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Course of lactate, pH and base excess for prediction of mortality in medical intensive care patients

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Abstract

Introduction: As base excess (BE) had shown superiority over lactate as a prognostic parameter in intensive care unit (ICU) surgical patients we aimed to evaluate course of lactate, base excess and pH for prediction of mortality of medical ICU patients.

Materials and Methods: For lactate, pH and base excess, values at the admission to ICU, at 24 ± 4 hours, maximum / minimum in the first 24 hours and in 24 – 48 hours after admission were collected from all patients admitted to the Medical ICU of the University Hospital Tübingen between January 2016 until December 2018 and investigated for prediction of in-hospital-mortality.

Results: Mortality in the cohort of 4067 patients was 22 % and significantly correlated with all evaluated parameters. Strongest predictors of mortality determined by ROC were maximum lactate in 24 h (AUROC 0.74, cut off 2.7 mmol/L, hazard ratio of risk group with value > cut off 3.20) and minimum pH in 24 h (AUROC 0.71, cut off 7.31, hazard ratio for risk group 2.94). Kaplan Meier Curves stratified across these cut offs showed early and clear separation. Hazard ratios per standard deviation increase were highest for maximum lactate in 24 h (HR 1.65), minimum base excess in 24 h (HR 1.56) and minimum pH in 24 h (HR 0.75). In multiple logistic regression analysis, age, minimum pH in 24 h, pH at 24 h after admission, maximum lactate in 24 h, maximum lactate in 24 – 48 h, minimum base excess in 24 h and minimum base excess in 24 – 48 h were independent predictors of mortality.

Discussion: Lactate, pH and base excess were all suitable predictors of mortality in internal ICU patients, with maximum / minimum values in 24 and 24-48 h after admission altogether stronger predictors than values at admission. Base excess and pH were not superior to lactate for prediction of mortality.

Keywords: Lactate, pH, base excess, clearance, medical ICU, mortality

Introduction

Estimation of the mortality of patients at intensive care unit (ICU) is necessary for treatment planning and treatment decisions as well as for support and advice for the patient's relatives. Various surrogate parameters and their significance for the assessment of mortality risk have been evaluated, in particular lactate as parameter of anaerobic metabolism and tissue perfusion [1,2]. Elevated lactate level is common in patients admitted to ICU and a strong predictor of mortality in unselected ICU patients [3,4] and lactate clearance was recently discovered as an even stronger parameter than initial lactate level for assessing mortality risk of critically ill patients [5,6].

To count for the ability to buffer a metabolic (lactate) acidosis, parameters of acid-base balance, such as base excess or pH, could represent the body's conditions as more general parameters than lactate. Acid-base parameters have recently been evaluated as parameters for estimation of mortality in different subgroups of patients: In patients after cardiac surgery, base excess at ICU admission was a stronger parameter for prediction of ICU mortality than lactate-levels [7]. Lactate, anion gap and base excess were interchangeable biomarkers of traumatic shock [8] and base excess was a strong predictor of mortality in a large cohort of trauma patients [9]. Bicarbonate and anion gap were associated with higher mortality in sepsis patients even if lactate levels were low [10]. Metabolic acidosis at admission to ICU and early pH changes correlated with higher mortality in a small Indian cohort of critically ill patients [11]. However, for evaluation of acid base parameters as predictors of mortality of patients requiring treatment at a medical ICU, there is still a lack of data. We therefore aimed to evaluate parameters of acid-base balance obtainable by blood gas analysis as predictors of mortality in critically ill medical patients.

Materials and Methods

Patients and blood gas analysis

Data from all patients admitted to the Medical ICU of the University Hospital Tübingen between January 2016 until December 2018 was collected from the patient data management system (ICCA, Philips GmbH) of the University and evaluated retrospectively. The study was evaluated by the local ethics committee of the University of Tuebingen (139/2019B02) and there were no objections to the conduct of the study since the requirements of §13(1) of German Data Protection Adaption Act (Landesdatenschutz-Anpassungsgesetz) in conjunction with Articles 5, 6, 9, 89 of Regulation (EU) 2016/679 are met. Age, gender and SAPS II score at admission to ICU and need for invasive ventilation or dialysis during the treatment at ICU were documented. Laboratory data obtained included base excess, pH and lactate from arterial or venous blood gas analysis at admission to ICU and during the first 48 hours after admission to ICU. All blood gas analyses were performed with a Radiometer ABL90 FLEX. The following parameters were evaluated as predictors of mortality (Figure 1): value at admission, value after 24 ± 4 hours, maximum (lactate) / minimum (pH, base excess) value in the first 24 hours and between 24 – 48 hours after admission and slope of lactate, pH and base excess. Slope of the variables was calculated as difference between maximum (lactate) or minimum (pH, base excess) value during the first 24 hours and value at admission. All analyses were performed with all available patient data at the respective time points.

Mortality was defined as positive if the patient died in hospital and negative if the patient was discharged from hospital alive. Primary diagnosis and cause of death were classified into groups according to the recorded ICD-10 (International Statistical Classification of Diseases and Related Health Problems) classification.

Statistical analysis

Statistical analyses were performed using R version 3.6.1, SAS JMP Pro 14.2.0 and MedCalc 19.1. Continuous variables were tested for normal and lognormal distribution. Distributions are reported as number (n) and percent for categorical parameters. Medians and interquartile range (IQ) are provided for continuous lognormal parameters. χ^2 test (nominal variables) and Wilcoxon test (continuous variables) were performed to test for differences between groups. Computation of receiver operating characteristics (ROC, C-statistics) was performed to evaluate the ability of parameters to predict mortality, with determination of the cut off value by Youden index (J = sensitivity + (specificity – 1)), and the area under the receiver operating characteristics curve (AUROC) is reported. Hazard ratios were determined from Cox regression for risk groups divided by cut offs from ROC, or per increase of the variable of 1 standard deviation (SD). Kaplan Meier curves were constructed for groups stratified by cut-offs from C-statistics using log-rank test to test for differences. All baseline parameters were included in a stepwise least square linear regression model with forward and backward direction mode, probability to enter $p = 0.05$ and probability to leave $p = 0.1$, to create a multiple regression model for prediction of mortality and identify independent predictors of mortality. Statistical significance was determined by two-sided tests with an alpha of 0.05 ($p < 0.05$).

Results

Study cohort

A total number of 4067 patients was admitted to intensive care treatment at the medical ICU of the University Hospital Tübingen between January 2016 until December 2018 and included in the analysis (Figure 1). N = 913 patients (22 %) died after a median of 8 (interquartile range 2 – 18) days. The characteristics of the study cohort are listed in table 1.

Causes of death in the cohort classified by ICD-10 category were I ('diseases of circulatory system', including stroke, intracranial bleeding, pulmonary embolism, myocardial infarction, cardiomyopathy, valvular diseases, cardiac arrhythmias; 21 %), J ('diseases of the respiratory system', including pneumonia, chronic obstructive pulmonary disease; 16 %), A + B ('certain infectious and parasitic disease', including sepsis; 16%), R57.0 ('cardiogenic shock'; 13 %), C + D ('neoplasms and diseases of the blood and hematopoietic organs and certain disorders involving the immune system'; 11 %), K ('diseases of the digestive system', including alcoholic cirrhosis of the liver; 7 %), and R57.2 ('septic shock'; 6 %).

