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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Stewart's Approach for Acid-Base Disorders: Does the Strong Ion Difference and Effects Have an Impact on Intensive Care Unit Mortality?

Asit Baz Bozukluklarına Stewart Yaklaşımı: Güçlü İyon Farkı Yoğun Bakım Mortalitesini Etkiler Mi?

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ABSTRACT *Objective:* The diagnosis and treatment of electrolyte and acid-base imbalances in intensive care unit (ICU) patients have critical importance. The value of Stewart's approach in revealing acid-base disorders is known. There are parameters defined according to this approach. This study investigates the impact of the ClEffect, NaEffect, Na-ClEffect, SIDnl and Cl/Na ratio values calculated according to Stewart's approach on ICU mortality.

Materials and Methods: 2000 patients whose Na, Cl, K, SBE, pH values were recorded and SIDnl, ClEffect, NaEffect, Na-ClEffect, APACHE II and SOFA scores calculated are included in this study. ClEffect, NaEffect, Na-ClEffect, SIDnl, Cl/Na ratio values were evaluated with a multivariable logistic regression model in terms of ICU mortality.

Results: Abnormal ranges of SIDnl (SIDnl<30 or SIDnl≥43) were significantly increased in non-survivors than survivors (p=0.026). ClEffect, NaEffect, Na-ClEffect, Cl/Na ratio and their percentages of abnormal ranges were similar between survivor and non-survivor patients.In the multivariate logistic regression model, the likelihood of mortality was 3.5-fold (2.9-4.3), 1.7-fold (1.4-2.1) and 1.2-fold (1.0-1.5) increased by APACHE-II ≥26, SOFA>7, and SIDnl<30 or SIDnl≥43 (p<0.001, p<0.001, p=0.041, respectively).

Conclusion: SIDnl is associated with ICU mortality, but pH, SBE, ClEffect, NaEffect, Na-ClEffect and Cl/Na ratio is not. SIDnl is one of the independent variables of Stewart's approach and is a valuable parameter in blood gas evaluations.

Keywords: Acid-base, strong ion difference, sodium, chloride, intensive care unit, mortality, outcome

ÖZ *Amaç:* Yoğun bakım ünitesi (YBÜ) hastalarında elektrolit ve asit-baz bozukluklarının tanı ve tedavisi kritik öneme sahiptir. Asit-baz bozukluklarını açıklamada Stewart yaklaşımının önemi bilinmektedir. Bu yaklaşıma göre tanımlanmış çeşitli parametreler vardır. Bu çalışmanın amacı, Stewart'ın yaklaşımına göre hesaplanan ClEffect, NaEffect, Na-ClEffect, SIDnl, Cl/Na oranı değerlerinin YBÜ mortalitesi üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntemler: Bilgisayar destekli karar destek sistemine Na, Cl, K, SBE, pH değerleri kaydedilen ve sisteme tanımlı formüller aracılığıyla SID, NaEffect, ClEffect, Na-Cl Effect, APACHE II ve SOFA skorları hesaplanan 2000 hasta bu çalışmaya dahil edilmiştir. ClEffect, NaEffect, Na-ClEffect, SIDnl, Cl/Na oranı değerleri multivariable lojistik regresyon modeli ile YBÜ mortalitesi açısından değerlendirildi.

Bulgular: Anormal SIDnl aralıkları (SIDnl<30 veya SIDnl≥43), ölen hastalarda hayatta kalanlara göre anlamlı olarak yüksekti(p=0.026). ClEffect, NaEffect, Na-ClEffect, Cl/Na oranı ve bunların anormal aralıkları, hayatta kalan ve ölen hastalarda benzerdi. Multivariable lojistik regresyon modelinde, ölüm olasılığı APACHE-II ≥26, SOFA>7 ve SIDnl<30 veya SIDnl≥43 olan hastalarda sırasıyla 3.5 kat (2.9-4.3), 1.7 kat (1.4-2.1) ve 1.2 kat (1.0-1.5) artmış olarak bulundu (p<0,001, p<0,001, p=0,041).

