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Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score

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Abstract *Objectives:* To describe risk factors for the development of acute renal failure (ARF) in a population of intensive care unit (ICU) patients, and the association of ARF with multiple organ failure (MOF) and outcome using the sequential organ failure assessment (SOFA) score. *Design:* Prospective, multi-center, observational cohort analysis. *Setting:* Forty ICUs in 16 countries. *Patients:* All patients admitted to one of the participating ICUs in May 1995, except those who stayed in the ICU for less than 48 h after uncomplicated surgery, were included. After the exclusion of 38 patients with a history of chronic renal failure requiring renal replacement therapy, a total of 1411 patients were studied. *Measurements and results:* Of the patients, 348 (24.7%) developed ARF, as diagnosed by a serum creatinine of 300 $\mu\text{mol/l}$ (3.5 mg/dl) or more and/or a urine output of less than 500 ml/day. The most important risk factors for the development of ARF present on admission were acute circulatory or respiratory failure; age more than 65 years, presence of infection, past history of chronic heart failure (CHF), lymphoma or leukemia, or cirrhosis. ARF patients developed MOF earlier than non-ARF patients (median

24 vs 48 h after ICU admission, $p < 0.05$). ARF patients older than 65 years with a past history of CHF or with any organ failure on admission were most likely to develop MOF. ICU mortality was 3 times higher in ARF than in other patients (42.8% vs 14.0%, $p < 0.01$). Oliguric ARF was an independent risk factor for overall mortality as determined by a multivariate regression analysis (OR = 1.59 [CI 95%: 1.23–2.06], $p < 0.01$). Infection increased the risk of death associated with all factors. Factors that increased the ICU mortality of ARF patients were a past history of hematologic malignancy, age more than 65 years, the number of failing organs on admission and the presence of acute cardiovascular failure. *Conclusion:* In ICU patients, the most important risk factors for ARF or mortality from ARF are often present on admission. During the ICU stay, other organ failures (especially cardiovascular) are important risk factors. Oliguric ARF was an independent risk factor for ICU mortality, and infection increased the contribution to mortality by other factors. The severity of circulatory shock was the most important factor influencing outcome in ARF patients.

Key words

Mortality · Oliguria · Multiple organ failure · Severity-of-illness · Prognosis · Scoring systems

Table 1 The SOFA score (*MAP* mean arterial pressure)

SOFA score	0	1	2	3	4
Respiration					
PaO ₂ /FIO ₂ (mmHg) (kPa)	> 400 > 5.3)	301–400 (4.1–5.3)	201–300 (2.8–4.0)	101–200 (1.4–2.7)	≤ 100 ≤ 1.3)
Coagulation					
Platelets (x10 ³ /mm ³)	> 150	101–150	51–100	21–50	≤ 20
Liver					
Bilirubin (mg/dl) (μmol/l)	< 1.2 < 20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	≥ 12.0 ≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl) (μmol/l) or urine output	< 1.2 < 110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440) < 500 ml/day	> 5.0 > 440) < 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in μg/kg/min)

Introduction

Acute renal failure (ARF) is a common and serious complication in critically ill patients. The incidence of ARF in intensive care unit (ICU) patients varies from 3 to 16%, depending on the population studied and the criteria used to define ARF [1, 2, 3]. The mortality rate in ARF patients remains high [1, 4, 5, 6, 7, 8, 9, 10, 11] despite improvements in renal replacement techniques. Possible explanations for this finding include the fact that ICU patients today are older and more debilitated than previously [12], and that the same pathophysiological factors involved in the development of ARF are also incriminated in the failure of other organs, so that ARF is often part of the multiple organ failure (MOF) syndrome [1, 13]. The aim of the present study was to define the profile of ARF patients in the critical care setting and to identify the risk factors related to the development of, and mortality from, ARF, and the association of ARF with failure of other organs. We used a large database to evaluate organ dysfunction/failure using a newly described organ failure assessment score [14] developed by consensus and validated by retrospective (1643 patients [15]) and prospective (1449 patients [14]) data collection.

