North East Italian Prospective Hospital Renal Outcome Survey on Acute Kidney Injury (NEiPHROS-AKI): Targeting the Problem with the RIFLE Criteria

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Acute kidney injury (AKI) in the intensive care unit (ICU) is associated with an enhanced mortality. The Acute Dialysis Quality Initiative group has proposed the RIFLE (Risk–Injury–Failure–Loss–ESRD) classification to standardize the approach to AKI. This study was performed to estimate the AKI incidence in ICU patients in northeastern Italy and describe clinical characteristics and outcomes of patients with AKI on the basis of their RIFLE class. A prospective multicenter observational study was performed of patients who fulfilled AKI criteria in 19 ICU in northeastern Italy. Data were analyzed using multivariate logistic regression and survival curve analysis. Of 2164 ICU patients who were admitted during the study period, 234 (10.8%; 95% confidence interval 9.5 to 12.1%) developed AKI; 19% were classified as risk (R), 35% as injury (I), and 46% as failure (F). Preexisting kidney disease was present in 36.8%. The most common causes of AKI were prerenal causes (38.9%) and sepsis (25.6%). At diagnosis of AKI, median serum creatinine and urine output were 2.0 mg/dl and 1100 ml/d, respectively. ICU mortality was 49.5% in class F, 29.3% in I, and 20% in R. Independent risk factors for mortality included RIFLE class, sepsis, and need for renal replacement therapy, whereas a postsurgical cause of AKI, exposure to nephrotoxins, higher serum creatinine, and urine output were associated with lower mortality risk. In this study, AKI incidence in the ICU was between 9 and 12%, with 3.3% of ICU patients requiring renal replacement therapy. Sepsis was a significant contributing factor. Overall mortality was between 30 and 42%, and was highest among those in RIFLE class F.

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Acute kidney injury (AKI) affects 5 to 7% of all hospitalized patients, and despite technological advances, it continues to be associated with poor outcomes (1,2). This syndrome is common in the intensive care unit (ICU), with a reported incidence of 1 to 25% depending on the population being studied and the criteria used to define its presence (1–4). AKI in this setting is associated with mortality rates of 50 to 70%, which have remained relatively constant in the past decades (3,5,6).

Although AKI is associated with a high risk for death, its epidemiology and outcome are not well determined, in part as a result of the lack of a standardized definition. More than 35 different definitions have been used in the literature, including one by Bellomo *et al.* (7), creating conflicting results and making comparisons difficult (8). A practical definition should be based on widely accepted foundations of pathophysiology, clinical behavior, response to treatment, histopathologic features, and prognosis. To define better AKI and its characteristics, the Acute Dialysis Quality Initiative (ADQI) developed a consensus definition for AKI, grading the severity of the disease from "risk" to "injury" to "failure" (Table 1) (9). Recently, a number of single-center studies evaluated the incidence and outcome of AKI using this classification (10–14). It has not been assessed, however, in a multicenter setting. This study estimates the incidence of AKI in ICU patients in northeastern Italy, describes the clinical characteristics of patients with AKI and their outcomes on the basis of their RIFLE (Risk–Injury–Failure–Loss–ESRD) category, and explores the relationship between the two components (serum creatinine and urine output) of the RIFLE criteria.

Materials and Methods

This study was conducted in 19 centers in the three regions in northeastern Italy from April to June 2003 (participating centers are listed at the end of the article). The study protocol was reviewed by the institutional review board of the parent study center (Ospedale San Bortolo) and subsequently adopted and approved by the participating centers. Because of the anonymous observational nature of the study, the need for informed consent was waived.

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Table 1. RIFLE classification for AKI[a]

RIFLE Classification	Creatinine and GFR Criteria	UO Criteria
Risk	Increased creatinine ×1.5 or GFR decrease >25%	UO <0.5 ml/kg per h ×6 h
Injury	Increased creatinine ×2 or GFR decrease >50%	UO <0.5 ml/kg per h ×12 h
Failure	Increased creatinine ×3 or GFR decrease >75%	UO <0.3 ml/kg per h ×24 h or anuria ×12 h
Loss[b]	Persistent ARF = complete loss of kidney function >4 wk	
ESRD[b]	ESRD (need for dialysis >3 mo)	

[a]AKI, acute kidney injury; ARF, acute renal failure; UO, urine output.
[b]"Outcome" categories.

