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【 ORIGINAL ARTICLE 】

Blood Gas Analysis Results and Serum Lactate Levels in Patients with Psychogenic Hyperventilation and Urinary Tract Infection with Suspected Sepsis: A Retrospective Comparative Study

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Abstract:

Objective The prognosis differs considerably between patients with psychogenic hyperventilation syndrome (HVS) and those with urinary tract infection (UTI)-associated sepsis; however, the nonspecific symptoms and signs make the diagnosis and management difficult. We herein report the utility of a blood gas analysis for distinguishing HVS from UTI with suspected sepsis.

Methods This single-center retrospective cohort study was conducted in a tertiary-care hospital in Japan. Patients ≥18 years old with a quick Sequential Organ Failure Assessment (qSOFA) score ≥2 and HVS or UTIs were included. The results of an arterial blood gas (ABG) or venous blood gas (VBG) analysis of the two groups were compared using the Mann-Whitney U test. We used a receiver-operating characteristic (ROC) curve analysis of the arterial pH and arterial PCO_2 to assess the ability of these analyses to distinguish HVS from UTI with suspected sepsis.

Results A total of 64 patients with HVS (ABG, n=14; VBG, n=50) and 53 with UTI with suspected sepsis (ABG, n=35; VBG, n=18) were included. Patients with HVS had alkalemia and lower PCO_2 levels than patients with UTI with suspected sepsis, but the serum lactate levels were similar between the groups. The ROC analysis determined the pH cut-off value to be 7.509 (sensitivity: 0.91; specificity: 0.86) and the PCO_2 cut-off value to be 21.6 mmHg (sensitivity: 1.00; specificity: 0.64).

Conclusion Elevated serum lactate levels alone cannot be used to differentiate between patients with HVS and those with UTI with suspected sepsis, but the degree of pH and PCO_2 abnormality can help with the differential diagnosis.

Key words: lactate, hyperlactatemia, hyperventilation, sepsis, urinary tract infection

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Introduction

The prevalence of psychogenic hyperventilation syndrome (HVS) in the general population is estimated to be approximately 9.5%, and individuals with HVS often visit emergency departments (EDs) (1, 2). Although HVS is a well-known condition, there are no widely accepted diagnostic criteria; thus, the diagnosis is often based on the exclusion of other conditions and the treating physician's experience (1). As the clinical presentation of HVS with tachypnea and/or an altered mental status and non-specific signs on a physical examination, is similar to that of some critical conditions, such as sepsis, the treating physicians must diagnose and manage patients with HVS carefully.

Urinary tract infections (UTIs) are also a common cause of sepsis in ED settings (3). The mortality rate of severe sepsis or septic shock is approximately 30% (4). It is important to exclude other organic diseases and critical conditions, as the diversity of presenting symptoms and nonspecific

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symptoms of UTIs can obscure the diagnosis (5, 6).

The definition of sepsis changed in 2016. The quick Sequential Organ Failure Assessment (qSOFA) for sepsis screening is now used in ED settings (7). Patients who meet at least two of the following qSOFA criteria are likely to have poor outcomes: an altered mental state, a systolic blood pressure of ≤100 mmHg, and a respiratory rate of ≥22 breaths/min (7). Patients with HVS and patients with UTI with suspected sepsis generally present with nonspecific signs, including a rapid respiratory rate and altered mental state. Although HVS is a self-limiting condition, sepsis can be fatal. Thus, it is important to distinguish between HVS and sepsis in the ED as early as possible.

Elevated serum lactate levels are sometimes present in patients with HVS, yet these patients have a good prognosis (8, 9), while patients with hyperlactatemia due to a critical condition, such as sepsis, have a poor prognosis (10-12). In patients with HVS, respiratory alkalosis and inverse correlation between PCO_2 and serum lactate levels are detected by blood gas analyses (9). However, no studies have directly compared the serum lactate levels or blood gas analysis results in patients with HVS and those with UTI with suspected sepsis.

