

Liver abscess in feedlot cattle: association with gastrointestinal histopathology, finishing diet composition, and other risk factors

by

Rachel Elena Champagne

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Approved by:

Major Professor
Dr. Phillip A. Lancaster PhD

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Abstract

Liver abscess (LA) is an ongoing issue in feedyard cattle and has served as a crucial topic of research in recent years for several reasons. Dairy-influenced animals have become a greater proportion of slaughtered fed cattle and have an increased prevalence of LA. Additional movements to increase sound antimicrobial stewardship practices when managing LA has increased the need for alternative control methods. As the significance of the LA issue has increased, the need has increased for better understanding of LA as a disease process to develop improved mitigation strategies. The objective of this thesis is to evaluate risk factors and potential pathophysiological associations of liver abscess in feedyard cattle. The first chapter is dedicated to a meta-regression of the current literature to evaluate potential associations of LA with finishing cattle performance, diet ingredient composition, and the digestion rate of dietary starch and neutral detergent fiber (NDF). The second study is an evaluation of feedyard mortalities across the feeding period to determine potential associations of liver abscess with comorbidities, cattle demographics, and gastrointestinal histopathology.

For the first study, a literature search was performed to identify published cattle finishing studies that provided LA prevalence, finishing diet composition, and other dietary and demographic information. After a literature search, 676 treatment groups (TG) were included from 160 different experiments across 121 different publications. Both LA prevalence and severe LA (SLA) prevalence were evaluated across three meta-regression model structures: total LA prevalence relative to the total cattle in TG, SLA prevalence relative to the total cattle with LA in TG, and SLA prevalence relative to the total cattle in TG. Diet-related moderators significantly associated with LA prevalence were grain (% dry matter), starch digestibility (%²/hour), and fibrous byproduct (FB) NDF digestibility (%²/hour). The only diet-related moderator associated

with SLA prevalence relative to the total cattle in TG was grain (% dry matter). The only diet-related moderator significantly associated with SLA prevalence relative to the total cattle with LA in TG was FB NDF digestibility (%²/hour). Overall, grain and fibrous byproduct inclusion rate and digestibility, but no moderators related to roughage ingredients or nutrient digestibility, were associated with LA prevalence and severity.

The second study evaluated findings from gross necropsy and histopathology evaluations of feedyard mortalities to identify factors associated with the presence of LA including cattle demographic factors, and gross and histologic gastrointestinal (GI) morphologic abnormalities. A cross-sectional, observational study was performed via gross necropsies of 935 feedyard cattle mortalities across 6 High Plains feedyards during the months of June and July of two consecutive years. The LA status of each mortality was recorded and samples for GI histopathological evaluation were collected from ventral sac of the rumen, duodenojejunal junction, and spiral colon. Grossly, GI pathology was recorded as either abnormal or normal for the mucosa, serosa, and contents of the rumen, small intestine (SI), and spiral colon (SC). Tissues collected were analyzed to collect multiple histologic measurements of various structures.

Overall, LA prevalence was lower than expected at 5.3%. Liver abscesses were observed in mortalities from across the feeding period, however there was a higher probability of LA if the animal was 100+ days on feed (DOF) compared to less than 50 DOF at death. Dairy-influenced mortalities, steer mortalities, and mortalities with peritoneal adhesions present at necropsy had a higher probability of LA at time of necropsy, though the observational nature of the study prevents any temporal conclusions of causation. Cases with LA had thinner rumen papillae width, reduced rumen papillae keratin thickness, reduced small intestine (SI) crypt depth, or reduced total SI proprial thickness. Although LA occurred at a lower rate than expected in

feedyard mortalities, LA occurred throughout the feeding period and was associated with several demographic factors and with histologic GI morphologic lesions but not with gross abnormalities in the GI tract.

In conclusion, both studies focused on liver abscess as the primary health outcome and sought to better quantify potential associations with concurrent pathologies, comorbidities, demographics, diet, and other risk factors. This thesis has contributed to the body of literature evaluating risk factors and comorbidities of liver abscess in feedyard cattle. By investigating LA disease process from multiple perspectives, at different time points, and both on the macroscopic and microscopic level this work will provide information to fill in knowledge gaps surrounding liver abscess development. Further work is needed to utilize risk factor and disease progression knowledge to develop novel mitigation strategies for LA in feedyard cattle.

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Introduction

The objective of this thesis is to provide more information about the risk factors surrounding liver abscess (LA) related to gastrointestinal health, diet composition in the finishing phase, cattle demographics, and cattle performance. Liver abscesses continue to be a persistent issue in feedlot cattle and can cause losses in performance and at harvest (Nagaraja and Chengappa, 1998; Brown and Lawrence, 2010). Several factors have contributed to the need for more information surrounding LA: the rising prevalence of dairy-influenced animals in feedlot scenarios which have greater propensity to developing LA, increased prevalence of severe LA (SLA) causing greater losses in harvested product and harvest efficiency, and the continued effort to emphasize antimicrobial stewardship (Grimes, 2022). The need for more effective mitigation methods leaves a void of knowledge to be filled.

The first study's objective was to use meta-regression to evaluate associations between finishing diets factors, cattle demographics, LA severity, and LA prevalence in treatment groups (TG) of feedlot cattle. A literature search was conducted to identify published cattle finishing studies that provided LA prevalence, finishing diet composition, and other dietary and demographic information. These data (121 publications; 676 treatment groups (TGs)) were used to perform meta-regressions. Both LA prevalence and severe LA prevalence were evaluated across three meta-regression model structures: total LA prevalence relative to the total cattle in TG, severe LA prevalence relative to the total cattle with LA in TG, and SLA prevalence relative to the total cattle in TG. The goal of this study was to evaluate primarily ration composition on both an ingredient inclusion and nutrient digestibility level to identify potential associations with LA prevalence and severity. LA prevalence was associated with grain (% dry matter) starch digestibility (%²/hr), and fibrous byproduct NDF digestibility (%²/hr). Severe LA relative to the

total cattle with LA in TG was associated with FB NDF digestibility (%²/hr). Severe LA relative to the total cattle in TG was associated with grain (% dry matter). Overall, grain and fibrous byproduct inclusion rate and digestibility, but no moderators related to roughage ingredients, were associated with LA prevalence and severity.

The second study evaluated findings of gross necropsy and gastrointestinal histopathology evaluations of feedyard mortalities to identify factors associated with the presence of LA including cattle demographic factors, and gross and histologic gastrointestinal (GI) morphologic lesions. A cross-sectional, observational study was performed via gross necropsies of 935 feedyard cattle mortalities across 6 High Plains feedyards during the months of June and July of two consecutive years. The LA status of each mortality was recorded and samples for GI histopathological evaluation were collected from ventral sac of the rumen, duodenojejunal junction, and spiral colon. Overall, LA prevalence was lower than expected when compared with current literature. Liver abscesses were observed in mortalities that died across the feeding period, especially those later in the feeding period. Liver abscesses were more likely to be found in mortalities that were dairy-influenced, steers, or mortalities that had abdominal adhesions present at necropsy though the observational nature of this study prevents any conclusions related to causality. Histologically, cases with LA had reduced rumen papillae width, reduced rumen papillae keratin thickness, reduced small intestine (SI) crypt depth, or reduced total SI proprial thickness compared to cases without LA.

Overall, both studies focused on LA as the primary health outcome and sought to identify concurrent pathologies, comorbidities, cattle demographics, diet composition, and other factors. By better understanding associations of these factors with LA prevalence and severity, pathogenesis, and risk factors may be better understood. This work sought to fill in knowledge

gaps in the LA disease complex and utilize novel methods for the evaluation of LA and its risk factors. More research is needed to continue research of risk factors in order to better inform novel mitigation strategies for LA in feedyard cattle.

Chapter 1 - Effect of finishing diet composition on prevalence and severity of liver abscess in feedlot cattle: a meta-regression

Abstract

Liver abscesses (LA) in feedlot cattle raise concerns surrounding performance losses, carcass contamination, and antimicrobial stewardship. Identifying factors associated with LA prevalence and severity (A+ LA score) provides more context on risk factors and intervention efforts. The study objective was to use meta-regression to evaluate associations between finishing diets factors, cattle demographics, LA severity, and LA prevalence in treatment groups (TG) of feedlot cattle. Dataset development via literature review yielded 121 publications (160 experiments; 676 TG; 88,786 cattle) which were fitted to multilevel mixed-effects meta-regression models with random effect of experiment nested in publication. Three models were evaluated: LA relative to the total cattle in TG (LA-TG; n=676 TG), severe LA (SLA) relative to the total cattle with LA in TG (SLA-LA; n=246 TG), and SLA relative to the total cattle in TG (SLA-TG; n=246 TG). All models showed moderate heterogeneity prior to putting moderators into model structures, with I^2 values ranging from 47–62%. Introducing selected moderators reduced heterogeneity by varying amounts depending on outcome (Null model I^2 values: 46.28–63.25% across all models; models with moderators I^2 values: 35.79–52.55% across all models), although considerable variation remained for most outcomes. Egger's regression intercepts were significant across all models, suggesting potential small-study effects or publication bias. In the LA-TG model, predicted LA prevalence was lowered by the inclusion of tylosin (0.13 vs. 0.21) and the inclusion of monensin (0.16 vs. 0.18) ($P<0.001$). Heifers had lower (0.12) prevalence than steer (0.21) or mixed sex TG (0.18) ($P<0.01$). Of the continuous variables, LA prevalence

was positively associated with final weight (0.0001 increase per kg; $P<0.05$), grain inclusion (0.002 per 1% dry matter (DM); $P<0.001$), starch digestibility (0.003 per 1 %²/hour; $P<0.001$), and fibrous byproduct NDF digestibility (0.20 per 1 %²/hour ; $P<0.001$). LA prevalence was negatively associated with gain:feed (-0.58 per 1.0 unit; $P<0.001$). In the SLA-LA model, tylosin lowered predicted prevalence of SLA among LA-affected cattle (0.32 vs. 0.37; $P<0.01$).

Prevalence of SLA was positively associated with final weight (0.001 per kg; $P<0.01$) and negatively associated with initial weight (-0.001 per kg; $P<0.001$) and fibrous byproduct inclusion (-0.003 per 1% DM; $P<0.001$). In the SLA-TG model, tylosin (0.07 vs. 0.10; $P<0.001$) and monensin (0.07 vs. 0.10; $P<0.001$) were associated with lower prevalence of S LA out of all cattle within a TG. Regional differences were also observed: studies performed in Canada (0.05) had lower A+ LA prevalence than the Other (0.10) category ($P<0.01$). Animals on trial diets for <100 days had lower predicted prevalence of S LA (0.04) compared to those on >100 days (0.08–0.15; $P<0.001$). Prevalence of SLA was positively associated with final weight (0.0001 per kg; $P<0.10$). These findings show associations between LA prevalence and severity with feed additives, diet composition, and other factors. By better understanding how diet ingredients and nutrient digestibility are associated with LA prevalence and severity, alternate methods to mitigate LA in feedlot cattle can be identified.

Key Words: Grain, Rate of digestion, NDF, Roughage, Starch

List of Abbreviations:

LA – Liver Abscess(es)

SLA – Severe/A+ liver abscess(es)

GI – Gastrointestinal

TG – Treatment Group

LA-TG – model for LA prevalence out of all animals within TG

SLA-LA – model for severe/A+ LA prevalence out of animals with LA within TG

SLA-TG – model for severe/A+ LA prevalence out of all animals within TG

ADG – Average Daily Gain

G:F – Gain-to-feed ratio

NEg – Net Energy for Gain

DMI – Dry Matter Intake

ADF – Acid Detergent Fiber

NDF – Neutral Detergent Fiber

HCW – Hot Carcass Weight

%DM – Percent Dry Matter

CA – Canada (Region)

MW – Midwest United States (Region)

SW – Southwest United States (Region)

Other – All other regions (excluding CA, MW, SW)

DOED – Days on experimental diet

Initial Weight – Weight at beginning of experimental finishing trial

Final Weight – Body weight at the end of experimental finishing trial

Introduction

Liver abscess (LA) is the most common cause for liver condemnation (61.4% of all liver condemnations) in feedyard cattle with 17.8% of all fed cattle affected (Eastwood et al., 2017). Liver abscesses are a major health concern that can result in significant economic and performance losses. Recent estimates for the total annual costs of LA to the US beef industry range from \$260 million to \$400 million or more (Broadway et al., 2024; Taylor et al., 2025). Even though LA prevalence has remained roughly the same over the years at 12-32% in feedyard cattle (Brink et al., 1990; Nagaraja and Chengappa, 1998; Brown and Lawrence, 2010; Grimes et al., 2024), prevalence of severe LA has been reported to have increased (Nagaraja and Lechtenberg, 2007). Liver scars are assumed to be areas from resolved LA and have been observed at harvest and in newly weaned calves – which calls into question when LA are forming (traditionally, later in the feeding phase while on high concentrate rations), how long it takes them to resolve, and the contribution of high concentrate diets (Broadway et al., 2024). While LA have been an issue in the beef cattle industry for decades, in recent years there has been greater focus on LA impact on the industry, risk factors, and control methods.

Animals with LA have been shown to have reductions in average daily gain (ADG), gain-to-feed ratio (G:F), 12th rib fat thickness, hot carcass weight (HCW), dressing percentage, and LM area (Brink et al., 1990; Brown and Lawrence, 2010; Rezac et al., 2014). Entire liver condemnation due to LA obviously contributes to economic losses; however, a larger cost is attributed to viscera or carcass contamination and potential production delays as LA rupture on the production line at harvest (Brown and Lawrence, 2010). Production and performance losses are more likely with severe LA and particularly with severe LA that are coupled with abdominal adhesions (Broadway et al., 2024). Another reason for increased concern is the greater

proportion of dairy-influenced slaughtered fed cattle since they are more predisposed to developing LA than traditional beef breeds (Amachawadi and Nagaraja, 2016; Grimes et al., 2024; Herrick et al., 2024). As LA prevalence and severity increase, the negative impact on overall revenue within the beef industry is exaggerated through reduced carcass parameters, compromised production efficiency, and shrinking profit margins (Broadway et al., 2024).

The current antimicrobial stewardship climate has encouraged the exploration of alternative methods to the industry-standard control method of incorporating tylosin phosphate in the feed (Nagaraja and Chengappa, 1998; Huebner et al., 2019). Alternative dietary additives such as probiotics or essential oils have been studied, although they have not been as effective as in-feed tylosin (Meyer et al., 2009; Pukrop et al., 2019). Diet alteration has also been explored. However, modifying dietary roughage and starch inclusion rate as well as ingredient processing method has had mixed results on LA prevalence (Zinn and Plascencia, 1996; Reinhardt and Hubbert, 2015). Studies focused on feed management and step up strategies have also showed varied results in effect on LA prevalence (Miller et al., 2012; Schneider et al., 2012; Paterson et al., 2024).

Previous literature suggests ruminal and perhaps other gastrointestinal (GI) lesions are the primary predisposing factor for LA (Nagaraja and Chengappa, 1998). Ruminal acidosis causes rumenitis and increased GI wall permeability for bacteria to translocate into systemic circulation where they are eventually drained from the abdomen to the portal vein and to the liver where they establish abscesses (Nagaraja and Chengappa, 1998; Owens et al., 1998). Typically, rapid fermentation which then leads to acidosis is attributed to grain-heavy diets that are typical in feedyard settings (Nagaraja and Lechtenberg, 2007). While review papers have been published to summarize studies over specific dietary factors or ingredients and their effect on LA, to our

knowledge there has not been a collective analysis on the potential associations between feedstuffs and nutrients with LA during the finishing phase (Reinhardt and Hubbert, 2015; Bryant and Jennings, 2022).

The objective of this study was to analyze previously published studies via meta-regression to identify dietary factors and other risk factors in feedyard cattle associated with LA prevalence and severe LA (SLA) prevalence. We hypothesized various factors in the finishing diet are associated with LA prevalence and severity; specifically, roughage inclusion (percent dry matter basis (%DM)), roughage NDF digestibility, ADF:NDF ratio, and antimicrobial feed additives are negatively associated while grain inclusion (%DM), starch digestibility are positively associated with both LA and SLA prevalence.

Materials and Methods

Ethical Statement

Approval from the Institutional Animal Care and Use Committee (IACUC) was not required as data used for analysis in this study were collected from previously performed trials and no procedures specific to this study were performed on live cattle.

Literature Search

An internet search engine (Google Scholar) was utilized to identify published journal articles, reports, and accepted theses for a meta-regression evaluating the association between finishing diet composition and the prevalence or severity of LA. “Feedyard”, “cattle”, and “liver abscess” were used as search terms. Items had to be published from 1970 to 2025 and were sorted by relevance within the search engine. Title and abstract of publications were initially

screened to establish whether it reported original prospective research data and was related to the finishing phase of beef cattle based on study objective and type. Further evaluation of studies meeting these criteria was performed to evaluate suitability for data extraction.

Inclusion and Exclusion Criteria

Publications were included in the dataset for meta-regression if they 1) were published from 1970 to 2025, 2) reported LA prevalence by treatment for each experiment (if more than one was included in the publication), 3) reported the number of animals included in each treatment for each experiment within the publication, 4) reported diet composition by ingredient inclusion percentage for each treatment within the publication, and 5) was a study that fed diets commonly utilized in a finishing feedyard. Publications were excluded if they were not original research (e.g., reviews, meta-analyses, etc.).

Data Extraction

Each publication was assigned a unique identification number and experiments (for publications that reported more than one trial) within that publication were assigned numbers beginning at 1 to allow for random effect nesting in later analysis. Variables that may have contributed to LA formation and severity were collected for each TG (including all replicates) within experiment. Availability of all variables did not determine eligibility of a treatment in the meta-regression. Information collected for each TG included state or country where the experiment was performed, number of animals, sex, breed, age, average initial weight, average final weight, days on experiment diet (DOED), average daily gain (ADG), average daily dry matter intake (DMI), average gain to feed ratio (G:F), average hot carcass weight (HCW), LA prevalence, LA score prevalence (Elanco Liver Check System (Elanco, Greenfield, IN) or

equivalent definitions), liver scar prevalence, and dietary factors. Dietary factors collected for each TG included: (1) inclusion of tylosin phosphate or monensin, (2) type and inclusion percentage of top two roughage ingredients, (3) type, processing method, and inclusion percentage of the top three grain ingredients, (4) type and inclusion percentage of fibrous byproducts (FB) ingredients, (5) dietary acid detergent fiber (ADF), (6) dietary neutral detergent fiber (NDF), (7) net energy for gain (NEg), and (8) number of feedings per day. Feed ingredients in the diet derived from other industries or as byproducts of production of another feed component (distillers grains, corn gluten feed, beet pulp, etc.) were included as FB. All ingredient inclusion percentages reported on an as fed basis were converted to a dry matter basis prior to entering them into the dataset.

Several new columns were calculated from collected data. A ratio of ADF to NDF was calculated for each TG to serve as a proxy for scratch factor provided in the diet of each TG. A total diet inclusion percentage on a dry matter basis was calculated for roughage, grain, and FB for each TG by summing the inclusion percentages for each ingredient in its respective category. National Research Council (NRC) Nutrient Requirements for Beef Cattle (National Research Council, 2000) were utilized to compile two data points (percent nutrient and nutrient digestion rate) for each ingredient type and processing method. For grains, the percent starch and starch digestion rate (kd CB1) were collected. For roughages and FBs, the percent NDF and NDF digestion rate (kd CB3) were collected. These values were used to create a reference table for each individual feed ingredient which was then used to compute the overall starch and NDF digestibility rate for the diet of each TG (Appendix Tables A.1, A.2).

For each diet ingredient the inclusion percentage, fiber or starch percentage, and starch or NDF digestibility rate were used in a formula to calculate the digestibility rate of that nutrient

within specific diet (termed “digestibility” for the remainder of the paper). This number provided another mechanism for evaluating ingredients included in finisher diets. Digestibility captured the proportion of the diet represented by that nutrient and the rate at which that nutrient would presumably be digested within the animal after ingestion. By calculating nutrient digestibility for specific ingredient types and processing methods, the information captured is more reflective of the potential effect on rumen function and health; although, calculations based on book values are a good estimate, they may not perfectly reflect the actual digestibility rate of the nutrient in the case of each TG. Digestibility for starch (Equation 1), roughage NDF (Equation 2), and FB NDF (Equation 3) were calculated as follows:

$$[1] \quad \text{Digestibility } (\%^2/\text{hr})_{\text{Starch}} = \frac{(\text{Ingredient inclusion, \%DM}) * (\text{Starch, \%})}{100} \times Kd \text{ (CB1), \%}/\text{hr}$$

$$[2] \quad \text{Digestibility } (\%^2/\text{hr})_{\text{Roughage}} = \frac{(\text{Ingredient inclusion, \%DM}) * (\text{NDF, \%})}{100} \times Kd \text{ (CB3), \%}/\text{hr}$$

$$[3] \quad \text{Digestibility } (\%^2/\text{hr})_{\text{FB}} = \frac{(\text{Ingredient inclusion, DM\%}) * (\text{NDF, \%})}{100} \times Kd \text{ (CB3), \%}/\text{hr}$$

Statistical Analysis

All statistical analyses were conducted using R statistical software (R Core Team, 2022). Collected variables were included as moderators in a meta-regression model to test potential sources of heterogeneity or differences in observed effects between TG outcome measurements (Viechtbauer, 2010; Harrer et al., 2021). Meta-regression was used to evaluate associations between moderators and three outcomes of interest: total LA prevalence relative to the total cattle in TG, SLA prevalence relative to the total cattle with LA in TG, and SLA prevalence relative to the total cattle in TG. Moderators evaluated included tylosin, monensin, region, sex, breed, age, initial weight, final weight, DOED, ADG, DMI, G:F, roughage (%DM), roughage NDF digestibility, grain (%DM), starch digestibility, FB (%DM), FB NDF digestibility, ADF,

NDF, ADF:NDF ratio, HCW, NEg, number of feedings per day. Categorized moderators included tylosin, monensin, region, sex, breed, age, DOED, and number of feedings per day. Descriptions of how data were categorized in these variables are included in Table 1.2.

