

# Metabolic acidosis in medical intensive care unit with indicators and their prognostic value- A prospective observational study



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## ABSTRACT

**Background:** Metabolic acidosis is a common abnormality in the intensive care unit. There has recently been a surge of interest in nontraditional approaches to the analysis of acid base disorders. **Aims and Objectives:** This study was undertaken to compare the application of the physicochemical method of Stewart and the traditional Henderson-Hasselbach equation with correction for albumin in quantification of acid base disorders. **Materials and Methods:** All patients with metabolic acidosis admitted to the ICU as defined by a base deficit of  $> 2.5$  were included in the study. The APACHE II score was calculated at admission and the predicted mortality was defined. The acid base disorders were quantified by the traditional approach with anion gap correction for serum albumin as well as by the Stewart method with calculation of the strong anion gap acidosis. **Results:** One-hundred forty patients were included in the study of which 58% were males. In 125 subjects (89%) acidosis was discovered by the Stewart method. The traditional method detected increased anion gap in 109 subjects (78%) but this increased to 124 (88.5%) when corrected for albumin. Both the strong ion gap (SIG) and the albumin corrected anion gap correlated strongly. Serum lactate levels and SIG predicted mortality as did albumin corrected anion gap. **Conclusion:** Albumin correction of the anion gap correlates well with acidosis as discovered by the SIG and therefore should be used in the ICUs rather than the traditional anion gap. With this modification, we can thus depend on the application of the intuitive traditional method rather than the more difficult to apply Stewart method for analysis of the acid base abnormalities in the ICU.

**Key words:** Anion gap, Henderson-hasselbach, Strong ion gap, Stewart model

## INTRODUCTION

Metabolic acidosis is one of the commonest disorders, among critically ill patients, faced by every clinician and intensivist on a day to day basis. It is associated with high morbidity and mortality irrespective of etiology.

Acid base analysis plays a very vital role in an intensive care unit. Metabolic acidosis may contribute to the morbidity and mortality associated with shock, although it may also have some protective effects in milder form.<sup>1</sup>

Abnormalities identified by various methods (strong ion gap (SIG), AG, lactic acidosis) appears to be more common in critically ill patients and are associated with increased mortality especially when it occurs early in the course of critical illness.<sup>2</sup>

Certain types of metabolic acidosis are strong independent predictors of mortality in critically ill patients and should be monitored in intensive care units.<sup>2</sup>

Lactic acidosis is commonly associated with mortality and hence Serum lactate is considered as a prognostic indicator of illness severity.<sup>3-5</sup>

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The history of arterial blood gas analysis goes back over more than forty years. The relationship between base excess (BE), anion gap, hyperchloraemia, 'unmeasured' strong anions, and mortality is still unclear and controversy persists till date. The optimal assessment of the underlying mechanism is unknown.

The traditional anion gap,  $(\text{Na}^+ + \text{K}^+) - (\text{Cl}^- + \text{HCO}_3^-)$ , does not account for the effect of weak acids, mostly albumin, which is commonly abnormal in critical illness.

Despite previous studies showing that neither base deficit nor anion gap are effective at discriminating between the presence or absence of hyperlactatemia,<sup>6-10</sup> there persists the commonly held belief that normal anion gap or the absence of base deficit rules out the presence of hyperlactatemia.

Various indices like anion gap corrected for albumin, lactate, phosphate and base excess of unmeasured anions (Fencl-Stewart) were evaluated in clinical assessment of metabolic acidosis to ascertain their prognostic value. The conclusions among studies are not yet clear.<sup>11-13</sup>

Strong ion Gap (SIG) has been shown to be better than blood lactate, pH, or injury severity scores in trauma patients and pediatric surgery patients as a predictor of mortality.<sup>14</sup> At the bedside, both the apparent and effective SID can be calculated and used to determine the strong ion gap (SIG), which can then be used in a manner similar to anion gap.

The benefits of the SIG rests in its detection of otherwise unidentified anions in plasma whenever the serum total protein, albumin, and phosphate concentrations are markedly abnormal.<sup>15</sup> SIG can be valuable in clinical settings or research studies investigating acid-base balance and help provide an understanding of acid-base properties of administered intravenous fluids.<sup>16,17</sup>

## AIMS AND OBJECTIVES

Studies pertaining to acid base disorders in Indian journals are meager. Metabolic acidosis is associated with high morbidity and mortality irrespective of aetiology.

