Acute kidney injury in the intensive care unit according to RIFLE*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain the meaning of RIFLE.
2. Describe the usefulness of RIFLE in the intensive care unit.
3. Use this information in a clinical setting.

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Objectives: To apply the RIFLE criteria "risk," "injury," and "failure" for severity of acute kidney injury to patients admitted to the intensive care unit and to evaluate the significance of other prognostic factors.

Design: Retrospective analysis of the Riyadh Intensive Care Program database.

Setting: Riyadh Intensive Care Unit Program database of 41,972 patients admitted to 22 intensive care units in the United Kingdom and Germany between 1989 and 1999.

Patients: Acute kidney injury as defined by the RIFLE classification occurred in 15,019 (35.8%) patients; 7,207 (17.2%) patients were at risk, 4,613 (11%) had injury, and 3,199 (7.6%) had failure. It was found that 797 (2.3%) patients had end-stage dialysis-dependent renal failure when admitted to an intensive care unit.

Interventions: None.

Measurements and Main Results: Patients with risk, injury, and failure classifications had hospital mortality rates of 20.9%, 45.6%, and 56.8%, respectively, compared with 8.4% among patients without acute kidney injury. Independent risk factors for hospital mortality were age (odds ratio 1.02); Acute Physiology and Chronic Health Evaluation II score on admission to intensive care unit (odds ratio 1.10); presence of preexisting end-stage disease (odds ratio 1.17); mechanical ventilation (odds ratio 1.52); RIFLE categories risk (odds ratio 1.40), injury (odds ratio 1.96), and failure (odds ratio 1.59); maximum number of failed organs (odds ratio 2.13); admission after emergency surgery (odds ratio 3.08); and nonsurgical admission (odds ratio 3.92). Renal replacement therapy for acute kidney injury was not an independent risk factor for hospital mortality.

Conclusions: The RIFLE classification was suitable for the definition of acute kidney injury in intensive care units. There was an association between acute kidney injury and hospital outcome, but associated organ failure, nonsurgical admission, and admission after emergency surgery had a greater impact on prognosis than severity of acute kidney injury. (Crit Care Med 2007; 35:1837–1843)

KEY WORDS: acute kidney injury; intensive care unit; RIFLE; outcome

Acute renal failure is classically defined as an abrupt and sustained decrease in renal function. However, there is neither agreement on the best method of assessing renal function nor consensus on the exact cutoffs for the diagnosis. Even the degrees to which the process is "abrupt" or "sustained" are variable. In 1994, Novis and colleagues (1) performed a systematic review of 28 studies on renal failure after surgery published between 1965 and 1989 and found that no study used the same criteria to define renal failure. Ten years later, a survey of 598 doctors and nurses who attended an international critical care nephrology meeting revealed that as many as 199 different definitions for acute renal failure were used in clinical practice (2). As a result, reported incidences of acute renal failure in the intensive care unit (ICU) range from 1% to 25% with mortality rates between 40% and 90% (2–10). This lack of a uniform

*See also p. 1983.

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Table 1. RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria for the definition of acute kidney injury

RIFLE Category	GFR Criteria	Urine Output Criteria
Risk	Increased serum creatinine × 1.5 or decrease of GFR >25%	Urine output <0.5 mL/kg/hr for 6 hrs
Injury	Increased serum creatinine × 2 or decrease of GFR >50%	Urine output <0.5 mL/kg/hr for 12 hrs
Failure	Increased serum creatinine × 3 or decrease of GFR >75% or serum creatinine ≥4 mg/dL	Urine output <0.3 mL/kg/hr for 12 hrs or anuria for 12 hrs
Loss	Complete loss of renal function for >4 wks	
End-stage kidney disease	Need for RRT for >3 mos	

GFR, glomerular filtration rate; RRT, renal replacement therapy.

definition not only leads to conflicting reports in the literature but also is believed to be a major obstacle to research in this field. Several nephrologists and critical care experts have called for consensus criteria (11–13). Furthermore, the term *acute kidney injury* (AKI) has been put forth as the preferred nomenclature to replace acute renal failure with the understanding that the spectrum of AKI is broad and includes different degrees of severity. The most recent proposal for a consensus definition for AKI stems from the Acute Dialysis Quality Initiative group, which suggested criteria for three grades of increasing severity (Risk of acute renal failure, Injury to the kidney, Failure of kidney function) and two outcome classes (Loss of kidney function and End-stage kidney disease) (RIFLE classification) (Table 1) (13).

