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Assessment of Clinical, Respiratory and Metabolic Parameters in Neonatal Calves in Different Courses of Aspiration Pneumonia

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A B S T R A C T

Iatrogenic aspiration pneumonia (AP), often caused by incorrect drenching and feeding with inappropriate bottles, is a frequent condition that can lead to sudden death depending on the amount of aspirated fluid. The evaluation of clinical scores and blood gas analytes may provide valuable insights into the complications that may arise due to AP in later stages. In this study, the AP Group consisted of 23 Holstein breed calves aged 1-14 days, which developed clinical signs such as cough, nasal and/or ocular discharge, and respiratory distress after forced feeding with inappropriate bottles. The Control Group consisted of 11 healthy calves with similar characteristics. Clinical examinations, Calf Health Score (CHS) evaluations, and venous blood gas analysis were performed. Based on anamnesis, calves with AP were classified as either Acute or Chronic AP. In clinical examination, heart and respiratory rates were higher in the Acute AP Group compared to the other groups ($P<0.001$). Total CHS was higher in the AP Group than that in the Control Group ($P<0.001$). The pH, sO_2, Cl and Hb levels of the AP Group were lower, and K and lactate levels were higher compared to the Control Group ($P<0.031$). Among all groups, the pCO_2 levels were highest in the Acute AP Group ($P<0.001$). The Na level of the Chronic AP Group was lower than that of the Control Group ($P<0.05$). The hematocrit level was lowest in the Chronic AP Group ($P<0.016$). These findings suggest that venous blood samples can be effectively used to classify the course of AP in neonatal calves; significant alterations in venous blood gas, electrolyte levels, and CHS can be observed in affected animals; sO_2 and pCO_2 levels are particularly important in distinguishing between acute and chronic cases of AP; and clinical and laboratory findings may be similar to those observed in healthy animals in chronic cases depending on the body's ability to compensate or tolerate the disease.

Keywords: aspiration pneumonia, acute and chronic AP, calf, calf health score, electrolyte balance

INTRODUCTION

Respiratory diseases are among the most common causes of economic losses in livestock, with a multivariate etiology resulting in clinical and pathological abnormalities in the respiratory tract. In addition to infectious etiologies, inhalation of foreign substances such as milk, liquid supplements, or medicines can damage lung parenchyma, causing severe and often fatal aspiration pneumonia (AP) (1). Although there is no clear data on the incidence of AP in calves, it is reported to be one of the most common causes of pneumonia in neonatal calves (2). Hence, AP is defined as inhalation pneumonia resulting from inhalation of foreign substances such as medicine, milk, and food or rumen contents following hypocalcemia, especially if the cow becomes cast, and after incorrect drenching (2,3). Many breeders/farmers use various liquid supplements or medicines by drenching them for the treatment or prevention of diseases. Improper administration methods or incorrect drenching/bottle-feeding techniques, as well as inexperienced personnel or farmers administering milk or medicines in liquid form, especially if the animal's tongue is sticking out, head held high, coughing and belching, are the most common cause of AP and it is considered as a major management issue (4,5).

Early diagnosis and accurate determination of etiology are important in the effective control of respiratory system diseases (6,7). Questioning the breeder during the anamnesis can reveal whether any liquid material or milk was given by drenching and suspicion of AP may be considered (2,8). In addition to anamnesis and clinical examinations, blood gas analysis is accepted as the gold standard in the evaluation of lung functions (9,10). Blood gas analysis in respiratory system diseases is an important method that provides useful information on the relationship between ventilation, oxygenation and metabolic status, qualitative and quantitative evaluation of metabolic and respiratory acid-base problems, evaluation of the severity of respiratory disease, and making therapeutic decisions (9-11). Although the correlation of some blood gas parameters such as venous pH, HCO3, BE, and lactate with arterial samples in critically ill and premature newborns has been evaluated, and has been reported that a single venous value cannot be used in the evaluation of arterial blood gas parameters, it is stated that the use of venous blood can be used in the diagnosis and screening of diseases (12). Also, since AP is an often-fatal emergency (1), it may be considered whether venous blood should be used, at least as used in the initial assessment in another respiratory disease with high mortality such as chronic obstructive pulmonary disease (COPD) (13). Moreover, it has been reported that arterial catheterization has many complications, and that venous blood gas and electrolyte analysis is an alternative method in individuals with respiratory critical disease (14), and the values of parameters such as pH, BE, HCO_3 and pCO_2 in venous samples are also reliable compared to their equivalent arterial blood samples (15,16). Recently, instead of comprehensive and equipment-requiring scanning devices, different scoring systems have been developed by standardizing clinical examination findings and scoring each of the clinical parameters according to the degree of importance (6,17). For this purpose, the Wisconsin Calf Health Score (CHS) system based on five clinical parameters including rectal temperature, cough, nasal discharge, ocular discharge and ear position was proposed and started to be used. According to this scoring system, calves with a total respiratory score of five or higher (provided that at least two abnormal parameters are observed) are considered as diseased. It is stated that screening calves with CHS at least twice a week before weaning provides a significant advantage in the early diagnosis and control of respiratory system diseases (6). Therefore, evaluation of parameters such as fever, cough, ocular or nasal discharge, abnormal breathing, and auscultation of abnormal lung sounds, which are typical findings of respiratory system diseases, may facilitate rapid antemortem diagnosis. However, since the evaluated parameters can also be observed in diseases such as otitis media and chronic pneumonia, it is recommended to investigate their sensitivity and specificity (7).

