Predictors of Recurrent AKI


*Tennessee Valley Healthcare System (TVHS), Veterans Administration (VA) Medical Center, Veteran’s Health Administration; †Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee; ‡Vanderbilt Center for Kidney Disease (VCKD), Nashville, Tennessee; §Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee; ‖Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, Tennessee; ¶Division of Nephrology, Department of Medicine, University of Washington, Washington, DC; **TVHS Geriatric Research Education and Clinical Centers; and ††Division of General Internal Medicine, Vanderbilt University Medical Center, Nashville, Tennessee

ABSTRACT

Recurrent AKI is common among patients after hospitalized AKI and is associated with progressive CKD. In this study, we identified clinical risk factors for recurrent AKI present during index AKI hospitalizations that occurred between 2003 and 2010 using a regional Veterans Administration database in the United States. AKI was defined as a 0.3 mg/dl or 50% increase from a baseline creatinine measure. The primary outcome was hospitalization with recurrent AKI within 12 months of discharge from the index hospitalization. Time to recurrent AKI was examined using Cox regression analysis, and sensitivity analyses were performed using a competing risk approach. Among 11,683 qualifying AKI hospitalizations, 2954 patients (25%) were hospitalized with recurrent AKI within 12 months of discharge. Median time to recurrent AKI within 12 months was 64 (interquartile range 19–167) days. In addition to known demographic and comorbid risk factors for AKI, patients with longer AKI duration and those whose discharge diagnosis at index AKI hospitalization included congestive heart failure (primary diagnosis), decompensated advanced liver disease, cancer with or without chemotherapy, acute coronary syndrome, or volume depletion, were at highest risk for being hospitalized with recurrent AKI. Risk factors identified were similar when a competing risk model for death was applied. In conclusion, several inpatient conditions associated with AKI may increase the risk for recurrent AKI. These findings should facilitate risk stratification, guide appropriate patient referral after AKI, and help generate potential risk reduction strategies. Efforts to identify modifiable factors to prevent recurrent AKI in these patients are warranted.


The increasing incidence of AKI highlights a need to develop strategies to reduce poor outcomes among survivors of AKI.1–3 Up to one-third of elderly patients hospitalized with AKI are rehospitalized with recurrent AKI within 12 months,4 and each episode of recurrence is associated with an increased risk for progression to advanced CKD.5 Preventing recurrent AKI may be an overlooked means to reduce long-term decline in kidney function following AKI.

A first step in preventing recurrent AKI is to identify patients at highest risk. Most studies examining risk factors for AKI focus on premorbid characteristics including demographics, baseline kidney function, or comorbid conditions.6,7 Little is known about which risk factors among
AKI survivors impact the risk for recurrence. We hypothesized that in addition to known premorbid risk factors, inpatient features associated with the index AKI event would help further profile patients at highest risk for future AKI. We tested this hypothesis by comparing the demographic, comorbid, and inpatient characteristics of patients experiencing and not experiencing recurrent AKI among a regional cohort of Veteran survivors of hospitalized AKI.

RESULTS

Patient Characteristics
A total of 11,683 first qualifying index AKI hospitalizations were examined (Figure 1). The baseline demographic, comorbid, and hospital data from the index hospitalization are shown in Table 1. The median age was 68 (interquartile range [IQR], 59–78) with a high prevalance of coronary artery disease, diabetes mellitus, hypertension, malignancy excluding nonmelanoma skin cancers, and congestive heart failure (CHF). Patients experiencing recurrent AKI were older and had a heavier comorbidity burden. Patients with recurrent AKI were also more likely to be hospitalized with a diagnosis of decompensated advanced liver disease (ALD), severe sepsis, malignancy, intravascular volume depletion, acute coronary syndrome, and a primary diagnosis of CHF.

The distribution of index AKI severity using the kidney disease improving global outcomes (KDIGO) staging system was stage I (80%), II (11%), and III (9%), respectively. Among patients experiencing recurrent AKI, the peak serum creatinine during index hospitalization was 1.9 (IQR, 1.5–2.4) mg/dl and the subsequent baseline serum creatinine used to define recurrent AKI was 1.2 (IQR, 1.0–1.5) mg/dl. We defined baseline serum creatinine for recurrent AKI as the lowest of either the most recent serum creatinine (inpatient or outpatient) beginning at discharge from the index AKI hospitalization or the admission creatinine of the recurrent AKI hospitalization (Figure 2). Forty-nine percent of index AKI survivors were rehospitalized at least once during the follow-up period with a mean±SD and median (IQR) number of hospitalizations of 1±1.5 and 0 (IQR, 0–1), respectively, and a range of 0–16. A total of 2954 patients (25%) were rehospitalized with recurrent AKI within 12 months. The median (IQR) time to hospitalized recurrent AKI in this population was 64 (IQR, 19–167) days. The mean±SD and median (IQR) number of recurrent AKI admissions were 0.4±0.8 and 0 (IQR, 0–1), respectively, with a range of 0–11. The mean±SD and median (IQR) number of admissions without recurrent AKI were 0.6±1.1 and 0 (IQR, 0–1), respectively, with a range of 0–13. The total 1-year mortality from the time of discharge was 23%. Patients who experienced recurrent AKI had a higher 1-year mortality (35%) than patients who did not experience recurrent AKI (18%), P<0.001. Approximately 40% of patients who died were rehospitalized with recurrent AKI before death.

