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A Novel Predictive Model for Hospital Survival in Patients who are Critically Ill with Dialysis-Dependent AKI: A Retrospective Single-Center Exploratory Study

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Key Points

- Predicting survival in patients who are critically ill with AKI-D is a patient-centered research topic that has prognostic and therapeutic implications.
- A single-center, retrospective data–based prognostic model was developed using disease acuity, comorbid illness, and clinical data at RRT start.
- Although robust test performance in predicting hospital survival was seen, external validation is needed to prove the generalizability of results.

Abstract

Background Mortality of patients who are critically ill with AKI initiated on RRT is very high. Identifying modifiable and unmodifiable clinical variables at dialysis start that are associated with hospital survival can help, not only in prognostication, but also in clinical triaging.

Methods A retrospective observational study was conducted on patients with AKI-D who were initiated on RRT in the medical and surgical intensive care units (ICUs) of a high-acuity academic medical center from January 2010 through December 2015. We excluded patients with suspected poisoning, ESKD, stage 5 CKD not on dialysis, or patients with AKI-D initiated on RRT outside of the ICU setting. The primary outcome was in-hospital mortality.

Results Of the 416 patients who were critically ill with AKI-D admitted to the medical (38%), surgical (41%), and cardiac (21%) ICUs, with nearly 75% on artificial organ support, the mean age 62.1±14.8 years, mean SOFA score was 11.8±4.3, dialysis was initiated using continuous RRT in 261 (63%) and intermittent hemodialysis in 155 (37%) patients. Incidence of survival to hospital discharge was 48%. Using multivariable logistic regression with stepwise backward elimination, a prognostic model was created that included the variables age, CKD, COPD, admission, and within 24 hours of the start SOFA score, refractory hyperkalemia and uremic encephalopathy as dialysis indications, BUN >100 mg/dl, serum creatinine, serum lactate, serum albumin, CRRT as initial modality, severe volume overload, and abdominal surgery. The model exhibited good calibration (goodness of fit test, $P=0.83$) and excellent discrimination (optimism-corrected C statistic 0.93).

Conclusions In this single-center, diverse, critically ill AKI-D population, a novel prognostic model that combined widely used ICU scores, clinical and biochemical data at dialysis start, and dialysis indication and modality, robustly predicted short-term survival. External validation is needed to prove the generalizability of the study findings.

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Introduction

Despite recent advances in critical care medicine and dialysis techniques, AKI in the intensive care unit (ICU), especially for those on dialysis, is associated with high mortality (1). Given the considerable costs and resources needed to provide critical care dialysis, strategies to optimize clinical outcomes in this population is a top-priority research topic in critical care nephrology (2). Despite the daunting ethical challenges in conducting randomized trials in critical care settings, recent multicenter randomized trials do not show incremental survival benefit, with protocolized early dialysis initiation on the basis of severity of AKI as compared with clinician-adjudicated emergent indications, underscoring the need to individualize, not generalize, the decision process (3).

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Given the absence of a clear-cut, evidence-based approach, novel methods, such as prognostication tools, can be used to simplify therapeutic decision making. Other than prognostication, such tools could also help in earlier utilization of RRT if a high-risk individual is identified on the basis of dialysis indications or modality. A key factor in this is the choice of patient-centered endpoints that also provide valid measures of processes of care, so quality of services can be improved. Keeping these objectives in mind, we designed this observational study, which sought to identify clinical and biochemical data, including dialysis-specific information at RRT start in these patients, then use this information to develop a mathematical model that predicts the probability of survival to hospital discharge.

Materials and Methods

Electronic medical records were obtained for all adult patients with dialysis-dependent AKI (AKI-D) initiated on RRT in the medical and surgical ICU of Medstar Washington Hospital Center, a high-acuity academic medical center. The observation period extended from January 2010 through December 2015. Exclusion criteria included patients with ESKD, advanced CKD (stage 5, not on dialysis), patients with confirmed or suspected poisoning, patients with AKI-D transferred from other centers, initiated on RRT outside the ICU within current admission, initiated on RRT in study-center ICU but subsequently transferred to outside hospitals, or patients with missing data on clinical course during index hospitalization. Of note, we did not exclude patients with AKI-D in prior hospitalization.

Definition and staging of AKI was on the basis of serum creatinine, per the Kidney Disease Improving Global Outcomes (KDIGO) consensus criteria (4). Data collection included demographic, clinical details, and biochemical tests at time of ICU admission, at, or within 24 hours of, dialysis initiation. Biochemical panel within 24 hours of RRT was defined as test panel closest to and before the exact time of RRT start, within a 24-hour period. Acuity of illness was quantified using the Sequential Organ Failure Assessment (SOFA) score and the Acute Physiologic and Chronic Health Evaluation scoring system II (5). Comorbidity burden was quantified using the Charlson comorbidity index (6).

