Prognostic value of acid-base changes and clinical signs of respiratory disease severity in hospitalized dairy calves

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SUMMARY

Bovine respiratory disease (BRD) represents a significant concern due to its negative effects on animal health, short- and long-term productivity, and substantial economic losses in both dairy and beef calves. This retrospective study aims to identify the predictors associated with outcomes in hospitalized calves affected by BRD.

From 2005 to 2020, 652 calves diagnosed with respiratory problems were admitted to the Veterinary Teaching Hospital of the University of Milan. Data on signalment, clinical signs, auscultatory findings, blood gas results, microbiological findings, and outcomes were collected. Among these, 184 Holstein Friesian calves aged 1 to 6 months (17 males and 167 females) with uncomplicated BRD were included in the study. Upon hospitalization, the calves were treated according to a standardized protocol involving antibiotics, mucolytics, and anti-inflammatory drugs. The potential clinical predictors of survival were evaluated using multivariable logistic regression. The association between predictors and outcome was considered significant when the p-value was <0.05.

Post-treatment, 130 calves were discharged in a healthy state, whereas 54 calves succumbed to the disease. A multivariable logistic regression model indicated that survival rate was significantly associated to auscultatory findings with a higher risk of survivor in calves with only increased breath sounds compared to calves with increased bronchial sound (P = 0.006; odds ratio: 7.359; 95% confidence interval: 1.857-29.156). In addition, increased base excess was found in survived calves compared to non-survived calves (P = 0.012; odds ratio: 1.14; 95% confidence interval: 1.013-1.226).

These findings suggest that calves with lower auscultatory scores are more likely to survive. Additionally, the presence of pathological bronchial sounds indicates more severe lung lesions compared to other alterations in normal breath sounds. Furthermore, a higher base excess value correlates with a better outcome. The increase in base excess indicates that the metabolic compensatory mechanisms in animals with a positive outcome effectively manage the respiratory acidosis induced by lung lesions, while in cases with a negative outcome, these compensatory mechanisms are either absent or inadequate.

KEY WORDS

Bovine Respiratory Disease, Prognostic factors, Dairy calves, Outcome.

INTRODUCTION

Bovine respiratory disease (BRD) is a multifactorial condition that affects cattle, causing significant economic losses due to mortality, morbidity, and long-term effects on growth and productivity (1-5). This disease is one of the most common and costly health issues in the cattle industry worldwide. It primarily affects the lower respiratory tract and can lead to severe pneumonia, impacting the overall health and performance of the animals (1-3). The causes of BRD are complex and involve a combination of stress factors, viral infections (such as infectious bovine rhinotracheitis virus and bovine viral diarrhea virus), bacterial pathogens (such as *Mannheimia haemolytica* and *Pasteurella multocida*), and environmental conditions (4,5).

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The clinical signs of BRD include cough, fever, and nasal discharge, but many animals have subclinical BRD, which means they do not exhibit obvious symptoms despite being infected. For this reason, clinical signs have demonstrated low diagnostic accuracy (6-8). Subclinical cases can go unnoticed and untreated, leading to a greater spread of the disease within a herd and increased economic losses.

In recent years, literature has focused on studying diagnostic methods to achieve greater diagnostic accuracy for this disease. Although no practical and affordable gold standard tests for the diagnosis of BRD are available (9), thoracic ultrasonography (TUS) represents the most accurate in vivo diagnostic method (10-12). TUS allows for the visualization of lung lesions and provides detailed information on the extent of lung involvement, making it a valuable tool for diagnosing BRD. Similarly, however, several studies have also focused on improving the diagnostic accuracy of clinical signs, which are often much more user-friendly than TUS (13-17).

In particular, studies have focused on the use of certain clinical scoring systems that take various clinical signs into account. The two most commonly used clinical scores are the Calf Respiratory Scoring Chart, which considers five different clinical signs (rectal temperature, presence of cough, nasal discharge, eye score, and ear score) on a 4-level scale (from 0 to 3) (13), and the California Respiratory Scoring System, which uses a dichotomous score for nasal discharge, ocular discharge, rectal temperature, ear position, spontaneous cough, and abnormal breathing. However, the weight assigned to different clinical signs is not the same (14). For both systems, animals with a total score of less than 5 are considered diseased (13,14).

