



# The Role of RIFLE, AKIN and KDIGO Criteria in Determining the Relationship Between Acute Kidney Injury and Mortality in Intensive Care Patients

Yoğun Bakım Hastalarında Akut Böbrek Hasarı ve Mortalite İlişisinin Belirlenmesinde RIFLE, AKIN ve KDIGO Kriterlerinin Yeri

✉ Nergiz BAYRAKÇI<sup>1</sup>, ✉ Sibel ERSAN<sup>2</sup>, ✉ Ali ÇELİK<sup>3</sup>, ✉ Caner ÇAVDAR<sup>3</sup>, ✉ Taner ÇAMSARI<sup>3</sup>, ✉ Hakan Alp BODUR<sup>4</sup>, ✉ Aykut SİFİL<sup>3</sup>

<sup>1</sup>Tekirdağ Namık Kemal University Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, Tekirdağ, Turkey

<sup>2</sup>University of Health Sciences Turkey, Tepecik Training and Research Hospital, Clinic of Nephrology, İzmir, Turkey

<sup>3</sup>Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, İzmir, Turkey

<sup>4</sup>UCLouvain University Namur (Sainte-Elisabeth) Hospital, Clinic of Obesity and Diabetes, Namur, Belgium

## ABSTRACT

**Aim:** Risk, injury, failure, loss, and end stage (RIFLE); acute kidney injury network (AKIN) and kidney disease: Improving global outcomes (KDIGO) classifications are the most commonly used criteria for the diagnosis of acute kidney injury (AKI). The aim of our study was to determine the relationship between the mortality and the severity of AKI diagnosed by using RIFLE, AKIN, and KDIGO classifications in critically ill patients.

**Materials and Methods:** Data of 1,491 patients hospitalized in tertiary intensive care unit were retrieved from electronic medical records and patients diagnosed with AKI were included in the study. AKI severity was determined according to the RIFLE, AKIN, and KDIGO classifications.

**Results:** One hundred fifty-five patients were included in the study. The percentages of patients in risk, damage, and failure stages according to the RIFLE criteria were 14.8%, 40.0%, and 45.2%, respectively. The percentages in stage 1, 2 and 3 were 45.6%, 30.6%, and 23.8% according to the AKIN criteria and 18.7%, 21.7%, and 54.1% according to the KDIGO criteria, respectively. There was a difference in mortality between the stages of AKI determined according to the AKIN and RIFLE criteria. Mortality was found to be higher in patients in KDIGO stage 3.

**Conclusion:** These three classifications do not consider the etiology of AKI. Therefore, it may be possible that they do not accurately reflect the relationship between mortality and AKI severity. However, the KDIGO classification, which emerged with the need arising from the inadequacy of the classifications used before it, seems to be more valid in this respect.

**Keywords:** Acute kidney injury, AKIN, KDIGO, mortality, RIFLE, intensive care

## ÖZ

**Amaç:** Akut böbrek hasarının (ABH) daha kesin biçimde tanımlanması ve takip sürecinin daha iyi yönetilmesi amacıyla çok sayıda sınıflama gündeme gelmiştir. Bunlar arasında en yaygın kabul görenler risk, injury, failure, loss, and end stage (RIFLE), acute kidney injury network (AKIN) ve kidney disease: Improving global outcomes (KDIGO) sınıflamaları olmuştur. Bu çalışmada, yoğun bakımda izlenen ve ABH tanısı alan hastalarda RIFLE, AKIN ve KDIGO kriterlerine göre ABH şiddeti ile mortalite arasındaki ilişkinin saptanması amaçlanmıştır.

**Gereç ve Yöntem:** Dahiliye yoğun bakım ünitesinde izlenen 1.491 hastaya ait veriler retrospektif olarak incelendi ve ABH saptanan hastalar çalışmaya dahil edildi. Tüm hastalar için RIFLE, AKIN ve KDIGO kriterlerine kullanılarak ABH şiddeti belirlendi.

**Bulgular:** Çalışmaya 155 hasta dahil edildi. RIFLE kriterlerine göre risk, hasar, yetmezlik evrelerinde yer alan hasta oranları sırasıyla; %14,8, %40,0, %45,2; AKIN kriterlerine göre evre 1, evre 2 ve evre 3'te yer alan hasta oranları sırasıyla; %45,6, %30,6, %23,8; KDIGO kriterlerine göre evre 1, evre 2 ve evre 3'te yer alan hasta oranları sırasıyla; %18,7, %21,7, %54,1 idi. AKIN ve RIFLE kriterlerine göre belirlenen ABH evreleri arasında mortalite oranları açısından farklılık saptanmazken, KDIGO evre 3'te yer alan hastalarda evre 1 ve evre 2 ABH gruplarına göre mortalite daha yüksek saptandı.

