Classifying AKI by Urine Output versus Serum Creatinine Level

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ABSTRACT

Severity of AKI is determined by the magnitude of increase in serum creatinine level or decrease in urine output. However, patients manifesting both oliguria and azotemia and those in which these impairments are persistent are more likely to have worse disease. Thus, we investigated the relationship of AKI severity and duration across creatinine and urine output domains with the risk for RRT and likelihood of renal recovery and survival using a large, academic medical center database of critically ill patients. We analyzed electronic records from 32,045 patients treated between 2000 and 2008, of which 23,866 (74.5%) developed AKI. We classified patients by levels of serum creatinine and/or urine output according to Kidney Disease Improving Global Outcomes staging criteria for AKI. In-hospital mortality and RRT rates increased from 4.3% and 0%, respectively, for no AKI to 51.1% and 55.3%, respectively, when serum creatinine level and urine output both indicated stage 3 AKI. Both short- and long-term outcomes were worse when patients had any stage of AKI defined by both criteria. Duration of AKI was also a significant predictor of long-term outcomes irrespective of severity. We conclude that short- and long-term risk of death or RRT is greatest when patients meet both the serum creatinine level and urine output criteria for AKI and when these abnormalities persist.

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Clinical trials of diagnostics and therapeutics for AKI can be challenging for several reasons.[1–3] The selection of short-term AKI end points requires an understanding of the relationship between AKI severity and duration and long-term outcomes. Severity of AKI is determined by relative azotemia, defined by an increase in serum creatinine (SC), or oliguria defined by a decrease in urine output (UO). However, patients manifesting both oliguria and azotemia and those in which these impairments are persistent are more likely to have worse disease and therefore worse outcomes.

AKI is very common in the critically ill. Upward of 75% of patients manifest the syndrome when defined by the full Kidney Disease Improving Global Outcomes (KDIGO) criteria.[4] However, spontaneous resolution (or rapid response to treatment) occurs in some patients. Such patients may be less appropriate for enrollment in clinical trials of novel therapeutics. Similarly, for various clinical trial applications, it may be important to select end points that are more closely tied to clinical outcomes.

Thus, we sought to investigate the relationship between maximum AKI severity and duration across

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creatinine and UO domains and the risk for RRT, and likelihood of renal recovery and survival.

RESULTS

Characteristics of Study Participants

Table 1 provides baseline characteristics of patients meeting maximum AKI severity by UO or SC criteria or both. Baseline characteristics were not very different between groups with the exception of surgical reason for admission (63.9% for UO versus 52% for SC), hospital admission creatinine (1.0 mg/dl for UO versus 1.8 mg/dl for SC), patients receiving vasopressors (23.3% for UO, 34.3% for SC, and 43% for both), and those suspected of having sepsis (11.9% for UO, 15.5% for SC, and 19.7% for both).

Outcomes of Patients with UO versus Creatinine Criteria

As shown in Table 2, outcomes for patients reaching maximum AKI stage according to UO criteria or SC criteria alone were less likely to receive RRT in the hospital (2.1% and 4.9%) compared with those reaching maximum AKI stage by both criteria (25%). Median intensive care unit (ICU) and hospital lengths of stay in hospital survivors were very similar for patients with maximum stage AKI due to UO (5 and 13 days) compared with patients with maximum stage AKI due to SC (4 and 14 days), and were greater than for patients without AKI

Table 1. Baseline characteristics for patients with maximum AKI severity by UO, SC, or both (*n*=23,866)