Another interesting method for the diagnosis of BRD, which has recently shown good results in terms of diagnostic accuracy, is auscultation (17). The main limitation of auscultation is the classification of respiratory sounds and inter-operator reproducibility, but the results obtained make it a practical and economical method under field conditions (16,17).

Nevertheless, the severity of BRD-related lung damage, clinical signs, and metabolic changes during episodes has been poorly explored. Two studies evaluated the use of TUS and clinical scoring to monitor the treatment of BRD in fattening bulls (18,19). In these studies, both methods (TUS and clinical scoring) showed improvement in bulls with successful treatment. For the metabolic changes, two studies specifically investigated lactate as a negative prognostic factor; in beef calves, L-lactate concentrations higher than 4 to 5 mmol/L are a good predictor of death and were used to assess BRD severity (20,21). Prognostic predictors can help practitioners distinguish between calves with favorable prognoses and those at high mortality risk. However, more data must be collected on the most easily obtainable clinical and laboratory findings associated with outcomes in calves affected by BRD. The current study aims to identify significant risk factors associated with survival in a hospitalized population of calves affected by BRD. Clinical data, thoracic auscultation findings, and blood gas analysis results were used to analyze predictors.

MATERIALS AND METHODS

Animals

The study population consisted of client-owned dairy calves admitted to the Veterinary Teaching Hospital of the University of Milan with respiratory signs upon preliminary examination. Calves were retrospectively recruited from patients admitted between January 2005 and June 2020, aged between 1 and 6 months. The clinical diagnosis of BRD was based on clinical examination and thoracic auscultation findings. Calves with other concurrent diseases (e.g., enteritis, arthritis, umbilical pathologies) or those presenting with aspiration pneumonia at the time of hospitalization were excluded from the study. This retrospective study was authorized by Ethical Committee of University of Milan (Protocol No. 2/2016 of 15.02.2016).

Clinical procedures

Information saved from medical records included clinical and laboratory findings from the initial examination, therapy, and outcome. For each animal, identification, sex, body weight (kg), age (d), rectal temperature (°C). During the preliminary visit, every calf underwent a clinical examination, and clinical data were recorded using the Calf Respiratory Scoring Chart (CRSC) developed by Wisconsin University (13). Briefly, CRSC requires assigning a score based on the survey of five clinical signs: rectal temperature, cough, nasal and eye discharge, and abnormal ear position. For each sign, a score from 0 to 3 was assigned based on severity (normal = 0, slightly abnormal = 1, abnormal = 2, and severely abnormal = 3). Eye discharge and ear position were considered together, recording only the highest score. The minimum score is 0 and the maximum is 12. Calves with a total respiratory score of 5 or higher were considered to BRD positive (13).

Each animal was auscultated using a conventional stethoscope. The auscultatory exam was performed on both hemithorax, starting from the upper-middle line, right behind the cranial edge of the lung projection area, proceeding by horizontal or vertical lines until the entire area was auscultated, focusing on each point for 2-3 inspiratory acts by the same operator. Lung sounds were scored as describe by Boccardo et al. (17). Briefly, AUSC0 (normal breath sounds) refer to the typical sounds heard during inhalation in lungs with normal aeration. AUSC1 (increased breath sounds) indicate a moderate amplification in the intensity of breath sounds audible during both inhalation and exhalation, with a clear distinction between the two phases. AUSC2 (crackles/ wheezes) refer to manifestations such as wheezes and crackles, indicative of bronchial diseases. AUSC3 (increased bronchial sound) indicate signs of lung consolidation, characterized by heightened bronchial sounds that mimic the tone heard during tracheal auscultation, further complicate the differentiation between inhalation and exhalation sounds. Finally, AUSC4 (pleural friction rubs) refer to abnormalities such as pleural friction rubs. When multiple abnormal sounds were present in the same calf, the highest score recorded from auscultation at six anatomical sites was used for assessment.