Sonuç: SIDnl, YBÜ mortalitesi ile ilişkili iken, pH, SBE, ClEffect, NaEffect, Na-ClEffect ve Cl/Na oranı değildir. Stewart yaklaşımının bağımsız değişkenlerinden biri olan SIDnl, kan gazı değerlendirmelerinde önemli bir parametredir.

Anahtar Kelimeler: Asit baz, güçlü iyon farkı, sodyum, klorür, yoğun bakım ünitesi, mortalite

Introduction

Acid-base disorders are commonly found in patients admitted to the intensive care unit (ICU) as a consequence of the underlying disease or inappropriate fluid resuscitation. They are associated with high mortality and morbidity, often accompanying critical diseases (1). Therefore, the assessment of acid-base disorders is critical for accurate diagnosis and effective treatment.

Debates on which approach is more logical and holistic in the analysis of acid-base balance have continued for many years (2). However, Stewart's approach is more comprehensive than the others, it can define subtle or combined acid-base disorders that cannot be detected using only the Henderson-Hasselbalch or base excess (BE) approaches (3, 4). Traditional approaches are insufficient to reveal causal mechanisms (5). Gilfix et al. devised an original Fencl concept showing the impact of changes in Strong Ion Difference (SID) and the total amount of weak acids (ATOT) on BE and designed simple formulas that do not require computers or calculators, aiming to make Stewart's approach accessible (6, 7). With this approach, complex acid-base abnormalities can be detected at the bedside, and early treatment targeting underlying causes can be started (8, 9).

This study aims to investigate the impact of the Chloride Effect (ClEffect), Sodium Effect (NaEffect), Sodium-Chloride Effect (Na-ClEffect), non-lactate Strong Ion Difference (SIDnl), Chloride/Sodium ratio (Cl/Na ratio) values calculated according to Stewart's approach by a computer-based decision support system on ICU mortality.

Materials and Methods

The retrospective observational study was approved by the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with a decision no. 2019/49. During the admission of all patients to the ICU, information and consent forms were signed by the relatives of the patients, stating that the patient data would be used in retrospective scientific studies.

Definitions and Calculations of the Effects and SID

The physicochemical approach is based on four mechanisms (6):

1) Sodium Effect (NaEffect): Changes in the amount of solvent (i.e. water) concentrate or dilute the solution, changing the SID (8). This diluting effect of water is called the "free water effect".

2) Chloride Effect (ClEffect): Indicates the amount of change from normal serum chloride (Cls) concentration. First of all, the correction should be made by considering the dilution effect on chloride. This correction (Clcorrected) is obtained by multiplying the measured serum chloride concentration (Cls) by the ratio of standard sodium (140 mmol/L) to the measured sodium (Nas).

3) Protein Effect: It shows the change of dominant weak acids such as albumin.

4) Other Effects: The effect of negative ions (lactate, ketoacids, formate, oxalate, salicylate, sulfate, and phosphate), most of which cannot be measured and cause strong ion gap (SIG) metabolic acidosis.

In our study, SID was calculated from the differences of strong ions other than lactate, also known as SIDnl (10). (See electronic supplement for formulas used in effects and SIDnl calculations).

Study Population

Data of 9038 patients hospitalized in Bakırköy Dr.Sadi Konuk Training and Research Hospital, Department of Anesthesia and Reanimation General Intensive Care Unit between 01.01.2013-31.12.2019 and registered with 'ImdSoft-Metavision/QlinICU Clinical Decision Support Software (Israel)' were obtained by SQL (Structured Query Language) inquiries. Radiometer ABL 800 (Denmark) was used for blood gas analysis. Patients who stayed in the ICU for less than 48 hours (3234) and patients whose APACHE II score was not calculated (2101) were excluded from the study. Out of 3703 patients, 2000 patients whose Nas, Cls, Ks, SBE, pH values were recorded and SIDnl, ClEffect, NaEffect, Na-ClEffect, Cl/Na ratio, APACHE II, and SOFA scores calculated are included in this study (Figure 1).