The `rma.mv` function from the `metafor` package (Viechtbauer, 2010) was used to run multi-level mixed-effects meta-regression models that reflected the hierarchical structure of these data (Harrer et al., 2021). The `escalc` function from `metafor` was used to generate sampling variances from raw binomial counts (LA count and treatment size (LA-TG), SLA count and treatment size (SLA-TG), S LA count and LA count (SLA-LA), respectively). Effect sizes were calculated as logit-transformed proportions (PLO) of LA prevalence or SLA score prevalence, based on `escalc()`-generated sampling variances. To control for the hierarchical structure of TG-within-experiment and of experiments-within-publications, a random effect of experiment identification number nested within publication identification number was included in all models (three level models) (Viechtbauer, 2010; Cheung, 2014). Models were fit by restricted maximum likelihood (REML). Moderator significance was assessed using Type III Q-tests (ANOVA-like tests). Model selection was conducted based solely on moderator Q-test significance rather than model-fit criteria (e.g., AIC, BIC).

Candidate moderators were first screened in univariate mixed-effects meta-regression models to reduce the full list to a subset of moderators that were more likely to reach significance in later model development steps. Univariate models were built as described above, including the random effect. Estimated marginal means (EMMs) and pairwise contrasts for group comparisons were obtained from univariate categorical model output using a patched wrapper for the `emmeans` package following the guidelines in the `emmeans` “Extending `emmeans`” vignette (Lenth et al., 2025) and examples provided in the `metafor` package

(Viechtbauer, 2022). Predicted probabilities and standard errors (SE) for outcome prevalence were generated directly from emmeans and pairwise contrasts outputs on the logit scale and back transformed to probabilities. Slopes (logit scale) were generated for continuous variables and the average predicted probability change per unit of moderator change were computed (e.g., percentage-point change in LA prevalence for every unit change in moderator), along with corresponding SE. This allowed for a more interpretable prediction of outcome prevalence in relation to continuous moderators. Moderators with a Type-III Q-test <0.30 (in their respective univariate model) were kept for subsequent selection and model building processes for final moderator selection.

Moderators who had a Type III Q-test <0.30 in their respective univariate model were assessed for completeness of reporting across all TGs. If a specific moderator was reported in $<90\%$ of all TGs (rows), then that moderator was removed from further analysis to maintain sufficient sample size and statistical power. Final moderator selection was accomplished by entering all moderators (1) selected by univariate screening and (2) sufficiently reported into a bi-directional stepwise inclusion function (forwards and backwards stepwise inclusion components) based on Type-III Q-tests. At each iteration, the least significant moderator (Type-III Q-Test >0.05) was removed and the model was re-fit. After each removal, previously excluded moderators were re-tested sequentially for significance upon re-inclusion (Type III Q-test <0.05 threshold). The re-added moderator was only retained in the model if it met the threshold for significance (Type III Q-test <0.05), otherwise it was excluded again. This process continued sequentially, until all variables in the final model were significant (Type III Q-test <0.05).

These final variables were then included in a final `rma.mv` model to generate final Type-III Q-tests. Potential collinearity among moderators in the final model was assessed by calculating variance inflation factors (VIFs) (Akinwande et al., 2015). Moderators with $VIF > 5$ were considered to have high collinearity and were excluded from the final model. From the final model, `emmeans` and pairwise comparisons (categorical moderators) and average predicted prevalence change for a one-unit change in moderator (continuous moderators) were generated as previously described. Probabilities of outcome prevalence as affected by moderators in the final model were calculated using the methods previously described.

Assessment of Heterogeneity

Heterogeneity was evaluated using a multilevel meta-regression approach to account for nested structure of data (experiments within publications) and the inclusion of multiple treatment-level moderators (Cheung, 2014). Intercept-only “Null” models were fitted using the `rma.mv` function in the `metafor` package in R (Viechtbauer, 2010), specifying random effects at three hierarchical levels: publication only (two-level model), experiment only (two-level model), and experiments nested within publications (three-level model). These models provided baseline estimates of variance and heterogeneity components (σ^2 , I^2 , H^2) without moderators (Viechtbauer, 2016). Three more models (with the same random effect structures as the Null models) were run with a group of final treatment-level moderators that were selected via univariate and bidirectional stepwise process as previously described. These models were used to determine how the addition of moderators affected variance and heterogeneity components (σ^2 , I^2 , H^2) and to calculate a pseudo R^2 .

Heterogeneity was quantified at each random-effect level (experiment or publication) and for each model overall using the estimated variance components. The notation σ^2 was used to

quantify level-specific variance (rather than τ^2) following best practices for multilevel meta-regression models (Viechtbauer, 2024). Overall I^2 and H^2 were derived from the summed variance components across levels. An I^2 value closer to 0% indicates that most variation is due to sampling error or very little heterogeneity is present, while values closer to 100% indicate variation in true effect sizes and greater heterogeneity between TGs (Higgins et al., 2003). Calculating overall and level-specific (publication-level versus experiment-level) I^2 estimates within the nested random effect (experiment nested within publication) allows accurate partitioning of variance between and within clusters of heterogeneity (i.e., within nested random effect levels) (Viechtbauer, 2016). Thresholds developed by Higgins et al. were used to classify heterogeneity (I^2) of collective meta-regression data as low (0-25%), moderate (26-50%), or high (75% and above) (Higgins, 2003). An H^2 value of 1 indicates that all observed variability can be explained by sampling error alone (i.e., no true heterogeneity), whereas values greater than 1 indicate that the observed variability exceeds what would be expected from sampling error alone. Pseudo R^2 was calculated as the percentage reduction in variance for each model containing moderators at each random-effect level and overall, relative to the corresponding Null model. Greater pseudo R^2 values indicate that the included fixed moderators accounted for a larger fraction of the observed heterogeneity. Unlike R^2 used in linear regression, pseudo R^2 in meta-regression does not represent the proportion of total variance explained, but instead the proportional reduction in between-study heterogeneity (σ^2) attributable to included moderators (Viechtbauer, 2010; Higgins & Thompson, 2002).

Residual Diagnostics

Residual diagnostics were conducted on the Null nested model to assess model adequacy. Raw and standardized residuals were examined from the Null nested model, and standardized

residuals exceeding $|2|$ were flagged as potentially influential (Viechtbauer, 2010). Plots of residuals were created and examined for patterns that may indicate heterogeneity of variance, misfit, or publication bias. These diagnostics provide insight into model fit and outlying studies, complementing variance-component–based heterogeneity measures.

Publication Bias Assessment

Publication bias was evaluated based on the three-level nested Null models. Publication bias refers to the tendency for studies with statistically significant or otherwise favorable results to be more likely to be published than studies with null or unfavorable findings, leading to a non-representative body of evidence and potentially inflated overall effect estimates. Residual-based funnel plots were generated for these models using the funnel function of metafor, plotting effect sizes against their standard errors, with a reference line at the model intercept to visualize potential asymmetry (Viechtbauer, 2010). In the absence of publication bias and other small-study effects, these plots are expected to exhibit a symmetrical, funnel-shaped distribution, as sampling variability decreases with increasing study precision (Viechtbauer, 2010). Multilevel Egger’s regressions based on standardized residuals were then performed for the same nested models, regressing standardized residuals on study precision to formally assess funnel plot asymmetry, indicative of small-study effects or potential publication bias (Viechtbauer, 2010; Cheung, 2014).

Results

Literature Review and Assessment

The database search yielded a total of 3,290 initial publication results. After the initial screening, a total of 121 publications met the inclusion criteria and were included in the meta-regression. The 121 publications represented 160 experiments, 676 TGs, and 88,786 cattle. References for the included publications can be found in Appendix A (Appendix Table A.10). Of the screened publications, those that did not meet inclusion criteria (n=39) are reported in Appendix A (Appendix Table A.9).

Upon initial data cleaning, outliers were removed in several categories to prevent skewed data from interfering with results. Treatment groups comprised of dairy-influenced cattle (n=19), on study in South America (n=7), and comprised of solely bulls (n=4) were removed from the analysis. The four TGs of bulls were dairy-influenced, thus the total number of TGs removed from the analysis was 26. This left 650 TGs that reported overall LA prevalence and 246 TGs that reported SLA prevalence available for further analysis.

LA-TG Results

LA-TG Model Results – Meta-regression

The results of all univariate models for initial moderator selection for the LA-TG model (n=650 TG) can be found in Appendix A (Appendix Table A.3, A.4). Of the univariate models that were run, 24 moderators had a P-value of <0.30: tylosin, monensin, region, sex, breed, age, DOED, number of feedings per day, initial weight, final weight, ADG, DMI, G:F, ADF, NDF, ADF:NDF ratio, HCW, NEg, roughage (%DM), roughage NDF digestibility, grain (%DM), starch digestibility, FB (% DM), and FB NDF digestibility.

Moderators removed for insufficient (<90% of all TGs) reporting included: Age (n=179), number of feedings per day (n=362), ADF (n=177), NDF (n=223), ADF:NDF ratio (n=127), HCW (n=507), and NEg (n=283). All univariate results of these moderators showed strong association with predicted LA prevalence within TG. Age of animals enrolled in a TG had a statistically significant effect on LA prevalence ($P<0.001$); however, the predicted prevalence was very similar between Yearling (0.19) and Other (0.19) categories and pairwise comparisons showed no significant difference. Feeding frequency was statistically associated with predicted LA prevalence ($P<0.001$). However, predicted prevalence values were nearly identical across TGs fed 1 (0.19), 2 (0.19), or 3 (0.20) times daily, and pairwise comparisons indicated no significant differences between feeding frequencies. ADF and NDF inclusion percentages were both negatively associated with predicted LA prevalence: LA prevalence decreased by 0.01 with each %DM increase in ADF ($P<0.001$) and decreased by 0.004 with each %DM increase in NDF ($P<0.001$). The ADF:NDF ratio also showed a negative relationship with predicted LA prevalence within TG (-0.33 per unit increase in ratio; $P<0.001$). In contrast, HCW and NEg were positively associated with predicted LA prevalence, with each 1 kg increase in HCW corresponding to a 0.0004 increase ($P<0.001$) and each 1 Mcal/kg increase in NEg corresponding to a 0.04 increase ($P<0.001$) in predicted LA prevalence.

After the 17 univariate-selected moderators ($P<0.30$) with sufficient representation were fed into the bi-directional stepwise selection function, the final moderators selected were tylosin, monensin, sex, final weight, ADG, G:F, grain (%DM), starch digestibility, and FB NDF digestibility. Liver abscess prevalence relative to the total cattle in TG (LA-TG; n=650) was evaluated in a final rma.mv model to determine potential associations between LA prevalence and final selected factors (Table 1.5, 1.6). All final moderators had VIF values less than 5 and

were included in the final model. Tylosin supplementation was associated with a lower predicted LA prevalence (0.13) compared to cattle not receiving tylosin (0.22) ($P<0.001$). Monensin supplementation followed a similar trend between TGs fed diets containing monensin (0.16) and those without (0.18) ($P<0.01$). Heifers (0.11) had a lower predicted LA prevalence than steers (0.23) or TG containing both heifers and steers (0.18) ($P<0.01$).

Final weight had a statistically significant positive effect on the predicted LA prevalence within TG (0.005 increase for each 25 kg; $P<0.01$). For every kg increase in ADG, predicted LA prevalence decreased by 0.03 ($P<0.05$); or for every 0.25 kg increase in ADG, LA predicted prevalence decreased by 0.0075. A 1-unit increase in G:F corresponded to a predicted decrease in LA prevalence of 0.50 ($P<0.01$). On a more realistic scale, each 0.01-unit increase in G:F corresponded to a predicted decrease in LA prevalence of 0.005. A 1% increase in total grain inclusion (on a %DM basis) increased predicted LA prevalence by 0.002 ($P<0.001$). Both starch digestibility and FB NDF digestibility had positive effects on predicted LA prevalence with each 1 %²/hour increase in digestibility increasing the predicted LA prevalence by 0.002 ($P<0.01$) and 0.21 ($P<0.001$), respectively.

LA-TG Results – Heterogeneity & Publication Bias Assessment

Dataset heterogeneity estimates differed across LA-TG model structures (Table 1.3). In the null models, the experiment-only model showed moderate heterogeneity ($\sigma^2 = 0.82$, $I^2 = 62.31\%$) and the publication-only model was slightly lower but was still within the moderate heterogeneity category ($\sigma^2 = 0.77$, $I^2 = 60.82\%$). The nested null model indicated that most heterogeneity was attributable to differences between publications ($\sigma^2 = 0.59$, $I^2 = 44.33$) rather than between experiments ($\sigma^2 = 0.24$, $I^2 = 18.31\%$). The nested model overall had similar heterogeneity when compared to the experiment-only model and was greater than the

publication-only model ($\sigma^2 = 0.83$, $I^2 = 62.64\%$). In the experiment-only model, adding moderators reduced variance ($\sigma^2 = 0.52$, $I^2 = 51.48\%$, pseudo $R^2 = 35.83\%$), while the publication-only model showed a greater reduction ($\sigma^2 = 0.55$, $I^2 = 52.55\%$, pseudo $R^2 = 28.66\%$). In the nested model, adding moderators reduced overall variance ($\sigma^2 = 0.52$, $I^2 = 51.48\%$, pseudo $R^2 = 36.74\%$). Within the nested model, experiment-level variance was practically eliminated by the addition of moderators ($\sigma^2 = 5.63 \times 10^{-9}$, $I^2 = 0.00\%$, pseudo $R^2 = 100.00\%$), while publication-level variance remained substantial ($\sigma^2 = 0.52$, $I^2 = 51.48\%$, $H^2 = 2.06$; pseudo $R^2 = 10.60\%$). Publication bias was detected in the nested null model as the Egger's regression indicated significant funnel plot asymmetry (intercept = -0.53 , SE = 0.050 , $P < 0.001$) (Table 1.4; Figure 1.1).

SLA-LA Results

SLA-LA Results – Meta-Regression

The results of all univariate models for initial moderator selection for the SLA-LA (n=246 TG) model can be found in Appendix A (Appendix Table A.5, A.6). Of the univariate models that were run, 24 moderators had a P-value of < 0.30 : tylosin, monensin, region, sex, breed, age, DOED, number of feedings per day, initial weight, final weight, ADG, DMI, G:F, ADF, NDF, ADF:NDF ratio, HCW, NEg, roughage (%DM), roughage NDF digestibility, grain (%DM), starch digestibility, FB (%DM), and FB NDF digestibility.

Moderators removed for insufficient ($< 90\%$ of all TGs) reporting included: Age (n=93), number of feedings per day (n=193), ADF (n=109), NDF (n=137), ADF:NDF Ratio (n=81), and NEg (n=142). Univariate results of these moderators showed varying degrees of association with predicted SLA prevalence within animals with LA. Age was again a significant moderator ($P < 0.001$) with regards to the SLA prevalence outcome, but differences between the Yearling

(0.34) and Other (0.33) categories were nonsignificant in pairwise comparisons. Feeding frequency was significantly associated with predicted SLA prevalence within animals with LA ($P<0.001$). Predicted prevalence values were 0.33, 0.42, and 0.56 on the logit scale for one, two, or three daily feedings, respectively, although pairwise comparisons indicated no significant differences between feeding levels. Among continuous variables, ADF (%DM), NDF (%DM), and ADF:NDF ratio were all negatively associated with predicted SLA prevalence relative to the total cattle with LA in TG, with estimated effects on prevalence of -0.02 ($P<0.05$), -0.01 ($P<0.001$), and -0.18 ($P=0.20$) for every 1-unit increase, respectively. In contrast, NEg was positively associated with predicted SLA prevalence relative to the total cattle with LA in TG, with each 1 Mcal/kg increase in NEg corresponding to a 0.18 increase in predicted prevalence ($P<0.001$).

After 18 univariate-selected moderators ($P<0.30$) with sufficient representation in the dataset were fed into the bi-directional stepwise selection function, the final moderators selected were tylosin, region, initial weight, final weight, and FB (%DM). Prevalence of SLA within TG ($n=246$) was evaluated in a final rma.mv model to determine potential associations between SLA prevalence relative to the total cattle with LA in TG and final selected factors (Table 1.7, 1.8). All final moderators had VIF values less than 5 and were included in the final model. Tylosin supplementation was associated with a slightly lower predicted SLA prevalence (0.35) compared to cattle not receiving tylosin (0.40) ($P<0.01$). Region also influenced predicted SLA prevalence ($P<0.05$), however, pairwise comparisons showed no significant differences between categories. Among continuous variables, initial weight and FB (%DM) were both negatively associated with predicted SLA relative to the total cattle with LA in TG. Each 1 kg increase in initial weight corresponded to a 0.001 decrease in SLA prevalence (each 25 kg increase corresponded to a

0.025 decrease in predicted SLA prevalence; $P < 0.001$) and each 1% increase in FB corresponded to a 0.008 decrease ($P < 0.05$). Conversely, final weight was positively associated with predicted SLA prevalence relative to the total cattle with LA in TG, with each 1 kg increase corresponding to a 0.001 increase in predicted SLA prevalence (each 25 kg increase corresponded to a 0.025 increase in predicted SLA prevalence; $P < 0.05$).

SLA-LA Results – Heterogeneity & Publication Bias Assessment

Dataset heterogeneity estimates again differed across SLA-LA structures (Table 1.3). In the null models, the experiment-only model showed moderate heterogeneity ($\sigma^2 = 0.62$, $I^2 = 46.24\%$), while the publication-only model indicated greater heterogeneity, although still falling within the moderate heterogeneity category ($\sigma^2 = 0.67$, $I^2 = 47.65\%$). The nested null model showed most heterogeneity was attributable to differences between experiments ($\sigma^2 = 0.42$, $I^2 = 30.19\%$) and a smaller portion to differences between publications ($\sigma^2 = 0.24$, $I^2 = 17.18\%$). The overall nested null model ($\sigma^2 = 0.66$, $I^2 = 47.37$) had greater heterogeneity than the experiment-only model but almost identical heterogeneity to the publication-only model. Incorporation of moderators reduced variance across all models with the exception of the experiment level of the nested model (Table 1.3). In the experiment-only model, adding moderators reduced variance ($\sigma^2 = 0.41$, $I^2 = 35.79\%$, pseudo $R^2 = 35.30\%$), while the publication-only model showed a lesser reduction ($\sigma^2 = 0.46$, $I^2 = 38.56\%$, pseudo $R^2 = 31.07\%$). In the nested model, overall heterogeneity was reduced by addition of moderators ($\sigma^2 = 0.46$, $I^2 = 38.30\%$, pseudo $R^2 = 31.05\%$). Within the nested model, experiment-level variance and heterogeneity slightly increased after adding moderators ($\sigma^2 = 0.44$, $I^2 = 36.59\%$, pseudo $R^2 = -3.37\%$), while publication-level variance was greatly reduced ($\sigma^2 = 0.02$, $I^2 = 1.71\%$, pseudo $R^2 = 91.52\%$) by addition of moderators. Publication bias was not detected in the nested null model as the Egger's

regression indicated no significant funnel plot asymmetry (Intercept = -0.03 , SE = 0.074 , $P=0.664$) (Table 1.4; Figure 1.1).

SLA-TG Results

SLA-TG Results – Meta-Regression

The results of all univariate models for initial moderator selection for the SLA-TG model ($n=246$ TG) can be found in Appendix A (Appendix Table A.7, A.8). Of the univariate models that were run, 24 moderators had a P-value of <0.30 : tylosin, monensin, region, sex, breed, age, DOED, number of feedings per day, initial weight, final weight, ADG, DMI, G:F, ADF, NDF, ADF:NDF ratio, HCW, NEg, roughage (%DM), roughage NDF digestibility, grain (%DM), starch digestibility, FB (%DM), and FB NDF digestibility.

Moderators removed for insufficient ($<90\%$ of all TGs) reporting included: Age ($n=93$), number of feedings per day ($n=193$), ADF ($n=109$), NDF ($n=137$), ADF:NDF ratio ($n=81$), and NEg ($n=142$). Univariate results of these moderators showed strong association with predicted SLA prevalence relative to the total cattle in TG. Age was strongly associated with predicted SLA prevalence ($P<0.001$), however pairwise comparisons showed no statistical difference between the Yearling (0.09) and Other (0.09) categories. Feeding frequency was significantly associated with predicted SLA prevalence relative to the total cattle with LA in TG ($P<0.001$). Predicted SLA prevalence values were 0.09 , 0.11 , and 0.11 for TGs fed one, two, or three times daily, respectively, although pairwise comparisons indicated no significant differences between feeding levels. Among continuous variables, ADF ($P<0.001$), NDF ($P<0.001$), and the ADF:NDF ratio ($P<0.001$) were all negatively associated with predicted SLA prevalence: for each unit increase, predicted SLA prevalence decreased by 0.01 , 0.004 , and 0.33 , respectively.

