Epidemiological evaluations of magnitude and the temporal distributions of feedlot heart disease and bovine respiratory disease

by

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B.S., Iowa State University, 2010
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AN ABSTRACT OF A DISSERTATION

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Department of Diagnostic Medicine/Pathobiology
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Abstract

The objective of this research was to quantify epidemiologic parameters and associations of risk factors of heart disease in feedlot cattle as well as to analyze temporal distributions of first treatment bovine respiratory disease (BRD) in cohorts with high and low morbidity. Three retrospective studies were conducted to evaluate risk and timing of heart disease in feedlot cattle evaluating different sample populations (individual and cohort data). An additional investigation was performed utilizing retrospective data from a different sample population to investigate BRD morbidity magnitude and timing. Individual first treatment records were utilized to determine if cohorts were high (≥ 15% BRD) morbidity or low (<15% BRD) morbidity, then data were analyzed by clustering on the cumulative distribution of timing of first BRD treatments. A risk association analysis was performed on cohort demographics and risk factors for respective clustering groups.

Feedlots utilized multiple diagnoses for heart disease, and multiple case definitions of heart disease increase the risk of potential misclassification. Deaths due to heart disease was seven per 10,000 cattle placed at a feedlot. Risk factors for a cohort having at least one heart disease death included sex, average cohort arrival weight, year of placement, length of cohort feeding period up until 325 days on feed, and number of cattle received per cohort. Timing of a heart disease death was found to have a mean and median days on feed of 110 days. Cohort demographics associated with the timing of heart disease were average cohort arrival weight which was modified by placement year. Year of placement was also modified by placement quarter on the timing of heart disease death. Steers were found to die later in the feeding phase compared to heifers.

The second investigation utilized individual animal treatment records and cohort data to analyze associations of disease treatment and risk of heart disease in feedlot cattle. This study found that cattle were removed from their respective cohort at a rate of nine per 10,000 cattle placed due to heart disease. Furthermore, cattle died with a heart disease diagnosis at a rate of six per 10,000 cattle placed resulting in a total of 15 heart disease cattle per 10,000 cattle received that did not finish with their respective cohort. The number of BRD treatments was associated with the risk of heart disease and the magnitude of risk was influenced by average cohort arrival weight. Treating cattle for acute interstitial pneumonia (AIP), BRD, and complex disease was associated with increased risk of terminal heart disease diagnosis. Heart disease risk was influenced by feedlot elevation and average cohort arrival weight.

The third and final investigation of heart disease reported risk and timing of right heart failure (RHF) when using a specific case definition in feedlot cattle from Canada and the U.S. These data found that cattle breed (beef, dairy, dairy-cross), type (yearling, calves), treatment of BRD (yes/no), cohort BRD morbidity (0 to 5%, 6 to 12%, 12.1 to 27% and >27%), elevation category, sex, arrival quarter and arrival year were associated with risk of RHF. These data also reported that cattle had an unadjusted risk of RHF of 7.8 cattle per 10,000 cattle placed. Timing of RHF death was on average of 179 days on feed and had a median of 174 days on feed unadjusted. The demographic and risk factors used to associate risk with RHF were also found to be associated with timing of RHF and several interactions were evaluated for their influence of timing of RHF.

The fourth investigation utilized individual and cohort data from 10 US feedlots. Cohorts were divided into HIGH (≥ 15% BRD) morbidity or LOW (<15% BRD) morbidity based on cumulative first treatment BRD within a cohort. Cohorts were clustered on the cumulative timing

of their respective first treatment BRD. Descriptive and statistical analysis were performed on all groups from the cluster analysis as well as the inclusion of cohorts that did not report any treatments for BRD. Results indicated shrink, average cohort arrival weight, ADG, sex, death loss, railed cattle, and number of cattle received were associated with clustering group.

In conclusion, the current research reported novel information on feedlot heart disease and descriptions of the temporal patterns of BRD from high and low BRD cohorts as well as data supporting previous findings of the respective diseases. These data reported many different demographic and risk factors with heart disease risk and timing, as well as, associating with specific clustering BRD timing patterns. This information could be useful in future research.

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Abstract

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The fourth investigation utilized individual and cohort data from 10 US feedlots. The cohorts were divided into HIGH (≥ 15% BRD) morbidity or LOW (<15% BRD) morbidity based on cumulative first treatment BRD within a cohort. Cohorts were clustered on the cumulative

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Dedication

This dissertation is dedicated to my wife (Abby), my children (Corbin and Renée), and my parents (Tony and Michele). I could not have done this without your love and support.

Chapter 1 - A review of literature: bovine heart disease syndrome with emphasis in feedlot cattle

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Abstract

Bovine heart disease (HD) is a syndrome in feedlot cattle that encompasses many different diagnoses and etiologies that share the commonality of mechanical heart failure. For the purposes of this literature review, only non-infectious heart diseases will be evaluated on its epidemiology. Historically, HD in cattle was primarily attributed to changes in altitude or elevation. However, there is growing concern in the number of cattle not finishing their feeding period due to HD. The objective of this review is to synthesize papers that describe the current understanding of feedlot cattle HD case definition, epidemiology, and risk factors of HD. Currently there is not an abundance of literature describing HD in feedlot cattle. Only four journal articles were found that describe case defined risk factors and timing associated with feedlot cattle diagnosed with HD. Case definitions of HD in feedlot cattle varied across studies including, right heart failure, congestive heart failure, non-infectious heart failure, and brisket disease. Risk of HD death was reported to range from 4 to 15 per 10,000 cattle placed in the feedlot. Factors associated with HD risk include the feedlot, gender, the time of year arrived at feedlot (arrival quarter), and which year data were collected. Timing of HD death was reported

to range throughout the feeding period with average timing to death after arrival to feedlot being 110 (IQR 64 to 153days) to 135 (IQR 90 to 190 days) days on feed depending on the study. In conclusion, this literature review found that many factors are associated with HD. The use of multiple case definitions creates confusion and potential misclassification between data sets. Additionally, cattle are being identified with suspect HD and removed prior to death during the feeding period, allowing for potential misdiagnosis and an underestimation HD prevalence. Lastly, cattle are dying from HD throughout the feeding period and not necessarily just in the later part of the feeding period.

Introduction

Heart disease (HD) was first described by Glover and Newsome (1914) in an epidemiological investigation of ranchers in Colorado and surrounding areas of high elevations having cattle die of a mystery disease coined “Dropsy”. The authors described a non-infectious and non-contagious disease with common clinical symptoms of subcutaneous brisket edema, jugular pulses, distended abdomen, lethargy, and anorexia. Additional clinical signs included development of a wet cough and diarrhea later in disease process. In the 1970’s HD became problematic in feedlot cattle when Jensen et al., (1976) described it as a one of the leading causes of mortality in yearling feedlot cattle in Colorado. However, HD was reported in cattle fed at higher elevations with little evidence reported in feedlots at lower elevations. Current investigations of HD reported an increase in the number of cases at lower, more moderate, elevations (Neary et al., 2016; Moxley et al., 2019). There are reports in literature that HD contributed to losses of more than $250,000 U.S. for a single producer and up to 7.5% of pen mortalities at a particular feedlot (Moxley et al., 2019). Cases of right heart failure (RHF) were reported to be increasing in the fed cattle population starting in 2002 and ending in 2012 in

Canadian cattle at moderate to lower elevations (Neary et al., 2016). It remains unknown if increasing number of cases were due to increase in disease or more efforts to better identify the disease. Furthermore, there is a lack of published literature on large population investigations of U.S. feedlot cattle with HD. The objective of this review is to synthesize papers that describe the current understanding of feedlot cattle HD case definition, epidemiology, and risk factors of HD.

Materials and Methods

Authors gathered and reviewed literature over the span of October 2019 through September 01, 2022. Data bases utilized for the presented literature include PubMed, Agricola, and the search engine Google Scholar®. Key terms used for searching were: 'bovine heart disease, 'Feedlot congestive heart failure', 'Heart failure', and 'brisket disease'. Some research was identified from referenced literature identified from the original literature search. The current review included original research articles, case reports, personal communications, and a published thesis report.

Results and Discussion

History

Error! Reference source not found. outlines the main manuscripts evaluated in this article. Glover and Newsome (1914) identified one of the first documentations of HD in cattle and described it as a disease-causing swelling of the brisket at high elevations. This mystery disease was reported as being more prevalent at 8,000 to 9,000 feet (2438 m to 2743 m), in the winter. Furthermore, the mystery disease was initially investigated as an infectious disease. However, the disease was later found to be non-infectious by taking blood from a clinical animal and injecting IV into another animal with no symptoms occurring thereafter. These first documentations were in range cattle (mature cattle and neonates) at high elevations where

ranchers were reporting losses of multiple cattle with common symptoms. Overall, Glover and Newsome (1914) described the most common pathological finding was “general dropsy” which included enlarged liver and dilated heart. The term “Dropsy” was later replaced as a medical diagnosis with congestive heart failure or general heart disease.

Later HD was described or referenced as “Brisket Disease” in research (Kuida et al., 1963). Brisket disease was being reported primarily in young calves associated with exposure to conditions existing on summer ranges on elevations greater than 8,000 ft (2,438m). Investigators noted that a significant number of animals recovered from brisket disease when brought down to an elevation of 4,500 ft (1,372m).

In the mid 1970’s HD (*Brisket disease*) ranked as the second leading cause of death following shipping fever, in yearlings on feed in Colorado (Jensen et al., 1976). Heart disease was later classified as right heart failure and described in feedlot cattle (Neary et al., 2016). Additionally, other reports described HD as congestive heart failure cases or non-infectious heart disease (Moxley et al., 2019; Johnson et al., 2021). Not all literature agrees on a HD case definition and the disease clinical diagnosis has evolved over the past century. A consensus for HD case definition is the heart is the main organ of the disease process that leads to the demise of the animal. The lack of a universally accepted case definition allows for the potential of multiple different disease processes which impact the heart. Unfortunately, multiple case definitions also result in differing estimates of HD magnitude of impact making it difficult to translate data from one operation to another.

Furthermore, cattle are currently dying of HD at lower elevations where previously HD was primarily observed at higher elevations. This could be the result of a different disease with similar clinical and pathological signs, or HD was potentially misdiagnosed or undiagnosed in

the past. This disease was reported in mature and neonate cattle in the early 1900's and now has evolved into non-mature cattle in feedlots and range production. The disease today remains problematic for range and feedlot cattle and there is growing concern that the disease is becoming more prevalent in feedlot cattle deaths.

Pathology

The pathogenesis of HD is thought to originate from increased volume of blood pumped, or an increased resistance to flow, or intrinsic weakness or disease of the myocardium (Alexander, 1978). Heart disease, specifically right heart failure, in any species results from the overwork of the right side of the heart (right ventricle). The cause of over-work was associated to either the heart itself or within the peripheral circulation or the pulmonary vascular bed (Alexander, 1978). Alexander (1978) further described congestive heart failure as either congenital or acquired disease. Congenital disease results from a volume overload of the heart, stenosis of the outflow tracts, or increased pulmonary vascular resistance from induced pulmonary vascular sclerosis. Acquired diseases of the heart (such as valvular disease) results from a failure of valvular incompetence or stenosis, or best described as diseases that weaken the heart to the point where myocardial failure is evident. Multiple different processes can impact the heart, the myocardium, pulmonary system, vasculature, or hepatic system. Multiple etiologies allow for different opportunities to insult the heart, which may or may not be diseased.

Clinical signs

Glover and Newsome (1914) first described symptoms of heart disease in cattle as appearing listless, dull, drooped ears. Authors described clinically affected cattle as gaunt and anorexic with some having a moist cough. Diarrhea would usually appear soon after other clinical symptoms. More recent reports describe cattle symptomatic with HD having varying

degrees of subcutaneous ventral edema extending up to the neck ("Brisket Disease"), ascites, hydrothorax, profuse fluid diarrhea, labored breathing, abducted elbows, jugular pulsations, and swayed back (Alexander, 1978; Malherbe et al., 2012; Neary et al., 2016; Bassett, 2019; Heaton et al., 2019; Krafsur et al., 2019; Moxley et al., 2019). Other clinical findings of affected cattle may include a presence of muffled heart sounds or murmur, venous distension, a venous pulse, edema, normal or reduced appetite, normal or dull mentation, and presence of abnormal or normal feces (Bexiga et al., 2008). Reef and McGuirk (2002) described the differences between congestive heart failure and heart failure is the presence of effusion and edema. The presence of fluid means a volume overload from either peripheral vasculature or valvular disfunction. Whereas lack of fluid may suggest a myocardial insult. Overall, literature on HD found that clinical signs vary depending on the animal, specific disease process/etiology, and the stage of the disease. Some animals show more clinical signs leading up to death, while others appear to have abrupt disease onset and death. It remains unclear if these are different disease processes or the same disease with individual variation.

Subclinical signs

Until more recent times, no research has evaluated if HD is present at slaughter from cattle that would be considered non-diseased or subclinical. A heart scoring system was developed by Dr. Tim Holt from Colorado State University for the use of categorizing hearts post-mortem from 1 to 5 grade. In short, Grade 1 is considered a normal heart, Grade 2 is classified as mild change in heart anatomy, Grade 3 has moderate change in heart anatomy with a reverse "D" appearance, Grade 4 hearts have severe changes compared to normal anatomy, Grade 5 hearts have the most severe change in heart architecture, flaccid, and very round in shape (Personal correspondence with Dr. Tim Holt Sept. 30, 2021).

Heffernan et al. (2020) reported that heart scores were positively related to mean pulmonary arteriole pressure (mPAP). Steers were PAP tested from two different time points (January 5, 2018, time point 1 and March 20th, 2018, timepoint 2) at the Beef Improvement Center in Saratoga, Wyoming then sent to two different feeding locations (Ft. Collins, CO and Akron, CO). Authors reported that performance was not different until cattle had a heart score of 4 or greater (Heffernan et al., 2020). Kukor et al. (2021) also investigated heart scoring, using the same scoring system as Heffernan et al. (2020), at slaughter and reported finding 34% of cattle having a heart score ≥ three, which is generally considered abnormal. Thus, there is evidence that subclinical disease is present at slaughter. However, no data was presented on other organ systems commonly effected with HD such as the liver. Furthermore, heart scoring has the potential for abundant subjectivity and the data were never compared to actual sire PAP scores. This leaves opportunities for future research investigating sire PAP scores effect on feedlot disease. The performance metrics of cattle with a heart score less than 4 being no different begs the question if scores of 1, 2, and 3 are impactful pathology or are within the variation of a normal heart. Considering all the unknowns, more research is needed on heart scoring of cattle in slaughter facilities.

Gross and histological changes

On necropsy, early literature reported clinical cases were described as having an emaciated carcass, subcutaneous tissues under the jaw and region of the brisket are infiltrated with a clear serum (Glover and Newsome, 1914; Alexander, 1978). Authors reported the abdomen was commonly filled with a large amount of fluid which was straw-colored (6-8 gal; 22.7L to 30.3L). The gastrointestinal lining was described as thickened and some areas of small hemorrhages. The liver was described as enlarged and tough and on cross section was grayish

mottled appearance with large cut veins (Alexander, 1978). This gross appearance was described as “nutmeg liver” by British anatomist Francis Kiernan in 1833 due to the similarity of looking like a cross-section of a nutmeg seed (Lin, 2018). The diseased heart was described grossly as enlarged, dilated, and flabby. Krafsur et al. (2019) reported gross pathological findings for heart disease were defined as hypertrophy/dilation of the right atrial and ventricular myocardium, dilated pulmonary trunk, hepatomegaly, ascites, mesenteric, mesocolonic, and intestinal edema. Cattle dying due to HD have multiple common pathologies at presentation. This suggests that once the mechanical function of the heart is compromised then classical pathologies become apparent (ascites, ventral edema, liver congestion, hepatomegaly etc.). Interestingly, the heart itself will have varying degrees of severity of pathological changes, which is likely due to the functionality of the valves, arteries, and veins.

At high elevations, cattle could succumb to *Cor pulmonale,* a type of heart disease developing from chronic hypoxia due to low oxygen saturation at high elevations. This causes an increased pulmonary vascular resistance at the precapillary level resulting in pulmonary hypertension, which leads to an increased right ventricular workload and subsequent failure (Alexander, 1978). Increasing altitude decreases the alveolar pulmonary oxygen (PO_2), which shortens the time necessary to develop severe pulmonary hypertension. The small pulmonary arteries and arterioles have medial thickening in the lumen resulting in restriction of blood flow which leads to a maintained vasotonic increased resistance. A wide variation has been described in cattle with a portion developing severe pulmonary hypertension while others have only a moderate increase in pulmonary hypertension from altitude (Alexander, 1978). Chronic pneumonia can also cause severe alveolar damage leading to chronic hypoxia, which can have similar effects as *Cor pulmonale* on the cardiopulmonary system.

Krafsur et al. (2019) performed a semi-quantitative histopathological assessment of cardiopulmonary tissues from feedlot cattle that suffered from HD and compared the tissues to non-diseased cattle of similar genetics and stage of life. Cattle for the study came from moderate to lower elevations (544 to 1420m). The study used the following clinical case definition for HD, "*cattle presenting distended jugular veins, diarrhea, and loss of body condition"*. Authors reported that symptomatic HD cattle exhibited perivascular and interstitial fibrosis of the left ventricular myocardium compared to the control group (Krafsur et al., 2019). Authors also reported right ventricular perivascular, interstitial, and replacement fibrosis were greater in symptomatic cattle vs. controls. The authors hypothesized that intensive fattening leads to dysregulation of the metabolic, vascular, and inflammatory pathways resulting in left ventricular fibrosis and intracardiac adipose deposition leading to LV stiffening and diastolic dysfunction (Krafsur et al., 2019).

Cor pulmonale is described as a pathological disease process of induced hypoxia to the alveoli leading to pulmonary changes and heart failure due to failure to meet the body's demands for oxygen. Congestive heart failure is described as a chronic disease process with an unclear cause where the heart was the cause of failure and death. The clinical signs of both these disease etiologies are similar and could have the potential to be classified as the same disease. However, *Cor pulmonale* is related to lack of oxygen exchange at the alveolus from high altitudes and congestive heart failure is related to chronic disease of the heart. Thus, animals at lower elevations should not be of concern of *Cor pulmonale* except if there is insult to the alveolus such as pneumonia.

Epidemiology

Historically HD investigations in feedlots were not reported until Jensen et al. (1976) performed an epidemiological survey of feedlot yearling cattle (n = 407,000; 4 feedyards) in Colorado. The most prevalent diseases diagnosed from necropsied (n=1,988) cattle out of a total of 3,943 mortalities were: pneumonia at 48%, diphtheria at 6%, brisket disease at 6%, hemorrhagic colitis at 5%, riding injury at 4%, bloat at 3%, calculosis at 2%, endocarditis at 2%, embolic pulmonary aneurysm at 1% and pulmonary edema at 1%. Many pitfalls were noted such as that only 1,988 of the 3,943 cattle that died were necropsied (Jensen et al., 1976). However, this was one of the first more "modern" epidemiological report of HD impact in fed cattle. From this study, the magnitude of the population at risk for any of the described diseases is unclear, however, 6% of the necropsied cattle were diagnosed with brisket disease (a form of HD). Reported brisket disease was slightly higher than more current reports with approximately 4% of the dead cattle diagnosed with HD (Johnson et al., 2021). However, Jensen et al. (1976) evaluated a yearling population whereas Johnson et al. (2021) reported a mixed population of calves and yearlings. Neary et al. (2016) reported a lower risk of HD in yearlings vs. calves (0.40, 95% CI 0.26, 0.60) in Canadian feedlots, but found that risk was greater for yearlings in US feedlots in 2012 (2.21 95% CI 1.38, 4.09). Authors suggested that the difference between US and Canadian RHF deaths in yearlings vs. calves may be altitude. Four of the five US feedlots in the Neary study were located at elevations > 1,142m and likely had cattle from similar elevations.

A more current large population evaluation of heart disease epidemiology was performed by Neary et al. (2016). Authors performed a retrospective observational study to evaluate risk of right heart failure (RHF, a form of HD) over multiple years in multiple feedlots. Authors

characterized some of the risk factors for RHF and how they affect the timing of RHF occurrence during the feeding period. Factors of interest that were investigated include: respiratory disease treatment, placement period, risk of BRD/UF (bovine respiratory disease/undifferentiated fever), and sex. Their investigation used data from 10 Canadian and five US feedlots over various years, 2000, 2004, 2008, 2012 for Canadian feedlots and 2012 for US feedlots, respectively. The feedlots selected were a subsample of available data and selected due to similar management software and health management team. For their statistical analysis, digestive disorders (DD) were used as a control (referent) to minimize confounding associated with common pathogenesis for the analysis.

Neary et al. (2016) reported that the odds for RHF over time varied from 1.58 (95% CI = 1.11, 2.26; 2004) to 2.69 (95% CI = 1.95, 3.70; 2008) and 1.51 (95% CI = 1.07, 2.13; 2012) in Canadian feedlots when controlling for DD, feedlot, age, risk of BRD/UF, sex and period of placement. In 2012 the likelihood of adjusted risk for RHF was 1.08 (95% CI = 0.89, 1.28) per 1,000 cattle in the US vs. 4.45 (95% CI = 3.52, 5.56) per 1,000 cattle digestive deaths. Johnson et al. (2021) reported that HD had a prevalence of 7 deaths per 10,000 cattle placed from a US population evaluating 22 feedlots. In addition, another study by Johnson et al. (2022) reported prevalence of HD in both cattle railed and cattle that were diagnosed at necropsy and found that railed cattle risk for HD was 9 per 10,000 cattle placed and death from HD was found to be 6 per 10,000 cattle placed. The differences of overall prevalence or risk could be in part due to case definition of HD between the studies. However, risk seemed to be somewhat similar between the studies of HD. The differences likely depend on location, which could be biased with how staff were trained and/or the cattle fed at a particular location and time (year) which the studies were performed.

Risk of RHF in Canadian feedlots doubled from the year 2000 to 2012 (Neary et al., 2016). Mean attack risk per 1,000 cattle for RHF was 0.21 (95% CI 0.11 to 0.31 for 2000), 0.28 (95% CI 0.17 to 0.39 for 2004), 0.47 (0.27 to 0.66 in 2008), and 0.40 (95% CI 0.24 to 0.56 for 2012) (Neary et al., 2016). Canadian cattle had approximately half the risk of RHF and DD in 2012 compared to US cattle, with cattle from both countries having a 5 times greater risk for a DD compared to a RHF in 2012. Risk of RHF was found to be different between each feedyards. Neary et al. (2016) also reported that risk of RHF in US feedyards did not parallel risk of a DD compared to Canadian cattle. The authors explained this by reporting that risk of a RHF was not different between feedlots. Whereas cattle in the four US feedlots reported greater risk of RHF between feedlots. However, there were only four US feedlots, and the range of elevations was greater for US feedlots (596m to 1,282m) compared to Canadian feedlots (657m to 1,145m).

Johnson et al. (2021) also reported a greater probability for cattle placed in quarters three and four for HD but was not significantly different between quarters. Furthermore, Johnson et al. (2021) also reported time of placed was influenced by arrival weight. However, one should caution extrapolation on risk between the two studies. Neary et al. (2016) reported risk of individual cattle whereas Johnson et al. (2021) reported risk of at least one HD death in a cohort. Time of year is associated with risk, but risk may be confounded or influenced by age/arrival weight.

Cattle in the US had a higher risk of RHF compared to Canadian cattle. Neary et al. (2016) reported that limitations of data could be a potential source of confounding, such as only reporting on data from four US feedlots, from one time-point, at relatively higher elevations, and comparing to the Canadian feedlots from multiple time-points and lower elevations. One interesting finding was that yearlings in Canada had a lower risk of RHF compared to calves,

whereas the US yearling population had a greater risk of RHF compared to calves. The increased risk over time was thought to have been attributed to either feeding cattle more intensively such that a hypoventilation becomes possible. The authors suggested that fat content around the thoracic cavity has increased over time.

Johnson et al. (2021) also performed a retrospective observational study on HD. Authors used a case definition of any non-infectious cause of heart disease at time of necropsy. The study compared the probability of a cohort having one case of HD and risk factors associated with HD. Overall, the probability of a cohort having at least one HD death was reported to be associated with sex, arrival quarter, number of cattle placed in a cohort, arrival year, and arrival weight category. Heart disease was found to be relatively low risk for cattle place on feed with no clear cause of HD.

Some other distinguishing findings reported from (Neary et al., 2016) were cattle treated for BRD were three times more likely to die from RHF than cattle not treated for BRD when controlling for likelihood of death from DD, year of placement, and feedlot. Johnson et al. (2022) looked at the risk of BRD and association of terminal HD. Authors reported the number of required BRD treatments was associated with terminal HD and modified by arrival weight category. Both studies identified BRD treatment associated with HD death, and this could be due to multiple factors including misdiagnosis of HD as BRD at the time of first treatment or significant BRD causing pulmonary dysfunction leading to HD. These data are not able to distinguish causality and further research may be useful to further discern relationship among these disease syndromes.

Low risk cattle were twice as likely to die from RHF vs high risk cattle. Male cattle in the US had 39% greater odds of RHF than females in the US, no difference were reported in

Canadian cattle. Neary et al. (2016) reported that age at arrival was not associated with the likelihood of a RHF in both US and Canadian cattle. Johnson et al. (2022) reported greatest risk of HD was found in 900lb or greater placed cattle and in 400 to 500lb placed cattle. Additionally, risk of HD was found to be subjective to feedlot elevation. Feedlots at higher elevation carried a higher risk of HD. This risk was further modified by disease treatment at the feedlot. Cattle that were treated for two or more independent disease events and fed at higher elevations (> 4,000 ft; 1219m) had the greatest risk of HD. There are inconsistencies in the data reported on the risk of age on RHF or HD. Neary et al. (2016) data on US populations was gathered from four out of five feedlots at higher elevations. Whereas Johnson et al. (2022) reported risks of HD across many feedlots at various (moderate <1600m) elevations. The inconsistencies between the studies could be due to study population or potentially a risk factor which was not controlled for in the modeling process.

The adjusted mean attack risk of RHF doubled from 2000 to 2012; however, risk of DD was still 4 to 5 greater in comparison, making RHF mortalities minor in their data set (Neary et al., 2016). Furthermore, the increase in mean attack risk was not significantly different from 2000 to 2012. Johnson et al. (2021) reported year was associated with HD. 2016 had lower risk of HD compared to 2017 and 2018. The two different studies compared risk of HD differently. Neary et al. (2016) compared risk of HD adjusting for digestive disease deaths while Johnson et al. (2021) compared the risk of having one HD per a cohort. This differs from how risk is reported and interpreted. However, when disease risk is very low-to-rare and randomly distributed, the estimates between the two studies should be similar. In the end, risk of HD is likely to have year-to-year variation with due to cattle type at a feedlot and management practices with respect to their current market conditions.

From the previous studies, risk factors for HD largely depended on elevation, placement weight, year, and previous disease (Neary et al., 2016; Johnson et al., 2021; Johnson et al., 2022). Unfortunately, one cannot determine cause and effect from observational research. The disease process appears to be a multifactorial process, which the previous authors suggested from their research. Also with the previous investigations, no reports determined characteristics that would place cattle at high-risk for HD.

Timing

Timing of heart disease is of interest to feedlot producers due to anecdotal evidence that much of the disease is in the later phases where more fattening occurs. Late days on feed deaths incur higher financial burden compared to deaths earlier in the respective feeding period. Neary et al. 2016 reported median days to death was 139 d for RHF and 129 d in DD in Canadian Feedlots and US feedlot had a median RHF death of 133 d and DD death of 107 d. Additionally, it was reported that median days to death in RHF did not change over time relative to the year 2000. These data do not support the speculation that heart disease is a late day disease in fed cattle. Moxley et al. (2019) reported that cattle in their investigative study (n=17) originated from one feedyard with a mean age at arrival of 205 d and mean time in the feedyard prior to death or slaughter was 180 days with mean age at death or slaughter being 385 d and 414kg (910lbs). In addition, Moxley et al. (2019) reported cattle died prior to the development of advanced obesity. Their data should be taken with caution as concern of over extrapolation from their small investigation. Johnson et al. (2021) evaluated timing of HD in an observational study and found that mean and median days on feed to death was 110 days. Authors further reported that temporal distribution of HD deaths was consistent throughout the feeding period. This may be the strongest evidence of consistent risk versus greater risk later in the feeding phase. Authors

further compared a risk factor association with timing of HD deaths and reported that model-estimated mean days to death when adjusting for arrival weight depended on arrival year. Lighter weight cattle died later in the feeding period compared to heavier placed cattle. However, the range of the SE was greater for the lighter and heavier placed cattle due to the lower number of cattle in those respective categories compared to moderate-weight cattle.

Studies reporting the timing of HD death have concluded that HD was found throughout the feeding period and not consistently represented in the final days on feed prior to finish. There were some cattle that died later in the fattening period, but not all cattle that died were reported as overtly obese. The exact timing to death of HD appears to also be multifactorial, which could depend on cattle type and/or location of feeding facility. Studies by a group at CSU are monitoring heart scores at harvest facilities and reporting increased heart sizes suggesting that cattle with subclinical disease are surviving to harvest (Heffernan et al., 2020; Kukor et al., 2021)

Elevation

Glover and Newsome, (1914) first reported elevation playing a role with heart disease. Alexander (1978) reported that altitude-induced heart disease was commonly seen in altitudes greater 1,200 to 1,500 meters. Jensen (1976) reported incidences of brisket disease in lower elevations at 1,200 to 1,500 meters. Malherbe et al. (2012) reported heart disease in Holstein heifers associated with elevation of 1,600m, whereas previously heart disease was not associated with Holsteins. Neary et al. (2013) described mortality rates of beef calves at five high-altitude ranches (greater than 2,438 meters). Authors investigated associations with sires selected over 20 years for low pulmonary arteriole pressure on mortality rates, in a herd where heart failure was found in half of the necropsied young calves. Furthermore, Neary et al. (2016) stated from their

investigation of feedlot cattle in the US from >1,600m could indicate that altitude play a factor causing hypobaric hypoxia. Data from 4 of the 5 US feedlots were located with altitudes above 1,142m (lowest was 686 m). Neary reported that cattle were 9 times more likely to die from RHF at their highest altitude feedyard compared to cattle at the lowest altitude. Risk of RHF in US cattle was found to range from 4 to 17 per 10,000 head entering feedlots with altitudes ranging from 596m to 1286 m. Johnson et al. (2022) used feedlot elevation as a risk factor for HD and reported that higher elevations increased risk of terminal HD. Given the previously evaluated studies, elevation plays an influential role in the risk of HD. However, it remains unclear on whether every disease is identical in the previous studies. Or if any disease under the HD syndrome is more sensitive to elevation.

Genetic evaluation

Glover and Newsome were the first to report that ranchers that raised their own bulls for replacement had lower incidence of dropsy (HD), which could be the earliest hypothesis of heart disease being a heritable condition (Holt and Callan, 2007). In 1960, pulmonary arteriole pressure (PAP) was first published in relationship to cattle with HD and by 1963 it was determined that cattle under chronic hypoxic conditions at high-altitude mountain pressures displayed increased PAP and the magnitude of PAP was related to the degree of hypertrophy of the small arteries (Holt and Callan, 2007). Currently PAPs are used as a tool to evaluate cattle for high genetic value when selecting for replacements. In a review by Holt and Callan (2007) interpretation of the PAP score depends on many factors. Cattle more than 12 months old with < 41mmHg at elevations greater than 1,500m (5,000ft) are likely to maintain and be acceptable stock for breeding. Cattle greater than 49mmHg should not be used for breeding stock, when tested under similar conditions, due to high risk for developing heart failure at high elevations.

