Published in final edited form as:

Am J Kidney Dis. 2012 March ; 59(3): 356–363. doi:10.1053/j.ajkd.2011.07.012.

The Risk of Infection-Related Hospitalization With Decreased Kidney Function

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Abstract

Background—Moderate kidney disease may predispose to infection. We sought to determine whether decreased kidney function, as estimated by serum cystatin C, was associated with the risk of infection-related hospitalization in older individuals.

Study Design—Cohort Study.

Setting & Participants—5,142 Cardiovascular Health Study participants with measured serum creatinine and cystatin C and without eGFR <15 ml/min/1.73 m² at enrollment.

Predictor—The primary exposure of interest was estimated glomerular filtration rate using serum cystatin C (eGFR_{SCysC}).

Outcome—Infection-related hospitalizations during a median follow-up of 11.5 years.

Results—In adjusted analyses, eGFR_{SCysC} categories of 60–89, 45–59, and 15–44 ml/min/1.73 m² were associated with 16%, 37%, and 64% greater risk of all-cause infection-related hospitalization, respectively, compared with an eGFR_{SCysC} ≥90 ml/min/1.73 m². When cause

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Findings from this study were presented as a Poster Presentation at the American Society of Nephrology Renal Week in Denver, CO on November 20, 2010.

Financial Disclosure: The authors declare that they have no relevant financial interests.

specific infection was examined, an $\text{eGFR}_{\text{SCysC}}$ of 15–44 ml/min/1.73 m² was associated with an 80% greater risk of pulmonary and 160% greater risk of genitourinary infection compared with an $\text{eGFR}_{\text{SCysC}} \geq 90$ ml/min/1.73 m².

Limitations—No measures of urinary protein, study limited to principal discharge diagnosis.

Conclusions—Lower kidney function, estimated using cystatin C, was associated with a linear and graded risk of infection-related hospitalization. These findings highlight that even moderate degrees of reduced kidney function are associated with clinically significant higher risks of serious infection in older individuals.

Keywords

renal disease; chronic kidney disease; infection; clinical epidemiology

Chronic kidney disease (CKD) is a rapidly emerging public health challenge, particularly among older individuals. Moderate to severe CKD is strongly associated with the risk of all-cause hospitalization, with a 10–50% increase among individuals with Stage 3 CKD ($\text{eGFR} = 30\text{--}59$ ml/min/1.73 m²) and a 110% increase among individuals with Stage 4 CKD ($\text{eGFR} = 15\text{--}29$ ml/min/1.73 m²).¹ Complications associated with CKD include both cardiovascular and non-cardiovascular disease hospitalizations and death.^{1–3}

Decreased kidney function leads to retention of metabolic waste products and hormonal disturbances that adversely impact multiple target tissues, including blood vessels, bone, and the immune system. Altered immune cell function is a known clinical complication of late stage kidney disease, as demonstrated by markedly high rates of infection and infection-related mortality among people who have end-stage kidney disease receiving dialysis.^{4–6} However, few studies have sought to determine whether less severely reduced kidney function is associated with infection risk. Existing studies in CKD populations are limited to evaluation of only specific types of infection such as bacteremia or pneumonia,^{7,8} and have relied on serum creatinine levels to estimate kidney function. Serum cystatin C-based estimates of kidney function may more accurately predict adverse outcomes associated with chronic kidney disease as compared to creatinine-based estimates of kidney function.

In our study, we sought to examine comprehensively the associations of kidney function with risks of infection-related hospitalization in Cardiovascular Health Study participants. We estimated kidney function using serum cystatin C, an alternate marker of glomerular filtration that does not depend on muscle mass and more precisely detects early loss of kidney function than serum creatinine;⁹ we also assessed associations with all infection-related hospitalizations and with specific infection types.

Methods

Study Population

The Cardiovascular Health Study (CHS) is a prospective cohort study of community-dwelling adults aged 65 years or older.¹⁰ Participants were randomly sampled from Health Care Financing Administration Medicare-eligibility lists in Sacramento County, CA; Allegheny County, PA; Forsyth County, NC; and Washington County, MD. Participants were initially recruited between 1989 and 1990. Exclusion criteria included: inability to provide informed consent or communicate with the interviewer; need of a proxy respondent for baseline examination; institutionalization; being homebound; receipt of hospice care; treatment with radiation or chemotherapy for cancer; or plans to move out of the community within 3 years.¹¹ An additional 687 African-American participants were recruited from 1992–1993. CHS participants were excluded from the current study if they had prevalent

end-stage renal disease, an eGFR <15 ml/min/1.73 m² based on either creatinine or cystatin C, or missing baseline serum creatinine or cystatin C measures.