Characteristic[a]	No AKI (*n*=8179)	Maximum AKI Severity			*P* Value[c]
		UO (*n*=14,177)	SC (*n*=4694)	Both (*n*=4995)	
Age (yr), mean (SD)	54.1 (17.9)	61.9 (16.4)	60.4 (17.5)	62.4 (15.7)	<0.001
Men	4786 (58.5)	8206 (57.9)	2605 (55.5)	2826 (56.6)	0.01
Race					<0.001
White	6549 (80.1)	11,283 (79.6)	3663 (78)	3833 (76.7)	
Black	613 (7.5)	973 (6.9)	405 (8.6)	395 (7.9)	
Other	1017 (12.4)	1921 (13.6)	626 (13.3)	767 (15.4)	
BMI (kg/m^2), mean (SD)	26 (5.7)	29.4 (8.3)	26.4 (7)	29.1 (8.7)	<0.001
Comorbid condition					
Diabetes	336 (4.1)	903 (6.4)	372 (7.9)	426 (8.5)	<0.001
Cardiac disease	496 (6.1)	1358 (9.6)	572 (12.2)	628 (12.6)	<0.001
Chronic renal disease	91 (1.1)	182 (1.3)	128 (2.7)	110 (2.2)	<0.001
History of liver transplant	85 (1)	265 (1.9)	158 (3.4)	195 (3.9)	<0.001
History of hypertension	1934 (23.6)	4719 (33.3)	1678 (35.7)	1883 (37.7)	<0.001
Myocardial infarction	267 (3.3)	522 (3.7)	198 (4.2)	194 (3.9)	0.25
Heart failure	277 (3.4)	995 (7)	463 (9.9)	518 (10.4)	<0.001
Chronic liver disease	254 (3.1)	1057 (7.5)	347 (7.4)	686 (13.7)	<0.001
Sequelae of chronic liver disease	90 (1.1)	397 (2.8)	139 (3)	232 (4.6)	<0.001
Neoplasms	987 (12.1)	1989 (14)	589 (12.5)	665 (13.3)	0.03
Malignant neoplasm	350 (4.3)	614 (4.3)	172 (3.7)	182 (3.6)	0.03
HIV	31 (0.4)	24 (0.2)	33 (0.7)	29 (0.6)	<0.001
Multiple comorbidities	2026 (24.8)	4798 (33.8)	1723 (36.7)	2062 (41.3)	<0.001
Surgical admission	4748 (62.6)	8494 (63.9)	2291 (52)	2813 (59.3)	<0.001
SC (mg/dl), mean (SD)					
Known baseline	0.9 (0.4)	1 (0.4)	1.1 (0.6)	1.1 (0.6)	<0.001
Hospital admission	0.9 (0.4)	1 (0.5)	1.8 (1.5)	1.7 (1.2)	<0.001
Reference	0.9 (0.3)	0.9 (0.4)	1 (0.6)	1 (0.6)	<0.001
Reference eGFR					
<30	69 (0.8)	235 (1.7)	189 (4)	221 (4.4)	<0.001
30–60	359 (4.4)	1433 (10.1)	525 (11.2)	586 (11.7)	
>60	7751 (94.8)	12,509 (88.2)	3980 (84.8)	4188 (83.8)	
APS-III score, mean (SD)[b]	46.2 (21.2)	63.4 (26.6)	67.8 (30.1)	79.1 (31.9)	<0.001
Fluids, mean (SD)[b]	3.8 (3.1)	4.1 (3.5)	4.4 (3.9)	5 (5)	<0.001
Vasopressors[b]	1220 (14.9)	3302 (23.3)	1610 (34.3)	2147 (43)	<0.001
Mechanical ventilation[b]	4037 (0.5)	9138 (64.5)	2514 (53.6)	3376 (67.6)	<0.001
Suspected sepsis[b]	458 (5.6)	1688 (11.9)	727 (15.5)	983 (19.7)	<0.001

Data are presented as *n* (%) unless otherwise indicated. BMI, body mass index; APS-III, Acute Physiology, Age, Chronic Health Evaluation III.

[a]Missing values for age (10 patients), sex (1 patient), BMI (26 patients), surgical versus medical admission (2020 patients), known baseline creatinine (19,613 patients), hospital admission creatinine (2115 patients), APS-III score (47 patients), and fluid volume in the first 24 hours (4805 patients).

[b]Conditions measured in the first 24 hours of ICU admission.

[c]*P* values are shown for difference among the three groups of AKI patients. Patients without AKI are shown but are not formally compared.

Table 2. Outcomes for patients with maximum AKI severity by UO, SC, or both (*n*=23,866)

Characteristic	No AKI (*n*=8179)	Maximum AKI Severity			*P* Value[c]
		UO (*n*=14,177)	SC (*n*=4694)	Both (*n*=4995)	
Duration of stage 3 AKI (d), mean (SD)	N/A	1.3 (0.6)	3.5 (4)	5.6 (6.9)	<0.001
RRT during hospital stay	4 (0)	304 (2.1)	232 (4.9)	1251 (25)	<0.001
Length of stay (d), median (Q1, Q3)[a]					
ICU	3 (2–4)	5 (3–9)	4 (2–6)	7 (4–15)	<0.001
Hospital	7 (5–11)	13 (8–22)	14 (8–24)	22 (12–38)	<0.001
Mortality					
Hospital	350 (4.3)	1761 (12.4)	788 (16.8)	1597 (32)	<0.001
30 days[b]	425 (5.2)	1822 (12.9)	808 (17.2)	1375 (27.5)	<0.001
90 days[b]	596 (7.3)	2710 (19.1)	1074 (22.9)	1890 (37.8)	<0.001
1 year[b]	1064 (13)	3966 (28)	1498 (31.9)	2395 (47.9)	<0.001

Data are presented as *n* (%) unless otherwise indicated. N/A, not applicable.
[a]Length of stay was calculated only in hospital survivors.
[b]Days from ICU admission.
[c]*P* values are shown for difference among the three groups of AKI patients. Patients without AKI are also shown but are not formally compared.

