Acute Renal Failure in Critically Ill Patients
A Multinational, Multicenter Study

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Context Although acute renal failure (ARF) is believed to be common in the setting of critical illness and is associated with a high risk of death, little is known about its epidemiology and outcome or how these vary in different regions of the world.

Objectives To determine the period prevalence of ARF in intensive care unit (ICU) patients in multiple countries; to characterize differences in etiology, illness severity, and clinical practice; and to determine the impact of these differences on patient outcomes.

Design, Setting, and Patients Prospective observational study of ICU patients who either were treated with renal replacement therapy (RRT) or fulfilled at least 1 of the predefined criteria for ARF from September 2000 to December 2001 at 54 hospitals in 23 countries.

Main Outcome Measures Occurrence of ARF, factors contributing to etiology, illness severity, treatment, need for renal support after hospital discharge, and hospital mortality.

Results Of 29 269 critically ill patients admitted during the study period, 1738 (5.7%; 95% confidence interval [CI], 5.5%-6.0%) had ARF during their ICU stay, including 1260 who were treated with RRT. The most common contributing factor to ARF was septic shock (47.5%; 95% CI, 45.2%-49.5%). Approximately 30% of patients had preadmission renal dysfunction. Overall hospital mortality was 60.3% (95% CI, 58.0%-62.6%). Dialysis dependence at hospital discharge was 13.8% (95% CI, 11.2%-16.3%) for survivors. Independent risk factors for hospital mortality included use of vasopressors (odds ratio [OR], 1.95; 95% CI, 1.50-2.55; $P<.001$), mechanical ventilation (OR, 2.11; 95% CI, 1.58-2.82; $P<.001$), septic shock (OR, 1.36; 95% CI, 1.03-1.79; $P=.03$), cardiogenic shock (OR, 1.41; 95% CI, 1.05-1.90; $P=.02$), and hepatorenal syndrome (OR, 1.87; 95% CI, 1.07-3.28; $P=.03$).

Conclusion In this multinational study, the period prevalence of ARF requiring RRT in the ICU was between 5% and 6% and was associated with a high hospital mortality rate.

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THE EPIDEMIOLOGY AND OUTcome of acute renal failure (ARF) in critically ill patients in different regions of the world are not well understood. Although there have been several epidemiological studies of ARF,[1-16] most are either single center[1-3,6-8,12] or if multicenter are confined to a single country.[4,5,9-11,13,15,16] The period prevalence and hospital mortality reported in these studies have varied widely (single-center studies: 1%-25%; multicenter studies: 39%-71%) and most studies are not comparable because they used different inclusion criteria. In 1 multinational study[14] that collected data for a general severity scoring system and provided further but limited and indirect information about the epidemiology of ARF, more than 90% of participating centers were in Europe or North America. All studies of ARF have been conducted in Australia, Europe, or North America.

We conducted a multinational, multicenter, prospective, epidemiological survey of ARF in intensive care unit (ICU) patients. The objectives of this study were to determine the period prevalence of ARF in ICU patients in multiple countries; to characterize differences in etiology, illness severity, and

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Table 1. Characteristics of Patients With Acute Renal Failure and Participating Centers

	No./Total (%)
Men	1105/1738 (63.6)
Renal function	
Normal	966/1738 (55.6)
Chronic impairment	512/1738 (29.5)
Unknown	260/1738 (15.0)
Mechanical ventilation	1312/1722 (76.2)
Vasopressors/inotropes	1189/1721 (69.1)
Mode of RRT	
Continuous	1006/1258 (80.0)
Intermittent	212/1258 (16.9)
Peritoneal dialysis and slow continuous ultrafiltration	40/1258 (3.2)
	Median (IQR)
Age of patients, y	67 (53-75)
Body weight of patients, kg	74 (63-85)
Length of hospital stay prior to ARF, d	5 (1-12)
SAPS II score*	48 (38-61)
Creatinine level, μmol/L	97 (79-150)
Estimated creatinine clearance, mL/min	35 (20-59)
Level at ICU admission	
Creatinine, μmol/L	179 (110-310)
Urea, mmol/L	15.0 (8.8-27.0)
	No.
Type of hospital	
Affiliated with a university	36
Large urban	14
Small urban	4
No. of beds in hospital	
<500	14
500-999	25
≥1000	15
Type of ICU	
General	45
Surgical	4
Cardiothoracic	3
Trauma	1
Bone marrow transplant	1
No. of beds in ICU	
<10	10
10-29	29
≥30	15

