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The association between Whisper ® lung scores and feedlot performance in crossbred calves

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The association between Whisper® lung scores and feedlot performance in crossbred calves

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The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this thesis. The Graduate College will ensure this thesis is globally accessible and will not permit alterations after a degree is conferred.

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ABSTRACT

A cohort study was conducted in a population of crossbred feeder steers at a commercial feedlot in central Iowa. This study assessed the relationship between Whisper® lung scores taken at feedlot arrival and feeding performance and health performance. Lung scores were taken at initial processing along with individual weights. Feeding performance outcomes included average daily gain (ADG), feed efficiency (FE), hot carcass weight (HCW), dressing percentage (DRESS), marbling score (MARB), fat thickness (FAT), and ribeye area (REA). Health outcomes included treatment for BRDC (RTX), death due to BRDC (RD), being diagnosed with chronic BRDC (RC), and dying after treatment for BRDC (RCF). A causal diagram was used to inform model building for linear and logistic regression models.

A total of 401 crossbred steer calves were enrolled in the study. Health data and ADG data from 389 steers were used in the health outcomes analyses and the ADG linear regression model. Carcass data from 227 steers were used in all other feeding performance analyses. Arrival age and arrival weight were found to be significant confounders and were included in the linear regression model analyzing arrival lung score's association with ADG. There was no significant association between arrival lung score and ADG, FE, HCW, DRESS, MARB, FAT, or REA. There was a significant increase in the odds ratio for RTX but only for calves with an arrival lung score of 5 (OR 1.27, 95% CI 1.03-1.57, p-value 0.005). There was a significant increase in the odds ratio for RD but only for calves with an arrival lung score of 4 (OR 1.06, 95% CI 1.00-1.13, p-value 0.02). There was no association between arrival lung score and being diagnosed with chronic BRDC or dying after treatment for BRDC. This study

demonstrates that arrival lung score may be associated with treatment for BRDC and death due to BRDC but more research needs to be done.

CHAPTER 1. LITERATURE REVIEW OF NON-HUMAN BRDC DIAGNOSTICS

Background

Bovine respiratory disease complex (BRDC) is a prominent problem in the cattle feeding industry. This complex is the most commonly diagnosed disease in feedlot cattle, affecting approximately 16.2% of all cattle on feed[37]. The negative impact of BRDC is due to multiple factors. Costs associated with treatment, labor, reduced feeding performance, reduced carcass value, and increased death loss all contribute to reduced profitability. On average, treatment for BRDC is more expensive than treatment of any other condition seen in the feedlot[37]. Severe lung lesions seen at slaughter are associated with decreases in average daily gain, hot carcass weight, less internal fat, and lower marbling scores[10]. Either untimely treatment of or undiagnosed BRDC can lead to these lesions and economic losses associated with them.

Finding cattle affected with BRDC is a challenge in all feedlots. Traditionally, feedlots have relied on a two-step approach for diagnosing BRDC. The first step is identifying sick animals in their home pens. The second step is confirming that those identified animals are truly sick and establishing a cause for their illness. The most common means of identifying sick animals in their home pens has been clinical evaluation or pen riding/walking. Traditionally, rectal temperature has been the most common means of confirming illness.

Various “non-human” diagnostic tests have been developed and investigated as a means of improving the accuracy of diagnosing BRDC in feeder cattle. All diagnostic tests used in a feedlot setting can be categorized as either detection tests (used to identify sick cattle in their home pen) or confirmatory tests (used to determine if BRDC is the cause of their symptoms). A lack of an ante-mortem gold standard for BRDC diagnosis has made establishing sensitivity and specificity of the diagnostic tests difficult.

Due to the lack of an ante-mortem gold standard, a statistical approach has been used in leu of a gold standard. In recent years, studies have started to use a Bayesian statistical approach to estimate sensitivity and specificity of clinical evaluation and more recently other diagnostic modalities by using two known imperfect tests[41]. Bayesian latent class analysis uses the known imperfections of the tests as well as the prevalence of the disease in the population to establish a more accurate sensitivity and specificity of the diagnostic test in question. Because the tests are already assumed to be imperfect, a true gold standard test is not necessary when using this statistical approach.

Diagnostic test analyses are often difficult to perform and lend themselves to bias. With a lack of a gold standard, classification bias is a major issue. Classification bias occurs when the reference test is not 100 per cent accurate. This results in the disease state to not always be correctly identified[28]. When diagnostic test accuracy varies based on the severity of the disease, spectrum bias becomes an issue as well[28]. Comparability of studies to each other becomes limited due to the number and variation of the diagnostic tests that are being used as gold standards in each study. This paper will attempt to present and evaluate the available data on the utility of diagnostic tests used to identify and confirm BRDC in cattle.

Detection Tests for BRDC

Tests used to detect cattle with BRDC in their home pen are focused on identifying early physiologic and behavioral changes associated with the disease. These changes include variation in feeding behavior, locomotion and movement, and internal and external temperature. Ideally, detection tests should be highly sensitive to detect all animals in the pen with BRDC.

Clinical Evaluation

While this paper's focus is on "non-human" methods of diagnosing BRDC, clinical evaluation of cattle in the pen needs to be discussed as well. Clinical evaluation is not a perfect test but is the standard by which other diagnostic tests are measured due to its wide application in commercial feeding operations. Most of the symptoms noted during evaluation are nonspecific physiologic reactions to any infection and subsequent fever. Symptoms such a depression, lethargy, rough hair coat, anorexia, and dehydration are often noted[14]. However, these symptoms are not specific for BRDC and can arise with fever of any origin[14]. Respiratory rate has also been described as a symptom noted during clinical evaluation. However, one study was not able to demonstrate a significant change in respiratory rate for calves subjected to a known infectious challenge[12].

Both White et al (2009) and Timsit et al (2016) have used clinical evaluation and lung lesions at slaughter in Bayesian models. White et al (2009) calculated the sensitivity and specificity of clinical evaluation to be 61.8% and 62.8% respectively. Timsit et al (2016) calculated the sensitivity and specificity of clinical evaluation to be 27% and 92% respectively. Timsit et al (2016) noted that their calculations had wide credible intervals and found significant heterogeneity among those studies that were evaluated in their meta-analysis. This study highlighted the fact that there is no standard set of clinical signs associated with BRDC and no standard for diagnosis.

Because of the statistical approach of these studies, they did not need a gold standard for BRDC diagnosis. Many studies do not take this same approach and use clinical evaluation as the gold standard by which their diagnostic test is measured. With known imperfections as a diagnostic test, its use as a gold standard is guaranteed to lead to bias in the study.

Feeding Behavior

When applying feeding behavior as a diagnostic, there are two aspects that have been investigated; meal time and meal volume. Meal time is simply tracking presence at the feed bunk and does not account for feed intake. When looking at meal time, the number of visits to the feed bunk as well as length of visits have been analyzed. Meal volume is tracking daily feed intake as well as intake of each individual meal. With either meal time or meal volume, analysis is based on deviation from an individual animal's average as an indicator for illness.

When using meal time as a diagnostic, studies have shown that that healthy steers (those not diagnosed with BRDC by clinical evaluation) spend more time at the feed bunk and go to the feed bunk more often than their sick counterparts[30,31]. Healthy steers spend 30% more time at the bunk[30] and have 0.6-1.5 times more feeding bouts than sick steers[31]. Using a cumulative sums statistical procedure on the total time spent within 50cm of the bunk, one study was able to predict illness in steer calves 3.7 to 4.5 days earlier than clinical evaluation[23]. This study reported a sensitivity of 90% but used clinical evaluation as a means of quantifying true disease state. This study contains a significant classification bias due to clinical evaluation being the only index test used as a gold standard.

Another study used rectal temperature, clinical evaluation, and serum concentrations of haptoglobin to quantify true disease status in feedlot cattle. This study found that the risk of developing BRDC decreased as meal frequency increased[42]. This study also found that their hazard model was able to predict BRDC in 81% of the cases three days before being detected by clinical evaluation using meal time alone[42]. These researchers looked at both meal time and meal volume as a BRDC diagnostic and found that meal volume was equivalent to meal time in predicting BRDC. This study did not attempt to use a combination of both meal time and meal volume in a prediction model. This same study found a reduction in mean meal intake for those calves diagnosed with BRDC via clinical evaluation, rectal temperature, lung auscultation score, pulse oximetry readings, and white blood cell count. When using multiple index tests to classify true disease state, the comparability becomes limited. Studies with this many index tests can truly only be compared to other studies that used the same set of index tests. Classification bias is probably less of an issue with many index tests but is still present in these studies. Spectrum bias also comes into play with this many index tests because only the most severe cases meet all the criteria to be considered a case.

Monitoring feeding behavior may lead to earlier detection of BRDC. Studies have claimed that changes in feeding behavior are evident one day to two weeks before an animal is found to be ill by clinical evaluation[16,23,42]. The highest accuracy in early prediction is approximately three to five days prior to clinical evaluation[23,42]. This would result in earlier treatment of those cases that would be identified by clinical evaluation, not identification of those cases being missed by clinical evaluation.

Continuous Temperature Monitoring

Continuous temperature monitoring relies on technology put in place at the beginning of the feeding period to monitor the internal or external temperature of an animal at regular intervals. This category of detection test does not include rectal temperature, which for the purposes of this paper, has been classified as a confirmatory test. There have been three methods of continuous temperature monitoring with published research on their validity; ruminal-reticular boluses, tympanic temperature monitoring, and infrared thermography of the orbit.

Of the three methods in this category, ruminal-reticular boluses have been the most extensively studied. It has been shown that ruminal-reticular temperature is highly correlated to rectal temperature and increases in the same manner after a known disease challenge[25,38]. Because of this correlation, it has been used to find previously undetected episodes of fever believed to be associated with BRDC. With the ability to monitor temperature continuously, it raises the question of how often should the temperature be checked. One study found that analyzing the average temperature in 30 minute intervals was the most accurate unit when it came to diagnosing BRDC[38]. Like feeding behavior this technology was able to detect BRDC 4 hours to 7 days earlier than clinical evaluation alone[25,34,35,38]. These undetected fevers were associated with a statistically significant reduction in average daily gain[35,38]. An association with reduction in production values does not mean an exclusive association with BRDC. Fever can be generated for a multitude of reasons, one of which is BRDC. There is likely a significant amount of classification bias due to other causes of fever. Much like using feeding behavior, continuous temperature monitoring can lead to earlier detection but not necessarily more complete detection of BRDC.

Tympanic temperature monitoring has not been well evaluated in the literature. Only one published report could be identified that discussed the utility of this technology. This report summarized data collected from 4 cohorts, totaling 131 calves. Using clinical score, rectal temperature, and blood leukocyte counts to determine true disease state, they attempted to determine the accuracy of the Fever Tag® devices[20]. While the devices did not seem to have any false positive results, repeated mechanical malfunction (i.e. the probe becoming dislodged from the ear) and a higher activation threshold than expected lead to a low sensitivity of BRDC detection for this technology. This study had a unique combination of index tests used as a gold standard. This limits its comparability and is not even truly comparable to other temperature monitoring device studies. Classification bias is a significant issue with this study as well as diagnostic review bias because rectal temperature and tympanic temperature are not independent of each other.

Infrared thermography of the orbit does not have any commercially available applications but has been studied as a means of measuring body temperature. The most successful prototype was set up to scan the orbit while the animal drank at the water tank[26]. This technology could identify animals with BRDC 4 to 6 days earlier than clinical evaluation[27]. While this technology does show promise for identifying sick animals, it needs to be developed for large scale applications. Future studies of this technology should include Bayesian latent class analysis to avoid classification bias.

Locomotion and Movement

Tracking locomotion and movement has been investigated as a means of diagnosing BRDC. One system called Remote Early Disease Identification (REDI) was evaluated by Kansas researchers[39]. This system consists of ear tag transmitters and readers positioned around the pen that then relay the position and movement data to a central server that uses an algorithm to evaluate the calves' movements and determine if they are sick. When compared to clinical evaluation, REDI is just as accurate in determining sick from healthy animals but was 0.75 days faster at identifying sick animals. Due to classification bias, the sensitivity and specificity of REDI in this study is hard to determine.

