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Recovery After Acute Kidney Injury

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At a Glance Commentary: *Scientific Knowledge on the Subject*- For many forms of acute kidney injury prevention will not be possible because patients tend to present with AKI that has already begun. Thus, efforts will need to target better recovery. Little is known about how recovery after acute kidney injury occurs or what different patterns of recovery mean for long-term outcomes. *What This Study Adds to the Field*- We have advanced a conceptual model of recovery from acute kidney injury and we identified distinct recovery phenotypes on the basis on the clinical course over the first week. These phenotypes are associated with dramatically different outcomes.

Abstract

Rationale: Little is known about how acute kidney injury (AKI) resolves and whether patterns of reversal of renal dysfunction differ among patients with respect to ultimate recovery.

Objectives: We sought to examine different patterns for AKI reversal that are found in patients and assess how they relate to post-discharge outcomes.

Methods: We studied 16,968 critically ill patients with Kidney Disease Improving Global Outcomes stage 2-3 AKI using an electronic database. Reversal of AKI was defined as alive and no longer meeting criteria for even stage 1. Recovery was defined as reversal at hospital discharge.

Measurements and Main Results: We observed five patterns. The most common (4508, 26.6%) was early reversal that was sustained through discharge but almost as many patients (4496, 26,5%) had no reversal at all. The remaining patients had late reversal after day 7 (9.7%), early reversal with one or more relapses but with ultimate recovery (22.5%) and relapsing without recovery (14.7%). Outcomes for patients with these phenotypes were quite different with age-adjusted 1-year survival varying from >90% for early reversal to <40% for patients never reversing. Relapses are common (37.3%) especially in the first 72 hours after reversal, and are associated with a 5-fold increased risk of death by 1 year compared to early sustained reversal.

Conclusions: We have identified five distinct recovery phenotypes on the basis of the clinical course over the first week after AKI manifestation. These phenotypes may identify patients amenable to therapeutic intervention. Long-term outcomes are associated with recovery status at hospital discharge.

Key words: Critical care, outcomes, survival, dialysis, renal failure

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Introduction

More than a decade ago an imperfect conceptual model for acute kidney injury (AKI) was proposed (1) and subsequently refined (2-4). Today, the consensus model serves as the basis for diagnosis, epidemiology, and clinical trials for AKI. The criteria specified in the model have been validated in terms of risk for death and dialysis (5,6), have also served as the basis for biomarker discovery and validation (7), and are in excellent agreement with expert adjudication (8). While new research will inevitably further refine this conceptual model there can be no doubt that it has advanced the field in numerous ways.

A major limitation of the AKI model is that it is based on kidney function, not injury per se (9). As a result, it may follow injury rather than identify it early. While new biomarkers may improve early recognition (7,8), they will not cause patients to seek medical attention earlier. This is compounded further by the fact that AKI does not have early symptoms that cause patients to seek care. Thus, for many forms of community acquired AKI, we will likely need to accept that prevention will be impossible (10). Even for hospital acquired AKI prevention may be ineffective and therefore our efforts will need to target better recovery. Doing so will require a conceptual model and may not be as simple as the reverse of the conceptual model for AKI. As we examine the various ways we might conceptualize recovery it is clear that return of renal function may take on multiple trajectories (11,12) and it is just as clear that these trajectories have not been described in any systematic way. For example, when renal function appears to normalize after AKI, (we term this "reversal"), does this lead to recovery by hospital discharge? Are there differences between patients that have AKI reversal early in their course as opposed to later? The various trajectories of renal recovery after AKI are also important because renal recovery is associated with long-term survival (10,12,13) and has been identified as an important endpoint for clinical trials (14).

In order for reversal and recovery of AKI to be used as endpoints for clinical trials or to guide follow-up or simply to be standardized so as to improve communication

and research, there is a need for detailed analysis of patient data. Using this analysis we hope to achieve a better understanding of how AKI reversal and ultimately, renal recovery might be defined and how various definitions might relate to long-term outcomes. Our proximate goals are to examine the different patterns for AKI reversal that are found in patients and assess how different time-based definitions for reversal describe these patterns. Our ultimate goal is to provide evidence for future development of a conceptual model for renal recovery that can be used both for trials and at the bedside.

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Methods

Conceptual Model

For our analyses we developed a working conceptual model for the study of the kinetics of AKI reversal and renal recovery (Figure 1) based on prior literature (1-6,11). Since AKI is an abrupt loss of renal function developing over 7 days or less (1) and because the actual start of AKI may not be identified, we defined "early reversal" as absence of AKI for at least 24 hour period within 7 days of first documented onset of AKI. We operationalized this conceptual model by limiting our analysis to patients with stage 2-3 AKI and defined reversal as the absence of any AKI stage, 1-3. This was done in order to avoid misclassification of minor changes in renal function (e.g. just above and below the cut offs for staging) or influences of fluid balance. We determined final recovery status at hospital discharge recognizing that recovery may occur after discharge in some patients. To examine the effect of the duration of AKI reversal we applied several rules. If multiple episodes of reversal occurred (i.e. reversal followed by relapse of stage 2-3 AKI) we considered the longest instance that reversal was sustained. We considered death prior to hospital discharge as "non-recovery" because renal recovery without survival is both rare and not patient-centered. This analysis provides three separate pieces of information. First, we can identify five groups of patients: i. those with AKI reversal within the first 7 days of reaching stage 2 or 3 that was sustained through hospital discharge; ii. those without AKI reversal within the first 7 days of reaching stage 2 or 3 that may or iii. may not be sustained through hospital discharge and iv. those with a "stuttering course" with at least one relapse that may or v. may not resolve prior to hospital discharge. Second, we can observe how these various groups differ in terms of outcomes at hospital discharge and out to 1 year. Third, we can better understand the patients exhibiting AKI reversal by stratifying on the basis of the duration of reversal. This is important because patients are treated in prospect and we should understand the risks of relapse as a function of how long after the initial reversal such relapses occur. Said another way, how long should a patient be followed closely after their kidney dysfunction has resolved? We can also determine sensitivity and

specificity for different duration of AKI reversal for predicting recovery at hospital discharge.

