Original Article

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Anion Gap is a Predictor of Elevated Serum Lactate in Patients Diagnosed with Sepsis without Shock in the Emergency Department

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Abstract:

Objective: To determine whether high anion gap levels predict increased serum lactate >2 mmol/L, and to determine the best AG cut-off point for predicting serum lactate levels greater than 2 mmol/L and greater than 4 mmol/L.

Material and Methods: This is a retrospective study among patients with sepsis without shock admitted to the emergency department of a tertiary care, university hospital. Anion gap and serum lactate were collected. Patients' baseline characteristics and laboratory results were also incorporated to calculate the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score. Analysis of diagnostic accuracy and Receiver Operator Characteristics (ROC) was used to demonstrate the appropriate cut-off point of the anion gap for predicting serum lactate >2 mmol/L.

Results: The study included 236 patients. Anion gap >12 mmol/L had a sensitivity of 93.3% (95%CI 88.2-96.6%) and a specificity of 13.7% (95%CI 6.8-23.8%) for predicting serum lactate >2 mmol/L. There was poor discriminative performance of the anion gap to predict serum lactate >2 mmol/L (area under ROC is 0.65; 95%CI 0.58-0.72). In contrast, there was good discriminative performance of the anion gap to predict serum lactate >4 mmol/L (area under ROC 0.83; 95%CI 0.77-0.88). The optimal cut-off point was anion gap > 18 mmol/L, which was good for predicting serum lactate >4 mmol/L.

Conclusion: An anion gap >12 mmol/L is not suitable for assessing lactate >2 mmol/L; however, an anion gap >18 mmol/L can predict serum lactate >4 mmol/L in patients with sepsis who had mean arterial pressure (MAP) >65 mmHg.

Keywords: anion gap, sepsis, septic shock, serum lactate

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Introduction

Sepsis is a common condition and a major public health problem worldwide. The World Health Organization (WHO) defines sepsis as a life-threatening infection that results in organ dysfunction, causing disability and high mortality[1]. According to research by Rudd et al., in 2017[2], 48.9 million sepsis cases occurred worldwide, accounting for 19.7% of deaths. Sepsis is among the leading causes of patient death worldwide. The factors associated with mortality in sepsis patients are delayed diagnosis, delayed antibiotics, severe bloodstream infection, and septic shock[3–5].

The Third International Consensus definitions for sepsis and septic shock (Sepsis-3) define sepsis as a condition in which life-threatening organ dysfunction is caused by a dysregulated host response to infection. A Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of more than 2 points is used to diagnose the patient. Septic shock is defined as sepsis with circulatory disorders, with higher mortality rates. After enough fluid has been retrieved, the diagnosis is considered in patients who also require vasopressors to regulate their mean arterial pressure (MAP) at more than 65 mmHg with serum lactate levels greater than 2 mmol/L[3]. "Non-hypotensive sepsis with elevated serum lactate" is defined as lactate >4 mmol/L and systolic blood pressure (SBP) greater than 90 mm Hg[7–9]. Previous research indicates that non-hypotensive sepsis with elevated serum lactate, like septic shock, is associated with a significant death rate[7,8]. Because lactate is a result of anaerobic metabolism in organs that are ischemic from shock, serum lactate levels are useful in the diagnosis of septic shock, based on the above evidence[10].

Serum lactate levels rise during septic shock, resulting in acidosis and a higher anion gap. Anion gap (AG) is calculated by Na^+-[Cl^-+HCO_3^-], with a value greater than 12 mmol/L combined with metabolic acidosis. This condition is known as wide anion gap metabolic acidosis[11]. According to research by Ganesh et al.[12], a study of patients diagnosed with sepsis in an Intensive Care Unit (ICU) reported that the patients had higher anion gap metabolic acidosis than the other types of metabolic acidosis, with lactic acidosis being the most common.