Although there are many studies on respiratory system diseases, which are important economic burdens for the cattle industry all over the world, field studies on AP are limited and the diagnosis can only be made at necropsy in animals without specific clinical findings (3,8). Therefore, in this study, it was aimed both to investigate whether aspiration pneumonia can be classified as acute or chronic from venous blood samples unlike in human medicine (18) and to determine the effect and possible correlations of the disease on clinical scores and blood gas and electrolyte parameters according to the course.

MATERIALS AND METHODS

Ethical Statement

This study was approved by the decision of the Ethics Committee of the Faculty of Veterinary Medicine of Harran University, with session number 2021/004, dated 07.05.2021 and numbered 01-08. All institutional and national guidelines for the care and use of study animals were followed. All calf breeders gave their consent before the commencement of the study.

Animals

Twenty-three calves of Holstein breed, 1-14 days old, who developed non-specific respiratory system symptoms such as cough, nasal and/or ocular discharge, and respiratory distress after being fed on milk/colostrum with inappropriate bottles constituted the Aspiration Pneumonia (AP) Group. Eleven clinically healthy calves with the same characteristics constituted the Control Group. All were admitted to Harran University Veterinary Faculty Animal Hospital for check-ups, diagnosis, and treatment purposes. Calves who were found to have any comorbid disease as a result of clinical examinations such as atresia, diarrhea, and ruminal drinking and were determined to be premature or those with any signs of respiratory system disease prior to drenching that indicate diseases such as bovine respiratory disease complex were not included in the study. In addition, calves with other etiologies such as meconium aspiration syndrome, dust, or toxic gas inhalation that might cause AP were not included in the study.

Anamnestic Data

In the anamnesis of all calves included in the AP Group, it was learned that symptoms such as cough, nasal discharge, and difficulty breathing developed on forced feeding on milk/colostrum with an inappropriate bottle.

AP-developed calves as a result of the administration of different liquid materials such as digestive stimulants or vitamin-mineral complex solutions were not included in the study as the alteration and severity of the investigated parameters may be affected by the character and acidity of the aspirated material. Thus, the fact that all the AP cases in the study were due to forced milk/colostrum and was confirmed both in the anamnesis and by observing the unsuitability of feeding bottles (leakage of milk when turned over) (Figure 1) in the farm from which the calf was brought.

Figure 1. Inappropriate bottle used for feding

Clinical Examinations and Evaluation of Calf Health Score

All calves included in the study were evaluated with CHS, along with clinical examinations including mucous membrane, palpable lymph node examinations, and lung auscultation. Body temperatures were measured using a rectal thermometer. The presence of a cough was detected by observation during inspection or induced by laryngeal palpation. Within the scope of CHS, it was accepted that points range from 0 to 3 as clinical signs progress from 0 (normal), to 1 (mildly abnormal), to 2 (moderately abnormal), and to 3 (severely abnormal). Calves with a total CHS of 5 or higher with AP were considered clinically diseased and included in the AP Group (n: 23). Calves with a total CHS of 4 or less and with no disease determined as a result of clinical and laboratory examinations were considered healthy (6) and included in the Control Group (n: 11).

Sample Collection and Analysis

Following the CHS evaluation, 4-5 mL of venous blood samples were obtained from all the calves using the jugular venipuncture technique with injectors containing heparin.

Blood gas and electrolyte analysis were performed within 5-10 min after the sampling using an autoanalyzer (epoc® Blood Analysis System, Siemens Healthineers, Germany). In this context, pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), bicarbonate (HCO_3), negative base excess (BE), oxygen saturation (sO_2), sodium (Na), potassium (K), calcium (Ca), Chlorine (Cl), hematocrit (Hct), hemoglobin (Hb), glucose (Glu) and lactate (Lac) levels were evaluated.

