Acute kidney injury (AKI) is associated with progression to advanced chronic kidney disease (CKD). We tested whether patients who survive AKI and are at higher risk for CKD progression can be identified during their hospital admission, thus providing opportunities to intervene. This was assessed in patients in the Department of Veterans Affairs Healthcare System hospitalized with a primary diagnosis indicating AKI (ICD9 codes 584.xx). In the exploratory phase, three multivariate prediction models for progression to stage 4 CKD were developed. In the confirmatory phase, the models were validated in 11,589 patients admitted for myocardial infarction or pneumonia during the same time frame that had RIFLE codes R, I, or F and complete data for all predictor variables. Of the 5351 patients in the AKI group, 728 entered the hospital with a diagnosis of AKI and were at especially high risk for progression to CKD. Hence, the severity of AKI is a robust predictor of progression to CKD.

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KEYWORDS: acute kidney injury; acute renal failure; albumin; chronic kidney disease; predicts; severity
critical. In this study, we set out to further risk stratify AKI patients who are more likely to progress to CKD, and develop a prediction tool to help clinicians identify these patients at the time of hospital discharge for nephrological outpatient follow-up.

RESULTS

There were 5351 patients in the AKI population. These subjects had a mean 10.2 ± 13.9 SC evaluations during the year before hospitalization, 9.8 ± 7.7 SC evaluations during their index hospitalization, and 15.0 ± 24.0 after hospitalization. In this group, 728 (13.6%) entered CKD4 after their index hospitalization, and 15.0 ± 0.82; Table 2, Figure 1a). Model parameters were: $y = 0.2141 + 0.0174 \cdot \text{age} - 0.1861 \cdot \text{AA} + 0.1223 \cdot \text{T} + 0.1067 \cdot \text{DM} + 0.4075 \cdot \text{(SC-Hosp)} - 0.5865 \cdot \text{(Alb-Base)} - 0.8942 \cdot \text{(Alb-Hosp)}$

Evaluation of models in control sample

1. **Model 1.** This prediction model included: sex, age, race, diagnosis of ATN, time at risk (T), presence of diabetes mellitus (DM), estimated glomerular filtration rate (eGFR)-pre, SC-Hosp, renal replacement therapy (RRT), teaching hospital, baseline serum albumin concentrations (Alb-Base), serum albumin during hospitalization (Alb-Hosp), baseline hemoglobin, and mean-hemoglobin during hospitalization. The final model was significant ($P<0.0001$), had moderate effect size ($D=64$), and good prediction accuracy (area under the receiver operating characteristic (ROC) curve = 0.82; Table 2, Figure 1a). Model parameters were: $y = 0.2141 + 0.0174 \cdot \text{age} - 0.1861 \cdot \text{AA} + 0.1223 \cdot \text{T} + 0.1067 \cdot \text{DM} + 0.4075 \cdot \text{(SC-Hosp)} - 0.5865 \cdot \text{(Alb-Base)} - 0.8942 \cdot \text{(Alb-Hosp)}$

2. **Model 2.** Predictors tested included age, Alb-Hosp, SC-Hosp, and time at risk. All variables were entered into the equation. This model was significant ($P<0.0001$), with moderate effect size ($D=0.61$), and good prediction accuracy (area under the ROC curve = 0.81; Figure 1b). Model parameters were: $y = -0.8249 + 0.0162 \cdot \text{age} + 0.1064 \cdot \text{T} + 0.3655 \cdot \text{(SC-Hosp)} - 1.1468 \cdot \text{(Alb-Hosp)}$

According to this model, each year of age raised the odds of reaching CKD4 by 2%, each 1.0 mg/dl SC increase raised the odds by 44%, and each 1.0 gm/dl albumin increase reduced the odds by 43%. Risk scores were computed for each AKI subject using the above equation. Using this risk score cut-point, the model had a sensitivity of 0.72 and specificity of 0.74. The odds of reaching CKD4 for those with a risk score above the cut-point were 7.27 worse (95% CI 5.98–8.84; Table 5) compared with those with risk scores below the cut-point.

