Acute kidney injury patterns and outcomes in low-risk versus high-risk critically ill patients admitted to the medical intensive care unit

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Abstract

Background: *Acute kidney injury (AKI) is often one component of multiple organ failure (MOF) in the intensive care unit (ICU). However, not all patients with MOF develop AKI, and AKI may develop in the absence of MOF. We compared the impact of AKI alone and in combination with MOF on the survival of patients admitted to a large tertiary care medical intensive care unit (MICU).*

Methods: *We abstracted data from the electronic medical records of patients admitted to the MICU from April 2012 through June 2013 and categorized patients as either high-risk or low-risk status based on use of vasopressor support or mechanical ventilation during the ICU stay. The outcomes we considered were in-hospital, 30 day, 90 day, 180 day, and 1 year mortality.*

Results: *Of the 834 critically ill patients, 743 (89%) developed some degree of AKI. Ninety-one percent of the high-risk cohort developed AKI and 87% of the low-risk cohort developed AKI. Patients with AKI had higher mortality at 1 year than patients without AKI (adjusted odds ratio [OR], 2.5; 95% confidence interval, 1.38 to 4.53); P interaction 0.003). Hospital mortality was greater for high-risk patients without AKI than for low-risk patients with AKI.*

Conclusion: *Acute kidney injury occurs at similar frequency in high- and low-risk ICU patients and has significant impact on survival in both groups. Cardiovascular collapse or respiratory failure has greater impact on short term mortality than AKI, but this effect diminishes over time. Conversely, the impact of AKI on mortality increased over time and remained an independent risk factor for mortality.*

Keywords: Acute kidney injury, intensive care unit, critically ill patients, mortality, length of stay

Introduction

Critical illness is a major predisposing factor for acute kidney injury (AKI), but AKI can develop in the absence of other organ failure. Patients with respiratory failure, cardiovascular failure, or sepsis are at high risk for mortality. Systemic illnesses that present with cardiovascular or respiratory organ failure often cause AKI. Critically ill patients without other organ failure, especially those without circulatory collapse or respiratory failure, are less likely to develop AKI. Conventional wisdom suggests that these patients are at low risk overall and are, therefore, less likely to receive interventions aimed at preventing AKI (avoidance of nephrotoxic drugs and radiocontrast, assessment of fluid status, and close monitoring of renal function).[1]

We sought to examine the risk of developing AKI and the outcomes associated with AKI in critically ill

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DOI: 10.12746/swrccc2017.0517.237

patients assigned to be at high or low-risk based on the recorded use of treatments for sepsis or for other acute organ failure. Sileanu et al previously demonstrated that, among individuals admitted to any ICU setting, low-risk patients with AKI had higher mortality than high-risk patients without AKI.[1] We sought to compare Sileanu's results with the mortality of our study population which was limited to patients admitted to the medical intensive care unit (MICU). We also compared the mortality outcomes of patients who developed different stages of AKI defined by Acute Kidney Injury Network (AKIN) criteria. Finally, we evaluated the effect of prior chronic kidney disease (CKD) using CKD stages defined by Kidney Disease Global Outcome (KDIGO) criteria on mortality.[2] In the United Kingdom, after a systematic review of the care and outcomes for patients with AKI, the National Health Service found that inadequate risk assessment is a common practice that often results in delays in preventive measures and treatment.[3] We believe our study should further define the degree of risk for mortality and for AKI in patients in high and low overall risk groups in the MICU setting.

Methods

Source Population. Our database included data on a source population of 856 patients admitted to the MICU of a single tertiary medical center (University Medical Center, Lubbock, Texas) from April 1, 2012, to June 30, 2013. The MICU at this institution is open for admissions by any member of the Internal Medicine or Family Medicine Departments; the majority of patients are admitted to the Internal Medicine MICU service. Patients admitted specifically for cardiac diagnoses are admitted to the hospital cardiac intensive care unit and are not included in this study, nor are trauma patients or surgical cases admitted to the MICU. For those individuals admitted on multiple occasions during the study interval, only the data from the initial admission were used to determine presence of AKI and risk status. Patients with serum creatinine ≥4.0 mg/dL, ESRD, CKD stage 5, or a history of kidney transplant were excluded from the study. The remaining 834 patients comprised the study population.

Design and data collection. We obtained approval for the study from the Institutional Review Board of Texas Tech University Health Sciences Center prior to its initiation. We conducted a pilot study from January 1, 2012, to March 31, 2012, which included 183 source patients. This pilot study established the number of cases which would be needed to obtain a sample of adequate size for the planned analysis, but these data were not included in the final study. The data of the included cases were abstracted from the hospital electronic medical records and entered into a de-identifiable database created for this study.

We ultimately abstracted data from the electronic medical records of all 834 patients admitted to the MICU of University Medical Center, Lubbock, Texas, from April 1, 2012, through June 30, 2013. The previous pilot study had determined that at least 750 records would be required to have sufficient data for analysis. The data abstracted included patient demographics, diagnoses, comorbidities, billing codes, laboratory and radiological investigations, death records for hospital mortality, vasopressor use, mechanical ventilation, medications, details of any renal replacement therapy (RRT), vital signs, and weight and height measurements. We reviewed records from the local funeral homes, obituary publications by local and national newspapers, and the Texas electronic death registry to determine mortality outcomes after hospital discharge. All patients were censored on February 1, 2015, at the conclusion of the follow-up period. Finally, the data were de-identified to protect medical privacy before they were analyzed for outcomes.

Study Cohorts. We first stratified patients into high-risk and low-risk cohorts. The high-risk cohort included all patients who had acute cardiovascular or acute respiratory organ failure during the ICU admission, determined by the use of mechanical ventilation or vasopressor support. The low-risk cohort included patients who required neither vasopressor support nor mechanical ventilation. Comorbid conditions were determined by assigned International Classification of Diseases, Ninth Revision (ICD-9) codes. The patient simplified acute physiology scores (SAPS II) were computed from electronic abstraction of all physiology variables present within 24 hours of ICU admission.