Fourteen studies have been published that used the RIFLE classification in specific patient populations (14–28). Abosaif et al. (14) applied the RIFLE criteria to 183 ICU patients, Kuitunen et al. (15) used the RIFLE classification to determine the incidence of AKI among 813 patients undergoing cardiac surgery, and Ahlstrom et al. (16) evaluated its predictive power among 668 ICU patients. The RIFLE criteria were also applied to patients on renal replacement therapy (RRT) (17, 28), 46 patients treated with extracorporeal membrane oxygenation (18), and 126 burn patients (19), as well as bone marrow transplant recipients (20), human immunodeficiency virus-infected patients (21), and patients with sepsis (26). Larger studies were undertaken by Hoste et al. (22), who validated the RIFLE criteria among 5,383 ICU patients, and Uchino et al. (23), who applied the RIFLE classification to 20,126 hospitalized patients. Last, Heringlake et al. (24) surveyed 81 cardiac centers in Germany and received creatinine data from 26 centers to determine the incidence of AKI after cardiac surgery. Outcome data were not collected. A correlation between the RIFLE criteria and outcome was demonstrated by all investigators but Heringlake et al. (24) and Maccariello et al (28). Interestingly, the latter two were also the only studies undertaken in more than one center. All other 12 studies were single-center studies with a specific patient population.

Our aim was to apply the RIFLE classification to a large cohort of >40,000 ICU patients admitted to several different ICUs in two countries. We assessed the correlation with hospital mortality and were particularly interested in evaluating the impact of AKI in the context of other risk factors.

MATERIALS AND METHODS

Study Population. We retrospectively analyzed the Riyadh Intensive Care Unit Program database with demographic and daily physiologic data of 41,972 adult patients over 153,958 ICU days. All patients were admitted to ICUs in 16 district hospitals and three teaching hospitals in the United Kingdom and three ICUs in teaching hospitals in Germany between June 1989 and October 1999.

Data Analysis. All patients without preexisting dialysis-dependent renal failure were categorized according to the RIFLE classification. Due to lack of data on 6- or 12-hr urine volumes, we only used the glomerular filtration rate (GFR) criteria to determine the RIFLE category. As recommended by the Acute Dialysis Quality Initiative working group, GFR was calculated using the simplified "modification of diet in renal disease" formula (GFR = 186 × [serum creatine]$^{-1.154}$ × [age]$^{-0.203}$ × [0.742 if female] × [1.210 if black]) (29). Patients were classified according to the change between baseline and daily GFR during their stay in the ICU. As suggested by the Acute Dialysis Quality Initiative working group, for patients whose preexisting renal function was not known, a normal GFR before admission to ICU was assumed (13). The most severe degree of AKI was recorded, that is, patients with injury to the kidney at admission to ICU who later developed failure of kidney function were classified as having failure. Similarly, patients who had failure at one stage and later recovered remained classified as having failure. We did not study the outcome classes of RIFLE (Loss and End-stage kidney disease) in this study.

The impact of associated organ failure was assessed by defining organ failure according to the criteria of Knaus and colleagues (30), supplemented by a definition for gastrointestinal failure (31). Maximum number of associated organ failure refers to the highest number of other failed organs (excluding renal failure) on any day during the stay in the ICU. The study was reviewed by the local ethics committee. The need for informed consent was waived because the study required neither an intervention nor breach of privacy or anonymity.