Patients could be assigned into groups based on primary diagnoses as follows (Figure 2A): Infectious = ICD R57.2 + A + B (n = 290), cardiac = ICD R57.0 + I (n = 1482), respiratory = ICD J (n = 726), malignant = ICD C + D (n = 421) and other / uncertain (n = 1148). Kaplan Meier curves of groups of primary diagnosis showed highest mortality in the infectious disease group during the first 20 days and highest mortality in the malignant disease group after more than 80 days (Figure 2B).

Figure 1: Flow chart study cohort and evaluated parameters

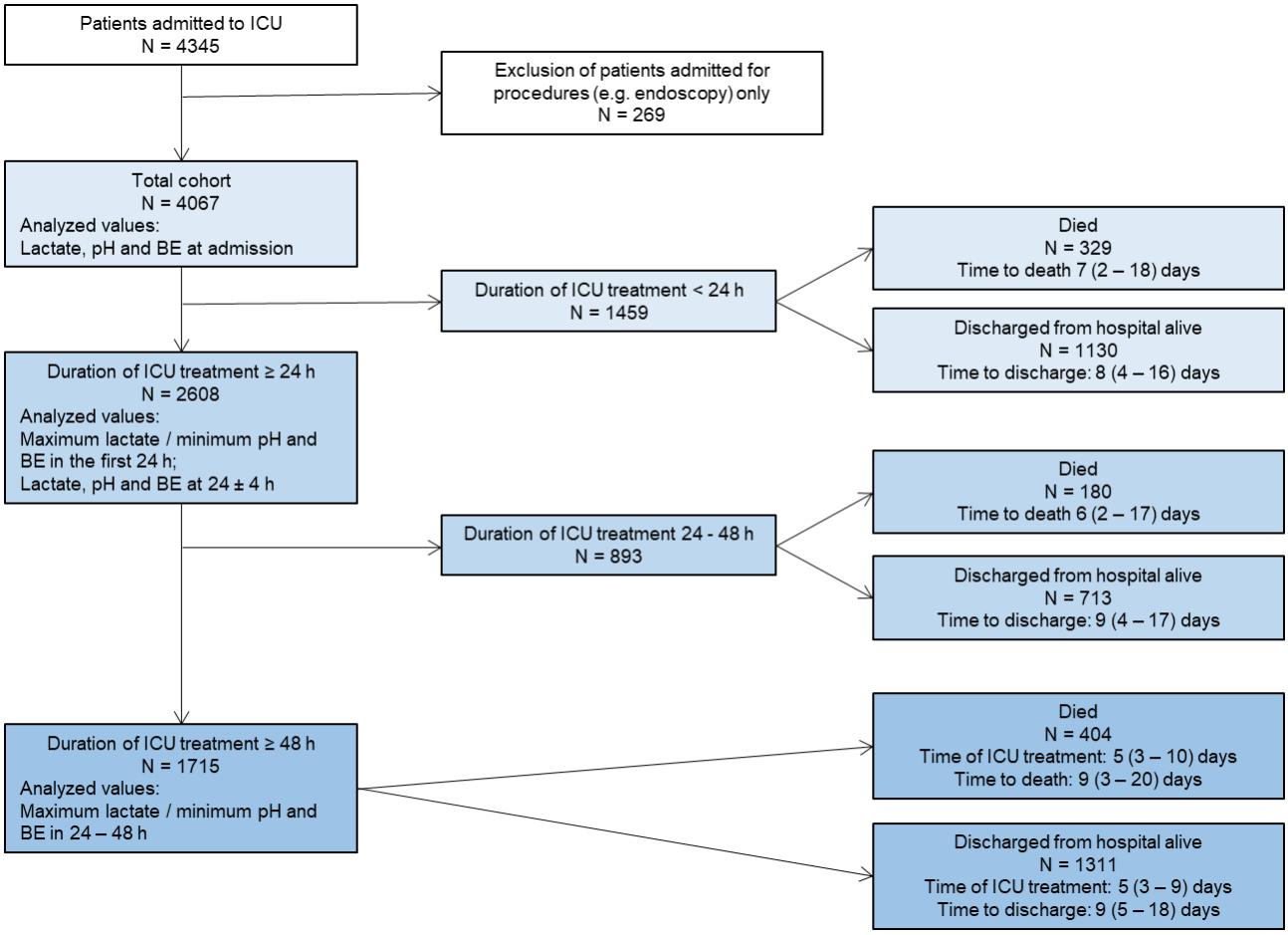
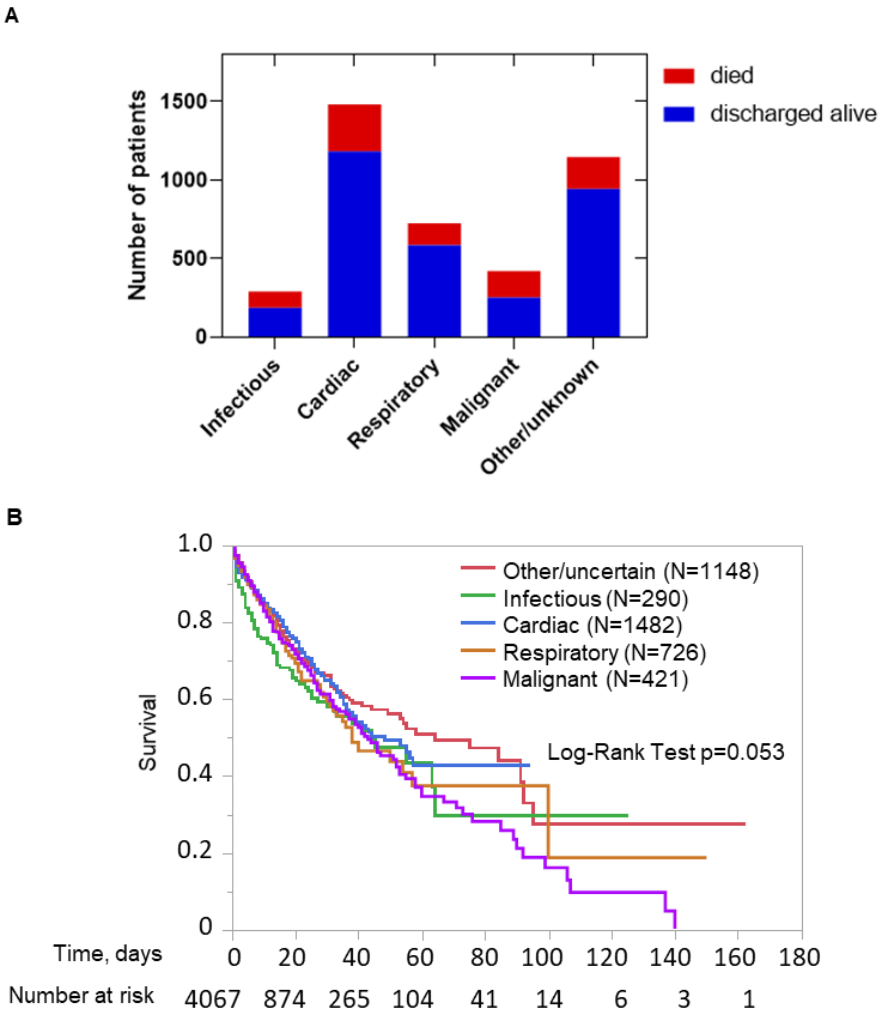


Table 1: Characteristics of study cohort

Values are n (%) for categorical variables and mean (interquartile range) for continuous variables. Differences of groups of patients who died, and patients discharged from hospital alive were tested and p values are reported from χ^2 test for nominal variables and Wilcoxon test for continuous variables.

