Acute Renal Failure in Patients with Sepsis in a Surgical ICU: Predictive Factors, Incidence, Comorbidity, and Outcome

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Abstract. Acute renal failure (ARF) is a common complication in intensive care unit (ICU) patients. Although there are several reports on outcome of septic patients with ARF, there are no data regarding predisposing factors for ARF. Therefore, the incidence of ARF was investigated in 185 sepsis patients admitted in a surgical ICU during a 16-mo period. Variables predisposing to ARF on day 1 of sepsis were evaluated with univariate and multivariable analyses. APACHE II and SOFA scores were compared during a 14-d period. Additionally, the impact of organ failure on mortality was evaluated. ARF developed in 16.2% of the patients, and 70.0% of these needed renal replacement therapy (RRT). Patients with ARF were more severely ill and had a higher mortality. Remarkably, serum creatinine was already increased on day 1. Creatinine $>$ 1 mg/dl and pH $<$ 7.30, both on day 1 of sepsis, were independently associated with ARF. Age, need for vasoactive therapy, mechanical ventilation, and RRT, but not ARF itself, were associated with mortality. In conclusion, ARF was a frequent complication in sepsis. Sepsis patients with ARF were more severely ill and had a higher mortality. Need for RRT was independently associated with mortality. A simple risk model for ARF, on basis of two readily available parameters on day 1 of sepsis, was developed. This model allows initiating specific therapeutic measures earlier in the course of sepsis, hopefully resulting in a lower incidence of ARF and needi for RRT, thereby lowering mortality.

Acute renal failure (ARF) is a common complication in patients admitted to the intensive care unit (ICU). Numerous causes are responsible for the development of ARF (1); moreover, ARF has often a multi-factorial etiology in critically ill patients. The relative importance of factors contributing to ARF will be different depending on the underlying pathology and patient characteristics. A patient population of young trauma patients developing ARF can probably not be compared with older patients with ischemic and congestive heart disease developing ARF after cardiac surgery. The large differences in mortality for patients with ARF, as reported in recent trials (varying between 28 and 83%) can possibly be explained by differences in patient population (2–25). On the other hand, the relatively stable mortality of patients with ARF over the past decades, despite advances in critical and renal care, is attributed to the changing pattern of associated pathology and patient populations (26–29).

Analysis of a well-described subgroup of ICU patients (*e.g.*, patients after cardiac surgery or sepsis patients) can reveal more precise information concerning the epidemiology and risk factors for development of ARF.

Sepsis is a common condition with an annual death toll in the United States comparable to that of acute myocardial infarction (30). Sepsis is also a well-known risk factor for the development of ARF, and 35 to 50% of ARF cases in the ICU can be attributed to sepsis (2,12,20,23). Mortality in this subgroup of patients is considerably higher than in other subgroups of ARF (2,20,23).

Despite these considerations, there are to the best of our knowledge hardly any data concerning risk factors associated with the development of ARF in patients with sepsis. Our own group found in 1993 that sepsis patients who developed ARF had more associated organ failure, more need for vasoactive therapy, and had a lower central venous pressure (CVP), despite more aggressive fluid therapy, compared with sepsis patients without ARF (31).

The aim of this study was to evaluate the incidence of ARF in critically ill patients with sepsis admitted in a surgical ICU and to identify predisposing factors leading to this condition. In addition, we evaluated the impact of the development of ARF and other organ dysfunctions during the ICU stay on outcome of this sepsis population.

Materials and Methods

Study Population

All adult patients hospitalized in the 22-bed surgical ICU of the Ghent University Hospital during a 16-mo observation period were screened to determine whether they fulfilled the inclusion criteria for sepsis. Sepsis was defined according to the ACCP/SCCM Consensus Conference: Infection and two or more of the following conditions: (*1*) temperature $>$ 38°C or $<$ 36°C; (*2*) heart rate $>$ 90/min; (*3*)

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respiratory rate > 20/min or $PaCO_2$ < 32 mmHg or need for ventilation; (*4*) white blood cell count > 12.000/mm^3 or < 4000/mm^3 (32). Patients with preexisting chronic renal insufficiency (defined by a serum creatinine > 1.5 mg/dl), patients who were treated for sepsis elsewhere before admission, and patients who were included in a clinical trial were excluded from analysis.

Data Collection

The study was designed as a retrospective cohort study. One of the authors (EH) reviewed the complete electronic ICU patient database for patients admitted during the study period. Patient files with a diagnosis of sepsis were retrieved and the individual files of each selected patient were subsequently screened to determine whether sepsis criteria were indeed fulfilled and whether there were no exclusion criteria. For every sepsis patient, two data nurses registered a set of physiologic and laboratory parameters during the first 14 d of the septic episode or when the ICU stay was shorter than 14 d, until ICU discharge or demise. For every parameter, the most abnormal value per day was registered. Need for organ support (vasoactive therapy, mechanical ventilation, and renal replacement therapy [RRT]) was scored for the whole ICU observation period. APACHE II score and predicted mortality were calculated on data collected during the first 24 h of admission (33). Additionally, the APACHE II score and the sepsis-related organ failure assessment score (SOFA) (34) were calculated daily during sepsis to evaluate the evolution of associated organ dysfunction and severity of illness. Both scores were calculated twice: once in the classical way, and once with omission of the points for renal dysfunction.

ARF was arbitrarily defined as a rise from normal creatinine (upper limit 1.0 mg/dl) to at least a serum creatinine ≥2 mg/dl.

