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Acute renal failure in patients with severe sepsis and septic shock—a significant independent risk factor for mortality: results from the German Prevalence Study

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Abstract

Background. Sound data about the prevalence of acute renal failure (ARF) among patients with severe sepsis and septic shock are lacking. Further, it is not known whether ARF is an independent risk factor for mortality in septic patients or merely an indicator of disease severity.

Methods. A prospective cross-sectional one-day prevalence study was carried out in a representative sample of German ICUs, divided into five strata (< 200 beds; 201–400 beds; 401–600 beds; > 600 beds; university hospitals). 3877 patients were screened of whom 415 had severe sepsis and septic shock.

Results. Fourteen patients (3.4%) had chronic dialysis-dependent RF and were excluded from analysis. Of the remaining 401 patients, 166 (41.4%) had ARF, as defined by a rise in creatinine above twice the upper limit of normal and/or a drop in urine output to < 0.5 ml/kg bodyweight. Median APACHE II score was 22 in patients with ARF and 16 in patients without ARF ($p < 0.0001$). Patients with severe sepsis/septic shock had an overall hospital mortality of 55.2%. Hospital mortality in patients with ARF was 67.3% and without ARF 42.8% ($p < 0.0001$). After adjustment for APACHE II score and age, ARF remained a significant independent risk factor for death [odds ratio (OR) 2.11, 95% confidence interval (CI) 1.27-3.52]. Mortality in septic patients was not associated with pre-existing, non-dialysis-dependent chronic kidney disease, whereas in dialysis-dependent patients with sepsis mortality increased to 86%.

Conclusion. In this representative survey in patients with severe sepsis/septic shock, prevalence of ARF is high with 41.4%. ARF represents a significant independent risk factor for mortality in these patients.

Keywords: acute renal failure; epidemiology; mortality; sepsis

Introduction

Acute renal failure (ARF) is defined as a significant acute decline in glomerular filtration rate (GFR), usually associated with uraemia, which may or may not be associated with a fall in urine output. It is a frequent complication in critically ill patients and associated with an excess mortality [1–3]. In fact, ARF is nowadays mostly observed as part of the multi-organ dysfunction syndrome in severe sepsis and septic shock [1].

Severe sepsis and septic shock are the most common causes of mortality in non-coronary intensive care units (ICUs) accounting for an estimated annual number of 60 000 deaths in Germany [4]. The 90-day mortality rates of severe sepsis and septic shock are as high as 54% [4]. The combination of ARF and severe sepsis was reported to carry a mortality of up to 70% whereas the mortality of ARF alone is 40–45% [5,6]. However, it is unclear whether such estimates are truly representative for all hospitalized patients, since tertiary care centres are probably overrepresented in clinical trials. Moreover, especially in septic patients, it remains controversial whether ARF is an independent predictor of death or merely an indicator of disease severity and whether ARF-associated mortality is related to other organ failures.

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Thus, the aim of the present study was to analyse the prevalence of ARF in patients with severe sepsis/septic shock and analyse its possible impact on patient outcome using data gathered during the German Prevalence Study of Severe Sepsis and Septic Shock [4].

Methods

The study was carried out by the German Sepsis Competence Network (SepNet) with 17 regional centres, a medical coordination centre (University of Jena) and a data management and biometry centre (University of Leipzig).

A detailed description of the methodology of the study has been published previously [4]. In short, data were collected on a cross-sectional, 1-day basis in a representative sample of German hospitals stratified by size: strata 1–4 comprised all non-university hospitals with $\leq$200, 201–400, 401–600 and >600 beds, respectively, and stratum 5 comprised all university hospitals.

A randomly selected study day between 15 January 2003 and 14 January 2004 was assigned to each participating hospital, distributed over a 1-year period to control for possible seasonal variations.

A total of 454 ICUs in 310 hospitals were visited by a trained ICU physician from the nearest SepNet regional centre. All patients admitted to an ICU bed between 6: 00 a.m. of the study day and 6.00 a.m. of the following day were screened for a sepsis-related condition as defined by modified consensus criteria of the American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) [7]. All patients who fulfilled the criteria of severe sepsis and septic shock on the study day were evaluated further. The visiting ICU physician decided if the patients qualified for the pre-defined criteria for ARF (see subsequently) on the study day. All data presented here is gathered from the patients records of this one study day. Hospital and ICU data were collected through an interview of the ICU director. Patient data were gathered anonymously. Electronic data entry, data management, quality control and analysis were performed at the SepNet study coordination centre. The study was approved by the responsible institutional ethics committees and by the federal data protection commissioner.