A blood sample was collected from the jugular vein in a 9-mL tube without anticoagulant to determine serum total protein (STP). Samples were allowed to clot and then centrifuged at 20°C for 10 minutes at 900 g. To determine STP concentration, a hand refractometer (MR514ATC, Milwaukee S.r.l, Gallarate, Italy) was used. Once centrifuged, the serum was aspirated into a soft plastic Pasteur pipette, and a drop of serum was then used for the analysis. A second blood sample was anaerobically collected from the jugular vein into a disposable heparinized 2.5 mL syringe for venous blood-gas analysis. Blood pH, bicarbonate ($HCO3^-$), partial pressure of carbon dioxide ($pCO2$), base excess (BE), blood sodium (Na^+), chlorine (Cl^-), potassium (K^+), anion gap (AG), packed cell volume (PCV), and hemoglobin (Hb) were immediately determined using a blood gas analyzer (AVL Opti CCA, Diamond Diagnostic, Holliston, USA).

Housing and outcome

During hospitalization, calves were housed in individual calf brick pens (1.8 m × 1.2 m) in an indoor stall with a controlled temperature of 18°C. The pens were bedded with straw and cleaned daily. Freshwater, hay, and calf starter were offered ad libitum. Calves were monitored twice daily with complete clinical examinations. Surviving calves were discharged from the hospital in a healthy state, i.e., normal hydration and vigor, good appetite, and normal breathing for at least two days.

Statistical Analysis

For all statistical analyses, SPSS 26.0 for Mac (IBM, Armonk, USA) was used. Descriptive statistics were performed, with continuous variables expressed as mean ± SD and categorical variables as frequencies and percentages. Continuous variables considered in the statistical analysis were age, body weight, STP, rectal temperature, and blood gas findings. Categorical variables included sex, WCRSC, and AUSC. To identify which variables correlated with mortality, a multivariable logistic regression model was performed. Only parameters with $P < 0.1$ were included in the final multivariable logistic regression model. Parameters with $P < 0.05$ were considered correlated with mortality.

RESULTS

The medical records of 184 calves met the criteria for inclusion in the study, from a total of 5626 cattle admissions over the same period. Six hundred and fifty-two animals were diagnosed with a respiratory airway condition. Of those, 294 animals were diagnosed with BRD, 60 with aspiration pneumonia, and 257 presented with other comorbidities (e.g., neonatal calf diarrhea, arthritis, omphalitis). Finally, the medical records of 184 calves (17 (9.24%) males, 167 (90.76%) females) met the criteria for inclusion in the study. Analysis of data retrieved from the medical records is summarized in Tables 1 and 2. No calves included in the study had an auscultation score of AUSC0 or AUSC4. One hundred and thirty (70.65%) calves survived after hospitalization, and 54 (29.35%) did not survive. The results of the first multivariable logistic regression revealed a statistically significant interaction between outcome and both BE and AUSC ($P < 0.1$). In contrast, CRS was not significantly correlated with outcomes in calves affected by BRD. BE and AUSC were thus included in the final model, which revealed that both these variables were correlated with outcomes as reported in Table 3 ($P = 0.012$ and $P = 0.006$, respectively).

DISCUSSION

The results of the present study suggested that the survival rate of calves with increased breath sounds (AUSC 1) and those with crackling and wheezing sounds (AUSC 2) increased by 7.35 and 1.91 times, respectively, compared to calves with increased bronchial sounds (AUSC 3). Crackles develop in bronchopneumonia as bronchiolar exudation increases, and in viral interstitial pneumonia, wheezes—caused by high-velocity air passing through a narrowed airway during forced respiration—may be audible (22, 23). When complete consolidation occurs, increased bronchial sounds, heard during inspiration and expiration, become louder if the bronchial lumen remains open and the surrounding lung tissue has been replaced by cells and tissues (23). Auscultation is an inexpensive diagnostic method used by practitioners and has been assessed to have good specificity (97 - 98%) and sensitivity (66 - 81%) compared to thoracic ultrasonographic assessment of lung lesions when the auscultatory findings are well categorized (17). However, auscultation is subjective (24), requiring a well-trained person with good acoustic abilities to recognize abnormal sounds correctly (25). In recent years, a computer-aided auscultation device has been developed to detect abnormal lung sounds automatically. This new technology is promising as a rapid and accurate method for BRD diagnosis, with sensitivity and specificity estimated at 93% and 90%, respectively (25). Such an instrument may improve case definition, risk assessment, and stratification of cattle by lung scores (26).

