

Serum osmolality and outcome in intensive care unit patients

B. HOLTGRETER¹, C. BANDT¹, S.-O. KUHN², U. GRUNWALD³, C. LEHMANN², C. SCHÜTT³ and M. GRÜNDLING²

¹Institute for Mathematics and Informatics, ²Department of Anaesthesiology and Intensive Care Medicine and ³Institute for Immunology and Transfusion Medicine, Department of Immunology, Ernst-Moritz-Arndt-University, Greifswald, Germany

Background: The aim of the present study was to compare 16 routine clinical and laboratory parameters, acute physiologic and chronic health evaluation (APACHE) and sequential organ failure assessment (SOFA) score for their value in predicting mortality during hospital stay in patients admitted to a general intensive care unit (ICU).

Methods: A retrospective observational clinical study was carried out in a 15-bed ICU in a university hospital. Nine hundred and thirty-three consecutive patients with ICU stay > 24 h (36.2% surgical, 29.1% medical and 34.7% trauma) were observed. Blood sampling, patient surveillance and data collection were performed. The primary outcome was mortality in the hospital. We used receiver operating characteristic (ROC) analyses and logistic regression to compare the 16 relevant parameters, APACHE II and SOFA scores.

Results: Two hundred and thirty-three out of the 933 patients died (mortality 25.0%). One laboratory parameter, serum osmolality [area under the curve (AUC) 0.732] had a predictive value for mortality which lay between that of APACHE II (AUC 0.784)

and SOFA (AUC 0.720) scores. When outcome prediction was restricted to long-term patients (ICU stay > 5 days), serum osmolality (AUC 0.711) performed better than either of the standard scores (APACHE AUC 0.655, SOFA AUC 0.636). Using logistic regression analysis, the association of clinical parameters, age and diagnosis group with mortality was determined.

Conclusion: Elevated serum osmolality at ICU admission is associated with an increased mortality risk in critically ill patients. Serum osmolality is cheaper and more rapid to determine than the scoring systems. However, further studies are needed to evaluate the predictive value of serum osmolality in different patient populations.

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THE aim of the present study is to identify routine parameters with predictive value on the day of intensive care unit (ICU) admission. Established outcome prediction, based on measurements during the first 24 h of ICU stay, includes acute physiology scores such as acute physiologic and chronic health evaluation (APACHE) II (1) and III (2), mortality probability models (3) or the simplified acute physiology score (4). Other scores including the multiple organ dysfunction score and the sequential organ failure assessment (SOFA) score (5–7) have been developed to evaluate a patient's morbidity and organ dysfunction. These scoring systems have been evaluated in many clinical studies (8–12).

However, scoring systems have several drawbacks, in particular their time-consuming evaluation. Some parts of the scores cannot be obtained by automatic equipment. The Glasgow coma score (GCS), which is integrated in several scoring systems, can only be

determined by expert staff and discrepancies can arise when it is determined by different individuals. Similar difficulties exist for other parameters such as those required to assess the necessity of catecholamine therapy, the evaluation of gastrointestinal tract function or the effects of medication. Files from patient data management systems (PDMSs) must be cross-checked manually. Thus, many ICUs do not determine any scores in daily practice (13).

Evaluating individual parameters may help to overcome these difficulties. Several investigations in different ICU populations identified parameters with prognostic value which are either registered in everyday clinical routine or can be obtained easily (14–21). Although single parameters are likely to provide less information than complex scores, they may nevertheless be valuable tools in ICU practice.

In our study, 16 routine parameters were investigated in a heterogeneous group of 933 consecutive

patients. We report that serum osmolality is a potentially useful parameter to estimate mortality risk, especially in long-term patients.

