AKI Complications in Critically Ill Patients: Association with Mortality Rates and RRT

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Abstract

Background and objectives AKI is associated with short- and long-term mortality. However, the exact contribution of AKI complications to the burden of mortality and whether RRT has any beneficial effect on reducing mortality rates in critically ill AKI patients are unknown.

Design, setting, participants, & measurements This was a retrospective analysis using data from the Multiparameter Intelligent Monitoring in Intensive Care II project. A total of 18,410 adult patients were enrolled from four intensive care units from a university hospital from 2001 to 2008.

Results Overall, 10,245 patients developed AKI. After adjustments, the odds ratios (ORs) for hospital mortality were 1.73 (95% confidence interval [95% CI], 1.52 to 1.98) for AKI stage 1, 1.88 (95% CI, 1.57 to 2.25) for stage 2, and 2.89 (95% CI, 2.41 to 3.46) for stage 3. Totals of 33%, 59%, and 70% of the excess mortality rates associated with AKI stages 1, 2, and 3, respectively, were attenuated by the inclusion of each AKI-related complication in the model. The main burden of excess hospital mortality associated with AKI was attenuated by metabolic acidosis and cumulative fluid balance. Long-term mortality was not attenuated by any of the associated complications. Next, we used two different approaches to explore the associations between RRT, AKI complications, and hospital mortality: multivariate analysis and propensity score matching. In both approaches, the sensitivity analysis for RRT was associated with a better hospital survival in only the following AKI-related subgroups: hyperkalemia (OR, 0.55; 95% CI, 0.35 to 0.85), metabolic acidosis (OR, 0.70; 95% CI, 0.53 to 0.92), cumulative fluid balance >5% of body weight (OR, 0.60; 95% CI, 0.40 to 0.88), and azotemia (OR, 0.57; 95% CI, 0.40 to 0.81).

Conclusions A majority of the excess risk of mortality associated with AKI was attenuated by its fluid volume and metabolic complications, particularly in severe AKI. In addition, this study demonstrated that RRT is associated with a better outcome in patients with AKI-related complications.

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Introduction

AKI is strongly associated with increased early and long-term patient morbidity and mortality (1–6). In the past, AKI was considered a surrogate marker for illness severity, and patient mortality was considered a consequence of the underlying disease (7,8). In intensive care unit (ICU) patients in particular, AKI develops as a result of another disease (*e.g.*, sepsis, cardiogenic shock, or trauma), which will lead to mortality in a certain number of patients (9). Although AKI is accepted as a consequence of severe diseases in critically ill patients, there is an abundance of epidemiologic data demonstrating that AKI itself also contributes to this elevated mortality rate (10).

Several complications may explain the association between AKI and mortality. Some of these complications are directly linked to AKI and can easily be measured (hyperkalemia, metabolic acidosis, volume overload, hyponatremia), whereas the effect on AKI-related mortality of other complications (inflammation, infection, organ cross-talk) is difficult to assess (11). Only recently was one of the complications of AKI (volume overload) investigated as a pathway leading to high hospital mortality (12,13). The overwhelming majority of studies investigating AKI in critically ill patients and its association with mortality have adjusted the models for markers related to demographic characteristics, comorbidities, and illness severity, but not for those related to metabolic or fluid AKI complications. Although these studies are important for assessing the importance of AKI in the context of mortality rates, they were unable to elucidate why patients with AKI die (14).

Another controversial topic related to AKI is RRT. Although this therapy cannot achieve the same level of homeostasis as a normally functioning kidney, RRT is partly efficient in correcting at least the directly related AKI complications (hyperkalemia, metabolic acidosis, volume overload, azotemia). Nevertheless, RRT is associated with complications, and recent observational studies suggested that RRT is associated with either similar or worse outcomes, even after

multiple adjustments (15–18). Again, previous studies have not attempted to adjust for all of the variables affecting an ICU stay, including hyperkalemia, the development of metabolic acidosis, cumulative fluid balance, urine output, and worsening azotemia.

In this study, we used a large and detailed electronic database to investigate (*1*) the influence of each directly related complication on the excess AKI-related mortality, and (*2*) the patients in whom RRT can be associated with hospital survival benefits through sensitivity analysis according to the AKI-related complications.

Materials and Methods

The Multiparameter Intelligent Monitoring in Intensive Care Database

The Multiparameter Intelligent Monitoring in Intensive Care II (MIMIC-II) project, maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology, contains data on patients hospitalized in an ICU at Beth Israel Deaconess Medical Center from 2001 to 2008 (19). The database is freely available, such that any researcher who accepts the data use agreement and has attended "protecting human subjects training" can apply for permission to access the data. This study was approved by the Institutional Review Boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center and was granted a waiver of informed consent. A description of MIMIC-II database is detailed in the Supplemental Appendix.