In order to describe which clinically relevant events are likely to occur soonest after discharge, we illustrated the cumulative incidence of different events experienced within the year following discharge from index AKI. Figure 3, A–C illustrates the cumulative incidence and Tables 2–4 report the corresponding proportion of patients experiencing each event. We first focused on the rates of recurrent AKI hospitalization and death. Figure 3A and Table 2 show the cumulative incidence of patients hospitalized with recurrent AKI and death/hospice referral as the first event experienced. We next performed a stratified analysis to illustrate the cumulative incidence of these events by index AKI severity (shown in Figure 3B and Table 3). Lastly, to better understand the overall risk of AKI survivors for rehospitalization (with and without recurrent AKI), we introduced an additional outcome of rehospitalization without recurrent AKI in Figure 3C and Table 4, which report the cumulative incidence of hospitalization without recurrent AKI, hospitalization with recurrent AKI, and death/hospice referral as the first event experienced. Of the 25% of all patients who experienced recurrent AKI, the majority (58%) occurred within the first 90 days of discharge from index AKI (Figure 3A, Table 2). Approximately one-third of index
AKI survivors were rehospitalized without recurrent AKI as their first event experienced (Figure 3C, Table 4). There was a dose-dependent relationship between AKI severity and the risk of mortality as the first event experienced (Figure 3B, Table 3).

Clinical Variables Associated with Recurrent AKI

We performed multivariable Cox regression analysis to identify risk factors for recurrent AKI. Factors associated with recurrent AKI are illustrated in Figure 4A as follows:

Demographic and Comorbid Risk Factors

Older age was associated with a higher risk of recurrent AKI. Baseline eGFR also showed a dose-dependent association with recurrent AKI. Comorbid conditions that were associated with recurrent AKI included CHF, ALD, dementia, diabetes, and coronary artery disease.

Discharge Diagnoses from the Index Hospitalization

Inpatient risk factors were selected a priori based on previously known association with developing AKI. Discharge diagnoses most strongly associated with recurrent AKI included congestive heart failure (primary diagnosis), decompensated ALD, malignancy, acute coronary syndrome, and volume depletion. Lower mean inpatient serum albumin also showed a dose-dependent association with recurrent AKI. The severity (i.e., stage) of index AKI was not associated with the risk for recurrent AKI.

Table 1: Index hospital characteristics of patients with and without recurrent AKI

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (n=11,683)</th>
<th>No Recurrent AKI (n=8729)</th>
<th>Recurrent AKI (n=2954)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>68 (59–78)</td>
<td>67 (58–77)</td>
<td>71 (60–79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>11,358 (97%)</td>
<td>8468 (97%)</td>
<td>2890 (99%)</td>
<td>0.02</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>10,180 (87%)</td>
<td>7617 (87%)</td>
<td>2563 (87%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>6340 (54%)</td>
<td>4575 (52%)</td>
<td>1765 (60%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>10,040 (86%)</td>
<td>7434 (85%)</td>
<td>2606 (88%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>5987 (51%)</td>
<td>4304 (49%)</td>
<td>1683 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>2577 (22%)</td>
<td>1693 (19%)</td>
<td>884 (30%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease (%)</td>
<td>1665 (14%)</td>
<td>1189 (14%)</td>
<td>476 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Advanced liver disease (%)</td>
<td>431 (4%)</td>
<td>281 (3%)</td>
<td>150 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>3025 (26%)</td>
<td>2172 (25%)</td>
<td>853 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple myeloma (%)</td>
<td>100 (1%)</td>
<td>67 (1%)</td>
<td>33 (1%)</td>
<td>0.08</td>
</tr>
<tr>
<td>HIV (%)</td>
<td>95 (1%)</td>
<td>69 (1%)</td>
<td>26 (1%)</td>
<td>0.64</td>
</tr>
<tr>
<td>Dementia (%)</td>
<td>1185 (10%)</td>
<td>843 (10%)</td>
<td>342 (12%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dl</td>
<td>1.14 (0.95–1.40)</td>
<td>1.10 (0.95–1.37)</td>
<td>1.20 (1.00–1.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CKD (baseline eGFR&lt;60)</td>
<td>4021 (34%)</td>
<td>2816 (32%)</td>
<td>1205 (41%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF (primary dx)</td>
<td>643 (6%)</td>
<td>402 (5%)</td>
<td>241 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>898 (8%)</td>
<td>637 (7%)</td>
<td>261 (9%)</td>
<td>0.007</td>
</tr>
<tr>
<td>Decompensated advanced liver disease</td>
<td>468 (4%)</td>
<td>308 (4%)</td>
<td>160 (5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Volume depletion</td>
<td>1747 (15%)</td>
<td>1266 (15%)</td>
<td>481 (16%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Severe sepsis</td>
<td>2118 (18%)</td>
<td>1543 (18%)</td>
<td>575 (19%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1561 (13%)</td>
<td>1103 (13%)</td>
<td>458 (16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/HONC</td>
<td>141 (1%)</td>
<td>108 (1%)</td>
<td>33 (1%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Procedures/surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>174 (1%)</td>
<td>147 (2%)</td>
<td>27 (1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Vascular surgery</td>
<td>1485 (13%)</td>
<td>1097 (13%)</td>
<td>388 (13%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>482 (4%)</td>
<td>379 (4%)</td>
<td>103 (3%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Left-heart catheterization</td>
<td>860 (7%)</td>
<td>620 (7%)</td>
<td>240 (8%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Inpatient chemotherapy</td>
<td>137 (1%)</td>
<td>82 (1%)</td>
<td>55 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Indicators of illness severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severity of AKI, stage I (%)</td>
<td>9381 (80%)</td>
<td>7005 (80%)</td>
<td>2376 (80%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Stage II (%)</td>
<td>1282 (11%)</td>
<td>948 (11%)</td>
<td>334 (11%)</td>
<td></td>
</tr>
<tr>
<td>Stage III (%)</td>
<td>1020 (9%)</td>
<td>776 (9%)</td>
<td>244 (8%)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>764 (7%)</td>
<td>572 (7%)</td>
<td>192 (6%)</td>
<td>0.92</td>
</tr>
<tr>
<td>ICU stay, days</td>
<td>3237 (28%)</td>
<td>2419 (28%)</td>
<td>818 (28%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>5.1 (2.9–9.8)</td>
<td>5.0 (2.8–9.4)</td>
<td>5.8 (3.0–10.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*p* values <0.05 denote statistical significance.