Thus, elevation and age are important when performing PAP scoring. Pulmonary arterial pressure heritability has been reported to range from 0.2 to 0.45(Shirley et al., 2008; Crawford et al., 2016; Speidel et al., 2020). Furthermore, Crawford et al. (2016) reported that selecting for lower PAP should have minimal influence on the growth and performance of yearling Angus bulls and heifers. These estimates of heritability considered to be moderately to highly heritable by most geneticists. Most of the PAP evaluations and research have been performed on Angus based genetics. However, Holt and Callan (2007) reported that testing over 150,000 cattle there appeared to be no breed that is resistant to the effects of high-altitude hypoxia. Unfortunately, there is not any available literature on a larger scale for feedlot cattle PAP scored at arrival on the risk of HD or studies evaluating sires PAP scores and outcomes at the feedlot. When performing PAP scores, many factors are important to obtain accurate scores, such as age at scoring, sex, and elevation at time of test.

Efforts to find genetic commonalities are underway with the advent of whole genome sequencing. Newman et al. (2015) reported a high association of *EPAS1* double variant in cattle with high-altitude heart disease and suggested that the *EPAS1* variant could be a tool for identifying cattle at high risk for heart disease. However, when the *EPAS1* was reevaluated in a group of cattle that were diagnosed with bovine CHF and compared to pen-mate controls, there was no difference in frequency of the *EPAS1* variant between cases and controls, which does not support *EPAS1* being a useful tool for genetic identification for bovine CHF (Heaton et al., 2019). Heaton then performed another analysis using the same animals for a genomic wide association study (GWAS). They reported that cattle with genomics regions containing the genes for ARRDC3 and NFIA are major risk factors for bovine CHF. The odds of BCHF increased 8-fold for animals that had two copies of risk alleles in either genos, homozygosity of risk alleles at

both genes increased underlying BCHF odds by 28-fold (Heaton et al., 2022). These data are promising for finding cattle at high risk of disease. Implementation of a genetic test could be a useful tool for nucleus breeding herds. Currently these tools do not appear to be economically advantageous for testing cattle at arrival to the feedlot, due to the low prevalence of HD currently present in most US feedlots.

Conclusions

Heart disease in beef cattle is not fully understood at the current time. Heart disease as a cause of death is mechanical failure of the heart to perfuse the body with necessary nutrients and oxygen. From the literature, heart disease is a disease process that can be attributed to many different factors that increase the risk of clinical disease. Key factors associated with HD include sex, age, country, elevation, BRD treatment, BRD risk, and timing of placement at the feedlot.

Incidence of heart disease in fed cattle was reported to grow from 2 in 10,000 to 11 per 10,000 cattle placed from 2000 to 2012. There appears to be a wide discrepancy of when cattle succumb to HD and there is little evidence of identification of disease prior to full clinical signs. Unfortunately, little can be done from a management standpoint by onset of full clinical signs. The average and median timing of RHF was reported to be later in the feeding period (around 130 days on feed); however, due to many different factors (management, feeding, cattle type). Timing of RHF is expected to range on based on those dependencies. There are speculations that HD is a late-day disease issue, however there is published literature that would contradict those speculations. There appears to be promising tests for identifying genetic risk for HD. However, these are not necessarily practical for conventional cattle placed at feedlots due to low HD prevalence. Subclinical HD has been found at slaughter and there could be a genetic link with no-fatal HD. No available research has repeatably found HD being overrepresented in the later

feeding period compared to earlier feeding deaths. In addition, reported no direct breed influence of HD in cattle. In conclusion, HD remains a problematic for feedlot operators, producers, and geneticist due to lack of progress in reducing HD at the feedlot level. Heart disease in feedlot cattle appears to be a multifactorial with major risk factors of elevation and genetics not fully understood. Furthermore, HD in feedlot cattle is rare compared to common feedlot diseases such as BRD or digestive diseases. There has been no direct causal link nor any therapeutic treatments for cattle with clinical HD reported in literature.

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Table 1-1. Bovine heart disease literature of case definitions and risk used for review analysis

Title	HD Case definition	RISK
Brisket disease (dropsy of high altitude)[1]	Brisket disease ("dropsy").	
Diseases of yearling feedlot cattle in Colorado[2]	Brisket disease	6% of necropsied cattle (n=1,988) Reported 3,943 mortalities
Brisket disease in yearling feedlot cattle[3]	Brisket disease	6% of necropsied cattle (n=1,988) Reported 3,943 mortalities
The interaction of pathogenetic mechanisms in bovine high mountain (brisket) disease.[4]	Brisket disease: "*a term that is generally used to identify the syndrome of congestive right heart failure in the bovine species, historically associated with residence at high altitude."*	Incidence of 0.5% to 2% in cow-calf operations around 2,200 m
Right ventricular hypertrophy with heart failure in Holstein heifers at elevation of 1,600 meters[5]	*A syndrome of right-sided heart failure in young Holstein cattle resembling a clinical presentation of brisket disease.*	Case-study with 10 cases over a multi-year study in Holstein population.
Right-Sided congestive heart failure in North American feedlot cattle[6]	*Brisket and ventral edema; hydroperitoneum; hydrothorax and secondary atelectasis; hepatomegaly and chronic passive congestion; intestinal and mesenteric edema; hydropericardium; right-ventricular hypertrophy and dilation.*	Retrospective observational study. From 10 Canadian feedlots over multiple years and 5 US feedlots from 2012. Population at risk 1.56 million cattle over a multi year study (2002, 2004, 2008, 2012).

		In 2012 for every 10,000 cattle entering the US feedlots 11 died from RHF. Median time to RHF death was 19 weeks (approximately 139 days)
Investigation of congestive heart failure in beef cattle in a feedyard at a moderate altitude in western Nebraska[7]	Right-sided heart congestive heart failure, and brisket disease. *Cattle exhibited clinical evidence of brisket edema and one or more of the antemortem signs of jugular pulse, dyspnea, or cyanosis; and 2) postmortem lesions of heart enlargement, pleural or pericardial effusion, or pulmonary edema with identification of heart enlargement postmortem being subjective to interpretation of size and shape.*	Case study n=17 cases (16 steers, 1 heifer) over a 15-month period.
Evaluation of EPAS1 variants for association with bovine congestive heart failure[8]	*Bovine congestive heart failure included two or more clinical signs specific to bovine congestive heart failure, ventral and intermandibular edema ('brisket' and 'bottle jaw') jugular vein distention and pulsation, ascites/abdominal swelling, and exophthalmia ('bug-eye'). Also, two more non-specific clinical signs: dyspnea, abducted elbows, depression, drooped ears, intermittent water orange diarrhea, tachycardia, exercise intolerance, open mouth breathing, and weight loss.*	Case-control study. Paired samples from 102 affect cattle and 102 nonaffected pen-mates from January 2017 to April 2018. Cattle were fed at four feedlots in Nebraska and Wyoming.
Evaluating the epidemiology and management of bovine congestive heart failure[9]	*Bovine congestive heart failure was defined as any animal showing one or more of antemortem clinical signs of congestive disease including ventral subcutaneous edema, abduction of the elbows, jugular pulse, and dyspnea.*	Data from one feedlot starting in 2011 to 2016. Cases per 100,000 head days at risk from 2011 to 2016 ranged from approximately 1 (2012) to as high as 3.1 (2016). Total cases of BCHF = 554 form a population of 111,329 cattle (4.97 BCHF per 1,000 cattle)
Retrospective analysis of cohort risk factors and	Any disease that was listed as primary cause of death impacting the heart from a noninfectious origin. *Diagnosis included HD Heart disease, HEA heart*	Observational study reported 7 HD deaths per 10,000 cattle placed from a population of 4.6

feeding phase timing associated with noninfectious heart disease deaths in U.S. feedlot cattle[10]	*failure, Heart Disease, Heart Failure, Heart failure left/right, Heart problem, Left heart failure, Mechanical heart failure, congestive heart failure.*	million cattle from 22 US commercial feedlots over three years.

[1]Glover and Newsome, (1914)
[2]Jensen et al. (1976)
[3]Jensen et al. (1976)
[4]Alexander, (1978)
[5]Malherbe et al.,(2012)
[6]Neary et al. (2016)
[7]Moxley et al. (2019)
[8]Heaton et al. (2019)
[9]Bassett, (2019)
[10]Johnson et al. (2021)

Chapter 2 - Retrospective analysis of cohort risk factors and feeding phase timing associated with non-infectious heart disease deaths in US fed cattle

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Abstract

Heart disease, specifically, congestive heart failure has become of increased interest to geneticists and cattle feeders. Data on cohort associations of risk factors related to heart disease and when heart disease deaths occur in US feedlot cattle are limited. The study objectives were to 1) determine potential associations between feedlot cohort demographics and the risk of at least one non-infectious heart disease (NIHD) death occurrence and 2) determine potential association between feedlot cohort demographics and the timing of NIHD deaths during the

feeding phase. Data were downloaded from commercial feedyard software and analyzed by constructing a generalized linear mixed model for both analyses. A binomial and Gaussian distribution for risk of NIHD death and timing of NIHD were utilized as link functions for their respective models. Our study population consisted of 28,950 cohorts (representing 4,596,205 cattle) that were placed in 22 US commercial feedlots from January 01, 2016 to January 01, 2019. There were 3,282 cases of NIHD deaths from a population of 75,963 cattle that died during the three-year study period. Average cohort arrival weight's effect on NIHD probability was influenced by arrival quarter and arrival year of placement ($P < 0.01$). Cohorts with steers were associated with a greater probability of at least one NIHD death (2.38%) compared to heifers (1.95%; $P < 0.01$). Increasing cohort size was associated with an increased probability of a cohort having at least one NIHD death ($P < 0.01$). The probability of at least one NIHD death in a cohort increased from 1.51%, to 2.12%, and 2.87% in d on feed categories 100-175, 176-250, and 251-326 respectively. Cattle > 326 d on feed were no different in the probability of a NIHD death compared to the other feeding categories. Timing of a NIHD death had a mean and median occurrence of 110 d on feed with an interquartile range of 64 to 153 d on feed. The effect of arrival weight on d at death was influenced by year placed with heavier cattle generally decreasing the model adjusted means of d on feed at NIHD death. Arrival quarter was influenced by year placed on model adjusted means on the timing of a NIHD death. Steers with NIHD died later compared to heifers ($P < 0.01$) diagnosed with NIHD. In conclusion, multiple factors are associated with probability and timing of a NIHD death. Probability of having at least one NIHD death within a cohort was low and half of the deaths occurred before 110 d on feed.

Keywords

brisket disease, cattle, congestive heart failure, feedlot, heart disease

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List of abbreviations

AIP, acute/atypical interstitial pneumonia
BRD, bovine respiratory disease
CHF, congestive heart failure
DOF, days on feed
GI, gastrointestinal
LCL, lower confidence limit
NIHD, non-infectious heart disease
RHF, right heart failure
UCL, upper confidence limit
UID, unique identification number
US, United States

Introduction

Heart disease, specifically congestive heart failure (CHF) or right heart failure (RHF), have been investigated recently (Neary et al., 2013; Neary et al., 2016; Heaton et al., 2019; Krafsur et al., 2019) in finishing cattle. Research has identified increases of cases classified as heart disease over time suggesting that prevalence of heart disease may be increasing. Neary et. al., 2016 reported the risk of right heart failure from 2000 to 2012 doubled from 0.21 to 0.40 per 1,000 head placed. Some individual producers in the Western Plains had annual losses exceeding $250,000 (Heaton et al., 2019). Previous research stated animals that succumb to heart disease in the feedlot tended to die later in the feeding phase (Neary et al., 2015; Neary et al., 2016). Neary

et al. (2016) found a median d on feed for a right heart failure death was 132 d for Canadian cattle and 133 d for US cattle. Due to the economic value of heart disease animals, including the cost of animal plus operational costs, and feed cost, there is a need to further investigate data to better understand heart disease risk and underlying factors that may influence heart disease. The purpose of this research is two-fold, 1) determine the risk of at least one non-infectious heart disease (NIHD) death within a cohort and the associated cohort demographics that may influence risk of heart disease in the population 2) evaluate when a NIHD death occurs during the feeding period and evaluate cohort demographics that influence the timing of heart disease deaths.

Materials and Methods

Animal Care and Use Committee approval was not obtained for this study due to retrospective data being obtained from existing privatized databases from commercial feedyards.

Data Source

Data used for analysis were under confidential agreement with participating feedyards. Cohort and individual mortality data were collected from cattle placed in 22 commercial US feedyards from January 1, 2016, to January 1, 2019 located throughout the mid and southern plains. After confirming that inclusion criteria were met, a total of 4,596,205 cattle were received comprising of 28,950 cohorts and 75,963 mortalities. A cohort is defined as a group of cattle that were acquired, managed, and marketed similarly but not necessarily commingled in the same physical location (pen) for the feeding phase. Data were exported from commercial feedyard systems and subsequently imported into R (R Core Team, 2020) for analysis.

Risk of NIHD cohort by enrollment criteria:

Enrolled cattle (Fig. 1) were categorized by animal identification, lot identification, average lot arrival weight (“in-weight”), arrival date to feedlot (“in-date”), death date (event

date), d on feed at death, sex, pen at death, number of cattle received in cohort, cause of death ("diagnosis"), and organization number (arbitrary identification number representing a unique feedyard). A unique identification number (UID) was created to distinguish animals within cohorts from their respective feedyard due to separate feedyards having similar cohort identification number systems. The UID was comprised of the organization identification number, feedyard identification number, and cohort identification number. Total d on feed was calculated as ship date less arrival date (total d on feed = ship date – arrival date). Estimated ship date was used when an actual ship date was not provided as the final date on feed for that lot in the total days on feed calculation. If no known ship date or estimated ship date were recorded, then the observation was omitted from the data set.

Included cohorts must have completed their respective feeding phase and be considered a closed cohort. Review of the data found multiple cohorts that had cattle remaining not shipped when they logically should have been (e.x. 3 cattle remaining in a cohort after multiple years since ship date). Thus, a new variable was created "current pen size" to evaluate for cohorts being closed. The following equation was used to calculate the parameters of current pen size: [Current Pen Size = cattle received – (cattle shipped + cattle railed + cattle dead) = 0]. Cattle shipped is defined as cattle who finished their feeding period and were shipped to a harvest facility. Cattle railed is defined as cattle who were removed and not finishing their respective cohorts feeding period due to health-related reasons (i.e., muscular skeletal injury, lack of thriving. Data evaluation revealed that multiple cohorts remained with -1 or ≤ 7 cattle in current pen size when they should have been 0 due to shipment date and time to data download with no new entries. Thus, authors deemed data acceptable to include a current pen size range from -1 to 7 cattle as a "closed pen" to accommodate for a likely accounting error.

Cohort inclusion criteria included: greater than 39 cattle were placed, cohort with current pen size at close-out of -1 to 7, average arrival weight was greater than or equal to 182 kg and less than or equal to 545 kg. Cohorts were limited to a sex listed as heifer or steer. Other options under the sex category including mixed sex, bulls, or Holstein were not included. Cohorts must have been on feed at least 100 d before shipping to harvest. For cohorts that met the inclusion criteria, a placement-quarter variable was created from the arrival month of placement. The following criteria was used to create the placement quarter variable: **1** = January through March, **2** = April through June, **3** = July through September, and **4** = October through December. Individual mortality data used in this analysis were gathered from their respective feedyard health software. Multiple diagnosis categories were utilized to define specific diseases common in fed cattle. For the purpose of this paper, entered diagnosis were evaluated and condensed into five disease categories: Acute/Atypical Interstitial Pneumonia (**AIP**), Bovine Respiratory Disease Complex (**BRD**), Gastrointestinal disease + Bloat (**GI+Bloat**), Non-Infectious Heart disease **(NIHD)**, and **Other** (any diagnosis that was not AIP, BRD, GI+Bloat, or NIHD) .

Days on feed analysis of heart deaths:

Cohorts meeting the inclusion criteria had their individual mortality data analyzed for when a NIHD death occurred during the feeding phase. A new variable was created and called "event days on feed". This was calculated by using the following formula [Event DOF (days) = Death date – Arrival date]. Individual deaths categorized for NIHD were included in the analysis. Infectious heart disease cases were removed from the heart disease category prior to analysis. Table 1 shows the diagnosis codes that comprised the heart disease category.

Statistical Analysis

Risk analysis for any non-infectious heart disease death within a cohort:

A generalized linear mixed-model was fit into R Studio (R Core Team, 2020) using the 'lme4' package (Bates et al. 2015) and 'glmer' function. Feedyard was included as a random intercept to account for lack of independence of cohorts within feedyard. A binomial outcome of 0 or 1 for heart death in lot was created, 0 = no NIHD deaths within the cohort and 1 = at least one NIHD death within cohort, for the outcome variable and fixed effects included: arrival quarter, days on feed, arrival weight, sex, arrival head received (lot size by quartiles), and arrival year. To avoid violating the assumption of linearity, total received head in each lot was categorized into four equal groups using the dplyr::ntile function in R (Wickham et al., 2019). Using this method there is the possibility of overlapping values in the groups; however, authors wanted to keep the groups as equal as possible with respect to the number of cohorts in each group. A univariate analysis was performed, and only significant factors ($P \leq 0.05$) were included. All factors of the model were found to be significant, and a second model was created incorporating interactions. All possible 2-way interactions were incorporated, and only significant 2-way interactions were included ($P \leq 0.05$). The final risk model was created utilizing a backwards elimination process (Dohoo et al., 2012), where all factors and interactions were included then eliminated when found to be non-significant ($P > 0.05$).

Days on feed of heart death individual analysis:

Individual heart disease mortalities (n = 3,282) and their associated cohort data were exported from 19 US commercial feedlots, three of the feedyards from the 22 used with the risk analysis reported no NIHD deaths and thus were not included in the NIHD d on feed analysis. A generalized linear mixed-model was fit in R Studio (R Core Team, 2020) using the 'lme4' package (Bates et al. 2015) and 'lmer' function to assess the association of head received, arrival quarter, gender, arrival weight and arrival year on the outcome d on feed at the time of a NIHD.

Feedyard was included as a random intercept to account for the lack of independence within feedyards. The final model was created by initially including all covariates and interactions, then a backwards variable elimination process was used to remove non-significant interactions and covariates ($P > 0.05$).

Results

Descriptive Statistics

The final data set consisted of 28,950 cohorts; 11,927 cohorts were heifers and 17,027 were steers. The total cattle received during the three-year observational study was 4,596,205. Figure 2 shows the total cattle received to the feedyards which died, (n = 75,963 cattle), during the feeding phase of various diseases expressed as a percent of total cattle received. Death loss for NIHD was 0.07% or a 7 in 10,000 cattle across all 22 feedyards over the three-year period. This number was calculated by total NIHD deaths divided by total cattle received (3,282 cattle / 4,596,205 cattle). There were 457 NIHD deaths in 2016 out of a population of 1,081,903 cattle accounting for 0.04% or 4 in 10,000 cattle. In 2017 NIHD accounted for 1,283 deaths out of a population of 1,637,876 cattle accounting for 0.078% or 8 in 10,000hd of cattle. Finally, in 2018 1,542 cattle died due to NIHD in a population of 1,876,426 cattle representing 0.08% (8 in 10,000 cattle). Non-infectious heart disease deaths accounted for approximately 4% of the total dead population (3,282 / 75,963). Variables significantly ($P < 0.05$) associated with the probability of having at least one NIHD death in a cohort included sex, cohort size, and cohort feeding length (d on feed) and the 2-way interactions between arrival weight and arrival year, arrival weight and quarter of placement. Variables significantly ($P < 0.05$) associated with influencing timing of NIHD death include sex and cohort size, and the 2-way interactions arrival year and arrival quarter, arrival year and arrival cohort average weight.

Association of cohort risk of at least one heart death within cohort:

The effect of cohort weight on the probability of a cohort having at least one NIHD death was influenced by cohort arrival quarter and year of placement. The association of arrival weight category with the risk of having a cohort with at least one NIHD death generally decreased with heavier weights influenced by arrival quarter (Fig. 4). Cattle placed in the second quarter had the same risk of NIHD death across all weight groups. The greatest risk of having a NIHD death within a cohort was found in the 273-318kg cohorts placed in the 4^{th} quarter compared to all other cattle placed at all other quarters. Cohorts placed in the first quarter at 182-227kg had the lowest risk (0.005% probability). However, the lighter weight cattle in our study (182-227kg) did not differ in the risk from the heavier placed cattle (445-500kg). The association of arrival weight with the probability of at least one NIHD death in a cohort was influenced by placement year (Fig. 6). In 2016, all placement weight categories had no differences in cohort probability of a NIHD death. Cattle placed in 2017 and 2018 had no differences in probabilities of a NIHD death across weight category except for 2018, 182-227kg placed cattle had a lower probability (0.009, LCL 0.003 UCL 0.02) of a NIHD death within cohort compared to 2017 (0.037, LCL 0.012; 0.11 UCL).

Additionally, steer cohorts were associated with having a greater model estimated means probability of a NIHD death compared to heifers [2.38% (LCL 1.0%, UCL 5.8%) vs 1.95% (LCL 0.78%, UCL 4.7%), respectively] ($P < 0.01$). The model estimated means probability of NIHD increased linearly with cohort size quartile from the lowest probability of 1.12% in quartile 1 to 3.82% in quartile 4. Quartile 4 was not different from quartile 1 but was different than quartile 2 and 3 (1.93% and 2.57% respectively).

The model estimated means probability of at least one NIHD death in a cohort increased with increasing d on feed for cohorts from 1.51% to 2.87% for cattle fed 100-175 d and 251-326 d respectively. Model estimated means estimate probability decreased to 2.33% in cattle that were fed > 326 d, which was not ($P = 0.90$, $P = 0.9985$, $P = 0.99$) different compared to the 100-175, 176-250, and 251-326 categories of d on feed, respectively.

Timing of non-infectious heart disease death modeled results:

Variables significantly ($P < 0.05$) associated with the d on feed of NIHD death in the final model were cohort size and sex and the 2-way interactions of arrival weight and arrival year, and arrival year and arrival quarter.

Cattle that died from NIHD died on average at 110 days on feed (Fig. 3). The median days on feed death was also found to be 110 days. The interquartile range of a NIHD death occurred between 64 and 153 days on feed in this study. Cattle placed at heavier weights tended to have a lower model estimated days-on-feed at NIHD death (Fig. 6) with the effect being influenced by placement-year. Placement-quarter's effect of when a NIHD death occur was also influenced by placement-year (Fig. 7). The effect of gender indicated that steers died later compared to heifers ($P < 0.01$). Steers that died due to NIHD died at model estimated means of 114 d, ± 4 d compared to heifers with a NIHD death at 102 d, ± 5 d. Lastly, cattle placed from cohorts' sizes of 60 to 101 cattle died approximately 8 d earlier (LCL 91 d, UCL 111 d) than other placement groups ($P < 0.01$).

Discussion

A problem with operational feedyard data is a lack of consistent standardized reporting of data across feedyards (Corbin and Griffin, 2007). Our retrospective data includes many case definitions of NIHD, which can be specific to a feedyard and/or organization and potentially

differ among trained personnel. Each feedyard entered a diagnosis for health data for their respective system for cause of death. To accommodate the inconsistent case definition of what defined heart disease, our study case definition included all non-infectious diseases that affected the heart which was labeled the primary cause of death.

Previous literature has described the individual risk of RHF and factors that affect risk of RHF in Canadian and US feedlot cattle (Neary et. al., 2016). Bassett (2019) performed an epidemiological investigation on CHF of one feedyard in western Nebraska over six years, which looked at number of CHF cases per 100,000 cattle head days and the timing of CHF diseases during the feeding period. The current study evaluated potential associations of cohort factors on the probability of at least one NIHD death and the timing of NIHD during the finishing phase. Our showed that the risk of NIHD death doubled from 4 per 10,000 cattle received in 2016 to 8 per 10,000 cattle received in 2017 and 2018. Differences from 2016 compared to 2017 & 2018 could be due to more contributing feedyard data during 2017 & 2018, cattle type procured at each respective feedyard, or other unknown reasons. Neary et al. (2016) estimated the incidence of RHF in cattle to be between 4-17 per 10,000 cattle entering US feedyards and reported an increase in mean risk per 1,000 Canadian cattle for RHF from 0.21 in 2000 to 0.4 in 2012. Bassett (2019) found that the proportion of cases of CHF doubled from 2011 to 2016. One concern with operational feedlot data is the accuracy of which the data is measured. stated that accuracy of measured health outcomes is a potential source of differential error. The question of whether NIHD deaths are increasing or are veterinarians and feedlot personnel getting better at diagnosing them, is still a valid confounding concern. Albeit the data presented here and saw increases in the number of cases throughout multiple different time periods and locations.

The effect of arrival weight on the probability of a NIHD death was influenced by quarter of feedyard placement in our data. Average cohort placement weight had the numerically lowest model estimated probability of a NIHD death in the 182 kg to 227 kg groups, while the 273kg to 318kg average cohort placement weights had numerically greater probability of a heart death when placed in the 4th quarter compared to other placement-weights and placement quarters. Cattle placed in the 2nd quarter had similar probability of a NIHD death across all weight classes. Light weight cattle had similar probability of a NIHD death to cattle placed at 445kg to 500 kg. Neary et al. (2016) reported that increasing weights at feedyard placement did not increase the risk of a RHF, with the assumption more weight to gain means more days on feed. Bassett (2019) evaluated cohort percent finish, which was defined as "Degree of Finish (% Finish) = d on feed at diagnosis / (lot end date – lot start date)", at the time of individual CHF death and reported that there was potential for clustering, but CHF was distributed throughout the feeding period and heavily skewed with increased deaths in greater percent finished cohorts. "Degree of finish" variable was designed to be a representation of an approximate degree of fattening with respect of timing to their respective cohort at the time of death. Our data found that that lighter weight (181kg-227kg) cattle had relatively similar probability of a heart disease death within cohort as heavier placed cattle (409-455kg). In addition, our data also found that weight was also affected by the year of placement into feedyard. In 2016, our data saw a numerically lower probability of a heart disease death across all weight classes compared to 2017 and 2018 data. Neary et al. 2016 found year to year variation in RHF with an overall 2-fold increase in risk from 2000 to 2012. Bassett, 2019 evaluated CHF in one feedyard over six years and saw increased number of cases per 100,000 cattle head-days from 2011 through 2016. Our data showed a numeric increase in a probability of at least one NIHD death within a cohort from 2016 to 2018,

suggesting that some potential factor (i.e., cattle type) within year is influencing cattle dying of NIHD.

Steer cohorts had a greater probability of a cohort having at least one NIHD death compared to heifers ($P < 0.01$). Neary et al. (2016) found that steers in the US had 39% greater odds of RHF compared to heifers, but no differences were observed in Canadian cattle sexes. Our data showed that steers had a 22% (2.38% vs 1.95%) greater probability of at least one NIHD death compared to heifers diagnosed with NIHD. A field investigation by Moxley et al. (2019) followed heart failure deaths over a 15-month period at one feedyard and found steer were overrepresented (16 steers) and one heifer. The steers originated from one herd located immediately adjacent to the feedlot and the one heifer originated from Cokeville, WY. Data suggests that gender plays a role in heart disease cases in finishing cattle.

It was hypothesized that increasing heavier finishing weight increases heart failure risk by increasing fat deposits around the cardiopulmonary structures (Krafsur et al., 2019). This would suggest there would be a longer average time from arrival at the feedyard to death due to NIHD. Our data found that median time from arrival to NIHD death (110 d) was shorter compared previous literature (Neary et. al., 2016) at 133 d. Our observation of near-normal distribution of time from feedlot arrival to at least one death due to NIHD, reinforces the finding that NIHD was not found to increase over the feeding phase. Bassett (2019) reported a relatively normal distribution of percent finished at time of death due to CHF, meaning approximately one-half the cases happened before the cohort was 50%-60% finished. These data suggests that NIHD is not necessarily a late-day disease in finishing cattle. However, our analysis found increasing d on feed for a cohort was associated with increased probability of having at least one NIHD death within the cohort from 100 to 326 d finishing periods. There was an increase in

model estimated mean cohort probabilities of a NIHD death from 100 (1.51%) to 326 (2.87%) d on feed. Feeding greater than 326 d showed no evidence of being different from other d on feed categories with a model estimated mean probability of 2.33%, meaning risk was no different in cattle fed for a considerable length of time compared to cattle earlier in the finishing period. These data are consistent with Neary et al. and Bassett (2016, 2019) where they found CHF throughout the feeding period. Furthermore, we found that half of the NIHD deaths occurred before 110 d. Neary et. al., 2016 found half of their heart disease deaths occurring after 19 weeks (> 133 d) on feed. Bassett (2019) showed that CHF cattle died in the greatest proportion between 121 d and 181 d after arrival to the feedyard. Thus, assessment of timing of NIHD deaths across multiple studies has shown that cattle dying from a heart disease event are not strictly dying during the later d of the feeding period where heavier and more fatten cattle would be represented.

In addition, the current study looked at average cohort arrival weight's effect on timing of NIHD death. Arrival weight category was significantly associated with the timing of NIHD death with heavier weights having a general trend of lower d on feed when they died. Heavier placed cattle had a model estimated means d on feed that was numerically lower than lighter placed cattle, however, there was considerable variation in the point estimate. This was likely due to having fewer cattle placed in heavier weight categories and consequently fed for a shorter period. However, one could argue they are not at risk for the same amount of time during the feeding period compared to a lighter (282-227 kg) placed cattle.

The results of this study indicated that multiple factors were associated with increased probability of having at least one NIHD death within a cohort. The current study's investigation found that interactions of the studied cohort factors have a role in the biology of risk of NIHD.

Additionally, the association of timing of a NIHD death was found to have a near normal distribution throughout the feeding period with half of the deaths occurring before 110 d. Overall, the risk associated with NIHD was very low in the current study and several factors were found to be associated with the probability of at least one NIHD death within a cohort. However, the probability of a cohort having at least one NIHD death was relatively minimal. Even at a low prevalence, heart disease in feedlot cattle remains troubling due to animals dying throughout the feeding phase, the financial impact of NIHD, and the lack of a clear causal pathway.

Limitations

In observational studies, there tends to be a lack of consistent, standardized reporting of data across feedyards (Corbin and Griffin, 2006). In our retrospective study, certain limitations need to be addressed. One is that our study was conducted on data that was entered from multiple feedyards having different personnel diagnose the diseased animals at necropsy with various training backgrounds. As previously stated, case definition varied between yards (Table 1), which carries the potential of misclassification bias. To help control some of this bias multiple heart disease categories were lumped into one category of NIHD. Additionally, the risk factors evaluated were not randomly dispersed among cohorts, as with all observational studies, and were subjected to unknown confounding factors. To help address bias and confounding, our analysis was set up as a multivariate mixed effects and had feedyard set as a random intercept. Thus, the results and conclusions are limited to the data presented and the cattle that fit our inclusion criteria.

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Conflict of Interest Statement

Authors declare no conflicts of interest**.**

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Table 2-1 Disease diagnosis categories incorporated into non-infectious heart disease (NIHD) case definition.