In 2016, White et al performed a follow-up study[40]. This study again used clinical evaluation and the REDI system to determine disease status of the animals on trial but used the Bayesian latent class analysis to calculate sensitivity and specificity. The imperfections of the REDI system and clinical evaluation were taken into account with both trials in this study and found the REDI system to have a sensitivity of 81.3% and a specificity of 92.9%. This was compared to clinical evaluation which was shown to have a sensitivity of 64.5% and a specificity of 69.1%. The use of the Bayesian statistical method did reduce issues with classification bias when compared to the first study but this study's comparability is limited due to the unique combination of imperfect tests used in the statistical methods. A summary of reported sensitivities and specificities of the discussed detection tests is give in Table 1.1.

Confirmatory Tests for BRDC

Confirmatory tests are chute side diagnostic tests used to determine if the cause of illness is truly BRDC. Confirmatory tests look for pathologic changes in the animal. Ideally, confirmatory tests should be highly specific and able to predict treatment outcome.

Rectal Temperature

Rectal temperature is used to determine if an animal is febrile. Fever is a non-specific response to infection[14]. While an infection in the lungs can cause a fever, not all fevers are caused by an infection in the lungs. It has been shown that rectal temperature will spike the same day an animal is given a known viral challenge but the rectal temperature will rapidly return to normal[12]. Rectal temperature has not been shown to have a strong correlation with treatment outcome[33]. One study found a weak correlation with treatment outcome but in low risk cattle only[3]. Another study found no difference in the probability of an animal being successfully harvested if their rectal temperature at time of first treatment for BRDC was between 103° Fahrenheit (F) and 104°F[33]. That same study did find that a rectal temperature greater than 104.5°F did reduce an animal's probability of having a successful harvest but the correlation was heavily influenced by the animal's arrival date, sex, and days on feed at time of first treatment. There is no current research that has attempted to quantify the sensitivity or specificity of rectal temperature as a BRDC diagnostic test. There is major concerns with classification bias of any study of rectal temperature due to the multitude of causes of fever. It is incredibly challenging to determine if the cause of the fever is truly to due BRDC or due to any of the other causes of fever.

Thoracic Ultrasound

Thoracic ultrasound has been used in the dairy industry to help predict reproductive performance and survival of dairy heifers[32]. Heifers with lung consolidation have a reduced chance of becoming pregnant and an increased chance of being culled before their first parturition[32]. However, ultrasonographic changes to the lung and BRDC treatment outcome have not been shown to have the same level of correlation. One study found ultrasonographic lesions consistent with lung consolidation at the time of first treatment was negatively correlated with treatment outcome[24]. However, another study that looked for changes in lung anatomy over a period of six weeks after the identification of illness was not able to find a significant correlation between abnormalities on thoracic ultrasound and treatment outcome[2]. Both of these trials used clinical evaluation and rectal temperature to define a case of BRDC. Even though these studies were not looking at sensitivity or specificity of ultrasound as a diagnostic, classification bias was still present in determining what cases were evaluated and followed.

Most pneumonia lesions develop cranial to the sixth intercostal space with the right cranial lobe, right middle lobe, and left cranial lobe being the most commonly affected lung lobes[22]. The ultrasound probe must be placed under the triceps muscle in order to visualize the cranial aspect of the cranial lung lobes. This means that the cranial aspect of the right and left cranial lung lobes can only be evaluated in cattle less than 6 months of age[22]. In feedlot cattle, the fourth intercostal space is the cranial most space that can be scanned[24]. For the authors of this study, a full thoracic ultrasound exam took approximately 45 minutes to conduct. The combination of these factors has led to very little adaptation of this technology in large commercial feeding operations.

Attempts have been made to determine the sensitivity and specificity of thoracic ultrasound. Since young calves (i.e. pre-weaned Holstein calves) have been the subject of much of this research, the only estimations of sensitivity and specificity are for the use of thoracic ultrasound in these calves. Sensitivity has been reported to be 79.4% and specificity has been reported to be 93.9%[6]. This study did use Bayesian latent class analysis to evaluate sensitivity and specificity. A calf respiratory scoring chart was the second imperfect test used in this study. Classification bias was limited in this study because of the statistical approach but comparability is limited because it was done in pre-weaned dairy calves. In pre-weaned dairy calves, the cranial most lung lobes can still be visualized which limits the comparability of these studies to studies done on feedlot sized animals. There is no published research that had determined the sensitivity or specificity of thoracic ultrasound in larger feedlot cattle.

Thoracic Auscultation

A group of veterinary consultants developed a system to score lung sounds heard on thoracic auscultation. Originally, a 10-point scale was used but was later simplified to a 5-point scale[8,18]. A lung score of 1 indicates normal lung sounds. A lung score of 2 indicates mild, acute pneumonia with mild crackles and rales. A lung score of 3 indicates moderate, acute pneumonia with moderate crackles and rales. A lung score of 4 indicates severe, acute pneumonia with severe crackles and rales. Finally, a lung score of 5 indicates the presence of pathology consistent with chronic pneumonia with diffuse, severe crackles and rales. Lung scores assigned by a human evaluator have been shown to correlate with lung lesions seen at necropsy performed immediately after lung scores were taken[8]. Training veterinarians and feedlot personnel to accurately score lung sounds can take an extended period of time and can require an individual to listen to numerous animals. Studies that use human-generated lung scores open themselves up to differential verification, i.e. differing accuracies of each person assigning lung scores, especially if multiple people are assigning lung scores in a given study.

A computer-aided lung auscultation system (Whisper®) was created to make lung auscultation scoring more objective and more widely applicable. The Whisper® system utilizes an electronic stethoscope to record lung sounds for 8 seconds. The recorded lung sounds are then wirelessly transmitted to a computer. Once received by the computer the lung sounds are analyzed by an algorithm and a lung score is assigned. The computer-generated lung scores have been shown to be significantly correlated to the human-generated lung scores[18]. The study implied that a single veterinarian took all the human-generated lung scores, meaning the computer-generated lung scores agree with one veterinarian's lung scores. More repetition would be needed with more trained evaluators to determine how well the computer-generated lung scores and human generated lung scores agree.

Both computer-generated and human-generated lung scores have been shown to correlate with retreatment rate as well as case fatality rate[8,17]. Each single point increase in lung score correlates to a nearly 50% increase in case fatality rate[18]. Sensitivity and specificity of computer-generated lung scores was calculated using a Bayesian statistical approach[18]. Whisper® lung scores of cattle pulled for first time BRDC treatment and clinical evaluation at time of being pulled were used as the two imperfect test. This study found the sensitivity and specificity to be 92.9% and 89.6% respectively. While this study did limit classification bias and diagnostic review bias by using the Bayesian method and blinding the clinical evaluator, the cases that were enrolled in this study were chosen by pen checkers using clinical evaluation. This raises an issue of spectrum bias, if only the more severe, noticeable cases of BRDC were enrolled.

Blood and Serum Tests

Currently, evaluation of blood and serum samples is confined to laboratory testing. But as technology continues to evolve, the ability to perform these tests chute-side grows closer to reality.

Complete Blood Count

Performing complete blood counts (CBC) on suspect cases of BRDC has been used to determine is the animal displays signs of inflammation in their blood. It has been used in many studies are part of a set of diagnostic tests to create a gold standard[26,27,42]. Few studies have investigated the utility and accuracy of CBC as a stand-alone BRDC diagnostic.

One study found that white blood cell counts (WBCC) were not statically, significantly different between true positive and true negative cases, even though WBCC was used as one of three criteria to determine disease state[26,27]. The other two criteria were rectal temperature and clinical score. The reported sensitivity of WBCC ranges from 78% down to 25%[26,27]. The reported specificity ranges from 82% to 94%[26,27]. Both studies are subject to selection and classification bias because WBCC was a diagnostic criteria. One study showed that only 52% of BRDC cases had a WBCC that was outside of the reference range[42]. That same study found that 84% of BRDC cases had a red blood cell count outside of the reference range. The abnormal counts were both below and above the given reference ranges. Classification bias is of concern in this study because true disease state was determined by rectal temperature and clinical score.

Blood Gas Analysis

Hand-held blood gas analysis machines are currently available and can offer relatively quick, chute-side results. These machines are temperature and humidity sensitive, so the chute-side environment must be controlled to an extent. Blood gas parameters have been evaluated as a means of measuring lung function to determine if they also relate to severity of disease.

A study in 1992 found a significant correlation between the partial pressure of oxygen in arterial blood (PaO_2) and the partial pressure of carbon dioxide (PCO_2) and clinical scores[7]. As clinical scores worsened, PaO_2 decreased and PCO_2 increased. This study did note that the calves they studied had chronic respiratory disease and that the correlations would probably not hold true in calves affected with relatively mild disease. This is spectrum bias. A study in 2005 compared blood gas parameters between calves sick with

BRDC that survived for more than 24 hours after blood sampling and calves that died within 24 hours after blood sampling[21]. They found that PCO_2 was significantly higher and PaO_2 was significantly lower in calves that died within 24 hours. Spectrum bias is an issue with this study because only cases that were severe enough to be hospitalized were used. A group of researchers from the Slovak Republic attempted to find a difference in blood gas parameters in calves with moderate clinical signs, severe clinical signs, and calves that died within 48 hours of being examined[29]. The only significant difference was between those calves that died in 48 hours and all other calves. Those calves that died in 48 hours had a significantly lower partial pressure of oxygen (PO_2). Much like the previous study, this study only evaluated cases that had been referred to a hospital leading to spectrum bias in the patient population. Another study did find a significant association between PaO_2 and the percentage of lung affected by pneumonia in a Bovine Respiratory Syncytial Virus challenge[9]. In this study all calves were euthanized so no correlation to outcome could be made. Also, this was a experimentally induced single challenge model, while most cases of naturally occurring BRDC is multi-factorial. This difference limits the comparability of this study to those that use naturally occurring BRDC. No published study has attempted to determine the sensitivity or specificity of blood gas analysis as a diagnostic test.

Acute Phase Proteins

Multiple acute phase proteins have been evaluated as potential indicators of BRDC. Haptoglobin has been found to be in greater concentrations in the serum of calves with more severe clinical scores[15]. The use of clinical scores opens this paper up to classification bias. In addition, a correlation was found between the amount of free haptoglobin in the serum and the percentage of lung involved in BRDC on necropsy[12]. A meta-analysis of papers evaluating acute phase proteins as BRDC diagnostics attempted to determine the sensitivity and specificity of haptoglobin. This paper was only able to determine a relatively wide range of potential values for both sensitivity and specificity due to the inconsistent clinical definition of BRDC[1]. For each study included in the meta-analysis, a point estimate and 95% confidence interval was calculated leading to a list of potential values. This same paper evaluated fibrinogen and serum amyloid A as BRDC diagnostics as well. Like haptoglobin, the sensitivity and specificity of each could only be expressed as a range of values due to the lack of consistent BRDC clinical definition[1]. Classification bias, comparability, and differential verification are all issues for this meta-analysis and the studies it included.

Haptoglobin-matrix metalloproteinase 9 (HpMM9) is a complex made of free haptoglobin and matrix metalloproteinase 9. These complexes are formed exclusively in neutrophils and their presence in the blood is a demonstration of acute inflammation[13]. Increased concentrations in the blood have been shown to correlate with the percentage of lung involvement in BRDC challenge models[13]. The correlation between HpMM9 and lung pathology was found to be stronger than the correlation between haptoglobin and percentage of lung involvement. Because this study used a controlled challenge model, its comparability is limited when applying to research to naturally occurring cases of BRDC. There has been no work to determine correlation with treatment outcome or sensitivity or specificity of this test.