3. **Model 3.** Predictors entered into the equation included age, time at risk, eGFR-Base, RRT, Alb-Hosp, and RIF score. This model was significant ($P<0.0001$), and had acceptable prediction accuracy ($D=0.54$; area under ROC curve = 0.77, Figure 1c). The prediction model parameters were: $y = -0.0394 + 0.00959 \cdot \text{age} + 0.1165 \cdot \text{T} - 0.00562 \cdot \text{(GFR-Base)} + 0.4384 \cdot \text{RRT} + 0.6326 \cdot \text{RIF} - 1.1214 \cdot \text{(Alb-Hosp)}$

In this model, each year of age added 1%, each 1 point increase in RIF score added 88%, and having dialysis during admission added 140% to the odds of reaching CKD4, each 1 point increase in GFR-Base reduced the odds by 1%, and each 1-point increase in Alb-Hosp reduced the odds of reaching CKD4 by 67% (Table 6). Those with a risk score above the cut-point had odds of reaching CKD4 that were 5.75 (95% CI 4.72–7.00; Table 7) times higher than those with scores below the cut-point.
each CON subject using the model 1 equation (Table 8). Using a cut-point of \( /C0 = 2.45 \), sensitivity was 0.71, specificity was 0.61, and the OR for CKD4 was 3.85 (95% CI 3.29–4.52). These results indicate little loss of prediction accuracy in the validation cohort of patients without a primary AKI diagnosis compared with the derivation sample of patients that had a primary AKI diagnosis, in the absence of CKD.

**Model 2.** Model 2 was significant in the CON population \((P<0.0001)\), it had moderate effect size \((D = 0.63)\), and good prediction accuracy \((c = 0.81; \text{Figure 2b})\). The model indicated that each year of age added 1%, and each 1.0 g/dl increase in SC-Hosp added 529% to the odds of reaching CKD4. Each 1.0 g/dl increase in Alb-Hosp reduced the odds by 47% (Table 8). Using a risk score cut-point of \(-2.2\), the model had sensitivity of 0.66, specificity of 0.66, and the odds of having CKD4 were 3.76 (95% CI 3.28–4.32) for those with risk scores above, as opposed to below the cut-point.

**Model 3.** When model 3 was tested in CON subjects, RRT was found to be highly collinear with the intercept, so this model was evaluated without the intercept. It was significant \((P < 0.0001)\), had moderate effect size \((D = 0.64)\) and good prediction accuracy \((c = 0.82; \text{Figure 2c})\). This model indicated that each year of age added 1%, and each 1 point increase in RIF added 343% to the odds of reaching CKD4, each 1 point increase in GFR-Base reduced the odds of reaching CKD4 by 3% and each 1.0 g/dl increase of mean

**Table 1 | Univariate relationships with CKD4**

| Variable          | No CKD4 \((n=4623)\) | CKD4 \((n=728)\) | Total \((N=5351)\) | Univariate odds ratio (95% CI) |
|-------------------|-----------------------|------------------|-------------------|-------------------------------|
|                   | \(n (\text{column %})\) | \(n (\text{column %})\) |                   |                               |
| **Race**          |                       |                  |                   |                               |
| African American  | 1444 (31.2)           | 212 (29.1)       | 1656 (31.0)       | 1.50 (0.78–2.89) **NS**       |
| Hispanic          | 275 (6.0)             | 57 (7.8)         | 332 (6.2)         |                               |
| Caucasian         | 2830 (61.2)           | 446 (61.3)       | 3276 (61.2)       |                               |
| Other             | 74 (1.6)              | 13 (1.8)         | 87 (1.6)          |                               |
| **Gender**        |                       |                  |                   |                               |
| Male              | 4519 (97.9)           | 713 (98.6)       | 5232 (98.0)       | 1.13 (0.96–1.33) **NS**       |
| Female            | 95 (2.1)              | 10 (1.4)         | 105 (2.0)         |                               |
| **DM pre-admission** |                  |                  |                   |                               |
| Yes               | 1767 (38.2)           | 257 (35.3)       | 2024 (37.8)       | 1.13 (0.96–1.33) **NS**       |
| No                | 2856 (61.8)           | 471 (64.7)       | 3327 (62.2)       |                               |
| **Dialysis***     |                       |                  |                   |                               |
| Never             | 4578 (99.0)           | 690 (94.8)       | 5268 (98.5)       | 1.13 (0.96–1.33) **NS**       |
| During hospitalization | 39 (0.8)            | 18 (2.5)         | 57 (1.1)          |                               |
| Post hospitalization | 6 (0.1)              | 2 (0.3)          | 8 (0.2)           |                               |
| **Hospital complexity** \((a)\) |                  |                  |                   |                               |
| 1A                | 2493 (54.0)           | 392 (53.9)       | 2885 (53.9)       | 1.13 (0.96–1.33) **NS**       |
| 1B                | 831 (18.0)            | 126 (17.3)       | 957 (17.9)        |                               |
| 1C                | 662 (14.3)            | 98 (13.5)        | 760 (14.2)        |                               |
| 2                 | 469 (10.2)            | 81 (11.1)        | 550 (10.3)        |                               |
| 3                 | 166 (3.6)             | 31 (4.3)         | 197 (3.7)         |                               |
| **Teaching hospital** |                  |                  |                   |                               |
| Yes               | 4080 (88.3)           | 630 (86.5)       | 4710 (88.1)       | 0.85 (0.68–1.07) **NS**       |
| No                | 541 (11.7)            | 98 (13.5)        | 639 (12.0)        |                               |
| **ATN diagnosis** |                       |                  |                   |                               |
| Yes               | 276 (6.0)             | 67 (9.2)         | 343 (6.4)         | 1.60 (1.21–2.11) **NS**       |
| No                | 4347 (94.0)           | 661 (90.8)       | 5008 (93.6)       |                               |