Congestive Heart Failure
HD HEART DISEAS
HEA HEART FAILURE
HEART DISEASE
HEART FAILURE
HEART FAILURE LEFT/RIGHT
HEART FAILURE LEFT\RIGHT
HEART PROBLEM
LEFT HEART FAILURE
Heart Failure
MECHANICAL HEART FAILURE
INFECTIOUS HEART FAILURE
CONGESTIVE HEART FAILURE

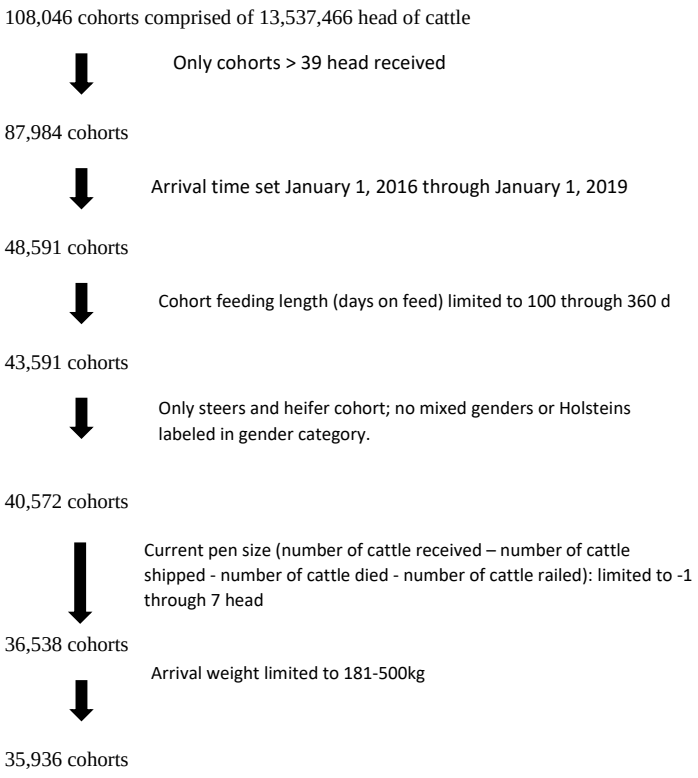

Figure 2.1 Data filtering from inclusion criteria applied to 22 US commercial feedlots.

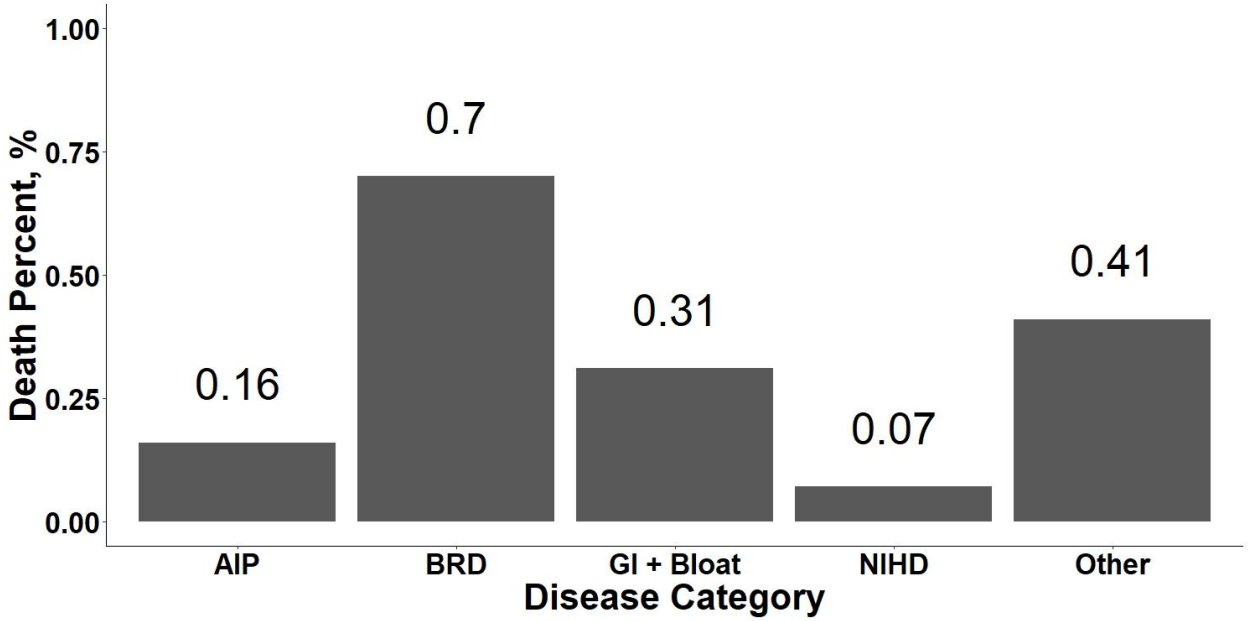

Figure 2.2 Percent of diagnosis per disease expressed as percent of total cattle received. (AIP = Atypical/Acute interstitial pneumonia; BRD = bovine respiratory disease, GI+Bloat = Gastrointestinal disorders and bloat, NIHD = Non-infectious heart disease, Other = All other non-categorized diseases).

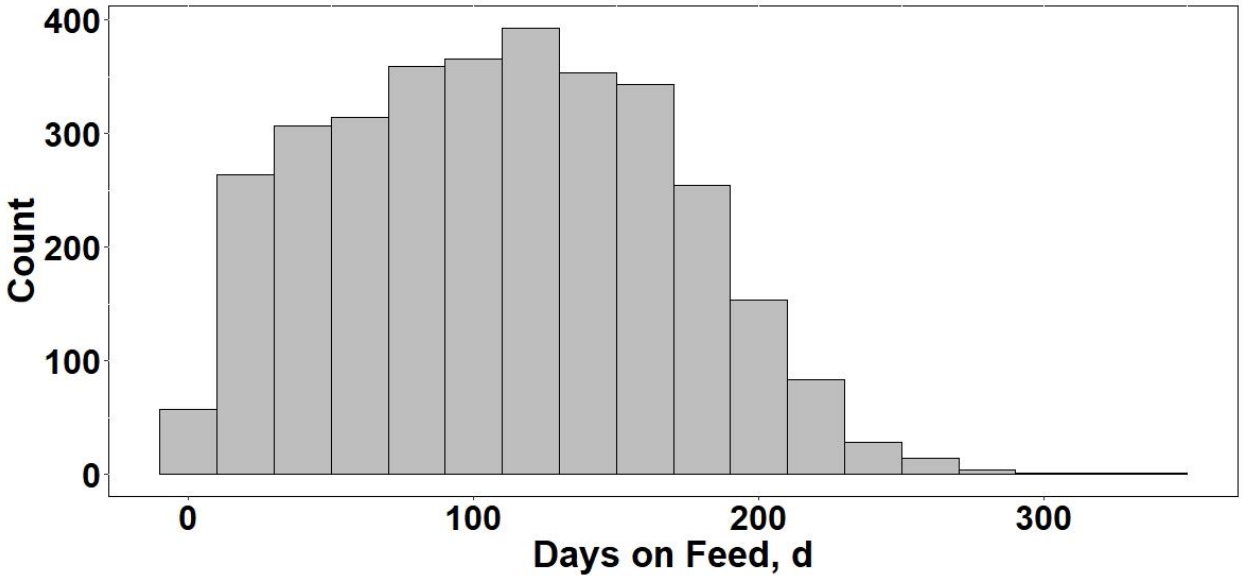

Figure 2.3 Count of non-infectious heart disease deaths by days on feed at the time of death, mean and median = 110 d; totaling 3,282 non-infectious heart disease deaths observed over three years from 19 US feedyards

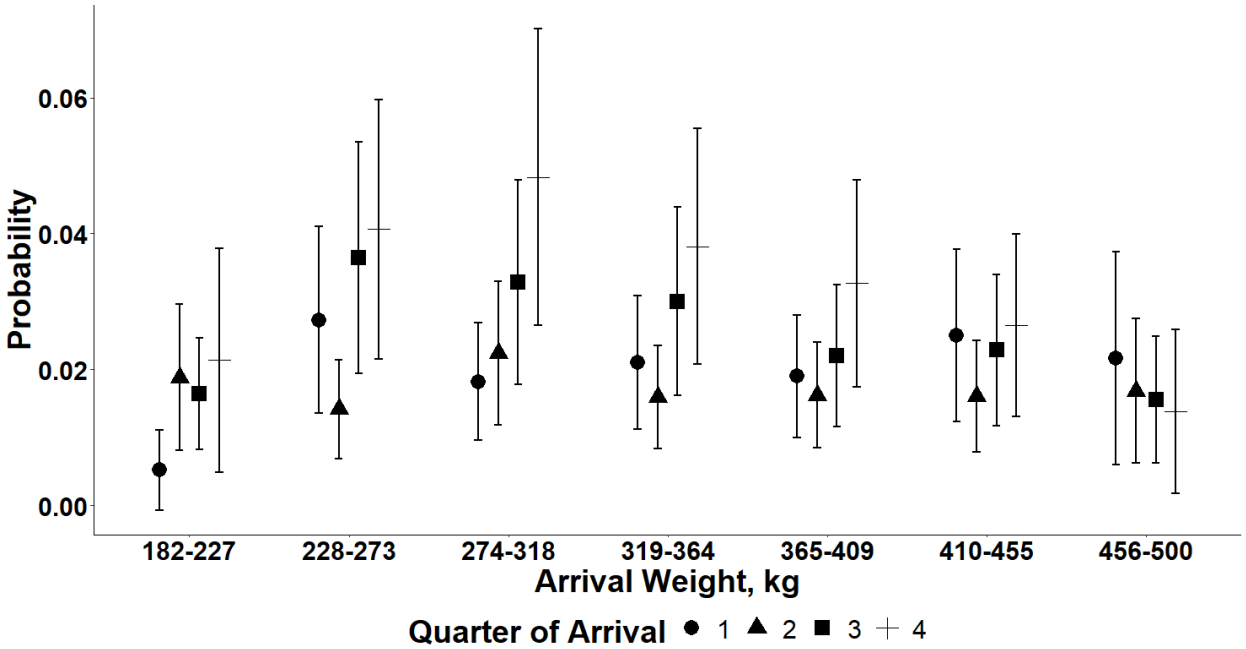

Figure 2.4 Model estimated means with one standard error probability of a non-infectious heart disease death by cohort arrival weight (x-axis) and cohort arrival quarter (shape)

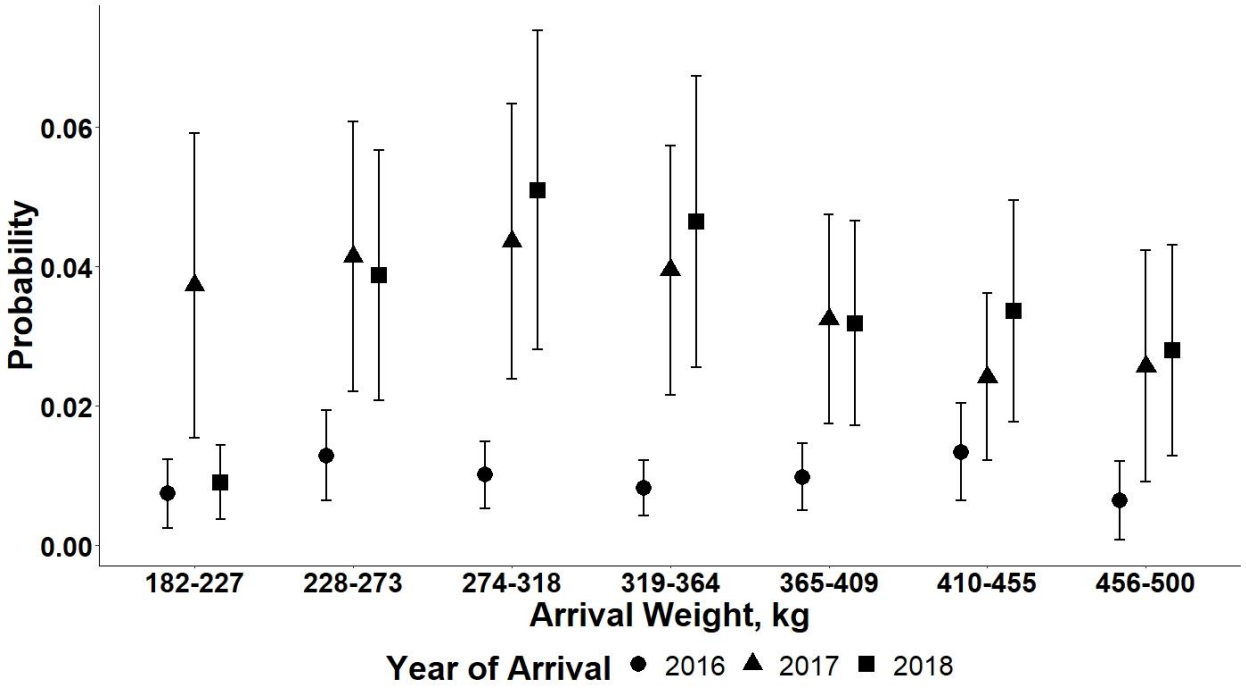

Figure 2.5 Model estimated means with one standard error of a non-infectious heart disease death by cohort arrival weight influenced by cohort arrival year (shape)

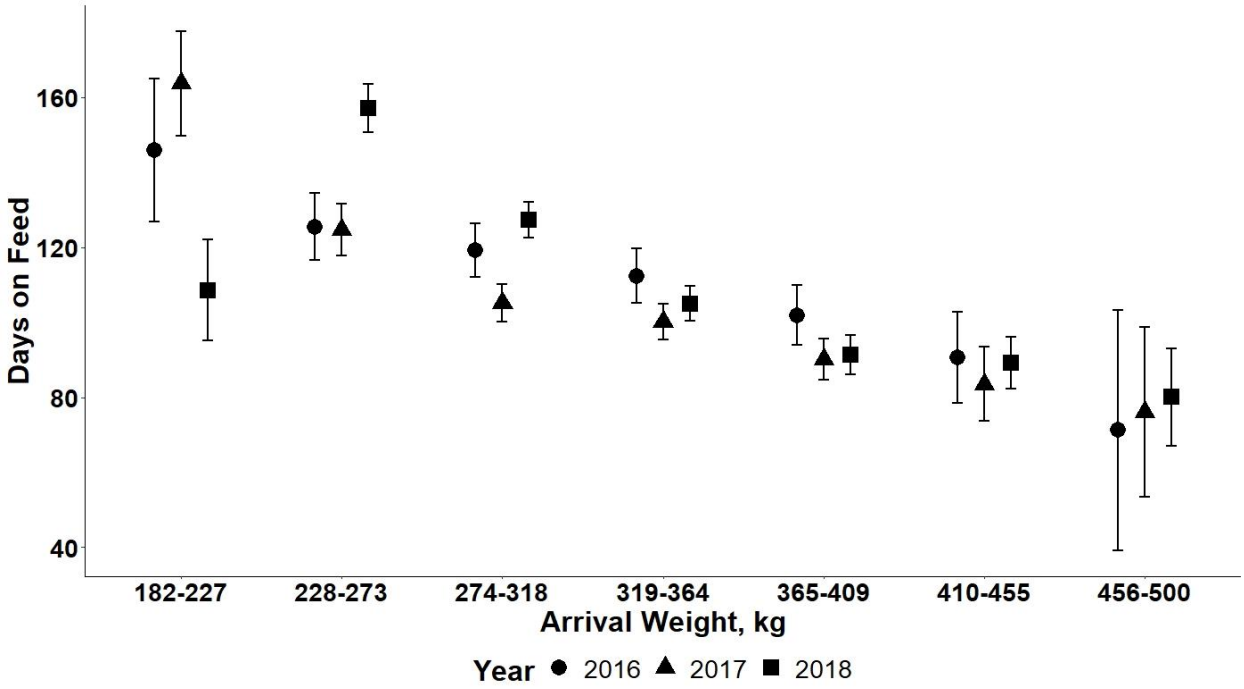

Figure 2.6 Model estimated means with one standard error of a non-infectious heart disease death (NIHD) event (days on feed) effected by average cohort arrival weight influenced by arrival year (shape).

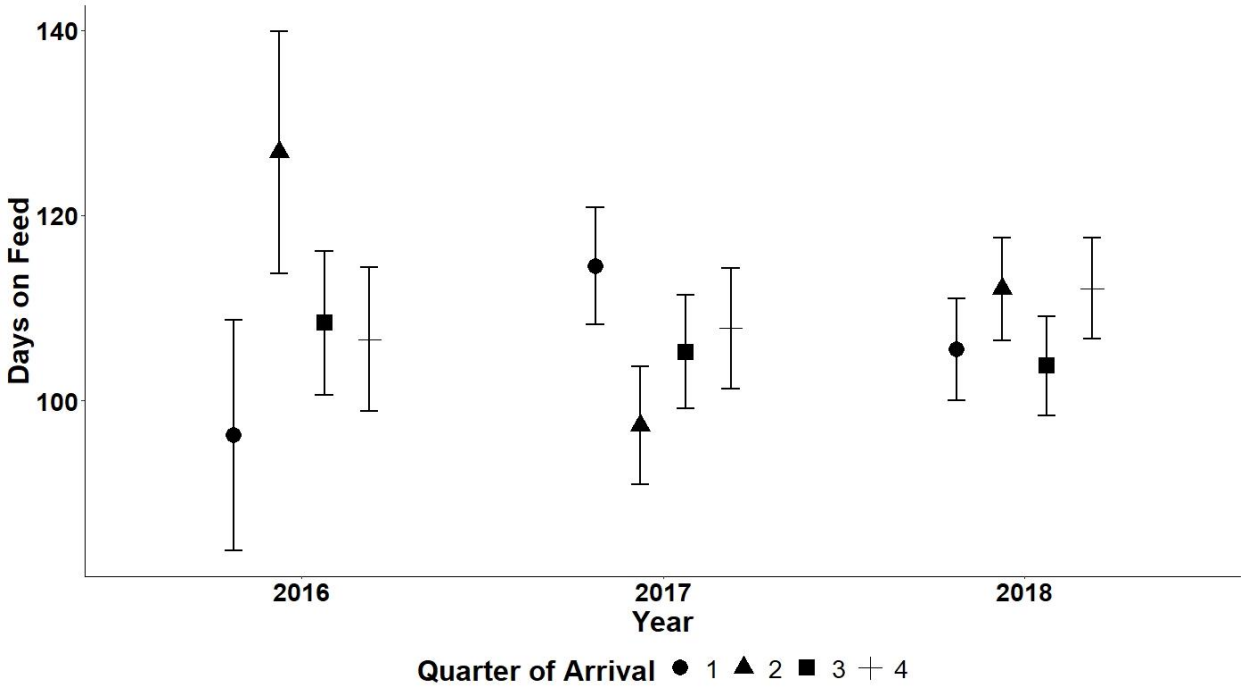

Figure 2.7 Model estimated mean estimates with one standard error of a non-infectious heart disease death event (days on feed) effected by cohort arrival year influenced by arrival quarter (shape)

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Chapter 3 - Association of feedlot disease treatment on the probability of heart disease syndrome in U.S. feedlot cattle

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Abstract

Data from 14 US feedlots were evaluated from January 1, 2017, through December 31, 2020, for disease treatment on the probability of being terminally diagnosed with heart disease (HD). The study objective was two-fold, 1) Determine the association between the number of bovine respiratory disease (BRD) treatments (0,1,2,3+) and HD, 2) Determine the association of common feedlot disease treatment (AIP, BRD, Complex Disease, GI+Bloat, Other), and cohort demographics with HD. Data were analyzed using generalized mixed effects models to evaluate the probability of terminal HD. Covariates of interest include: BRD treatments, feedlot disease category, average cohort arrival weight, arrival year, arrival quarter, feedlot elevation, and sex. The number of BRD treatments was associated with HD ($P < 0.01$). Cattle requiring additional

BRD treatments increased their probability of not finishing the feeding period due to HD. The magnitude of this association was influenced by average cohort arrival weight, feedlot elevation, sex, and arrival quarter ($P < 0.01$). Feedlot disease categories were associated with the probability of not finishing the feeding phase due to a HD diagnosis ($P < 0.01$). The magnitude of this association was influenced by average cohort arrival weight, and feedlot elevation ($P < 0.01$). Sex was influenced by feedlot elevation on the probability of a not finishing due to HD diagnosis ($P < 0.01$) with higher elevations having a greater probability of HD. Overall, HD remains relatively low at 15 per 10,000 cattle received. The majority (9 of the 15) HD cattle railed prior to death at the feedlot.

Key Words

BRD, Complex Disease, Feedlot, Heart Disease,

Introduction

Bovine respiratory disease **(BRD)** remains the leading cause of morbidity and mortality in most feedlots and has been associated with large, negative economic effects in the feedlot industry[1]. None-the-less, heart disease **(HD)** has gained interest from producers, veterinarians, and geneticists as potentially increasing as a contribution to total feedlot mortalities over time[2]. Recent literature has documented HD increasing in prevalence over time in the feedlot population of Canadian and U.S. cattle at moderate elevations which is in contrast with the previous assumptions of HD being a problem only at high elevation[2,3]. Common feedlot demographics have been analyzed to determine their associations to right heart failure[2–4]. Previous literature reported that cattle treated for BRD were found to be up to three times more likely to die from right heart failure (RHF) than cattle not treated for BRD when controlling for

likelihood of dying from a digestive death, year of placement, and feedlot[3]. Currently there is a gap in literature on the association of HD with number of BRD treatments as well as other feedlot diseases. The objectives of this study were 1) determine the association of the number of BRD treatments with HD and 2) determine the association of feedlot disease treatments (Atypical Interstitial Pneumonia (**AIP**), BRD, Gastrointestinal Disease + Bloat (**GI+Bloat**), heart disease (**HD**), **Other** (any disease that is not **AIP**, **GI+Bloat**, **Heart Disease**, or **BRD**), and **Complex** (an animal treated for more than one disease category within the feeding phase period) on the probability of a terminal diagnosis of HD.

Materials and Methods

Animal Care and Use Committee approval was not obtained for this study due to retrospective data being obtained from existing privatized databases from commercial feedlots.

Data source

Data used for analysis were obtained under confidentiality agreements with participating feedlots. Individual treatment, mortality, and cohort data were sourced from 14 US commercial feedlots located throughout the central US and plains feeding regions from 2017 through 2020. A cohort is defined as a group of cattle that were purchased, managed, and marketed at a similar endpoint. The cohort may or may not have been housed and fed in the same pen throughout the finishing period. Cohort data was limited to demographic variables such as sex, arrival date, total head received, average cohort arrival weight, that define the population of cattle placed at the feedlot. Individual animal data were collected at a time of an event during the production phase (e.g. treatment definition, treatment date, and therapy regimen, and necropsy defined death diagnosis). An event is defined as an individual record for treatment, observation, or item given

to an individual at the time of occurrence following the caretaker's animal health protocol previously established by a licensed veterinary health professional.

Data preparation:

All data manipulations were performed in R[5], utilizing the tidyverse package[6]. The original data consisted of individual treatment data, 780,776 events, with multiple events (rows) per individual. Individual treatment events were matched with individual terminal events (n = 62,191), which included date and diagnosis of terminal event. All terminal events were recorded by trained feedlot personnel and were defined as either death or rail events. A railed animal is considered an animal that was removed from its cohort and sold for salvage value prior to the completion of the feeding period for the cohort. Data was concatenated from 780,776 observations to 291,552 observations (number of cattle treated for disease) to get individual events to one event per row, while creating new variables (columns) to account for multiple events within the individual's feeding phase. Individual level data was matched to the cohort data, which consisted of 14,480 unique cohorts (Figure 2.1).

Original individual data were filtered using an inclusion criterion to create a uniform population to represent common U.S. fed cattle demographics and to limit potential confounding variables. In short, each treated animal's cohort data was tied to individual data records then filtered by inclusion criteria for completeness. Cattle used for this study were included if feedlot placement timeframe was between January 1, 2017 through December 31, 2020. Cattle were also included if average cohort placement weight was between 400 to 1100lbs (182 kg to 500 kg). Cohort feeding period was limited to cattle fed between 100 to 400 days on feed. Sex was limited to steers and heifers. Holsteins, mixed sex groups of steers and heifers, as well as bulls were not included in the current study. Furthermore, due to nature of retrospective data, castration status

cannot be confirmed. An individual's treatment event was limited to ≥ - 7 days on feed. Authors allowed a grace period of -7 days on feed as cattle were potentially being grouped before a cohort's defined start date was initiated. Treatment and disease diagnosis were grouped into six categories: heart disease (**HD**), atypical interstitial pneumonia (**AIP**), bovine respiratory disease (**BRD**), gastrointestinal and bloat (**GI + Bloat**), other (**Other**), and complex (**Complex**). Heart disease cases were limited to diseases of a non-infectious origin at diagnosis (example: heart disease, right heart failure, brisket disease, CHF etc.). Infectious causes such as endocarditis, myocarditis, pericarditis events were removed from analysis. The category 'Other' encompassed a wide variety of events and diseases. To limit 'Other' to disease events, list categories that were similar to procedural events were removed (e.g. import, reimplant, moving cattle, check weight, etc.). Complex disease treatment was defined as an animal which was pulled and treated for more than one of the previously described diseases within the feeding period. Disease categories were mutually exclusive whereas cattle could only be in one treatment category if treated for disease, otherwise if an individual were treated for multiple different diseases it would be placed in the complex disease treatment category. The number of times individuals were treated were not evaluated for this analysis.

Simulated individual data:

To account for cattle which did not require any treatment and finished the feeding phase as part of the cohort, a simulated "indicator" observations (new row of data) were created. Simulated observations were created by taking the difference between number of cattle placed within a cohort and subtracting the number of individual records (death and/or treatment records) within cohort to get the number of cattle not requiring treatments and not dying within the feeding period ("non-treated cattle" = total cattle placed within cohort – total number of

unique/distinct observations within cohort). Deaths and treatment records were cross referenced to only have on record per individual. A total of 2,216,121 observations were created to represent the cattle which did not require treatment and finished the feeding phase. Matching column variables were created to bind the simulated data to the filtered master data set. Lot demographic data was tied to the simulated observations.

Variable creation:

New variables were created to group and filter cattle into categories for data analysis and modeling of non-infectious heart disease death. Continuous variables were grouped into categorical variables based on biological break points to avoid violating assumptions of linearity. The study case definition of BRD was an animal pulled for BRD and treated with an antimicrobial. A new variable (brd_trt_cat) was created with four categories: 0, 1, 2, 3+ based on the number of individual BRD treatments. Cattle were only represented in their highest respective category, (i.e., cattle treated three times were only included in the 3+ category and not counted in 1 or 2 brd_trt_cat). A unique identifier number (UID2) was created to tie an individual observation to lot demographic data represented the concatenation of "yardid", "lotid", and "lot arrival year". A second unique identifier was created to group multiple events to one individual using an individual's "yardid", "lotid", "arrival year" and "tag number". To account for total number of treatments a variable called treatment count (Trt_Count) was created which grouped data to one observation (one row per individual) by summing up all treatment counts on an individual to one row of all treatment counts (Trt_Count). Binary variable categories were created to account for whether an animal was ever treated for one of the six mutually exclusive disease categories (**HD, AIP, BRD, GI + Bloat, Other,** and **Complex**). A

‘1’ indicated an animal was treated for a specific disease category and ‘0’ indicated no treatment for the specific disease category.

To account for arrival period, cattle were grouped by the quarter which they arrived. The variable was created from the feedlot arrival date (arrival_qrt). Cattle that arrived from January to March were labeled as one, cattle that arrived April to June were labeled as two, July to September were labeled as three, and October through December were labeled as four.

A variable for feedlot elevation was developed (elevation_cat_ft). The specific feedlot elevation was found using readily available websites and the feedlot’s current mailing address[7,8]. Elevations were grouped in 3 categories: < 3000 ft, 3,001 ft to 3,999ft, ≥ 4,000ft (< 914.4 m, 914.7 m to 1218.9 m, ≥ 1219.2 m). All 14 feedlots were as equally distributed as possible within the three mutually exclusive categories (n = 4, 5, and 5 feedlots per respective category).

Statistical Analysis:

The current study used generalized mixed effects multivariate logistic regression to analyze study objectives. Data was analyzed in R using the glmer function in the lme4 package[5,9]. The first objective modeled the probability of developing HD and not finishing the feeding phase as the outcome variable. Factors of interest include: BRD treatment categories (0,1,2,3), average cohort arrival weight, arrival quarter, elevation category, and sex as covariates. Authors limited the number of interactions included to: BRD category and elevation category, sex and BRD category, BRD category and average cohort arrival weight, and BRD and cohort arrival quarter due to biological reasoning.

To accomplish the second objective, authors modeled the probability of developing HD and not finishing the feeding phase as the outcome variable while conditioning on disease category (AIP, BRD, GI + Bloat, Other, and Complex Disease), average cohort arrival weight,

elevation category, and sex. Interactions in the second model were limited to, sex and disease category, average cohort arrival weight and disease category, elevation category and disease category, elevation category and average cohort arrival weight, and elevation category and sex.

Random intercepts of lot within yard and arrival year were included in both analyses to account for lack of independence and hierarchical structure of the data. A significance of $P < 0.05$ was established *a priori*.

Predetermined interactions were included in the model and removed using a backwards elimination process to finalize the model[10]. Final model was selected by comparing models and selecting the model with the lowest Bayesian Information Criterion (BIC). Pairwise comparisons for significant interactions or main effects were performed for each model using emmeans package with Tukey method adjustment for family-wise error rate[11].

Results:

The final model data set included 2,380,165 individual cattle. There were 182,620 cattle treated for BRD (67.2%) out of 271,814 individual treatment records. Data included 14,480 distinct cohorts and individual data comprised of 732,932 heifers and 1,647,233 steers. Maximum feedlot elevation was 4,551 ft (1,387 m) and minimum was 1,949 ft (594 m). Table 1 shows number of cattle received by year and feedlot elevation as well as the percent of cattle treated for BRD and subsequently diagnosed with heart disease. Table 3-2 shows counts of cattle not finishing, either by death or railed events, and treatments by disease code. There were 3,656 cattle with HD observed in the data set which represented 1,174 heifers and 2,482 steers from both railer and death events. Heart disease events accounted for 0.15% of total cattle received (15 per 10,000 cattle) during the four-year study period. There were 2,130 cattle railed due to HD and 1,526 cattle died due to HD over the four-year study period. Prevalence of HD death

was found to be 0.06% (6 in 10,000 cattle), and prevalence of HD rails was 0.09% (9 in 10,000 cattle) over the four-year study period. In 2017, there were 384 terminal HD diagnoses observed in a population of 109,591 cattle received (0.35%; 35 per 10,000 cattle). Whereas 2018 had 1,246 terminal HD diagnosis observed from population of 801,267 cattle (16 per 10,000 cattle). The lowest frequency of HD was observed in 2019 at 1,373 cattle from a population of 1,088,621 (13 per 10,000 cattle). The final year of the current study had 653 terminal HD observed in 420,026 received cattle (16 per 10,000 cattle).