Study Population

Patients who were older than 18 yr and who were admitted to one of the participating ICU during the study period were considered for study inclusion. From this population, only incident patients who fulfilled criteria for the risk, injury, and failure categories of the RIFLE criteria for AKI were included in the study (9). Either the serum creatinine or urine output criterion was used to diagnose AKI and determine the RIFLE classification of each patient, using the criteria that led to the worst possible classification (Table 1). The RIFLE classification at the time of diagnosis of AKI (also called RIFLE "initial") was considered for analysis. For patients in whom baseline serum creatinine values were not known (22%), the value was estimated using the Modification of Diet in Renal Disease equation (assuming average baseline GFR of 75 ml/min per 1.73 m^2), as recommended by the ADQI workgroup (9,15). Patients who had stage 5 chronic kidney disease and were undergoing long-term renal replacement therapy (RRT) were excluded from the study. Two patients were admitted twice to the ICU during the study period for different reasons; in each case, the second admission was counted as a new case.

Data Collection

Multiple data elements were prospectively collected on each patient with AKI at study inclusion and were recorded on a standardized case report form that was developed for this study, which was pilot-tested in one of the participating centers (Ospedale San Bortolo) before dissemination to the other study sites. Requested data included demographics, premorbid renal function, use of potentially nephrotoxic drugs, medical history, urine output, serum creatinine levels, and associated laboratory abnormalities at time of AKI diagnosis. For patients who were treated with RRT, we collected data regarding the initial and subsequent (if any) RRT modality, as well as the type of medical and nursing personnel who initiated and managed the therapy at bedside. Indications, frequency, duration, and operational characteristics of RRT were individualized for each patient by the treating physicians at each site. There were no prespecified criteria for initiation or withdrawal of RRT or for any of its aspects. ICU mortality was the primary outcome of interest. We also collected data on cause of death and ICU length of stay, as well as recovery of renal function, defined as a serum creatinine <1.5 mg/dl (133 μmol/L) and urine output >800 ml/d, or a return to baseline level of renal function at time of ICU discharge or death.

For calculation of the incidence of AKI, summary data on all ICU admissions from April to June 2003 were obtained from each participating center. This included the total number of admissions; frequency distribution of age, gender, and ICU length of stay for all ICU admissions; and the overall ICU mortality for that time period. Individual patient data were not available for patients without AKI.

Statistical Analyses

Continuous data are presented as the mean (95% confidence interval [CI]) or the median (interquartile range), as appropriate, and nominal data are presented as percentages. Comparisons among multiple groups were performed using the Fisher or the χ^2 test for nominal variables, and ANOVA (with Bonferroni correction) or Kruskal-Wallis test was used for numerical variables where appropriate. Kaplan-Meier survival analysis was used to compare 28-d ICU mortality among the RIFLE categories. Patients who were alive at ICU discharge were censored. The log-rank statistic was used to test differences between groups. Exploratory univariate analysis for several variables was performed to identify possible predictors of ICU mortality. $P < 0.05$ was considered as statistically significant. Serum creatinine levels and urine output were evaluated as both continuous variables (actual values and natural log) and dichotomous variables (above or below a particular level). Previous exposure to potentially nephrotoxic agents was explored in three different forms: "Angiotensin-converting enzyme inhibitors/angiotensin II type 1 receptor blockers (ACEI/ARB) or nonsteroidal anti-inflammatory drugs," "ACEI/ARB and nonsteroidal anti-inflammatory drugs together," or "any nephrotoxic agent." The form "any nephrotoxic agent" had the strongest association with both mortality and need for RRT and was used for the final analysis.