| **Mean ± s.d.** |          |          |          |          |
|-----------------|----------|----------|----------|----------|
| Age**           | 66.1 ± 12.2 | 67.8 ± 12.6 | 66.3 ± 12.3 | 1.01 (1.005–1.02) **NS** |
| Alb-Base***     | 3.7 ± 0.6 | 3.3 ± 0.7 | 3.61 ± 0.6 | 0.38 (0.33–0.43) **NS** |
| Alb-Hosp***     | 3.3 ± 0.7 | 2.7 ± 0.7 | 3.24 ± 0.8 | 0.31 (0.27–0.36) **NS** |
| Hgb-Base***     | 12.9 ± 1.9 | 12.4 ± 1.8 | 12.9 ± 1.9 | 0.86 (0.82–0.89) **NS** |
| Hgb-Hosp***     | 11.7 ± 1.9 | 10.8 ± 1.8 | 11.6 ± 1.9 | 0.74 (0.71–0.78) **NS** |
| Residency slots | 35.3 ± 18.5 | 35.8 ± 19.6 | 35.3 ± 18.7 | 1.00 (1.00–1.01) **NS** |
| Baseline eGFR   | 80.4 ± 17.3 | 81.6 ± 18.1 | 80.6 ± 17.4 | 1.00 (1.00–1.01) **NS** |
| Time at risk (years)*** | 2.35 ± 1.62 | 2.79 ± 1.67 | 2.41 ± 1.67 | 1.18 (1.12–1.23) **NS** |

Abbreviations: Alb-Base, baseline serum albumin; Alb-Hosp, serum albumin during hospitalization; ATN, acute tubular necrosis; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; Hgb-Base, baseline serum hemoglobin; Hgb-Hosp, serum hemoglobin during hospitalization; ICU, intensive care unit; NS, not significant.

* \( P < 0.01 \) ** \( P < 0.001 \) *** \( P < 0.0001 \).

*VA hospital complexity is an administrative rating where ‘1’ indicates treatment of high-risk patients, presence of specialty providers, high volume, complex ICU services, and research.
albumin during hospitalization reduced the odds by 41% (Table 8). Having required RRT during admission raised the risk of entering CKD4 by 5218%. Risk scores were computed using model 3 in the CON subjects. Using a cut-point of $-1.8$, the model had sensitivity 0.70, specificity 0.70, and OR = 5.62 for those with risk scores above, as opposed to below, the cut-point (95% CI 4.87–6.49). These were very similar to those obtained in the validation cohort when compared with the derivation sample.

DISCUSSION

Before the era of CKD staging, it was generally accepted that patients who recovered from AKI had ‘good’ renal outcomes as assessed by a low incidence of end stage renal disease (ESRD). These previous long-term studies were hampered by different definitions, variable follow-up times, and low overall numbers. From 2008 through 2010, four studies assessing four different cohorts of patients demonstrated that patients who survive an episode of AKI have a significant risk for the development of advanced CKD (stage 4/5). In this analysis, we were able to identify risk factors for progression to advanced CKD. Our data suggest that advanced age, low serum albumin levels, presence of diabetes, and severity of AKI, as assessed by RIFLE score or mean SC levels during hospitalization are strong predictors of poor long-term renal outcome. The strong predictive value of serum albumin levels is a novel finding, but it is not surprising because these levels have been associated with poor outcomes in a variety of diseases including end stage renal disease (ESRD), surgical illness, and acute stroke. Low levels of serum albumin can be due to either nutritional related factors, high levels of inflammation, or a combination of these factors. With respect to age, a recent meta-analysis indicated that a higher proportion of elderly survivors of AKI did not recover renal function as well as younger control subjects. Although it is intuitive that severity of AKI would be associated with progression to advanced CKD, these data are the first to show this link (Figure 3). In particular, we have shown that patients