Statistical Analysis. Demographic data were presented as mean ± SD and 95% confidence intervals or median and range. Student's *t*-test, chi-square test, Fisher's exact test, and Mann-Whitney test were employed in univariate analyses to evaluate statistical significance ($p < .05$). Multivariate logistic regression analysis was conducted to identify independent predictors of all-cause hospital mortality and to obtain the odds ratios. Variables that were found to be significant risk factors in univariate analyses were entered simultaneously in the multivariable model (enter method). These variables included nine categorical variables (gender; presence of preexisting end-stage chronic illness; need for mechanical ventilation; RIFLE categories of risk, injury, and failure; RRT for AKI; emergency surgery; elective surgery; nonsurgical admission; and admission after cardiac surgery) and four numerical variables (age, Acute Physiology and Chronic Health Evaluation II score on admission to ICU, number of failed organs on admission to ICU, and maximum number of associated organ failure). Odds ratios were estimated from the b coefficients obtained, with respective 95% confidence intervals. Calibration of the model was assessed by the goodness-of-fit statistic test from Hosmer-Lemeshow, and discrimination capability was evaluated by determining the area under the receiver operating characteristic curve. The statistical package SPSS (version 14.0, Woking, UK) was used for all statistical analyses. We considered $p < .05$ to be statistically significant.

RESULTS

Baseline Demographics. We analyzed data of 41,972 adult ICU patients (63.5%

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Table 2. Characteristics and outcome depending on degree of renal function

	No AKI (n = 26,153)	Risk (n = 7,207)	Injury (n = 4,613)	Failure (n = 3,199)
Age, yrs				
Mean	57.3	66.5	67.3	63.7
95% CI	57.2–57.5	66.2–66.7	66.9–67.7	63.2–64.2
SD	16.01	12.9	13.2	14.5
Range	16–99	16–99	16–97	16–96
APACHE II score at admission to ICU				
Median	11	15	19	22
Range	1–64	1–44	1–62	1–52
No. of associated failed organs at admission to ICU[a]				
Median	0	0	1	1
Range	0–5	0–6	0–6	0–6
Maximum no. of associated failed organ systems[a]				
Median	1	1	1	2
Range	0–5	0–6	0–6	0–6
Outcome				
ICU mortality, n (%)	1,307 (5.0)	1,057 (14.7)	1,686 (36.5)	1,523 (47.6)
Hospital mortality, n (%)	2,204 (8.4)	1,505 (20.9)	2,104 (45.6)	1,816 (56.8)
Survivors' ICU length of stay, days				
Median	1	2	3	6
Range	1–112	1–270	1–219	1–193
Nonsurvivor's ICU length of stay, days				
Median	2	2	3	5
Range	1–90	1–73	1–110	1–104

AKI, acute kidney injury; CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

[a]Excluding renal failure.

males) with a mean age of 60.5 yrs (SD 15.7); 12,790 patients (30.5%) were admitted to ICUs in three teaching hospitals in the United Kingdom, 15,493 patients (36.9%) were admitted to ICUs in 16 district hospitals in the United Kingdom, and 13,689 patients (32.6%) were admitted to ICUs in three teaching hospitals in Germany. All participating ICUs were able to provide RRT. There were 2,872 patients (6.8%) who were transfers from other hospitals. The overall ICU mortality was 13.7%, and hospital mortality was 18.8% (standardized mortality ratio 1.07). Three patients had incomplete data to determine their RIFLE category and were excluded from the subsequent analysis.

Incidence of AKI and Outcome. There were 15,019 patients (35.8%) who fulfilled the criteria for AKI, of whom the majority were classified as being in the RIFLE category risk (Table 2); 26,153 patients (62.3%) had no evidence of AKI according to the RIFLE classification. There were 797 patients who had preexisting dialysis-dependent renal failure.