Cardiovascular dysfunction was defined as the need for vasoactive medication (epinephrine, norepinephrine, vasopressin, dopamine when administered in a dose > 5 μg/kg per min, or dobutamine), pulmonary dysfunction as need for mechanical ventilation, coagulation abnormalities when platelet count was < 150 × 10^3/mm^3, and liver dysfunction when serum bilirubin was > 2 mg/dl.

Volume balance was calculated by subtracting urinary volume, gastric residue, and fluid loss from drains from the total volume of fluids infused (colloids, crystalloids, and dextrose).

Patient Management

All patients were treated according to an existing protocol for hemodynamic management. A minimum mean arterial pressure (MAP) of 65 to 75 mmHg was pursued; when MAP was lower, adequate fluid resuscitation was checked by means of central venous pressure or pulmonary artery occlusion pressure and corrected by crystalloid or colloid infusions. Therapy with vasoactive medication was initiated when the MAP remained < 65 mmHg. Pulmonary artery catheterization using a semi-continuous cardiac output catheter and monitor (Vigilance; Baxter Healthcare Corporation, McGaw Park, IL), was performed when the patient remained oliguric despite adequate fluid resuscitation and/or when there was need for additional vasoactive therapy. RRT was instituted in patients with acute renal failure fulfilling at least one of the following criteria: urea > 200 mg/dl; fluid overload and oligo-anuria (< 400 ml/d); bicarbonate < 15 mEq/L; or potassium > 6.0 mmol/L. The indication for RRT was independently made by the attending renal consultant, who was not involved in this analysis.

Statistical Analyses

The data are expressed as median (interquartile range). The Mann-Whitney *U* test and χ^2 test were used for univariate analysis. A stepwise forward logistic regression model was constructed on basis of demographic, hematologic, biochemical, hemodynamic, and ventilatory variables. Variables were selected for inclusion in the logistic regression model when the difference between ARF and non-ARF patients had a significance of 0.25 or less in bivariate analysis. When variables described more or less the same (*e.g.*, pH and HCO_3^-), only the variable that was most significant in univariate analysis was included in the analysis. To assess the relationship between a continuous variable and the outcome and to subsequently analyze whether a continuous variable needed to be transformed or categorized, we used a smoothing scatter plot (Lowess of fit). Goodness-of-fit of the model was assessed with the Hosmer and Lemeshow test. Additionally, the model was evaluated using receiving operating characteristic curve analysis (ROC). ROC analysis gives a graphical representation of the sensitivity and 1-specificity of the studied model to predict either mortality or the development of acute renal failure. The discriminative power is maximal when the area under the curve is 1, and there is no discriminative power when the area under the curve is 0.5. Significance was accepted for a two-sided *P* value of < 0.05. The statistical software package SPSS 11.0.1 (SPSS Inc. Chicago, IL) was used.

Results

Epidemiology of ARF and Need for RRT in Patients with Sepsis

During the 16-mo observation period, 185 of 1875 admitted patients fulfilled the inclusion and exclusion criteria for the study. Of these 185 patients, 30 (16.2%) developed ARF (definition of ARF fulfilled on median day 3 of sepsis; interquartile range, 1 to 5), and 21 (70.0% of the patients with ARF) were treated with RRT. Serum creatinine reached its peak on day 4 (3–9) of sepsis in patients with ARF and on day 2 (1–4) in patients without. In patients with ARF, serum creatinine rose to a maximum of 3.47 mg/dl (2.78 to 5.92) compared with 0.98 mg/dl (0.85 to 1.21) in patients without ARF ($P < 0.001$).

Aminoglycosides were used in three (10.0%) and amphotericin B in another two (6.7%) patients who developed ARF. None of the patients who developed ARF were treated with vancomycin. The proportion of patients who were treated with these nephrotoxic drugs was not significantly different from the patients without ARF. Radio-contrast media were administered in four patients (13.3%) who developed ARF and in 19 patients (12.3%) who did not develop ARF; again, this was not significantly different.

The demographic characteristics of patients who did and those who did not develop ARF are described in Table 1. There was no difference in focus of infection between patients who developed ARF and those who did not.

APACHE II score on admission was correct in predicting mortality in the whole group of sepsis patients and for the patients without ARF. The observed hospital mortality in the whole group of sepsis patients was 33.0%, and the expected mortality based on the APACHE II score on admission was 29.5% (14.9 to 46.5) ($P = 0.306$). In patients without ARF, the observed mortality was 28.4% and the expected mortality was 29.1% (14.9 to 42.7; $P = 0.698$). In patients with ARF, APACHE II on admission underestimated the mortality (observed and expected mortality were 56.7% and 42.9% [18.6 to 68.8%], respectively; $P = 0.012$; Table 1). Serial evaluation

Table 1. Patient characteristics and clinical outcome of patients with sepsis who did and did not develop acute renal failure (ARF)[a]

	Patients without ARF	Patients with ARF	*P*
Demographic data			
n	155 (83.8%)	30 (16.2%)	
gender (male/female)	106/49	20/10	0.853
age (yr)	53 (33.6 to 67.0)	62 (48.0 to 69.5)	0.063
APACHE $II_{admission}$	16 (10.0 to 20.0)	21 (13.0 to 29.5)	**0.002**
APACHE II expected mortality (%)	29 (14.9 to 42.7)	43 (18.7 to 68.8)	**0.009**
time in hospital before ICU (d)	0 (0 to 2)	0 (0 to 3)	0.309
Source of infection			
lung	107 (69.0%)	18 (60.0%)	0.333
abdomen	16 (10.3%)	6 (20.0%)	0.134
other causes	32 (20.6%)	6 (20.0%)	0.936
Clinical outcome			
LOS_{ICU} (d)	10 (5.0 to 18.0)	20 (13 to 27)	**0.001**
LOS_{Hosp} (d)	30 (15.0 to 60.0)	27 (19.8 to 51.5)	0.734
$mortality_{ICU}$ (%)	35 (22.6%)	16 (53.3%)	**0.002**
$mortality_{Hosp}$ (%)	44 (28.4%)	17 (56.7%)	**0.007**