Inclusion criteria: All patients older than 17 years were admitted to the medical or surgical intensive care unit.

Exclusion criteria: Patients hospitalized for less than 48 hours and whose Nas, Cls, Ks, SBE, pH values were not recorded or effects, SIDnl, scores not calculated.

Statistical Analysis

Data were analyzed using SPSS 22 for Windows (IBM Corp., Armonk, NY, USA). Mean±standard deviation (SD), median (interquartile range [IQR]), frequencies and percentages were used for descriptive data. The conformity

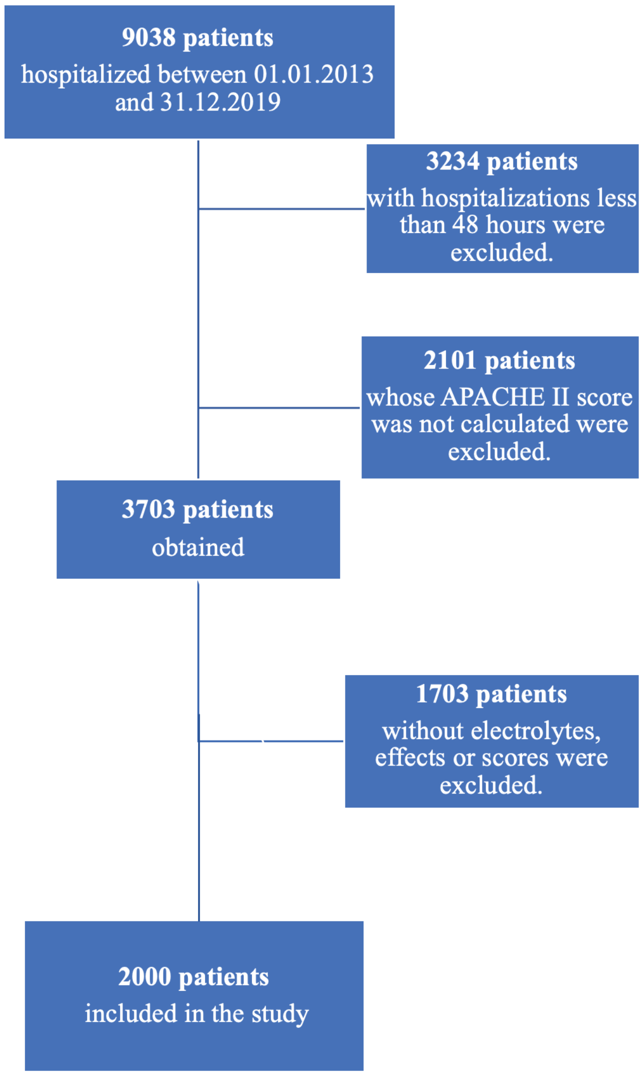

Figure 1. Flow chart of study participants

of the quantitative data to the normal distribution was tested with the Kolmogorov-Smirnov test and graphical examinations. Student's t-test and Mann Whitney U test were used for comparisons between two groups (survivors and nonsurvivors) of quantitative variables. Pearson chi-square test was used to compare qualitative data. The optimal cut-off level for APACHE-II score, SOFA score, SBE and pH to affect mortality was evaluated with ROC analysis using the Youden index. Multivariate logistic regression analysis was used for the likelihood of mortality. APACHE-II score, SOFA score, SIDnl, SBE and pH were added to the multivariate model. A p-value of <0.05 was used to determine the significance.