Multivariable logistic regression analysis was then conducted to investigate independent predictors for ICU mortality and need for RRT. The analysis was conducted with backward stepwise method (exclusion probability 0.20; inclusion probability 0.10) for the following covariates: Age, sepsis, postsurgical cause of AKI, previous use of nephrotoxic agents, need for RRT, serum creatinine (natural log), and urine output (natural log). The model's goodness of fit was tested with the Hosmer-Lemeshow statistic. Agreement between the creatinine and urine output criteria of the RIFLE classification was evaluated with the κ test. For exploration of the contribution of each criterion to the outcomes of interest, multivariable logistic regression analysis was repeated using the RIFLE class based on serum creatinine only (RIFLE-c) and again using the RIFLE class based on urine output only (RIFLE-o). Patients who failed to fulfill criteria for R_c or R_o are labeled as class 0_c or 0_o, respectively. All statistical analyses were performed using SPSS 11.5.1 (SPSS, Chicago, IL). A two-sided $P < 0.05$ was considered significant.

Results

We evaluated a total of 2164 admissions in 19 ICU during the study period. Characteristics of the participating centers are shown in Table 2. Patients who were admitted to these ICU had a mean age of 64.3 yr, and 62.2% were male. The overall ICU mortality was 13.4% (95% CI 11.0 to 16.0%) and ranged from 3.4 to 27.4% in the individual study sites. The mean length of stay for survivors was 5.7 d.

During the study period, 234 (10.8%) patients (95% CI 9.5 to 12.1%) developed AKI during their ICU stay. The incidence ranged from 1.0 to 29.1% in the various study centers. The clinical characteristics of the AKI cohort are shown in Table 3. Compared with all ICU admissions, patients with AKI tended to be older and be of male gender. Preexisting hypertension and diabetes were common. Previous exposure to potentially nephrotoxic medications was reported in 30.8%, the most common being ACEI and ARB. Some patients were exposed to more than one of these agents. Thirty-seven percent of patients were transferred to the ICU from medical units, 28% came from surgical departments, and 30% were direct admissions to the ICU. Three quarters of patients with AKI were admitted for medical rather than surgical reasons; the most common diagnostic grouping was cardiovascular conditions (20.5%), followed by pulmonary (15%) and sepsis (14.2%). The most commonly cited cause for AKI was a prerenal cause (38.0%), followed by sepsis (25.6%). At the time of AKI diagnosis, the median serum creatinine was 2.0 mg/dl (177 μmol/L). Median urine output was 1100 ml/d, and 19.7% were considered oliguric, with a urine output of <400 ml/d. Also at the time of AKI diagnosis, more than half of the patients had associated acid-base and hematologic abnormalities, and a significant proportion exhibited hypoalbuminemia and elevation of transaminase levels.

Among 234 patients with AKI, 19% were classified as risk (R), 35% as injury (I), and 46% as failure (F; Table 3). As expected on the basis of the RIFLE criteria, F patients had a significantly higher creatinine and lower urine output at the time of diagnosis of AKI. There was concordance between the serum creatinine and urine output criteria in 34% of cases (Table 4). In 53% of cases, the creatinine criteria led to a worse RIFLE class, whereas in 13% of cases, it was the urine output criteria that led to a worse RIFLE class. κ was 0.132 ($P < 0.001$).

Table 2. Characteristics of participating centers[a]

Characteristic	*n* (%)
Type of hospital	
public	13 (68.4)
university affiliated	6 (31.6)
No. of hospital beds	
<300	3 (15.8)
300 to 600	7 (36.8)
601 to 1000	3 (15.8)
>1000	6 (31.6)
No. of ICU beds	
<10	11 (57.9)
10 to 20	8 (42.1)

[a]ICU, intensive care unit.

RRT

Seventy-one (30.3%) patients with AKI (95% CI 19.6 to 41.0%) were treated with RRT. Patients in class F were more likely to need RRT (Table 3). Independent predictors for need for RRT were exposure to any nephrotoxic drug, higher serum creatinine level, lower urine output, and younger age. The overall utilization of continuous RRT (CRRT) was exceptionally high, with 98.6% of patients receiving CRRT for all or part of their dialysis course. The most common initial RRT modality was continuous venovenous hemofiltration (50.7%); intermittent hemodialysis (IHD) was performed first in 14.1%. Nine of the 10 patients who started with IHD were subsequently shifted to CRRT. Only one patient was treated with IHD alone during the AKI episode. No CRRT patients were shifted to IHD.