**Address for Correspondence:** Nergiz BAYRAKÇI MD, Tekirdağ Namık Kemal University Faculty of Medicine, Department of Internal Medicine, Division of Nephrology, Tekirdağ, Turkey

**Phone:** +90 282 250 73 20 **E-mail:** nbayrakci@nku.edu.tr **ORCID ID:** orcid.org/0000-0002-5923-953X

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**Sonuç:** Her üç tanı ve evreleme sistemi de ABH etiyolojisini dikkate almamaktadır. Bu nedenle mortalite ve ABH şiddeti arasındaki ilişkiyi doğru yansıtmamaları söz konusu olabilir. Bununla birlikte, kendisinden önce kullanılan evreleme sistemlerindeki eksikliklerden doğan ihtiyaçla ortaya çıkan KDIGO evreleme sistemi bu açıdan daha geçerli görünmektedir.

**Anahtar Kelimeler:** Akut böbrek hasarı, AKIN, KDIGO, mortalite, RIFLE, yoğun bakım

## INTRODUCTION

Acute kidney injury (AKI), defined as sudden and progressive deterioration of kidney functions, is among the leading causes of mortality in hospitalized patients. The reported incidence of AKI in patients followed in the intensive care unit is between 20% and 50%, and this rate exceeds 70% in the presence of sepsis. A mortality rate of 15-70% has been reported in this group<sup>1-4</sup>. The lack of consensus on the definition of AKI and the presence of different definitions over 35 currently in use are likely reasons for the large variability in reported frequency and mortality rates. This situation made it difficult to make comparisons among studies on AKI, and caused inadequacy in the evaluation of prognostic indicators.

Based on the need for diagnostic standardization, risk, injury, failure, loss, and end stage (RIFLE) was defined in 2004 by the Bellomo et al.<sup>1</sup> Then, the classifications of Mehta et al.<sup>5</sup> acute kidney injury network (AKIN) in 2007 and Kellum et al.<sup>6</sup> kidney disease: Improving global outcomes (KDIGO) in 2012 were defined. Although they have some limitations, criteria for the diagnosis and staging of AKI are the most agreed and widely studied subjects in these classifications<sup>2</sup>. In all three classifications, serum creatinine and urine amount are taken into account and the severity of AKI is defined in 3 stages. In RIFLE staging, differently, there are 2 stages associated with the outcome as "L-loss" and "E-end-stage renal disease". Unlike the other two, in the AKIN classification, creatinine and urine changes in the 48-hour period are taken into account. KDIGO classification can be interpreted as an integrated version of AKIN and RIFLE classifications.

In the majority of related studies, it has been reported that all three classifications can be used to predict mortality and that mortality increases as the AKI stage increases<sup>7-15</sup>.

In our study, it was aimed to determine the severity of AKI according to AKIN, RIFLE and KDIGO criteria and to evaluate its relationship with mortality in patients who were followed up in the internal medicine intensive care unit of a tertiary hospital and developed AKI.

## MATERIALS AND METHODS

The information of 1,491 adult patients who were followed up in the tertiary internal medicine intensive care unit between August 2003 and May 2010 were analyzed through the hospital information system, patient files and the registry

system of the intensive care unit. The study protocol was prepared in accordance with the Declaration of Helsinki and Ethics Committee approval of Dokuz Eylül University Faculty of Medicine was obtained (approval number: 252/2009). Among 589 patients with elevated serum creatinine, those who stayed in the intensive care unit for less than 48 hours (n=185), those with a history of chronic kidney failure and kidney transplantation (n=128), those with insufficient diagnostic data (n=75), and those who had highest serum creatinine levels at admission to the intensive care unit but had regression in the follow-up (late AKI, n=46) were excluded and 155 patients were included in the study. Patients' age, gender, indication for intensive care unit, co-morbidities, presence of sepsis, acute physiology and chronic health evaluation score-II (APACHE-II) and simplified acute physiology score-II (SAPS-II) scores, duration of monitorization in intensive care, need for invasive mechanical ventilation, basal and peak serum creatinine values, need for hemodialysis following the diagnosis of AKI, and outcome data were recorded. Co-morbidities were grouped as cardiovascular disease (diabetes, hypertension, cerebrovascular event, coronary artery disease, heart failure), malignancy (metastatic or non-metastatic solid and hematological malignancies), chronic obstructive pulmonary disease, liver failure and other. APACHE-II and SAPS-II scores were calculated by considering the worst parameters in the first 24 hours of admission to the intensive care unit. Even if the serum creatinine value decreased to basal level, the outcome was accepted as "death" if death occurred during the follow-up period,