Sepsis patients with lactate >2 mmol/L or >4 mmol/L are associated with high mortality[7,8,10], but difficult to diagnose because of their normal blood pressure. As a result, serum lactate testing is used to aid in the early stages of resuscitation. Although serum lactate is useful for sepsis treatment planning, most hospitals are unable to provide the test. From a survey of 20 hospitals in a large province, Chiang Mai, Thailand, only 5 hospitals were able to deliver serum lactate tests. For this reason, our study was focused on determining whether high anion gap levels can predict an increase in serum lactate >2 mmol/L. Furthermore, we were interested in determining the correlation of AG with serum lactate and mortality in sepsis patients with normal blood pressure. We expect our findings to be useful in decision-making in early resuscitation and to reduce the mortality rate.

Material and Methods

Study design

A retrospective analytical study was performed on patients admitted to the Emergency Department (ED) of Maharaj Nakorn Chiang Mai Hospital, which is a university, tertiary-care, 1400-bed hospital with an estimated 70,000 patients per month receiving healthcare services. About 40 patients per month are admitted to the ED. The protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University. Informed consent was waived by exemption review (Permission no. EME-2563-07410) because of the study's retrospective design.

This study collected information on patients admitted to the ED who were diagnosed with sepsis without shock between June 2019 and September 2020. The inclusion

criteria were patients older than 15 years of age diagnosed with sepsis using the Third International Consensus definition for sepsis (Sepsis-3), with an increased Sequential Organ Failure Assessment (SOFA) score of at least 2 points and a mean arterial pressure (MAP) of ≥65 mmHg. The exclusion criteria were patients referred from another hospital, outpatient treatment, and incomplete data.

Data collection

The patients were recruited using the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) referred for sepsis (include A41, R65, R57) from the hospital electronic medical records (EMR; provided by Digicard 2007® and SMI®, Chiang Mai, Thailand). The chart review was done by data collectors consisting of healthcare providers and technicians. We collected the data of baseline characteristics, including age, sex, comorbidities, source of infection, body temperature, pulse rate, respiration rate, blood pressure, oxygen level, and the Glasgow Coma Scale (GCS), all of which were recorded as hemodynamic parameters. The SOFA scores of all the patients were recorded using laboratory results (platelets, PaO_2, creatinine). In some patients without a PaO_2 value, PaO_2 was retrospectively estimated from O_2 saturation using the hemoglobin-oxygen ($Hb-O_2$) dissociation curve for SOFA score calculation. Other laboratory data were recorded, including sodium (Na^+), chloride (Cl^-), and bicarbonate (HCO_3). The anion gap was calculated using the formula $AG=Na^+-[Cl^-+HCO_3^-]$. Also documented were serum lactate and the patient's condition before discharge from the hospital. Following the sepsis protocol, all laboratory data, including serum lactate, as well as laboratory data utilizing estimated anion gap and SOFA score, were collected at the same time.

The primary endpoint used AG >12 mmol/L as a screening test for serum lactate >2 mmol/L in sepsis patients not in shock. The secondary endpoints were to determine the association between AG and lactate, and to determine the best AG cut-off point for predicting serum lactate levels greater than 2 mmol/L and greater than 4 mmol/L.

The estimating infinite population proportion formula[13] was used in this study to calculate the sample population. No previous study indicated the sensitivity of a wide anion gap (>12 mmol/L) to help diagnose the likelihood of serum lactate >2 mmol/L in sepsis patients without shock. We reviewed patients who were expected to be used in the study (pilot cases) to determine the sensitivity, and we computed sample sizes. Pilot cases were used in a sample of the 42 sepsis patients who were treated between February and April 2020. Patients with blood lactate >2 mmol/L and AG >12 mmol/L had a sensitivity of 93%. A sample size of 116 patients was calculated using the estimating infinite population proportion formula. Sepsis patients with serum lactate >2 mmol/L between June 2019 and September 2020 had a prevalence of 59%. A sample of 197 participants was required, with a 20% data loss allowance computed for 236 samples and an average length of at least 7 months.

Statistical analysis

Data analysis used descriptive statistics; the normally distributed numerical variables were presented as mean±S.D., and other numerical variables as median (interquartile range). Test characteristics (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) were analyzed. The area under the receiver operating characteristic (ROC) curve was analyzed to determine the appropriate cut-off point of AG for predicting serum lactate >2 mmol/L and serum lactate >4 mmol/L. Stata version 16 (Stata Corp LLC, College Station, TX, USA) was used for statistical analysis.