Outcomes

Overall ICU mortality for all patients with AKI was 36.3% (95% CI 30.1 to 42.5%), significantly higher than that in the entire ICU cohort ($P < 0.001$). The top three reported causes of death were sepsis (35%), cardiac causes (12.8%), and pulmonary causes (4.7%). ICU mortality was highest among class F (49.5%), followed by class I (29.3%) then class R (20%). Kaplan-Meier survival analysis was statistically significant ($P = 0.03$ by log rank test; Figure 1). The results of the multivariate logistic regression analysis are shown in Table 5. RIFLE classification was the strongest predictor of ICU mortality. With respect to class R, the odds ratio (OR) was 2.2 for class I and 4.9 for class F ($P = 0.01$). Other variables that were associated with increased risk for ICU mortality were sepsis as the cause of AKI and need for RRT. A postsurgical cause for AKI, previous exposure to any nephrotoxic agent, higher serum creatinine, and urine output were associated with a lower risk for death. Mortality was not significantly different between patients with a prerenal cause of AKI (30 *versus* 39% [other cause of AKI]; $P = 0.17$). Thirty-six percent of patients with AKI recovered renal function at the time of death or ICU discharge. Recovery of renal function was seen more frequently among class R (57.8%) and I (43.9%) patients than among F patients (20.6%; $P < 0.001$). The median ICU length of stay for AKI survivors was 10 d (interquartile range 3 to 24 d), significantly longer than that of the entire ICU cohort ($P < 0.001$). ICU length of stay was not significantly different among the three RIFLE classes. The analysis was repeated using the RIFLE class only on the basis of serum creatinine criteria (RIFLE-c). With respect to class 0_c, the OR was 3.0 (95% CI 0.2 to 38.3) for R_c, 7.3 (95% CI 0.6 to 88.7) for I_c, and 18.2 (95% CI 1.2 to 267.4) for F_c. However, when the analysis was performed with RIFLE class only on the basis of urine output criteria (RIFLE-o), it did not emerge as an independent predictor of mortality.

Discussion

This study is, to our knowledge, the first multicenter study to appraise the performance of the RIFLE classification for AKI.

Table 3. Characteristics of study population by RIFLE class[a]