Any degree of AKI was associated with a significantly increased all-cause ICU and hospital mortality compared with not having AKI (Tables 2 and 3). Without controlling for any other risk factors, compared with not having AKI, we found that the odds ratio for death in hospital was 2.11 for patients in the risk category, 5.15 for patients in the injury category, and 8.27 for patients in the failure category. The RIFLE classes also correlated with length of stay in ICU: Median length of stay was shortest among patients without AKI and increased with increasing severity of AKI (Table 2).

There were 1,836 patients who received RRT for AKI, of whom 1,473 patients (80.2%) were treated with a continuous mode alone (continuous arteriovenous hemofiltration or continuous veno-venous hemo[dia]filtration), 95 patients (5.2%) who received intermittent hemodialysis, and 12 patients (0.7%) who were treated with peritoneal dialysis alone. There were 243 patients (13.2%) treated with a combination of a continuous mode and intermittent hemodialysis and 12 patients (0.7%) who received a continuous mode followed by peritoneal dialysis. One patient had incomplete data related to type of RRT.

During the time periods 1989–1993, 1994–1996, and 1997–1999, the mean GFR at time of initiation of RRT was 23.8 mL/min/1.73 m^2 (SD 26.6), 23.7 mL/min/1.73 m^2 (SD 22.2), and 24 mL/min/1.73 m^2 (SD 21.7), respectively. Within individual units, the average GFR at time of RRT did not change significantly, but there were differences between units ranging from an average GFR 14 mL/min/1.73 m^2 to 43 mL/min/1.73 m^2.

There were 2,872 patients transferred from other hospitals. The exact reasons for transfer could not be retrieved. There were 455 transferred patients (including 16 patients with dialysis-dependent renal failure) treated with RRT during their stay in the ICU, of whom 259 patients received renal support within 24 hrs after transfer.

Impact of Confounding Factors. There was a correlation between severity of AKI and Acute Physiology and Chronic Health Evaluation II score as well as number of failed organs on the day of admission to ICU (Table 2). In all RIFLE categories, hospital mortality increased as the maximum number of associated failed organ systems increased (Table 4). Similarly, among patients with the same maximum number of failed organs, outcome was worse in patients with more severe AKI.

Within each RIFLE category, a proportion of patients were treated with RRT. In a univariate analysis, mortality was higher among patients who received RRT than in patients within the same RIFLE category but not receiving RRT (Table 5).

Multivariate Analysis. Age, Acute Physiology and Chronic Health Evaluation II score on admission to ICU, presence of preexisting end-stage chronic illness, mechanical ventilation, maximum number of failed organ systems, nonsurgical admission, admission after emergency surgery, and RIFLE categories of risk, injury, and failure were found to be independently associated with all-cause hospital mortality (Table 6). Maximum number of associated organ failures, admission after emergency surgery, and nonsurgical admission were the strongest predictors of hospital outcome. Male gender and admission after cardiac surgery were independently associated with reduced hospital mortality. In contrast, preexisting dialysis-dependent renal failure and treatment with RRT for AKI were not associated with a worse outcome. The area under the receiver operating characteristic curve was 0.897 (Hosmer-Lemeshow chi-square = 48.32; 2 *df*, $p < .001$).

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Table 3. Univariate analysis of the characteristics of hospital survivors and nonsurvivors