We therefore investigated blood gas analysis data and serum lactate levels in patients with HVS and a qSOFA ≥2 as well as in patients with UTI with suspected sepsis to determine the utility of blood gas analyses for early differentiation between the two conditions in the ED.

Materials and Methods

Study design

This study was a retrospective comparative study, conducted in a single tertiary-care center. We compared the vital signs, serum lactate level, and blood gas results of patients with HVS who visited the ED between January 2015 and December 2018 and patients with UTIs who visited the ED between January 2017 and December 2017.

Setting

Kurashiki Central Hospital is a 1,131-bed tertiary-care center in western Japan. The ED manages approximately 70,000 patients annually, including approximately 10,000 patients who are transported by ambulance or helicopter. The final diagnosis of patients at discharge from the ED is recorded in the electronic medical records. Treating ED physicians order laboratory tests and imaging studies of patients at their discretion.

The study protocol was approved by the institutional review board of Kurashiki Central Hospital (No.2970). The requirement for informed consent was waived because of the retrospective design of the study.

Participants

We included patients ≥18 years old with HVS, transported by ambulance to the ED between January 2015 and December 2018. We confirmed the final diagnosis at discharge from the ED and extracted the patient data. HVS was defined as follows: (i) an episode of hyperventilation reported by the patient or a witness and (ii) a respiratory rate of ≥22 breaths/min on arrival. We excluded patients for the following reasons: (i) the cause of hyperventilation was suspected to be an organic or somatic disease based on vital signs, history, electrocardiography, chest X-ray, or laboratory test results; or (ii) the evaluation in the ED resulted in hospital admission. We included patients with HVS with a qSOFA ≥2 who underwent an arterial blood gas (ABG) or venous blood gas (VBG) analysis for the initial assessment through to the final diagnosis.

We also included patients ≥18 years old transported by ambulance to the ED with UTIs between January and December 2017, who were admitted after the ED evaluation. We confirmed the final diagnosis at discharge from the ED and extracted the patient data. UTIs were defined according to the following criteria: (i) an episode of symptoms related to the urinary tract; (ii) bacteriuria, pyuria, and nitrites detected by a urinalysis; and (iii) the exclusion of non-UTI causes of a fever in the ED. We excluded patients in whom the cause of admission was anything other than a UTI based on their history, electrocardiography, X-ray, CT, ultrasound, or laboratory test results. We included UTI patients with qSOFA ≥2 who underwent an ABG or VBG analysis for initial assessments through to the final diagnosis.

As there are no definitive diagnostic criteria for HVS or UTI, the inclusion and exclusion criteria were based on indicators that are practical for use in clinical settings and were defined by discussion among the three authors.

Measurements

We reviewed all medical records and extracted data regarding age, sex, initial vital signs on arrival, lowest blood pressure during staying in the ED, pH, oxygen partial pressure (PO_2), carbon dioxide partial pressure (PCO_2), bicarbonate ion (HCO_3^-), sodium ion (Na^+), potassium ion (K^+), chloride ion (Cl^-), ionized calcium ion (Ca^{2+}), and serum lactate level. We set the reference serum lactate level as ≤2.0 mmol/L (7, 13). In the ED, arterial blood was collected from the radial or femoral artery, and venous blood was collected from any peripheral vein using a heparinized plastic syringe. The collected sample was immediately analyzed with an ABL800 FLEX (Radiometer Medical, Tokyo, Japan) in the ED. Results were recorded in the medical records automatically.