Characteristic	All AKI	Risk	Injury	Failure	*P*
n	234	45	82	107	
Demographics					
age (yr; mean [95% CI])	68.5 (66.6 to 70.4)	63.6 (59.5 to 67.7)	72.0 (69.3 to 74.7)	67.1 (64.1 to 70.1)	0.001
male gender (%)	176 (75.2)	40 (88.9)	62 (75.6)	74 (69.2)	0.036
diabetes (%)	60 (25.6)	7 (15.6)	23 (28)	30 (28)	0.476
hypertension (%)	137 (58.5)	27 (60)	57 (69.5)	53 (49.5)	0.040
NSAID (%)	30 (12.8)	6 (13.3)	13 (15.9)	11 (10.3)	0.521
ACEI or ARB (%)	45 (19.2)	9 (20)	23 (28)	13 (12.1)	0.023
Department of origin					0.004
direct ICU admission	69 (29.5)	20 (44.4)	26 (31.7)	23 (21.5)	
medical	87 (37.2)	14 (31.1)	23 (28)	50 (46.7)	
surgical	65 (27.8)	7 (15.6)	31 (37.8)	27 (25.2)	
transfer from other ICU	13 (5.6)	4 (8.9)	2 (2.4)	7 (6.5)	
Baseline renal characteristics					
abnormal renal function (%)	86 (36.8)	13 (28.9)	30 (36.6)	43 (40.2)	0.001
proteinuria or microhematuria (%)	16 (6.8)	3 (6.7)	6 (7.3)	7 (6.5)	0.977
Diagnosis of AKI					
serum creatinine (mg/dl; median [IQR])	2 (2.0 to 3.0)	1.8 (1.5 to 2.0)	2 (2.0 to 2.0)	3.2 (3.0 to 5.0)	<0.001
diuresis (ml/d; median [IQR])	1100 (520 to 1760)	1655 (1235 to 2075)	1490 (958 to 1910)	500 (100 to 1000)	<0.001
oliguria (%)	44 (19.7)	0 (0)	0 (0)	44 (45.4)	<0.001
Associated abnormalities					
acid-base (%)	130 (55.6)	17 (37.8)	47 (57.3)	66 (61.7)	0.02
electrolytes (%)[b]	128 (54.7)	19 (42.2)	43 (52.4)	66 (61.7)	0.08
hepatic enzymes (%)	76 (32.5)	9 (20)	27 (32.9)	40 (37.4)	0.11
cardiac enzymes (%)	64 (27.4)	9 (20)	25 (30.5)	30 (28)	0.44
hypoalbuminemia (%)	102 (43.6)	13 (28.9)	30 (36.6)	59 (55.1)	0.003
hematologic (%)[c]	115 (49.1)	19 (42.2)	38 (46.3)	58 (54.2)	0.33
coagulation (%)	87 (37.2)	10 (22.2)	31 (37.8)	46 (43)	0.053
Cause of AKI					
prerenal (%)	89 (38.0)	14 (31.1)	49 (59.8)	26 (24.3)	<0.001
sepsis (%)	60 (25.6)	9 (20)	20 (24.4)	31 (29)	0.49
ischemic ATN (%)	34 (14.5)	7 (15.6)	10 (12.2)	17 (15.9)	0.76
radiocontrast (%)	1 (0.4)	0 (0)	0 (0)	1 (0.9)	
nephrotoxic ATN other than contrast (%)	13 (5.6)	2 (4.4)	4 (4.9)	7 (6.5)	0.83
other (%)	12 (5.1)	2 (4.4)	2 (2.4)	8 (7.5)	0.29
Treatment of AKI					<0.001
any RRT (%)	71 (30.3)	2 (4.4)	15 (18.3)	54 (50.5)	
no RRT (%)	163 (69.7)	43 (95.6)	67 (81.7)	53 (49.5)	
RRT modality (% of those who needed RRT)					0.96
CRRT only (%)	61 (85.9)	2 (100)	13 (86.7)	46 (85.2)	
CRRT then IHD (%)	0 (0)	0 (0)	0 (0)	0 (0)	
IHD only (%)	1 (1.4)	0 (0)	0 (0)	1 (1.9)	
IHD then CRRT (%)	9 (12.7)	0 (0)	2 (13.3)	7 (13)	
Outcome					
ICU mortality (%)	85 (36.3)	9 (20)	24 (29.3)	52 (49.5)	0.001
renal recovery at time of death or ICU discharge (%)	84 (35.9)	26 (57.8)	36 (43.9)	22 (20.6)	<0.001
length of stay (d; median [IQR])	10 (3 to 24)	10 (2 to 20)	8 (3 to 23)	12 (4 to 29)	0.16

[a]RIFLE class was determined at time of AKI diagnosis. To convert serum creatinine from mg/dl to μmol/L, multiply by 88.4. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II type 1 receptor blocker; ATN, acute tubular necrosis; CI, confidence interval; CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; RIFLE, risk–injury–failure–loss–ESRD; RRT, renal replacement therapy.

[b]Abnormalities in serum or plasma sodium, potassium, calcium, or phosphorus.

[c]Includes anemia, leukocytosis, leukopenia, and thrombocytopenia.

We evaluated 2164 ICU patients in 19 ICU in northern Italy, 234 (10.8%) of whom developed AKI. We noted that mortality increased almost linearly from the risk category to the failure category. Using R as the reference category, the OR for ICU mortality adjusted for several variables (Table 5) were 2.2 for I and 4.9 for F.

Table 4. RIFLE class by serum creatinine and urine output criteria[a]

RIFLE-c	RIFLE-o				
	0_o	R_o	I_o	F_o	Total
0_c	0	5	0	2	7
R_c	1	39	3	2	45
I_c	0	70	9	17	96
F_c	10	37	7	32	86
Total	11	151	19	84	234

[a]RIFLE class was determined at time of AKI diagnosis. Class 0 denotes the patients did not reach criteria for risk by serum creatinine (0_c) or urine output (0_o). RIFLE-c, RIFLE class by serum creatinine criteria; RIFLE-o, class by urine output criteria.