(3 and 7 days). However, patients reaching maximum stage AKI with both criteria had much longer lengths of stay (7 and 22 days). Similarly 90-day and 1-year mortality were similar for patients with AKI maximum stage by UO (19.1% and 28%) compared with SC (22.9% and 31.9%) but were much higher for patients with both maximum criteria (37.8% and 47.9%).

Table 3 and Supplemental Table 5 shows the distribution of patients classified by various combinations of UO and SC criteria for AKI. In our cohort, 8179 patients (26%) had no evidence of AKI by either criteria and hospital mortality was 4.3%. Interestingly, 17,198 patients (54%) had no AKI by SC criteria and a hospital mortality of 5.9%, whereas far fewer (11,057; 35%) were free of AKI by UO criteria and had a hospital mortality rate of 5.6%. Patients with AKI by stage 3 criteria had the highest risk of death (40.3% by SC and 42.6% by UO) and use of RRT (36.6% by SC, 34.6% by UO). However, combinations of SC and UO criteria resulted in generally much worse outcomes. For example, stage 3 AKI by SC had a hospital mortality of 11.6% absent of any UO criteria but mortality increased to 38.6% when just stage 1 UO criteria were also present. Similarly, stage 3 AKI by UO had a hospital mortality of 17.7% absent any SC criteria but mortality increased to 32.1% when just stage 1 SC criteria was also present. For illustrative purposes, we reduced the number of groups to six based on similar rates of RRT and hospital mortality.

Renal Recovery and 1-Year Survival

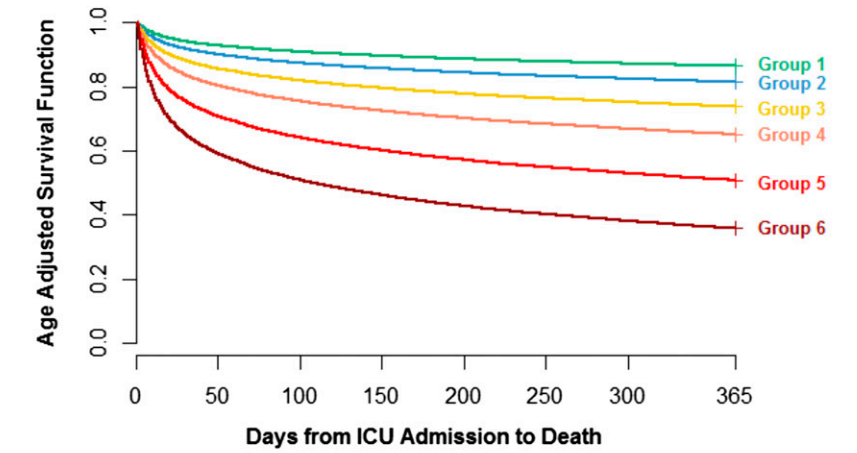
Age-adjusted survival and freedom from RRT (ESRD) over 1 year after ICU admission (Figure 1) followed a similar pattern as short-term outcomes shown in Table 3. For survival, there was separation among the six groups depicted in Table 3 (shown in color in Supplemental Table 5) ($P<0.001$); for ESRD, groups 1 and 2 were not different ($P=0.41$) and groups 3 and 4 were also very similar to each other ($P=0.56$). Groups 5 and 6 showed significant separation ($P<0.001$) but overall rates of progression to ESRD were quite low except for group 6 (Figure 1).