Patients

Approval was obtained from the University of Pittsburgh Institutional Review Board. We analyzed data on 45,568 adult patients admitted to any of 8 ICUs at the University of Pittsburgh Medical Center during an 8-year period (July 2000-October 2008). After excluding patients who never developed stage 2-3 AKI, received hemodialysis or renal transplant prior to hospital admission, those with known baseline creatinine ≥ 3.5 mg/dl; those receiving large blood transfusion (>4 units packed red blood cells within any 24 hour period), or those with incomplete data (see Figure 2) our analysis cohort included 16,968 patients with stage 2 and 3 AKI.

Variables and outcomes

We calculated the acute physiology components of the APACHE III score (APS-III) (15), and defined suspected sepsis as the ordering of blood cultures and antibiotics within 24 hours of each other, as defined previously (16). Baseline, admission and reference serum creatinine were determined as previously described (5,17,18). We classified patients according to the KDIGO criteria (4) using serum creatinine (SC) and urine output (UO) criteria. Hourly SC was interpolated linearly from point to point provided that the gap between 2 recorded values was ≤ 48 hours. If two SC values were separated by more than 48 hours then the 2nd value became the new starting point for the interpolation. The last available SC value was dragged down to the next integer hour. Available UO data was redistributed hourly as previously described (5). If multiple episodes of AKI occurred we only considered the first occurrence of stage 2-3 AKI for purposes of defining reversal. Subsequent events were considered “relapses”.

We defined AKI reversal as the absence of any stage of AKI by either SC or UO criteria. For example, a patient with stage 2 AKI would have to have a decrease in SC to less than 150% of baseline and be free of periods of oliguria (UO <5ml/kg/hr)

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longer than 6 hours. For each patient we determined the timing and duration of reversal. We ascertained AKI status in 24 hour intervals from the time of reversal over the first 7 days from stage 2-3 AKI.

Any subsequent occurrence of stage 2-3 AKI after initial reversal was considered as a relapse. Following 7 days we only assessed AKI status again at hospital discharge. In order to be defined as completely recovered at discharge, a patient had to be alive, and in the 3 calendar days prior to discharge off RRT and free of AKI by either SC or UO criteria. Thus, a total of five patterns of recovery can be identified: Early Sustained Reversal (defined as reversal starting within 7 days and sustained through hospital discharge); Late Reversal (defined as reversal after 7 days and sustained through hospital discharge); Relapsing AKI with complete recovery at hospital discharge; Relapsing AKI without complete recovery at hospital discharge; and Never Reversed AKI. We considered death prior to hospital discharge as "non-recovery" because renal recovery without survival is both rare and not patient-centered, as suggested by international consensus recommendations (11,14).

For patients who exhibited AKI reversal within the 7 day "early reversal window" we calculated the duration of reversal in days. If there were multiple reversal periods we only considered the longest reversal period for purposes of duration. For convenience and to limit the total number of groups to those representing >10% we considered all durations ≥5 days (120 hours) as one group. For patients discharged prior to 5 days after first meeting reversal criteria we assigned these patients to the ≥5 day group if their reversal was sustained through discharge. In the unusual event that a patient died while meeting reversal criteria, the duration of reversal was truncated to the time of death.

Our primary outcomes were survival and need for chronic dialysis at one year after ICU admission. Vital status was determined from the National Center for Health Statistics National Death Index database or the Social Security Administration's Death Master File. Chronic dialysis was determined by querying the United States Renal Data System (USRDS) database.

Statistical analysis

Statistical analyses were performed using the STATA software, version SE 13.1, with statistical significance set at $p < 0.05$. Survival graphs were created using the R package 'survival', version 2.38-1. Comparisons across groups were performed using the χ^2 asymptotic test for categorical variables and the Kruskal–Wallis one-way analysis of variance by ranks for continuous variables. We used multivariable logistic regression to identify risk factors associated with: i. recovery at hospital discharge; ii. late reversal vs. no reversal of AKI. Wald tests were used to assess the significance of each risk factor retained in the final models reporting individual odds ratios (OR) for each. Cox proportional hazards model was used to graphically describe the age-adjusted survival at 1 year after ICU admission. In the survival model, Breslow method was used for ties, the likelihood ratio test was used to test the overall statistical significance of the model and Wald tests were used to do pairwise comparisons between groups.

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Results

Patients and Recovery Status at Discharge

Among the 16,968 patients with KDIGO stage 2-3 AKI (Figure 2) 9,976 (58.8%) patients had complete recovery of renal function (no longer met any criteria for AKI) at hospital discharge. Patients recovering at hospital discharge can be further subdivided into those with early sustained reversal 4,508 (26.6%), those with late sustained reversal 1,642 (9.7%), and those with relapsing AKI who ultimately recovered by discharge 3,826 (22.5%). The remaining 6,992 patients who did not have complete renal recovery at hospital discharge can also be subdivided into those who exhibited reversal but then relapsed without subsequent recovery 2,496 (14.7%), and those who had no AKI reversal at any time point 4,496 (26.5%). Baseline characteristics for these patients are provided in Table 1. Patient characteristics associated with non-recovery in multivariable models are shown in Table 2. Panel A shows a model with the outcome of non-recovery at hospital discharge. Increasing age and comorbidities increased the odds of not recovering while surgical admission and increasing urine output favored recovery. Panel B examines the variables associated with recovery in patients who do not exhibit early reversal (i.e. comparing late reversal to no reversal). Older patients, blacks, medical patients, patients with lower reference creatinine and those without respiratory failure all had higher odds of not recovering (Table 2b). Panel C compares patients with a relapse (with or without subsequent recovery) to patients with early sustained reversal. Interestingly, sepsis is a strong indicator of a relapse (OR 1.34 95%CI 1.18-1.52 P<0.001) as is black race (OR 1.37 95%CI 1.13-1.67 P<0.001).