The APACHE II scores were retrieved from patient medical records. Thirty-three patients could not be assigned SAPS II scores due to missing data, and 235 patients could not be assigned APACHE II scores due to missing data. Hence, the SAPS II score was used to assess the severity of illness because there were fewer charts lacking these data. The systemic inflammatory response syndrome (SIRS) was defined as the presence of at least two of the following: heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, white blood cell count > 12,0004,000/μL or < 4,000/μL, and temperature > 100.4ºF or < 96.8ºF. Sepsis was defined as the presence of SIRS with an identified source of infection. Since sepsis is generally widely under-reported, we reviewed the laboratory and radiological investigations of all patients who met the criteria for SIRS to determine source of infection, and if an infection was found to be present, the patient was considered to have sepsis for purposes of the study.

Chronic kidney disease stages were defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria. Glomerular filtration rate was estimated by the four variable Modification by Diet of Renal Disease (MDRD) equation using baseline serum creatinine or by use of reference serum creatinine if the baseline serum creatinine were unavailable. Baseline serum creatinine was the lowest serum creatinine measured within six months of hospital admission. Reference serum creatinine was the lowest serum creatinine recorded during the hospital admission prior to initiation of RRT, or after a minimum of five days following discontinuation of RRT, or up to six months post discharge. Obesity was classified based on the body mass index (BMI). The classification used for the study was: underweight, BMI <18.5 kg/m^2; normal weight, BMI range from 18.5 to 24.9 kg/m^2; overweight, BMI range from 25 to 29.9 kg/m^2; mild obesity, BMI range from 30 to 34.9 kg/m^2; moderate obesity, BMI from 35 to 39.9 kg/m^2; and morbid obesity, BMI ≥40 kg/m^2.

AKI Classification. The presence of AKI was determined by the increase in the patient's serum creatinine from the patient's baseline serum creatinine according to the maximum KDIGO criteria met during ICU admission. The severity of AKI was initially classified by both RIFLE (Risk, Injury, Failure, Loss, or End Stage Kidney Disease) and AKIN criteria, and CKD stage was defined by KDIGO criteria.[3] Among patients who did not have a baseline serum creatinine, the reference serum creatinine (defined above) was used in place of baseline serum creatinine. Due to inconsistencies in urine output collection and charting, we were restricted to using changes in serum creatinine from baseline to determine the presence of AKI and for estimating the severity of AKI according to AKIN and RIFLE criteria.

Risk factors and exposures. The literature was reviewed to identify risk factors for AKI in critically ill patients. Several studies identified the following risk factors for the development of AKI: age, sex, race, body mass index (BMI), hypertension, diabetes mellitus, cardiac disease, CKD, admission type (medical versus surgical), SAPS II score, hypotension, sepsis, nephrotoxic drug use, and COPD.[4-6]

Outcome Assessment. For our study, the defined patient outcomes were in-hospital mortality, mortality at 30 days, 90 days, 180 days, and 365 days from ICU admission. We also analyzed the data for effects of AKI, CKD, and high-risk/low-risk classification on ICU length of stay (LOS) and hospital LOS.

Statistical Analysis. Statistical analyses were performed using the SAS software and the MedCalc software with statistical significance set at P value <0.05. Categorical variables were summarized as number (percentage) and continuous variables were summarized as mean ± (SD or SEM) if normally distributed or median ± interquartile range if skewed. Multiple risk factors and comorbidities were adjusted for by using the multiple variable logistic regression model for each risk factor when comparing the difference in magnitude of association between AKI and mortality (hospital, 30 day, 90 day and 365 day mortality) between the low-risk and high-risk cohorts. We also conducted multiple variable logistic regression models to assess the degree of association between multiple variables and the severity of AKI by AKIN criteria. All initially selected variables were retained in the model regardless of significance level. We used Kaplan-Meier survival analysis to graphically describe

the following survival curves: 1) between AKI versus no AKI classification; 2) between AKI and low-and high-risk groups at study censor point on February 1, 2015; and 3) between different stages of AKI per AKIN criteria.

Results

Demographics. Of the 834 patients who met the inclusion criteria, 743 (89%) developed AKI. These patients had a mortality rate of 52% at end of the follow up period on February 1, 2015. Among the demographic factors, age, body mass index, and race had statistically significant impacts on survival. Mortality increased with age and Hispanic ancestry; survival was better in patients of African descent and in patients who were overweight or had mild to moderate obesity (Table 1). Of the several identified risk factors known to affect mortality, congestive heart failure (CHF), coronary artery disease (CAD), and sepsis had a negative impact on survival (Table 1). However, after adjustment for multiple covariates, sepsis and CHF had statistically significant impacts on mortality at 1 year, but CAD did not (Table 4). There was no statistically significant impact of CKD, HTN, smoking, morbid obesity, underweight, sex, and chronic obstructive pulmonary disease (COPD) on survival (Table 1). Tables 2 and 3 highlight the baseline characteristics and demographics of patients based on AKI status and risk group stratification, respectively.

Survival Outcomes based on AKI status. After adjusting for multiple risk factors and severity of illness defined by SAPS II scores, patients with AKI had higher mortality rates at 180 and 365 days than patients without AKI (Table 4). The Kaplan-Meier survival curve analysis of patients with AKI shows a progressive increase in mortality over time when compared to patients without AKI whose mortality outcome appeared to plateau after 100 days (Figure 1). Patients with AKIN 1, AKIN 2 and AKIN 3 all had higher mortality at 365 days than patients with no AKI (adjusted odds ratios [OR] 2.16, 3.03, and 3.34 with P interaction 0.017, 0.001, and <0.001,

