

Outcome of Acute Kidney Injury in Critical Care Unit, Based on AKI Network

Seyed Mohammadreza Hashemian¹,
Hamidreza Jamaati², Behrooz Farzanegan
Bidgoli¹, Farin Rashid Farrokhi³, Majid
Malekmohammad⁴, Sepehr Roozdar¹,
Seyed Amir Mohajerani¹, Ahmad Bagheri¹,
Golnar Radmnand¹, Behzad Hatami¹,
Mandana Chitsazan¹

¹Chronic Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, ²Tobacco Prevention and Control Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ³Telemedicine Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, ⁴Tracheal Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Correspondence to: Roozdar S

Address: Chronic Respiratory Disease Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Email address: roozdars@gmail.com

INTRODUCTION

Acute Kidney Injury continues to remain a significant problem in hospitalized patients and has a high mortality rate. Furthermore, the incidence of AKI continues to increase and currently there is no definitive therapy for it (1). It is a complex functional or structural disorder, which occurs abruptly, usually within 48 hours of hospitalization and is defined as a sudden onset of reduced kidney function (2). Previous studies highlight the importance of early recognition of AKI as well as the association of AKI

Background: Acute Kidney Injury (AKI) is an unsolved clinical problem in critical care patients with a high mortality rate, increasing incidence, and no definitive therapy. We studied the incidence, risk factors, and mortality associated with AKI in ICU patients.

Materials and Methods: In a prospective study, patient demographics, reason for hospitalization, reason for ICU admission, Length of ICU stay, laboratory data, and Vital signs were recorded in prepared forms during the ICU stay. AKI was defined as an increase in serum creatinine (SCr) of $\geq 0.3\text{mg/dl}$ from the baseline.

Results: A total of 200 patients who were enrolled in our study; 134 (67%) did not develop AKI during their ICU stay while 66 (33%) developed AKI (SCr ≥ 0.3) according to the AKIN definition. Patients with AKI had higher APACHE II scores (12.3 ± 5.6 vs. 6.9 ± 3.6 ; $P < 0.001$), longer ICU stays (7.6 ± 7.6 vs. 3.7 ± 2.8 days respectively; $P < 0.001$), and higher mortality (19.7% vs. 0.7%; $P < 0.001$).

Conclusion: The AKIN criteria are clinically valid and can be a good predictor of mortality and patient outcome in addition to APACHE II score in ICU patients.

Key words: Acute kidney injury, Intensive care unit, Glomerular filtration rate

with increased mortality in hospitalized patients (3). The clinical spectrum of AKI ranges from slight elevations in serum creatinine to anuric renal failure. Acute kidney injury causes disturbances in fluid balance, electrolytes, and acid-base status due to decreased solute clearance and decreased glomerular filtration rate (GFR) (urine < 0.5 ml/kg/hr for > 6 hrs). In critically ill patients the dilution of SCr by fluid accumulation may lead to underestimation of the severity of AKI and delayed diagnosis of AKI (4).

Oliguria is common in ICU patients and might be better in identifying patients with AKI compared to serum creatinine criterion (5). There is an association between AKI and patient outcomes. However, associated organ failure had a greater impact on prognosis than severity of AKI (6). 5-7% of the hospitalized patients and 30% of ICU patients develop AKI (7). Although risk factors for AKI are not fully understood, it has severe consequences (8). The reported mortality rate associated with AKI is 20-90%, which has not changed significantly over the last 15 years. Mortality rate depends on the patient's general condition, age, and the severity of illness. Among patients who are admitted to the ICU because of AKI, older patients experience higher rates of AKI. There used to be no uniform definition of AKI in the literature until the Acute Kidney Injury Network (AKIN) developed a new definition based on scientific investigation (9). As minor increases in serum creatinine ($\geq 0.3\text{mg/dl}$) are associated with increased mortality, AKIN chose changes in SCr as the basis of their definition of AKI (10). Besides mortality, AKI increases other morbidities, which are associated with increased costs (11), increased length of hospital stay (12,13), and increased risk of developing chronic kidney disease (CKD), including end-stage kidney disease (14-17).