Inclusion and Exclusion Criteria

We included all adult patients with an ICU length of stay >24 hours. Patients with insufficient laboratory tests, those who underwent RRT on the day of or before their hospital admission, and those who did not achieve a serum creatinine level <4 mg/dl during their hospital stay were categorized as having ESRD and were therefore excluded. All patients who died during the ICU stay were assessed for palliative care indications; if indicated, they were excluded.

AKI Definition

AKI was defined according to the Kidney Disease Improving Global Outcome (KDIGO) criteria (20). Briefly, serum creatinine levels were used to classify the stage of AKI. Because the MIMIC-II database does not include previous serum creatinine information, the lowest value during the hospital stay was used to determine baseline renal function (21). The worst serum creatinine increases or urine outputs over 7-day periods were examined. Patients receiving RRT were considered as AKI stage 3. In general, urine output measurements were entered hourly. Patients with at least 6 consecutive hours of data and valid output measurements were included, and we calculated the weight-normalized total urine output over this 6-hour period. In patients with insufficient urine output measurements, only the criterion of serum creatinine was applied.

AKI-related complications were defined in accordance with the following cut-off values: hyperkalemia, serum potassium >5 mEq/L; metabolic acidosis, corresponding to serum bicarbonate <24 mEq/L; excessive cumulative fluid balance >5% of body weight; and azotemia, corresponding to serum blood urea >60 mg/dl. These cut-off values were defined by sensitivity analysis. We tested several points to determine the most sensitive cut-off values, namely, those with which RRT remained associated with a better outcome in the multivariate analysis. All patients requiring RRT received continuous therapy.

The outcomes recorded were hospital and late mortality. Late mortality was assessed by data from the Social Security Death Index. Imputed means were used for all variables with missing or implausible values when they comprised <5% of the total sample. Regarding body weight, <15% of the records were missing data, and the missing values were imputed as sex-specific means. Only the first ICU admission was considered for each patient.

Statistical Analyses

First, we used descriptive statistics, including means with SDs or frequencies, to describe the population as appropriate. We aimed to investigate the association of AKI stage as a categorical variable and RRT with in-hospital mortality. For the univariate analysis, we used chi-squared tests, *t* tests, and one-way ANOVAs to evaluate statistical significance. All tests were two-sided, and a P value <0.05 was considered significant. For the multivariate analysis, we performed several logistic regression analyses using a dependent variable (in-hospital mortality rate) after the collinearity tests were performed. In all of the models, the following covariates were considered to be related to the mortality and morbidity of critically ill patients: age, sex, type of initial ICU, admission sequential organ failure assessment (SOFA) score and simplified acute physiology score (SAPS)-I, AKI severity, sepsis diagnosis, need for mechanical ventilation/vasoactive drugs, and the main comorbidity groups obtained from the International Classification of Diseases (Ninth Revision) Clinical Modification codes using the Elixhauser Comorbidity Index. As described in the results section, other variables were added to the models to investigate the influence of AKI-related complications on hospital mortality. Interaction terms were calculated to determine possible effect modification between AKI complications and were inserted in the models. The specific covariates that were used in each logistic regression model are specified in the text and/or tables. We also performed a subgroup analysis to search for interactions between the AKI-related complications to investigate the association between RRT and hospital mortality.

To investigate whether AKI-related complications had any influence on the effect of AKI on long-term survival, we performed a multivariate Cox regression analysis in all patients discharged alive from the hospital. The statistical analysis was performed using SPSS 19.0 for Windows.

Propensity Score Matching

Patients were assigned a propensity score for dialysis initiation during the ICU stay. The propensity to initiate dialysis was estimated using a logistic regression model. Model selection was performed using stepwise regression, retaining all covariates with a P value <0.20. This level of significance was chosen to ensure the inclusion of all variables that could influence the initiation of RRT (22). Covariates included age, admission SAPS-I/SOFA score, maximum BUN, cumulative fluid balance, minimum

bicarbonate, maximum serum potassium, and main comorbidities, including heart failure. Interaction terms were calculated to determine possible effect modification between AKI complications and were inserted in the model. In addition, alternative therapies to RRT were included (diuretic and alkali administration). Although urine output is already included in the AKI classification, the reduced time necessary to classify AKI (6 hours in some cases) was insufficient to trigger the initiation of RRT; therefore, a minimum 24-hour urine output was also included in the model. To match patients with similar propensity scores, 1:1 nearest neighbor matching was utilized without replacements using a 0.2-SD caliper. Exact matching was not required for any of the variables.

