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Outcome prediction of acute renal failure in medical intensive care *

J.-H. Schaefer, F. Jochimsen, F. Keller, K. Wegscheider and A. Distler

Department of Internal Medicine, Klinikum Steglitz of the Free University of Berlin, FRG

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Abstract. Data acquired prospectively from 134 patients with acute renal failure requiring dialysis in a medical intensive care unit (ICU) were analysed in order to derive indicators predicting ICU-survival. Mortality in the ICU was 56.7%. Linear discriminant analysis correctly predicted outcome in 79.9% at the start of dialysis, and 84.7% at 48 h after the first dialysis. The most important predictive variables were mechanical ventilation and low blood pressure. On the other hand, the total correct classification rates achieved by a standardised system for scoring ICU-patients (APACHE II) did not exceed 58.2%. It is concluded that outcome prediction by APACHE II and even by the discriminant functions is too inaccurate to become the basis for clinical decisions either concerning the initiation or the continuation of dialysis treatment in ARF.

Key words: Acute renal failure – Intensive care medicine – Outcome prediction – APACHE II

Acute renal failure (ARF) occurring in the intensive care unit (ICU) is still a severe complication with a mortality up to 86% [1]. Especially when ARF has reached a degree which makes dialysis treatment inevitable, a prognostic estimation would be very helpful. Several attempts have been made to derive prognostic indices for patients with ARF [2–6], but few studies have differentiated between intensive care patients and those admitted to a general ward [7, 8]. As Butkus demanded [9], it is necessary to more accurately define study populations in order to achieve comparability, including a measure of the severity of the underlying illness. We therefore examined patients admitted to a medical ICU and assessed the Acute Physiology and Chronic Health Evaluation (APACHE II) as a method of determining the severity of illness.

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Demographic and anamnestic characteristics as well as clinical and laboratory variables obtained before the initiation of dialysis, and during the first 48 hours thereafter, were examined in order to answer the following questions: 1) Which of the variables distinguish between survivors and non-survivors? 2) Is it possible to derive a prognostic index that identifies patients without a chance of survival? 3) How well do standardised scoring systems for intensive care such as APACHE II predict outcome?

Patients and methods

All patients admitted to the medical ICU of Klinikum Steglitz, Free University of Berlin, between January 1985 and February 1988 ($n = 4130$) were included prospectively in an observational study by acquisition of clinical and laboratory data through standardised forms. The study was approved of by the ethics committee of Klinikum Steglitz. All patients treated by haemodialysis because of ARF were selected for evaluation in the present study. Chronic dialysis and kidney transplantation were exclusion criteria.

Dialysis was initiated in the presence of at least one of the indications specified in Table 1. Haemodialysis was performed for 4 h at least 3 times per week using a 1.2 m^2 capillary dialyser (ultrafiltration factor of 6–8) with a blood flow rate of 200 ml/min, a dialysate flow rate of 500 ml/min (acetate dialysate) and 1000 IU/h heparin.

The variables listed in Table 1 were analysed to derive prognostic indicators immediately before the initiation of dialysis therapy (P0) as well as 24 (P24) and 48 h (P48) thereafter. All variables represented clinical parameters obtained from routine monitoring and therapy. The prognostic criterion was defined as death or survival in the ICU. All variables were entered as dichotomous predictors according to the definitions given in the table. They were derived from the worst values within 24 h.

Multiple organ failure (MOF) was assessed as an additional variable by adding up the number of organ dysfunctions apart from ARF. The failure of the respiratory, hepatic and neurological organ systems was based on the definitions by Jordan et al. [17] and cardiac failure was defined as radiological or clinical signs of congestion. This variable was not included in the discriminant analysis as a single variable; we were interested in the relevance of the particular organ systems, which were therefore entered separately.