Patients and methods

Forty participating centers in 16 countries (see Appendix) enrolled all patients admitted to the ICU during May 1995, excluding patients under 12 years of age and those remaining in the ICU for less than 48 h after uncomplicated elective surgery. A total of 1449 patients were included. Thirty-eight patients with chronic re-

nal failure requiring renal replacement therapy were eliminated from this study population. For the remaining 1411 patients, admission data related to demography, previous health status and presence of infection were obtained. Daily evaluation of organ function was performed based on a set of clinical and laboratory parameters and the most abnormal value for each system in each 24 h period was noted according to the sequential organ failure assessment score (SOFA, Table 1).

The patients were separated into two groups, depending on the presence or absence of ARF at any time during their ICU stay. ARF was defined by a creatinine concentration of 300 μmol/l (3.5 mg/dl) or more, and/or oliguria (a daily urine output < 500 ml). The previous health status of each patient was determined on admission: CHF was defined as the presence of Class III or IV symptoms of the New York Heart Association classification, while the definitions of acquired immunodeficiency syndrome (AIDS), cancer, cirrhosis, chronic obstructive pulmonary disease (COPD) and diabetes were left to each physician. Infection, on admission and/or during the ICU stay, was assessed by each physician according to clinical, laboratory and microbiological parameters following the criteria of the Center for Disease Control. Organ failure was defined as a SOFA score (Table 1) of 3 or more for any system. MOF was defined as the simultaneous presence of two or more organ failures, other than renal, at any time during the ICU stay. We identified individual risk factors for developing ARF and, in patients with ARF, predictors of MOF and mortality.

Data were analyzed using a Statistical Package for Social Sciences (SPSS, release 5.0.1 for Windows, SPSS, Chicago, Ill.) software. Categorical data were expressed in proportion, and subgroups were analyzed by a χ^2 -statistic (with Yates' correction where applicable). Continuous data were expressed as median and subgroups were evaluated by a non-parametric rank test (Mann-Whitney-Wilcoxon U). Risk factors were evaluated in univariate analysis, and in multivariate analysis by a multiple logistic stepwise regression procedure [16]. The relationship between different factors and mortality was evaluated by a Cox Proportional Hazards Model [17], and survival curves were constructed. Variables with *p* less than 0.05 were included in the model. Odds ratios were estimated from the b coefficients obtained, with respective

95 % confidence intervals (CI 95 %). Calibration of the model was assessed by \hat{C}_g , goodness-of-fit statistic test from Hosmer-Lemeshow [18], and discrimination capability was evaluated by determination of the area under the receiver operating characteristics (ROC) curve [19]. In all comparisons, a p less than 0.05 was considered statistically significant.

Results

Risk factors for acute renal failure

Of the 1411 patients, 348 (24.7 %) developed ARF during their ICU stay, and the presence of ARF prolonged the ICU stay by 3 days (median ICU stay 7 versus 4 days in non-ARF patients, $p < 0.01$) (Table 2). Patients who developed ARF were older (median age 63 vs 57 years, $p < 0.01$), more likely to be infected on admission (43.4 % vs 28.2 %; OR = 1.52 [CI 95 %: 1.51–2.50]; $p < 0.01$) and more often admitted for medical than surgical reasons (49.7 % vs 44.4 %; OR = 1.26 [CI 95 %: 1.05–1.51]; $p = 0.01$) than patients who did not develop ARF. Patients who developed ARF more frequently had a history of chronic disease (36 % vs 24 %, $p < 0.01$), including CHF (10.6 %; OR = 2.18 [CI 95 %: 1.12–4.44]; $p = 0.02$), cirrhosis (5.7 %; OR = 2.18 [CI 95 %: 1.16–4.10]; $p = 0.01$) or lymphoma/leukemia (6.0 %; OR = 2.23 [CI 95 %: 1.02–7.10]; $p = 0.04$). ARF patients had more other organ failures on admission than non-ARF patients (1.4 ± 1.1 vs 0.6 ± 0.7 , $p < 0.01$). Cardiovascular failure (OR = 1.84 [CI 95 %: 1.32–2.56], $p < 0.01$) and respiratory failure (OR = 1.44 [CI 95 %: 1.09–1.88], $p = 0.01$) were individual risk factors for developing ARF. Table 3 shows the results of a logistic regression analysis. The sensitivity of this model to predict ARF was 94 %, with a specificity of 32 % (correct classification of 76 %).