Institutional Review Board approval for the Cardiovascular Health Study was obtained from each of the participating clinical centers and the coordinating center at the University of Washington.

Measurements

Extensive baseline data were ascertained including: demographics (age, sex, and self-reported race), prevalent disease (coronary heart disease, congestive heart failure, hypertension, chronic obstructive pulmonary disease, stroke, and diabetes), blood pressure, weight, height, laboratory measures (serum creatinine, cystatin C, albumin, C-reactive protein (CRP), and interleukin-6 (IL-6)), medications, tobacco use, and education. The CHS laboratory procedures have been outlined in detail previously.¹² Serum creatinine was measured by a colorimetric method (Ektachem 700, Eastman Kodak). Serum cystatin C was measured by particle-enhanced immunonephelometric assay (N Latex Cystatin C, Siemens; www.usa.siemens.com); interassay coefficient of variation (CV) of 2.3–3.1%.¹³ CRP was measured by ELISA (developed by the CHS central lab); CV of 8.9%. IL-6 was measured by HS-ELISA (R&D Systems; www.rndsystems.com); CV of 6.3%.¹⁴

The primary exposure of interest was kidney function, as measured by serum cystatin C-based eGFR (eGFR_{SCysC}), at study entry. The eGFR_{SCysC} was calculated using the following equation: $eGFR = 76.7 \times CysC^{-1.19}$.¹⁵ Secondary analyses were conducted to examine how findings differed when serum creatinine-based measures of eGFR were employed. The CKD-EPI (CKD Epidemiology Collaboration) eGFR (eGFR_{SCr(CKD-EPI)}) equation was used to estimate the glomerular filtration rate based on serum creatinine (SCr): $eGFR = 141 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$ where $\kappa = 0.7$ for females and 0.9 for males, $\alpha = -0.329$ for females and -0.411 for males, min indicates the minimum of SCr/ κ or 1 and max indicates the maximum of SCr/ κ or 1.¹⁶

The primary outcome of interest was hospitalization for infection. Infection-related hospitalization was defined as any hospitalization with a principal discharge diagnosis of bacteremia, septicemia, endocarditis, pulmonary, genitourinary, gastrointestinal, soft tissue, bone or joint infection. Discharge diagnoses were based on *International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)* codes (see Item S1, available as online supplementary material).¹⁷ During follow-up, participants were contacted semi-annually to ascertain clinically relevant events including hospitalization. Contact was by telephone alternating with annual examination visits through 1999 and subsequently by semi-annual telephone contact. At the semi-annual contacts, participants were asked about major illnesses and hospital admissions. Medical records were obtained for all reported hospitalizations. All hospitalizations during follow-up (through June 30, 2007) were examined and included in the analyses if the principal discharge diagnosis was an infection of interest. Participants were followed for infection-related hospitalization until the time of death, loss to follow-up or study end. Secondary to the very low number of episodes of endocarditis (n=8) and bone and joint infections (n=0), these types of infection were not examined further.

Statistical Analyses

We analyzed baseline eGFR_{SCysC} as a continuous variable and according to categories (15–44, 45–59, 60–89, or ≥ 90 ml/min/1.73 m²). Age-adjusted rates and 95% confidence intervals for all-cause and cause-specific infection-related hospitalizations were calculated

by $eGFR_{SCysC}$ categories. Poisson regression was used to examine whether kidney function, as measured by $eGFR_{SCysC}$, was associated with the risk of infection-related hospitalization(s). The first multivariable model included age, sex, race, body mass index (BMI), diabetes, coronary heart disease, heart failure, cancer, chronic obstructive pulmonary disease, stroke, tobacco use and serum albumin. To examine whether the association between $eGFR_{SCysC}$ and infection changed with inclusion of markers of inflammation, CRP and IL-6 were added to the second model. We tested for overdispersion and found no such violation in our Poisson model. We also evaluated whether the association between kidney function and the risk of all-cause infection was modified by age, sex, or race using interaction terms.