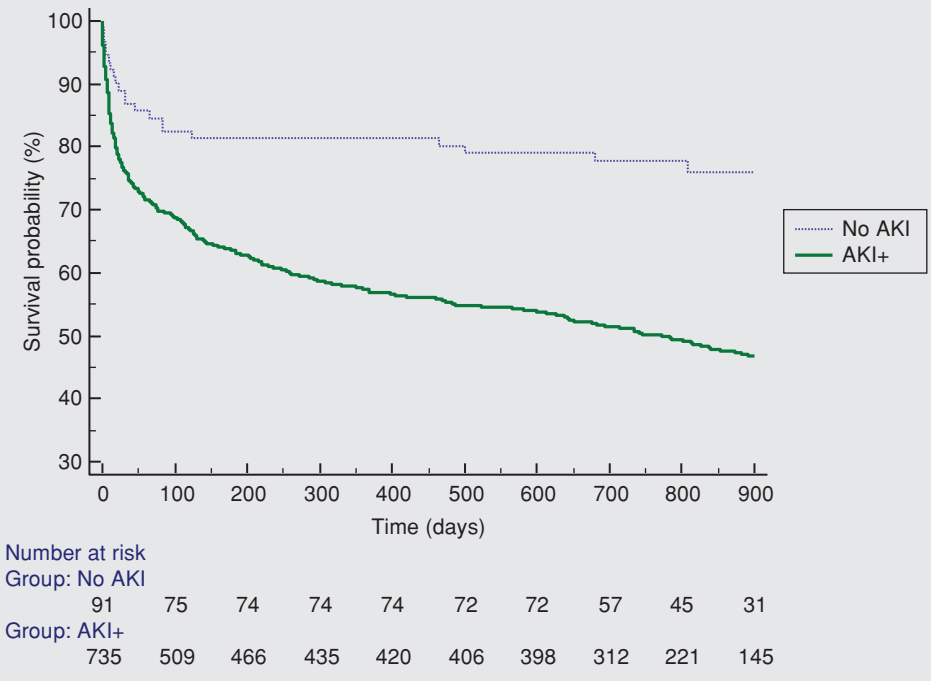

Figure 1. Kaplan-Meier survival curves for AKI versus no AKI cohorts. The graph illustrates the impact of AKI on survival. All degrees of AKI are included. The effect is present early in the ICU stay and the difference widens over the duration of the study.

Table 1. Demography and baseline characteristics of study population

Characteristic	*n*	%	Mortality*	OR	95%CI	P value
Population	834	100.0	48.7			
SAPS II derived score (mean ± *SD*)	32.7	12.8			4.75 to 8.19	<0.001
BMI (mean ± *SD*)	29.7	11.3				0.212
Normal Weight	264	31.7	57.6	Reference		
Under weight	51	6.1	54.9	0.97	0.53 to 1.78	0.919
Overweight	182	21.8	45.6	0.62	0.42 to 0.90	0.013
Mild Obesity	136	16.3	42.7	0.55	0.36 to 0.83	0.005
Moderate Obesity	57	6.8	31.6	0.31	0.17 to 0.58	<0.001
Morbid Obesity	93	11.2	47.3	0.66	0.41 to 1.06	0.087
Length of stay						
HOSPITAL (mean ± *SD*)	9.1	8.0				0.706
ICU (mean ± *SD*)	4.8	5.8				0.131
Age (mean ± *SD*)	65.2	16.8				<0.001
Gender						
Female	384	46.0	46.6	Reference		
Male	450	54.0	50.7	1.19	0.90 to 1.56	0.214
Race						
African American	77	9.2	42.9	Reference		
White	536	64.3	46.1	1.14	0.70 to 1.85	0.595
Hispanic	168	20.1	61.9	2.17	1.25 to 3.75	0.006
Other	28	3.4	60.7	2.06	0.85 to 4.98	0.108
No reply	25	3.0				
Diabetes mellitus	262	31.4	48.9	1.01	0.75 to 1.35	0.945
CAD	260	31.2	58.1	1.73	1.29 to 2.33	<0.001
CHF	251	30.1	60.2	1.94	1.43 to 2.62	<0.001
COPD	97	11.6	56.7	1.44	0.94 to 2.21	0.094
Hypertension	440	52.5	48.9	1.00	0.76 to 1.31	0.978
Smoking	188	22.5	48.9	1.01	0.73 to 1.40	0.937
CKD Stage						
stage 0 & 1	337	40.4	50.7	Reference		
stage 2	264	31.7	44.3	0.76	0.55 to 1.05	0.098
stage 3A	112	13.4	49.1	0.94	0.61 to 1.44	0.760
stage 3B	79	9.5	53.1	1.10	0.67 to 1.80	0.698
stage 4	80	9.6	27.5	1.12	0.59 to 2.15	0.724
Sepsis	545	65.4	53.4	1.66	1.24 to 2.22	<0.001
Renal replacement therapy	44	5.3	54.6	1.43	0.75 to 2.74	0.281
IHD	14	1.7	35.7			
CVVHD	33	4.0	72.7			
Both IHD and CVVHD	3	0.4	33.3			
AKI						
No	91	10.9	24.2	Reference		
Yes	743	89.1	51.8	3.46	2.08 to 5.77	<0.001
Mechanical ventilation	263	31.5	59.3	1.86	1.38 to 2.50	<0.001
Vasopressor	329	39.5	59.9	2.07	1.56 to 2.75	<0.001
Risk group						
Low-risk group	410	4926	40.7	Reference		
High-risk group	424	50.8	56.6	1.73	1.42 to 2.10	<0.001
Admitting service						
Medicine team	259	31.1	37.5			
Family medicine	52	6.2	57.7			
MICU team	91	10.9	67.0			
Private Network Physicians	416	49.9	49.8			
Surgery	16	1.9	50.0			

95%CI, 95% Confidence interval; CKD, chronic kidney disease; SAPS II, simplified acute physiology score II; LOS, length of stay; BMI, body mass index; *SD*, standard deviation; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive disease; IHD, intermittent hemodialysis; CVVHD, continuous venovenousl hemodialysis; mortality*, mortality at end of study on Feb 1, 2015 expressed in percentage; OR, odds ratio; *n,* number except otherwise specified.