Results

The MIMIC-II database contains the records of 32,425 patients, 24,581 of whom were adults aged ≥15 years at the time of admission. Patients with an ICU length of stay <24 hours (n=3549), patients with ESRD (n=538), and deceased patients identified as receiving palliative care (n=74) were excluded from the analysis (Figure 1).

The final cohort, therefore, contained 18,410 patients (almost 80% of all adult patients admitted to the ICU during this period). Of these patients, 891 (4.8%) were classified only by creatinine-based KDIGO criteria because of insufficient urine output measurements. During the ICU stay, 10,245 (55.6%) patients developed AKI. The distribution of patients according to AKI stage is shown in Figure 1. The mean age at admission was 63.9±17.6 years, and 7962 of the patients (43.2%) were women. The overall ICU and hospital mortality rates were 7.6% and 11.1%, respectively. Complete patient data according to AKI stage are shown in Table 1.

Metabolic Acidosis, Hyperkalemia, and Positive Fluid Balance Attenuates Early AKI-Related Mortality

Patients with AKI had higher hospital mortality rates (16.2% versus 4.7%, P<0.001). The unadjusted hospital mortality odds ratios (ORs) were 3.1 (95% confidence interval [95% CI], 2.7 to 3.5), 4.6 (95% CI, 3.9 to 5.4), and 8.8 (95% CI, 7.5 to 10.3) for patients with AKI stages 1, 2, and 3, respectively, compared with patients with no AKI (P<0.001 for all). We performed a multivariate logistic regression analysis that included age, sex, main comorbidities, diagnosis at hospital discharge, sepsis, initial ICU care unit type, admission SAPS and SOFA scores, and the need for mechanical ventilation and vasoactive drugs. After adjusting for all of these variables, AKI had the following adjusted ORs for hospital mortality: 1.73 (95% CI, 1.52 to 1.98) for AKI stage 1, 1.88 (95% CI, 1.57 to 2.25) for stage 2, and 2.89 (95% CI, 2.41 to 3.46) for stage 3 (Figure 2, model 1).

To analyze the association of AKI-related complications with mortality, we included in the above multivariate logistic regression model each variable, one by one, in the following order: maximum serum potassium, minimum serum bicarbonate, and cumulative fluid balance. There was a progressive reduction in the ORs as the AKI stage increased, as shown in Figure 2. The major attenuation in the ORs was seen for AKI stage 3. In this stage, maximum serum potassium attenuated the OR for hospital mortality by 19%; minimum serum bicarbonate, by an additional 32%; and cumulative fluid balance, by 46%. The overall attenuation of AKI stage 3–related complications in the OR was 70%. In AKI stages 1 and 2, the overall OR attenuation was 33% and 59%, respectively. None of the tested interactions were statistically significant. The attenuation of OR on addition of cumulative fluid balance was almost absent in AKI stage 1 mortality (Figure 2). Regarding hyponatremia, adding the minimum sodium level to model 1 changed the OR by

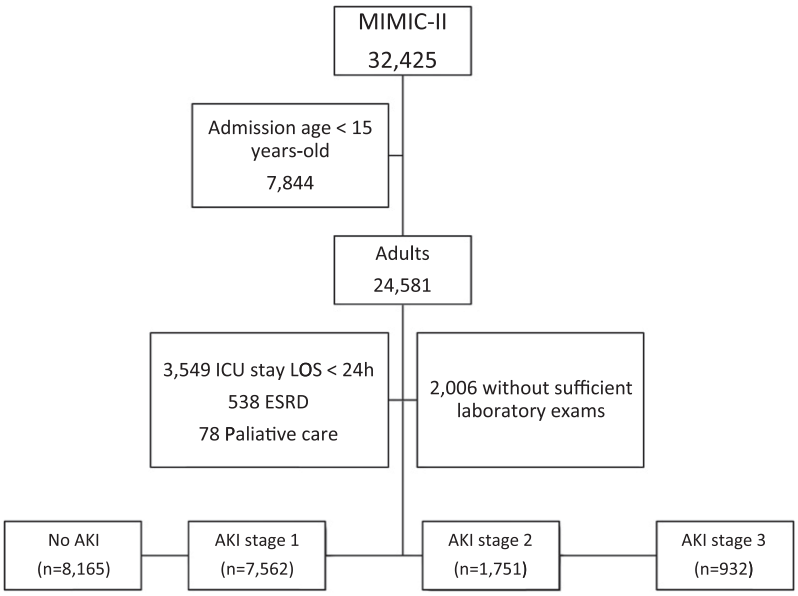


Figure 1. | Patient distribution in the MIMIC-II database and exclusion criteria. ICU, intensive care unit; LOS, length of stay; MIMIC-II, Multiparameter Intelligent Monitoring in Intensive Care II.