Forming Subgroups

Neonatal calves included in the AP Group were divided into two subgroups, acute AP and Chronic AP mainly on the basis of anamnesis and venous sO_2 level. The duration of symptoms was 1 (1-2) days in the Acute AP group and 6 (4-10) days in the Chronic AP group ($P<0.001$). The anamnestic data and blood gas results were consistent with those reported in human medicine (18). Thus, 14 neonatal calves with AP were included in the Acute AP and 9 in the Chronic AP Group.

Statistical Analysis

Statistical software program SPSS 25.00 (SPSS for Windows®) was used for the data analysis. One-sample Kolmogorov-Smirnov test was used to investigate whether all data were parametric or not. Non-parametric data were presented as median (min, max) using Mann-Whitney U, Kruskal-Wallis test. The Pearson correlation test was used to determine possible correlations between CHS and blood gas and electrolyte parameters using the same statistical software. In addition, Receiver Operating Characteristic (ROC) analysis was performed to evaluate the diagnostic performance of the parameters that were determined to be statistically significant between the groups. Within the scope of ROC analysis, the parameters of area under the curve (AUC), cut-off, sensitivity, specificity and observed power (Op) were evaluated. Statistical significance was accepted as $P\leq0.05$ for all data.

RESULTS

Clinical Examinations and Calf Health Score

Clinical examination findings are presented in Table 1. Respiratory and heart rates were significantly higher in the Acute AP group compared to the Control and Chronic AP groups ($P<0.001$). Body temperature was statistically insignificant between the groups ($P=0.773$). CHS of calves with AP was higher than that of the ones in the Control Group ($P<0.001$). Although the CHS of the Acute AP Group was numerically higher compared to the calves with Chronic AP, no statistical difference was detected ($P>0.05$). CHS findings are presented in Table 2.

Blood Gas and Electrolyte

Compared to the Control Group, the pH, sO_2, Cl, and Hb levels of the Acute and Chronic AP groups were lower ($p<0.021$). In comparison with the other groups, the pCO_2 level was highest in the Acute AP Group ($P<0.001$). Na level was lower in calves with chronic AP compared to the healthy ones in the Control Group ($P<0.05$). Compared to the Control Group, calves with Acute AP had higher K levels ($p<0.031$). Among all the groups, the Hct level was the lowest in the Chronic AP Group ($p<0.016$). Lactate level was higher in calves with AP compared to the Control Group ($p<0.001$). The results of blood gas and electrolyte analysis are presented in Table 3

Table 1. Clinical Examination Findings of Calves: Median values with ranges (minimum and maximum) for each group

	Parameters				
Group	**Body weight (kg)**	**Heart rate (beat/min)**	**Respiratory rate (min)**	**Body temperature (°C)**	**Calf Health Score**
Control Group (n=11)	47 (39-55) ^{ab}	98.0 (78.0-120) ^{b}	44 (36-55) ^{b}	38.3 (37.9-38.6)	1 (0-2) ^{b}
Acute AP Group (n=14)	47 (34-54) ^{b}	152 (130-178) ^{a}	72 (62-90) ^{a}	38.2 (35.6-39.7)	8 (3-12) ^{a}
Chronic AP Group (n=9)	52 (45-55) ^{a}	110 (86.0-130) ^{b}	42 (38-52) ^{b}	38.8 (35.7-39.9)	7 (3-10) ^{a}
P-value	0.047	<0.001	<0.001	0.773	<0.001

$^{a-b}$ Values in a column with different superscript letters significantly different ($P \leq 0.05$)

Table 2. Calf Health Score evaluation of calves

Parameters	**Score**	**Control Group (n= 11)**	**Acute AP Group (n=14)**	**Chronic AP Group (n=9)**
Rectal temperature (°C)	0	n=3 (27.3%)	n=3 (21.4%)	n=3 (33.3%)
	1	n=8 (72.7%)	n=8 (57.1%)	n=2 (22.2%)
	2	n=0 (0.00%)	n=1 (7.14%)	n=2 (22.2%)
	3	n=0 (0.00%)	n=2 (14.3%)	n=2 (22.2%)
Coughing	0	n=11 (100%)	n=2 (14.3%)	n=0 (0.00%)
	1	n=0 (0.00%)	n=9 (64.3%)	n=5 (55.6%)
	2	n=0 (0.00%)	n=2 (14.3%)	n=3 (33.3%)
	3	n=0 (0.00%)	n=1 (7.14%)	n=1 (11.1%)
Nasal discharge	0	n=10 (90.9%)	n=0 (0.00%)	n=2 (22.2%)
	1	n=1 (9.09%)	n=3 (21.4%)	n=4 (44.4%)
	2	n=0 (0.00%)	n=7 (50.0%)	n=1 (11.1%)
	3	n=0 (0.00%)	n=4 (28.6%)	n=2 (22.2%)
Ocular discharge/Ear position	0	n=9 (81.8%)	n=1 (7.14%)	n=2 (22.2%)
	1	n=2 (18.2%)	n=1 (7.14%)	n=4 (44.4%)
	2	n=0 (0.00%)	n=9 (64.3%)	n=1 (11.1%)
	3	n=0 (0.00%)	n=3 (21.4%)	n=2 (22.2%)
Fecal score	0	n=10 (90.9%)	n=4 (28.6%)	n=4 (44.4%)
	1	n=1 (9.09%)	n=3 (21.4%)	n=1 (11.1%)
	2	n=0 (0.00%)	n=1 (7.14%)	n=1 (11.1%)
	3	n=0 (0.00%)	n=6 (42.9%)	n=3 (33.3%)