Table 2. Baseline characteristics based on AKI status

Characteristics	No AKI (n = 91)	AKI (n = 743)
Age	65.1(18.4)	65.21(16.6)
Gender		
Female	46(50.6)	338(45.5)
Male	45(49.4)	405(54.5)
Race		
White	70(76.9)	466(62.7)
Black	8(8.8)	69(9.3)
Hispanic	9(9.9)	159(21.4)
Other	2(2.2)	26(3.5)
CKD		
Stage 0&1	33(36.3)	304(40.9)
Stage 2	39(42.9)	225(30.3)
Stage 3	17(18.7)	175(23.6)
Stage 4	2(2.2)	39(5.3)
Smoking		
No	69(75.8)	577(77.7)
Yes	22(24.2)	166(22.3)
BMI		
Normal	29(31.9)	235(31.6)
Overweight	19(20.9)	163(21.9)
Mild obesity	20(22.0)	116(15.6)
Moderate obesity	5(5.5)	52(7)
Morbid obesity	8(8.8)	85(11.4)
Underweight	5(5.5)	46(6.2)
No data	5(5.5)	46(6.2)
Hypertension		
No	50(55.0)	346(46.6)
Yes	41(45.1)	397(53.4)
Diabetes		
No	65(71.4)	507(68.2)
Yes	26(28.6)	236(31.8)
CAD		
No	67(73.6)	507(68.2)
Yes	24(26.4)	236(31.8)
CHF		
No	65(71.4)	518(69.7)
Yes	26(28.6)	225(30.3)
COPD		
No	76(83.5)	661(89.0)
Yes	15(16.5)	82(11.0)
Mechanical Ventilation		
No	73(80.2)	498(67.0)
Yes	18(19.8)	245(33.0)
Vasopressor(s)		
No	65(71.4)	440(59.2)
Yes	26(28.6)	303(40.8)
Sepsis		
No	46(50.6)	243(32.7)
Yes	45(49.5)	500(67.3)
Lowest Creatinine	0.89(0.5)	1.1(0.8)
Highest Creatinine	1.2(0.5)	2.6(2.0)
SAPS II derived score	27.6(10.2)	33.4(12.9)

Data are presented as n(%) or mean(± SD) unless otherwise specified; CKD, chronic kidney disease; SAPS II, simplified acute physiology score II; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive disease

Table 3. Baseline characteristics of low-risk and high-risk groups

Characteristics	Low risk (n = 410)	High risk (n = 424)
Age	67.5(17.4,98.2)	65.4(20.1,95.6)
Gender		
Female	191(46.6)	193(45.5)
Male	219(53.4)	231(54.5)
Race		
White	267(67.3)	269(65.3)
Black	38(9.6)	39(9.5)
Hispanic	77(19.4)	91(22.1)
Other	15(3.8)	13(3.2)
CKD		
Stage 0&1	142(34.6)	195(46.0)
Stage 2	132(32.2)	132(31.1)
Stage 3	111(27.1)	81(19.1)
Stage 4	25(6.1)	16(3.8)
Smoking		
No	327(80.2)	315(74.6)
Yes	81(19.9)	107(25.4)
BMI		
Normal	137(35.9)	127(31.7)
Overweight	89(23.3)	93(23.2)
Mild obesity	70(18.3)	66(16.5)
Moderate obesity	25(6.5)	32(8.0)
Morbid obesity	41(10.7)	52(13.0)
Underweight	20(5.2)	31(7.7)
No data	28(6.8)	23(5.4)
Hypertension		
No	188(46.1)	204(48.3)
Yes	220(53.9)	218(51.7)
Diabetes		
No	281(68.9)	287(68.0)
Yes	127(31.1)	135(32.0)
CAD		
No	285(69.9)	285(67.5)
Yes	123(30.2)	137(32.5)
CHF		
No	295(72.3)	284(67.3)
Yes	113(27.7)	138(32.7)
COPD		
No	366(89.7)	367(87.0)
Yes	42(10.3)	55(13.0)
Mechanical Ventilation		
No	N/A	161(38.0)
Yes	N/A	263(62.0)
Vasopressor(s)		
No	N/A	95(22.4)
Yes	N/A	329(77.6)
Sepsis		
No	184(44.9)	105(24.8)
Yes	226(55.1)	319(75.2)
Lowest Creatinine	1.0(0.2,7.3)	0.8(0.2,4.4)
Highest Creatinine	1.8(0.5,18.6)	2.0(0.3,26.1)
SAPS II derived score	27(6,58)	36(6,86)

Data are presented as n(%) or median(minimum, maximum) unless otherwise specified; CKD, chronic kidney disease; SAPS II, simplified acute physiology score II; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive disease

Table 4. Logistic regression models comparing outcomes between AKI versus no AKI with multiple risks factors

	Hospital mortality		30 day mortality		90 day mortality		180 day mortality		365 day mortality	
Characteristic	**OR**	**P**	**OR**	**P**	**OR**	**P**	**OR**	**P**	**OR**	**P**
AKI										
No										
Yes	0.88	0.753	1.37	0.414	1.24	0.500	2.42	0.003	2.50	0.003
Age	0.99	0.074	1.00	0.653	1.01	0.317	1.02	<0.001	1.02	0.005
CAD	1.11	0.669	1.05	0.839	1.09	0.673	1.20	0.327	1.12	0.548
CHF	1.21	0.452	1.46	0.098	1.63	0.018	1.45	0.051	1.50	0.036
COPD	1.68	0.129	1.62	0.119	1.79	0.035	1.33	0.274	1.66	0.051
CKD										
stage 0&1										
stage 2	0.80	0.426	0.68	0.116	0.73	0.149	0.63	0.019	0.63	0.021
stage 3	1.12	0.711	0.88	0.649	0.83	0.464	0.73	0.162	0.74	0.182
stage 4	0.38	0.119	1.07	0.892	1.00	0.995	1.00	0.994	1.12	0.772
Diabetes mellitus	0.84	0.485	0.81	0.338	0.94	0.758	1.06	0.756	1.00	0.991
Hypertension	0.75	0.212	0.69	0.074	0.93	0.710	0.92	0.624	0.82	0.247
BMI										
Normal weight										
Overweight	0.89	0.675	0.86	0.566	0.70	0.132	0.68	0.077	0.68	0.072
Mild obesity	0.86	0.653	0.56	0.061	0.57	0.040	0.57	0.022	0.57	0.023
Moderate obesity	0.40	0.113	0.29	0.020	0.33	0.011	0.37	0.007	0.32	0.003
Morbid obesity	1.04	0.923	0.71	0.335	0.64	0.168	0.79	0.399	0.72	0.259
Underweight	0.68	0.402	0.75	0.479	0.90	0.774	0.70	0.293	0.72	0.333
Male	0.75	0.215	0.86	0.474	0.96	0.821	1.07	0.691	1.02	0.885
Smoking	0.93	0.798	0.70	0.157	0.77	0.229	1.04	0.851	0.92	0.678
Sepsis	2.13	0.007	2.69	<0.001	2.25	0.001	1.53	0.016	1.51	0.022
SAPS II derived score	1.08	<0.001	1.07	<0.001	1.06	<0.001	1.03	<0.001	1.04	<0.001

OR, adjusted odds ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; P value for interaction between AKI and no AKI

respectively, Table 5). Figure 2 illustrates the Kaplan-Meier survival curve analysis of different stages of AKI by AKIN scoring criteria. The results were similar when RIFLE criteria were used.