Rivers et al,<sup>14</sup> utilized hypotension and elevated serum lactate levels to identify patients in shock and demonstrated that emergency department patients with presumed sepsis and a serum lactate level of  $\geq 4.0$  mmol/L and/or frank hypotension are at a significant risk of death (38–59% mortality).

This false belief was probably the reason that measurement of serum lactate was not considered a part of standard

admission battery of laboratory tests. The other reason would be the affordability issue in this part of the world.

Some studies have suggested an independent association between low pH or standard base excess (SBE) and mortality,<sup>11</sup> whereas others have not.<sup>12</sup>

Park et al,<sup>13</sup> showed that the use of standard base excess (SBE) with a cut off value of  $< -2.0$  was able to detect 100% of measures with metabolic acidosis.

Our intention was to detect suspected clinical cases of metabolic acidosis, and to include those with a base excess cut off value  $< -2.5$ . And these groups were analyzed by various bedside metabolic acid-base indices and their relationship to lactate concentrations and outcomes in form of survival were noted. The various metabolic acid-base indices used to detect the unmeasured ions were anion gap (traditional method), strong ion gap (Stewart's), anion gap corrected for albumin and lactate (ACAG, ALCAG) and base excess of unmeasured anion (Fencl-Stewart method). Their relationships with each other were also noted.

To summarize, the study objectives are as follows:

1. To quantify acid base disorders according to the underlying mechanism of metabolic acidosis.
2. To compare the traditional and physicochemical methods of quantifying metabolic acidosis in patients admitted to an ICU among survivors and non-survivors.
3. To compare these variable's predictive value in terms of ICU mortality with serum lactate levels and APACHE II score.

We hope this study would be a refresher to all the clinicians and intensivists in India.

## MATERIALS AND METHODS

All patients with suspected cases of metabolic acidosis admitted in the medical ICU. Approval for the study was obtained from the Ethics Review Board of Kerala Institute of Medical Sciences, Anayara, Thiruvananthapuram.

### Sampling

Arterial blood-gas samples were taken anaerobically and lactate samples were analyzed at the best without significant delay. APACHE II scoring and predicted risk of mortality<sup>18,19</sup> was calculated on admission. Electrolytes, BUN, serum Creatinine and serum albumin were measured in plasma. Table 1 provides a summary of measurement methodology. Sample size calculation was done as per the below mentioned formula.

**Table 1: Epidemiological, clinical and outcome variables**

No. of cases	140
Age (in years)	55±17
Gender, %male	54%
APACHE II on admission	15±6
APACHE II, Mortality risk (%)	24±16
Admission type (%)	
Sepsis	47
Gastrointestinal	25
Respiratory	19
Renal	10
Endocrine/Metabolic	8
Neurological	7
Hematological	6
Genitourinary	5
Malignancy	3
Overdosage/toxins	3
Miscellaneous	7

$$N = (Z_{2-\alpha} \times p \times q) / d^2$$

Where p – prevalence of acidosis among those admitted in the ICU of

KIMS hospital = 0.80

$Z_{\alpha} = 1.96$  for  $\alpha = 0.05$

d (precision) = 10% of the prevalence = 0.08

$$N = \{(1.96)^2 \times 0.8 \times 0.2\} / (0.08)^2 = 96 \sim 100$$

Sample size was also comparable based on several similar studies.<sup>20</sup>

### Period of Study

From Sept 1 2008 to Feb 2009

### Study Design

Prospective, observational study.

### Setting

Department of General Medicine at Kerala Institute of Medical Sciences, Thiruvananthapuram

### Inclusion Criteria

1. Patients aged  $\geq 18$
2. Either sex
3. Suspected case of metabolic acidosis with a SBE of  $< -2.5$

### Exclusion Criteria

1. Those with incomplete data.
2. Patients with primary respiratory components (Respiratory acidosis and alkalosis)

### Study Variables

Patients who were included in the study had the following variables included:

1. Age
2. Sex
3. Reason for admission
4. Hemoglobin (Hb)
5. Acid base variables – pH, pCO<sub>2</sub>, HCO<sub>3</sub>, SBE
6. Renal function tests BUN, S.Cr
7. Serum electrolytes – Na, K, Cl, Mg, Ca, Phos
8. Serum Albumin
9. Serum Lactic acid (Fluoride)

### Outcome Variables

1. Corrected serum anion gap for albumin
2. Corrected serum anion gap for albumin, lactate and phosphate
3. SID apparent (SIDa) and effective (SIDE)
4. Strong ion gap (SIG)
5. APACHE score

### Measurements and Calculations

On admission, demographic data (age, gender) were recorded. Acute Physiology and Chronic Health Evaluation (APACHE) II score and predicted mortality rate 28, 29 were calculated on admission. All samples were analyzed in the hospital's main laboratory (cobas® 6000 analyzer series; Roche Diagnostics Limited, Roche Diagnostics GmbH, Mannheim, Germany). Serum samples were collected in a serum separator tube and sent to the central laboratory for processing.