AKI Trajectories

Figure 2 illustrates three patterns of patient course based on evidence for AKI reversal in the first week after stage 2-3 criteria were met. The most common pattern observed (37.3%) was a relapsing course where patients met reversal criteria but did not remain without AKI on subsequent days. The second most common pattern was non-reversal in the first week (36.2%). The prognosis for relapsing versus non-recovery in the first week were quite different with 60.5% of

the former group (3,826 of 6,322) ultimately recovering renal function while only 26.8% (1,642 of 6,138) of patients with no reversal from 0-7 days ultimately recovering (p <0.001). For patients that exhibited early sustained reversal the median time to reversal was 30 hours compared to 43 hours (p-value<0.001) and 47 hours (p-value<0.001) for patients with relapse with subsequent recovery or not respectively.

Outcomes

Unadjusted outcomes by recovery status are shown in Table 3. Early reversal was associated with the shortest ICU and hospital lengths of stay and best prognosis (one year survival 90.2%) and those patients who never recovered or had reversal with relapse had the longest lengths of stay and worst prognosis (one year survival about 40%). Patients recovering late did better than those with no recovery but not as well as those recovering early (AKI reversal sustained). One year age-adjusted survival by group is shown in Figure 3. The same patterns observed in unadjusted analyses were seen in the adjusted model in that early reversal does best, but late reversal still does better than no reversal.

Duration of AKI reversal

Patients exhibiting AKI reversal within the early reversal window are further stratified by the duration of reversal in Table S1. When one examines the course for patients exhibiting an AKI reversal event within the first week after meeting stage 2-3 criteria we can see that 10,830 patients (63.8%) had reversal of renal dysfunction at least temporarily. For 6,077 patients (35.8%) this reversal was sustained for at least 5 consecutive days (sum of the last two columns). An additional 840 patients (5%) had reversal for 4 days and 969 (5.7%) had reversal lasting for 3 days. Finally, we found an additional 1,347 (7.9%) and 1,597 (9.4%) who had AKI reversal that was sustained for only 48 or 24 hours, respectively. Thus, depending on how sustained the AKI reversal (i.e. duration), the percentage of patients classified as AKI reversal varied from 63.8% (1 day) to 35.8% (5 days). Characteristics for these various patient groups are shown in Table S1. Finally, if we ask how well various

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durations of reversal predict recovery at hospital discharge we can see sensitivity, specificity, positive and negative predictive values (PPV, NPV) in Table S2. Specificity for recovery at hospital discharge does not exceed 80% until reversal is sustained for at least 72 hours.

Sensitivity analyses

To help assess generalizability, we included treatment year as a variable in our models since practice patterns may change (as do providers) over time. Our results remained unchanged. Finally, we repeated our primary analysis after changing the definition of reversal/recovery to be less stringent (considered to be reached when no AKI stage 2-3 was present—i.e. stage 1 was considered reversal/recovery). Our results are summarized in Table S3 and are virtually identical to our primary analysis (Tables 1 and 3). We also repeated the models shown in table 2 after removing in-hospital deaths. The results were similar (see Table S4).

Discussion

To our knowledge this is the first study to characterize the various patterns of recovery following an episode of AKI and relate these patterns to long-term outcomes. Our results have implications for patient care and health care policy. For example, non-recovery after AKI is common (approximately 40%) and associated with rather poor prognosis. Indeed patients who were not recovered at hospital discharge (whether they had early reversal or not) were twice as likely to be dead at one year (59%) compared to patients that experienced late recovery (with or without early reversal) (29%).

Interestingly, late recovery is also very common with more than half of patients who ultimately recover, doing so after day 7 (i.e. no early reversal or relapsing). While these patients do not achieve the same survival statistics as patients with early sustained reversal, their prognosis is markedly better than those who do not recover and these differences persist for at least one year following discharge. Given the frequency and effect on survival for late recovery, efforts to understand this phenomenon and target it for therapies would seem critical. Indeed, early reversal usually occurred within the first 72 hours (Table S1) and fully half of all early reversal occurred in the first 30 hours—perhaps before many treatments could be initiated. Focusing on identification of patients who have not had early reversal could dramatically change the current treatment paradigm.

Another interesting result of our analysis is that recovery that appears to start (early reversal) but then relapse or recur is actually the most common pattern following AKI. This unstable pattern has a better prognosis than patients not exhibiting any improvement within the first week—60.5% ultimately recovering renal function compared to only 26.8%. However, there may be opportunities to stabilize these patients (effectively moving them into the early recovery group) or increase their numbers by moving patients out of the non-recovery group. Unfortunately, modifiable risk factors were not identified (Tables 2a and 2b) but various at-risk groups can be seen. One such group is defined by lower baseline serum creatinine. Worse outcomes from AKI in patients with lower creatinine has

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been observed previously (19), and could reflect poor surveillance or general health deficits (decreased muscle mass).

Finally, as we follow patients clinically who exhibit recovery after AKI, we need to keep in mind that specificity for predicting recovery at discharge is rather low until about 72 hours. Patients with 24 or even 48 hours of reversal still commonly "slip back". Thus, careful monitoring of these patients would seem to be indicated. In addition, this observation may have value on deciding when it is safe to re-initiate medications that may have been discontinued during the initiation of AKI. Given the results of late recovery, it likely just as important not to "write off" kidney function in a patient who has no evidence of early reversal.