Results

The study was conducted with 2000 patients, 40.1% (n=803) female and 59.9% (n=1197) male (Table 1). The median age of the patients was 67 years. The median values of SOFA and APACHE-II scores were 8 (6-11) and 26 (21-31), respectively (Table 1). The mortality rate was 53.5% (n=1069). The percentages of abnormal ranges of ClEffect, NaEffect, Na-ClEffect, SIDnl and Cl/Na ratio were differently found (Table 1).

In non-survivors, SBE, pH, duration of invasive mechanical ventilation (IMV) and length of ICU stay (LOS-ICU) were significantly decreased whereas SOFA and APACHE II scores were significantly increased than survivors (p<0.001, p<0.001, p=0.034, p<0.001, p<0.001 and p<0.001 respectively) (Table 2).

Although median values of SIDnl were similar between the two groups, the percentage of abnormal ranges of SIDnl (SIDnl<30 or SIDnl≥43) were significantly increased in non-survivors than survivors (p=0.390, p=0.026) (Table 2).

On the other hand, ClEffect, NaEffect, Na-ClEffect, Cl/Na ratio and their percentages of abnormal ranges were also similar between survivor and non-survivor patients (p=0.846, p=0.309; p=0.072, p=0.612; p=0.981, p=0.903; p=0.706, p=0.218) (Table 2).

Cut-off and area under curve (AUC) values of SOFA score, APACHE-II, SBE and pH were >7 (0.66 [0.64-0.69]), ≥26 (0.74 [0.72-0.76]), ≤-4.4 mmol/L (0.59 [0.56-0.61]) and <7.33 (0.57 [0.54-0.59]), respectively (p<0.001 for all) (Table 3).

In the multivariate logistic regression model, the likelihood of mortality were 3.5-fold (2.9-4.3), 1.7-fold (1.4-2.1) and 1.2-fold (1.0-1.5) increased by APACHE-II ≥26, SOFA>7, and SIDnl<30 or SIDnl≥43, respectively (p<0.001, p<0.001, p=0.041) (Table 4).

Discussion

In the present study, it was shown that SOFA score, APACHE II and abnormal SIDnl values (<30 or ≥43) at the ICU admission were associated with mortality. This highlights the importance of the Stewart approach and its metabolic component, SID. Unlike some studies, we didn't find any relationship between SBE, pH and mortality (11-14). SBE and pH are known as dependent variables, hence, we think that it can be the reason for this result. Discussions on the superiority of approaches to the diagnosis and treatment of acid-base disorders continue today (15-18). However, the

Table 1. Patients' chracteristics and outcomes	
Patients, n	2000
Age, years	67 (55-78)
Male, n (%)	1197 (59.9)
BMI, (kg/m²)	26.1 (24.2-29.4)
SOFA score	8 (6-11)
APACHE II	26 (21-31)
Diagnosis, n (%)	
Medical	1862 (93.1)
Surgery	138 (6.9)
pH	7.33 (7.23-7.40)
$PaCO_2$, (mmHg)	40.2 (33.4-49.0)
SBE, (mmol/L)	-4.5 (-9.2 ; -0.2)
Cl_s, (mmol/L)	107 (103-112)
Na_s, (mmol/L)	139 (136-144)
K, (mmol/L)	4.0 (3.6-4.4)
Cl_{Effect}, (mmol/L)	-5.1±9.0
$-14.1 \leq Cl_{Effect} \leq 4.9$	1465 (73.2)
$Cl_{Effect} < -14.1$ or $Cl_{Effect} > 4.9$	535 (26.8)
Na_{Effect}, (mmol/L)	0.0 (-1.2-1.2)
$-1.2 \leq Na_{Effect} \leq 1.2$	1127 (56.3)
$Na_{Effect} < -1.2$ or $Na_{Effect} > 1.2$	873 (43.7)
$Na\text{-}Cl_{Effect}$, (mmol/L)	-4.9±10.5
$-15.5 \leq Na\text{-}Cl_{Effect} \leq 4.6$	1384 (69.2)
$Na\text{-}Cl_{Effect} < -15.5$ or $Na\text{-}Cl_{Effect} > 4.6$	616 (30.8)
SID_{nl}, (mmol/L)	37 (30-43)
$30 \leq SID_{nl} \leq 43$	1092 (54.6)
$SID_{nl} < 30$ or $SID_{nl} \geq 43$	908 (45.4)
Cl/Na ratio	0.77 (0.72-0.81)
0.72≤Cl/Na ratio≤0.81	1161 (58.1)
Cl/Na rati<0.72 or Cl/Na ratio>0.81	839 (41.9)
Lactate, (mmol/L)	1.4 (1.0-2.0)
Urea, (mg/dL)	44 (27-70)
Creatine, (mg/dL)	0.7 (0.5-1.13)
Duration of IMV, (h)	88 (20-272)
Length of ICU stay, (h)	124 (48-306)
AKI, n (%)	796 (39.8)
Mortality, n (%)	1069 (53.5)