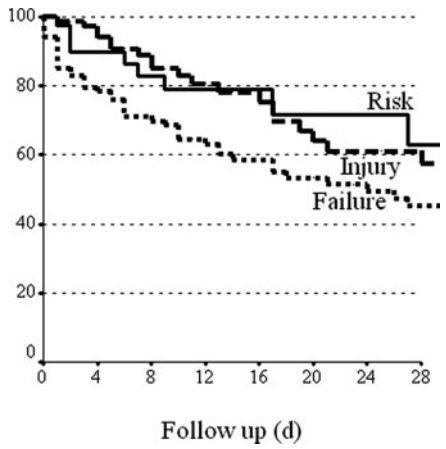

Figure 1. Kaplan-Meier curve for intensive care unit survival by RIFLE class; log-rank statistic $P = 0.03$. Solid line, risk; dashed line, injury; dotted line, failure.

Four retrospective, single-center studies have reported the use of the RIFLE classification in ICU patient populations (Table 6) (10–13) and one in a general hospital population (14). The incidence of AKI in the ICU, that is, the aggregate of the R, I, and F categories, ranged from 19 to 67% (10,13), and the need for RRT ranged from 2.5 to 4.1% (10,11,13). In contrast to our study, in which we classified patients into RIFLE categories at time of diagnosis of AKI (RIFLE "initial"), others classified the patients on ICU admission (12), at peak creatinine levels (10), or maximum RIFLE class attained (13). Mortality, variably reported as hospital mortality, 30- or 90-d mortality, in class R ranged from 8 to 38.3%, in class I from 11.4 to 50%, and in class F from 26.3 to 74.4%. In all of these studies, mortality was, similar to our findings, significantly higher in class F. Kuitunen *et al.* (10) analyzed 813 consecutive cardiac surgery patients during an 8.5-mo period. Patients were classified into R, I, or F on the basis of the change between the preoperative and peak levels of plasma creatinine and urine output. Abosaif *et al.* (12) from the United Kingdom applied the RIFLE criteria to 183 ICU patients who had a serum creatinine level >1.7 mg/dl (150 μmol/L) and compared them with 24 control patients without AKI. They found a greater need for RRT in class F and noted a higher mortality as compared with our own and other studies, regardless of RIFLE class. ICU mortality in their F group was 74.4%. One possible explanation is that patients who already have AKI at the time of ICU admission have a poorer prognosis than those who develop AKI later in their ICU stay. The published literature is not clear on this issue. An earlier study from France showed delayed occurrence of AKI as an independent risk factor for mortality (6); however, a second French study did not find the same association (16). Bell *et al.* (11) studied 207 patients who were treated with CRRT in the ICU during a 6-yr period, 188 of whom were categorized into R, I, and F. The authors did not specifically state when the patients were classified. The remaining 16 patients were dialysis dependent before their ICU admission (considered as ESRD, RIFLE category E), and three were classified into the loss category. Being the only study that included exclusively patients who were treated with RRT, one would anticipate that this was a group with more advanced AKI and, therefore, a worse outcome. However, their mortality for all three categories was lower than that in the UK study (12) (Table 6). This may be due to a difference in case mix and center-specific practices regarding dialysis. It is possible that the Swedish center (11) may have been more aggressive in initiating RRT (criteria for CRRT not described), or patients with AKI on ICU admission have a worse prognosis. In the multivariate analysis in this study, only the RIFLE category, specifically class F, remained an independent predictor of mortality; class I had a mortality risk equal to that of class R (11). Recently, Hoste *et al.* (13) reported their experience with a large cohort of patients from seven ICU in a single center. In this retrospective study, they were also able to examine the progression from the initial RIFLE category to the maximum or peak RIFLE class attained by patients. They reported that more than half of R patients go on to progress to I or F, and more than one third of I patients progress to F. In terms of long-term follow-up, the Swedish study showed that only 4.8% of survivors were dialysis dependent at 6 mo (11); likewise, the UK study reported that survivors had significantly improved creatinine after 1 and 6 mo (12).

It is interesting that the range of reported incidence of AKI using the RIFLE definition remains wide, perhaps in part because of the use of slightly different populations (Table 6). Hoste *et al.* (13) report an exceptionally high incidence of 67%, although their rate of RRT use in the ICU was similar to both our results and the reported literature. Our study population consisted of patients in mostly public hospitals, more than half of which had fewer than 600 beds.