[a] Values are expressed as median (interquartile range). ARF, acute renal failure; APACHE $II_{admission}$, APACHE II score calculated on basis of data from the first 24 h of admission to the ICU; APACHE II expected mortality was calculated according to the APACHE II score and the admission category; $LOS_{ICU/Hosp}$, length of stay in the ICU and hospital, respectively; $mortality_{ICU/Hosp}$, mortality in the ICU and hospital, respectively. *P* values in bold are significant.

during the first 14 d of sepsis of the APACHE II and the SOFA score of patients with and without ARF is illustrated in Figure 1. The APACHE II score differentiated patients who developed ARF from those who did not during the first week of sepsis (Figure 1A). The APACHE II score calculated without the points for renal dysfunction was, however, the same in both groups, throughout the observation period (Figure 1B). SOFA score was significantly higher in patients who developed ARF compared with those who did not from day 2 of sepsis on (Figure 1C). Again, however, there was no difference in SOFA score between both groups when the points for renal dysfunction were not included in the calculation (Figure 1D).

Length of stay in the ICU was longer for patients with ARF; on the other hand, length of stay in the hospital was the same in both groups (Table 1). Mortality, both in the ICU and for the total hospital stay, was higher in patients who developed ARF. The excess mortality in patients who developed ARF could be entirely explained by the high mortality in patients treated with RRT (72.7% mortality in patients treated by RRT *versus* 10.0% in ARF patients without need for RRT; $P = 0.001$).

Risk Factors on the First Day of Sepsis for the Development of ARF

In Table 2, the parameters of patients who did and did not develop ARF on the first day of sepsis are illustrated. Sepsis patients who developed ARF had a lower mean arterial BP, despite a higher central venous pressure or pulmonary artery occlusion pressure, received more aggressive fluid loading, and were treated in a higher proportion with vasoactive medication. Although there was no difference in the need for ventilation between both groups, patients with ARF had a more pronounced impairment of gas exchange, as reflected by a lower PaO_2/FIO_2 ratio. Renal function was already impaired, and metabolic acidosis was already present on the first day of sepsis in patients who developed ARF. Patients who developed ARF had a somewhat lower hematocrit, possibly explained by the more positive fluid balance causing dilution.

A multivariable analysis was performed to identify variables on the first day of sepsis, associated with the development of ARF later in the course of sepsis. For this analysis, we excluded the patients that already developed ARF on the first day of sepsis ($n = 8$). APACHE II score on admission, age, central venous pressure, need for vasoactive therapy, PaO_2/FIO_2, serum creatinine, hematocrit, potassium, and pH were included in this logistic regression equation. According to the Lowess of fit line of the scatter plot comparing the individual continuous variables with the predicted probability for ARF, we recoded pH and serum creatinine to dichotomous variables with a cutoff value of 7.30 and 1.0 mg/dl, respectively. Additionally, central venous pressure was recoded into three categories: patients with CVP lower than 5 mmHg, CVP between 5 and 10 mmHg, and CVP higher than 10 mmHg. After a stepwise forward procedure, $pH < 7.30$ and serum creatinine > 1.0 mg/dl, both on the first day of sepsis, were identified as independent covariates for the development of ARF (Table 3). This model predicted 89.1% of the ARF episodes correctly and had a goodness-of-fit, according to the Hosmer and Lemeshow test with a *P* value of 0.334, which indicates that there was a minimal difference between the predicted and the observed number of cases. The corresponding ROC graph had an area