Table 3. Comparison of blood gases, electrolytes, and some hemogram parameters between groups

Parameters	**Control Group (n= 11)**	**Acute AP Group (n=14)**	**Chronic AP Group (n=9)**	**P-value**
pH	7.39 (7.35-7.45) ^{a}	7.26 (6.81-7.40) ^{b}	7.18 (7-7.44) ^{b}	0.011
pCO_2 (mmHg)	40.8 (32.9-46.6) ^{b}	56.15(40.3-87.9) ^{a}	47.9 (37.4-60.9) ^{b}	0.000
pO_2 (mmHg)	31.9 (23.4-43.10)	26.4 (8.6-41.6)	24.6 (22.3-40.5)	0.061
HCO_3 (mmol/L)	22.4 (19.4-27.4)	19.9 (13.1-38.3)	23.8 (13.8-33.80)	0.857
BE (mmol/L)	-1.2 (-4.4-4.8)	-6.75 (-18.5-13)	-7.2 (-13.3-8.8)	0.507
sO_2 (%)	69.6 (44.9-79.1) ^{a}	36.9 (5.8-50.8) ^{b}	40.2 (11-53.9) ^{b}	0.000
Na (mmol/L)	145 (130-154) ^{a}	139.5 (116-149) ^{ab}	135 (126-147) ^{b}	0.050
K (mmol/L)	3.9 (3-4.7) ^{b}	4.95 (3.4-12) ^{a}	4.6 (4.3-5) ^{ab}	0.031
Ca (mmol/L)	0.99 (0.79-1.33)	1.33 (0.25-1.42)	1.25 (1.02-1.31)	0.172
Cl (mmol/L)	106 (96-119) ^{a}	99 (90-108) ^{b}	100 (84-113) ^{b}	0.021
Hct (%)	39 (21.5-56.3) ^{a}	27 (16-60) ^{ab}	24 (19-32) ^{b}	0.016
Hb (g/dL)	14.4 (11.2-22.8) ^{a}	9.1 (5.6-13.8) ^{b}	8.3 (6.4-11.2) ^{b}	0.000
Glucose (mg/dL)	87 (73-103)	84.5 (21-196)	80 (28-106)	0.402
Lactate (mmol/L)	0.7 (0.2-1.1) ^{b}	5.18 (0.30-13.33) ^{a}	3.8 (0.95-11.19) ^{a}	0.002

AP: Aspiration pneumonia; pH: Power of hydrogen; pO_2: Partial pressure of oxygen; pCO_2: Partial pressure of carbondioxide; HCO_3: Bicarbonate; BE: Base excess; sO_2: Oxygen saturation; Na: Sodium; K: Potassium; Ca: Calcium; Cl: Chlorine; Hct: Hemotocrit; Hb: Hemoglobin

As a result of the Pearson correlation analysis, a moderate negative correlation was found between CHS and sO_2 ($P<0.05$). There was no significant correlation between the other parameters and CHS. Between blood gas and electrolyte parameters, a moderate negative correlation between pH and pCO_2, a strong positive correlation between pH and BE, a moderate negative correlation between pCO_2 and sO_2, and a strong positive correlation between HCO_3 and BE were found. Correlation analysis results are presented in Table 4.

ROC-based diagnostic performance analyses were performed to investigate the effectiveness of statistically significant clinical and laboratory parameters in differentiating the course of the disease and/or diagnosis. It was accepted that an AUC of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the disease or condition based on the test), 0.6 to 0.8 is acceptable, 0.8 to 0.9 is excellent, and more than 0.9 is outstanding. As a result of the analysis, it was determined that the diagnostic performances of Na, K, Cl, Hct and lactate levels were acceptable in the evaluation of the presence of the disease with AUC>0.7; pH, pCO_2 and CHS were good with AUC>0.8; and sO_2 and Hb levels were excellent with AUC>0.9 in distinguishing the disease chronology and the presence of the disease. ROC-based diagnostic performance analyses are presented in Table 5 and ROC curves are presented in Figure 2.