Table 3. Relationship between UO and SC criteria and clinical outcomes

SC Only (KDIGO Stage)	UO Only				
	No AKI	Stage 1	Stage 2	Stage 3	Total
No AKI					
Patients	8179[a]	3158[b]	5421[b]	440[d]	17,198
Dead	4.3[a]	5.3[b]	7.9[b]	17.7[d]	5.9
RRT	0.0[a]	0.0[b]	0.1[b]	1.1[d]	0.1
Stage 1					
Patients	1889[b]	1262[c]	3485[c]	842[e]	7478
Dead	8.0[b]	11.3[c]	13.0[c]	32.1[e]	13.6
RRT	0.3[b]	0.7[c]	0.6[c]	10.9[e]	1.7
Stage 2					
Patients	618[c]	476[d]	1533[d]	831[e]	3458
Dead	11.3[c]	23.9[d]	21.5[d]	44.2[e]	25.5
RRT	1.0[c]	1.3[d]	1.7[d]	21.7[e]	6.3
Stage 3					
Patients	371[c]	321[e]	1019[e]	2200[f]	3911
Dead	11.6[c]	38.6[e]	28.0[e]	51.1[f]	40.3
RRT	3.2[c]	17.8[e]	14.2[e]	55.3[f]	36.6
Total					
Patients	11,057	5217	11,458	4313	32,045
Dead	5.6	10.5	13.0	42.6	14.0
RRT	0.3	1.4	1.7	34.6	5.6

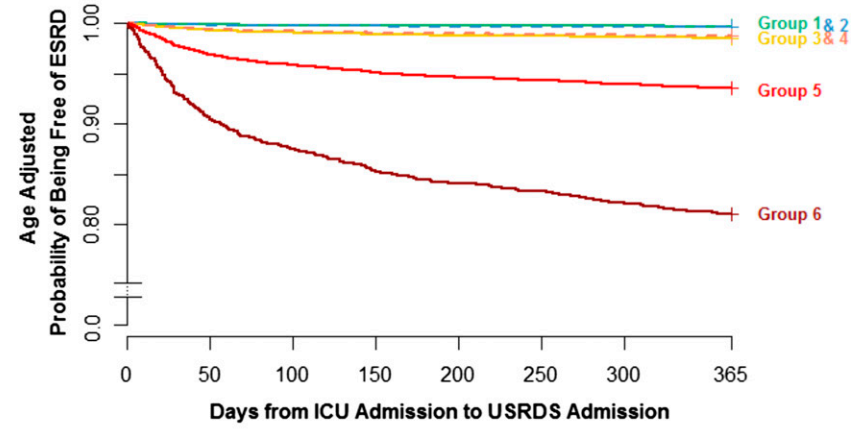
Data are presented as the number of patients, percentage of hospital mortality, and percentage of RRT for patients by maximum AKI criteria (UO, SC, or both). Superscript letters denote similar outcome patterns.
[a]Group 1, no AKI by either criterion.
[b]Group 2, stages 1–2 by UO criteria but no AKI by SC or stage 1 by SC and no AKI by UO.
[c]Group 3, stages 1–2 by UO plus stage 1 by SC or stages 2–3 by SC alone.
[d]Group 4, stages 1–2 by UO plus stage 2 by SC or stage 3 by UO alone.
[e]Group 5, stage 3 by UO plus stages 1–2 by SC or stage 3 by SC plus stages 1–2 by UO.
[f]Group 6, stage 3 by both criteria.

Figure 2 shows age-adjusted 1-year survival for patients with AKI by only one criterion (UO or SC). Overall, increasing stage is associated with lower survival ($P<0.001$). However, when AKI is defined only by UO and no AKI is present by SC criteria (Figure 2, top), stage 1 does not separate from no AKI



No. at risk

Group 1	8174	7680	7553	7447	7356	7278	7214	7111
Group 2	10465	9405	9101	8905	8744	8605	8473	8335
Group 3	5734	4813	4549	4382	4264	4155	4057	3972
Group 4	2449	1832	1722	1650	1583	1549	1519	1492
Group 5	3013	1910	1698	1592	1533	1489	1465	1436
Group 6	2200	1143	973	899	847	815	793	768



No. at risk

Group 1	7117	7107	7103	7100	7097	7097	7096	7096
Group 2	8344	8335	8328	8324	8323	8320	8316	8311
Group 3	3982	3966	3956	3946	3937	3930	3927	3920
Group 4	1499	1492	1490	1486	1485	1483	1480	1479
Group 5	1464	1410	1397	1386	1383	1381	1374	1366
Group 6	813	723	697	683	674	672	665	663

Figure 1. Age-adjusted survival and RRT rates by AKI severity. Groups refer to combinations of UO and creatinine criteria depicted in Table 3 and Supplemental Table 5. Group 1 (green), no AKI by either criterion; group 2 (blue), stages 1–2 by UO criteria but no AKI by SC or stage 1 by SC and no AKI by UO; group 3 (yellow), stages 1–2 by UO plus stage 1 by SC or stages 2–3 by SC alone; group 4 (orange), stages 1–2 by UO plus stage 2 by SC or stage 3 by UO alone; group 5 (red), stage 3 by UO plus stages 1–2 by SC or stage 3 by SC plus stages 1–2 by UO; and group 6 (dark red), stage 3 by both criteria. The top panel shows age-adjusted 1-year survival for all patients (10 patients had missing age). The bottom panel shows age-adjusted 1-year dialysis rates for patients that entered the USRDS before 1 year. Patients who died before 1 year are excluded. Overall differences by groups are significant for both sets ($P<0.001$).

