

# Importance of RIFLE (Risk, Injury, Failure, Loss, and End-Stage Renal Failure) and AKIN (Acute Kidney Injury Network) in Hemodialysis Initiation and Intensive Care Unit Mortality

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## What's Known

- Appropriate initiation time of renal replacement treatment in ICU patients is not known.
- There is a paucity of relevant data in the existing literature.

## What's New

- Our study is the first study to evaluate the initiation time of RRT according to the RIFLE and AKIN classifications in the ICU.

## Abstract

Our study evaluated the differences between early and late hemodialysis (HD) initiation in the intensive care unit (ICU) according to the RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure) and AKIN (Acute Kidney Injury Network) classifications. On the assumption that early initiation of HD in critical patients according to the RIFLE and AKIN criteria decreases mortality, we retrospectively evaluated the medical records of 68 patients in our medical ICU and divided the patients into 2 groups: Those undergoing HD in no risk, risk, or injury stage according to RIFLE and in stage 0, I, or II according to AKIN were defined as early HD and those in failure stage according to RIFLE and in stage III according to AKIN were defined as late HD. The median age of the patients was 66.5 years, and 56.5% were male. HD was started in 25% and 39.7% of the patients in the early stage in the RIFLE and AKIN classification, respectively. According to RIFLE, HD was started in 61.5% of the surviving patients in the early stage; this rate was 16.4% in the deceased patients ( $P=0.001$ ). HD was commenced in 69.2% of the surviving patients in AKIN stages 0, I, and II and in 32.7% of the deceased patients ( $P=0.026$ ). Sepsis (61.5% vs. 94.5%;  $P=0.001$ ) and mechanical ventilation (30.8% vs. 87.3%;  $P<0.001$ ) during HD increased ICU mortality, whereas HD initiation in the early stages according to RIFLE decreased ICU mortality (61.5% vs. 16.4%;  $P=0.001$ ). In conclusion, in critically ill patients, HD initiation in the early stages according to the RIFLE classification decreased our ICU mortality.

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**Keywords** • Acute kidney injury • Intensive care units • Renal dialysis

## Introduction

Acute kidney injury (AKI) is a sudden deterioration of renal functions. It can be defined as an increase in the serum creatinine of 0.3 mg/dL in 48 hours or a 1.5-fold increase compared to the baseline value in 7 days or urine output  $<0.5$  mL/kg/h for over 6 hours. The incidence of AKI is between 5% and 60% in the intensive care unit (ICU). Five to ten percent of critically ill patients

with AKI require hemodialysis (HD) to support their fluid and metabolic balances.<sup>1-3</sup>

The HD initiation criteria are clearly defined in patients with chronic renal disease. However, in AKI, some specialists tend to start HD late (after 2 or more definite criteria have occurred), while others tend to start it early (only 1 criterion as hypervolemia or acidosis). In the literature, there are different parameters to define the timing of HD.<sup>2-4</sup>

The classifications of RIFLE (Risk, Injury, Failure, Loss, and End-stage renal failure) and AKIN (Acute Kidney Injury Network) have been developed to determine the diagnosis and prognosis in AKI. These classifications, which are based on the increase in serum creatinine and decrease in the global filtration rate (GFR) and urine output, have been used to determine the time to start HD and to predict mortality in AKI.<sup>4,5</sup>

The aim of the present study was to define the criteria for HD initiation in our medical ICU patients and to determine the effects of early vs. late HD initiation according to the RIFLE and AKIN classifications on ICU mortality.

## Patients and Methods

Sixty-eight patients who were admitted to the Medical ICU of Gazi University Hospital between January 2009 and August 2014 and underwent HD during their ICU stay were included in this retrospective study. The ethics committee of our institution approved the study (#25901600/79, decision date: 01.29.2015). Patients with chronic renal disease, HD initiation before ICU admission, and ICU stay <48 hours were excluded from the study.