A semiquantitative method to grade volume overload was used as follows: 0, no O_2 need, no peripheral edema; 1+, peripheral edema but no O_2 need; 2+, documentation of pulmonary edema on clinical examination or chest x-ray±peripheral edema; 3+, ventilator dependent pulmonary edema.

Severity of liver disease was scored as follows: 0, no liver disease/Child Pugh class A; 1, compensated liver disease/Child Pugh class B; and 2, decompensated liver disease/Child Pugh class C.

Hyperkalemia severity was graded as follows: 0 if serum K <5.5 mmol/L; 1+ if serum K 5.5–6.5 mmol/L; 2+ if serum K 6.5–7.5 mmol/L; and 3+ if serum K >7.5 mmol/L.

Acidosis was categorized as severe if arterial pH <7.2 versus mild if >7.2, whereas BUN elevation was categorized as mild if <100 mg/dl and severe if >100 mg/dl. Details of nephrology or intensivist note were used to identify the cause of AKI, indication for RRT, and details of dialysis modality, prescription details, dialysis-related complications, and clinical outcome of hospitalization. To minimize misclassification bias, data abstractors were trained to collect data using a standard data abstraction form. Data from different abstractors were reviewed periodically to ensure accuracy and reproducibility. The principal investigator was responsible for maintaining data integrity and confidentiality. Using an anticipated probability of survival to hospital discharge of around 40% for patients admitted to the ICU with AKI-D (1,2), and keeping a margin of error ≤0.05, a minimal sample size of 369 was considered.

Statistical Methods

Analyses were performed with STATA (StataCorp 2019, Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.). Continuous variables were compared using a *t* test or the Wilcoxon signed-rank test, where appropriate, whereas categorical variables were compared using the chi-squared test or Fisher's exact test as appropriate. Multiple imputation was used for missing data.

The prognostic model was constructed in the following steps:

Step 1: Identification of Candidate Variables

This was done using binary logistic regression for candidate variables using a complete dataset.

Step 2: Construction of the Regression Model

Clinically relevant covariates identified in univariate analysis with $P<0.25$ were included in the initial multivariable regression model. Total number of covariates were chosen using the rule of one variable per ten events (7). Stepwise logistic regression using backward elimination was done using an α-critical value of 0.15 for the exit from the previous model. All continuous covariates were assumed to have linear and additive relationships with log-odds of outcome. Wherever clinical data existed with respect to clinical outcomes, continuous variables were converted to categorical variables to simply model.

Step 3: Internal Validation

Model discrimination was assessed using area under the receiver operating characteristic curve, whereas model calibration was assessed using a calibration plot. A bootstrap validation technique using 1000 repetitions was used to generate optimism-corrected *C* statistics for the final model.

Step 4: Model Specification

All of the β coefficients from the final model were used to create a risk calculator on an Excel spreadsheet.

Study protocol was approved by the institutional review board. The manuscript was prepared in accordance with strengthening the reporting of observational studies in epidemiology statement for observational studies (8) and transparent reporting of a multivariable prediction model for individual prognosis or diagnosis statement for multivariable prediction model (9).

Results

Preliminary dataset obtained using International Classification of Diseases 9th revision codes (using ICU admission status CM 359.81, renal dialysis status V45.1, extracorporeal dialysis V56.0, hemodialysis PS 39.95, and procedure codes for dialysis 58001C, 58027C, 58029C for charts retrieved through September 2015) and International Classification of Diseases 10th revision codes (using ICU admission status 99291, dialysis dependence Z99.2, and dialysis procedure codes 90935, 90945, 90947, and 90999 for charts after September 2015), which yielded a general list of 968 patients, of whom 432 were excluded due to misclassification error, 97 for RRT initiated outside the ICU, and 23 because they were either transferred to other institutions or underwent organ transplantation. Final data analysis included 416 patients and included those who opted for withdrawal of care.

Baseline characteristics of patients are shown in Table 1. Mean age of patients was 62.1±14.8 years, and they were mostly male (58%) and Black (64%). The mean Charlson comorbidity index was 5.2±2.9, with nearly 48% of patients having baseline CKD. Etiology of AKI was overwhelmingly acute tubular necrosis (82%), followed by cardiorenal syndrome (12%). An even spread of patients across medical (38%), surgical (41%), and cardiac (21%) ICUs was seen, indicating a well-represented ICU population. Details of artificial organ support at RRT start (Table 1) included 71% on mechanical ventilator, 8% on a left ventricular assist device (LVAD), and 4% on extracorporeal membrane oxygenator (ECMO). Mean acuity scores at RRT start were 28.9±7.6 by Acute Physiology and Chronic Health Evaluation Score (APACHE) score and 11.8±4.3 by SOFA score. Majority of cardiovascular surgeries were emergent (67%). Dialysis modality at start was continuous RRT in 63% of patients and intermittent hemodialysis in 37% of patients. Mean time from hospitalization to ICU admission was 3.6±0.5 days. The median time lag from KDIGO stage 3 AKI to RRT start was 14 hours. The most common indication for RRT was volume overload (62%), followed by metabolic acidosis (41%), and hyperkalemia (28%). In most patients (67%), there was more than one indication for RRT initiation. The percentage of missing data varied from 0.24% to 4%.

