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Original Article

Effect of pH, lactate, electrolyte, and strong ion difference variability on prediction of intensive care unit mortality: A retrospective study

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ABSTRACT

Objective: To investigate the effect of the variability of Na_s, Cl_s, K_s, lactate values and sodium effect (Na_{Effect}), chloride effect (Cl_{Effect}), non-lactate strong ion difference (SID_{nl}) values calculated according to Stewart's approach on predicting intensive care unit (ICU) mortality.

Methods: The study was conducted on 1 539 patients, retrospectively. Serum Na (Na_s), serum Cl (Cl_s), serum K (K_s), serum Ca (Ca_s), serum Mg (Mg_s), lactate, pH values and SID_{nl}, Na_{Effect}, Cl_{Effect}, APACHE II (first, last), and SOFA (first, last) scores were recorded. Radiometer ABL 800 (Denmark) was used for blood gas analysis. The variability of each parameter was calculated. The effect of variability of each parameter on 30-day ICU mortality was analyzed.

Results: The variability of lactate ($P<0.001$, $OR=0.580$, 95% $CI=0.505$-0.652), pH ($P=0.001$, $OR=0.004$, 95% $CI=0.000$-0.104), Na_{Effect} ($P<0.001$, $OR=0.550$, 95% $CI=0.378$-0.592), K_s ($P<0.001$, $OR=0.385$, 95% $CI=0.244$-0.565) values were protective factors of ICU mortality and Cl_s value was a risk factor ($P=0.004$, $OR=1.095$, 95% $CI=1.024$-1.164). Variability of Cl_{Effect}, SID_{nl} values did not affect ICU mortality.

Conclusions: The variability of electrolytes is important. Electrolyte, effects, and lactate variability can guide treatment and fluid applications in ICU.

KEYWORDS: Electrolyte; Variability; Mortality; Sodium; Chloride; Lactate; ICU

is increasingly used by intensive care physicians, revealed that electrolyte imbalance and acid-base disorders should be evaluated together[2].

In the Stewart approach, there are three main determinants of acid-base status: *in vivo* partial pressure of carbon dioxide (pCO_2), total non-volatile weak acids (A_{TOT}), and strong ion difference (SID). SID is the primary metabolic factor of the physicochemical approach[3]. Gilfix *et al.* explained the effect of changes in non-lactate strong ion difference (SID_{nl}) and A_{TOT} on pH with 4 simple mechanisms [sodium effect (Na_{Effect}), chloride effect (Cl_{Effect}), albumin effect, other effects][4].

Nowadays, we can interpret the instant biochemical values of the patients as well as the former values and the change between them, through computer programs used in the intensive care unit (ICU).

Significance

Our study measures three important electrolytes (Na, Cl, K) and lactate variabilities together in a large population of intensive care patients and also focuses on the non-lactate strong ion difference variability. We find that variability of lactate, pH, Na_{Effect}, K_s values are protective factors of intensive care unit mortality and Cl_s value is a risk factor. Electrolyte, effects and lactate variability can guide treatment and fluid applications in intensive care unit.

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1. Introduction

Electrolyte imbalance is a common problem in the critically ill. It is related to mortality and morbidity[1]. The Stewart approach, which

Recently, variability in serum electrolytes has attracted attention as a new risk factor for in-hospital mortality in critically ill patients[5]. The variability, which helps us to follow the trend in addition to instant biochemistry measurements, is important in the follow-up of serum electrolyte values in critically ill patients. Our aim in this study was to investigate the relationship between variability of serum electrolyte values (Na_s, Cl_s, K_s), lactate, effects (Na_{Effect}, Cl_{Effect}), and SID_{nl} on 30-day ICU mortality.

2. Patients and methods

2.1. Ethical statement

The study was approved by the Health Sciences University Bakırköy Dr.Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with the approval number 2021-16-06. Informing and consent forms were obtained from patients or relatives.

2.2. Study population

Patients who were admitted to Intensive Care Unit, Department of Anesthesiology and Reanimation, Bakırköy Dr.Sadi Konuk Training and Research Hospital from 31 December 2013 to 31 December 2020 were included and divided into two groups (survivors and non-survivors). This study was registered to 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software (Israel)'.

2.3. Inclusion and exclusion criteria

All patients above the age of 17 who were admitted to medical and surgical ICU were included. Patients with hospitalizations less than 30 day and patients without APACHE Ⅱ and SOFA scores, electrolytes, effects, or scores were excluded.

2.4. Definitions and calculations of the effects and SID

The four effects suggested by Gilfix *et al* are as follows[4]:

1) Na_{Effect}: The SID is found by subtracting the concentration of the positively charged strong ions and the negatively charged strong ions. Changes in the amount of solvent, *i.e.* water, concentrate, or dilute the solution, thereby changing the SID[6]. This diluting effect of water is called the "free water effect";

2) Cl_{Effect}: It measures the effect of Cl_s deviation from normal. However, due to the dilution effect on Cl_s, corrected Cl_s ($Cl_{corrected}$) must be calculated;

3) Albumin effect: It shows the effect of albumin change on standard base excess (SBE);

4) Other effects: It is found by subtracting the sum of the other 3 effects from SBE.