Table 2 | Results model 1 for CKD4

| Variable          | Estimate | s.e. | $P$ | Adjusted OR | 95% CI   |
|-------------------|----------|------|-----|-------------|----------|
| Intercept         | 0.2141   | 0.437| 0.62| NA          | NA       |
| Age               | 0.0174   | 0.0047| 0.0002| 1.02      | 1.01–1.03|
| Time at risk      | 0.1223   | 0.0405| 0.0026| 1.13      | 1.04–1.22|
| DM                | 0.1067   | 0.0585| 0.068| 1.24      | 0.98–1.56|
| SC-Hosp           | 0.4075   | 0.0286| $< 0.0001$| 1.50     | 1.42–1.59|
| African American  | $-0.1861$| 0.0638| 0.0036| 0.69      | 0.54–0.89|
| Alb-Base          | $-0.5865$| 0.1033| $< 0.0001$| 0.56    | 0.45–0.68|
| Alb-Hosp          | $-0.8942$| 0.0947| $< 0.0001$| 0.41    | 0.34–0.49|

Abbreviations: Alb-Base, baseline serum albumin; Alb-Hosp, serum albumin during hospitalization; CI, confidence interval; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; NA, not applicable; OR, odds ratio; RRT, renal replacement therapy; SC-Hosp, serum creatinine during hospitalization.

Predictors that were tested included sex, age, race, ATN, time-at-risk, DM, eGFR-Base, SC-Hosp, RRT, teaching hospital, Alb-Base, Alb-Hosp, mean-hemoglobin-pre, mean-hemoglobin-during.

Forward selection was used with $P < 0.1$ required to enter the equation. There were 3180 subjects with all data non-missing, who were included in the analysis, 474 of whom (14.9%) reached CKD4. Somer’s $D$ was 0.64, $c = 0.82$, and likelihood ratio $\chi^2$ was 565.8 (df=7, $P < 0.0001$).

Figure 1 | Receiver operating characteristic (ROC) curves for models 1–3 in acute kidney injury (AKI) population. (a) ROC curve for model 1 in AKI subjects, $c = 0.82$. (b) ROC curve for model 2 in AKI subjects, $c = 0.81$. (c) ROC curve for model 3 in AKI subjects, $c = 0.77$. Dotted line shows minimum Euclidean distance from ROC curve to the point of optimum sensitivity and specificity.
In CON (cross-validation sample) In AKI (derivation sample)

Indicator
glomerular hypertrophy, or development of fibrosis after leading to vascular dropout, nephron loss followed by multitude of possible mechanisms: acute endothelial injury that leads to CKD progression. Pre-clinical studies suggest findings raise questions about the pathophysiology of AKI progression to CKD by 500-fold (over 5000%). These to CKD than patients with less severe AKI. In the validation who require dialysis are at much higher risk for progression to CKD than patients with less severe AKI. In the validation

were included in the analysis, 581 of whom (14.2%) reached CKD4. Somer’s

Abbreviations: Alb-Hosp, serum albumin during hospitalization; CI, confidence interval; CKD, chronic kidney disease; NA, not applicable; OR, odds ratio; SC-Hosp, serum creatinine during hospitalization.

Predictors tested included age, Alb-Hosp, SC-Hosp, time-at-risk. All variables were entered into the equation. There were 4095 subjects with all data non-missing, who were included in the analysis, 582 of whom (14.0%) reached CKD4. Somer’s $D = 0.61, c=0.81$, and likelihood ratio $\chi^2 = 643.2 \text{ (d.f.}=4, P < 0.0001)$. who require dialysis are at much higher risk for progression to CKD than patients with less severe AKI. In the validation portion of the study, need for RRT increased the likelihood of progression to CKD by 500-fold (over 5000%). These findings raise questions about the pathophysiology of AKI that leads to CKD progression. Pre-clinical studies suggest a multitude of possible mechanisms: acute endothelial injury leading to vascular dropout, nephron loss followed by glomerular hypertrophy, or development of fibrosis after sustaining AKI. To prevent AKI from progressing to CKD, the pathophysiological mechanisms that underlie this process will need to be further elucidated.

To make these data accessible to clinicians, we developed three multivariable models to identify those AKI survivors who were at highest risk for progression to CKD. Model 1 was developed by stepwise regression and had a rank correlation between predicted and observed CKD4 of 0.64 (area under ROC curve = 0.82). To try and simplify model 1, we developed model 2, which was based on the most heavily weighted factors from model 1. This model had a rank

Table 3 | Performance of model 1 in the derivation and cross-validation samples, at various cut-points

| Indicator | Cut-point |
|-----------|-----------|
| In AKI (derivation sample) | Sensitivity | Specificity | PPV | NPV | Rel risk (pos) | OR (pos) |
| -3.0 | 0.96 | 0.90 | 0.77 | 0.64 | 0.46 | 0.31 | 0.20 |
| -2.5 | 0.90 | 0.73 | 0.61 | 0.48 | 0.32 | 0.26 | 0.20 |
| -2.0 | 0.81 | 0.57 | 0.51 | 0.37 | 0.25 | 0.17 | 0.12 |
| -1.5 | 0.64 | 0.39 | 0.29 | 0.19 | 0.12 | 0.07 | 0.04 |
| -1.0 | 0.40 | 0.26 | 0.17 | 0.11 | 0.06 | 0.03 | 0.01 |
| 0.0 | 0.20 | 0.11 | 0.07 | 0.05 | 0.03 | 0.02 | 0.01 |