	Total cohort	Patients who died	Patients discharged from hospital alive	p value
Number	4067	913	3154	
Age	68 (55 – 78)	71 (60 – 80)	67 (53 – 77)	<0.0001
Gender (m, male; f, female)	m 2270 (56 %) f 1797 (44 %)	m 511 (56 %) f 402 (44 %)	m 1757 (56 %) f 1395 (44 %)	0.9151
SAPS II score, points	42 (28 – 54)	44 (29 – 57)	41 (28 – 53)	0.0383
Invasive ventilation	1894 (47 %)	480 (53 %)	1416 (45 %)	<0.0001
Dialysis	531 (13 %)	143 (16 %)	388 (12 %)	0.0079
Primary diagnosis, - Infectious - Cardiac - Respiratory - Malignant - Other / uncertain	 290 (7%) 1482 (36%) 726 (18%) 421 (10%) 1148 (28%)	 103 (11%) 298 (33%) 140 (15%) 168 (18%) 204 (22%)	 187 (6%) 1184 (38%) 586 (19%) 253 (8%) 944 (30%)	<0.0001
Duration to death or discharge, days		8 (2 – 18)	9 (4 – 17)	0.0042
Base excess at admission, mmol/L	0.2 (-4.2 – 3.9)	-3.4 (-9.2 – 2.3)	0.8 (-2.9 – 4.3)	<0.0001
Base excess at 24h, mmol/L	1.1 (-2.2 – 5.0)	-0.3 (-4.0 – 3.4)	1.8 (-1.4 – 5.5)	<0.0001
Base excess minimum in 24h, mmol/L	-1.0 (-5.8 – 2.8)	-5.7 (-12.1 – 0.4)	-0.3 (-4.2 – 3.1)	<0.0001
Base excess minimum in 24-48h , mmol/L	3.2 (0.1 – 7.2)	1.85 (-1.5 – 5.8)	3.7 (0.6 – 7.5)	<0.0001
Lactate at admission, mmol/L	1.4 (0.9 – 2.4)	2.3 (1.2 – 5.8)	1.2 (0.8 – 2.0)	<0.0001
Lactate at 24h, mmol/L	1.1 (0.8 – 1.7)	1.5 (0.9 – 2.5)	1.0 (0.7 – 1.5)	<0.0001
Lactate maximum in 24h, mmol/L	1.7 (1.1 – 2.9)	3.0 (1.6 – 9.0)	1.5 (1.0 – 2.3)	<0.0001
Lactate maximum in 24-48h, mmol/L	1.4 (0.9 – 2.1)	2.0 (1.3 – 3.6)	1.2 (0.8 – 1.8)	<0.0001
pH at admission	7.39 (7.33 – 7.44)	7.35 (7.23 – 7.43)	7.40 (7.35 – 7.44)	<0.0001
pH at 24h	7.42 (7.37 – 7.47)	7.40 (7.33 – 7.45)	7.43 (7.39 – 7.47)	<0.0001
pH minimum in 24h	7.37 (7.28 – 7.41)	7.28 (7.13 – 7.37)	7.38 (7.32 – 7.42)	<0.0001
pH minimum in 24-48h	7.45 (7.41 – 7.49)	7.43 (7.39 – 7.49)	7.46 (7.42 – 7.5)	<0.0001

Figure 2: Distribution of patients (A) and Kaplan Meier curves (B) by primary diagnosis group



Definition of primary diagnosis groups: Infectious = ICD R57.2 + A + B; Cardiac = ICD R57.0 + I; Respiratory = ICD J; Malignant = ICD C + D; Other / uncertain

ICD-10:
A + B = Certain infectious and parasitic diseases;
C + D = Neoplasms and Diseases of the blood and hematopoietic organs and certain disorders involving the immune system;
E = Endocrine, nutritional and metabolic diseases;
F = Mental and behavioral disorders;
G = Diseases of the nervous system;
I = diseases of circulatory system;
J = Diseases of the respiratory system;
K = Diseases of the digestive system;
R57.0 = Cardiogenic shock; R57.1 = Hypovolemic shock; R57.2 = Septic shock.

Note: Pneumonia and ARDS classified in category J (disease of respiratory system)

Univariate analysis: ROC and Cox regression

All evaluated variables (value at admission, value after 24 ± 4 hours, maximum (lactate) / minimum (pH, base excess) value in the first 24 hours and in 24 – 48 hours after admission and slope of lactate, pH and base excess) showed significant differences between groups of patients discharged alive or died (Table 1) and were associated significantly with mortality in univariate analysis (Table 2). The variables with the highest area under the receiver operating characteristics curve (AUROC) were maximum lactate in the first 24 hours after admission (AUROC 0.74, sensitivity 0.56 and specificity 0.81 at a cut off value of 2.7 mmol/L, Figure 3A) and minimum pH in the first 24 hours after admission (AUROC 0.72, sensitivity 0.60 and specificity 0.76 at a cut off value of 7.31, Figure 3B).

In proportional hazard analyses using the cut-offs from ROC analyses for stratification of risk groups, the highest hazard ratios were found for base excess, lactate and pH at admission and for minimum base excess, minimum pH and maximum lactate in 24 hours after admission (Table 2), with hazard ratio for minimum / maximum values in the first 24 h overall higher than for values at admission. In proportional hazards determined per standard deviation, maximum lactate in 24 h, lactate at admission, minimum base excess in 24 h and minimum pH in 24 h showed highest or lowest hazard ratio per SD (Table 2).

Results of proportional hazard analyses in the subgroups of primary diagnoses overall resembled the results in the total cohort (Table 3): Maximum lactate in 24 h was a strong predictor of mortality in all groups; lactate values were overall strong predictors of mortality, and the interval-related maximum / minimum values of all markers were overall stronger predictors of mortality than values at admission. Additionally, base excess at admission and minimum base excess in 24 h were strong predictors of mortality in the cardiac disease group; and age was a strong predictor of mortality in the respiratory disease group (Table 3).

