MODIFIED KDIGO FOR PREDICTING MORTALITY IN ICU PATIENTS RECEIVING CONTINUOUS RENAL REPLACEMENT THERAPY FOR ACUTE RENAL FAILURE: KDIGO-URINARY OUTPUT VS. KDIGO-SERUM CREATININE LEVEL

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ABSTRACT

Introduction: *Acute Renal Injury (ARI) is a constant problem for patients in intensive care and Continuous Renal Replacement Therapy (CRRT) is an ever-more important part of acute renal injury (ARI) treatment. Various criteria have been used for the diagnosis and classification of acute renal failure, including RIFLE (Risk-Injury-Failure-Loss-End stage), AKIN (Acute Kidney Injury Network) and most recently KDIGO (Kidney Disease: Improving Global Outcomes). Many studies have only evaluated urinary output or serum creatinine when categorizing ARI. Our aim was to determine the predictors of mortality in intensive care patients treated with CRRT and to compare mortality with ARI level as determined by KDIGO-Serum Creatinine (KDIGO-SCr) and KDIGO-urinary output (KDIGO-UO)*

Materials and methods*: This retrospective study was performed on intensive care patients receiving CRRT at our institute between January 2010-December 2011. Patient files were reviewed and demographic data, hospitalization time, laboratory findings, CRRT commencement and ARI levels were noted.*

Results*: Seventy patients were included in the study. Mortality was found to be associated with patients' age, Glascow Coma Scale (GCS) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score and adjusted predicted death rate. (p<0,01). Receiver Operating Curve (ROC) area under the curve was statistically significant for determination of mortality using KDIGO-SCR (p<0.01) although the same was not true for KDIGO-UO (p>0.05).*

Conclusions*: We believe that RIFLE, AKIN, KDIGO criteria are each good predictors of mortality. In the case of KDIGO criteria, based solely on serum creatinine or urinary output, KDIGO-SCr was found to be a better predictor of mortality when compared to KDIGO-UO.*

Key words*: KDİGO, Acute Renal Injury, Critical Care, Creatinine.*

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Introduction

Acute Renal Injury (ARI) is a constant problem for patients in intensive care and Continuous Renal Replacement Therapy (CRRT) is an ever-more important part of ARI treatment[1-3]. Despite continuing discussion on the choice of patients and timing of treatment, many authors have reported decreasing mortality with early CRRT[2-5].

Classification systems have been used to define early or late CRRT, while some authors have used serum creatinine, serum urea, urinary output and blood potassium levels[3, 4, 6, 7]. Despite numerous studies, there is no absolute and widely-accepted definition for early or late CCRT[3, 4, 6-8].

Various criteria have been used for the diagnosis and classification of acute renal failure, including RIFLE (Risk-Injury-Failure-Loss-End stage),

AKIN (Acute Kidney Injury Network) and most recently KDIGO (Kidney Disease: Improving Global Outcomes). RIFLE and AKIN have more frequently been utilized for patients requiring renal replacement therapy in intensive care settings[9-12]. Glomerular filtration rate (GFR), basal serum creatinine levels and urinary output are criteria used for diagnosing ARI in RIFLE; contrariwise, GFR is not utilized in KDIGO or AKIN, which use serum creatinine and urinary output.

The diagnosis of ARI by KDIGO is defined as an ≥0.3 mg/dl increase in serum creatinine levels within the last 48 hours or known/estimated increase in serum creatinine of ≥1.5 times in the last 7 days or urinary output <0.5 ml/kg/hour during the last 6 hours[13]. Definition and classification of AKI by KDIGO is shown at Table 1.

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline	<0.5 ml/kg/h for 6–12 hours
	OR	
	≥0.3 mg/dl (≥26.5 mmol/l) increase	
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 hours
3	3.0 times baseline	<0.3 ml/kg/h for ≥24 hours
	OR	OR
	Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l)	Anuria for ≥12 hours
	OR	
	Initiation of renal replacement therapy	
	OR,	
	In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m2	

Table 1: Staging of AKI by KDİGO[13].