Methods

This retrospective study was carried out in a 15-bed ICU in the Department of Anaesthesiology and Intensive Care Medicine at Ernst-Moritz-Arndt-University in Greifswald, Germany. The unit has an average of 700 patients per year. The patient to nurse ratio was 1 : 3 and there were seven physicians working in a three shift system. During the study period of 42 months, 933 patients with an ICU stay longer than 24 h were treated. The patient group was heterogeneous, including trauma, 34.7% (multiple, brain, chest or abdominal), surgery, 36.2% (abdominal, chest or neurosurgery), and medical 29.1% (pulmonary or cardiac decompensation, other diseases). All patients received standard treatment.

For 16 clinically relevant laboratory parameters, the worst value during the day of ICU admission was considered (see Table 1). As proposed in the original publications, APACHE II and SOFA scores were calculated from the worst values during the first 24 h after ICU admission. Parameters for the calculation of the acute physiology score (vital and laboratory parameters) were collected using the PDMS and verified by the nurse. Physicians determined the

Glasgow coma and chronic health scores. Demographic parameters, as well as ICU and hospital outcome, were also recorded.

Statistical analysis was carried out using SPSS (SPSS, Version 11.5 for Windows; SPSS Inc., Chicago, IL), JMP IN (JMP IN[®] 5.1 for Windows, JMP[™]; SAS Institute Inc., Cary, NC) and R (free shareware, www.r-project.org). All parameters were screened for their capacity to predict hospital outcome both by *t*-tests for the difference of means of survivors and non-survivors and by univariate logistic regressions. *P*-values were corrected with Bonferroni's adjustment for multiple testing, $p_{corr} = P \times n$, where *n* is the total number of accomplished tests (*n* = 18). $p_{corr} < 0.05$ was considered statistically significant. For osmolality, we compared the logistic regression function with a non-linear regression, using a slightly larger class of logistic functions. Areas under receiver operating characteristic (ROC) curves (AUC) were calculated (22) and compared with the Z-statistic (23). A multivariate analysis of the influence of clinical and demographic parameters on hospital outcome was performed with backward logistic regression.

Results

Mean age of the patients was 53 (SD 19) years, with a range from 8 to 91 years. 63.2% of the patients were

Table 1

Univariate analysis of clinical parameters in ICU patients.

	Mean ± SD		<i>p</i> _{corr}	
	Survivors	Non-survivors	<i>t</i> -test	Logistic regression
APACHE II score	20.3 ± 7.7	28.4 ± 7	7 × 10 ^{-41*}	2 × 10 ^{-29*}
Osmolality (mOsm/kg)	297 ± 16.7	312 ± 22.1	8 × 10 ^{-17*}	7 × 10 ^{-18*}
SOFA score	6.6 ± 3	9.3 ± 3.5	1 × 10 ^{-16*}	4 × 10 ^{-16*}
Glucose (mmol/l)	9.4 ± 3.5	12.0 ± 4.6	7 × 10 ^{-13*}	2 × 10 ^{-14*}
Urea (mmol/l)	7.6 ± 7.2	11.9 ± 10.2	1 × 10 ^{-7*}	9 × 10 ^{-9*}
Lactate (mmol/l)	2.6 ± 1.9	4.0 ± 3.6	4 × 10 ^{-6*}	1 × 10 ^{-8*}
Sodium (mmol/l)	138 ± 5.1	141 ± 7.1	5 × 10 ^{-5*}	5 × 10 ^{-6*}
Creatinine (μmol/l)	98.5 ± 87.8	138.5 ± 104.2	5 × 10 ^{-6*}	1 × 10 ^{-5*}
Leucocytes (Gpt/l)	11.5 ± 5.3	13.7 ± 7.6	0.0008*	7 × 10 ^{-5*}
pH value	7.416 ± 0.084	7.382 ± 0.124	0.0017*	7 × 10 ^{-5*}
International normalized ratio	1.251 ± 0.341	1.379 ± 0.418	0.0005*	0.0003*
Procalcitonin (ng/ml)	4.96 ± 19	19.4 ± 78.3	0.13	0.018*
Bilirubin (μmol/l)	20.1 ± 19.7	24.6 ± 25.8	0.32	0.16
CRP (mg/l)	87.7 ± 88.1	105.5 ± 105.8	0.43	0.26
Thrombocytes (Gpt/l)	175 ± 99	158 ± 97	0.44	0.45
Albumin (g/l)	28.4 ± 6.5	27.2 ± 8.0	0.97	0.59
Protein (g/l)	46.8 ± 10.5	47.4 ± 13	1	1
Bicarbonate (mmol/l)	26.5 ± 3.7	26.0 ± 4.3	1	1