Table 1. General characteristics of patients according to AKI stage

Characteristic	All Patients (*n*=18,410)	No AKI (*n*=8157)	AKI Stage 1 (*n*=7367)	AKI Stage 2 (*n*=1634)	AKI Stage 3 (*n*=1252)	*P*
Age (yr)	63.9±17.6	61.7±17.8	66.6±17.2	63.6±17.7	62.4±16.1	<0.001
Men	10,434 (56.7)	4829 (59.2)	4148 (56.3)	786 (48.1)	671 (53.6)	<0.001
Hypertension	6103 (33.2)	2936 (36.0)	2440 (33.1)	477 (29.2)	250 (20.0)	<0.001
Diabetes mellitus	3587 (19.5)	1501 (18.4)	1534 (20.8)	307 (18.8)	245 (19.6)	0.002
Congestive heart failure	3622 (19.7)	1058 (13.0)	1730 (23.5)	438 (26.8)	396 (31.6)	<0.001
COPD	3096 (16.8)	1208 (14.8)	1368 (18.6)	303 (18.5)	217 (17.3)	<0.001
Liver disease	900 (4.9)	293 (3.6)	354 (4.8)	113 (6.9)	140 (11.2)	<0.001
Solid tumors	2780 (15.1)	1117 (13.7)	1262 (17.1)	248 (15.2)	153 (12.2)	<0.001
Lymphoma	290 (1.6)	104 (1.3)	141 (1.9)	25 (1.5)	20 (1.6)	0.01
Metastatic cancer	823 (4.5)	301 (3.7)	408 (5.5)	67 (4.1)	47 (3.8)	<0.001
Sepsis	2087 (11.3)	399 (4.9)	855 (11.6)	355 (21.7)	478 (38.2)	<0.001
ICU first service						<0.001
Medical	6701 (36.4)	2592 (31.8)	2853 (38.7)	671 (41.1)	585 (46.7)	
Surgical	979 (5.3)	465 (5.7)	393 (5.3)	83 (5.1)	38 (3.0)	
Cardiac care	3974 (21.6)	1733 (21.2)	1629 (22.1)	352 (21.5)	260 (20.8)	
Cardiac surgery	6.756 (36.7)	3367 (41.3)	2492 (33.8)	528 (32.3)	369 (29.5)	
SAPS on ICU admission	14 (10–18)	12 (8–16)	14 (10–18)	16 (13–20)	18 (13–21)	<0.001
SOFA on ICU admission	6 (2–9)	4 (1–7)	6 (3–9)	8 (5–11)	9 (6–13)	<0.001
Hyperkalemia	1604 (8.7)	276 (3.4)	647 (8.8)	278 (17.0)	403 (32.2)	<0.001
Azotemia (BUN >60 mg/dl)	1775 (9.6)	98 (1.2)	734 (10.0)	331 (20.3)	612 (48.9)	<0.001
Cumulative fluid balance >5% body wt	7359 (54.2)	2359 (40.9)	3157 (57.5)	1007 (77.0)	836 (82.8)	<0.001
Hyponatremia	5252 (28.5%)	1570 (19.2)	2179 (29.6)	756 (46.3)	747 (59.7)	<0.001
Metabolic acidosis	12,828 (69.7)	4843 (59.4)	5442 (73.9)	1409 (86.2)	1134 (90.6)	<0.001
Alkali therapy	1137 (6.2)	161 (2.0)	434 (5.9)	196 (12.0)	346 (27.6)	<0.001
Diuretic use during ICU stay	7722 (41.9)	2549 (31.2)	3439 (46.7)	1009 (61.8)	725 (57.9)	<0.001
Need for vasoactive drugs	6001 (32.6)	2266 (27,8)	2304 (31.3)	778 (47.6)	653 (52.2)	<0.001
Need for mechanical ventilation	10,483 (56.9)	3840 (47.1)	4290 (58.2)	1325 (81.1)	1028 (82.1)	<0.001
ICU LOS, d	5.6±3.6	2.6±1.7	4.9±2.8	11.7±7.7	18.9±8.8	<0.001
ICU mortality	1394 (7.6)	205 (2.5)	657 (8.9)	238 (14,6)	294 (23.5)	<0.001
In-hospital mortality	2046 (11.1)	385 (4.7)	978 (13.3)	303 (18.5)	380 (30.4)	<0.001

Data are expressed as the mean±SD, *n* (%), or median (interquartile range). Alkali and diuretic therapy were considered only if administered before RRT. COPD, chronic pulmonary obstructive disease; ICU, intensive care unit; SOFA, sequential organ failure assesment; SAPS, simplified acute physiology score; LOS, length of stay.