Many studies have only evaluated urinary output or serum creatinine when categorizing RIFLE as urinary output can be effected by multiple factors in ICU patients. Other studies have also investigated the superiority of using urinary output and serum creatinine levels for predicting mortality[14-20]. To our knowledge, there is no study comparing the use of KDIGO-UO and KDIGO-SCr as separate classifications.

In this study, we compared KDIGO-UO and KDIGO-SCr as predictors of mortality.

Materials and methods

This retrospective study was performed between January 2010 and December 2011 at a tertiary intensive care center. Using our institute's Intensive Care Unit patient database, which includes all patient demographic and medical data, we analyzed the data of patients who had received Continuous Veno-Venous Hemofiltration for ARI at least once. Patients with terminal stage malignancy, burns ≥ 2nd degree in more than 50% of body and those readmitted to ICU were excluded due to an increased rate of mortality. Patients in ICU for less than 24 hours were excluded due to short ICU stay and patients under 18 years of age were excluded from the study (n=14) as ARI is evaluated differently in children than in adults.

Records of patients were retrospectively reviewed and the following were noted as factors effecting mortality and/or acute renal failure: age, gender, history of chronic illness, patients' diagnosis, Glasgow Coma Scale at admission, APACHE II score within first 24 hours, length of ICU stay, ICU discharge or exitus status, ICU admission laboratory levels (arterial blood gasses, albumin, creatinine, urea, hematocrit, potassium) and average arterial pressure. Patients' adjusted predicted death rates were calculated from http://www.sfar.org/scores2/apache22.html. APDR.

For CRRT, day of commencement or therapy and number of treatments were noted. Patients' worst creatinine levels and hourly urine outputs were compared with RIFLE, AKIN and KDIGO severity stages. KDIGO was calculated using urinary output and serum creatinine levels separately (KDIGO-UO and KDIGO-SCr). It should be noted that patients who started on CRRT will fall into stage 3 KDIGO classification automatically. However, we defined the ARI classification for our study based on patients' pre-CRRT clinical evaluation as reported previously[17,19,20].

The local ethics committee (Kartal Dr. Lutfi Kırdar Education & Research Hospital Ethics Committee) confirmed that Research and Ethics approval was not required for this study, as all data was collected retrospectively. The need for informed consent was also waived because the study required neither an intervention nor breach of privacy or anonymity.

Statistical analysis

When evaluating the findings obtained in this study, statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows 15.0 software (SPSS Inc, Chicago, USA). When evaluating the data, in addition to descriptive statistical methods (mean, standard deviation), for quantitative data with parameters showing normal distribution Student t test was used for comparison between two groups, whereas for parameters not showing normal distribution the Mann Whitney U test was used. In the comparison of qualitative data Chi-Square test, Fisher's Exact test and Continuity Correction (Yates) was used. For KDIGO-SCr and KDIGO-UO ROC analysis was performed. Significance was evaluated at p <0.05 level.

Results

Demographic data

Seventy patients, aged between 21 to 91 years, undergoing CRRT due to ARI in ICU were included in the study. Patients' average age was 57.04±20.82 years. There were 27 females and 43 males. While 72.9% of patients died in ICU (n=51), 27.1% (n=19) were discharged. The Adjusted predicted death rates calculated through APACHE II scores were between 11.9% - 99.6% and averaged 69.95%±23.36%. ICU stays lasted from 2-51 days and the average stay was 11.96±10.59 days.

Indications for intensive care admittance was electrical burns in 5, cardiopulmonary insufficiency in 19, neurological disease in 12, post abdominal surgery in 4, sepsis in 8, trauma in 8 and burns (20-50%) in 14 patients. There were 38 patients with chronic diseases (32 with diabetes mellitus, 9 with chronic obstructive pulmonary disease, 17 hypertension and 4 with congestive heart disease).