In our study, clinical signs were not associated with survival. As reported by Šoltésová et al. (27), clinical examination, which evaluates clinical symptomatology and only partially disease

Table 1 - Mean ± standard deviation for the considered continuous variables at admission in 184 survived and deceased Holstein Friesian calves affected by BRD. To identify which of these variables correlated with mortality, an initial multivariable logistic regression model was performed. Only parameters with $P < 0.1$ were included in the final multivariable logistic regression model (P value[1]). The parameters with $P < 0.05$ were considered as correlating with mortality (P value[2]).

Variables	Survived calves	Deceased calves	P value[1]	P value[2]
Age (d)	62.554 ± 38.506	72.796 ± 45.517	-	-
Body weight (kg)	68.65 ± 33.372	70.90 ± 36.812	-	-
Rectal temperature(°c)	39.370 ± 0.822	39.004 ± 1.102	0.249	-
Serum total protein (g/dl)	5.83 ± 1.068	5.25 ± 1.314	-	-
Ph	7.4133 ± 0.06541	7.3227 ± 0.10189	0.260	-
Partial pressure of carbon dioxide (mmHg)	48.3618 ± 6.720	47.5583 ± 11.667	0.526	-
Blood bicarbonate (mmol/l)	29.885 ± 5.666	24.604 ± 7.341	0.234	-
Base excess (mmol/l)	5.659 ± 5.533	0.521 ± 8.394	0.005	0.012
Blood sodium (mmol/l)	136.067 ± 8.02381	132.850 ± 8.725	0.510	-
Blood potassium (mmol/l)	4.109 ± 0.661	4.312 ± 1.368	0.498	-
Blood chloride (mmol/l)	100.811 ± 6.695	100.252 ± 7.784	0.287	-
Anion gap (mmol/l)	10.191 ± 4.823	13.179 ± 8.819	0.234	-
Packed cell volume (%)	29.295 ± 5.351	30.785 ± 9.753	0.220	-
Hemoglobin (g/dl)	10.466 ± 2.317	10.607 ± 3.179	0.231	-
Cardiac frequency	113.975 ± 25.622	118.519 ± 28.006	0.893	-
Respiratory rate	70.697 ± 24.757	67.654 ± 22.678	0.703	-

Table 2 - Frequencies and percentages of the categorical variables at admission for surviving and deceased calves.

Variables	Score	Survived calves	Deceased calves
Auscultatory score	1	44 (33.8%)	2 (3.7%)
	2	20 (15.4%)	14 (25.9%)
	3	48 (36.9%)	36 (66.7%)
Dehydration score	0	97 (74.6%)	27 (50.0%)
	1	18 (13.8%)	11 (20.4%)
	2	7 (5.4%)	9 (16.7%)
	3	1 (0.8%)	6 (11.1%)
Calf respiratory score	0	5 (3.5%)	5 (9.3%)
	1	5 (3.5%)	0
	2	23 (17.7%)	7 (13.0%)
	3	20 (15.4%)	12 (22.2%)
	4	10 (7.7%)	8 (14.8%)
	5	29 (22.3%)	8 (14.8%)
	6	13 (10.0%)	4 (7.4%)
	7	11 (8.5%)	3 (5.6%)
	8	6 (4.6%)	2 (3.7%)
	9	3 (2.3%)	1 (1.9%)
	10	0	0
	11	0	0
	12	0	0

severity, represents the starting point in diagnosing lung diseases. Clinical examination alone makes it difficult or impossible to sufficiently assess morphological and functional changes, leading to delayed treatment and uncertain prognosis.