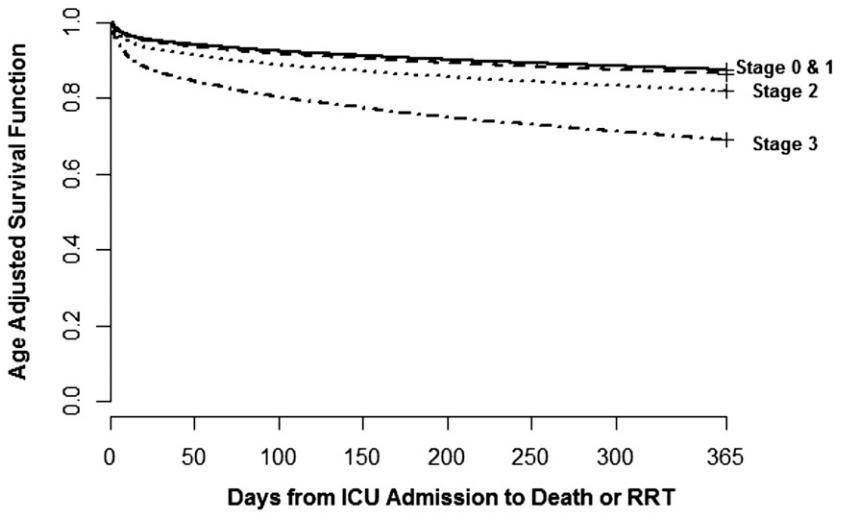
($P=0.12$). Conversely, when AKI is defined only by SC and no AKI is present by UO criteria, stages 2 and 3 do not separate ($P=0.27$).

Influence of AKI Duration

Mean duration of stage 3 AKI was 1.3 days (SD 0.6) for patients whose maximum stage was reached on the basis of UO criteria, 3.5 days (SD 4) for patients whose maximum stage was reached by SC criteria, and 5.6 days (SD 6.9) for patients who reached the same maximum stage by both criteria (Table 2). The relationships between AKI duration (persistence) and long-term outcomes are depicted in Figure 3. Figure 3, A and B, shows persistence of AKI by SC with Figure 3B showing results limited to hospital survivors. When in-hospital deaths are considered (Figure 3A), outcomes appear to be influenced in the positive direction by persistence (except for stage 1); however, when these patients are excluded, persistent AKI is associated with significantly greater risk of death or dialysis ($P<0.001$). This association remained in multivariable analyses ($P<0.001$). A similar pattern is apparent for persistence of oliguria in both univariate and multivariable models ($P<0.001$) (Figure 3, C and D).

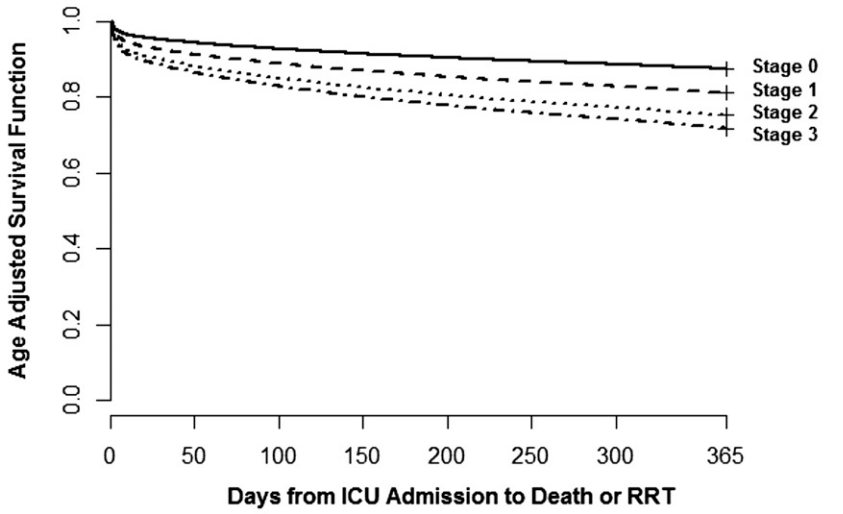
Sensitivity and Supplemental Analyses

We performed a number of additional analyses, the results of which are provided in the Supplemental Appendix. We performed subgroup analyses by baseline creatinine (<0.6 mg/dl and 0.6–1.2 mg/dl) and the results are shown in Supplemental Figure 1. Baseline characteristics and outcomes by AKI stage based solely on UO criteria, based solely on SC criteria, and based both (maximum severity) SC and UO criteria are shown in Supplemental Tables 1–3, respectively. Supplemental Table 4 provides the reference creatinine values according to the method used.