Mortality

General Assessment of Mortality (Table 2): The average age, GCS score, GCS groups, APACHE II scores, APACHE II groups and Adjusted Predicted Death Rate (APDR) averages were statistically higher in the deceased patients when compared to those transferred to a ward (p<0.01). Evaluation of mortality and ARI (Tables 3-4, Figure 1): There was a statistically significant difference between AKIN, RIFLE, KDIGO-SCr and KDIGO stages (p<0.01). There was no statistically significant correlation between KDIGO-UO and mortality (p>0.05).

		Ward Transfer	Exitus	
		Ave±SD (median)	Ave±SD (median)	P
Age (years)		41,42±16,16	62,86±19,41	[1]**0,001****
ICU Hospitalization (day)		14,47±9,43 (13)	11,01±10,94 (7)	[2]**0,059**
Albumin		2,97±0,75 (3,06)	2,62±0,68 (2,56)	[2]**0,091**
APACHE-II		15,95±7,15 (16)	32,59±8,23 (33)	[2]**0,001****
APDR %		40,37±18,42(38,1)	80,97±13,19(81)	[2]**0,001****
GCS		13,16±2,52 (15)	7,57±3,80 (8)	[2]**0,001****
		n (%)	**n (%)**	
Gender	**Female**	5 (%26,3)	22 (%43,1)	[3]**0,313**
	Male	14 (%73,7)	29 (%56,9)	
APACHE-II	**< 20**	13 (%68,4)	1 (%2)	[4]**0,001****
	20-30	6 (%31,6)	20 (%39,2)	
	≥ 30	0 (%0)	30 (%58,8)	
GCS	**< 6**	0 (%0)	17 (%33,3)	[4]0,001**
	9-Jun	4 (%21,1)	21 (%41,2)	
	> 9	15 (%78,9)	13 (%25,5)	
Albumin	**0-2.49**	5 (%27,8)	22 (%43,1)	[3]**0,386**
	≥ 2.5	13 (%72,2)	29 (%56,9)	

Table 2: Patient demographics, CRRT application and mortality.
*[1]Student t test; [2]Mann-Whitney U test; [3]Continuity Correction (Yates) test; [4]Chi-Square test; **p<0.01*

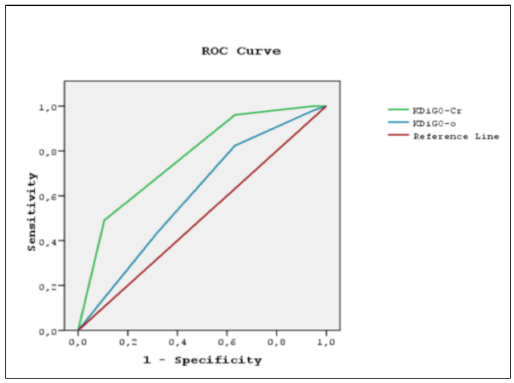

Figure 1: ROC Curve for KDIGO-SCr and KDIGO-UO, demonstrating difference between two groups.

		Ward Transfer	Exitus	
		n (%)	n (%)	P
AKIN	Stage 1	6 (%31,6)	1 (%2)	**0,001****
	Stage 2	6 (%31,6)	14 (%27,5)	
	Stage 3	7 (%36,8)	36 (%70,6)	
RIFLE	R	6 (%31,6)	1 (%2,0)	**0,001****
	I	6 (%31,6)	15 (%29,4)	
	F	7 (%36,8)	35 (%68,6)	
KDİGO-Cr	0	1 (%5,3)	0 (%0)	**0,001****
	1	6 (%31,6)	2 (%3,9)	
	2	10 (%52,6)	24 (%47,1)	
	3	2 (%10,5)	25 (%49)	
KDİGO-uo	0	1 (%5,3)	1 (%2)	**0,398**
	1	6 (%31,6)	8 (%15,7)	
	2	6 (%31,6)	20 (%39,2)	
	3	6 (%31,6)	22 (%43,1)	
KDİGO	1	5 (%26,3)	1 (%2)	**0,002****
	2	7 (%36,8)	14 (%27,5)	
	3	7 (%36,8)	36 (%70,6)	