The APACHE II score was calculated as described in the original publication [10], and the admission diagnostic categories were used to estimate the risk of death. The patients were divided into diagnostic subgroups according to their underlying disease: septic, gastrointestinal,

Table 1. List of variables and definitions for bivariate and multivariate analysis

Variable	Definition
Indications for dialysis:	
Serum creatinine	>500 µmol/l
Oliguria	<400 ml/day
Volume overload	Clinical/radiologic evidence of congestion or CVP>20 cmH_2O, unresponsive to conventional treatment
Metabolic acidosis	pH<7.37 and HCO_3^- <21 mmol/l in the presence of high serum creatinine or oliguria (as above)
Hyperkalemia	>6 mmol/l in the presence of oliguria (as above)
Uremia	Pericarditis, coma, convulsions after exclusion of other causes
Annamnestic/demographic data:	
Gender	Female
Age	>60 years
Diabetes mellitus	Yes
Heart failure	Congestive/right heart (NYHA III/IV)
Hypertension	Yes
Renal insufficiency	Without dialysis
Alcoholism	Without liver cirrhosis
Liver cirrhosis	Yes
Immune deficiency	Neoplastic diseases, AIDS, treatment with immunosuppressive agents
Clinical/laboratory data:	
Mechanical ventilation	All sorts of ventilator support
Volume overload	Clinical/radiologic evidence of congestion, CVP>20 cmH_2O
Liver failure	According to the definition by Jordan [17]
GI-bleeding	Nasogastric aspirate of blood, haematemesis
CNS depression	Stupor, coma
Thrombocytopenia	<60000 µl
Hypotension	Systolic blood pressure<80 mmHg persistent for 1 h or recurrent readings within 6 h or cardiopulmonary resuscitation
Vasoactive medication	Use of epinephrine, norepinephrine, or high doses of dopamine (>3 µg/kg/min)
Centralised circulation	Cyanosis or cold, clammy extremities
Volume depletion	CVP<0 cmH_2O for 6 h
Volume substitution	>1000 ml of blood, albumin or colloidal solutions
Infection	Suspect of infection: temperature>38 °C with clinical symptoms of infection
Septic shock	Temperature>38 °C and hypotension
Serum lipase	Serum lipase>200 U/l
Surgery	any surgery
Mean blood pressure	<70 mmHg
Heart rate	>119/min
Body temperature	>37.9 °C
Sodium	>145 mmol/l
Serum urea	>30 mmol/l
Blood glucose	>10 mmol/l
Prothrombin time	<50%
WBC	>15000/µl
Haemoglobin	<9 g/dl

GI – gastrointestinal, CNS – central nervous system, CVP – central venous pressure, and WBC – white blood cells

cardiovascular, neurological, and endocrine. The APACHE II score was assessed on admission, at P0, P24 and P48.

Bivariate statistical analysis for the prognostic variables was performed using the χ^2-test (SPSSX). A p-value lower than 0.05 was considered statistically significant.

All variables were entered into a linear discriminant procedure (BMDP Statistical Software, 1983), for stepwise selection of the predictor variables including all variables with an F-value of at least 4.0. The resulting variables were tested for reliability using the 'leaving-one-out' method', which is a jack-knifing procedure. This approach is superior to the method of resubstitution, because it avoids falsely optimistic results [11]. Since the 'leaving-one-out' method is not feasible for logistic regression analysis, the linear discriminant model was preferred in this study. The analysis was performed for the three points named above. At P24 and P48, the corresponding variables were added to those obtained at earlier time points. Sensitivity was defined as the correct prediction of death, specificity as the correct prediction of survival.

Classification rates for APACHE II were calculated at two different risk cut-off-points (0.5 and 0.7). A comparison of the classification rates obtained by APACHE II at a cut-offpoint of 0.5 and by the discriminant functions was performed by χ^2-test. The overall accuracy of the variable MOF was calculated using a maximum-likelihood approach with a cutpoint of 0.5 and was compared to the discriminant functions by χ^2-test as well.

Results

Of 134 patients haemodialysed for ARF, 76 died and 58 survived, yielding a mortality of 56.7%. After 48 h, 10 patients had died and 6 had been transferred to a normal ward for continued dialysis since they did not need further ICU monitoring. Thus, at P48, 118 patients remained for the analysis (66 non-survivors and 52 survivors).

Of the patients 68 (32 non-survivors and 36 survivors) were dialysed immediately after admission or on the day of admission. In 18 patients dialysis was initiated more than 5 days after admission; 15 of these patients died.

Non-survivors did not differ significantly from surivors with respect to age and gender. The majority of the patients suffered from sepsis (74.6%). The median APACHE II value of the population at P0 was 22.5.

