Clinical Kidney Journal, 2017, vol. 10, no. 3, 332–340

doi: 10.1093/ckj/sfw107
Advance Access Publication Date: 13 December 2016
Original Article

Acute kidney injury in patients with severe sepsis or septic shock: a comparison between the 'Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease' (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications

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Abstract

Purpose: Using the Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE), Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) systems, the incidence of acute kidney injury (AKI) and their ability to predict in-hospital mortality in severe sepsis or septic shock was compared.

Materials and methods: We performed a retrospective analysis of 457 critically ill patients with severe sepsis or septic shock hospitalized between January 2008 and December 2014. Multivariate logistic regression was employed to evaluate the association between the RIFLE, AKIN and KDIGO systems with in-hospital mortality. Model fit was assessed by the goodness-of-fit test and discrimination by the area under the receiver operating characteristic (AUROC) curve. Statistical significance was defined as $P < 0.05$.

Results: RIFLE (84.2%) and KDIGO (87.5%) identified more patients with AKI than AKIN (72.8%) ($P < 0.001$). AKI defined by AKIN and KDIGO was associated with in-hospital mortality {AKIN: adjusted odds ratio [OR] 2.3[95% confidence interval (CI) 1.3–4], $P = 0.006$; KDIGO: adjusted OR 2.7[95% CI 1.2–6.2], $P = 0.021$} while AKI defined by RIFLE was not [adjusted OR 2.0 (95% CI 1–4), $P = 0.063$]. The AUROC curve for in-hospital mortality was similar between the three classifications (RIFLE 0.652, $P < 0.001$; AKIN 0.686, $P < 0.001$; KDIGO 0.658, $P < 0.001$).

Received: June 2, 2016. **Accepted:** September 22, 2016

Conclusions: RIFLE and KDIGO diagnosed more patients with AKI than AKIN, but the prediction ability for in-hospital mortality was similar between the three systems.

Key words: acute kidney injury, definition, incidence, mortality, sepsis

Introduction

Numerous definitions have been proposed to define acute kidney injury (AKI) [1], resulting in great discrepancy in the reported incidence of AKI. This heterogeneity of data has made the comparison of various published studies focusing on AKI difficult, and in many cases impossible. The development of two new classification systems for AKI over the last decade [Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN)] [2, 3] has led to enhanced knowledge concerning the epidemiology of AKI, demonstrating greater sensitivity and specificity in the diagnosis and stratification of AKI [4]. The RIFLE classification system (Table 1) was published in 2004 [2]. It stratifies AKI according to three classes of severity—risk, injury and failure—based on serum creatinine (SCr) or glomerular filtration rate (GFR) and on changes in urine output (UO) over a predetermined period of time and two classes of outcome—loss of kidney function and end-stage kidney disease—based on time of renal replacement therapy dependency. Worsening of renal function must occur over a period of 7 days and persist for >24 h for AKI to be deemed present. In the absence of a pre-existing history of chronic kidney disease (CKD) and when baseline SCr is unknown, a baseline GFR between 75 and 100 mL/min/1.73 m^2 should be assumed and the Modification of Diet in Renal Disease (MDRD) equation should be used to calculate an estimated baseline SCr. However, some modifications were warranted due to the knowledge that even small increases in SCr are associated with poor outcomes [5], the fact that formulas that estimate GFR presume a steady state that is absent in AKI and, lastly, due to differences in accessibility and indications for initiation of renal replacement therapy among different institutions and countries. Therefore, in 2007, the AKIN classification (Table 1), also known as the modified RIFLE [3], was proposed and published with the intention of improving diagnostic accuracy. Instead of depending on either SCr or GFR, the AKIN classification relies solely on the former, calling for at least two measurements over a 48-h period, thereby discarding the requirement for known baseline SCr levels. The diagnosis of AKI and classification of patients into the various groups is carried out only after the hydration status has been optimized and after excluding urinary obstruction as a cause for renal dysfunction, and the AKIN classification does not consider outcome classes, as happens with the RIFLE classification. AKIN has not proved to be advantageous over RIFLE regarding the severity and outcomes of AKI despite showing a higher diagnostic sensitivity [6–8]. Recently, the RIFLE and AKIN classifications were merged into the Kidney Disease: Improving Global Outcomes (KDIGO) classification (Table 1), with the purpose of providing integrated yet simplified criteria to be applied in clinical activity, research and public health surveillance [9]. In this classification, severity has been stratified in the same way as AKIN, except for a simplification of the criteria required to reach stage 3. Theoretically, KDIGO offers advantages over the other two systems in identifying patients with AKI and in predicting outcome.

Sepsis is the leading cause of AKI in the intensive care unit (ICU) and patients with septic AKI are clinically distinct from those with non-septic AKI. Septic AKI is associated with high disease severity scores, non-renal organ failure, requirement for mechanical ventilation, need for vasoactive drugs, extended lengths of ICU and hospital stay, higher in-hospital mortality and increased probability of renal function recovery at hospital discharge [10, 11]. Consequently, a profound understanding of septic AKI is essential for the nephrologist and the intensivist to appropriately formulate diagnoses, treatment options and follow-up strategies, in addition to predicting patient outcome.