Overall survival to hospital discharge was 49%, with 23% recovering from a dialysis-dependent state, 23% on maintenance dialysis, and 2% receiving hospice care at time of discharge. Key clinical variables associated with primary outcome are shown in Tables 2 and 3. In the univariate analysis, positive correlation was seen with pre-existing CKD, initial ICU admission APACHE II and SOFA scores, BUN and serum creatinine and serum albumin at RRT start, time from KDIGO stage 3 to RRT start (in hours), and hyperkalemia or uremic encephalopathy as the indication for RRT start. Key factors linked with poor survival were age, ICU admission for cardiac surgery, pre-existing chronic obstructive pulmonary disease (COPD), APACHE II and SOFA score at/within 24 hours of dialysis start, serum lactate at/within 24 hours or RRT start, oliguria for >48 hours before dialysis, continuous RRT as initial RRT modality, use of either ventilatory support, ECMO, intra-aortic balloon pump or LVAD, and severity of volume overload, or severe metabolic acidosis at RRT start.

Table 1. Baseline characteristics of patients

Clinical Characteristics (n=416)[a]	Values
Age, yr, mean±SD	62.1±14.8
Sex, *n* (%)	
M/F	242/174 (58/42)
Ethnicity, *n* (%)	
Black	266 (64)
Non-Hispanic White	119 (29)
Others (Hispanic, Asian)	31 (7)
Comorbidity profile	
Charlson comorbidity score, mean±SD	5.2±2.9
Pre-existing CKD, *n* (%)	201 (48)
Pre-existing diabetes mellitus, *n* (%)	188 (45)
Pre-existing CAD, *n* (%)	147 (35)
Pre-existing CHF, *n* (%)	165 (40)
Active malignancy, *n* (%)	29 (7)
Active hematologic malignancy, *n* (%)	15 (4)
Cause of AKI	
Acute tubular necrosis, *n* (%)	340 (82)
Cardiorenal syndrome, *n* (%)	48 (12)
Other causes (transplant rejection, obstructive uropathy, vascular events, vasculitis, AIN), mean±SD	28 (7)
APACHE II score, mean±SD	28.9±7.6
SOFA score, mean±SD	11.8±4.3
Composition of ICU patients, *n* (%)	
Medical ICU	158 (38)
Surgical ICU	170 (41)
Cardiac ICU	88 (21)
Artificial organ support, *n* (%)	
Ventilator dependent	296 (71)
LVAD	33 (8)
IABP	31 (8)
ECMO	15 (4)
Dialysis modality used in initiating RRT in ICU, *n* (%)	
Intermittent hemodialysis	155 (37)
CRRT	261 (63)
Median length of stay, d	16
Mean duration from hospital admission to ICU transfer, d, mean±SD	3.6±0.5
Median time-lag from KDIGO Stage 3 to RRT start, h	14
Clinical outcomes, *n* (%)	
Death	218 (52)
Discharge with recovery from dialysis dependence	97 (23)
Discharge on dialysis	95 (23)
Discharge on hospice	6 (2)

M/F, male/female; CAD, coronary artery disease; CHF, congestive heart failure; AIN, acute tubulointerstitial nephritis; APACHE II, Acute Physiology and Chronic Health Evaluation Score; SOFA, Sequential Organ Failure Assessment Score; ICU, intensive care unit; LVAD, left ventricular assist device; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; CRRT, continuous RRT; KDIGO, Kidney Disease Improving Global Outcomes.
[a]Missing data not imputed.

Table 2. Comparison of clinical characteristics at dialysis initiation: Survivors and nonsurvivors