Our study does have important limitations. Although we studied a large number of patients from several ICUs our patients were all cared for in a single large healthcare system with practice patterns that may be different from other institutions. Mitigating this concern somewhat is our observation that over time (as providers and treatment practices change) our results remain stable. Furthermore, our overall rates of AKI and outcomes agree well with a recent international cross-sectional study performed in 97 centers (6) and our results indicating low mortality for patients with recovery is consistent with our prior work in septic shock patients from a 31-center trial of resuscitation strategies (10). Our decision to study patients with moderate-severe AKI (stage 2-3) was pragmatic because distinguishing clinically relevant AKI from mild fluctuations in renal function can be quite challenging for stage 1. Similar pragmatism led us to exclude patients with short ICU stays or receiving large volume blood transfusions since missing or uninterpretable data (creatinine) could be an issue in such patients. Finally, the definitions for renal recovery have not been standardized and although consensus exists regarding basic principles (1, 20), variation in specific implementations abound (11). Our primary definition, absence of "any AKI" has construct validity but may be no better than other definitions. In particular, we cannot exclude ongoing "subclinical" injury. However, return of function is a fairly a common index for recovery in other areas of medicine. Future studies might expand recovery to include dynamic measures of

function that could be more sensitive (21-22). The results of our various sensitivity analyses are reassuring in that our primary results were robust to changing our definitions to treat return to stage 1 or less as reversal/recovery.

In conclusion, we have identified at least three distinct recovery phenotypes on the basis on the clinical course over the first week after AKI manifestation (early reversal, relapsing, and no reversal). These phenotypes are associated with dramatically different long-term outcomes. However, long term outcomes are associated with recovery status at hospital discharge. We have proposed a conceptual model for AKI recovery to guide future research.

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Table 1. Patient characteristics stratified by patterns of AKI reversal

Characteristic[a]	Early Sustained Reversal (N = 4,508)	Late Sustained Reversal (N = 1,642)	Relapse Recovery (N = 3,826)	Relapse No Recovery (N = 2,496)	Never Reversed (N = 4,496)	P-Value[b]
Age, median (Q1-Q3)	60 (49-72)	64 (52-75)	65 (53-76)	67 (54-77)	67 (54-77)	<0.001
Males	2,630 (58.3)	924 (56.3)	2,226 (58.2)	1,374 (55)	2,381 (53)	<0.001
Race						
White	3,618 (80.3)	1,321 (80.5)	3,021 (79)	1,932 (77.4)	3,348 (74.5)	<0.001
Black	355 (7.9)	129 (7.9)	291 (7.6)	169 (6.8)	323 (7.2)	
Other	535 (11.9)	192 (11.7)	514 (13.4)	395 (15.8)	825 (18.3)	
BMI, median (Q1-Q3)	28.1 (24.4-33.0)	28.8 (24.7-34.9)	27.7 (24.1-32.3)	27.4 (23.6-32.2)	27.4 (23.6-32.9)	<0.001
Comorbid conditions						
Hypertension	1,514 (33.6)	597 (36.4)	1,438 (37.6)	938 (37.6)	1,619 (36)	0.001
Diabetes	787 (17.5)	353 (21.5)	816 (21.3)	550 (22)	927 (20.6)	<0.001
Cardiac disease	745 (16.5)	351 (21.4)	820 (21.4)	565 (22.6)	997 (22.2)	<0.001
Liver transplant	118 (2.6)	54 (3.3)	103 (2.7)	70 (2.8)	149 (3.3)	0.24
Chronic renal disease	191 (4.2)	105 (6.4)	191 (5)	131 (5.2)	278 (6.2)	<0.001
Multiple comorbidities	2,097 (46.5)	797 (48.5)	1,988 (52)	1,286 (51.5)	2,252 (50.1)	<0.001
Surgical admission	2,857 (68.5)	1,102 (70.2)	2,568 (70.8)	1,548 (66.2)	2,176 (51.9)	<0.001
Creatinine, mg/dl, median (Q1-Q3)						
Hospital admission	1 (0.8-1.3)	1.1 (0.9-1.8)	1 (0.8-1.4)	1 (0.8-1.4)	1.4 (0.9-2.3)	<0.001
Known baseline value	0.9 (0.7-1.2)	1 (0.7-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1 (0.7-1.3)	0.001
Reference value	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1)	0.9 (0.8-1.1)	<0.001
APS-III score[c] median (Q1-Q3)	59 (43-79)	63 (45-84)	66 (50-85)	70 (52-90)	75 (54-101)	<0.001
Weight adjusted urine output (ml/kg), median(Q1-Q3)[d]	17.9 (12.9-26.8)	15.8 (10.2-24.8)	17.5 (12.5-26.5)	17.4 (11.8-26.4)	14.2 (7.3-23.9)	<0.001
Suspected sepsis	520 (11.5)	223 (13.6)	593 (15.5)	414 (16.6)	883 (19.6)	<0.001
Vasopressors[c]	989 (21.9)	511 (31.1)	981 (25.6)	749 (30)	1,845 (41)	<0.001
Mechanical ventilation[c]	2,665 (59.1)	1,059 (64.5)	2,484 (64.9)	1,656 (66.3)	2,792 (62.1)	<0.001

[a] Missing data: age (n=4), BMI (n=3,313), surgical admission (n=1,073), hospital admission creatinine (n=1,071), known baseline value (n=10,015), APS-III score (n=22), weight adjusted urine output (n=670)

[b] Pearson Chi-Square Asymptotic Test for categorical variables; Kruskal-Wallis test for continuous variables

[c] On the day of ICU admission

[d] The available urine in the 24 hours after ICU was summed and divided by the weight

Table 2. Multivariable logistic regression models for renal recovery

A. Outcome: No Recovery vs. Recovery

Variable	OR	95% CI for OR	P-Value
Age, by 5 years	1.04	1.03-1.06	<0.001
Male	0.87	0.82-0.94	<0.001
Race			
Black vs. white	0.93	0.81-1.06	0.26
Other vs. white	1.28	1.16-1.42	<0.001
Hypertension	0.89	0.82-0.97	0.005
Cardiac disease	1.14	1.04-1.25	0.007
Surgical admission	0.64	0.59-0.68	<0.001
APS-III score[a], by units of 10	1.13	1.11-1.14	<0.001
Weight adjusted urine output[b], by 100ml	0.54	0.43-0.68	<0.001
Vasopressors[a]	1.51	1.40-1.62	<0.001
Mechanical ventilation[a]	0.88	0.81-0.95	0.002