HONC, hyperosmotic nonketotic coma; ICU, intensive care unit.
We performed an additional analysis with recurrent AKI defined as moderate to severe (i.e., KDIGO stages II and III injury) (Figure 4B). Eight hundred and forty-three (7.2%) patients experienced an episode of moderate to severe recurrent AKI. In contrast to the primary analysis, the severity of the index AKI event did show a dose-dependent relationship with the risk for moderate to severe recurrence [stage II adjusted hazard ratio (aHR) 1.30 [95% confidence interval, (95% CI)], 1.06 to 1.60], stage III aHR 1.62 (95% CI, 1.30 to 2.02). Other risk factors that remained associated with a higher risk of moderate to severe recurrent AKI included comorbid diagnoses of CHF, ALD, and dementia. Similarly, discharge diagnoses of decompensated ALD, malignancy, volume depletion, and acute coronary syndrome, and lower mean serum albumin also remained associated with recurrent AKI. Chemotherapy did not remain statistically significant after multivariable adjustment. A comorbid diagnosis of HIV was associated with recurrent AKI in this analysis.

Supplemental Analyses

1. In order to provide more information on death following AKI and the potential effects of censoring, we performed an adjusted analysis using a competing risk model with recurrent AKI remaining the primary outcome and death or hospice referral treated as a competing risk. In multivariable competing risk analysis, inpatient risk factors associated with a higher risk of recurrent AKI were similar to the primary analysis except that age and acute coronary syndrome were no longer statistically significant (Supplemental Figure 1).

2. To further reduce the possibility of fluctuating or nonrecovery of renal function following index AKI being misclassified as recurrent AKI, we also performed an analysis in which hospitalizations for recurrent AKI occurring within the first 90 days were not counted. In this analysis, 1634 (55%) of the original 2954 recurrent AKI episodes occurred after 90 days. A primary discharge diagnosis of CHF, discharge diagnoses of decompensated ALD, malignancy, and volume depletion remained associated with recurrent AKI. However, inpatient chemotherapy, acute coronary syndrome along with age, gender, and comorbid diagnoses of ALD and dementia were no longer statistically significant (Supplemental Figure 2).

3a. To better understand the risk for recurrence among patients more likely to have acute tubular necrosis, we performed two supplemental analyses. First, we examined whether duration of index AKI was associated with recurrent AKI. Our rationale was that acute tubular necrosis is the most common inpatient AKI etiology when injury persists and is an equally important long-term prognostic factor as is the change in serum creatinine. Tertiles of qualifying AKI days were studied (<2 days, 2 days, and >2 days) with 45%, 23%, and 32% of patients falling into these groups, respectively. Using <2 days as a reference group, the HRs for recurrent AKI for 2 days and >2 days injury were 1.17 (95% CI, 1.06 to 1.29) and 1.32 (95% CI, 1.20 to 1.45), respectively. Including duration had minimal impact on the strengths of the associations identified in our main analysis (data not shown).