Definitions

Severe Sepsis/Septic Shock were defined according to modified ACCP/SCCM consensus criteria [7]. Patients with a proven or suspected infection, two or more systemic inflammatory response syndromes (SIRS) criteria and an infection-induced organ dysfunction were classified as having severe sepsis. Septic shock was diagnosed when the systolic arterial blood pressure remained <90 mmHg despite adequate fluid resuscitation.

ARF was defined as a rise in creatinine above twice the upper limit of normal (in patients with previously normal renal function) and/or a drop in urine output to <0.5 ml/kg bodyweight for at least 4 h despite fluid resuscitation. Therefore, according to the newly proposed 'consensus recommendations for defining ARF' [8], patients in this study had acute renal risk (R), injury (I) or manifest acute renal failure (F). Patients with chronic kidney disease (CKD) and baseline serum creatinine levels above the upper limit of normal according to the local laboratory were classified as acute on chronic disease, RIFLE-F_c. In these patients, the decrease in urine output was the only diagnostic criterion.

Statistical analysis

SPSS 11.0.1 (SPSS Inc., Chicago, IL, USA) was used for all data analyses. Categorical outcome data are reported as absolute or relative frequencies where appropriate. The chi-square test, the Kruskal–Wallis H-test and the Mann–Whitney U-test were applied to compare categorical and continuous variables where appropriate.

Multivariate logistic regression analysis was used to identify risk factors for mortality. The model included only those factors that were found to be significantly predictive in preceding univariate analyses.

The Acute Physiology And Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) score were calculated from documented physiological and chronic disease variables as described elsewhere [9,10]. If a single parameter was not documented, the corresponding subscore value was set to zero. To investigate the impact of ARF on morbidity and outcome further, we also calculated the non-renal APACHE score and non-renal SOFA score. This means that in these scores the renal parameters were omitted.

Results

General epidemiology

Of the 3877 screened patients, 415 suffered from severe sepsis/septic shock. Fourteen patients were excluded from analysis because of pre-existing CKD requiring regular haemodialysis (HD) (Figure 1). Of the remaining

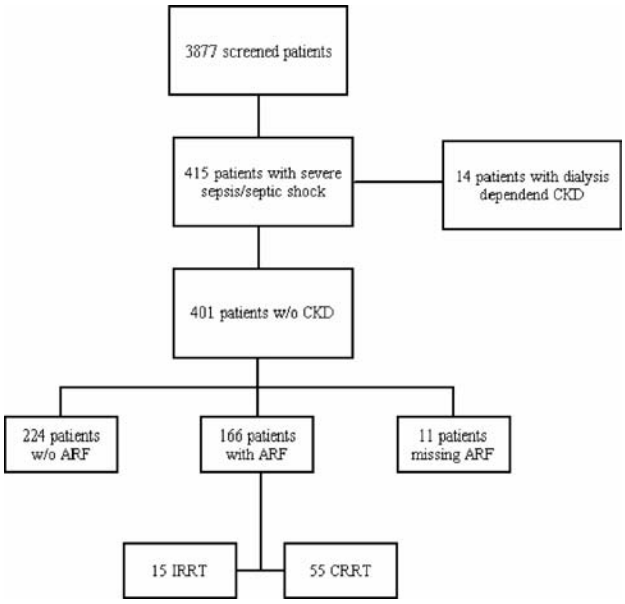

Fig. 1. Distribution of septic patients among all screened patients and their mode of RRT.

401 patients, 166 (41.4%) patients were diagnosed to have ARF according to the above definitions on the study day. This implies a prevalence of septic ARF of 4.3% [95% confidence interval (CI) = 3.7–5.0%] among all screened patients and of 42.6% (95% CI = 37.8–47.5%) among all septic patients.

Patients characteristics are given in Table 1. The median age of patients with ARF was higher ($P = 0.0008$) compared with patients without ARF. With respect to bodyweight, sex distribution, site of infection and concomitant illnesses the two groups were similar. The occurrence of chronic obstructive pulmonary disease and heart failure was slightly, though not significantly higher, while more patients with ARF had pre-existing CKD (see subsequently).