Statistical analyses

Continuous variables were presented as medians and interquartile ranges (IQRs), and the values in the two groups were compared using the Mann-Whitney U test due to a non-normal data distribution. The sex distribution of the two groups was compared using Fisher's exact test. Several studies have shown an inverse correlation between PCO_2 and se-

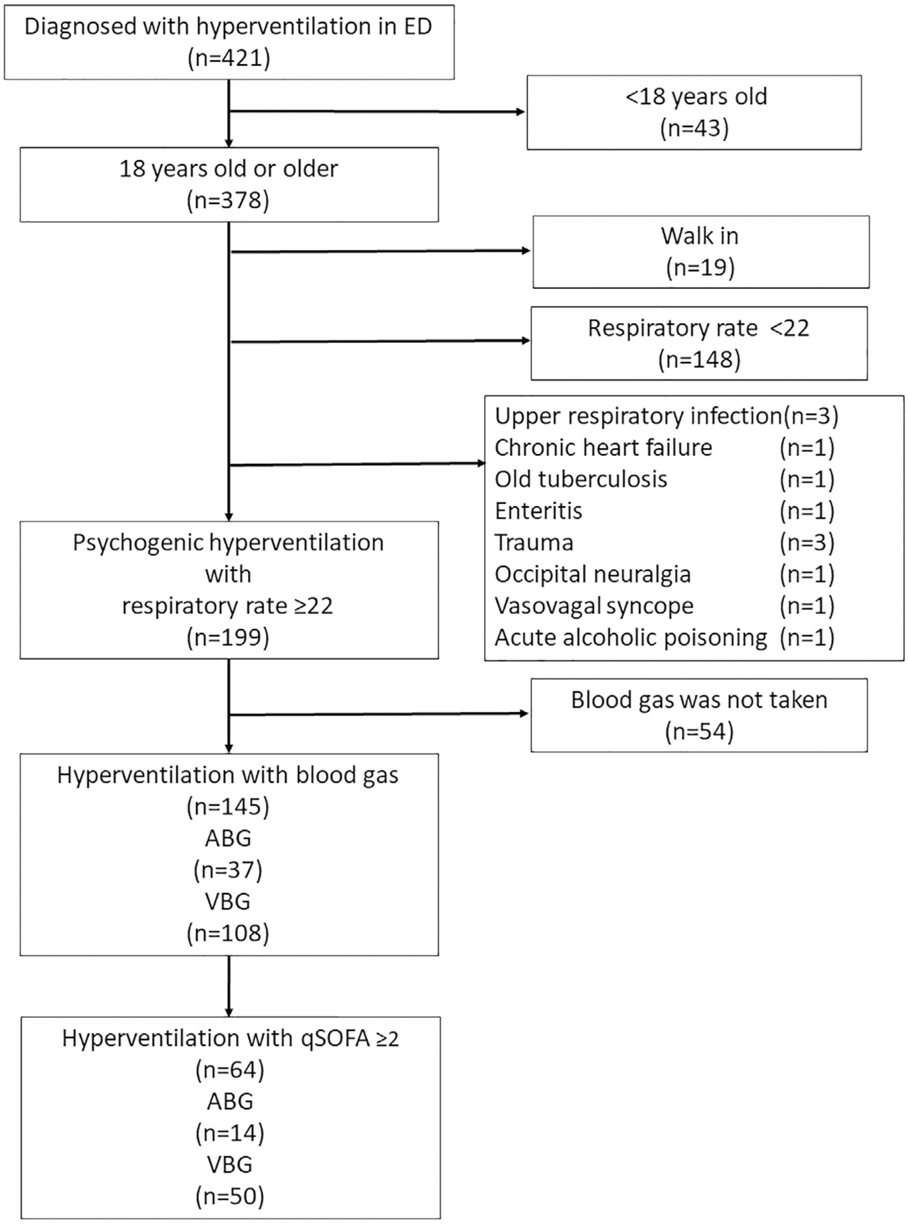

Figure 1. **Selection of study participants with psychogenic hyperventilation with qSOFA ≥2. ABG: arterial blood gas, ED: emergency department, qSOFA: quick Sequential Organ Failure Assessment, VBG: venous blood gas**

rum lactate levels in patients with HVS (8, 9). Thus, we investigated the correlation between PCO_2 and serum lactate levels with patients who met two of the three qSOFA criteria in both the HVS and UTIs groups using Spearman's rank correlation coefficient. We plotted the receiver-operating characteristic (ROC) curves for arterial pH and arterial PCO_2 to assess their ability to distinguish HVS from UTIs associated with sepsis and determined the cut-off, sensitivity, and specificity. We determined the cut-off using the value that maximized the sum of the sensitivity and specificity. Statistical analyses were conducted using EZR version 1.37 (14).