Results

Baseline characteristics

The study involved 236 sepsis patients; 137 were men (58%) with an average age of 71 years. Most patients had hypertension (57.2%), hyperlipidemia (36.7%), diabetes mellitus (27.1%), cardiovascular disease (27.1%), and chronic kidney disease (21.6%). The most prevalent site of infection was the respiratory tract, which accounted for 46% of all infections, followed by urinary tract infections (39%), and gastrointestinal infections (9%). The average SOFA score change was 3.89 (S.D. 1.77), the serum lactate level was 3.62 (S.D. 2.95), and the anion gap was 17.59 (S.D. 5.46). The average mean arterial pressure (MAP) was 91 mmHg. Most of the patients (85.2%) were alive when they were discharged from the hospital (Table 1).

Among the 236 patients enrolled, 163 patients with serum lactate >2 mmol/L had AG >12 mmol/L, a sensitivity of 93.3% (95% CI 88.2-96.6%), specificity of 13.7 (95% CI 6.8-23.8%), and PPV of 70.7% (95% CI 64.1-76.7%). NPV was 47.6% (95% CI 25.7-70.2%).

The area under the ROC curve for AG as a predictor of serum lactate >2 mmol/L was 0.65 (95% CI 0.58-0.73), indicating poor discrimination (Figure 1). We did not compute the best cut-off point of AG because the results showed a poor relationship between the anion gap and serum lactate >2 mmol/L. Whereas the area under the ROC curve for AG as a predictor of serum lactate >4 mmol/L was 0.82 (95% CI 0.77-0.88), indicating good discrimination (Figure 2), and the best cut-off point of AG was >18 mmol/L to predict serum lactate >4 mmol/L calculated by the Youden

Table 1 Baseline characteristics (n=236)

Variables	N (%)
Male	137 (58.05)
Age: years*	71.24 (16.21)
Comorbidities	
Hypertension	135 (57.20)
Hyperlipidemia	87 (36.86)
Diabetes mellitus	64 (27.12)
Cardiovascular disease	64 (27.12)
Chronic kidney disease	51 (21.61)
Cancer	38 (16.10)
Others (COPD, HIV, Gout, DLP, BPH, CVA, Parkinson, Dementia, AF)*	104 (44.07)
Source of infection	
Respiratory tract	109 (46.19)
Urinary tract	91 (38.56)
Gastrointestinal tract	21 (8.90)
Hepatocellular	6 (2.54)
Skin	10 (4.24)
Others	37 (15.68)
Delta SOFA score*	3.89 (1.77)
MAP initial at ED visit*	91.25 (19.20)
MAP before admission*	88.17 (13.44)
Lactate*	3.62 (2.95)
Anion Gap*	17.59 (5.46)
Status before discharge	
Alive	201 (85.17)

*Mean (S.D.), ED=emergency department, MAP=mean arterial pressure, SOFA=sequential (sepsis-related) organ failure assessment score, COPD=chronic obstructive pulmonary disease, HIV=human immunodeficiency virus, DLP=Dyslipidemia, BPH=benign prostatic hyperplasia, CVA=cerebrovascular accident, AF=atrial fibrillation.