Risk factors for multiple organ failure

One hundred and seven of the non-ARF patients developed MOF (10.1 %). Of the 348 ARF patients, 241 (69.3 %) developed MOF. These patients more frequently presented with infection on admission (124/241 MOF patients [51 %] vs 27/107 non-MOF patients [25 %], $p < 0.01$). ARF patients developed MOF earlier than other patients (median 24 vs 48 h after ICU admission, $p = 0.013$). There was no clear pattern of onset of organ failure, but a strong relationship between the onset of MOF and the onset of ARF. Of the 241 patients, 65 % developed MOF at the same time as ARF, 10 % developed MOF after ARF and 25 % developed MOF before ARF. Older age or past history of CHF increased the risk of MOF (Table 4). In a multivariate analysis, cardiovascular failure was the most important indepen-

Table 2 Demography of study population (ARF acute renal failure, ICU intensive care unit)

	ARF	No ARF	p
Number of patients	348	1063	
Age (years)*	63 (13–86)	57 (12–82)	< 0.001
Source of admission			
Emergency room	106 (30.5 %)	407 (38.3 %)	
Hospital ward	107 (30.7 %)	252 (23.7 %)	
Operating room	81 (23.3 %)	287 (27.0 %)	
Other hospital	48 (13.8 %)	99 (9.3 %)	
Others	6 (1.7 %)	18 (1.6 %)	
Type of admission			
Elective surgery	44 (12.6 %)	260 (18.0 %)	
Emergency surgery	64 (18.4 %)	253 (17.5 %)	
Trauma	32 (9.2 %)	181 (12.5 %)	
Medical	173 (49.7 %)	641 (44.4 %)	
Acute coronary	26 (7.5 %)	78 (5.4 %)	
Others	9 (2.6 %)	36 (2.2 %)	
ICU stay (days)*	7 (1–34)	4 (1–45)	< 0.001
ICU mortality**	149 (42.8 %)	199 (14.0 %)	< 0.001
Hospital mortality**	171 (49.1 %)	188 (17.7 %)	< 0.001

* values expressed in median (range); p values obtained by Mann-Whitney-Wilcoxon U test

** values expressed in proportions; p value obtained by χ^2 test

Table 3 Risk factors for developing acute renal failure in the study population (obtained by logistic regression) (OR odds ratio)

Factor	OR (95 % CI)	p value
Age ≥ 65 years	1.50 (1.16–1.92)	0.002
Infection on admission	1.52 (1.16–2.03)	0.003
Cardiovascular failure	1.84 (1.32–2.56)	0.007
Cirrhosis	2.18 (1.16–4.10)	0.01
Respiratory failure	1.44 (1.09–1.88)	0.01
Chronic heart failure	2.18 (1.12–4.44)	0.02
Lymphoma/leukemia	2.23 (1.02–7.10)	0.04

Table 4 Risk factors for developing multiple organ failure in acute renal failure patients (obtained by logistic regression) (CHF chronic heart failure, OR odds ratio)

Factor	OR (95 % CI)	p value
Cardiovascular failure	15.50 (15.25–15.75)	< 0.01
Hepatic failure	9.06 (8.65–9.47)	< 0.01
Coagulation failure	6.23 (5.80–6.66)	< 0.01
Neurologic failure	4.14 (4.02–4.26)	< 0.01
Age ≥ 65 years	1.19 (1.05–1.33)	< 0.01
Past history of CHF	2.27 (1.63–3.17)	0.02

dent risk factor for the development of MOF. The presence of MOF prolonged the ICU stay by 5 days (median 9 vs 4 days, $p < 0.01$).

