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Original Paper

Prehospitalization Risk Factors for Acute Kidney Injury during Hospitalization for Serious Infections in the REGARDS Cohort

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Key Words
Acute kidney injury · Infections · Risk prediction · Epidemiology

Abstract
Background/Aims: Acute kidney injury (AKI) frequently occurs in hospitalized patients. In this study, we determined prehospitalization characteristics associated with AKI in community-dwelling adults hospitalized for a serious infection. ***Methods:*** We used prospective data from 30,239 participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national cohort of community-dwelling adults ≥45 years old. We identified serious infection hospitalizations between 2003 and 2012. Using the Kidney Disease Improving Global Outcomes (KDIGO) criteria, we defined AKI as an increase in serum creatinine (sCr) ≥0.3 mg/dl from the first inpatient sCr measurement during the first 7 hospitalization days. We excluded individuals with a history of renal transplant or preexisting end-stage renal disease as well as individuals with <2 sCr measurements. We identified baseline characteristics (sociodemographics, health behaviors, chronic medical conditions, biomarkers, and nonsteroidal anti-inflammatory, statin, or antihypertensive medication use) independently associated with AKI events using multivariable generalized estimating equations. ***Results:*** Over a median follow-up of 4.5 years (interquartile range 2.4–6.3), we included 2,074 serious infection hospitalizations among 1,543 individuals. AKI occurred in 296 of 2,074 hospitalizations (16.5%). On multivariable analysis, prehospitalization characteristics independently associated with AKI among individuals hospitalized for a serious infection included a history of diabetes [odds ratio (OR) 1.38; 95% CI 1.02–1.89], increased cystatin C (OR 1.73 per SD; 95% CI 1.20–2.50), and increased albumin-to-creatinine ratio (OR 1.19 per SD; 95% CI 1.007–1.40). Sex, race, hypertension, myocardial infarction, estimated glomerular filtration rate, high-sensitivity C-reactive

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protein, and the use of nonsteroidal anti-inflammatory, statin, or antihypertensive medications were not associated with AKI. ***Conclusions:*** Community-dwelling adults with a history of diabetes or increased cystatin C or albumin-to-creatinine ratio are at increased risk for AKI after hospitalization for a serious infection. These findings may be used to identify individuals at high risk for AKI.

Introduction

Acute kidney injury (AKI) may result from decreased renal blood flow, obstruction of the outflow tract, or damage to the renal filtration system [1]. In the United States, there are over 600,000 hospitalizations and 120,000 deaths associated with AKI [2]. Those who survive AKI are at heightened risk of significant consequences including chronic kidney disease, cardiovascular events, and the need for chronic dialysis [3, 4].

Prevention is an important potential strategy for reducing the consequences of AKI [3]. Current scientific and clinical efforts focus upon the detection of AKI at its earliest stages. For example, novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 have been investigated as early markers of AKI [5–10]. In some cases, individuals may present to the hospital with AKI already in progress [11, 12]. In this context, the identification of individuals at heightened risk of AKI prior to the onset of illness could provide important advantages. Prior studies have provided only limited insights into baseline prehospitalization characteristics associated with subsequent AKI risk [13–16].

Infections and sepsis (the syndrome of exaggerated systemic inflammatory response to a serious microbial infection) are among the most common causes of AKI [17, 18]. Animal and human evidence collectively suggests that infection- and sepsis-induced AKI is distinct from AKI due to other conditions, encompassing pathophysiologic mechanisms such as mitochondrial dysfunction, apoptosis, endothelial dysfunction, acidosis, thrombosis, and impaired vascular tone [17, 19]. In this study, we sought to determine prehospitalization characteristics associated with the development of AKI among community-dwelling adults hospitalized for a serious infection.

Materials and Methods

Study Design

We used data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, one of the largest population-based longitudinal cohorts of community-dwelling adults in the United States [20]. Designed to identify the reasons for geographic and racial disparities in stroke mortality in the US, REGARDS includes 30,239 community-dwelling adults ≥45 years old from the 48 contiguous US states and the District of Columbia [20]. The REGARDS study oversampled blacks and individuals living in the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina, and Georgia (the 'stroke buckle') and 35% from the remainder of North Carolina, South Carolina, and Georgia plus Tennessee, Mississippi, Alabama, Louisiana, and Arkansas (the 'stroke belt'). The REGARDS study is 42% African-American and 45% male, with 69% of participants >60 years old.