No. at risk

Stage 0	8174	7673	7544	7436	7342	7264	7199	7096
Stage 1	3158	2915	2845	2804	2772	2731	2697	2659
Stage 2	5419	4802	4624	4510	4411	4341	4267	4192
Stage 3	440	344	324	314	303	297	286	279



No. at risk

Stage 0	8174	7673	7544	7436	7342	7264	7199	7096
Stage 1	1888	1683	1621	1578	1548	1518	1490	1460
Stage 2	618	528	508	490	474	460	445	432
Stage 3	369	310	290	278	270	266	260	252

Figure 2. Age-adjusted 1-year risk for death or RRT for AKI staging based solely on UO or creatinine criteria. Shown are death or RRT rates over 1 year (includes in-hospital events) for patients with AKI staging based solely on UO (no AKI by SC; 7 patients had missing age) (top) and those with AKI based solely on SC (no AKI by UO; 8 patients had missing age) (bottom). Overall differences by stage are significant for both sets ($P<0.001$).

DISCUSSION

Using a large heterogeneous series of patients cared for over an 8-year period in multiple ICUs in one large academic medical center, we examined the associations between AKI and both short-term and long-term outcomes as functions of UO and SC criteria both alone and in combination. We also examined the effect of persistence of AKI defined as the time in which a criterion for diagnosis of AKI was present. We used hard clinical end points (death and dialysis) to assess the significance of AKI events and to examine differences among various groups defined by the domains of criteria (UO versus SC), severity (stage), and time (persistence).

Our results demonstrate several surprising findings. First, despite relatively minor (although statistically significant) differences in baseline characteristics (Table 1), patients meeting both UO and SC criteria for AKI have dramatically worse outcomes compared with patients who manifest AKI solely or predominantly by one criterion. Indeed, as seen in Table 3, hospital mortality was <18% and RRT was <3.5% for the 11,897 patients (37.1%) manifesting AKI by only one parameter. Meanwhile, mortality reached 51.1% and RRT 55.3% for the 2200 patients (6.9%) meeting stage 3 criteria by both UO and SC. Even stage 3 criteria in one domain with stage 1 criteria in another was associated with >30% hospital mortality and >10% use of RRT. These results establish the absolute necessity for UO assessment in critically ill patients for staging of AKI. They also appear to contrast with prior work by Ralib and colleagues, who found that the oliguria threshold of 0.5 ml/kg per hour was not predictive of survival, whereas 0.3 ml/kg per hour was.[5] These authors did not examine the effects of UO and SC together and their sample size was only 725 patients, limiting their statistical power. Other investigators have found UO to be a sensitive and early marker for AKI and to be associated with adverse outcomes in critically ill patients.[6] UO is also affected by renal tubular function as evidenced by response to a "furosemide stress test."[7]

Second, 1-year outcomes parallel the hospital outcomes for the various combinations of UO and SC criteria. Indeed, the

