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Research Article

Relationship of Hospital Mortality with Metabolic Acidosis Severity in Critically Ill Patients

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ABSTRACT

Background: Metabolic acidosis (MA) is a common pathologic process with fatal consequences in critically ill (CI) patients. The more the severity of acidosis the more mortality rate is expected. To evaluate the relationship of hospital mortality with MA severity in CI patients admitted to emergency department (ED).

Methods: In this prospective cohort study, we enrolled CI patients (based on physician clinical assumption), most at level 1 or 2 emergency severity index triage system. Patients were followed and evaluated in 2 parallel groups, one with and the other without MA. The severity of acidosis, chief complaints, final diagnosis, demographic data, acute physiologic assessment and chronic health evaluation II (APACHE II) score, serum lactate and bicarbonate level, need for intubation and mechanical ventilation, admission ward, hospital length of stay and in hospital mortality were compared between the 2 groups.

Results: A total of 1811 CI patients including 60.2% males and 39.8% females with and without MA were evaluated. The most common age range was 65-55 years old (31.7%) with the mean±SD of 61.34±8.23. The most common complaints and diagnoses were weakness (40.5%) and pneumosepsis (35.1%), respectively. Patients with severe acidosis had higher lactate level and APACHE II score ($p<0.05$). Mortality rate was 10.4%. Most of our cases had severe MA. Expired cases had higher lactate level and APACHE II score ($p<0.05$).

Conclusion: Lactate level, bicarbonate level and APACHE II score were all significant independent predictors of hospital mortality in CI patients.

Introduction

Metabolic acidosis (MA) is a pathologic process in which the hydrogen ion concentration in blood increases in the meantime bicarbonate (HCO3) level may decrease. Acidemia is when the blood potential of hydrogen (PH) reaches below 7.35 [1]. MA especially lactic acidosis and tissue hypoxia can happen concomitantly and endanger the outcome in critically ill (CI) patients. CI is called when the patient has one or more organ system failure so that the probability of deterioration and life-threatening consequences are formidable yet inevitable [2-3]. MA is a common finding in CI patients admitted to intensive care unit (ICU) and its severity is associated with higher mortality rate (twice as likely to die as patients without MA) [4-7]. It is shown that lactate level in this group of patients can be a strong independent predictor of mortality [6].

Approximately, 80% of patients admitted to ICU remain in the acute event briefly and survive finally. In contrast, some cases do not have the same disease course

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and they recover slowly. These chronically CI patients comprise 5-10% of ICU admitted cases [8]. Having an artificial airway support and being ventilated mechanically for quite a long period of time define chronically CI (8). ICU mortality rate depends exactly on the severity of illness. Up to 40% of CI patients are reported to die in ICU despite intensive care medicine [9].

Nowadays, because of overcrowding and not having enough admission beds in ICUs, more and more CI patients are being admitted and managed to emergency department (ED)s. ED boarding makes ED physicians and nurses to be trained to appropriately care and timely manage such group of patients in an overcrowded environment with many distractions but few resources. In the present study, we decided to assess the relationship of hospital mortality with MA severity in CI patients admitted to ED. Knowing the main determinants of outcome in CI patient population would help us to predict the real prognosis and also apply the best approach towards their disease course right from the very first moment of admission in ED.

Methods

In this prospective cohort study, all CI patients (based on the mentioned definition and objective estimation of the physician), who were admitted to ED of Dr. Shariati hospital were enrolled in our study from 2020-2021. The study was approved by the Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICINE.REC.1397.181). The privacy of data was maintained according to the Helsinki Declaration of biomedical ethics. Informed written consent was taken from patients or their guardian before enrolment.

Patients were evaluated in 2 parallel groups one with MA and the other without MA. Patients in both groups were followed and their ultimate outcome recorded. All data were evaluated and registered by the third-grade emergency physician in a predesigned checklist. Enrollment was by convenient sampling. Exclusion criteria were: respiratory acidosis component, unwilling to participate in our study, referral cases being managed in other centers before admission to our ED and discharge against medical advice.