The demographics of the patients; ICU admission reasons; comorbidities; severity scores; etiologies of AKI; levels of blood urea, creatinine, sodium, potassium, phosphorus, albumin, blood pH, and bicarbonate; urine outputs; estimated GFRs; and RIFLE and AKIN classes at admission and immediately before the initiation of HD were recorded retrospectively. The Cockcroft–Gault formula was used to calculate the estimated GFR. The values were normalized for a body surface area of 1.73 m<sup>2</sup> and gender. Additional morbidities during ICU stay (mechanical ventilation support, development of sepsis/septic shock, etc.) and mortality were recorded. The patients were divided into 2 groups of surviving and deceased. The patients with no risk, risk, and injury according to RIFLE and in stage 0, I, or II according to AKIN were defined as early HD and the patients in failure stage according to RIFLE and in stage III according to

AKIN were defined as late HD. The differences in ICU mortality were compared between the early and late HD groups.

## Statistical Analysis

SPSS, version 17 (SPSS Inc., Chicago, IL, USA), was used in the statistical analyses. The Mann–Whitney *U*-test and the  $\chi^2$  test were employed in the comparisons. The parameters that were significant in the univariate analysis were included in the logistic regression analysis, and the independent risk factors were defined for ICU mortality. *P* values <0.05 were considered statistically significant.

## Results

A total of 2183 patients were admitted to our ICU during the study period, and 311 of them received HD. After the application of the exclusion criteria, 68 patients were included in the study. The median age of the patients was 66.5 years, and 56.5% of them were male. The rates of intermittent and continuous HD were 63.2% and 50%, respectively. The most common indications for HD initiation were decreased urinary output (70.6%), estimated GFR<30 mL/min (66.2%), and hypervolemia due to congestive heart failure (50%). HD was started in 25% of the patients in the early stage according to the RIFLE classification, while HD was commenced in 39.7% of the patients in the early stage according to the AKIN classification.

At the end of the study period, 19.1% of the patients survived and 80.9% of them died. The rates of HD initiation in the early stage according to the RIFLE classification of the surviving and deceased groups were 61.5% and 16.4%, correspondingly (*P*=0.001). The rates of HD initiation in the early stage according to the AKIN classification in the surviving and deceased groups were 69.2% and 32.7%, respectively (*P*=0.026). The rates of sepsis (61.5% vs. 94.5%; *P*=0.001) and mechanical ventilation support (30.8% vs. 87.3%; *P*<0.001) during HD were higher in the deceased group. The rates of intermittent HD were 92.3% and 56.4% in the surviving and deceased groups, correspondingly (*P*=0.016).

There was no difference in ICU mortality between the groups according to creatinine levels <3 mg/dL and ≥3 mg/dL (30.8% vs. 29.1%; *P*=0.935) and blood urea nitrogen ≥100 mg/dL and <100 mg/dL (7.7% vs. 32.7%; *P*=0.342) at the time of HD initiation (table 1).

The length of the ICU stay of the patients that received HD in the early stage according to the RIFLE and AKIN classifications (6 vs. 14,