Table 4. Pearson correlation analysis of calf health score and blood gas and electrolyte parameters

Parameters	Correlations							
	pH	pCO_2	pO_2	HCO_3	BE	sO_2	CHS	pH
pH	1	-0.620**	0.083*	0.590**	0.741**	0.558**	-0.434*	1
pCO_2 (mmHg)		1	-0.484**	0.097*	-0.072*	-0.625**	0.487**	
pO_2 (mmHg)			1	-0.220*	-0.165*	0.597**	-0.389**	
HCO_3 (mmol/L)				1	0.954**	0.094*	-0.102*	
BE (mmol/L)					1	0.245*	-0.218*	
sO_2 (%)						1	-0.676**	
CHS							1	

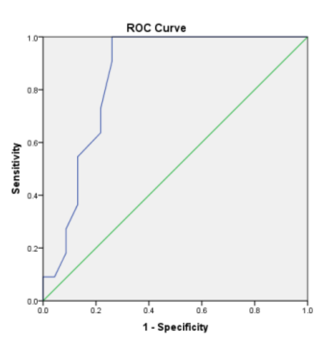
** Sig. (2-tailed) <0.05, * Sig. (2-tailed) >0.05 (Pearson correlation)

Table 5. ROC analysis of parameters determined to be statistically significant between groups

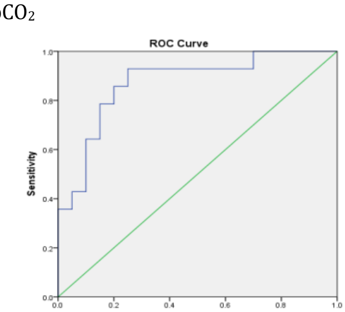
Parameters	AUC	Std. Error	P-value	Asymp. %95 CI		Cut-off	Sensitivity	Specificity	Observed Power
				Lower Bound	Upper Bound				
pH	0.850	0.066	0.001	0.721	0.979	7.34	100%	73.1%	64.9%
pCO_2 (mmHg)	0.871	0.064	0.000	0.747	0.996	46.65	92.6%	75%	71.8%
sO_2 (mmHg)	0.984	0.018	0.000	0.949	1.000	44.50	100%	82.6%	60.2%
Na (mmol/L)	0.735	0.094	0.028	0.551	0.920	139.5	81.8%	60.9%	54.2%
K (mmol/L)	0.738	0.093	0.020	0.556	0.919	4.45	71.4%	60%	74.1%
Cl (mmol/L)	0.771	0.086	0.012	0.602	0.940	100.5	81.8%	65.2%	74.3%
Hct (%)	0.783	0.088	0.008	0.610	0.955	31.4	81.8%	69.6%	70.9%
Hb (g/dL)	0.968	0.025	0.000	0.919	1.000	11.05	100%	82.6%	71.6%
actate (mmol/L)	0.771	0.085	0.008	0.605	0.938	1.14	92.9%	65%	71.8%
CHS	0.838	0.068	0.001	0.705	0.970	4	92.9%	60%	100%

AUC: Area under curve; Std. Error: Standart error; pH: Power of hydrogen; pCO_2: : Partial pressure of carbondioxide; sO_2: Oxygen saturation; Na: Sodium; K: Potassium; Cl: Chlorine; Hct: Hemotocrit; Hb: Hemoglobin; CHS: Calf Health Score