Abbreviations: ARF, acute renal failure; ICU, intensive care unit; IQR, interquartile range; RRT, renal replacement therapy; SAPS II, Simplified Acute Physiology Score.
SI conversion factors: To convert creatinine to mg/dL, divide by 88.4; creatinine clearance to mL/s, multiply by 0.0167; urea in mmol/L to urea nitrogen in mg/dL, divide by 0.357.
*The score range is 0 to 163.

clinical practice; and to determine the association of these differences with patient outcomes.

METHODS

This study was conducted at 54 centers in 23 countries from September 2000 to December 2001 (participating centers are listed at the end of the article). The study protocol was reviewed by the ethics committees or investigational review boards at each participating site. Because of the anonymous and noninterventional fashion of this study, the ethical committees of most study centers waived the need for informed consent. At centers in which the ethics committees or investigational review boards required informed consent, formal written consent was obtained from patients or surrogates.

Study Population

All patients who were older than 12 years (several ICUs treated adolescents) and who were admitted to 1 of the participating ICUs during the observational period were considered for study inclusion. From this population, only patients who were treated with renal replacement therapy (RRT) other than for drug poisoning or who had at least 1 of the predefined criteria for ARF were included in the study.

The criteria for ARF were oliguria defined as urine output of less than 200 mL in 12 hours and/or marked azotemia defined as a blood urea nitrogen level higher than 84 mg/dL (>30 mmol/L). These criteria were chosen because they are simple, objective, numerically identifiable, and likely to be considered triggers for the initiation of RRT in the ICU. While other definitions for ARF exist and recent consensus criteria for acute renal dysfunction include less severe forms,[17,18] our intent was to study severe ARF that likely would be treated with RRT. Patients with any dialysis treatment before admission to the ICU or patients with end-stage renal failure and receiving dialysis were excluded.

Data Collection

The following information was prospectively obtained at study inclusion and was recorded on a standardized case report form developed for this study: sex, date of birth, body weight (measured or estimated at ICU admission), date of hospital admission, premorbid renal function (any evidence of abnormal serum level of creatinine or creatinine clearance prior to hospital admission), premorbid creatinine level, date of ICU admission, the Simplified Acute Physiology Score[19] (SAPS II) on the day of ICU admission, creatinine and blood urea nitrogen levels at ICU admission, and primary diagnosis.

The contributing factors to ARF were identified from a list of 7 possible choices (septic shock, cardiogenic shock, hypovolemia, drug-induced, obstructive uropathy, major surgery, and other) according to the judgment of the treating clinician. More than 1 contributing factor could be selected in each case. When a patient was treated with RRT, the initial mode of RRT was recorded. Renal replacement therapy was defined as either peritoneal dialysis or any technique of renal support requiring an extracorporeal circuit and an artificial membrane. Need for mechanical ventilation and inotropes/vasopressors at inclusion into the study, date of ICU discharge, date of hospital discharge, survival at ICU and hospital discharge, and need for RRT at hospital discharge were obtained.

Data were collected by means of an electronically prepared Excel-based data collection tool (Microsoft Corp, Seattle, Wash), which was made available to participating centers with instructions. All centers were asked to complete data entry and e-mail the data to the central office, where the data were screened in detail by a dedicated intensive care specialist for any missing information, logical errors, insufficient detail, or addition of queries. Any queries generated an immediate e-mail inquiry and were to be resolved within 48 hours.