The KDIGO classification system has been recently assessed in several published studies [12–18]; however, its applicability to septic AKI and its comparison with the two previous classifications has not yet been performed or validated in this setting. Therefore, we sought to evaluate the incidence of AKI according

Table 1. RIFLE [2], AKIN [3] and KDIGO [9] classifications

Class/ stage	SCr/GFR			UO		
	RIFLE	AKIN	KDIGO	RIFLE	AKIN	KDIGO
Risk/1[a]	↑ SCr ×1.5 or ↓ GFR >25%	↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑ SCr ≥150–200% (1.5–2×)	↑ SCr ≥26.5 μmol/L (≥0.3 mg/dL) or ↑ SCr ≥150–200% (1.5–2×)	<0.5 mL/kg/h (>6 h)	<0.5 mL/kg/h (>6 h)	<0.5 mL/kg/h (>6 h)
Injury/2[a]	↑ SCr ×2 or ↓ GFR >50%	↑ SCr >200–300% (>2–3×)	↑ SCr >200–300% (>2–3×)	<0.5 mL/kg/h (>12 h)	<0.5 mL/kg/h (>12 h)	<0.5 mL/kg/h (>12 h)
Failure/ 3[a]	↑ SCr ×3 or ↓ GFR >75% or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑ SCr 44.2 μmol/L (>0.5 mg/dL)	↑ SCr >300% (>3×) or if baseline SCr ≥353.6 μmol/L (≥4 mg/dL) ↑SCr ≥44.2 μmol/L (≥0.5 mg/dL) or initiation of renal replacement therapy	↑ SCr >300% (>3×) or ↑SCr to ≥353.6 μmol/L (≥4 mg/dL) or initiation of renal replacement therapy	<0.3 mL/kg/h (>24 h) or anuria (>12 h)	<0.3 mL/kg/h (24 h) or anuria (12 h)	<0.3 mL/kg/h (24 h) or anuria (12 h)

[a]Risk class (RIFLE) corresponds to stage 1 (AKIN and KDIGO), injury class (RIFLE) corresponds to stage 2 (AKIN and KDIGO) and failure class (RIFLE) corresponds to stage 3 (AKIN and KDIGO).

Table 2. Patients' baseline characteristics

Characteristic	Value
Age (years), mean ± SD	64.1 ± 16.4
Gender (Male), *n* (%)	264 (57.9)
Race (Caucasian), *n* (%)	433 (94.7)
Weight (kg), mean ± SD	76.2 ± 18.2
Hypertension, *n* (%)	212 (46.5)
Co-morbidities, *n* (%)	
Diabetes	103 (22.6)
CVD	125 (27.4)
COPD	38 (8.3)
Cirrhosis	18 (3.9)
Malignancy	109 (23.9)
Medical admission, *n* (%)	253 (55.5)
Infection source, *n* (%)	
Abdominal	187 (41.0)
Respiratory	138 (30.3)
Kidney	57 (12.5)
Skin	34 (7.5)
Other	26 (5.7)
Unknown	14 (3.1)
SAPS II, mean ± SD	49.4 ± 17.3
Baseline SCr (mg/dL)[a], mean ± SD	1.3 ± 0.6
Admission SCr (mg/dL)[b], mean ± SD	2.3 ± 1.5
Haemoglobin (g/dL)[c], mean ± SD	10.4 ± 2.0
Serum albumin (g/dL)[c], mean ± SD	1.9 ± 0.6
Mechanical ventilation, *n* (%)[d]	350 (76.8)
Vasopressors, *n* (%)[d]	316 (69.3)
Fluid balance (L)[d], mean ± SD	4.5 ± 5.7
RRT, *n* (%)[d]	108 (23.7)
LOS in hospital (days), mean ± SD	37.1 ± 39.4
LOS in ICU (days), mean ± SD	10.0 ± 10.0
ICU mortality, *n* (%)	108 (23.7)
In-hospital mortality, *n* (%)	153 (33.6)

LOS, length of stay; RRT, renal replacement therapy; SD, standard deviation.
[a]Used in RIFLE and KDIGO classifications.
[b]Used in AKIN classification.
[c]On ICU admission.
[d]During ICU stay.

to these three classifications (RIFLE, AKIN and KDIGO) and compared their ability to predict in-hospital mortality in a cohort of critically ill patients with severe sepsis or septic shock.

Materials and methods

The present study is retrospective in nature, including all patients with severe sepsis or septic shock admitted to the Division of Intensive Medicine of the Centro Hospitalar Lisboa Norte (Lisbon, Portugal) between January 2008 and December 2014. Centro Hospitalar Lisboa Norte is an academic and referral centre for 3 000 000 inhabitants.

The study was approved by the Ethical Committee at the Centro Hospitalar Lisboa Norte, EPE, in agreement with institutional guidelines. Informed consent was waived by the Ethical Committee due to the retrospective and non-interventional nature of the study.

Participants

Selection of potentially eligible patients was conducted based on the ICU patient admission register. All adult patients (≥18 years of age) with severe sepsis or septic shock admitted to the Division of Intensive Medicine were selected. Sepsis was defined by historical criteria in accordance with the American College of Chest Physicians and the Society of Critical Care Medicine consensus [19].

Exclusion criteria included (i) CKD patients already on renal replacement therapy, (ii) patients who underwent renal replacement therapy 1 week before ICU admission and (iii) patients who were discharged or died <2 days after admission in the ICU.