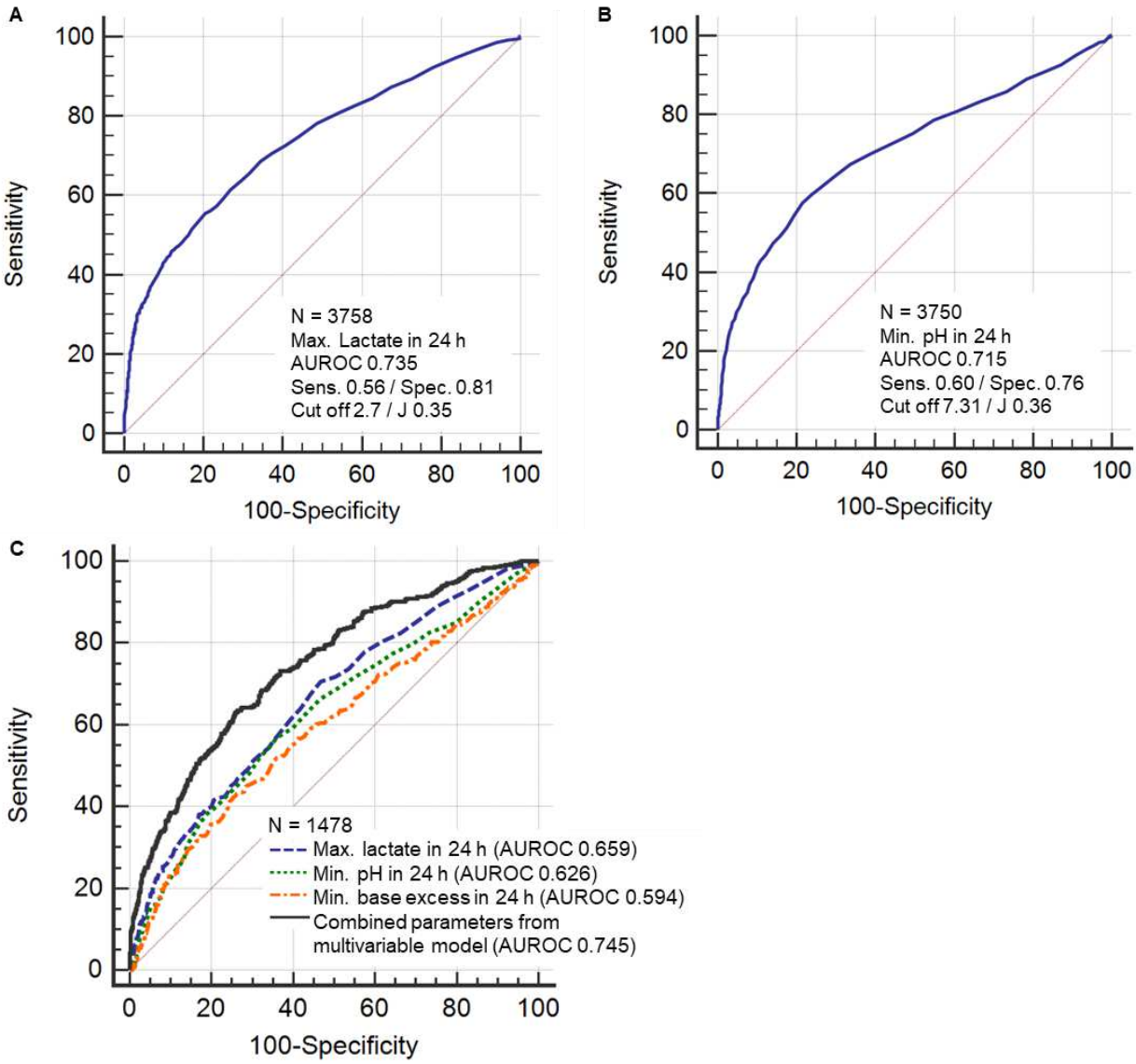
Table 2: Univariate correlations with mortality: ROC and Cox regression

Hazard ratios are of risk group defined by cut off from ROC (e.g. risk group with age ≥ 58 years compared to group with age < 58 years) and per standard deviation increase.
Values with $p < 0.05$ are listed only. There was no significant correlation of gender and mortality. Highest AUROC and highest or lowest hazard ratios are marked in bold.

Abbreviations: AUROC, Area under the receiver operating characteristic curve; HR, hazard ratio; CI, confidence interval; n.s., not significant; min, minimum; max, maximum.

Parameter	AUROC	Risk group (Cut off)	HR of risk group (95% CI)	HR per SD (95% CI)
Age, years	0.575	> 58	1.61 (1.37 – 1.90)	1.35 (1.26 – 1.46)
SAPS II score, points	0.529	> 53	1.28 (1.07 – 1.53)	1.09 (1.01 – 1.19)
Base excess at admission, mmol/L	0.649	< -3.8	**2.27** (1.99 – 2.59)	0.69 (0.65 – 0.74)
Base excess at 24h, mmol/L	0.604	< -1.2	1.57 (1.32 – 1.86)	0.79 (0.72 – 0.86)
Base excess min in 24h, mmol/L	0.680	< -4.9	**2.47** (2.15 – 2.83)	**0.64** (0.61 – 0.68)
Base excess min in 24-48h, mmol/L	0.602	< 2.2	1.53 (1.28 – 1.82)	0.76 (0.69 – 0.84)
Base excess slope , mmol/L	0.589	< -2.4	1.52 (1.31 – 1.75)	0.84 (0.81 – 0.89)
Lactate at admission, mmol/L	0.698	> 2.1	**2.93** (2.57 – 3.34)	**1.39** (1.34 – 1.44)
Lactate at 24h, mmol/L	0.652	> 1.4	2.06 (1.74 – 2.44)	1.26 (1.21 – 1.32)
Lactate max in 24h, mmol/L	**0.735**	> 2.7	**3.20** (2.79 – 3.67)	**1.40** (1.35 – 1.44)
Lactate max in 24-48h, mmol/L	0.702	> 1.7	2.20 (1.84 – 2.64)	1.30 (1.24 – 1.36)
Lactate slope, mmol/L	0.574	< -1.0	1.62 (1.40 – 1.86)	0.84 (0.80 – 0.88)
pH at admission	0.630	< 7.31	**2.60** (2.28 – 2.97)	0.72 (0.68 – 0.75)
pH at 24h	0.640	< 7.36	1.89 (1.59 – 2.26)	0.76 (0.71 – 0.81)
pH min in 24h	**0.715**	< 7.31	**2.94** (2.56 – 3.38)	**0.64** (0.61 – 0.67)
pH min in 24-48h	0.592	< 7.43	1.73 (1.45 – 2.07)	0.77 (0.71 – 0.83)
pH slope	0.612	< -0.05	1.54 (1.36 – 1.80)	0.95 (0.93 – 0.98)

Figure 3: ROC analysis of mortality by maximum lactate (A) and minimum pH (B) in the first 24 h after admission, and multivariable ROC of mortality (C)



Combined parameters from multivariable model (Table 4) are age, minimum pH in 24 h, pH at 24 h after admission, maximum lactate in 24 h, maximum lactate in 24 – 48 h, minimum base excess in 24 h and minimum base excess in 24 – 48 h.

Pairwise comparison of multivariable ROC curves:
Combined parameters and maximum lactate $p < 0.0001$; combined parameters and minimum pH in 24 h $p < 0.0001$; combined parameters and minimum base excess in 24 h $p < 0.0001$; maximum lactate in 24 h and minimum pH in 24 h $p = 0.0947$; maximum lactate in 24 h and minimum base excess in 24 h $p < 0.0001$; minimum pH in 24 h and minimum base excess in 24 h $p = 0.0477$.

Abbreviations: AUROC, Area under the receiver operating characteristics curve; max., maximum; min., minimum; sens., sensitivity; spec., specificity; J, Youden-Index.

Table 3: Hazard ratios for subgroups of primary diagnosis

Values are Hazard ratio per standard deviation increase and 95 % confidence interval. Highest or lowest hazard ratios for every group of primary diagnosis are marked. For definition of primary diagnosis groups see Table 1.
n.s. = not significant; for all other tests p-value was < 0.05.

Abbreviations: min, minimum; max, maximum.