AKI stage was determined for all patients according to the RIFLE, AKIN, and KDIGO criteria (Table 1). The last 2 stages in the RIFLE classification were not included in the staging because they were related to patient outcome. When staging AKI according to the RIFLE criteria, the patient's basal serum creatinine value, if known, was used, and if it is unknown, the serum creatinine value corresponding to 75 mL/min/1.73 m<sup>2</sup> glomerular filtration rate (GFR) according to the modification of diet in renal disease formula was used<sup>1,16</sup>. RIFLE staging was performed according to the highest serum creatinine and lowest GFR value in the 7-day period following the trend of increasing serum creatinine level. While AKI was staging according to the AKIN criteria, the lowest serum creatinine value was determined as basal serum creatinine in the 48-hour period in which AKI was detected; AKI severity was determined at the time of diagnosis according to the highest serum

creatinine value<sup>5</sup>. Those who underwent hemodialysis within the first 48 hours of being diagnosed with AKI were classified as stage 3. When staging AKI according to the KDIGO criteria, the basal serum creatinine value of the patient, if known, and the lowest serum creatinine value before the development of AKI, if not known, was determined as the basal value. AKI severity was determined according to the highest serum creatinine value in the 7-day period after the serum creatinine level started to increase. Those who underwent hemodialysis within 7 days were classified as stage 3<sup>6,16</sup>.

Since daily urine output data were not sufficient in all patients, the urine amount criterion was not used in the diagnosis and staging of AKI.

**Statistical Analysis**

Statistical Package for the Social Sciences (Windows, version 25) software was used for data recording and analysis. P value <0.05 was considered significant. The homogeneity of variances was tested by the Kolmogorov-Smirnov analysis. The groups were compared with the ANOVA analysis of variance, Kruskal-Wallis test, Mann-Whitney U test or chi-square tests according to whether they were parametric or non-parametric. Logistic regression analysis was used to determine the effect of variables on mortality.

**RESULTS**

**General Characteristics of the Patients**

In our study, in which the data of 1,491 intensive care patients were analyzed, the rate of AKI was found to be 18.5%. One hundred fifty-five adult patients with sufficient data were included in the study. The median age was 62 (18-89) years, and the female sex rate was 42.6% in patients with a mean follow-up period of 12.7 (2-105) days. The most common comorbidity was cardiovascular diseases (50.3%), and 43.6% of the patients had more than two comorbidities. In 59.4% of the patients, the indication for follow-up in the intensive care unit was sepsis or systemic inflammatory response syndrome. The rate of patients who needed invasive mechanical ventilation was 92.3%, and

sepsis and respiratory failure were found to coexist in 45.8% of the patients. The mean APACHE-II score was 24.6±8.8 and the SAPS-II score was 55.9±19.7. The rate of patients who received hemodialysis at any time during the follow-up was found to be 33.5%. The mortality rate was 77.4% (Table 2). There was no significant difference in mortality between the patients who underwent and did not undergo hemodialysis (p=0.054). Logistic regression analysis, including age, AKI stages, APACHE-II and SAPS-II scores, hemodialysis need, and mechanical ventilator and vasopressor needs, did not reveal any mortality-related parameter.

**Characteristics of AKI Stages According to RIFLE Criteria**

Of the 155 patients included in our study, 14.8% were included in the risk stage, 40.0% in the damage stage, and 45.2% in the failure stage. Mortality rates in the stages of risk, damage and failure were determined as 65.2%, 77.4% and 81.4%, respectively. No significant difference was found between the stages in this respect. There was no significant difference between RIFLE stages in terms of age, comorbid diseases, presence of sepsis and need for mechanical ventilation. While there was no significant difference between the stages in terms of APACHE-II scores, the mean SAPS-II score of the risk stage was found to be lower than the other stages (p=0.049). In the intensive care follow-up after the diagnosis of AKI, hemodialysis was applied to 3 (13.0%) patients in the risk stage, 12 (19.4%) patients in the failure stage, and 37 (52.9%) patients in the damage stage (p=0.000) (Table 3).