OR, odds ratio; CI, confidence interval. [a] On the day of ICU admission

[b] The available urine volume in the 24 hours after ICU was summed and divided by the weight

Values measured at ICU capture the 24 hours after ICU admission

N=15,266; ROC (95%CI) = 0.647 (0.638-0.656); Goodness-of-fit p-value 0.37

B. Outcome: No Reversal vs. Late Reversal

Variable	OR	95% CI for OR	P-Value
Age, by 5 years	1.02	1.00-1.04	0.03
Race			
Black vs. white	1.42	1.07-1.89	0.01
Other vs. white	1.09	0.86-1.38	0.48
Surgical admission	0.54	0.47-0.62	<0.001
Reference creatinine[a]	0.85	0.76-0.94	0.002
APS-III score[a], by 10 units	1.14	1.11-1.17	<0.001
Vasopressors[a]	1.40	1.22-1.60	<0.001
Mechanical ventilation[a]	0.75	0.64-0.86	<0.001

OR, odds ratio; CI, confidence interval. [a]Captured in the 24 hours after ICU admission

N=5,405; ROC (95%CI): 0.661 (0.646-0.678); Goodness-of-fit p-value 0.79

C. Outcome: Relapse vs. Early Sustained Reversal

Variable	OR	95% CI for OR	P-Value
Age, by 5 years	1.05	1.03-1.06	<0.001
Race			<0.001
Black vs. white	1.37	1.13-1.67	0.001

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Other vs. white	1.01	0.86-1.18	0.9
Diabetes	1.16	1.04-1.29	0.01
Cardiac disease	1.30	1.16-1.46	<0.001
APS-III score[a], by 10 units	1.08	1.06-1.1	<0.001
Suspected sepsis[a]	1.34	1.18-1.52	<0.001
Mechanical ventilation[a]	1.13	1.03-1.24	0.01

OR, odds ratio; CI, confidence interval. [a]Captured in the 24 hours after ICU admission

N=9,861; ROC (95%CI): 0.661 (0.6-0.622); Goodness-of-fit p-value <0.001

Table 3. Outcomes stratified by recovery pattern

Outcome	Early Sustained Reversal (N = 4,508)	Late Sustained Reversal (N = 1,642)	Relapse Recovery (N = 3,826)	Relapse No Recovery (N = 2,496)	Never Reversed (N = 4,496)	P-Value[a]
In Hospital RRT	n/a	248 (15.1)	75 (2)	264 (10.6)	964 (21.4)	<0.001
Length of stay, days, median (Q1-Q3)						
ICU	4 (3-7)	6 (3-14)	7 (4-15)	8 (4-16)	5 (3-10)	<0.001
Hospital	12 (8-18)	17 (9-32)	20 (11-31)	23 (14-38)	12 (6-24)	<0.001
Mortality						
ICU	n/a	n/a	n/a	545 (21.8)	1,559 (34.7)	<0.001
Hospital	n/a	n/a	n/a	1,141 (45.7)	2,154 (47.9)	0.08
30 Days	44 (1)	43 (2.6)	124 (3.2)	889 (35.6)	2,034 (45.2)	<0.001
90 Days	159 (3.5)	173 (10.5)	519 (13.6)	1,246 (49.9)	2,400 (53.4)	<0.001
365 Days	443 (9.8)	414 (25.2)	1,177 (30.8)	1,450 (58.1)	2,687 (59.8)	<0.001

Where there is a not applicable (n/a) the p-value represents the comparison between groups with values.

[a] Pearson Chi-Square Asymptotic Test for categorical variables; Kruskal-Wallis test for continuous variables.

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Figure Legends

Figure 1. Conceptual model

Acute Kidney Injury (AKI) is an abrupt loss of renal function developing over 7 days or less.(1) While the actual start of AKI may not be identified (more than half of AKI cases are community-acquired) and many cases may not resolve rapidly, we defined "early reversal" as absence of AKI for at least 24 hours within 7 days of first documented AKI. *Recovery status was determined at hospital discharge but we recognize that recovery may proceed out further and a true final status would be better assessed at 90-days or longer.

Figure 2. Study flow

Source population included all patients admitted to the ICU. *Exclusions: Not stage 2-3 AKI (23,587); End-stage kidney disease, creatinine >3.5 or receiving dialysis before ICU admission (3,839); Massive blood transfusion (1,174); ICU stay <48hrs (3,631).

Figure 3. Age adjusted survival by recovery patterns

Survival differences are highly significance overall ($p < 0.001$). All pair-wise comparisons are also significant. For example, late sustained reversal vs. relapse recovery HR (95%CI): 0.86 (0.77-0.96), $p = 0.005$; relapse no recovery vs. never reversed HR (95%CI): 0.81 (0.76-0.86), $p < 0.001$.

Acknowledgements

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Figure 1. Conceptual model

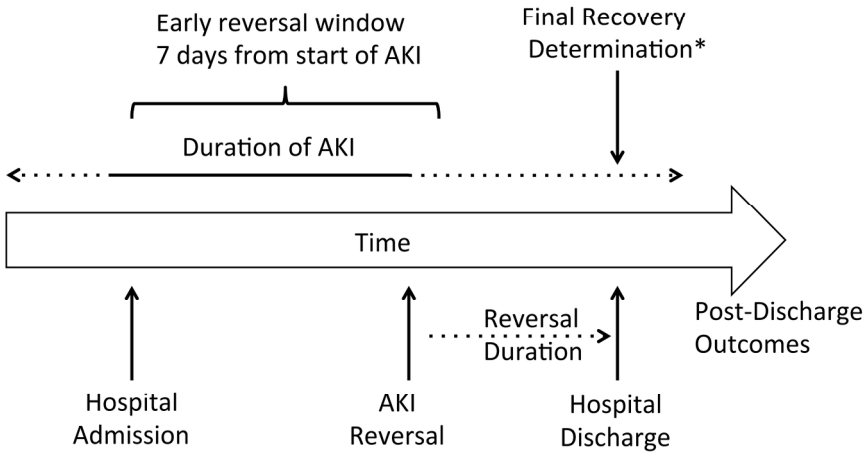

Figure 1. Conceptual model

97x55mm (600 x 600 DPI)