**Table 1:** General characteristics of all, surviving and deceased, patients in the study population

Parameters	All patients (N=68)	Surviving patients (n=13)	Deceased patients (n=55)	P value
Age (y) (median, interquartile range)	66.5 (54-76.8)	69 (47-80)	66 (55-75)	0.963
Gender (male, %)	39 (56.5)	4 (30.8)	35 (63.6)	0.059
Length of ICU stay (d) (median, interquartile range)	10.5 (5-21)	7 (5-17)	12 (5-26)	0.232
Length of hospital stay (d) (median, interquartile range)	20.5 (13.3-33.5)	20 (10-24.5)	21 (13-37)	0.454
APACHE II score (median, interquartile range)	24 (18.3-28)	20 (11-24)	25 (19-29)	0.020
SOFA score on admission (median, interquartile range)	7 (5-11)	5 (4-8)	8 (6-12)	0.003
SOFA score on discharge (median, interquartile range)	14 (9-17)	4 (2.5-6)	15 (10-18)	<0.001
Charlson comorbidity score (median, interquartile range)	3 (2-4)	3 (2.5-4)	2 (2-4)	0.42
Reasons for admission to the ICU (n, %)				
Respiratory insufficiency	46 (67.6)	9 (69.2)	37 (67.3)	0.892
Sepsis/septic shock	46 (67.6)	5 (38.5)	41 (74.5)	0.012
Cardiovascular	10 (14.7)	2 (15.4)	8 (14.5)	0.939
Gastrointestinal	16 (23.5)	2 (15.4)	14 (25.5)	0.441
Renal	28 (41.2)	7 (53.8)	21 (38.2)	0.357
Comorbidities (n, %)				
Diabetes mellitus	19 (28)	3 (23.1)	16 (29.1)	0.664
Cardiovascular	27 (39.7)	6 (46.2)	21 (38.2)	0.754
Hypertension	32 (47.1)	8 (61.5)	24 (43.6)	0.356
Cancer	30 (44.1)	4 (30.8)	26 (47.3)	0.36
Respiratory (COPD)	13 (19.1)	7 (53.8)	6 (11)	<0.001
Gastrointestinal	8 (11.8)	1 (7.7)	7 (12.7)	0.612
Neurological	11 (16.2)	2 (15.4)	9 (16.4)	0.931
RIFLE classes on admission (n, %)				
No risk	19 (27.9)	1 (7.7)	18 (32.7)	0.07
Risk	24 (35.3)	7 (53.8)	17 (30.9)	0.12
Injury	25 (36.8)	5 (38.5)	20 (36.4)	0.888
AKIN stages on admission (n, %)				
AKIN 0	21 (30.4)	1 (7.7)	20 (36.4)	0.044
AKIN I	27 (39.1)	8 (61.5)	19 (34.5)	0.114
AKIN II	20 (29.4)	4 (30.8)	16 (29.1)	0.905
Possible causes of AKI (n, %)				
Sepsis	39 (57.4)	2 (15.4)	37 (67.3)	0.001
Colistin usage	9 (13.2)	0	9 (16.4)	0.117
Diuretics	10 (14.7)	2 (15.4)	8 (14.5)	0.939
Amphotericin B	4 (5.8)	0	4 (7.3)	0.316
Acyclovir usage	3 (4.4)	0	3 (5.5)	0.389
Hypervolemia	4 (5.8)	3 (23.1)	1 (1.8)	0.003
Radiocontrast agent	5 (7.4)	1 (7.7)	4 (7.3)	0.958
HD modalities (n, %)				
Intermittent HD	43 (63.2)	12 (92.3)	31 (56.4)	0.016
Continuous HD	34 (50)	2 (15.4)	32 (58.2)	0.011
Reasons for HD initiation (n, %)				
BUN $\geq$ 100 mg/dL	19 (27.9)	1 (7.7)	18 (32.7)	0.342
Potassium $\geq$ 6 mEq/L	6 (8.8)	0	6 (11)	0.251
Hypervolemia	34 (50)	7 (53.8)	27 (49.1)	1
Creatinine $\geq$ 3 mg/dL	20 (29.4)	4 (30.8)	16 (29.1)	0.935
Hyperuricemia	3 (4.4)	0	3 (5.5)	0.410
Intoxication	1 (1.5)	0	1 (1.8)	0.624
pH<7.20	18 (26.5)	2 (15.4)	16 (29.1)	0.911
Phosphorus $\geq$ 7 mg/dL	6 (8.8)	0	6 (11)	0.237
Refractory hypernatremia( $\geq$ 150 mEq/L)	9 (13.2)	1 (7.7)	8 (14.5)	0.725

(Contd...)