3b. We next performed a subgroup analysis among patients with index AKI lasting >2 days excluding patients with a primary discharge diagnosis of CHF, a discharge diagnosis of decompensated ALD, or receiving chemotherapy. Among 3173 qualifying patients (27% of the original cohort), 873 (28%) experienced recurrent AKI. Inpatient factors that remained associated with a higher risk of recurrent AKI included malignancy and acute coronary syndrome, while cardiac and abdominal surgeries remained associated with a lower risk. In this analysis, baseline eGFR was associated with recurrent AKI along with female gender (protective), and comorbid diagnoses of CHF, dementia, and HIV (Supplemental Figure 3).
Figure 3. Cumulative Incidence of First Event Experienced Among Survivors of Hospitalized AKI. The y-axis denotes the cumulative proportion of AKI survivors experiencing the event and the x-axis represents time in days on the upper line with the number of patients who have not experienced any event below it. Once a patient experiences any event, they are censored. (A) Cumulative incidence of...
Table 2. Cumulative incidence rates of hospitalization with recurrent AKI or death/hospice referral as the first event experienced

<table>
<thead>
<tr>
<th>Time</th>
<th>30 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk (11,683)</td>
<td>10,137</td>
<td>9038</td>
<td>8174</td>
<td>7125</td>
</tr>
<tr>
<td>Recurrent AKI hospitalization (%) (95% CI)</td>
<td>8.5% (8.0 to 9.0)</td>
<td>14.6% (14.0 to 15.3)</td>
<td>19.5% (18.8 to 20.2)</td>
<td>25.3% (24.5 to 26.1)</td>
</tr>
<tr>
<td>Death or hospice referral (%) (95% CI)</td>
<td>5.0% (4.6 to 5.4)</td>
<td>8.1% (7.7 to 8.6)</td>
<td>10.6% (10.1 to 11.2)</td>
<td>13.8% (13.2 to 14.4)</td>
</tr>
</tbody>
</table>

DISCUSSION

AKI is a risk factor for CKD progression and future mortality. In this study, we demonstrate that recurrent AKI is common in the first year following hospitalization and that longer injury duration, along with inpatient diagnoses of decompensated ALD, CHF (primary), malignancy with or without chemotherapy, acute coronary syndrome, and volume depletion are independent risk factors for recurrent AKI.

The path to ESRD is often nonlinear and marked by one or more episodes of AKI. One-third of elderly AKI survivors are rehospitalized with recurrent AKI within 12 months, with one in eight experiencing two recurrences (i.e., three AKI episodes in 12 months).

Traditional AKI risk stratification often focuses on static susceptibility risk factors including age or CKD. While important, these findings indicate that the risk for AKI is dynamic and varies greatly as underlying disease evolves. Our results extend on the literature by highlighting that the residual or ongoing effects of acute illness and its associated treatments are equally or more important to consider in assessing proximal AKI risk. This may be particularly true in certain survivors of AKI, in whom these effects combined with recent AKI, may confer additional susceptibility that overshadows the risk associated with more remote difference in baseline eGFR. For example, patients with decompensated ALD often experience AKI due to altered systemic and regional hemodynamics, fluid shifts from loss of oncotic pressure or accumulation of interstitial fluid, and a predisposition to infection. These complications may improve by discharge, but the risk for relapse is high, tending to worsen in the absence of transplantation. Treatment also often involves antibiotic exposure or more aggressive diuretic strategies, which may further increase the risk for AKI. However, the persistence of decompensated ALD as a risk factor when using stricter definitions for recurrent AKI suggests these risks extend beyond mere dilution and concentration of serum creatinine. Similarly, the effects of decompensated CHF on kidney function are well known, and the repercussions of AKI on cardiac function and mortality are being actively studied.

The bidirectional nature of these interactions may be mediated by vascular congestion, as classically observed in the cardiorenal syndrome. In our study, patients hospitalized with a primary discharge diagnosis of CHF who experienced recurrent AKI were more likely to die than those who did not experience recurrent AKI (37% versus 26%). Preventing recurrent AKI in this population may also be important given literature indicating a lower likelihood of renal recovery following AKI.

We also found that patients with AKI in the setting of acute coronary syndrome were at risk for recurrent AKI. These findings may help explain the observations made by others that some patients who experience AKI following coronary angiography appear to be at risk for long-term decline in kidney function. Potential mechanisms for this observation include the effects of renovascular or atheroembolic disease, future or repeat angiography, and selection of patients with decreased renal reserve, compromised hemodynamics, and diffuse disease less amenable to cardiac surgery. The latter may also partially explain the apparent lower risk for recurrence among the select group of cardiac surgery patients than those with acute coronary syndromes.

Another group of patients we identified to be at risk for recurrent AKI were those with malignancy or receiving chemotherapy. Ongoing improvements in the approach to prevention and treatment of cancer have led to an estimated reduction in cancer-related mortality by 20% over the past 20 years. The improved survival along with advances in available, but potentially nephrotoxic therapies, has resulted in cancer becoming an increasingly important contributor to the changing AKI case mix. Not surprisingly, the need to enhance our
understanding of the potential renal sequelae (i.e., “onconephrology”) is recognized by the American Society of Nephrology as a growing area of interest.28 Whether the risk of AKI recurrence in this population is mediated by exposure to chemotherapy or from underlying cancer is not known, highlighting an important area for future study. However, we did find that inpatient chemotherapy was no longer associated with recurrent AKI beyond 90 days, suggesting that the timing of renal complications relating to inpatient chemotherapy or its re-administration is likely to occur earlier.