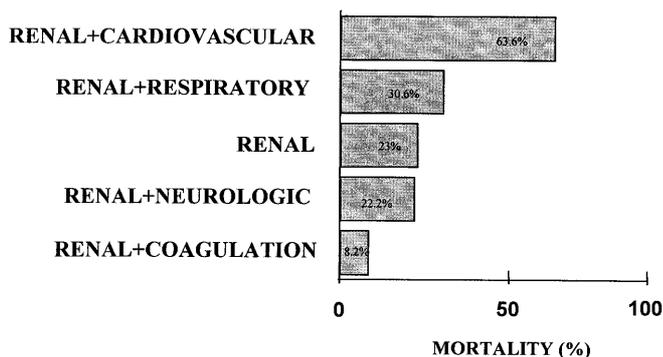


Fig.1 Intensive care unit mortality and association of organ failures in acute renal failure (ARF) patients. Bar shows the percentage mortality among ARF patients, alone or associated with other organ failures. The association of ARF and acute cardiovascular failure presented the highest mortality rate

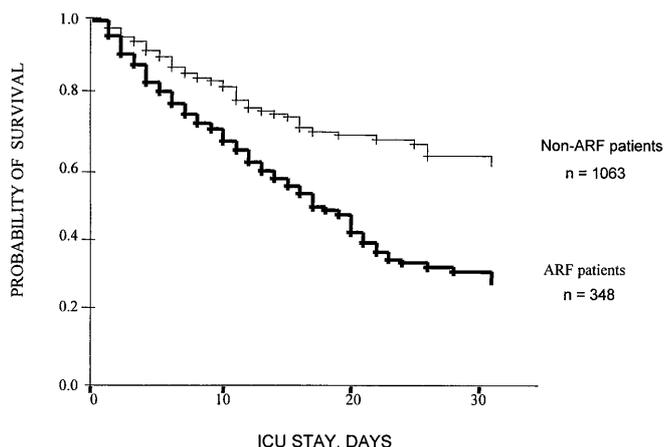


Fig.3 Survival curve for the first month in intensive care unit constructed using estimates of Cox regression model. Hazards seem to be constantly proportional with no evidence of violation of the principles of analysis. Difference between the curves estimated by Breslow test (to equality of survival distributions) was 29.33 ($p < 0.01$)

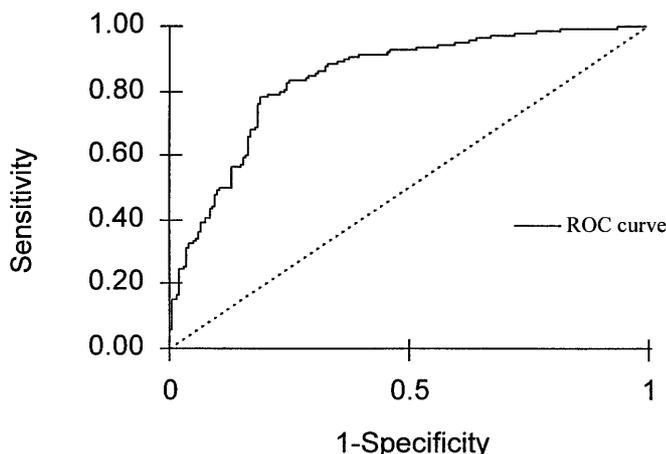


Fig.2 Receiver operating characteristics curve of the model predicting death. The area under the curve was 0.82 ± 0.02 ($p = 0.001$), indicating a good capability of the model to discriminate between survivors and non-survivors

Risk factors for death

Mortality was about 3 times higher in patients with ARF than in those without, both in the ICU and in the hospital (42.8% vs 14.0% and 49.1% vs 17.7%, respectively, both $p < 0.01$). Among the ARF patients, the du-

ration of ICU stay was the same in survivors and non-survivors (median 7 days); non-survivors were older than survivors (median 65 vs 61 years, $p < 0.01$) and more commonly developed infection during the ICU stay (53.7% vs 27.1%, $p < 0.01$). Oliguria was more frequent in the non-survivors (46.7% vs 24.2%, $p < 0.01$) and was an independent risk factor for mortality (OR = 1.59 [CI 95%: 1.21–1.95], $p < 0.01$). In the total study population, the presence of oliguric ARF was an independent risk factor for death (OR = 1.59 [CI 95%: 1.23–2.06], $p < 0.01$).