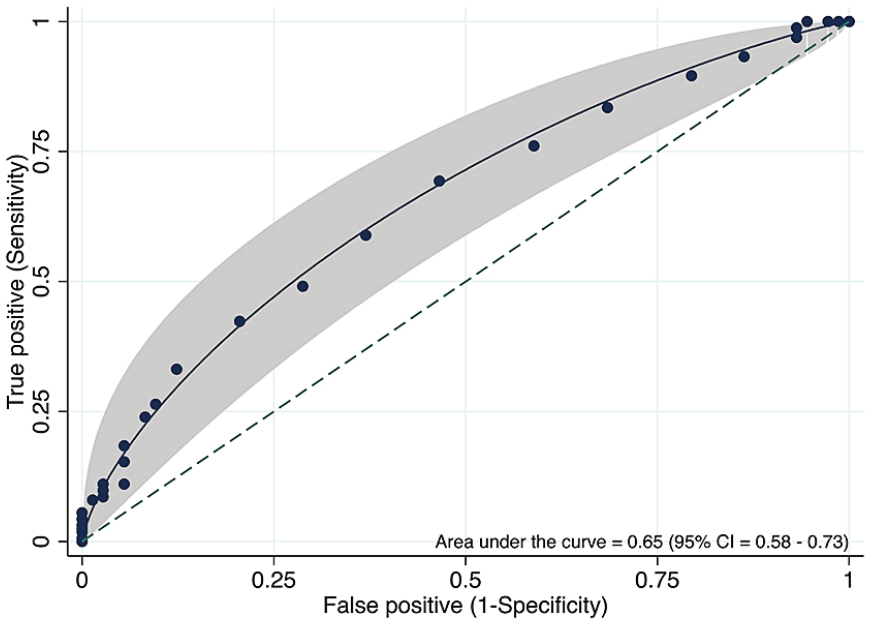

Figure 1 Parametric ROC curve analysis of anion gap to predict serum lactate >2 mmol/L

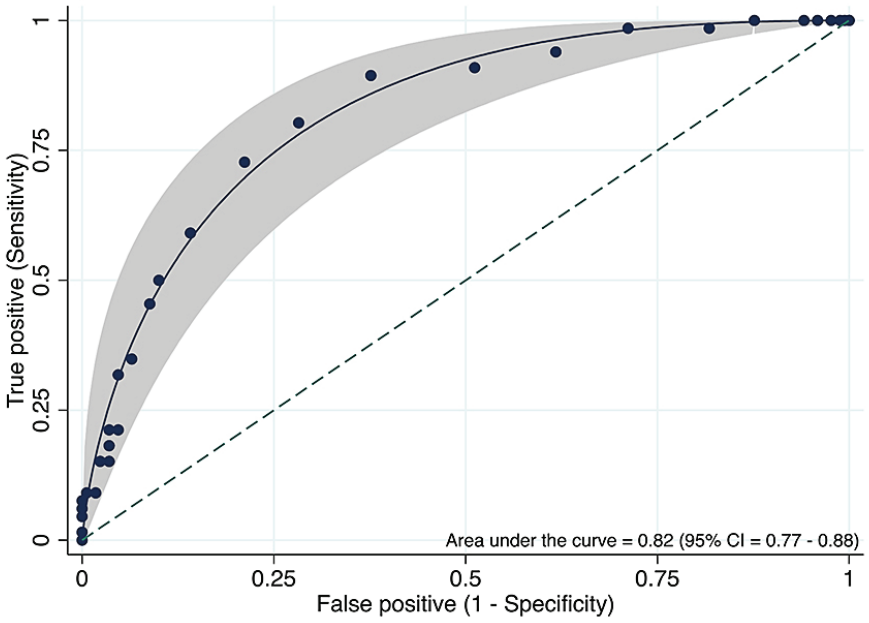

Figure 2 Parametric ROC curve analysis of anion gap to predict serum lactate >4 mmol/L

Index. AG >18 mmol/L was obtained with a sensitivity of 80.3% (95%CI 68.7-89.1%), specificity of 71.8% (95% CI 64.4-78.4%), PPV was 52.5% (95% CI 42.3-62.5%), NPV was 90.4% (95% CI 84.1-94.8%), and area under the ROC curve for this cut-off point was 0.76 (95%CI 0.70-0.82), showing acceptable discrimination.

The sensitivity of AG >12 mmol/L for predicting mortality was 97.1% (95% CI 85.1-99.9%), specificity was 10% (95% CI 6.2-14.9%), PPV was 15.8% (95% CI 11.2-21.4%), NPV was 95.2% (95%CI 76.2-99.9%), and the area under ROC was 0.54 (95%CI 0.50-0.57), indicating poor discrimination.