Lastly, volume depletion has traditionally been considered to be a more self-limited and benign cause of AKI. However, we found that volume depletion was a risk factor for recurrent AKI that persisted even with more severe definitions for recurrence. These findings suggest that while pre-renal AKI may be reversible, factors which confer the initial risk of developing volume depletion may persist and be associated with a risk for future morbidity, including more severe AKI. Whether this relates to primary illness, concurrent therapy, or is simply a marker of intrinsic renal susceptibility is unknown; however, these findings highlight that the risk for future AKI in patients experiencing volume depletion does not fully resolve at hospital discharge.

Although baseline eGFR was modestly associated with recurrent AKI in the primary analysis, this association was more robust in patients with sustained index AKI after excluding hospitalizations for CHF, ALD, and chemotherapy in our supplemental analysis. This may be due to selection of patients with diminished renal reserve whose susceptibility (as reflected by baseline eGFR) becomes more prominent in the absence of the above diseases. The severity of AKI also did not independently predict the risk of recurrent AKI when using sensitive KDIGO criteria. However, when we used a more specific definition of recurrent AKI, the severity of the index AKI episode did emerge as a dose-dependent risk factor. A potential explanation for these findings is that when sensitive definitions for AKI are applied, the effect of underlying conditions associated with acute variations in serum creatinine, such as CHF and ALD, predominantly influence the risk for recurrent AKI. However, with a more specific definition for recurrent AKI, the impact of more severe index AKI on risk becomes apparent suggesting that AKI may lower the threshold for future tissue injury in a dose-dependent manner. The biologic basis for susceptibility may be rooted in experimental and early clinical data indicating that AKI leads to impairments in vascular autoregulation.32–34 Nevertheless, these findings underscore that similar to the prognostic significance of a transient ischemic attack or angina,35 even mild episodes of AKI may be a harbinger (i.e., or failed stress test) for future, more devastating AKI.

The optimal care following AKI remains to be defined and the transition of care may be an opportunity to prevent long-term loss of kidney function and its sequelae.36 We previously demonstrated that few AKI survivors are referred for follow-up nephrology care.12 Subsequent studies suggest that referral may benefit survivors of dialysis-requiring AKI.37 However, better understanding of the care driving this potential benefit and a more efficient approach to identify high risk patients are needed. This may be especially appropriate during the first 3–4 months following discharge from AKI, when most of the

### Table 3. Cumulative incidence rates of hospitalization with recurrent AKI or death/hospice referral as the first event experienced stratified by index AKI stage

<table>
<thead>
<tr>
<th>Time</th>
<th>30 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index stage I AKI number at risk (n=9386)</td>
<td>8240</td>
<td>7367</td>
<td>6688</td>
<td>5822</td>
</tr>
<tr>
<td>Index stage I AKI recurrent AKI hospitalization (% (95% CI))</td>
<td>8.2% (7.7 to 8.8)</td>
<td>14.3% (13.6 to 15.0)</td>
<td>19.3% (18.5 to 20.1)</td>
<td>25.3% (24.4 to 26.2)</td>
</tr>
<tr>
<td>Index stage I AKI death or hospice referral (%) (95% CI)</td>
<td>4.3% (3.9 to 4.7)</td>
<td>7.3% (6.8 to 7.9)</td>
<td>9.5% (8.9 to 10.1)</td>
<td>12.7% (12.0 to 13.4)</td>
</tr>
<tr>
<td>Index stage II AKI number at risk (n=1282)</td>
<td>1084</td>
<td>962</td>
<td>861</td>
<td>748</td>
</tr>
<tr>
<td>Index stage II recurrent AKI hospitalization (% (95% CI))</td>
<td>9.1% (7.6 to 10.8)</td>
<td>15.3% (13.4 to 17.3)</td>
<td>20.5% (18.4 to 22.8)</td>
<td>26.1% (23.7 to 28.5)</td>
</tr>
<tr>
<td>Index stage II death or hospice referral (%) (95% CI)</td>
<td>6.6% (5.3 to 8.0)</td>
<td>9.8% (8.2 to 11.5)</td>
<td>12.5% (10.7 to 14.4)</td>
<td>15.6% (13.7 to 17.6)</td>
</tr>
<tr>
<td>Index stage III AKI number at risk (n=1015)</td>
<td>813</td>
<td>709</td>
<td>625</td>
<td>555</td>
</tr>
<tr>
<td>Index stage III AKI recurrent AKI hospitalization (%) (95% CI))</td>
<td>10.2% (8.4 to 12.1)</td>
<td>16.8% (14.5 to 19.1)</td>
<td>19.9% (17.5 to 22.4)</td>
<td>24.0% (21.5 to 26.7)</td>
</tr>
<tr>
<td>Index stage III AKI death or hospice referral (%) (95% CI)</td>
<td>10.0% (8.2 to 11.9)</td>
<td>13.6% (11.6 to 15.8)</td>
<td>18.5% (16.2 to 21.0)</td>
<td>21.4% (18.9 to 24.0)</td>
</tr>
</tbody>
</table>

### Table 4. Cumulative incidence rates of hospitalization with recurrent AKI, hospitalization without recurrent AKI, or death/hospice referral as the first event experienced