**Characteristics of AKI Stages According to AKIN Criteria**

Of the 155 patients included in the study, 8 remained outside the definition of AKI. 45.6% of the patients were included in the 1<sup>st</sup> stage, 30.6% in the 2<sup>nd</sup> stage, and 23.8% in the 3<sup>rd</sup> stage. Mortality rates of AKIN stage 1, stage 2 and stage 3 were determined as 77.6%, 77.8% and 80.0%, respectively, and no difference was found between the stages in this respect. There was no significant difference between AKIN stages in terms of age, co-morbidity, presence of sepsis and need for mechanical ventilation. While there was no significant difference between

**Table 1. RIFLE, AKIN, KDIGO criteria according to serum creatinine value**

Stage	Serum creatinine		
	RIFLE*	AKIN**	KDIGO**
<b>Risk/stage 1</b>	≥1.5 fold increase	1.5-2 fold increase or ≥0.3 mg/dL increase	1.5-1.9 fold increase or ≥0.3 mg/dL increase
<b>Damage/stage 2</b>	≥2 fold increase	>2-3 fold increase	>2-2.9 fold increase
<b>Failure/stage 3</b>	≥3 fold increase or when 4 mg/dL, sudden increase of 0.5 mg/dL and over	>3 fold increase or when 4 mg/dL, sudden increase of 0.5 mg/dL and over	≥3 fold increase or >4 mg/dL

\*In addition to the serum creatinine value, a 25-50% decrease in glomerular filtration rate is defined as "risk", a 50-75% decrease as "damage", and a decrease of 75% or more as "failure". \*\*The need for dialysis corresponds to stage 3 acute kidney injury, regardless of other criteria. RIFLE: Risk, injury, failure, loss of kidney function; end-stage kidney disease, AKIN: Acute kidney injury network, KDIGO: Kidney disease: Improving global outcomes

the stages in terms of SAPS-II score, the mean APACHE-II score of AKIN stage 1 was found to be higher than the other stages ( $p < 0.019$ ). Hemodialysis was applied to 17 (25.4%) patients in stage 1, 13 (28.9%) patients in stage 2, and 20 (57.1%) patients in stage 3 during the intensive care follow-up after the diagnosis of AKI ( $p = 0.004$ ) (Table 3).

### Characteristics of AKI Stages According to KDIGO Criteria

Of the 155 patients included in our study, 18.7% were classified as stage 1, 27.1% as stage 2, and 54.2% as stage 3. Mortality rates in stage 1, stage 2 and stage 3 were found to be 72.4%, 64.3% and 85.7%, respectively, and the mortality rate in stage 3 was higher than in other stages ( $p = 0.02$ ). There was no difference between KDIGO stages in terms of age, comorbid diseases,

presence of sepsis, need for mechanical ventilation, APACHE-II and SAPS-II scores. In the intensive care follow-up after the diagnosis of AKI, there was no patient in need of dialysis in stage 1, while hemodialysis was applied in 9.5% of patients in stage 2 and 57.1% of patients in stage 3 ( $p = 0.000$ ) (Table 3).

### DISCUSSION

In our study, 155 patients diagnosed with AKI were evaluated in terms of AKI severity and AKI-related mortality according to 3 different staging systems. According to the RIFLE criteria, the distribution rates in risk, damage and failure stages were determined as 14.8%, 40.0% and 45.2%, respectively. When similar studies were examined, the rates of 16.9–53% for the risk stage, 24.1–38.8% for the damage stage and 17.4–45.4% for the failure stage were reported and compared to the rates in our study, it was observed that the rates of patients in the risk stage were higher in most of these studies<sup>4,7,9-11,14,17-20</sup>. In our study, the distributions in the AKI stages determined according to the AKIN criteria for the same patients were 45.6%, 30.6% and 23.8% for stages 1, 2, 3, respectively, and it was seen that the number of patients was higher in the early AKI stages, compared to other classifications. In addition, 8 patients remained outside the definition of AKI. In similar studies, patient distribution rates were reported as 24.1–59.2% in stage 1, 12.5–20.7% in stage 2, and 27.2–48.5% in stage 3, and similar to our study, most of them were observed to be in the early stages<sup>4,10,11,14,17-19,21</sup>. When the KDIGO classification was used for AKI staging in the study group, the distribution rates of stage 1, stage 2, and stage 3 patients were found as 18.7%, 21.7% and 54.2%, respectively. In similar studies, the reported patient rates for stages 1, 2 and 3 were 19.5–70.9%, 11.7–28.3% and 12–45%, respectively<sup>4,13,14,17-19</sup>. In our study, distributions in KDIGO staging were generally similar to those in the literature. Although all of the aforementioned studies were intensive care reports, it was observed that the distribution of patients in AKI stages was different from each other due to some factors such as the use of the urine criterion, the consideration of different criteria in determining the basal creatinine value, the difference in the monitorization periods selected to determine the severity of AKI, and the different characteristics of the study groups in some studies. This situation makes it difficult to comment on which classification is more accurate in determining the diagnosis and stage of AKI.