In contrast, NEg was positively associated with predicted SLA prevalence, with each 1 Mcal/kg increase in NEg corresponding to a 0.06 increase in predicted SLA prevalence ($P<0.001$).

After 18 univariate-selected moderators ($P<0.30$) with sufficient representation in the dataset were fed into the bi-directional stepwise selection function, the final moderators selected were tylosin, monensin, region, DOED, grain (%DM), and FB NDF digestibility. Prevalence of SLA relative to the total cattle in TG (n=246) was evaluated in a final rma.mv model to determine potential associations between SLA prevalence and final selected factors (Table 1.9, 1.10). Fibrous byproduct NDF digestibility (%²/hour) was excluded from the final model due to VIF>5; all other final moderators had VIF values less than five and were included in the final model. Tylosin supplementation was associated with a slightly lower predicted SLA prevalence (0.07) compared to cattle not receiving tylosin (0.10) ($P<0.001$). Monensin supplementation also had a similar effect, with TGs receiving monensin showing a predicted SLA prevalence of 0.07 versus 0.10 for cattle not receiving monensin ($P<0.001$). Region influenced predicted SLA prevalence as well: TG from CA (0.05) had lower ($P<0.001$) predicted SLA prevalence than TG from Other regions (0.12), while TG from MW (0.06) or SW (0.12) were not statistically different from CA or Other. Treatment groups with fewer than 100 DOED (0.04) had a significantly lower predicted SLA prevalence than all other TG ($P<0.001$), and TG with 100-149 DOED (0.09) had significantly lower predicted SLA prevalence than TG with 200+ DOED (0.15), but TG with 150-199 DOED were not statistically different from those having 100-149 or 200+ DOED ($P<0.001$). Among continuous variables, grain (%DM) tended to be positively associated with predicted SLA prevalence: with each 1% increase in grain corresponding to a 0.0003 increase in predicted prevalence ($P=0.09$).

SLA-TG Results – Heterogeneity & Publication Bias Assessment

Dataset heterogeneity estimates differed across SLA-TG model (n= 246 TG) structures (Table 1.3). In the null models, the experiment-only model showed low heterogeneity ($\sigma^2 = 0.20$, $I^2 = 28.78\%$), while the publication-only model showed moderate heterogeneity ($\sigma^2 = 0.86$, $I^2 = 63.25\%$). The nested null model indicated that most heterogeneity was attributable to differences between publications ($\sigma^2 = 0.84$, $I^2 = 62.85\%$), with minimal contribution from differences between experiments ($\sigma^2 = 2.52 \times 10^{-8}$, $I^2 = 0.00\%$). Overall heterogeneity of the nested model ($\sigma^2 = 0.84$, $I^2 = 62.85\%$) was similar to the publication-only model and substantially higher than the experiment-only model. Incorporation of moderators reduced variance across the publication-only and nested models (Table 1.3). In the experiment-only model, adding moderators decreased variance and heterogeneity ($\sigma^2 = 0.42$, $I^2 = 45.90\%$, pseudo $R^2 = 49.85\%$), while the publication-only model showed a reduction ($\sigma^2 = 0.38$, $I^2 = 43.95\%$, pseudo $R^2 = 55.10\%$). In the nested model, overall heterogeneity and variance were also reduced by addition of moderators ($\sigma^2 = 0.42$, $I^2 = 45.90\%$, pseudo $R^2 = 49.85\%$). Within the nested model, experiment-level variance continued to contribute minimally ($\sigma^2 = 6.93 \times 10^{-9}$, $I^2 = 0.00\%$, pseudo $R^2 = 72.48\%$), while publication-level variance decreased ($\sigma^2 = 0.42$, $I^2 = 45.90\%$, pseudo $R^2 = 49.85\%$). Publication bias was detected in the nested null model, as the Egger's regression indicated significant funnel plot asymmetry (intercept = -0.42 , SE = 0.068 , $P < 0.001$) (Table 1.4; Figure 1.1).

Discussion

Liver abscesses continue to cause major concerns in feedlot cattle with regards to performance, economic losses, and antimicrobial stewardship. Due to the recent trends in increased prevalence and severity of LA, efforts to find alternative control methods while also utilizing feed-through antimicrobials prophylactically persist. Pathophysiology of LA has been

long-accepted to involve gastrointestinal insult, microbial translocation across the rumen wall, and bacterial embolization upon reaching the liver to form abscesses (Nagaraja and Chengappa, 1998; Broadway et al., 2024). The effect of diet formulation on both GI health and LA has been explored in previous literature (Bryant & Jennings, 2022; Schneid et al., 2024a). While other studies have evaluated the effect of certain feed ingredients, ingredient inclusion rates, and feed additives on LA, the goal of this study was to use a meta-regression approach of quantifying the association of finishing diet factors with LA prevalence and severity in feedlot cattle.

Univariate Models

There were several moderators that had significant univariate results, however, were not reported in 90% or more of all TG and thus were excluded from further moderator selection processes. The following moderators fell into this category across all three models: Age, number of feedings per day, ADF, NDF, ADF:NDF ratio, HCW (only LA-TG), and NEg. Both categorical variables in this group, Age and number of feedings per day, were statistically significant across all univariate model structures ($P < 0.001$ in each instance), however, the Tukey-adjusted pairwise comparisons consistently showed no difference between the Yearling and Other categories or between 1, 2, or 3 feedings per day, respectively. The lack of difference in pairwise comparisons is likely due to reduced statistical power following correction for multiple comparisons.

Age of animals at enrollment may serve as a proxy for several different characteristics: ability to adapt to high starch finisher diets, time on feed required to reach the ideal finish composition, feed consumption habits, and previous backgrounding history contributing to overall health status (Kleen et al., 2003; Reinhardt and Hubbert, 2015; Schoonmaker et al.,

2002). Age is closely associated with body weight, which is likely why age is reported less often and may contribute to confounding between the two moderators. Schneid et al showed that irregular feeding times and quantities did not affect LA frequency compared to consistent feeding times and amounts (Schneid et al., 2024a). However, they did not evaluate LA severity or the effect of different feeding frequencies per day. Statistical power was limited in the present study due to a disproportionate number of TG fed two and three times daily compared to TG fed once daily.

Within the continuous moderators, ADF ($P<0.001$ in LA-TG and SLA-TG; $P<0.05$ in SLA-LA), NDF ($P<0.001$ in all models), and ADF:NDF ratio ($P<0.001$ in LA-TG and SLA-TG; $P<0.5$ in SLA-LA) consistently had negative associations with the outcome across all models. This pattern agrees with previous research linking greater levels of dietary physically effective fiber to improved rumen health due to multiple effects: increased buffering ability, slowing the rate of rapid starch fermentation, reduced overall total digestible nutrients, and increased scratch factor (Nagaraja and Chengappa, 1998; Weiss, 1998; Reinhardt and Hubbert, 2015; Pereira et al., 2021). Multiple studies have found that increasing fiber or forage inclusion rates in finisher rations was associated with reductions in overall LA prevalence and severity which aligns with previous literature outlining contributions of rumen health to LA pathophysiology (Wilson et al., 2023; Amachawadi and Nagaraja, 2022; McDaniel et al., 2024; Paterson et al., 2024).

Both HCW (under-represented & thus removed in LA-TG model; $P<0.001$) and NEg ($P<0.001$ in all models) showed positive associations with outcome across all univariate models. The positive association of TG HCW with LA prevalence in the LA-TG model mirrors the positive association of final weight with LA throughout the univariate and multivariate models. From this standpoint, we see that as TGs finish at heavier weights (as reflected by HCW) the

predicted LA prevalence increases. Much of the current literature reports that, on an individual basis, animals with LA have impaired carcass traits due to both reduced performance in the yard and carcass trimming at the plant (Grimes et al., 2024, Herrick et al., 2024). This is an example of a common shortfall in meta-analyses: ecological fallacy. Ecological fallacy describes the scenario when group-based data either over- or under-represents true biology on an individual level (Geissbühler et al., 2021).

Across all model structures, NEg was positively associated with LA prevalence and severity. This agrees with current literature that finds increased grain content and use of processing methods to increase starch digestibility (i.e., available energy) are associated with higher LA prevalence (Nagaraja and Chengappa, 1998; Kleen et al., 2003; Bryant and Jennings, 2022). Batista & Holland, however, found NEg was not associated with LA prevalence on a pen basis which again brings up the issue of ecological fallacy (Geissbühler et al., 2021; Batista and Holland, 2022).

Due to significance of these moderators in univariate evaluation, these moderators may provide additional context to understanding risk factors for LA and SLA. However, standard reporting of these datapoints in future studies is needed to provide 'statistical power to clarify their significance with regards to LA prevalence and severity in the finishing phase.

Multivariate Results

Several moderators were significantly associated with LA prevalence and/or severity across multiple models. Tylosin, for example, was significant across all three models with TG receiving tylosin having lower predicted LA and SLA prevalence than those without. This aligns with previous work and current industry standards which have long held in-feed tylosin

supplementation as the gold standard control method for LA prevalence and severity in feedlot cattle (Nagaraja and Chengappa, 1998; Reinhardt and Hubbert, 2015; Amachawadi and Nagaraja, 2016; Weinroth et al., 2019). Collectively, the results of the present study align with previous work that tylosin inclusion is associated with reductions in overall LA risk and shifts the distribution of LA away from the most severe (A+) category. Tylosin and monensin were not found to be collinear in this study, most studies included in the present work included each of them as unique treatment interventions and controlled for them accordingly.

Monensin was significant in the LA-TG and SLA-TG models. In both models, TG receiving monensin had a lower predicted LA prevalence than those not receiving monensin. Current literature shows that monensin, in addition to controlling coccidiosis, improves feed efficiency and reduces prevalence of digestive issues such as subacute ruminal acidosis, acidosis, and bloat (Duff and McMurphy, 2007; Harris et al., 2015; Bowman-Schnug et al., 2025). Furthermore, monensin has been consistently shown to alter feeding behavior to tend towards smaller, more frequent meals throughout the day with provides consistent input to the ruminal environment, further reducing acidosis risk (Erickson et al, 2003). Literature directly evaluating the association of monensin and LA have mixed results: some studies show no significant effect on LA prevalence while others show monensin supplementation reduced the prevalence of severe LA when combined with tylosin, however, did not evaluate monensin as a individual additive (Heinemann et al., 1978; Nagaraja and Chengappa, 1998; Meyer et al., 2009). The findings of the present study reflect the findings and logical progression of current literature: monensin inclusion either directly or indirectly reduces LA prevalence and severity.

Geographical region was significant in the SLA-LA and SLA-TG models. However, pairwise comparisons only showed differences between region categories in the SLA-TG model:

Canada had a lower SLA prevalence out of all animals within TG than the Other category but was not statistically different from the Midwest or Southwest categories. Geographical region of cattle finishing location has been shown to influence LA prevalence in previous work which was not found in the present study (LA-TG model). Herrick et al found that the greatest LA prevalence was found in the Pacific Northwest (absorbed into “Other” in this study) and the least occurring in the Northeast (also absorbed into “Other”) (Rezac et al., 2014; Herrick et al., 2022). Perhaps the lack of difference in the present study is due to categorization differences. Few studies have evaluated the association of geographical region with LA severity, however Reinhardt and Hubbert showed that both overall LA and severe LA prevalence were increased in the Great Plains region (Reinhardt and Hubbert, 2015) but this is the only study known to these authors to have evaluated associations between geographical location and LA severity. Geographical region is likely confounded by breed type and available feedstuffs within region (Broadway et al., 2024), making evaluation of direct regional effect on LA difficult. The potential confounding was mitigated within the model by including breed as a moderator and by converting all feed ingredients to their primary nutrient dry matter inclusion (starch or NDF) and nutrient digestibility.

Final weight was positively associated with LA (LA-TG) and SLA (SLA-LA) prevalence. Brink et al found that animals with SLA had lower ($P < 0.10$) average final body weights than animals without LA, but there were no differences between animals with healthy livers and those with A or A- scores (Brink et al., 1990). Schneid et al found that final body weight did not differ between cattle with any severity of LA compared to those with normal livers (Schneid et al., 2024a). Most of the current literature surrounding LA focuses on associated losses in performances due to decreased weight gain, feed efficiency, and HCW

(Brown and Lawrence, 2010; Reinhardt and Hubbert, 2015). The positive association in the present study between model outcome (LA prevalence and SLA prevalence) with final weight may be a true reflection of associations or ecological fallacy may be playing a role in this discrepancy: Brinks et al evaluated individual animal outcomes while the present study evaluated TG averages (Geissbühler et al., 2021). On the other hand, this finding may be related to the present study's structure: not all experimental TG included in this meta-regression were reflective of a complete finishing phase that takes animals from entry to ideal finish point. The association between a heavier final weight and LA prevalence/severity may be confounded by DOED in that cattle on a finisher diet for a longer period would foreseeably have both a greater final weight and more DOED at risk for LA or severe LA.

Grain (%DM) was positively associated with LA (LA-TG) and SLA (SLA-TG) prevalence. This reflects trends seen in literature showing that higher grain inclusion leads to higher rates of acidosis and LA (Nagaraja and Lechtenberg, 2007; Reinhardt and Hubbert, 2015; Amachawadi and Nagaraja, 2022). This trend is exacerbated as grains are processed to enhance starch digestibility. As grain inclusion and starch digestibility increase, in turn, so does the risk of acidosis, resulting epithelial damage, and seeding of the liver to form LA (Nagaraja and Chengappa, 1998). Based on current literature, the inclusion rate and source of grain and roughage components of a diet appear to have the highest influence on LA prevalence (Bryant and Jennings, 2022; Schneid et al., 2024a).

A surprising finding across all model structures was the lack of association of roughage (%DM) or roughage NDF digestibility. These two moderators were not selected for inclusion in either of the three final models. Current literature repeatedly shows that roughage inclusion is one of the most important factors for reducing prevalence and severity of LA aside from grain

inclusion/fermentability (Nagaraja and Chengappa, 1998; Batista and Holland, 2022). Previous work has shown that LA prevalence is either unchanged (Stock et al., 1990; B. Holland et al., 2018; Jennings et al., 2021) or decreases as dietary roughage inclusion level increases (Zinn and Plascencia, 1996; Wilson et al., 2023; Schneid et al., 2024b). A wide range of roughage inclusion was observed across TG in the present study, however the majority of diets (82.5% of TG had <15% roughage (%DM)) included levels of roughage reflective of typical finishing diet practices. While the lack of significant association with roughage moderators in the present study may be an accurate representation of LA risk, perhaps more statistical power is required across varying levels of roughage inclusion to detect the protective effect observed in previous studies. In addition, the expected protective effect of increased roughage may be inherently captured within the grain (%) moderator: as grain inclusion increases, proportion of roughage included decreases.

LA-TG Multivariate Model

When LA were evaluated relative to the total cattle in TG, moderators included in the final model included: tylosin, monensin, sex, ADG, G:F, final weight, grain (%DM), starch digestibility, and FB NDF digestibility. All moderators except for sex, ADG, G:F, starch digestibility, and FB NDF digestibility have been discussed previously. Heifers had a significantly lower predicted LA prevalence than steers or mixed sex TG. This aligns with current literature and could be due to trends surrounding feed consumption and growth rate differences between sexes (Smith, 1998; Grimes, 2022; Grimes et al., 2024). Acidosis may be a higher risk for steers due to greater feed consumption and growth rates (Hicks et al., 1990; Amachawadi and Nagaraja, 2015). A greater risk of acidosis, and thus rumenitis, amongst a larger percentage or entirety of a TG would contribute to a higher average LA prevalence. In

addition, heifers are smaller framed and reach an ideal finish composition earlier than steers – thus limiting their days at risk for developing LA while receiving a grain-based finisher diet (Nagaraja and Chengappa, 1998; Amachawadi and Nagaraja, 2016). Herrick et al did report heifers to have a numerically greater LA prevalence than steers, however the difference was small (Herrick et al., 2022).

Individual animals with LA have been shown in previous work to have impaired performance parameters; in the present study, ADG and G:F were negatively associated with LA prevalence (Brown and Lawrence, 2010; Batista and Holland, 2022). In fact, reductions have been as high as 14% reduction in ADG and 13% reduction in G:F (Brink et al., 1990). Schneid et al found that steers fed a high concentrate diet had higher LA prevalence and SLA prevalence as well as lowered reduced ADF and other performance parameters on a TG level (Schneid et al., 2024a). Although this is not a direct tie between LA and reduced performance during the finishing phase, it follows the same trends. Decreased performance of LA cattle may be influenced by changes in liver function, metabolic efficiency, increased net energy for maintenance energy requirements, or reductions in DMI (Brink et al., 1990; Owens et al., 1998; Batista and Holland, 2022; Amachawadi et al., 2023).

In the LA-TG model, starch digestibility was positively associated with LA prevalence. As was previously discussed, grain (%DM) was also positively associated with LA prevalence as has been shown in published literature. The positive relationship of starch digestibility follows similar trends with work demonstrating that higher levels of grain ingredient processing increases rumen starch availability and digestibility (Zinn, 1990; Reinhardt and Hubbert, 2015). Other literature shows that while grain type and processing method affect fermentation profile, there is little evidence showing a direct effect on LA (Mader et al., 1991; Loerch, S.C. and

Fluharty, F.L., 1999). In fact, Reinhardt and Hubbert conclude that “in a high-grain finishing diet, the roughage level and form have a much greater effect on LA than does grain source or degree of processing” (Reinhardt and Hubbert, 2015). The present study finds an association between LA prevalence and starch digestibility. Unique to this study is both the method of calculating digestibility values for overall starch, roughage NDF, and FB NDF and evaluating dietary effect on LA prevalence and severity regardless of whether diet was the imposed treatment of the study or not. Perhaps the method of quantifying digestibility as was done in the present study allows an objective method of comparing digestibility of diets across multiple studies to provide greater statistical power.

A positive association of FB NDF digestibility with LA prevalence was also observed. FB ingredients were intended be used to substitute portions of the grain component in finishing diets, sparing some of the fermentable carbohydrate load without sacrificing nutrition for performance outcomes (Klopfenstein et al., 2008). However, the majority of studies show no reduction in overall LA prevalence or rumenitis with the inclusion of FB on a %DM basis (Depenbusch et al., 2008a; May et al., 2011; Meyer et al., 2013; Amat et al., 2014; Koch et al., 2020). The lack of difference between groups receiving FB and those not receiving FB has led some to state “that the neutral detergent fiber (NDF) of grain byproducts does not function in a manner similar to NDF from traditional roughage sources” (Reinhardt and Hubbert, 2015; Galyean and Hales, 2022). This may be in part due to the high level of sulfuric acid in FB products such as distillers grains or corn gluten feed which may negate potential rumen buffering effect of the FB as evidenced by several studies that show FB ingredients provide no advantage over grain products with regards to rumen pH (Al-Suwaiegh et al., 2002; Holtshausen et al., 2011; Walter et al., 2012). On the other hand, FB inclusion has been shown to reduce LA

prevalence (Corrigan et al., 2007). Perhaps the inclusion of FB ingredients in a diet has a neutral effect on LA prevalence until the FB inclusion rate is high enough to reduce available NDF from traditional roughage sources that buffer rumen pH and provide scratch factor.

SLA-LA Multivariate Model

When SLA were evaluated relative to the total cattle with LA in TG, moderators included in the final model included: tylosin, region, initial weight, FB (%DM), and final weight. All moderators except for initial weight and FB (%DM) have been discussed previously ; both variables were negatively associated with SLA prevalence. Initial weight has been studied frequently in the literature as it relates to LA, which is likely due to the normal practice of blocking experimental animals to treatment group by initial body weight. This practice allows more comparable TG, however, it means initial body weight (initial weight in this study) is not a typical component evaluated. In the present study, the negative association between initial weight and SLA prevalence may be reflective of baseline health status and maturity of the TG, step-up or backgrounding effect, or shorter DOED until finish (and thus lower accrued number of days at risk for severe LA) (Theurer et al., 2021; Galyean and Hales, 2022; Hales, 2024; Schneid et al., 2024a). Particularly in this model, where factors associated with SLA out of all LA within the TG are being evaluated, factors like overall health and DOED could have large impacts on whether LA becomes severe and the overall prevalence of severe LA (Castillo-Lopez et al., 2014).

As discussed in the previous section, the majority of current literature shows no difference in LA prevalence with the addition of FB ingredients to the diet (Depenbusch et al., 2008b; Reinhardt and Hubbert, 2015; Galyean and Hales, 2022). This could be due to the NDF contained in FB ingredients not having the same characteristics and effects as NDF from

roughage sources (Reinhardt and Hubbert, 2015). However, in the present study the addition of FB on a %DM basis is shown to reduce SLA prevalence. Beliveau and McKinnon found that FB inclusion had no effect on LA scores but also found there to be no effect on performance parameters (Beliveau and McKinnon, 2008). There may be no true effect to be observed in this instance, or perhaps there is a component of the added NDF from FB that allows continued performance goals to be met, all the while preventing progressing of LA severity (Corrigan et al., 2007; Beliveau and McKinnon, 2008; Amat et al., 2014).