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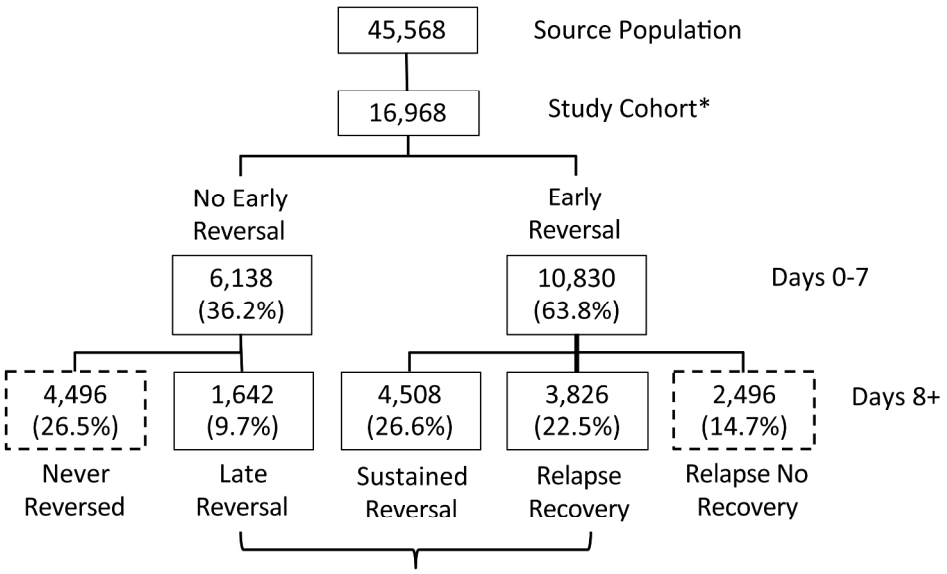
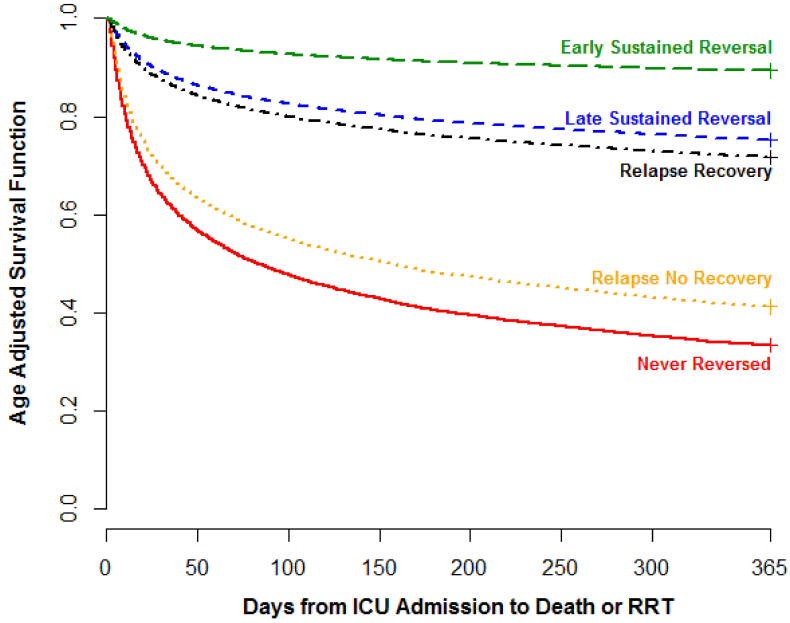


Figure 2. Study flow

267x170mm (300 x 300 DPI)

Figure 3. Age adjusted survival by recovery patterns



No. at risk								
Early Sustained Reversal	4507	4404	4317	4235	4176	4122	4070	4026
Late Sustained Reversal	1642	1529	1424	1357	1310	1272	1242	1203
Relapse Recovery	3823	3535	3245	3061	2910	2818	2719	2625
Relapse No Recovery	2496	1386	1190	1114	1075	1052	1027	1008
Never Reversed	4496	2127	1922	1826	1757	1709	1678	1648

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Supplemental Appendix:

Recovery After Acute Kidney Injury

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Table S1. Patient characteristics and outcomes stratified by reversal duration