Table 3: Relationship between acute renal injury classification models and status of patient.
*Chi-Square test; **p<0.01*

	Area	Std. Error	P	%95 CI	
				Lower Bound	Upper Bound
KDIGO-SCr	0,770	0,064	**0,001****	0,644	0,895
KDIGO-UO	0,603	0,079	0,187	0,448	0,759

Table 4: ROC analysis for KDİGO-SCr and KDİGO-Uo, showing statistical significant difference of KDIGO-SCr.

KDIGO-SCr used for prediction of mortality had ROC area under the curve of 0.770 with standard error of 0.064. Confidence interval was 0.644 - 0.895 which was statistically significant (p<0.01).

KDIGO-UO used for prediction of mortality had ROC area under the curve of 0.603 with a standard error of 0.079. Confidence interval was 0.448 - 0.759 which was statistically insignificant.(p>0.05).

Blood levels at admittance compared with mortality are shown in Table 5.

Discussion

Renal failure requiring renal replacement therapy is frequently seen in intensive care patients. Renal replacement therapy is frequently used in reanimation units for acute and chronic renal failure[2]. Different results have been reported in studies looking into the effect of CRRT for acute renal failure on mortality, in intensive care patients[1, 2, 5-7, 12].

In a meta-analysis performed by Osterrman et al[14], mortality of patients undergoing CRRT was

		Ward Transfer	Exitus	
		Ave±SD (median)	Ave±SD (median)	P
pH		7,29±0,09	7,22±0,11	[1]**0,008****
HCO3		19,93±4,53	17,30±4,50	[1]**0,073**
Urea		82,33±45,4 (61,5)	135,44±84,06 (96)	[2]**0,004****
Creatinine		2,24±2,09 (1,11)	3,04±1,89 (2,41)	[2]**0,008****
K		4,52±0,89	5,21±1,19	[1]**0,030***
Hct		34,63±7,42 (34,75)	33,44±6,59 (35)	[2]**0,717**
MAP		7,84±20,51 (72)	63,76±16,19 (57)	[2]**0,207**
		n (%)	n (%)	
pH	≤ 7.15	2 (%10,5)	12 (%23,5)	[3]**0,014***
	7.16 – 7.29	6 (%31,6)	28 (%54,9)	
	≥ 7.30	11 (%57,9)	11 (%21,6)	
HCO3	≤ 10	0 (%0)	4 (%7,8)	[3]**0,016***
	10 – 20	6 (%33,3)	32 (%62,7)	
	≥ 20	12 (%66,7)	15 (%29,4)	
Urea	< 100	13 (%72,2)	27 (%52,9)	[3]**0,059**
	100-200	5 (%27,8)	11 (%21,6)	
	≥ 200	0 (%0)	13 (%25,5)	
Creatinine	0-2	12 (%66,7)	14 (%27,5)	[3]**0,005****
	2-4	2 (%11,1)	26 (%51)	
	≥ 4	4 (%22,2)	11 (%21,6)	
K	≤ 3.5	2 (%11,1)	4 (%7,8)	[3]**0,001****
	3.5-6	16 (%88,9)	26 (%51)	
	≥ 6	0 (%0)	21 (%41,2)	
Hct	≤ 30	2 (%11,1)	15 (%29,4)	[4]**0,203**
	> 30	16 (%88,9)	36 (%70,6)	
MAP	< 60	6 (%31,6)	27 (%52,9)	[5]**0,186**
	> 60	13 (%68,4)	24 (%47,1)	

Table 5:Comparison of various admittance blood levels and mortality. K: Potassium, Hct: Hematocrit, MAP: Mean Arterial Pressure.;
*[1]Student t test; [2]Mann-Whitney U test; [3]Chi-square test; [4]Fisher's Exact test; [5]Continuity Correction (Yates) test; *p<0.05; **p<0.01*

found to be 37.5% - 85%. Similarly, we have found the rate of mortality to be 72.9% in these patients.