Sensitivity: 0.96, 0.90, 0.77, 0.62, 0.46, 0.30, 0.17
Specificity: 0.30, 0.15, 0.09, 0.05, 0.03, 0.02, 0.01

Abbreviations: AKI, acute kidney injury; CON, control; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Table 4 | Results for model 2 for CKD4

| Variable | Estimate | s.e. | P | Adjusted OR | 95% CI |
|----------|----------|-----|---|-------------|-------|
| Intercept | -0.8249 | 0.3661 | 0.0243 | NA | NA |
| Age | 0.0162 | 0.0041 | <0.0001 | 1.02 | 1.01-1.03 |
| Time at risk | 0.1064 | 0.0341 | 0.0018 | 1.11 | 1.04-1.19 |
| SC-Hosp | 0.3655 | 0.0234 | <0.0001 | 1.44 | 1.38-1.51 |
| Alb-Hosp | 0.8756 | 0.0707 | <0.0001 | 0.32 | 0.28-0.37 |

Abbreviations: SC-Hosp, creatinine during hospitalization; CI, confidence interval; CKD, chronic kidney disease; NA, not applicable; OR, odds ratio.

Table 5 | Performance of model 2 in the derivation and cross-validation samples, at various cut-points

| Indicator | Cut-point |
|-----------|-----------|
| In AKI (derivation sample) | Sensitivity | Specificity | PPV | NPV | Rel risk (pos) | OR (pos) |
| -3.0 | 0.96 | 0.90 | 0.77 | 0.62 | 0.46 | 0.30 | 0.17 |
| -2.5 | 0.90 | 0.73 | 0.61 | 0.48 | 0.32 | 0.26 | 0.20 |
| -2.0 | 0.81 | 0.57 | 0.51 | 0.37 | 0.25 | 0.17 | 0.12 |
| -1.5 | 0.64 | 0.39 | 0.29 | 0.19 | 0.12 | 0.07 | 0.04 |
| -1.0 | 0.40 | 0.26 | 0.17 | 0.11 | 0.06 | 0.03 | 0.01 |
| 0.0 | 0.20 | 0.11 | 0.07 | 0.05 | 0.03 | 0.02 | 0.01 |

Sensitivity: 0.96, 0.90, 0.77, 0.62, 0.46, 0.30, 0.17
Specificity: 0.30, 0.15, 0.09, 0.05, 0.03, 0.02, 0.01

Abbreviations: AKI, acute kidney injury; CON, control; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.

Table 6 | Results for model 3 for CKD4

| Variable | Estimate | s.e. | P | Adjusted OR | 95% CI |
|----------|----------|-----|---|-------------|-------|
| Intercept | -0.0394 | 0.5192 | 0.94 | NA | NA |
| Age | 0.0096 | 0.0041 | 0.019 | 1.01 | 1.00-1.02 |
| Time at risk | 0.1165 | 0.0328 | 0.0004 | 1.12 | 1.05-1.20 |
| SC-Hosp | 0.0556 | 0.0029 | 0.052 | 0.99 | 0.99-1.00 |
| Alb-Hosp | 0.4384 | 0.1024 | 0.0063 | 1.20 | 1.18-1.22 |
| RRT score | 0.6326 | 0.0725 | <0.0001 | 1.88 | 1.63-2.17 |
| Alb-Hosp | 0.0752 | 0.3237 | <0.0001 | 0.33 | 0.29-0.37 |

Abbreviations: SC-Hosp, serum albumin during hospitalization; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NA, not applicable; OR, odds ratio.

Table 7 | Performance of model 3 in the derivation and cross-validation samples, at various cut-points

| Indicator | Cut-point |
|-----------|-----------|
| In AKI (derivation sample) | Sensitivity | Specificity | PPV | NPV | Rel risk (pos) | OR (pos) |
| -3.0 | 0.98 | 0.95 | 0.89 | 0.77 | 0.55 | 0.36 | 0.16 |
| -2.5 | 0.95 | 0.87 | 0.82 | 0.64 | 0.48 | 0.30 | 0.12 |
| -2.0 | 0.92 | 0.78 | 0.73 | 0.60 | 0.40 | 0.24 | 0.09 |
| -1.5 | 0.88 | 0.71 | 0.61 | 0.48 | 0.31 | 0.19 | 0.07 |
| -1.0 | 0.84 | 0.66 | 0.57 | 0.44 | 0.30 | 0.16 | 0.05 |
| 0.0 | 0.80 | 0.61 | 0.52 | 0.40 | 0.27 | 0.13 | 0.04 |