APACHE II, acute physiologic and chronic health evaluation; SOFA, sequential organ failure assessment; CRP, C-reactive protein. Mean and standard deviation (SD) for survivors and non-survivors were calculated separately. For the *t*-test and the univariate logistic regression, *P*-values with Bonferroni's correction (*n* = 18) are given. *indicates that $p_{corr} \leq 0.05$. Parameters are ranked by the last *P*-value.

male. Median length of stay was 7 days, with a minimum of 25 h and a maximum of 175 days. Overall ICU mortality was 23.9% and mortality during hospital stay 25.0%.

Parameter screening

Table 1 summarizes the ranges mean ± SD of survivors and non-survivors for all parameters, along with p_{corr} values for *t*-tests and univariate logistic regressions. Bilirubin, C-reactive protein (CRP), thrombocytes, albumin, protein and bicarbonate did not differ significantly between survivors and non-survivors using either method. Procalcitonin with $p_{corr} = 0.13$ for the *t*-test and $p_{corr} = 0.018$ for regression was accepted for further analysis. In view of the distribution of procalcitonin, the Mann–Whitney *U*-test would be more appropriate ($p_{corr} = 7 \cdot 10^{-9}$). The remaining parameters differ significantly between survivors and non-survivors using both methods, some of them with extremely small p_{corr} .

ROC analysis

We evaluated the prognostic value of 10 selected parameters using the area under the ROC curve (AUC). Table 2 indicates that APACHE II score (AUC 0.784) was the best prognostic marker, followed by osmolality (AUC 0.732), SOFA score (AUC 0.720), and glucose (AUC 0.698).

For all parameters, patients are predicted to survive if the measured value is below a certain cut-off. Appropriate cut-offs in Table 2 were chosen such that *sensitivity + specificity* (percentage of correctly predicted non-survivors and survivors, respectively) was maximized. For example, for 61.3% of the survivors osmolality was lower than 298 mOsm/kg (specificity) on ICU admission, while for 76.4% of

the non-survivors osmolality was greater than 298 mOsm/kg (sensitivity).

Because osmolality was not measured on Saturdays and Sundays, 15% of the values are missing. For the SOFA score, 29% of values are missing because exact FiO₂ values on admission were not reported. When all patients with missing SOFA scores were excluded, AUC values (Table 2) changed by ± 0.01, except for APACHE II (AUC 0.755).

A graphical comparison of ROC curves for osmolality and APACHE II score is presented in Fig. 1. The curve for APACHE II score runs slightly closer to the upper-left corner of the graph than for osmolality, reflecting the higher AUC value.

Connection with ICU stay

We distinguished short- (ICU stay > 1 and ≤ 5 days) and long-term (ICU stay > 5 days) patients. AUC values were higher for most parameters for short-term patients (Table 3), and in particular for APACHE II (0.936) and SOFA (0.862). For the laboratory parameters, glucose predicted best (AUC 0.796), whereas osmolality and lactate had AUC values around 0.75. However, when analysis was restricted to long-term patients only osmolality discriminated well (AUC 0.711). For this patient group, the APACHE and SOFA scores had AUC values below 0.66, comparable to those of glucose, creatinine, urea, and procalcitonin.