Survival outcomes based on AKI and risk stratification. Patients in the high-risk cohort had higher mortality in-hospital and at 30, 90, 180, and 365 days than the low-risk cohort both before and after adjusting for multiple risk factors (Tables 6 and 7). Patients with cardiovascular failure, respiratory failure, or sepsis (the high-risk cohort) had a six fold increase in mortality in-hospital, but only a twofold increase in mortality at one year when compared to those patients who did

Table 5. Logistic regression models comparing mortality outcomes of different stages of AKI by AKIN criteria with multiple risk factors

	Hospital mortality		30 day mortality		90 day mortality		365 day mortality	
Characteristic	**OR**	**P**	**OR**	**P**	**OR**	**P**	**OR**	**P**
AKIN Stage 0 (no AKI)								
AKIN Stage 1	0.81	0.631	1.18	0.683	1.06	0.862	2.16	0.017
AKIN Stage 2	0.93	0.878	1.43	0.404	1.30	0.471	3.03	0.001
AKIN Stage 3	1.23	0.640	2.12	0.074	1.83	0.089	3.34	<0.001
Age	0.99	0.113	1.01	0.440	1.01	0.170	1.02	0.002
CAD	1.09	0.721	1.02	0.922	1.07	0.737	1.10	0.604
CHF	1.24	0.396	1.51	0.072	1.69	0.012	1.53	0.029
COPD	1.71	0.117	1.67	0.101	1.84	0.029	1.71	0.040
CKD stages								
CKD stage 0&1								
CKD stage 2	0.87	0.627	0.75	0.261	0.80	0.313	0.66	0.044
CKD stage 3	1.23	0.501	1.01	0.968	0.94	0.813	0.82	0.400
CKD stage 4	0.39	0.127	1.07	0.884	1.01	0.981	1.19	0.671
Diabetes mellitus	0.81	0.399	0.76	0.223	0.90	0.583	0.97	0.844
Hypertension	0.77	0.255	0.71	0.102	0.96	0.829	0.83	0.273
BMI								
Normal weight								
Overweight	0.87	0.647	0.85	0.529	0.69	0.121	0.67	0.064
Mild obesity	0.84	0.598	0.53	0.047	0.55	0.032	0.55	0.018
Moderate obesity	0.38	0.100	0.28	0.016	0.32	0.009	0.31	0.002
Morbid obesity	0.99	0.984	0.66	0.251	0.61	0.123	0.69	0.191
Underweight	0.64	0.333	0.68	0.346	0.83	0.615	0.65	0.215
Male	0.77	0.247	0.89	0.572	0.99	0.943	1.05	0.785
Smoking	0.93	0.796	0.70	0.157	0.77	0.243	0.92	0.682
Sepsis	2.05	0.011	2.54	<0.001	2.14	0.000	1.45	0.039
SAPS II derived score	1.08	<0.001	1.06	<0.001	1.05	<0.001	1.03	<0.001

OR, adjusted odds ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; P value for interaction between different stages of AKI by AKIN criteria.

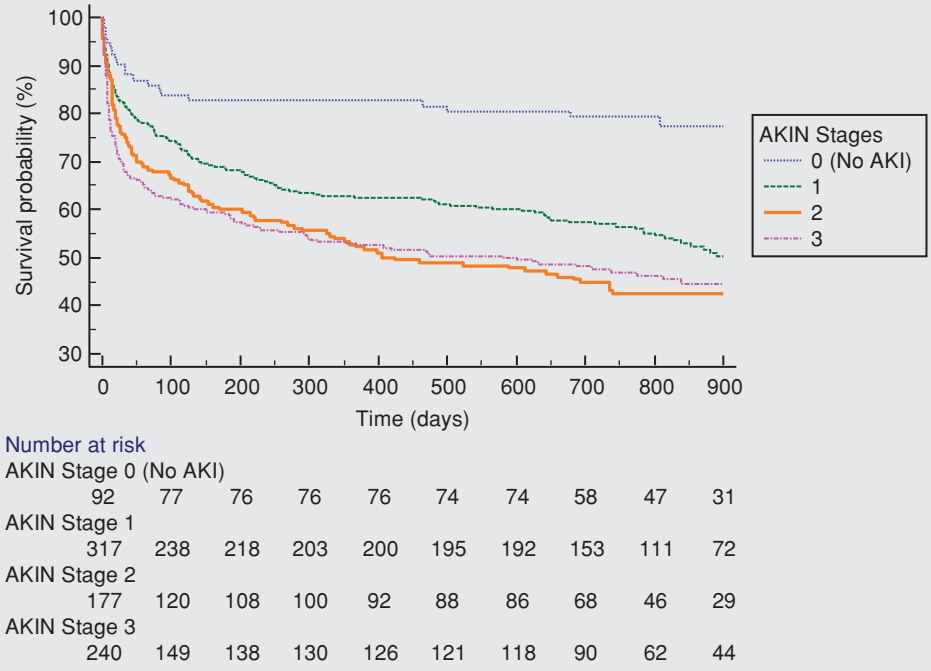

Figure 2. Kaplan-Meier survival curves for different stages of AKI by AKIN. The graph indicates the impact of the severity of AKI on survival. Notably, AKI 1 is seen to reduce survival. Details of significance are reviewed in the text and tables.

not have any of these risk factors (Table 6). Among the low-risk patient group, the presence of AKI had a significant impact on mortality (34.7% versus 15.1%) at 365 days (raw OR, 2.99; P interaction, 0.006). However, any effect of AKI on mortality for patients in the low-risk group was attenuated at the in-hospital, 30, 90, and 180 day points. The mortality rate was greater for high-risk patients with AKI than for high-risk patients without AKI at 90 days (mortality, 40.4% versus 21.1%; raw OR, 2.54; P interaction, 0.023), 180 days (mortality, 45.6% versus 23.7%; raw OR, 2.70; P interaction, 0.012), and 365 days (mortality, 50.5% versus 23.7%; raw OR, 3.29; P interactions, 0.003) as shown in Table 7.