Characteristics	Survivors (n=198)	Nonsurvivors (n=218)	Odds Ratio	95% Confidence Interval	P Value for Odds Ratio
Age, yr, mean±SD	60.0±14.5	64.0±14.4	0.981	0.967 to 0.994	0.006
Sex, *n*					
M/F	109/89	133/85	0.783	0.529 to 1.156	0.219
Reason for ICU admission					0.063
Medical causes, *n*	122	117	Reference		
Cardiac surgery, *n*	31	59	0.504	0.305 to 0.834	0.008
Vascular surgery, *n*	18	20	0.863	0.434 to 1.712	0.674
Abdominal surgery, *n*	19	11	1.656	0.756 to 3.630	0.207
Trauma surgery, *n*	3	4	0.719	0.158 to 3.283	0.671
Burns, *n*	2	5	0.384	0.073 to 2.016	0.258
Neurosurgery, *n*	3	2	1.438	0.787 to 8.764	0.693
Length of stay, d, mean±SD	26.6±18.4	16.1±17.1	1.034	1.024 to 1.052	<0.001
Hospital admission to ICU transfer, d, mean±SD	2.4±5.0	4.6±12.5	0.966	0.937 to 0.997	0.030
Charlson comorbidity score, mean±SD	5.2±3.2	5.2±2.5	1.010	0.944 to 1.080	0.769
No diabetes mellitus, *n* (%)	111 (56)	117 (54)	1.057	0.718 to 1.556	0.778
CAD, *n* (%)	69 (35)	78 (36)	0.960	0.642 to 1.436	0.843
CHF, *n* (%)	79 (40)	86 (40)	1.019	0.688 to 1.600	0.925
COPD, *n* (%)	21 (11)	38 (17)	0.562	0.317 to 0.996	0.048
Decompensated liver disease, *n* (%)	4 (2)	11 (5)	0.623	0.122 to 1.124	0.110
Baseline CKD, *n* (%)	118 (60)	83 (38)	1.733	1.205 to 2.550	0.003
Active malignancy (non-heme), *n* (%)	14 (7)	15 (7)	1.029	0.484 to 2.191	0.939
Hematologic malignancy, *n* (%)	3 (2)	12 (6)	0.265	0.074 to 0.955	0.042
APACHE II score, mean±SD[a]					
On ICU admission	25.0±7.8	26.7±9.4	0.978	0.957 to 1.001	0.059
At/within 24 hours of RRT start	26.5±7.0	31.1±7.5	0.916	0.890 to 0.945	<0.001
SOFA score, mean±SD[a]					
On ICU admission	9.0±3.9	10.8±4.6	0.906	0.866 to 0.950	<0.001
Within 24 hours of RRT start	9.8±4.0	13.6±3.8	0.791	0.748 to 0.837	<0.001
BUN at start, mg/dl, mean±SD	86.0±42.8	70.3±33.6	1.011	1.005 to 1.016	<0.001
S. creatinine at start, mg/dl, mean±SD	5.77±4.95	3.68±2.29	1.334	1.202 to 1.480	<0.001
S. potassium at start, mmol/L, mean±SD	5.2±1.4	4.8±1.2	1.243	1.068 to 1.446	0.005
Arterial pH at start, mean±SD[a]	7.29±0.12	7.27±0.14	3.755	0.820 to 17.191	0.087
pCO_2 at start, mm Hg, mean±SD	38±0.9	39±1	0.991	0.977 to 1.006	0.273
S. HCO_3 at start, mmol/L, mean±SD	19.3±5.9	19.3±6.3	0.999	0.968 to 1.031	0.943
S. albumin, g/dL, mean±SD	2.6±1.1	2.2±0.7	1.825	1.393 to 2.391	<0.001
S. lactate, mmol/L at 24 hours of start[a], mean±SD	2.0±2.0	4.4±4.4	0.756	0.683 to 0.837	<0.001
CRRT/IHD as initial RRT modality	88/110	173/45	0.208	0.135 to 0.320	<0.001

Table 2. (Continued)

Characteristics	Survivors (n=198)	Nonsurvivors (n=218)	Odds Ratio	95% Confidence Interval	P Value for Odds Ratio
RRT start from stage 3 AKI, h, mean±SD	47.8±109.2	25.6±48.3	1.005	1.001 to 1.009	0.013
Ventilatory support at RRT start, n (%)	115 (58)	181 (83)	0.283	0.180 to 0.445	<0.001
ECMO at RRT start, n (%)	0 (0)	15 (7)	—	—	—
IABP at RRT start, n (%)	22 (10)	9 (5)	0.422	0.189 to 0.940	0.035
LVAD support at RRT start, n (%)	10 (5)	23 (11)	0.448	0.208 to 0.968	0.041
SCUF before RRT start, n (%)	25 (12)	21 (11)	0.937	0.506 to 1.734	0.836

M/F, male/female; ICU, intensive care unit; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation Score; SOFA, Sequential Organ Failure Assessment Score; S., serum; pCO_2, partial pressure of CO_2; HCO_3, serum bicarbonate level; CRRT, continuous RRT; IHD, intermittent hemodialysis; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; SCUF, slow continuous ultrafiltration.
[a]Only for complete patients.

In the initial multivariable logistic regression model, 19 variables (Table 4) were included. Stepwise logistic regression by backward elimination was conducted using an α-critical value for an exit of 0.15. This resulted in only 14 variables being included in the final model (Table 4). Comparison for any postsurgical patient was made with patients admitted to medical ICU. Formal tests of multicollinearity for the final model using variance inflation factor method indicated that all independent variables had variance inflation factor close to 1, so multicollinearity was minimal.