AKI, acute kidney injury; APACHE, Acute Physiology Assessment and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; PaCO2, partial carbon dioxide pressure; s, serum; SBE, standard base excees; SIDnl, non-lactate strong ion difference; SOFA, Sequential Organ Failure Assessment

physicochemical approach is thought to provide a broader perspective. In patients with normal pH and SBE values, it was shown that low SID, which can only be detected by Stewart's approach, is associated with prolonged hospitalization even at neutral pH (19). Furthermore, it is also known that SID and SIDnl were associated with increased ICU mortality and length of stay in ICU (10, 20, 21). For this reason, SID, especially SIDnl, is a more important blood-gas parameter which affects outcomes in the ICU.

Actually, SIDnl is a parameter which is used to detect electrolyte effect on acid-base status. And, a few electrolyte evaluation approaches are defined in the literature such as Fencl's corrections, base excess chloride (BECl) and Cl/Na ratio (6, 7, 22, 23). In our study, we didn't observe any relationship among all serum levels of electrolytes (Cls, Nas, Ks), effect values of them (ClEffect, NaEffect, Na-ClEffect), Cl/Na ratio and ICU mortality except for SIDnl. Effect values (ClEffect, Na-ClEffect), which are suitable for the Fencl concept that we used in our study, take into account the Clcorrected instead of the Cls in chloride measurements (6, 7). The lack of mention of any correction in Stewart's approach has caused the Fencl concept to be criticized in this respect (23, 24). Gucyetmez et al. claimed that the best chloride evaluation approach was the BECl (23). Indeed, SIDnl and BECl mainly refer to the difference between Na and Cl in accordance with their formulas (23). Our results obviously show that approaches based on the difference between Na and Cl such as SIDnl and BECl are also more valuable parameters to lead electrolyte effects on mortality in the ICU. For this reason, we can argue that the serum values of electrolytes should be evaluated without any correction.

Surprisingly, the median lactate value (1.4 mmol/L) was higher in survivor patients than in non-survivor patients (1.3 mmol/L) in our study. Therefore, no relationship was found between lactate and mortality. However, it is known that high lactate levels are associated with high mortality (25-28).

In this study, it was also found that APACHE II ≥ 26 and SOFA Score > 7 were associated with higher mortality. This result is consistent with previous studies (29-31). In addition, as expected, the duration of mechanical ventilation and the length of stay in the ICU were found to be longer in non-survivor patients.

Limitations

Although all parameters of the quantitative method have been previously defined in the software, it is not known how effectively these data are used by intensive care physicians