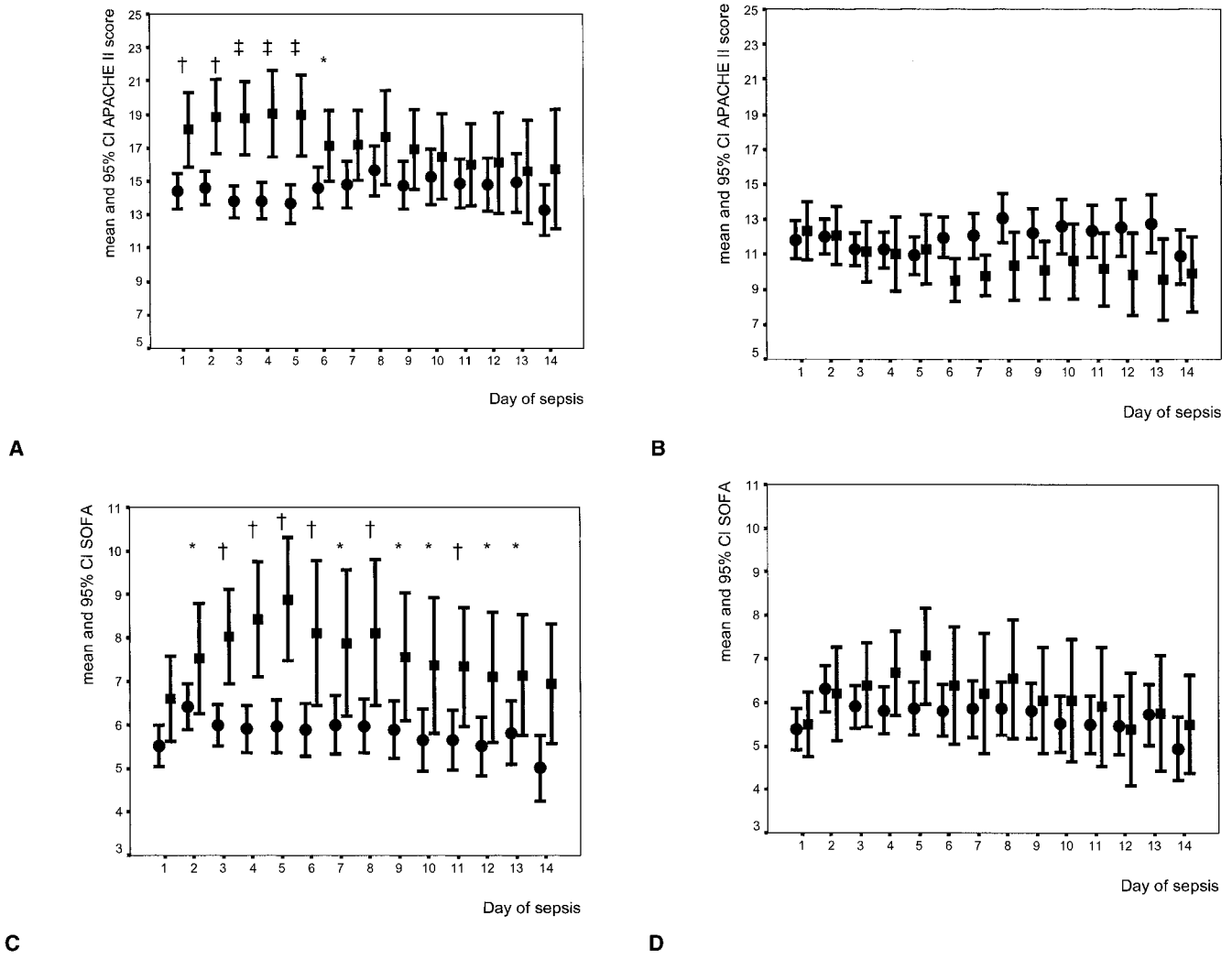

Figure 1. (A) Evolution of APACHE II score, (B) evolution of APACHE II score without scoring for renal dysfunction, (C) evolution of SOFA score, and (D) evolution of SOFA score without scoring for renal dysfunction in patients who did not develop acute renal failure (ARF; ●) and those who did develop ARF (■). CI, confidence interval; * $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.

under the curve of 0.806 (95% confidence interval, 0.703 to 0.910; Figure 2).

Mortality and Organ Dysfunction during the Observation

Not surprisingly, a higher proportion of nonsurvivors developed respiratory or cardiovascular dysfunction, acute renal failure, or need for RRT (Table 4). In a second logistic regression model, the various organ dysfunctions, age, gender, and APACHE II score on admission were incorporated. Increasing age, need for vasoactive therapy, and need for RRT were independently associated with mortality in this model (Table 5). The model correctly predicted mortality in 76.0% and had minimal difference between observed and expected cases (Goodness-of-fit according to Hosmer and Lemeshow: P value = 0.875). The corresponding ROC curve for this logistic model is illustrated in Figure 3.

Discussion

Sepsis is an important problem in ICU patients, not only because of its high incidence, but also because of the high mortality associated with this condition. It is a well-known fact that sepsis is an important risk factor for the development of ARF, and mortality in this specific subgroup of ARF patients is considerably higher than in others (2,12,20,23). There are however surprisingly few data on risk factors for the development of ARF in sepsis patients. To the best of our knowledge, we could find only six recent studies that compared critically ill patients with and without renal failure and that explored factors responsible for the development of ARF (5,10,14,18,24,35). None of these specifically evaluated sepsis patients. On the basis of these considerations, we decided to evaluate the development of ARF in the specific subgroup of surgical ICU patients with sepsis.

ARF had an incidence of 16.2% in sepsis patients admitted to a surgical ICU. This was, not surprisingly, much higher than

Table 2. Comparison of patients with sepsis who did and did not develop ARF on the first day of sepsis[a]