The REGARDS study enrolled participants between 2003 and 2007, obtaining baseline data for each participant using both phone interview and in-person evaluations. Baseline information included medical history, functional status, health behaviors, physical character-

istics (height, weight), physiologic measures (blood pressure, pulse, electrocardiogram), and an inventory of medications. Additional questionnaires evaluated diet, family history of diseases, psychosocial factors, and prior residences. The study collected blood and urine specimens from each participant.

The REGARDS study contacted study participants at 6-month intervals by telephone, identifying the date, location, and attributed reason for all hospitalizations during the follow-up period. The study then retrieved medical records for specific health events. If the participant died, the study team reviewed death certificates and medical records and interviewed proxies to ascertain the circumstances of the participant's death and assign an underlying cause of death.

Identification of Hospitalization Events for Serious Infection

Using the taxonomy of Angus et al. [21], we identified all hospitalizations (Emergency Department visits and/or hospital admission) attributed by participants to a serious infection. Two trained abstractors independently reviewed all relevant medical records to identify clinical and laboratory information, confirm the presence of a serious infection on initial hospital presentation, and to verify the relevance of the serious infection as a major reason for hospitalization. An initial review of 1,349 hospital records indicated excellent interrater agreement for the presence of a serious infection ($\kappa = 0.92$). We included hospitalization events during the follow-up period February 5, 2003, through December 31, 2012.

Outcomes – Definition of AKI

We defined AKI using the Kidney Disease Improving Global Outcomes (KDIGO) criteria [22]. We used the first serum creatinine (sCr) measurement during hospitalization as the index value. We determined the rise in creatinine using all creatinine values during the first 7 days of hospitalization. We excluded hospitalizations with fewer than 2 creatinine measurements. We also excluded patients with a prior history of dialysis or kidney transplantation. We used the first inpatient sCr as a reasonable approximation of the participant's baseline value because we did not have access to outpatient sCr measurements. Although the REGARDS study measured sCr at each participant's entry into the study, we opted not to use these values because the median elapsed time to infection hospitalization was 4.5 years.

Baseline Participant Characteristics

Participant characteristics were determined upon REGARDS enrollment. Demographic characteristics included age, sex, race, and self-reported annual household income and education (years of school). Health behaviors included smoking status and alcohol use. Alcohol use categories included none, moderate (1 drink per day for women or 2 drinks per day for men), and heavy (>1 drink per day for women and >2 drinks per day for men) [23].

Chronic medical conditions included atrial fibrillation, chronic lung disease, deep vein thrombosis, diabetes, dyslipidemia, hypertension, myocardial infarction, obesity, peripheral artery disease, and stroke. Atrial fibrillation was based upon participant self-report or baseline electrocardiographic evidence. Diabetes was defined as a fasting glucose ≥126 mg/l (or a glucose ≥200 mg/l for those not fasting) or the use of insulin or oral hypoglycemic agents. Dyslipidemia consisted of low-density lipoprotein cholesterol >130 mg/dl or the use of lipid-lowering medications. Hypertension included a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the self-reported use of antihypertensive agents. Myocardial infarction included individuals with a self-reported history of myocardial infarction or baseline electrocardiographic evidence of myocardial infarction.

Obesity encompassed those with a waist circumference >102 cm for males or >88 cm for females, or a body mass index ≥30 [24]. Participants self-reported a prior history of stroke

(including transient ischemic attacks) or deep vein thrombosis. Peripheral artery disease included a self-reported history of lower-extremity arterial bypass or leg amputation. We defined participant use of pulmonary medications (β-agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, ipratropium, cromolyn, aminophylline, and theophylline) as a surrogate for chronic lung disease.

Medication Use

At the initial interview, REGARDS obtained an inventory of all medications used by the participants. We considered medications potentially associated with AKI risk, including nonsteroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and mineralocorticoid receptor antagonists [25–29]. Participants reported medication adherence using the four-question version of the Morisky Medication Adherence Scale, which provides a measure of individual compliance with medication use [30]. We defined Morisky medication adherence as 0 = good and 1–4 = poor.