SLA-TG Multivariate Model

When SLA were evaluated relative to the total cattle in TG, moderators included in the final model included: tylosin, monensin, region, DOED, and grain (%DM). All moderators other than DOED have been discussed previously. In the present study, animals that had been on study for less than 100 DOED had a lower probability of SLA than animals in all other categories. Additionally, animals that had been on study for greater than 200 DOED had a greater probability of SLA than animals with 100-149 DOED, but not different than animals with 150-199 DOED. There is no literature known to these authors that assesses the potential association between LA severity and DOED. Findings of the present study mimic those of current literature that suggests LA occur more commonly later in the feeding period due to step up diets containing more starch, higher cumulative risk of LA over a larger number DOED, and increased variation in daily DMI observed in heavier cattle (Nagaraja and Lechtenberg, 2007; Castillo-Lopez et al., 2014). Some studies have suggested that transition period animals are also at a higher risk for ruminal acidosis as they are transitioned onto a high starch diet (Brown et al., 2006; Meyer and Bryant, 2017) which may translate to a higher risk for other health incidents, such as LA, as well (Theurer et al., 2021). While the present study findings reflect most of the

literature surrounding LA and DOED today, there is again the semantics of DOED definition to consider. Days on feed in the present study signifies the number of days an animal was on experimental diet which may or may not also correspond to the number of days it took the animal to reach the ideal finish point. This may contribute to DOED being included as a moderator in the final model for SLA-TG and not included in the other two models.

Heterogeneity

Moderate heterogeneity across almost all models indicates that true differences in LA prevalence and severity across the data are not fully explained by sampling error or random noise and instead are consistent with true biological variation and methodological differences (Higgins and Thompson, 2002; Riley et al., 2011). With the exception of one model (SLA-LA), heterogeneity and variance estimates (σ^2 , I^2 , and H^2) consistently indicate that most variability in effect sizes arises between publications as opposed to between individual experiments within publication, when appropriate nesting of experiment within publication is accounted for. This is to be expected as experiments published in the same manuscript often shared portions of experimental methods, data collection, or reporting styles – all of which would contribute to data variation. The nested structure provides the most accurate decomposition of total heterogeneity because it avoids inaccuracies caused by combining experiment-attributable variation with publication-attributable variation (Assink and Wibbelink, 2016). Thus, we understand that differences between experiments (design, management, reporting, etc.) drives the variability in prevalence in the SLA-LA model. Perhaps there are factors unique to the progression in severity of LA as a disease process that are more accurately captured by experimental-level factors: in

other words, perhaps the risk of having a progressive and severe LA is related to different factors than the risk of having a LA or an SLA at all.

Moderator inclusion substantially improved model fit and meaningfully reduced σ^2 and I^2 . Nested model structures were especially improved by moderators which indicates better alignment between moderators and hierarchical structure of the model (Konstantopoulos, 2011; Cheung, 2014). The improvement offered by moderator inclusion demonstrates that the meta-regression captured key contextual factors (Higgins and Thompson, 2002; Viechtbauer, 2010). Minor increases in heterogeneity with moderator inclusion in some cases likely reflect overfitting or residual variance at unmodeled levels (e.g., SLA-LA Nested model (experiment level)). In all other cases, heterogeneity was reduced by the addition of moderators but was not eliminated entirely. The remaining heterogeneity emphasizes that publication-level context, reporting differences, and unmeasured moderators continue to be crucial determinants of observed variation in LA prevalence and severity outcomes (Riley et al., 2011; Harrer et al., 2021).

Publication Bias

Significant Egger's test intercepts for LA-TG and SLA-TG indicate funnel plot asymmetry, suggesting potential small-study or selective reporting bias. In the results for both models, the Egger's test results indicate smaller studies reported larger effect sizes and were more likely to report fewer liver abscesses (rather than being equally likely to report fewer or greater number of liver abscesses) compared to the overall estimated effect size for both LA-TG and SLA-TG (Figure 1.1). This bias implies that pooled estimates for these outcomes may understate the true magnitude of moderator effects (Egger et al., 1997; Lin and Chu, 2018). Thus, results of these meta-regressions should be interpreted cautiously in light of apparent publication

bias. Assessment of funnel plots developed for the LA-TG and SLA-TG models shows there are fewer studies represented in the lower right quadrant, which indicates a lack of smaller studies reporting LA and SLA prevalences that fall higher than the overall estimated effect. In contrast, the non-significant Egger's intercept in the SLA-LA model supports that remaining heterogeneity primarily reflects genuine experimental differences rather than reporting asymmetry. Any given study is more likely to be published in a scientific journal if its findings are statistically significant, thus naturally creating publication bias (Lin and Chu, 2018).

However, funnel plot asymmetry can be caused by sources other than publication bias (Lin and Chu, 2018), such as poor methodological design or the existence of multiple subgroups (Sterne et al., 2011). Although both the SLA-LA and SLA-TG models have the same number of rows, they evaluate SLAs with different denominators and Egger's regression does not necessarily have the same power across both structures. Power to detect funnel-plot asymmetry depends not only on the size of the dataset evaluated but also on the distribution of study precisions, the magnitude of any effect-precision correlation, between-study heterogeneity (σ^2/I^2), and the degree of clustering in the data (Simmonds, 2015). Consequently, a significant Egger's intercept for SLA-TG but not SLA-LA may reflect true small-study effects (lower precision with more extreme results) for the population-level metric (SLA-TG) or other denominator- or clustering-related differences between outcomes. Beyond the aforementioned factors contributing to a significant Egger's intercept for LA-TG, industry and literature norms may contribute true publication bias in some instances. Meaning, since more studies within this dataset emphasize overall LA prevalence as a reportable outcome rather than SLAs, publication bias may be present if this emphasis creates stronger incentives to publish studies showing significant reductions in LA prevalence than those focused on LA severity (SLA). Overall, these findings suggest that effect

estimates for LA-TG and SLA-TG should be interpreted with caution, as small-study effects and potential publication bias may inflate perceived differences between studies, whereas estimates for SLA-LA are more likely to reflect genuine experimental variation.

Results of the present study showed grain and fibrous byproduct inclusion rate and related nutrient digestibility, but no moderators related to roughage ingredients, were associated with LA prevalence and severity. This is an interesting finding when considering the multiple published studies that show a reduction in LA with increased roughage inclusion. However, it is possible that while including roughage may reduce LA, grain and FB ingredient characteristics may be more important (or serve as an indirect proxy for roughage inclusion level) and thus were significant in the present study even when roughage was not. Identifying risk factors for LA and severe LA in feedyard cattle has great implications for attempts to generate more effective control methods. Without accurate knowledge of what predisposes an animal to develop LA or for LA to progress to severe levels, decisions for mitigation are less informed and at worst, ineffective. More research is needed to continue to characterize risk factors for LA and SLA in order to better understand the pathophysiology and prospective mitigation strategies for LA in feedyard cattle.

Limitations of the present study include ecological fallacy which has been shown as a major pitfall of most studies utilizing meta-regression techniques (Thompson and Higgins, 2002; Geissbühler et al., 2021). Ecological fallacy, otherwise known as aggregation bias, is based on the “logical fallacy in the interpretation of observed data, and findings at the group level may be either an under- or overestimation of the real association between patient-level characteristics and treatment effect” (Geissbühler et al., 2021). The associations between TG averages and certain group characteristics do not necessarily reflect the association to individual-level

characteristics with accuracy. As previously stated, significant publication biases were found in portions of this study and therefore results of the LA-TG and SLA-TG models should be interpreted with caution as they may be over-inflated. While the final moderators within these models may have over-inflated significant associations, the majority of results in these models align with previous research findings which adds to their credibility. Another limitation of the study was that not all publications included in the meta-regression described experimental trials that accurately portrayed the industry-standard finishing phase – either through altered duration, cohort size, finishing point, or management styles. This reduces the external validity of this study and adds an element of variation that is difficult, if not impossible, to quantify.

Author Contributions

Rachel Champagne (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Phillip Lancaster (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—review & editing), Brad White (Conceptualization, Methodology, Validation, Visualization, Writing—review & editing), Bob Larson (Conceptualization, Methodology, Validation, Visualization, Writing—review & editing)

Disclosures

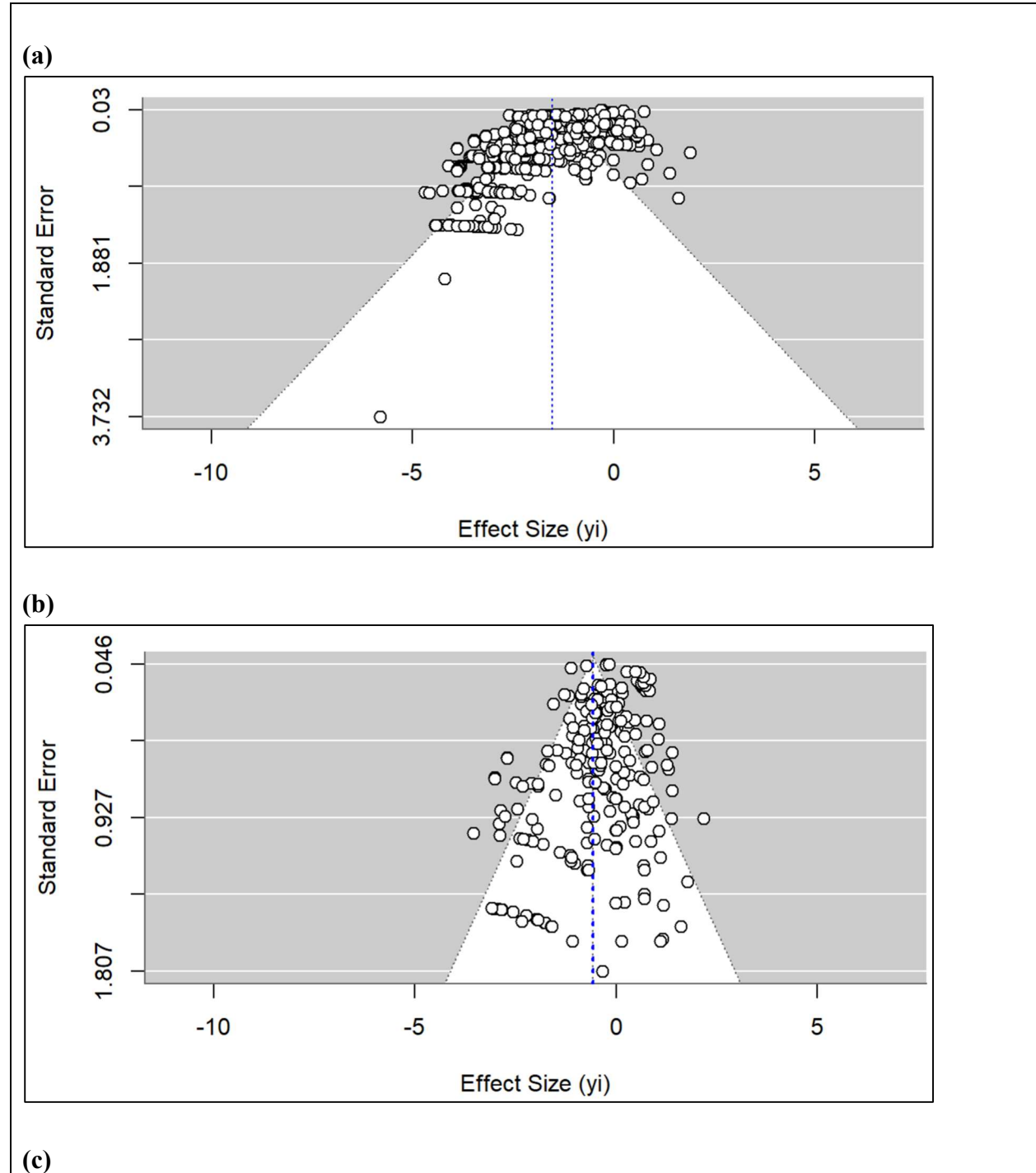
Authors claim no conflict of interest and have nothing else to disclose.

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Figures

Figure 1.1 Funnel plots of the three meta-analyses performed on published studies in finishing cattle: (a) liver abscess (LA) relative to the total cattle in treatment group (TG), (b) severe LA (SLA) relative to the total cattle with LA in TG, and (c) SLA relative to the total cattle in TG. Each circle represents a TG. The middle blue dashed line represents the overall estimated effect size while its 95% confidence limits are within the white triangle.



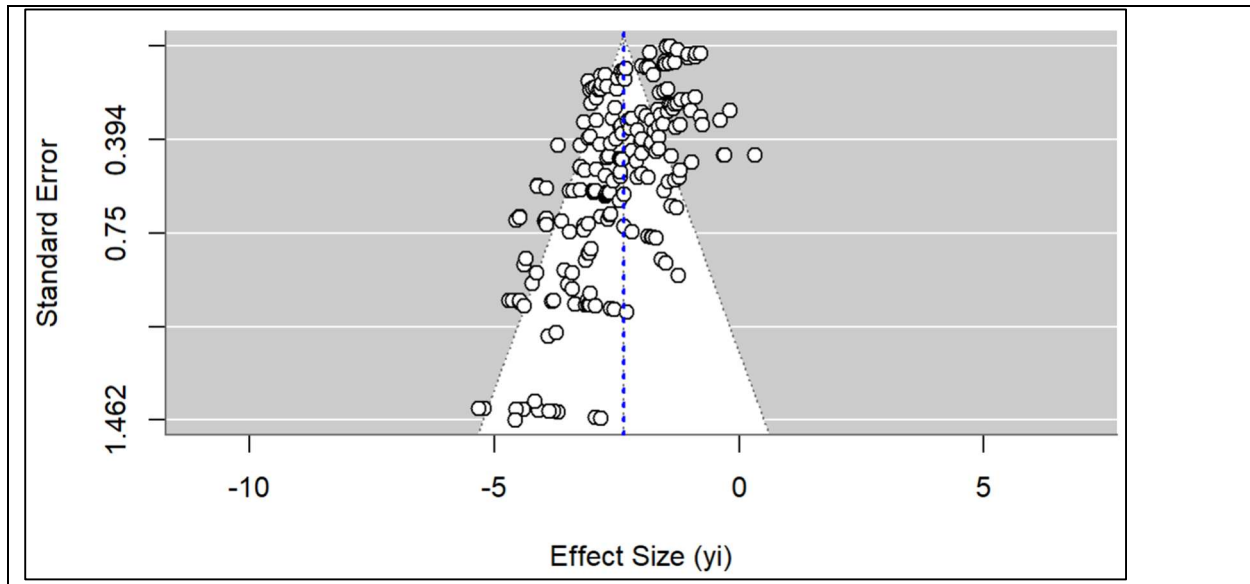
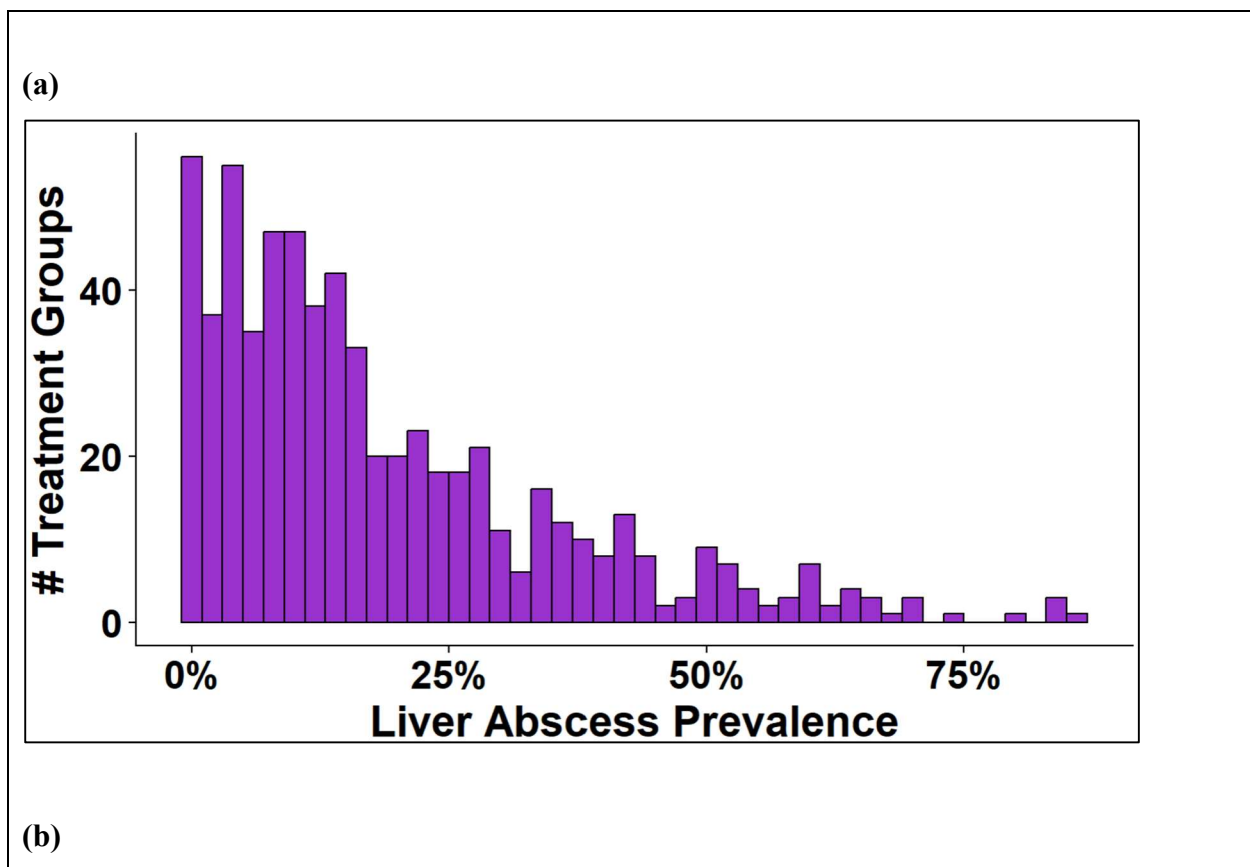
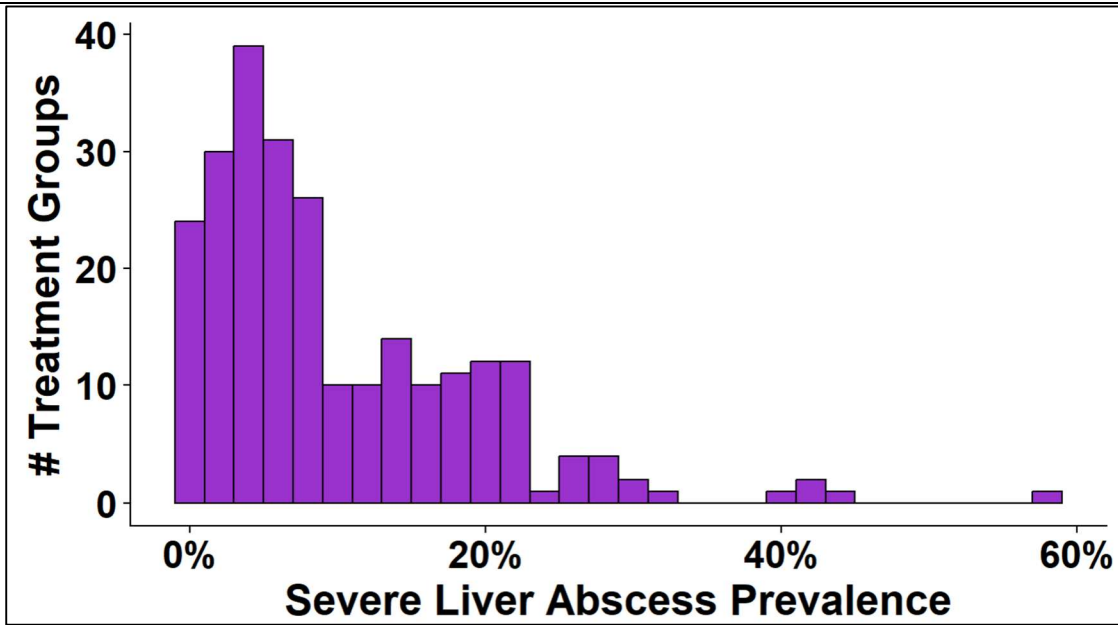
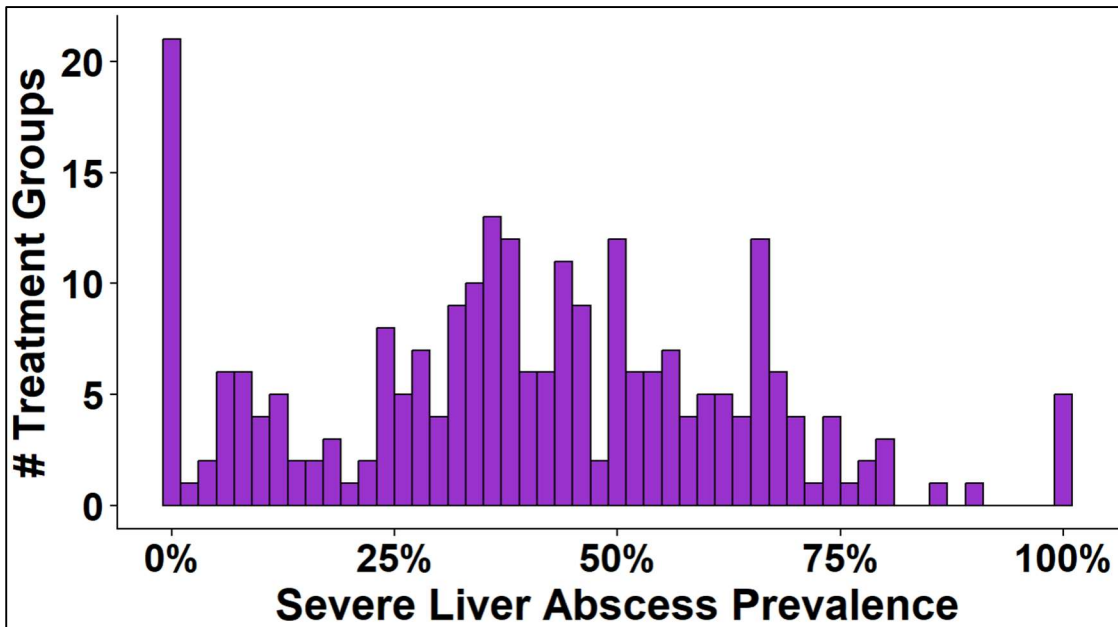


Figure 1.2 Histograms of (a) liver abscess (LA) relative to the total cattle in treatment group (TG), (b) severe LA (SLA) relative to the total cattle with LA in TG, and (c) SLA relative to the total cattle in TG.