Table 2. Comparison between survivors and non-survivors			
	Survivors (n=931)	**Non-survivors (n=1069)**	**p**
Age, years	67 (54-77)	68 (56-78)	0.100
Male, n (%)	564 (60.6)	633 (59.2)	0.534
BMI, (kg/m^2)	26.1 (24.5-29.4)	26.1 (24.2-29.4)	0.329
SOFA Score	7 (5-9)	9 (7-12)	***<0.001***
APACHE II	23 (18-27)	29 (24-33)	***<0.001***
Diagnosis, n (%)			
Medical	860 (92.4)	1002 (93.7)	
Surgery	71 (7.6)	67 (6.3)	0.232
pH	7.34 (7.26-7.41)	7.31 (7.21-7.40)	***<0.001***
$PaCO_2$, (mmHg)	40.4 (33.8-48.4)	40.1 (33.0-49.6)	0.827
SBE, (mmol/L)	-3.6 (-7.3 ; 0.0)	-5.6 (-10.8 ; -0.7)	***<0.001***
Na_s, (mmol/L)	139 (137-143)	139 (136-144)	0.682
Cl_s, (mmol/L)	108 (103-112)	107 (102-112)	0.152
K_s, (mmol/L)	4.0 (3.6-4.5)	3.9 (3.5-4.4)	0.144
Cl_{Effect}, (mmol/L)	-5.2±8.8	-5.1±9.2	
$-14.1 \leq Cl_{Effect} \leq 4.9$	692 (74.3)	773 (72.3)	0.846
$Cl_{Effect} < -14.1$ or $Cl_{Effect} > 4.9$	239 (25.7)	296 (27.7)	0.309
Na_{Effect}, (mmol/L)	0.0 (-0.9 ; 1.2)	-0.3 (-1.2 ; 1.2)	
$-1.2 \leq Na_{Effect} \leq 1.2$	519 (55.7)	608 (56.9)	0.072
$Na_{Effect} < -1.2$ or $Na_{Effect} > 1.2$	412 (44.3)	461 (43.1)	0.612
$Na\text{-}Cl_{Effect}$, (mmol/L)	-5.0 (-11.6 ; 1.3)	-5.1 (-11.7 ; 2.0)	
$-15.5 \leq Na\text{-}Cl_{Effect} \leq 4.6$	643 (69.1)	741 (69.3)	0.981
$Na\text{-}Cl_{Effect} < -15.5$ or $Na\text{-}Cl_{Effect} > 4.6$	288 (30.9)	328 (30.7)	0.903
SID_{nl}, (mmol/L)	36 (31-43)	37 (30-44)	
$30 \leq SID_{nl} \leq 43$	533 (57.3)	559 (52.3)	0.390
$SID_{nl} < 30$ or $SID_{nl} \geq 43$	398 (42.7)	510 (47.7)	***0.026***
Cl/Na ratio	0.76 (0.73-0.81)	0.77 (0.72-0.81)	
0.72≤Cl/Na ratio≤0.81	554 (59.5)	607 (56.8)	0.706
Cl/Na ratio<0.72 or Cl/Na ratio>0.81	377 (40.5)	462 (43.2)	0.218
Lactate, (mmol/L)	1.4 (1.1-2.1)	1.3 (1.0-1.9)	0.068
Urea, (mg/dL)	44 (27-70)	44 (28-71)	0.587
Creatinine, (mg/dL)	0.71 (0.47-1.15)	0.72 (0.46-1.11)	0.979
AKI, n (%)	540 (58.0)	664 (62.1)	0.085
Duration of IMV, (h)	89 (0-272)	88 (26-272)	***0.034***
Length of ICU stay, (h)	139 (52-328)	111 (48-286)	***<0.001***

AKI, acute kidney injury; APACHE, Acute Physiology Assessment and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; IMV, invasive mechanical ventilation; $PaCO_2$, partial carbon dioxide pressure; s, serum; SBE, standard base excees; SID_{nl}, non-lactate strong ion difference; SOFA, Sequential Organ Failure Assessment

Table 3. Cut-off and area under curve values of significantly difference variables in non-survivors

	Cut-off values	AUC (95% CI)	p
APACHE II	≥26	0.74 (0.72-0.76)	*<0.001*
SOFA Score	>7	0.66 (0.64-0.69)	*<0.001*
SBE, (mmol/L)	≤-4.4	0.59 (0.56-0.61)	*<0.001*
pH	<7.33	0.57 (0.54-0.59)	*<0.001*