Internal validation of the final model yielded excellent discrimination (Figure 1), with a C score of 0.93 (95% confidence interval, 0.92 to 0.95). The GiViTI calibration belt shown in Figure 2 indicated good calibration (goodness of fit test, P=0.83). Additionally, the optimism corrected C statistics using bootstrapping technique for 1000 repetitions was 0.93 (95% confidence interval, 0.91 to 0.95) showing minimal optimism in the model developmental process. An Excel sheet was prepared using the final model to calculate survival probability. Given the exploratory nature of study, external validation or model updating could not be done.

Discussion

AKI affects 5%–6% of all patients in the ICU, 28%–70% of whom need dialysis at some point (1,10). Mortality in AKI sustained in the ICU is as high as 50%, with the highest incidence reported in AKI-D and varying from 45% to 79% (1,10–12). Although RRT is supposed to mitigate the detrimental effects of metabolic derangements and volume overload in AKI, their apparent lack of incremental benefit highlights the confounding effect of coexisting multiorgan failure (10,11). This paradoxical relationship between RRT and mortality in patients who are critically ill with AKI-D has recently been highlighted by the failure to demonstrate any incremental benefit of "early" or protocolized dialysis start over "usual" or "standard" initiation for emergent indications in randomized trials when patients were well matched in terms of comorbidities and acuity of illness Standard versus Accelerated Initiation of Renal-Replacement Therapy in Acute Kidney Injury (STARRT-AKI trial) (3). In view of this, strategies to optimize clinical outcomes in this high-risk cohort involve individualizing treatment thresholds on the basis of disease trajectory, while using prognostic data for informed decision making and palliative therapies.

In the last three decades, several prognostic scores dedicated to AKI and AKI-D in the critical care setting have been published, and a recent systematic review summarizing these studies is mentioned (13). Although these survival models have shown robust internal validity, utility in contemporary practice settings is limited, due to a lack of standard definition of AKI, variable inclusion-exclusion criteria, and poor performance in external validation studies (14–21). Additionally, these scores also have no utility in decision making or triaging, because prognostic variables do not include data centered around the choice of dialysis modality or clinical indication. Finally, many of the survival models use endpoints such as 7- or 60-day or ICU mortality, which may not be valid because early mortality could be confounded by the severity of extrarenal disease, whereas late mortality, extending beyond the hospitalization period, may be affected by clinical events unrelated to AKI or its therapy (19,22). To address these shortcomings, we chose a study population that was similar to major clinical trials in terms of baseline clinical acuity, comorbidities (3), and use of CRRT as the predominant dialysis modality (3,19). As a result, our clinical outcomes were similar to these studies (3,19).

Our prognostic model validated several prognostic variables for AKI-D, such as age (13,19), serum albumin (19), serum creatinine (19,22), and serum lactate (22), although

Table 3. Dialysis specific factors associated with survival outcomes

Clinical Characteristics	Survivors (n=198)	Nonsurvivors (n=218)	Odds Ratio	95% Confidence Interval	P Value
Indications, *n* (%)					
Volume overload	117 (60)	139 (64)	0.870	0.752 to 1.006	0.061
Hyperkalemia	73 (37)	44 (20)	2.309	1.489 to 3.582	<0.001
Metabolic acidosis	79 (40)	93 (43)	0.892	0.603 to 1.319	0.568
Uremic encephalopathy	54 (27)	38 (17)	1.839	1.159 to 2.919	0.010
Unclear/nonemergent	16 (8)	25 (12)	0.679	0.351 to 1.312	0.249
Oliguria >48 hours before start[a]	84 (42)	122 (56)	0.610	0.415 to 0.896	0.012
Degree of volume overload					0.060
None, *n*	68	64	Ref	Ref	—
Mild, *n*	10	7	1.344	0.483 to 3.745	0.571
Moderate, *n*	37	28	1.243	0.684 to 2.262	0.475
Severe, *n*	83	119	0.656	0.422 to 1.021	0.062
Acidosis (pH <7.35) at start, *n* (%) [a]	131 (66)	156 (72)	0.777	0.513 to 1.178	0.235
Severe acidosis (pH <7.2) at start, *n* (%)	38 (19)	57 (26)	0.671	0.421 to 1.068	0.093
Degree of hyperkalemia mmol/L at start					0.222
None (<5.5), *n*	130	166	Ref	Ref	
Mild (5.5–6.5), *n*	31	26	1.502	0.850 to 2.654	0.162
Moderate (6.5–7.5), *n*	17	14	1.529	0.727 to 3.217	0.263
Severe (>7.5), *n*	18	13	1.743	0.824 to 3.690	0.146
BUN >100 mg/dl at start, *n* (%)	67 (34)	45 (21)	1.966	1.265 to 3.055	0.003
Effluent/dialysate flow rate of CRRT, ml/kg per hour, mean±SD	23.8±10.4	23.3±8.8	1.006	0.979 to 1.034	0.668

CRRT, continuous RRT; Ref, reference.