Primary diagnosis	Infectious n = 290	Cardiac n = 1482	Respiratory n = 726	Malignant n = 421	Uncertain / other n = 1148
Age	1.24 (1.00 – 1.56)	1.27 (1.09 – 1.49)	**2.13 (1.65 – 2.79)**	n.s.	**1.61 (1.40 – 1.85)**
SAPS II score	n.s.	n.s.	n.s.	1.28 (1.05 – 1.57)	n.s.
Base excess at admission	0.76 (0.62 – 0.93)	**0.54 (0.49 – 0.61)**	0.77 (0.66 – 0.90)	0.75 (0.63 – 0.90)	0.75 (0.67 – 0.85)
Base excess at 24h	n.s.	0.76 (0.62 – 0.93)	0.79 (0.69 – 0.93)	n.s.	0.72 (0.59 – 0.87)
Base excess min in 24h	0.75 (0.63 – 0.90)	**0.53 (0.47 – 0.59)**	0.73 (0.62 – 0.86)	0.71 (0.60 – 0.84)	0.63 (0.56- 0.72)
Base excess min in 24-48h	n.s.	n.s.	0.79 (0.65 – 0.95)	n.s.	0.65 (0.52 – 0.80)
Base excess slope	0.86 (0.77 – 0.97)	0.85 (0.77 – 0.95)	0.83 (0.73 – 0.96)	n.s.	0.83 (0.77 – 0.90)
Lactate at admission	1.37 (1.23 – 1.51)	1.46 (1.38 – 1.54)	1.49 (1.20 – 1.79)	1.40 (1.21 – 1.59)	1.33 (1.23 – 1.42)
Lactate at 24h	**1.40 (1.25 – 1.55)**	1.30 (1.16 – 1.42)	1.17 (1.00 – 1.32)	1.18 (1.03 – 1.37)	1.28 (1.19 – 1.37)
Lactate max in 24h	1.32 (1.20 – 1.45)	**1.53 (1.44 – 1.62)**	**1.52 (1.28 – 1.76)**	**1.56 (1.01 – 1.26)**	**1.46 (1.36 – 1.57)**
Lactate max in 24-48h	1.34 (1.19 – 1.50)	1.29 (1.18 – 1.39)	1.48 (1.13 – 1.85)	1.14 (1.00 – 1.25)	1.41 (1.29 – 1.52)
Lactate slope	n.s.	0.79 (0.69 – 0.93)	0.78 (0.73 – 0.84)	n.s.	n.s.
pH at admission	0.72 (0.63 – 0.84)	0.64 (0.60 – 0.69)	0.76 (0.66 – 0.87)	0.85 (0.76 – 0.96)	0.73 (0.65 – 0.82)
pH at 24h	0.70 (0.59 – 0.85)	0.69 (0.60 – 0.80)	0.81 (0.72 – 0.93)	0.78 (0.65 – 0.94)	0.72 (0.63 – 0.85)
pH min in 24h	0.71 (0.62 – 0.82)	0.60 (0.55 – 0.64)	0.66 (0.58 – 0.75)	0.76 (0.68 – 0.86)	0.61 (0.54 – 0.69)
pH min in 24-48h	0.82 (0.69 – 0.98)	0.75 (0.64 – 0.88)	0.75 (0.63 – 0.91)	0.76 (0.63 – 0.93)	0.73 (0.61 – 0.88)
pH slope	0.80 (0.65 – 1.00)	n.s.	**0.54 (0.44 – 0.69)**	0.64 (0.50 – 0.84)	**0.58 (0.49 – 0.70)**

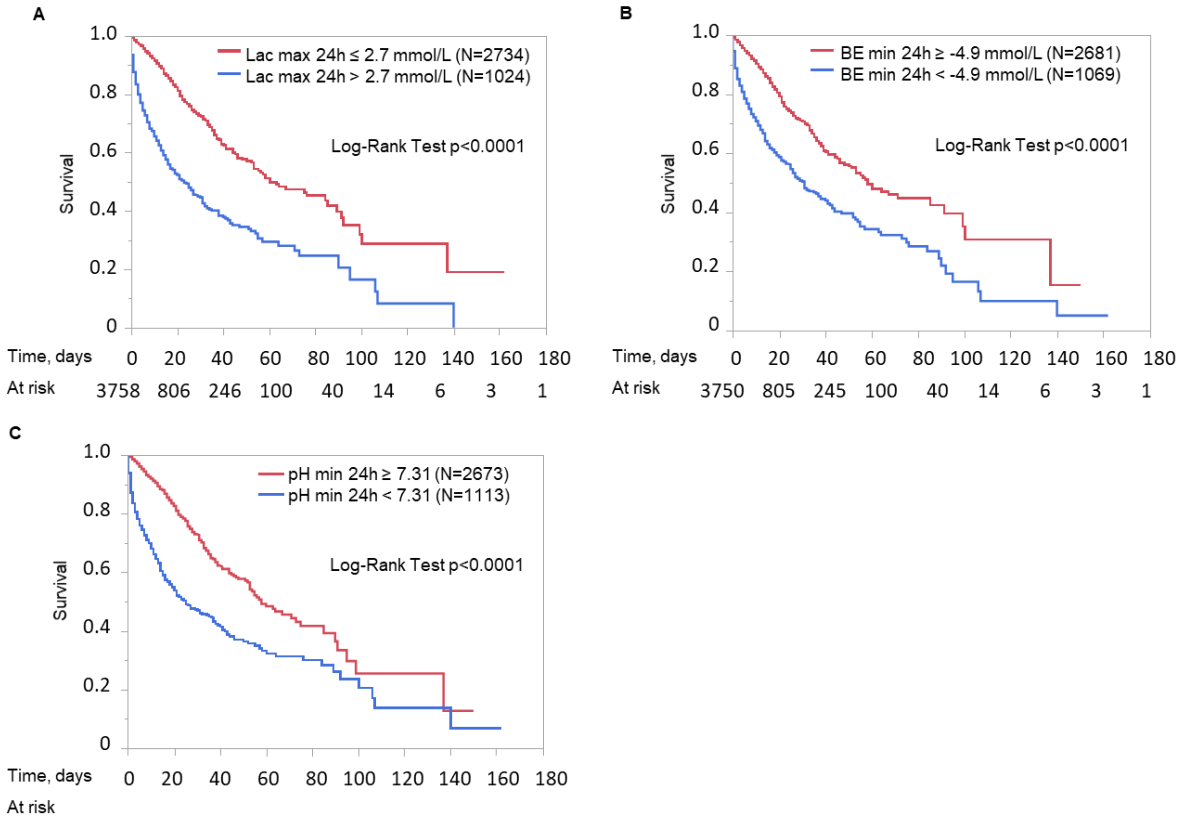
Kaplan Meier Curves

Kaplan Meier curves for groups stratified by cut offs from C-statistics are shown as an example for maximum lactate in 24 h after admission and minimum base excess and minimum pH in 24 h after admission (Figure 4A, B, C). Kaplan Meier curves for the cut offs maximum lactate in 24 h > 2.7 mmol/l, minimum base excess in 24 h < -4.9 mmol/L and minimum pH in 24 h < 7.31 showed a clear separation particularly in the first 20 days after admission to ICU (Figure 4A, B, C).

Figure 4: Kaplan Meier curve of mortality by maximum lactate (A), minimum base excess (B) and minimum pH (C) in the first 24 h after admission

Cut off values used for stratification in risk groups were determined by ROC analysis.

Abbreviations: Lac, lactate; BE, base excess.



Multivariable logistic regression

Regressors of the multivariable logistic regression models fitted on mortality were selected from all baseline variables by a stepwise approach as described in the methods section. Age, minimum pH in 24 h, pH at 24 h after admission, maximum lactate in 24 h, maximum lactate in 24 – 48 h, minimum base excess in 24 h and minimum base excess in 24 – 48 h entered the final nominal logistic model and were independently associated with mortality (Table 4).