As expected, both hospital and ICU length of stay (LOS) were longer in the high-risk cohort than in the low-risk cohort (Table 7). In the low-risk group, the mean ICU and hospital LOS were greater for patients with AKI than for patients without AKI (mean ICU LOS, 2.4 days with AKI versus 2.0 days without AKI; mean hospital LOS, 6.7 days with AKI versus 5.0 days without AKI). Similarly, but with a wider margin, there was an increase in both ICU and hospital LOS among high-risk patients with AKI compared to high-risk patients without AKI (mean ICU LOS 7.3 with AKI versus 5.3 days without AKI; mean hospital LOS 12.0 days with AKI versus 8.2 days without AKI). The impact of AKI on both ICU and hospital LOS was greater in the high-risk cohort than in the low-risk cohort (difference in mean ICU LOS, 2.0 days in high-risk cohort versus 0.4 day in low-risk cohort; difference in mean hospital LOS, 3.8 days in high-risk cohort versus 1.7 days in low-risk cohort, Table 7).

High-risk patients with AKI had the highest mortality while low-risk patients without AKI had the lowest mortality (Table 6 and Figure 3). High-risk patients without AKI had higher hospital mortality than low-risk patients with AKI (adjusted OR 3.79; 95% confidence interval, 1.22 to 11.78; P interaction 0.022) or, as presented in the Table 8, the OR for low risk plus AKI was 0.26 versus high risk without AKI. This trend reversed at about 100 days from which time low-risk patients with AKI had numerically higher mortality rates than high-risk patients without AKI (Figure 3), but this difference was no longer significant at 365 days (adjusted

Table 6. Logistic regression models comparing outcomes between low and high risks groups with multiple risk factors

	Hospital mortality		30 day mortality		90 day mortality		365 day mortality	
Characteristic	**OR**	**P**	**OR**	**P**	**OR**	**P**	**OR**	**P**
Low-risk								
High-risk	6.21	<0.001	3.27	<0.001	2.52	<0.001	1.86	<0.001
Age	1.00	0.866	1.01	0.036	1.02	0.007	1.02	<0.001
CAD	1.30	0.268	1.25	0.302	1.23	0.281	1.22	0.268
CHF	1.17	0.512	1.40	0.118	1.55	0.027	1.46	0.041
COPD	1.23	0.525	1.33	0.326	1.52	0.115	1.43	0.154
CKD								
stage 0&1								
stage 2	1.02	0.961	0.79	0.235	0.80	0.280	0.68	0.046
stage 3	1.22	0.506	0.95	0.847	0.90	0.646	0.82	0.372
stage 4	1.24	0.691	2.00	0.111	1.70	0.192	1.74	0.154
Diabetes Mellitus	0.86	0.523	0.86	0.468	0.97	0.874	1.02	0.895
Hypertension	0.68	0.072	0.67	0.036	0.88	0.481	0.82	0.236
BMI								
Normal weight								
Overweight	0.77	0.343	0.76	0.250	0.65	0.056	0.64	0.033
Mild obesity	0.69	0.231	0.47	0.010	0.50	0.007	0.50	0.003
Moderate obesity	0.23	0.010	0.19	0.002	0.24	0.001	0.26	<0.001
Morbid obesity	0.59	0.161	0.50	0.045	0.51	0.030	0.62	0.084
Underweight	0.74	0.463	0.75	0.432	0.93	0.826	0.79	0.457
Male	0.85	0.454	0.92	0.659	1.01	0.953	1.07	0.664
Smoking	0.76	0.282	0.63	0.055	0.70	0.097	0.85	0.392
Sepsis	2.03	0.006	2.62	<0.001	2.34	<0.001	1.67	0.003

OR, adjusted odds ratio; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; P value for interaction between low-risk and high-risk groups.

OR 2.0; 95% confidence interval, 0.83 to 4.85; P interaction 0.124, Table 8).

Finally, patients with mild or moderate obesity had lower mortality than patients with normal weight at 90 days (adjusted OR, 0.57; P interaction, 0.04; and adjusted OR, 0.33; P interaction, 0.01, respectively), 180 days (adjusted OR, 0.57; P interaction, 0.02; and adjusted OR, 0.37; P interaction, 0.006, respectively) and 365 days (adjusted OR, 0.57; P interaction, 0.023; and adjusted OR, 0.32; P interaction, 0.003, respectively, Table 4). Morbid obesity showed no correlation with mortality in-hospital (adjusted OR, 1.04; P interaction, 0.92), at 30 days (adjusted OR, 0.71; P interaction, 0.34), at 90 days (adjusted OR, 0.64; P interaction, 0.17), at 180 days (adjusted OR, 0.79; P interaction, 0.40), and at 365 days (adjusted OR, 0.72; P interaction, 0.26).