identifying some novel associations. For example, baseline CKD as a good prognostic variable has previously been reported in AKI (11,23), and is speculated to be due to earlier renal consultation or ischemic preconditioning (23). Baseline COPD is another variable not previously reported, although recent observational studies have shown AKI is a risk factor for COPD exacerbation or hospitalization (24,25). Better survival after abdominal surgery is another unique observation that, we speculate, could be due to overall good prognosis for postoperative AKI (16,19,22). Although prior studies showed the highest incidence of perioperative AKI-D and mortality with cardiac and vascular surgeries, our studies showed significant association with clinical outcomes only in univariate association. This is notable, because the majority of cardiac and vascular surgeries were emergent, indicating the dominant role of multiorgan failure in determining clinical outcomes perioperatively. Our study and others (14–16,19) reiterated the negative association of mechanical ventilation on survival, although this variable was not selected in model development because ventilator dependence is a component of the SOFA score. Other artificial organ support in our study, such as ECMO, intra-aortic balloon pump, or LVAD showed similar association with the outcomes of other studies (26–28), although this was not significant in the final model, indicating they may represent surrogate markers of disease acuity. Of note, we could not test the independent association of ECMO support with outcomes, because no patients survived to hospital discharge. This leaves the question of whether ECMO use is a perfect predictor variable, or if sample representativeness was unsolved.

Our study reinforced previous data linking low serum creatinine at RRT start with poor clinical outcomes, given its association with low muscle mass and poor nutritional status (18,19,29). Serum lactate was identified as a key predictor variable in our study, underscoring the pivotal role of tissue hypoxia or circulatory failure in predicting outcomes in AKI-D (22,30–32), as in any other patient who is critically ill (33,34). In fact, recent prognostic models have demonstrated that serum lactate could potentially predict survival in patients with septic shock on CRRT (22,31). The favorable implications of elevated BUN at dialysis start in our study reflect continued uncertainty in literature about its biologic effects in uremia (34), with studies showing either no association (35) or negative association with survival (36). A possible explanation for this effect could be that BUN may be inversely related to acuity of illness, as seen previously (35).

Table 4. Stepwise logistic regression using backward selection

Models and Variables	Full Model				Final Model			
	Odds Ratio	Standard Error	*P* Value	95% Confidence Interval	Odds Ratio	Standard Error	*P* Value	95% Confidence Interval
Age, yr	0.965	0.009	0.000	0.948 to 0.984	0.965	0.009	0.000	0.948 to 0.983
Baseline CKD	1.384	0.238	0.058	0.989 to 1.935	1.687	0.302	0.004	1.187 to 2.396
Baseline COPD	0.161	0.058	0.000	0.080 to 0.326	0.146	0.054	0.000	0.071 to 0.300
Admission SOFA score	1.140	0.415	0.001	1.058 to 1.229	1.225	0.046	0.000	1.137 to 1.319
SOFA score within 24 hours of RRT start	0.689	0.031	0.000	0.631 to 0.753	0.653	0.030	0.000	0.597 to 0.715
Refractory hyperkalemia as indication	3.512	1.026	0.000	1.982 to 6.225	3.763	1.103	0.000	2.118 to 6.685
Uremic encephalopathy as indication	0.558	0.156	0.037	0.322 to 0.965	0.317	0.077	0.000	0.197 to 0.510
BUN >100 mg/dl at start	1.495	0.415	0.148	0.867 to 2.577	1.855	0.503	0.023	1.090 to 3.152
S. creatinine mg/dl at start	1.151	0.070	0.021	1.021 to 1.297	1.206	0.077	0.003	1.065 to 1.366
S. albumin >3.5 g/dl at start	2.284	1.053	0.073	0.925 to 5.639	3.289	1.472	0.008	1.368 to 7.907
CRRT chosen as initial RRT modality	0.450	0.136	0.011	0.293 to 0.853	0.514	0.141	0.015	0.301 to 0.879
Lactate at start, mmol/L	0.809	0.039	0.000	0.737 to 0.889	0.805	0.037	0.000	0.735 to 0.882
Severe volume overload at start	1.657	0.424	0.048	1.004 to 2.735	1.440	0.362	0.148	0.879 to 2.358
ICU after abdominal surgery	3.870	2.161	0.015	1.296 to 11.562	3.766	2.128	0.019	1.244 to 11.396
ICU after cardiac surgery	1.156	0.334	0.617	0.655 to 2.038	—	—	—	—
Active hematologic malignancy	0.434	0.350	0.301	0.090 to 2.107	—	—	—	—
Severe acidosis at start	1.217	0.481	0.620	0.561 to 2.639	—	—	—	—
On LVAD at start	1.516	0.588	0.284	0.708 to 3.242	—	—	—	—
On IABP at start	1.215	0.509	0.643	0.534 to 2.761	—	—	—	—
Constant	155.413	131.238	0.000	29.696 to 813.353	123.778	100.556	0.000	25.185 to 608.344
LR chi^2		439.45				576.54		
Prob >chi^2		0.0000				0.0000		
Pseudo R^2		0.4565				0.5094		

COPD, chronic obstructive pulmonary disease; SOFA, sequential organ failure assessment score; S., serum; CRRT, continuous RRT; ICU, intensive care unit; LVAD, left ventricular assist device; IABP, intra-aortic balloon pump; LR, likelihood ratio.