Variables and data sources

All variables were collected from electronic and handwritten patient clinical records. The analysed variables included patient demographic characteristics (age, gender, ethnicity and body weight), comorbidities [diabetes mellitus, hypertension, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), cirrhosis and malignancy], primary diagnosis (medical versus surgical), source of infection, serum haemoglobin, serum albumin, SCr, UO, disease severity according to the Simplified Acute Physiologic Score (SAPS) II [20] as determined by the worst variables recorded during the first 24 h, fluid balance, need for mechanical ventilation, vasopressor use and requirement for renal replacement therapy. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria [21] and hypertension was diagnosed according to the seventh report of the Joint National Committee [22]. CVD was considered whenever a history of cerebrovascular disease, chronic heart failure, cardiac ischaemic disease and peripheral arterial disease was present, and COPD included emphysema and chronic bronchitis. For CVD and COPD, a previous diagnosis on clinical records was considered sufficient. In-hospital mortality was considered the outcome measure.

The development of AKI within the first week of ICU hospitalization was diagnosed and classified using the RIFLE, AKIN and KDIGO classifications based on both SCr and UO criteria (Table 1). The criteria that led to the worst classification were used and the maximum RIFLE, maximum AKIN and maximum KDIGO were reported. In this ICU, SCr is determined at least once a day and UO is recorded hourly for all patients. Pre-admission SCr (SCr within the previous 3 months) was considered as baseline SCr for RIFLE and KDIGO classifications and SCr on ICU admission was considered as baseline SCr for AKIN classification. When pre-admission SCr values were unavailable they were estimated from the MDRD equation [23] assuming the lower limit of a normal baseline GFR of 75 mL/min/1.73 m^2. Hourly recorded urine output was available for all patients and 6-h periods were used to diagnose and classify AKI.

Statistical methods

Continuous variables were presented as the mean ± standard deviation and categorical variables as the total number and percentage of cases for each category. RIFLE classes, AKIN stages and KDIGO stages were compared using Student's *t*-test for normally distributed continuous variables, Mann–Whitney *U* test for non-normally distributed continuous variables and chi-square test for categorical variables.

Multivariate logistic regression analysis was employed to evaluate the association between RIFLE criteria, AKIN criteria and KDIGO criteria with in-hospital mortality. Model fit was assessed by the goodness-of-fit test and discrimination was assessed by the area under the receiver operating characteristic (AUROC) curve. Data were expressed as odds ratios (ORs) with

Table 3. Demographic and clinical characteristics of patients according to the development of AKI defined by the RIFLE, AKIN and KDIGO classifications