Statistical Analyses

Data are presented as median and interquartile range (IQR; 25th to 75th percentiles) or percentages (95% confidence intervals [CIs]). Multivariable logistic regression analysis was conducted to investigate risk factors for hospital mortality (proc LOGIST version 6.12, SAS Institute Inc, Cary, NC). The following variables were investigated as independent risk factors using a backward elimination approach: type and size of hospital, type and size of ICU, age, sex, body weight, premorbid renal function, hospital stay prior

to ARF, SAPS II score, serum creatinine and urea nitrogen levels at ICU admission, use of mechanical ventilation, use of vasopressors or inotropes, reason for ICU admission, and factors contributing to ARF. Variables were allowed to remain in the models if the multivariable analysis yielded a $P<.05$. Mode of RRT was not used as a variable because patients not receiving RRT were included. The contribution of dummy variables, such as ICU admission diagnosis and study center, to the model was assessed using a likelihood ratio χ^2. All other variables were assessed based on the Wald χ^2; $P<.05$ was considered statistically significant.

RESULTS

Epidemiology of ARF

From September 2000 to December 2001, 29 269 critically ill patients were admitted to the ICUs at 54 study centers (TABLE 1) in 23 countries (2 centers did not provide the number of ICU admissions). The median screening period at each study center was 183 days (IQR, 131-215 days). Among these patients, 1738 patients (5.7%; 95% CI, 5.5%-6.0%) had ARF sometime during their ICU stay as defined by the study criteria (57 patients from the 2 centers that did not provide the number of ICU admissions were excluded from this calculation). The period prevalence ranged from 1.4% to 25.9% across all study centers. Of the patients with ARF documented by study criteria, 1260 patients (4.2%; 95% CI, 4.0%-4.4%) were treated with RRT and 478 (1.6%; 95% CI, 1.4%-1.7%) had ARF but were not treated with RRT.

Patient demographics are shown in Table 1. The median age of patients with ARF was 67 years (IQR, 53-75 years). The median SAPS II score was 48 (IQR, 38-61). The median body weight was 74 kg (IQR, 63-85 kg). Approximately 30% of patients had chronic renal dysfunction but were not receiving dialysis treatment. Estimated creatinine clearance at ICU admission was 35 mL/min (IQR, 20-59 mL/min) (0.58 mL/s; IQR, 0.33-0.99 mL/s). Among the patients who were treated with RRT, continuous RRT was the most common initial modality used (80.0%), followed by intermittent RRT (16.9%), and peritoneal dialysis and slow continuous ultrafiltration (3.2%).

The major reason for ICU admission was medical in 58.9% of patients and surgical in the remaining 41.1%. Cardiovascular surgery was the most common diagnostic grouping, followed by medical respiratory, medical cardiovascular, gastrointestinal tract surgery, medical gastrointestinal tract, and sepsis. In 47.5% of patients, ARF was associated with septic shock. Thirty-four percent of ARF was associated with major surgery, 27% was related to cardiogenic shock, 26% was related to hypovolemia, and 19% of ARF was potentially drug-related. Medical and surgical ICU admissions by diagnostic groups and the distribution of other possible contributing factors to ARF appear in TABLE 2.

Table 2. Medical and Surgical Intensive Care Unit Admissions and Contributing Factors to Acute Renal Failure

	No. (%)
Medical admission (n = 1736)	1023 (58.9)
Respiratory tract	225 (13.0)
Cardiovascular	197 (11.3)
Gastrointestinal tract	175 (10.1)
Sepsis	174 (10.0)
Hematologic	77 (4.4)
Metabolic	65 (3.7)
Renal	39 (2.2)
Neurological	37 (2.1)
Trauma	34 (2.0)
Surgical admission (n = 1736)	713 (41.1)
Cardiovascular	402 (23.2)
Gastrointestinal tract	198 (11.4)
Trauma	39 (2.2)
Respiratory tract	31 (1.8)
Renal	17 (1.0)
Orthopedic	11 (0.6)
Neurological	9 (0.5)
Gynecologic	6 (0.3)
Contributing factors (n = 1726)	
Septic shock	820 (47.5)
Major surgery	592 (34.3)
Cardiogenic shock	465 (26.9)
Hypovolemia	442 (25.6)
Drug-induced	328 (19.0)
Hepatorenal syndrome	99 (5.7)
Obstructive uropathy	45 (2.6)
Other	211 (12.2)