<1% (data not shown). Another known and measurable AKI complication, azotemia, was not evaluated because its marker, BUN, is also an AKI biomarker and therefore presents a greater collinearity with serum creatinine.

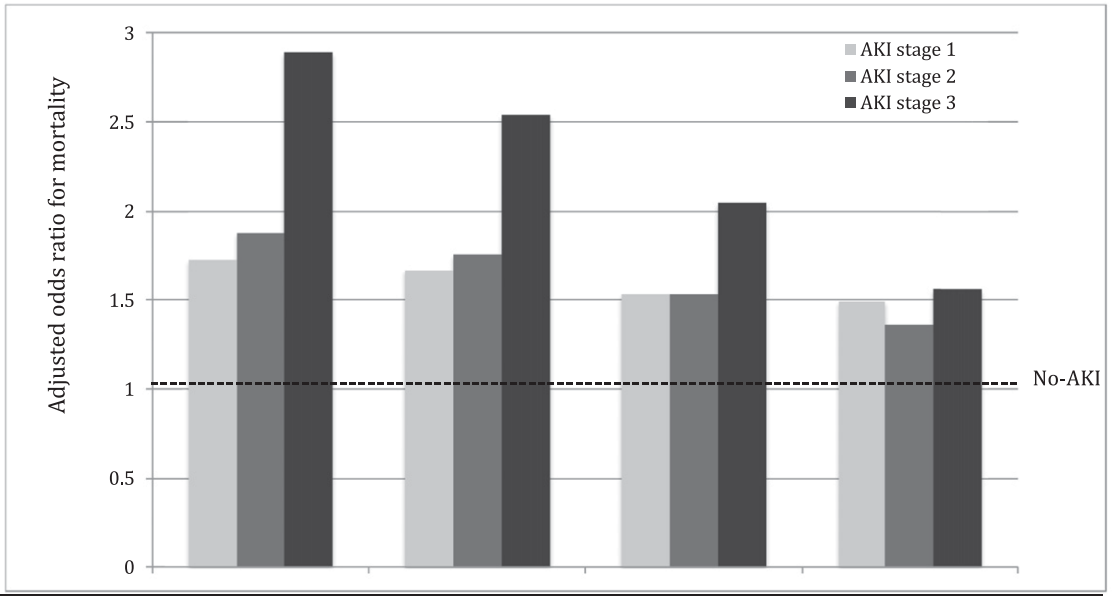
Although AKI-related hospital mortality was at least partly attenuated by its direct complications, the same was not true for long-term mortality. After evaluating 15,377 patients who were alive 90 days after hospital admission during a 24-month period, no AKI-related complications were able to modify the AKI hazard ratio by >5%. When all of the AKI-related complications were added to the Cox model, the maximum attenuation was only 5.3% (see Supplemental Table 1).

Association of RRT with Mortality in Complicated AKI Cases

During the ICU stay, RRT was performed in 532 patients. Generally, RRT patients had more comorbidities and higher severity scores (Table 2), and the crude hospital mortality rate was higher in these patients (32.0% versus 10.4% for non-RRT patients, $P<0.001$). The majority of patients receiving RRT had two or more AKI-related complications (*n*=516; 79.2%).

A multivariate logistic regression model adjusted for age, sex, main comorbidities, diagnosis at hospital discharge, sepsis, initial ICU care unit type, admission SAPS and SOFA scores, need for mechanical ventilation/vasoactive drugs, alternative therapies to RRT (diuretic and alkali administration), and other variables influencing the decision to initiate RRT (maximum BUN and urine output <400 ml/24 h) was used. In this model, RRT was not associated with a lower hospital mortality (OR, 1.18; 95% CI, 0.94 to 1.50). When the AKI-related complications (metabolic acidosis, hyperkalemia, cumulative fluid balance) were added to the model, RRT was associated with better hospital survival (OR, 0.75; 95% CI, 0.58 to 0.96). Again, none of the tested interactions were statistically significant.