Table 1: (Continued)

Parameters	All patients (N=68)	Surviving patients (n=13)	Deceased patients (n=55)	P value
Severe metabolic acidosis (bicarbonate<15 mEq/L with pH<7.20)	26 (38.2)	1 (7.7)	25 (45.5)	0.012
Lactate≥4 mEq/L	10 (14.7)	0	10 (18.2)	0.143
GFR<30 mL/min	45 (66.2)	9 (69.2)	36 (65.5)	0.796
Urine output<0.5 mL/kg/h	48 (70.6)	6 (46.2)	42 (76.4)	0.066
Uremic encephalopathy	2 (2.9)	0	2 (3.6)	0.485
RIFLE classes at the time of HD initiation (n, %)				
No risk	3 (4.4)	1 (7.7)	2 (3.6)	0.522
Risk	7 (10.3)	3 (23.1)	4 (7.3)	0.092
Injury	7 (10.3)	4 (30.8)	3 (5.5)	0.007
Failure	49 (72.1)	5 (38.5)	44 (80)	0.003
Loss	2 (2.9)	0	2 (3.6)	0.485
No risk, risk, injury (total)	17 (25)	8 (61.5)	9 (16.4)	0.001
AKIN stages on HD initiation (n, %)				
0	4 (5.8)	1 (7.7)	3 (5.5)	0.758
I	6 (8.8)	3 (23.1)	3 (5.5)	0.044
II	17 (25)	5 (38.5)	12 (21.8)	0.213
III	41 (60.3)	4 (30.8)	37 (67.3)	0.026
0, I, and II (total)	27 (39.7)	9 (69.2)	18 (32.7)	0.026
Mechanical ventilation during HD	52 (76.5)	4 (30.8)	48 (87.3)	<0.001
Sepsis during HD	60 (88.2)	8 (61.5)	52 (94.5)	0.001

ICU: Intensive care unit; APACHE II Score: Acute physiology and chronic health evaluation II score; SOFA Score: Sequential organ failure assessment score; COPD: Chronic obstructive pulmonary diseases; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal failure; AKIN, Acute Kidney Injury Network; HD: Hemodialysis; AKI: Acute Kidney Injury; BUN: Blood urea nitrogen; GFR, Global filtration rate

P=0.008 RIFLE; 7 vs. 15, P=0.002 AKIN) was shorter than that of the patients who received HD in the late stages according to RIFLE and AKIN (table 2).

In the multivariate analysis, HD initiation in the early stage according to the RIFLE classification was found to be an independent factor in the decreased ICU mortality (OR=0.7, 95% CI=0.008–0.62; P=0.017). Mechanical ventilation support (OR=12.35, 95% CI=1.78–85.8; P=0.011) and sepsis (OR=22.36, 95% CI=1.5–333.3; P=0.024) were the factors that increased ICU mortality during HD.

## Discussion

In the literature, there are a large number of studies on the timing of renal replacement therapy (RRT) in AKI, especially in critically ill patients. Studies on the evaluation of the RIFLE and AKIN criteria vis-à-vis HD initiation are very limited. In our study, we hypothesized that early initiation of RRT in critically ill patients according to the RIFLE and AKIN classifications decreases ICU mortality. We found that early HD initiation according to the RIFLE classification decreased ICU mortality. Additionally, we found that sepsis and mechanical ventilation during RRT were bad prognostic factors for mortality during HD.

According to a study from Canada, life-threatening high serum potassium levels, presence of pulmonary edema due to hypervolemia, and severity of edema are the criteria considered by clinicians during HD initiation.<sup>6</sup> In our study, decreased urinary output, decreased GFR (<30 mL/min), and hypervolemia were the most common reasons for HD initiation.

In a study by Shiao et al.,<sup>7</sup> the rate of mortality was decreased in a situation where HD was started when the serum creatinine value was 1.5–2-fold compared to when the serum creatinine level was more than twofold the normal value. Elsewhere, the mortality rate was reported to show an increase in patients who were started on HD when their creatinine levels were <3.5 mg/dL (309 µmol/L).<sup>8,9</sup> In our study, we did not find any difference in mortality between the low creatinine group (<3 mg/dL) and the high creatinine group (≥3 mg/dL), suggesting that creatinine levels was not a major determinative parameter for HD initiation in our ICU.