(c)



Tables

Table 1.1 Descriptives of studies included in meta-analysis.

Category	Meta-Analysis Dataset*
Publications	115
Experiments	153
Treatments (rows; n)	650
Range (treatments/experiment)	1-16
Average (treatments/experiment)	4.26
Total Number of Animals	84,536
Tylosin (# Treatments)	
Number Rows reporting value	650
Yes	306
No	344
Monensin (# Treatments)	
Number Rows reporting value	650
Yes	406
No	244
Region (# Treatments)	
Number Rows reporting value	650
Canada (CA)	89
Midwest USA (MW)	347
Southwest USA (SW)	104
Other	110
Treatment Size (# cattle/treatment)	
Number Rows reporting value	650
Average	130
Range	5-4431
Sex (# cattle/treatment)	
Number Rows reporting value	650
Steer	501
Heifer	111
Mixed	38
Breed (# Treatments)	
Number Rows reporting value	610
Beef-influenced	567
Bos indicus-influenced	20
Mixed	23
Age (# Treatments)	
Number Rows reporting value	179
Yearling	158
Other	21
Initial Weight (kg) (per Treatment)	

Number Rows reporting value	647
Average	350
Range	213-545
Final Weight (kg) (per Treatment)	
Number Rows reporting value	635
Average	553
Range	197-757
Days on Feed (# Treatments)	
Number Rows reporting value	633
<100	87
100-149	335
150-199	189
200+	22
Average Daily Gain (kg) (ADG/treatment)	
Number Rows reporting value	644
Average	1.50
Range	0.83-2.86
Dry Matter Intake (kg/day/treatment)	
Number Rows reporting value	630
Average	9.63
Range	5.14-14.32
Gain:Feed (per treatment)	
Number Rows reporting value	642
Average	0.1561
Range	0.0659-0.2230
Acid Detergent Fiber (ADF) (% dry matter per treatment)	
Number Rows reporting value	177
Average	8.86
Range	2.8-24.4
Neutral Detergent Fiber (NDF) (% dry matter per treatment)	
Number Rows reporting value	223
Average	18.25
Range	4.6-39.9
ADF:NDF Ratio (per treatment)	
Number Rows reporting value	127
Average	0.52
Range	0.30-0.85
Hot Carcass Weight (Average kg/treatment)	
Number Rows reporting value	507
Average	356.58
Range	210-466.4
Net Energy for Gain (Mcal/kg/treatment)	
Number Rows reporting value	283

Average	1.35
Range	0.23-1.93
Feedings Per Day (# Treatments)	
Number Rows reporting value	362
1	265
2	85
3	12
Roughage (% dry matter per treatment)	
Number Rows reporting value	650
Average	10.28
Range	0-81.53
Roughage NDF Digestibility (%²/hr per treatment)	
Number Rows reporting value	624
Average	0.30
Range	0.04-2.55
Grain (% dry matter per treatment)	
Number Rows reporting value	650
Average	72.1
Range	12.9-97.0
Starch Digestibility (%²/hr per treatment)	
Number Rows reporting value	650
Average	11.8
Range	1.31-23.87
Fibrous Byproduct (% dry matter per treatment)	
Number Rows reporting value	650
Average	9.23
Range	0-60.0
Fibrous Byproduct NDF Digestibility (%²/hr per treatment)	
Number Rows reporting value	650
Average	0.21
Range	0.00-1.71
Liver Abscess (% cattle in treatment)	
Number Rows reporting value	650
Median	13.35
Range	0-87.0
Liver Abscess Score A+ (% LA cattle in treatment)	
Number Rows reporting value	246
Median	6.9
Range	0-57.9
Liver Abscess Score A (% LA cattle in treatment)	

Number Rows reporting value	180
Median	4.11
Range	0-43.48
Liver Abscess Score A- (% LA cattle in treatment)	
Number Rows reporting value	175
Median	6.30
Range	0-27.3
Liver Scars (% cattle in treatment)	
Number Rows reporting value	4
Median	20.0
Range	14.46-26.36
* These values are prior to excluding outliers in the dataset. Data values were entered as value per treatment group (row). Outcome variables (liver abscess, A+ liver abscess, A liver abscess, A- liver abscess) were reported as mean percentage or number affected out of the treatment group size.	

Table 1.2 Description of categorical moderators evaluated in the liver abscess (LA) prevalence and severe LA prevalence models and their respective categories.

Moderator	Category
Tylosin	Yes
	No
Monensin	Yes
	No
Region	Canada (CA)
	Midwest (MW)
	Southwest (SW)
	Other
Sex	Steer
	Heifer
	Mixed
Breed	Beef-influenced
	Bos-indicus-influenced
	Mixed
Age	Yearling
	Other
Days on Feed	<100
	100-149
	150-199
	200+
Feedings per Day	1
	2
	3

Table 1.3 Heterogeneity analysis of each final rma.mv model ran in the present study with and without moderators. Models included in the present study are as follows: liver abscess (LA) out of all animals in a treatment group (TG), severe LA (SLA) out of all animals with LA within TG, and SLA out of all animals within TG. Moderators were selected through a backwards and forwards stepwise selection process based on moderator significance within the model.

Model	σ^2	I2 (%)	H2	Pseudo R2 (%)
LA-TG[†] – Null				
Experiment Only	0.82	62.31	2.65	-
Publication Only	0.77	60.82	2.55	-
Experiment nested in Publication	0.83	62.65	1.84	-
Experiment (1level)*	0.24	18.31	1.49	-
Publication (1level)*	0.59	44.33	2.19	-
LA-TG[†] – Moderators				
Experiment Only	0.52	51.48	2.06	35.83
Publication Only	0.55	52.55	2.11	28.66
Experiment nested in Publication	0.52	51.48	1.53	36.74
Experiment (1level)*	5.63x10 ⁻⁹	0.00	1.00	100.00
Publication (1level)*	0.52	51.48	2.06	10.60
SLA-LA[‡] – Null				
Experiment Only	0.62	46.28	1.86	-
Publication Only	0.67	47.65	1.91	-
Experiment nested in Publication	0.66	47.37	1.45	-
Experiment (1level)*	0.42	30.19	1.57	-
Publication (1level)*	0.24	17.18	1.33	-
SLA-LA[‡] – Moderators				
Experiment Only	0.41	35.79	1.56	35.30
Publication Only	0.46	38.56	1.63	31.07
Experiment nested in Publication	0.46	38.30	1.31	31.05
Experiment (1level)*	0.44	36.59	1.59	-3.37
Publication (1level)*	0.02	1.71	1.03	91.52
SLA-TG[§] – Null				
Experiment Only	0.84	62.85	2.69	-
Publication Only	0.86	63.25	2.72	-
Experiment nested in Publication	0.84	62.85	1.85	-
Experiment (1level) *	2.52x10 ⁻⁸	0.00	1.00	-
Publication (1level) *	0.84	62.85	2.69	-
SLA-TG[§] – Moderators				
Experiment Only	0.42	45.90	1.85	49.85
Publication Only	0.38	43.95	1.77	55.10

Experiment nested in Publication	0.42	45.90	1.42	49.85
Experiment (1 level) *	6.93x10 ⁻⁹	0.00	1.00	72.48
Publication (1 level)*	0.42	45.90	1.85	49.85
*Italicized rows are the amount of heterogeneity attributable to that level (experiment or publication) within the nested structure of the “Experiment nested in Publication” model †LA-TG model evaluates liver abscess (LA) relative to total cattle within treatment group (TG). ‡SLA-LA model evaluates severe LA (SLA) relative to total cattle with LA within TG. §SLA-TG model evaluates SLA relative to total cattle within TG.				

Table 1.4 Egger’s Regression tests performed on asymmetry of funnel plots for all three models ran in the present study: liver abscess (LA) out of all animals in a treatment group (TG), severe LA (SLA) out of all animals with LA within TG, and SLA out of all animals within TG.

Model [†]	Term	β (estimate)	SE (estimate)	t / Wald F*	P-Value (estimate)
LA Prevalence					
	Intercept	-0.53	0.050	-10.55	<0.001
	Precision	0.11	0.011	10.30	<0.001
SLA Prevalence (n=animals with LA within treatment)					
	Intercept	-0.03	0.074	-0.44	0.664
	Precision	0.06	0.018	3.12	0.002
SLA Prevalence (n=treatment size)					
	Intercept	-0.42	0.068	-6.21	<0.001
	Precision	0.10	0.013	7.53	<0.001
*t-statistics are reported for the intercept terms while Wald F-statistics are reported for precision terms. †Funnel plots were created using a null (containing no moderators) rma.mv model with a random effect of experiment nested within publication.					

Table 1.5 Probability of liver abscess out of all animals in a treatment group based on categorical demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Liver Abscess		P-value
Tylosin					<0.001
Yes	-1.90	0.100	0.13	a	

No	-1.29	0.098	0.22	b	
Monensin					<i><0.01</i>
Yes	-1.66	0.098	0.16	a	
No	-1.52	0.102	0.18	b	
Sex					<i><0.01</i>
Steer	-1.23	0.231	0.23	b	
Heifer	-2.05	0.159	0.11	a	
Mixed	-1.50	0.075	0.18	b	

Table 1.6 Probability of liver abscess out of all animals in a treatment group based on continuous demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Slope (logit)	SE (logit)	Average Change in Predicted Prevalence of Liver Abscess (per unit change)	P-value
Final Weight (kg)	0.003	0.0009	0.0002	<i><0.01</i>
Average Daily Gain (kg)	-0.45	0.226	-0.03	<i><0.05</i>
Gain:Feed	-6.11	2.158	-0.50	<i><0.01</i>
Grain (% dry matter)	0.03	0.004	0.002	<i><0.001</i>
Starch Digestibility (%²/hr)	0.03	0.010	0.002	<i><0.01</i>
Fibrous Byproduct NDF Digestibility (%²/hr)	1.41	0.164	0.21	<i><0.001</i>

Table 1.7 Probability of severe liver abscess out of all animals with liver abscess in a treatment group based on categorical demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Severe Liver Abscess		P-value
Tylosin					<i><0.01</i>
Yes	-0.62	0.142	0.35	a	

No	-0.39	0.132	0.40	b	
Region					<i><0.05</i>
Canada (CA)	-0.84	0.140	0.30	a	
Midwest (MW)	-0.77	0.278	0.32	a	
Southwest (SW)	-0.15	0.235	0.46	a	
Other	-0.26	0.195	0.43	a	

Table 1.8 Probability of severe liver abscess out of all animals with liver abscess in a treatment group based on continuous demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Slope (logit)	SE (logit)	Average Change in Predicted Prevalence of Severe Liver Abscess (per unit change)	P-value
Initial Weight (kg)	-0.01	0.002	-0.001	<i><0.001</i>
Final Weight (kg)	0.003	0.0015	0.001	<i><0.05</i>
Fibrous Byproduct (% dry matter)	-0.01	0.005	-0.003	<i><0.05</i>

Table 1.9 Probability of severe liver abscess out of all animals in a treatment group based on categorical demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Severe Liver Abscess		P-value
Tylosin					<i><0.001</i>
Yes	-2.60	0.139	0.07	a	
No	-2.21	0.131	0.10	b	
Monensin					<i><0.001</i>
Yes	-2.58	0.134	0.07	a	
No	-2.24	0.140	0.10	b	
Region					
Canada (CA)	-2.87	0.147	0.05	a	<i><0.001</i>
Midwest (MW)	-2.75	0.241	0.06	ab	
Southwest (SW)	-1.99	0.352	0.12	ab	
Other	-2.02	0.203	0.12	b	

Days on Feed					
<100	-3.30	0.302	0.04	a	<i><0.001</i>
100-149	-2.31	0.155	0.09	b	
150-199	-2.24	0.236	0.10	bc	
200+	-1.77	0.166	0.15	c	

Table 1.10 Probability of severe liver abscess out of all animals in a treatment group based on continuous demographic and ration variables included in final multivariate rma.mv model (# variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Average Change in Predicted Prevalence of Severe Liver Abscess (per unit change)	P-value
Grain (% dry matter)	0.01	0.005	0.0003	<i><0.10</i>

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Chapter 2 - Association of liver abscess with demographic factors, gross pathology, and gastrointestinal histologic morphology in feedyard mortalities

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Abstract

Liver abscesses (LA) are a major cause of hepatic condemnation in feedlot cattle (~20% beef carcasses) creating concerns surrounding carcass contamination, impaired performance, and antimicrobial stewardship. Due to antemortem limitations in determining LA status, risk factors for LA during the feeding phase are poorly characterized. The objective was to identify factors associated with the presence of LA in feedlot mortalities at necropsy, including demographic factors, and gross and histologic gastrointestinal (GI) morphologic lesions. Systematic necropsies (n=900) were performed in 6 central U.S. commercial feedyards (June/July 2022 and 2023). Gross morphologic diagnoses were determined by technicians and confirmed by a veterinarian. Formalin-fixed sections of rumen, small intestine (SI), and spiral colon (SC) were collected from LA cases (n = 40) and time-, feedlot-matched controls (CON; no LA; n=40). Demographic data collected included sex, days on feed at death (DOF), arrival weight, number of disease treatments, and estimated weight at death. Morphologic features were measured in GI tissues

using hematoxylin and eosin stain and alcian blue stain was used to evaluate goblet cell area in SI and SC. General and linear mixed-effects models were used to evaluate LA association with demographic, gross lesions, and histomorphologic changes identified in LA and CON cases. Steers had greater ($P<0.01$) probability of LA than heifers (0.16 vs. 0.06, respectively). Dairy-influenced cases had a greater ($P=0.04$) probability of LA than traditional beef breeds (0.30 vs. 0.03, respectively). Cases that were 101 + DOF had a greater ($P<0.01$) probability of LA than those <50 DOF (0.20 vs 0.06, respectively). Cases with peritoneal adhesions had a greater ($P<0.01$) probability of having LA than cases without peritoneal adhesions. Liver abscess cases had wider ($P = 0.03$) rumen papillae and thinner ($P=0.05$) keratin layer lining papillae in the rumen, and shallower ($P=0.02$) crypts and thinner ($P=0.02$) propria in the SI than CON cases. A tendency ($P=0.08$) for LA cases to have a lower percent area of goblet cells in the SI than CON cases was observed. No differences in SC morphology were observed. Although results are biased to only feedlot mortalities, these findings indicate an association of LA with histomorphologic measures, gross pathology, and demographic factors. Further investigation is required to better understand factors influencing LA formation in feedlot cattle.

Key words: histology; morphology; necropsy; gastrointestinal

List of Abbreviations:

LA – Liver Abscess(es)

CON – mortalities without a liver abscess

GI – Gastrointestinal

SI – Small Intestine

SC – Spiral Colon

DOF – Days on Feed at death

Introduction

Liver abscesses (LA) are a major health issue in feedyard cattle and result in significant economic and performance impacts (Herrick et al., 2024). Liver abscesses were the most common (61.4% of all liver condemnations) cause for liver condemnation and affected 17.8% of all livers from fed cattle (Eastwood et al., 2017). Liver abscess prevalence varies (0% to 95.5% in beef cattle) but is usually between 12% to 32% in most feedlot cattle (Brink et al., 1990; Nagaraja and Chengappa, 1998; Brown and Lawrence, 2010; Grimes et al., 2024). Prevalence seems to depend on multiple factors: roughage level, feedstuff particle size, grain type, breed, sex, etc. (Utley et al., 1973; Fulton et al., 1979; Stock et al., 1987, 1990; Nagaraja and Chengappa, 1998; Amachawadi and Nagaraja, 2016) making it difficult to develop management strategies to reduce prevalence of LA.

The increase in incidence of LA was identified as the most significant finding in the processing floor audit portion of the 2016 National Beef Quality Audit (Eastwood et al., 2017). Overall, LA incidence is relatively constant, however, the proportion of severe abscesses is increasing causing losses in production (Nagaraja and Lechtenberg, 2007). Condemned livers reduce the value of the overall carcass while simultaneously reducing hot carcass weight and carcass yield, particularly if abscesses are severe (Nagaraja and Lechtenberg, 2007; Brown and Lawrence, 2010). Liver abscesses may burst during evisceration causing entire viscera condemnation or carcass contamination which slows the production line (Nagaraja and

Lechtenberg, 2007). In addition, LA have been shown to reduce performance parameters during the feeding phase (Brink et al., 1990; Brown and Lawrence, 2010; Rezac et al., 2014).

Cattle with severe LA have been observed to have reductions in average daily gain as severe as 14% and gain-to-feed ratios that are decreased by as much as 13% (Brink et al., 1990). Carcass characteristics of 12th rib fat thickness and LM area were also reduced in carcasses that had LA (Brown and Lawrence, 2010; Rezac et al., 2014). Severe liver abscessation and abscesses potentially bursting during harvest lead to reduced hot carcass weight and red meat yield due to carcass trimming.

Little work has been done to characterize incidence and risk factors for LA during the feeding phase due to difficulty in diagnosing LA status antemortem. Cattle with LA do not exhibit clinical signs and blood culture or blood biomarker tests for diagnosing LA have been explored with variable results (Nagaraja and Lechtenberg, 2007; Herrick et al., 2020; Thompson et al., 2025). The liver is ideal for ultrasonographic imaging due to its location and tissue consistency (Nagaraja and Chengappa, 1998). However, ultrasound cannot visualize the entire liver and is impractical to employ in a commercial feedyard setting (Nagaraja and Chengappa, 1998; Nagaraja and Lechtenberg, 2007). Since diagnosis of LA can only accurately be performed at harvest or necropsy, there is no reliable way in live animals to know how LA develop throughout the feeding period.

Historically, LA etiology has been thought to begin with GI wall pathology. Most studies found associations between rumen lesions and LA and explain that rumenitis, due to acidosis and other insults, leads to increased permeability of ruminal epithelium allowing microbes access to the liver via the portal vein and embolize in the liver to form abscesses (Smith, 1944; Jensen et al., 1954; Nagaraja and Chengappa, 1998; Rezac et al., 2014). However, not all studies have

shown an association of LA with ruminal lesions (Amachawadi and Nagaraja, 2016). Longer periods of lower rumen pH damage the ruminal wall (Steele et al., 2011; Sun et al., 2018; Hu et al., 2022) and steers with LA have lower ruminal pH for longer periods of time than steers without LA (Theurer et al., 2021). Acidotic conditions damage GI mucosa and change GI microbial populations (Kleen et al., 2003; Steele et al., 2016). Acidosis can take many forms: acute ruminal acidosis, subacute ruminal acidosis (SARA), and hindgut acidosis (Galyean and Rivera, 2003; Schwartzkopf-Genswein et al., 2003; Steele et al., 2011). It is not uncommon to see concurrent hindgut acidosis with acute acidosis or SARA. Acidosis in the hindgut may intensify the effects of mucosal damage and microbial leakage due to histologically thinner mucosa compared to the rumen (Li et al., 2012). The role of hindgut acidosis has been of interest since the discovery of LA containing *Salmonella* which indicates LA etiology may involve the SI and SC more than previously thought (Amachawadi and Nagaraja, 2015). Previous work has found associations between changes in GI organ acidity and alterations to corresponding GI epithelium (Plaizier et al., 2008; Steele et al., 2009), which is consistent with the GI damage involved in the current proposed pathophysiology of LA. However, no literature exploring GI histopathology as it directly relates to LA is available. A few studies have found differences in the transcriptomes of rumen and ileal tissue in LA cases compared to controls indicating changes in metabolic function (Abbas et al., 2020; LindholmPerry et al., 2024). Improved understanding of LA disease process, timing, and risk factors will ultimately allow for improved therapeutic interventions.

Based on available literature, we hypothesize that LA occurs throughout the feeding period and are associated with both gross and histologic GI lesions. The objective of the current

study was to determine associations of LA at necropsy with demographic factors, gross and histomorphologic lesions in the GI tract of feedyard mortalities.

Materials and methods

No IACUC approval was required for the current study after concurrent agreement with the Institutional Animal Care and Use Committee (IACUC) since evaluations were only performed on cattle mortalities.

Experimental Design

A cross-sectional, observational case control study (observational unit: individual animal feedyard mortalities) was designed to evaluate LA lesions observed throughout the feeding period in cattle mortalities from all causes of death. Necropsies were performed at six high plains feedyards during the months of June and July in consecutive years (2022 & 2023). All yards incorporated tylosin phosphate in the diet at label recommended levels (60 to 90 mg per head per day) for the entirety of the feeding period to address LA risk. Finishing rations were based on steam-flaked corn with target bulk density of 0.33 kg/L (26 lb/bu) and contained ~6% roughage, consistent with finishing rations used in High Plains feedyards. Mortalities enrolled in the study had died within 18 hours of postmortem examination and/or had minimal to no gross autolysis. Autolysis was determined by the individual performing the postmortem examination based on external appearance, tissue color, smell, and texture.