We also performed a stratified analysis according to the AKI-related complications. Because the majority of patients



	Model 1	Model 1 + hyperkalemia	Model 1 + hyperkalemia + metabolic acidosis	Model 1 + hyperkalemia + metabolic acidosis + cumulative fluid balance
No-AKI	Reference			
AKI stage 1	1.73 (1.52-1.98)	1.67 (1.47-1.91)	1.53 (1.34-1.75)	1.49 (1.30-1.71)
AKI stage 2	1.88 (1.57-2.25)	1.76 (1.46-2.11)	1.53 (1.27-1.84)	1.36 (1.12-1.64)
AKI stage3	2.89 (2.41-3.46)	2.54 (2.09-3.07)	2.05 (1.68-2.49)	1.56 (1.25-1.94)

Figure 2. | **Increments of hospital mortality rates according to AKI stage.** Model 1 is adjusted for age, sex, main comorbidity diagnosis at hospital discharge, sepsis, admission SAPS and SOFA scores, and the need for mechanical ventilation and vasoactive drugs. SAPS, simplified acute physiology score; SOFA, sequential organ failure assessment.

developed more than one AKI-related complication, the OR was adjusted for other AKI-related complications in each subgroup analysis. The results of this analysis are shown in Figure 3. In the subgroup analysis, RRT was associated with a better hospital outcome only in patients exhibiting metabolic acidosis, hyperkalemia, cumulative fluid balance >5% of body weight, or BUN>60 mg/dl. In the analysis of their counterparts, the same result was not observed.

Propensity Score Matching

To further analyze the association between RRT and hospital mortality, we performed propensity score matching (1:1). Of the 532 patients in whom RRT had been initiated, 502 were matched with 502 patients in whom RRT had not been initiated (Table 2). The remaining 30 patients could not be matched because of an inadequate number of non-RRT patients with a sufficiently high propensity for receiving RRT. The area under the receiver operating characteristic curve of the propensity score predicting dialysis was 0.93 (95% CI, 0.93 to 0.94), indicating that the model had outstanding predictive ability (Supplemental Figure 1).

Table 2 illustrates the matched covariates within the matched cohort and demonstrates the balance across all of the measured covariates after propensity score matching. In the full cohort, the initiation of RRT was strongly associated with mortality (unadjusted OR, 5.05; 95% CI, 4.21 to 6.07). After propensity score matching, patients who did not receive RRT had a higher mortality rate (42.0% versus 34.5%, P=0.02), demonstrating the marginal protection associated with RRT (OR, 0.72; 95% CI, 0.55 to 0.95). Again, subgroup analysis using an unadjusted OR after propensity score matching revealed that only patients presenting with AKI-related complications had better hospital survivals associated with the use of RRT (Table 3).

Discussion

In this study, we demonstrated that AKI complications explained most of the severe AKI-attributed hospital mortality; however, late AKI-related mortality remained basically unaltered after adjusting for these complications. In addition, RRT was associated with a better outcome only in the subgroups with AKI-related complications.

Several studies have assessed AKI-related mortality in critically ill patients, and the majority of these studies agreed that AKI is associated with higher short-term mortality (4–6). Although AKI has several and detrimental clinical consequences (acid-base disorders, hypervolemia, hyperkalemia,

Table 2. General characteristics according RRT during ICU stay before and after propensity-scoring matching

Characteristic	Before Matching			After Matching		
	No RRT (*n*=17,878)	RRT (*n*=532)	*P*	No RRT (*n*=502)	RRT (*n*=502)	*P*
Age (yr)	63.9±17.6	64.1±15.5	0.73	64.8±17.2	64.5±15.2	0.87
Men	10,116 (56.6)	318 (59.8)	0.21	302 (60.2)	299 (59.6)	0.98
Hypertension	6032 (33.7)	71 (13.3)	<0.001	128 (25.5)	66 (13.1)	<0.001
Diabetes mellitus	3473 (19.4)	114 (21.4)	0.25	107 (21.3)	107 (21.3)	1.00
Congestive heart failure	3405 (19.0)	217 (40.8)	<0.001	197 (39.2)	203 (40.4)	0.70
COPD	3018 (16.9)	78 (14.7)	0.18	86 (17.1)	78 (15.5)	0.49
Liver disease	830 (4.6)	70 (13.2)	<0.001	64 (12.7)	64 (12.7)	1.00
Solid tumors	2737 (15.3)	43 (8.1)	<0.001	44 (8.8)	43 (8.6)	0.91
Lymphoma	280 (1.6)	10 (1.9)	0.57	12 (2.4)	10 (2.0)	0.67
Metastatic cancer	813 (4.5)	10 (1.9)	0.003	8 (1.6)	10 (2.0)	0.63
Sepsis	1868 (10.4)	219 (41.9)	<0.001	188 (37.5)	194 (38.6)	0.70
SAPS on ICU admission	14 (10–17)	18 (13–22)	<0.001	17 (12–21)	18 (13–21)	0.48
SOFA on ICU admission	5 (2–8)	10 (7–14)	<0.001	10 (6–13)	10 (6–14)	0.62
Hyperkalemia	1399 (7.8)	205 (38.5)	<0.001	164 (32.7)	190 (37.8)	0.22
Azotemia (BUN>60 mg/dl)	1456 (8.1)	319 (60.0)	<0.001	289 (57.6)	290 (57.8)	0.95
Cumulative fluid balance > 5% body wt	7035 (53.5)	324 (76.8)	<0.001	312 (76.1)	299 (75.5)	0.84
Hyponatremia	4930 (27.6)	322 (60.5)	<0.001	273 (54.4)	289 (57.6)	0.50
Urine output <400 ml/24 h	4150 (23.7)	414 (84.8)	<0.001	360 (71.7)	375 (74.7)	0.95
Metabolic acidosis	12,352 (69.1)	476 (89.5)	<0.001	436 (89.2)	446 (88.8)	0.38
Alkali therapy	955 (5.3)	182 (34.2)	<0.001	161 (32.1)	158 (31.5)	0.84
Diuretic use during ICU stay	7463 (41.7)	259 (48.7)	0.001	228 (45.4)	243 (48.4)	0.38