Objective one: BRD and HD Association

The number of times cattle were treated for BRD was associated with HD ($P< 0.001$), and this effect was modified by arrival weight ($P < 0.01$), sex ($P = 0.01$), and arrival quarter ($P < 0.01$). The model-estimated probability for HD increased as arrival weight increased and increased with additional BRD treatments (Figure 3.2). For example, Cattle placed at 600lbs to 700lbs and never treated for BRD (274 to 318kg) had an estimated probability 0.03% (SE = 0.02%) of developing HD. The probability increased with increasing number of BRD treatments from 0.27% (SE = 0.14%), to 0.45 (SE = 0.23%), and 0.73% (SE = 0.38%) for BRD categories 1, 2, and +3 respectively.

Quarter of placement influenced the effect of BRD treatment category on an individual's HD probability (Figure 3.3). Cattle in the 0 BRD treatment category had the lowest HD estimated probability, with cattle placed in quarter two having the lowest overall estimated probability of a HD diagnosis at 0.014%. As the number of BRD treatments increased for quarter 2 placed cattle, the estimated probability of a HD increased from 0.30% (SE = 0.10%) to 0.66% (SE = 0.30%), and finally 0.70% (SE = 0.40%) respectively. Cattle in the 3+ BRD treatment category had the highest estimated probability of HD when placed in quarter 1 (1.1%, SE =

0.60%). However, the probability was not different within the 3+ BRD treatment category across all placement quarters. No difference was seen in cattle placed in quarter 2 with 3+ BRD treatments compared to cattle in BRD treatment category 2 and BRD treatment category 1 in quarters 1, 2, and 4. Cattle fed at higher elevations had a numerically greater probability of being diagnosed with HD. The magnitude of the probability was influenced by number of BRD treatments (Figure 3.4). The highest model-estimated mean probability was seen in cattle treated three or more times and fed at elevations > 4,000 ft at 2.35% (SE = 1.80%). Cattle fed at lower elevations had numerically lower model adjusted probabilities of HD. However, animals that were never treated for BRD had the lowest model adjusted probability of developing HD at < 0.06%.

Objective two: Feedlot disease association with HD

The final model found that three interactions were associated with not finishing due to a terminal diagnosis of HD. Arrival weight by disease treatment category was associated with not finishing due to HD ($P < 0.01$). Lighter placed cattle and non-diseased had the lowest probability of not finishing the feeding period due to HD with estimated probabilities < 0.01% (Figure 3.6). Cattle placed and treated as complex disease (requiring treatment for multiple diseases) treatments had between 1.79% and 2.85% (SE = 1.06% and SE = 1.74%, respectively) estimated probability of not finishing the feeding period due to HD. Cattle placed at 501 to 600lbs (227 to 272 kg) and treated for AIP had an estimated probability of not finishing the feeding period due to HD at 3.38% (SE = 3.01%).

Feedlot disease treatment category was influenced by feedlot elevation category on its associated with not finishing due to HD ($P < 0.001$). Cattle treated for complex disease category and fed in feedlots >4,000 ft (1219 m) had the highest numerical model-estimated probability of

not finishing the feeding period due to HD (3.55% and 5.53% respectively). Cattle having no disease treatments had the lowest estimated probability of not finishing the feeding period due to HD regardless of their feedlot elevation (Figure 3.5).

Finally, sex by feedlot elevation category interaction was associated with not finishing the feeding period due to HD ($P < 0.01$). There were numerically different estimated probabilities influenced by feedlot elevation but were not different between sex and feedlot elevation.

Discussion

Previous data reported that HD in feedlot cattle was 4 in 10,000 cattle and 7 to 8 in 10,000 cattle received[3,2]. The current study found 15 in 10,000 cattle were railed or died due to HD. To the authors knowledge, this is the first study to include railed cattle in terminal diagnosis for HD. Previous studies only reported cattle diagnosed with HD at necropsy. Over the four-year period, the number of cattle that died due to HD were found to be 6.4 in 10,000 cattle received. The number of cattle railed due to HD diagnosis was approximately 9 in 10,000 cattle received. These data indicate that HD is being identified regularly with over half of the total disease cases railed prior to death. However, confirmation of true disease remains ambiguous. Case definitions varied greatly from yard to yard as in previous literature[2]. Data generated from the current study gives a more comprehensive industry prevalence of HD. Heart disease varied greatly from year to year in prevalence. Many factors could have played a role in the variation seen from year to year such as cattle type, market demand, and environmental factors; most of which were not able to be accounted for in the current study and could potentially contribute to confounding[12].

Bovine respiratory disease remains the most common disease treated for in feedlot cattle[1]. Neary et al. (2016) reported cattle treated for BRD had a 2.52 to 3.14 times odds of

developing right heart failure when controlling for the likelihood of death from digestive disorders, year of placement, risk of BRD/UF (undifferentiated fever), age, and sex in 10 Canadian and 5 US feedlots compared to cattle never treated for BRD/UF. Authors hypothesized cattle were misidentified at treatment due to similar clinical signs of disease (BRD and HD). Cattle pulled for BRD exhibit clinical signs of disease such as depression, labored breathing/respiratory issues, and anorexia[13]. Likewise, cattle with HD have been described in detail as in respiratory distress, open mouthed breathing, abducted elbows, sunken eyes, off feed, brisket edema, swayed back, and distended abdomen[14]. There is potential for misclassification of disease, especially early in the disease process. Accuracy of BRD identification remains a major obstacle for feeding operations[15]. Prevalence of BRD morbidity is far greater than HD in the findings of the current study (BRD = 7.55% of cattle received, HD = 0.11% of cattle received). USDA, 2011 reported 16.2% of cattle placed were affected by shipping fever (BRD) throughout a wide range in different regions. The difference in prevalence between diseases make cattle more likely to have experienced BRD during the feeding phase compared to HD. In addition, BRD has abundant therapeutic options for treatment and prevention with average cost of therapy close to $24 per animal (USDA, 2011). Whereas therapeutic options for cattle with HD are limited and likely result in railing the animal earlier in the feeding phase for salvage value unless in the advanced clinical stages with euthanasia being the only humane option.

The role of elevation's influence with BRD on HD has not been previously described. Interestingly, risk of HD seems to increase with additional BRD treatments suggesting that cattle could be misclassified (incorrectly identified for a particular disease). Brisket or "high mountain" disease has been documented and well-established[3,16–18]. Cattle in higher elevations are more susceptible to brisket disease due to low oxygen saturation and the cattle's poor lung capacity to

body size ratio[18]. Cattle with compromised cardiovascular/pulmonary systems at higher elevations could be more prone to pulmonary hypertension. This can lead to restricted blow flow and cardiac overload in the right heart leading either to successful compensation or the animal will succumb to disease. The current study included feedlot elevation in the modeling process. However, all feedlots in the current study would be deemed to be in low to moderate elevations; < 5,280 ft (1600 m)[19]. Other reports have shown increasing prevalence of RHF in fed cattle at moderate elevations[3,20]. Prior cattle placement elevation could potentially add more value to the model. However due to the limitations of data, the current study was limited to known information of feedlot location for elevation. Cattle fed at higher elevations could have been sourced from higher or similar elevations (> 5,280 ft: 1600 m). Cattle from higher elevations have been previously described of having a higher risk of HD development[19]. To the author's knowledge, elevation and BRD categories have not been used as a predictor for associating probability of HD in cattle. The current findings support anecdotal speculations of HD at greater prevalence in higher elevations. However, in cattle never treated for BRD there is no difference between elevation categories for risk of HD.

Cattle placed at heavier weights and treated multiple times for BRD were at an increased probability of not finishing the feeding period due to HD diagnosis. Previous research found risk of HD was found to be similar across weight groups of received cattle[2]. However, BRD was not controlled for in the previous modeling process. The current study further supports an assumption for HD being very low in disease prevalence (compared to BRD, GI and AIP) and appears to be consistent throughout the feeding period of feedlot production especially in cattle not treated for BRD. Other research reported mixed results that varied based on classification at

arrival. Yearling cattle placed in Canadian feedlots had 60% the risk of RHF compared to calves, and 138% the risk compared to calves in US feedlots[3].

There is lack of published knowledge describing cattle with multiple disease treatments in US feedlots. In the current study, cattle treated for at least two different diseases (complex disease treatment) had numerically higher model-estimated probabilities of not finishing the feeding period due to a HD diagnosis compared to most other disease categories, apart from cattle treated for HD. The most prevalent disease in fed cattle is BRD[21]. Bovine respiratory disease treatment carries an average first treatment success between 75 to 80% [22]. Whereas cattle failing their first BRD treatment require additional therapy. Cattle that are diseased earlier on in the feeding period could have a higher risk for future disease development. Furthermore, an insult to the respiratory system and vasculature could increase the workload on the heart which could increase the risk of future HD. One possibility is that BRD can lead to HD. The other possibility is that cattle were misclassified as BRD when they were in early HD. Due to the nature of the study, it is impossible to decipher if one disease caused another or predisposed the animal to other diseases. The need for further research on relationships of cattle treated for BRD and their risk of subsequent disease development is warranted. As well as cattle treated for complex diseases on potentially being misclassified for disease therapy. This would help better identify and diagnose cattle for more appropriate management decisions.

Limitations

Data from the current study showed a wide variation from year to year on the distribution of health events. Differences in health outcomes can be attributed to many things, in particular management decisions[12]. In observational data differentiation between cause and event cannot be explicitly determined[10]. Additionally, observational studies run a higher risk to systematic

error[12,23]. For the current study, inclusion criteria and case definitions were set in place prior to the study to help address some of the systematic bias. Overall, one should exercise caution drawing conclusions and extrapolating findings to cattle populations outside the selected study parameters.

Conclusions

The current study found that cattle removed from feeding phase due to HD diagnosis was 15 per 10,000 cattle received over a four-year period. Railed cattle accounted for approximately 9 of the 15 HD diagnosed per 10,000 cattle and deaths accounted for 6 per 10,000 of the 15 diagnosed per 10,000 cattle. Heart disease would generally be considered relatively low risk compared to common feedlot disease such as BRD (16% morbidity risk or 16 per 100 cattle). The association of the number of BRD treatments with an individual's probability of HD was influenced by average cohort arrival weight, arrival quarter, sex, and feedlot elevation on the individual risk of HD. In general, cattle treated two or more times increased their probability of not finishing their respective feeding period due to HD and risk was further increased by heavier average cohort arrival weights. Cattle treated for multiple diseases throughout the feeding period had a greater probability of not finishing due to HD. This effect was influenced by feedlot elevation and average cohort arrival weight. The risk of HD was relatively low and consistent in cattle not treated for BRD or any feedlot disease regardless of their average cohort placement weight, quarter, sex, or feedlot elevation.

Conflicts of interest

Authors report no conflicts of interest.

Contribution

All authors contributed to the design, analysis and writing of the current study.

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Table 3-1 Descriptive of 14 U.S. commercial feedlots of cattle treated for Bovine Respiratory Disease and terminal diagnosis of heart disease by elevation category and arrival year.

Elevation Category	Year	Cattle	Steers	Heifers	HD Deaths*	HD Rails†	HD and BRD Cat‡ 0, %	HD and BRD Cat‖ 1, %	HD and BRD Cat§ 2, %	HD and BRD Cat¶ 3+, %
< 3,000	2017	22,884	47%	53%	11	0	0.01	0.28	0.70	0.00
3,000-3,999	2017	17,455	69%	31%	11	29	0.07	0.49	1.16	1.88
> 4,000	2017	78,759	62%	38%	108	225	0.23	2.18	3.48	5.75
< 3,000	2018	242,081	79%	21%	96	0	0.02	0.39	0.52	0.09
3,000-3,999	2018	406,370	55%	45%	183	416	0.09	0.52	1.04	1.10
> 4,000	2018	162,264	59%	41%	222	329	0.18	1.93	3.22	5.40
< 3,000	2019	355,542	60%	40%	87	1	0.01	0.33	0.37	0.61
3,000-3,999	2019	491,546	69%	31%	222	355	0.06	0.63	1.12	1.43
> 4,000	2019	203,573	78%	22%	306	402	0.19	1.65	3.70	4.07
< 3,000	2020	133,486	75%	25%	41	3	0.01	0.42	0.79	2.08
3,000-3,999	2020	182,688	77%	23%	78	169	0.07	1.03	1.40	1.42
> 4,000	2020	83,517	71%	29%	161	201	0.24	1.67	3.48	4.73

Footnotes:

*HD Deaths = Deaths diagnosed as heart disease

†HD Rails = Rails diagnosed as heart disease

‡HD and BRD Cat 0= heart disease terminal diagnosis and never treated for Bovine Respiratory Disease, expressed as percent of cattle that had terminal diagnosis of heart disease out of number of cattle with 0 BRD treatments.

‖HD and BRD Cat 1= heart disease terminal diagnosis and previously treated for Bovine Respiratory Disease 1x, expressed as percent of cattle that had terminal diagnosis of heart disease out of number cattle with 1 BRD treatment.

§HD and BRD Cat 2= heart disease terminal diagnosis and previously treated for Bovine Respiratory Disease 2x, expressed as percent of cattle that had terminal diagnosis of heart disease out of number of cattle with 2 BRD treatments.

¶HD and BRD Cat 3+= heart disease terminal diagnosis and previously treated for Bovine Respiratory Disease 3 or more times, expressed as percent of cattle that had terminal diagnosis of heart disease out of number of cattle with 3 or more BRD treatments.

Table 3-2 Data of 14 U.S. commercial feedlots showing counts of deaths and rails of cattle treated for disease and partitioned by arrival year and feedlot elevation. Each treatment category is mutually exclusive.

					Treatments													
					None[†]		AIP[‡]		BRD[‖]		HD[*]		Complex[§]		GI+Bloat[¶]		Other[‡‡]	
Elevation	Year	Cattle	Deaths	Rails	Rails	Deaths	Rails	Deaths	Rails	Deaths	Rails	Deaths	Rails	Deaths	Rails	Deaths	Rails	Deaths
<3000	2017	22,884	674	0	0	8	0	11	0	569	0	0	0	42	0	4	0	40
3000-3999	2017	17,455	462	258	3	2	0	1	117	393	8	3	64	40	5	10	61	13
>4000	2017	78,759	704	731	4	4	18	30	115	378	96	15	232	163	18	5	248	109
<3000	2018	242,081	3230	500	0	47	0	28	6	2069	0	0	55	134	12	59	427	893
3000-3999	2018	406,370	5330	3119	46	105	0	5	1194	4228	262	60	576	369	36	89	1005	474
>4000	2018	162,264	1178	975	10	9	13	28	220	662	116	31	224	196	22	40	370	212
<3000	2019	355,542	3370	980	2	36	0	23	60	2355	0	1	399	330	8	62	511	563
3000-3999	2019	491,546	4828	3862	90	82	1	1	1546	3619	225	60	635	434	57	113	1308	519
>4000	2019	203,573	1738	1175	3	20	13	62	247	920	165	74	331	304	26	31	390	327
<3000	2020	133,486	1040	370	1	13	1	29	13	686	0	0	139	103	3	21	213	188
3000-3999	2020	182,688	1625	1361	15	14	4	4	559	1203	96	21	183	111	25	47	479	225
>4000	2020	83,517	851	528	1	6	11	23	98	432	60	39	131	155	15	22	212	174
	Totals	2,380,165	25,030	13,859	175	346	61	245	4,175	17,514	1,028	304	2,969	2,381	227	503	5,224	3,737

Footnotes:
[*]HD = Heart Disease
[†]None = Cattle not treated for any disease
[‡]AIP = Acute or Atypical Interstitial Pneumonia,
[‖]BRD = Bovine Respiratory Disease,
[§]Complex = Cattle treated for more than one of the disease categories,
[¶]GI+Bloat = Cattle treated for gastrointestinal disease or bloat,
[‡‡]Other = Cattle treated for any other disease not fitting any of the above categories.

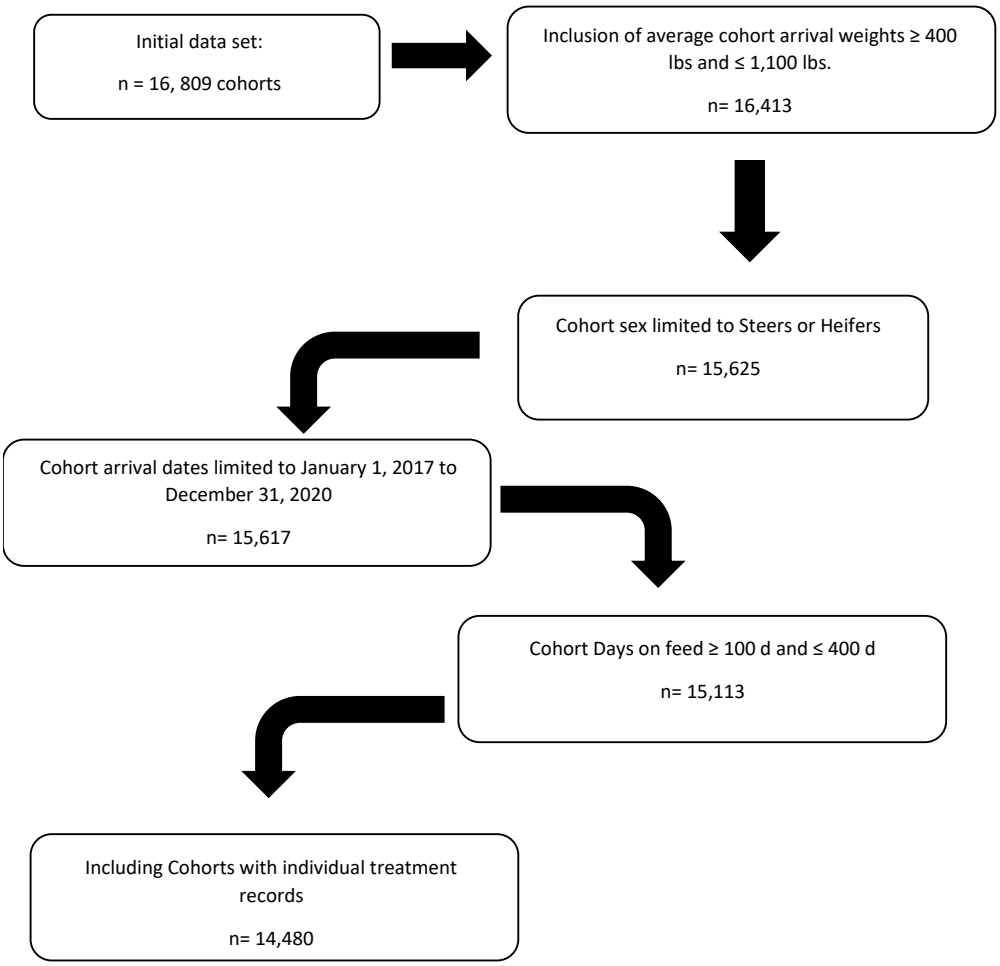

Figure 3.1 Flow chart showing inclusion of cohort level data from 14 U.S. commercial feedlot used for final model.

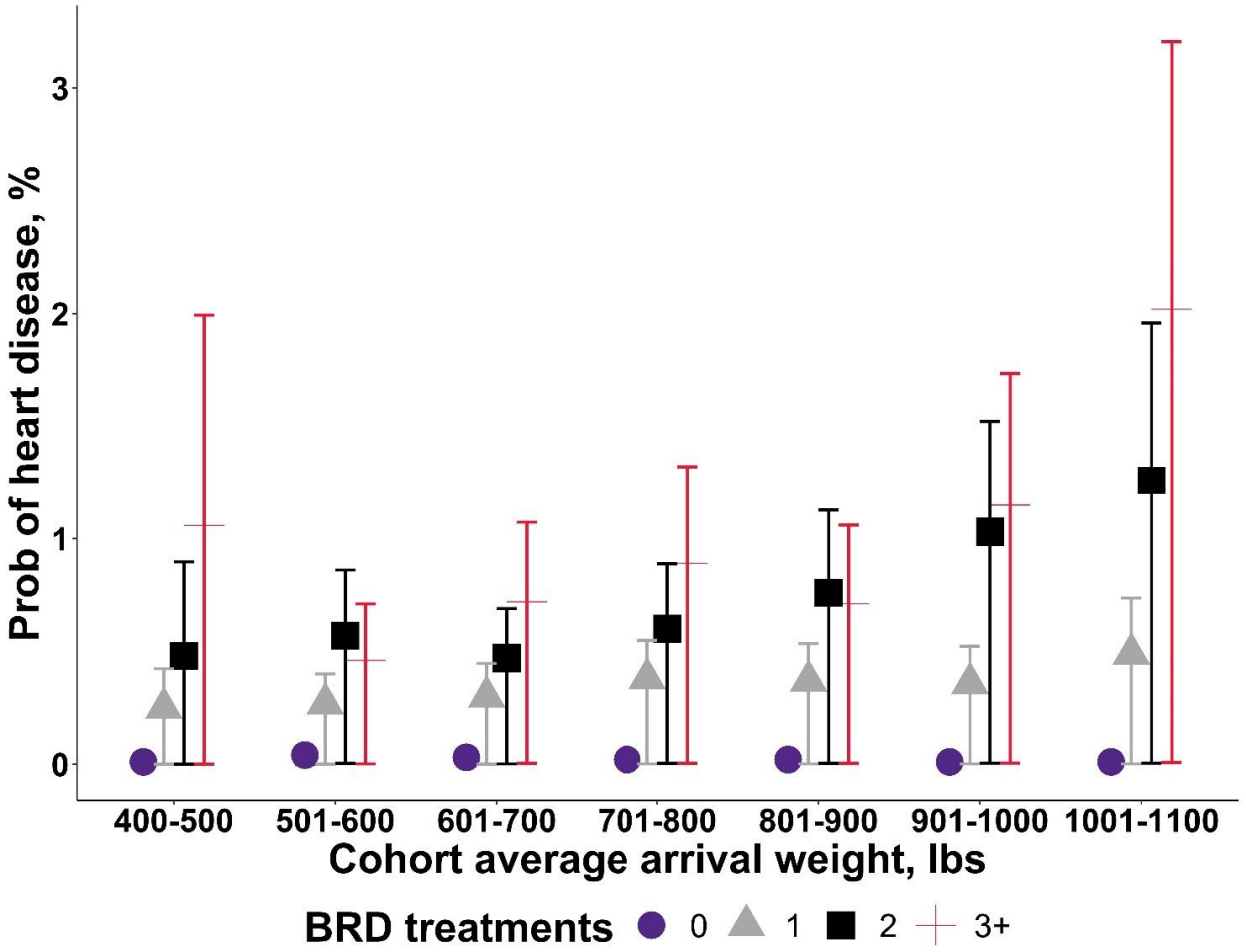

Figure 3.2 Model-estimated probabilities plus one SE for heart disease by cohort arrival weight (lbs) modified by number of times treated for bovine respiratory disease. Legend shows mutually exclusive BRD treatment categories as: circle (purple) is "0 or no treatments", triangle (grey) = "one treatment", square (black) = "two treatments", plus-sign(red) = "three or more treatments". Estimates are adjusted for cohort arrival quarter, cohort sex, and feedlot elevation with random intercepts of cohort within yard and cohort arrival year.

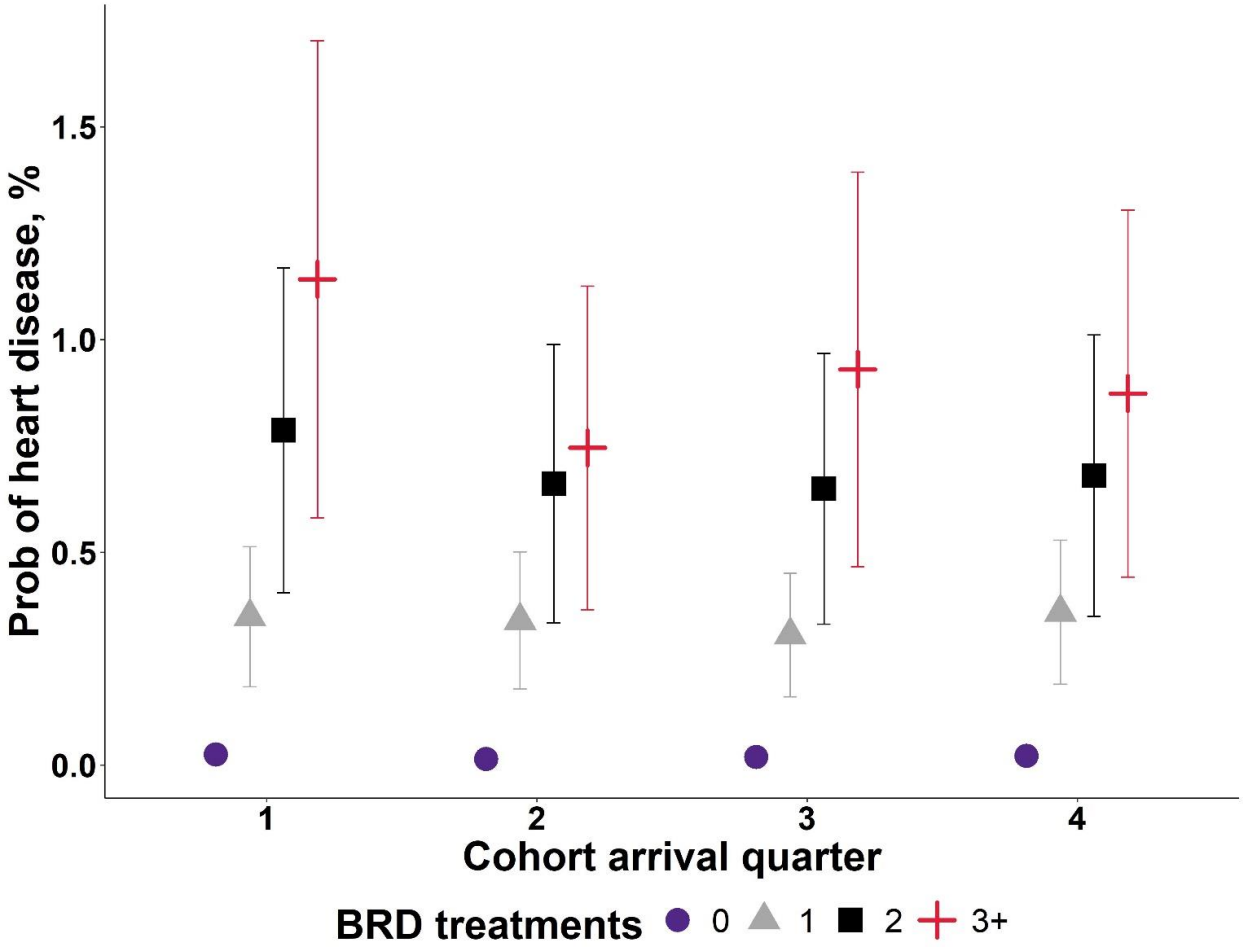

Figure 3.3 Model-estimated probabilities plus one SE of developing heart disease influenced by BRD treatment categories. Legend shows mutually exclusive BRD treatment categories as: circle (purple) is "0 or no treatments", triangle (grey) = "one treatment", square (black) = "two treatments", plus-sign (red) = "three or more treatments". Estimates are adjusted for average cohort arrival weight (lbs.), cohort sex, and feedlot elevation. Model also included random intercepts for cohort within yard, yard, and cohort arrival year.

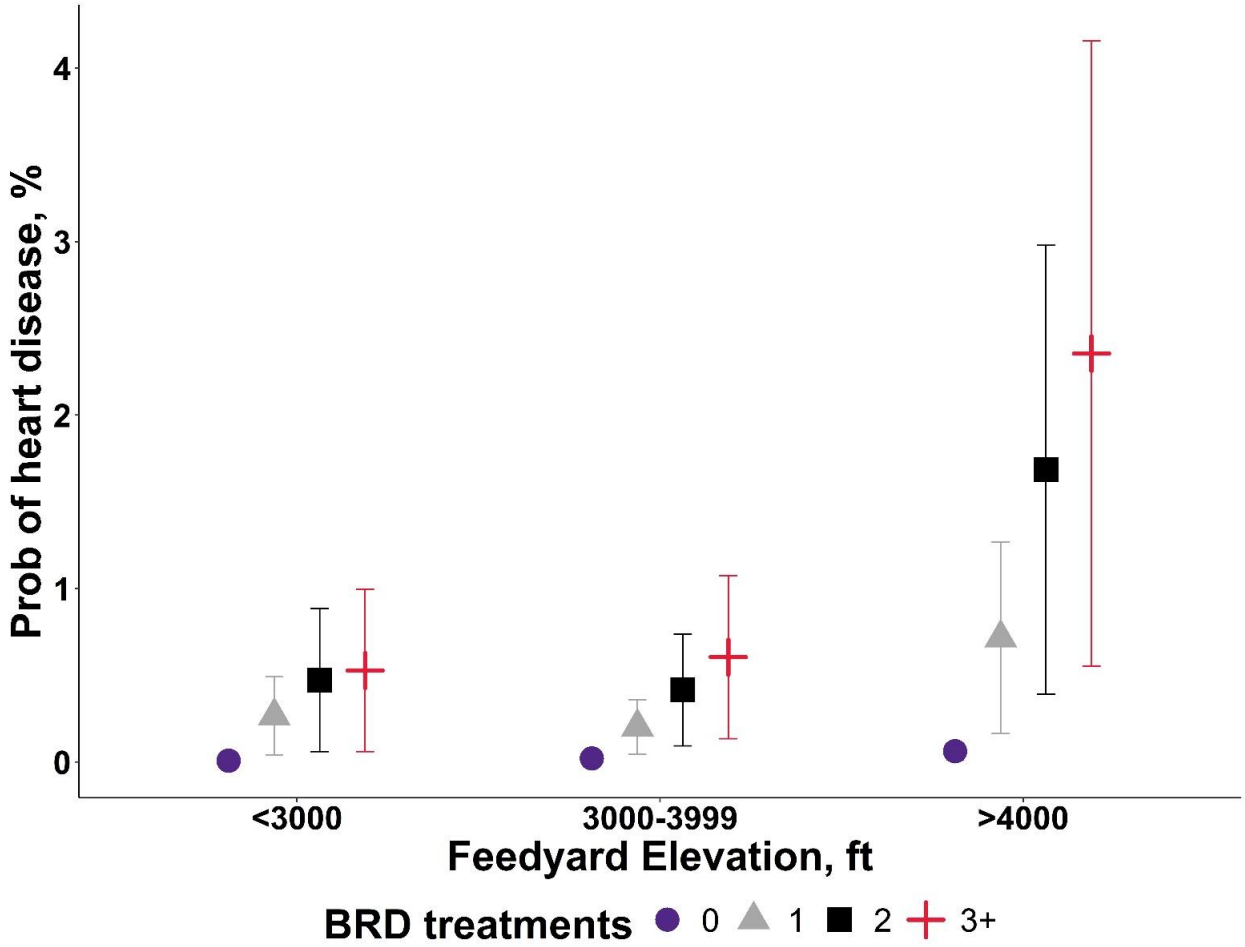

Figure 3.4 Model-estimated probabilities plus one SE for heart disease by elevation category (ft) influenced by bovine respiratory disease treatment category. Legend shows mutually exclusive BRD treatment categories as: circle (purple) is "0 or no treatments", triangle (grey) = "one treatment", square (black) = "two treatments", plus-sign(red) = "three or more treatments". Estimate are adjusted for average cohort arrival weight (lbs.), cohort arrival quarter, and cohort sex. Model included random intercepts to account for data clustering for feedlot, cohort within feedlot and cohort arrival year.