Blood gas samples were collected in a heparin syringe and arterial blood gas analyzed. Blood gas analysis included pH, partial arterial CO<sub>2</sub> tension, base deficit (SBE) and standard bicarbonate value (SB). Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> were measured in the laboratory with the use of an indirect ion-selective electrode technique. Albumin was measured with a bromocresol dye colorimetric technique, Mg<sup>2+</sup> by a chlorophosphonazo method, phosphate by a phosphomolybdate complex colorimetric technique, and Ca<sup>2+</sup> by an ortho-cresolphthalein complex method. Lactate was measured with lactate oxidase peroxidase (LOPOD) complex.

The subjects were studied in three parts: first part comprised of comparisons of mean of the metabolic variables between survivors and non-survivors, by independent-samples 't' test assuming unequal variances. Also correlations between various metabolic parameters (AG, BE and SIG) within the group was studied.

## RESULTS

One hundred and forty (140) patients were included. Their epidemiologic, clinical, and outcome variables are

shown in the Table 1. Most of the patients were admitted to ICU directly from the emergency room and a few were admission in ICU from the wards/rooms (inpatients).

We were able to demonstrate a significant correlation between survival and albumin levels Table 2. In our study we had found that hypoalbuminemia (serum albumin <3.5 g/dl) were present in 110/140 (78.6%) of all patients and 24/26 (92.3%) of those who had died. Hypoalbuminemia as a predictor of mortality with a RR of 3.3 (95% CI, 1.19 – 13.0), PPV 21.8%, NPV 93.3%.

The Arterial acid base variables in the present study is shown in Table 3 among the measured and the derived variable serum albumin was  $3.0 \pm 0.6$ g/dl & derived variables SIG was  $12.2 \pm 7.4$ .

**Table 2: Correlations between albumin and survival**

Correlations	Albumin (g/dl)	Survival
Albumin (g/dl)		
Pearson correlation	1	0.231**
Sig. (2-tailed)		0.006
Sum of squares and cross-products	50.661	7.576
Covariance	0.364	0.055
N	140	140
Survival		
Pearson correlation	0.231**	1
Sig. (2-tailed)	0.006	
Sum of squares and cross-products	7.576	21.171
Covariance	0.055	0.152
N	140	140

\*\* . Correlation is significant at the 0.01 level (2-tailed)

**Table 3: Arterial acid base variables**

	Normal (our lab)	All cases (n=140)
Measured variables		
Na <sup>+</sup> , meq/L	136-145	132±9
K <sup>+</sup> , meq/L	3.5-5.1	4.2±1.0
Ca <sup>2+</sup> , mg/dL	8.8-10.2	8.2±1.1
Mg <sup>2+</sup> , mg/dL	1.7-2.55	2.1±0.5
Cl <sup>-</sup> , mmol/L	98-107	98±8.6
Pi <sup>-</sup> , mmol/L	2.7-4.5	3.7±2.2
Albumin, g/dL	3.5-5.2	3.0±0.6
pH	7.35-7.45	7.33±0.1
pCO <sub>2</sub> , mmHg	35-45	27.8±9.5
Lactate, mmol/L	0-2	4.07±3.1
Derived variables, mmol/L		
HCO <sub>3</sub> <sup>-</sup>	22-28	15.8±5
AG <sub>observed</sub>	12-17	22.2±7.6
AG <sub>corrected</sub>	12-17	24.6±7.5
BE	-2 to+2	-9.2±5.1
BE <sub>ua</sub> (FencI-Stewart)	-2 to+2	-9.4±8.0
SID <sub>apparent</sub>	40±2	37.7±6
SIG	2±2	12.2±7.4

The characteristics of patients presented according to outcome in the present study are shown in Table 4 among the measured and the derived variable among survivors and non survivors. Lactate levels were low  $3.7 \pm 2.8$  in survivors and  $5.6 \pm 4$  among non survivors which was statistically not significant. However among the derived variable APACHE score II was  $14.6 \pm 5.9$  among survivors and  $45 \pm 16.8$  among non survivors.