Characteristics and Outcomes[a]	Not Reversed in Days 0-7	Maximum Sustained Reversal (hours)						P Value[b]
		24<48	48<72	72<96	96<120	≥120 but not through d/c	Sustained through d/c	
	(N = 6,138)	(N = 1,597)	(N = 1,347)	(N = 969)	(N = 840)	(N = 1,569)	(N = 4,508)	
Age, median (Q1-Q3)	66 (53-76)	67 (55-77)	68 (54-77)	66 (55-77)	65 (53-76)	63 (50-74)	60 (49-72)	<0.001
Males	3,305 (53.9)	889 (55.7)	741 (55)	573 (59.1)	491 (58.5)	906 (57.7)	2,630 (58.3)	<0.001
Race								
White	4,669 (76.1)	1,220 (76.4)	1,076 (79.9)	783 (80.8)	647 (77)	1,227 (78.2)	3,618 (80.3)	<0.001
Black	452 (7.4)	110 (6.9)	103 (7.6)	61 (6.3)	67 (8)	119 (7.6)	355 (7.9)	
Other	1,017 (16.6)	267 (16.7)	168 (12.5)	125 (12.9)	126 (15)	223 (14.2)	535 (11.9)	
Comorbid condition								
Hypertension	2,216 (36.1)	587 (36.8)	517 (38.4)	383 (39.5)	335 (39.9)	554 (35.3)	1,514 (33.6)	<0.001
Diabetes	1,280 (20.9)	348 (21.8)	305 (22.6)	204 (21.1)	175 (20.8)	334 (21.3)	787 (17.5)	<0.001
Cardiac disease	1,348 (22)	305 (19.1)	311 (23.1)	236 (24.4)	188 (22.4)	345 (22)	745 (16.5)	<0.001
Liver transplant	203 (3.3)	36 (2.3)	28 (2.1)	28 (2.9)	24 (2.9)	57 (3.6)	118 (2.6)	0.04
Chronic renal disease	383 (6.2)	73 (4.6)	56 (4.2)	62 (6.4)	37 (4.4)	94 (6)	191 (4.2)	<0.001
Multiple comorbidities	3,049 (49.7)	784 (49.1)	707 (52.5)	523 (54)	449 (53.5)	811 (51.7)	2,097 (46.5)	<0.001
Surgical admission	3,278 (56.9)	979 (65)	840 (65.3)	633 (69.7)	535 (68.1)	1,129 (76.4)	2,857 (68.5)	<0.001
Creatinine, mg/dl, median (Q1-Q3)								
Hospital admission	1.3 (0.9-2.2)	1 (0.8-1.4)	1 (0.8-1.4)	1 (0.8-1.4)	1 (0.8-1.4)	1 (0.8-1.4)	1 (0.8-1.3)	<0.001
Known baseline value	1 (0.7-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.3)	0.9 (0.7-1.2)	0.01
Reference value	0.9 (0.8-1.1)	0.8 (0.7-1)	0.9 (0.7-1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.8-1.1)	<0.001
APS-III score, median (Q1-3)	72 (52-97)	66 (49-85)	66 (50-86)	65 (49-84)	68 (52-88)	70 (53-90)	59 (43-79)	<0.001
Weight adjusted urine output (ml/kg), median(Q1-Q3)[c]	15 (8-24)	17 (12-25)	17 (12-26)	19 (12-27)	18 (12.3-26)	18 (13-28)	18 (13-26.8)	<0.001
Suspected sepsis[d]	1,106 (18)	246 (15.4)	206 (15.3)	135 (13.9)	140 (16.7)	280 (17.8)	520 (11.5)	<0.001
Vasopressors	2,356 (38.4)	396 (24.8)	337 (25)	251 (25.9)	243 (28.9)	503 (32.1)	989 (21.9)	<0.001
Mechanical ventilation	3,851 (62.7)	1,042 (65.2)	862 (64)	605 (62.4)	529 (63)	1,102 (70.2)	2,665 (59.1)	<0.001
Recovered at discharge[e]	1,642 (26.8)	869 (54.4)	840 (62.4)	660 (68.1)	568 (67.6)	889 (56.7)	3,951 (87.6)[f]	
In Hospital RRT	1,212 (19.7)	105 (6.6)	59 (4.4)	37 (3.8)	31 (3.7)	107 (6.8)	0 (0)	<0.001
Length of Stay, Days, Median (Q1-Q3)								
ICU	5 (3-11)	7 (4-14)	7 (4-15)	7 (4-14)	7 (4-13)	10 (5-20)	4 (3-7)	<0.001
Hospital	14 (7-26)	16 (10-28)	18 (10-29)	18 (11-29)	18 (12-31)	30 (21-46)	12 (8-18)	<0.001
Mortality								
ICU	1,559 (25.4)	212 (13.3)	120 (8.9)	58 (6)	34 (4)	121 (7.7)	0 (0)	<0.001
Hospital	2,154 (35.1)	360 (22.5)	219 (16.3)	131 (13.5)	105 (12.5)	326 (20.8)	0 (0)	<0.001
30 Days	2,077 (33.8)	350 (21.9)	225 (16.7)	132 (13.6)	91 (10.8)	215 (13.7)	44 (1)	<0.001
90 Days	2,573 (41.9)	530 (33.2)	368 (27.3)	239 (24.7)	183 (21.8)	445 (28.4)	159 (3.5)	<0.001
365 Days	3,101 (50.5)	728 (45.6)	539 (40)	393 (40.6)	321 (38.2)	646 (41.2)	443 (9.8)	<0.001

[a] Missing data: age (n=4), BMI (n=3,313), surgical admission (n=1,073), admission creatinine (n=1,071), known baseline creatinine (n=10,015), APS-III score (n=22), urine output (n=670)

[b] Pearson Chi-Square Asymptotic Test for categorical variables; Kruskal-Wallis test for continuous variables

[c] The available urine in the 24 hours after ICU was summed and divided by the weight

[d] Ordering of blood cultures and antibiotics within 24 hours of each other

[e] Alive and off RRT in the 3 calendar days prior to d/c and the last known AKI stage in the last 3 days prior to d/c was 0

[f] Number is lower than 4,508 because of missing data in the 3 calendar days prior to discharge

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Table S2. Predicting recovery at discharge by duration of AKI reversal

	Hours				
	24<48	48<72	72<96	96<120	≥120 but not through d/c
PPV	77.0%	80.9%	84.0%	86.2%	88.8%
NPV	73.2%	67.5%	63.1%	60.1%	58.0%
Sensitivity	83.5%	74.8%	66.4%	59.8%	54.1%
Specificity	64.3%	74.7%	82.0%	86.4%	90.3%

PPV, Positive predictive value; NPV, Negative predictive value

Table S3. Sensitivity Analysis: Reversal/Recovery defined as stage 1 or less.