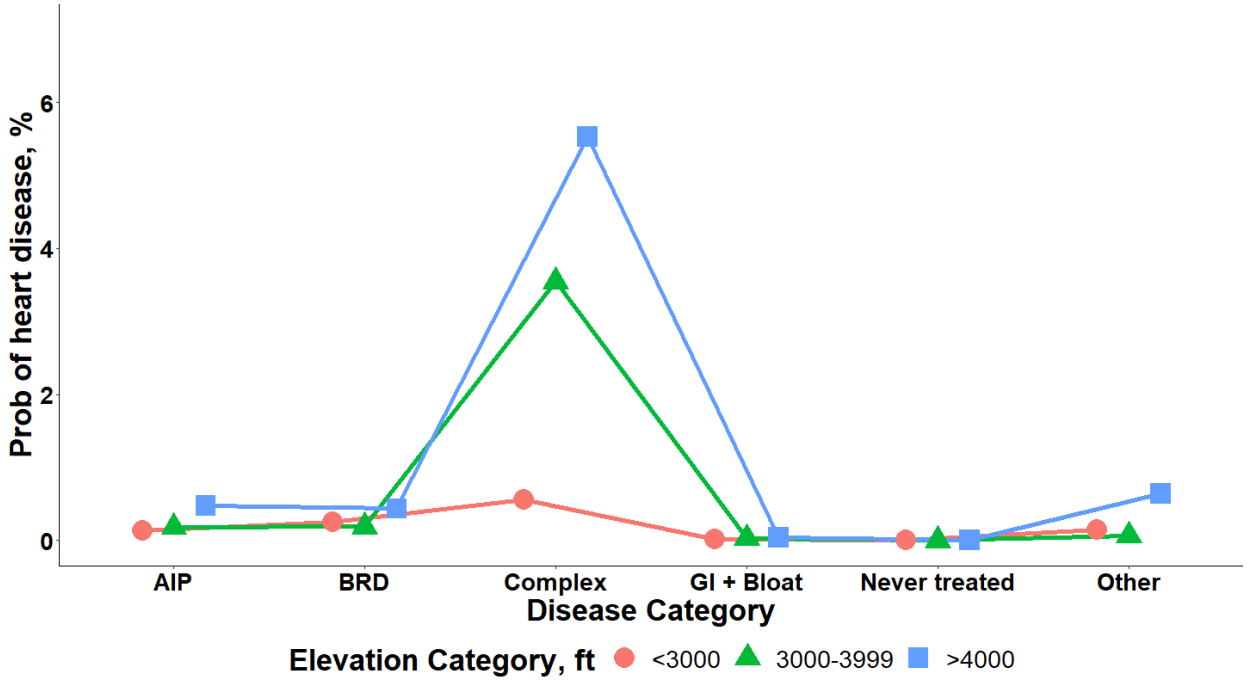

Figure 3.5 Model-estimated probabilities of developing heart disease by feedlot treatment category influenced by feedlot elevation. Legend shows circle (red) as "< 3,000 ft", triangle (green) as "3,000 ft to 3,999 ft" and square (blue) as "> 4,000 ft". Estimates are adjusted for average cohort arrival weight (lbs.), sex and include random intercepts for feedlot and cohort within feedlot, and cohort arrival year.

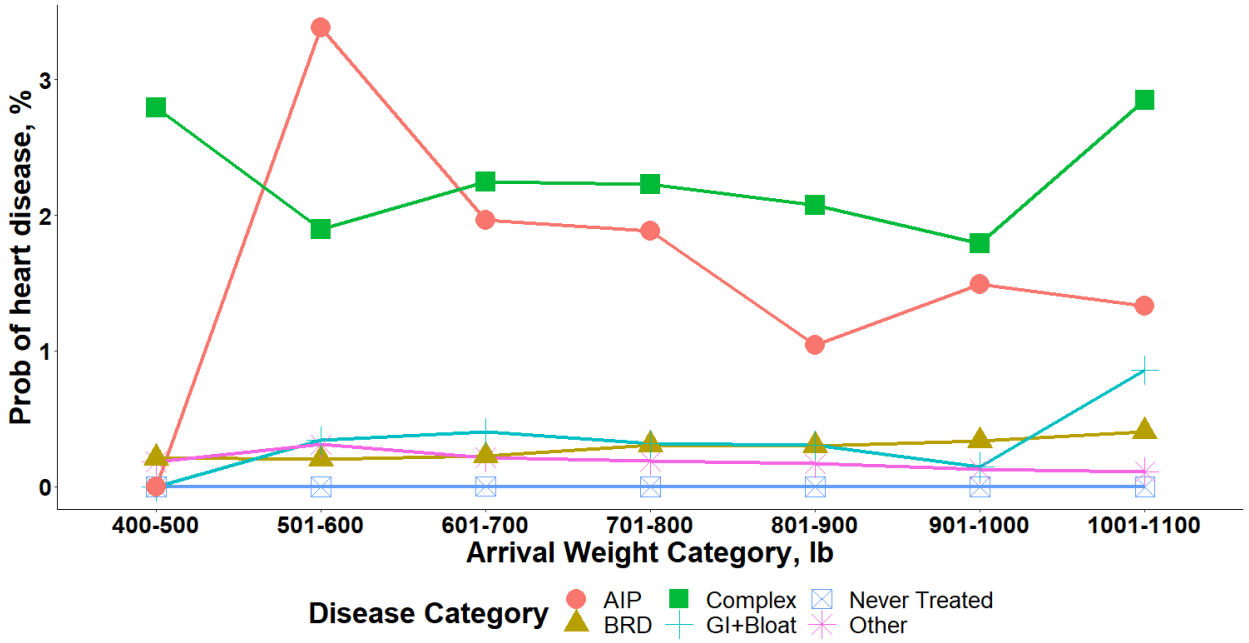

Figure 3.6 Model-estimated probability of developing heart disease by average cohort arrival weight category influenced by feedlot disease treatment. Legend shows mutually exclusive disease categories being circle (red) as AIP (atypical/acute interstitial pneumonia), square (green) as Complex (cattle are treated for at least two different feedlot disease categories, cattle may have been treated multiple times), square with cross (light blue) as "cattle that were never treated for a disease", Triangle (gold) as BRD (Bovine Respiratory Disease, cattle may have been treated more than once for BRD in this category), plus-sign(turquoise) as "GI + Bloat" (cattle treated for any gastrointestinal disease and /or blot, may have been treated more than once within this category), Asterix (pink) as "Other" cattle which were treated for any disease not lumped into the previous categories (excluding heart disease). Heart disease was excluded from the visual due to its high probability of animals being removed and skewing the visual. Estimates are averaged over elevation categories, sex and include random intercepts for feedlot, cohort within feedlot, and cohort arrival year.

Chapter 4 - Risk and timing of death from right heart failure in U.S. and Canadian feedlot cattle

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Abstract

Previous literature reported a rise in risk of right heart failure (RHF). The objective of the current study was to use a validated case definition of RHF to determine the risk and timing of RHF. Data were analyzed using mixed effects models to evaluate the risk of RHF and timing of RHF in 13 US and Canadian feedlots from January 2016 through December 2020. Cohort-level covariates of interest include breed (beef, dairy, dairy-cross), type (yearlings, calves), bovine respiratory disease (BRD) risk at arrival (high, medium, low), BRD morbidity category (0 to 5%, 6 to 12%, 12.1 to 27% and > 27%), elevation category, sex, arrival quarter, average cohort

arrival weight, and arrival year. The non-adjusted risk over the study population was 7.8 in 10,000 cattle received and mean and median unadjusted timing to RHF death was 179 and 174 DOF, respectively. Arrival year was associated with RHF and was influenced by arrival quarter on the magnitude of risk of RHF ($P < 0.01$). Bovine respiratory disease risk category's association with risk of RHF, was influenced by placement year and by feedlot elevation ($P < 0.01$). Elevation category association with risk of RHF was influenced by breed (beef, dairy, or dairy-cross) ($P < 0.01$). Heifers had a risk ratio of 1.23 compared to steers (LCL = 1.06, UCL = 1.43) ($P < 0.01$). BRD risk category association with timing of RHF was influenced by average cohort arrival weight ($P < 0.01$). Cattle that died due to RHF and were treated for BRD died 11 days (LCL = 1.33, UCL = 20.2 days) sooner than cattle never treated for BRD ($P = 0.03$). Cattle breed was also found to be associated the timing of RHF ($P = 0.01$). Dairy-cross cattle that died due to RHF died approximately 37 days earlier in the feeding period (SE = 13.0 days, $P = 0.01$) compared to beef cattle. Overall, many factors affected the risk and timing of RHF in feedlot cattle.

Key words: feedlot, heart disease, brisket disease, right heart failure, congestive heart failure.

Introduction

Right heart failure (RHF) related deaths continue to be problematic for feeding operations and cattle owners due to unclear cause and insufficient ability to identify high-risk individuals or cohorts. Historically RHF were only described in cattle populations at higher elevations, > 2130m (Alexander, 1978; Glover and Newsome, 1914; Jensen et al., 1976). More recently, risk of feedlot RHF has gained interest and has been more commonly reported at moderate elevations (Bassett, 2019; Heaton et al., 2019; Johnson et al., 2021; Krafsur et al., 2019; Moxley et al., 2019; Neary et al., 2016). The epidemiology of RHF at moderate elevations and across

international production systems has been more recently described (Bassett, 2019; Johnson et al., 2021; Neary et al., 2016). In comparison to bovine respiratory disease (BRD) and gastrointestinal (GI) disease, RHF is considered a lower-risk disease for much of the cattle feeding population. Some data would support that populations of fed cattle experience high-risk of RHF at moderate elevations regardless of a generalized low-risk for HD (Heaton et al., 2019). Heart disease can be confusing due to many different diagnostic names such as congestive heart failure, right heart failure, heart failure, *cor pulmonale*, brisket disease, etc. Due to many different names describing clinical signs associated with failure of effective heart function, we combined all these diseases into one syndrome name, RHF, to avoid confusion. A knowledge gap exists related to whether risk of RHF in fed cattle is increasing. Furthermore, cattle with dairy genetic influence have grown as a percent of fed cattle and how this increase influences risk and timing of RHF remains unknown.

Therefore, there were two objectives for the current study. 1) Evaluate previously identified factors on the risk of RHF in commercially fed cattle using a common case definition across multiple feedlots. 2) Evaluate the timing of RHF in fed cattle using a validated case definition.

Materials and Methods

Animal Care and Use Committee approval was not obtained for this study due to retrospective data being obtained from existing privatized databases from commercial feedlots. Case definitions:

All RHF deaths classified in the current study were diagnosed by a licensed veterinarian. In some instances, a veterinarian conducted the post-mortem examination on site. In other instances, trained personnel prosected the dead animals using a standardized method to capture

appropriate digital images and electronically transfer them to the veterinarian for diagnosis (Wildman et al., 2000). The case definition of RHF for the current study was previously described by Neary et al. (2016) as the following: “The postmortem lesions included brisket or ventral edema; hydroperitoneum, hydrothorax and secondary atelectasis; hepatomegaly, and chronic passive congestion; intestinal mesenteric edema; hydropericardium; right-ventricular hypertrophy and dilation.” Cattle treated for BRD include cattle treated under the following conditions: cattle with a fever at arrival, cattle pulled and treated for undifferentiated fever, and cattle pulled with clinical signs attributable to BRD but had no fever detected. BRD risk classification is a grouping assigned by the feedlot at arrival to the cohort for their apparent risk of BRD. The risk classification includes: ‘high’, ‘medium’, or ‘low’.

Data cohort risk analysis

Two datasets comprised of individual RHF deaths and cohort level data were collected from 13 U.S. and Canadian commercial feedlot operations from 2016 through 2020. A cohort is defined as cattle that are purchased during a similar timeframe and managed in an equivalent manner and fed to a similar endpoint but not necessarily fed in the same pen. A total of 7,591 cohort and 1,572 individual (mortalities) data were collected by (D.A.D) for the current study. Cohort variables of interest include average cohort arrival weight, cattle class (yearlings vs. calves), breed (beef, dairy, dairy-cross), BRD morbidity (percentage of cattle in the cohort treated for BRD), number of cattle in the cohort, BRD risk (low, medium, and high), sex, and feedlot elevation in feet (and meters). Specific feedlots’ location and identification were masked for data analysis, and a random unique identification variable was assigned to each of the 13 feedlots. Data were collected under a confidentiality agreement between the participating feedlots and the data manager. All data were imported into R programming version 4.1.2 (Team,

2021) for data manipulation and statistical analysis. Variable creation and data wrangling were performed using the tidyverse package (Wickham et al., 2019).

Variable creation

A new variable, "uid", was created to tie individual RHF deaths to cohort data by grouping the feedlot identification number, cohort identification number, and year within individual heart deaths, where uid = ("feedlotID.cohortID.year"). This unique identification number was also created at the cohort data level and used to tie individual data to cohort data to get identify the number of RHF deaths per cohort.

Timing of arrival was categorized into arrival quarters by creating a new variable. Cattle classified as a "1" arrived at the feedlot between January 1st and March 31st, "2" are cattle that arrived at the feedlot between April 1st and June 30th, "3" are cattle that arrived at the feedlot between July 1st and September 30th, "4" were cattle that arrived between October 1st and December 31st.

For data at the cohort level data, average arrival weight was categorized into 42.5kg. categories for the analysis to avoid violating the assumption of linearity and making assumptions more externally generalizable. Initial average cohort arrival weights ranged from 136kg to greater than 544kg prior to selection criteria. For the second portion of the objective, assessing timing of RHF death by DOF the assumption of linearity was checked by plotting arrival weights against timing of death from RHF (DOF) and showed a non-linear relationship. To avoid violation of linearity and be more externally generalizable, individual arrival weights were categorized into 45.5kg categories. Feeding elevation was identified by physical location of the feedlot. Feedlot operations were grouped into one of three categories depending on elevation of the feedlot to balance data and create equal representation of number of feedlots within elevation

categories. Feedlots with elevation less than 900m were grouped into the first category ("1"). Feedlots that were between 950m to 1,050m were grouped into the second ("2") category. Any feedlot at an elevation greater than or equal to 1,050m were grouped in the final elevation category ("3").

A new variable was created to categorize each cohort's BRD morbidity into one of 4 groups. Cohorts were categorized based on summary statistics of percent of cohort treated for BRD. The minimum percent morbidity for BRD was found to be 0% and maximum was 95% with an inner quartile range (IQR) of 5% to 27%, respectively. Cut off points were established based on IQR of BRD morbidity for 'brd_cat' groups as follows: 0 to 5% BRD morbidity "0-5", >5 to 12% BRD morbidity "6-12", 12.1 to 27% BRD morbidity "12.1 – 27" and >27% BRD morbidity ">27". This put 1,711 cohorts in the 0 to 5% BRD morbidity group, 1,183 cohorts in the 6 to 12% BRD morbidity group, 1,417 cohorts in the 12.1 to 27% BRD morbidity group and 1,216 cohorts in the >27% morbidity group, respectively.

Inclusion criterion:

Cohort data were included if average arrival weight categories of cattle placed were between 136kg to 500kg. Only cohorts that were determined to be 'Heifers' or 'Steers' were included in the final data set. Cohorts were included in the final data set if total cattle received was ≥ 40 cattle. Cohort days on feed were not evaluated due to constraints of linking data to multiple ship dates within cohort. Individual data were matched to final cohort level data for inclusion in risk analysis and timing of RHF.

Statistical analysis:

Analyses were performed using R programming version 4.1.2 (Team, 2021). Descriptive data were summarized with confidence intervals using the tidyverse package (Wickham et al.,

2019). Three statistical models were used for evaluating the risk of RHF: Poisson, negative binomial regression, and zero inflated binomial regression. Data were initially fit into a Poisson model using number of heart deaths in a cohort as an outcome and log transformation of number of cattle received as an offset to calculate the risk ratio of RHF. The risk ratio was back transformed to a risk per 10,000 cattle. The initial Poisson model included fixed effects for arrival weight category, cattle class, breed, sex, elevation category of feedlot, arrival quarter, BRD morbidity category, and arrival year which were previously reported as significant for heart disease (Johnson et al., 2021). A dispersion perimeter was calculated for the Poisson model using the performance (Lüdecke et al., 2021) package. The Poisson model was found to be over dispersed (dispersion ratio = 2.020, Pearson's Chi-squared = 11,719.457, P-value $\leq$ 0.001) and thus data were then modeled in a negative binomial and zero-inflated negative binomial mixed effects regression model. Two family functions were evaluated using the negative binomial models (nbinom1 and nbinom2). Only two-way interactions estimated to imply biological significance were evaluated in the models. Interactions were included in the final model if $P < 0.05$. Final model was selected by the lowest Akaike's Information Criterion (AIC), which was determined to be a negative binomial model with a nbinom1 family and log-link function. Feedlot ID was used as a random intercept to account for lack of independence of cohort within feedlot for RHF timing analysis. Post-hoc comparisons were performed using the emmeans package (Lenth, 2022) using a Tukey-Kramer multiple comparison adjustment and a offset of log (10,000) to get the risk per 10,000 cattle.

To accomplish the second portion of the study objective, a linear mixed effects model was used to evaluate the timing of RHF in days on feed with the 'lme4' package (Bates et al., 2015). Days on feed at death from RHF was the outcome of interest for individual timing

analysis. Fixed effects included for the analysis included sex, cattle class (yearling or calves), breed (beef, dairy, dairy-cross), BRD treatment (yes = '1', no = '0'), elevation category (1, 2, 3), arrival weight category, and BRD risk classification. Univariate analyses were performed to determine significant factors to include in the model that were not previously found to be significant (Johnson et al., 2021). A random intercept for feedlot ID and cohort ID within feedlot were used to account for hierarchical structure of the data. Several two-way interactions of fixed effects were assessed and only interactions with $P \leq 0.05$ were included in the final model.

Results

Descriptive statistics:

A summary of the data from the final dataset is displayed in Table 4-1. These data showed a total of 1,717,356 cattle placed in 13 U.S. and Canadian feedlots which accounted for 5,527 cohorts of cattle. Total death loss due to RHF was 7.8 per 10,000 cattle placed. Feedlot elevation ranged from minimum of 71m to a maximum of 1,311m. The number of RHF per cohort ranged from 0 to 30 with an IQR of 0 to 0 with a mean and median of 0.24 and 0, respectively. Cohort size ranged from 40 to 6,856 cattle placed with an IQR of 97 to 452 cattle. The mean and median number of cattle placed per cohort was 311 and 216 cattle, respectively. Figure 4.1 shows the unadjusted cumulative risk of RHF by days on feed. Summary statistics of RHF days on feed (DOF) resulted with a minimum DOF of 0 and maximum DOF of 609 mean and median RHF DOF was 179 and 174, respectively. The IQR of RHF DOF was 110 to 239. Figure 4.2 is a histogram of the counts of RHF across DOF at the time of death. Figure 4.4 is a raincloud plot displaying the distributions of timing of RHF as a density plot and individual points (death events) for the timing of RHF deaths by arrival year for the duration of the study.

Cohort RHF Risk:

Cattle breed (beef, dairy, or dairy-cross) was associated with RHF and influenced by arrival year (Figure 4.5). Beef cattle had numerically higher risk of RHF estimates compared to dairy or dairy-cross cattle but were not different across all 5 years of the study. Furthermore, placement year was influenced by BRD morbidity category (0 to 5%, 6 to 12%, 12.1 to 27% and >27%) on the risk of RHF ($P < 0.01$). Cattle placed in 2016 with cohorts having between 0 to 5% BRD morbidity had the lowest RHF risk at 1.67 SE = 0.49. Figure 4.7 shows the association of arrival year being influenced by arrival quarter on risk of RHF ($P = 0.02$). Estimated risk of RHF ranged from 4 (Q4-2016) to 10 (Q3-2019) per 10,000 cattle. Quarter 3 in 2019 had the highest estimated risk of RHF at 10 per 10,000 cattle which was significantly different compared to Q4-2016 (4 per 10,000 cattle, SE = 0.91) and Q3-2018 (4.39 per 10,000 cattle, SE = 1.10) and Q4-2017 (4.93 per 10,000 cattle, SE = 1.12). Quarter 4-2016 was found to be lower compared to Q4-2019 at 4 vs 7.56 per 10,000 cattle diagnosed with RHF. Risk of RHF were found to be no different across other quarters and years in the study comparison.

Cattle risk category was influenced by feedlot elevation on the magnitude of RHF ($P < 0.01$). No meaningful differences were found in comparisons within BRD risk groups (Figure 4.6). Right heart failure was associated with feedlot elevation and modified by breed (beef, dairy, or dairy-cross) on the risk of RHF ($P < 0.01$). Beef cattle placed in elevation category 3 had 0.54 times the risk of RHF as dairy cattle placed in at similar elevations ($P = 0.03$, LCL = 0.31; UCL = 0.962). In addition, dairy cattle had 2.04 times the risk of RHF as dairy-cross cattle ($P = 0.05$, LCL = 1.00, UCL = 4.14). No other differences were found with elevation category and breed classification. Finally, heifers died of RHF 1.23 times that of steers when adjusting over arrival

quarter, arrival year, risk category, elevation category, and BRD morbidity category ($P < 0.01$, LCL = 1.06, UCL = 1.43).

Timing of RHF

The current study found that the association of BRD risk was influenced by arrival weight category on the timing of RHF ($P < 0.01$) (Figure 4.9). Low BRD risk cattle having an average cohort arrival weight <136kg had an estimated 80 DOF (SE = 22 days) to RHF death. This was different than high risk-cattle placed at <136kg (161 d, SE = 11.0, $P < 0.01$), low-risk cattle placed at 227-272kg (174 d, SE =12.9, $P < 0.01$), high-risk cattle placed at 227-272kg (177d, SE=11.0,$P < 0.01$), high-risk cattle placed at 181-226kg (182d, SE=15.1, $P = 0.01$).

Furthermore, the current study found that cattle dying due to RHF that were treated for BRD died 11 days (SE = 4.8 d) sooner than cattle that were not treated for BRD. Cattle breed classification were associated with the timing of RHF ($P = 0.01$). Dairy-cross cattle were found to die due to RHF approximately 37 days earlier in the feeding period (SE = 13.0, $P = 0.01$) compared to beef genetically influenced cattle. No significant differences were found comparing the timing of RHF in beef genetically influence cattle to dairy genetically influenced cattle (estimated difference of 16 days SE = 12.5, $P = 0.39$).

Discussion

The current study evaluated risk of RHF across multiple populations of cattle fed at different elevations, across two predominant cattle feeding countries. To the authors knowledge this is the first study that evaluated RHF associations that incorporated cattle breed type (dairy, beef, and dairy-cross) as a predictor of RHF. Literature from a similar case definition of RHF reported cattle that developed RHF at 4 to 17 per 10,000 cattle received (Neary et al., 2016). Other literature reported cattle dying from heart disease from all non-infectious origins (not necessarily

limited to RHF) at 7 in 10,000 cattle placed (Johnson et al., 2021). Similar estimates of heart disease reported cattle dying at 6-7 per 10,000 cattle placed and cattle being railed at a risk of 9 per 10,000 cattle placed, giving broadly defined heart disease an overall prevalence of 15 per 10,000 cattle placed (Johnson et al., 2022). The current study found overall risk of RHF was within range of previously published research at 7.8 RHF per 10,000 cattle placed. These data would support using a broad case definition of heart disease and finding similar death risk in commercial production settings. However, the current study could not look at railed cattle (cattle removed earlier from their respective feeding period prior to finishing with cohort) due to data limitations and thus no associations were drawn for those animals. Current estimates are likely to be conservative due to not including railer cattle. Overall disease impact is a higher risk than reported by the current study. However, there is the potential for country differences in the ability to rail cattle. In Canada, railing options are not as abundant as the U.S. due to the size of the feedlot industry and cattle exhibiting RHF symptoms are more likely to be condemned (R.D.M).

Differences between US cattle and Canadian cattle risk could also play a role in variation between previously reported data. Another consideration for variation of RHF between the current study and previously reported literature would be the study case definition. Johnson et al. (2021 and 2022) used an all-encompassing case definition of heart disease, which included all diagnosis from a non-infectious origin contributing to heart disease. Authors reported using such a case definition due to the higher variability in feedlot personnel training and variability between feedyards. Whereas the current study and previously reported literature (Neary et al., 2016) used a more specific case definition of heart disease; right heart failure (RHF). Both HD and RHF have similarities, but RHF encompasses a specific criteria for an animal to be

diagnosed as RHF. Furthermore, all diagnoses were performed by veterinarians in the current study and in Neary et al. (2016), which would decrease some of the variability across feedlots and give a more robust estimate of RHF disease impact within the feedlot industry. However, given the differences in case definition, risk of RHF appears to be similar to risk of HD as previously reported.

Data from the current study reflected year-to-year variation on the risk of RHF with many comparisons between arrival year and quarter not being different. Johnson et al. (2021) previously reported year-to-year variation feedlots reported an average prevalence between 7 and 9 HD per 10,000 cattle dying of non-infectious HD. The current study found that arrival year and quarter ranged between 4 and 10 RHF per 10,000 cattle placed which is similar to previous literature (Bassett, 2019; Johnson et al., 2021; Neary et al., 2016). This suggests multiple factors effect cattle health in feedlots year-to-year. The current study was performed over a period where RHF was being more thoroughly documented compared to previous times when heart disease was gaining interest and focus within the feedlot industry. This would suggest that in the past five years that RHF does not seem to be increasing in prevalence compared to previous literature (Neary et al., 2016).

The risk of RHF was not found to be linear with increasing elevation in the current study. Johnson et al. (2022) reported that cattle fed at higher elevations had a greater risk of heart disease compared to cattle fed at lower elevations (Johnson et al., 2022). It has been hypothesized that cattle with greater risk of heart disease could have originated from higher elevations (Neary et al., 2016). Due to limitations in the data, previous location and elevation prior to the feedlot were not able to be analyzed due to many missing data. The current study found higher risk of RHF in cattle that were fed at moderate elevations (Elevation category 2:

900m to 1,050m). At this elevation, cattle would not be considered at high-risk for pulmonary hypertension due to hypobaric conditions (Newman et al., 2011). Johnson et al. (2022) reported that as elevation increased, the probability of a terminal heart disease diagnosis increased. However, the magnitude of risk (probability) was influenced by disease category (AIP, BRD, GI, Other, Complex Disease) or how many BRD treatments an individual received. The current study did not find a significant interaction between lot BRD morbidity category and elevation. Whereas Johnson et al. (2022) reported an interaction of BRD treatments and elevation. Differences could be explained in the available data for analysis whereas authors only had first treatment BRD data for analysis in the current study, thus multiple treatments records could not be evaluated as were in previous literature.

Unadjusted timing of RHF death was found to be greater than previous reported literature by 30 to 60 days (Bassett, 2019; Johnson et al., 2022; Neary et al., 2016). Increasing average days on feed to death from 178 compared to previous reports of 110 could support the theory that cattle being on feed longer in comparison to previous timing of RHF reports impacting RHF. However, Figure 4.4 shows distributions of timing of RHF over the five-year study period with median days on feed at death diagnosis and these data do not support any dramatic shift in median/mean days on feed at death when cattle are managed under similar health and performance recommendations, which is what one would expect if feeding periods increased (Neary et al., 2016). Data in the current study implemented a similar inclusion criterion as Johnson et al. (2021) and timing of RHF was much greater for the current study by 60 days. Differences in timing could be related to breed of cattle (beef, dairy, and dairy-cross) included in the current study, which were not accounted for in the former study. Dairy cattle are typically fed for a longer period compared to beef cattle. There was a difference between dairy-beef cross

cattle compared to beef cattle with beef cattle dying later in their respective feeding period numerically compared to dairy-cross cattle. However, no differences were found between beef and dairy cattle on the timing of RHF. Lastly, management strategies and cattle populations likely play a role in timing of RHF.

The current study reported that average cohort arrival weight category had different affects compared to previous literature (Johnson et al., 2021). Johnson et al. (2021) reported increasing average arrival weight categories was associated with cattle dying earlier in their respective feeding period. The current study found a similar timing to death across weight groups with effect modifications by BRD risk category. Again, management of cattle or type (dairy, beef, dairy-cross) could have played a role timing of RHF or that the industry is feeding cattle longer. Furthermore, the current study used the same case definition of RHF as Neary et al. (2016); however, differs from other previously reported research (Johnson et al., 2022, 2021). Different case definitions and methods for diagnosis have a strong possibility of causing variability in reported literature.

Conclusions

In summary, risk of RHF deaths were found to be similar to previously reported literature from fed cattle populations greater than 10 years ago. However, we cannot rule out if cattle are being identified and railed prior to death for true disease impact. Risk of RHF vary numerically across different breed types at different elevations and years. Timing of RHF varies among the genetic influence of cattle (beef vs. dairy-cross vs. dairy) and timing in the last 5 years appears to have increased in number of days on feed to death from previous research. These data support cattle are dying later in the feeding period; however, the distribution does not appear to be

skewed or an overrepresentation of RHF deaths in late feeding periods which suggests that RHF is not exclusively a late DOF disease problem.

Limitations:

Data were observational in nature and thus caution from drawing conclusions should be exercised as observational studies run a high-risk of bias (Dohoo, 2014; Theurer et al., 2015). Authors attempted to limit such bias with inclusion criteria and statistical analyses. Inferences outside data range should be disregarded.

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Conflicts of interest

Two authors work for Feedlot Health by TELUS Agriculture (DAD, RDR). Authors declare no other conflicts of interest for this study.