Table 1. Clinical characteristics of patients with and without ARF on admission to ICU

Characteristics	Patients with ARF ($n = 166$)	Patients without ARF ($n = 224$)	*P*-value
Age (Years), Median (IQR)	71 (60–76)	64 (50–73)	0.0008
Sex, No. (%)			
Male	105 (63.3)	117 (52.2)	0.0423
Bodyweight, median (IQR) (kg)	80 (70–87)	80 (65–90)	0.9275
Site of infection, No (%)			
Lung	98 (59.0)	146 (65.2)	0.6277
Abdomen	47 (28.3)	53 (23. 7)	0.2023
Gastrointestinal	17 (10.2)	15 (6.7)	0.1786
Bone/soft tissue	16 (9.6)	18 (8.0)	0.5965
Urogenital	13 (7.8)	12 (5.4)	0.2865
Wound infection	16 (9.6)	16 (7.1)	0.3377
Concomitant diagnosis, No (%)			
Diabetes	48 (28.9)	52 (23.2)	0.2023
Hypertension	74 (44.6)	96 (42.9)	0.7347
Heart failure	44 (26.5)	41 (18.3)	0.0524
Stroke/peripheral artery disease	30 (18.1)	26 (11.6)	0.0718
COPD	15 (9.0)	35 (15.6)	0.0543
Dyslipidaemia	10 (6.0)	15 (6.7)	0.7887
Thyroid disease	6 (3.6)	14 (6.3)	0.2433
Pre-existing CKD	22 (13.3)	15 (6.7)	0.0289

Seventy patients (42%) with ARF were treated with renal replacement therapy (RRT) on the study day. RRT was performed as continuous RRT in 55 patients (79%) and as intermittent HD (IHD) in 15 patients (21%) (Figure 1). The distribution of patients with septic ARF was not statistically different in hospitals of different size ($P = 0.1048$, Figure 2). In non-university hospitals, the proportion of patients with ARF ranged from 32% to 48%. In university hospitals, 49% of septic patients had ARF.

Characteristics and mortality of patients with and without ARF

Table 2 presents clinical data and findings in patients with and without ARF collected on the study day. As expected, creatinine and urea were significantly elevated while the urine output, base deficit and platelets were significantly lower in patients with ARF compared with patients without ARF. Patients with ARF needed significantly higher dose of vasopressor therapy compared with patients without ARF. The groups were comparable with respect to other organ

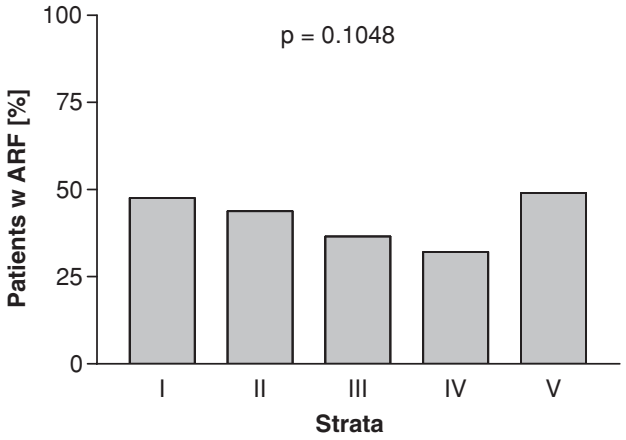

Fig. 2. Percentage of patients with ARF according to the stratum (strata 1–4 comprised all non-university hospitals with ≤200, 201–400, 401–600 and >600 beds, respectively, and stratum 5 comprised all university hospitals).

Table 2. Clinical characteristics in patients with and without ARF on the study day