Lipopolysaccharide binding protein (LBP) is a polypeptide that binds to bacterial lipopolysaccharide and presents it to monocytes[15]. This study did find LBP in higher concentrations in the serum of calves with more severe clinical BRDC scores but was unable to determine if there was a linear correlation. Once again the use of clinical scores opens this study to classification bias.

L-lactate is a biomarker associated with hypoperfusion of tissues. This biomarker has been shown to be a negative prognostic indicator for various conditions[5]. L-lactate can be measured in the blood quickly with a portable machine making it ideal for a chute side diagnostic. Evaluation of L-lactate found that temperament of the calf greatly impacted the concentration of L-lactate in the serum and there was no difference in serum concentrations between calves that survived a BRDC event and calves that did not[5]. Using BRDC death does limit the classification bias of this study but temperament is a serious confounder that obscures the results.

Metabolomics

Metabolomics is the study of metabolites in biological fluids. Rather than trying to isolate a single chemical that is different, metabolomics looks at the change in all measurable chemicals to determine a metabolite profile. Samples can be analyzed by nuclear magnetic resonance, mass spectrometry, or ultra-performance liquid chromatography.

The first published use of this technology associated with BRDC was in 2015. Researchers looked at the metabolite compounds in the plasma of calves before and after vaccination with an intranasal vaccine containing three viral BRDC agents[11]. They found 12 compounds that differed between the before and after samples proving that differences could be identified. In 2016, another group of researchers set out to determine if the metabolite profiles of sick animals presented to a teaching hospital were different from the metabolite profiles of healthy animals from a local teaching farm[4]. This study did find 10 compounds that were at different levels in the plasma of sick and healthy animals. This study lends itself to classification bias as well as spectrum bias due to the cases being referred to a teaching hospital. In 2018, Iowa researchers evaluated the metabolite profiles of feeder cattle diagnosed with BRDC and of healthy counter parts from the same commercial feedlot[19]. They evaluated both nasal secretions and serum from both sets of cattle. These researchers found four compounds in nasal secretions and five compounds in serum that differed between the sick and healthy animals. Like most diagnostic test analysis studies, this study did have issues with classification bias because clinical evaluation was used to determine disease status. Spectrum bias was also present because multiple criteria needed to be met in order to be classified as a sick animal. Metabolomic technology is still in its infancy but these trials show promise that one day metabolomics could be a useful tool in diagnosing BRDC. A summary of reported sensitivities and specificities of the discussed confirmatory tests is give in Table 1.2.

Summary

While clinical evaluation is widely used in feedlots for detection of BRDC, it is an imperfect test. This has led to the investigation of non-human means of detecting BRDC. Monitoring feeding behavior has shown the most promise for detecting BRDC in the pen but due to the cost of installing the equipment, it has not been widely adapted. Continuous temperature monitoring, specifically ruminal-reticular boluses, do not present the same cost hurdle as monitoring feeding behavior but is also a less sensitive test. More research is needed to determine the utility of other detection tests.

There are a long list of tests that have been evaluated as confirmatory tests for BRDC. However, due to a lack of a gold standard for BRDC diagnosis, determining the sensitivity and specificity of these tests remains difficult. Rectal temperature is most commonly used but has no correlation with treatment outcome. Thoracic ultrasound has been extensively used in the dairy industry to find lesions in the lungs of calves. The accuracy of this test wanes as cattle mature because the most diagnostics portions of the lung cannot be imaged due the anatomical limitations. Computer aided thoracic auscultation has a loose association with lung lesions but does correlate with treatment outcome. Various markers in the blood have been investigated but none have proven to be specific enough to the utilized consistently.

With a lack of a gold standard for BRDC diagnosis, evaluating diagnostic tests remains quite difficult. Finding the association between diagnostic test results and production measures is easier. Determining which animals are suffering from BRDC is about mitigating production losses associated with this disease. Rather than trying to find a test that is highly sensitivity and specificity, the industry would benefit from any test that could predict production losses due to BRDC.

References

1. Abdallah A, Hewson J, Francoz D, et al. Systematic review of the diagnostic accuracy of haptoglobin, serum amyloid A, and fibrinogen versus clinical reference standards for the diagnosis of bovine respiratory disease. *J Vet Intern Med* 2016; 30:1356-1368.

2. Abutarbush SM, Pollock CM, Wildman BK, et al. Evaluation of the diagnostic and prognostic utility of ultrasonography at first diagnosis of presumptive bovine respiratory disease. *Ca J Vet Res* 2012; 76:23-32.

3. Avra TD, Abell KM, Shane DD, et al. A retrospective analysis of risk factors associated with bovine respiratory disease treatment failure in feedlot cattle. *J Anim Sci* 2017; 95:1521-1527.

4. Basoglu A, Baspinar N, Tenori L, et al. Plasma metabolomics in calves with acute bronchopneumonia. *Metabolomics* 2016; 21:128

5. Bucsinski S, Rademacher RD, Tripp HM, et al. Assessment of L-lactatemia as a predictor of respiratory disease recognition and severity in feedlot steers. *Pre Vet Med* 2015; 118:306-318.

6. Buczinski S, Ollivett TL, Dendukuri N. Bayesian estimation of the accuracy of the calf respiratory scoring chart and ultrasonography for the diagnosis of bovine respiratory disease in pre-weaned dairy calves. *Pre Vet Med* 2015; 119:227-231.

7. Collie DDS. Pulmonary function changes and clinical findings associated with chronic respiratory disease in calves. *Br Vet J* 1992; 148:33-40.

8. DeDonder K, Thomson DU, Loneragan GH, et al. Lung auscultation and rectal temperature as a predictor of lung lesions and bovine respiratory disease treatment outcome in feedyard cattle. *Bov Pract* 2010; 44(2):146-153.

9. Ellis J, Waldner C, Gow S, et al. Relationship of the extent of pulmonary lesions to the partial pressure of oxygen and the lactate concentration in arterial blood in claves experimentally infected with bovine respiratory syncytial virus. *Ca J Vet Res* 2013; 77:205-210.

10. Gardner BA, Dolezal HG, Bryant LK, et al. Health of finishing steers: effects on performance, carcass traits, and meat tenderness. *J Anim Sci* 1999; 77:3168-3175.

11. Gray DW, Welsh MD, Doherty S, et al. Identification of systemic immune response markers through metabolomics profiling of plasma from calves given an intra-nasally delivered respiratory vaccine. *Vet Res* 2015; 46:7.

12. Hanslicek GA, White BJ, Mosier D, et al. Serial evaluation of physiologic, pathological, and behavioral changes related to disease progression of experimentally induced Mannheimia haemolytica pneumonia in postweaned calves. *Am J Vet Res* 2010; 71:359-369.

13. Hanthorn CJ, Dewell GA, Dewell RD, et al. Serum concentrations of haptoglobin and haptoglobin-matrix metalloproteinase 9 (Hp-MMP 9) complexes of bovine calves in a bacterial respiratory challenge model. *BMC Vet Res* 2017; 10:285-294.

14. Hart BL. Biological basis of the behavior of sick animals. *Neuroscience & Biobehavioral Reviews* 1988; 12:123-137.

15. Idoate I, Vander Ley B, Schultz L, et al. Acute phase proteins in naturally occurring respiratory disease of feedlot cattle. *Vet Immun Immunopath* 2015; 163:221-226.

16. Jackson KS, Carstens GE, Tedeschi LO, et al. Changes in feeding behavior patterns and dry matter intake before clinical symptoms associated with bovine respiratory disease in growing bulls. *J Anim Sci* 2016; 94:1644-1652.

17. Lowe J, Brattain K, Taylor G, et al. The value of using enhanced case definitions for the management of BRD in commercial feedlots. *AABP Proceedings* 2015; 48:177-178.

18. Mang AV, Buczinski S, Booker CW, et al. Evaluation of a computer-aided lung auscultation system for diagnosis of bovine respiratory disease in feedlot cattle. *J Vet Intern Med* 2015; 29(4):1112-1116.

19. Maurer DL, Koziel JA, Engelken TJ, et al. Detection of volatile compounds emitted from nasal secretions and serum: towards non-invasive identification of diseased cattle biomarkers. *Separations* 2018; 5:18.

20. McCorkell R, Wynne-Edwards K, Windeyer C, et al. Limited efficacy of fever tag temperature sensing ear tags in claves with naturally occurring bovine respiratory disease or induced bovine viral diarrhea virus infection. *Can Vet J* 2014; 55:688-690.

21. Nagy O, Seidel H, Paulikova I, et al. Use of blood gasses and lactic acid analyses in diagnosis and prognosis of respiratory diseases in calves. *Bull Vet Inst Pulawy* 2006; 50:149-152.

22. Ollivet TL, Buczinski S. On-farm use of ultrasonography for bovine respiratory disease. *Vet Clin Food Anim* 2016; 32:19-35.

23. Quimby WF, Sowell BF, Bowman JGP, et al. Application of feeding behavior to predict morbidity of newly received claves in commercial feedlot. *Can J Anim Sci* 2001;315-320.

24. Rademacher RD, Buczinski S, Tripp HM, et al. Systematic thoracic ultrasonography in acute bovine respiratory disease of feedlot steers: impact of lung consolidation on diagnosis and prognosis in a case-control study. *Bov Pract* 2014; 48(1):1-10.

25. Rose-Dye TK, Burciaga-Robles LO, Krehbiel CR, et al. Rumen temperature change monitored with remote rumen temperature boluses after challenges with bovine viral diarrhea virus and Mannheimia haemolytica. *J Anim Sci* 2011; 89:1193-1200.

26. Schaefer AL, Cook NJ, Bench C, et al. The non-invasive and automated detection of bovine respiratory disease onset in receiver calves using infrared thermography. *Res in Vet Sci* 2012; 93:928-935.

27. Schaefer AL, Cook NJ, Church JS, et al. The use of infrared thermography as an early indicator of bovine respiratory disease complex in calves. *Res in Vet Sci* 2007; 83:376-384.

28. Schmidt RL, Factor RE. Understanding sources of bias in diagnostic accuracy studies. *Arch Pathol Lab Med* 2013; 137:558-565.

29. Šoltésová H, Nagy O, Tóthová C, et al. Blood gases, acid-base status and plasma lactate concentrations in calves with respiratory diseases. *Acta Veterinaria-Boegrad* 2015; 65(1):111-124.

30. Sowell BF, Bowman JGP, Branine ME, et al. Radio frequency technology to measure feeding behavior and health of feedlot steers. *Applied Animal Behavior Science* 1998; 59:277-284.

31. Sowell BF, Branine ME, Bowman JGP, et al. Feeding and watering behavior of healthy and morbid steers in commercial feedlot. *J Anim Sci* 1999; 77:1105-1112.

32. Teixeira AG, McArt JA, Bicalho RC. Thoracic ultrasound assessment of lung consolidation at weaning in Holstein dairy heifers: reproductive performance and survival. *J Dairy Sci* 2017; 100:2985-2991.

33. Theurer ME, White BJ, Larson RL, et al. Relationship between rectal temperature at first treatment for bovine respiratory disease complex in feedlot calves and the probability of not finishing the production cycle. *J Am Vet Med Assoc* 2014; 245:1279-1285.

34. Timsit E, Assié S, Quiniou R, et al. Early detection of bovine respiratory disease in young bulls using reticulo-rumen temperature boluses. *The Veterinary Journal* 2011; 190:136-142.

35. Timsit E, Bareille N, Seegers H, et al. Visually undetected fever episodes in newly received beef bulls at a fattening operation: occurrence, duration, and impact on performance. *J Anim Sci* 2011; 89:4272-4280.

36. Timsit E, Dendukuri N, Schiller I, et al. Diagnostic accuracy of clinical illness for bovine respiratory disease (BRD) diagnosis in beef cattle placed in feedlots: a systematic literature review and hierarchial Bayesian latent-class meta-analysis. *Pre Vet Med* 2016; 135:67-73.

37. USDA. Part IV: Health and management on U.S. feedlots with a capacity of 1,000 or more head. 2011. https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV_1.pdf. Accessed February 23, 2019.