	Patients without ARF	Patients with ARF	*P*
Hemodynamic data			
heart rate (/min) (*H*)	110 (94.0 to 123.3)	113 (97.3 to 124.8)	0.556
MAP (mmHg) (*L*)	72 (63.0 to 81.5)	66 (57.0 to 70.3)	**0.004**
CVP (mmHg) (*L*)	5 (3.0 to 8.0)	8 (4.0 to 13.0)	**0.008**
patients with PAC (%)	44 (28.4%)	13 (43.3%)	0.105
PAOP (mmHg) (*L*)	6 (4.0 to 8.0)	9 (5.0 to 12.5)	0.074
CO (L/min) (*L*)	6.4 (5.60 to 8.05)	7.2 (4.60 to 8.50)	0.771
vasoactive therapy (%)	56 (36.1%)	17 (56.7%)	**0.035**
NOR (μg/kg per min) (*H*)	0.22 (0.13 to 0.28)	0.17 (0.09 to 0.32)	0.664
Ventilatory data			
ventilatory support (%)	113 (72.9%)	24 (80.0%)	0.417
PaO_2/FIO_2 (*L*)	208 (120.0 to 278.0)	121 (95.0 to 161.5)	**0.003**
PaO_2 (mmHg) (*L*)	92 (73 to 124)	76 (63 to 91)	**0.014**
$PaCO_2$ (mmHg) (*L*)	33 (30 to 38)	37 (31 to 46)	**0.028**
Hematologic data			
WBC count ($10^3/mm^3$) (*H*)	14.7 (10.7 to 19.2)	16.3 (11.8 to 20.3)	0.347
hematocrit (%) (*L*)	30.5 (25.9 to 35.3)	27.9 (24.3 to 32.0)	**0.028**
platelet count ($10^3/mm^3$) (*H*)	182 (114 to 252)	159 (116 to 217)	0.252
Biochemistry data			
Na^+ (mmol/L)	139 (135 to 141)	137 (134 to 142)	0.492
K^+ (mmol/L)	3.6 (3.4 to 4.0)	3.9 (3.5 to 4.3)	0.068
glycemia (g/dl) (*H*)	1.63 (1.43 to 2.08)	1.79 (1.27 to 2.73)	0.612
urea (mg/dl) (*H*)	40 (20 to 50)	55 (40 to 162.5)	**<0.001**
creatinine (mg/dl) (*H*)	0.91 (0.75 to 1.05)	1.43 (1.05 to 2.4)	**<0.001**
AST (U/L)	35 (20 to 78)	37 (24 to 93)	0.286
pH (*L*)	7.37 (7.33 to 7.42)	7.27 (7.19 to 7.33)	**<0.001**
HCO_3^- (mmol/L) (*L*)	22 (20 to 24)	19 (17 to 24)	**0.027**
Fluid management			
volume balance (L/24 h)	1.0 (0.05 to 1.84)	2.1 (1.52 to 3.12)	**<0.001**
urinary volume (L/24 h)	1.6 (0.92 to 2.33)	0.9 (0.44 to 1.41)	**<0.001**

[a] Values (highest (*H*) or lowest (*L*)) are recorded during the first day of sepsis, and are expressed as median (interquartile range). ARF, acute renal failure; MAP, mean arterial BP; CVP, central venous pressure; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; NOR, dosage of norepinephrine; WBC, white blood cell count. *P* values in bold are significant.

Table 3. Logistic regression model for variables on the first day of sepsis associated with the development of ARF[a]

	Odds ratio	95% CI	*P*
pH <7.35	6.25	1.92 to 20.41	0.002
Serum creatinine >1 mg/dl	7.56	2.16 to 26.49	0.002

[a] CI, confidence interval.

the incidence of ARF in patients after cardiac surgery (1.1 to 7.7%) (5,14) and was comparable to the incidence of ARF described in a general medical ICU population (16 to 24.7%) (24,35). In contrast to earlier reports ARF did not occur late in the clinical course of severe illness (1); ARF, as defined in the present study, appeared on average 3 d after the beginning of sepsis. One may speculate that this shift to early development (and the absence of a late peak in the incidence for ARF) is caused by improvements in the clinical care of these patients.

Patients who developed ARF were already early in the course of their disease and more severely ill compared with patients who did not develop ARF, as illustrated by the higher APACHE II score on admission and during the first week of sepsis and by the higher SOFA score from day 2 of sepsis on. The APACHE II and the SOFA score evaluate organ dysfunction, including renal dysfunction; it is therefore not surprising that patients with ARF had a higher score in these scoring methods. When renal dysfunction was not scored, there was for both scoring methods no significant difference between the two patient groups. ARF itself was therefore the main factor that discriminated severity of illness and organ dysfunction score.

The excess mortality in patients with ARF, over that predicted by the APACHE II score, is most probably an illustration of the failure of the APACHE II system to predict mortality accurately in subgroups of ICU patients.

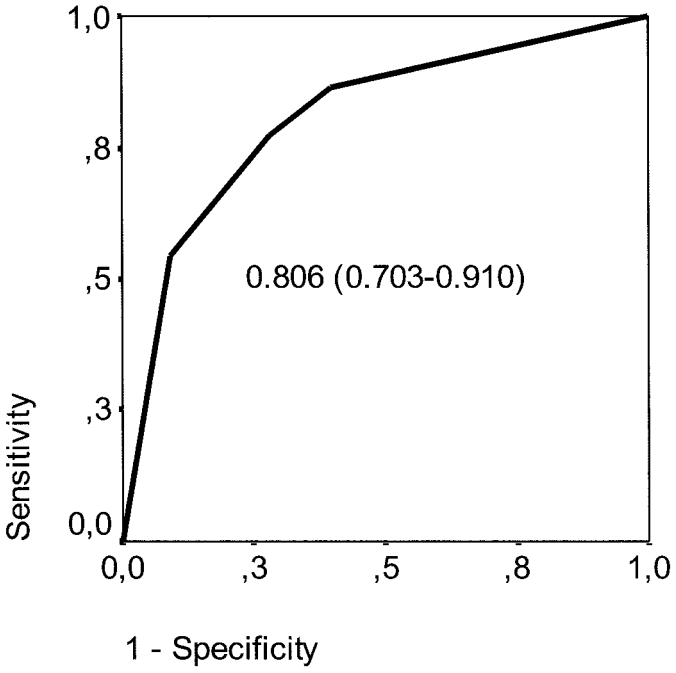

Figure 2. Receiver operator characteristic curve of the logistic regression model predictive for ARF. Area under the curve and the 95% confidence interval are given inside the ROC curve.