The blood urea level has been noted to play a role in the timing of HD and the prognosis of the patients in some studies, while it was not significant in the studies performed by Jamale et al.<sup>10</sup> and Demirkilic et al.<sup>11</sup> Similar to these studies, we did not find any difference in ICU mortality according to the blood urea level.

**Table 2:** Comparison of early and late HD groups according to the RIFLE and AKIN classifications

Parameters	All patients (N=68)	Early HD (according to RIFLE) 17 (25%)	Late HD (according to RIFLE) 51 (75%)	P value	Early HD (according to AKIN) 27 (39,7%)	Late HD (according to AKIN) 41 (60,3%)	P value
Age (y) (median, interquartile range)	66.5 (54-76.8)	58 (39.5-70.5)	68 (57-78)	0.062	64 (44-72)	70 (57.5-79)	0.114
Gender (male, %)	39 (56.5)	8 (47.1)	31 (60.8)	0.322	14 (51.9)	25 (61)	0.617
Length of ICU stay (d) (median, interquartile range)	10.5 (5-21)	6 (2-16)	14 (6-26)	0.008	7 (3-12)	15 (7.5-27.5)	0.002
APACHE II (median, interquartile range)	24 (18.3-28)	24 (17-33)	24 (19-28)	0.580	25 (18-31)	23 (19-28)	0.411
SOFA score (median, interquartile range)	7 (5-11)	6 (4-6)	8 (5-11)	0.216	7 (4-10)	8 (5-11)	0.293
Reasons for admission to the ICU (n, %)							
Respiratory insufficiency	46 (67.6)	11 (64.7)	35 (68.6)	0.772	18 (66.7)	28 (68.3)	1.000
Sepsis/septic shock	46 (67.6)	9 (52.9)	37 (72.5)	0.148	17 (63)	29 (70.7)	0.599
Cardiovascular	10 (14.7)	1 (5.9)	9 (17.6)	0.236	4 (14.8)	6 (14.6)	0.984
Gastrointestinal	16 (23.5)	3 (17.6)	13 (25.5)	0.509	6 (22.2)	10 (24.4)	0.837
Renal	28 (41.2)	11 (64.7)	17 (33.3)	0.044	14 (51.9)	14 (34.1)	0.208
Comorbidities (n, %)							
Diabetes mellitus	19 (28)	4 (23.5)	15 (29.4)	0.640	6 (22.2)	13 (31.7)	0.425
Cardiovascular	27 (39.7)	4 (23.5)	23 (45.1)	0.156	9 (33.3)	18 (43.9)	0.453
Hypertension	32 (47.1)	6 (35.3)	26 (51)	0.401	9 (33.3)	23 (56.1)	0.085
Cancer	30 (44.1)	9 (52.9)	21 (41.2)	0.415	13 (48.1)	17 (41.5)	0.625
Respiratory (chronic obstructive lung diseases)	13 (19.1)	4 (23.5)	9 (17.6)	0.593	6 (22.2)	7 (17.1)	0.754
Gastrointestinal	8 (11.8)	2 (11.8)	6 (11.8)	0.844	3 (11.1)	5 (12.2)	0.705
Neurological	11 (16.2)	1 (5.9)	10 (19.6)	0.183	2 (7.4)	9 (22)	0.111
Mechanical ventilation during HD (n, %)	52 (76.5)	9 (52.9)	43 (84.3)	0.018	18 (66.7)	34 (82.9)	0.150
Sepsis during HD (n, %)	60 (88.2)	14 (82.4)	46 (90.2)	0.385	22 (81.5)	38 (92.7)	0.161
Mortality in the ICU (n, %)		9 (52.9)	46 (90.2)	0.001	18 (66.7)	37 (90.2)	0.026