38. Voss B, Laue HJ, Hoedemaker M, et al. Field-trial evaluation of an automatic temperature measurement device placed in the reticulo-rumen of pre-weaned male calves. *Livestock Science* 2016; 189:78-81.

39. White BJ, Goehl DR, Amrine DE. Comparison of remote early disease identification (REDI) system to visual observations to identify cattle with bovine respiratory diseases. *Intern J Appl Res Med* 2015; 13:23-30.

40. White BJ, Goehl DR, Amrine DE, et al. Bayesian evaluation of clinical diagnostic test characteristics of visual observation and remote monitoring to diagnose bovine respiratory disease in beef calves. *Pre Vet Med* 2016; 126:74-80.

41. White BJ, Renter DG. Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. *J Vet Diagn Invest* 2009; 21:446-453.

42. Wolfger B, Schwartzkopf-Genswein KS, Barkema HW, et al. Feeding behavior as an early predictor of bovine respiratory disease in North American feedlot systems. *J Anim Sci* 2015; 93:377-385.

Table 1.1 *Reported sensitivity and specificity of various antemortem BRDC detection tests*

Detection Test	Sensitivity (95% CI)	Specificity (95% CI)	Study
Clinical Evaluation	61.8% (55.7-68.4) 27% (12-65)	62.8% (60.0-65.7) 92% (72-98)	41 36
Feeding Behavior - Meal Time	88% (not given) 81% (not given)	83% (not given) 77% (not given)	23 42
Feeding Behavior - Meal Volume	82% (not given)	78% (not given)	42
Ruminal-Reticular Boluses	71% (not given)	98% (not given)	38
Fever Tag	47% (not given)	100% (not given)	20
Infrared of Orbit	69% (not given)	76% (not given)	27
REDI	67% (not given) 81.3% (55.5-95.8)	93% (not given) 92.9% (88.2-96.9)	39 40

Table 1.2 *Reported sensitivity and specificity of various antemortem BRDC confirmatory tests*

Confirmation Test	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Study**
Rectal Temperature	N/A	N/A	
Thoracic Ultrasound	79.4% (66.4-90.9)	93.9% (88.0-97.6)	6
Thoracic Auscultation (Computer Aided)	92.9% (71-99)	89.6% (64-99)	18
White Blood Cell Count	77.8% (not given) 25.4% (not given)	82.1% (not given) 94.3% (not given)	26 27
Blood Gas Analysis	N/A	N/A	
Haptoglobin	70% (51-85) 63% (48-76) 100% (97-100) 70% (51-85) 85% (66-96) 76% (53-92) 61% (41-78) 93% (66-100)	90% (73-98) 91% (79-98) 80% (44-97) 100% (63-100) 93% (68-100) 95% (88-98) 97% (85-100) 86% (57-98)	1
Fibrinogen	57% (37-76) 63% (48-76) 57% (34-78) 80% (61-92)	94% (81-99) 89% (76-96) 95% (88-98) 90% (73-98)	1
Serum Amyloid A	100% (88-100) 59% (39-78) 82% (63-94) 65% (50-78) 53% (43-62)	43% (10-82) 80% (52-96) 94% (81-99) 87% (74-95) 90% (55-100)	1
Haptoglobin-matrix metalloproteinase 9	N/A	N/A	
Lipopolysaccharide binding protein	N/A	N/A	
L-Lactate	N/A	N/A	
Metabolomics	N/A	N/A	

CHAPTER 2. THE ASSOCIATION BETWEEN WHISPER® LUNG SCORES AND FEEDLOT PERFORMANCE IN CROSSBRED CALVES

Modified from a manuscript to be submitted to The Bovine Practitioner

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Introduction

Bovine respiratory disease complex (BRDC) is a prominent problem in the cattle feeding industry. This complex is the most commonly diagnosed disease in feedlot cattle, affecting approximately 16.2% of all cattle on feed[7]. The economic impact is multifaceted from treatment costs to negative impacts on production. On average, treatment for BRDC is more expensive than treatment of any other condition seen in the feedlot[7]. Severe lung lesions seen at slaughter are associated with decreases in average daily gain, hot carcass weight, less internal fat, and lower marbling scores[3]. Either untimely treatment or undiagnosed BRDC can lead to these lesions and economic losses associated with them.

If it could be predicted which animals will suffer from BRDC when they arrive at a feedlot, some of the expense associated with treatment could be avoided. It has been shown that breed, arrival weight, and season of arrival at the feedlot are associated with risk of BRDC[5]. There is potential that those animals with characteristics consistent with an increased risk of BRDC could be managed differently to reduce this risk.

Auscultation of the lungs is a common part of physical exams for veterinarians. In 2010, DeDonder et al showed that lung scores assigned by trained personnel could be used to help predict case outcomes of BRDC treatments. When compounded with rectal temperature, lung score was shown to correlate with a calf's risk of death due to BRDC[2]. This correlation was seen in calves already affected with BRDC. There has been no published research to determine if lung scores could predict a calf's risk of death before being diagnosed with BRDC. Furthermore, there has been no published research about how lung scores correlate with feeding performance.

The objective of this study was to determine the Whisper® Stethoscope's ability to identify an association with production losses due to BRDC. The first aim was to determine if the lung score taken at arrival was correlated with feeding performance, specifically average daily gain (ADG) and feed efficiency (FE). The second aim was to determine if the arrival lung score was associated with health outcomes during the feeding period. The third aim was to determine if the arrival lung score was correlated with carcass quality.

Materials and Methods

Study Design

This was a cohort study where subjects were followed from feedlot arrival through slaughter. The experimental unit was each calf, the exposure of interest was arrival lung score, and the primary outcome of interest was ADG. Other feeding performance outcomes that were investigated included feed efficacy (FE), hot carcass weight (HCW), dressing percentage (DRESS), marbling score (MARB), fat thickness (FAT), and ribeye area (REA). Health outcomes of interest that were investigated were treatment for BRDC (RTX), death due to BRDC (RD), being diagnosed with chronic BRDC (RC), and dying after treatment for BRDC (RCF).

Setting

This study took place on a commercial feedlot in central Iowa. It started on August 29th, 2017 and was completed on September 28th, 2018. This study was approved by the Institutional Animal Care and Use Committee of Iowa State University (IACUC Log number 4-17-8496-B). Feeding pens were 882.6 square meter, concrete floor, outdoor lots with guard rail fencing on three sides and feed bunk for the fourth side. Each pen had 25.6 linear meters of bunk space and 3.7 linear meters of water space. Calves were fed a total mixed ration twice a day that met or exceeded the National Research Council's requirements for growth. Water was provided ad labium via automatic fence-line waterers.

Participants

Power calculations were performed to determine the sample size for this trial. The primary outcome of interest was a change in ADG. It was determined that a change of 0.05 kilograms per day (kg/d) in ADG would be an economically significant difference to detect. This was based on conversations with producers and economists. In order to detect this difference at a significance level of 0.05 and a power level of 80%, approximately 400 animals would need to be enrolled in the study. Therefore, 4 loads of approximately 100 calves each would be enrolled in this study.

Dairy/beef crossbred steer calves were procured from calf growing operations in northern Indiana. The number of calves on a given load was determined by the number of calves deemed ready for shipment at the time of cattle procurement. Criteria for shipment to the feedlot was based on vigor, weight, and frame size. Calves were transported to the research feedlot via tractor trailer. Because date of arrival and grower operation source were seen as potential confounders, each trailer load of calves from a single source was placed in a separate pen and no other calves were added to the pen. Each pen was one lot of cattle.

On arrival, calves were placed immediately in their home pen and allowed to rest for 48 hours. At the time of initial processing, calves were vaccinated with a five-way modified live virus respiratory vaccine[a] and a seven-way clostridial vaccine[b], poured with a permethrin and piperonyl butoxide topical[c] and orally drenched with fenbendazole[d] according to label directions. They also received a single extended release growth promoting implant[e] under the skin of the left ear. Calves were given sequentially numbered ear tags and an ear notch was collected for bovine viral diarrhea virus (BVDV) immunohistochemistry to determine if any calf was persistently infected with the virus. Finally, an arrival lung score was collected. No metaphylaxis or feed grade antibiotics were used for the control or treatment of BRDC at any point throughout the feeding period. At approximately 200 days on feed, cattle were re-implanted with a terminal growth promoting implant[j] placed under the skin of the left ear.

Calves were monitored for sickness once daily. Any calf displaying physical signs consistent with BRDC (depression, decreased rumen fill, increased respiratory effort) was removed from its home pen and taken to the treatment chute for further evaluation. Once in the chute, a rectal temperature was taken. Any calf with a rectal temperature greater than 40° Celsius (C) or a depression score greater than 2 on a scale of 0 to 4[f] received treatment for BRDC. First time BRDC treatment was a single subcutaneous injection of tildipirosin[g] at a rate of 4mg/kg of body weight. A 7-day post treatment interval was observed for any calf treated with tildipirosin[g]. Second time BRDC treatment was a single subcutaneous injection of florfenicol[h] at a rate of 40mg/kg of body weight. A 4-day post treatment interval was observed for any calf treated with florfenicol[h]. Third time BRDC treatment was a single subcutaneous injection of oxytetracycline[i] at a rate of 30mg/kg of body weight. Any animal that was not maintaining its body weight in its home pen or had a depression score of 3 or higher[f], regardless of the number of times it had been treated, was removed from its home pen, placed in a hospital pen, and labeled a “chronic”. When an animal was removed from its home pen, a final weight was collected and that animal’s end point in the trial was labeled as “chronic”. Any animal that died while on trial, had a final dead weight collected and was recorded as “dead”. A post-mortem exam was conducted on every animal that died to determine cause of death. A final live weight was collected at the feedlot 4 to 7 days prior to shipment for harvest. Carcass data was collected on an individual animal basis in the harvest facilities.

Variables

All subjects were classified by their arrival lung score. The Whisper® stethoscope was placed in the instructed location on the right side of the calf’s chest and a recording was taken for 8 seconds. Each lung score was deemed appropriate by the algorithm software. Any lung score deem insufficient for analysis was retaken. The stethoscope was operated by a single investigator who was blinded to the scores. Scores were recorded by an assistant who did not evaluate calves in the pen for sickness. The proprietary algorithm used was developed as an aid in treatment decisions and has been shown to be associated with treatment outcome[2]. A lung score of 1 indicates normal lung sounds. A lung score of 2 indicates mild, acute pneumonia with mild crackles and rales. A lung score of 3 indicates moderate, acute pneumonia with moderate crackles and rales. A lung score of 4 indicates severe, acute pneumonia with severe crackles and rales. Finally, a lung score of 5 indicates the presence of pathology consistent with chronic pneumonia with diffuse, severe crackles and rales. Cattle with a lung score of 1 were the referent.

Age of each calf at arrival was determined by the birth date written on an ear tag and expressed in months. Those calves missing their ear tag, did not have an age recorded and the missing data was omitted from the statistical evaluation. Individual arrival weights were collected in the chute at the time of initial processing for each calf. A final weight was collected in the chute 4 to 7 days prior to slaughter for each individual calf.

The outcome of interest was ADG. This was a continuous variable expressed in kilograms per day (kg/d). This was calculated by subtracting the calf's arrival weight from the final weight to establish total weight gained and dividing by the number of days on feed at the time the final weight was taken. A higher ADG was the desired result. Feed efficiency (FE) was calculated by Mr. Matthew Groves of the Tri-County Steer Carcass Futurity Cooperative, Lewis, Iowa using the proprietary formula developed by the cooperative. A lower FE was the desired result. Hot carcass weight (HCW), dressing percentage (DRESS), marbling score (MARB), fat thickness (FAT) and ribeye area (REA) were collected at the harvest facility by a contracted data collection service which was blinded to arrival lung score. All were expressed as continuous variables.