Two sensitivity analyses were conducted to examine whether multiple infection-related hospitalizations in the same individual contributed to the observed findings. In the first sensitivity analysis, any infection-related hospitalizations that occurred within two weeks of a previous infection-related hospitalization were excluded. In the second sensitivity analysis, only the first infection-related hospitalization was examined using a Cox proportional hazards model.

The associations of $eGFR_{SCysC}$ and $eGFR_{SCR(CKD-EPI)}$ with all-cause infection were compared visually by using splines to assess the functional form; splines were created using a penalized Cox model. The association between $eGFR_{SCR(CKD-EPI)}$ and infection-related hospitalization was also examined using Poisson regression, using the same approach as outlined above for $eGFR_{SCysC}$. All analyses were performed using S-Plus (version 8.0, Tibco, Seattle, WA), SPSS statistical software (version 15.0.1.1, SPSS, Inc., Chicago, IL) and Stata (version 10.1, StataCorp LP, College Station, TX).

Results

Among the 5,888 original CHS participants, 80 were excluded for missing serum creatinine measurements, 651 for missing cystatin C, and 15 for $eGFR < 15$ ml/min/1.73 m² or renal replacement therapy, resulting in a final study sample of 5,142. Participants excluded were more likely to be older, male, non-black, have prevalent diabetes and cancer, and higher hemoglobin, IL-6, serum creatinine and cystatin C concentrations. Excluded participants had lower BMIs and a lower prevalence of coronary heart disease as compared with included participants. Among the study participants, 13% had stage 3a CKD ($eGFR_{SCysC} = 45\text{--}59$ ml/min/1.73 m²) and 5% had stage 3b or stage 4 CKD ($eGFR_{SCysC} = 15\text{--}44$ ml/min/1.73 m²). Participants who had lower $eGFR_{SCysC}$ were more likely to be older and male, more likely to smoke, and had a higher prevalence of diabetes, hypertension, and cardiovascular disease (Table 1). Lower kidney function was also associated with higher serum levels of the inflammatory markers, CRP and IL-6.

Median follow-up was 11.5 years. During follow-up, 20% of the cohort had one infection-related hospitalization and 10% had two or more infection-related hospitalizations. Lower estimated kidney function was associated with a significantly greater age-adjusted risk of all infection-related hospitalizations as well as pulmonary and genitourinary infections (Figure 1). The association of $eGFR_{SCysC}$ with all infection-related hospitalizations was generally linear across the measured range of kidney function (Figure 2a).

After adjustment for demographics, BMI, tobacco use, prevalent coronary heart disease, stroke, heart failure, diabetes, cancer, COPD and serum albumin, lower $eGFR_{SCysC}$ categories were associated with significantly greater risks of all-cause, pulmonary, and genitourinary infection-related hospitalizations (Table 2). Further adjustment for serum CRP and IL-6 concentrations did not materially alter these estimates. In contrast, lower estimated

kidney function was not associated with gastrointestinal or soft-tissue infections or bacteremia and septicemia. The $eGFR_{SCysC}$ categories of 60–89, 45–59, and 15–44 ml/min/1.73 m² were associated with 16%, 37%, and 64% greater risks of all infection related hospitalizations compared to an $eGFR_{SCysC} \geq 90$ ml/min/1.73 m². When analyzed as a continuous variable, lower $eGFR_{SCysC}$ was associated with 8%, 7%, and 11% higher adjusted risks of all-cause, pulmonary, and genitourinary infection related hospitalization. The association between $eGFR_{SCysC}$ and infection was not modified by age, sex or race. Results did not substantively differ when infection-related hospitalizations that occurred within two weeks of prior infection-related hospitalization were excluded (result not shown). When only the first infection-related hospitalization was examined, findings were generally similar except that statistically significant associations were observed between an $eGFR_{SCysC}$ of 45–59 ml/min/1.73 m² and bacteremia/septicemia and pulmonary infection (results not shown).

Given the high rates of pulmonary infections, we also examined rates of vaccination at study entry by $eGFR$ categories. The proportion of participants with influenza vaccination was 43%, 44%, 48%, and 49% whereas the proportion with pneumococcal vaccination was 26%, 26%, 27%, and 26% for $eGFR_{SCysC}$ categories ≥ 90 , 60–89, 45–59, and 15–44 ml/min/1.73 m², respectively.