Table 7. Patient outcome by AKI and risk status

Characteristic	AKI+	AKI−	AKI+ versus AKI−		
			OR	95% CI	P value
Low-risk group					
Patients, *n*	357	53			
Mortality, %					
Hospital	5.60	3.77	1.51	0.34 to 6.67	0.584
30-day	13.16	5.66	2.53	0.76 to 8.43	0.132
90-day	20.17	15.09	1.42	0.64 to 3.15	0.386
180-day	27.17	15.09	2.10	0.95 to 4.61	0.065
365-day	34.73	15.09	2.99	1.37 to 6.55	0.006
Length of stay, days					
ICU, mean (± SEM)	2.4 (0.28)	2 (0.73)	N/A	0.03 to 2.37	0.044
Hospital, mean (± SEM)	6.7 (0.40)	5 (1.04)	N/A	1.09 to 4.42	0.001
High-risk group					
Patients, *n*	386	38			
Mortality, %					
Hospital	28.50	18.42	1.77	0.75 to 4.13	0.190
30-day	33.68	18.42	2.25	0.96 to 5.25	0.061
90-day	40.41	21.05	2.54	1.14 to 5.69	0.023
180-day	45.60	23.68	2.70	1.25 to 5.86	0.012
365-day	50.52	23.68	3.29	1.52 to 7.13	0.003
Length of stay (days)					
ICU, mean (± SEM)	7.3(0.27)	5.3(0.86)		2.95 to 5.28	<0.001
Hospital, mean (± SEM)	12(0.38)	8.2(1.22)		2.52 to 5.91	<0.001

OR, odds ratio; 95% CI, 95% confidence interval; p-value compares AKI− and AKI+; SEM, standard error of the mean; N/A, not applicable, P value is for the comparison of AKI− and AKI+.

Discussion

Multiple studies have evaluated the impact of AKI on mortality and defined the risk factors that contribute to the development of AKI in critically ill patients. However, very few studies have examined the impact of AKI in the absence of respiratory or cardiovascular failure on mortality or compared mortality for AKI with and without these cofactors. To our knowledge, the study done by Sileanu et al is the only study to have examined these associations.[1] Sileanu et al included only patients who developed acute kidney injury within one week of ICU admission and excluded patients with mild AKI (KDIGO stage 1) as having no AKI. This approach presumes a low impact of mild AKI on mortality and excludes patients who developed AKI prior to or at the time of ICU admission or after seven days of ICU admission. We decided to include all patients who developed AKI before and during the entire course of ICU admission and who had less severe forms of AKI (AKIN stage 1) as having AKI.

AKI was found to be an independent risk factor for mortality. Although the impact of moderate to severe AKI

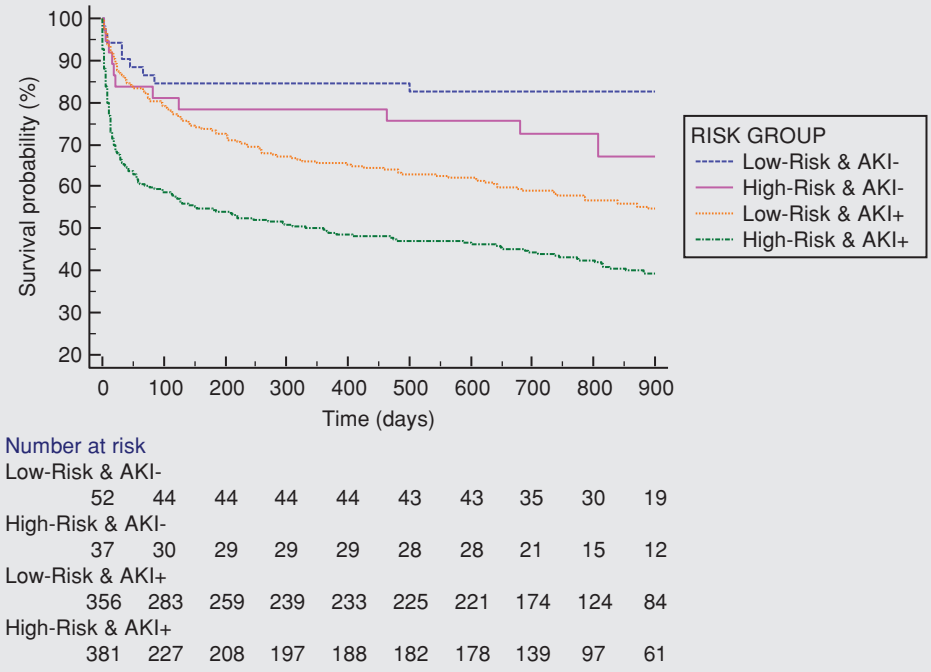

Figure 3. Kaplan Meier survival curves for low-risk and high-risk groups based on AKI stratification. The combined effects of AKI and high- and low-risk cohort status on survival are shown. The impact of risk cohort and AKI status seem to be additive. Details of statistics are in the text and tables.

(AKIN 2 and AKIN 3) on mortality became statistically significant from 180 days, mild AKI (AKIN stage 1) also had statistically significant impact on mortality at 365 days. This underscores the importance of using measures aimed at preventing even the mildest form of AKI (AKIN 1) in the intensive care unit, because failure to do so doubles the odds of death at one year (Table 5).

Despite major differences in study design between our study and Sileanu's study[1], we also found a trend toward higher mortality among patients in the low-risk group who have AKI compared to patients in the high-risk group who did not have AKI. This developed about 100 days after the ICU admission, but the difference did not reach statistical significance (Figure 3). As might be expected, patients in the high-risk cohort without AKI had statistically significant higher in-hospital mortality than the low-risk cohort with AKI, but this trend reversed after 100 days as discussed earlier (Figure 3). This finding differs from the observations of Sileanu et al that showed increased in-hospital mortality among the low-risk group with AKI compared to the high-risk group without AKI. Perhaps if we had excluded the patients who had mild AKI, we may have arrived at the same result.

The inclusion of patients with increases in creatinine fitting AKI stage one criteria notably resulted in an extreme incidence of AKI, approximately 90%, in among both high- and low-risk groups in our patient population. Why this occurred is not clear, but possible explanations include the exclusion of individuals with primary cardiac diagnoses, such as unstable angina and post-operative cases who might otherwise be medically stable, and the application of stringent, but undefined, admission criteria. Notably, the incidence of AKI and the mortality rate were similarly increased.