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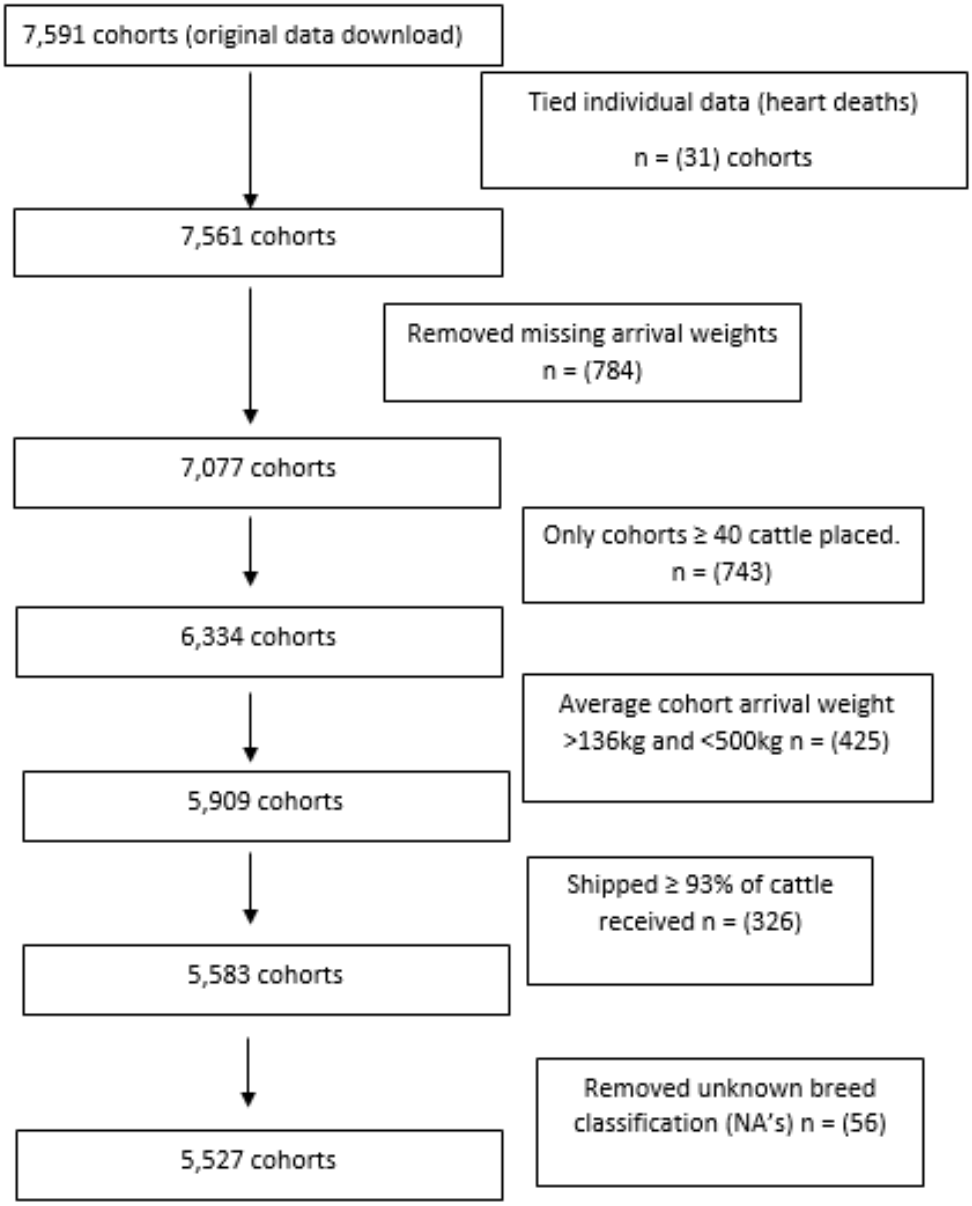

Figure 4.1 Data inclusion criteria for 13 U.S. and Canadian feedlots analysis of right heart failure risk

Table 4-1 13 U.S. and Canadian commercial feedlots descriptive data used to model risk of right heart failure (RHF)

Yard	Elevation, m	Lots	Cattle Received	Percent of calves	Percent of yearlings	Beef, % rcvd	Dairy, % rcvd	Dairy-Cross, % rcvd	Heart Deaths	BRD Morb, %	Heart per 10K
F	932	158	113,626	86.1	13.9	100	0	0	233	15	20.5
G	1,016	84	61,586	41.6	58.4	77.3	22.7	0	90	7	14.6
A	562	127	119,287	81.3	18.8	100	0	0	58	12	4.9
H	1,004	302	156,434	74.7	25.3	100	0	0	288	9	18.4
B	896	62	31,994	81.9	18.1	100	0	0	40	11	12.5
C	850	181	70,814	100.0	0.0	0	97.4	2.6	63	17	8.9
D	653	326	129,910	62.3	37.7	87.2	12.4	0.3	78	12	6.0
J	1,311	543	148,218	92.1	8.0	64.6	2.5	32.7	156	23	10.5
K	1,194	296	41,343	66.2	32.8	89.3	8	2.2	40	20	9.7
L	1,181	511	137,094	76.1	23.9	72.2	25.4	2.4	42	16	3.1
M	1,093	526	254,767	69.1	30.9	37.2	43.3	19.3	142	10	5.6
I	944	1,123	305,730	15.7	84.3	82.6	8.1	9.3	96	8	3.1
E	71	1,288	146,553	99.8	0.2	5.6	28	66.3	10	35	0.7
	Total		5,527	1,717,356						1,336	7.8

- m = meters, ft = feet
- % rcvd = percent cattle received
- Beef = genetically beef origin, Dairy = genetically dairy origin, Dairy-cross = genetically a dairy x beef animal.
- Morb, % = Morbidity percent = (number of first treatment BRD / cattle received) *100
- Heart per 10K = heart deaths per 10,000 cattle received (total heart deaths / cattle received) * 10,000

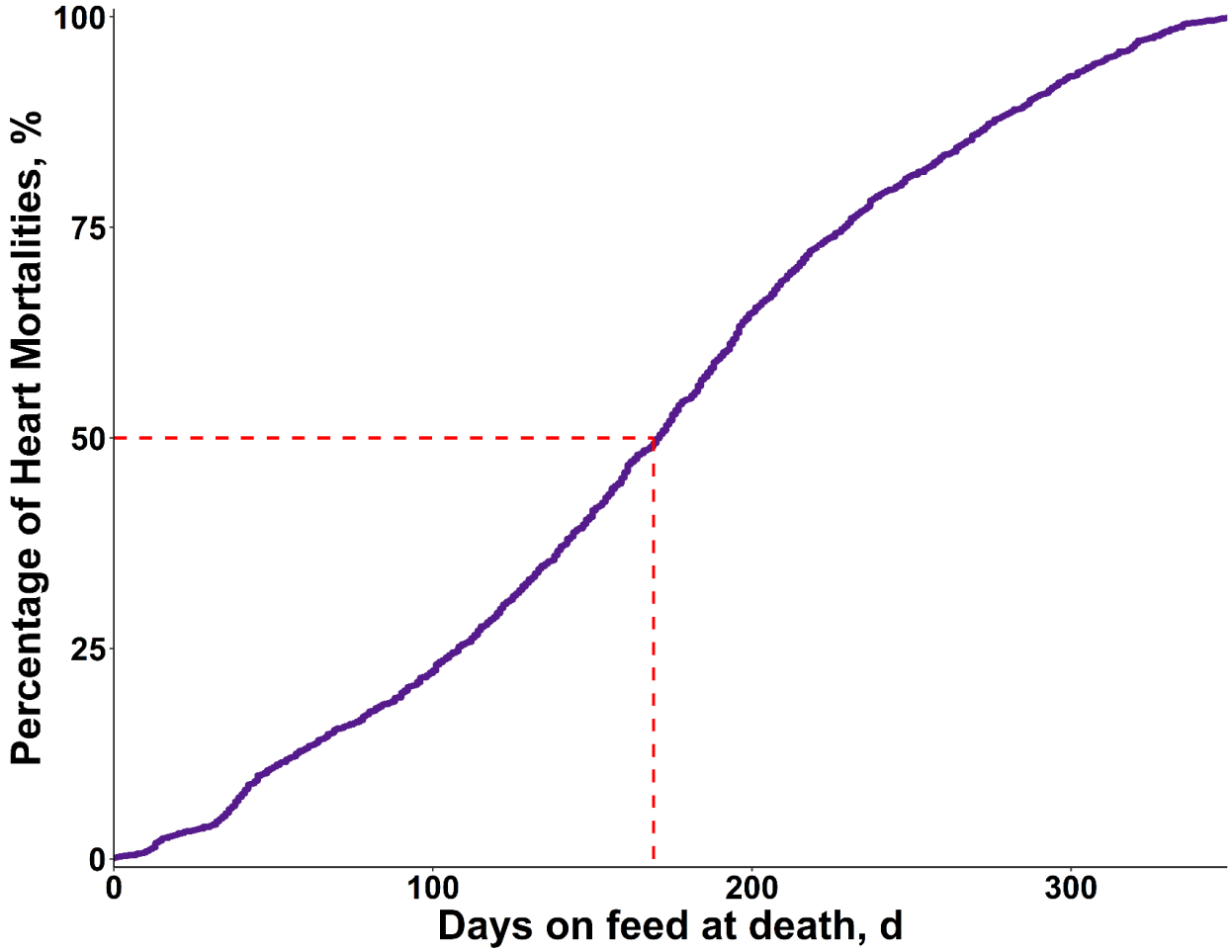

Figure 4.2 Cumulative incidence of right heart failure (RHF) mortalities from 13 U.S. and Canadian feedlots by days on feed at death with red dashed line representing 50% mortalities and corresponding DOF (174 d = median).

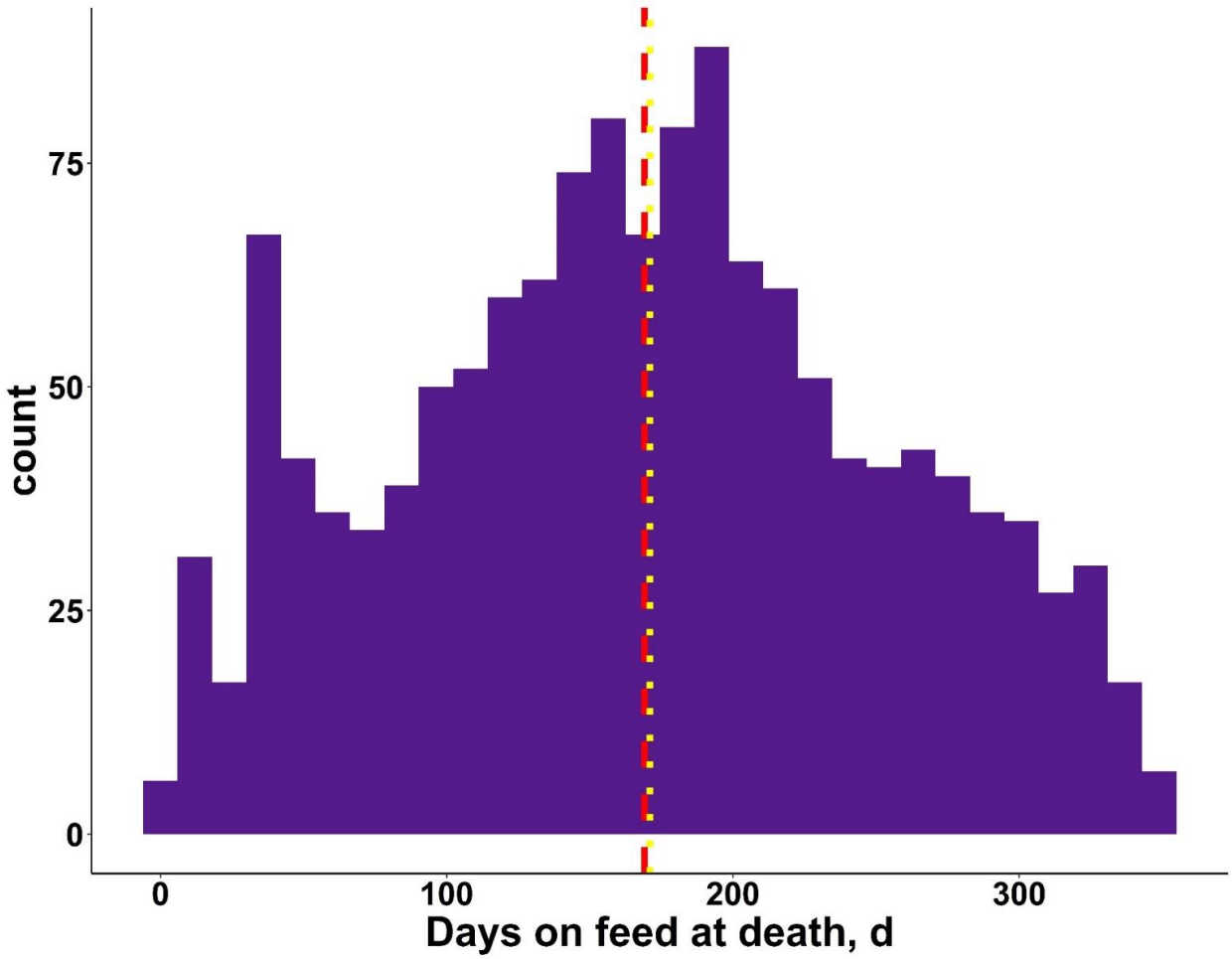

Figure 4.3 Histogram of days on feed of right heart failure mortality counts from 13 U.S. and Canadian feedlots. Red line (median = 174 d) and yellow dotted line (mean = 178 d).

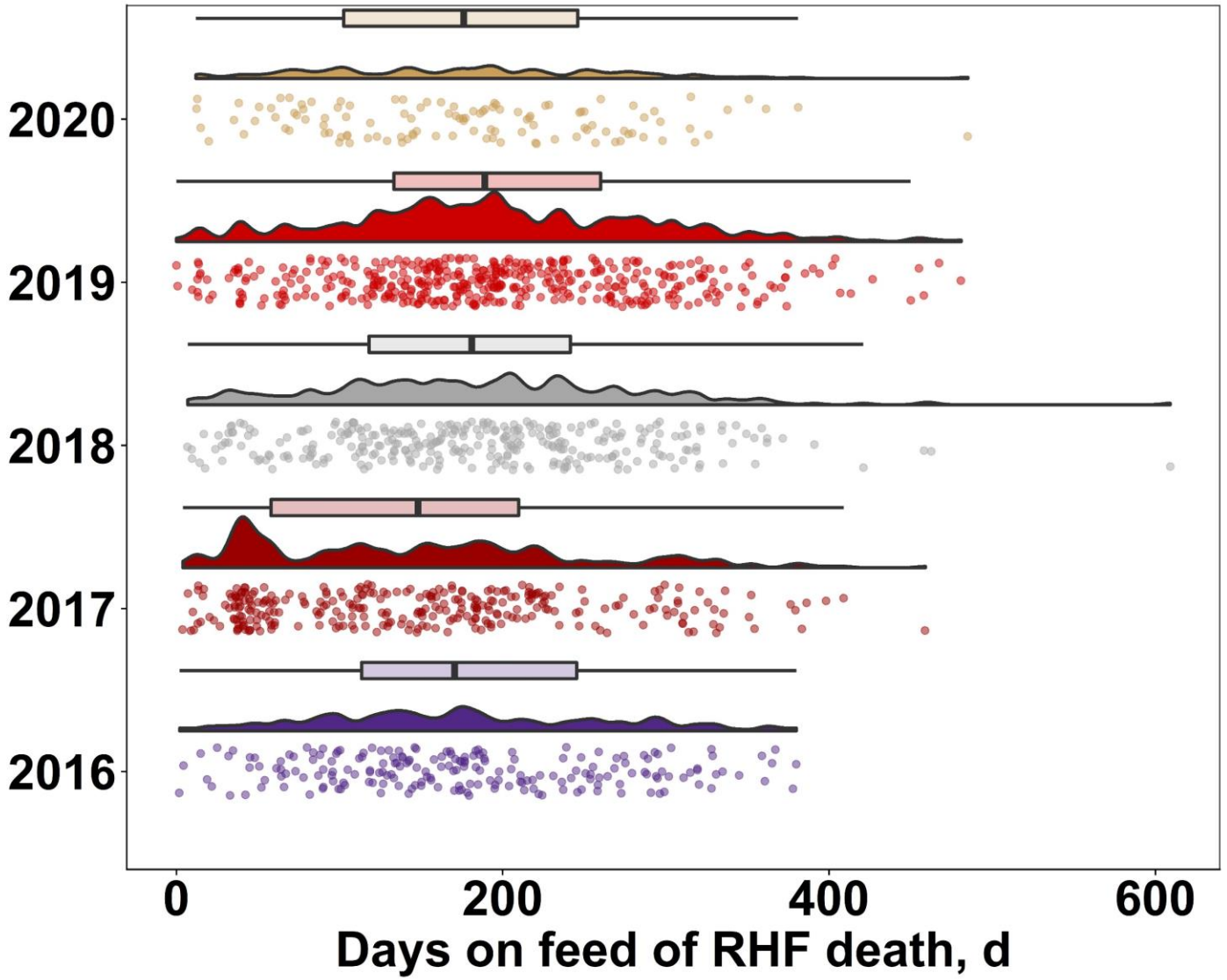

Figure 4.4 Raincloud with box-plot showing timing and density of right heart failure (RHF) deaths by days on feed categorized by arrival year (n = 1,336).

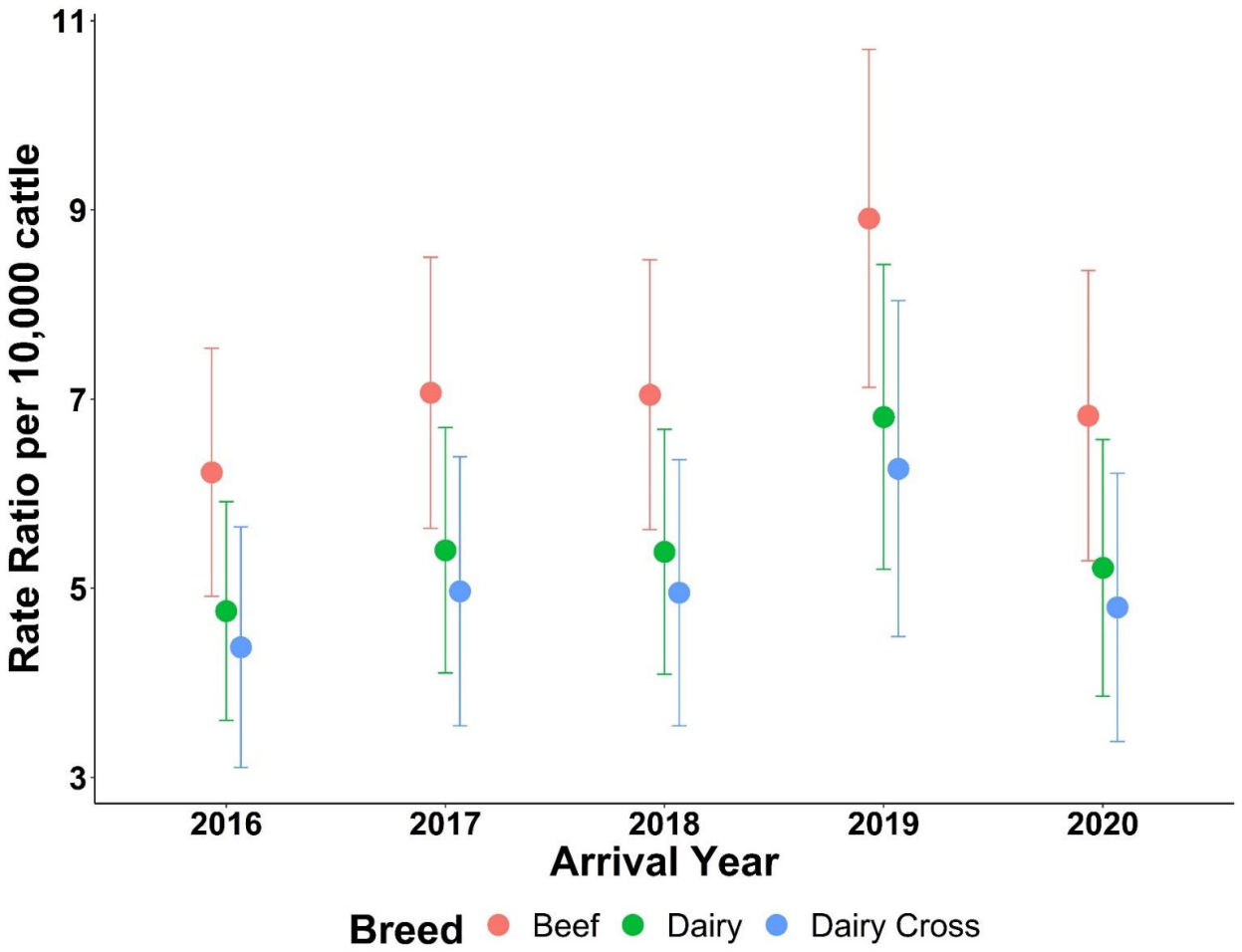

Figure 4.5 Model estimated risk ratio and SE for right heart failure (RHF) on breed (Beef, Dairy, or Dairy-cross) influenced by placement year from 13 U.S. and Canadian feedlots. Model estimates adjusted over arrival quarter, elevation category, sex, and BRD morbidity category.

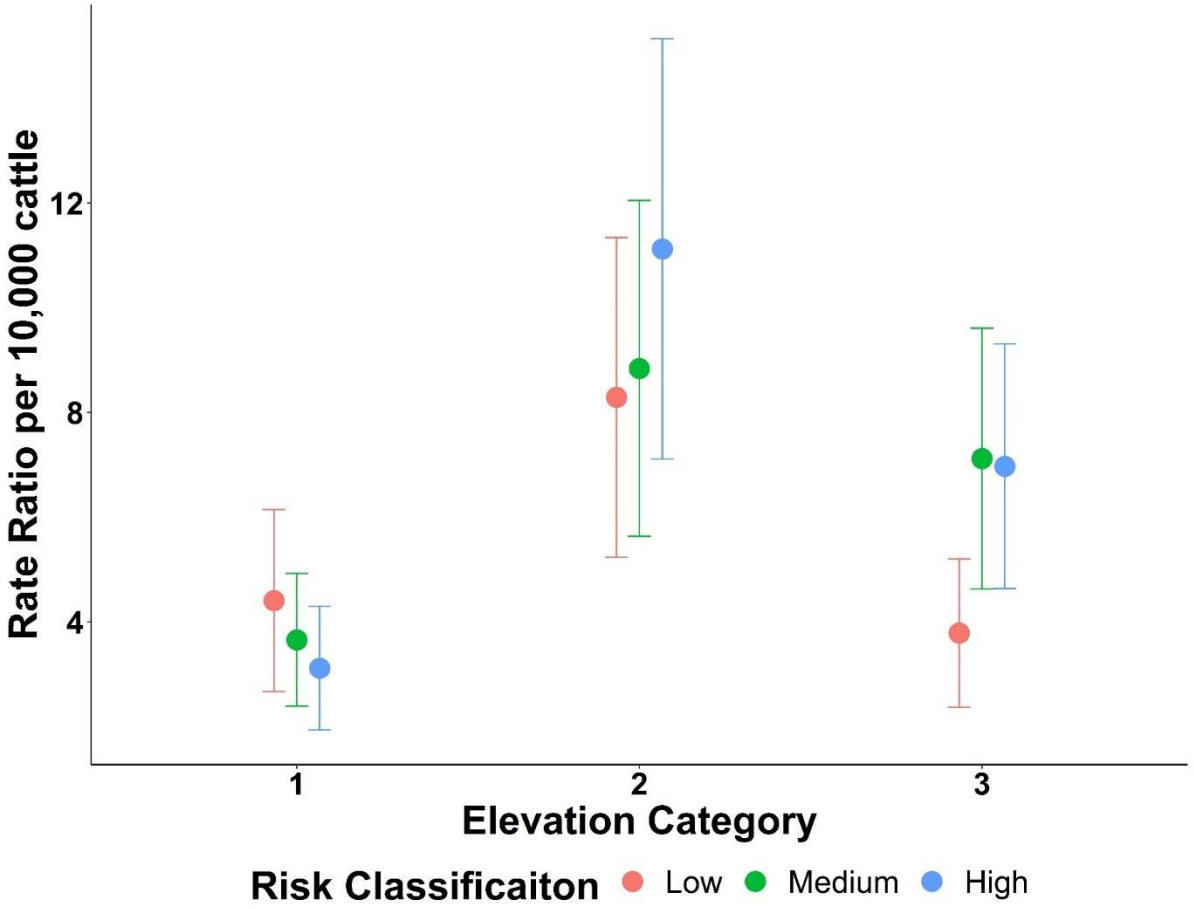

Figure 4.6 Model estimated risk ratio and SE for right heart failure (RHF) by bovine respiratory disease (BRD) risk classification influenced by elevation category (1,2, or 3) from 13 U.S. and Canadian feedlots. Model estimates adjusted over arrival quarter, breed, arrival year, sex, and BRD morbidity category

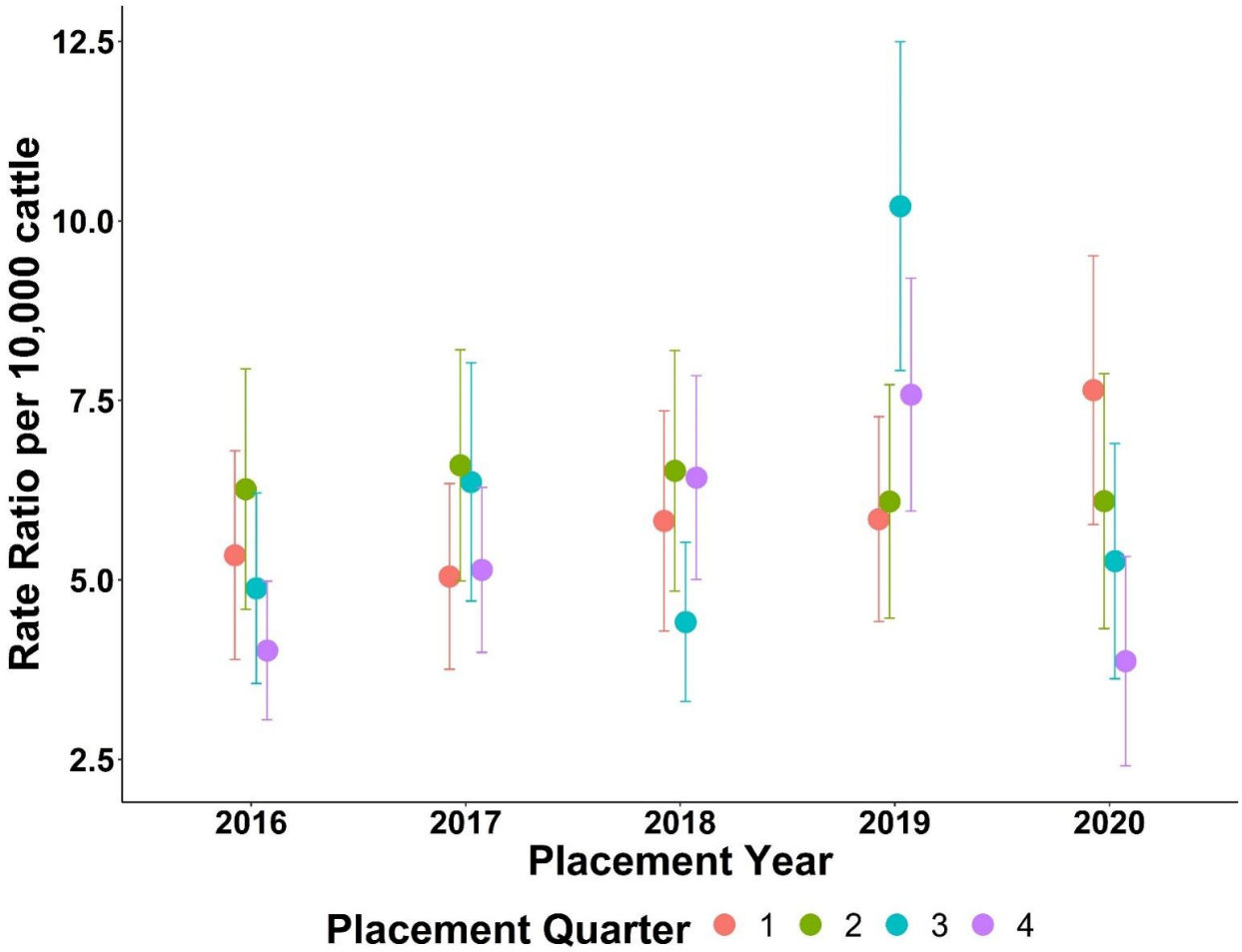

Figure 4.7 Model estimated rate ratio and SE for cattle placement quarter influenced by placement year for right heart failure (RHF) from 13 U.S. and Canadian feedlots. Model estimates adjusted over breed, elevation category, risk, sex, and BRD morbidity category.

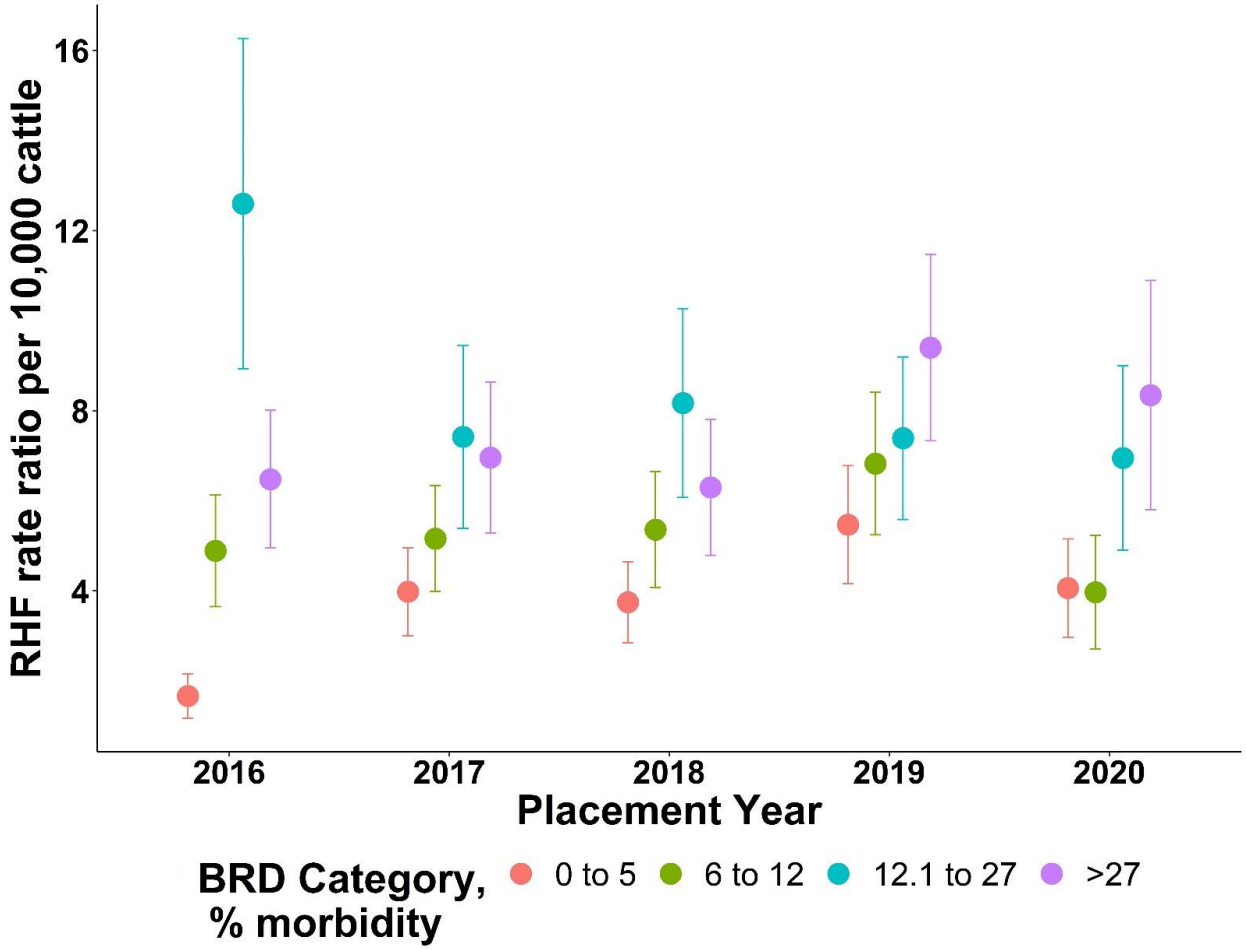

Figure 4.8 Model estimated rate ratio and SE of right heart failure (RHF) of cattle placed by arrival year influenced by BRD morbidity category. Model estimates adjusted over arrival quarter, breed, elevation category, risk, and sex.