Results

Characteristics of study participants

A total of 421 patients were diagnosed with HVS at discharge from the ED, of whom 145 met the criteria for inclusion in the HVS group in this study. Of these 145 patients, 37 underwent an ABG analysis, and 108 underwent a VBG analysis. A total of 64 patients met the criteria of HVS with qSOFA ≥2. Of these 64 patients, 14 underwent an ABG analysis, and 50 underwent a VBG analysis (Fig. 1).

A total of 293 patients were diagnosed with UTIs in the ED and admitted to the hospital. Of these 293 patients, 53 met the criteria for UTI with suspected sepsis. Of these 53

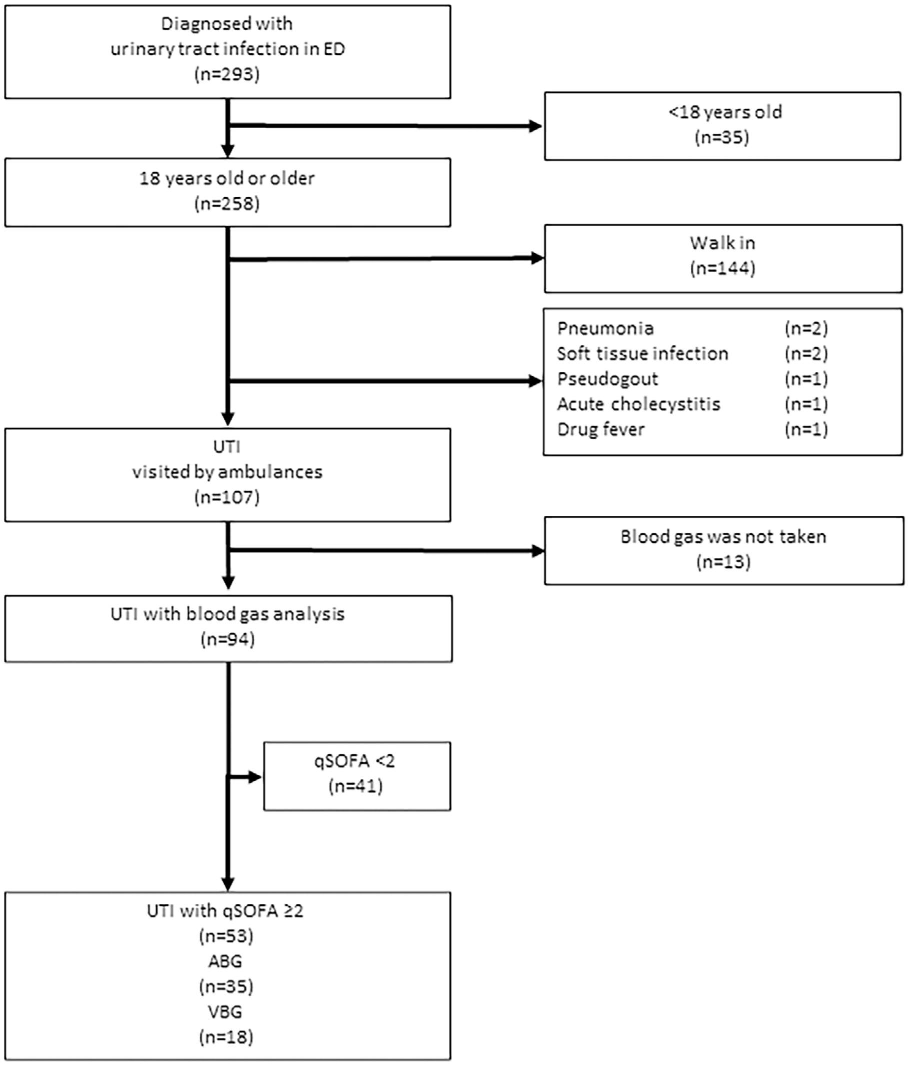

Figure 2. Selection of study participants with urinary tract infection with suspected sepsis. ABG: arterial blood gas, ED: emergency department, qSOFA: quick Sequential Organ Failure Assessment, VBG: venous blood gas

patients, 35 underwent an ABG analysis, and 18 underwent a VBG analysis (Fig. 2).