HD: Hemodialysis; ICU: Intensive care unit; APACHE II Score: Acute physiology and chronic health evaluation II score; SOFA Score: Sequential organ failure assessment score; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal failure; AKIN: Acute Kidney Injury Network

Oliguria was selected as a criterion to start RRT in many studies, and this was found to be more sensitive than urea or creatinine levels in predicting the prognosis.<sup>12</sup> Oliguria was defined as <100 mL of urine in 8 hours, <400 mL of urine in 24 hours, or <30 mL of urine hourly in 6 hours. In our study, urine output <0.5 mL/kg/h in more than 6 hours was accepted as oliguria. Also, we found that there was no difference in ICU mortality when HD was started on the basis of this criterion.

A direct association between increased ICU mortality and volume overload of patients has been known for a long time. Therefore, some studies have suggested that HD be started when volume overload is >10% of the body weight and is unresponsive to diuretic treatment.<sup>4</sup> Hypervolemia was assessed in our study periodically, and it was accepted as an important criterion for HD initiation. Nevertheless, our results demonstrated no effect on ICU mortality.

Ostermann et al.<sup>8</sup> reported increased mortality in patients in whom HD was started

with a pH < 7.2. The threshold level for pH was considered 7.2 in our study. Mortality was similar in the groups of patients in whom HD was commenced with pH levels lower or higher than this level. However, the rate of mortality increased in the patients in whom HD was initiated when the HCO<sub>3</sub> level was <15 mEq/L in blood gas analysis.

The RIFLE and AKIN classification systems have been drawn upon to determine the prognosis of AKI. Nonetheless, they are also currently utilized to determine the timing of RRT. Bagshaw et al.<sup>13</sup> suggested that in the presence of severe AKI (i.e., RIFLE category failure or AKIN category III) and/or rapidly deteriorating kidney function, RRT initiation be considered, particularly if there was failure to respond to initial therapy.

Hoste et al.<sup>14</sup> found that of those developing RIFLE class risk, 56% progressed to either class injury or failure, and of those developing RIFLE class injury, 36% progressed to RIFLE

class failure. The patients in RIFLE class failure had a worse clinical outcome, characterized by a 2.7- (95% CI=2.0–3.6) fold increased risk of hospital death and longer durations of stay in both ICU and hospital. Yet, of these RIFLE class failure patients, only 14.2% received HD. However, no specific analysis was performed in their study to explore whether the higher mortality for that group (RIFLE class failure) was modified by earlier HD initiation.

Shiao et al.<sup>7</sup> evaluated the effects of early and late RRT initiation according to the RIFLE classification. Mortality was lower in the patients in whom RRT was started early (43% vs. 75%; P=0.002) in their study, which chimes in with our study.

Bell et al.<sup>15</sup> stratified their study population by RIFLE class at the time of HD initiation and found that those in RIFLE class failure had considerably higher 30-day mortality than those in whom RRT was initiated in either RIFLE class risk or injury (adjusted HR=3.4, 95% CI=1.2–9.3, crude 30-day mortality =57.9% for failure vs. 23.5% for risk vs. 22.0% for injury).

There are some limitations in our study. Firstly, it is a retrospective study. Secondly, it is a single-center study. Thirdly, the study group is very small. Fourthly, all the patients in the study population are medical patients, not traumatic or surgical patients. For all these reasons, the results obtained from this study cannot be generalized. Fifthly, we calculated the estimated GFR with the Cockcroft–Gault formula. This formula is less valuable, but easy to calculate at bedside. The use of this formula may reduce the dependability of the GFR calculation. However, we did not use the estimated GFR to classify the patients according to RIFLE. Despite these limitations, our study is an important study in that it demonstrates the importance of the RIFLE classification in early HD initiation and its relation to ICU mortality.

## Conclusion

In critically ill patients with AKI, the RIFLE/AKIN criteria can provide the possibility of a more quantitative characterization of the timing of HD initiation.

**Conflict of Interest:** None declared.

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