The calculation of the effects and SID_{nl} with the formulas of Stewart's approach, which was previously defined in the Decision Support System, was made by the system and the following formulas were used[4,6.7]:

$Na_{Effect} = 0.3 \times (Na_s - 140)$ (mmol/L)

$Cl_{corrected} = $ Measured $Cl_s \times$ [Standart Na_s (140 mmol/L)/Measured Na_s]

$Cl_{Effect} = 102 - Cl_{corrected}$ (mmol/L)

$SI_{Dnl} = Na_s + K_s + Ca_s + Mg_s - Cl_s$

2.5. Measurement

Na_s, Cl_s, K_s, Ca_s, Mg_s, lactate, pH values and their SID_{nl}, Na_{Effect}, Cl_{Effect}, APACHE Ⅱ (first, last), and SOFA (first, last) scores were recorded. Radiometer ABL 800 (Denmark) was used for blood gas analysis. The variability of each parameter was calculated. Variability is defined as the 30-day standard deviation of the daily mean of all measurements performed in the ICU. The effect of variability of each parameter on 30-day ICU mortality was analyzed.

2.6. Statistical analysis

Data obtained from the Clinical Decision Support system were transferred to an Excel file. The collected data were evaluated by SPSS version 22.00 (SPSS Inc., Chicago, IL). Median (range/IQR), frequencies, and percentages were used for descriptive data. The normal distribution of the quantitative data was tested with the Kolmogorov-Smirnov test and graphical examinations. Survivor and non-survivor groups were compared with Mann Whitney *U* for continuous variables, Chi-square, and Fisher exact test for categorical variables. Potential factors affecting ICU mortality were analyzed by logistic regression analysis. A *P*-value of <0.05 was considered significant.

3. Results

A total of 1 539 patients were included as shown in Figure 1, including 39.4% (*n*=607) female and 60.6% (*n*=932) male. The median age of the patients was 67 years (54-78). The mortality rate was 64.84% (*n*=998). A total of 1 385 patients were admitted to the ICU for non-surgical reasons and 154 for surgical reasons. The differences in age, height, APACHE II_last, SOFA_first, and SOFA_last were statistically significant between non-survivor patients and survivor patients (*P*<0.01) (Table 1). The levels of lactate, pH, Cl_s, K_s, Na_{Effect} variability were statistically higher in non-survivor patients than in survivor patients (*P*<0.01) (Table 2).

The variability of lactate, pH, K_s, and Na_{Effect} values were protective factors of 30-day ICU mortality. The variability of Cl_s values was a risk factor for 30-day ICU mortality (*P*=0.004, *OR*=1.095, 95% *CI*=1.024-1.164) (Table 3).

Table 1. Demographic and clinical characteristics.

Characteristics	Total, *n*=1 539	Survivors, *n*=541	Non−survivors, *n*=998	U/χ^2	*P*
Female (*n*, %)	607 (39.4%)	217 (40.1%)	390 (39.1%)	0.192	0.827
Age (year, median, range)	67 (54-78)	56 (45-70)	62 (54-73)	211 453	<0.001
Weight (kg, median, range)	80 (70-85)	80 (75-90)	80 (70-90)	258 419	0.161
Height (m, median, range)	1.70 (1.60-1.75)	1.70 (1.64-1.76)	1.70 (1.64-1.75)	243 780	0.002
BMI (kg/m², median, range)	26.1 (24.2-29.4)	27.7 (25.5-30.1)	27.2 (24.5-29.7)	266 881	0.211
Admission reason (*n*, %)					
Non-surgery	1 385 (89.9%)	491 (90.7%)	894 (89.5%)	0.157	0.615
Surgery	154 (10.1%)	50 (9.3%)	104 (10.5%)		
APACHE Ⅱ first (median, range)	26 (22-31)	26 (21-31)	26 (22-30)	268 921	0.901
APACHE Ⅱ last (median, range)	27 (19-33)	17 (14-21)	31 (27-35)	33 624	<0.001
SOFA first (median, range)	8 (6-11)	7 (5-10)	9 (6-12)	162 656	<0.001
SOFA last (median, range)	9 (5-13)	4 (3-6)	12 (8-15)	46 462	<0.001
Length of stay in ICU (day, median, range)	6.6 (3.1-13.1)	13.2 (6.3-20.0)	7.5 (3.0-13.6)	268 479	0.932

APACHE: Acute Physiology Assessment and Chronic Health Evaluation; BMI: body mass index; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment.

Table 2. Analysis of lactate, electrolytes, strong ion difference and effects.