	With ARF ($n = 166$)	Without ARF ($n = 224$)	*P*-value
Temperature (°C) median (IQR)	38.0 (37.2–38.6)	38.3 (37.6–38.8)	0.0034
Creatinine (mg/dl) median (IQR)	2.3 (1.5–3.4)	1.0 (0.6–1.4)	<0.0001
Urea (mg/dl) median (IQR)	103 (69–147)	56 (33–87)	<0.0001
Urine output (ml) median (IQR)	935 (81–2530)	3057 (2184–4000)	<0.0001
Base excess median (IQR)	−0.3 (−4.3 to 2.4)	1.7 (−1.7 to 4.5)	<0.0001
Norepinephrine dose (μg/kg/min) median (IQR)	0.09 (0.0–0.38)	0.0 (0.0–0.12)	<0.0001
MAP (mmHg) median (IQR)	60 (54–75)	63 (55–70)	0.6231
Haematocrit (%)	28 (25–32)	30 (27–33)	0.0045
RBC-transfusions (pats;%)	37 (22.3)	42 (18.8)	0.2468
Respirator therapy, No (%)	135 (81.3)	159 (71.0)	0.0515
PaO_2/FiO_2 ratio median (IQR)	184 (133–238)	178 (136–226)	0.8141
Bilirubin (mg/dl) median (IQR)	0.3 (0.1–7.0)	0.1 (0.1–2.7)	0.0372
Platelets (G/L) median (IQR)	137 (74–240)	223 (130–326)	<0.0001
Lactate (mg/dl) median (IQR)	18 (12–32)	13 (9–23)	0.0217
CrP median (IQR)	14.9 (8.1–22.7)	14.8 (6.8–23.6)	0.9209

ARF, Acute renal failure; MAP, mean arterial pressure; RBC, red blood cell; CrP, C-reactive protein.

Table 3. Clinical outcome parameters in patients with and without ARF

	With ARF ($n = 166$)	Without ARF ($n = 224$)	P-value
In-hospital mortality (%)	67.3[a]	42.8[b]	<0.0001
ICU mortality (%)	64.6[c]	39.5[d]	<0.0001
Median (IQR) APACHE II score (points)	22 (17–28)	16 (11–22)	<0.0001
Median (IQR) Non-renal APACHE II score (points)	18 (13–23)	15 (10–21)	0.0002
Median (IQR) SOFA score (points)	10 (7–13)	7 (5–9)	<0.0001
Median (IQR) Renal SOFA score (points)	2 (1–4)	0 (0–1)	<0.0001
Median (IQR) Non-renal SOFA score (points)	8 (5–11)	7 (4–8)	0.0023

ARF, acute renal failure; ICU, intensive care unit; IQR, interquartile range. [a]Ten patients with no information about mortality.
[b]Twenty-three patients with no information about mortality.
[c]Twenty-two patients with no information about mortality.
[d]Thirty-four patients with no information about mortality.

Table 4. Univariate and multivariate logistic regression of risk factors for mortality

	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
Non-renal APACHE II	1.065	1.033–1.098	<0.0001	1.046	1.006–1.087	0.0223
Age	1.016	1.002–1.031	0.0254	1.013	0.995–1.030	0.1527
PLT	1.186	0.714–1.967	0.5101	#		
ALI	0.895	0.588–1.364	0.6058	#		
ARF	2.753	1.780–4.256	<0.0001	2.112	1.266–3.523	0.0042
Metabolic acidosis	2.334	1.302–4.187	0.0044	1.653	0.776–3.522	0.1931
Septic shock	1.976	1.293–3.018	0.0016	1.463	0.886–2.416	0.1367
Pre-existing CKD	1.068	0.535–2.134	0.8513	#		
Norepinephrine dose	2.457	1.111–5.432	0.0264	1.192	0.685–2.074	0.5347
Heart failure	1.514	0.909–2.519	0.1109	#		

ARF, acute renal failure; PLT, platelets; ALI, acute lung injury (defined as a PaO_2/FiO_2 ratio <250 mmHg); CKD, chronic kidney disease; #, not included in multivariate analysis.

dysfunctions such as respiratory and liver failure. Although the haematocrit was lower in patients with ARF, the number of units of packed red blood cells (RBCs) and the proportion of patients having received a transfusion was similar in both groups. Lactate levels were significantly higher among patients with ARF, but the levels of C-reactive protein (CrP) were similar.

The most frequent sites of infection were pulmonary (59%) and abdominal (28%) in all 401 septic patients. There was no significant difference in the site of infection between patients with and without ARF (Table 1).

The median length of ICU stay was 6 [interquartile range (IQR) 2–14] days for patients with ARF *vs* 6 days (IQR 3–16) for patients without ARF ($P = 0.0480$; chi-square test). Median hospital stay was significantly longer in patients with ARF compared with patients without ARF [38 (IQR 24–53) *vs* 30 (IQR 20–35); $P = 0.0058$].