In univariate analysis, the incidence of ARF was significantly higher in nonsurvivors. This was, however, entirely caused by the high mortality in ARF patients with need for RRT. ARF and need for RRT are so closely related to each other that multiple logistic regression analysis probably could not identify the independent contribution of each variable, a phenomenon known as multicollinearity. The need for RRT resulted in a 6 times increased odds for dismal outcome. This is an affirmation of data from the recent literature showing that patients who needed RRT had a significantly higher mortality compared with patient groups without need for RRT (2–4,11,17,18,20,22,35). It underlines the importance of further research regarding the optimal timing, dose, and mode of RRT. Furthermore, this highlights the importance of a logistic regression model for prediction of ARF. When the patients at risk for development of ARF can already be identified on the first day of sepsis, greater effort can be put in measures to prevent the evolution to ARF and need for RRT; this would also potentially result in a better outcome. One could argue, however, that the decision for starting RRT in patients with ARF is not always taken on objective grounds. In our patient population, the decision was taken by the consulting nephrologist, who has not been involved in the analysis of these data.

Renal function of patients who developed ARF was already impaired in the very early course of sepsis. It seems that a certain patient group was already predestined to develop ARF, despite the fact that the fluid balance was more positive. The fact that patients who developed ARF had more need for vasoactive therapy, despite greater volumes of fluid infused, can indicate that fluid therapy was insufficient. This can be explained by a more pronounced capillary leak syndrome resulting in intravascular hypovolemia and hemodynamic instability. These circulatory abnormalities could have led to tissue hypoxia and eventually to organ dysfunction. Following this line of reasoning, early and more aggressive fluid therapy and/or optimization of cardiac output by means of dobutamine can possibly restore imbalances in renal oxygen delivery and oxygen demand and development of ARF. This is in agreement with the observation that restoration of imbalances in oxygen delivery and demand, already on admission, in patients with sepsis leads to less organ dysfunction and better outcome (36). When comparable therapy is instituted later in the course of sepsis, no benefit regarding the reduction of organ dysfunction or mortality could be found (37,38).

The high incidence of ARF, despite volume therapy, could also lead to an alternative conclusion: volume repletion alone could not prevent ARF in all patients; therefore, additional therapeutic measures such as activated protein C might be necessary to reduce ARF, or other organ dysfunctions and mortality in patients with sepsis may be needed (39).

On the basis of the odds ratios from the logistic regression model, the risk for ARF can already be estimated on the first day of sepsis. The risk for development of ARF was increased 6 times when the pH was < 7.30, and 7.5 times when serum creatinine was > 1.0 mg/dl. This simple model might provide an elegant and easy-to-use bedside tool for the clinician on the basis of readily available parameters, but it is obvious that it needs further prospective confirmation in larger groups of patients, preferably recruited in a multicenter setting, before it can be recommended in daily practice.

A remarkable finding in the present study was that older age was not associated with development of ARF in sepsis, although common sense would suggest the opposite. The patient sample studied had relatively few patients of older age: the upper interquartile range was 67 yr in patients without ARF and 69.5 yr in patients with ARF. Therefore, it remains an open question whether another patient population with a wider age distribution would have altered the conclusion. Data in the literature are ambiguous on this point. Two community-based studies found that older age was associated with a higher incidence of ARF (11,40). In a general medical ICU population and in a population of patients undergoing myocardial revascularization, age was an independent factor associated with the development of ARF in multivariable analysis (14,24,35). On the other hand, older age was not included in another multivariable model for prediction of ARF after cardiac surgery (5) or in a model for a group of trauma patients (10). More recently, univariate analysis could also not reveal a difference in age between patients with and without ARF in a general ICU setting (18). An explanation for the fact that older age was not associated with ARF could be that in our septic patient population the impact of the underlying diseases leading to ARF (hemodynamic instability caused by sepsis, or trauma, or preexisting cardiovascular, pulmonary, and/or renal dysfunction) is so overwhelming compared with older age that it cannot be identified as an independent factor in multivariable analysis. Another explanation could be that older patients with more

Table 4. Patient characteristics and organ dysfunction of patients with sepsis who did and did not survive[a]

	Survivors	Non-Survivors	*P*
n	124 (67%)	61 (33%)	
Age	50 (31 to 66)	62 (45 to 70)	**0.004**
Gender (male/female)	70%/30%	64%/36%	0.393
APACHE $II_{admission}$	15 (10 to 19)	19 (14 to 26%)	**0.001**
LOS_{ICU} (d)	12 (5 to 20)	13 (6 to 20)	0.974
LOS_{Hosp} (d)	40 (23 to 78)	15 (9 to 26)	**<0.001**
Organ dysfunction developed ARF (%)	13 (11%)	17 (28%)	**0.003**
need for RRT (%)	5 (4%)	16 (26%)	**<0.001**
mechanical ventilation (%)	96 (77%)	60 (98%)	**<0.001**
vasoactive therapy (%)	54 (44%)	50 (82%)	**<0.001**
thrombocytopenia ($<150 \cdot 10^3/mm^3$)	77 (62%)	46 (75%)	0.071
bilirubin >2 mg/dl	45 (36%)	27 (44%)	0.296

[a] Values are expressed as median (interquartile range), and percentage. APACHE $II_{admission}$, APACHE II score calculated on basis of data from the first 24 h of admission to the ICU; $LOS_{ICU/Hosp}$, length of stay in the ICU and hospital, respectively; ARF, acute renal failure; RRT, renal replacement therapy. *P* values in bold are significant.

Table 5. Logistic regression model for variables associated with mortality[a]

	Odds Ratio	95% CI	*P*
Need for vasoactive medication	4.61	1.97 to 10.77	<0.001
Age (/decade)	1.40	1.13 to 1.72	0.002
Need for RRT	6.02	1.69 to 21.46	0.006
Need for mechanical ventilation	6.64	0.81 to 54.51	0.078

[a] CI, confidence interval; RRT, renal replacement therapy.