Of the patients who underwent blood gas analyses, hyperlactatemia (>2 mmol/L) was observed in 94 (64.8%) of the 145 HVS patients and 39 (41.5%) of the 94 UTI patients ($p < 0.001$).

Main results

The age, sex, vital signs, and blood gas analyses of patients with HVS and qSOFA ≥2 and patients with UTI with suspected sepsis are shown in Table 1. The patients with HVS were younger than the patients with UTI with suspected sepsis. There were no marked differences in the respiratory rate, initial systolic blood pressure, or Glasgow Coma Scale scores between the two groups. The heart rate and body temperature were higher, and the lowest blood pressure during the ED stay was lower in the patients demonstrating UTI with suspected sepsis than in those with HVS.

The ABG and VBG analyses both showed a higher incidence of alkalemia and lower level of PCO_2 in the patients with HVS with a qSOFA ≥2 than in the patients demonstrating UTI with suspected sepsis. The ABG analysis showed a similar degree of serum lactate elevation in the patients with HVS and those demonstrating UTI with suspected sepsis. In contrast, the VBG analysis revealed elevated serum lactate levels in the patients with HVS but not in those demonstrating UTI with suspected sepsis. There was no marked difference in the HCO_3^- level between the patients with HVS and those demonstrating UTI with suspected sepsis.

The correlation between the PCO_2 and lactate levels

The Spearman's rank correlation coefficients (ρ) for the association between the PCO_2 and serum lactate level in patients with HVS whose qSOFA ≥2 and patients with UTI with suspected sepsis are shown in Table 2. The coefficients in the patients who underwent an ABG analysis were -0.64 and -0.073 in those with HVS and UTI with suspected sepsis, respectively, while the coefficients in the patients who underwent a VBG analysis were -0.46 and -0.37 in those

Table 1. Characteristics and Blood Gas Analysis of Patients with Hyperventilation Syndrome (qSOFA ≥2) and Patients with Urinary Tract Infection with Suspected Sepsis.