Outcomes

Fifty-two percent of all ARF patients died in the ICU and another 8% died in the hospital after discharge from the ICU, resulting in the overall hospital mortality of 60.3% (95% CI, 58.0%-62.6%); whereas SAPS II predicted mortality was 45.6% ($P<.001$) (TABLE 3). Of patients who survived to hospital discharge, 13.8% (95% CI, 11.2%-16.3%) required RRT at the time of discharge. The median length of ICU stay was 10 days (IQR, 5-22 days) and the median length of hospital stay was 22 days (IQR, 11-44 days). The period prevalence and mortality (observed and predicted) by country appear in Table 3. However, these data are shown for illustrative purposes and comparisons across countries are not possible because sampling was not representative in any country.

The following variables were entered in the backward elimination model building process of multivariate regression analysis and were not found to be significant independent predictors of outcome, so did not contribute to the final model: sex, premorbid renal impairment, estimated creatinine clearance, some of the contributing factors to ARF (major surgery, hypovolemia, drug-induced, and obstructive uropathy), type of hospital (academic or nonacademic), and number of hospital beds. In the final model, important risk factors for outcome included vasopressors, mechanical ventilation, sepsis/septic shock, cardiogenic shock, hepatorenal syndrome diagnostic grouping, type of ICU, and number of beds in each ICU. The complete results of multivariate regression analysis appear in TABLE 4. As a separate analysis, we repeated the multivariate regression using ICU mortality as the dependent variable and the results were essentially the same (data not shown).

COMMENT

This study is, to our knowledge, the first large international investigation of the epidemiology and outcome of ARF in critically ill patients. We screened nearly

30 000 patients and found that the period prevalence of ARF associated with critical illness using our simple inclusion criteria was 5.7%. This is the largest and most globally representative study of the period prevalence of ARF in the ICU. The period prevalence of ARF had been reported from 1.5% to 24%, depending on populations studied and criteria used.[2,5,6,13,14] In our study, period prevalence of ARF varied among study centers to a nearly identical extent (1.4%-25.9%) despite our use of a single set of criteria. We recognize that even though we studied only 54 centers and 23 countries, we speculate that the worldwide period prevalence of ARF (according to our definition) in critically ill patients is approximately 6%. Based on our research, the worldwide period prevalence of acute RRT in the ICU is approximately 4% (or two thirds of those with ARF).

Septic shock was the most common contributing factor to ARF. The frequency in which it was a contributing factor to the development of ARF was around 50% in all centers. Logistic regression showed that study center, older age, time between hospital and study inclusion, SAPS II score, use of mechanical ventilation, and vasopressors were all independent significant risk factors for mortality. These findings are consistent with previous findings.[2-5,13,16] The effects of time between hospital admission and study inclusion (development of ARF) suggests that the delayed development of ARF while in the hospital selects a particular group of patients with a poor prognosis.

We found that observed mortality was significantly higher than SAPS II predicted mortality (60.3% vs 45.6%; $P<.001$). The developmental cohort for the SAPS II score excluded burn, coronary care, and cardiac surgery patients.[19] In our study, there were approximately 300 cardiac surgery patients and 10 burn patients. Six study centers included some patients from their coronary care units, although such patients contributed to a small population. Therefore, we recalculated observed and predicted mortality after excluding cardiac surgery patients and found that the difference in observed vs predicted mortality still remained significant (61.3% vs 46.1%; $P<.001$). Several epidemiological studies of SAPS II[11-13,15] for ARF have previously reported various relationships between observed and predicted mortality (from overestimation to underestimation). Considering that our study is multinational and thus fairly representative of a variety of populations, it is likely that SAPS II generally underestimates mortality in ARF patients.