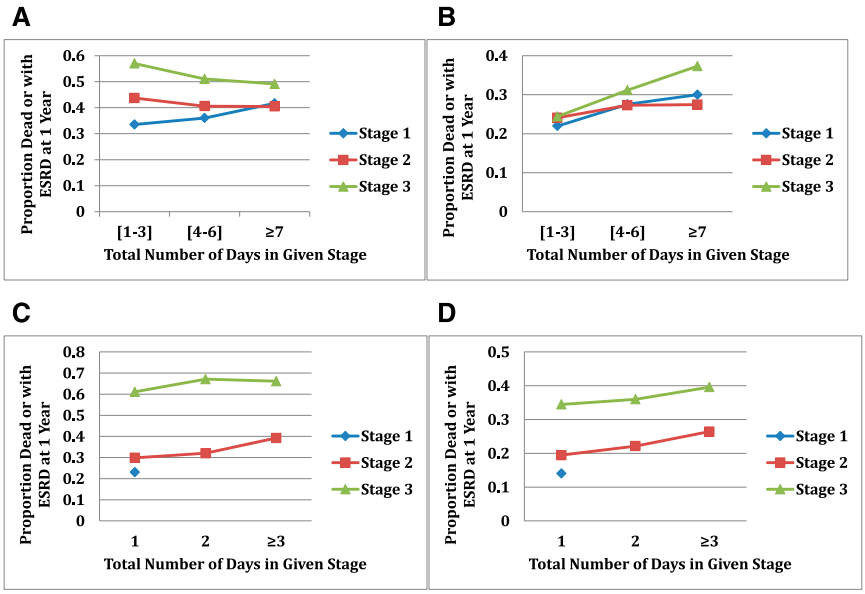


Figure 3. Relationship between duration of AKI and death or dialysis at 1 year after ICU admission. (A) Duration of AKI by SC criteria (in all patients with or without AKI by UO) and likelihood of death or dialysis at 1 year. Likelihood of death or dialysis is significantly different by stage and also by time ($P<0.001$ and $P=0.02$, respectively) and the interaction between time and stage is significant ($P<0.001$). (B) Duration of AKI by SC criteria and likelihood of death or dialysis at 1 year (excludes death or RRT during the index hospitalization). Likelihood of death or dialysis is significantly different by stage and also by time ($P=0.01$ and $P<0.001$, respectively). (C) Duration of AKI by UO criteria (in all patients with or without AKI by SC) and likelihood of death or dialysis at 1 year. Likelihood of death or dialysis is significantly different by stage and also by time (analysis limited to only patients with stages 2–3) ($P<0.001$). (D) Duration of AKI by UO criteria and likelihood of death or dialysis at 1 year (excludes death or RRT during the index hospitalization). Likelihood of death or dialysis is significantly different by stage and also by time (analysis limited to only patients with stages 2–3) ($P<0.001$).

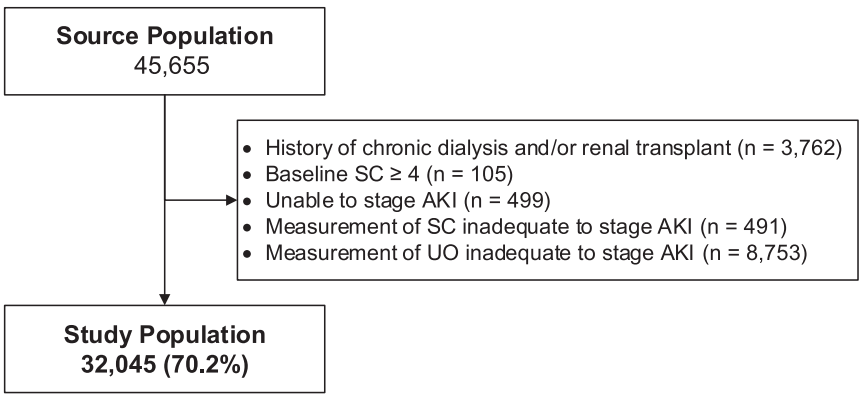


Figure 4. The source population included all patients cared for in an ICU over the 8-year study period. The study population included 32,045 patients (70.2% of the source population) after excluding missing data (mainly urine output) and ESRD.

survival curves continue to separate for much of the year after an AKI event. Although less common than death, postdischarge RRT rates also continued to rise over the year for patients incurring a stage 3 event (either UO or SC) plus at least a stage 1 event in the other domain. These results again emphasize the importance of both UO and SC in the assessment of AKI but also emphasize the importance of follow-up in this population.

Third, isolated oliguria (no SC criteria present) is surprisingly frequent and appears to be associated with a long-term hazard. Figure 2 shows that stages 2 and 3 AKI by UO criteria alone are associated with decreased 1-year survival. To the best of our knowledge, this has not been reported previously, and if the relationship is causal, the mechanisms are unknown. Several studies have emphasized the importance of fluid overload both in terms of its effect on clinical outcomes[7–9] and on SC measurements.[10] It is likely that most oliguric patients are volume overloaded and it is reasonable to deduce that this represents an adverse effect on survival. It is also conceivable that volume overload masks some degree of azotemia; thus, profound oliguria is not just an early indicator of AKI, and it may be the only indicator. Because our data suggest that even mild azotemia (stage 1) dramatically increases mortality in oliguric patients (Table 3), it does seem likely that some patients who did not fulfill SC criteria nevertheless had some degree of azotemia and that this too influenced outcomes.