An exemplary multivariable ROC analysis is shown in Figure 3C for minimum or maximum values in 24 h after admission for lactate, pH and base excess, respectively, and combined parameters from multivariable logistic regression. AUROC of combined parameters from the multivariable model was 0.745 and significantly higher than AUROC of each individual parameter in multivariable ROC (Figure 3C), however only slightly higher than the univariate AUROCs of the individual parameters (Figure 3A, B and Table 2). From the individual parameters investigated in the multivariable ROC, maximum lactate in 24 h had the highest AUROC, which was significantly different from the AUROC of minimum base excess in 24 h but not from the AUROC of minimum pH in 24 h (Figure 3C).

Table 4: Multivariable logistic regression model of ICU mortality

All baseline parameters were included in a stepwise least square multiple regression model with forward and backward direction mode, probability to enter p = 0.05, probability to leave p = 0.1.

Abbreviations: AUROC, Area under the receiver operating characteristic curve; min, minimum; max, maximum.

Parameter	Estimate	Standard error	Chi Square	p value
n = 1478; r^2 = 0.1458; p < 0.0001; combined AUROC 0.748				
Intercept	-42.20	6.55	41.51	<0.0001
Base excess min in 24-48h	0.05	0.02	6.70	0.0096
Base excess min in 24h	-0.06	0.02	11.52	0.0007
Lactate max in 24-48h	-0.25	0.04	35.11	<0.0001
Lactate max in 24	-0.12	0.03	16.96	<0.0001
pH at 24h	3.90	1.08	13.15	0.0003
pH min in 24h	2.25	0.83	7.28	0.0070
Age	-0.02	0.01	30.58	<0.0001

Discussion

In our cohort of medical ICU patients, all investigated parameters, lactate, pH and base excess, were suitable predictors of ICU mortality. Cut off values at admission to ICU for prediction of mortality were with 2.1 mmol/L for lactate and -3.8 mmol/L for base excess in a range consistent with the values determined in other studies (around 1.5 – 2.5 mmol/L for lactate and -4 - -6 mmol/L for base excess) [4,12-14].

However, base excess and pH were not superior to lactate for prediction of mortality in this unselected cohort of medical ICU patients. This is in contrast to patients after heart surgery at admission to ICU, where base excess was superior to lactate for prediction of mortality [7] and trauma patients, where base excess has been found a strong predictor of mortality [9,14]. In our analyses, lactate was the strongest predictor of ICU mortality, followed by pH: Lactate values showed the highest AUROC in univariate and multivariable ROC analyses and the highest Hazard ratio per standard deviation increase; pH values had the second highest AUROC in multivariable ROC analysis; Kaplan Meier curve stratified by maximum lactate over the first 24 h and minimum pH over the first 24 h showed the clearest separations.

For lactate, prognostic significance of the course or clearance has been evaluated [3,13,15-17]. In sepsis patients, lactate at 24 hours was found to be strongest predictor of mortality in serial lactate measurements [17] and early lactate clearance was associated with improved outcome [16]. In other unselected cohorts of ICU patients, mortality was higher in patients developing high lactate levels after more than 24 hours following ICU admission or missing lactate clearance in the first 12 hours [3] and lactate at 24 hours after admission to ICU was strongest for prediction of mortality [18]. There are systematic reviews available, that found that across different ICU cohorts lactate clearance was associated with a better outcome [19,20]; the significance of the course of lactate was thereby independent of the initial value and it was recommended to monitor the lactate level by measurements every 1 to 2 hours [21]. Lactate-guided therapy with monitoring the course of lactate levels after admission to ICU has been suggested to improve

treatment outcome [22]. Our findings are consistent with these reports: In our cohort of medical ICU patients, from all lactate values, maximum lactate during the first 24 hours and during 24 to 48 hours after admission to ICU were strongest predictors for mortality in the total cohort and in primary diagnosis subgroups. Altogether, lactate values both at admission and during 48 hours after admission to the ICU are valuable indicators for prognosis assessment.

This results in the question, whether the course of values in the first hours after initiation of intensive care treatment should also be considered for other markers used for evaluation of mortality risk. In patients with extracorporeal life support after out of hospital cardiac arrest, lactate and base excess both showed best predictive power for values measured 3 h after initiation of extracorporeal life support [23]. In our cohort of medical ICU patients, initial values of pH and base excess were less predictive than values in the first 24 to 48 hours of the ICU stay. The strongest predictors were the maximum or minimum values during the first 24 hours after admission. These were also superior to the slope between value at admission and maximum or minimum value in the first 24 hours. Our study therefore corroborates the prognostic significance of the values of all parameters, lactate, pH and base excess, in the first 24 to 48 hours after admission to intensive care unit compared to the single value at admission.

SAPS II predicted mortality risk showed an AUROC of only 0.529 in our cohort, compared to 0.86 in the original validating sample from 1993 [24]. This could be due to a changed cohort of patients undergoing intensive care and improved methods and possibilities of treatment. Parameters and scores used for assessment of mortality risk must be reviewed repeatedly. Combination of parameters resulted in a marginal increase of AUROC for prediction of mortality, indicating that mortality remains difficult to assess as it is dependent on many influenceable and non-influenceable factors.

The study is limited by the retrospective and single-center design. Additionally, the influence of treatment on the investigated biomarkers could only be assessed to a limited extent, whereby the response to therapy is likely to be reflected in the course of the parameters: A better

prediction of mortality by biomarkers assessed after admission to the ICU, compared with values at admission to ICU, reflects the association of poor response to therapy, and thus poor recovery of organ function and normalization of acid-base balance, with mortality. The study complements previous studies in the field of mortality prediction in critically ill patients by highlighting the analytes pH and base excess in addition to lactate and their course over the first 48 hours after admission to ICU in medical ICU patients.

In conclusion, lactate, pH and base excess appear to be consistently valid parameters for estimating mortality, and monitoring changes in these parameters during the first hours of intensive care treatment can improve the accuracy of mortality estimates.

Data availability

The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions statement

AS analyzed and interpreted the data and drafted the manuscript. RR and MH provided the data, supported the analysis and interpretation of the data and reviewed the manuscript. KM helped analyzing and interpreting the data. RW was a major contributor of the analysis and interpretation of the data and reviewed the manuscript. All authors read and approved the final manuscript.

Additional information

The authors declare no competing interests.