Scores based on many parameters are expected to measure severity on a broad scale and hence should differentiate between short- and long-term survivors. For both scores (APACHE II and SOFA), we found that survivors exhibit smaller values for short- (APACHE mean 17, SOFA mean 5) than for long-term patients (APACHE mean 23, SOFA mean 8). However, no significant differences were found in the

Table 2

Receiver operating characteristics (ROC) analyses for parameters with predictive value.

Parameter	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Cut-off	Mv
APACHE II score	0.784 (0.752–0.816)	73.0	70.2	25	1 (0.001%)
Osmolality (mOsm/kg)	0.732 (0.692–0.772)	76.4	61.3	298	139 (15%)
SOFA score	0.720 (0.678–0.762)	90.8	40.0	6	268 (29%)
Glucose (mmol/l)	0.698 (0.660–0.737)	66.5	65.1	9.5	1 (0.001%)
Creatinine (μmol/l)	0.669 (0.628–0.710)	56.2	71.6	95	30 (3.2%)
Urea (mmol/l)	0.661 (0.619–0.703)	49.4	77.0	9	32 (3.4%)
Lactate (mmol/l)	0.652 (0.609–0.694)	49.3	71.4	3	158 (17%)
Procalcitonin (ng/ml)	0.641 (0.598–0.683)	51.8	69.3	1.5	72 (7.7%)
Sodium (mmol/l)	0.610 (0.566–0.654)	47.0	73.1	141	1 (0.001%)

APACHE II, acute physiologic and chronic health evaluation; SOFA, sequential organ failure assessment. Area under the curve (AUC) values and their confidence interval (95% CI) are shown along with the number of missing values (Mv). Sensitivity and specificity correspond to the optimized cut-off value.

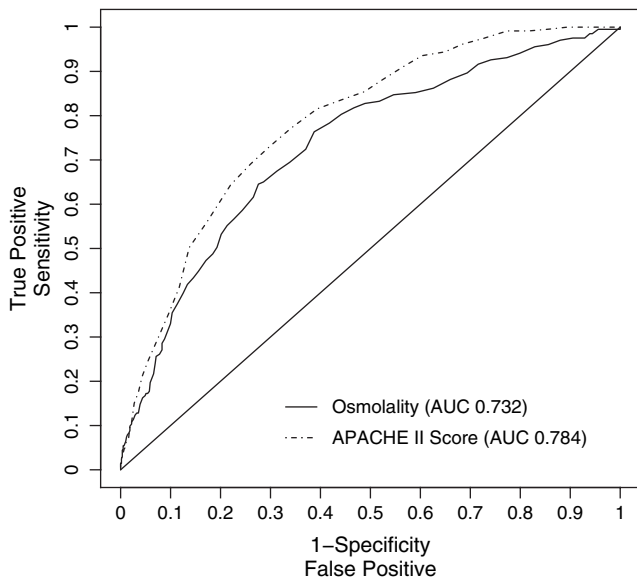


Fig. 1. Prediction of hospital mortality by receiver operating characteristic (ROC) curves for osmolality and acute physiologic and chronic health evaluation (APACHE) II score upon intensive care unit (ICU) admission.

score values for non-survivors. For osmolality, the distributions of short- and long-term patients coincided for non-survivors as well as for survivors. Thus, osmolality does not provide a broad scale. Osmolality beyond 300 mOsm/kg indicates a critical state, but a value far below 300 does not imply that the patient is in good shape or will have a short ICU stay.

Multivariate analysis

Using osmolality as a control variable showed that creatinine, urea, sodium, pH and international normalized ratio (INR) were no longer significantly correlated with outcome ($P > 0.13$). Correlations of leucocytes and procalcitonin with outcome also lost significance ($P = 0.02$).

In a backward logistic regression, creatinine, urea, sodium, INR and pH proved to be not significant ($P > 0.25$). Though these parameters are predictive (see Tables 1 and 2), the remaining parameters (osmolality, glucose, lactate, leucocytes, and procalcitonin) are more valuable and were therefore used for logistic regression. Categorical variables gender, age (≤ 65 or > 65), diagnosis group (trauma, surgical or medical) and their interactions were added (Table 4). While age, gender and diagnosis group failed, the combination of age and trauma did not. Results of the logistic regression are shown in Table 4. For example, an increase of osmolality by one unit increases the mortality risk by factor 1.033. Risk is multiplied by 3.145 for old trauma patients.