Table 5 shows the measured and derived variables according to hyperlactatemia serum creatinine among the hyperlactatemia was  $2.4 \pm 2.7$  and SIG was  $11 \pm 6.5$ .

Table 6 and Figure 1-6 shows the characteristics of Hyperlactatemia patients (serum lactate >2mmol/L) were present in 105 patients (75%). Hyperlactatemia was severe (serum lactate >5 mmol/L) in 36 patients (25%). Hypoalbuminemia was present in 101 patients (72%). One-hundred thirty patients (92.8%) had low serum bicarbonate level. With Stewart method metabolic acid base alterations were detected in 125 patients (89%). Of which 109 patients (78%) were cases of metabolic acidosis

**Table 4: Characteristics of patients presented according to outcome**

	Survivors (n=114)	Non-survivors (n=26)	P value
Measured variables			
Age	54.8±17.3	56.5±17.6	0.64
Hb (g/dl)	11.6±2.4	11.2±3.6	0.59
PCV (%)	37±8	36±15	0.83
Total count (in 1000's)	13±6	17±10	0.04
Na <sup>+</sup> , meq/L	133±8.3	129±11.4	0.10
K <sup>+</sup> , meq/L	4.3±1.1	4.1±0.9	0.52
Ca <sup>2+</sup> , mg/dL	8.2±1.1	8.1±0.9	0.65
Mg <sup>2+</sup> , mg/dL	1.8±0.3	1.7±0.5	0.75
Cl <sup>-</sup> , mmol/L	99.2±8	96.3±11	0.22
Pi <sup>-</sup> , mmol/L	3.5±1.6	4.9±3.6	0.003
Albumin, g/dL	31.3±6	27.8±6	0.01
pH	7.34±0.10	7.28±0.13	0.03
pCO <sub>2</sub> , mmHg	27.3±7.8	30±14.6	0.37
Lactate, mmol/L	3.7±2.8	5.6±4	0.03
S.Creatinine, mg/dL	2±1.9	4.6±13	0.33
Derived variables,			
HCO <sub>3</sub> <sup>-</sup>	16±4.3	14.7±6.2	0.33
AG <sub>observed</sub>	22.1±6.6	22.1±10	1.0
AG <sub>corrected</sub>	24.3±6.3	25.2±10.4	0.67
AG <sub>corrected (Lact&amp;alb)</sub>	22.9±7.2	19.6±8.5	0.07
BE	-8.6±4.6	-11.4±6.4	0.05
BE <sub>ua</sub> (FencI-Stewart)	-8.9±6.9	-11.6±11.3	0.25
SID <sub>apparent</sub>	38.3±5.8	35±6.5	0.02
SID <sub>effective</sub>	25.7±5	24.6±6.7	0.45
SIG	12.6±6.9	10.4±9.1	0.25
SBENa	-2.05±2.5	-3.2±3.4	0.10
SBECI	-2.3±5	-2.4±6.5	0.95
SBEalb	30.6±13.1	38.2±14	0.01
SBEIact	-2.7±2.8	-4.6±4	0.02
SBEsig	-32±12.8	-39.4±16	0.04
APACHE score II	14.6±5.9	23.2±5.2	0.000
Predicted Mortality	22.8±13.9	45±16.8	0.000

detected by low SID. However, 109 (78%) of these patients had increased anion gap and 124 (88.5%) had increased albumin corrected anion gap. Consequently the use of albumin corrected anion gap among critically ill patients permitted the additional diagnosis of 15 patients with metabolic acidosis. SIG and albumin corrected AG strongly correlated and showed narrow 95% limits of agreement (0.77-0.95) in critically ill patients. The mean duration of stay  $5.0 \pm 2.8$  days.

Among the non-survivors, 78.1% (8/26) of the deaths were attributed by base deficit due to unmeasured anions.

Among the non-survivors, 42.3% (11/26) of the deaths were attributed by hyperlactatemia (serum lactate  $> 5$  mEq/L).