Figures

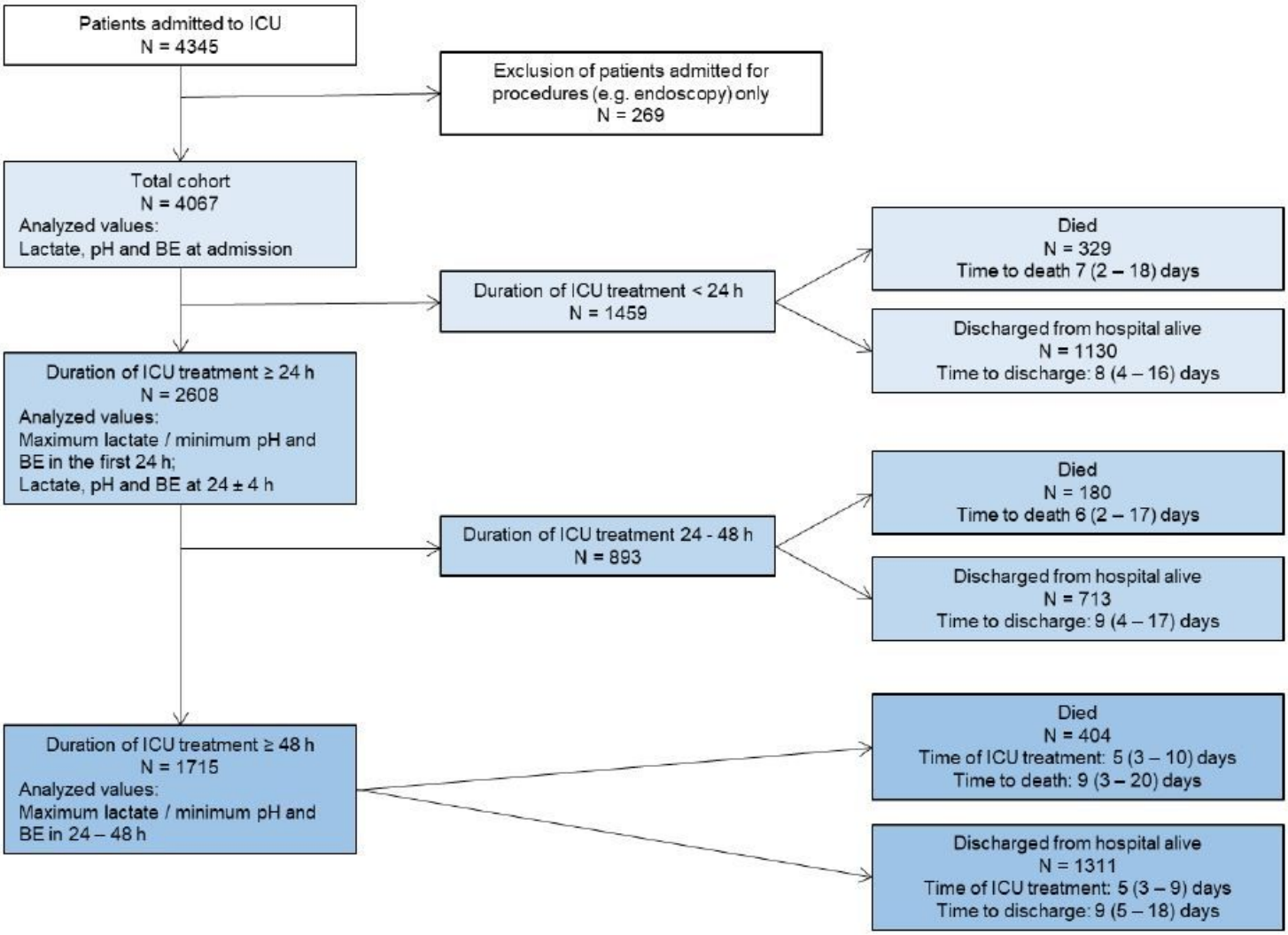

Figure 1

Flow chart study cohort and evaluated parameters

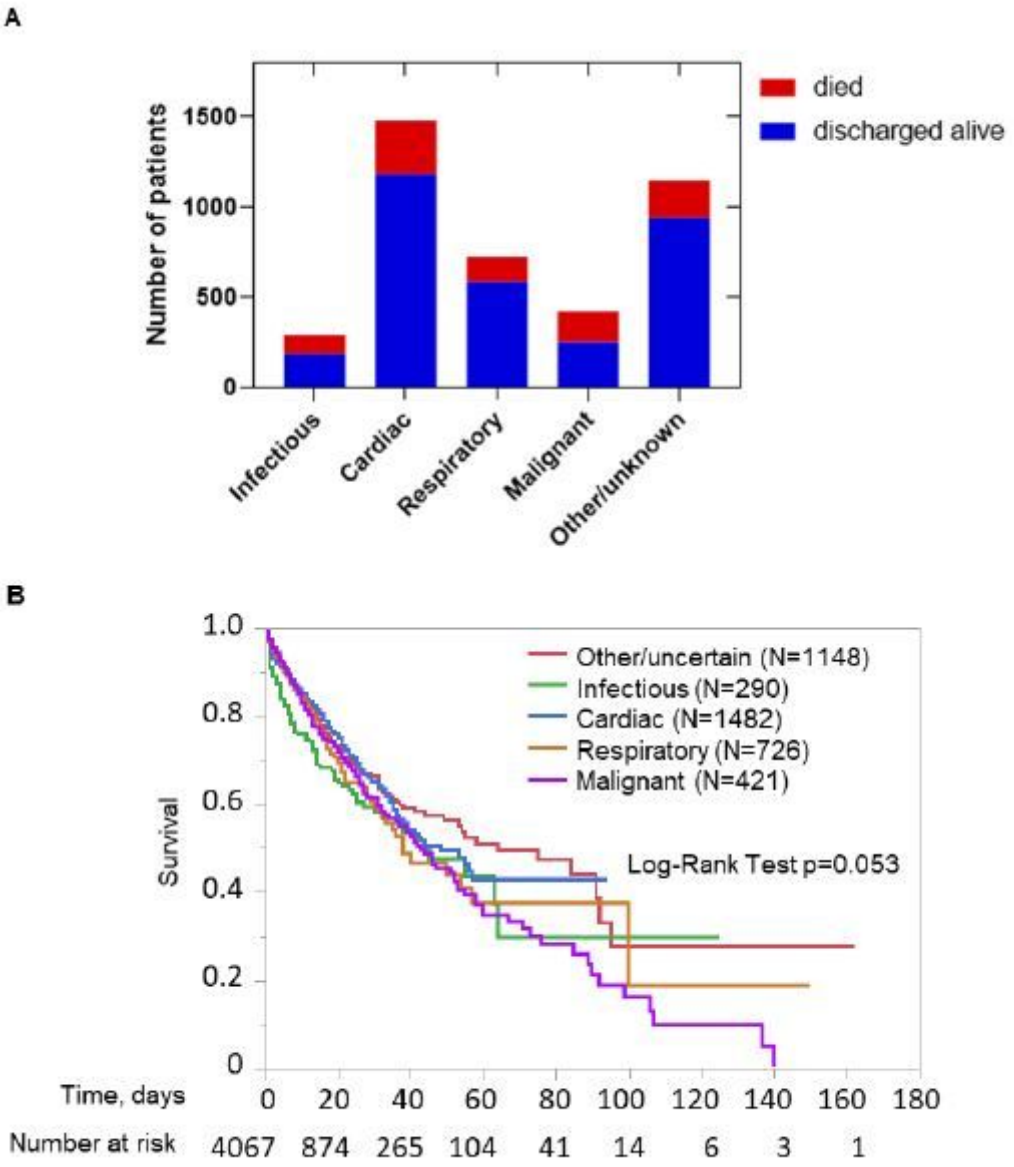

Figure 2

Distribution of patients (A) and Kaplan Meier curves (B) by primary diagnosis group