Furthermore, we compared Table 4 with cross-tables of factors and mortalities. In comparison to surgical and medical patients, trauma patients displayed the lowest mortality rate (21.6%, 24.6% and 29.5%, respectively). Mortality did not differ between females and males (25.9% and 24.4%). Patients with age > 65 had higher mortality (32.4%) than the younger ones (21.5%). However, this age dependence was considerable for trauma patients (16.4% mortality for age ≤ 65 compared with 43.5% for age > 65) and less for surgical cases (21.8% and 28.8%), whereas for medical patients it was negligible (29.0% and 30.4%).

The odds ratios for univariate logistic regressions in Table 4 confirm the result of the multivariate analysis. However, for the mortality probability function calculated from the multivariate model, the AUC value is 0.781 (CI 0.743–0.819) which is significantly higher [$P = 0.001$, Z-statistic (23)] than for the univariate model with osmolality alone (AUC 0.732). Restricted to long-term patients, the multivariate regression predicts with AUC = 0.738 which is better than all values in Table 3. Comparison of the

Table 3

Parameters with predictive value.			
AUC (95% CI)	All patients (n = 933)	Short-term (n = 405)	Long-term (n = 528)
APACHE II score	0.784	0.936 (0.911–0.960)	0.655 (0.604–0.705)
Osmolality (mOsm/kg)	0.732	0.756 (0.685–0.827)	0.711 (0.661–0.761)
SOFA score	0.720	0.862 (0.816–0.908)	0.636 (0.575–0.696)
Glucose (mmol/l)	0.698	0.796 (0.741–0.852)	0.636 (0.585–0.687)
Creatinine (μ mol/l)	0.669	0.696 (0.631–0.761)	0.648 (0.595–0.702)
Urea (mmol/l)	0.661	0.642 (0.572–0.712)	0.664 (0.612–0.717)
Lactate (mmol/l)	0.652	0.747 (0.676–0.818)	0.587 (0.533–0.642)
Procalcitonin (ng/ml)	0.641	0.608 (0.528–0.689)	0.641 (0.590–0.692)
Sodium (mmol/l)	0.610	0.688 (0.616–0.759)	0.553 (0.497–0.609)

APACHE II, acute physiologic and chronic health evaluation; SOFA, sequential organ failure assessment; AUC: area under ROC curve. ROC analysis was carried out for short- (ICU stay > 1 and ≤ 5 days) and long-term (ICU stay > 5 days) patients.

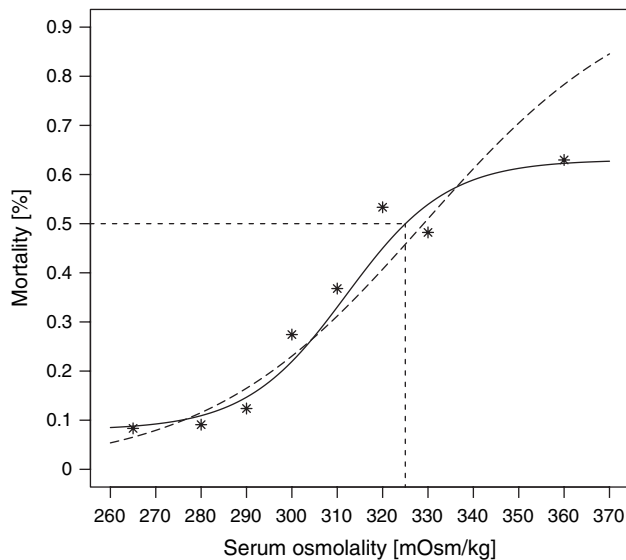


Fig. 2. Relationship between osmolality and hospital mortality given using univariate logistic regression (dashed line) and by a non-linear regression with a larger class of functions (solid line, $r^2 = 0.977$). Asterisks denote the hospital mortality calculated for each of the eight equally spaced osmolality classes. The dashed line displays the osmolality value for an estimated mortality of 50%.