We found that most survivors of ARF (86%) were dialysis-independent at hospital discharge. Although these results are consistent with recent clinical trials of ARF,[20-22] they are better than estimates from large epidemiological studies in the United States in which roughly 65% of surviving patients are thought to be free of dialysis at hospital discharge.[3,23] These findings could significantly impact the way in which interventional trials are designed in the future.

Our study has several limitations. First, centers chose to participate in this study and are most likely not representative of any single country. Therefore, it is likely that there was a self-selection bias toward centers with a particular interest in ARF and its management. These centers might have managed more ARF patients, treated them more aggressively, used continuous RRT more frequently, and produced different outcomes compared with other institutions. However, the period prevalence of ARF, the demographic features of the patients, and overall mortality were similar to previous studies.

Second, this is an observational study not a randomized controlled trial. However, the sample size is the largest in the

Table 3. Period Prevalence of Acute Renal Failure and Mortality by Country*

	No. of Participating Centers (N = 54)	No. of Patients (N = 1738)	Period Prevalence (95% CI), %	Predicted Mortality, %†	Hospital Mortality (95% CI), %
Australia	6	293	6.3 (5.6-7.0)	47.0	53.4 (47.7-59.1)
Belgium	3	163	8.8 (7.5-10.1)	43.2	57.7 (50.1-65.3)
Brazil	4	153	4.8 (4.0-5.5)	43.6	76.8 (70.1-83.6)
Canada	2	93	4.6 (3.7-5.6)	56.8	59.8 (49.8-69.8)
China	2	77	8.8 (6.9-10.7)	48.5	61.0 (50.1-71.9)
Czech Republic	1	21	16.8 (10.2-23.4)	44.6	61.9 (41.1-82.7)
Germany	2	129	3.3 (2.7-3.8)	39.4	61.9 (53.4-70.4)
Greece	1	5	2.4 (0.3-4.5)	62.2	80.0 (44.9-100.0)
Indonesia	1	25	4.4 (2.7-6.1)	41.4	72.0 (54.4-89.6)
Israel	1	10	2.1 (0.8-3.4)	61.3	100.0
Italy	6	109	5.4 (4.4-6.4)	32.0	50.5 (41.1-59.8)
Japan	4	90	5.5 (4.4-6.6)	40.8	64.0 (54.1-74.0)
The Netherlands	2	113	6.1 (5.0-7.2)	49.5	62.5 (53.5-71.5)
Norway	2	50	3.7 (2.7-4.7)	46.6	62.0 (48.5-75.5)
Portugal	2	36	22.1 (15.7-28.5)	53.7	63.9 (48.2-79.6)
Russia	1	14	2.6 (1.3-3.9)	82.6	61.5 (35.1-88.0)
Singapore	2	31	6.3 (4.2-8.4)	59.3	74.2 (58.8-89.6)
Spain	2	16	10.5 (5.6-15.3)	32.2	43.8 (19.4-68.1)
Sweden	1	9	4.7 (1.7-7.7)	25.7	22.2 (0-49.4)
Switzerland	1	26	3.2 (2.0-4.4)	44.3	65.4 (47.1-83.7)
United Kingdom	1	52	20.6 (15.6-25.5)	63.7	73.1 (61.0-85.1)
United States	6	194	8.0 (6.8-9.3)	44.2	52.1 (45.0-59.2)
Uruguay	1	29	12.9 (8.5-17.3)	35.6	65.5 (48.2-82.8)
Overall			5.7 (5.5-6.0)	45.6	60.3 (58.0-62.6)

Abbreviation: CI, confidence interval.
*Countries are provided for illustrative purposes only because sampling was not representative of any given country.
†Calculated with Simplified Acute Physiology Score II.

literature and the data were collected in 23 countries around the world. As such, this study provides the first available estimates of global treatment and outcomes for ARF. We did not include some potentially important variables in the multivariate analysis, such as mode and intensity of RRT, timing of the beginning of treatment, and hospital admission diagnosis. We did not include mode or intensity of RRT as variables in the logistic regression analysis because approximately one third of patients were not treated with RRT. Mode and intensity of RRT might affect outcome of ARF patients but available data are inconsistent.[20-22,24-26]

Third, we only considered baseline clinical variables and data obtained at study inclusion in our analysis. This component of the study focuses on the epidemiological aspects of ARF, and this choice likely affected our findings. Had we collected information at hospital or ICU admission, we might have found that other variables influenced final outcome. However, the focus of our investigation related to the onset of ARF in the ICU and the understanding of what factors detectable at that time might have influenced subsequent outcome.

