer	1006	102	21.5	Reference	Reference	Reference	Reference
Intermediate-utilizer	1633	273	38.3	1.78 (1.42 – 2.23)	1.79 (1.42 – 2.26)	1.66 (1.31 – 2.10)	1.65 (1.30 – 2.09)
High-utilizer	135	28	55.6	2.53 (1.67 – 3.85)	2.26 (1.47 – 3.48)	2.07 (1.34 – 3.19)	1.90 (1.21 – 2.96)
	ESKD-censored death						
	N	No. Events	Events per 1000 person-years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Low-utilizer	1006	81	17.1	Reference	Reference	Reference	Reference
Intermediate-utilizer	1633	238	33.4	1.96 (1.53 – 2.53)	1.63 (1.26 – 2.11)	1.50 (1.15 – 1.95)	1.47 (1.13 – 1.91)
High-utilizer	135	35	69.5	4.11 (2.76 – 6.11)	3.62 (2.40 – 5.45)	3.19 (2.10 – 4.86)	2.91 (1.91 – 4.43)

Sensitivity analysis introduced a 1-year lag, starting survival time at the year 5 visit after baseline, with adjustment for covariates at year 4.

Model 1 is unadjusted
Model 2 is stratified by center and adjusts for age, sex, race, ethnicity, income level, education level, health insurance
Model 3 is Model 2 with further adjustment for systolic blood pressure, body mass index, smoking status, diabetes mellitus, any cardiovascular disease, ACEi/ARB, beta-blockers, statins, anti-platelet drugs
Model 4 is Model 3 with further adjustment for hemoglobin, serum albumin, natural log transformed proteinuria, and eGFR

Supplemental Table 3. Risks of ESKD and death by hospitalization trajectory formed through the year 2 visit

Trajectory Groups (N = 3497)	ESKD						
	N	**No. Events**	**Events per 1000 person-years**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 HR (95% CI)**
Low-utilizer	1827	360	29.5	Reference	Reference	Reference	Reference
Intermediate-utilizer	1595	448	48.3	1.62 (1.41 –1.86)	1.58 (1.37 – 1.82)	1.48 (1.28 – 1.71)	1.33 (1.15 – 1.54)
High-utilizer	75	28	92.6	3.02 (2.05 – 4.43)	2.72 (1.83 – 4.04)	2.28 (1.53 – 3.42)	2.29 (1.52 – 3.45)
	ESKD-censored death						
	N	**No. Events**	**Events per 1000 person-years**	**Model 1 HR (95% CI)**	**Model 2 HR (95% CI)**	**Model 3 HR (95% CI)**	**Model 4 HR (95% CI)**
Low-utilizer	1827	235	19.3	Reference	Reference	Reference	Reference
Intermediate-utilizer	1595	317	34.2	1.80 (1.52 – 2.13)	1.64 (1.38 – 1.94)	1.47 (1.23 – 1.75)	1.44 (1.20 – 1.71)
High-utilizer	75	26	86.0	4.66 (3.11 – 6.99)	5.25 (3.44 – 8.02)	4.35 (2.83 – 6.69)	4.04 (2.63 – 6.23)

Model 1 is unadjusted

Model 2 is stratified by center and adjusts for age, sex, race, ethnicity, income level, education level, health insurance

Model 3 is Model 2 with further adjustment for systolic blood pressure, body mass index, smoking status, diabetes mellitus, any cardiovascular disease, ACEi/ARB, beta-blockers, statins, anti-platelet drugs

Model 4 is Model 3 with further adjustment for hemoglobin, serum albumin, natural log transformed proteinuria, and eGFR

Supplemental Table 4. Risks of ESKD and death by hospitalization trajectory after adjustment for baseline hospitalization status

Trajectory Groups (N = 3012)	ESKD				
	N	No. Events	Events per 1000 person-years	Fully Adjusted*	Further adjustment for baseline hospitalization status**
Low-utilizer	1066	137	23.7	Reference	Reference
Intermediate-utilizer	1802	368	41.4	1.49 (1.22 – 1.84)	1.52 (1.22 – 1.90)
High-utilizer	144	39	64.8	1.75 (1.20 – 2.56)	1.83 (1.20 – 2.80)
	ESKD-censored death				
	N	No. Events	Events per 1000 person-years	Fully Adjusted*	Further adjustment for baseline hospitalization status
Low-utilizer	1066	100	17.3	Reference	Reference
Intermediate-utilizer	1802	299	33.6	1.48 (1.17 – 1.87)	1.44 (1.12 – 1.85)
Rapid-utilizer	144	38	63.2	2.58 (1.74 – 3.83)	2.44 (1.57 – 3.78)

*Model is stratified by center and adjusts for age, sex, race, ethnicity, income level, education level, health insurance, systolic blood pressure, body mass index, smoking status, diabetes mellitus, any cardiovascular disease, ACEi/ARB, beta-blockers, statins, anti-platelet drugs, hemoglobin, serum albumin, natural log transformed proteinuria, and eGFR

**Model is further adjusted for hospitalization within the first year (baseline to the year 1 visit)

Supplemental Table 5. Risks of ESKD and death by number of hospitalizations in the first year of the CRIC Study

Hospitalization groups (N = 3775)	ESKD			
	N	No. Events	Events per 1000 person-years	Fully Adjusted*
0 hospitalizations	2618	632	30.0	Reference
1 hospitalization	789	247	43.4	1.16 (1.00 – 1.35)
>1 hospitalization	368	123	50.7	1.18 (0.96 – 1.44)
	ESKD-censored death			
	N	No. Events	Events per 1000 person-years	Fully Adjusted*
0 hospitalizations	2618	392	18.6	Reference
1 hospitalization	789	155	27.2	1.24 (1.03 – 1.50)
>1 hospitalization	368	99	40.8	1.81 (1.44 – 2.27)

*Model is stratified by center and adjusts for age, sex, race, ethnicity, income level, education level, health insurance, systolic blood pressure, body mass index, smoking status, diabetes mellitus, any cardiovascular disease, ACEi/ARB, beta-blockers, statins, anti-platelet drugs, hemoglobin, serum albumin, natural log transformed proteinuria, and eGFR