P-values in Table 4 confirms that osmolality is by far the most significant parameter.

Figure 2 shows the univariate logistic regression curve for osmolality (dashed line)

$$m = \frac{1}{1 + \exp[-0.0415 \times (\text{osmolality} - 329)]}$$

along with dots indicating the mortality in our data for eight equally spaced segments of osmolality values. This logistic model assumes that the mortality m is near zero for very small and near one for very large osmolality. Assuming that a certain part q of deaths occurs independently of osmolality and some

percentage q' of patients survive despite high osmolality a more general kind of logistic model can be derived. Non-linear regression with least squares was applied to fit such model. The resulting function with $q = 0.08$ and $q' = 0.63$,

$$m = 0.08 + \frac{(0.63 - 0.08)}{1 + \exp[-0.09 \times (\text{osmolality} - 312)]}$$

is depicted in Fig. 2 (solid line). Both functions disagree for the extreme values which were rarely observed, but they agree on a large interval including most of our data.

Discussion

Risk prediction is an important issue in intensive care. The APACHE II score is commonly used as a severity score during the first 24 h on the ICU while the SOFA score was developed to estimate morbidity during ICU stay. Both were evaluated in extensive studies. For SOFA, Timsit et al. reported an AUC value of 0.72 for hospital outcome (24). Moreno et al. and Peres Bota et al. obtained AUC values 0.772 and 0.872 on the admission day (6,7). In a prospective study with more than 12,000 ICU patients, Suistomaa et al. found an AUC of 0.84 for the APACHE II score taken during the first 24 h (25).

In the present retrospective one-center study with 933 consecutive ICU patients, AUC was 0.720 for SOFA and 0.784 for APACHE II score, which agrees with (24) and is somewhat smaller than that reported in Moreno et al. and Peres Bota et al. (6,7). However, in the present study the median length of ICU stay (LOS) of 7 days and the hospital mortality of 25.0% were rather large, indicating inclusion of only few intermediate care patients. In contrast, median LOS was 3 and 5 days in Moreno et al. (6) and Peres Bota

Table 4

Risk factors in outcome prediction – backward logistic regression analysis of clinical parameters and factors in mortality prediction.

Risk factor	P (Wald's test)	Multivariate analysis OR (95% CI)	Univariate analysis OR (95% CI)
Osmolality (mOsm/kg)	2×10^{-9}	1.033 (1.022–1.044)	1.042 (1.033–1.052)
Lactate (mmol/l)	0.0002	1.176 (1.080–1.280)	1.256 (1.169–1.350)
Leucocytes (Gpt/l)	0.017	1.039 (1.007–1.073)	1.059 (1.034–1.085)
Glucose (mmol/l)	0.02	1.061 (1.009–1.115)	1.167 (1.123–1.212)
Procalcitonin (ng/ml)	0.038	1.008 (1.001–1.015)	1.010 (1.004–1.016)
Age (> 65) × trauma	0.021	3.145 (1.185–8.349)	2.490 (1.472–4.213)
Trauma	0.089	0.608 (0.343–1.079)	0.754 (0.548–1.038)
Age (> 65) × surgical	0.425	1.472 (0.570–3.805)	1.256 (0.834–1.893)
Age (> 65)	0.868	0.944 (0.482–1.852)	1.752 (1.287–2.384)
Surgical	0.990	1.004 (0.540–1.867)	0.966 (0.709–1.315)

Only significant variables and interactions are listed with their significance value P , odds ratio (OR) and 95%-confidence interval. Age (> 65 years), trauma and surgical diagnosis were defined as indicator variables. Six hundred and eighty-seven cases (73.6%) were included.

et al. (7). Suistomaa et al. reported that mean LOS was 3.4 days, hospital mortality 19.8% and for 4639 patients with LOS ≤ 1 day, AUC was 0.91 for APACHE II, whereas for 1312 patients with LOS > 7 days, AUC was only 0.65 (25). This agrees well with our results: APACHE II predicted well in 405 patients with LOS > 1 and ≤ 5 days (AUC 0.936), while for 528 patients with LOS > 5 days prediction was worse (AUC 0.655).