Aside from the RIFLE category, we noted that sepsis and need for RRT were independent predictors for ICU mortality. Sepsis and septic shock have been associated with increased mortality risk in several studies (1–3,17,18). Our results show that a postsurgical cause for AKI was associated with a lower risk. This is congruent with an Australian study in which patients who came from various surgical units had lower odds for hospital mortality (14). This would also be in agreement with the lower overall ICU mortality reported by Kuitenen *et al.*

Table 5. Multivariate regression analysis for ICU mortality[a]

Parameter	OR (95% CI)	*P*
RIFLE class		
risk	1.0 (reference)	
injury	2.245 (0.837 to 6.019)	0.108
failure	4.882 (1.396 to 17.074)	0.013
Sepsis	1.933 (0.977 to 3.823)	0.058
Need for RRT	1.843 (0.904 to 3.758)	0.092
Postsurgical cause of AKI	0.491 (0.239 to 1.010)	0.053
Any nephrotoxic agent	0.462 (0.227 to 0.940)	0.033
Serum creatinine (log)	0.349 (0.162 to 0.755)	0.007
Diuresis (log)	0.299 (0.086 to 1.044)	0.058
Constant	1.036	0.956

[a]OR, odds ratio; RRT, renal replacement therapy.

Table 6. Studies on the RIFLE classification in ICU populations

Parameter	This Study	Kuitunen *et al.* (10)	Bell *et al.* (11)	Abosaif *et al.* (12)	Hoste *et al.* (13)
Country	Italy	Finland	Sweden	United Kingdom	United States
Study design	Prospective multicenter	Single center	Retrospective single center	Retrospective single center	Retrospective single center
Study population	ICU admissions	Cardiac surgery	ICU patients needing CRRT	ICU patients with serum creatinine >1.7 mg/dl on admission	ICU admissions
Basis of RIFLE	Creatinine, urine output	Creatinine	Creatinine, urine output	Creatinine, urine output	Creatinine, urine output
At what point was RIFLE assessed?	Initial	Peak postoperative	NS	ICU admission	Maximum
Total population	2164	813	8152	NS	5383
No. with AKI[b]	234	156[c]	188 RIF 19 LE	183	3617
Incidence of AKI (%)	10.8	19.2	2.5 needed CRRT	NA	67.2
Risk (*n*)	45	88	17	60	670
% of ICU patients	2.1	10.9	0.2	NA	12.4
% of patients with AKI	19.2	56.4	9.0	32.8	18.5
Injury (*n*)	82	28	50	56	1436
% of ICU patients	3.8	3.5	0.6	NA	26.7
% of patients with AKI	35.0	17.9	26.6	30.6	39.7
Failure (*n*)	107	40	121	43	1511
% of ICU patients	4.9	5.0	1.5	NA	28.0
% of patients with AKI	45.7	25.6	64.4	23.5	41.8
Patients treated with RRT	71	25[d]	207	71	219
% of ICU patients	3.3	3.1	2.5	NA	4.1
% of patients with AKI	30.3	16.0	NA[e]	38.8	6.0
Mortality end point	ICU	90 d	30 d	ICU	Hospital
Mortality R (%)	20.0	8.0	23.5	38.3	8.8
Mortality I (%)	29.3	21.4	22.0	50.0	11.4
Mortality F (%)	49.5	32.5	57.9	74.4	26.3

[a]To convert serum creatinine from mg/dl to μmol/L, multiply by 88.4. NA, not applicable because denominator not available; NS, not stated in article.
[b]Represents the aggregate of risk, injury, and failure groups.
[c]One patient who was treated with RRT and was classified as RIFLE class 0 was not included.
[d]Numbers for ICU subpopulation not provided in article.
[e]Only patients who needed RRT were included in the study.