While odds of death due to respiratory or cardiovascular failure decreased over time (Table 6), the odds of death due to AKI increased over time (Table 4). From this observation, one might infer that the greatest impact of AKI on mortality is long term while acute respiratory or acute cardiovascular failure has its greatest impact on short term mortality. The impact of AKI on ICU and hospital length of stay was greater among the high-risk group compared to the

Table 8. Logistic regression models comparing mortality outcomes of patients in low-risk group with AKI versus patients in high-risk group without AKI

Characteristic	Hospital mortality			365 day mortality		
	OR	95% CI	P	OR	95% CI	P
LR & AKI+ versus HR & AKI−	0.26	0.09 to 0.82	0.022	2.00	0.83 to 4.85	0.124
Age	1.03	1.00 to 1.06	0.068	1.04	1.02 to 1.06	<0.001
CAD	1.69	0.61 to 4.66	0.312	0.90	0.51 to 1.58	0.719
CHF	0.68	0.22 to 2.08	0.494	1.72	0.95 to 3.11	0.074
CKD						
Stage 0&1						
Stage 2	0.80	0.30 to 2.17	0.664	0.58	0.31 to 1.06	0.077
Stage 3	0.19	0.05 to 0.79	0.023	0.72	0.37 to 1.40	0.334
Stage 4	0.45	0.05 to 4.33	0.489	1.63	0.56 to 4.75	0.370
COPD	2.74	0.76 to 9.87	0.124	1.36	0.59 to 3.12	0.467
DM	0.45	0.15 to 1.32	0.145	0.76	0.46 to 1.27	0.297
Hypertension	0.47	0.18 to 1.18	0.106	0.88	0.53 to 1.46	0.617
BMI						
Normal weight						
Overweight	0.41	0.12 to 1.35	0.142	0.67	0.36 to 1.25	0.205
Mild obesity	0.70	0.19 to 2.60	0.590	0.67	0.33 to 1.37	0.270
Moderate obesity	0.40	0.03 to 4.63	0.463	0.51	0.16 to 1.64	0.258
Morbid obesity	0.92	0.19 to 4.34	0.913	0.72	0.31 to 1.66	0.439
Underweight	0.92	0.17 to 5.09	0.927	0.34	0.11 to 1.05	0.061
Male	0.72	0.30 to 1.77	0.476	1.18	0.71 to 1.95	0.525
Smoking	0.73	0.24 to 2.24	0.582	1.58	0.86 to 2.90	0.142
Sepsis	3.62	1.25 to 10.5	0.018	1.39	0.86 to 2.27	0.181

OR, adjusted odds ratio; LR, low-risk; HR, high-risk; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; P value for interaction between risk group and AKI

low-risk group; again this finding contrasts that found by Sileanu et al.[1]

Given the effect of acute kidney injury on mortality, most authors have advocated strategies aimed at predicting and preventing the development of AKI. These measures are highlighted by the KDIGO AKI work group.[2] In addition, several biochemical parameters, including Cystatin C and Kidney Injury Molecule 1 (KIM-1), may provide biomarkers that accurately predict the development of AKI prior to a rise in creatinine. Biomarkers that have shown some promise in recent studies include the product of [TIMP-2] and [IGFBP-7] and KIM-1.[7,8] Neutrophil gelatinase associated lipocalin (NGAL), interleukin 18, tissue inhibitor metalloproteinase 2 (TIMP-2), neutrophil elastase 2, insulin growth factor binding protein 7 (IGFBP-7), and liver type fatty acid binding protein (L-FABP) are currently being evaluated in the evolution of AKI. Some authors have advocated electronic alert systems to

promptly identify patients with AKI.[9] Currently, the serum creatinine still remains the test used for GFR estimation during evolution of AKI.

There has been a recent controversy on the effect of obesity on mortality outcomes of patients admitted to the intensive care unit. In a recent meta-analysis by Akinnusi et al, a subgroup analysis comparing the outcomes in obese (BMI 30 to 39.9 kg/m^2) and non-obese (BMI < 30 kg/m^2) critically ill patients in intensive care units found improved survival among obese patients when compared to non-obese patients.[10] Oliveros et al also showed improved survival among obese (BMI 30 to 39.9 kg/m^2) critically ill patients compared to patients with normal BMI (18.5 to 24.9 kg/m^2), but there was no correlation between morbid obesity (BMI ≥ 40 kg/m^2) and mortality.[11] Our study also reveals an apparent protective effect of mild and moderate obesity on mortality compared to normal weight at 90, 180 and 365 days (Table 4). These results are similar to those reported by Akinnusi et al and Olivaros et al.[10,11] Conversely, we found no association between mortality and morbid obesity among critically ill-patients admitted to the intensive care setting, similar to the results found by Oliveros et al.[11] Although the pathophysiology of the protective role of mild and moderate obesity, but not morbid obesity, on mortality in critically ill patients admitted to the intensive care units have not been fully explained, increased adipose tissue stores during high catabolic states may have a beneficial role. Several authors have postulated that the adipocyte-secreted hormones leptin and interleukin-10 have immune-modulatory properties that might decrease inflammatory response and improve survival.[10] However, this does not explain why morbid obesity does not have a similar protective effect on mortality. Perhaps the threshold BMI of 39.9 kg/m^2 is critical, above which the risk of death associated with the high comorbidities and complications due to morbid obesity outweighs the protective effects of high adipose tissue on mortality. Further studies will be needed to test this hypothesis.

Conclusion

Our study confirms that AKI is an independent risk factor for long term mortality. Cardiovascular collapse and respiratory failure have greater impact on short term mortality than AKI, but the effect of these two factors diminishes over time, whereas the association of AKI with mortality persists. These data also provide evidence that low-risk patients with AKI have worse survival outcomes over time than high-risk patients without AKI. The absence of cardiovascular or respiratory failure should therefore not exclude ICU patients from strategies and interventions aimed at preventing AKI. The importance of this recommendation is based on the impact of AKI on survival even in low-risk patients. Finally, in this study as in other prior publications, mild and moderate obesity had a protective effect on survival in critically ill patients admitted to the medical ICU. Although counterintuitive, if only the known effects of obesity on survival in the general population are considered, this result might reflect the benefit of nutritional reserves during the stress of an ICU hospitallization.

Article citation: Anaele CU, Suarez G, Kennedy-Prieto S, Bashir M, Laski M, Yang S. Acute kidney injury patterns and outcomes in low-risk versus high-risk critically ill patients admitted to the medical intensive care unit. The Southwest Respiratory and Critical Care Chronicles 2017;5(17):17-31.
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Submitted: 9/7/2016
Accepted: 1/10/2017
Reviewers: Vaqar Ahmed MD, Kenneth Nugent MD
Conflicts of interest: none

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