In contrast to the linear association between $eGFR_{SCysC}$ and infection risk, the association of $eGFR_{SCr(CKD-EPI)}$ with all-cause infection-related hospitalization was U-Shaped (Figure 2b). A summary of the spline model for $eGFR_{SCr(CKD-EPI)}$ showed no significant linear effect ($p=0.4$), but revealed a marginally significant nonlinear effect ($p=0.05$). Because of the U-shaped relation between $eGFR_{SCr(CKD-EPI)}$ and infection, $eGFR_{SCr(CKD-EPI)}$ was divided into finer categories in the adjusted analyses (≥ 105 , 90–104, 75–89, 60–74, 45–59, and 15–44 ml/min/1.73 m²) and $eGFR_{SCr(CKD-EPI)}$ of 60–74 ml/min/1.73 m² was selected as the referent group. When compared with an $eGFR_{SCr(CKD-EPI)}$ of 60–74 ml/min/1.73 m², participants with an $eGFR_{SCr(CKD-EPI)}$ of 15–44 had a 24% higher risk of all-cause infection (p -value=0.05) and a 54% higher risk of pulmonary infection (p -value=0.008). Other ranges of $eGFR_{SCr(CKD-EPI)}$ were not significantly associated with risk of infection-related hospitalization (see Table S1).

Discussion

When kidney function was assessed by $eGFR_{SCysC}$, we found that it was linearly associated with higher risk of infection-related hospitalization. As compared with participants with an $eGFR_{SCysC} \geq 90$ ml/min/1.73 m², participants with Stage 3a CKD ($eGFR_{SCysC} = 45–59$ ml/min/1.73 m²) had a nearly 40% increase in the risk of infection-related hospitalization and participants with Stages 3b or 4 CKD ($eGFR_{SCysC} = 15–44$ ml/min/1.73 m²) had a more than 60% increase in risk. These findings highlight that even moderately decreased kidney function is associated with clinically significant greater risks of serious infection.

In contrast to the linear association observed between $eGFR_{SCysC}$ and the risk of infection, we found a U-shaped relation between $eGFR$ and the risk of infection when a creatinine-based measure of $eGFR$ was utilized. Only an $eGFR_{SCr(CKD-EPI)}$ of 15–44, when compared to an $eGFR_{SCr(CKD-EPI)}$ 60–74 ml/min/1.73 m², was associated with an increased risk of infection-related hospitalization. Our findings are similar to other CHS studies that have found cystatin C-based estimates of kidney function to be more strongly and linearly associated with adverse health outcomes as compared to creatinine-based estimates.^{3,18} Our findings further highlight that cystatin C based measures of kidney function may more accurately estimate the risks of serious adverse outcomes such as infection that are associated with kidney disease.

Interestingly, few studies have examined the risk of infection among individuals who have CKD that does not require dialysis, and the current study is the first to our knowledge that uses cystatin C to quantify the risks of serious infection among older patients. To date, the largest studies have focused on specific infections such as bacteremia or pneumonia and have relied on creatinine based measures to estimate kidney function. For example, James *et al.* found that among adults 66 years and older, the risk of bloodstream infections was higher for persons with lower eGFR, finding approximately 25%, 60%, and 250% higher risk among older persons with eGFR of 45–59, 30–44, and <30 ml/min/1.73 m², respectively, compared to persons with an eGFR ≥60 ml/min/1.73 m².⁷ In our study we did not find a significant increase in the risk of bacteremia or septicemia with declining levels of kidney function. The discrepancy in findings with our study may be due to key differences in the study by James *et al.* including: 1) ascertainment of co-morbidities from administrative data, potentially resulting in residual confounding and higher risk estimates; 2) the combination of all bloodstream infections including *Escherichia coli*, *Pseudomonas*, and *Klebsiellapneumoniae* bacteremia, which would likely have been classified as site-specific infection in our study, such as genitourinary or pulmonary; and 3) the inclusion of pre-dialysis participants with an eGFR <15 ml/min/1.73 m² in the James *et al.* study, a particularly high risk group. In a separate study among adults, James *et al.* found that kidney function was independently associated with risk of pneumonia diagnosis during hospitalization and the risk was modified by age.⁸ In adults 75 years or older, a significant increase in risk was only observed for eGFRs < 30 ml/min/1.73 m², and these patients had an 80% increase in the risk of pneumonia when compared to patients with an eGFR of 60–104 ml/min/1.73 m². Although differences in study design limit direct comparison of findings, participants in our study with an eGFR_{SCysC} of 15–44 ml/min/1.73 m² or an eGFR_{SCr(CKD-EPI)} of 15–44 ml/min/1.73 m² had a significant increase in the risk of pulmonary infections, similar to the James *et al.* study. Importantly, in the study by James *et al.*, a significant increase in the incidence of pneumonia was also observed among participants with an eGFR ≥105 ml/min/1.73 m²; rates of incident pneumonia were similar to or higher than those observed in patients with Stage 3b CKD.⁸ We found a similar U-shaped risk when creatinine-based measures of eGFR (eGFR_{SCr(CKD-EPI)}) were used to examine the relationship between kidney function and infection risk. Of interest, the proportion of CHS participants that reported influenza vaccination at study entry was highest in the lowest eGFR_{SCysC} categories whereas pneumococcal vaccination was overall similar across eGFR categories.

