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

Henry E. Wang a  T. Clark Powell a  Orlando M. Gutiérrez b, d  Russell Griffin d  Monika M. Safford c

a Department of Emergency Medicine, and Divisions of b Nephrology and c Preventive Medicine, Department of Medicine, University of Alabama School of Medicine, and d Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Ala., USA

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
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, Louisianan, 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 (κ = 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 m² 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 PCO₂ <32 mm Hg, and (4) leukocytosis (white blood cells >12,000 or <4,000 cells/mm³ or >10% band forms) [33]. We used asynchronous combinations of abnormal vital signs and laboratory tests observed during the initial 24 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].
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
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).

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

|                     | 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**

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.

**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

|                    | AKI (n = 296 events) | No AKI (n = 1,778 events) | p value<sup>b</sup> |
|--------------------|----------------------|---------------------------|---------------------|
| **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 m² | 70.8 ± 23.7         | 77.8 ± 21.8               | <0.001              |
| eGFR <60 ml/min/1.73 m² | 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<sup>c</sup> | 30.4 | 29.6 | 0.77 |

Values are means ± standard deviations or numbers. BMI = Body mass index; waist circumference. <sup>a</sup> Includes 2,074 serious infection hospitalization events among 1,557 individuals. <sup>b</sup> Associations evaluated by GEE accounting for clustering by participant. <sup>c</sup> 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 AKIa

|                          | AKI (n = 296 events) | No AKI (n = 1,778 events) | p valueb |
|--------------------------|----------------------|---------------------------|----------|
| 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 admissionc | 73.0                  | 61.3                      | <0.001   |
| 28-hour SOFA scored      | 2 (1–4)              | 1 (0–2)                   | <0.001   |
|                          | 28.6                 | 28.4                      |          |
|                          | 24.0                 | 20.0                      |          |
|                          | 23.3                 | 18.1                      |          |
|                          | 24.3                 | 6.6                       |          |
| MEDS scoree              | 11 (8–14)            | 9 (8–13)                  | 0.06     |
|                          | 3.4                  | 3.7                       | 0.14     |
|                          | 16.2                 | 19.5                      |          |
|                          | 47.6                 | 50.5                      |          |
|                          | 17.2                 | 15.0                      |          |
|                          | 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 infectiona

|                                | 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.

Acknowledgements

This study was supported by award R01-NR012726 from the National Institute for Nursing Research, UL1-RR025777 from the National Center for Research Resources, as well as by grants from the Center for Clinical and Translational Science and the Lister Hill Center for Health Policy of the University of Alabama at Birmingham. The parent REGARDS study was supported by cooperative agreement U01-NS041588 from the National Institute of
Neurological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies. Representatives of the funding agencies have been involved in the review of the manuscript but not directly involved in the collection, management, analysis, or interpretation of the data.

The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at http://www.regardsstudy.org and http://www.regardssepsis.org.

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.