## DISCUSSION

One-hundred forty patients were included in our prospective observational study. On the basis of the mechanism of metabolic acidosis, we categorized them into hyperlactatemia/lactic acidosis (Serum lactate  $> 2.5$  meq/l), SIG acidosis ( $>5$  meq/l), and hyperchloremic acidosis (as an entity which may not be explained by lactic acidosis or SIG acidosis).<sup>21,22</sup>

The physicochemical approach described by Stewart provides an accurate way of quantifying metabolic acidosis. There is a strong correlation between the SIG, the albumin- and lactate corrected anion gap.<sup>23</sup> In our study we also demonstrated a strong correlation. Lactic acidosis and high SIG has been shown to be associated with adverse outcomes.<sup>24-26</sup>

In our study, we noticed that 60.5% of survivors and 77% of non-survivors had an increased lactic acid level of  $>2.5$  meq/l, and 89% of survivors and 77% of non survivors had SIG acidosis. Probably these results reflect the on-admission levels which no doubt will be elevated, albeit, there were no serial levels for comparison.<sup>27</sup>

Anion gap or the albumin corrected anion gap was insensitive in detecting hyperlactatemia  $>2.5$  and ROC shows us that lower levels anion gap increases sensitivity in detecting hyperlactatemia.

Acute renal failure is defined as a creatinine value of  $>150\mu\text{mol/L}$ .<sup>28,29</sup> Our study had a total of 56 patients who had their serum creatinine levels above  $150\mu\text{mol/L}$ . Out of the 26 patients who died, the majority of the cause of death was attributed by Sepsis (38.6%), followed by gastrointestinal (35%) (Mostly chronic liver disease).

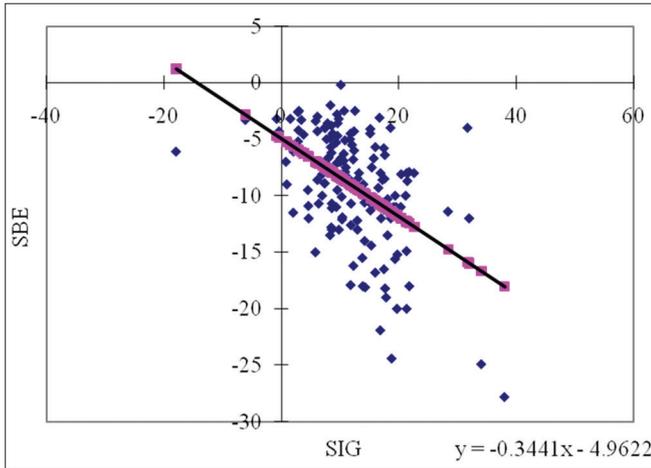
**Table 5: Characteristics of patients presented according to hyperlactatemia ( $>5\text{mmol/L}$ )**

	Lactate level $>5$ mmol/L (n=38)
Measured variables	
Age	59±14
Na <sup>+</sup> , meq/L	132±9.9
K <sup>+</sup> , meq/L	4.6±1.2
Mg <sup>2+</sup> , mg/dL	1.7±0.4
Cl <sup>-</sup> , mmol/L	97.8±9.4
Albumin, g/L	4.4±2.5
pH	7.27±0.12
pCO <sub>2</sub> , mmHg	28.5±12.4
Lactate, mmol/L	8.2±2.9
Serum Creatinine, mg/dL	2.4±2.7
Derived variables,	
HCO <sub>3</sub> <sup>-</sup>	14.3±5
AG <sub>observed</sub>	24.6±7
AG <sub>corrected</sub>	27.3±6.7
AG <sub>corrected (Lact&amp;alb)</sub>	20±7.3
BE	-11.5±5.4
BE <sub>ua</sub> (FencI-Stewart)	
SID <sub>apparent</sub>	34.4±5.5
SID <sub>effective</sub>	23.5±5.4
SIG	11±6.5
SBENa	-2.3±2.9
SBEcl	-1.5±5.1
SBEalb	34.7±14.8
SBEact	-7.2±2.9
SBEsig	-35±15
APACHE score II	19.6±7.2
Predicted Mortality	35.3±20