Our study assessed the role of base excess (BE) as a predictor of outcomes in calves affected by BRD. Among laboratory variables, only BE ($P = 0.012$; odds ratio: 1.14; 95% confidence interval: 1.013-1.226) was significantly correlated with outcomes. These results show that a higher BE value is correlated with a better outcome. To our knowledge, only a few studies have evaluated the prognostic value of BE in calves affected by BRD. Šoltésová et al. (27) reported that mean BE values were higher in sick animals, even in calves with less severe respiratory clinical signs, compared to healthy ones, which had lower BE values. Literature research shows that Husain et al. (28), Davis et al. (29), Sauaia et al. (30), and Paladino et al. (31) investigated this topic in species other than bovine, relating it to multiorgan failure caused by shock. In those studies, BE was correlated as a predictor of outcomes in traumas resulting in tissue hypoxia. Although not directly related to bovine species, it is supposed that a similar condition of tissue hypoxia may be found in calves affected by severe BRD. Similarly, previous studies also assessed base deficit as a marker for outcomes and used it as an indirect measure of lactic acidosis, often related to tissue hypoxia. Husain et al. (28) found significant differences in BE between survivors and non-survivors. Paladino et al. (31) investigated metabolic parameters such as base deficit and lactate, which were highly sensitive indicators of blood loss by measuring tissue perfusion, improving the identification of major injury after trauma.

Table 3 - Multivariable logistic regression results for exploring the relationship between medical records and outcome.

Variables [a]	Odds Ratio	95% Confidence Interval
AUSC1	7.359	1.857 - 29.158
AUSC2	1.919	0.520 - 7.089
AUSC3	1	/
Base excess (mmol/L)	1.114	1.013-1.226

[a]The reference category is surviving calves; AUSC1: increased breath sounds; AUSC2 crackles/ wheezes; AUSC3: increased bronchial sound. AUSC1 and AUSC 2 have been compared to AUSC 3.

Metabolic indices of acid-base balance reflect possible compensating regulatory processes in the body in response to disturbed homeostasis due to respiratory acidosis development (32). Thus, it is plausible that increased BE indicates that the metabolic compensatory mechanisms in animals with a positive outcome can manage the respiratory acidosis induced by lung lesions, while these mechanisms are inadequate or absent in cases with negative outcomes.

In this retrospective study, blood gas analysis data were from venous blood drawn from the jugular vein and not arterial blood. During respiratory diseases, an arterial blood sample is crucial for evaluating lung dysfunctions, providing more information about partial pressure of oxygen (pO2) and tissue oxygenation. Compared to partial pressure of carbon dioxide (pCO2), pO2 alterations can be observed even in mild lung affections (27, 28).

The description of blood-gas changes in calves affected by BRD was recently provided by Boccardo et al. (33). The alterations highlighted in our study were not found in Boccardo et al. (33) research, which instead emphasized blood glucose as the most affected parameter by BRD. However, our study results are challenging to compare because Boccardo et al. (33) used arterial blood samples from BRD-affected calves that did not require hospitalization. Furthermore, their study did not analyze factors associated with outcome, and survival was not a considered outcome measure.

Our study has limitations, with the most significant being the lack of thoracic ultrasound use as a method for BRD diagnosis. This data could not be analyzed because the study period spans a wide range, and the introduction of thoracic ultrasound as a more accurate diagnostic method for BRD was first described in 2016 (34). Further studies including the use of thoracic ultrasound are necessary in the future.

CONCLUSION

Auscultatory scores and BE values are among the easiest clinical and laboratory findings to obtain during preliminary examinations. The results of this retrospective study indicate that BE and AUSC can differentiate calves affected by BRD at higher mortality risk from those with a greater probability of a better outcome. Calves with AUSC 1 and AUSC 2 have better outcomes than calves with AUSC 3. Moreover, higher BE values are useful as a predictor of better outcomes, while lower BE values indicate a higher mortality risk.

Future studies should aim to identify a cut-off value for BE to help practitioners distinguish between calves with a positive prognosis and those with a high mortality risk.

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