References

1. KDIGO clinical practice guideline for acute kidney injury. Section 2: AKI definition. Kidney Int Suppl 2012; 2: 19–36.
2. Hoste EA, Kellum JA: Acute kidney injury: epidemiology and diagnostic criteria. Curr Opin Crit Care 2006; 12: 531–537.
3. Bellomo R, Kellum JA, Ronco C: Acute kidney injury. Lancet 2012; 380: 756–766.
4. Grams ME, Rabb H: The distant organ effects of acute kidney injury. Kidney Int 2012; 81:942–948.
5. Ostermann M, Philips BJ, Forni LG: Clinical review: biomarkers of acute kidney injury: where are we now? Crit Care 2012; 16: 233.
6. Bagshaw SM, Bennett M, Haase M, Haase-Fielitz A, Egi M, Morimatsu H, D'Amico G, Goldsmith D, Devarajan P, Bellomo R: Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med 2010; 36:452–461.
7. Martensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR: Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med 2010; 36:1333–1340.
8. Han WK, Walker RS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV: Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008; 73:863–869.
9. Liangos O, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, Bonventre JV, Jaber BL: Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers 2009; 14:423–431.
10. Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, Frampton CM, Bennett MR, Ma Q, Sabbisetti VS, Vaidya VS, Walcher AM, Shaw GM, Henderson SJ, Nejat M, Schollum JB, George PM: Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. Kidney Int 2011; 79:1119–1130.
11. Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO: Epidemiology and outcome of community-acquired acute kidney injury. Nephrology 2014; 19:282–287.
12. Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A: Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. Clin J Am Soc Nephrol 2014; 9:1007–1014.
13. Bagshaw SM, George C, Bellomo R, Committee ADM: Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care 2008; 12:R47.
14. Murugan R, Karajala-Subramanyam V, Lee M, Yende S, Kong L, Carter M, Angus DC, Kellum JA: Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival. Kidney Int 2010; 77:527–535.
15. Plataki M, Kashani K, Cabello-Garza J, Maldonado F, Kashyap R, Kor DJ, Gajic O, Cartin-Ceba R: Predictors of acute kidney injury in septic shock patients: an observational cohort study. Clin J Am Soc Nephrol 2011; 6: 1744–1751.
16. Finlay S, Bray B, Lewington AJ, Hunter-Rowe CT, Banerjee A, Atkinson JM, Jones MC: Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. Clin Med 2013; 13: 233–238.
Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J: Albuminuria and estimated glomerular filtration rate in independent association with acute kidney injury. J Am Soc Nephrol 2010;21:1757–1764.

Doi K, Leelahavanichkul A, Hu X, Sidransky KL, Zhou H, Qin Y, Eisner C, Schnermann J, Yuen PS, Star RA: Pre-existing renal disease promotes sepsis-induced acute kidney injury and worsens outcome. Kidney Int 2008;74:1017–1025.

Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014;371:58–66.

Knight EL, Verhave JC, Spiegelman D, Hillege HL, de Zeeuw D, Curhan GC, de Jong PE: Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int 2004;65:1416–1421.

Powell TC, Donnelly JP, Gutierrez OM, Griffin RL, Safford MM, Wang HE: Cystatin C and long term risk of community-acquired sepsis: a population-based cohort study. BMC Nephrol 2015;16:61.

Venot M, Weis L, Clec'h C, Darmon M, Allaouchiche B, Goldgran-Toledano D, Garrouste-Orgeas M, Adrie C, Timsit JF, Azoulay E: Acute kidney injury in severe sepsis and septic shock in patients with and without diabetes mellitus: a multicenter study. PLoS One 2015;10:e0127411.

Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, Saran R, Wang AY, Yang CW: Chronic kidney disease: global dimension and perspectives. Lancet 2013;382:260–272.

Thakar CV, Christianson A, Himmelfarb J, Leonard AC: Acute kidney injury episodes and chronic kidney disease risk in diabetes mellitus. Clin J Am Soc Nephrol 2011;6:2567–2572.

Girman C, Kou TD, Brodovicz K, Alexander CM, O'Neill EA, Engel S, Williams-Herman DE, Katz L: Risk of acute renal failure in patients with type 2 diabetes mellitus. Diabet Med 2012;29:614–621.

Shelton LM, Park BK, Copple IM: Role of Nrf2 in protection against acute kidney injury. Kidney Int 2013;84:1090–1095.

Der Mesrobian PJ, Kalamaras JS, Eisele G, Phelps KR, Asif A, Mathew RO: Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. Clin Nephrol 2014;81:174–184.

Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW: Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365–3370.

McDonald JS, McDonald RJ, Lieske JC, Carter RE, Katzberg RW, Williamson EE, Kallmes DE: Risk of acute kidney injury, dialysis, and mortality in patients with chronic kidney disease after intravenous contrast material exposure. Mayo Clin Proc 2015;90:1046–1053.