APACHE, Acute Physiology, Assessment and Chronic Health Evaluation ; AUC, area under curve; CI, confidence interval; SBE, standard base excees; SOFA, Sequential Organ Failure Assessment

Table 4. Multivariate logistic regression model for likelihood of mortality

	OR (95% CI)	p
APACHE II≥26	3.5 (2.9-4.3)	**<0.001**
SOFA Score>7	1.7 (1.4-2.1)	**<0.001**
SID_{nl}<30 or SID_{nl}≥43, (mmol/L)	1.2 (1.0-1.5)	**0.041**
SBE≤-4.4, (mmol/L)	1.2 (0.9-1.5)	0.102
pH<7.33	0.9 (0.8-1.2)	0.872

APACHE, Acute Physiology, Assessment and Chronic Health Evaluation ; CI, confidence interval; OR, odds ratio; SBE, standard base excees; SID_{nl}, non-lactate strong ion difference; SOFA, Sequential Organ Failure Assessment

and how they affect the treatment of patients. Also, due to the retrospective nature of our study, we could not test the adequacy of the sample size.

Conclusion

The importance of Stewart's approach, especially in defining complex acid-base disorders, is known. The results of our study show that SIDnl is associated with ICU mortality, but pH, SBE and Na-ClEffect are not. Therefore, SIDnl is a valuable parameter in blood gas evaluations.

Ethics

Ethics Committee Approval: The retrospective observational study was approved by the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee with a decision no. 2019/49.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.T., S.A., K.A.T., Concept: F.T., S.A., Z.Ç., Design: F.T., S.A., Data Collection and Process: F.T., S.A., B.Ö.B., K.A.T., Z.Ç., Analysis or Interpretation: F.T., S.A., B.Ö.B., G.Ö.Y., K.A.T., Z.Ç., Literature Search: F.T., Z.Ç., Writing: F.T., S.A., G.Ö.Y., K.A.T., Z.Ç.

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Electronic Supplement

Supplementer Data

SID (strong ion difference), Sodium Effect, Chloride Effect, Sodium Chloride Effect were calculated using the formulas defined in ImdSoft-Metavision/QlinICU Clinical Decision Support Software over the laboratory parameters of the patients with the software language as shown below (1-4):

Chloride Effect

```
If Parameters.Uvalue("Cl")>0 then
cl=Parameters.Uvalue("Cl")
Else
cl=0
End If
If Parameters.Uvalue("Na+")>0 then
na=Parameters.Uvalue("Na+")
Else
na=0
End If
If na>0 and cl>0 then
Return_Value=Round(((140/na)*cl),2)
Else
Return_Value="--"
End If
If Parameters.Uvalue("Cl")>0 then
cl=Parameters.Uvalue("Cl")
Else
cl=0
End If
If Parameters.Uvalue("Na+")>0 then
na=Parameters.Uvalue("Na+")
Else
na=0
End If
If cl>0 and na>0 then
Return_Value=102-(Round(((140/na)*cl),2))
Else
Return_Value="--"
End If
```

Sodium Effect

```
If Parameters.Uvalue("Na+")>0 then
Na=Parameters.Uvalue("Na+")
Else
Na=0
End If
If na>0 then
Return_Value=Round((0.3*(Na-140)),2)
Else
Return_Value="--"
End If
```

Sodium Chloride effect

```
Value"Sodium Effect"+ Value" Chloride Effect"
```

Chloride /Sodium Ratio

```
a=("Klor")
b=  ("Sodyum")
if  a>0 and  b>0 then
result=Round((a/b),2)
else
result=" "
end if
Return_Value =result

SIDnl
if ("Na+")>0 then
s=("Sodyum")
k=("Klor")
p=("Potasyum")
Return_Value=Round(((s+p)-k),0)
```

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