Although general ICU scores are extensively used in critical care settings, their performance in AKI-D is very poor (13,21,37) because the developmental cohort included very few patients with AKI (38–40). Nonetheless, given their ability to predict in-hospital mortality in diverse settings such as after surgery (41), emergency room presentation (42), ICU (43), and CRRT (31,44) the SOFA score was used in our study. Another reason for using SOFA scores is that several of its component variables have shown an association with prognosis in AKI-D, such as mean arterial pressures (15,19), use of pressors (22,31), mechanical ventilation use (14–16,19,45), serum bilirubin (16,19), level of

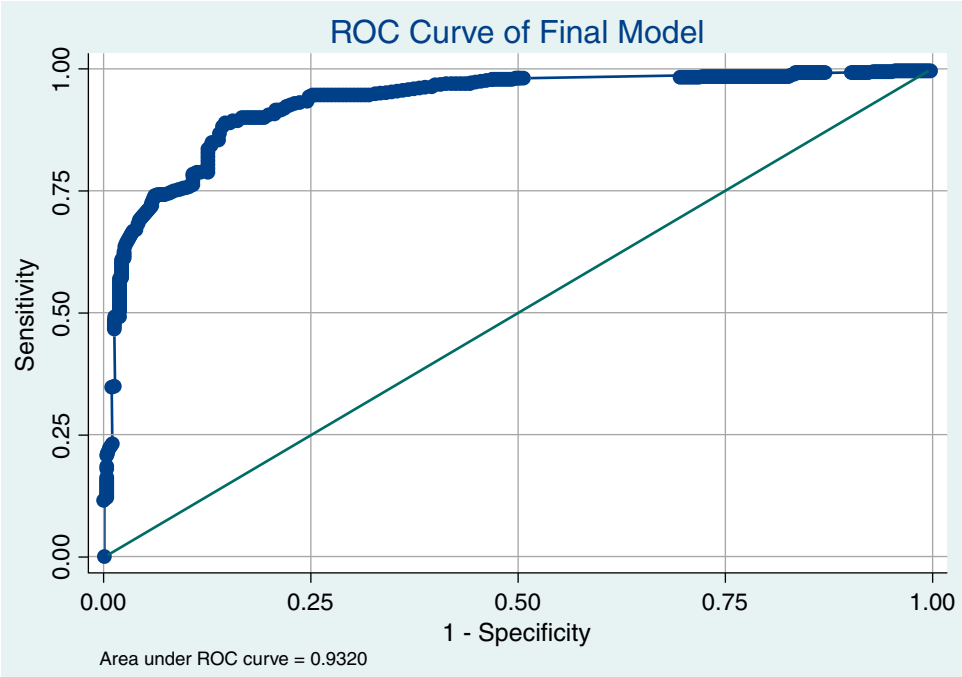

Figure 1. | Receiver operating characteristic (ROC) curve for final model with the *y* axis representing sensitivity and *x* axis showing 1−specificity. The sensitivity of model is 90%, specificity 81%, positive likelihood ratio 4.86, negative likelihood ratio 0.12, positive predictive value 89%, and negative predictive value 84%.

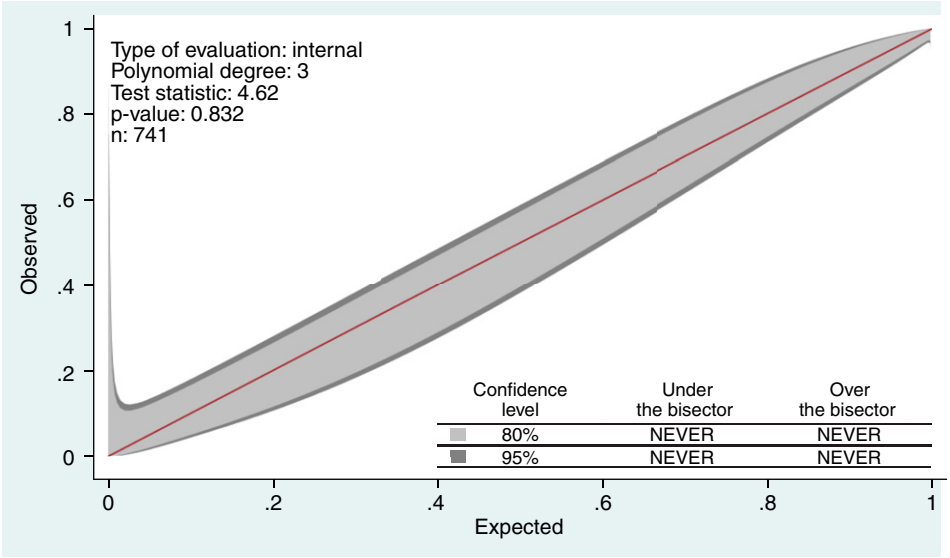

Figure 2. | Calibration belt showing goodness of fit of final model using STATA that graphically shows significant deviation from perfect calibration that is paired to formal hypothesis testing.