In our study group, in which the rates of sepsis and mortality were very high, the rate of late-stage AKI was found to be higher in both when the KDIGO and RIFLE classifications were used. In the AKIN classification, the rate was higher in the early stage AKI group. Compared to KDIGO and RIFLE classifications, it was observed that the median of basal serum creatinine value was higher in the AKIN classification, and the median of the highest serum creatinine value that determined the AKI stage

Characteristics	Whole population (n=155)
Age (year)	62 (18-89)
Gender (female), n (%)	66 (42.6)
Duration of intensive care monitorization (day)	8 (2-2190)
APACHE-II	24.6±8.8
SAPS-II	55.9±19.7
<b>Comorbidity, n (%)</b>	
Cardiovascular disease	78 (50.3)
COPD	26 (16.8)
Cirrhosis	37 (23.9)
Malignancy	16 (10.3)
Sepsis, n (%)	92 (59.4)
Those with the need of vasopressor, n (%)	148 (95.5)
Those with the need of mechanical ventilator, n (%)	143 (92.3)
Those undergoing hemodialysis, n (%)	52 (33.5)
Mortality, n (%)	120 (77.4)
<b>Basal creatinine (mg/dL)</b>	
RIFLE*	0.85 (0.42-1.3)
AKIN**	0.98 (0.42-3.1)
KDIGO*	0.85 (0.42-13)
<b>Highest creatinine (mg/dL)</b>	
RIFLE*	2.39 (1-7.91)
AKIN**	1.9 (0.79-7.60)
KDIGO*	2.39 (1-7.91)
*The creatinine value corresponding to 75 mL/min/1.73 m <sup>2</sup> of glomerular filtration rate according to the modification of diet in renal disease study formula was accepted as the basal value in patients whose basal creatinine value was unknown.	
**The lowest value in the first 48 hours evaluated for acute kidney injury was accepted as the basal creatinine value. AKI: Acute kidney injury, APACHE: Acute physiology and chronic health evaluation, SAPS: Simplified acute physiology score, COPD: Chronic obstructive pulmonary disease, RIFLE: Risk, injury, failure, loss of kidney function, AKIN: Acute kidney injury network, KDIGO: Kidney disease: Improving global outcomes	

was lower. Therefore, due to the small difference between these two values, more patients seem to be in the early stage AKI group. In addition, the limitation of AKIN staging to the 48-hour period ignores the possible increase in serum creatinine compared to the 1-week evaluation period in the RIFLE and KDIGO classifications. This may be another reason for why more patients are included in earlier AKI stages in AKIN-based classification compared to other staging systems. For similar reasons, was reported that when the AKIN classification was applied, more patients were not diagnosed with AKI compared to other classifications. There are studies in the literature with similar comments regarding the AKIN classification<sup>10,13,14,17,18</sup>.

In our study, it was observed that mortality increased in parallel with the severity of AKI determined according to each of the 3 staging systems, but this increase was found to be statistically significant in favor of stage 3 only in the KDIGO classification. However, AKI stages were not found to be determinative for

mortality in all three classifications. In most of the similar studies, correlation was found between AKI severity and mortality in all three classifications<sup>8,13,15,17,18</sup>. The patient groups in these studies are quite heterogeneous. On the other hand, in a study of Pereira et al.<sup>4</sup> that included 457 septic patients and compared the relationship of RIFLE, AKIN, and KDIGO classifications with mortality, although AKIN and KDIGO classifications were the predictors of mortality, no correlation was found between AKI stages and mortality. In another study in which 1.036 patients were evaluated, a correlation was found between stage 2 and 3 AKI and mortality in all three classification systems<sup>19</sup>.