The investigators that monitored the calves' health and administered treatments were blinded to the arrival lung scores. Treatment for BRDC was a dichotomous variable; calves were either treated for BRDC at least once or not treated at all. Death due to BRDC and being diagnosed with chronic BRDC were also dichotomous variables; either calves died of BRDC or they did not and calves were either diagnosed with chronic BRDC or not. A respiratory case fatality was defined as any calf that died of BRDC after being treated for

BRDC. This was also a dichotomous variable. All fatal BRDC cases were classified as RD but only those that died of BRDC that had been treated at least once were classified as a RCF.

Statistical Methods

A causal diagram was used to determine the appropriate set of covariates to estimate both total and direct effect of the exposure of interest (arrival lung score) on the outcome of interest (ADG). The DAGitty[k] software was used to identify covariates that would need to be controlled for in the linear regression model. The causal diagram was created with the help of industry experts.

Individual linear regression models were used to evaluate correlations between arrival lung score and FE, HCW, DRESS, MARB, FAT, and REA for those animals that were successfully harvested. Logistic regression models were used to evaluation associations between arrival lung score and RTX, RD, RC, and RCF. A two-tailed p-value less than or equal to 0.05 was considered significant. Residual plots were created to determine if significant outliers were present in the data. Significant outliers were removed from the data set. Arrival lung score was evaluated as both a continuous variable as well as a factor variable. A lack of linearity in the logit would conclude that arrival lung score should be evaluated as a factor and not a continuous variable.

Finally, a survival analysis was performed and a survival curve was created for each lung score. This was done to determine if timing of cattle death or diagnoses of chronic BRDC was impacted by arrival lung score.

Results

Participants

In total, 401 steers were enrolled at the start of the trial in 4 lots. No calves were persistently infected with bovine viral diarrhea virus. Eleven animals were removed from the trial due to lost identification and 1 animal was removed because it was found to be a bull instead of a steer. Health data from 389 steers was used for the health outcomes analyses and ADG analysis. Due to errors in data collection at one of the harvest facilities, carcass data was collected on only 227 steers. This resulted in the inclusion of only 227 steers in the FE calculations and analysis.

Descriptive Data

The average arrival weight of all steers was 220kg with a range from 149kg to 319kg. Average arrival age was 6.75 months with a range from 5 months to 8.8 months. The average arrival lung score was 3. At arrival 33 calves (8.2%) had a lung score of 1, 107 calves (26.7%) had a lung score of 2, 137 calves (34.2%) had a lung score of 3, 69 calves (17.2%) had a lung score of 4, and 55 calves (13.7%) had a lung score of 5. Figure 2.1 shows the distribution of lung scores for all 401 calves. Figure 2.2 shows the distribution of lung scores in each of the 4 lots.

Of the 389 steers with available health data, 132 steers (33.9%) were treated at least once for BRDC. A total of 15 steers died (3.9%). Of those 15 dead steers, 8 (2.1%) died of BRDC and 7 (1.8%) died of other causes. A total of 40 steers (10.3%) were labeled as chronic during the trial. Of those 40, 18 (4.6%) were labeled with chronic BRDC and 22 (5.7%) were labeled with other chronic illnesses. Table 2.1 displays the descriptive data and the incidence of each health metric by lot. Table 2.2 displays the descriptive data by arrival lung score.

Main Results

The causal diagram displayed in Figure 2.6 showed that both age and weight at arrival were significant covariates. Lot was added to the linear mixed model as a fixed effect. Arrival lung score was evaluated as a factor variable. While ADG numerically increased with lung score, the increase was not shown to be statistically significant for any of the lung scores (p-values >0.05). The mean ADG and standard error for arrival lung score is displayed in Table 2.3. Feed efficiency did numerically improve as lung score increased but this improvement was only statistically significant for calves with arrival lung scores of 4 (p-value 0.02) and 5 (p-value 0.005). Feed efficiency data is displayed in Table 2.4.

Hot carcass weight was decreased in cattle with lung scores 3 through 5. Dressing percentage was not affected by lung score at arrival. Marbling score was decreased in cattle with lung scores greater than 1. Fat thickness was reduced in cattle with lung scores greater than 1. Ribeye area was decreased in cattle with lung scores greater than 2. Univariate linear models for HCW, DRESS, MARB, FAT, and REA all showed no significant association between the variables and arrival lung score. Carcass data is displayed in Table 2.4.

The percentage of cattle treated for BRDC numerically increased as lung score increased. Death loss due to BRDC was greatest among those cattle with a lung score of 4. Chronic BRDC rate was greatest in cattle with a lung score of 3. The case fatality rate for BRDC treatments was highest among cattle with a lung score of 4. The differences in these variables were not statistically significant. The incidence of various health parameters within each arrival lung score is displayed in Table 2.5.

The odds of being treated for BRDC did increase with an increase in lung score. The only lung score that was significantly different from the referent (lung score 1) was lung score 5 (p-value 0.02). The only lung score that was statistically significantly different from the referent in the odds of dying of BRDC was lung score 4 (p-value 0.04). The odds of being diagnosed with chronic BRDC did not change with arrival lung score. The odds of being a fatal case of BRDC also did not change with arrival lung score. Unadjusted odds ratios and 95% confidence intervals are displayed in Table 2.6.

Survival curves of all five lung scores did not differ significantly at any point in time. Survival to slaughter did not differ among lung scores. The survival curves are depicted in Figure 2.7.

Discussion

In general, a diagnostic test analysis can be difficult to perform. In cases where there is no gold standard, a diagnostic test analysis becomes nearly impossible. Classification bias was a major concern in this trial. With no gold standard for the diagnosis of BRDC, it became impossible to know the true association between a lung score taken at arrival and true incidence of BRDC. As a result, measures of cattle feeding performance (ADG and FE) were used as a proxy for BRDC incidence. Cattle with BRDC are known to have reductions in average daily gain as well as impaired feed efficiency. The economic variables are easier and more reliably quantified. There is less classification bias in measuring average daily gain and feed efficiency than measuring health metrics such as BRDC diagnosis and treatment as well as a diagnosis of chronic BRDC.

Before the trial began it was unknown what the distribution of lung scores would be. Originally, it was hypothesized that the distribution would be front end loaded with the majority of cattle having lung scores of 1 and 2 and few cattle having lung scores of 4 and 5. This was derived from previous research using the Whisper® stethoscope as a diagnostic tool[2]. The distribution of lung scores in cattle pulled for illness was heavily skewed to the left with only 1.5% to 3.0% of cattle having a lung score of 4 or 5. However, the distribution of lung scores in this group of calves showed a bell curve centered at lung score 3. Both lung scores of 4 and 5 were more common than lung score 1. This drastic difference could be due to the population of calves that live with undiagnosed BRDC. It has been shown that clinical evaluation fails to identify all cases of BRDC in the feedlot[6,9]. This trial evaluated every animal in the group both treated and untreated. More cattle need to be evaluated at feedlot arrival in order to better understand the normal distribution of lung scores at arrival.

The discrepancies seen between the lung score distribution does not impact the generalizability of this study to other populations. While ADG was not significantly impacted by ALS, FE was. This impact was evident only in those calves with ALS of 4 and 5. This study had a higher proportion of cattle with lung score 4 and 5 which made the association easier to identify but does not mean that the association does not exist in a population of cattle with fewer lung scores 4 and 5.

Scatter plots were constructed to examine the impact uncontrollable factors could have on lung score. A scatter plot of ALS by arrival age showed that the older calves tended to have higher lung scores. This could be explained knowing the production systems in which these calves were raised. Calves are deemed ready for shipment to the feedlot based mostly on weight; an average shipping weight of 500 pounds is a common goal in this production system. If previous cases of BRDC impaired a calf's ability to grow and gain weight, then it would be older than its counter parts when it reached the target weight for shipment. The older calves having higher lung scores could be an indication of previous lung damage. Scatter plots of ALS by arrival weight and ALS by processing order (calves processed first versus calves processed last) did not reveal any trends. These scatter plots can be seen in Figures 2.3, 2.4, and 2.5.

Previous research has demonstrated the utility of using causal diagrams to determine the appropriate set of covariates for which to adjust[4,5]. Figure 2.7 displays the causal diagram used to determine the necessary covariates needed to model the effect of arrival lung score on ADG. Arrival weight and arrival age were the only two covariates that needed to be included in the final model. Lot was included in the linear mixed model as a fixed effect because it accounted for source, date of arrival, and pen density in which the calves were fed. These were the only three variables that differed among the feeding groups.

Average daily gain did numerically increase as arrival lung score increased. However, once the linear mixed model adjusted for arrival weight, arrival age, and controlled for lot, there was no significant difference between any of the lung scores. The numerical trends could be explained by the increased rate of BRDC in increasing lung scores. In 2017, Wilson et al found an increase in ADG for those calves treated for BRDC compared to those calves that were never treated[8]. He speculated that increase in ADG was due to compensatory gain seen after treatment. Increased rates of treatments among calves with arrival lung scores of 4 and 5 could be a result of the same phenomenon that Wilson et al (2017) described. These calves were also on feed for an extended period of time. The maximum days on feed was 367 days. Cattle were shipped when contracted dates could be arranged with the harvest facilities. It is possible that the effects of ALS could be mitigated by the extended period of time these cattle spent on feed. Those with worse lung scores had more time to accumulate compensatory gain later in the feeding period.

Calculated feed efficiency improved as lung score increased as well with lung score 4 and 5 being significantly better. Busby (2010) found that steers treated for BRDC at least once had significantly improved FE[1]. He hypothesized that this was due to a reduction in feed intake. Feed efficacy is simply a ratio of feed taken in to weight gained. If disease is reducing feed intake by a greater proportion than it is reducing the weight gain, then cattle will appear to be more efficient. Since more of the calves with lung scores 4 and 5 were treated, more calves could have had a reduction in feed intake which led to an seemingly improved FE.

None of the carcass metrics showed a trend or association with arrival lung score. Previous research has shown that steers treated for BRDC have lighter carcasses, less fat, and lower quality grades at slaughter[3]. Calves with an arrival lung score of 5 were the only group with a statically significantly increased risk of being treated for BRDC. Without a strong association with BRDC treatment, it would not be expected that carcass traits would be associated with arrival lung score. There is also selection bias in the reported carcass metrics. Theses cattle were harvested at two separate harvest facilities. One of those facilities only slaughtered cattle that were black hided and could qualify for the Certified Angus Beef program. Because of this, cattle were sorted by coat color when they were harvested. Data was lost from only one plant. The carcass data that was successfully collected was not a random sample of the cattle on this trial. Cattle with ALS of 4 and 5 were disproportionately over represented in the carcass data. Over all the relatively small number of cattle that did have complete carcass data made it difficult to find significant differences due to a lack of power coming from a reduced sample size.

The incidence of treatment for BRDC did numerically increase as arrival lung score increased. The only lung score with a significant odds ratio for treatment of BRDC was lung score 5; arrival lung scores 2 through 4 did not have odds ratios that were significantly different from 1. Those calves with an arrival lung score of 5 are only 27% more likely to be treated for BRDC than calves with any other lung score. Classification bias is almost certainly an issue with this metric. There is no gold standard for diagnosis of BRDC. This is not the odds ratio for suffering from BRDC; it is the odd ratio for being diagnosed with and treated for BRDC. The odds ratio for dying from BRDC was only significantly different for those calves with an arrival lung score of 4. These calves had a 6% increase in the odds of dying from BRDC. Death due to BRDC is a more accurate metric than treatment for BRDC. Cause of death can be accurately and definitively diagnosed by performing a necropsy. This is a more reliable and realistic number but due to the small number of BRDC deaths, significant differences between lung scores became hard to find.

The survival curve did not show any difference in timing of death due to BRDC or being diagnosed with chronic BRDC. Arrival lung score did not show any association with the odds of being diagnosed with chronic BRDC or dying after treatment for BRDC. It was hypothesized that those animals with more damaged lungs would be treated sooner and develop chronic BRDC sooner. However, the survival curve does not show a difference in timing for any of the lung scores.