Cruz et al.[15] compared the RIFLE, AKIN and KDIGO criteria in intensive care patients for mortality prediction, and all three were found to be good predictors of mortality and the ROC analysis results were indicated to be similar. Our study also found RIFLE, AKIN and KDIGO to be good predictors of mortality.

In some studies, the RIFLE criteria were classified according to urinary output and creatinine values as RIFLE-SCr and RIFLE-UO using a different perspective[15-18]. In a study by Lopes et al.[18] where the authors compared RIFLE and AKIN criteria in 703 intensive care patients with ARI, they took both systems into subgroups as creatinine and urinary output. The authors reported that RIFLE-SCr, which is determined based on serum creatinine values, is a better predictor of mortality when compared to RIFLE-UO and also RIFLE.

However, we were unable to find any publications where such classification regarding KDIGO criteria was used. We believe that our study will be a first in this regard. Patients in our study were evaluated according to RIFLE, AKIN, KDIGO-SCr and KDİGO-UO and KDIGO criteria. The similarity between mortality rates of the RIFLE, AKIN and KDIGO groups and the numbers in the patient groups is noteworthy. All three criteria were found to be statistically significant on the prediction of mortality in a similar way to the study of Cruz et al[15].

The real differences are observed in the KDIGO-SCr and KDIGO-UO groups. The relatively higher mortality of stage 0 and 1 patients according to urinary output in comparison with the KDIGO-SCr group stands out. It gives rise to the thought that KDIGO-UO according to ROC analysis is not a significant predictor of mortality in comparison with KDIGO-SCr, and that KDIGO-UO is not appropriate to use as a marker for mortality. This can be regarded as a similar situation to the comparison of RIFLE-SCr and RIFLE-UO by Lopez et al.[18].

In the prospective study comparing RIFLE with and without urinary output by Wladzimirow et al[19] on 260 ICU patients; it has been stated that the number of patients with an ARI diagnosis has dropped where only creatinine is used for assessment, and that this situation is associated with increased mortality.

In our study, when only one of these two criteria is used it can be seen that of 43 patients who are stage 3/R, 16 according to KDIGO-SCr and 15 according to KDIGO-UO were evaluated as stage 1/R or stage 2/1. We believe, as also stated by Wladzimirow et al.[19], that this will lead to a delay in diagnosis and increase in mortality.

In a study by Macedo et al.[20] on urinary output value in ARI diagnosis in intensive care patients, they stated that hourly or six hourly urine output monitoring was more valuable in comparison with creatinine values in the diagnosis of ARI. Our study does not support this assertion.

Urinary output and serum creatinine levels have been utilized in the diagnosis and classification of acute renal failure, both alone and together. There are several studies evaluating the value of RIFLE, RIFLE-UO and RIFLE-SCr as predictors of mortality. However, since 2012, KDIGO has been recommended for the classification of ARI. This study is the first to use KDIGO-UO and KDIGO-SCr for modified classification of ARI. With this study, the superiority of RIFLE-SCr over RIFLE-UO has been demonstrated to be similar in KDIGO-SCr versus KDIGO-UO too. Prospective studies are required to further demonstrate the accuracy of our findings.

Conclusion

We believe that RIFLE, AKIN, KDIGO criteria are each good predictors of mortality. In the case of KDIGO criteria based solely on serum creatinine or urinary output, we believe that this can lead to mistakes in ARI diagnosis and an increase in mortality. However, KDIGO-SCr is superior to KDIGO-UO as a prediction of mortality.

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