Many ICUs do not use scores in their daily work because of lack of time. Schönhofer et al. reported that 80% of intensive care physicians had no practical experience with the SOFA score, although half of those interviewed consider scores to be important and helpful. On average, score determination required 37 min per patient and week (13).

Therefore, the purpose of this study was to identify routine parameters with prognostic relevance which can be determined in a rapid, simple and inexpensive way. Glucose demonstrated prognostic relevance in non-diabetic and diabetic patients with trauma, cardiovascular diseases, and in post-operative and medical/surgical patients (26–30). In different ICU populations, an association between lactate and lactate clearance with mortality was observed (31–33). In previous studies, kidney function parameters proved to be relevant (18,34–36). The prognostic relevance of osmolality was confirmed in patients with different underlying diseases (20,21,36–39). Especially in elderly patients, hyperosmolality on admission was associated with increased mortality (40,41). In our study, the predictive value of osmolality was independent of age.

Among 16 clinically relevant parameters in our study of 933 patients with ICU stay > 24 h, serum osmolality had the largest predictive value (AUC 0.732), followed by other metabolic and kidney-related parameters including glucose, creatinine, urea, lactate and sodium, and procalcitonin (Tables 1 and 2). For long-term patients (LOS > 5 days), prediction by osmolality was even better than by APACHE II. However, for short-term patients, the scores provided a more reliable prediction (Table 3). In a multivariate logistic analysis, outcome prediction by osmolality could not be improved by other kidney-related parameters. Osmolality with lactate, leucocytes, glucose, procalcitonin, and the interaction of age with diagnosis gave a multivariate model with an AUC of 0.781, which in view of the number of parameters seems only slightly better than osmolality alone.

The essential role of the renal system in critically ill patients has often been emphasized. Acute kidney

failure as a symptom of the multiple organ dysfunction syndrome still results in a mortality of up to 60% (42). Sensitivity of the kidney to critical microcirculatory changes was considered a main cause for multiple organ failure, and early diagnosis and therapy of critical situations in microcirculation could improve patient outcome (43,44). Moreover, micro albuminuria at admission was associated with high mortality and frequent occurrence of organ failure (14,45). Micro albuminuria also reflects changes in capillary permeability and can be measured simply. Perhaps osmolality plays a similar role.

Van de Berghe et al. reported a successful trial of strict blood glucose control using insulin therapy (28). Although the APACHE II values were relatively low in that study (median 9 in survivors and non-survivors), compared with our study (20 and 29, respectively), the relevance of glucose was confirmed here. Patients with an admission blood glucose ≤ 6.1 mmol/l had a mortality rate of 11% compared with 43% for patients with glucose > 11 mmol/l. Glucose is an early marker which is inexpensive to measure and, in contrast to osmolality and lactate, can be controlled by intensive insulin therapy. However, it is not clear to what extent this therapy is capable of reducing mortality in different patient populations (46,47).

The predictive capacity of osmolality and glucose in our study of 933 patients in a single ICU remains to be verified by multicentre studies. If the results were confirmed, this could provide a simple method for risk prediction and lead to consequences for therapy.

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Address:

Matthias Gründling

Department of Anaesthesiology and Intensive Care Medicine

Ernst-Moritz-Arndt-University

Friedrich-Loeffler-Straße 23b

D-17487 Greifswald

Germany

e-mail: gruendli@uni-greifswald.de