Fourth, our definition of ARF was probably skewed toward a high level of severity. On the other hand, no accepted or validated definitions of ARF exist. We did not provide clinicians with a standardized definition of chronic renal failure. No consensus definition exists in this setting and the diagnosis is complex and involves data obtained from history, biochemical analysis, body size, sex, hematological information, and imaging. We consider it unlikely that this would have influenced our major findings because the period prevalence was essentially the same as that found in previous studies.[2,5,6,13,14] Unlike some of these studies, we did not find that patients with chronic renal failure had a better outcome once we corrected for other variables. This difference may reflect the effect of study centers outside of developed countries, the greater numbers of variables available for analysis, and differences in the impact of premorbid care and comorbidites once patients from developing countries are included.

Fifth, although we did not have the resources to conduct an onsite data audit, all data inconsistencies were immediately resolved by electronic communication and data completeness was more than 99% at the time of statistical analysis. Nonetheless, the lack of independent data validation is a significant limitation of our database.

Finally, our database did not include long-term follow-up and thus the outcomes for patients following hospital discharge are unknown. For this reason, we chose not to analyze data using survival rates (eg, Cox proportional hazards) because we would have had to assume that survival postdischarge resembled in-hospital survival rates and this seems unlikely. Furthermore, our intent was to examine all-cause hospital mortality truncated at 28 days rather than survival rates because hospital mortality has been the most common end point for clinical trials of ARF. There is controversy as to whether prolonging in-hospital survival represents a benefit if hospital mortality is the same. However, the absence of postdischarge information is a significant limitation of our study.

In summary, we have conducted a multinational, multicenter, prospective, epidemiological study of ARF that includes the largest and most representative sample of ICUs and ARF patients so far. We found a period prevalence of ARF in the ICU of approximately 6%, with close to two thirds of such patients receiving RRT. In this study, premorbid renal dysfunction was common, sepsis was the dominant cause of ARF in the ICU, SAPS II scores underestimated mortality, and most survivors were dialysis-independent at hospital discharge. This information may be helpful in the design of future international interventional trials, which would apply to worldwide practice, in regard to the statistical power and choice of appropriate outcome measures.

Table 4. Multivariable Logistic Regression Analysis for Hospital Mortality in Critically Ill Patients With Acute Renal Failure*

Independent Variables	OR (95% CI)	*P* Value
Demographics		
Age in 1-year increments	1.02 (1.01-1.03)	<.001
Duration between hospital admission and inclusion to study in 1-day increments	1.02 (1.01-1.03)	<.001
SAPS II in 1-point increments	1.02 (1.01-1.03)	<.001
Mechanical ventilation	2.11 (1.58-2.82)	<.001
Vasopressors/inotropes	1.95 (1.50-2.55)	<.001
Diagnostic medical groupings		
Cardiovascular	1.00	
Metabolic	0.37 (0.18-0.76)	.007
Hematologic	2.70 (1.32-5.50)	.006
Contributing factors to ARF		
Sepsis/septic shock	1.36 (1.03-1.79)	.03
Cardiogenic shock	1.41 (1.05-1.90)	.02
Hepatorenal syndrome	1.87 (1.07-3.28)	.03
Features of intensive care unit		
Type		
General	1.00	
Specific	1.64 (1.07-2.52)	.02
No. of beds		
≥30	1.00	
10-29	0.81 (0.63-1.03)	.08
<10	0.57 (0.37-0.86)	.008

Abbreviations: ARF, acute renal failure; CI, confidence interval; OR, odds ratio; SAPS II, Simplified Acute Physiology Score.
*Model fit was good (Hosmer-Lemeshow *c* test, 20.01; *P* = .33).

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