	RIFLE			AKIN			KDIGO		
Characteristic	No AKI (*n* = 72)	AKI (*n* = 384)	P-value	No AKI (*n* = 124)	AKI (*n* = 332)	P-value	No AKI (*n* = 57)	AKI (*n* = 399)	P-value
Age (years), mean ± SD	62.4 ± 18.2	64.4 ± 15.6	0.321	62.6 ± 17.1	64.6 ± 15.6	0.215	64.1 ± 17.4	64.1 ± 16.0	0.994
Gender (male), *n* (%)	16 (63.9)	218 (56.8)	0.262	73 (58.9)	191 (57.5)	0.796	35 (61.4)	229 (57.4)	0.566
Race (Caucasian), *n* (%)	67 (93.1)	366 (95.3)	0.422	116 (93.5)	317 (95.5)	0.401	54 (94.7)	379 (95.0)	0.936
Weight (kg), mean ± SD	71.01 ± 14.5	77.2 ± 18.7	0.009	73.1 ± 15.7	77.4 ± 19.0	0.024	70.9 ± 14.3	77.0 ± 18.6	0.019
Co-morbidities, *n* (%)									
Hypertension	34 (47.2)	178 (46.4)	0.892	59 (47.6)	153 (46.1)	0.776	30 (50.2)	182 (45.6)	0.320
Diabetes	17 (23.6)	86 (22.4)	0.821	29 (23.4)	74 (23.3)	0.803	15 (26.3)	88 (22.1)	0.472
CVD	17 (23.6)	108 (28.1)	0.431	29 (23.4)	96 (28.9)	0.239	14 (24.6)	111 (27.8)	0.606
COPD	6 (8.3)	32 (8.3)	1.000	12 (9.7)	26 (7.8)	0.526	5 (8.8)	33 (8.3)	0.898
Cirrhosis	2 (2.8)	16 (4.2)	0.579	3 (2.4)	15 (4.5)	0.306	1 (1.8)	17 (4.3)	0.363
Malignancy	18 (25)	91 (23.7)	0.812	33 (26.6)	76 (22.9)	0.407	13 (22.8)	96 (24.1)	0.836
Medical admission, *n* (%)	41 (56.9)	212 (55.2)	0.768	67 (54.0)	186 (56.0)	0.703	31 (54.4)	222 (55.6)	0.859
Infection source, *n* (%)									
Abdominal	23 (31.9)	164 (42.7)	0.088	47 (37.9)	140 (42.2)	0.410	19 (33.3)	168 (42.1)	0.208
Respiratory	22 (30.6)	116 (30.2)	0.953	40 (32.3)	98 (29.5)	0.571	16 (28.3)	122 (30.6)	0.700
Kidney	16 (22.2)	41 (10.7)	0.007	24 (19.4)	33 (9.9)	0.007	14 (24.6)	43 (10.8)	0.003
Skin	3 (4.2)	31 (8.1)	0.247	5 (4.0)	29 (8.7)	0.089	2 (3.5)	32 (8.0)	0.225
Other	7 (9.7)	19 (4.9)	0.109	7 (5.6)	19 (5.7)	0.975	6 (10.5)	20 (5.0)	0.093
Unknown	1 (1.4)	13 (3.4)	0.367	1 (0.8)	13 (3.9)	0.087	0 (0.0)	14 (3.5)	0.151
SAPS II, mean ± SD	42.8 ± 15.3	50.7 ± 17.4	<0.001	44.3 ± 15.3	51.3 ± 17.6	<0.001	42.8 ± 15.6	50.4 ± 17.3	0.002
Baseline SCr (mg/dL)[a], mean ± SD	1.4 ± 0.6	1.3 ± 0.6	0.169				1.4 ± 0.7	1.3 ± 0.6	0.185
Admission SCr (mg/dL)[b], mean ± SD				2.1 ± 1.5	2.3 ± 1.5	0.176			
Haemoglobin (g/dL)[c], mean ± SD	10.1 ± 2.1	10.4 ± 2.0	0.248	10.1 ± 1.8	10.5 ± 2.1	0.047	10.0 ± 1.7	10.5 ± 2.0	0.078
Serum albumin (g/dL)[c], mean ± SD	2.1 ± 0.6	1.9 ± 0.6	0.018	2.1 ± 0.6	1.9 ± 0.6	0.003	2.1 ± 0.6	1.9 ± 0.6	0.003
Mechanical ventilation, *n* (%)[d]	51 (70.8)	85 (77.9)	0.195	88 (71)	262 (78.9)	0.074	41 (71.9)	309 (77.4)	0.357
Vasopressors, *n* (%)[d]	35 (48.6)	281 (73.2)	<0.001	66 (53.2)	250 (75.3)	<0.001	26 (45.6)	290 (72.7)	<0.001
Fluid balance (L)[d], mean ± SD	3.9 ± 6.9	4.6 ± 5.4	0.335	3.7 ± 5.9	4.8 ± 5.6	0.065	3.6 ± 6.9	4.6 ± 5.4	0.180
RRT, *n* (%)[d]		108 (28.1)			108 (32.5)			108 (27.1)	
LOS in hospital (days), mean ± SD	41.4 ± 54.3	36.3 ± 35.9	0.314	36.6 ± 37.2	37.2 ± 40.2	0.879	39.5 ± 44.8	36.7 ± 38.6	0.625
LOS in ICU (days), mean ± SD	9.9 ± 9.9	10.0 ± 10.1	0.913	9.4 ± 9.4	10.2 ± 10.3	0.431	9.8 ± 10.3	10.0 ± 10.0	0.881
ICU mortality, *n* (%)	10 (13.9)	98 (25.5)	0.033	18 (14.5)	90 (27.1)	0.005	7 (12.3)	101 (25.3)	0.030
Hospital mortality, *n* (%)	16 (22.2)	137 (35.7)	0.026	26 (21.0)	127 (38.3)	0.001	10 (17.5)	143 (87.5)	0.006

[a]Used in RIFLE and KDIGO classifications.
[b]Used in AKIN classification.
[c]On ICU admission.
[d]During ICU stay.

95% confidence intervals (CIs). Statistical significance was defined as a P-value <0.05. Analyses were performed with the statistical software package SPSS for Windows (version 21.0; SPSS, Chicago, IL, USA). The comparison between AUROC curves was made using the method of DeLong with the statistical software MedCalc for Windows (version 16.2; MedCalc Software, Ostend, Belgium).

Results

Participants

After analysis of the ICU patient admission register, 723 patients were selected as potentially eligible. Of these, 266 were excluded: 122 had CKD on renal replacement therapy and 144 had been hospitalized for less than 48 h. None required renal replacement therapy in the week preceding ICU admission. Consequently, we focused on a final cohort of 457 patients. Patient baseline characteristics are described in Table 2.

Demographic and clinical characteristics of the studied population according to AKI development are described in Table 3. Pre-admission SCr was available in 185 patients (40.6%) and in the remaining cases [*n* = 272(59.4%)] it was estimated using the MDRD formula, assuming a baseline eGFR of 75 mL/min/1.73 m^2. As expected, when compared with patients not developing AKI, AKI patients were more likely to have significantly higher SAPS II values (P < 0.001 for RIFLE and AKIN; P = 0.002 for KDIGO) and to require vasopressors (P < 0.001 for RIFLE, AKIN and KDIGO). Lower serum albumin values were also more commonly found among AKI patients (P = 0.018 for RIFLE; P = 0.003 for AKIN and

Table 4. Patients with AKI classified by creatinine criteria, UO criteria or both

	SCr	UO	SCr + UO
RIFLE classification, %			
Risk	53.2	31.2	15.6
Injury	65.4	26.7	7.9
Failure	46.2	38.3	15.5
Any category	52.6	33.9	13.5
AKIN classification, %			
Stage 1	50.5	32.1	17.4
Stage 2	44.1	55.9	0
Stage 3	28.1	64.7	7.2
Any category	38.8	52.1	9.1
KDIGO classification, %			
Stage 1	49.1	34.2	16.7
Stage 2	31.0	67.3	1.7
Stage 3	34.7	55.9	9.4
Any category	38.7	50.9	10.4