Bivariate analysis of the anamnestic data revealed a significant difference between the non-survivors and survivors for the history of liver cirrhosis only. Assessment of the variables at P0 including the indications for dialysis, revealed a significant difference between survivors and non-survivors for mechanical ventilation, volume overload, volume substitution, mean arterial pressure, heart rate, body temperature, and blood glucose level. A high serum creatinine level also reached significance and identified the survivors unexpectedly. This phenomenon was not reflected by the serum urea level, for which no significant difference was observed. The comparison of peak creatinine levels also yielded significantly higher results for the survivors, median values being 545 µmol/l compared to 380 µmol/l ($p = 0.0224$ Mann-Whitney U test).

At P24, the pattern had not changed substantially. Only the clinical suspicion of bacterial infection and the presence of high serum lipase levels were additionally significant, high serum lipase levels, again surprisingly, identifying the survivors. At P48, hypotension was signif-

Table 2. Significant results of bivariate analysis

Variable	Total *n*	Non-survivors		Survivors		χ^2	*p*
		n	%	*n*	%[a]		
Anamnestic/demographic:							
Liver cirrhosis	28	21	27.6	7	12.1	3.92	0.0476
Indications for dialysis:							
Serum creatinine	43	17	22.4	26	44.8	6.62	0.0101
Volume overload	56	38	50.0	18	31.0	4.12	0.0425
Data obtained immediately before first dialysis (PO):							
Ventilator support	56	46	60.5	10	17.2	23.59	<0.0001
Volume overload	56	38	50.0	18	31.0	4.12	0.0425
Volume substitution	31	24	31.6	7	12.1	5.99	0.0144
Mean pressure	59	47	61.8	12	20.7	20.97	<0.0001
Heart rate	73	51	67.1	22	37.9	10.14	0.0014
Body temperature	69	47	61.8	22	37.9	6.61	0.0102
Blood glucose	69	50	65.8	19	32.8	13.08	0.0003
Data 24 h after first dialysis (P24):							
Ventilator support	59	46	60.5	13	22.4	17.83	<0.0001
Serum creatinine	47	18	23.7	29	50.0	8.88	0.0029
Infection	63	42	55.3	21	36.2	4.06	0.0439
Serum lipase	20	6	7.9	14	24.1	5.62	0.0178
Mean pressure	78	56	73.7	22	37.9	15.85	0.0001
Heart rate	88	61	80.3	27	46.6	15.12	0.0001
Data 48 h after first dialysis (P48):							
Ventilator support	61	48	72.7	13	25.0	24.65	<0.0001
Hypotension	28	24	36.4	4	7.7	11.67	0.0006
Vasoactive drugs	50	39	59.1	11	21.1	15.62	0.0001
Volume overload	52	35	53.0	17	32.7	4.09	0.0431
Volume substitution	40	29	43.9	11	21.2	5.76	0.0164
Infection	67	45	68.2	22	42.3	6.92	0.0085
Septic shock	41	33	50.0	8	15.4	13.88	0.0002
Mean pressure	80	66	86.8	14	24.1	51.18	<0.0001
Heart rate	70	48	72.7	22	42.3	9.93	0.0016
Prothrombin time	45	34	51.5	11	21.2	10.11	0.0015
WBC	62	41	62.1	21	40.4	4.67	0.0306

GI – gastrointestinal, CNS – central nervous system, and WBC – white blood cells

[a] these columns display the frequencies of the variables in the groups of nonsurvivors and survivors, respectively

icantly different between survivors and non-survivors, together with the use of vasoactive drugs, septic shock, leukocytosis and a prothrombin time below 50%. Significant results are displayed in Table 2.

MOF was assessed as a summary variable, adding the number of organ failures apart from renal failure. The correlation of outcome with the number of organ failures is shown in Fig. 1. There was an obvious increase of mortality with rising numbers of organ dysfunction.