If arrival lung scores are a proxy for previous lung damage due to BRDC, then the lung pathology can lead in an increased risk of BRDC treatment and death. Knowing that higher lung scores come with a higher risk of treatment or death, interventions could be used to help mitigate some of that risk. These calves could be selectively treated at arrival with antibiotics or placed in a lower stress environment, such as on pasture, to combat the increased risk of treatment and death. Since arrival lung score is not associated with being diagnosed with chronic BRDC or an increase in BRDC case fatality, it stands to reason these calves with increased lung scores would still respond positively to selective treatment based on lung score.

Conclusion

Average daily gain tends to increase as arrival lung score increases. However, due to the small sample size of this project no significant correlations could be made. Feed efficiency tended to improve as lung score increased with a significant improvement in those calves with lung scores of 4 and 5 at arrival. Odds of being treated for BRDC and dying of BRDC tend to increase with lung score as well but the increase is small and only significant in calves with the highest lung scores. The algorithm used in this study was designed to aid in treatment decisions and associate with treatment outcome. The idea of developing a different algorithm that could be used at feedyard arrival to better predict feeding and health performance should be explored. Further investigation is needed to determine if a Whisper® stethoscope lung score taken at arrival is associated with feeding performance or health performance.

Endnotes

a. Vista 5 ®, Merck Animal Health, Whitehouse Station, NJ

b. Vision 7 ®, Merck Animal Health, Whitehouse Station, NJ

c. Ultra Boss ®, Merck Animal Health, Whitehouse Station, NJ

d. Safe-Guard ®, Merck Animal Health, Whitehouse Station, NJ

e. Revalor-XS ®, Merck Animal Health, Whitehouse Station, NJ

f. Apley MD. Feedlot Pharmaceutical Documentation. *Vet Clin Food Anm* 2015; 31:3-5-315

g. Zuprevo ®, Merck Animal Health, Whitehouse Station, NJ

h. Nuflor ®, Merck Animal Health, Whitehouse Station, NJ

i. 300 Pro LA ®, Norbrook Labratories, Newry, Northern Ireland

j. Revalor 200 ®, Merck Animal Health, Whitehouse Station, NJ

k. DAGitty v2.3, http://www.dagitty.net/dags.html#

References

1. Busby, D. Tri-County steer carcass futurity data. *AABP Proceedings* 2010; 43:71-81.

2. DeDonder K, Thomson DU, Loneragan GH, et al. Lung auscultation and rectal temperature as a predictor of lung lesions and bovine respiratory disease treatment outcome in feedyard cattle. *Bov Pract* 2010; 44(2):146-153.

3. Gardner BA, Dolezal HG, Bryant LK, et al. Health of finishing steers: effects on performance, carcass traits, and meat tenderness. *J Anim Sci* 1999; 77:3168-3175.

4. Hay KE, Barnes TS, Morton JM, et al. Risk factors for bovine respiratory disease in Australian feedlot cattle: use of causal diagram-informed approach to estimate effects of animal mixing and movements before feedlot entry. *J Prevet Med 2014*; 117:160-169.

5. Hay KE, Morton JM, Mahony TJ, et al. Associations between animal characteristics and environmental risk factors and bovine respiratory disease in Australian feedlot cattle. *J Prevet Med* 2016; 125:66-74.

6. Timsit E, Dendukuri N, Schiller I, et al. Diagnostic accuracy of clinical illness for bovine respiratory disease (BRD) diagnosis in beef cattle placed in feedlots: a systematic literature review and hierarchial Bayesian latent-class meta-analysis. *Pre Vet Med* 2016; 135:67-73.

7. USDA. Part IV: Health and management on U.S. feedlots with a capacity of 1,000 or more head. 2011. https://www.aphis.usda.gov/animal_health/nahms/feedlot/downloads/feedlot2011/Feed11_dr_PartIV_1.pdf. Accessed February 23, 2019.

8. Wilson BK, Step DL, Maxwell CL, Gifford CA, Richards CJ, Krehbiel CR. Effect of bovine respiratory disease during the receiving period on steer finishing performance, efficiency, caracass characteristics, and lung score. *The Professional Animal Scienctist* 2017; 33(1):24-36.

9. White BJ, Renter DG. Bayesian estimation of the performance of using clinical observations and harvest lung lesions for diagnosing bovine respiratory disease in post-weaned beef calves. *J Vet Diagn Invest* 2009; 21:446-453.