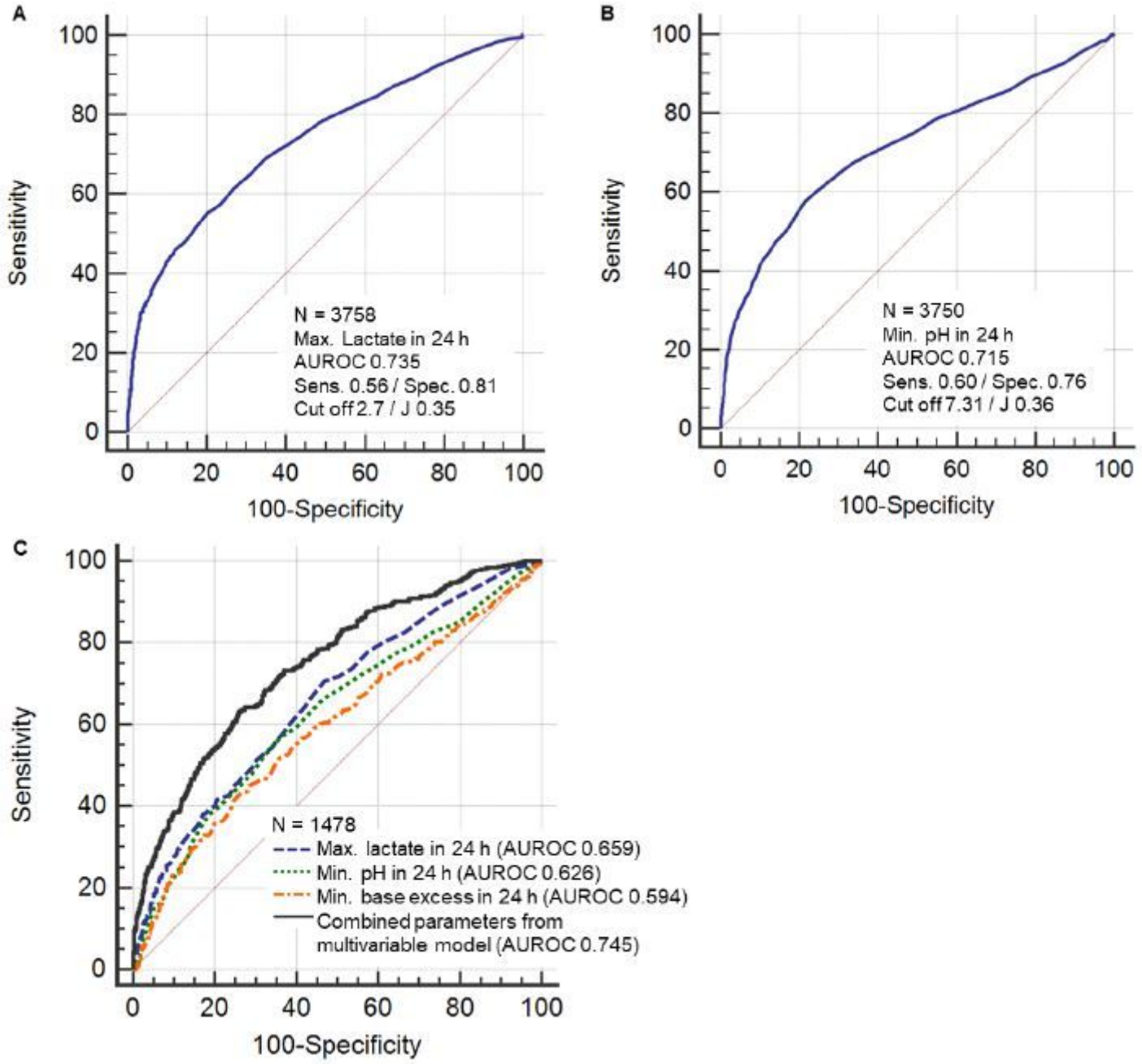

Figure 3

ROC analysis of mortality by maximum lactate (A) and minimum pH (B) in the first 24 h after admission, and multivariable ROC of mortality (C)

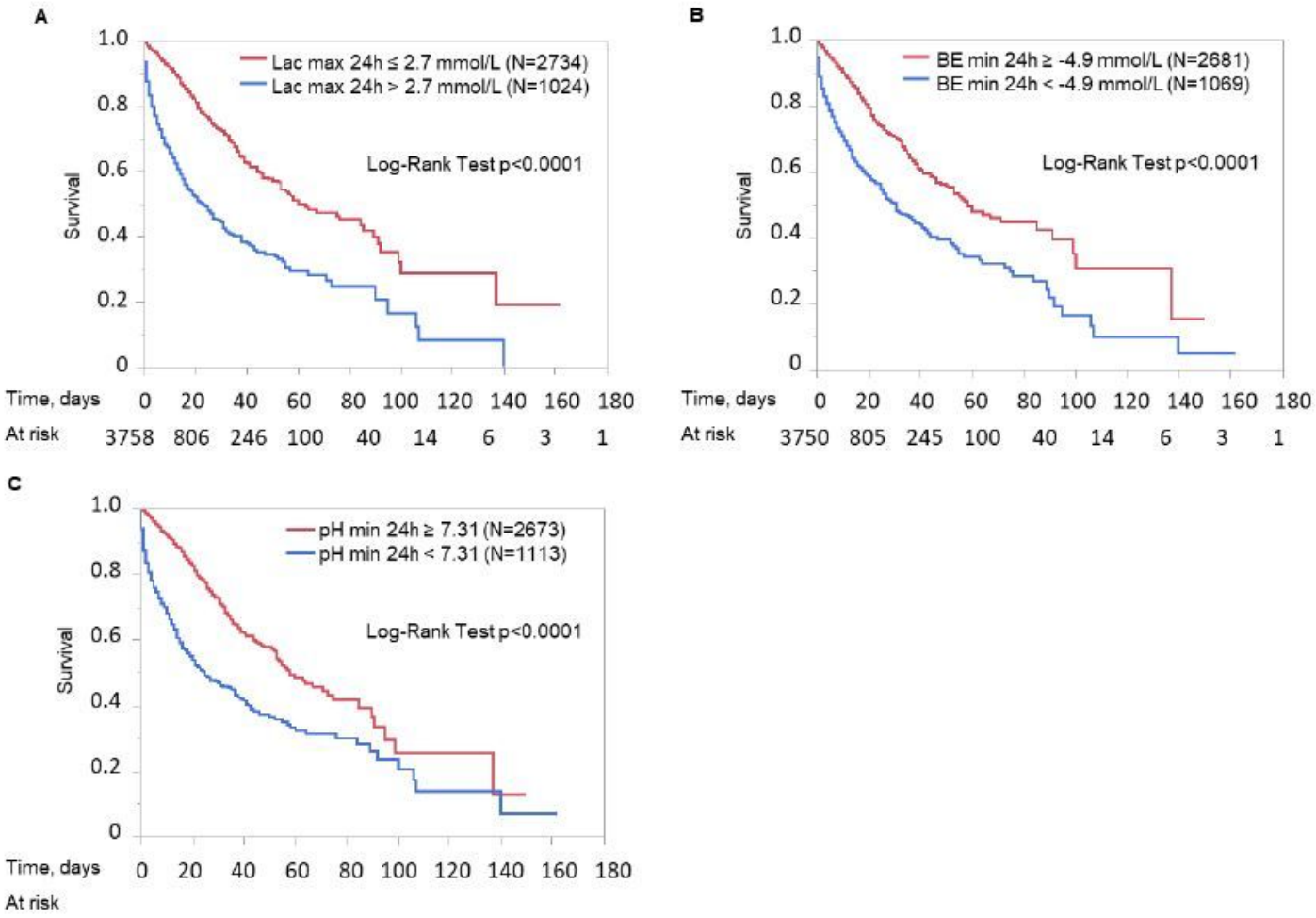

Figure 4

Kaplan Meier curve of mortality by maximum lactate (A), minimum base excess (B) and minimum pH (C) in the first 24 h after admission Cut off values used for stratification in risk groups were determined by ROC analysis. Abbreviations: Lac, lactate; BE, base excess.