### Study Limitations

The main limitation of our study is the small number of patients compared to similar studies in the literature. Moreover, we think that the similarity of hospitalization indications in our study group reduces the heterogeneity among patients. Another limitation of ours is the inability to use the urine criterion in

**Table 3. Comparison of AKI stages determined according to RIFLE, AKIN and KDIGO classifications**

Parameter	Stage			p
<b>RIFLE</b>	<b>Risk</b>	<b>Damage</b>	<b>Failure</b>	
Number of patients, n (%)	23 (14.8)	62 (40.0)	70 (45.2)	-
Age (years)	59 (26-87)	62 (18-88)	65 (18-89)	0.687
Comorbidity, n (%)	20 (87.0)	57 (91.9)	63 (90.0)	0.782
APACHE-II	23.4±9.1	23.7±8.5	25.8±9.0	0.319
SAPS-II	46.7±19.0	56.3±19.9	58.4±19.0	0.049
Sepsis, n (%)	12 (52.2)	39 (62.9)	41 (58.6)	0.659
Hemodialysis, n (%)	3 (13.0)	12 (19.4)	37 (52.9)	0.000
Death, n (%)	15 (65.2)	48 (77.4)	57 (81.4)	0.272
<b>AKIN</b>	<b>Stage 1</b>	<b>Stage 2</b>	<b>Stage 3</b>	
Number of patients, n (%)	67 (45.6)	45 (30.6)	35 (23.8)	-
Age (years)	61 (26-89)	61 (18-81)	60 (18-88)	0.581
Comorbidity, n (%)	61 (91.0)	42 (93.3)	30 (85.7)	0.699
APACHE-II	22.8±9.1	25.0±8.9	28.0±7.8	0.019
SAPS-II	51.4±18.4	58.4±20.6	59.6±19.7	0.068
Sepsis, n (%)	40 (59.7)	26 (57.8)	23 (65.7)	0.757
Hemodialysis, n (%)	17 (25.4)	13 (28.9)	20 (57.1)	0.004
Death, n (%)	52 (77.6)	35 (77.8)	28 (80.0)	0.763
<b>KDIGO</b>	<b>Stage 1</b>	<b>Stage 2</b>	<b>Stage 3</b>	
Number of patients, n (%)	29 (18.7)	42 (27.1)	84 (54.2)	-
Age (years)	62 (26-87)	62 (18-88)	65 (18-89)	0.709
Comorbidity, n (%)	24 (82.8)	40 (95.2)	76 (90.5)	0.216
APACHE-II	23.4±8.1	23.7±8.8	25.5±9.1	0.408
SAPS-II	48.1±18.5	56.1±19.6	58.4±19.6	0.055
Sepsis, n (%)	19 (65.5)	21 (50.0)	52 (61.9)	0.332
Hemodialysis, n (%)	0 (0)	4 (9.5)	48 (57.1)	0.000
Death, n (%)	21 (72.4)	27 (64.3)	72 (85.7)	0.020

\*A p value of <0.05 was considered statistically significant. RIFLE: Risk, injury, failure, loss of kidney function, end-stage kidney disease, AKIN: Acute kidney injury network, KDIGO: Kidney disease: Improving global outcomes, AKI: Acute kidney injury, APACHE-II: Acute physiology and chronic health evaluation, SAPS: Simplified acute physiology score

the diagnosis and staging of AKI, since the urine output of all patients could not be followed closely and appropriately. Finally, our high mortality rate, possibly due to causes other than AKI, made it difficult to compare mortality rates between AKI stages.

## CONCLUSION

AKIN staging seems to be more applicable than the RIFLE and KDIGO criteria since it eliminates the need for baseline creatinine, includes the need for hemodialysis in the diagnosis, and suggests a shorter time window for the timing of diagnosis. However, due to these reasons, it is possible to reflect the severity of AKI as lower than it is. The last of the three staging systems, the KDIGO criteria, which have been reported to diagnose AKI with a higher frequency in comparative studies and to predict the relationship between AKI severity and outcomes more accurately, have been used more frequently in recent years. However, the etiology of AKI is ignored in all three diagnostic systems. Considering the etiology-related parameters and the presence of early histological changes in the AKI process, we think that the inclusion of biomarkers in the diagnostic criteria may significantly increase the validity of existing classifications and contribute positively to patient follow-up.

## Ethics

**Ethics Committee Approval:** Ethics Committee approval of Dokuz Eylül University Faculty of Medicine was obtained (approval number: 252/2009).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: N.B., S.E., A.Ç., C.Ç., T.Ç., A.S., Design: N.B., S.E., A.Ç., C.Ç., T.Ç., A.S., Data Collection or Processing: N.B., S.E., H.A.B., Analysis or Interpretation: N.B., A.S., Literature Search: N.B., H.A.B., Writing: N.B.

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