Despite available evidence about the impact of AKI on morbidity and mortality, there are inadequate data on epidemiology and outcomes associated with AKI in different parts of the world. Besides, the definition of AKI needs to be validated in order to accurately predict patient outcome. As more studies are conducted our understanding of the disease, its risk factors, and associated mortality will improve. In the current study we investigated the incidence, risk factors, and mortality associated with AKI in the ICU population.

MATERIALS AND METHODS

Study Design

We conducted a prospective observational study from Feb 2010 to Aug 2010 in our tertiary referral center. All study protocols were reviewed and approved by the

institutional ethics committee of National Research Institute of Tuberculosis and Lung diseases (NRITLD), Shahid Beheshti University of Medical Sciences. Informed consent was obtained from patients or their legal surrogates and all patient information were kept confidential. Patient demographics, reason for hospital admission, reason for ICU admission, length of ICU stay, laboratory data, and vital signs were recorded during their ICU stay. Vital signs included heart rate, respiratory rate, blood pressure, and Glasgow Coma Scale score.

Datasheets were completed by a physician who was blinded to the study to reduce the possibility of bias. Statistical analysis was carried out by a statistician who was blinded to the study design as well. Daily visits were carried out by attending intensivists. All physical examinations prior to admission and during the ICU stay were performed by the attending intensivist. As comorbidities are important in predicting mortality, all comorbidities including cardiovascular diseases, gout, cirrhosis, glomerulonephritis or any other kidney disease such as chronic kidney disease were recorded. Other conditions which could potentially predispose patients to kidney injury, such as hemorrhage, diarrhea, vomiting, hyperthermia or fever, and administration of nephrotoxic agents were recorded. We adjusted drug doses based on the patients' kidney function. The amount of urine produced by each patient was measured hourly. Laboratory tests including electrolytes, blood urea nitrogen and serum creatinine were measured at baseline (before admission), at 6 AM every day during ICU stay, when AKI was diagnosed, and at 24 and 48 hours after AKI was diagnosed. The ability of AKIN criteria for predicting hospital mortality was compared to that of the APACHE II score, age, and multi-organ failure.

Patient Selection

Acute kidney injury was defined as an increase in serum creatinine (SCr) of $\geq 0.3\text{mg/dl}$ from the baseline. The lowest value of SCr during the ICU stay or within 24 hours before admission was considered the baseline SCr. Patients were categorized into two groups: AKI and Non-

AKI. The patients in the AKI group had an increase in SCr of ≥ 0.3 mg/dL during their ICU stay as previously specified. Intensive care unit mortality, length of ICU stay, and renal replacement therapy (RRT) use were compared between the two groups.

Statistical analysis

Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL). All continuous data are presented as mean \pm SD. Student's t-test was applied to compare normally distributed means. Chi-squared or Fisher's exact tests were used to compare discrete variables. Univariate logistic regression was used in order to demonstrate AKI as an independent predictor of hospital mortality. Multivariate analysis was performed in order to evaluate the predictive value of variables on mortality and LOS. The cut-off point for LOS was 5 days (the 75% percentile of all LOS). The means of continuous independent variables were used as cut-off points in logistic regression analysis. Variables with significant association to patient outcomes in univariate analysis were used in the regression analysis. Maximizing the Youden index was also used to find the best cut-off points for age and APACHE II score in comparison of predictors. A P-value < 0.05 was considered statistically significant.