The observed association between kidney function and infection-related hospitalization may be due to an increased susceptibility to infection and/or an increased severity of infection in older patients with CKD. Biologically, kidney disease is a metabolic disorder and is associated with numerous alterations in immune function. Although not well studied in pre-dialysis chronic kidney disease, end-stage renal disease and its associated metabolic consequences result in an acquired immunodeficiency with numerous alterations in immune function; findings include: 1) impaired polymorphonuclearchemotaxis, phagocytosis, oxidative metabolism and intracellular killing;^{19–21} and 2) inadequate co-stimulation of T cells by antigen presenting cells resulting in impaired activation of helper T cells.²² Furthermore, the observed immune dysfunction can result in vaccine hyporesponsiveness.^{21,23} Kidney disease is a continuum and alterations in immune cellular function may develop well before end-stage renal disease, similar to other metabolic abnormalities associated with kidney disease.

Our study contributes to the current literature in several important ways. First, we estimated kidney function using cystatin C, allowing us to examine more directly the association between kidney function and infection. In contrast to creatinine, cystatin C is produced by all nucleated cells and is not correlated with muscle mass,²⁴ a particular concern in older

populations who may have low serum creatinines secondary to low muscle mass or malnutrition. Biologically, it is unlikely that normal kidney function increases the risk of infection-related hospitalization, and the apparent U-shaped relation between creatinine-based measures of kidney function and infection observed in our study and others⁸ is likely secondary to misclassification of kidney function when using creatinine-based estimates. Second, our study included comprehensive ascertainment of important co-morbidities and health behaviors, reducing the likelihood of residual confounding and allowing for more precise estimates of the excess infection risk associated with kidney disease. Third, our study examined a broad range of infections and found that multiple types of infections contributed to the overall risk of infection-related hospitalization.

Our study has several limitations. First, the CHS participants were 65 years of age or older at study entry, so our findings are only applicable to older patients with kidney disease. However, CKD is most common in this age group and therefore these findings in the elderly are important. Second, we only examined principal discharge diagnoses, so our study likely underestimates the true burden of infection in older patients with CKD. Third, we did not have measures of proteinuria and therefore cannot draw conclusions regarding the impact of proteinuria on the observed findings. Fourth, we cannot exclude residual confounding contributed to some of the observed association between reduced kidney function and infection. Fifth, we only examined kidney function at study entry and therefore cannot determine whether progression of kidney disease influenced the risk of infection. Sixth, we used *ICD-9-CM* codes to identify infections of interest as opposed to validated clinical criteria for specific types of infection, potentially resulting in misclassification. Finally, given the low number of specific types of infection (e.g., soft tissue, gastrointestinal, septicemia) and the limited number of participants with severe chronic kidney disease, our study may not be able to detect important differences in the risk of certain types of infections with respect to reduced kidney function. Despite these limitations, our study has important implications for the care of older patients with kidney disease.