Arterial and venous blood gas	HVS (n=64)	Sepsis (n=53)	p value
Male/Female	13/51	27/26	
Female (%)	79.7	49.1	<0.001*
Age	46 (31-68)	83 (77-90)	<0.001†
Initial systolic blood pressure (mmHg)	137 (120-150)	129 (101-155)	0.16†
Lowest blood pressure (mmHg)	127 (102-145)	96 (85-109)	<0.001†
Heart rate (/min)	90 (78-101)	112 (92-124)	<0.001†
Respiratory rate (/min)	29 (24-32)	26 (24-33)	0.26†
Body temperature (/min)	36.7 (36.3-37.0)	38.6 (37.4-39.6)	<0.001†
Glasgow Coma Scale	14 (14-14)	14 (13-14)	0.63
Arterial blood gas	n=14	n=35	
Male/Female	5/9	19/16	
Female (%)	64.3	45.7	0.07*
Age	72 (58-79)	84 (77-89)	0.004†
Serum lactate >2 mmol/L (%)	9 (64.3)	20 (57.1)	0.76*
Initial systolic blood pressure (mmHg)	144 (125-162)	129 (105-150)	0.11†
Lowest blood pressure (mmHg)	141 (99-150)	94 (86-103)	0.002†
Heart rate (/min)	81 (72-95)	113 (96-125)	<0.001†
Respiratory rate (/min)	27 (24-30)	27 (23-34)	>0.99†
Body temperature (/min)	36.6 (36.3-36.7)	39.2 (37.5-40.1)	<0.001
Glasgow Coma Scale	14 (14-15)	14 (12-14)	0.06
pH	7.63 (7.53-7.67)	7.47 (7.40-7.49)	<0.001
PCO_2 (mmHg)	20.3 (14.9-25.3)	29.3 (26.8-32.7)	<0.001
HCO_3^- (mmol/L)	20.0 (17.6-22.3)	20.3 (18.1-22.6)	>0.99†
Lactate (mmol/L)	3.1 (1.8-4.1)	2.3 (1.5-4.6)	0.97†
K (mEq/L)	3.5 (3.2-3.6)	3.9 (3.5-4.3)	0.007†
Venous blood gas	n=50	n=18	
Male/Female	8/42	8/10	
Female (%)	84	55.6	0.39*
Age	40 (29-60)	82 (77-90)	<0.001†
Serum lactate >2 mmol/L (%)	33 (66.0)	6 (33.3)	0.23*
Initial systolic blood pressure (mmHg)	134 (119-146)	124 (99-164)	0.51†
Lowest blood pressure (mmHg)	127 (103-141)	96 (85-131)	0.03†
Heart rate (/min)	91 (80-102)	104 (83-117)	0.05†
Respiratory rate (/min)	30 (24-35)	26 (24-32)	0.30†
Body temperature (/min)	36.8 (36.4-37.2)	38.4 (37.4-38.9)	<0.001†
Glasgow Coma Scale	14 (13-14)	14 (14-15)	0.04†
pH	7.52 (7.44-7.61)	7.43 (7.40-7.45)	<0.001†
PCO_2 (mmHg)	28.3 (21.3-33.5)	37.4 (34.1-40.2)	<0.001†
HCO_3^- (mmol/L)	22.6 (20.8-24.6)	23.8 (22.6-25.2)	0.09†
Lactate (mmol/L)	2.7 (1.9-3.7)	1.5 (1.3-2.4)	<0.002†
K (mEq/L)	3.5 (3.3-3.8)	3.7 (3.3-4.3)	0.10†

The data are presented as median with interquartile range.
*: Fisher's exact test
†: Mann-Whitney U test
HCO_3^-: bicarbonate ion, HVS: psychogenic hyperventilation syndrome, K: potassium ion, PCO_2: partial pressure of carbon dioxide, UTI: urinary tract infection

with HVS and UTI with suspected sepsis, respectively.

Results of an ROC analysis

In our study, the prevalence of UTI with suspected sepsis was 71.4%. The ROC curves for arterial pH and arterial PCO_2 for distinguishing between HVS with qSOFA ≥2 and UTIs associated with sepsis are shown in Figs. 3 and 4, respectively. For pH, the cut-off value was 7.509 with a sensi-

Table 2. Spearman's Rank Correlation Coefficient between PCO_2 and Lactate in Patients with Hyperventilation Syndrome and Patients with Urinary Tract Infection with Suspected Sepsis.

	ABG		VBG	
	ρ	p	ρ	p
HVS with qSOFA ≥2	-0.64	0.024	-0.46	<0.001
UTI with suspected sepsis	-0.073	0.68	-0.37	0.137

ABG: arterial blood gas, HVS: psychogenic hyperventilation syndrome, PCO_2: partial pressure of carbon dioxide, qSOFA: quick Sequential Organ Failure Assessment, UTI: urinary tract infection, VBG: venous blood gas

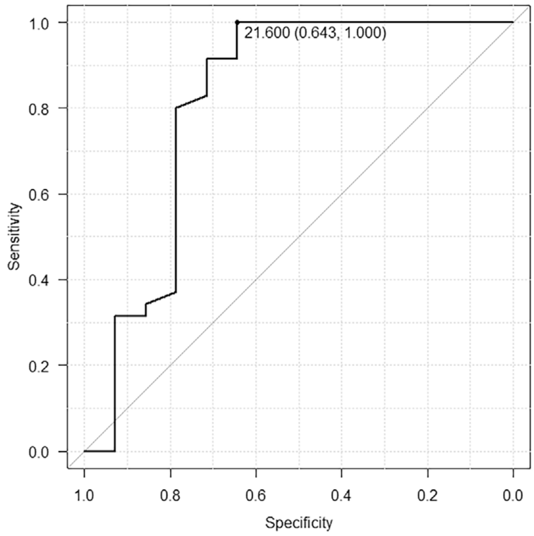

Figure 4. Receiver-operating characteristic curve of arterial blood gas carbon dioxide partial pressure for distinguishing hyperventilation syndrome from urinary tract infection with suspected sepsis.