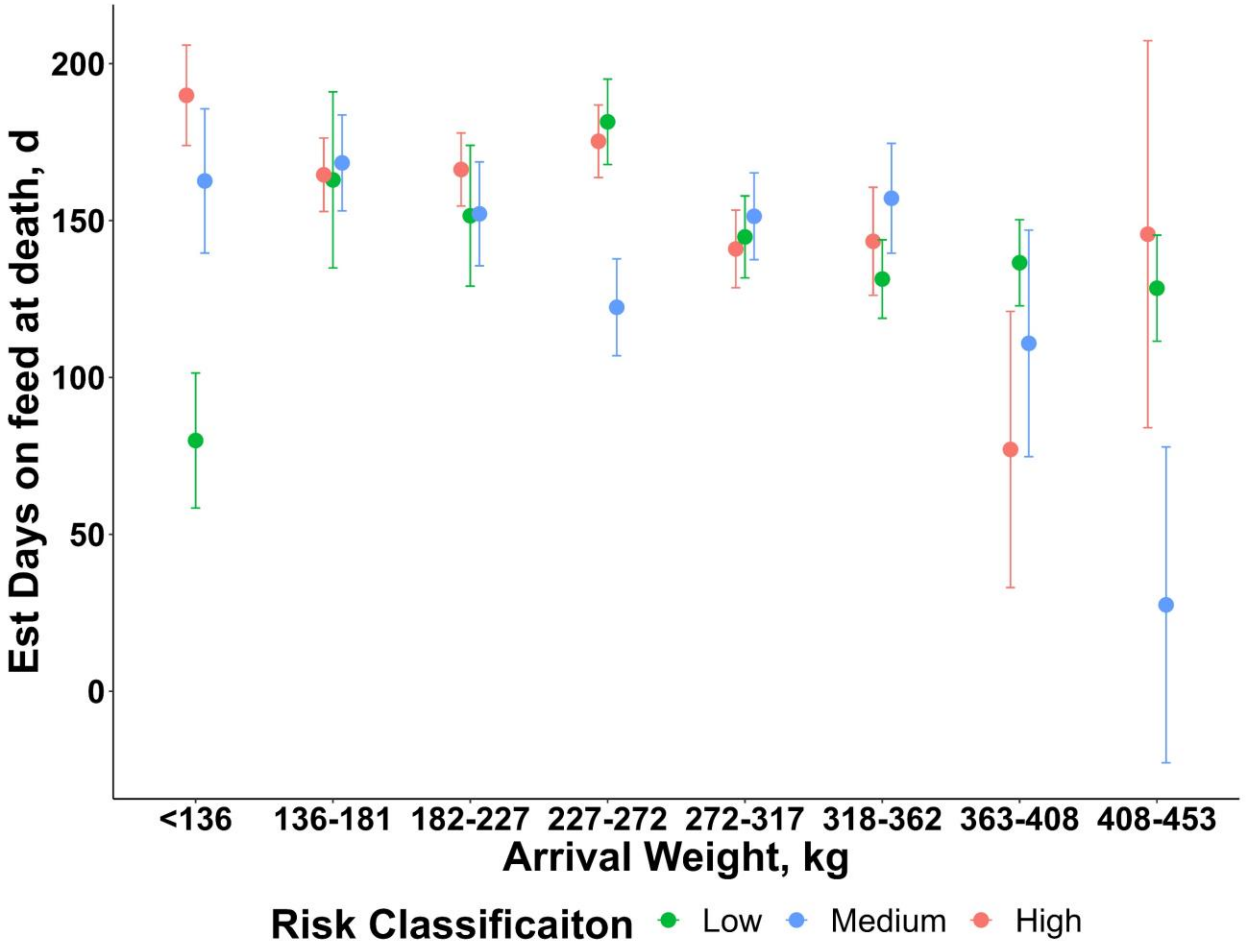

Figure 4.9 Model estimated timing and SE for right heart failure (RHF) by arrival weight category influenced by bovine respiratory disease (BRD) risk classification of cattle from 13 U.S. and Canadian feedlots. Model estimates adjusted for sex, cattle class, breed and BRD treatment categories.

Chapter 5 - An evaluation of temporal distributions of high, low, and zero cohort morbidity of cumulative first treatment bovine respiratory disease and their associations with demographic, health, performance outcomes in US feedlot cattle

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Abstract

Timing and magnitude of bovine respiratory disease (BRD) has the potential to impact intervention and overall economics of cattle on feed. Currently there is a need to better describe when cattle are being treated for BRD. The current study consisted of two study objectives. The first objective was to compute a cluster analysis on the temporal distributions of cumulative first treatment BRD from HIGH (≥ 15% of cattle received treated for BRD) and LOW cohorts (< 15% of cattle received treated for BRD) to assess cohort-level timing (days on feed) of BRD first treatments. The second study objective was to determine potential associations among cluster groups (temporal patterns) and demographic risk factors (arrival characteristics), health outcomes (morbidity, mortality, and railing rate) and performance (ADG). Data were collected

from 10 US commercial feedlot operations from January 02, 2019 through December 15, 2021 located in the central US. Data included a total of 7,735 cohorts representing 1,016,873 feedlot cattle with 66.1% heifers and 33.9% steers. Cohorts were grouped based on the number of total first BRD treatments per cattle received and divided into HIGH (≥15%), LOW (<15%) or ZERO (0%) cohort morbidity. Hierarchical cluster analyses were performed on both HIGH and LOW groups based on cohort-level cumulative timing of first treatment BRD. Cluster groups were optimally generated for HIGH (n = 6; named H1 through H6), and LOW (n = 7; named L1 through L7) morbidity groups. Cohorts with ZERO BRD morbidity were added for descriptive and statistical comparisons. Univariate and multivariate mixed model analyses were performed evaluating relationships between clustering groups and cohort demographics, health, and performance outcomes. Descriptive statistics (univariate) were performed on cohort arrival demographics of clustering group, which included the following: cattle received, shrink, probability of being steer, and average cohort arrival weight. Multivariate analyses included average daily gain, BRD morbidity, total death loss, rails (cattle removed from the cohort prior to finish date), and days to 50% cohort BRD morbidity. Feedlot was included as random intercept for all analyses. Data illustrated all demographic factors evaluated were associated with clustering group ($P < 0.01$). Total death loss was greater in HIGH groups H1 through H5 compared to LOW and ZERO groups ($P < 0.01$). Groups L7 and ZERO had the lowest estimated total death loss at 1.64 and 0.93 (SE = 0.32 and 0.27) respectively. Cluster H1 had the greatest estimated death lost at 4.19% (SE = 0.26) compared to all other clusters except H2 (4.15, SE = 0.25). Cattle in HIGH (H1 through H5) had greater estimated rail risk compared to cattle in LOW ($P < 0.01$). Cluster H1 had the highest estimated rate for rails at 11.9 (SE = 3.3) cattle per 1,000 cattle received however was no different than H2 or H3. Cattle in ZERO cluster had the

lowest estimated rate of rails at 1.8 (SE = 0.65). However, was no different that cattle in group L7 (2.8, SE = 1.0). Days on feed to 50% cumulative BRD were different between all clustering groups ($P < 0.05$). Cluster H6, L5, L6, and L6 treated half of their respective BRD first treatments by days 59.8, 61.2, 60.6, and 109.8 days on feed, respectively, with the remaining clusters treating half of their total first BRD treatments by day 44 on feed These data could be used as a tool for earlier identification and potential interventions for cohorts with later days on feed BRD treatments. However, more research is needed to evaluate and predict which cohorts will follow similar distributions.

Key Words: Feedlot, Bovine Respiratory Disease, Cluster Analysis, Epidemiology

Introduction

Bovine respiratory disease (BRD) has remained the most economically important disease in feedlot cattle for over the past half century (Johnson and Pendell, 2017). The level of BRD morbidity and mortality has not dramatically decreased even with the currently available antimicrobial therapies and management strategies (USDA, 2013). There is growing concern cattle are exhibiting increased number of treatments for BRD later in their respective feeding period. Bovine respiratory disease affects cattle typically within the first 30 to 35 days on feed. However, many changes from economic to genetic have impacted how cattle are fed and the duration of their respective time at a feedlot. Cattle that have late-day feeding BRD carry the potential of an increased risk of death due to late-day BRD, which incurs larger financial burden (feed, cost of treatment, yardage, and interest) compared to the same animal experiencing early onset BRD at the feedlot.

The timing of cumulative first BRD treatments have been previously reported and analyzed (Babcock et al., 2010). However, there are gaps in knowledge of potential differences

in BRD temporal patterns based on overall magnitude of BRD within a cohort. A better understanding of the timing and magnitude of BRD within cohorts along with the association of risk factors could provide economic advantages for producers through decreased health problems and increased performance. In consideration of these goals, two study objectives were developed. The first objective was to compute two cluster analyses on the distributions of cumulative first treatment BRD, one on HIGH (≥ 15% of cattle received treated for BRD) and one on LOW cohorts (< 15% of cattle received treated for BRD) based timing of BRD treatments occur (days on feed). The second study objective was to determine potential associations among cluster groups (temporal patterns) and demographic risk factors (arrival characteristics), health outcomes (morbidity, mortality, and railing rate) and performance (ADG).

Materials and Methods

Animal Care and Use Committee approval was not obtained for this study due to retrospective commercial data being obtained from privatized databases.

Data from 10 commercial feedlots located in the central US were utilized in the current study. Study data encompassed cattle placed on feed from January 02, 2019, to December 15, 2021. Individual treatment and cohort data were downloaded from privatized commercial feedlot software into R® studio (Team, 2021) for data wrangling, cleaning, and analysis. The current study used a case definition of a cohort defined as a group of cattle purchased within a similar timeframe and managed similarly to a common endpoint but not necessarily fed in the same pen throughout their feeding period. For the purposes of this study, a BRD treatment was defined as cattle that were identified with clinical BRD and treated with an antimicrobial. The association analysis included cohorts with no or zero BRD treatments. However, cohorts with zero BRD

treatments were not included in the temporal distribution cluster analysis since groups were clustered by their timing of first treatment BRD.

Data management: variable creation

A new variable was created using yard identification, lot identification number, pen, and arrival year to a unique identification number "uid2" to tie individual treatment records to the cohort level data. For individual record data, a new variable was created to represent days on feed at event by taking the event date (treatment date) less the arrival date (days on feed = event date – arrival date). Variables were created for cohort level data that represented total number of BRD treatments within each cohort both as a number and as a percent of cattle received. Another variable was created that grouped individual animal treatment data to cumulative daily cohort BRD treatments, expressed as percent of cattle received "cumulative BRD percent". A variable was created to represent the cohorts timing to 50% BRD treatments by taking individual BRD treatment records and determining the days on feed at which 50% of cumulative BRD treatments were reached. A variable for arrival quarter "in_qrt" was created by taking the month of arrival and categorizing into 1 (January through March), 2 (April through June), 3 (July through September), or 4 (October through December). Shrink was calculated by taking average cohort payweight less average cohort arrival weight and dividing by payweight then multiplying by 100 to get percentage, (shrink, % = ((payweight – arrival weight)/payweight) *100). Performance variables were created from cohort closeout. Only animals that shipped for harvest were used in the performance variable calculations (deads out). A variable for average daily gain (ADG) were created from the difference between average cohort shipping weight (deads out) and average cohort arrival weight divided by number of days on feed (DOF) (ADG = (shipping weight – arrival weight)/ DOF).

Cluster Analysis:

Individual animal treatment records from the defined study period were obtained for each cohort included in potential cluster analysis. The cluster analysis only utilized cohorts with pen morbidity of ≤ 100 percent first treatment. The raw data had two cohorts with > 100 percent pen morbidity, which were removed from analysis. Cohorts were split into HIGH BRD morbidity (total cohort first treatment BRD ≥ 15% of cattle received), LOW BRD morbidity (total cohort first treatment BRD < 15% of cattle received), or ZERO BRD morbidity (no BRD treated cattle) depending on their respective cumulative BRD morbidity.

Two cluster analyses were performed, one for HIGH and one for LOW morbidity groups; no cluster analysis was performed on BRD timing for the ZERO morbidity group as there were no treatments. Individual first treatment BRD data were aggregated to daily cohort level cumulative BRD morbidity (percent BRD treatments per cattle received) data for cluster analysis. Cohorts were clustered on temporal distributions (days on feed) of cumulative BRD treatments, expressed as a percent ((cumulative BRD treatments / initial cattle received) *100) using the hclust function from the stats package in R (R Core Team, 2022). Cluster distancing was performed utilizing the "ward.D" method (Ward, 1963). Clustering groups were evaluated similar to (Babcock et al., 2010). In short, computed cluster height were plotted by creating an elbow plot in ggplot2 (Wickham, 2016). These graphical figures plot cluster height against the successive number of clusters to determine the step (cluster) at which further reduction resulted in a substantial increase in relative change of height values. Optimal cluster groups were determined when relative change in height values were first minimized.

Descriptive statistics and association analysis

Descriptive statistics were computed for each clustering group within HIGH and LOW and the group containing ZERO BRD treatments ("0"). For each cluster a mean, standard deviation and range were computed using cohort performance and individual health data. Medians were calculated for cohort BRD morbidity and timing to 50% BRD treatment days on feed. Frequency tables were created for non-continuous data.

Average cohort arrival weight was categorized into seven 45.5kg categories ("181kg to 226kg", "227kg to 272kg", "272.1kg to 317kg", "318kg to 362kg", "363kg to 408kg", "408kg to 453kg", "454kg to 498kg") to avoid lack of model convergence. Clustering groups were concatenated into one factor with 13 levels and ZERO (H1, H2, H3, H4, H5, H6, L1, L2, L3, L4, L5, L6, L7 and 0) for the statistical analysis.

Association analyses were performed in R (R Core Team, 2021) using the lmer4 package (Bates et al., 2015). Linear and logistic regression mixed models were created to compare the association of arrival characteristics and performance characteristics to clustering groups. Descriptive statistics were created to determine association of shrink, cohort size (number of cattle received), at arrival with clustering group. Multivariate models were created to determine association of clustering groups with performance (average daily gain) and health (total death loss percentage, BRD morbidity, total head railed (cattle removed from a cohort prior to the cohort's shipment date), and days to 50% BRD treatments) factors. Covariates used in each multivariate model included arrival weight class category, arrival quarter, and sex. The BRD morbidity model also included average daily gain as a covariate. All continuous outcomes were assessed for linearity. Any outcomes that were identified as non-linear were transformed either by taking the log or square root of the outcome and assessed for overall fit for final model. The

best fit model from transformed data is reported in the results. All models were built by using backwards eliminations technique (Dohoo, 2012). Any of the above covariates that were not significant ($P > 0.05$) were removed from the final model. Multivariate models were assessed for collinearity utilizing the "performance" package "check_collinearity" function in R (Lüdecke et al., 2021). No variables were identified as being colinear.

Feedlot was used as random intercepts to account for hierarchical data structure and lack of independence of lot within feedlot for both descriptive and multivariate analysis. Model comparisons were created using the emmeans package (Lenth, 2022) using a Tukey Kramer adjustment for multiple comparisons. Model predictions were weighted by cells using method = "cells" in emmeans. Models which required outcomes to be transformed to meet the assumption of linearity were back transformed within the model estimates in the *post hoc* comparisons using emmeans. A significance of $P < 0.05$ was determined *a priori.*

Results

The final data set used to model demographic and risk associations and cluster analyses contained 7,735 cohorts representing 1,016,873 fed cattle. There were 66.1% heifers and 33.9% steers. Average cohort arrival weight was 343kg and range from 182kg to 497kg. Number of cattle received per cohort averaged 132 cattle and ranged from 40 to 892 cattle per cohort. Average cohort overall death loss was 1.32% and ranged from 0% to 43.1% across enrolled cohorts. The average feeding length (DOF) per cohort was 157 days and ranged from 60 days to 350 days. On average cohorts had a 2.1% shrink, however ranged from -94.87% to 25.1%. There were 950 cohorts with negative shrink with two cohorts reporting a shrink less than -10%. A negative shrink percentage indicates an average cohort weight gain from purchase to arrival at feedlot in the current study. Average days to reach 50% cohort BRD morbidity was 32 days and

ranged from 0 to 197 days on feed. There were 5,903 (76.3%) cohorts in the low morbidity group, 1,597 (20.6%) cohorts in the high morbidity group, and 235 (3.01%) cohorts which reported zero morbidity due to BRD.

Cluster analysis:

Results from the cluster analysis found that optimal number of clustering groups for HIGH morbidity were 6 clusters and LOW morbidity cohorts were 7 clusters. For the LOW clustering groups increasing from 7 to 8 indicated little distances between clusters and reducing from 7 to 6 clustering groups resulted in dramatic curve changes which is suggestive of a combination of two dissimilar clusters (Babcock et al., 2010; Ward, 1963). Figure 5.1 and Figure 5.2 show the distance (y axis) versus number of cluster groupings (x axis). Distance between clustering groups indicates dissimilarity, the greater number of groups that are clustered together the smaller the distance between groups, indicating little difference between groups. For the remainder of this study HIGH was divided into H1 through H6 and LOW is divided into L1 through L7 to represent their respective clustering group. Table 5-1 shows the frequency and distribution of cohorts within clustering groups and by factors of interest.

Risk association analysis

The association of cohort demographic risk factors with clustering group is reported in Table 5-2 and Table 5-3. The number of cattle received was also found to be associated with clustering groups ($P < 0.01$). No differences were found within HIGH clusters among estimated head received. Cohorts in Zero had the lowest estimated cattle received per cohort at 93 (SE = 8.22). Cohorts in L2 had estimated cattle received per cohort of 145 (SE = 7.31) which were greater than all of HIGH, Zero, and L1, and L7.

Shrink was found to be associated with clustering group ($P < 0.01$). Clusters in LOW (L1 through L7) had a smaller estimated arrival shrink compared to cohorts in HIGH (H1 through H5). Cohorts in ZERO cluster had the lowest shrink loss at 1.24% (SE = 0.39). However, were no different than cattle in H6, L5, and L7. Shrink was greatest for cohorts placed in H1(3.65, SE = 0.32) but different compared to H6 (2.12, SE = 0.31) within the HIGH group as well as different compared to LOW and ZERO.

Arrival weight was found to be associated with clustering groups ($P < 0.01$). Cohorts in HIGH had lower arrival weights compared to cohorts in LOW or ZERO. Cohorts in H4 and H6 reported the lowest arrival weight at 295kg and 295kg, respectfully (SE = 8.3 and 8.2). Cohorts in H6 were no different compared to H3 and H1. Cohorts in ZERO reported the heaviest arrival weights at 376kg (SE = 9.1), which was significantly greater than all cohorts except L7.

Finally, the probability of a cohort being steer was associated with clustering group ($P < 0.01$). Cluster L6 had a lower probability 0.27 (SE = 0.03) of being steer compared to H1, H2, L1, and ZERO (0.40 and 0.35, 0.35 SE = 0.04, 0.04, 0.3 and 0.04, respectively).

Table 5-3 displays the association analysis of performance and health metrics with clustering groups. Average daily gain (ADG) was associated with clustering group ($P < 0.01$). Cohorts in clusters H1 through H6 had lower reported ADG compared to L2 through L7 and Zero. Cohorts in Zero had the highest ADG at 1.66kg/d (SE = 0.05). Cohorts in H6 had the lowest reported ADG at 1.33kg/d (SE = 0.05) but was no different compared to other cohorts within H1 through H5.

Bovine respiratory disease was associated with clustering group ($P < 0.01$). Cohorts in HIGH (H1 through H6) reported higher estimated BRD compared to cohorts in LOW (L1 through L7) and ZERO. H1 was estimated to have the highest predicted BRD morbidity at

27.25% (SE = 0.82). ZERO has the lowest estimated BRD (0.01, SE = 0.02), which was found to be no different compared to L7 at 2.33% (SE = 0.32).

Total death loss was associated with clustering group ($P < 0.01$) with higher death loss estimated for cohorts in H1 through H5 versus LOW (L1 through L7), H6, and ZERO clustering groups. H1 had the greatest model estimated death loss at 4.19% (SE = 0.26) but was not different compared to H2 (4.15%, SE = 0.25). Cohorts in cluster group ZERO (1.15) were not different from L7 (1.84) but had lower death loss than all other groups. There were no differences in death losses between cohort in cluster groups H6 and all of the LOW cluster groups. Cohorts in ZERO reported the lowest total death loss at 0.93 (SE = 0.27), but was not different compared to L7 (1.64, SE = 0.32).

Clustering group was associated with number of railed cattle ($P < 0.01$). Model estimated rail rates were greater for HIGH (H1 through H6) clusters compared to LOW (L1 through L7) cluster and ZERO. Cluster H2 had the highest estimated railing rate at 13.6 rails per 1,000 head received (SE = 3.7) but was not different compared to H1 and H3 at 11.9 and 11.2 per 1,000 cattle received (SE = 3.3 and 2.7; $P > 0.05$), but greater than all other cohorts. Cohorts in the ZERO clustering group had the lowest number of estimated rails per 1,000 cattle received at 1.8 (SE = 0.5; $P < 0.05$), which was no different that L7 clustering group at 2.8 cattle per 1,000 cattle received (SE = 1.0). L1 and L6 reported lower estimated railing rates compared to L2 (4.0 and 3.6 cattle per 1,000 cattle received (SE = 1.1 and 1, respectively) versus 5.1 cattle per 1,000 cattle received, SE = 1.4, respectively).

Days to 50% cohort morbidity was found to be associated with cluster group ($P < 0.01$). There were differences between HIGH and LOW clusters and within HIGH and LOW clusters. Cohorts in H6, L5, L6, and L7 had estimated days to 50% cohort BRD at 59.8 (SE = 1.77), 61.2

(SE = 0.82), 60.6 (SE = 0.63) and 109.8 (SE = 2.19), respectively. These clusters were much later compared to H1 through H5 and L1 through L4.

Discussion

These data identified BRD temporal patters at two levels of cohort morbidity (HIGH ≥15% and LOW <15%). In addition, these data showed several important risk factors associated with clustering group such as shrink, number of cattle received, and sex. Performance and health metrics were also found to be associated with clustering group when adjusting for other factors such as ADG, BRD morbidity, death loss, and rail cattle. The creation of these temporal distributions and model estimates may lead to future research to aid in the ability to predict when cohorts would likely experience BRD.

Hierarchical clustering methods have been previously employed to describe temporal patters of BRD in feedlot cattle (Babcock et al., 2010). One of the weaknesses of the previously described temporal patterns was the inability to relate the magnitude of BRD of a cohort within its temporal distribution pattern. Babcock et al. (2010) reported that assessing both the timing and magnitude of disease lead to clusters being driven almost exclusively on magnitude of disease. Authors of the current study also experienced the previously stated conundrum as a major obstacle. Efforts to address this obstacle led authors to cluster feedlot cohorts into HIGH or LOW BRD to better stratify the magnitude of BRD within temporal distributions. The current study set a threshold of 15% to distinguish cohorts that were categorized as HIGH or LOW similar to previous research (Rojas et al., 2022).

Babcock et al. (2010) reported seven clusters optimally fit their study data, and the current study found seven clusters were optimal in LOW with six optimal in HIGH. The major difference between the two studies was accounting for BRD magnitude. The current study

partitioned BRD morbidity into two groups, which produced 13 different levels of groupings for clustering on the timing of BRD and one level of 0 (ZERO) BRD morbidity.

For arrival demographic associations with clustering group, the current study analyzed cohort size (number of cattle received), shrink, arrival weight, and sex in univariate analyses with cohort clusters. LOW (L1 through L7) clusters were estimated to have greater cohort sizes with greater average number of cattle received but this was not the case for ZERO cohort sizes. Model estimated average cohort size for cattle in ZERO grouping were 93 cattle, which resulted in the lowest estimated average cohort size overall but not different from L7 or H6. This could be due groups of local, ranch direct cattle kept in a similar cohort, since ZERO also reported a low estimated shrink (1.24%, SE = 0.39). The ZERO may have been comprised of cohorts backgrounded or managed differently prior to entering the feedyard and older due to a higher arrival weight 376kg (SE = 9.1kg).

Shrink was lowest in cohorts reporting no BRD morbidities (ZERO) and highest in HIGH (H1 through H5) cluster groups. Previous research reported that cattle with greater shrink (body weight loss from purchase to feedlot arrival) had greater BRD morbidity risk as well as lower body weights (Cernicchiaro et al., 2012). The authors suggested this was likely due to the stress incurred during transport and distance traveled.

Arrival weights were estimated to be heavier for cohort in L1 through L7 clusters or ZERO compared to cohorts in HIGH clusters, and cohorts with ZERO morbidity had the largest estimated average arrival weight compared to all other clusters except L7. Clusters in H1 though H6 had lowest estimated average cohort arrival weight compared to LOW and zero clusters. In a literature review on the epidemiology of BRD, Taylor et al. (2010) reported several studies that associated lower body weights with higher BRD morbidity, which was also consistent in other

previous literature (Babcock et al., 2010; Cernicchiaro et al., 2012; Babcock et al., 2013). Thus, the HIGH clusters have overall lower weights and carry higher risk for BRD morbidity. However, the cluster that reported the lowest estimated arrival weight was not the cluster with the highest reported BRD morbidity (H4 = lowest estimated average cohort arrival weight. This was significantly different compared to H1, which highest estimated cohort BRD morbidity significantly different compared to H4). The timing to 50% BRD was different between the two clusters (H1 = 10.1 days on feed to 50% cohort BRD vs. H4 = 40 days on feed to 50% cohort BRD). Differences in BRD magnitude and timing between the H1 and H4 groups could be different pathogens, or backgrounding methods (vaccination status, nutritional status, etc.) none of which could be controlled for in the current study.

Model estimates for ADG reported that LOW L2, L3, L4, L6, and ZERO outperformed all the HIGH clusters (H1 through H6). This is consistent with other research reporting ADG was negatively associated with BRD. The decreased performance was hypothesized that that the cause was presumably due to anorexia and inflammation (Cusack et al., 2007).

Estimates for average cluster morbidity showed variation within HIGH and LOW clustering groups. Data were split by cohort morbidity, thus differences between HIGH and LOW were to be expected. However, the variation within each HIGH and LOW clustering groups is interesting because it could suggest that the timing of BRD treatments could potentially be related to the amount of BRD a cohort experiences. HIGH groups that were clustered in H4, H5, H6 reported estimates that were after 30 days for >50% of their BRD compared to H1, H2, and H3 which experienced 50% of their BRD by 22 days on feed. Potential reasons for the reported differences in timing to 50% disease could be the pathogen causing disease such as viral vs. bacterial. However, literature on the timing of clinical disease from observational research

appears to be limited. Experimentally induced disease typically appears clinically sooner than 21 days for both viral and bacterial agents (Grissett et al., 2015).

Differences in cohort level morbidity could be associated with the amount of stress from transport if shrink is considered a measurable metric of stress due to transport. Clusters H1 through H3 had higher numerically estimated shrink compared to H4 through H6. Total death loss was found to follow similar patterns as BRD. The amount of death loss attributed to BRD has previously been reported to range from 41% to 52% of the dead population (Smith, 1998). Since morbidity of BRD follows similar death loss patterns it is likely that most death loss is driven by BRD. Total death loss was lower for cohorts in LOW (L1 though L7) and ZERO compared to HIGH (H1 through H5), except for H6 which was no different than LOW but greater than ZERO. Death loss was no different in the LOW groups, however, ZERO BRD morbidity demonstrated the lowest death loss, which was different from L1 through L6 but no different than L7. Thus, it would appear with greater shrink came greater amount of BRD with earlier days on feed.

Railing rate estimates appear to be higher in HIGH (H1 through H6) vs. LOW (L1 through L7) and HIGH (H1 through H6) vs. ZERO pattern. The rates for railing cattle do not follow the same patters as BRD morbidity or death loss. Thus, cattle are being railed likely for other diseases outside BRD, such as lameness/muscular-skeletal, which was reported in previous research (Horton et al., 2021). Cattle in low clustering groups were estimated to have fewer cattle railed (per 1,000 cattle received) compared to HIGH cluster groups. These data reported that rates differed more in cohorts that were within the HIGH clusters, with cluster H2 having the highest rail rate. In addition, differences in railing rates were reported in estimates within the LOW cluster groups. Babcock et al. (2013) used a multivariate model to describe risk for culling

and mortality and reported a higher risk for cohorts with lower arrival weights. This was also found consistent with the current study whereas arrival weights with HIGH having lower estimated arrival weight vs LOW and ZERO. ZERO had the heaviest average cohort arrival weight of 376kg (SE=9.1).

Model estimated DOF to 50% cumulative BRD first treatments drastically differed between HIGH and LOW clusters and notably within respective clusters. Four cluster groups stand out in this analysis: H6, L5, L6, and L7 which were estimated to hit 50% of their first BRD treatment by d 59.8, 61.2, 60.6 and 109.8, respectively on feed. These clusters would be considered much later from industry normal. Babcock et al. (2009) reported that 74% of BRD cases occurred within the first 42 days on feed, which many of the cluster groups achieved. However, a few clustering groups were outside 42 days on feed, which could be a relation to what industry is describing for mid to late-day BRD (Smith et al., 2022; Theurer et al., 2021). The LOW clusters had overall lower morbidity which means even regardless of timing, fewer cattle were treated. Thus, when comparing the percentages of cattle treated one must consider the total number of cattle treated (denominator) relative to timing of treatments.

In consideration of study, these data are retrospective and observational which carry a greater inherent risk of bias (Dohoo, 2014). Caution should be used when generalizing these data to other populations not like the current study population. Furthermore, the study population contained a higher-than-average heifer population compared to most feedlot operations. Operational data are known to be susceptible to confounding (Theurer et al., 2015). Measures were taken to remove incomplete or missing data. Risk factor inclusions were limited to available data. Other important risk factors such as previous location/distance travel, genetics,

number of intact males in steer cohorts, weather, and carcass performance were not included in the current analysis as with previous research (Taylor et al., 2010).

In consideration of the current study, the objective was to describe when BRD occurred during the feeding period while incorporating the magnitude of cohort morbidity from the study population. Previous work (Babcock et al., 2010) utilized a technique to limit the evaluation period to 100 days after arrival resulting in all cohorts with cattle at risk for each day in the study. A limitation of the current work is the evaluation period (up to 275 days) included days when cohorts were not at risk for additional BRD treatments as they had been sold. The study objective was to determine temporal risk patterns during the entire feeding period; thus, an evaluation of the entire period was selected. After cattle left the facility their number of BRD treatments did not change (increase or decrease). Thus, these data were modeled to strictly evaluate the days on feed of when a cohort's first treatment BRD occurred.

Moreover, the clustering technique required a creation of artificial days on feed for some cohorts to create a similar days on feed for the cluster analysis. For example, a cohort could have been on feed 100 days then sent to harvest whereas a different cohort could have been on feed for 210 days then sent to harvest. These two cohorts have different risk periods for treatment of BRD, cohort 1 could have only had BRD treatments up to 100 days on feed whereas cohort 2 could have had BRD treatments up to 210 days on feed. To analyze the two cohorts 110 days of 100% BRD would need to be created for cohort 1 to perform a cluster analysis between the two. This inherently creates an artificial risk period for cohort 1. However, one could argue that after 100% of BRD treatments have occurred and cattle are no longer at risk for BRD, due to being sent to harvest, any artificial days on feed past 100 should not matter due to the cattle have experienced all the BRD they were physically allowed. On the contrary, one could argue that the

artificial risk period could misconstrued cohorts that have later BRD treatments on days on feed, placing them in clusters where the later day BRD are potentially misrepresented due to their dissimilarity (Euclidean distance between days). Both arguments were discussed and weighed against research objective and authors elected to perform the cluster analysis as presented, with creation of artificial days on feed to accomplish the research objective.