Baseline Biomarkers

REGARDS participants provided blood and urine samples following a 10- to 12-hour fast. Research personnel centrifuged samples to separate serum or plasma within 2 h of collection. All samples were shipped overnight on ice packs to the laboratories at the University of Vermont. Receiving laboratory personnel performed additional centrifugation at 30,000 *g* and 4°C and either immediately analyzed (general chemistries) or stored the samples at −80°C.

Biomarkers included in the analysis included sCr, serum high-sensitivity C-reactive protein (hsCRP), serum cystatin C (Cyst-C), and urinary albumin-to-creatinine ratio (ACR). We determined serum hsCRP and Cyst-C using particle-enhanced immunonephelometry (N Latex Cyst-C, N hsCRP, Siemens AG, Munich, Germany). Unlike conventional CRP assays, the hsCRP technique is able to detect levels as low as 0.04 mg/l. We determined sCr by colorimetric reflectance spectrophotometry (Ortho Vitros Clinical Chemistry System 950IRC, Johnson & Johnson Clinical Diagnostics, Raritan, N.J., USA). We assessed urinary albumin via nephelometry (BN ProSpec Nephelometer, Dade Behring, Siemens Healthcare, Deerfield, Ill., USA) and urinary creatinine with a rate-blanked Jaffé procedure (Modular P Analyzer, Roche/Hitachi, Roche Diagnostics, Indianapolis, Ind., USA).

We estimated the glomerular filtration (eGFR) rate using the CKD-EPI equation, defining eGFR <60 ml/min/1.73 m^2 as abnormal [31]. Consistent with our prior study, we defined hsCRP >3.0 mg/dl as abnormal [32]. We defined Cyst-C measurements above the fourth quartile of values observed in the REGARDS cohort (≥1.1 mg/dl) as abnormal. We defined ACR ≥30 mg/g as abnormal.

Hospital Course

We identified hospitalizations meeting criteria for sepsis, defined as a serious infection plus ≥2 systemic inflammatory response syndrome criteria, including (1) heart rate >90 beats/min, (2) fever (temperature >38.3 or <36°C), (3) tachypnea (>20 breaths/min) or PCO_2 <32 mm Hg, and (4) leukocytosis (white blood cells >12,000 or <4,000 cells/mm^3 or >10% band forms) [33]. We used asynchronous combinations of abnormal vital signs and laboratory tests observed during the initial 28 h of hospitalization, allowing for Emergency Department and up to 1 full day of inpatient treatment.

Other variables associated with the hospital course included infection type; Sequential Organ Failure Assessment (SOFA) for respiratory, renal, hepatic, cardiovascular, hematologic, and neurologic systems; Mortality in Emergency Department Sepsis (MEDS) score; admission to intensive care unit; provision of inpatient dialysis, and hospital mortality [34, 35].