RESULTS

Of the 200 patients who were enrolled in our study 66 (33%) developed AKI according to the AKIN definition (SCr increase ≥ 0.3). The mean age of the patients in the non-AKI group, and that of the patients in the AKI group were 43.9 ± 18.7 and 54.5 ± 19.1 years, respectively ($p < 0.001$). Seventy-six (56.7%) patients in the non-AKI group and 38 (57.6%) in the AKI group were men. Patient demographic data, diagnoses, and referring services are shown in tables 1 and 2. Patients who developed AKI had higher APACHE II scores (12.3 ± 5.6 vs. 6.9 ± 3.6 ; $P < 0.001$), longer ICU stays (7.6 ± 7.6 vs. 3.7 ± 2.8 days respectively; $P < 0.001$), and higher mortality rates (19.7% vs. 0.7% ; $P < 0.001$). Mortality rate in patients with AKI was 13 times higher than that of those

who did not develop AKI. Also the number of days on mechanical ventilation, duration of vasoactive drug infusions, and duration of dobutamine infusion were longer in the patients who developed AKI compared to those who did not develop AKI. ($P < 0.001$; $P = 0.007$). Serum creatinine clearance before admission to ICU was 0.91 ± 0.26 in the non-AKI patients and 0.93 ± 0.3 in those who developed AKI ($P = 0.654$). APACHE II scores were significantly different between the two groups (6.86 ± 3.6 in non-AKI vs. 12.3 ± 5.6 in AKI; $P < 0.001$). Acute kidney injury was a significant predictor of mortality after adjusting for other comorbidities in the multivariate logistic regression. Our data revealed that AKI patients had a higher rate of complications (54% vs. 23%; $P = 0.012$) and multi organ failure (43% vs. 12%; $P = 0.031$) (Tables 3 and 4).

Age, APACHE II score, AKI, and dobutamine use were independent predictors of mortality. Development of AKI was the strongest predictor of mortality after adjusting for all other variables in the multiple logistic regression analysis (OR adjusted=14.8; 95%CI: 1.8-121.98) and had the same sensitivity as APACHE II score for predicting mortality (Sensitivity = 0.93). Median length of ICU stay was 5 days for the AKI group and 3 days for the non-AKI group ($p = 0.001$).

We did not find a significant difference between LOS in dead and alive patients in the AKI group. Multivariate logistic regression analysis showed that AKI is a powerful predictor of LOS. Acute kidney injury, defined according to the AKIN criteria, can predict mortality with 71% specificity and 93% sensitivity. APACHE II score can predict ICU mortality with 75% specificity and 93% sensitivity, while age and dobutamine use had a lower sensitivities (0.57 vs. 0.21) compared to those of AKI and APACHE II score. AKIN criteria and APACHE II score are equally good predictors of ICU mortality. Youden index for these two criteria are 0.64 and 0.68 respectively. Youden index for age and dobutamine use are 0.21 and 0.18, respectively, which are considered weak.

Table 1. Patient demographic and clinical characteristics of patients with AKI vs. those who did not develop AKI. Relative risk of mortality stratified across demographic and clinical variables.

	Total	Non-AKI	AKI	RR	95% CI	P Value
Frequency, n(%)	200(100)	134(67)	66(33)			NA
Age, yrs						
Mean ± SD	47.42±19.4	43.9±18.7	54.5±19.1	2.4	1.3-3.88	<0.0001
Median (IQR)	49(30.25-64)	45(26-60)	58(44.7-70.25)			<0.0001
Gender						
Male, n(%)	114(57)	76(56.7)	38(57.6)	2.7	0.9-4.7	0.908
Female, n(%)	86(43)	58(43.3)	28(42.4)	1.5	0.5-3.3	0.908
APACHE II						
Mean ± SD	8.65±5.02	6.86±3.6	12.3±5.6	7.2	3.49-25.6	<0.0001
Median (IQR)	8(5-11.75)	7(4-9)	12(8-17)			<0.0001
First SCr						
Mean ± SD	0.914±0.28	0.91±0.26	0.93±0.3	2.7	1.1-3.8	0.654
Median (IQR)	0.9(0.7-1.1)	0.9(0.77-1.1)	0.8(0.7-1.2)			0.960
LOS						
Mean ± SD	5±5.2	3.7±2.8	7.6±7.6	1.76	0.9-2.8	<0.0001
Median (IQR)	3(2-5)	3(2-4)	5(3-8.25)			<0.0001
MVD						
Mean ± SD	1.31±3.6	0.38±1.1	3.2±5.6	2.28	0.88-3.95	<0.0001
Median (IQR)	0(0-1)	0(0-0)	1(0-3.25)			<0.0001
Time of vasoactives						
Mean ± SD	0.37±1.2	0.14±0.6	0.82±1.9	1.23	0.7-1.67	0.007
Median (IQR)	0(0-0)	0(0-0)	0(0-1)			<0.0001
Dobutamin n (%)	9(4.5)	2(1.5)	7(10.6)	3.45	1.7-5.45	0.007
Mortality n (%)	14(7)	1(0.7)	13(19.7)			<0.0001