Non-survivors developed more organ failures than survivors (median 2 vs 1, $p < 0.01$). Cardiovascular failure was the associated organ failure with the worst prognosis in ARF patients (Fig.1). Using a forward logistic regression method, we identified the maximum cardiovascular score during the ICU stay, the number of organ failures on admission, age more than 65 years and a past history of lymphoma or leukemia as independent risk factors of mortality in ARF patients (Table 5). The presence of infection at any time during the ICU stay increased the risk of death caused by other factors, except advanced age. This model had a good calibration, estimated by the Hosmer-Lemeshow goodness-of-fit ($\hat{C}g^* = 1.444$, $p = 0.99$) and good discriminative power (area under ROC curve = 0.82 ± 0.02 , $p = 0.001$) (Fig.2). These results were used to construct a survival curve (Fig.3) illustrating the shorter estimate of survival time in ARF patients (Breslow test = 29.3, $p < 0.01$).

Table 5 Risk factors for death in acute renal failure patients (obtained by logistic regression) (OR odds ratio)

Factor	OR (CI 95%)	<i>p</i>
Maximum cardiovascular score	1.37 (1.18–1.60)	< 0.01
No. of organ failures on admission	1.24 (1.03–1.50)	0.02
Age \geq 65 years	1.22 (1.01–1.49)	0.04
Past history of lymphoma/leukemia	2.31 (1.03–5.16)	0.04

Discussion

The factors implicated in the development of ARF and its associated poor prognosis are not well defined in the literature and studies aimed at identifying risk factors could assist in our understanding of this disease process. Improved comprehension of which patients are likely to develop ARF could also assist in more appropriate patient selection for clinical trials of potential new therapies.

In our study of a heterogeneous adult ICU population, we found that 25% of the patients developed ARF. This incidence is higher than in some other studies [1, 2, 3] but this may be explained by our exclusion of elective postoperative admissions and by the diagnostic criteria used for the definition of ARF. In our study, ARF was defined by a serum creatinine concentration greater than or equal to 300 $\mu\text{mol/l}$ (3.5 mg/dl) and/or a urine output less than, or equal to, 500 ml/day. We believe that the combination of these two aspects is important, as oliguria may precede a rise in creatinine concentration. As in other studies [5, 6, 8, 10, 13], oliguria was an important prognostic factor; it independently doubled the risk of death for the entire population.

Some of the most important risk factors for ARF were already present on admission to the ICU and included advanced age, the presence of infection, a past history of certain chronic diseases and the presence of other failing organs. Age [1, 9, 11, 20, 21, 22], infection [5, 7] and preexisting chronic disease [1, 9, 13] have all been reported as risk factors in other studies.

Interestingly, although ARF occurred at various time intervals, sometimes present on admission, sometimes developing after a prolonged ICU stay, ARF survivors and non-survivors had similar overall lengths of ICU stay, as some non-survivors died early. In addition, the proportional, estimated survival in ARF patients, compared to non-ARF patients, was reduced throughout the first 30 days. The 43% ICU mortality rate of ARF patients in our study population is comparable to recent values quoted in the literature [3, 4, 5, 6, 7, 8, 10, 11, 12]. In the present study, mortality was 3 times higher in those with, than in those without, ARF. Factors most associated with mortality in our ARF patients included advanced age, past history of hematological malignancies, the number of organ failures on admission and the severity of cardiovascular failure, confirming the observations of previous studies [1, 5, 7, 10, 23]. In many studies shock is identified as a poor prognostic factor in ARF patients [1, 2, 4, 5, 6, 24, 25, 26, 27], and in our study circulatory shock was the most important factor associated with mortality. No other single organ failure significantly contributed to mortality, but the number of dysfunctional organs did, again in agreement with the findings of others [1, 6, 23, 25, 26] and stressing the role of associated organ

failure as an important prognostic determinant in these patients.