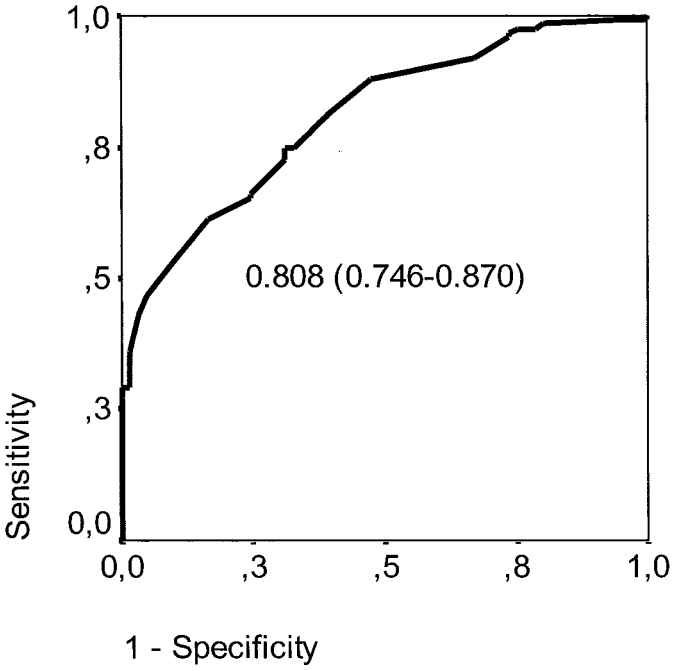

Figure 3. Receiver operating characteristic curve analysis of the logistic regression model predictive for mortality. Area under the curve and the 95% confidence interval are given inside the ROC curve.

co-morbidity (*e.g.*, higher baseline serum creatinine) were excluded from elective surgery and/or admission to the ICU, leading to a selection bias.

Mechanical ventilation probably exerts negative effects on renal function (41), and some studies found an association between mechanical ventilation and ARF (10,35). In our patient population, pulmonary failure was however not associated with an increased risk for ARF. The high proportion of patients needing mechanical ventilation, and the impact of other risk factors for development of ARF made it less likely that mechanical ventilation could be identified as an independent risk factor in this particular study population.

Conclusions

This is to the best of our knowledge the first article that evaluates risk factors for the development of ARF in a subgroup of ICU patients with sepsis; additionally, the incidence and course of ARF in this patient population are described.

One of six patients developed ARF early during the course of sepsis, and most of them needed RRT. ARF patients were already more severely ill on admission and on the first day of sepsis and had a higher mortality compared with sepsis patients who did not develop ARF; moreover, RRT was an independent risk factor for mortality.

On the basis of this database, an easy-to-use bedside tool for identification of patients at higher risk for ARF on day 1 of sepsis was developed.

Patients who developed ARF had already a higher serum creatinine, a lower urinary volume, and more need for vasoactive therapy on the first day of sepsis, despite a more positive fluid balance. To prevent ARF, restoration of hemodynamic status should therefore be started earlier and be applied more

aggressively, and awareness on low and medium care wards should be raised to stimulate early transfer to the ICU and/or early aggressive treatment. Our findings add indirectly to the evidence that the timing of therapy is crucial in patients with sepsis. Alternatively, they also suggest that besides hemodynamic resuscitation, additional therapies will be needed to prevent the development of organ dysfunction in the course of sepsis. Finally, they also underline the potential importance of the developed risk stratification system for early detection of sepsis patients at risk for ARF.