Table 5. Incidence of AKI according to RIFLE, AKIN and KDIGO criteria

	RIFLE	AKIN	P-value
Risk/stage 1	77 (16.9)	110 (24.1)	0.007
Injury/stage 2	100 (21.9)	70 (15.5)	0.011
Failure/stage 3	207 (45.4)	152 (33.3)	0.002
Any category	384 (84.2)	332 (72.8)	<0.001
	RIFLE	KDIGO	P-value
Risk/stage 1	77 (16.9)	89 (19.5)	0.303
Injury/stage 2	100 (21.9)	103 (22.6)	0.811
Failure/stage 3	207 (45.4)	207 (45.4)	1
Any category	384 (84.2)	399 (87.5)	0.154
	AKIN	KDIGO	P-value
Risk/stage 1	110 (24.1)	89 (19.5)	0.092
Injury/stage 2	70 (15.5)	103 (22.6)	0.005
Failure/stage 3	152 (33.3)	207 (45.4)	<0.001
Any category	332 (72.8)	399 (87.5)	<0.001

Values given as *n* (%).

KDIGO). Furthermore, ICU mortality (P = 0.033 for RIFLE; P = 0.005 for AKIN; P = 0.03 for KDIGO) and in-hospital mortality (P = 0.026 for RIFLE; P = 0.001 for AKIN; P = 0.006 for KDIGO) were also higher in AKI patients than in non-AKI patients.

AKI stratified by the RIFLE, AKIN and KDIGO criteria

AKI occurred in 84.2% of patients with a maximum RIFLE category: risk in 16.9%, injury in 21.9% and failure in 45.4%. According to AKIN and KDIGO criteria, AKI occurred in 72.8% of patients (24.1% with stage 1, 15.4% with stage 2 and 33.3% with stage 3) and 87.5% of patients (19.5% with stage 1, 22.6% with stage 2 and 45.4% with stage 3), respectively (Table 4). RIFLE and KDIGO criteria allowed for the identification of more patients as having AKI than AKIN criteria (P < 0.001, respectively) and classified more patients with injury (P = 0.011)/stage 2 of KDIGO (P = 0.005) and failure (P = 0.002)/stage 3 of KDIGO (P < 0.001), although AKIN identified more patients with stage 1 than RIFLE (P = 0.007). There were no significant differences in AKI incidence (overall AKI and severity classes/stages) between RIFLE and KDIGO classifications (Table 5).

Creatinine criteria led to a maximum RIFLE in 52.6% of patients, a maximum AKIN in 38.8% of patients and a maximum KDIGO in 38.7% of patients, while UO criteria led to a maximum RIFLE in 33.9% of patients, a maximum AKIN in 52.1% of patients and a maximum KDIGO in 50.9% of patients, whereas in almost 10% of patients it was both the UO and creatinine criteria that led to a maximum RIFLE, a maximum AKIN and a maximum KDIGO (Table 4).

Table 6. In-hospital mortality for AKI defined and classified according to RIFLE, AKIN and KDIGO criteria

	RIFLE	AKIN	P-value
Risk/stage 1	25 (18.2)	23 (18.2)	0.767
Injury/stage 2	32 (23.0)	38 (30.0)	0.455
Failure/stage 3	66 (48.3)	72 (56.6)	0.579
Any category	49 (35.7)	49 (38.3)	1
	RIFLE	KDIGO	P-value
Risk/stage 1	25 (18.2)	30 (21.3)	0.487
Injury/stage 2	32 (23.0)	33 (23.3)	0.898
Failure/stage 3	66 (48.3)	69 (48.3)	0.78
Any category	49 (35.7)	51 (35.8)	0.832
	AKIN	KDIGO	P-value
Risk/stage 1	23 (18.2)	30 (21.3)	0.425
Injury/stage 2	38 (30.0)	33 (23.3)	0.537
Failure/stage 3	72 (56.6)	69 (48.3)	0.783
Any category	49 (38.3)	51 (35.8)	0.832

Values given as *n* (%).

In-hospital mortality

AKI defined by AKIN and KDIGO based on SCr and UO criteria was independently associated with increased in-hospital mortality [AKIN: any category 38.3%, adjusted OR 2.3 (95% CI 1.3–4), P = 0.006; KDIGO: any category 35.8%, adjusted OR 2.7 (95% CI 1.2–6.2), P = 0.021], while AKI defined by RIFLE was not [any category 35.7%, adjusted OR 2.0 (95% CI 1–4), P = 0.063]. In addition, failure [48.3%, adjusted OR 1.4 (95% CI 1.1–1.8), P = 0.009], as well as stage 3 of AKIN and KDIGO [AKIN 56.6%, adjusted OR 1.6 (95% CI 1.3–2.1), P < 0.001; KDIGO 48.3%, adjusted OR 2.7 (95% CI 1.2–6.2), P = 0.021], was also independently associated with an increased risk for death. In contrast, risk and stage 1 of AKIN and KDIGO, as well as injury and stage 2 of AKIN and KDIGO, were not associated with increased in-hospital mortality (Tables 6 and 7).