<table>
<thead>
<tr>
<th>Time</th>
<th>30 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>365 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number at risk (11,683)</td>
<td>8951</td>
<td>7218</td>
<td>6031</td>
<td>4667</td>
</tr>
<tr>
<td>Recurrent AKI hospitalization (%) (95% CI)</td>
<td>7.8% (7.4 to 8.3)</td>
<td>12.1% (11.5 to 12.7)</td>
<td>14.9% (14.3 to 15.5)</td>
<td>17.8% (17.1 to 18.5)</td>
</tr>
<tr>
<td>Recurrent hospitalization without recurrent AKI (%) (95% CI)</td>
<td>11.5% (10.9 to 12.1)</td>
<td>19.6% (18.9 to 20.4)</td>
<td>25.4% (24.6 to 26.2)</td>
<td>32.6% (31.8 to 33.5)</td>
</tr>
<tr>
<td>Death or hospice referral (%) (95% CI)</td>
<td>4.5% (4.1 to 4.9)</td>
<td>6.7% (6.3 to 7.2)</td>
<td>8.2% (7.7 to 8.7)</td>
<td>9.7% (9.2 to 10.2)</td>
</tr>
</tbody>
</table>
recurrent AKI seems to occur. Notably, we did not find an independent association between markers of illness severity including mechanical ventilation or intensive care unit stay and recurrent AKI. This may have been driven, in part, by higher rates of death observed in this population (data not shown). However, these results should be interpreted with caution and do not suggest a lack of benefit from more intensive care or surveillance in survivors of critical illness.

The strengths of this study include the use of a large cohort of frequent users of the Veterans Administration (VA) system, creatinine-based definitions to capture index and recurrent AKI, and power to examine multiple potential confounders. However, as the study population is predominantly male, generalizability to women is limited. We also limited our detection of recurrent AKI to hospitalized AKI, which may underestimate the actual number of episodes. We did not examine multiple AKI episodes occurring during the index hospitalization as we believe significant: (1) Demographics and comorbid conditions: hypertension, peripheral vascular disease, HIV infection, multiple myeloma, malignancy, and (2) Inpatient factors/discharge diagnoses: AKI severity, diabetic ketoacidosis/hyperosmotic nonketotic coma, rhabdomyolysis, multiple myeloma, severe sepsis, left heart catheterization, vascular surgeries, mechanical ventilation, intensive care unit stay, and length of stay. (B) Forest plot indicating the aHR of risk factors for recurrent AKI when recurrent AKI is defined using KDIGO stage II and III injury using a Cox proportional hazards model. Confidence intervals that do not cross 1 denote statistical significance. The model was also adjusted for the following additional covariates whose associations with recurrent AKI were not statistically significant: (1) Demographic and comorbid conditions: age, gender, race, baseline eGFR, coronary artery disease, diabetes mellitus, hypertension, peripheral vascular disease, multiple myeloma, malignancy, and (2) Inpatient factors/discharge diagnoses: congestive heart failure (primary diagnosis), diabetic ketoacidosis/hyperosmotic nonketotic coma, rhabdomyolysis, multiple myeloma, severe sepsis, left heart catheterization, cardiac surgeries, vascular surgeries, inpatient chemotherapy, mechanical ventilation, intensive care unit stay, and length of stay.

Figure 4. Risk factors identified for recurrent AKI. (A) Forest plot indicating the aHR of risk factors for recurrent AKI using a Cox proportional hazards model. Confidence intervals that do not cross 1 denote statistical significance. The model was also adjusted for the following additional covariates whose associations with recurrent AKI were not statistically significant: (1) Demographic and comorbid conditions: hypertension, peripheral vascular disease, HIV infection, multiple myeloma, malignancy, and (2) Inpatient factors/discharge diagnoses: AKI severity, diabetic ketoacidosis/hyperosmotic nonketotic coma, rhabdomyolysis, multiple myeloma, severe sepsis, left heart catheterization, vascular surgeries, mechanical ventilation, intensive care unit stay, and length of stay. (B) Forest plot indicating the aHR of risk factors for recurrent AKI when recurrent AKI is defined using KDIGO stage II and III injury using a Cox proportional hazards model. Confidence intervals that do not cross 1 denote statistical significance. The model was also adjusted for the following additional covariates whose associations with recurrent AKI were not statistically significant: (1) Demographic and comorbid conditions: age, gender, race, baseline eGFR, coronary artery disease, diabetes mellitus, hypertension, peripheral vascular disease, multiple myeloma, malignancy, and (2) Inpatient factors/discharge diagnoses: congestive heart failure (primary diagnosis), diabetic ketoacidosis/hyperosmotic nonketotic coma, rhabdomyolysis, multiple myeloma, severe sepsis, left heart catheterization, cardiac surgeries, vascular surgeries, inpatient chemotherapy, mechanical ventilation, intensive care unit stay, and length of stay.
the pathophysiology probably differs, but acknowledge it as a needed area of study. Although we examined the first AKI observed in our dataset, our longitudinal records are limited in duration and we cannot be certain that some of our patients did not have a remote prior episode of AKI. We believe, however, that this does not detract from the main findings of this study, whose aim was to identify and examine the impact of inpatient risk factors for recurrent AKI. Lastly, we cannot be certain that ascertainment bias in measuring outpatient serum creatinine measurement did not contribute to the diagnosis of recurrent AKI in some patients. However, we found a low percentage of recurrent AKI hospitalizations (4.8%) in which AKI was the primary reason for admission (primary discharge diagnosis).