Conclusions

By splitting the data in HIGH and LOW morbidity groups we were able to show different temporal patterns of cumulative first treatment BRD while giving some reference to the magnitude of BRD within the cohorts represented in their respective cluster. The descriptive and statistical associations of risk factors for each cluster better describes the cattle represented within each cluster. These data have potentially identified and described clusters that could fit the industries concern of late-day BRD. Three of the clusters are in the LOW morbidity group with one in the HIGH (L5, L6, L7 and H6). Cohorts never treated for BRD had the lowest shrink, lowest number of railed cattle, heaviest average cohort arrival weight, and reported no BRD treatments in the raw data. More research is needed to understand the potential economic impact each cluster has on feedlot production. In addition, these data could be used in predictive modeling, whereas if one could predict a cohorts timing and magnitude of BRD one could potentially identify interventions to mitigate disease burden and economic impacts.

Declarations

Authors disclose no conflicts of interest for this study.

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Table 5-1 Descriptive statistics of HIGH, LOW, and ZERO cumulative bovine respiratory disease morbidity clusters and risk factors. Data from 10 US commercial feedlots were used to analyze hierarchical clustering of cumulative distributions of first treatment BRD in HIGH (≥ 15%) LOW (<15%) or ZERO (0%) cohorts.

	High						Low							Zero
Cluster Class	**H1**	**H2**	**H3**	**H4**	**H5**	**H6**	**L1**	**L2**	**L3**	**L4**	**L5**	**L6**	**L7**	**0**
Lots (n)	352	437	246	225	267	70	1163	1428	734	1392	385	717	84	235
heifers	201	278	160	155	164	42	696	897	471	857	232	503	58	120
steers	151	159	86	70	103	28	467	531	263	535	153	214	26	115
Average Arrival Wt, kg	318	316	312	303	322	305	347	341	351	349	337	345	364	387
SD	49	47	42	45	41	48	51	44	43	44	45	47	38	42
Average Shrink	3.49	3.16	3.21	3	2.86	1.76	2.05	2	2	1.92	1.32	1.54	1.39	1.04
SD	2.72	2.33	2.32	2.57	2.18	2.21	2.46	2.43	2.48	3.64	2.81	2.47	2.38	2.28
Average number Cattle received	111	116	119	120	117	105	130	145	133	139	138	139	117	84
SD	49	54	48	47	52	46	77	65	63	72	59	64	56	34
Received Cattle														
< 75 cattle	109	129	56	50	80	19	342	273	187	296	65	147	29	135
76 to 129	122	136	90	76	72	31	317	339	187	371	115	204	28	70
130 to 167	76	97	63	57	66	13	213	304	144	285	82	142	11	20
>167	45	75	37	42	49	7	291	512	216	440	123	224	16	10
Arrival Quarter														
Quarter 1	71	99	61	63	87	17	331	351	193	326	118	175	30	54
Quarter 2	37	90	54	60	78	24	228	433	244	394	123	238	24	60
Quarter 3	88	92	64	62	60	19	329	385	215	456	68	200	18	73

Quarter 4	156	156	67	40	42	10	275	259	82	216	76	104	12	48
Average Death Loss, %	4.17	4.21	2.93	2.84	3.06	2.09	1.24	1.44	1.28	1.3	1.38	1.26	1.23	0.51
SD	4.86	4.45	2.28	2.29	2.56	1.57	1.37	1.3	1.34	1.32	1.26	1.21	1.48	0.83
Average Morbidity	31.03	27.86	24.15	22.05	25.3	20.25	6.08	6.83	5.69	6.56	5.08	4.89	2.33	0
SD	13.25	11.79	8.39	6.76	9.97	4.79	4.18	3.49	3.76	3.95	2.98	3.3	1.75	0
Average BRD to 50%	9.76	21.57	21.25	40.8	34.38	61.33	13.22	31.22	44.37	27.65	64.55	61.79	110.76	0
Median BRD to 50%	10	21	22	41	34	57	13	31	44	28	61	61	109	0
SD	3.52	4.96	7.24	7.91	4.74	19.09	5.92	13.31	7.45	7.65	27.63	14.9	19	0
Mean Railers per cohort	1.78	2.42	1.62	1.56	1.68	0.77	0.64	0.82	0.66	0.78	0.57	0.48	0.25	0.18
Median Railers per cohort	1	1	1	1	1	0	0	0	0	0	0	0	0	0
SD	2.34	7.33	2.15	1.75	1.94	1.14	1.18	1.96	1.24	1.39	1.15	0.88	0.56	0.44
Mean days on feed, DOF	169	157	176	183	171	181	145	162	153	152	168	156	148	137
Median DOF	168	161	173	179	168	178	146	158	151	151	160	151	145	137
SD	37	38	31	33	31	29	32	27	27	26	31	28	25	18
Mean ADG	1.55	1.63	1.69	1.54	1.64	1.44	1.61	1.61	1.58	1.56	1.61	1.62	1.61	1.58
SD	0.84	1.50	1.66	0.65	1.52	0.26	1.85	1.06	0.67	0.50	1.10	0.86	0.49	0.20

Table 5-2 Univariate model estimates of cohort demographics and their association by temporal clustering group. Feedlot data were grouped into High (≥ 15%) or Low (< 15%) BRD cohort morbidity for clustering analysis.

BRD Status	High						Low							Zeros
Cluster	H1	H2	H3	H4	H5	H6	L1	L2	L3	L4	L5	L6	L7	0
Cattle received[6]	114^{b}	119^{b}	121^{bcd}	123^{bcde}	120^{bc}	103^{ab}	134^{cde}	145^{g}	135^{defg}	143^{fg}	137^{cdefg}	137^{efg}	117^{abcde}	93^{a}
SE	7.86	7.71	8.16	8.25	8.07	10.30	7.34	7.31	7.48	7.31	7.81	7.50	9.85	8.22
Shrink, %[7]	3.65^{f}	3.26^{ef}	3.47^{f}	3.08^{ef}	2.96^{ef}	2.13^{abcde}	2.27^{cd}	2.30^{d}	2.24^{bcd}	2.19^{bcd}	1.68^{ab}	1.90^{abc}	1.74^{abcd}	1.24^{a}
SE	0.32	0.30	0.30	0.32	0.32	0.31	0.41	0.28	0.28	0.29	0.28	0.30	0.29	0.39
Arrival weight, lbs	309^{bc}	315^{c}	302^{ab}	295^{a}	312^{bc}	295^{ab}	340^{ef}	333^{d}	341^{fg}	341^{f}	332^{de}	338^{def}	358^{gh}	376^{h}
SE	8.3	8.1	8.0	8.3	8.3	8.2	9.4	7.9	7.9	7.9	7.9	8.1	7.9	9.1
Prob of being Steer[8]	0.40^{b}	0.35^{b}	0.31^{ab}	0.28^{ab}	0.35^{ab}	0.36^{ab}	0.35^{b}	0.33^{ab}	0.32^{ab}	0.35^{ab}	0.35^{ab}	0.27^{a}	0.27^{ab}	0.41^{b}
SE	0.04	0.04	0.04	0.04	0.04	0.06	0.03	0.03	0.03	0.03	0.04	0.03	0.05	0.04

Model estimates for univariate models plus standard error (**SE**) of risk factors and their association with clustering groups. Model means and comparisons were computed using emmeans in R programming with a Tukey Kramer adjustment for multiple comparisons and model estimates weighted using "cells". Significance was set at $\alpha = 0.05$. Data were from 10 US commercial feedlot operations cohorts were dived into high and low morbidity groups on their cohort Bovine Respiratory Disease morbidity. High ≥ 15 % and Low < 15% BRD Morbidity. Zeros (no BRD treatments) were also added as their own group for this analysis.

[6]Cattle Received = Model estimated number of cattle received per clustering group
[7]Shrink = Model estimated shrink (difference in pay-weight from average cohort arrival weight * 100) expressed as percent
[8]Prob of being steer = Model estimated probability of a cohort being steer within clustering group.

Table 5-3 Model estimates of performance and health metrics and their association by temporal clustering group. Feedlot data were grouped into High (≥ 15%) or Low (< 15%) BRD cohort morbidity for clustering analysis.

BRD Status	High						Low							Zeros
Cluster	H1	H2	H3	H4	H5	H6	L1	L2	L3	L4	L5	L6	L7	0
ADG[1]	1.41^{ab}	1.46^{abc}	1.46^{abcd}	1.42^{ab}	1.45^{abc}	1.33^{a}	1.51^{bc}	1.57^{de}	1.58^{e}	1.57^{de}	1.55^{cde}	1.59^{e}	1.63^{cde}	1.66^{e}
SE	0.04	0.04	0.04	0.04	0.04	0.05	0.04	0.04	0.04	0.04	0.04	0.04	0.06	0.05
BRD Morb, %[2]	27.25^{j}	25.37^{i}	21.07^{gh}	19.43^{fg}	22.53^{h}	17.69^{f}	5.73^{d}	6.47^{e}	5.42^{d}	6.29^{e}	4.68^{c}	4.73^{c}	2.33^{b}	0.01 ^{a}
SE	0.82	0.77	0.76	0.74	0.77	0.93	0.34	0.36	0.34	0.36	0.34	0.32	0.32	0.02
Death loss, %[3]	4.19^{e}	4.15^{e}	2.94^{cd}	2.76^{cd}	3.06^{d}	2.08^{bc}	1.53^{b}	1.65^{b}	1.52^{b}	1.54^{b}	1.56^{b}	1.54^{b}	1.64^{ab}	0.93^{a}
SE	0.26	0.25	0.26	0.27	0.26	0.33	0.24	0.24	0.24	0.24	0.24	0.24	0.32	0.27
Rails/Culls[4]	11.9^{gh}	13.6^{h}	11.2^{fhg}	9.9^{fg}	6.6^{f}	7.6^{efg}	4.0^{b}	5.1^{de}	4.2^{bc}	4.4^{bc}	5.3^{cde}	3.6^{b}	2.8^{abcd}	1.8^{a}
SE	3.3	3.7	2.7	2.7	2.6	2.3	1.1	1.4	1.1	1.2	1.5	1.0	1.0	0.5
Days to 50% BRD[5]	9.4^{b}	21.3^{d}	20.5^{d}	40.3^{h}	34.2^{g}	59.8^{j}	12.5^{c}	29.5^{f}	44.0^{i}	27.0^{e}	61.2^{j}	60.6^{j}	109.8^{k}	0.0^{a}
SE	0.33	0.45	0.57	0.84	0.71	1.77	0.24	0.34	0.53	0.33	0.82	0.63	2.19	0

Model estimates for multivariate models plus standard error (**SE**) of risk factors and their association with clustering groups. Model comparisons were computed using emmeans in R programming with a Tukey Kramer adjustment for multiple comparisons. Model predictions are weighted by "cells". Significance was set at $\alpha = 0.05$. Data were from 10 US commercial feedlot operations cohorts were dived into high and low morbidity groups on their cohort Bovine Respiratory Disease morbidity. High ≥ 15 % and Low < 15% BRD Morbidity. Zeros (no BRD treatments) were also added as their own group for this analysis.

Footnotes:
[1]ADG = Model estimated Average Daily Gain (kg/day) = (Ship weight – Arrival weight) / days on feed
[2]BRD Morb = Model estimated cohort Bovine Respiratory Disease morbidity expressed as percentage of cattle received.
[3]Death Loss = Model estimated total death less per cohort expressed as percent of cattle received.
[4]Rails/Culls = Model estimated rails/culls (cattle removed from cohort prior to shipment for harvest) per 1,000 cattle received.
[5]Days to 50% BRD = Model estimated days on feed for a cohort within cluster to reach 50% of their respective BRD first treatments.
[6]Cattle Received = Model estimated number of cattle received per clustering group
[7]Shrink = Model estimated shrink (difference in pay-weight from average cohort arrival weight * 100) expressed as percent
[8]Prob of being steer = Model estimated probability of a cohort being steer within clustering group.

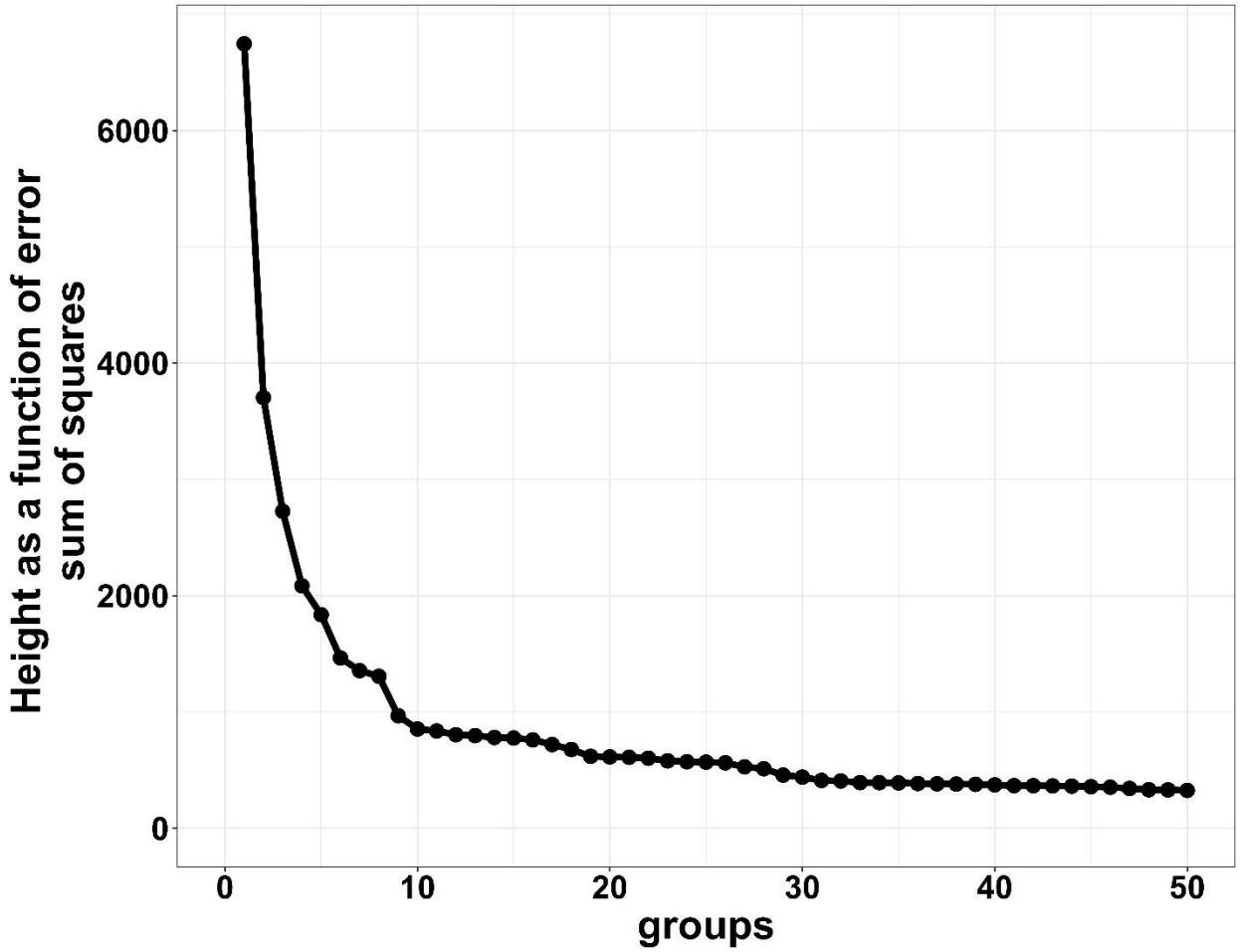

Figure 5.1 Elbow plot of HIGH (≥ 15%) bovine respiratory disease (BRD) morbidity cohorts demonstrating height as a function of error sum of squares for clustering cohorts with bovine respiratory disease from 10 US commercial feedlots. Distance between points is a difference in height of error some of squares. Greater heights are suggestive of larger differences between groups.

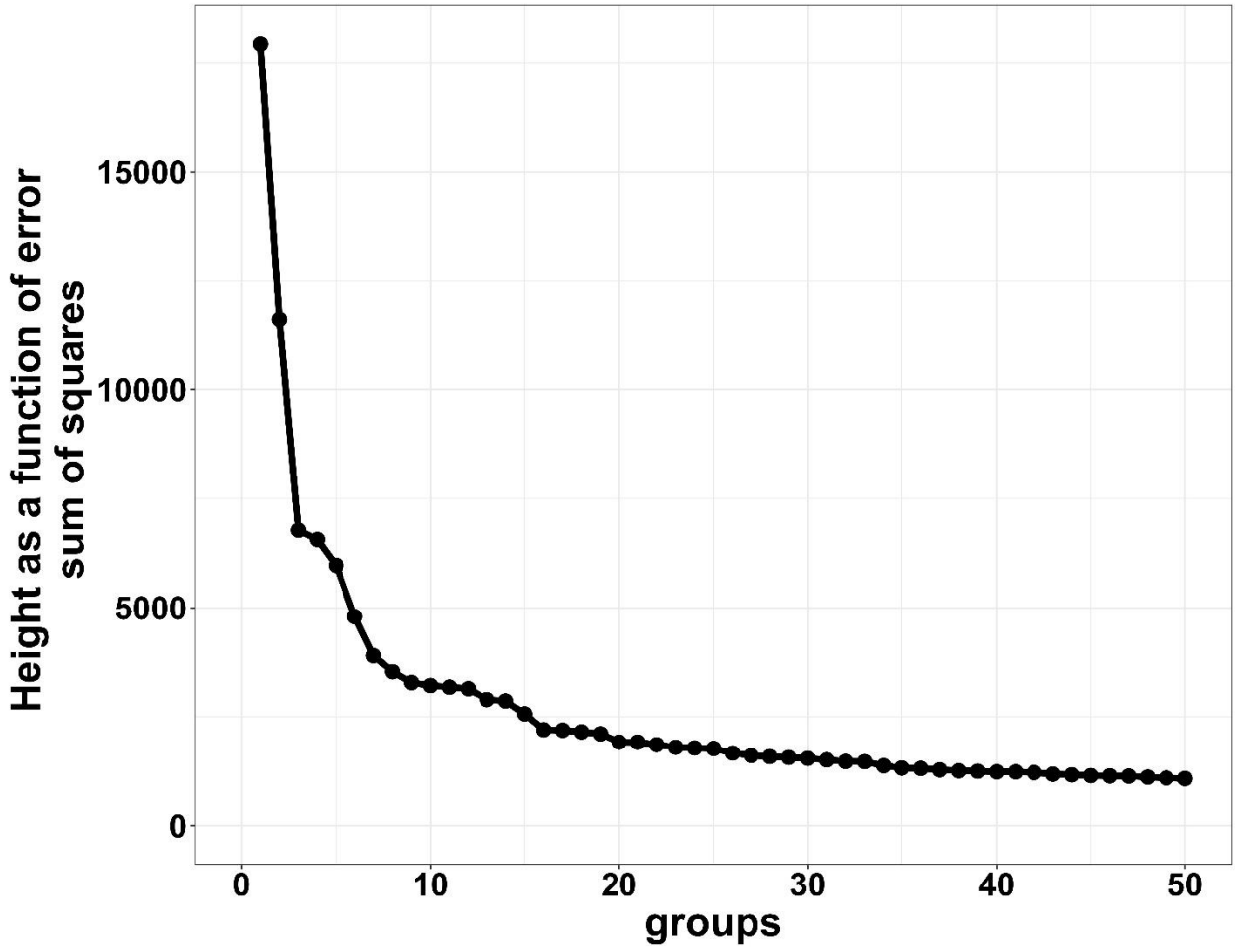

Figure 5.2 Elbow plot of Low (< 15%) bovine respiratory disease (BRD) morbidity cohorts demonstrating height as a function of error sum of squares for clustering cohorts with bovine respiratory disease from 10 US commercial feedlots. Distance between points is a difference in height of error some of squares. Greater heights are suggestive of larger differences between groups.

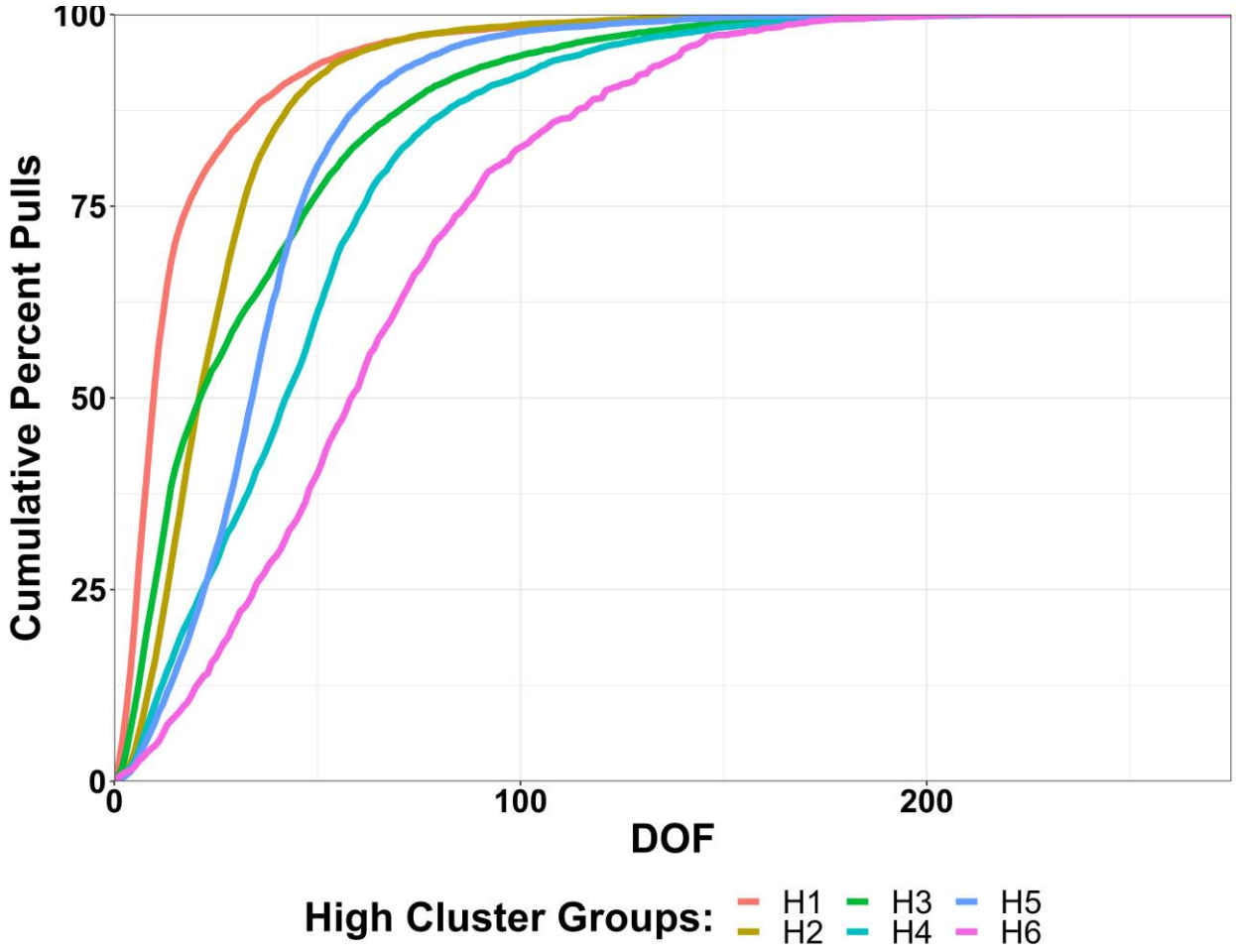

Figure 5.3 Data from 10 US feedlots were used to perform a cluster analysis of cohorts having ≥ 15% bovine respiratory disease (BRD) morbidity based on the cumulative timing, days on feed (DOF).

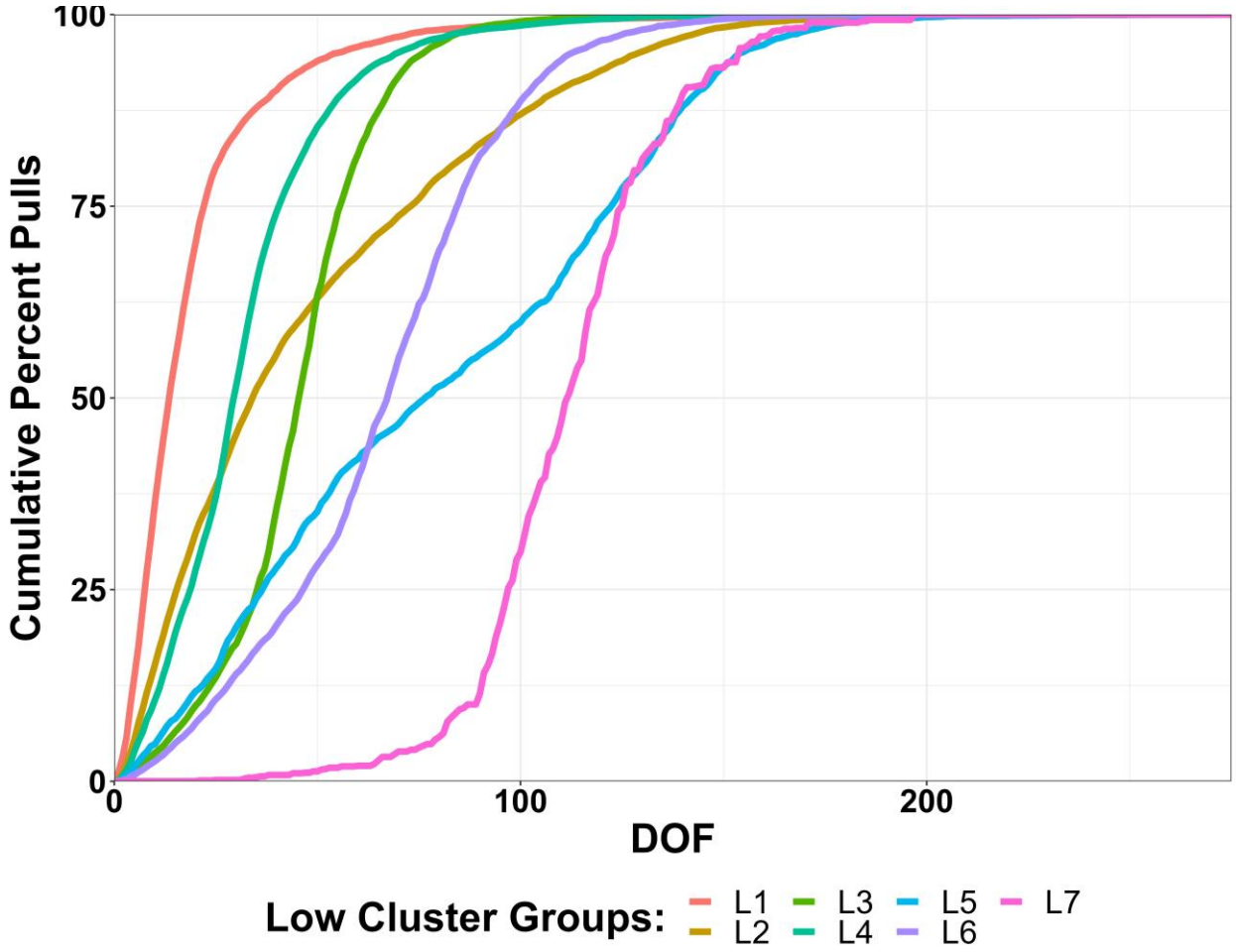

Figure 5.4 Data from 10 US feedlots were used to perform a cluster analysis of cohorts having < 15% bovine respiratory disease (BRD) morbidity based on the cumulative timing, days on feed (DOF).

Chapter 6 - Conclusions and future research

B.T. Johnson

The title of the presented thesis was *Epidemiological evaluations of magnitude and the temporal distributions of feedlot heart disease and bovine respiratory disease*. These research projects focused on feedlot heart disease (HD) and BRD timing and magnitude, and potential associations with risk factors of interest. The first four chapters evaluated heart disease in feedlot cattle. Chapter 1 focused on currently available research pertaining to feedlot HD. Chapter 2 was a retrospective observational study focused on evaluating the risk of a cohort having a HD death during the feeding period as well as the timing of HD deaths that occurred. Chapter 3 was also a retrospective observational study that evaluated potential associations of HD with treatment for BRD and other common feedlot diseases.

The fourth chapter evaluated HD risk using a consistent case definition similar to previously published literature (Neary et al. 2016). The objective was to see if risk of HD was similar using a validated case definition as compared to a grouping to multiple case definitions of HD. In addition, the risk of HD was compared to previously reported risk to determine if risk has changed since 2012. The fifth and concluding chapter focused on evaluating the timing of BRD by clustering first treatment BRD cases from a cohort and describing the cohorts that comprised the clusters, with the goal of taking the knowledge gained and incorporating into predictive models to determine usefulness for producers. Whereas a tool capable of predicting the timing and magnitude of BRD could be used by producers/managers to mitigate the impacts of disease and improve the economic outcome for the producer.

In consideration of data presented on HD, risk of death from HD does not appear to be rising at least from the 2012 data and relatively low compared to other feedlot diseases.

Furthermore, there does not appear to be any direct causal link from a cohort demographic standpoint that could reported from the observational analyses. However, there are promising data investigating the genetic link for causal HD (Heaton et al., 2019; Heaton et al., 2022). There continues to be questions on the amount and risk of HD occurring in late feeding period regardless of the current presented data. Thus, leaving an opportunity to better describe the risk of late day HD and its economic impact in feedlot cattle such as a future prospective cohort study. In addition, many questions have arisen on the association of beta agonists with HD. Here again would be a great opportunity to add to the current knowledge base on HD and address industry concerns. Other research that would add value to the beef industry on HD would be to better understand the impact of subclinical HD on feedlot performance and economics for producers. Currently there is research looking at subclinical heart disease at the packing plants (Heffernan et al., 2020; Kukor et al., 2021), but there appears to be areas of improvement and future research. A particular room for improvement would be on heart score classification. Adding objective measurements to hearts would better scale the disease present and mitigate the discrepancies and potential flaws in previous data analysis. Lastly, there is a lack of research comparing conventional feeding systems to natural and/or organic cattle systems and if the amount of disease within those populations. Data from those populations could provide information if certain practices are influencing the rate of HD as well as some potential for genetic evaluation within those populations.

In consideration of chapter 5, as state before, the goal was to create information on classifying timing and magnitude of BRD to incorporate into a predictive modeling. The predictive model could serve as a production tool for feedlot managers and health professionals to potentially make interventions on BRD if we could predict the timing and magnitude of BRD.

Ultimately, more research is needed in understanding the usefulness of predictive models. Predictive algorithms are highly dependent on the data of which is used to build the algorithms. Currently there is an abundance of data being collected every day which leaves an opportunity to understand use of the collected data different applications. The use of data analytics and computing tools is only to improve as time goes on with more research. Currently there is a demand for precision agriculture, which is what many systems are utilizing to improve efficiency of current systems to meet future demands without compromising current needs (sustainability).

In conclusion, the current research demonstrated an example solving producer/industry concerns by incorporating data science with biology. Future research on incorporating data science and biology appears to be area that could provide the most benefit for beef cattle, or any population, research. Many avenues can be addressed such as sustainability, efficiency, genomic/epigenetics, and profitability by adding more research which incorporates data science and biology.

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