Discussion

Our results indicate that an AG >12 mmol/L has a high sensitivity (93.3%) but low specificity (13.7%) for predicting serum lactate >2 mmol/L. Utilizing AG to predict lactate level >2 mmol/L has poor predictive outcomes due to the area under the ROC curve being 0.65. As a result, AG was found to be a poor predictor of high serum lactate >2 mmol/L; this result is similar to the findings of Aronovich et al.[14], who performed a retrospective study in patients with suspected shock, showing serum lactate levels can be elevated not associated with an increase in anion gap, in contrast with research from Songklanagarind Hospital[15], which showed an acceptable correlation of using AG to predict SL >2 mmol/L (area under the ROC curve 0.76). Sonklanagarind Hospital selected septic shock patients, but our study selected sepsis patients with normal blood pressure; this may have caused the difference in the results.

When an anion gap was used to predict serum lactate >4 mmol/L, it was found to be correlated and used effectively to predict an area under the ROC curve of 0.82. The most suitable cut-off point value for predicting serum lactate >4 mmol/L was AG >18 mmol/L. These results were close to the research results from the Songklanagarind Hospital15 septic shock patient data, which found the ideal anion gap level for predicting lactate greater than 4 mmol/L to be 18.5. In addition, this result is also correlated with research by Berkman et al.[16] that shows AG is a good predictor of elevated serum lactate >4 mmol/L with an area under the ROC curve of 0.84. This unexpected finding that increasing anion gap is not well correlated with serum lactate >2 mmol/L could be due to the fact that we did not identify any other causes of metabolic acidosis with a wide anion gap (methanol, uremia, diabetic ketoacidosis, iron, ethanol, salicylate, etc.). However, when serum lactate rises over 4 mmol/L, hyperlactatemia takes precedence over other causes of wide anion gaps, and hence, the anion gap is closely linked to greater serum lactate. From our results and previous studies, an anion gap >18 mmol/L may be useful in predicting whether a patient has a lactate level >4 mmol/L, which could help community hospitals in deciding whether to refer the patient for further evaluation at a more suitable hospital.

When examining the relationship between anion gap and mortality rate, AG >12 mmol/L was capable of predicting mortality with a high sensitivity (97.1%), but it had a relatively low specificity (10%) and an area under ROC of 0.54, indicating poor discrimination. In contrast to research by Aronovich et al.[14] in which AG could be used to predict the death rate, with an AG >20 mmol/L, indicating a threefold increase in mortality rate. Our study may not be able to forecast mortality because the mortality rate in our results was below 15%. Some factors make the results of the study different due to the population in the study. Mohr et al.[17] included patients diagnosed with both sepsis and septic shock, which is usually associated with a higher mortality rate than sepsis, whereas our study only included sepsis patients. Doctors may have to resuscitate or perform additional treatment when abnormal laboratory results are discovered that could lead to reductions in patient mortality.

Our study has several limitations. First, it was a single-center study based on retrospective records.

Second, we have not adjusted for other factors that may affect anion gaps, such as albumin or ethanol. However, it is important to note that our study's primary aim was to utilize a simple and readily available method to predict serum lactate. Adjusting for additional factors would necessitate more extensive laboratory testing, potentially complicating the method's practicality and accessibility. Additionally, we acknowledge the limitation regarding albumin data: the absence of albumin data for all patients may have impacted the accuracy of anion gap measurements. Third, we did not identify any other causes of wide anion gap metabolic acidosis (methanol, uremia, diabetic ketoacidosis, iron, ethanol, salicylate, etc.), but we believe that lactic acidosis is the most common type of wide anion gap metabolic acidosis, based on previous research[12]. Finally, because this was a retrospective analysis and not all the patients had arterial blood gas results, we used oxygen dissociation from O_2 saturation to calculate PaO_2, which is one component of the SOFA score.

Conclusion

An anion gap >12 mmol/L is not suitable for assessing lactate >2 mmol/L due to its very low specificity. However, if the anion gap is >18 mmol/L in patients with non-hypotensive sepsis, this value can predict lactate >4 mmol/L.

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Conflict of interest

There were no conflicts of interest in this study.

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