Characteristics	Survivors (n = 34,065) n	Survivors %	Nonsurvivors (n = 7,904) n	Nonsurvivors %	Odds Ratio (95% CI)	*p*
Male sex	21,937	64.4	4,700	59.5	0.81 (0.77–0.85)	<.0001
Mean age, yrs (95% CI)	59.4 (59.3–59.6)		64.9 (64.5–69.2)			<.0001
Median APACHE II score at admission to ICU (range)	12 (0–49)		21 (0–64)			<.0001
Median APACHE II score on day of AKI (range)[a]	15 (2–45)		22 (3–62)			<.0001
Degree of AKI						
No AKI	23,949	70.3	2,204	27.9		
Risk	5,702	16.7	1,505	19.0	2.11 (2.02–2.21)[b]	<.0001
Injury	2,509	7.4	2,104	26.6	5.15 (4.91–5.4)[b]	<.0001
Failure	1,383	4.06	1,816	22.98	8.27 (7.78–8.8)[b]	<.0001
Type of admission						
Nonsurgical	11,508	33.8	5,499	69.6	4.48 (4.25–4.73)	<.0001
Elective surgery	18,945	55.6	1,058	13.4	0.12 (0.12–0.13)	<.0001
Emergency surgery	3,612	10.6	1,347	17.0	1.73 (1.62–1.85)	<.0001
Source of admission						
Operating room	21,744	63.8	2,237	28.3	0.22 (0.21–0.24)	<.0001
Emergency room	5,038	14.8	1,531	19.4	1.38 (1.3–1.47)	<.0001
Ward	3,974	11.7	2,936	37.1	4.47 (4.25–4.73)	<.0001
Hospital transfers	2,064	6.1	808	10.2	1.77 (1.62–1.92)	<.0001
Recovery room	891	2.6	189	2.4	0.91 (0.77–1.07)	NS
Other	355	1.0	204	2.6	2.48 (2.08–2.95)	<.0001
Chronic end-stage diseases present	6,666	19.6	2,387	30.2	1.78 (1.68–1.88)	<.0001
Hb at admission to ICU						
≥9 g/dL	29,198	85.7	6,421	81.2		
<9 g/dL	4,867	14.3	1,483	18.8	1.39 (1.3–1.48)	<.0001
Patients admitted after cardiac surgery[c]	8,559	25.1	455	5.8	0.18 (0.17–0.20)	<.0001
Patients ventilated	19,583	57.5	6,388	80.8	3.12 (2.94–3.31)	<.0001
Renal replacement therapy						
RRT for AKI or ESRD	912	2.68	1288	16.3	7.08 (6.48–7.73)	<.0001
RRT for AKI only	708	2.1	1128	14.3	7.84 (7.1–8.65)	<.0001
Failed organs at day of admission to ICU						
0	20,433	59.98	1,635	20.7		<.0001
1	10,579	31.06	2,760	34.9	3.26 (3.05–3.48)	<.0001
2	2,573	7.6	2,133	27.0	10.4 (9.60–11.18)	<.0001
≥3	480	1.4	1,376	17.4	35.8 (31.9–40.2)	<.0001
Maximum no. of associated organ failures during entire ICU stay (including AKI)						
0	14,153	41.5	437	5.5		
1	12,042	35.4	1,262	5.97	1.62 (1.57–1.67)	<.0001
2	5,664	16.6	2,253	28.5	2.93 (2.85–3.01)	<.0001
3	1,761	5.2	2,375	30.0	7.63 (7.28–8.00)	<.0001
>3	445	1.3	1,577	19.95	25.7 (23.37–28.23)	<.0001
Maximum no. of associated organ failures during entire ICU stay (excluding AKI)						
0	18,544	54.4	932	11.8		
1	11,427	33.5	2,325	29.4	1.87 (1.82–1.92)	<.0001
2	3,421	10.0	2,827	35.8	4.83 (4.66–5.01)	<.0001
3	588	1.7	1,305	16.5	18.98 (17.4–20.71)	<.0001
>3	85	0.2	515	6.5	78.0 (62.4–97.51)	<.0001

CI, confidence interval; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury; Hb, hemoglobin; ICU, intensive care unit; RRT, renal replacement therapy; ESRD, end-stage dialysis-dependent renal failure.

[a]Only patients with AKI; [b]compared with patients with no AKI; [c]coronary artery bypass surgery and/or valve surgery.