consciousness (31,45), or platelet count (16,19), thereby avoiding model instability or overfitting due to multicollinearity (46). In this regard, we used a two-point SOFA score assessment—one at ICU admission and second at RRT start was used, because delta SOFA has been shown to have greater diagnostic accuracy (43).

Among dialysis-related factors, choice of CRRT was independently associated with poor clinical outcomes. Although a protopathic bias is suspected using this variable, because CRRT is typically chosen for patients who are hemodynamically unstable and typically have poor outcomes, modality choice may be a surrogate marker for unknown covariates influencing decision making. Hyperkalemia as an indication for RRT, is a unique association and its favorable implication for survival could be due to the relative ease of correcting this metabolic complication with dialysis. As previous studies (47,48), we found severe fluid overload at RRT start to be associated with

poor outcomes in univariate analysis. However, the magnitude and direction of this association changed in multivariate analysis, indicating there may be effect modifiers, such as acuity of illness at RRT start, which were not reported in previous studies (47,48) Finally, we showed presumed uremic encephalopathy at RRT start was associated with poor outcomes. Although RRT is supposed to mitigate any uremic complication, there is a possibility of misclassification of encephalopathy from nonuremic causes. This can potentially create a spurious association, especially because a lower level of consciousness, due to any reason, is associated with poor outcomes in AKI-D (12,49).

Our study has several limitations, including a small sample size, single-center data, and an absence of external validation. Some of the semiquantitative scores used in our study, such as the degree of volume overload, have not been externally validated previously, so could introduce misclassification bias. Other potential sources of error could include selection or referral bias, and indication bias. Additionally, given the absence of a contemporary dataset, applicability to the current ICU population, especially during the coronavirus disease 2019 pandemic, is questionable. Other confounders could be the inclusion of patients moving to a hospice, because this could potentially inflate mortality rates although lower the specificity of the survival model. Another potential confounder could be the dynamic nature of biochemical tests, such as serum potassium or bicarbonate before dialysis start, reflecting the confounding effects of medical treatment. Finally, given the observational nature of study, we cannot exclude the possibility of residual confounders

Despite these limitations, our retrospective data, which analyzed time elapsed from onset of AKI stage 3 to dialysis initiation as a continuous variable, showed no association with survival. This supports the conclusions of interventional data that dichotomized time to RRT start as "early" or "accelerated" versus "standard" or "usual" start strategies (3). Our data suggest that certain dialysis indications, such as hyperkalemia or volume overload, could potentially be the "low-hanging fruit" in considering early dialysis. Third, elevated serum lactate at RRT start has profound implications on outcomes in AKI-D, as for other patients who are critically ill. Fourth, specific comorbidities not overall comorbidity scores may affect survival in AKI-D. Finally, a survival model that assimilates baseline and dynamic clinical data with specific details of RRT indication and modality can potentially predict hospital survival.

To conclude, in this retrospective, exploratory single-center study, several clinical variables including specific comorbidities, illness trajectory, dialysis modality, and certain RRT indications were found to robustly predict survival to hospital discharge in patients who were critically ill with AKI-D. Future research is needed to externally validate this model for it to be an effective instrument in guiding clinical practice.

Disclosures

J. Veis reports having an advisory or leadership role with Davita as a Member of the Acute Dialysis Council; and reports other interests or relationships as a Member of the Medical Advisory Board of the National Kidney Foundation, Washington, DC, Affiliate. All remaining authors have nothing to disclose.

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Author Contributions

A. Ganguli, J. Moore, M. Sherman, and J. Veis conceptualized the study; S. Adhikari, N. Desai, S. Farooq, A. Ganguli, and V. Shah were responsible for the data curation; A. Ganguli was responsible for the formal analysis; S. Adhikari, N. Desai, S. Farooq, and V. Shah were responsible for the investigation; N. Desai was responsible for the methodology; A. Ganguli and V. Shah were responsible for the project administration; J. Moore, V. Shah, and J. Veis were responsible for the resources; A. Ganguli, J. Moore, M. Sherman, and J. Veis provided supervision; N. Desai and S. Farooq were responsible for the software; A. Ganguli and J. Veis were responsible for the validation; V. Shah and M. Sherman were responsible for the visualization; A. Ganguli wrote the original draft; A. Ganguli, M. Sherman, and J. Veis reviewed and edited the manuscript.

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