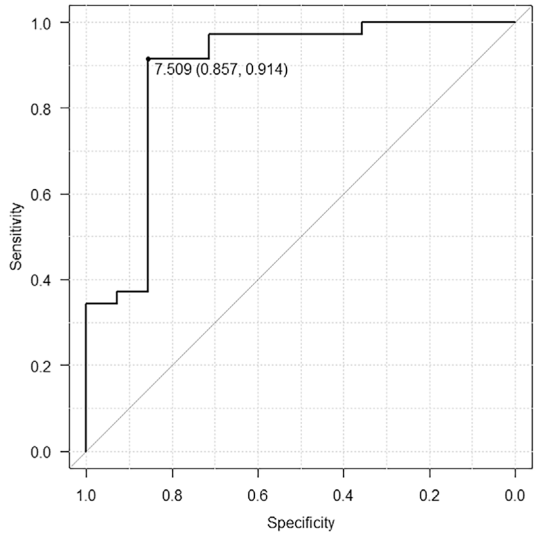

Figure 3. Receiver-operating characteristic curve of arterial blood gas pH for distinguishing hyperventilation syndrome from urinary tract infection with suspected sepsis.

tivity of 0.91 and a specificity of 0.86, and the area under the curve was 0.89 (95% confidence interval: 0.76-1.00) (Fig. 3). With a pH cut-off value of 7.509, the positive predictive value (PPV) and negative predictive value (NPV) for UTI with suspected sepsis were 94.1% and 80.0%, respectively. For PCO_2, the cut-off value was 21.6 mmHg with a sensitivity of 1.00 and a specificity of 0.64, and the area under the curve was 0.81 (95% confidence interval: 0.64-0.99) (Fig. 4). With a PCO_2 cut-off value of 21.6 mmHg, the PPV and NPV for UTI with suspected sepsis were 87.2% and 90.0%, respectively.

Discussion

To our knowledge, this is the first study to compare the blood gas values and serum lactate levels between patients with HVS and those with UTI with suspected sepsis. The pH was significantly higher (more alkaline) in the patients with HVS than in those with UTI with suspected sepsis. The serum lactate levels did not differ significantly between groups among patients who underwent an ABG analysis, but among those who underwent a VBG analysis, the HVS group had significantly higher lactate levels than the UTI with suspected sepsis group.

HVS causes respiratory alkalosis, and sepsis causes lactic acidosis with coexisting respiratory alkalosis (15). In HVS, carbon dioxide is lost through expiratory breathing, and the serum PCO_2 levels decrease, causing respiratory alkalosis (16, 17). The alkalosis increases the activity of phosphofructokinase, which regulates the rate of the glycolytic pathway, resulting in elevated serum lactate levels (16, 18, 19). The liver is one of the main organs to metabolize lactate, but this process is inhibited when the pH is outside the optimal range. Thus, the half-life of lactate increases in conditions of respiratory alkalosis (18), leading to elevated serum lactate levels in patients with HVS. In contrast, tissue hypoperfusion is the main cause of elevated serum lactate levels in patients with sepsis. Macro- or microcirculatory dysfunction, tissue hypoxia, and nutrient extraction by peripheral tissues can all occur in patients with sepsis or septic shock (12).