Postmortem Evaluation

A full systematic necropsy was performed by modifying previously described procedures (Griffin, 2020; Schmidt et al., 2023). If pathology or abnormalities were present in any of the body systems evaluated during necropsy (cardiovascular, GI, integument, lymphatic, musculoskeletal, respiratory, urogenital), they were documented in the case's necropsy record and pictures were collected. Necropsies were conducted in groups of two veterinary technicians [REC, PHS, MM, MJ, LC, KL, KN] with one technician performing the postmortem examination, determining gross lesions and appropriate morphologic diagnosis. Systematic evaluations of cardiovascular, GI, integumentary, lymphatic, musculoskeletal, respiratory, and urinogenital systems were conducted for each carcass. Postmortem morphologic diagnoses based on gross findings were confirmed by a veterinarian [BJW]. Individual case demographics were collected from the feedyard following necropsy.

During necropsy, livers were examined externally and then incised in 2.5-cm thick cross sections to observe the interior hepatic parenchyma for lesions. Hepatic abscesses were scored using a modified Elanco Liver Check System (Elanco, Greenfield, IN). A score of "O" indicated no abscesses in the liver. An "A" indicated one or two small abscesses or up to 2 to 4 well-organized abscesses (generally under 2.54 cm in diameter). An "A+" indicated 1 or more large abscesses (over 2.54 cm in diameter). All cases were classified as either O, A, or A + in the dataset.

Histology

Gastrointestinal samples were collected from all LA cases throughout the study. Once a case with LA was identified and GI samples were collected, GI samples were collected from a

case without LA from the same feedlot as soon as possible, to provide a location and temporally matched control (CON) for each LA case. Gastrointestinal samples were collected as a 1 × 1 cm square from three locations: ventral sac of rumen, duodenojejunal junction, and SC. All three samples were preserved in one container of 10% neutral buffered formalin per mortality case.

Samples were trimmed, embedded in paraffin, and sectioned by the histopathology laboratory at the Kansas State Veterinary Diagnostic Laboratory for histologic analysis. Routine staining was completed using hematoxylin and eosin (H&E) and alcian blue (pH 2.5 with brazilian blue counterstain). One slide per case per tissue was generated. For histologic and goblet cell analysis, slides were scanned on brightfield Leica Aperio AT2 scanner at 400x magnification to create digitalized versions of the slides (Leica Biosystems, Milton Keynes, United Kingdom; 400x). Morphologic measurements were obtained from H&E slides using the measuring tool in Aperio eSlide Manager software (Version 12.4.3.5008, Leica Biosystems, Deer Park, IL). To evaluate goblet cell area, five digital images per Alcian Blue slide were collected at 20x magnification in Aperio eSlide Manager. Goblet cell area for SI and SC tissues from the images were quantified using the Colour Deconvolution2 tool in the open-source image analysis software Fiji (Ruifrok and Johnston, 2001; Schindelin et al., 2012; Landini et al., 2021). Goblet cell area was expressed as percent area of goblet cells stained by Alcian Blue per high power field. All slides were examined and measured by one operator [REC, with guidance from BLP] who was blinded to gross diagnosis determined in the field during the histologic measurement collection process. Collection of five replicates of each measurement was attempted from each tissue. Examples of images from histology slides are included in Figure 2.1. Criteria for morphologic measurements collected are summarized in Table 2.1.

Statistical Analysis

Descriptive statistics were performed on all cases meeting inclusion criteria relative to known demographic factors, gross necropsy observations, and histology. Two datasets were created from the raw data.

Gross Necropsy Dataset

To evaluate the relationship of LA occurrence with demographic factors and gross pathologic lesions, a Gross Necropsy dataset was created. To be included in the Gross Necropsy dataset, a necropsy case was required to be of a mortality that occurred ≤ 18 hours prior, received LA score, and had data on demographic factors.

First, the association between liver abscess status and each demographic and gross pathologic variable evaluated was evaluated using Cramer's V and a Chi-squared analysis. Cramer's V provides a relative measure of association between categorical variables. Values range from 0, indicating no association, to 1, indicating a very strong association. Cramer's V was computed using `cramerV` function in R statistical software (<https://cran.r-project.org/web/packages/>; 31 October 2022), and Chi-square analysis performed using `chisq.test` function.

Second, linear mixed-effects models were created to evaluate the association of LA with demographic factors and gross pathologic lesions using the `lmer` function from the `lme4` package of R statistical software. A multivariate model was developed using backward stepwise techniques where all variables with $P \leq 0.30$ from univariate models were included in the initial multivariate model and only variables with $P < 0.10$ were included in the final model. Feedyard and year were included as random effects to account for the lack of independence among cases.

Factors evaluated included: LA score, breed, arrival weight, current estimated weight, days on feed (DOF), number of disease treatments, sex, autolysis, and factors for assessing gross pathology (SI serosa, SI mucosa, SI content, SI total*, SC serosa, SC mucosa, SC content, SC total*, rumen mucosa, rumen content, rumen total*, abomasum mucosa, peritoneal fluid, peritoneal adhesions, mesenteric lymph nodes, liver color, kidney, spleen, other organs total*). Descriptions of how data were categorized in these variables are included in Appendix Table B.1. Two-way interactions were tested and removed when not significant.

*“Total” indicates factors that were developed by combining all categories pertaining to the respective organ to classify the entire organ as “normal” or “abnormal.” (Ex: “SI total” combines SI serosa, SI mucosa, and SI content into one variable; if any one of the contributing variables was recorded as “abnormal,” the “SI total” variable was recorded as “abnormal”).

Histologic dataset

To determine differences in histologic features of the GI system between LA and CON cases, a histologic dataset was created using the formalin-fixed GI tissues and the corresponding case information. To be included in the Histologic dataset, a necropsy LA case required 1) minimal autolysis, 2) the liver to be evaluated for abscesses upon necropsy, 3) demographic information to be available, 4) formalin-fixed GI samples to be collected, and 5) a time-, feedyard-matched non-abscessed liver case that also met the inclusion criteria for the Histologic dataset.

First, a principal component analysis followed by a multivariate analysis of variance (MANOVA) was performed to evaluate the combined effect of liver abscess status on gastrointestinal morphology. Principal components were computed across all gastrointestinal

histologic measurements encompassing both years and all feedyards using `prcomp` function in R statistical software. The Scree plot was used to assess the most important principal components, which were used in the MANOVA. Multivariate analysis of variance was accomplished using the `manova` function in R statistical software. A backward stepwise technique was used where the initial model included all demographic and gross pathology variables and only variables with $P < 0.10$ were included in the final model.

Second, linear mixed-effects models were created using the `lmer` functions from the `lme4` package of R Studio to evaluate differences in histologic features of rumen, SI, and SC between LA and CON cases. A model was created for each histologic measurement (Table 2.1) where histologic measurement was the outcome variable. All multivariate models were developed using backward stepwise techniques where all variables with $P \leq 0.30$ from univariate models were included in the initial multivariate model and only variables with $P < 0.10$ were included in each final model. Feedyard, year, and individual animal case number were used as random effects to account for lack of independence between the 5 replicate histologic measurements on each sample. The independent variable of interest was LA vs. CON, and other factors were evaluated in the model to account for potential confounding factors which included breed, arrival weight, current estimated weight, days on feed, number of disease treatments, sex, autolysis, and factors for assessing gross pathology (SI serosa, SI mucosa, SI content, SI total*, SC serosa, SC mucosa, SC content, SC total*, rumen mucosa, rumen content, rumen total*, abomasum mucosa, peritoneal fluid, peritoneal adhesions, mesenteric lymph nodes, liver color, kidney, spleen, other organs total*). Descriptions of how data were categorized in these variables are included in Appendix Table B.1. Least-square means for morphologic measurements are presented for the variable of interest but not for other significant variables in the models.

Results

Nine hundred and thirty-five necropsies were performed. After exclusion criteria were applied to the Gross Necropsy dataset, thirty-five cases were excluded. Thirteen cases were excluded due to severe gross autolysis. Two cases were excluded for incomplete necropsy due to carcass removal for rendering prior to full necropsy completion. Fifteen cases were excluded due to incomplete demographic data from the feedyards. Five cases were excluded due to failure to record presence/absence of LA. Nine hundred complete necropsies met the inclusion and exclusion criteria for the Gross necropsy dataset. Case demographics are presented in Table 2.2. Heifers made up 67.7% of the cases, while the remaining 32.3% were steers, which was consistent with the feedyards' live cattle enrollment at the time of the study. Cattle of traditional beef breed origin accounted for 96.8% of the cases. Dairy or dairy-influenced cases made up the remaining 3.2%. Arrival weight ranged from 160 to 537 kg, with the majority (58.9%) of cases presenting arrival weights between 272 and 363 kg. The mean arrival weight was 332 kg (SD = 53). Days on feed (DOF) at death ranged from 1 to 226 d with cases relatively evenly distributed between 0 to 50 d (33.7%), 51 to 100 d (25%), and >100 d (41.3%). The mean DOF was 88 (SD = 55). Overall performance data of cattle cohorts from which feedyard mortalities came is detailed in Appendix Table B.2. Liver abscesses were observed in forty-eight cases across six feedyards. Of these, two LA cases were excluded due to severe autolysis and one LA case was excluded due to the case not having demographic data from the feedyard. Thus, forty-five cases met the inclusion criteria for fixed GI tissue sample collection (ventral sac of rumen, duodenojejunal junction, and SC) at the time of necropsy. Four LA cases (and their corresponding CON cases) were excluded due to inadequate labeling of the sample containers.

One LA case (and its corresponding CON case) was excluded from the final dataset due to incomplete feedyard history records on the CON case. In the case that an individual tissue sample was not collected at necropsy, the tissues obtained were included in the final analysis and the absent tissue was recorded as “Did not obtain” (DNO).

Gastrointestinal samples from eighty cases met the inclusion and exclusion criteria and were considered in the Histologic dataset (Table 2.2). Heifers made up 60% of the cases, while the remaining 40% were steers. Cattle of traditional beef breed origin accounted for 95% of the cases. Dairy or dairyinfluenced cases made up the remaining 5%. Arrival weight ranged from 253 to 502 kg, with the majority (61.2%) of cases having arrival weights between 272 and 363 kg. Days on feed (DOF) at death ranged from 5 to 222 d. Most of the cases were on feed for more than 100 d (55.0%).

When GI tissue samples were evaluated with microscopy, some measurements could not be obtained in five replicates as attempted. Multiple factors contributed to the collection of less than five replicates including tissue microscopic autolysis, tissue fracturing/crushing during slide preparation, or poor staining. When possible, tissues were recut and re-stained to make a new slide in an attempt to yield more measurable results. However, in some cases the goal of five replicates per measurement per tissue still could not be achieved. In this case, the measurements that could be collected were used in the dataset (these are detailed in Appendix Table B.3).

Gross Results

Of the nine hundred cases with gross necropsy results, forty-eight cases had LA (5.3%). Cases that had LA (n = 48) and cases that didn't have LA (n = 852) were evaluated to determine potential associations between LA and other factors. Initial evaluation indicated that current

estimated weight, days of feed at death, sex, presence/absence of peritoneal adhesions, and normal/abnormal mesenteric lymph nodes were significantly associated ($P \leq 0.05$) with LA (Appendix Table B.4). However, the associations were weak with Cramer's V ranging from 0.07 to 0.15. None of the other demographic or gross pathology variables were associated ($P > 0.10$) with LA.

In the multivariate models, the interaction between DOF and arrival weight on LA probability was tested and not included in the final gross necropsy model ($P = 0.53$). The presence of LA was associated with sex ($P < 0.01$) with steers having a greater probability than heifers (0.16 versus 0.06, respectively; Table 2.3). When breed was evaluated, dairy-influenced cases had a greater ($P = 0.04$) probability than traditional beef breeds (0.30 vs. 0.03, respectively). Cases that were 101 d or more on feed at death were more likely ($P < 0.01$) to have LA than cases on feed less than 50 d (0.20 vs. 0.06, respectively). However, no difference was detected between cases 50 to 100 DOF and either of the other groups (100 DOF). The presence of peritoneal adhesions at necropsy was positively associated ($P < 0.01$) with having LA (adhesions present: 0.18 vs. adhesions absent: 0.05). Cases < 273 kg at arrival and cattle 273 to 363 kg at arrival had a greater ($P = 0.09$) probability of LA than cattle having arrival weight >363 kg (0.14 and 0.13 vs. 0.05). Cases with normal rumen mucosa at necropsy tended ($P = 0.08$) to have a greater probability of LA than cases with abnormal mucosa (0.14 vs 0.07). Cases with normal mesenteric lymph nodes tended ($P = 0.10$) to have a greater probability of LA than cases with abnormal mesenteric lymph nodes (0.15 vs. 0.07). No other variables, including gross GI pathology, were significantly associated with having LA.

Of the forty-eight cases with LA, twenty received an abscess score of "A" (41.7%), twenty-eight received an abscess score of "A+" (58.3%). The remaining eight hundred and fifty-

two (94.7%) cases received an abscess score of “O” to indicate no abscesses present. Of the cases with LA ($n = 48$), a case had a greater probability of having a score of “A+” if the case had concurrent peritoneal adhesions ($P=0.01$) or abnormal SC content ($P = 0.01$) as shown in Table 2.4. A tendency ($P=0.09$) was observed for LA cases with grossly normal SI to be more likely to have “A+” abscesses.

Histologic Results

Analysis of the combined gastrointestinal histologic measurements resulted in 18 principal components (Appendix Table B.5) and based on the Scree plot (Appendix Figure B.1), the top 4 principal components, which explained 58% of the variation in the histologic measurements, were further evaluated. Small intestine villus width, crypt depth, and crypt width were the top 3 most important variables contributing to principal component 1, rumen papillae length, papillae area, and papillae width were the top 3 most important variables contributing to principal component 2, rumen papillae keratin, spiral colon goblet cell area, and small intestine propria thickness were the top 3 most important variables contributing to principal component 3, and rumen stratum spinosum, stratum granulosum, and stratum corneum were the top 3 most important variables contributing to principal component 4 (Table 2.5). Results of MANOVA revealed that liver abscess status explained a significant ($P=0.04$) amount of variation in the principal components (Table 2.6) while accounting for possible confounding demographic and gross pathology variables [sex ($P=0.01$), number of pulls ($P<0.01$), autolysis ($P<0.01$), rumen content ($P=0.04$), rumen total ($P=0.02$), small intestine mucosa ($P=0.08$), small intestine content ($P<0.01$), small intestine total ($P=0.02$), spiral colon content ($P=0.03$), peritoneal adhesions ($P=0.01$)].

Individual histologic tissue measurements from cases with LA (n = 40) and CON cases (n = 40) were evaluated to determine potential differences in histologic measurements (Table 2.7). Cases that had LA had wider rumen papillae ($P=0.03$) and thinner papillae keratin thickness ($P=0.05$) compared with CON cases (Figure 1a and b). Cases with LA also tended ($P=0.10$) to have a thinner rumen stratum granulosum layer. Cases with LA had shallower ($P=0.02$) crypts and thinner total propria ($P=0.02$) in the SI than those without LA (Figure 2.1c and d). A tendency ($P=0.08$) for cases with LA to have a lower percent area of goblet cells in the SI was observed. No differences were detected in SC morphology between LA and CON cases. Other demographic and gross pathologic factors significant in histologic statistics models are presented in Appendix Tables B.6, B.7, and B.8.

Discussion

Liver abscesses continue to be a major health issue in feedyard cattle with many important performance and economic issues. While much research has been done to determine LA prevalence and associations with concurrent pathologic lesions, the majority of work has been done at harvest due to the limitations of pre-mortem examination of LA. postmortem examinations at the feedyard allow LA and other necropsy lesions status to be evaluated throughout the feeding phase. Pairing necropsies with histologic evaluation of GI tissue provides a valuable method to better understand potential LA etiopathogenesis and characteristics of the affected animals. The goal of the current study was to identify associations of LA at necropsy with demographic factors, gross and histomorphologic GI lesions in feedyard mortalities.

Gross Necropsy

As diagnosed upon necropsy, 5.3% of cases had LA. In previous studies, much larger LA prevalences have been observed in feedyard cattle with a typical range of 12% to 32% or higher (Herrick et al., 2022; Grimes et al., 2024). The prevalence of LA observed in the current study varies from previous work due to differences in study population. The current study included postmortem evaluations of feedyard mortalities from deaths of various causes occurring at various times across the feeding period (<50 to >150 DOF). Previous studies commonly used data collected from animals at harvest, which by definition did not die during the feeding phase in order to be evaluated at harvest. Currently, we have no previous work utilizing a similar population of feedyard mortalities to form an expected prevalence for LA. Thus, the overall prevalence of LA being different in the current study when compared to previous work is expected since population type and size is vastly different. The current study population was also predominantly heifers, which has been shown (in the current study and previous work) to be associated with a lower probability of LA (Smith, 1998; Grimes et al., 2024). Liver abscess prevalence and severity also vary by season and geographic location (Herrick et al., 2022) which may have also affected prevalence in the current study; reported prevalence in harvest fed cattle was 25.5% in the Central Plains. Additional cross-sectional studies in different locations and at varied times of year would be helpful to better describe LA prevalence in feedyard mortalities at a range of DOF.

When demographic and gross necropsy data were evaluated for associations with LA, cases had a larger probability of having LA if it had dairy-influence, was a steer, was greater than 100 DOF, or had peritoneal adhesions present at necropsy. Liver abscesses are well-documented as having a higher prevalence in Holstein cattle than in traditional beef breeds at

harvest (Amachawadi and Nagaraja, 2016; Herrick et al., 2022; Grimes et al., 2024). Beef-dairy crossbreds have a prevalence of LA greater than either Holsteins and traditional beef breeds (Grimes, 2022). It has been suggested that the increased prevalence in beef-dairy crossbreds is multifactorial. Dairy-influenced animals spend more DOF at the feedyard (Amachawadi and Nagaraja, 2016) resulting in more time on high-concentrate finishing diets and increased opportunity to develop LA. Dairy-influenced animals have been reported to have a greater feed intake than beef animals as well as an increased incidence of digestive-related upsets and deaths (Nagaraja and Chengappa, 1998). Ingestion of non-feedstuff materials (such as hair, soil, rocks, plastic, etc.) has also been shown to be more common in dairy-influenced cattle which may contribute to rumen wall irritation with or without acidosis being present (Amachawadi and Nagaraja, 2016). All these differences may play a role in dairy-influenced animals having greater prevalence of LA, which could exacerbate the LA issue as beef-dairy cross calves increase in proportion of cattle at feedyards.

Trends around feed consumption and growth rates also may account for the difference in LA probability based on sex. The current study found that steers are more likely to have LA than heifers, which agrees with previous studies (Smith, 1998; Grimes, 2022; Grimes et al., 2024). Greater feed consumption and growth rates observed in steers may predispose them to acidotic episodes (Hicks et al., 1990; Amachawadi and Nagaraja, 2015, 2016). A greater frequency of acidosis would, in theory, contribute to the pathogenesis of GI mucosal damage leading to LA. Additionally, heifers are smaller framed and have lighter finishing weights which may allow them to finish the feeding phase in a shorter time period than steers, thus limiting their days at risk for LA (Nagaraja and Chengappa, 1998; Amachawadi and Nagaraja, 2016). One study did

report heifers to have a numerically greater incidence of LA than steers, however the difference was small (Herrick et al., 2022).

Finally, the only significant gross lesion observed at necropsy that had an association with LA was peritoneal adhesions. In previous studies, finding peritoneal adhesions with LA was common enough that authors classified these animals in a separate scoring category from those with LA alone (Brown and Lawrence, 2010; Herrick et al., 2022; Linneen et al., 2023; Grimes et al., 2024; McDaniel et al., 2024). Cattle with LA and adhesions have reduced HCW, require more carcass trimming, and have reduced performance at the feedyard (Nagaraja and Chengappa, 1998; Brown and Lawrence, 2010; Reinhardt and Hubbert, 2015). Studies have reported LA associated with adhesions to be the largest cause of lost revenue and efficiency at processing on top of the performance reductions during feeding (Broadway et al., 2024). The existence of LA and peritoneal adhesions together in the same animal is logical considering the location of the liver in the abdomen and the infectious nature of abscesses. However, due to the observational nature of the current study, causation cannot be determined. A LA may have ruptured and served as the inciting cause for adhesion formation, or there may have been primary peritonitis as evidenced by peritoneal adhesions that then infected the liver and caused abscess formation. More research is needed to understand these potential pathways more clearly. Peritoneal adhesions were also associated with having a worse abscess score among LA cases. Previous work agrees and has shown that animals with LA and peritoneal adhesions were a larger source of losses at harvest than animals with only LA (Nagaraja and Lechtenberg, 2007; Brown and Lawrence, 2010; Amachawadi and Nagaraja, 2015).