Stepwise discriminant analysis detected 6 variables contributing towards the differentiation of non-survivors from survivors at P0. These were the two anamnestic characteristics of liver cirrhosis and heart failure, the 3 clinical variables of requirement for mechanical ventilation, mean arterial pressure and septic shock and the 1 laboratory parameter; the blood glucose level. The overall jack-knifed correct classification rate was 79.9% with a sensitivity of 75% and a specificity 86.0%. When the variables obtained at P24 were added, the classification did not improve. The first 2 variables selected did not

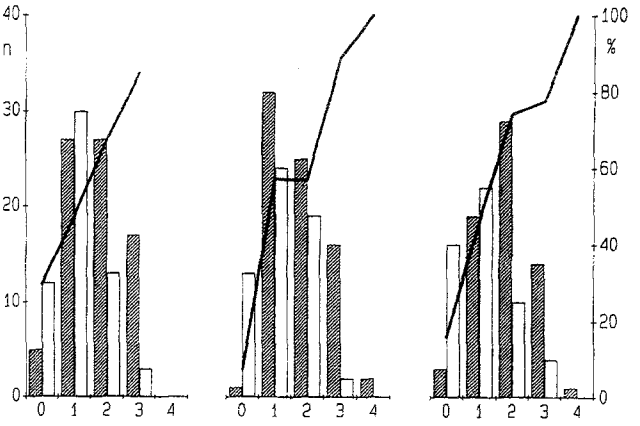

Fig. 1. Multiple organ system failure: number of organ functions involved apart from renal at P0 (*left*), P24 (*middle*) and P48 (*right*) and corresponding mortality. Non-survivors: ▨; Survivors: □; Mortality: —

change (requirement for mechanical ventilation and mean arterial pressure), and the only variable additionally chosen was heart rate. An overall correct classification rate of 79.1% was achieved with a sensitivity of 73.7% and a specificity of 86.2%. Adding the variables assessed at P48 yielded a correct classification of 84.7%, sensitivity and specificity being 87.9% and 80.8% respectively. The relevant variables consisted of the mean arterial pressure and prothrombin time at P48 in addition to blood glucose level and mechanical ventilation at P0. The only contributory anamnestic factor was heart failure. Tables 3 and 4 illustrate the 3 discriminant functions.

APACHE II was calculated for admission and the 3 points named above (P0, P24 and P48). Median values did not differ significantly between survivors and non-survivors (Table 5). On calculating the probability of dying with a risk cut-off-point of 0.5, death was only predicted with a sensitivity of 52.6% and survival with a specificity of 63.8% at P0, the total correct classification being 57.5%. The classification did not improve substantially at P24 and P48, or with a risk cutpoint of 0.7.

The overall correct classification rates obtained with APACHE II and the variable MOF were compared to the discriminant functions by a χ^2-test (Table 6) for the three points. All three discriminant functions performed significantly better than the APACHE II risk functions. Calculation of sensitivities at a specificity of 100% yielded 44.3%, 0% and 32.8% for the discriminant functions at P0, P24 and P48, and 2.6%, 0% and 0% for APACHE II.

Discussion

The aim of this study was to evaluate the possibility of predicting survival in ARF treated by dialysis in the ICU.

Study inclusion was established at the very moment when the decision to dialyse was made, so that the necessity of a prognostic estimation arose. Outcome prediction at the time of decision making (P0) was compared to that after 24 h (P24) and 48 h (P48), respectively. Linear discriminant analysis was used to develop a prognostic function, which predicted outcome correctly in 79.9% at

Table 3. Variables and function coefficients of multivariate stepwise linear discriminant analysis compared to bivariate *p*-variables listed in order of entry

P0			P24			P48		
Variable	Function coefficient	Bivariate *p*-value	Variable	Function coefficient	Bivariate *p*-value	Variable	Function coefficient	Bivariate *p*-value
Mechanical ventilation[1]	0.58711	<0.0001	Mechanical ventilation[1]	0.55220	<0.0001	Mean pressure[3]	4.45892	<0.0001
Mean pressure[1]	0.51897	<0.0001	Mean pressure[1]	0.52621	<0.0001	Blood glucose[1]	2.25054	0.0003
Liver cirrhosis[0]	0.48142	0.0476	Heart rate[2]	0.51229	0.0001	Prothrombin time[3]	2.56843	0.0015
Blood glucose[1]	0.44313	0.0003				Heart failure[0]	2.24830	NS
Heart failure[0]	0.32542	NS				Mechanical ventilation[1]	2.22227	<0.0001
Septic shock[1]	−0.34577	NS						
Constant	1.81243			−1.78523			−2.38171	

P0, wen dialysis was initiated, and amounted to 84.7% at P48, 48 h after the first dialysis. The most important predictive variables were requirement for mechanical ventilation and the presence of a low mean arterial pressure. Compared to APACHE II, the classification rates of the discriminant functions were significantly better, the overall correct classification with APACHE II not exceeding 58.2%.