Characteristics and Outcomes[a]	Early Sustained Reversal (N = 5,910)	Late Sustained Reversal (N = 1,040)	Relapse Recovery (N = 3,547)	Relapse No Recovery (N = 3,149)	Never Reversed (N = 3,322)	P Value[b]
Age, median (Q1-Q3)	61 (49-73)	64 (52-75)	65 (53-76)	68 (56-78)	66 (53-77)	<0.001
Males	3,404 (57.6)	616 (59.3)	2,041 (57.5)	1,692 (53.7)	1,782 (53.6)	<0.001
Race						
White	4,753 (80.4)	833 (80.1)	2,798 (78.9)	2,444 (77.6)	2,412 (72.6)	<0.001
Black	449 (7.6)	81 (7.8)	273 (7.7)	215 (6.8)	249 (7.5)	
Other	708 (12)	126 (12.1)	476 (13.4)	490 (15.6)	661 (19.9)	
Comorbid condition						
Hypertension	2,005 (33.9)	375 (36.1)	1,352 (38.1)	1,209 (38.4)	1,165 (35.1)	0.001
Diabetes	1,064 (18)	225 (21.6)	766 (21.6)	708 (22.5)	670 (20.2)	<0.001
Cardiac disease	1,033 (17.5)	214 (20.6)	776 (21.9)	728 (23.1)	727 (21.9)	<0.001
Liver transplant	159 (2.7)	34 (3.3)	101 (2.8)	101 (3.2)	99 (3)	0.63
Chronic renal disease	263 (4.5)	67 (6.4)	184 (5.2)	176 (5.6)	206 (6.2)	0.002
Multiple comorbidities	2,807 (47.5)	491 (47.2)	1,829 (51.6)	1,670 (53)	1,623 (48.9)	<0.001
Surgical admission	3,769 (68.9)	681 (68.6)	2,386 (70.6)	1,896 (64.2)	1,519 (49)	<0.001
Creatinine, mg/dl, median (Q1-Q3)						
Hospital admission	1.0 (0.8-1.4)	1.1 (0.8-1.8)	1.0 (0.8-1.4)	1.1 (0.8-1.6)	1.5 (1.0-2.5)	<0.001
Known baseline value	0.9 (0.7-1.2)	1.0 (0.8-1.4)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.7-1.4)	<0.001
Reference value	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.7-1.1)	0.9 (0.8-1.0)	0.9 (0.8-1.1)	<0.001
APS-III Score[c], median (Q1-Q3)	61 (45-81)	59 (41-82)	65 (49-84)	72 (53-92)	78 (55-105)	<0.001
Weight adjusted urine output (ml/kg), median(Q1-Q3)[c,d]	18.2 (12.9-27.2)	15.7 (9.3-24.5)	17.0 (12.1-26.0)	17.0 (11.3-25.9)	13.0 (5.8-22.6)	<0.001
Suspected sepsis[e]	735 (12.4)	130 (12.5)	538 (15.2)	553 (17.6)	677 (20.4)	<0.001
Vasopressors[c]	1,404 (23.8)	319 (30.7)	911 (25.7)	1,008 (32)	1,433 (43.1)	<0.001
Mechanical ventilation[c]	3,567 (60.4)	659 (63.4)	2,287 (64.5)	2,049 (65.1)	2,094 (63)	<0.001
In Hospital RRT	n/a	219 (21.1)	104 (2.9)	400 (12.7)	828 (24.9)	<0.001
Length of Stay, Days, Median (Q1-Q3)						
ICU	5 (3-8)	4 (2-12)	7 (4-16)	8 (4-16)	4 (3-10)	<0.001
Hospital	13 (9-21)	14 (7-30)	19 (11-33)	21 (13-36)	11 (5-23)	<0.001
Mortality						
ICU	n/a	n/a	n/a	821 (26.1)	1,283 (38.6)	<0.001
Hospital	n/a	n/a	n/a	1,575 (50)	1,720 (51.8)	0.16
30 Days	71 (1.2)	27 (2.6)	120 (3.4)	1,271 (40.4)	1,645 (49.5)	<0.001
90 Days	299 (5.1)	101 (9.7)	490 (13.8)	1,724 (54.7)	1,883 (56.7)	<0.001
365 Days	753 (12.7)	257 (24.7)	1,100 (31)	1,991 (63.2)	2,070 (62.3)	<0.001

[a] Missing data: age (n=4), surgical admission (n=1,073), hospital admission creatinine (n=1,071), known baseline value (n=10,015), APS-III score (n=22), weight adjusted urine output (n=670)

[b] Pearson Chi-Square Asymptotic Test for categorical variables; Kruskal-Wallis test for continuous variables

[c] On the day of ICU admission

[d] The available urine in the 24 hours after ICU was summed and divided by the weight

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Table S4. Sensitivity Analysis: Multivariable logistic regression models for renal recovery *excluding in-hospital deaths*

A. Outcome: No Recovery vs. Recovery

Outcome: No recovery vs. Recovery at d/c [a]	OR	95% CI for OR		P-Value
Age, by 5 years	1.02	1.00	1.03	0.01
Male	0.83	0.76	0.90	<0.001
Diabetes	1.15	1.02	1.29	0.02
Multiple comorbidities	0.86	0.78	0.95	<0.001
Surgical admission	0.88	0.80	0.96	0.003
APS-III score at ICU, by 10 units	1.02	1.01	1.04	0.009
Weight adjusted urine output[b], by 100 units	0.68	0.51	0.91	0.009
Suspected sepsis at ICU	0.83	0.73	0.94	0.003
Vasopressors at ICU	1.33	1.21	1.46	<0.001

[a] Recovery at d/c - late, relapse and early recovery groups; no-recovery - never and relapse no recovery groups

N=12,256; ROC (95%CI): 0.559 (0.547-0.571); Goodness-of-fit p-value 0.45

B. Outcome: No Reversal vs. Late Reversal

Outcome: No Reversal vs. Late Reversal	OR	95% CI for OR		P-Value
Male	0.87	0.75	0.99	0.04
Surgical admission	0.78	0.67	0.91	0.00
Reference Creatinine[a]	0.84	0.74	0.96	0.01
APS-III score[a], by 10 units	1.03	1.00	1.05	0.06
Vasopressors[a]	1.17	1.00	1.36	0.04
Mechanical ventilation[a]	0.80	0.68	0.93	0.005

[a] Captured in the 24 hours after ICU admission

N=3,457; ROC (95%CI): 0.562 (0.542-0.581); Goodness-of-fit p-value 0.44