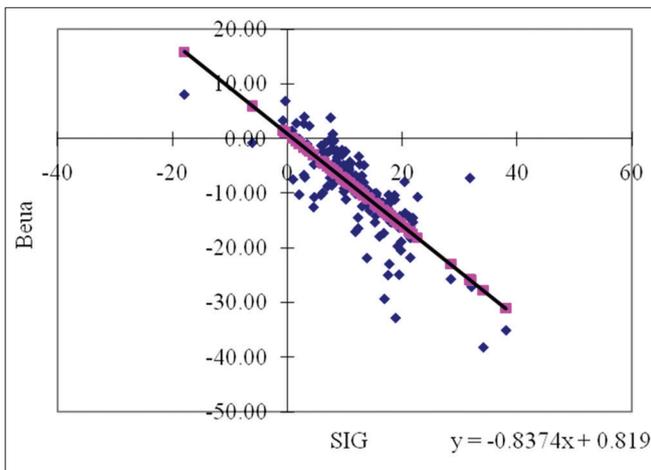
**Table 6: Correlation and logistic regression analysis for lactate**

	Pearsons correlation	P value	Area under ROC curve (95%CI)	P value
SBE	-0.328	0.000	0.682 (0.57-0.78)	0.001
BE <sub>ua</sub>	-0.321	0.000	0.676 (0.58-0.77)	0.001
AG <sub>observed</sub>	0.244	0.004	0.360 (0.25-0.46)	0.011
AG <sub>alb</sub>	0.282	0.001	0.329 (0.22-0.43)	0.002
AG <sub>AL</sub>	0.237	0.005	0.639 (0.53-0.74)	0.012
SID <sub>a</sub>	-0.408	0.000	0.737 (0.64-0.83)	0.000
SID <sub>e</sub>	-0.250	0.003	0.664 (0.55-0.76)	0.003
VanSlyke's Eq	-0.288	0.001	0.672 (0.56-0.77)	0.002
Wooten's Eq	-0.262	0.002	0.652 (0.54-0.76)	0.006

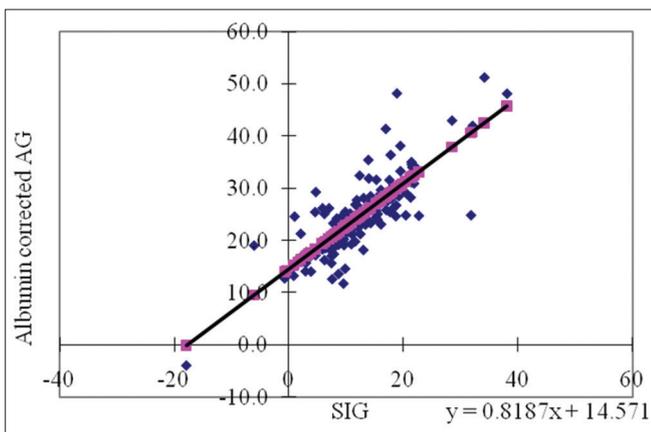
ROC, receiver operating characteristic; CI, confidence interval; SBE standard base excess; BE<sub>ua</sub>, base excess caused by unmeasured anions; AG<sub>alb</sub>, anion gap corrected for albumin; AG<sub>AL</sub>, AG corrected for albumin and lactate; SID<sub>e</sub>, strong ion difference effective; SID<sub>a</sub>, strong ion difference apparent