Sensitivity: 0.98, 0.95, 0.89, 0.77, 0.55, 0.36, 0.16
Specificity: 0.15, 0.10, 0.06, 0.03, 0.01, 0.00, 0.00

Abbreviations: AKI, acute kidney injury; CON, control; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value.
correlation of 0.61 between predicted and observed CKD4 (area under ROC curve = 0.81). Model 2 performs well, but because it includes mean SC-Hosp, its use would be limited to electronic medical records that can calculate that variable automatically. Therefore, we developed model 3 for use as a ‘bedside’ model, which is based on sentinel clinical events (RIFLE stage, need for dialysis, and so on). This model performs well with a rank correlation of 0.54 between predicted and observed CKD4 (area under ROC curve = 0.77). We then tested these equations in a separate large cohort of hospitalized veterans. All three equations were significant when tested in the CON populations (P < 0.001) and had c-statistics ≥ 0.81, signifying good reproducibility for all three models. We believe that these equations should undergo further validation and recalibration in other large population cohorts. In addition, because these endpoints are accessible, clinicians can use these equations to risk stratify AKI survivors who are at highest risk for progression to CKD. Once fully validated, hospitals with computerized medical record systems might use software based on prediction formulas like these, to generate a warning linked to the patient’s discharge that a particular patient is at risk for progression to CKD after experiencing an episode of AKI. This is particularly important when one considers that only a very small fraction of AKI patients are currently followed by a nephrologist after discharge.25

Most AKI patients are seen by a primary care provider following an AKI episode. At 30 days after AKI discharge, 74.5% have seen a primary physician compared with 11.9 and

![Figure 2 | ROC curves for models 1–3 in CON population. (a) ROC curve for model 1 in CON subjects, c = 0.81. (b) ROC curve for model 2 in CON subjects, c = 0.81. (c) ROC curve for model 3 in CON subjects, c = 0.82.](image)

| Variable | Estimate | s.e. | P   | Adjusted OR | 95% CI | 95% CI |
|----------|----------|-----|-----|-------------|--------|--------|
| Model 1  | Intercept| -4.0348 | 0.4116 | < 0.0001 | NA      | NA     |
|          | Age      | 0.0108  | 0.0038 | 0.0041     | 1.01   | 1.003–1.02 |
|          | Time at risk | 0.1630 | 0.0298 | < 0.0001   | 1.18   | 1.11–1.25  |
|          | DM       | 0.0943  | 0.0430 | 0.0285     | 1.21   | 1.02–1.43  |
|          | SC-Hosp  | 1.9199  | 0.0740 | < 0.0001   | 6.82   | 5.90–7.89  |
|          | African American | -0.4418 | 0.1068 | < 0.0001   | 0.64   | 0.52–0.79  |
|          | Alb-Base | -0.1903 | 0.0867 | 0.0281     | 0.83   | 0.70–0.98  |
|          | Alb-Hosp | -0.5614 | 0.0743 | < 0.0001   | 0.57   | 0.49–0.66  |
| Model 2  | Intercept| -4.5327 | 0.3247 | < 0.0001 | NA      | NA     |
|          | Age      | 0.0117  | 0.0034 | 0.0006     | 1.01   | 1.01–1.02  |
|          | Time at risk | 0.1506 | 0.0255 | < 0.0001   | 1.16   | 1.11–1.22  |
|          | SC-Hosp  | 1.8394  | 0.0646 | < 0.0001   | 6.29   | 5.55–7.14  |
|          | Alb-Hosp | -0.6316 | 0.0565 | < 0.0001   | 0.53   | 0.48–0.59  |
| Model 3  | Intercept| NA      | NA     | NA         | NA      | NA     |
|          | Age      | 0.0058  | 0.0034 | 0.088      | 1.01   | 1.00–1.01  |
|          | Time at risk | 0.1789 | 0.0251 | < 0.0001   | 1.20   | 1.14–1.26  |
|          | RIF (0–3) | 1.4881  | 0.0464 | < 0.0001   | 4.43   | 4.04–4.85  |
|          | GFR-base | -0.0263 | 0.0023 | < 0.0001   | 0.97   | 0.97–0.98  |
|          | Alb-Hosp | -0.5350 | 0.0561 | < 0.0001   | 0.59   | 0.53–0.65  |
|          | RRT      | 1.9868  | 0.3955 | < 0.0001   | 53.18  | 11.28–250.64 |

Abbreviations: AKI, acute kidney injury; Alb-Base, baseline serum albumin; Alb-Hosp, serum albumin during hospitalization; CON, control; DM, diabetes mellitus; NA, not applicable; OR, odds ratio; SC-Hosp, serum creatinine during hospitalization.