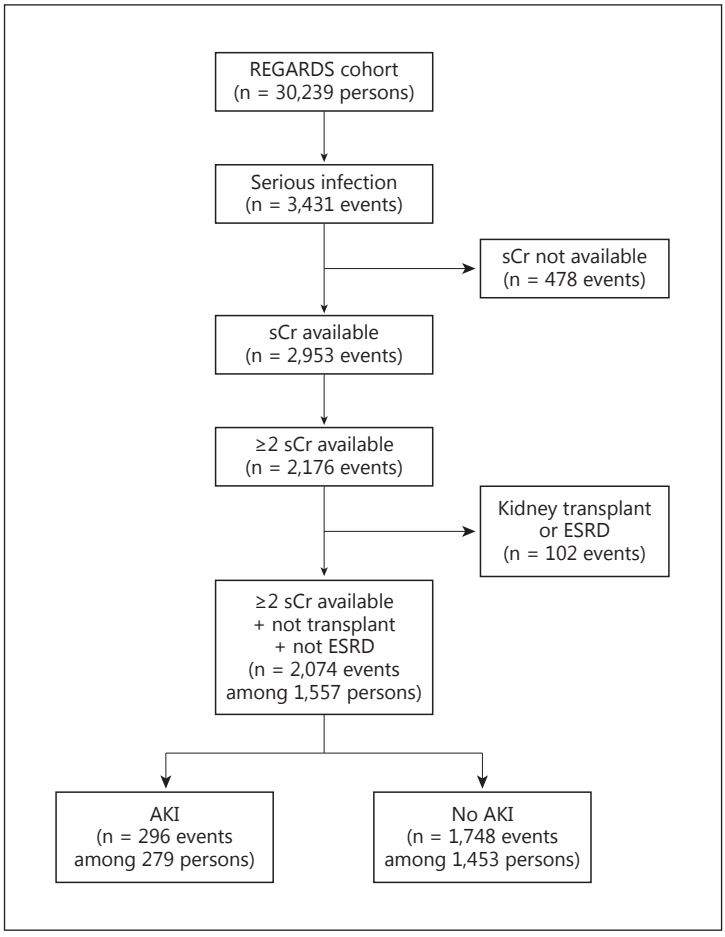

Fig. 1. Selection of cases included in the analysis. ESRD = End-stage renal disease.

Data Analysis

We compared prehospitalization characteristics between participants who did and did not develop AKI during hospitalization for a serious infection. Because an individual may have experienced multiple serious infection hospitalizations (up to 9 events in this cohort), we evaluated univariate associations using generalized estimating equations (GEE) models, defining AKI as the dependent variable and each participant characteristic as the independent variable, accounting for clustering by individual participant. We used exchangeable correlational structure and robust standard error estimates in these models.

To determine the factors independently associated with AKI, we fit a multivariable GEE model incorporating AKI as the dependent variable and participant characteristics that were statistically significant on univariate analysis as independent variables. We examined two-way multiplicative interactions between statistically significant variables remaining in the model. We conducted all analyses using Stata v.14.0 (Stata, Inc., College Station, Tex., USA).

Results

Serious Infection Hospitalizations

Among 30,239 REGARDS participants, there were 3,431 hospitalizations for a serious infection (fig. 1). sCr measurements were available for 2,953 hospitalizations, and at least 2 sCr values were available for 2,176 hospitalizations. After excluding 102 hospitalizations for

Table 1. Characteristics of sCr measurements among participants hospitalized for a serious infection[a]

	AKI (n = 296)	No AKI (n = 1,778)
sCr measurements		
Number of sCr measurements	5 (4–7)	3 (2–5)
Initial sCr, mg/dl	1.5 (1.0–2.2)	1.2 (0.9–1.6)
Maximum sCr, mg/dl	2.2 (1.6–3.4)	1.2 (1.0–1.7)
Maximum rise in sCr from index sCr, mg/dl	0.6 (0.4–1.0)	0.0 (0.0–0.1)
Number of measurements to maximum sCr	3 (2–5)	1 (1–2)
Time to maximum sCr, days	2.0 (1.0–3.5)	0.0 (0–0.6)
*AKI KDIGO stage*b		
Stage 0 (rise in sCr <0.3 mg/dl or <1.5 times baseline)	–	1,778
Stage 1 (rise in sCr ≥0.3 mg/dl or 1.5–1.9 times baseline)	270 (91.2)[c]	–
Stage 2 (rise in sCr 2.0–2.9 times baseline)	4 (1.4)[c]	–
Stage 3 (rise in sCr ≥3.0 times baseline or initiation of dialysis)	22 (7.4)[c]	–

Values are medians (interquartile ranges) or numbers (%). [a] Excludes individuals with a prior history of kidney transplant or end-stage renal disease, or individuals receiving <2 sCr measurements during hospitalization. [b] AKI stages defined using the KDIGO criteria and based upon rise from the first sCr during the first 7 days of hospitalization. [c] Reflects percentage of 296 AKI events.

individuals with a history of kidney transplant or end-stage renal disease, we analyzed 2,074 serious infection events among 1,543 persons. The median time between baseline data collection and hospitalization for serious infection was 4.5 years (interquartile range 2.4–6.3).

AKI Events and Univariate Associations with AKI

AKI occurred in 296 of 2,074 serious infection hospitalizations (16.5%; table 1). The 296 AKI events encompassed 308 individuals; 264 experienced 1 AKI event, 13 experienced 2 AKI events, and 2 experienced 3 AKI events.