DISCUSSION

Many nephrologists and intensivists agree that criteria for AKI are needed to facilitate clinical research and to allow comparison between different studies and institutions (11, 12). Ultimately, the ideal AKI classification needs to be accurate and predictive of relevant clinical outcomes. We previously showed that the proposed criteria by Bellomo et al. (acute renal injury, acute renal failure syndrome, severe acute renal failure syndrome) fulfilled this requirement (32). Application of the RIFLE criteria to the same database again confirms a correlation between severity of AKI and outcome. Patients with AKI had a longer stay in ICU and a significantly higher all-cause ICU and hospital mortality than patients without AKI. Even when we controlled for confounding factors in a multiple variable regression analysis, the RIFLE categories of risk, injury, and failure remained independent risk factors for hospital mortality. These findings are in keeping with previous studies. Kuitunen et al. (15) applied the RIFLE classification to a group of 813 patients who had undergone cardiac surgery and found that 156 patients (19.2%) developed AKI postoperatively. Ninety-day mortality was significantly higher in patients with RIFLE failure compared with patients with RIFLE risk (32.5% vs. 8%). Abosaif et al. (14) applied the RIFLE classification to 183 ICU patients and found that ICU mortality increased from 38.3% among patients with RIFLE risk to 50% in the injury group and to 74.5% among patients with RIFLE failure. Ahlstrom et al. (16) determined the incidence and outcome of AKI according to the RIFLE classification within the first 3 days in ICU and found that hospital mortality among 668 patients increased from 13% in the risk group to 23% in patients with failure. Hoste et al. (22) observed a similar correlation between severity of AKI and outcome among 5,383 ICU patients. Hospital mortality increased from 5.5% among patients without AKI to 8.8% in patients with RIFLE risk, 11.4% in patients with RIFLE injury, and 26.3% in patients with RIFLE failure. Uchino et al. (23) validated the RIFLE classification in 20,126 hospitalized patients and showed an almost linear increase in hospital mortality from "no AKI" to the failure category (no AKI 4.4%, risk 15.1%, injury 29.2%, failure 41.1%). All studies, including our own data, confirm that even moderate degrees of kidney dysfunction pose a significant risk of death. However, the question remains at which level of renal impairment mortality increases; that is, where is the exact cutoff between normal renal function and AKI with an increased risk of death? The RIFLE classification requires patients to have a reduction in GFR by ≥25% or a decrease in urine output to <0.5 mL/kg/hr in order to be

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Table 4. Association between maximum number of failed organs and hospital outcome

Maximum No. of Failed Organs (Excluding AKI)	No AKI (n = 26,153)		Risk (n = 7,207)		Injury (n = 4,613)		Failure (n = 3,199)	
	No. of Patients (%)	Died in Hospital (%)	No. of Patients (%)	Died in Hospital (%)	No. of Patients (%)	Died in Hospital (%)	No. of Patients (%)	Died in Hospital (%)
0	14,590 (55.8)	437 (3.0)	3,067 (42.6)	204 (6.7)	1,050 (22.8)	153 (14.6)	434 (13.6)	87 (20)
1	8,418 (32.2)	767 (9.1)	2,582 (35.8)	495 (19.2)	1,578 (34.2)	550 (34.9)	916 (28.6)	428 (46.7)
2	2,583 (9.9)	695 (26.9)	1,135 (15.7)	507 (44.7)	1,318 (28.6)	843 (64)	1,079 (33.7)	700 (64.9)
3	471 (1.8)	243 (51.6)	354 (4.9)	244 (68.9)	479 (10.4)	381 (79.5)	531 (16.6)	392 (73.8)
>3	91 (0.3)	62 (68.1)	69 (0.96)	55 (79.7)	188 (4.0)	177 (94.1)	239 (7.5)	209 (87.4)

AKI, acute kidney injury.