In conclusion, the risk for AKI is dynamic among AKI survivors and recurrence is common. The risk for recurrent AKI is likely to be due both to intrinsic susceptibility, which may increase after an episode of AKI, as well as the risk conferred by the residual effects of acute illness or its therapies. These factors are critical considerations in caring for recent AKI survivors. Further studies to identify potential risk reduction strategies in patients at highest risk for recurrence may generate optimism for reducing long-term morbidity in this growing population.

CONCISE METHODS

Study Population and Setting
This study involved data from five VA medical centers located in Tennessee, Kentucky, and West Virginia. The clinical enterprise encompasses acute inpatient hospitals, outpatient primary care and subspecialty clinics, outpatient pharmacies, rehabilitation facilities, and long-term care facilities and domiciliaries. A retrospective cohort of adults (≥18 years) was formed among patients hospitalized for at least 24 hours between January 2003 and December 2010. Qualifying hospitalizations were required to last ≥24 hours, have at least one inpatient serum creatinine measurement, and at least one outpatient serum creatinine measurement 7–365 days prior to admission. We excluded patients with a history of renal failure defined as chronic dialysis, baseline eGFR<15 ml/min per 1.73 m², or renal transplant prior to hospitalization. We also excluded index hospitalizations involving nephrectomy, renal transplant, acute nephritis or urinary obstruction, and those in which patients died or were referred to hospice care prior to discharge, or received dialysis within 48 hours of discharge. Lastly, to reduce misclassification of worsening index AKI as recurrent AKI, we also excluded patients whose serum creatinine peaked at the time of discharge from the index hospitalization.38

Index and Recurrent AKI Definitions
The primary outcome was hospitalization complicated by recurrent AKI within 12 months of discharge from the index AKI event. Acute kidney injury was defined as a 0.5 mg/dl or 50% increase in serum creatinine using the difference between peak hospitalization and baseline creatinine and staged according to KDIGO criteria.9 We defined index baseline serum creatinine as the mean outpatient serum creatinine 7–365 days prior to admission.39 The ‘index’ AKI hospitalization was defined as the first of all qualifying hospitalizations to meet study AKI criteria. For recurrent AKI hospitalization, we defined baseline serum creatinine as the lowest of either the most recent serum creatinine (inpatient or outpatient) beginning at discharge from the index AKI hospitalization or the admission creatinine of the recurrent AKI hospitalization (Figure 2). The rationale for the latter was to account for recovery of kidney function, which several studies have found can extend up to months following an episode of AKI.12–14

Data Sources
Data extracted from the regional data warehouse included general demographic information (e.g., age, gender, race, admitting service, and location), inpatient and outpatient procedures and diagnoses [using Current Procedural Terminology (CPT) and International Classification of Disease, version 9 (ICD-9) codes] (Supplemental Appendix), laboratory data, and computerized physician order entry. Comorbidities used in Table 1 were collected from data prior to the index hospital admission. The Tennessee Valley Health System (TVHS) Veteran’s Health Administration institutional review board and research and development committees approved this study.

Dialysis was defined using ICD-9 and CPT procedural codes. Death was ascertained through VA administrative codes (updated through the national death index), as well as patient family reports, VA personnel direct family contact, and federal third party notifications. eGFR for all serum creatinine measures was derived using the abbreviated modification of diet and renal disease equation.40 Chronic kidney disease was defined as a calculated eGFR<60 ml/min per 1.73 m² from the index baseline creatinine value. Comorbid conditions and inpatient diagnoses were also defined using ICD-9 diagnosis codes41–48 (Supplemental Appendix).