AKI: acute kidney injury; APACHE: Acute Physiology and Chronic Health Evaluation; SCr: Serum Creatinine; LOS: Length of Stay; MVD: Mechanical Ventilation Duration.

Table 2. Main diagnosis for hospitalization and the referring services in AKI and Non-AKI groups

Diagnosis	Total	Non-AKI	AKI
COPD	19(9.5)	9(6.7)	10(15.2)
Empyema	5(2.5)	3(2.2)	2(3)
Pulmonary emboli	13(6.5)	10(7.5)	3(4.5)
Hemothorax/pneumothorax	3(1.5)	3(2.2)	0(0)
Sleep apnea	3(1.5)	2(1.5)	1(1.5)
CABG	27(13.5)	14(10.4)	13(19.7)
PNET	1(0.5)	1(0.7)	0(0)
MVR	6(3)	2(1.5)	4(6.1)
Hydatid cyst	22(11)	20(14.9)	2(3)
Pneumonia	7(3.5)	1(0.7)	6(9.1)
Mesothelioma	3(1.5)	3(2.2)	0(0)
Tracheal Stenosis	25(12.5)	22(16.4)	3(4.5)
Hemoptysis	7(3.5)	6(4.5)	1(1.5)
TB	5(2.5)	3(2.2)	2(3)
Esophageal Problem	3(1.5)	2(1.5)	1(1.5)
Cancer	12(6)	7(5.2)	5(7.6)
Asthma	1(0.5)	1(0.7)	0(0)
Tumors	13(6.5)	10(7.5)	3(4.5)
Others	25(12.5)	15(11.2)	10(15.2)
Referrer groups			
Internal	59(29.5)	30(22.4)	29(43.9)
Surgery	102(51)	84(62.7)	18(27.3)
Heart Surgery	39(19.5)	20(14.9)	19(28.8)

PNET: Primitive neuroectodermal tumors, MVR: Mitral valve regurgitation, TB: Tuberculosis; CABG: Coronary artery bypass graft

Table 3. Predictors of ICU mortality and length of stay in patients with AKI - Univariate and Multivariate Analysis

Predictors	Mortality		LOS	
	Relative risk	95%CI	Relative risk	95% CI
Univariate analysis				
Age >48	1.58	0.51-4.899	2.508	1.351-4.656
APACHE > 9	27.3	3.49-213.56	1.866	1.020-3.412
AKI	32.6	4.16-255.6	3.987	2.125-7.481
Dobutamin	8.182	1.801-37.174	4.262	1.031-17.614
Multivariate Logistic Regression				Standard error
APACHE > 9	12.7	1.53-104.9	0.8	0.742
AKI	14.8	1.8-121.98	1.21	0.808
Dobutamin	3.412	0.591-19.7	3.28	0.796

CI, confidence interval; AKI, Acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4. Comparative Predictors of Mortality

	Total	Mortality%	Sensitivity	Specificity	Youden Index ^a	PPV	NPV	Accuracy ^b
Age≥55.5	76	10%	0.57	0.63	0.21	0.10	0.95	0.63
APACHE ≥10.5	59	22%	0.93	0.75	0.68	0.22	0.99	0.76
AKI	66	20%	0.93	0.71	0.64	0.20	0.99	0.73
Dobutamin	9	33%	0.21	0.97	0.18	0.33	0.94	0.90

PPV, Positive predictive value; NPV, Negative predictive value; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, Acute Kidney Injury.