**Figure 1:** Regression analysis between SIG (mmol/L) and BE (mmol/L)

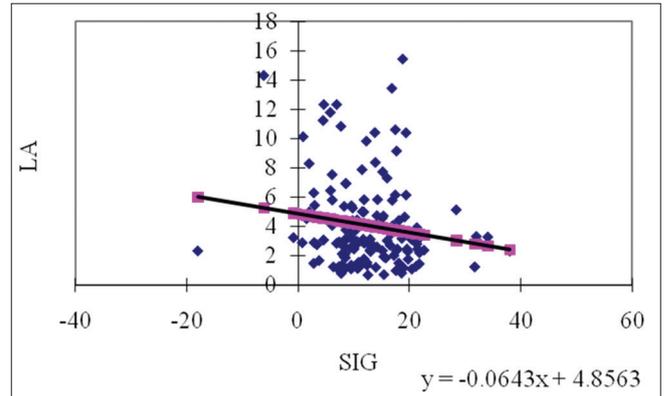


**Figure 2:** Regression analysis between SIG (mmol/L) and BEua (mmol/L)

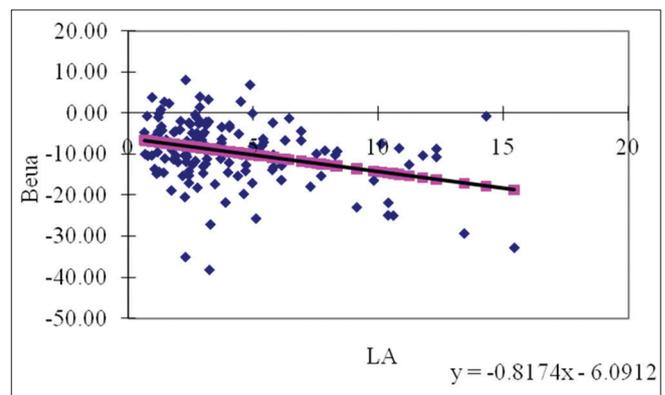


**Figure 3:** Regression analysis between albumin corrected anion gap (mmol/L) and SIG (mmol/L)

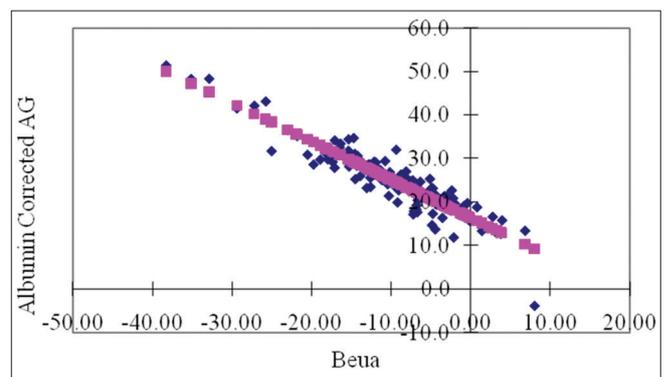
In a study among patients admitted in the ICU with acute asthmaticus, those who had lower arterial pH within 24 h of hospital admission were associated with increased mortality.<sup>30</sup>



**Figure 4:** Regression analysis between Lactic acid (mmol/L) and SIG (mmol/L)



**Figure 5:** Regression between BEua (FencI-Stewart method) and Lactic acid



**Figure 6:** Regression between albumin corrected AG and BEua

Whereas several other studies had demonstrated that delay of academia recovery as opposed to initial pH value was associated with increased mortality in the ICU.<sup>31,32</sup> In our study, we were able to demonstrate that pH was able to predict the risk of death with a RR of 2.94 (CI, 1.14-7.59). In our study we had found that hypoalbuminemia (serum albumin <3.5 g/dl) were present in 101/140 (72%) of all patients and 24/26 (92.3%) of those who had died. Hypoalbuminemia as a predictor of mortality with a RR of 4.8 (95% CI, 1.02 – 23.1), PPV 21.8%, NPV 93.3%.

Length of stay in hospital and in ICU did not differ significantly between the different groups of metabolic acidosis. Hyperlactatemia (serum lactate >2mmol/L) were present in 105 patients (75%). Hyperlactatemia was severe (serum lactate >5 mmol/L) in 36 patients (25%). One-hundred thirty patients (92.8%) had low serum bicarbonate level. With Stewart method metabolic acid base alterations were detected in 125 patients (89%). Of which 109 patients (78%) were cases of metabolic acidosis detected by low SID. However, 109 (78%) of these patients had increased anion gap and 124 (88.5%) had increased albumin corrected anion gap. Consequently the use of albumin corrected anion gap among<sup>32</sup> critically ill patients permitted the additional diagnosis of 15 patients with metabolic acidosis. SIG and albumin corrected AG strongly correlated and showed narrow 95% limits of agreement (0.77-0.95) in critically ill patients. The mean duration of stay  $5.0 \pm 2.8$  days. Among the non-survivors, 15.4% (4/26) of the deaths were attributed by hyperchloremia (Cl > 110 meq/L).

### Strengths of our Study

- Studies pertaining to this type of acid base analysis is meager in India and we hope this could be a refresher for all clinicians.
- Understanding of complex acid-base disturbances and their mechanisms will lead to more targeted treatments of acid-base and electrolyte disorders especially in ICU/critically ill patients.

### Limitations

Our study had a few limitations

- Serial lactate measurements would have let us to evaluate the prognostic value and access its risk of mortality.

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**Authors Contribution:**

**AKN and PAJ-** Concept, collected data and design of the study, reviewed the literature, manuscript preparation and critical revision of the manuscript; **MT and SB-** Conceptualized study, literature search, interpreted and review of study.

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