(10) in their cardiac surgery patients. Prerenal azotemia is traditionally regarded as a less problematic form of AKI. It is interesting that patients with a prerenal cause of AKI seem to have a mortality similar to those with other causes of AKI, although we may not have sufficient statistical power to detect a small difference. Although serum creatinine levels and urine

output at AKI diagnosis are the basis of the RIFLE classification, they remain as independent predictor variables for mortality when placed in a multivariable analysis with RIFLE. Low urine output and anuria have been long known to be associated with poor outcomes (1,19,20). In our analysis, lower creatinine concentrations at the time of AKI diagnosis were associated with an increased risk for death. Other authors have also noted a similar pattern in their cohorts (19–21). They hypothesized that low serum creatinine, particularly after adjustment for age and gender, probably reflects loss of muscle mass. However, it could also be related to volume overload and its diluting effect on the serum creatinine. Previous studies have reported the association between volume overload and mortality, in both adults and children (22,23). We also noted that a previous exposure to nephrotoxic agents was associated with a lower risk for death. One possible explanation for this favorable prognosis is that it is a readily reversible cause of AKI, and definitive management (*i.e.*, withdrawal of the offending agent) is relatively simple to carry out.

In our study, the use of CRRT was high, particularly with respect to the practice in the United States as reported by the Program to Improve Care in Acute Renal Disease (PICARD) study (24). The reason for the difference in center practices is not clear. We found that a collaborative effort between the nephrologist and the intensivist, as well as the ICU and dialysis nurse (data not shown), predominates among our centers, which may differ from the practices in "closed" ICU systems (25).

In our analysis, the serum creatinine criteria of the classification seemed to be a better predictor of mortality than urine output. However, the very wide CI suggest an unstable statistical model that should be interpreted with caution, which may in part be related to the relatively small number of patients in the I_o category. A rise in serum creatinine is an earlier sign of worsening renal function than oliguria. In >50% of our patients with AKI, the creatinine criteria led to a worse RIFLE class than urine output. That the predictive value of the "true" RIFLE class (using both creatinine and urine output criteria) was statistically more stable underlines the clinical utility of using the composite criteria to define the wide range of disease spectra in AKI.

The results of our study support the utility of the RIFLE classification in prognosticating the outcome of patients with AKI. The study included a large cohort of patients from multiple centers, using both serum creatinine and urine output criteria, as was intended by ADQI. To our knowledge, this is the first prospective, multicenter evaluation of the RIFLE classification and the first to evaluate the performance of the creatinine and urine output criteria. We acknowledge that there are several limitations to the data presented here. First, we had a predominantly white population, and our findings may not be applicable to more culturally diverse centers. Because of the study design, we were unable to compare directly patients with and without AKI. However, we were able to compare basic demographics and outcomes, such as ICU mortality and length of stay, between patients with AKI and the ICU population as a whole. We also did not include severity of illness scores in our evaluation. There was a need to assume a baseline creatinine value using the Modification of Diet in Renal Disease (MDRD) equation in patients in whom this value was not known. This assumption can obviously lead to misclassification of some patients. However, a true baseline is often unknown for many patients who are admitted to the ICU (13). The ADQI Committee was well aware of this contingency, and for this reason, they sought to develop a standardized rule for assuming the level of baseline renal function (9). Patient outcome in our study was evaluated at exit from the ICU, which underestimates the impact of AKI on outcome. Bell *et al.* (11) showed a difference of 19.8% between ICU and 2-mo mortality and 25.1% between ICU and 6-mo mortality. Last, because changes in serum creatinine and urine output lag behind real-time changes in renal function, there are some limits to the utility of the RIFLE classification, although it represents a tool that was hitherto unavailable. Ultimately, serum and urine biomarkers will redefine how we classify, treat, and monitor AKI.

Conclusion

The incidence of AKI in our ICU was between 9 and 12%, with 3.3% of ICU patients requiring RRT. Overall mortality was between 30 and 42% and was lowest in RIFLE class R and highest in class F. Our findings support the utility of the RIFLE classification for AKI and demonstrate that even more moderate degrees of kidney function pose a significant risk for death. Perhaps appropriate intervention in earlier stages of AKI may have a positive impact on patient outcomes. Until serum and urine biomarkers for AKI become widely available for clinical use, a simple and clinically applicable method for identifying these patients across different centers, such as the RIFLE classification, would help in recruitment of patients for future trials.

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Disclosures

None.

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