Statistical Analyses
Patients’ baseline characteristics, demographics, and injury stage were summarized as medians and IQRs for continuous variables and frequencies (%) for categorical variables. We used multivariable Cox regression analysis to identify predictors of recurrent AKI at hospital discharge from the index AKI event. Proportional hazards assumptions were verified using Schoenfeld residual plots.49 The list of predictors of recurrent AKI included demographics, comorbidities, as well as inpatient diagnoses and procedures from the index AKI hospitalization. Patients were censored at death, hospice or at the end of the data acquisition period (i.e., a year after the index AKI). aHRs were reported together with 95% CIs. As a sensitivity analysis, we also used proportional hazard competing risk regression by Gray and Fine with recurrent AKI as the main outcome and treating death/hospice as a competing risk.50 Adjusted hazard ratios were calculated for our covariates of interest. Cumulative incidence functions were evaluated in order to report cumulative probabilities of recurrent AKI and death/hospice over the study period.51,52 Aalen’s variance estimator was used to estimate confidence intervals of cumulative probabilities.53 Our rationale of using competing risk analysis was to provide additional information on the cumulative incidence of death/hospice in this high-risk population and to examine for possible inflation of HRs due to censoring by death.54 All analyses
included the same a priori-defined set of covariates chosen based on
known associations with AKI including: demographics (age, gender,
race), pre-existing conditions (baseline eGFR, coronary heart disease,
diabetes mellitus, hypertension, peripheral vascular disease, CHF, ALD,
HIV infection, multiple myeloma, malignancy excluding nonmelanoma
skin cancer, and dementia), inpatient markers of illness severity (intensive
care unit stay, mechanical ventilation, length of stay, AKI stage),
discharge diagnoses (CHF [primary], ALD, malignancy, diabetic keto-
cidosis/hyperosmotic nonketotic coma, multiple myeloma, rhabdo-
myolysis, acute coronary syndrome [myocardial infarction or unstable
angina], severe sepsis, intravascular volume depletion), or procedures
(chemotherapy, left heart catheterization), or surgeries (cardiac, vascu-
lar, abdominal). Age and serum albumin were modeled as nonlinear
effects using restricted cubic splines. All analyses were performed in R,
free software for statistical computing, version 2.12.1 (http://www.r-
project.org/). Restricted cubic splines for competing risk model were
implemented using the code that can be found at github.com, DOI

ACKNOWLEDGMENTS

Dr. Siew was supported by National Institutes of Health (NIH) K23-
DK089964-03 from the National Institute of Diabetes and Digestive and
Kidney Diseases (NIDDK), the Vanderbilt Center for Kidney Disease,
and the Veterans Administration HSR&D Merit Award IIR 13-073-3.
Dr. Ikizler was supported in this work by NIDDK K24-DK62849.
Dr. Matheny was supported by Veterans Health Administration Health
Services Research & Development (HSR&D) Career Development Award
CDA 08-020 and Investigator Initiated Research (IIR 11-292).
Dr. Parr (SKP) is supported by NIH Training Grant 5T32-DK007569-
25.
Dr. Bansal (NB) is supported by K23-DK088865.
Dr. Abdel-Kader is supported by K23-DK090304.
Dr. Hung is supported by Veterans Administration CSR&D Merit
Award 1H01CX00982-01A1.

This work was also partially supported by the Assessment and Serial
Evaluation of the Subsequent Sequelae of Acute Kidney Injury Study
(SU01DK92192-07).

Preliminary findings of this manuscript were presented in abstract
form at the Annual Meeting of the American Society of Nephrology in
November of 2014, in Philadelphia, PA.

DISCLOSURES

None.

REFERENCES

1. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY: Temporal changes in
1:37–42, 2013
injury episodes and chronic kidney disease risk in diabetes mellitus. Clin
3. Hsu CY, Ordoñez JD, Chertow GM, Fan D, McCulloch CE, Go AS: The
risk of acute renal failure in patients with chronic kidney disease. Kidney
Int 74:101–107, 2008
4. (USRDS) USRDS: Annual Data Report 2013, Chapter 6, Acute Kidney
Injury, 2013
6. Coca SG, King JT Jr, Rosenthal RA, Perkal MF, Parikh CR: The duration of
postoperative acute kidney injury is an additional parameter predicting
7. Coca SG, Singanamala S, Parikh CR Chronic kidney disease after acute
kidney injury: a systematic review and meta-analysis. Kidney Int 81:
442–448, 2012
8. Siew ED, Peterson JF, Eden SK, Hung AM, Speroff T, Ikizler TA,
Matheny ME: Outpatient nephrology referral rates after acute kidney
9. Macedo E, Zanetta DM, Abdulkader RC: Long-term follow-up of pa-
SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz
HM: Incidence, predictors at admission, and impact of worsening renal
23:2529–2600, 2010
12. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA,
Himmelfarb J, Collins AJ: Incidence and mortality of acute renal failure
1142, 2006
injury episodes and chronic kidney disease risk in diabetes mellitus. Clin
14. Liaño F, Felipe C, Tenorio MT, Rivera M, Abraira V, Sáez-de-Urturi JM,
Ocaña J, Fuentes C, Severiano S: Long-term outcome of acute tubular
16. Forman DE, Butler J, Wang Y, Abraham WT, O'Gara PT, Yeh RW:
Epidemiology, aortic stenosis, and cardiovascular outcomes in patients with
18. Moreau R, Lebrec D: Acute renal failure in patients with cirrhosis: per-
19. Moreau R, Lebrec D: Diagnosis and treatment of acute renal failure in
patients with cirrhosis. Best Pract Res Clin Gastroenterol 21:111–123,
2007
Circulation 121:2592–2600, 2010
prognosis of acute kidney injury after acute myocardial infarction. Arch
SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz
HM: Incidence, predictors at admission, and impact of worsening renal
23:2529–2600, 2010
23. Testani JM, Brisco MA, Chen J, McAuley BD, Parikh CR, Tang WH:
Timing of hemococoncentration during treatment of acute decomp-
pensated heart failure and subsequent survival: importance of sus-

199

1199


Recurrent AKI Predictors

This article contains supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2014121218/-/DCSupplemental.