pH



pCO_2



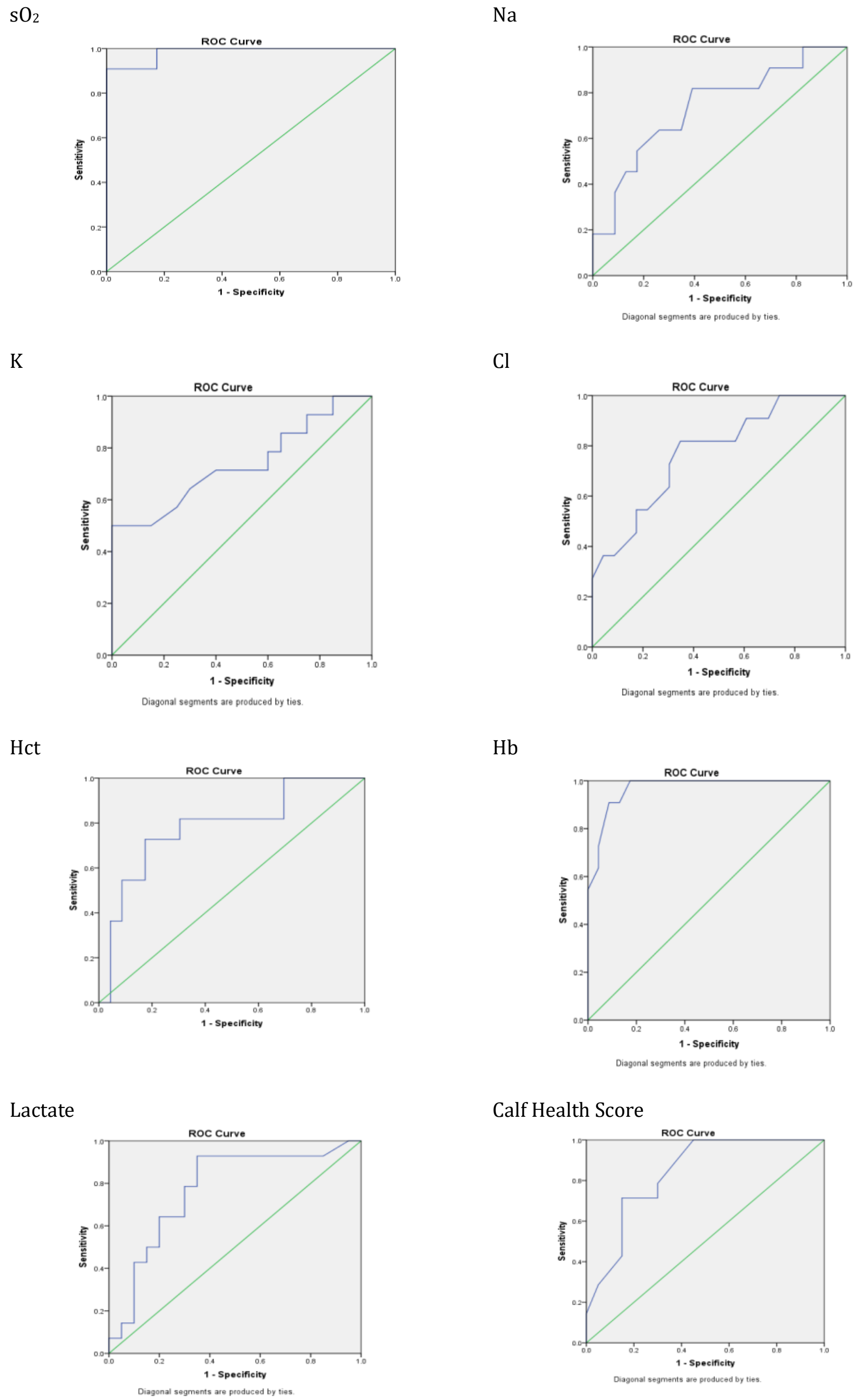


Figure 2. ROC curves of the parameters determined to be statistically significant between groups

Discussion

In this study, significant alterations were detected in venous blood gas and electrolyte analytes and CHS assessment. Compared to the Control Group, calves with AP had lower pH, sO_2, Na, Cl, Hct and Hb levels, and higher CHS, pCO2, K, and lactate levels. Only the pCO_2 level was statistically different between calves with acute and chronic AP and determined to be higher in acute cases. ROC-based diagnostic performance analysis revealed that the diagnostic performances of pH, sO_2, Na, Cl, Hct, and Hb levels were to distinguish calves with AP from healthy ones; pCO2 level was to differentiate acute and chronic cases were high. As a result, it was concluded that venous blood samples can be used to classify the course of the disease, significant changes can be observed in venous blood gas and electrolyte levels in calves with AP, CHS was negatively correlated with sO_2 level, and pCO2 level could provide important information in differentiating acute and chronic AP cases.

Incidental inhalation of large amounts of usually liquid foreign material result in aspiration pneumonia and the most common cause is using an inappropriate bottle for drenching or an unsuitable drenching technique (1). If large volumes of fluid have been aspirated, death is almost instantaneous, but gangrenous bronchopneumonia may also develop due to the irritant characteristics of the aspirated material (2). However, as the clinical and pathological features of aspiration pneumonia are quite variable, the onset of clinical signs is often insidious (2,19).