Multivariate analysis was repeated using the RIFLE, AKIN and KDIGO classifications based either on creatinine criteria or on UO criteria (Table 7). On the one hand, AKI defined by SCr criteria, as well as any of its classes/stages, was not associated with increased risk for in-hospital death. On the other hand, when AKI was defined and categorized by UO criteria, any category of AKI [adjusted OR 2.7 (95% CI 1.7–4.5), P < 0.001], as well as injury/stage 2 [adjusted OR 1.8 (95% CI 1.2–2.7), P = 0.004] and failure/stage 3 [adjusted OR 1.8 (95% CI 1.4–2.3), P < 0.001], was significantly associated with increased in-hospital mortality.

When considering both creatinine and UO criteria, the AUROC curve for in-hospital mortality was 0.652 for RIFLE criteria (P < 0.001), 0.686 for AKIN criteria (P < 0.001) and 0.658 for KDIGO criteria (P < 0.001) (Figure 1). There were no statistically significant differences in AUROC curves between the three classifications (RIFLE versus AKIN, P = 0.227; RIFLE versus KDIGO, P = 0.156; AKIN versus KDIGO, P = 0.147). The AUROC curves of these classifications for in-hospital mortality were significantly higher when defining AKI only by UO criteria as compared with SCr criteria (RIFLE, P < 0.001; AKIN, P < 0.001; KDIGO, P = 0.004).

Table 7. Multivariate regression analysis of in-hospital mortality for the RIFLE, AKIN and KDIGO classifications

Criteria	OR (95% CI)	P-value	AUROC curve (95% CI)
RIFLE criteria (SCr + UO)			
Risk	0.9 (0.3–2.4)	0.820	0.652 (0.607–0.696)
Injury	1.3 (0.8–2.1)	0.284	
Failure	1.4 (1.1–1.8)	0.009	
Any category	2.0 (1.0–4.0)	0.063	
AKIN criteria (SCr + UO)			
Stage 1	0.9 (0.4–1.9)	0.768	0.686 (0.642–0.729)
Stage 2	1.3 (0.8–2.0)	0.234	
Stage 3	1.6 (1.3–2.1)	<0.000	
Any stage	2.3 (1.3–4.0)	0.006	
KDIGO criteria (SCr + UO)			
Stage 1	1.5 (0.5–4.3)	0.486	0.658 (0.612–0.701)
Stage 2	1.7 (0.9–3.1)	0.085	
Stage 2	1.6 (1.1–2.1)	0.005	
Any stage	2.7 (1.2–6.2)	0.021	
RIFLE criteria (SCr)			
Risk	1.1 (0.6–2.2)	0.737	0.506 (0.449–0.562)
Injury	1.1 (0.8–1.5)	0.456	
Failure	1.0 (0.8–1.3)	0.779	
Any category	1.1 (0.7–1.9)	0.626	
AKIN criteria (SCr)			
Stage 1	1.0 (0.6–1.7)	0.955	0.528 (0.472–0.585)
Stage 2	0.9 (0.5–1.4)	0.508	
Stage 3	1.4 (1.1–1.9)	0.014	
Any stage	1.6 (1.0–2.6)	0.057	
KDIGO criteria (SCr)			
Stage 1	1.1 (0.5–2.3)	0.872	0.605 (0.549–0.661)
Stage 2	0.8 (0.5–1.3)	0.466	
Stage 2	1.2 (1.0–1.5)	0.076	
Any stage	1.3 (0.7–2.4)	0.322	
RIFLE, AKIN and KDIGO criteria (UO)			
Risk	0.8 (0.4–1.6)	0.466	0.701 (0.647–0.754)
Injury	1.8 (1.2–2.7)	0.004	
Failure	1.8 (1.4–2.3)	<0.000	
Any category	2.7 (1.7–4.5)	<0.000	

Multivariate analysis included age, gender, race, diabetes mellitus, hypertension, CVD, COPD, cirrhosis, malignancy, medical admission, illness severity evaluated by SAPS II, haemoglobin, serum albumin, need for vasopressors or mechanical ventilation and fluid balance.

Discussion

We conducted a single-centre study comprising 457 critically ill patients admitted to the ICU with severe sepsis or septic shock, aiming to evaluate the incidence of AKI according to the new definitions/classifications for AKI—the RIFLE, AKIN and KDIGO systems—and to compare their ability in predicting in-hospital mortality of those patients.

In the present study, the incidence of AKI was high, varying between 72.8 and 87.5% depending on the definition used. These results are in accordance with other retrospective studies carried out primarily in sepsis cohorts and that have also reported a high occurrence of septic-associated AKI. In these studies, >60–70% of patients with septic shock suffered AKI [24, 25].