Demographic data, chief complaint, final diagnosis, bicarbonate or vasopressor administration, the disease severity based on Acute Physiology and Chronic Health Evaluation II (APACHE II) score, blood lactate level, admission ward after ED (hospital ward or ICU), need for intubation and mechanical ventilation, discharge and mortality rates, vital signs, venous blood gas parameters and severity of MA (mild: 7.2<PH<7.3-moderate:7.1<PH<7.2-severe: PH<7.1) (mild: 13<HCO3<15- moderate:10<HCO3<13-severe: HCO3<10 mmol/L) were all recorded and compared between the 2 groups. Moderate to severe hyperlactatemia was considered to be 3-5 mmol/L.

Primary and secondary endpoints

Our primary outcome was to define the relationship of hospital mortality with acidosis severity in CI patients. Our secondary outcomes were assessment of other study variables with acidosis severity.

Statistical analysis and sample size calculation

Based on Gunnerson et al study [6], the mean mortality was considered 25% in nonacidotic cases and 35% in different classes of acidotic cases (the ratio of acidotic group with 3 subclasses to nonacidotic group was 3 to 1). With power 90% and accuracy 95%, we estimated a sample size of at least 309 cases in nonacidotic group and a sample size of 927 cases in acidotic group. By Bonferroni correction (error=0.01), the sample size was calculated to be 434 and 1302 in each group respectively. After gathering all data, they were inserted into SPSS (ver. 25.0) and Stata (ver. 15.0) software. Data were assessed for normal distribution using a Kolmogorov-Smirnov test. The descriptive indices such as frequency (percentage) and mean (standard deviation (SD)) were used to express the results. Chi-square test, independent t-test or nonparametric tests were used as required. A logistic regression model was used to identify independent predictors of mortality. The level of significance was 0.05.

Results

In this study, 87 cases were initially excluded based on the exclusion criteria while 1811 CI patients were enrolled. Most patients were males (1091 cases (60.2%)). Age had a mean±SD of 61.34±8.23 years (most between 55 to 65 years old (31.7%)). The most common chief complaints were: fatigue (40.5%), dyspnea (13.9%) and fever (13.9%). The most common final diagnosis were: pneaumosepsis (35.1%), urosepsis (17.0%) and diabetic ketoacidosis (9.7%). Length of hospital stay was 7.93±1.25 days (most between 5 to 10 days (59.5%)). Cases with severe MA had significantly longer hospital stay in comparison to other groups (p=0.0001).

Among all patients, 1239 cases (68.4%) had MA (91 (5.0%) mild, 364 (20.0%) moderate and 784 (43.4%) severe MA) and 572 cases (31.6%) had no MA.

Potential of hydrogen (PH) showed acidosis (lactic acidosis) in most cases with a mean±SD of 7.16±0.19. More than half of cases had normal blood bicarbonate level (59.5%) with a mean±SD of 18.28±7.01 mmol/L. Most cases had increased blood lactate level (78.7%) with a mean±SD of 5.04±1.12 mmol/L. APACHE II score showed a mean±SD of 24.72±5.17. All these variables were significantly different in cases with severe acidosis in comparison to other groups (p=0.0001).

Vasopressor and bicarbonate administration rates were significantly higher in severe acidosis (p=0.0001).

As expected, APACHE II score was significantly higher in severe acidosis cases (p=0.0001). in general, most cases in this study were admitted in hospital wards including ED (81.1%). Need for intubation and mechanical ventilation were higher in severe acidosis group (p=0.0001). Data is shown in detail in (Table 1).

Comparison of main studied variables to mortality rate is shown in (Table 2). Mortality rate (10.4%) was significantly higher in severe acidosis cases (p=0.0001). Age and gender showed no statistically significant differences between expired and survived groups. Hospital length of stay and lactate level were significantly higher in the expired group (p=0.003 and 0.0001 respectively). PH and bicarbonate level were significantly lower in the expired group (both p=0.0001). Patients in both expired and survived groups suffered from more severe MA and most of expired cases had severe acidosis (p=0.0001). APACHE II score was significantly higher in the expired group (p=0.004). Most expired cases were admitted in ICU rather than hospital wards (p=0.0001). Need for intubation and mechanical ventilation was the same in both groups (p=0.073).

Logistic regression analysis revealed that lactate level, bicarbonate level and APACHE II score were all significant independent predictors of mortality. Data is shown in (Table 3).