It is generally accepted that the underlying disease plays a major part in the prognosis of ARF [12, 13].

As we have already reported, the majority (74.6%) of patients requiring dialysis for ARF in this medical ICU suffered from sepsis [14]. This may be one explanation for the fact that infection-related variables hardly contributed to the discrimination; infection did contribute in more heterogeneous patient groups, as described by Lien and Corwin [5, 15]. Furthermore, our results also differed from the literature emphasizing the significance of surgical procedures [4]. They were a rare event in the medical ICU and could therefore not be evaluated.

In agreement with Liano [6], the requirement for mechanical ventilation proved to be one of the most important predictors. This emphasizes the role of MOF [16], which clearly distinguished ARF in the ICU from purely nephrological diseases. The correlation of outcome with the number of organ failures apart from renal failure in our data supports these findings (Fig. 1). Although the correlation between the number of organ systems involved and the mortality rate is well known [17], we did not include MOF in the discriminant analysis as a single variable, because we were interested in the relevance of the particular organ systems, which were therefore entered separately. When the overall correct classification rates obtained by the use of MOF only was compared to the discriminant functions, the results of the discriminant functions were significantly better at P0. At P24 and P48

Table 4. Jack-knifed classification results of multivariate stepwise linear discriminant analysis

	Expected to be				Total correct classification
	Dead	Alive	Sensitivty	Specificity	
P0					
Non-survivors	57	19	75.0	86.2	79.9
Survivors	8	50			
P24					
Non-survivors	56	20	73.7	86.2	79.1
Survivors	8	50			
P48					
Non-survivors	58	8	87.9	80.8	84.7
Survivors	10	42			

P0 = immediately before dialysis, P24 = 24 h after first dialysis, P48 = 48 h after first dialysis

Table 5. Performance of APACHE II

Median values of APACHE II:	Non-survivors	Survivors
APACHE on admission	24.0	22.0
APACHE at P0	22.5	22.5
APACHE at P24	25.0	22.0
APACHE at P48	24.0	22.0

Classification results	Expected		Sensitivity	Specificity	Total correct classification
	dead	alive			
(cut-off-point 0.5)					
P0					
Non-survivors	40	36	52.6	63.8	57.5
Survivors	21	37			
P24					
Non-survivors	48	28	63.2	51.7	58.2
Survivors	28	30			
P48					
Non-survivors	39	27	59.1	51.9	55.9
Survivors	25	27			
(cut-off point 0.7)					
P0					
Non-survivors	22	54	28.9	86.2	53.7
Survivors	8	50			
P24					
Non-survivors	22	54	28.9	79.3	50.8
Survivors	12	46			
P48					
Non-survivors	18	48	27.3	86.5	53.4
Survivors	7	45			

P0 = immediately before dialysis, P24 = 24 h after first dialysis, P48 = 48 h after first dialysis

Table 6. Comparison of classification results with APACHE II and the variable MOF to the discriminant functions: Correct classification rates with discriminant analysis compared to APACHE II and MOF

Point of time	Discriminant function	APACHE II (out-offpoint 0.5)	χ^2	p
P0	79.9%	57.5%	15.6	0.0014
P24	79.1%	58.2%	13.6	0.0035
P48	84.7%	55.9%	23.5	<0.0001
Point of time	Discrinant function	MOF (cut-offpoint 0.5)	χ^2	p
P0	79.9%	64.2%	8.2	0.0427
P24	79.1%	65.7%	6.0	NS
P48	84.7%	69.5%	7.8	NS

the differences did not reach the significance level, but nevertheless the classification rates with the discriminant functions exceeded those of the variable MOF (Table 6).

The other variables discriminating between survivors and nonsurvivors in multivariate analysis could be summarized as hemodynamic parameters consisting of mean arterial pressure, which was always included in the discriminant functions, heart rate and volume overload, accompanied by history of heart failure. The importance of hemodynamic parameters and septic shock has already been stressed by Menashe and Coratelli [7, 18]. Apart from that, only septic shock, blood glucose level, liver cirrhosis and prothrombin time contributed towards the discrimination. In contrast to the other variables, septic shock had a negative function coefficient. However, this does not imply a favourable effect of septic shock, since the variables of the discriminant functions can never be evaluated separately, but must always be considered in their particular combination. Bivariate analysis revealed that septic shock, although not significant at P0, was present in 32.9% of the on-survivors, compared to only 22.4% of the survivors. At P48 the difference became statistically significant, and septic shock was associated with a poor prognosis.