Table 5. Impact of renal replacement therapy (RRT)

	Without RRT		With RRT		
	Incidence, No. (%)	Hospital Mortality, No. (%)	Incidence, No. (%)	Hospital Mortality, No. (%)	p
No AKI (n = 26,153)	26,085 (99.7)	2,190 (8.4)	68 (0.3)	14 (20.6)	.0007
Risk (n = 7,207)	7,126 (98.9)	1,449 (20.3)	81 (1.1)	56 (69.1)	<.0001
Injury (n = 4,613)	4,207 (91.2)	1,791 (42.6)	406 (8.8)	313 (77.1)	<.0001
Failure (n = 3,199)	1,918 (60)	1,071 (55.8)	1,281 (40)	745 (58.2)	.21

AKI, acute kidney injury.

Table 6. Multivariate logistic regression analysis: Impact of risk factors on risk of death in hospital

Variables	B	p	OR (95% CI) for Hospital Mortality
Admission after cardiac surgery	−0.698	.000	0.5 (0.44–0.57)
Male gender	−0.070	.036	0.93 (0.87–0.995)
No. of failed organs at admission to ICU	−0.085	.001	0.92 (0.87–0.97)
Age	0.023	.000	1.02 (1.02–1.03)
APACHE II score at admission to ICU	0.092	.000	1.097 (1.09–1.104)
Preexisting chronic end-stage disease	0.153	.000	1.17 (1.08–1.26)
Mechanical ventilation	0.42	.000	1.52 (1.41–1.65)
Renal function			
No AKI			
Risk	0.335	.000	1.40 (1.28–1.53)
Injury	0.675	.000	1.96 (1.80–2.14)
Failure	0.461	.000	1.59 (1.43–1.76)
ESRD	−0.99	.330	0.91 (0.74–1.11)
Maximum no. of failed organ systems	0.754	.000	2.13 (2.03–2.23)
Admission after emergency surgery	1.124	.000	3.08 (2.77–3.42)
Nonsurgical admission	1.367	.000	3.92 (3.58–4.30)
RRT for AKI	−0.014	.84	0.99 (0.86–1.13)
Constant	−4.951	.000	0.007

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; AKI, acute kidney injury; ESRD, end-stage dialysis-dependent renal failure; RRT, renal replacement therapy.

classified as being at risk, the mildest category of AKI. However, Chertow et al. (33) demonstrated that even an increase in serum creatinine of only 0.3–0.4 mg/dL while in hospital resulted in a 70% increase in the risk of dying relative to patients with less or no change in serum creatinine. The recently established Acute Kidney Injury Network acknowledged this important finding and accordingly modified the new staging system for AKI (which is based on the RIFLE classification) (34).

In our study, the overall incidence of AKI in ICU was lower compared with the data by Hoste et al. (22) (35.8% vs. 67.2%). The most likely explanations are differences in patient case mix and factors related to single-center studies vs. multicenter studies. However, it is also possible that the incidence of AKI has truly changed in the last decade. Our study included data from 1989 to 1999, whereas Hoste et al. analyzed data of patients admitted between 2000 and 2001. For clarification, we analyzed the data of all patients who were admitted to one of the large tertiary referral centers included in our database between 2001 and 2004 and found that 54% of all patients admitted during this time period fulfilled the RIFLE criteria for AKI. Changes in clinical practice, case mix, and referral patterns to the ICU may be the reason for this increased incidence of AKI over time. Other explanations may be related to differences in the types of ICU, as shown by Uchino et al. (7), who observed a significantly higher incidence of AKI in specific ICUs vs. general ICUs as well as in larger units vs. smaller ones.

Patients with AKI have significant morbidity as judged by their Acute Physiology and Chronic Health Evaluation II score and associated organ failure or Sequential Organ Failure Assessment score (7, 18, 19). Although it is well known that AKI in ICU often occurs in the context of failure of other organs, either as a byproduct or as a significant contributor (35), our study is the only one that controlled for associated organ failure when validating the RIFLE classification. This may explain why the odds ratios for hospital mortality among patients with AKI were lower in our study compared with the results by Uchino et al (23).