Table 1- Basic data comparison of study variables in patients with and without metabolic acidosis

Variable		No metabolic acidosis	Metabolic acidosis severity			Total	P value
			Mild	Moderate	Severe		
Age (year) Mean±SD		21.9±54.62	5.12±58.23	60.73±6.22	10.25±59.5	8.23±61.34	0.071
Gender N (%)	Male	286 (26.3%)	63 (5.8%)	217 (19.9%)	525 (48.1%)	1091 (100%)	0.0001
	Female	286 (39.8%)	28 (3.9%)	147 (20.4%)	259 (35.9%)	720 (100%)	
Hospital length of stay (day) Mean±SD		5.86±3.04	6.09±1.94	8.34±1.68	10.12±2.52	7.93±1.25	0.0001
Venous blood gas analysis	Potential of hydrogen	7.30±2.74	7.23±1.64	7.15±0.32	7.02±0.85	7.16±0.19	0.0001
	Partial pressure of carbon dioxide(mmHg)	48.11±0.65	34.02±2.62	29.19±3.41	27.22±1.34	29.43±3.14	
	Partial pressure of oxygen (mmHg)	44.61±1.42	35.08±1.24	37.12±0.82	32.23±3.03	44.22±5.12	
Bicarbonate level (mmol/L)		22.42±3.02	13.51±2.50	10.38±1.04	8.07±0.95	18.28±7.01	0.0001
Lactate level (mmol/L)		2.02±1.13	3.33±1.07	4.72±0.83	6.46±2.09	5.04±1.12	0.0001
Vasopressor administration N (%)		26 (3.2%)	22 (2.7%)	195 (24.0%)	567 (70.1%)	810 (100%)	0.0001
Bicarbonate administration N (%)		0 (0%)	28 (2.4%)	357 (30.5%)	784 (67.1%)	1169 (100%)	0.0001
APACHE II score Mean±SD		21.13±0.54	24.40±8.24	26.11±8.01	28.61±1.05	24.72±5.17	0.0001
Admission ward N (%)	Hospital ward	569 (38.7%)	242 (16.4%)	309 (21.0%)	350 (23.9%)	1470 (100%)	0.0001
	Intensive or cardiac care unit	3 (0.8%)	51 (14.9%)	118 (34.6%)	169 (49.7%)	341 (100%)	
Need for intubation and mechanical ventilation N (%)		21 (4.5%)	21 (4.5%)	77 (16.7%)	343 (74.2%)	462 (100%)	0.0001
Mortality rate N (%)		14 (7.4%)	14 (7.4%)	21 (11.1%)	140 (74.1%)	189 (100%)	0.0001

Table 2- Basic data comparison of study variables in survivor vs non-survivor patients

Variable		Survivors	Non-survivors	P value
Age (year) Mean±SD		10.03±59.72	61.65±5.21	0.141
Gender N (%)	Male	978 (89.6%)	113 (10.4%)	0.054
	Female	644 (89.4%)	76 (10.6%)	
Hospital length of stay (day) Mean±SD		4.35±2.04	8.49±1.36	0.003
Venous blood gas analysis	Potential of hydrogen	7.36±0.35	6.97±0.14	0.0001
	Partial pressure of carbon dioxide(mmHg)	43.01±1.25	32.41±5.26	
	Partial pressure of oxygen (mmHg)	54.09±1.44	47.02±3.16	
Metabolic acidosis severity N (%)	Mild	77 (84.6%)	14 (15.4%)	0.0001
	Moderate	343 (94.2%)	21 (5.8%)	
	Severe	644 (82.1%)	140 (17.9%)	

Bicarbonate level (mmol/L)		21.02±3.19	9.72±2.75	0.0001
Lactate level (mmol/L)		3.92±1.13	6.94±1.10	0.0001
Vasopressor administration N (%)		627 (77.4%)	183 (22.6%)	0.0001
Bicarbonate administration N (%)		980 (83.8%)	189 (16.2%)	0.0001
APACHE II score Mean±SD		25.13±2.54	29.37±2.19	0.004
Admission ward N (%)	Hospital ward	1459 (99.2%)	11 (0.8%)	0.0001
	Intensive or cardiac care unit	163 (47.9%)	178 (52.1%)	
Need for intubation and mechanical ventilation N (%)		273 (59.0%)	189 (41.0%)	0.073

Table 3- Independent predictors of mortality using logistic regression

Variable	Value(Mean±SD)	Odds ratio	95% CI	P value
Lactate level (mmol/L)	5.04±1.12	1.04	0.89 1.28	0.003
Bicarbonate level (mmol/L)	18.28±7.01	0.58	0.21 0.85	0.001
APACHE II score (mmol/L)	24.72±5.17	1.11	1.03 1.24	0.008

Discussion

In this study, we found that lactate level, bicarbonate level and APACHE II score were all significant independent predictors of mortality. In this referral center, most of our CI patients had severe MA. The estimated 10.4% mortality rate, was significantly higher in cases with severe MA (p=0.0001).