In humans, it has been reported that clinical findings such as tachycardia, tachypnea, and prolonged expiration time are more prominent in acute cases than in chronic cases (18). The clinical findings in the Acute AP Group of the present study were consistent with previous reports (2,20). Heart and respiratory rates were higher in the Acute AP Group compared to the other groups ($p<0.001$). Findings such as cyanosis, tachypnea, and dyspnea in the Acute AP Group were thought to be related to the cardiovascular compensation response to the respiratory distress and hypoxemic state due to AP in order to optimize perfusion and improve gas exchange (21). It was reported that the body temperature is usually elevated within a range of 39.5° to 41 °C in cattle with AP (1,3). Compared with the other groups, numerically lower body temperature of the calves of the Acute AP Group was associated with possible development of sepsis, vasodilation or decreased tissue perfusion and the presence of Gram-negative bacteria (22). In addition, the low body temperature of the Acute AP Group may also be associated with pulmonary edema, a common manifestation of aspiration pneumonia (23,24). Body temperature, heart and respiratory rates of the Chronic AP Group which were determined to be similar to healthy calves were thought to be related to the body's compensation/tolerance response to the aspirated fluid (2,25).

There is no gold standard for antemortem diagnosis of respiratory system diseases of young dairy calves (7,8,26). Although there is significant morbidity, mortality, economic loss, welfare and management problems, screening of cattle for respiratory system disease is rarely practiced in the farm environment and comprehensive disease screening tools have disadvantages such as costliness and requirement of expertise (8). For this reason, it has been reported that a standardized scoring system is needed to detect respiratory system diseases in a timely manner (7). In the present study, CHS was used to evaluate the clinical course and severity of AP and it was determined that calves with AP had higher scores than healthy ones ($p<0.001$), but no statistical difference was observed between acute and chronic AP cases. The highest scores of the Acute AP Group were observed in cough, nasal discharge, eye or ear and fecal score parameters. In the Chronic AP Group, the highest score was in the cough score. It was thought that the low CHS of the calves with chronic AP was related to the compensation response of the body to the aspirated fluid (2). This finding may be related to the body's ability to tolerate continuous and/or small amounts of fluid aspiration in calves, similar to chronic AP cases reported in humans (20,25). Although the high CHS of the present study were consistent with the studies performed in calves with respiratory disease (27), they had low efficiency in differentiating the chronology of AP cases. Nevertheless, CHS assessment can be helpful for farmworkers in identifying the calves that need further examination and in the diagnosis of other respiratory diseases including AP or in selecting the appropriate diagnostic test, minimizing antibiotic use, and preventing chronic respiratory diseases (7).

The effects of respiratory diseases on the oxygenation of tissues and removal of CO2 from the body cause changes in blood gas and acid-base balance at various degrees in calves with respiratory system disease (10,11,28,29). Thus, the evaluation of blood gas and electrolyte parameters is an indispensable tool for the evaluation of the metabolic and respiratory conditions of the animal (16). Ventilation, pulmonary diffusion, pulmonary hemodynamic disorders and/or deterioration in ventilation-perfusion balance in the pathogenesis of respiratory tract diseases of neonatal calves cause a decrease in blood pO_2 levels (10).

Alveolar hypoventilation, acute hypoxemic respiratory failure, severe hypercapnia vasodilatation and impaired perfusion cause profound effects on acid-base regulation (30). The increase in blood pCO_2 levels is due to severe damage to the lung parenchyma and the deterioration of CO2 elimination due to large atelectasis areas (27). Since the clinical presentation of AP cases is highly variable, further classifying the cases as acute or chronic also enables the evaluation of complications that may occur due to AP (18). It is reported that the most common findings in blood gas analyses of AP cases in humans are high pCO2 and low pO_2 and sO_2, which may be lower in acute cases and normal in chronic cases. In addition, respiratory acidosis with hypoxia and hypercapnea is a common finding (27). In the present study, compared to the Control Group, low pH, sO_2 and high lactate levels of calves with AP and high pCO_2 levels of the Acute AP Group were though to be associated with hypoxia (31). In addition, the pCO_2 level of the Chronic AP Group, which was similar to the healthy calves, was interpreted as the ability of the lungs to activate the compensation mechanisms in order to remove CO_2 sufficiently so that it would not accumulate in the blood. Moreover, acidosis due to insufficient use of lactate and high lactate concentrations were associated with anaerobic metabolism in calves with AP (32). Since the changes in the blood gas analysis may differ depending on the balanced compensation mechanisms given by the body, values such as BE and HCO_3, which were found to be statistically insignificant in the present study, were thought to be related to the insufficient compensation response of the calf to respiratory acidosis. This finding was consistent with the fact that patients with chronic AP in human medicine may have normal blood gas values even in venous blood samples (18).