An interesting finding in the Gross Necropsy portion of the current study was the absence of significant association between LA and gross pathology in the rumen, SI, and SC. Gross GI

pathology was observed in one or more organs in 50% of cases in the current study, which aligns with previous work demonstrating approximately 20% to 50% of animals at harvest have ruminal lesions alone (Smith, 1944; Jensen et al., 1954; Rezac et al., 2014). No published studies have thoroughly evaluated the association of LA with prevalence of SI or SC lesions in fed cattle. However, when evaluated for significance in the current study, no gross GI pathologies were found to be associated with LA. The lack of significant association was the opposite of what was expected as the current pathogenesis of LA indicates bacteria leakage through damaged GI mucosa to form abscesses in the liver, and previous work has found gross GI lesions to be associated with LA prevalence (Jensen et al., 1954; Smith, 1998; Rezac et al., 2014). Later studies confirmed the pathogenesis by detecting corresponding microbial isolates from LA and ruminal walls in the same animals (Narayanan et al., 1997; Tadepalli et al., 2009). However, some work has found lower magnitude of association between LA and GI lesions or no association at all (Rezac et al., 2014). Interestingly, associations were found in the current study between LA cases with an “A+” score and GI/abdominal pathology. A potential alternative etiology of LA may be increased GI permeability due to causes other than widespread inflammation such as focal abrasion due to foreign objects (Broadway et al., 2024).

A secondary study objective was to determine the prevalence of LA throughout the feeding period. In previous research performed at harvest, researchers had no way of determining when the observed LA had initially formed. Previous work has suggested that LA occur more commonly later in the feeding period due to rations containing more starch, increased risk of LA accrued over more DOF, and the increased variation in feed consumption seen in heavier cattle (Nagaraja and Lechtenberg, 2007; Castillo-Lopez et al., 2014). It has also been suggested that cattle are at greater risk of ruminal acidosis if not transitioned to high-concentrate rations

appropriately (Brown et al., 2006; Meyer and Bryant, 2017). Increased risk for ruminal acidosis may also imply increased risk for other related health issues, such as LA, in transition animals (Theurer et al., 2021), but the incidence of ruminal acidosis may increase later in the feeding period (Castillo-Lopez et al., 2014) when animals are consuming large amounts of highly fermentable starch. Filling in the gaps of LA pathogenesis, such as when they form, allows better identification of animals at risk and better therapeutic efforts. In the current study, LA was observed throughout the feeding period. However, the probability of LA was greater in cases that had been on feed for longer than 100 d compared to those on feed less than 50 d. More research on LA throughout the feeding period is needed to fully characterize abscess formation and development patterns.

Histologic Dataset

While research evaluating histologic parameters as they relate to LA has not been performed, some previous research on the effects of diet, feed restriction, acidosis, etc. on histologic GI features is available (Dirksen et al., 1985; Kvidera et al., 2017a, 2017b; DeClerck et al., 2020). Still, little is known about the effects that diet, acidosis, LA, and other factors may have on specific GI morphology and vice versa. More work needs to be done to evaluate the microscopic changes within various GI tissues in relation to these conditions, and particularly LA. Since GI pathology is an integral part of the proposed LA etiology, exploring microscopic anatomy of the GI system will fill these knowledge gaps.

The rumen mucosa serves as a barrier between rumen contents and portal circulation (Graham and Simmons, 2005). Of the eight rumen parameters that were measured in the current study, only two were found to have significant differences between LA status—rumen papilla

width and papilla keratin thickness. Wider rumen papillae provide more surface area for nutrient and volatile fatty acid (VFA) absorption (Dirksen et al., 1985). Previous studies have shown varying results of factors affecting papilla size, shape, and area. Some have shown higher energy rations leading to increased papillae size (Dirksen et al., 1985). Others have shown decreased papillae size with higher energy rations (Steele et al., 2011; DeClerck et al., 2020). Still other studies showed no effect of diet on papillae size but did show differences in gene expression in the rumen epithelium (Novak et al., 2019). Likely the differences can be at least partially explained by the differences in time spent on feed in these studies as some work suggests differences between short-term and long-term responses of the rumen epithelium to high-concentrate diets (Dieho et al., 2016; Ferguson et al., 2022). No research has been done evaluating associations between LA and rumen papillae size. The results of the current study indicated that rumen papillae width was significantly greater in LA than CON cases. Cattle will adapt to low rumen pH by increasing VFA absorption through greater papillae size (Dirksen et al., 1985; Hu et al., 2022) indicating that LA cases may have been adjusting to rumen acidosis. In addition, the keratin layer on the papillae was thinner in cattle with LA when compared to CON cases. The reduction in rumen keratin layer has been shown to make the epithelium more absorptive to VFAs (Dirksen et al., 1985; Steele et al., 2009). It logically follows that a thinner keratin layer would also be more permeable to bacterial translocation. More research is needed to evaluate the relationship between rumen papillae parameters and other factors such as diet and LA.

Similar inconsistency in study results exists for rumen epithelial layers, particularly the stratum corneum and stratum granulosum. Some studies observed increased stratum corneum and stratum granulosum thickness with a larger proportion of cereal grains included in the ration

(Ferguson et al., 2022). While other studies found these parameters to be decreased when placed on a high grain diet as a means to induce ruminal acidosis (Steele et al., 2009, 2011). Differences may once again be related to differences in DOF and the speed at which animals were transitioned to a high-concentrate ration. Keratin forms a layer on the surface of the ruminal epithelium that serves as a protective measure from caustic substances (such as acid) that may be in the rumen (Lavker and Matoltsy, 1970). In the current study, cases with LA had thinner layers of keratin on rumen papillae than controls. A thinner keratin layer could contribute to greater permeability of the rumen wall and more translocation of bacteria into the abdomen, particularly under acidotic conditions. In addition, cases with LA tended to have a thinner stratum granulosum. Stratum granulosum has the most desmosomes and tight junctions of any of the four layers of rumen epithelium (Graham and Simmons, 2005) and is believed to contribute the most to the barrier function of the rumen epithelium (Ji et al., 2021). A thinner stratum granulosum would drastically change rumen wall permeability and make it easier for microbes to migrate into the abdomen to potentially form LA. More work is needed in evaluating the ruminal epithelium and its relationship/response to multiple conditions including acidosis and the effect on development of LA.

The post-ruminal GI system has recently been a topic of interest for both acidosis and LA research. Recent LA pathogen discoveries have suggested that acidosis can extend into the hindgut which includes the SI, large intestine, and cecum (Li et al., 2012; Amachawadi and Nagaraja, 2015; Broadway et al., 2024). Six parameters were evaluated in the SI, but only reduced crypt depth and reduced overall proprial thickness were significantly associated with LA. Crypts in the SI are invaginations that house multiple types of cells (Crosnier et al., 2006), which of particular interest include germ cells and goblet cells. Germ cells allow the animals to

regenerate lost epithelium (Crosnier et al., 2006). Thus, reduced crypt depth may lead to reduced function of germinal cells and the reduced capacity of SI for regeneration and repair after insult. Reduced repair capacity may lead to increased permeability of the SI wall and increased likelihood or permissiveness for translocation of bacteria.

Goblet cells are highly differentiated cells that secrete mucin in the SI and SC (Crosnier et al., 2006; Chase and Kaushik, 2019). They help form the brush border which is a crucial part of mucosal immunity in the GI tract. The mucous layer secreted by goblet cells prevents microbes from interacting directly with tissue and translocating into the body (Chase and Kaushik, 2019; Dao and Le, 2024). In the current study, a tendency for cases with LA to have a lower percent area of goblet cells in the SI was observed. Percent goblet cell area is important for two reasons: 1) the number of goblet cells can be up- and down-regulated throughout life (particularly downregulated in chronic disease) and 2) lack of goblet cells indicates mucosal immaturity and high mucosal turnover rates. Because goblet cells are a highly differentiated cell type, animals with reduced goblet cell area likely lacking full functional absorptive or regenerative capacity of their GI tract (Crosnier et al., 2006; Chase and Kaushik, 2019; Dao and Le, 2024). As a model of “leaky gut syndrome” in dairy cows, feed restriction was found to lead to reduced SI crypt depth and goblet cell area (Kvidera et al., 2017b). Chemically inhibiting crypt cell differentiation in the SI led to reduced cell proliferation and higher levels of lipopolysaccharide in the plasma (Kvidera et al., 2017a) in dairy cows. These findings reinforce the importance of both crypts and goblet cells in the functionality of mucosal immunity of the intestine. Thus, an immature non-differentiated epithelium is more likely associated with barrier dysfunction and more permeable to microbes and related toxins.

No differences were detected in the current study between the SC morphology in CON as compared to LA cases. No significant differences detected is interesting considering previous studies have found associations between induced SARA, cecal acidosis, and lipopolysaccharide (LPS) concentrations (Li et al., 2012). Li and associates suggested that the monolayer configuration of large intestine epithelium contributes to greater susceptibility to injury and pathologic permeability compared with the multi-layered epithelium of the rumen (Li et al., 2012). Other studies have also found associations between LA and increased genetic expression that relates to increased inflammation and decreased mucosal integrity (Abbas et al., 2020; Lindholm-Perry et al., 2024). The majority of the existing studies looking at histologic associations/ reactions with diet, acidosis, LA, etc. have evaluated segments of SI. Thus, the lack of differences in specific SC histology between LA and CON cases may be a true representation of the disease process. The majority of organ damage may be occurring more proximal in the GI tract, thus leaving the SC less involved in histologic damage and transmucosal leakage to form LA.

While the association between LA status and GI histologic parameters was the primary focus of the current study, that was not the only variable affecting or associated with GI histology (Appendix Table B.6–B.8). Of note, Number of Pulls was significantly associated with multiple rumen and SI measurements and could serve as a major confounding factor in the current study. It would be reasonable to presume that cattle that have been pulled for treatment multiple times would also be more likely to have reduced feed intake for longer periods due to disease-induced anorexia. Restricted feed intake has been shown to affect the absorptive capacity of the rumen (Zhang et al., 2013a, 2013b; Pederzoli et al., 2018). Alterations to GI absorptive

capacity are likely occurring due to microscopic changes in organ structure and histological morphology.

Another factor that was found to be associated with multiple measurements collected from the rumen, SI, and SC was autolysis of the mortality at time of necropsy. Autolysis is unfortunately a confounding factor that is difficult to control for in the current study since necropsies were performed as technicians were notified of mortalities occurring. There was no way to perform necropsies at a repeatable interval after death. In addition, other factors that vary between mortalities affect the rate of autolysis such as cause of death, ambient weather, carcass location at time of death, etc.

In the SI specifically, Peritoneal Adhesions was significantly associated with multiple histologic measurements. The association of Peritoneal Adhesions with SI histologic measurements could present a potential confounding factor between overall abdominal health and SI health because it is impossible to determine causation or sequence of events from these observational data. Similarly, SI Total was significantly associated with multiple histologic measurements in the SC. Thus, the inclusion of the demographic and gross pathology variables in the statistical model was performed to account for these confounding factors allowing a clearer interpretation of the association between liver abscess status and histological measurements.

Results of the current study indicated that LA is not as common and does not show the same associations with gross GI lesions in feedyard mortalities as in studies completed at harvest. Identifying what cattle are more at risk for LA is crucial to inform better management and treatment techniques. A better understanding of the affected animals will fill in gaps in LA etiopathogenesis by identifying specific risk factors and mechanisms. In addition, LA was found

to occur in cattle throughout the feeding period, but LA is more likely to occur if an animal is on feed longer than 100 d. Time at the feedyard may also be the reasoning behind why dairy-influenced breeds are more likely to have LA than traditional beef breeds. More knowledge of when LA form and how they progress as a disease is important for issues of management as well as potential prevention or intervention. Gastrointestinal lesions have been evaluated in previous studies, but few have included full histomorphologic assessment. In the current study, we demonstrated that histologic changes in the rumen and SI are altered significantly in cattle with LA. Post-ruminal lesions likely deserve similar attention when exploring LA etiology. In addition, the association of GI lesions and LA was only detected at a histologic level in the current study. Due to the observational nature of the current study, we were unable to explore potential cause-and-effect relationships between LA and histomorphology of the GI tract. Histologic evaluation is an important part of determining the role of the GI tract during the origin and development of LA and should be pursued as a topic of future research.

Limitations of the current study are that samples and data were collected based on availability of deceased animals during limited periods of time in six different feedyards. Power was limited by the number of mortalities that occurred within the study period and how many mortalities had LA. Due to the limited number of LA mortalities in the current study, higher power would be needed to increase confidence in the accuracy of the associations found. Since the current study population only included mortalities, the population does not represent the entire feedlot cattle population as LA are neither necessary nor sufficient to cause mortality in feedyard cattle. Many animals with LA continued through the production cycle to finish at harvest and were not included in the current dataset. These animals would have provided additional power to our study by being enrolled in both datasets had mortality occurred during

the feeding phase. A significant limitation of the current study was the reduced histologic quality of rumen tissues (particularly LA cases from 2023) which led to reduced data points and measurement duplicates being obtained. The disparity in number of measurements collected between LA cases and controls was accounted for by the statistical models but the lack of differences in rumen parameters may be affected by the reduction of study power due to the lower number of measurements available. In addition, sampling for the Histologic dataset was limited by the number of LA cases observed at necropsy which has been shown to vary by season of the year and geographical location (Herrick et al., 2022).

Supplementary Data

Supplementary data are available in Appendix B or at Translational Animal Science online.

Author Contributions

Rachel Champagne (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing—original draft, Writing—review & editing), Phillip Lancaster (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing—review & editing), Brad White (Conceptualization, Investigation, Methodology, Validation, Visualization, Writing—review & editing), Paige Schmidt (Data curation, Investigation, Resources, Writing—review & editing), Madeline Mancke (Data curation, Investigation, Resources, Writing—review & editing), Makenna Jensen (Data curation, Investigation, Resources, Writing—review & editing), Brandon Depenbusch (Funding acquisition, Resources, Writing—review & editing), Cody Nichols

(Funding acquisition, Resources, Writing— review & editing), Brandon Plattner (Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing—review & editing), Laura Carpenter (Data curation, Investigation, Writing—review & editing), Katie Long (Data curation, Investigation, Writing—review & editing), and Kady Nuncio (Data curation, Investigation, Writing— review & editing).

Conflict of Interest Statement

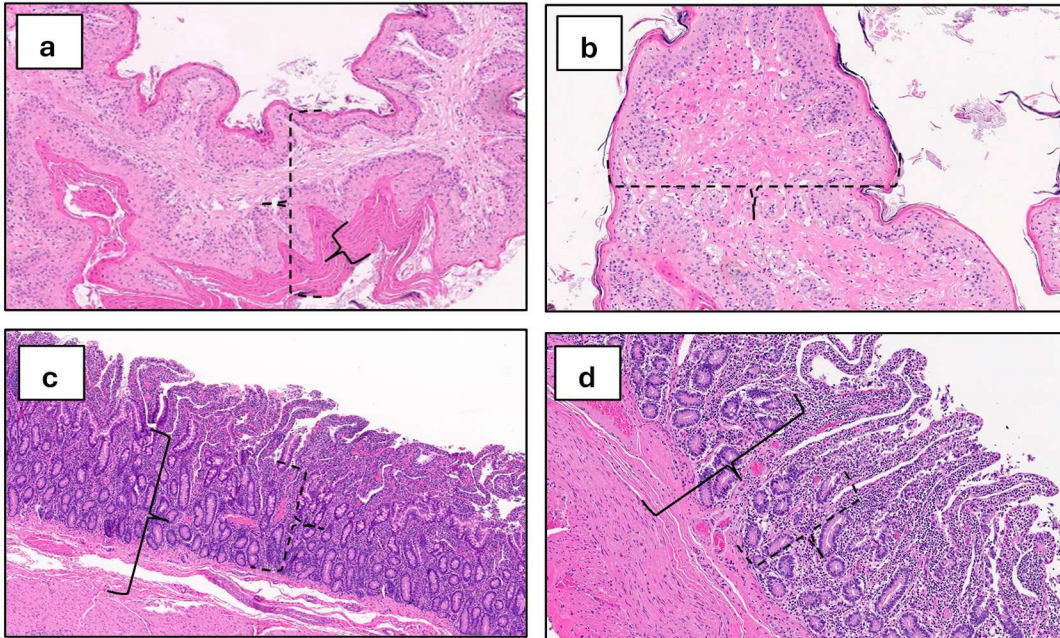
Authors claim no conflict of interest and have nothing else to disclose.

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Figures

Figure 2.1 Gastrointestinal samples were collected at necropsy from cases with liver abscess and from time-matched, feedyard-matched control cases (without liver abscess) for histologic measurement collection. Representative sections of rumen (a & b) and small intestine (c & d) samples collected from control cases (a & c) and liver abscess cases (b & d). Rumen papillae width (dashed line) and the keratin layer (solid line) are shown (a & b). Small intestine crypt depth (dashed line) and propria thickness (solid line) are shown (c & d).



Tables

Table 2.1 Description of histologic measurements collected from rumen, small intestine, and spiral colon samples using Aperio eSlide Manager software (5 replicates of each measurement were collected per tissue per case to account for biological variation).

Measurement Name (units)	Measurement Definition
Rumen	
Papilla Length (μm)	Papilla tip to papilla base
Papilla Width (μm)	Measured at mid-papilla height
Papilla Area (μm ²)	Papillae length x papilla width
Papilla Keratin Thickness (μm)	Measured from mucosal surface of papilla to where SG began or where nucleated SC cells ended
Stratum Corneum thickness ¹ (μm)	Measured from epithelial surface to SG
Stratum Granulosum thickness ¹ (μm)	Measured from SG to SS
Stratum Spinosum thickness ¹ (μm)	Measured from SG to SB
Stratum Basale thickness ¹ (μm)	Measured from SS to muscularis mucosa
Small Intestine	
Villus Length (μm)	Villus tip to villus base
Villus Width (μm)	Measured at mid-villus height
Crypt Depth (μm)	Measured from villus base to base of deepest crypt
Crypt Width (μm)	Measured across crypt at most even plane of section
Total Proprial Thickness (μm)	Measured from villus-base interface to muscularis mucosa
Spiral Colon	
Gland Depth (μm)	Measured from epithelium to base of deepest gland present
Gland Width (μm)	Measured across gland at most even plane of section
Total Proprial Thickness (μm)	Measured from epithelium surface to muscularis mucosa

¹All rumen epithelium measurements made on mucosa surface (not papillae).

Table 2.2 Descriptive statistics of demographic variables of feedyard necropsy cases that met inclusion criteria for the Gross Necropsy and Histologic datasets.

Category	Gross Necropsy Dataset (Count; n=900)	Histologic Dataset (Count; n=80)
Sex		
Heifer	609 (67.7%)	48 (60.0%)
Steer	291 (32.3%)	32 (40.0%)
Breed Type		
Beef	871 (96.8%)	76 (95.0%)

Dairy-influenced	29 (3.2%)	4 (5.0%)
Arrival Weight (kg)		
<226	22 (2.4%)	0 (0.0%)
227-271	103 (11.1%)	9 (11.2%)
272-317	229 (25.4%)	20 (25.0%)
318-363	302 (33.5%)	29 (36.2%)
364-408	192 (21.3%)	17 (21.3%)
409-454	42 (4.7%)	3 (3.8%)
>455	10 (1.1%)	2 (2.3%)
Days On Feed		
0-50	303 (33.7%)	18 (22.5%)
51-100	225 (25.0%)	18 (22.5%)
>100	372 (41.3%)	44 (55.0%)

Table 2.3 Probability of liver abscess in feedyard mortalities based on demographic and gross pathology variables included in the Gross Necropsy dataset.

Variable Name ¹	Probability of Liver Abscess	Standard Error (SE)	P-value
Breed			=0.04
Beef-influenced	0.03	0.010	
Dairy-influenced	0.30	0.277	
Sex			< 0.01
Heifer	0.06	0.044	
Steer	0.16	0.098	
Days on Feed at Death (days)			< 0.01
<50	0.06	0.045	
50-100	0.08	0.122	
>100	0.20	0.069	
Arrival Weight (kg)			=0.09
<272	0.14	0.100	
273-363	0.13	0.083	
>363	0.05	0.039	
Mesenteric Lymph Nodes			=0.10
Normal	0.15	0.087	
Abnormal	0.07	0.053	
Rumen Mucosa			=0.08
Normal	0.14	0.085	
Abnormal	0.07	0.053	
Peritoneal Adhesions			< 0.01
Absent	0.05	0.038	
Present	0.18	0.109	

¹SE = standard error of the probability; Mesenteric Lymph Nodes, Rumen Mucosa, and Peritoneal Adhesions are from necropsy evaluation of gross organ pathology classified into binary outcomes.

Table 2.4 Probability of a feedyard necropsy with liver abscesses (n = 48) having a liver score of A + (scored using modified Elanco Liver Check System) based on demographic and gross pathology variables included in the Gross Necropsy dataset.

Variable Name ¹	Probability of A+ Liver Score	Standard Error (SE)	P-value
Abdominal Adhesions			=0.01
Absent	0.55	0.151	
Present	0.90	0.072	
Spiral Colon Content			=0.01
Normal	0.49	0.128	
Abnormal	0.92	0.071	
Small Intestine Total			=0.09
Normal	0.87	0.093	
Abnormal	0.61	0.136	

¹SE = standard error of the probability; Peritoneal Adhesions, Spiral Colon Content, and Small Intestine Total are from necropsy evaluation of gross organ pathology classified into binary outcomes.

Table 2.5 Importance of histologic measurements in the rumen, small intestine, and colon to each of the top 4 principal components.