In a systematic review by Vincent et al in 2016, the outcome of CI patients was assessed based on serial blood lactate level check. Their review resulted in an important observation which was a better outcome in almost all groups of patients in relation to decreasing lactate concentration [10]. Our study supports the value of blood lactate level in CI patients. Baseline lactate level was significantly higher in the expired group (p=0.0001).

Gao et al in 2019, stated that cirrhotic CI patients had a high mortality rate and a poor outcome because of having severe MA. Lactic acidosis had the worst prognosis in all MA types [11].

In hospital mortality of pneumonia was evaluated in Demirel et al study in 2018. In their study, mortality rate was 21.8% and lactate level was 3.53 ± 3.59. Its best cutoff point of predicting mortality was 3.35 mmol/mm3. They finally recommended that lactate level could be used as risk stratification in this group of patients in ED [12]. Our study used baseline lactate level and showed the same result in all CI patients in ED.

Allyn et al in 2016, studied 77 cases with severe MA (PH<7) in ICU. Mortality rate was 67.5%. Mortality rate was 100% in cases who experienced cardiac arrest [13]. In our study, mortality rate in severe MA group was 17.9% which was definitely the highest mortality rate between all groups. Our ED is a tertiary referral center with a very high admission rate of cases with malignancy and immunocompromise.

In a retrospective observational study by Haas et al in 2016, lactate clearance and mortality were evaluated in CI cases admitted in ICU. It was determined that severe hyperlactatemia (lactate >10 mmol/L) was associated with 78.2% mortality rate. The most common diagnosis among this population was sepsis following cardiogenic shock [14]. In the present study, we did not observe severe hyperlactatemia but the higher lactate level patient had the higher mortality rate was seen. The most common final diagnosis were pneaumosepsis, urosepsis and diabetic ketoacidosis.

Severe MA was related to higher mortality rate in our study. Boniatti et al in 2011, designed a prospective cohort study on ICU patients. Severe MA in this study was associated with higher mortality rate [15]. Also, Jung et al in 2011 found that 8% of CI patients in ICU had severe MA. Almost all patients needed mechanical ventilation and vasopressors during their ICU stay. They expressed that severe MA was associated with 57% mortality rate in ICU [16]. As it is obvious, our mortality rate in ED was lower in comparison to previous studies. This might be related to lower blood lactate level and lower severe hyperlactatemia our cases had.

The impact of bicarbonate administration in the outcome assessment of lactic acidosis was evaluated in some studies but they could not address any significant change in morbidity or mortality reduction [17-20]. bicarbonate administration did not show any benefits in terms of reducing mortality in our study. All expired cases received bicarbonate therapy.

Biradar et al in 2021, assessed outcome of CI patients with severe MA. They concluded that higher lactate level and stronger anion gap were associated with higher mortality rate. Admission APACHE II score was significantly higher in the expired vs survived group in their study (p<0.001) [21].

Liu et al in 2015 showed that APACHE II score might supply a powerful prognostic utility in mortality of sepsis. They suggested a best cutoff point of >15 for APACHE II in prediction of unfavorable outcome [22]. Our study emphasized the same result. Expired cases with severe MA in our study had significantly higher APACHE II score (p=0.004).

Limitations of the study

The most important limitation in our study was that it was performed in a single center giving services to CI patients with high malignancy and immunocompromise rate.

Conclusion

Most of our patients had severe MA. The more severe MA, the higher lactate level and APACHE II score they had. Significantly higher rates of mortality, vasopressor and bicarbonate administration and need for mechanical ventilation were observed in severe MA. Lactate level, bicarbonate level and APACHE II score were all significant independent predictors of hospital mortality in CI patients.

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