Electrolyte abnormalities are the most common complication of various etiologies of pneumonia, including coronavirus disease 2019 (COVID 19) (33). Hyponatremia is an important cause of morbidity and mortality for different diseases such as lung diseases, myocardial infarction, heart failure and pulmonary embolism. Gas exchange disorders due to lung diseases also affect the release of renin, aldosterone, atrial natriuretic peptide and vasopressin. Decreased renal blood flow increases sodium and water retention, and finally hyponatremia occurs with pulmonary edema (34). Low Na levels ($P<0.05$) of the Chronic AP Group of the present study were associated with water and Na retention due to hormonal disorders. In addition, the fact that Na levels in acute AP cases were similar to healthy calves was interpreted as the response of hormonal and endothelial factors to gas exchange disorders that may occur in the later stages of the disease (33). The increase in venous potassium in hypoxic conditions has been associated with the role of extrinsic nerves in potassium release. Sympathetic nerves supplying skeletal muscle are strongly activated in hypoxia in reflex response to chemoreceptor activation, and therefore, these nerves may directly or indirectly mediate potassium release. In addition, hypoxia with or without respiratory acidosis may alter membrane action potentials and reabsorption kinetics, and vasodilation in the peripheral circulation in hypoxia may increase circulating potassium (35). In the present study, high potassium level ($p<0.031$) in the Acute AP Group was associated with the severity of hypoxia and impaired reabsorption kinetics in the acute phase of AP. It is well-known that acute dyspnea or even apnea, cyanosis, pulmonary edema and hypoxia may occur in cases of AP (20). Elevations in hemoglobin and hematocrit levels were reported as a result of compensatory processes reflecting chronic pulmonary disease and stimulation of erythropoiesis (10). However, opposite changes were reported by several researchers (36,37). Therefore, it was interpreted that the low hemoglobin and hematocrit levels of the calves with AP of the present study may be associated with failure of activation of erythropoiesis (38). In addition, the numerically lower hematocrit level of the Chronic AP Group may be related to chronic inflammation and the fact that the failure is more severe.

It was thought that pH and pCO_2, pCO_2 and sO_2, which were found to be negatively correlated with each other in the present study, may be related to the extent of lung damage and the severity of respiratory distress (31). In addition, the negative correlation between CHS and sO_2 was consistent with previous reports recommending the evaluation of CHS in respiratory diseases of calves (27). As a result of ROC-based diagnostic performance analysis, it was determined that the diagnostic performances of pH, sO_2, Na, Cl, Hct and Hb in differentiating calves with AP from healthy ones, and pCO_2 level in differentiating acute and chronic cases were high. In the present study, CHS was evaluated for the first time in calves with AP and a moderately strong negative correlation was determined. It is recommended to evaluate CHS and determine its diagnostic performance by ROC analysis in naturally developed AP cases in a larger number of animals.

The use of arterial blood samples has been suggested in the evaluation of lung ventilation, and it has been reported that there is a weak correlation between arterial sO_2 and pO_2 and venous sO_2 and pO_2 values (32). Despite the fact that the main limitation of this study is the use of venous blood samples, the technical difficulty of obtaining arterial blood samples under farm conditions in veterinary medicine causes the preference of venous blood samples. Venous blood is collected the most frequently and there are many studies in which respiratory system diseases in calves are evaluated with venous samples (16,27,29,31,39). Also, it was suggested that the venous blood gas analysis could be considered supportive rather than an alternative to the clinical evaluation (40). Even though examination of venous blood does not yield complete information on the respiratory functions (39), it can be considered for initial assessment in respiratory diseases with high mortality such as AP and COPD and this may simplify the care pathway (13). This study confirms previous studies evaluating venous blood samples in calves with respiratory diseases, but it is recommended to validate the present data to demonstrate the severity of AP, not in determining the course of the disease, in arterial blood samples.

It was observed that neonatal calves with AP developed as a result of incorrect drenching and feeding with inappropriate bottles can be classified as chronic and acute on the basis of venous oxygen saturation. In addition, it was determined that the compensation mechanisms in the body were activated in chronic cases, and the clinical findings along with pCO2 and sO2 levels were similar to the healthy ones, and that they had excellent diagnostic performance in the chronological classification of the disease. Although the CHS evaluation was useful in distinguishing calves with AP from the healthy ones, it was observed that it did not have sufficient performance in classifying the cases as acute and chronic. As a result, it was concluded that important alterations can be observed in venous blood gas, electrolyte and CHS parameters in neonatal calves with AP; certain clinical and laboratory parameters of chronic cases were similar to the healthy ones; pCO2 and sO2 levels were important in classifying the course of the disease, which may enable the evaluation of complications that may occur due to AP in further stages of the disease.

Venous blood samples can be used to classify the course of the disease; significant alterations in venous blood gas, electrolyte, and CHS can be observed in neonatal calves with AP such as decreased pH, sO2, Cl, Hb, and increased CHS, K, and lactate levels. In addition, it is recommended to use a polyethylene terephthalate bottle with a silicone nipple (7 cm) and a flow control dial in order to avoid or minimize the risk of the occurrence of aspiration pneumonia.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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