Notably, the initial blood pressure, respiratory rate, and Glasgow Coma Scale in the UTI with suspected sepsis group did not differ significantly from those values in the HVS group. These results suggest that the qSOFA criteria alone cannot be used to distinguish between these benign and critical conditions early in the ED setting. The study results also reveal that an elevated serum lactate level in patients with tachypnea does not necessarily mean that the patient has a severe medical condition, such as sepsis. The serum lactate levels alone were unable to distinguish between patients with HVS and those with UTI with suspected sepsis. Furthermore, the venous serum lactate level should not be used to rule out critical conditions such as UTI with suspected sepsis, as the venous serum lactate level can be lower in some patients with UTI with suspected sepsis than in those with HVS. The study results suggest that an inverse correlation between serum lactate levels and PCO_2 is more likely to occur in patients with HVS than those with UTI. The ROC curve results suggest that the degree of alkalemia or PCO_2 depression in ABG may help distinguish HVS from UTI with suspected sepsis. The results further suggest that patients with a typical medical history and physical examination findings as well as an increased degree of respiratory alkalosis and low PCO_2 level are more likely to experience HVS, even if their serum lactate level is high, than UTI with suspected sepsis (8, 9). Conversely, when managing tachypneic patients with high serum lactate levels who do not have significant respiratory alkalosis or low PCO_2, physicians should consider critical conditions, such as sepsis. As blood gas analysis results can be obtained sooner than the results of a complete blood count, biochemical tests, or urinary sediment examination, the use of a blood gas analysis can help treating physicians prepare for monitoring or therapeutic intervention earlier in the ED setting.

Limitations

Several limitations associated with the present study warrant mention. First, only patients with UTI with suspected sepsis were included in the sepsis group. Although the common causes of sepsis in the ED are UTIs and pneumonia (3), pneumonia can be diagnosed early based on the medical history, physical examination, and chest X-ray findings. Furthermore, lung lesions associated with pneumonia might affect PO_2 or PCO_2. In contrast, UTIs have variable presentations and severity and are not readily diagnosed based on a history or physical examination (6). While HVS is a self-limiting condition, sepsis due to UTIs is a critical condition that can sometimes mimic HVS. Thus, we excluded sepsis patients with respiratory infections and selected only those with UTI with suspected sepsis. Second, we did not focus on differences in vital signs between the two conditions. Although patients with UTI tend to present with a fever, while those with HVS do not, some patients with sepsis have a normal or low body temperature and can thus initially be overlooked, delaying the administration of antibiotics. Patients with sepsis without a fever have a longer length of stay in the intensive-care unit (ICU) and a higher mortality rate than those with a fever (19). In our study, 9 of the 53 patients with UTI with suspected sepsis had a body temperature ≤37.0 °C. Of these 9 patients, 4 (44%) were admitted to the ICU. Of the remaining 44 patients, 12 (27%) were admitted to the ICU ($p=0.427$). Thus, using only vital signs, such as body temperature, may be insufficient to distinguish HVS from sepsis. Third, of the patients with sepsis in our study, 37% (13/35) of those who received an ABG analysis and 17% (3/18) of those who received a VBG analysis were admitted to the ICU. This suggests that in the sepsis group, the more critical patients underwent an ABG analysis. This represents a measurement bias and may explain why the venous serum lactate levels were not elevated in the sepsis group. Fourth, blood gas analyses were not performed for all patients with UTI or HVS. We compared the characteristics of the participants who did and did not, have their blood gas measured (Supplementary material). Most of the characteristics were similar in both groups, suggesting that the sampling bias was low. However, the HVS patients who did not have their blood gas measured were younger than those who had their blood gas measured. This suggests that it might be easier to diagnose HVS in younger patients, so physicians might decide not to perform a blood gas analysis in the ED. Fifth, the study was small, and the design was retrospective; thus, a larger prospective study is needed to confirm the findings.

Conclusion

Patients with psychogenic HVS and those with UTI with suspected sepsis may have a similar degree of elevation of serum lactate levels on an ABG analysis. In such patients with hyperlactatemia, the pH and PCO_2 on ABG analyses might be useful for distinguishing psychogenic HVS from UTI with suspected sepsis early in the diagnostic assessment.

The authors state that they have no Conflict of Interest (COI).

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