Data are expressed as the mean±SD, *n* (%), or median (interquartile range). Alkali and diuretic therapy were considered only if administered before RRT.

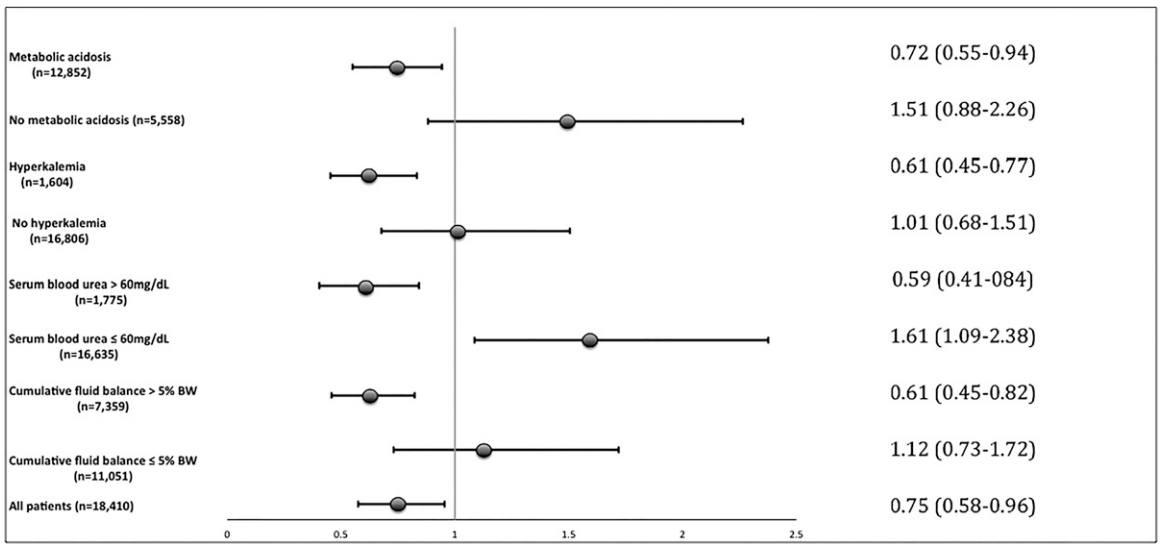


Figure 3. | Fully adjusted odds ratio values for hospital mortality in patients receiving or not receiving RRT according to subgroups defined by AKI complications. BW, body weight.

uremia, immune system depression, inflammation), some of which can be quantified in clinical practice, no study has evaluated its effect on AKI-attributed mortality. Previous studies evaluating the effect of AKI on critically ill patients have adjusted mortality only based on the laboratory values at ICU admission or during the first 24 hours, including one study using patients from the MIMIC-II database (23). In our analysis, we aimed to adjust for the main AKI-related complications, namely, hyponatremia, hyperkalemia, acid-base disorders, and cumulative fluid balance.

Of the above AKI-related complications, only volume overload has gained recent attention as a pathway by which

Table 3. Sensitivity analysis according AKI complications

Complication	Odds Ratio (95% Confidence Interval)	*P*
Metabolic acidosis		
Yes (*n*=882)	0.70 (0.53 to 0.92)	0.01
No (*n*=122)	0.70 (0.44 to 3.37)	0.70
Hyperkalemia		
Yes (*n*=354)	0.55 (0.35 to 0.85)	0.01
No (*n*=650)	0.91 (0.57 to 1.25)	0.44
Azotemia		
Yes (*n*=579)	0.57 (0.40 to 0.81)	0.002
No (*n*=425)	1.05 (0.68 to 1.63)	0.81
Excessive cumulative fluid balance		
Yes (*n*=611)	0.60 (0.40 to 0.88)	0.003
No (*n*=393)	1.10 (0.55 to 2.17)	0.79
Overall (*n*=1004)	0.72 (0.55 to 0.95)	0.02

An unadjusted odds ratio is shown for hospital mortality after propensity score matching. RRT was not associated with better hospital survival in patients without AKI-related complications.

patients with AKI die. Bouchard *et al.* reported that a positive fluid balance is associated with mortality in patients with AKI, regardless of whether they undergo RRT (24), and other studies have also confirmed this finding (13,25).