On univariate analysis of baseline characteristics, AKI events were more likely to involve blacks, persons with a history of alcohol use, diabetes, hypertension, or myocardial infarction (table 2). AKI events were more likely to occur among individuals with reduced eGFR, elevated Cyst-C, and elevated ACR. AKI was not associated with elevated hsCRP. AKI was more common among persons who regularly used ACEI, ARB, and mineralocorticoid receptor antagonists.

Among hospitalization characteristics, AKI events were more often associated with lung infections and sepsis (table 3). AKI was less likely to be associated with abdominal and skin infections. AKI hospitalizations were more likely to meet sepsis criteria and were associated with higher admission SOFA scores. Intensive care unit admission and hospital mortality were higher among AKI hospitalizations.

Multivariable Associations with AKI

On multivariable analysis, a history of diabetes and increased Cyst-C and ACR were independently associated with AKI during hospitalization for a serious infection (table 4). Two-way multiplicative interactions [(diabetes × Cyst-C), (diabetes × ACR), (Cyst-C × ACR)] were not statistically significant. Of 2,074 participants included in the analysis, 346 used ARBs, 602 used ACEIs, and 32 used both. The adjusted odds ratio (OR) for AKI was not higher for those taking both ACEI and ARBs (OR 1.40; 0.49–3.26).

Table 2. Characteristics of participants hospitalized for a serious infection, stratified by the absence or presence of AKI during hospitalization[a]

	AKI (n = 296 events)	No AKI (n = 1,778 events)	p value[b]
Demographics			
Age, years	69.8±8.8	69.1±9.1	0.23
Male sex	56.1	50.8	0.09
Black race	38.9	31.3	0.01
Income			
<20,000 USD	26.4	24.1	0.42
20,000–34,000 USD	26.0	28.9	
35,000–74,000 USD	28.0	26.2	
≥75,000 USD	7.4	10.0	
Unknown	12.2	10.8	
Education			
Less than high school	21.6	16.3	0.07
High school graduate	27.4	26.2	
Some college	27.7	28.9	
College or higher	23.0	28.6	
Missing	0.3	0.2	
Health behaviors			
Tobacco use			
Never	31.8	36.1	0.29
Past	52.7	48.3	
Current	15.2	15.2	
Missing	0.3	0.5	
Alcohol use			
None	72.0	66.5	0.04
Moderate	22.3	27.8	
Heavy	1.7	3.8	
Missing	4.1	2.0	
Chronic medical conditions			
Atrial fibrillation	17.6	13.8	0.07
Chronic lung disease	22.0	18.8	0.19
Deep vein thrombosis	8.5	9.5	0.59
Diabetes	48.3	32.3	<0.001
Dyslipidemia	66.2	63.8	0.42
Hypertension	76.7	68.6	0.005
Myocardial infarction	27.0	21.3	0.02
Obesity (abnormal BMI or WC)	4.1	59.3	0.28
Peripheral artery disease	4.1	4.3	0.96
Stroke	14.9	12.4	0.24
Biomarkers			
eGFR, ml/min/1.73 m^2	70.8±23.7	77.8±21.8	<0.001
eGFR <60 ml/min/1.73 m^2	31.8	20.1	<0.001
hsCRP, mg/dl	8.9±17.0	6.3±10.0	0.001
hsCRP >3.0 mg/dl	52.0	46.9	0.08
Cyst-C, mg/dl	1.29±0.56	1.18±0.30	<0.001
Cyst-C ≥1.11 mg/dl	63.5	43.6	<0.001
ACR, mg/g	269.9±843.2	85.5±340.1	<0.001
ACR ≥30 mg/g	40.2	23.5	<0.001
Medication use and adherence			
NSAID	17.6	16.3	0.64
Statin	38.2	38.6	0.91
ACEI	37.5	29.4	0.006
ARB	24.0	17.3	0.006
Mineralocorticoid receptor antagonist	4.7	2.3	0.01
Fair or poor medication adherence[c]	30.4	29.6	0.77

Values are means ± standard deviations or numbers. BMI = Body mass index; waist circumference. [a] Includes 2,074 serious infection hospitalization events among 1,557 individuals. [b] Associations evaluated by GEE accounting for clustering by participant. [c] Morisky medication adherence score 1–4.