For each model, the predictor variables used in the AKI sample were entered in a single step in the CON sample.

Model 1 Likelihood ratio χ² (LRC)=1219.8, d.f.=7, P < 0.0001; Somer’s D=0.62, c=0.81.
Model 2 LRC=1470.2, d.f.=4, P < 0.0001; Somer’s D=0.63, c=0.81.
Model 3 LRC=10810.0, d.f.=6, P < 0.0001; Somer’s D=0.64, c=0.82.
increases to 48.6% within one year of discharge. To our knowledge, this is the first risk assessment tool for CKD progression in AKI survivors. If reliable risk stratification tools can be validated, patients at high risk can be identified and targeted for intervention and follow-up.

Because our study examined a cohort of patients selected by ICD-9 codes that may suffer from low sensitivity, we chose to validate our predictive formulas in a large data set of patients who suffered an episode of AKI based on SC values, but were not classified as such at discharge. Our results indicate that the proposed equations may be valuable tools when applied to all hospitalized patients who experience an episode of AKI, whether diagnosed or not.

Limitations of this study include its focus on US veterans: findings may not be representative of other populations, especially women. In addition, our study excluded patients with preexisting CKD, so these prediction models may not be accurate in that population. Our ability to make causal inferences regarding the effects of predictors on outcomes is limited. On the other hand, our study strategy allowed us to access healthcare information for large derivation and validation samples, and to have long-term follow-up using both diagnoses and laboratory evaluations.

Because the mechanisms for AKI to CKD progression are currently unknown, the obvious question remains: when a survivor of AKI is identified, what measures can be used to reduce risk of progression to advanced CKD? Progression may be forestalled by: (1) regular follow-up with serial creatinine assessment to detect reversible causes of renal ischemia, (2) rigorous control of blood pressure within accepted guidelines, and (3) avoidance of medications that have significant nephrotoxic properties (for example, amphotericin, NSAIDs). More importantly, we believe that risk assessment tools such as the ones we propose can be used to identify patients for clinical trials. We envision a study wherein AKI survivors at risk for CKD progression are enrolled into a prospective longitudinal trial. Agents and interventions that might mitigate the progression to CKD include but are not limited to: tight blood pressure control, angiotensin II blockade, low protein diet, HMG Co-A reductase inhibitors, and anti-proliferative agents. Given the increasing incidence of AKI in the aging US population, we believe this is a critical issue. More research is needed to gain insight into the pathophysiology of progression from AKI to CKD with particular attention to hemodynamically induced glomerulosclerosis and inflammatory processes that may lead to scarring and tubular dropout.

In conclusion, we have shown that it is possible to identify variables that predict CKD progression in an incident AKI patient population, and that factors, such as AKI severity, decreased serum albumin concentration, and advanced age, are associated with progression to CKD after an episode of AKI. AKI patients who require dialysis and then recover are at especially high risk for AKI progression, and warrant follow-up after hospital discharge. We have developed and validated three equations to risk stratify those survivors of AKI who are at highest risk for CKD progression. We propose that these equations be used for identification of patients who should receive additional follow-up and participate in interventional clinical trials.

**MATERIALS AND METHODS**

Subjects included all patients in the Veterans Affairs (VA) healthcare system who were admitted with a primary diagnosis indicating AKI (ARF or ATN ICD9 codes 584.xx) during the period 1 October 1999 through 31 December 2005 as previously described. For each subject we recorded all SC, albumin, and other laboratory values during the year before the index hospitalization, and from the hospital admission date until either the end of the data collection period or the patient’s death. eGFR was calculated using the Modification of Diet in Renal Disease equation. Patients with no SC evaluations before their admission date and patients with preexisting CKD or any dialysis treatments were removed from the data set. This was done by removing patients who entered CKD stage 3, 4, or 5, or whose mean eGFR was $<60$ ml/min per $1.73\,m^2$, during the year before index hospitalization. Entry into CKD4 is defined as the first date on which the eGFR decreased below $30$ ml/min per $1.73\,m^2$ without ever going above $30$ ml/min per $1.73\,m^2$ again for that patient. Mean laboratory values were computed during the baseline year, and during the 30 days after the