In our study, only hyponatremia had no or minimal effect on AKI-related mortality. Hyperkalemia, although known to be a harmful complication of AKI, had a lower effect than metabolic acidosis and cumulative fluid balance on AKI-related mortality. This result was most likely due to the detrimental effects of hyperkalemia observed by the attending physician and the prompt institution of effective treatment in the form of RRT, diuretics, or other treatments. Additional AKI complications involve slow installations (volume overload) and/or are not associated with standardized thresholds for initiating treatment (volume overload and metabolic acidosis), making it difficult to make decisions regarding the initiation of adequate therapy.

In the most severe stages of AKI, more numerous and severe are its complications; therefore, it is comprehensible AKI complications explain almost all of the excess mortality in patients with stage 3 AKI, although AKI complications explain mortality in only one third of the patients with stage 1 AKI. The remaining unexplained excess mortality is most likely due to the currently unassessed effects of AKI, such as immune dysfunction, inflammation, organ crosstalk, and uremia, which is a complication that is difficult to measure apart from the assessment of renal function.

The second part of this study evaluated the effectiveness of RRT in treating patients with or without AKI complications. In the past 4 years, some studies have questioned the benefits of RRT with respect to the mortality of critically ill patients (15–17,26). Elseviers *et al.* (15) disclosed that RRT initiation was associated with poor outcomes after adjusting a severity scoring system for AKI (Stuivenberg Hospital Acute Renal Failure score) and other variables. Two other studies (16,17) demonstrated a similar risk of mortality in patients who did or did not receive RRT after matching patients by propensity analysis scoring. In the most recent study, RRT was associated with a better survival only in patients with a high level of serum creatinine (>4.2 mg/dl) (27), leading the authors to speculate that these findings could be explained by metabolic differences between the patients with low and high creatinine levels. However, these studies did not include all of the AKI complications and urine output as adjusted variables. The only study that included urine output and volume overload variables was performed by Clec'h *et al.* (16). However, in this study, metabolic derangement was considered only up to the moment at which the maximum AKI severity class was achieved, even though many AKI complications can emerge after this point, influencing the decision to start RRT and/or the overall prognosis.

In our study, RRT was associated with better hospital survival only when AKI complications were added to the multivariate model. The results of the multivariate regression analysis were similar to those derived from propensity score matching, demonstrating that RRT can be beneficial when taking all AKI-related complications into account.

In the sensitivity analysis, only those subgroups with AKI complications had a better survival when RRT was initiated. A preliminary conclusion we could reach is that RRT must be initiated only in patients with AKI with complications; however, several studies have suggested that early RRT initiation can have some advantages (28,29). Considering the studies evaluating the use of early RRT, we suggest that our challenge now is to recognize those patients prone to developing AKI-related complications early in the treatment course. In addition, it is important to emphasize that the majority of patients undergoing RRT had two or more AKI-related complications. Thus, the presence of one such complication alone does not necessarily warrant the initiation of RRT.

Our study has several limitations: first, this was a retrospective analysis; second, there was a lack of baseline serum creatinine information before hospital admission; and third, there was a lack of real-time data when a patient was admitted into the MIMIC-II project. Thus, it was not possible to explore the temporal trends regarding hospital mortality. However, the main limitation of this study was the lack of consensus regarding the timing of RRT initiation. Although we were able to match 502 patients who did or did not receive RRT, there are likely other variables that also influence decisions that are not included in our propensity score model, such as the physician's perception of early AKI recovery. These limitations can likely only be overcome with the use of clinical trials. Nevertheless, the identification of patients with AKI complications had a potential beneficial effect with RRT can help in design of these trials.

In conclusion, although many unexplained and/or immeasurable mechanisms are implicated in the high rate of mortality in AKI, this study demonstrated that at least some of these mechanisms can be explained by the fluid volume and metabolic complications related to AKI, particularly in its most severe stages. Moreover, for the first time, we demonstrated that RRT was associated with better hospital survival in patients with AKI-related complications.

Disclosures

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