A small number of recently published studies have compared the incidence of AKI as defined and categorized by the RIFLE, AKIN and KDIGO systems, as well as their prediction performance in different medical settings. In the FINNAKI study, the incidence of AKI defined by the AKIN and KDIGO criteria among the 2901 ICU patients studied was identical (39%) [12]. In a prospective study enrolling 637 patients hospitalized for acute decompensated heart failure, the incidence of AKI as defined by RIFLE, AKIN and KDIGO criteria was also similar and there were only slight differences in the predictive ability between RIFLE and KDIGO in relation to clinical outcomes at 30 days (AUROC 0.76 and 0.74, respectively) [13]. In a cohort of 1050 patients diagnosed with acute myocardial infarction, KDIGO criteria detected significantly more AKI patients than RIFLE criteria (36.6 versus 14.8%) and those patients diagnosed as having AKI by KDIGO criteria, but not RIFLE criteria, had a substantially higher early and late mortality (adjusted hazard ratio for 30-day death of 3.51 by RIFLE and 3.99 by KDIGO; adjusted hazard ratio for 1-year mortality of 1.84 by RIFLE and 2.43 by KDIGO) [14]. The incidence of AKI was identical between the RIFLE, AKIN and KDIGO classification systems in a retrospective analysis of 1881 adult patients who underwent cardiac surgery, however, the AUROC curve was significantly greater when using the AKIN as compared with the RIFLE criteria (0.86 versus 0.78, $P < 0.001$) [15]. In a recent retrospective cohort study considering 31 970 hospitalizations, the incidence of AKI was similar between the RIFLE, AKIN and KDIGO systems, as were their adjusted ORs for in-hospital death [16]. In a Chinese prospective study of 3107 ICU patients, KDIGO criteria diagnosed more AKI patients than both RIFLE (51 versus 46.9%, $P = 0.001$) and AKIN criteria (51 versus 38.4%, $P < 0.001$) and the AUROC curves for in-hospital mortality were 0.738 ($P < 0.001$) for RIFLE, 0.746 ($P < 0.001$) for AKIN and 0.757 ($P < 0.001$) for KDIGO. KDIGO was shown to be more predictive than RIFLE for in-hospital mortality ($P < 0.001$), but there were no differences between KDIGO and AKIN ($P = 0.12$) regarding this outcome [17]. Fujii *et al.* [18] recently completed a retrospective analysis of 49 518 hospitalizations and reported that the RIFLE and KDIGO criteria identified more patients with AKI than AKIN (11 versus 4.8%) and proved to have a higher discrimination ability for in-hospital mortality (AUROC curve for RIFLE 0.77; AUROC curve for KDIGO 0.78; AUROC curve for AKIN 0.69).

In our analysis, we found that RIFLE and KDIGO criteria permitted the identification of more patients as having AKI than AKIN criteria and classified more patients with injury/stage 2 of KDIGO and failure/stage 3 of KDIGO. However, AKIN recognized more patients with stage 1 AKI than RIFLE criteria. No significant differences in AKI incidence (overall AKI and severity classes/stages) were found when comparing RIFLE and KDIGO classifications. Furthermore, the prediction performance for in-hospital mortality was similar between the three classifications.

The pre-admission SCr level (1.3 ± 0.6 mg/dL) was much lower than the mean SCr level on the day of admission to the ICU (2.3 ± 1.5 mg/dL), implying that AKI may have already been present on the day of ICU admission or even earlier. In accordance with the definition of AKI by AKIN criteria, AKI was diagnosed by two creatinine measurements within 48 h. Unfortunately, most patients did not have a daily creatinine measurement prior to the ICU admission. Therefore, when using creatinine at ICU admission, some AKI cases may have been undeniably overlooked [26–28]. In addition, patients with a slow but progressive decrease in renal function may have also gone unnoticed when using the AKIN criteria for diagnosis [29].

In the current study, approximately one-third of patients with AKI as defined by the RIFLE classification system and one-half of patients with AKI defined by the KDIGO and AKIN systems were diagnosed as so based merely on UO criteria. We speculate that the higher percentage of AKI patients identified by UO criteria alone compared with those in whom AKI was diagnosed only by SCr criteria could be related to more pronounced oliguria often seen in septic patients, hemodilution