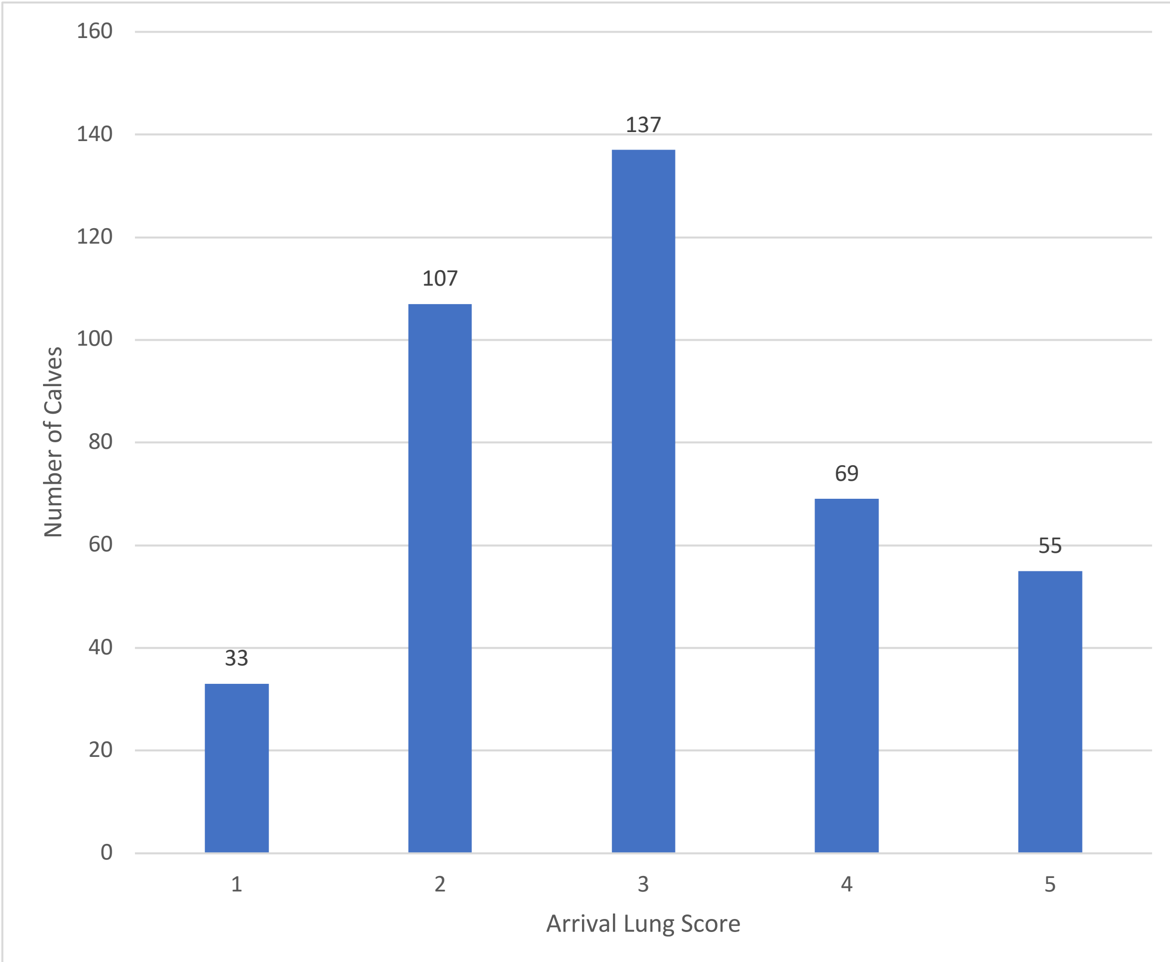

Figure 2.1. *Distribution of arrival lung scores for 401 calves*

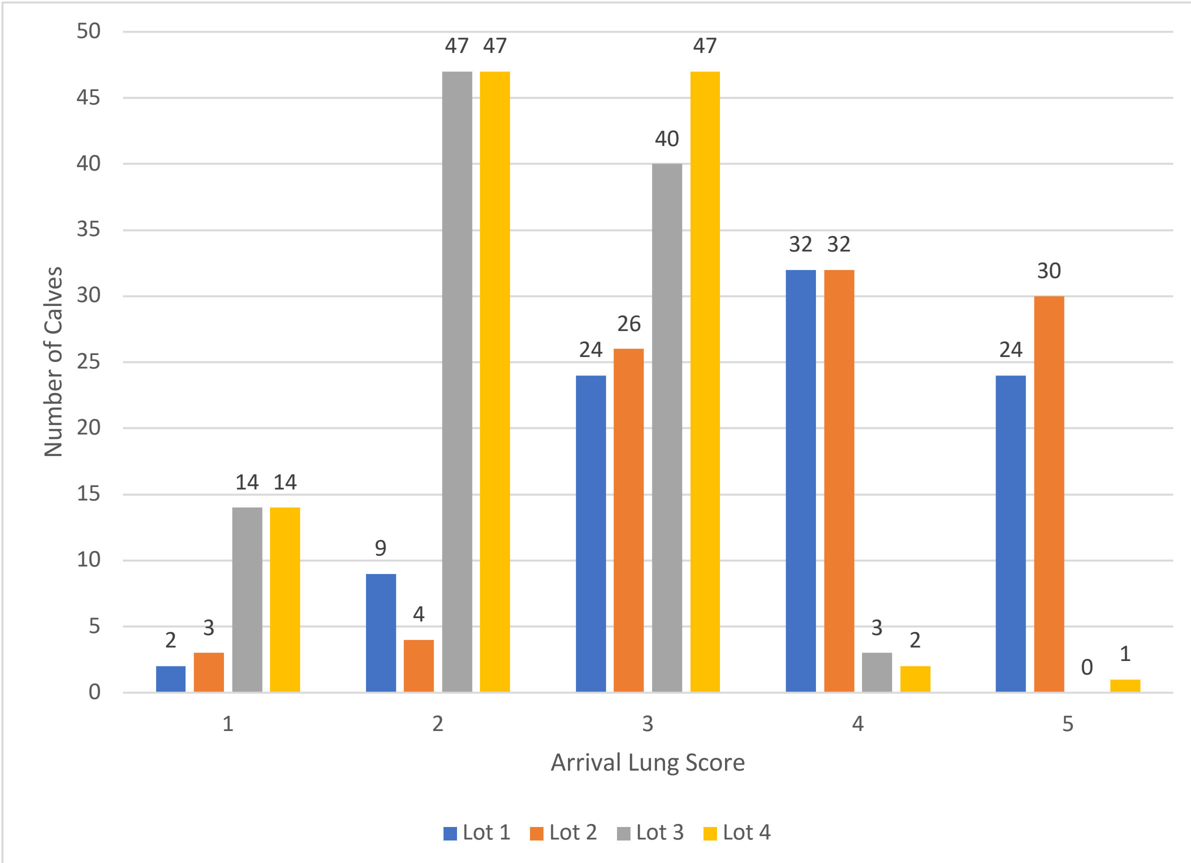

Figure 2.2. *Distribution of arrival lung scores by lot*

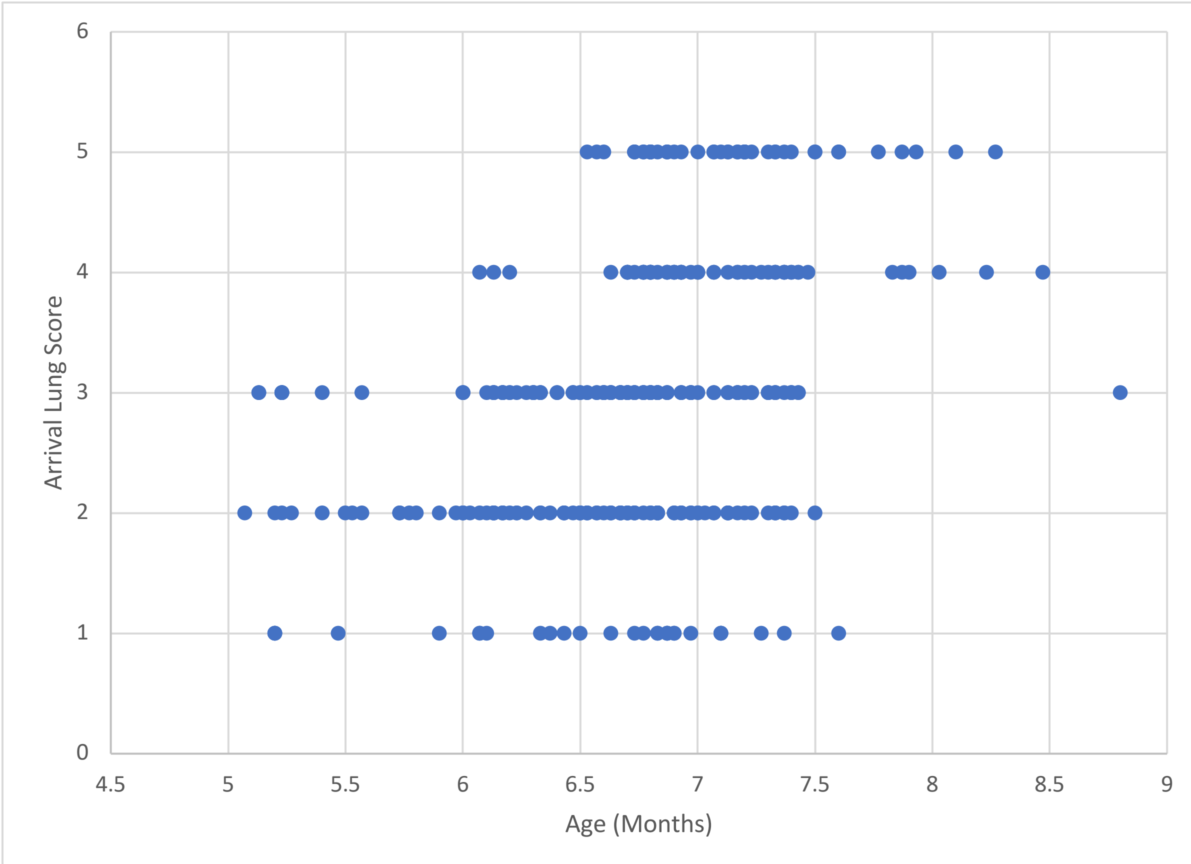

Figure 2.3. *Scatter plot of arrival lung scores by arrival age*

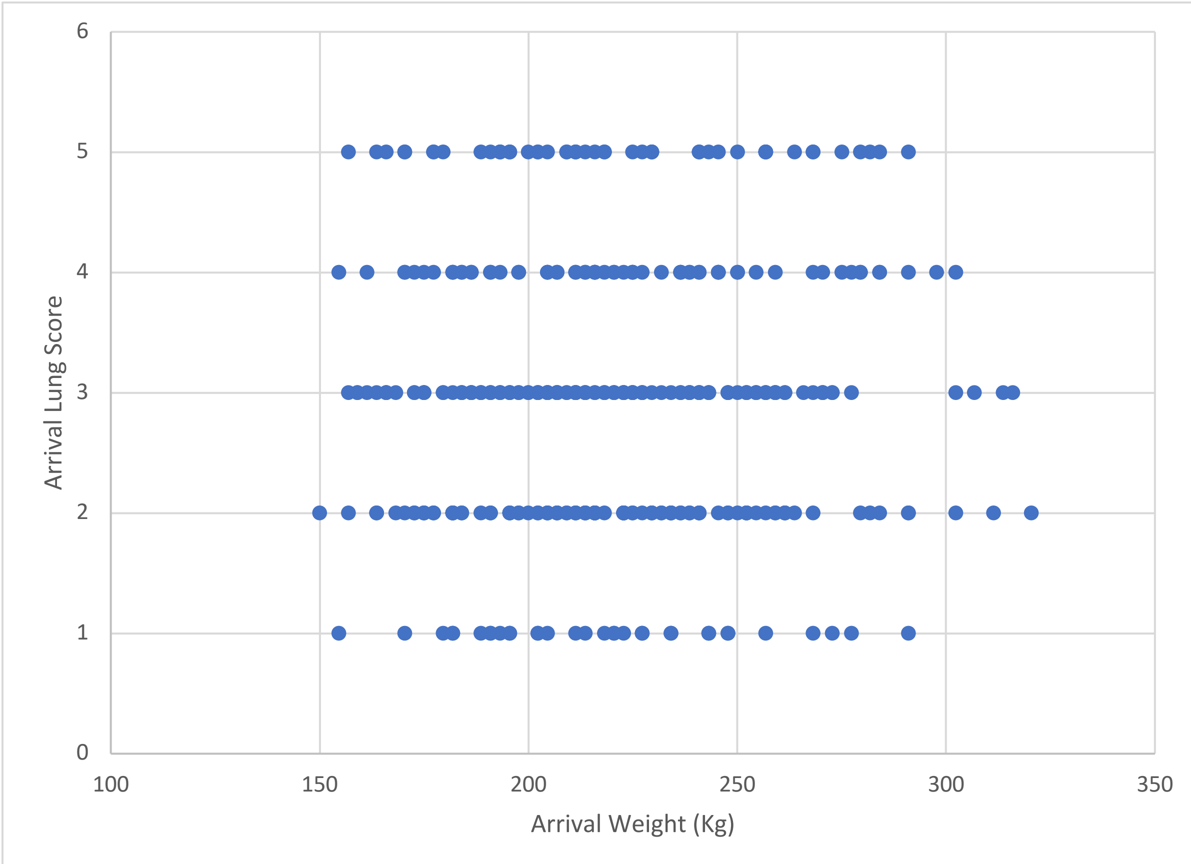

Figure 2.4. *Scatter plot of arrival lung scores by arrival weight*

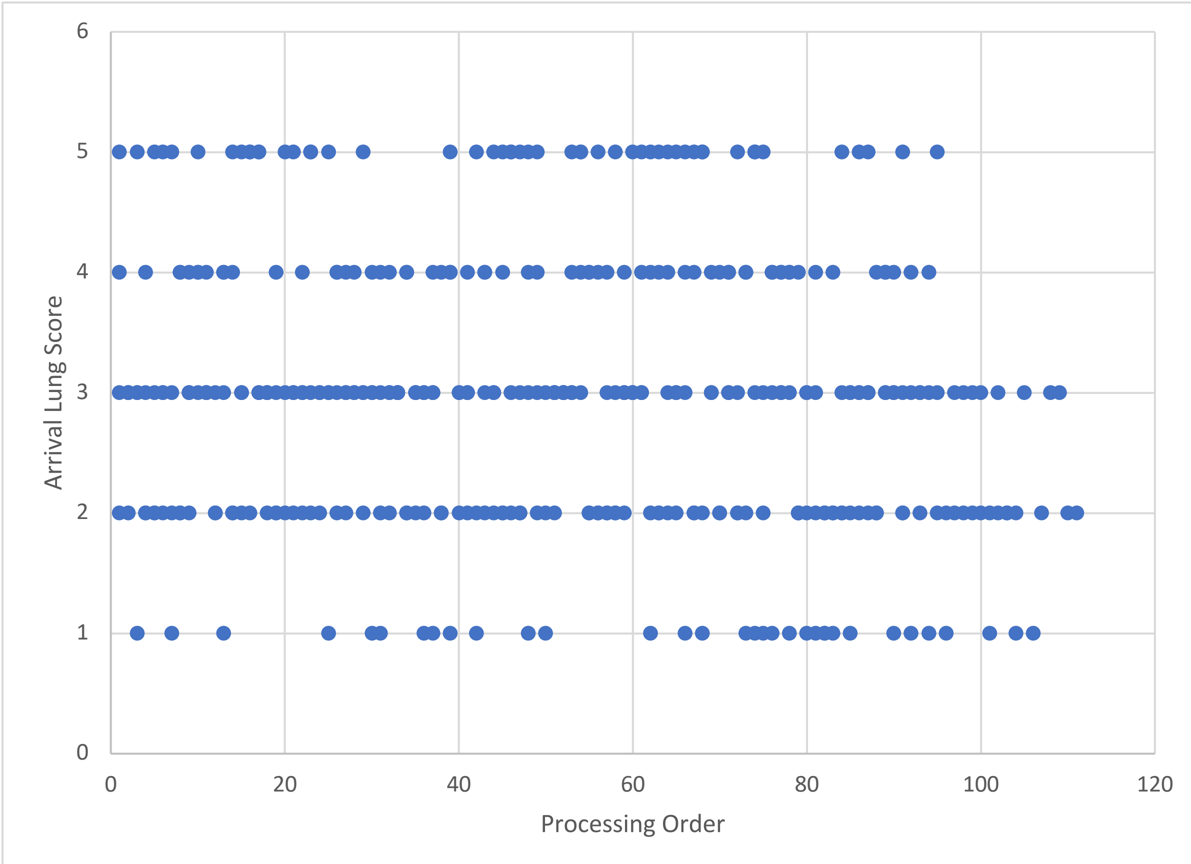

Figure 2.5. *Scatter plot of arrival lung scores by processing order*

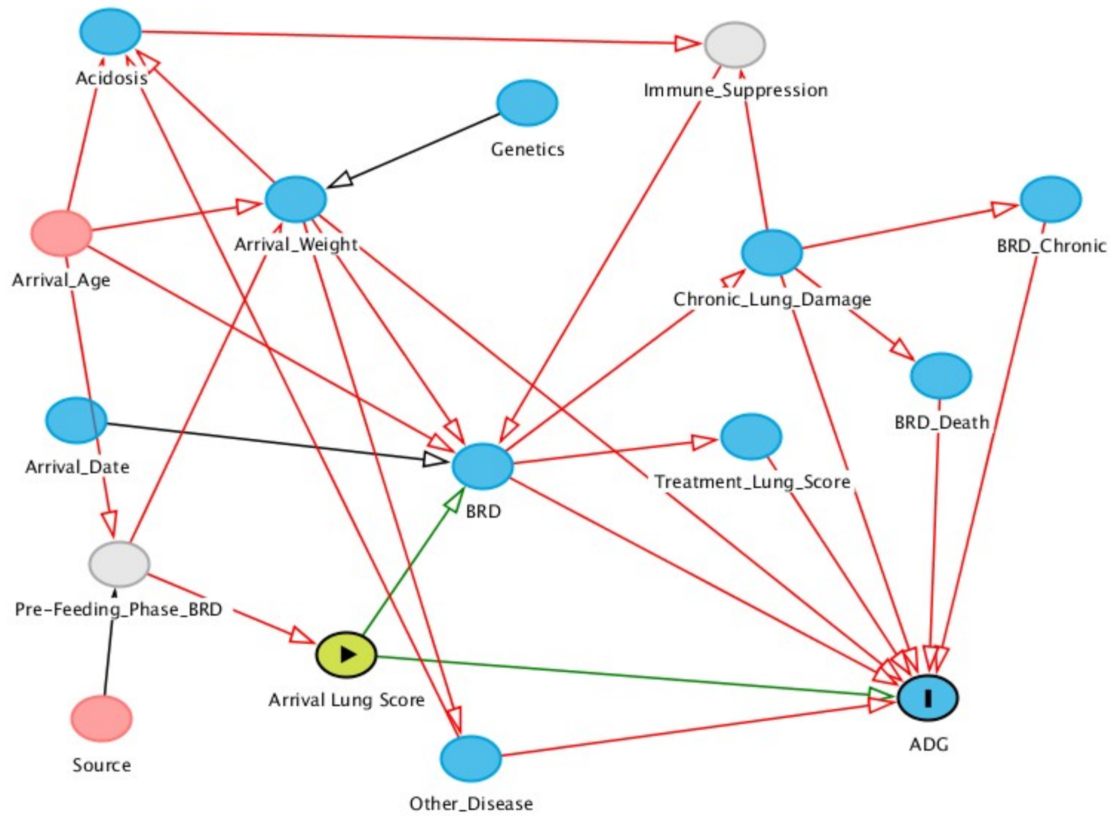

Figure 2.6. *Causal diagram created for model building*

Table 2.1. *Descriptive data for 389 calves by lot*

Variable (N=389)	**Lot 1 (N=80)**	**Lot 2 (N=95)**	**Lot 3 (N=103)**	**Lot 4 (N=111)**
Average Arrival Age, months	6.9	7.3	6.2	6.7
Maximum Arrival Age, months	7.9	8.8	7.4	7.4
Minimum Arrival Age, months	6.5	6.1	5.1	6.1
Average Arrival Weight, kg	228.7	230.2	223.6	203.3
Maximum Arrival Weight, kg	320.5	313.6	315.9	290.9
Minimum Arrival Weight, kg	154.5	165.9	159.1	150.0
Number ALS 1 N=33 (8.5%)	2 (2.5%)	3 (3.2%)	14 (13.6%)	14 (12.6%)
Number ALS 2 N=105 (27.0%)	8 (10.0%)	4 (4.2%)	46 (44.7%)	47 (42.3%)
Number ALS 3 N=134 (34.4%)	21 (26.3%)	26 (27.4%)	40 (38.8%)	47 (42.3%)
Number ALS 4 N=66 (17.0%)	29 (36.25%)	32 (33.7%)	3 (2.9%)	2 (1.8%)
Number ALS 5 N=51 (13.1%)	20 (25.0%)	30 (31.6%)	0 (0.0%)	1 (0.9%)
Treatment for BRDC N=132 (33.9%)	27 (33.8%)	37 (38.9%)	37 (35.9%)	31 (27.9%)
Death due to BRDC N=8 (2.1%)	2 (2.5%)	1 (1.1%)	1 (0.9%)	4 (3.6%)
Diagnosed with chronic BRDC N=18 (4.6%)	1 (1.3%)	3 (3.2%)	5 (4.8%)	9 (8.1%)
Death due to BRDC after treatment for BRDC N=7 (5.3%)	2 (7.4%)	1 (2.7%)	1 (2.7%)	3 (9.6%)

Table 2.2. *Descriptive data for 389 calves by arrival lung score*

Variable (N=389)	**ALS 1 (N=33)**	**ALS 2 (N=105)**	**ALS 3 (N=134)**	**ALS 4 (N=66)**	**ALS 5 (N=51)**
Average Arrival Age, months	6.5	6.5	6.7	7.1	7.1
Maximum Arrival Age, months	7.6	7.5	8.8	8.5	8.3
Minimum Arrival Age, months	5.2	5.1	5.1	6.1	6.5
Average Arrival Weight, kg	218.5	221.0	219.3	223.1	220.3
Maximum Arrival Weight, kg	290.9	320.5	315.9	302.3	290.9
Minimum Arrival Weight, kg	154.5	150.0	156.8	154.5	156.8
Number Lot 1 N=80 (20.6%)	2 (6.1%)	8 (7.6%)	21 (15.7%)	29 (43.9%)	20 (39.2%)
Number Lot 2 N=95 (24.4%)	3 (9.1%)	4 (3.8%)	26 (19.4%)	32 (48.5%)	30 (58.8%)
Number Lot 3 N=103 (26.5%)	14 (42.4%)	46 (43.8%)	40 (29.9%)	3 (4.5%)	0 (0.0%)
Number Lot 4 N=111 (28.5%)	14 (42.4%)	47 (44.8%)	47 (35.1%)	2 (3.0%)	1 (2.0%)

Table 2.3. *Mean ± SE of average daily gain by arrival lung score. Deads not included.*

N=389	**LS 1 (N=33)**	**LS 2 (N=105)**	**LS 3 (N=134)**	**LS 4 (N=66)**	**LS 5 (N=51)**
Average Daily Gain, kg/day	1.15 ± 0.04	1.14 ± 0.02	1.16 ± 0.02	1.18 ± 0.02	1.21 ± 0.02

Table 2.4. *Mean ± SE of feed efficacy and carcass characteristics by arrival lung score. Deads not included.*

Outcome (N=227)	**LS 1 (N=12)**	**LS 2 (N=47)**	**LS 3 (N=67)**	**LS 4 (N=56)**	**LS 5 (N=45)**
Feed Efficiency, kg feed/kg gain	8.01 ± 0.25	7.75 ± 0.13	7.63 ± 0.10	7.42 ± 0.08*	7.30 ± 0.09◊
Hot Carcass Weight, kg	375.01 ± 40.94	377.21 ± 14.15	360.32 ± 16.18	372.69 ± 14.95	365.89 ± 16.17
Dressing Percentage, %	59.1 ± 1	61.9 ± 0	59.8 ± 1	61.6 ± 1	59.4 ± 1
Marbling Score	510.08 ± 27.58	465.60 ± 16.60	457.69 ± 14.58	469.22 ± 14.57	462.05 ± 16.34