In summary, lower levels of kidney function are associated with a higher risk of infection, including even moderately reduced kidney function. Future studies are needed to understand the factors that contribute to this observed risk. Important areas in need of further research include the effect of moderately reduced kidney function on immune cell function, vaccine responsiveness in older patients with kidney disease, and the short and long-term outcomes of serious infections in persons with CKD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: This research was supported by contracts N01-HC-85239, N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, and grant HL080295 from the National Heart, Lung, and Blood Institute (NHLBI), with additional contribution from the National Institute of Neurological Disorders and Stroke (NINDS). Additional support was provided through AG-023629, AG-15928, AG-20098, AG-027058, and AG-027002 from the National Institute on Aging, and UL1 RR024146 from the National Center for Research. The CHS was funded through contracts with NHLBI and included substantial NHLBI involvement in the design and conduct of the study, and the collection and management of the data. The funding source was not involved in data analysis, interpretation of the data, preparation, review, or approval of the manuscript. The contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH. A full list of principal CHS investigators and institutions can be found at www.chsnhlbi.org/pi.htm.

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Figure 1.

Age-Adjusted Rates of All-Cause and Cause-Specific Infection by kidney Function. Age adjusted rates per 100 person-years of all-cause and cause-specific infection by category of serum cystatin C-based eGFR (ml/min/1.73 m²).

Figure 2.

The Association between kidney Function and the Risk of Infection-Related Hospitalization.

(a) The association between serum cystatin C-based eGFR and the risk of all-cause infection-related hospitalization

(b) The association between serum creatinine-based estimated glomerular filtration rate as calculated using the CKD-EPI equation and the risk of all-cause infection-related hospitalization

Table 1Baseline Characteristics of Included CHS Participants by eGFR_{SCysC} Category

	eGFR _{SCysC} (ml/min/1.73 m ²)			
	≥90 (n=1279)	60–89 (n=2962)	45–59 (n=648)	15–44 (n=253)
Age	71 +/- 4	72 +/- 5	75 +/- 6	77 +/- 7
Men	377 (30)	1210 (41)	298 (46)	125 (49)
Black	259 (20)	442 (15)	90 (14)	44 (17)
Smoking History				
Never	609 (48)	1395 (47)	274 (42)	122 (48)
Former	543 (42)	1201 (41)	288 (44)	88 (35)
Current	127 (10)	366 (12)	86 (13)	43 (17)
BMI, kg/m ²	25.8 +/- 4.2	27.0 +/- 4.8	27.6 +/- 5.1	27.0 +/- 5.2
Diabetes	193 (15)	440 (15)	124 (19)	55 (22)
Hypertension	654 (51)	1704 (58)	458 (71)	211 (83)
Cancer	145 (11)	412 (14)	110 (17)	45 (18)
CHF	25 (2)	113 (4)	54 (8)	43 (17)
CHD	172 (13)	589 (20)	183 (28)	86 (34)
Stroke	22 (2)	118 (4)	53 (8)	34 (13)
COPD	157 (12)	381 (13)	85 (13)	27 (11)
Albumin, g/dL	4.0 +/- 0.3	4.0 +/- 0.3	4.0 +/- 0.3	3.9 +/- 0.3
Hemoglobin, g/dL	13.9 +/- 1.4	14.1 +/- 1.3	13.8 +/- 1.5	13.3 +/- 1.7
CRP, mg/L	2.02 (0.98; 3.66)	2.47 (1.31; 4.33)	3.45 (1.97; 7.47)	4.29 (2.52; 9.50)
IL-6, pg/mL	1.33 (0.95; 2.00)	1.67 (1.16; 2.50)	2.28 (1.52; 3.38)	2.92 (2.02; 3.92)
SCr, mg/dL	0.8 +/- 0.2	0.9 +/- 0.2	1.2 +/- 0.3	1.6 +/- 0.5
SCysC, mg/L	0.8 +/- 0.05	1.0 +/- 0.1	1.4 +/- 0.1	1.9 +/- 0.4
eGFR _{SCr} (CKD-EPI) (ml/min/1.73 m ²)	86 +/- 12	73 +/- 14	57 +/- 13	40 +/- 14
eGFR _{SCysC} (ml/min/1.73 m ²)	103 +/- 11	76 +/- 8	54 +/- 4	37 +/- 6

Data are presented as mean +/- sd, number (%) of subjects, or median (25th; 75th percentile).