Table 3. Hospital course of 2,074 hospitalization events for a serious infection, stratified by the absence or presence of AKI[a]

	AKI (n = 296 events)	No AKI (n = 1,778 events)	p value[b]
Infection type			
Lung	44.3	50.3	0.004
Kidney	16.4	15.2	
Abdominal	18.8	13.2	
Skin	11.1	8.8	
Sepsis	4.7	9.1	
Other	4.7	3.4	
Sepsis criteria on admission[c]	73.0	61.3	<0.001
28-hour SOFA score[d]	2 (1–4)	1 (0–2)	<0.001
0	10.5	27.6	<0.001
1	17.9	27.8	
2	24.0	20.0	
3–4	23.3	18.1	
≥5	24.3	6.6	
MEDS score[e]	11 (8–14)	9 (8–13)	0.06
0–4	3.4	3.7	0.14
5–7	16.2	19.5	
8–12	47.6	50.5	
13–15	17.2	15.0	
≥16	15.5	11.4	
Admission to intensive care unit	21.3	9.6	<0.001
Inpatient dialysis	6.1	0.0	<0.001
Hospital mortality	22.6	5.6	<0.001

Values are medians (interquartile ranges) or numbers. [a] Includes 2,074 serious infection hospitalization events among 1,557 individuals. [b] Associations evaluated by GEE accounting for clustering by participant. [c] ≥2 systemic inflammation response syndrome criteria. [d] SOFA scores range from 0 to 20. [e] MEDS scores range from 0 to 27.

Table 4. Multivariable associations between baseline subject characteristics and OR for AKI after hospitalization for a serious infection[a]

	OR (95% CI) for AKI
Black race	1.34 (0.98–1.83)
Alcohol use	
None	referent
Moderate	0.96 (0.69–1.36)
Heavy	0.67 (0.27–1.64)
History of diabetes	1.38 (1.02–1.89)
History of hypertension	1.12 (0.79–1.57)
History of myocardial infarction	1.04 (0.74–1.45)
Cyst-C (normalized by SD)	1.73 (1.20–2.50)
ACR (normalized by SD)	1.19 (1.007–1.40)
hsCRP (normalized by SD)	1.06 (0.92–1.83)
ACEI use	1.33 (0.97–1.83)
ARB use	1.40 (0.96–2.06)
Mineralocorticoid receptor antagonist use	1.62 (0.82–3.21)

SD = Standard deviation. [a] Includes 2,074 serious infection hospitalization events among 1,557 individuals. Analysis performed by GEE with clustering by participant.

Discussion

An important step in reducing the incidence and impact of acute disease such as AKI is to identify the individuals at greatest risk for the condition. In this study, we found that those with a history of diabetes or increased ACR or Cyst-C are at increased risk of AKI during hospitalization for a serious infection. These results suggest that it may be possible to identify individuals at a stable phase of health who are at increased risk for AKI.

Only limited data describe prehospitalization risk factors independently associated with AKI during hospital treatment for a severe infection. These prior studies have important limitations, including focus on intensive care unit patients, identification of premorbid medical conditions retrospectively, and the inability to assess longitudinal risk [13–16, 36]. For example, in a study of 120,000 patients, Bagshaw et al. [13] found that comorbid disease burden was associated with increased risk of AKI, but their study was limited to patients admitted to the intensive care unit. In a study of 316 medical inpatients at 10 hospitals in the UK, Finlay et al. [16] found that chronic kidney disease and diabetes were independently associated with AKI, but the authors determined comorbid conditions retrospectively. Other studies have focused on AKI in narrow cohorts such as those with HIV, major trauma, hip fracture rhabdomyolysis, or those undergoing surgical or coronary procedures [37–42]. However, infection is the most common etiology for AKI, and infection-associated AKI is believed to have a distinct pathophysiology compared with other AKI subtypes.

In contrast to these prior efforts, our study has several important strengths. We used data from the REGARDS study, one of the nation's largest cohort of community-dwelling adults. While most AKI studies do not have reliable prehospitalization data, the REGARDS study used structured methods for determining comorbid conditions and medication use and systematically collected serum for biomarker analysis on all participants [43]. Furthermore, these data were obtained from each participant at a stable phase of health. We were also able to associate baseline risk factors with AKI episodes occurring over a 10-year span.