Fat Thickness, inch	0.41 ± 0.08	0.38 ± 0.02	0.38 ± 0.02	0.40 ± 0.02	0.38 ± 0.02
Ribeye Area, square inch	14.83 ± 0.34	14.87 ± 0.21	14.21 ± 0.24	14.40 ± 0.25	14.36 ± 0.28

* p-value 0.02

◊ p-value 0.005

Table 2.5. *Incidence of each health metric by arrival lung score.*

Outcome (N=389)	**LS 1 (N=33)**	**LS 2 (N=105)**	**LS 3 (N=134)**	**LS 4 (N=66)**	**LS 5 (N=51)**
Treatment for BRDC N=132 (33.9%)	7 (21.2%)	30 (28.6%)	49 (36.6%)	23 (34.8%)	23 (45.1%)
Death Due to BRDC N=8 (2.1%)	0 (0.0%)	2 (1.9%)	0 (0.0%)	4 (6.1%)	2 (3.9%)
Diagnosed with Chronic BRDC N=18 (4.6%)	0 (0.0%)	5 (4.8%)	10 (7.5%)	1 (1.5%)	2 (3.9%)
Death due to BRDC after treatment for BRDC N=7 (5.3%)	0 (0.0%)	2 (6.7%)	0 (0.0%)	4 (17.4%)	1 (4.3%)

Table 2.6. *Unadjusted odds ratios and 95% confidence intervals of univariate health performance models*

Outcome	**LS 1**	**LS 2**	**LS 3**	**LS 4**	**LS 5**
Treatment for BRDC	1.00	1.07 (0.90-1.30)	1.16 (0.97-1.39)	1.15 (0.94-1.39)	1.27 (1.03-1.57)*
Death Due to BRDC	1.00	1.02 (0.96-1.07)	1.00 (0.95-1.05)	1.06 (1.00-1.13)◊	1.04 (0.98-1.11)
Diagnosed with Chronic BRDC	1.00	1.05 (0.97-1.14)	1.07 (0.99-1.16)	1.02 (0.93-1.11)	1.04 (0.95-1.14)
Death due to BRDC after treatment for BRDC	1.00	1.23 (0.71-2.16)	1.17 (0.69-2.01)	1.12 (0.63-1.97)	0.93 (0.53-1.67)

* p-value 0.02

◊ p-value 0.04

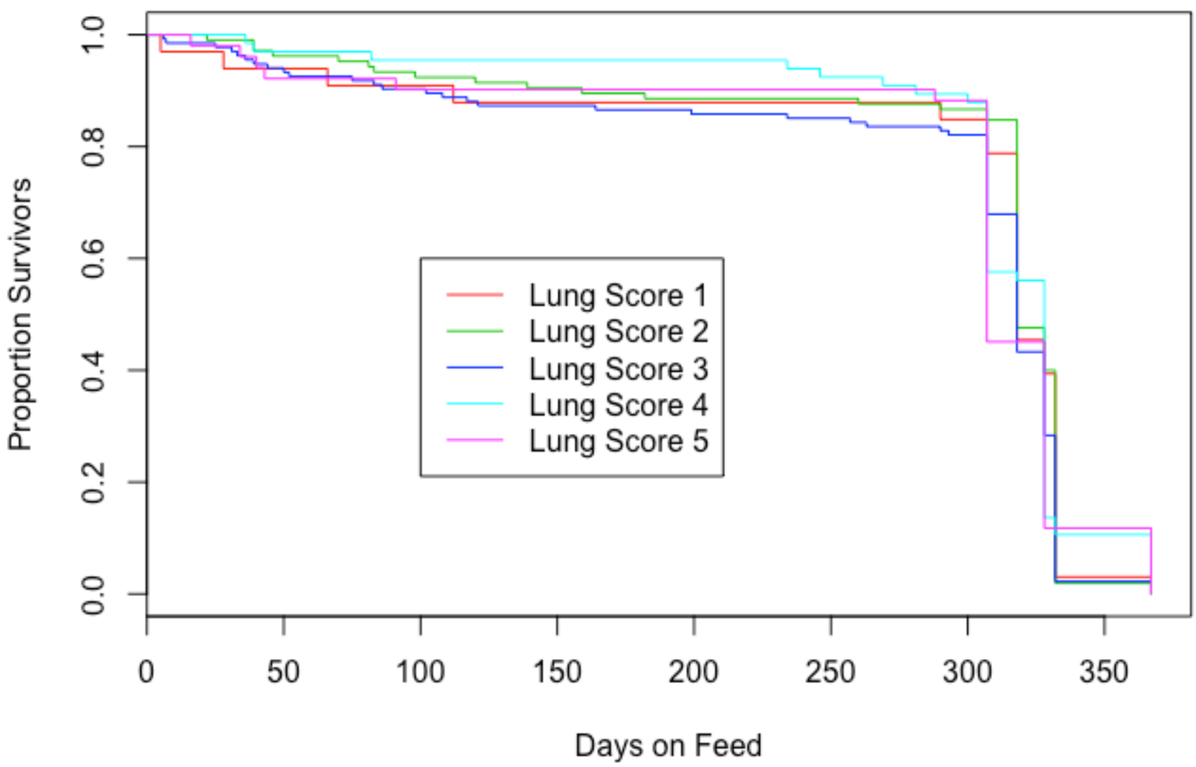

Figure 2.7. *Survival curve by arrival lung score*

CHAPTER 3. GENERAL CONCLUSION

Monitoring feeding behavior has shown the most promise for detecting BRDC in the pen but due to the cost of installing the equipment, it has not been widely adapted. Continuous temperature monitoring, specifically ruminal-reticular boluses, do not present the same cost hurdle as monitoring feeding behavior but is also a less sensitive test. More research is needed to determine the utility of other detection tests. Rectal temperature is most commonly used confirmatory test but has no correlation with treatment outcome. Thoracic ultrasound has been extensively used in the dairy industry to find lesions in the lungs of calves. Computer aided thoracic auscultation has a loose association with lung lesions but does correlate with treatment outcome. Various markers in the blood have been investigated but none have proven to be specific enough to the utilized consistently.

There was no significant association between arrival Whisper® lung score and ADG, FE, HCW, DRESS, MARB, FAT, or REA. There was a significant increase in the odds ratio for RTX but only for calves with an arrival lung score of 5 (OR 1.27, 95% CI 1.03-1.57, p-value 0.005). There was a significant increase in the odds ratio for RD but only for calves with an arrival lung score of 4 (OR 1.06, 95% CI 1.00-1.13, p-value 0.02). There was no association between arrival lung score and being diagnosed with chronic BRDC or dying after treatment for BRDC. This study demonstrates that arrival lung score may be associated with treatment for BRDC and death due to BRDC but more research needs to be done. The algorithm used in this study was designed to aid in treatment decisions and associate with treatment outcome. The idea of developing a different algorithm that could be used at feedyard arrival to better predict feeding and health performance should be explored.