Overall 90-day in-hospital mortality was 55.2% and differed significantly between patients with ARF (67.3%) and those without ARF (42.8%) ($P < 0.0001$). ICU mortalities were 64.6 and 39.5%, respectively ($P < 0.0001$). The median non-renal APACHE II score (18 *vs* 15, respectively; $P = 0.0002$), the median SOFA score (10 *vs* 7) as well as the renal SOFA score (2 *vs* 0) and non-renal SOFA score (8 *vs* 7) were significantly higher in patients with ARF than in those without ARF. The median APACHE II score including renal parameters was also significantly higher in patients with ARF compared with those without ARF (Table 3).

Table 4 shows predictors of mortality in univariate and multivariate logistic regression analysis. In this model, the presence of ARF was the only organ dysfunction that was predictive for mortality [odds ratio (OR) 2.112; $P = 0.0042$], whereas thrombocytopenia, acute lung injury, metabolic acidosis, septic shock and norepinephrine dose were not. Median urine output differed significantly between survivors and non-survivors (2960 *vs* 1975 ml; $P = 0.0001$).

Influence of pre-existing CKD on outcome

Thirty-seven patients had pre-existing non-dialysis-dependent CKD. Among patients with ARF the proportion of non-dialysis-dependent CKD was higher compared with patients without ARF (13.3 *vs* 6.7%; $P = 0.0289$; Table 1). In patients without ARF, the presence of pre-existing, non-dialysis-dependent CKD was associated with a non-significant increase in hospital mortality (57.1 *vs* 41.7%). Interestingly, in septic patients with ARF, mortality tended to be lower in patients with pre-existing CKD compared with patients without (54.5 *vs* 69.4%). Within the multivariate logistic regression model, however, pre-existing CKD was not predictive for mortality (Table 4). In contrast, patients with pre-existing dialysis-dependent renal failure ($n = 14$) had a markedly increased ICU and hospital mortality (85.7%) compared with patients with non-dialysis-dependent CKD or without ARF.

Influence of different treatment modalities

Haemodynamic stabilization was comparable between the two groups. Volume resuscitation in patients with and without ARF was similar with respect to type of fluids (colloid *vs* crystalloid) and amount given on the study day. Also, the type and amount of vasopressors used was similar. The mode of RRT had no impact on survival. The hospital mortality was 62.0% in ARF patients on continuous RRT (CRRT) and 71.4% in patients on IHD. Finally, there was no significant mortality difference in ARF patients with or without RRT (64.1 *vs* 69.6%).

Discussion

The goal of the present study was to investigate the epidemiology of ARF in severe sepsis and septic shock in the frame of a nationwide representative cross-sectional survey. The main findings are (i) that the prevalence of ARF in patients with severe sepsis/septic shock is 42.6% and (ii) that the risk of death in patients with ARF is more than twice as high as in septic patients without ARF even after adjustment for non-renal APACHE II score and age. Moreover, ARF appeared to represent a strong independent risk factor for mortality in septic patients.

This observation adds to previous studies in different patient populations suggesting that the development of ARF is associated with adverse outcomes. It has been shown that renal failure occurring after the application of contrast media substantially impaired outcome [11]. In a case–control study, patients with contrast nephropathy showed an increase in mortality from 7% to 34%. The adjusted OR for mortality was found to be 5.5 ($P < 0.01$) [12]. This OR is substantially higher than in patients included in the present study. This may be explained by the fact that mortality in septic patients is much higher than in patients with contrast nephropathy. This shows that the development of ARF has a greater impact in this cohort of patients.

After cardiac surgery mortality also increases with the occurrence of ARF [13]. Interestingly, a disease severity-dependent effect was seen [14]. In patients without prior renal dysfunction the OR of death increased with decreasing GFR [14]. Recently, it has been shown that even minimal perioperative changes of serum creatinine predict prognosis in patients after cardiothoracic surgery [15]. Due to the 1-day prevalence study design we cannot comment on a possible change in mortality with different degrees of renal dysfunction. However, in patients with acute on chronic renal failure, mortality was similar to that in ARF patients without prior renal insufficiency. Interestingly, the presence of chronic renal insufficiency in patients without ARF tended to increase mortality, but the difference was not significant. If, however, pre-existing kidney disease was so severe that patients required chronic haemodialysis, mortality increased markedly.