Surprisingly, high serum creatinine levels were associated with survival in our data. Hence, it cannot be concluded that the initiation of dialysis treatment at high creatinine levels necessarily implies a poor prognosis. No significant difference was found concerning urea levels, and non-survivors obviously had an elevation of urea out of proportion to creatinine reflecting their enhanced catabolism. Although dialysis was started at lower creatinine levels in these patients, outcome did not improve, which confirmed the prognostic importance of catabolism in ARF [19, 20]. In addition, further factors might have been responsible for this phenomenon, such as patient selection. In patients who appeared to be doing generally better dialysis treatment might have been started later than in patients in poor condition. On the other hand, not only creatinine levels at the beginning of dialysis, but also peak creatinine levels were significantly higher in the survivors, when tested as a genuine variable, so that neither the cut-off chosen for the definition of high serum creatinine (Table 1) nor the point of time when dialysis was started were responsible for the phenomenon. Nevertheless, with a dialysis protocol based on clinical decisions, it cannot be excluded that the factors discussed above biased the results to suggest that a higher creatinine level associated with a better outcome.

High serum lipase levels were also associated with a better prognosis. No obvious explanation could be derived from the data, but again, factors like patient referral and selection might have led to this result. In 9 patients, acute pancreatitis was diagnosed clinically on admission, so that, at least in these cases, one could argue that acute pancreatitis, although being complicated by ARF still had a better prognosis than ARF-accompanied septic diseases.

For comparison with a standardised score, we applied the APACHE II system designed by Knaus et al. [10] to grade the severity of illness, which is now frequently used as a predictor of outcome [21, 22]. Results have recently been published on the ability of APACHE II to predict outcome in ICU patients treated by haemodialysis [22]. At a death risk of 0.7 or more, a correct prediction of 100% specificity and 25.8% sensitivity was reported. The authors recommend APACHE II as a predictor of outcome for these patients. In our study, this scoring system did not meet these expectations. At a death risk cut-off-point of 0.5, the prediction was no better than chance – the choice of a 0.7 cut-off-point did not improve the total correct classification rates (Table 5). The use of APACHE II as a prognostic tool thus led to a misclassification of 57 patients at P0, 56 patients at P24 and 52 patients at P48. The APACHE II had originally been designed to predict outcome on admission; its poor performance could be due partly to the fact that it was used in the clinical course in this case, as described by Dobkin et al. [22] and by Chang et al. in a modified version [21]. On the other hand, the calculation of APACHE II on admission did not yield better results, which is not surprising since more than 50% of the study population received their first dialysis treatment directly after admission; APACHE II at P0 was equal to APACHE II on admission in these cases. Looking at the variables used in APACHE II and comparing them to their predictive value in this study, reveals that a high serum creatinine, which was associated with survival in our study, could account for up to 8 points in the score, whereas mechanical ventilation, one of the most important predictors, was not represented in APACHE II directly, but only through blood gas analyses and respiratory frequency. These effects probably contributed to the poor performance of the score in this sub-group with ARF, which does not necessarily mean that the predictive value of the score might not be higher in a larger and more heterogeneous population.

The discriminant predictor variables evaluated outcome better than APACHE II, although they were not able to classify more than 80% of the patients correctly during the first 24 h of dialysis. This high error rate renders them unsuitable as predictors for individual patients. We conclude that the inaccuracy in outcome prediction does not allow us to withhold dialysis treatment from any

patient on account of these methods of judgement. The improvement of predictive power from P0 to P48 indicates that the relevant changes under dialysis therapy should be considered in decision making. Withdrawal of therapy should only be discussed if the patient deteriorates further in spite of dialysis treatment.

It should be emphasized that the analysed population consisted of medical ICU patients, a rather homogeneous group in contrast to other study populations [3, 6]. Results may be different in surgical or nephrological patients, but these populations should be examined separately to avoid over-optimistic results in predictive power, at least partially due to different survival rates of populations with incomparable underlying diseases.

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Dr. J.-H. Schäfer
Klinikum Steglitz der FU
Medizinische Intensivstation
Hindenburgdamm 30
1000 Berlin 45
FRG