BMI, body mass index; CHF: Congestive heart failure; CHD: Coronary heart disease; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; IL-6: interleukin-6; eGFR_{SCr}(CKD-EPI): estimated glomerular filtration rate using the serum creatinine-based CKD-EPI equation; eGFR_{SCysC}: estimated glomerular filtration rate using serum cystatin C; SCr, serum creatinine; SCysC, serum cystatin C; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CHS, Cardiovascular Health Study

Conversion factors for units: albumin g/dL to g/L, ×10; serum creatinine in mg/dL to μmol/L, ×88.4; glomerular filtration rate in mL/min/1.73 m² to mL/s/1.73 m², ×0.01667; hemoglobin in g/dL to g/L, ×10.

Table 2

Association of All-Cause and Cause-Specific Infection-Related Hospitalizations with eGFR_{SCysC}

Infection-Related Hospitalization	Continuous (per 10-ml/min/1.73 m ² decrease)	eGFR _{SCysC} (ml/min/1.73 m ²)			
		≥90 (n=1279)	60–89 (n=2962)	45–59 (n=648)	15–44 (n=253)
All-cause infection [†]					
No. of events (total of 2405)		505	1369	363	168
RR (95% CI), model 1 [*]	1.09 (1.06, 1.12)	1.00 (ref)	1.20 (1.06, 1.36)	1.44 (1.20, 1.72)	1.79 (1.41, 2.28)
RR (95% CI), model 2 ^{**}	1.08, (1.04, 1.11)	1.00 (ref)	1.16 (1.02, 1.32)	1.37 (1.14, 1.66)	1.64 (1.28, 2.12)
Pulmonary					
No. of events (total of 1088)		213	631	156	88
RR (95% CI), model 1 [*]	1.08 (1.03, 1.12)	1.00 (ref)	1.29 (1.05, 1.57)	1.33 (0.99, 1.77)	1.83 (1.27, 2.63)
RR (95% CI), model 2 ^{**}	1.07 (1.02, 1.12)	1.00 (ref)	1.22 (0.99, 1.54)	1.27 (0.94, 1.71)	1.81 (1.25, 2.63)
Gastrointestinal					
No. of events (total of 404)		114	222	56	12
RR (95% CI), model 1 [*]	1.06 (0.99, 1.13)	1.00 (ref)	0.99 (0.76, 1.30)	1.49 (1.01, 2.20)	0.95 (0.44, 2.04)
RR (95% CI), model 2 ^{**}	1.05 (0.98, 1.13)	1.00 (ref)	0.99 (0.75, 1.32)	1.50 (0.99, 2.28)	0.82 (0.34, 1.97)
Genitourinary					
No. of events (total of 347)		76	191	53	27
RR (95% CI), model 1 [*]	1.14 (1.05, 1.25)	1.00 (ref)	1.11 (0.78, 1.59)	1.56 (0.95, 2.56)	3.03 (1.67, 5.48)
RR (95% CI), model 2 ^{**}	1.11 (1.01, 1.21)	1.00 (ref)	1.08 (0.75, 1.56)	1.17 (0.67, 2.05)	2.63 (1.40, 4.96)
Bacteremia & Septicemia					
No. of events (total of 366)		76	203	64	23
RR (95% CI), model 1 [*]	1.06 (0.98, 1.16)	1.00 (ref)	1.12 (0.79, 1.59)	1.46 (0.89, 2.38)	1.01 (0.44, 2.34)
RR (95% CI), model 2 ^{**}	1.06 (0.97, 1.15)	1.00 (ref)	1.10 (0.77, 1.58)	1.55 (0.93, 2.57)	0.77 (0.29, 2.03)
Soft Tissue					
No. of events (total of 200)		26	122	34	18
RR (95% CI), model 1 [*]	1.07 (0.96, 1.20)	1.00 (ref)	1.58 (0.93, 2.69)	1.50 (0.71, 3.15)	1.78 (0.66, 4.82)
RR (95% CI), model 2 ^{**}	1.07 (0.95, 1.21)	1.00 (ref)	1.59 (0.90, 2.79)	1.68 (0.77, 3.65)	1.56 (0.53, 4.56)

ref, reference; RR, rate ratio; CI, confidence interval; eGFR_{SCysC}: estimated glomerular filtration rate using serum cystatin C

model 1 adjusted for age, sex, race, tobacco use, body mass index, diabetes mellitus, coronary heart disease, stroke, heart failure, cancer, chronic obstructive pulmonary disease, and serum albumin

model 2 further adjusted for CRP & IL-6

Note: Only those infections shown are included in the all-cause count