Parameters	Survivors, *n*=541	Non−survivors, *n*=998	B	S.E.	Wald	Exp(B)	*P*
Lactate (meq/L, median, IQR)	0.62 (0.58)	1.01 (1.46)	−0.556	0.065	72.124	0.574	<0.001
SID_{nl} (median, IQR)	3.38 (2.34)	3.33 (2.49)	0.055	0.069	0.646	1.057	0.687
pH (median, IQR)	0.06 (0.04)	0.08 (0.05)	−5.566	1.685	10.909	0.004	<0.001
Cl_s (meq/L, median, IQR)	4.58 (2.99)	4.77 (3.82)	0.088	0.033	7.151	1.092	0.005
Na_s (meq/L, median, IQR)	4.04 (2.47)	4.70 (3.87)	0.122	0.134	8.623	1.873	0.124
K_s (meq/L, median, IQR)	0.54 (0.29)	0.65 (0.36)	−0.991	0.215	21.317	0.371	<0.001
Na_{Effect} (meq/L, median, IQR)	1.21 (0.74)	1.41 (1.16)	−0.749	0.115	42.509	0.473	<0.001
Cl_{Effect} (meq/L, median, IQR)	3.50 (2.14)	3.48 (2.21)	0.163	0.045	6.754	1.065	0.221

IQR: interquartile range; s: serum; SID_{nl}: non-lactate strong ion difference.
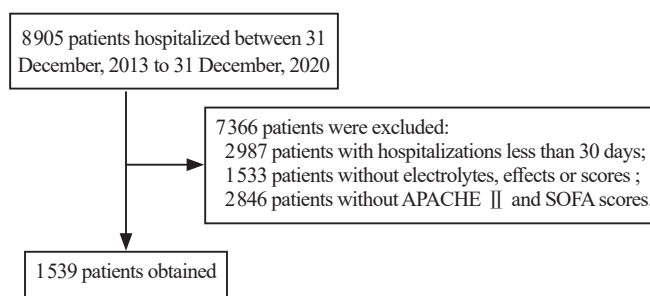
Figure 1. Diagram showing artificial intelligence (AI)-based algorithm approach.

Table 3. Multivariate logistic regression analysis for 30-day mortality.

Items	Odd ratio	*P*	95% CI
Lactate	0.580	<0.001	0.505-0.652
pH	0.004	0.001	0.000-0.104
Cl_s	1.095	0.004	1.024-1.164
K_s	0.385	<0.001	0.244-0.565
Na_{Effect}	0.550	<0.001	0.378-0.592

4. Discussion

Intensive care specialists make great efforts to manage problems with fluids, electrolytes, blood pH, and maintain acid-base balance[8]. The optimum pH range for human cells is 7.35-7.45. Below or above this narrow range is called acidemia or alkalemia. Both acidemia and alkalemia are associated with mortality in ICU[9]. It is also known that pH predicts mortality in ICU patients[10]. Our study finds that low pH variability is protective against mortality.

Control of Cl_s concentration could regulate the acid-base balance and maintain homeostasis[11]. Cl_s concentration varies depending on the change in the body's acid-base balance, *via* renal excretion and transfer from the cell membrane due to Donnan effects[12]. Higher Cl_s variability was associated with increased mortality. However, Cl_{Effect} variability is not associated with mortality. The Cl_{Effect} formulation described by Gilfix *et al* uses $Cl_{corrected}$ instead of Cl_s. This correction was criticized in the previous study[13]. Alterations in Cl_s levels and hyperchloremia have been reported to be associated with increased hospital mortality[14-17]. These studies also show that Cl_s should be considered without correction.

Na_s concentration is under hormonal control for the control of plasma osmolality and water balance. Na_s variability was not associated with mortality, while decreased Na_{Effect} variability was found to be protective against mortality. The free water effect is

common but minor, a 10 mmol/L decrease in Na_s concentration contributes to a -3.3 mmol/L change in SBE[6]. Despite this, the results of our study show that the free water effect cannot be ignored in the acid-base balance of the human body, which consists of 50%-80% water from birth to death. Our study reveals that Na_{Effect} is a valuable parameter when evaluating the contribution of Na_s to acid-base balance.

The decreased K_s and lactate variability were found to be protective against mortality. It has been shown that low K_s variability has a reducing effect on mortality[18,19]. It is already known that high lactate levels[20-23] and decreased lactate clearance[21-24] are associated with high mortality. This condition is associated with adequate tissue oxygenation and oxygen utilization.

The main determinant of SID_{nl}, which is the key to the pH control mechanism in the body, is the concentration difference between Na_s and Cl_s ions[3]. Although the relationship between SIDnl values and mortality is known, SID_{nl} variability did not significantly affect mortality in our study.

The retrospective observational nature of this study is limiting. Including SBE and bicarbonate in the study would have enriched the study.

The variability, whose importance has increased recently, may be useful in the follow-up of intensive care patients. Electrolyte, effects and lactate variability can guide our treatment and fluid applications in ICU. In this study, lower pH, lactate, Na_{Effect}, and K_s variability were associated with decreased ICU mortality and higher Cl_s variability was associated with increased ICU mortality.

Conflict of interest statement

The authors declare no conflict of interest.

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Authors' contributions

F.T., S.A., B.O.B.: Concept and design of study or acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content.

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