Fourth, our results are notable for what they tell us about the effect of persistent AKI. Although Figure 3, A and C, does not suggest much of an effect of duration of AKI on outcome, this is due to immortality bias. In order to remain in the cohort on day 2, a patient had to survive day 1. When hospital nonsurvivors are removed (Figure 3, B and D), it is clear that AKI persistence has a substantial influence on outcome. For example, 4 days at stage 3 (SC) AKI results in an approximately 30% rate of death or dialysis at 1 year. It requires more than a week at stage 1 to incur the same hazard. Persistence of oliguria is more constrained because after 3 days, almost all patients resolve, die, receive RRT, or develop significant azotemia. Nevertheless, even over 3 days, one can observe an effect of duration on outcomes independent of stage (Figure 3D). These results are consistent with the findings of Coca *et al.*, who demonstrated that duration of AKI based on creatinine after surgery was independently associated with subsequent outcome.[11]

Finally, our results do not suggest that small absolute changes in SC in patients with low baseline creatinine are less significant than larger changes in the same relative magnitude in patients with high baseline levels—as has been suggested by others.[12] Supplemental Figure 1 shows that even in ICU patients with very low baseline creatinine, AKI is associated with adverse long-term outcomes.

Our study has important limitations. Most notably, we cannot comment on AKI outside the ICU and although we examined a very large cohort, the patients are all from a single medical center (although the center includes multiple ICUs in different hospitals). However, our overall event rates and outcomes agree well with recent epidemiologic studies of AKI from around the world.[12–14] Because our study was observational, we cannot establish causality; indeed, the association between AKI (severity and duration) and adverse long-term outcomes may very well be confounded by other factors that we could not measure. Finally, we could not quantify duration of RRT because patients discharged on dialysis but no longer receiving it by 90 days (and thus absent from US Renal Data System [USRDS] data) had an indeterminate duration. We therefore chose to measure AKI duration exclusive of RRT. Similarly, long-term progression of or to CKD could not be assessed except for ESRD.

In summary, our results show that risk for death or dialysis over the index hospital stay and over the following year is greatest for patients that meet both UO and SC criteria for AKI and for those in whom the abnormalities persist longer. However, even a brief episode of isolated oliguria without subsequent azotemia appears to be associated with decreased 1-year survival.

CONCISE METHODS

We analyzed data on 32,045 adult patients admitted to any of eight ICUs at the University of Pittsburgh Medical Center during an 8-year period (from July 2000 to October 2008) after excluding patients who received hemodialysis or a renal transplant before hospital admission, those with known baseline creatinine≥4 mg/dl, or those with incomplete data (see Figure 4). The study protocol was approved by the University of Pittsburgh Institutional Review Board.

We calculated the acute physiology components of the Acute Physiology, Age, Chronic Health Evaluation III score,[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 SC were determined as previously described.[17,18]

We classified patients according to the maximum KDIGO criteria[19] met during hospitalization using SC and UO criteria. If multiple episodes of AKI occurred, we only considered the most severe. Because we used RRT as an outcome, we did not apply it as a rule to the small number of participants that were started on RRT before achieving stage 3 criteria by UO or creatinine. In addition, RRT was not included in the duration of AKI. Duration of AKI was determined separately for SC and UO criteria. Patients with gaps in SC>48 hours were excluded. Patients were grouped based on their maximum AKI stage during hospital stay and duration was determined in 24-hour intervals for that stage. Persistence for UO was based on the hourly UO data and was assessed in the same 24-hour fashion as for the creatinine rule. However, duration for UO criteria did not include the duration required for the stage. For example, a patient with 71 hours of oliguria would be in stage 3 for 2 days because the first 24 hours is required for stage 3 and the oliguria resolved before the third day.

Our primary outcomes were provision of RRT, hospital mortality, and survival up to 1 year. Chronic RRT was defined by the entrance date into the USRDS. Mortality at 1 year was determined from the National Center for Health Statistics National Death Index database or the Social Security Administration Death Master File.

Statistical analyses were performed using the STATA software (version SE 11.2), with statistical significance set at $P<0.05$. Survival graphs were created using the R 'survival' package (version 2.37-7). Comparisons across groups were performed using the chi-squared test for categorical variables and using either ANOVA or the Kruskal–Wallis one-way ANOVA by ranks for continuous variables. We used Cox proportional hazards model to describe the various age-adjusted survival curves at 1 year after ICU admission. The 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 perform pairwise comparisons between groups. The relationship between the duration of AKI, the stage of AKI, and death or dialysis was assessed through age- and comorbidity-adjusted logistic regression, and Wald tests were used for hypothesis testing. As a sensitivity analysis, we repeated our primary analysis without adjusting for age and by stratifying by patients with baseline SC<0.6 mg/dl and 0.6–1.2 mg/dl.

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DISCLOSURES

None.

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