While chronic kidney disease is a recognized AKI risk factor, our study suggests that infection-associated AKI is more strongly associated with ACR and Cyst-C than creatinine-based eGFR [44–47]. The latter finding is particularly interesting because some experts believe that Cyst-C is not strictly a marker of kidney function; Cyst-C may also reflect systemic inflammation [48]. We have previously found that Cyst-C is independently associated with sepsis risk, even after adjustment for eGFR and ACR [49]. Thus, there may be additional biologic pathways linking elevated Cyst-C with increased AKI risk after a serious infection.

While our study found an association between diabetes with AKI, the link between diabetes and AKI risk is an area of considerable controversy, with studies both affirming and challenging this relationship [50–53]. Of note, none of the other participant sociodemographics (age, sex, and race), health behaviors (tobacco and alcohol use), or chronic medical conditions (history of atrial fibrillation, myocardial infarction, hypertension, dyslipidemia, deep vein thrombosis, stroke, chronic lung disease, or obesity) exhibited associations with AKI. This latter observation is important, excluding these factors as targets for AKI prediction or prevention.

There is considerable interest in the longitudinal risk of AKI from the chronic use of medications such as NSAIDs, statins, ACEIs, ARBs, and aldosterone inhibitors [25–29]. In this study, we did not detect associations between AKI episodes and the regular use of NSAIDs, statins, ACEIs, ARBs, or mineralocorticoid receptor antagonists. We also did not detect an increased risk of AKI with combination ACEI/ARB use. Numerous studies have linked ACEI, ARB, and their combination use with an increased risk of AKI, potentially by blunting the kidney's ability to respond to decreased perfusion [25, 28]. We are cautious in interpreting our findings, as the REGARDS study determined medication use and medication adherence at

a single time point (without follow-up evaluations) and did not account for medication dosages.

While some may question the biologic connection between baseline characteristics and AKI occurring in the distant future, this is in fact the novel observation of our study; that characteristics detected at an early stable phase of health may be linked to AKI episodes far in the future. The current mainstays of AKI 'prevention' encompass hemodynamic optimization and avoidance of nephrotoxic medications at the earliest stages of acute illness [3, 19]. Our findings highlight that an individual's propensity for AKI may be recognized well before the onset of acute illness. While the interventions available to prevent AKI are currently limited, our findings would prove important with the development of novel AKI treatments or strategies; for example, for the identification of high-AKI-risk individuals to target novel AKI-preventive pharmacotherapy [54]. Additional studies must continue to identify opportunities to prevent and manage AKI.

Limitations

We focused on AKI occurring in individuals hospitalized for a serious infection. Recall or reporting biases may have resulted in underidentification of serious infection events, including repeat hospitalizations. AKI may have occurred but not been detected in individuals receiving fewer than 2 sCr measurements. We focused on AKI developing during hospitalization, not patient presentation to the hospital with community-acquired AKI [11, 12, 55]. As commonly done in AKI studies, we used the first inpatient sCr as an approximation of each participant's baseline sCr, an approach which may miss individuals who arrived at the hospital with ongoing AKI [56]. However, we did not have access to outpatient prehospitalization sCr values, which is necessary to capture cases of ongoing AKI [11, 12]. We also did not have information on the use of intravenous contrast agents, which may cause AKI [57].

We examined only eGFR, ACR, and Cyst-C. Additional studies must evaluate other biomarkers potentially tied to AKI risk. We were also limited to baseline conditions identified by the REGARDS study; for example, the study did not identify chronic liver disease, a history of rheumatic disease, or a history of organ transplant. Our study identified comorbid medical conditions, medication use, and a single measurement of each biomarker at the beginning of the REGARDS study. Over the 10-year observation period, participants may have developed additional chronic medical conditions or changes in their biomarker profiles. A repeat examination of all REGARDS subjects is in progress and may allow future examination of these changes.

Conclusions

AKI after hospitalization for a serious infection was independently associated with a history of diabetes and increased baseline ACR and Cyst-C. These observations may aid in the identification of individuals at increased risk for AKI.

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Disclosure Statement

Dr. Safford reports the following potential conflicts of interest: Amgen: salary support to study patterns of statin use in Medicare and other large databases; diaDexus: consulting to help with FDA application; NIH, AHRQ: salary support for research grants. Drs. Wang, Griffin, Gutiérrez, and Powell do not report any related conflicts of interest.

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