Sepsis is frequently implicated in the development and worsening of ARF [1, 7, 24], as well as in the prognosis of these patients [5, 8, 12, 26]. In our study, we preferred to refer to the more specific word infection, rather than sepsis, since signs of sepsis are common in critically ill patients even without evidence of infection [28]. In our study population, the presence of infection during the ICU stay increased the risk of death by virtually all other factors, especially circulatory failure. In many studies, sepsis and shock are mentioned together, suggesting a strong correlation of the two factors in the analysis of mortality [2, 4, 5, 6, 24, 25, 26]. Groeneveld et al. [1] reported that, in the absence of shock, sepsis did not worsen the prognosis of their ARF patients. However, our findings suggest that infection can increase the development of organ failure (renal failure included) in ARF patients and, as discussed above, organ failure is a major prognostic determinant.

Our study has important limitations. It was developed from a large database obtained on a voluntary basis. To encourage participation, we had to limit the amount of data to be collected, and thought it would not be possible to obtain a meaningful analysis of some potentially important risk factors for ARF, such as the use of nephrotoxic agents [24] or radiocontrast material [4]. Other limitations included the difficulty in defining the degree of hypotension over time so that, in general, the use of adrenergic agents was used as a surrogate measure to define acute cardiovascular failure. Clearly, separation of the effects of hypotension and of vasoconstrictive agents on renal function was impossible. Specific admission diagnoses and, in particular, causes of renal failure such as rhabdomyolysis or glomerulonephritis were not recorded. Finally, we used a multivariate analysis to estimate risks, and such methods have their limitations [29].

Despite these limitations, we believe our results add useful data to currently available literature on this subject. First, the database was large and reflected the usual mixed ICU population. Second, we were able to compare ARF patients to non-ARF patients, in contrast to many other studies including only critically ill patients with ARF [3, 5, 7, 8, 10, 12, 13, 20, 23, 25, 26]. Third, multivariate analysis of survival factors was based on a time-to-event occurrence rather than a single assessment, as in most multivariate models used [30, 31, 32], providing a daily approach to survival analysis, which is more appropriate in evaluating the dynamics between different factors.

In conclusion, our study identifies a number of important risk factors for the development and outcome of ARF in ICU patients: Infection is an important risk factor for both ARF and mortality; the presence of circulatory shock in ARF patients carries the greatest risk

of mortality; and our data confirm MOF as the most important determinant of outcome in ARF patients. These factors should be taken into account when testing new approaches for the prevention and treatment of ARF and other organ dysfunction in the critically ill.

Participating centers in the SOFA study

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Free University Hospital (L.G. Thijs, Amsterdam, the Netherlands); Cattinara Hospital (G. Berlot, Trieste, Italy); Hospital Senhora da Oliveira (M. Lafuente, Guimarães, Portugal); Academisch Ziekenhuis (J. Goris, Nijmegen, the Netherlands); Academisch Ziekenhuis Dijkzigt (H. Bruining, Rotterdam, the Netherlands); Comp. Hosp. Sta. Casa (G. Friedman, Porto Alegre, Brazil); Hôpital Boucicaut (J. Labrousse, Paris, France); Western General Hospital (I. Grant, Edinburgh, United Kingdom); Hosp. Geral de St. António dos Capuchos (R. Moreno, Lisboa, Portugal); Bristol Royal Infirmary (S. Willats, Bristol, United Kingdom); KAT General Hospital (H. Ioanidou, Athens, Greece); C.H.U. de Nantes (D. Villers, Nantes, France); C.S. Santa Marcelina (S. Blecher, São Paulo, Brazil); Guy's Hospital (R. Beale, London, United Kingdom); St Elizabeth Ziekenhuis Tilburg (L. Leenen, Tilburg, the Netherlands); University Hospital (P. Nightingale, Manchester, United Kingdom); Royal Prince Alfred Hospital (S. Smith, Sydney, Australia); C.H.U. de Liège (P. Damas, Liège, Belgium); C.H.R.U. de Marseille (C. Martin, Marseille, France); Hosp. Israelita Albert Einstein (E. Knobel, São Paulo, Brazil); The Toronto Hospital (J.C. Marshall, Toronto, Canada); Hospital General de Castello (A. Abizanda, Castellon, Spain); C.H.U. Cochin Port Royal (J.F. Dhainaut, Paris, France).

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