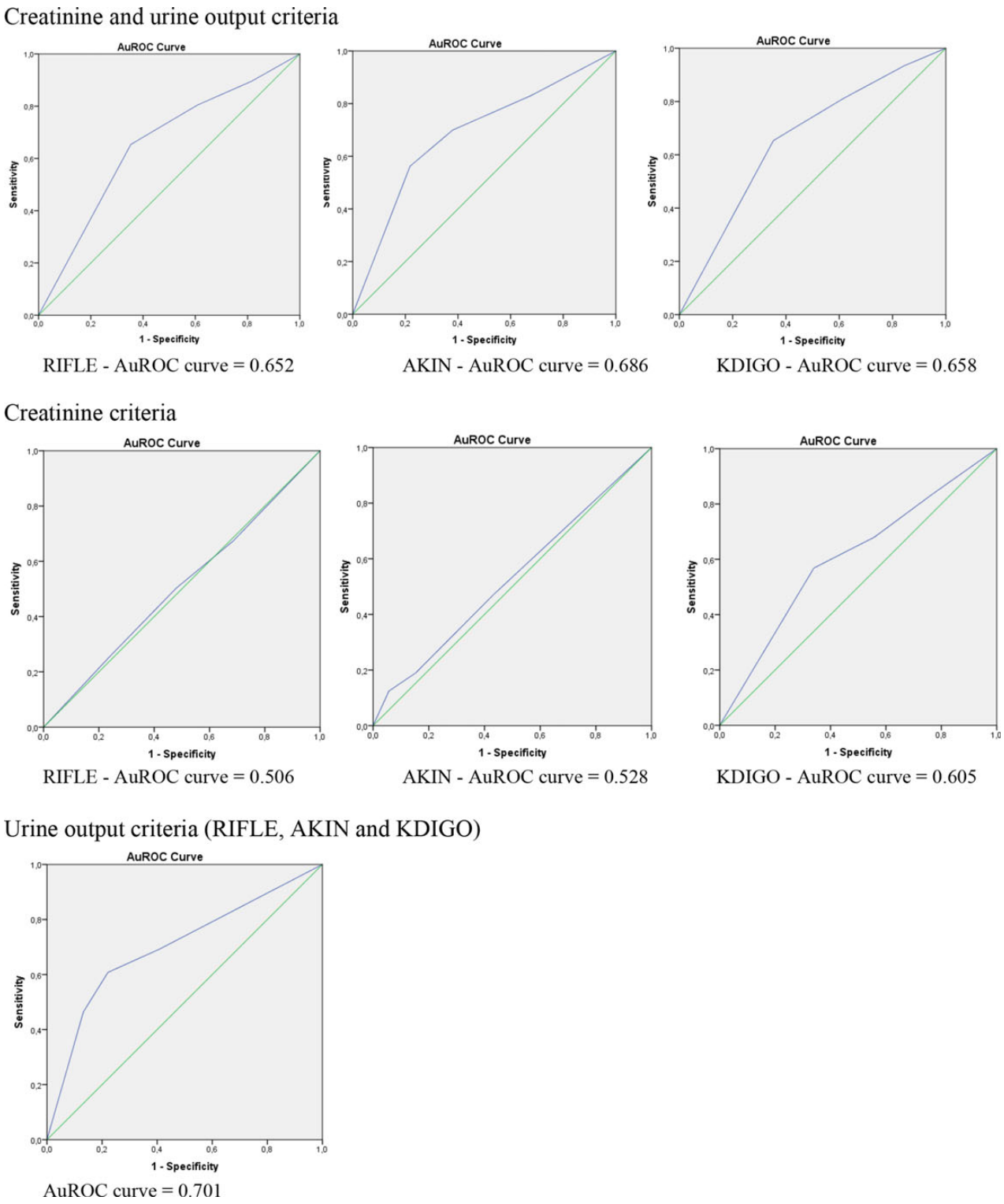

FIGURE 1: Area under the receiver operating characteristic (AUROC) curves for in-hospital mortality according to the Risk, Injury, Failure, Loss of kidney function, End-stage kidney disease (RIFLE), the Acute Kidney Injury Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) classifications based on serum creatinine and urine output criteria.

due to aggressive fluid resuscitation and greater degrees of positive fluid balance usually achieved in septic patients, resulting in lower SCr values, and reduced production of endogenous creatinine in sepsis [30–32].

There is a lack of conclusive data on the impact of AKI defined by SCr and/or UO on mortality. For example, in a systematic review, the relative risk for death among studies that used RIFLE based on SCr and UO was lower than in those using RIFLE

based exclusively on SCr [33]. Nevertheless, in a previous study we did not find any difference in terms of mortality for RIFLE based on SCr and UO and RIFLE based on SCr alone [6] and, similar to a North East Italian multicentre prospective study in 2164 ICU patients concerning AKI classified by the RIFLE criteria [34], the SCr criteria appeared to be a better predictor of mortality than UO. In contrast, in a recent prospective cohort study of critically ill patients, in those with AKI diagnosed exclusively by UO criteria, the need for renal replacement therapy was more frequent, the length of ICU stay was longer and the mortality rate was higher than in those patients without AKI [35]. We determined that AKI defined only by UO criteria was superior in the prediction of in-hospital mortality than AKI defined either by SCr itself or by both SCr and UO. Hence, UO seems to be a valid criterion with prognostic value in patients with septic AKI.

The present study has some limitations, including, first, its single-centre retrospective nature and relatively small cohort of patients. Second, the pre-admission SCr level was unknown to us in almost 60% of patients, compelling us to calculate an estimated baseline function using the MDRD equation, as recommended (assuming the lower limit of the normal baseline GFR of 75 mL/min/1.73 m^2) and previously applied [2, 6, 36, 37]. The estimation of a baseline SCr from the MDRD equation when pre-admission SCr is unavailable appears to perform reasonably well only if and when pre-admission GFR is near normal; however, in patients with supposed CKD, use of the MDRD equation to estimate baseline SCr overestimates the incidence of AKI and should not be employed [38]. Third, notwithstanding having measurements of UO on an hourly basis, data regarding additional factors that could influence UO, such as the use of diuretic therapy, was not available to us. Overall, we recognize that the presence of any biases would ultimately influence all three classifications, and thus would not significantly impact our conclusions.

Despite these limitations, our study has numerous strengths. To the best of our knowledge, this is the first study comparing the incidence of AKI as defined by the RIFLE, AKIN and KDIGO criteria and comparing their prognostic capability in critically ill patients with severe sepsis or septic shock. Moreover, we used both creatinine criteria and UO criteria to define and categorize AKI. Finally, notwithstanding the retrospective nature of the study, most of the studied variables were routinely registered during daily clinical practice.

Conclusions

Granting that the RIFLE and KDIGO criteria potentially diagnose more ICU patients with severe sepsis or septic shock as having AKI than the AKIN criteria, the prediction ability for discerning in-hospital mortality was similar between the three systems. Nonetheless, future prospective studies enrolling a larger number of patients are still warranted to better determine the sensitivity and prognostic performance of these classifications in critically ill patients with severe sepsis or septic shock.

Conflict of interest statement

None declared.

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