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References

1. Klahr S, Miller SB: Acute oliguria. *N Engl J Med* 338: 671–675, 1998
2. Brivet F, Kleinknecht D, Loirat P, Landais P, The French Study Group on Acute Renal Failure: Acute renal failure in intensive care units-causes, outcome, and prognostic factors on hospital mortality: A prospective, multicenter study. *Crit Care Med* 24: 192–198, 1996
3. Rialp G, Roglan A, Betbese A, Perez-Marquez M, Ballus J, Lopez-Velarde G, Santos J, Bak E, Net A: Prognostic indixes and mortality in critically ill patients with acute renal failure treated with different dialytic techniques. *Ren Fail* 18: 667–675, 1996
4. Liano F, Pascual J, the Madrid Acute Renal Failure Study Group: Epidemiology of acute renal failure: A prospective, multicenter, community-based study. *Kidney Int* 50: 811–818, 1996
5. Chertow G, Lazarus J, Christiansen C, Cook E, Hammerstein K, Frederick G, Daley J: Preoperative renal risk stratification. *Circulation* 95: 878–884, 1997
6. Schwilk B, Wiedeck H, Stein B, Reinelt H, Treiber H, Bothner U: Epidemiology of acute renal failure and outcome of haemodiafiltration in intensive care. *Intensive Care Med* 23: 1204–1211, 1997
7. Douma CE, Redekop WK, Van Der Meulen JH, Van Olden RW, Haeck J, Struijk DG, Krediet RT: Predicting mortality in intensive care patients with acute renal failure treated with dialysis. *J Am Soc Nephrol* 8: 111–117, 1997
8. Chertow GM, Levy EM, Hammermeister KM, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 104: 343–348, 1998
9. Chertow GM, Lazarus J, Paganini E, Allgren R, Lafayette R, Sayegh M: Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. *J Am Soc Nephrol* 9: 692–698, 1998
10. Vivino G, Antonelli M, Moro M, Cottini F, Conti G, Bufi M, Cannata F, Gasparetto A: Risk factors for acute renal failure in trauma patients. *Intensive Care Med* 24: 808–814, 1998
11. Pascual J, Liaño F, the Madrid Acute Renal failure Study Group: Causes and prognosis of acute renal failure in the very old. *J Am Geriatr Soc* 46: 721–725, 1998
12. Liano F, Junco E, Pascual J, Madero R, Verde E, the Madrid Acute Renal Failure Study Group: The spectrum of acute renal failure in the intensive care unit compared to that seen in other settings. *Kidney Int* 53[Suppl 66]: S16-S24, 1998
13. Lombardi R, Zampedri L, Rodriquez I, Alegre S, Ursu M, Di Fabio M: Prognosis in acute renal failure of septic origin: A multivariate analysis. *Ren Fail* 20: 725–732, 1998
14. Mora Mangano C, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT, for the Multicenter Study of Perioperative Ischemia Research Group: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. *Ann Intern Med* 128: 194–203, 1998
15. Noble JS, MacKirdy FN, Donaldson SI, Howie JC: Renal and respiratory failure in Scottisch ICUs. *Anaesthesia* 56: 124–129, 2001
16. Mehta RL, McDonald B, Gabbai FB, Pahl M, Pascual MTA, Farkas A, Kaplan RM, for the Collaborative Group for the Treatment of ARF in the ICU: A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int* 60: 1154–1163, 2001
17. Mehta RL, Pascual MT, Carmencita GG, Zhuang S, Chertow GM, for the PICARD Study Group: Refining predictive models in critically ill patients with acute renal failure. *J Am Soc Nephrol* 13: 1350–1357, 2002
18. Clermont G, Acker CG, Angus DC, Sirio CA, Pinsky MR, Johnson JJ: Renal failure in the ICU: Comparison of the impact of acute renal failure and end-stage renal disease on ICU outcomes. *Kidney Int* 62: 986–996, 2002
19. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Kidney Dis* 39: 930–936, 2002
20. Neveu H, Kleinknecht D, Brivet F, Loirat P, Landais P, the French Study Group on Acute Renal Failure: Prognostic factors in acute renal failure due to sepsis. Results of a prospective multicentre study. *Nephrol Dial Transplant* 11: 293–299, 1996
21. Ronco C, Bellomo R, Homel P, Brendolan A, Dan M, Piccinni P, La Greca G: Effect of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. *Lancet* 356: 26–30, 2000
22. Guerin C, Girard R, Selli J-M, Perdrix J-P, Ayzac L, for the Rhone-Alpes Area Study Group on Acute Renal Failure: Initial versus delayed acute renal failure in the intensive care unit. A multicenter prospective epidemiological study. *Am J Respir Crit Care Med* 161: 872–879, 2000
23. Cole L, Bellomo R, Silvester W, Reeves JH, for the Victorian Severe Acute Renal Failure Study Group: A prospective, multicenter study of the epidemiology, management, and outcome of severe acute renal failure in a "closed" ICU system. *Am J Respir Crit Care Med* 162: 191–196, 2000
24. de Mendonca A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F: Acute renal failure in the ICU: Risk factors and outcome evaluated by the SOFA score. *Intensive Care Med* 26: 915–921, 2000
25. Schiffl H, Lang SM, Fischer R: Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med* 346: 305–310, 2002
26. Druml W: Prognosis of acute renal failure 1975-1995. *Nephron* 73: 8–15, 1996
27. Turney J, Marshall D, Brownjohn A, Ellis C, Parsons F: The evolution of acute renal failure, 1956–1988. *Q J Med* 74: 83–104, 1990
28. Biesenbach G, Zazgornik J, Kaiser W, Grafinger P, Stuby U, Necek S: Improvement in prognosis of patients with acute renal failure over a period of 15 years: An analysis of 710 cases in a dialysis center. *Am J Nephrol* 12: 319–325, 1992

29. McCarthy JT: Prognosis of patients with acute renal failure in the intensive care unit: A tale of two eras. *Mayo Clin Proc* 71: 117–126, 1996
30. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR: Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 29: 1303–1310, 2001
31. Vogelaers D, Vanholder R, Colardyn F, Lameire NH: Acute renal failure in an ICU population with sepsis: Retrospective analysis on risk factors for outcome [Abstract]. Presented at: 3rd International Symposium on Acute Renal Failure, Halkidiki, Greece, 1993
32. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest* 101: 1644–1655, 1992
33. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: A severity of disease classification system. *Crit Care Med* 13: 818–829, 1985
34. Vincent J-L, Moreno R, Takala J, Willatts S, de Mendonça A, Bruining H, Reinhart CK, Suter PM, Thijs LG: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 22: 707–710, 1996
35. Groeneveld A, Tran D, van der Meulen J, Nauta J, Thijs L: Acute renal failure in the medical intensive care unit: Predisposing, complicating factors and outcome. *Nephron* 59: 602–610, 1991
36. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, the Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345: 1368–1377, 2001
37. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D: Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med* 330: 1717–1722, 1994
38. Gattinoni L, Brazzi L, Pelosi P, Latini R, Tognoni G, Pesenti A, Fumagalli R, for the SvO2 Collaborative Group: A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med* 333: 1025–1032, 1995
39. Bernard GR, Vincent JL, Laterre P-F, LaRosa SP, Dhainaut J-F, Lopez-Rodriquez A, Steingrub JS, Garber GE, Helterbrand JD, Ely EW, Fisher CJ, for the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group: Efficacy and safety of recombinant human activated protein C for severe sepsis. *New Engl J Med* 344: 699–709, 2001
40. Feest TG, Round A, Hamad S: Incidence of severe acute renal failure in adults: Results of a community based study. *BMJ* 306: 481–483, 1993
41. Pannu N, Mehta RL: Mechanical ventilation and renal function: An area for concern? *Am J Kidney Dis* 39: 616–624, 2002