^aYouden index = sensitivity+Specificity – 1 ; ^baccuracy = (true results/ all results)

DISCUSSION

The purpose of this study was to investigate the outcomes associated with AKI in ICU patients and to determine the predictors of mortality in patients who develop AKI during their ICU stay in a prospective observational study, using the AKIN criteria to diagnose AKI. Oliguria lasting for more than 12 hours and ≥ 3 more episodes of oliguria are associated with increased mortality and are sensitive markers for AKI and are associated with adverse outcomes in ICU patients (18). Previously RIFLE criteria were used to diagnose kidney injury (19). However, newer evidence suggests that smaller rises in SCr (≥ 0.3 mg/dL) should be used to diagnose kidney injury (20). A simplified definition of AKI which uses elevations in SCr is more helpful and advantageous than hourly measurements urine output and is able to predict patient outcomes more accurately.

Our findings show that patients who have met the AKIN criteria for AKI had higher ICU morbidity and mortality. In addition, patients who developed AKI had significantly longer hospital stays and required RRT more than those who did not develop AKI. Using other definitions for acute renal failure, previous studies have demonstrated that mortality and hospital length of stay was significantly higher in patients who developed acute renal failure during their ICU stay (19, 21). These investigators used different diagnostic criteria and definitions for AKI (more than 20 different definitions) and found incidence of AKI to be more than 50% in ICU patients. In those studies RRT was an accurate predictor. Patients who needed RRT had longer hospital stays and higher mortality (50%>70%). In our study, average ICU mortality during the study period was 7% but this rate was 19.8% in patients who developed AKI. Barrantes et al. (9)

and Uchino et al. (14) found higher mortality rates in their studies (39% and 60% respectively). Barrantes et al. (9) used the AKIN criteria while Uchino et al. used different criteria to diagnose AKI; they defined acute renal failure as need for RRT, BUN > 84 mg/dL, or a decrease in urine output (<200 ml/12 hrs). Both studies had a greater sample size compared to our study. Comparing our results with those from other studies that used different criteria is difficult and emphasizes the need for a uniform definition for AKI, which can accurately predict patient outcomes. The relationship between AKI and mortality in ICU was significant in our study (odds ratio 3.99; 95% CI 2.125-7.481), which is consistent with findings from other studies (22). We found a strong association between AKI and mortality with a high sensitivity (93%), while Barrantes et al. reported a lower sensitivity (56%). This disagreement may be the result of different study designs (prospective vs. retrospective). Similar to our findings, Barrantes et al. reported 77% specificity (71% in our study). This yielded a Youden index of 0.64 for our study in comparison to a Youden index of 0.33 in Barrantes's study. High sensitivity and specificity, as well as high Youden index make AKIN criteria for AKI highly predictive of ICU mortality.

Our study had several limitations including small sample size from a single center, even though we tried to include a broad range of ICU patients (post surgical patients, patients with coronary disease, and those with respiratory complications, etc.) as detailed in Table 2. Moreover, we excluded patients with pre-existing kidney complications. Additionally, we selected patients with normal baseline SCr. It is unclear whether baseline SCr levels affect patient outcomes or not.

In conclusion, we investigated AKIN criteria for AKI as predictor of ICU mortality and demonstrated that AKIN criteria is clinically valid and can be a good predictor of mortality and patient outcomes in addition to APACHE II score in ICU patients. Future studies with larger sample sizes are needed to confirm our findings and validate

AKIN criteria for AKI. These indexes help patients at risk of AKI receive closer attention and perhaps have better outcomes.

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