An ideal scoring method would be accurate and useful in the prediction of outcome. Our study adds to the evidence that the RIFLE classification is a system that describes AKI and correlates with hospital mortality. However, there are still some unresolved issues. First, the RIFLE classification in its current format does not include criteria for progression of AKI or timing. AKI, like any other organ failure, is a dynamic process (36). Hoste et al. (22) demonstrated that in some patients, AKI progresses from the

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RIFLE category risk to RIFLE categories injury or failure. Similarly, patients may be admitted with the RIFLE failure category but improve rapidly in response to resuscitation. In both cases, patients would be classified as having RIFLE failure although their overall prognosis is different. Similar to Hoste et al. (22) and Uchino et al. (23), we documented the worst degree of AKI independent of timing. In contrast, Ahlstrom et al. (16) classified patients according to their maximum score in the first 3 days in ICU, and Lin et al. (18), who applied the RIFLE classification to patients on extracorporeal membrane oxygenation, used only the values on the first day of extracorporeal membrane oxygenation. Second, the RIFLE classification does not include any criteria for RRT. Data by Hoste et al. (22) as well as our results show that all RIFLE categories included patients who received RRT. This is not surprising, given the lack of consensus criteria for the initiation, mode, and dose of RRT and large variation in practice between units and sometimes individual doctors within the same unit. As a result, the exact incidence of patients with different RIFLE categories may vary depending on whether RRT was started early (so that serum creatinine levels were maintained near normal) or late, when serum creatinine levels had increased by >200%. Ahlstrom et al. (16) dealt with this issue by categorizing all patients who received RRT as having failure. The recently founded Acute Kidney Injury Network decided that patients receiving RRT should be considered to have met criteria for stage 3 (i.e., the worst stage) irrespective of their creatinine level or urine output (34). However, further work and consensus are necessary to overcome the wide variability related to the practice of RRT.

Our study is one of 15 studies that used the RIFLE classification. It is important to consider its strengths and weaknesses. It is the largest multicenter study with incidence and outcome data. Therefore, results of this large cohort of >40,000 patients who were heterogenous in terms of nature of admission, source of admission, and comorbidity may be representative of a wide ICU population. As already alluded to, it is also the only study that controlled for associated organ failure as part of the validation process. On the other hand, we performed a retrospective analysis of data from a 10-yr period, during which time modern critical care may have changed. Since our database only includes information obtained during ICU stay, we were unable to provide data postdischarge from ICU, including data on the incidence and outcome of patients classified as RIFLE loss category or end-stage kidney disease category, that is, patients with AKI who received RRT for >30 days. We also did not have any data on treatment preadmission to ICU, including information on treatment of the 2,872 patients who were transferred from other hospitals. Nine percent of all transferred patients received RRT within 24 hrs after transfer, but we are unable to say how many patients were transferred solely for the purpose of RRT.

With regard to the actual RIFLE criteria, we encountered the same problem as Uchino et al. (23): Our database does not contain any information on 6- and 12-hr urine output, and we therefore classified patients using only the GFR criteria. Whether the inclusion of urine output criteria would have changed the results is not possible to say. Hoste and Kellum (37) summarized the results of ten studies that had used the RIFLE classification and found that patients in the RIFLE risk category defined by creatinine criteria were more severely ill compared with patients in the risk category defined by urine criteria alone. In another series, Hoste et al. (22) observed that patients in the RIFLE failure category based on GFR criteria had a slightly higher hospital mortality than patients in the RIFLE failure category based on urine output criteria (27.9% vs. 21.9%). Last, we did not have any information on the exact etiologies of AKI, the indications for RRT, the delivered dose of RRT, or the number of patients who died because active treatment was withdrawn.

CONCLUSIONS

We agree with previous authors that the RIFLE classification provides useful criteria for AKI that correlate with outcome. There was an association between AKI and hospital outcome, but associated organ failure, nonsurgical admission, and admission after emergency surgery had a greater impact on prognosis than severity of AKI. The recently founded Acute Kidney Injury Network has already modified the RIFLE classification slightly and incorporated new findings related to AKI. More work is necessary, especially related to the standardization of RRT.

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