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**Figure 3** Acute kidney injury (AKI) patients who survived > 1 year. (a) Mean eGFR over time (tertiles). (b) AKI patients who survived > 1 year. Mean serum creatinine over time (tertiles). Tertiles were defined based on scores at 1-5 years post-admission. Error bars show the 95% confidence interval at each time point.
date of hospitalization. Teaching hospital was coded yes when the number of Medical Residents was $\geq 5$ and VA complexity rating was 1 (indicating treatment of high-risk patients, specialty providers, high volume, complex intensive care unit services, and research). Time at risk was defined as years from diagnosis date to either the end of the data collection period or date of death, whichever came first. Patients in the AKI group had no admissions for myocardial infarction (MI) or pneumonia (see below). We first examined univariate associations between the predictors and outcome using likelihood ratio $\chi^2$ for categorical variables and univariate logistic regression models for continuous variables. In the exploratory phase of the study, we used logistic regression to test multivariate prediction models for entry into CKD4. Potential predictors included sex, age, race (AA, Hispanic), diagnosis of ATN, diagnosis date, presence of DM, mean baseline SC, mean SC-Hosp, need for RRT during hospitalization (RRT), hospital complexity, and mean Alb-Base concentrations, mean Alb-Hosp, mean baseline serum hemoglobin, and mean serum hemoglobin during hospitalization. A full-information model was tested including all available predictor variables (sex, age, race, teaching hospital; DM, baseline eGFR (GFR-Base), RRT, Alb-Hosp, Alb-Base, baseline serum hemoglobin, serum hemoglobin during hospitalization, RRT, and SC-Hosp) using a forward-entry stepwise procedure with a threshold of $P<0.10$ to enter the regression equation. For the equations that were developed, $T$ was time at risk, GFR-Base was mean eGFR before index hospitalization, RRT was dialysis during hospitalization (yes = 1, no = 0), Alb-Hosp was mean albumin (g/dl) during hospitalization, and RIF was RIFLE score during hospitalization (coded 0 for none, $R = 1$, $I = 2$, and $F = 3$; patients requiring dialysis were not coded as RIFLE F, but were coded separately as requiring dialysis during their index hospitalization (RRT)).

In addition to this model, we also tested several more simple $a priori$ models that might be useful for clinicians who do not have access to all the predictor variables in our full model. Wald $\chi^2$ values were tested to determine whether individual predictor variables had significant associations with the dependent variable after accounting for the effects of other predictors in the model. ORs were computed with 95% Wald confidence intervals. The $c$ statistic (a measure of area under the ROC curve) was examined as an indicator of overall prediction accuracy, and Somer’s $D$ was used to indicate the effect size. This is an estimate of the rank correlation between predicted and observed CKD4. To test for multi-collinearity, we examined tolerance and variance inflation using weighted regression, in which weight was based on the logistic regression maximum likelihood risk estimate, as recommended by Allison, as well as the diagnostics produced with the ‘collin’ option in SAS Proc Reg. If all tolerances were $>0.40$ and all condition indices were $<30$, we considered this to indicate that there was no multi-collinearity.

We calculated the optimal cut-point on the ROC curve in the AKI sample by finding the point on the ROC curve that minimized the distance from the curve to the point of best prediction (that is, the point where sensitivity = 1 and 1-specificity = 0). This is the point on the curve that minimizes the function square root of $[(1-\text{specificity})^2 + (1-\text{sensitivity})^2]$. Results are reported as mean $\pm$ s.d. unless otherwise noted. $P<0.05$ was the level of significance.

Validation of models
To test whether the results of prediction models cross-validated in a new sample, in the confirmatory phase of the study, we examined all VA patients who were admitted for MI or pneumonia during the same time frame as previously described. We selected all VA patients admitted with a primary diagnosis of MI (ICD9 410.xx) or pneumonia (ICD9 486.xx), who were never admitted for an AKI diagnosis, and who did not have CKD per the definition above, but who did have a rise in SC during their index admission that indicated a RIFLE score of either B, I, or F. We refer to these subjects as CON. To test a model’s ability to cross-validate in this new sample, we ran each model that was derived in the AKI sample, in the CON sample, using the same predictor variables and options. As a first step, we examined the association between predictors and dependent variable, the effect size, and the area under the ROC curve.

To further test a model’s ability to cross-validate in the CON sample, we used the logistic regression parameters that were generated in the AKI sample, to compute a predicted risk value in CON patients, based on the formula:

$$y = \text{int} + b_1\text{val}_1 + b_2\text{val}_2 + b_3\text{val}_3 + \ldots + b_n\text{val}_n$$  \hspace{1cm} (1)

where int is the intercept, $b_1$ to $b_n$ are the parameter estimates in the regression model, and val, to val, are the subject’s scores on the predictor variables. We then examined $2 \times 2$ $\chi^2$ values of predicted risk versus actual CKD4, for a series of cut-points on $y$. For each of these $\chi^2$ values, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and OR for the positive risk score as a predictor for developing CKD4.

**DISCLOSURE**
All the authors declared no competing interests.

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