Length of stay (LOS) in the ICU was not different between those patients with and without ARF. Hospital LOS, however, was significantly longer in patients with ARF. Obviously, the duration of ARF and possible RRT extended the hospital stay in patients who experienced ARF.

A large study on the impact of ARF needing RRT in over 17 000 critically ill patients demonstrated a 4-fold increased mortality in patients requiring RRT [3]. This study, however, included patients with critical illness in general and not specifically with severe sepsis. In the EPISEPSIS study, it was also found that the presence of RRT-dependent ARF was associated with an increased risk of dying [16]. In both trials, patients suffered from a more severe degree of renal dysfunction than our patients. Patients in the study by Metnitz and co-workers were dependent on RRT, while patients in the EPISEPSIS study had to have a renal SOFA score of ≥ 3. In the present study, we also included patients with relatively mild organ dysfunction in the analysis. But even in this cohort of patients the presence of ARF has a significant impact on survival. Therefore, our data support the notion that ARF may exert an independent effect on patient outcome and also show that renal dysfunction not yet requiring RRT is associated with an adverse outcome in septic patients.

This possible negative impact of ARF on the outcome of patients with severe sepsis and septic shock might be explained either by physiological imbalances due to ARF itself or by possible side-effects of its management including RRT.

First, patients with ARF may have an impaired immunocompetence and organ function [17]. Increased oxidant stress and a reduced capacity of the oxygen radical scavenger system have been described [18]. The presence of ARF may further, contribute to the accumulation of oxygen radical species. Second, it has been shown recently that anaemia in patients with dialysis-dependent ARF is an independent risk factor for death [19]. It is of note that the haematocrit in our study is lower in the ARF group than in patients without ARF. Third, the presence of ischaemia-induced ARF in an animal model was shown to increase tumour necrosis factor-α levels and cardiac apoptosis [20], leading to impaired systolic and diastolic cardiac function [20]. Therefore, the presence of ARF in the absence of other organ dysfunctions seems to have distant effects, in this case on cardiac function. Interestingly, we could demonstrate in our study that patients with ARF had more need of vasopressors and showed a significantly higher non-renal morbidity (as expressed by the non-renal SOFA and non-renal APACHE II score) than patients without ARF.

Certainly RRT itself may be associated with side-effects impairing the outcome of septic patients with ARF. The most frequently used mode of RRT in this study was continuous haemofiltration (CVHF). This is known to initiate several pathways of inflammation and coagulation. Moreover, RRT has potential effects on the antioxidant status by depleting antioxidants or generating radical oxygen species [18]. The type of filter membrane used should not be of relevance in this study. First, the treatment of choice was CVHF and here mostly synthetic, so-called 'biocompatible' membranes are used. Second, it has been shown that the use of two different types of membranes (cuprophane *vs* polysulphone) is not of relevance for the outcome of RRT-dependent ARF in an ICU [6]. Interestingly, there was a trend to improved outcome in patients treated with CRRT compared with IHD. The numbers of patients, however, are small and this fact must be interpreted with caution. It

is not possible to comment on the effect of dose of RRT, because such information had not been gathered. However, others have shown that the dialysis dose does have an impact on the outcome in critically ill patients with ARF [21].

Although the present survey comprised a large and thoroughly selected representative nationwide sample of hospitals and ICUs in Germany, its cross-sectional design carries certain limitations. The study was planned as a 1-day prevalence study, therefore the incidence of ARF may only be estimated. Also, there is no data regarding the course of the disease and therefore interventions such as RRT may not be mirrored correctly. Further, diseases with a longer duration are more likely to be overrepresented in 1-day point prevalence studies, possibly slightly overestimating the number of patients to suffer from sepsis and ARF. This error, however, should be of minor importance as a relationship between LOS and ARF could not be proven.

Conclusion

This study may suggest that the occurrence of ARF has a strong and independent negative impact on outcome in septic and septic shock patients. In accordance with previous studies, ARF should therefore be seen as a strong independent risk factor for mortality rather than merely an organ dysfunction associated with oliguria and rising creatinine values. As kidney injury and ARF play such an important role, efforts should be undertaken to prevent its occurrence and facilitate its early diagnosis. Measures must be implemented to identify patients at risk of developing kidney injury and nephrotoxic agents should be avoided as much as possible.

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Conflict of interest statement. None declared.

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