Item ¹	PC1	PC2	PC3	PC4
Papillae Length	0.15	-0.42	0.28	-0.09
Papillae Area	0.06	-0.51	0.26	0.00
Papillae Width	0.03	-0.38	0.13	0.11
Papillae Keratin Thickness	0.02	-0.27	-0.36	0.22
Stratum Basale Thickness	0.31	-0.01	-0.31	-0.24
Stratum Corneum Thickness	0.03	-0.32	-0.16	0.34
Stratum Spinosum Thickness	0.16	0.00	-0.07	-0.59
Stratum Granulosum Thickness	0.19	-0.28	-0.19	-0.44
Villus Height	0.21	-0.01	-0.32	0.09
Villus Width	0.38	-0.06	0.08	0.20
Crypt Depth	0.37	0.06	0.04	0.17
Crypt Width	0.41	0.04	-0.08	0.12
SI Propria Thickness	0.31	0.08	0.34	-0.04
SI Goblet Cell Area	0.26	-0.01	0.12	-0.04
Gland Depth	0.26	0.26	0.12	0.05
Gland Width	0.10	0.07	-0.25	-0.18
SC Propria Thickness	0.21	0.25	0.31	0.10
SC Goblet Cell Area	0.17	0.07	-0.36	0.28

¹PC = principal component; SI = small intestine; SC = spiral colon.

Table 2.6 Multivariate analysis of variance of principal components of histologic measurements to evaluate overall effect of liver abscess status on gastrointestinal morphology.

Variable	Wilks lambda	F-value	P-value
Liver Abscess	0.69	2.92	0.04
Sex	0.60	4.41	0.01
Number of Pulls	0.23	2.43	< 0.01
Autolysis	0.40	3.71	< 0.01
Rumen Content	0.69	2.91	0.04
Rumen Total	0.64	3.58	0.02
Small Intestine Mucosa	0.73	2.35	0.08
Small Intestine Content	0.52	6.00	< 0.01
Small Intestine Total	0.64	3.56	0.02
Spiral Colon Content	0.68	3.06	0.03
Peritoneal Adhesions	0.60	4.40	0.01

Table 2.7 Effect of liver abscess on histologic measurements in rumen, small intestine, and spiral colon tissues in the Histologic dataset.

	Liver Abscess ¹			
Measurement (units)	Yes	No	SEM	P-value
Rumen				
Papillae Length (μm)	2282	2222	293.0	0.23
Papillae Width (μm)	458 ^a	379 ^b	33.9	0.03
Papillae Area (μm ²)	1398680	1133182	228303.0	0.15
Papillae Keratin Thickness (μm)	36.2 ^a	47.2 ^b	6.78	0.05
Stratum Corneum (μm)	29.4	31.1	4.38	0.43
Stratum Granulosum (μm)	11.0 ^x	12.2 ^y	0.61	0.10
Stratum Spinosum (μm)	27.7	28.9	2.51	0.63
Stratum Basale (μm)	11.2	12.6	1.30	0.71
Small Intestine				
Villus Length (μm)	365	383	42.9	0.59
Villus Width (μm)	59.9	57.4	6.74	0.62
Crypt Depth (μm)	218 ^a	312 ^b	44.2	0.02
Crypt Width (μm)	37.1	34.6	2.53	0.28
Proprial Thickness (μm)	850 ^a	1056 ^b	84.3	0.01
SI Goblet Cell Area (%)	1.41 ^x	3.53 ^y	2.558	0.08
Spiral Colon				
Gland Depth (μm)	390	369	37.9	0.38
Gland Width (μm)	46	48.2	6.26	0.69
Proprial Thickness (μm)	789	785	114.0	0.95
SC Goblet Cell Area (%)	3.75	4.47	4.321	0.73

¹Yes = liver score of A or A + (based on modified Elanco Liver Check System); No = liver score of O (based on modified Elanco Liver Check System); SEM = standard error of the mean.

^{a,b}Means with different superscripts within a row are different ($P < 0.05$).

^{x,y}Means with different superscripts within a row are different ($P < 0.10$).

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Conclusions

Liver abscess (LA) in feedlot cattle has been an industry-wide issue for some time; however, LA prevalence and severity have increased in recent years. Economic losses due to reduced performance and compromised carcasses at harvest fuel the negative impact of LA on the beef industry. Additionally, multi-disciplinary efforts to practice judicious use of anti-microbials have incentivized the pursuit of mitigation alternatives to tylosin. Due to increased industry awareness of the rising issue of LA, an increased effort to understand risk factors for LA has been made. The purpose of this thesis was to evaluate LA in feedlot cattle and potential associations with gastrointestinal health, diet composition in the finishing phase, cattle demographics, and cattle performance.

Factors contributing to LA in feedlot cattle have traditionally included dietary factors such as high levels of grain inclusion and abrupt changes in dietary ration. Based on previous work, LA pathophysiology involves rumenitis leading to translocation of bacteria across the ruminal wall and being absorbed into systemic circulation which is then drained through the portal vein to the liver. Analyzing the LA literature has shown that dietary factors such as grain inclusion, starch digestion rate, and neutral detergent fiber digestion rate attributable to fibrous byproduct ingredients were associated with LA prevalence and severity. While roughage inclusion has been shown previously to be protective against LA, perhaps the detrimental effect of higher grain inclusion (and thus reduced roughage inclusion) is a more precise measure of LA risk.

The majority of previous literature focuses on ruminal mucosa damage and its contribution to LA formation, however the concept of hindgut acidosis and resulting intestinal damage has recently gained interest as a potential contributor to LA. Multiple histologic changes

in the rumen and small intestine were found to be associated with LA when compared to non-LA controls. These changes included parameters that logically correspond to reduced function of the gastrointestinal tract: thinning mucosa, decreased brush barrier function, reduced absorption capacity. Animals that had concurrent abdominal adhesions at necropsy, were dairy-influenced, or were steers were also found to have a higher probability of LA.

Across both studies, LA was utilized as the primary health outcome and study design was utilized to identify concurrent pathologies, comorbidities, cattle demographics, and diet composition. Through better understanding factors associated with LA prevalence and severity, more information is available to better outline the cattle most at risk for developing LA and possible areas where intervention strategies can be employed to reduce losses. Overall, dietary factors and multiple gastrointestinal morphology findings were found to be associated with a higher probability of LA. While more research is needed to further define LA risk factors, these data highlight potential risk factors for LA and associations with gastrointestinal morphology in multiple sectors of the gastrointestinal tract.

Appendix A - Supplement to Chapter 1

Appendix Table A.1 Reference table created to match grain ingredients with the National Research Council (NRC) feed composition reference table values for percent starch and starch digestibility.

Feedstuff	Processing Method	Starch (%)	Starch Digestion Rate, kd CB1 (%/hr)
Bakers Products	N/A	37.6	16
Barley	Cracked	53.6	10
Barley	Dry Rolled	56.7	30
Barley	Flaked	59.3	30
Barley	Grain	56.7	30
Barley	Ground	56.7	35
Barley	High Moisture	56.7	35
Barley	Rolled	56.7	30
Barley	Steam Flaked	59.3	30
Corn	Cracked	66.5	15
Corn	Dry Rolled	67.8	15
Corn	Flaked	67.8	25
Corn	Germ	19.7	50
Corn	Grain	72.1	15
Corn	Ground	67.8	25
Corn	High Moisture	71.3	30
Corn	Rolled	67.8	15
Corn	Steam Flaked	76.2	25
Corn	With Cobb	60.7	18
Rye	Steam Flaked	58.3	40
Sorghum	Cracked	62.4	30
Sorghum	Dry Rolled	53.6	10
Sorghum	Flaked	75.2	25

Sorghum	Grain	71.2	10
Sorghum	Ground	71.2	15
Sorghum	High Moisture	72.9	10
Sorghum	Rolled	53.6	10
Sorghum	Steam Flaked	59.9	15
Sunflower Seed	Ground	1.1	35
Wheat	Cracked	62.4	40
Wheat	Dry Rolled	62.4	40
Wheat	Flaked	62.4	45
Wheat	Grain	62.4	40
Wheat	Ground	62.7	40
Wheat	High Moisture	62.4	45
Wheat	Midds	36.5	70
Wheat	Rolled	62.4	40
Wheat	Steam Flaked	64.9	40
Wheat	Sprouted, Dry Rolled	62.4	40
Wheat	Steam Rolled	83	45
Wheat	Temper Rolled	62.4	45

Appendix Table A.2 Reference table created to match forage and fibrous byproduct (FB) ingredients with the National Research Council (NRC) feed composition reference table values for percent neutral detergent fiber (NDF) and NDF digestibility.

Feedstuff	NDF (%)	Fiber Digestion Rate, kd CB3 (%/hr)
Roughages		
Alfalfa Hay	41.7	5.5
Alfalfa Meal	55.4	10
Alfalfa Pellets/Cubes	45.5	5.5
Barley Silage	56.8	4
Corn Silage	41	6
Ground Alfalfa Hay	41.7	5.5

Mixed Hay	72.7	3.5
Sudan Grass Hay	65.8	3
Oat Straw	73.8	3
Alfalfa Haylage	42.5	10
Corn Stalks	70.8	5
Wheat Silage	56.5	6
Wheat Straw	73.6	3
Fescue Hay	65	3
Sorghum Silage	60.8	5
Alfalfa Silage	47	5.5
Ground Timothy Hay	63.8	3
Wheat Hay	57.9	3
Brewers Grain, Dried	52.1	6
Cottonseed Hulls	81.1	6
Soybean Straw	70	3
Oat Hulls	64.4	4
Corn Cobs	78.3	4
Forage Sorghum Sudan	59.8	5
Oat Silage	58.1	5
Peanut Hulls	68.5	6
Triticale Silage	58.6	5
Triticale Hay	57.7	3
Rice Hulls	53.8	6
Fibrous Byproducts (FB)		
Wet Distillers Grains & Solubles	31.5	7
Dried Distillers Grains & Solubles	33.7	7
Wet Corn Gluten Feed	38.5	5
Dry Corn Gluten Feed	35	5

Soybean Hulls	64.8	8
Beet Pulp	41.3	8
Modified Distillers Grains & Solubles	28.7	7
Corn Gluten Feed	38.5	5

Appendix Table A.3 Probability of liver abscess across all animals in a treatment group based on categorical demographic and ration variables included in initial univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Liver Abscess		P-value
Tylosin					<0.001
Yes	-1.88	0.074	0.13	a	
No	-1.23	0.073	0.23	b	
Monensin					<0.001
Yes	-1.68	0.080	0.16	a	
No	-1.20	0.084	0.23	b	
Region					<0.001
Canada (CA)	-1.72	0.097	0.15	a	
Midwest (MW)	-1.64	0.182	0.16	a	
Southwest (SW)	-0.79	0.197	0.22	b	
Other	-1.29	0.188	0.22	ab	
Sex					<0.001
Steer	-1.02	0.272	0.27	b	
Heifer	-1.85	0.168	0.14	a	
Mixed	-1.48	0.088	0.19	ab	
Breed					<0.001
Beef-influenced	-1.52	0.084	0.18	a	

Bos-indicus-influenced	-2.43	0.441	0.08	a	
Mixed	-1.61	0.384	0.17	a	
Age					<0.001
Yearling	-1.46	0.432	0.19	a	
Other	-1.48	0.150	0.19	a	
Days on Feed					<0.001
<100	-1.84	0.194	0.14	a	
100-149	-1.67	0.178	0.16	ab	
150-199	-1.55	0.102	0.18	ab	
200+	-1.38	0.126	0.20	b	
Feedings (#/day)					<0.001
1	-1.45	0.749	0.19	a	
2	-1.45	0.219	0.19	a	
3	-1.37	0.135	0.20	a	

Appendix Table A.4 Probability of liver abscess across all animals in a treatment group based on continuous demographic and ration variables included in initial univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Slope (logit)	SE (logit)	Average Change in Predicted Prevalence of Liver Abscess (per unit change)	P-value
Arrival Weight (kg)	1.15×10^{-3}	0.001	1.72×10^{-4}	<0.001
End Weight (kg)	2.49×10^{-5}	0.001	6.96×10^{-5}	<0.001
Average Daily Gain (kg)	-0.59	0.169	-0.08	<0.001

Dry Matter Intake (kg/day)	0.03	0.036	4.98×10^{-3}	<0.001
Gain:Feed	-9.07	1.876	-1.41	<0.001
Acid Detergent Fiber (ADF) (% total Dry Matter)	-0.08	0.022	-0.01	<0.001
Neutral Detergent Fiber (NDF) (% total Dry Matter)	-0.03	0.009	-4.48×10^{-3}	<0.001
ADF:NDF Ratio	-1.75	0.810	-0.33	<0.001
Hot Carcass Weight (kg)	0.003	0.0013	3.75×10^{-4}	<0.001
Net Energy for Gain (Mcal/kg)	0.23	0.314	0.04	<0.001
Total Roughage (% total Dry Matter)	-0.03	0.005	-2.37×10^{-3}	<0.001
Total Roughage NDF Digestibility (%/h)	-0.76	0.162	-0.07	<0.001
Total Grain (% total Dry Matter)	0.01	0.002	1.14×10^{-3}	<0.001
Total Starch Digestibility (%/h)	0.04	0.008	5.54×10^{-3}	<0.001
Total Fibrous Byproduct (% total Dry Matter)	-0.002	0.0020	-2.44×10^{-4}	<0.001
Total Fibrous Byproduct NDF Digestibility (%/h)	-0.05	0.090	-7.27×10^{-3}	<0.001

Appendix Table A.5 Probability of severe liver abscess out of all animals with liver abscess within treatment group based on categorical demographic and ration variables included in initial

univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Liver Abscess		P-value
Tylosin					<0.001
Yes	-0.74	0.130	0.32	a	
No	-0.52	0.121	0.37	b	
Monensin					<0.001
Yes	-0.66	0.120	0.34	a	
No	-0.40	0.131	0.40	b	
Region					<0.001
Canada (CA)	-0.86	0.151	0.30	a	
Midwest (MW)	-0.42	0.376	0.40	a	
Southwest (SW)	-0.11	0.289	0.47	a	
Other	-0.21	0.208	0.45	a	
Sex					<0.001
Steer	-0.53	0.134	0.37	a	
Heifer	-0.73	0.247	0.33	a	
Mixed	-0.55	0.363	0.37	a	
Breed*					<0.001
Beef	-0.75	0.723	0.32	a	
Mixed	-0.60	0.127	0.35	a	
Age					<0.001
Yearling	-0.65	0.561	0.34	a	
Other	-0.73	0.192	0.33	a	
Days on Feed					<0.001
<100	-1.47	0.323	0.19	a	
100-149	-0.57	0.156	0.36	ab	
150-199	-0.56	0.269	0.37	ab	

200+	-0.31	0.169	0.42	b	
Feedings (#/day)					<0.001
1	-0.70	0.173	0.33	a	
2	-0.32	0.311	0.42	a	
3	0.25	0.816	0.56	a	
*No Bos Indicus bred cattle represented in treatment groups with severe liver abscess (only breed levels represented in severe liver abscess population: beef, mixed)					

Appendix Table A.6 Probability of severe liver abscess out of all animals with liver abscess within treatment group based on continuous demographic and ration variables included in initial univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Slope (logit)	SE (logit)	Average Change in Predicted Prevalence of Liver Abscess (per unit change)	P-value
Arrival Weight (kg)	-0.003	0.0016	-0.001	<0.001
End Weight (kg)	0.001	0.0016	0.0003	<0.001
Average Daily Gain (kg)	-0.06	0.361	-0.01	<0.001
Dry Matter Intake (kg/day)	-0.01	0.070	-0.003	<0.001
Gain:Feed	0.18	3.927	0.04	<0.001
Acid Detergent Fiber (ADF) (% total Dry Matter)	-0.07	0.041	-0.02	<0.05

Neutral Detergent Fiber (NDF) (% total Dry Matter)	-0.02	0.019	-0.01	<0.001
ADF:NDF Ratio	-0.75	1.300	-0.18	=0.20
Hot Carcass Weight (kg)	0.001	0.0029	0.0003	<0.001
Net Energy for Gain (Mcal/kg)	0.89	0.538	0.18	<0.001
Total Roughage (% total Dry Matter)	-0.01	0.011	-0.002	<0.001
Total Roughage NDF Digestibility (%/h)	-0.21	0.358	-0.05	<0.001
Total Grain (% total Dry Matter)	0.01	0.004	0.001	<0.001
Total Starch Digestibility (%/h)	0.01	0.014	0.002	<0.001
Total Fibrous Byproduct (% total Dry Matter)	-0.01	0.004	-0.002	<0.001
Total Fibrous Byproduct NDF Digestibility (%/h)	-0.29	0.160	-0.06	<0.001

Appendix Table A.7 Probability of severe liver abscess out of all animals within treatment group based on categorical demographic and ration variables included in initial univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Predicted Prevalence of Liver Abscess	P-value
Tylosin				<0.001

Yes	-2.74	0.128	0.06	a	
No	-2.22	0.122	0.10	b	
Monensin					<0.001
Yes	-2.58	0.123	0.07	a	
No	-1.97	0.128	0.12	b	
Region					<0.001
Canada (CA)	-2.77	0.155	0.06	a	
Midwest (MW)	-2.42	0.279	0.08	ab	
Southwest (SW)	-1.63	0.417	0.16	ab	
Other	-1.75	0.207	0.15	b	
Sex					<0.001
Steer	-1.44	0.387	0.19	b	
Heifer	-2.70	0.237	0.06	a	
Mixed	-2.37	0.133	0.09	ab	
Breed*					<0.001
Beef	-2.76	0.761	0.06	a	
Mixed	-2.40	0.131	0.08	a	
Age					<0.001
Yearling	-2.31	0.634	0.09	a	
Other	-2.34	0.214	0.09	a	
Days on Feed					<0.001
<100	-3.50	0.347	0.03	a	
100-149	-2.61	0.263	0.07	ab	
150-199	-2.32	0.162	0.09	b	
200+	-1.99	0.178	0.12	b	
Feedings (#/day)					<0.001
1	-2.37	0.173	0.09	a	
2	-2.14	0.694	0.11	a	
3	-2.13	0.340	0.11	a	

*No Bos Indicus bred cattle represented in treatment groups with severe liver abscess (only breed levels represented in severe liver abscess population: beef, mixed)

Appendix Table A.8 Probability of severe liver abscess out of all animals within treatment group based on continuous demographic and ration variables included in initial univariate rma.mv models (24 variables). Outlier rows removed (n=26): Dairy-influenced (Breed; n=19), South America (Region; n=7), Bull (Sex; n=4 but already removed due to Breed).

Moderator Name	Estimate (logit)	SE (logit)	Average Change in Predicted Prevalence of Liver Abscess (per unit change)	P-value
Arrival Weight (kg)	-0.001	0.0018	-6.78×10^{-5}	<0.001
End Weight (kg)	0.002	0.0015	6.47×10^{-5}	<0.001
Average Daily Gain (kg)	-0.11	0.373	-0.03	<0.001
Dry Matter Intake (kg/day)	0.09	0.068	0.007	<0.001
Gain:Feed	-9.21	3.589	-0.69	<0.001
Acid Detergent Fiber (ADF) (% total Dry Matter)	-0.13	0.038	-0.01	<0.001
Neutral Detergent Fiber (NDF) (% total Dry Matter)	-0.05	0.016	-0.004	<0.001
ADF:NDF Ratio	-3.13	1.227	-0.33	<0.001
Hot Carcass Weight (kg)	0.001	0.0027	7.74×10^{-5}	<0.001
Net Energy for Gain (Mcal/kg)	0.84	0.535	0.06	<0.001

Total Roughage (% total Dry Matter)	-0.03	0.009	-0.002	<0.001
Total Roughage NDF Digestibility (%/h)	-0.95	0.298	-0.06	<0.001
Total Grain (% total Dry Matter)	0.01	0.003	7.09×10^{-4}	<0.001
Total Starch Digestibility (%/h)	0.03	0.012	0.002	<0.001
Total Fibrous Byproduct (% total Dry Matter)	-0.01	0.003	-0.001	<0.001
Total Fibrous Byproduct NDF Digestibility (%/h)	-0.29	0.126	-0.02	<0.001

Appendix Table A.9 Summary of papers that met inclusion criteria but were not included in final analysis due to exclusion criteria (n=39). Treatment sizes are included by experiment within paper (n=58).

Authors	Publication Year	Document Type	Publication	Experiment Number	Treatment Size	Inclusion Criteria not met	Reason for Exclusion
Vasconcelos, et al	2008	Journal Article (4 treatments)	J. Anim. Sci.		35	1	Unable to calculate accurate treatment means from effect means
Bartle, et al	1988	Journal Article	J. Anim. Sci.		28	1	Overall liver abscess prevalence not reported by treatment.
Bittner, et al	2016	Journal Article	PAS	1	42	1	No liver data collected/reported.
				2	40	1	No liver data collected/reported.
Burrin, et al	1988	Journal Article	Nebraska Agricultural Research Division - University of Nebraska - Lincoln	1	9	1	Overall liver abscess prevalence not reported by treatment.
				2	42-43	1	Overall liver abscess prevalence not reported by treatment.

Chandra Deb, et al	2024	Thesis	North Carolina State University		150	4	Stochastic-created animals utilized in analysis instead of real animal subjects.
Childress, et al	2025	Journal Article	Appl. Anim. Sci.		8	4	Not a finishing study.
Colling, et al	1979	Journal Article	Nebraska Agricultural Research Division - University of Nebraska - Lincoln		47-48	1	Overall liver abscess prevalence not reported by treatment.
Crookshank, et al	1973	Journal Article	J. Anim. Sci.		91-93	3	Incomplete ration data.
Davedow, et al	2020	Journal Article	Front. Vet. Sci.		2525-2526	3	Incomplete ration data.
Elam, et al	2009	Journal Article	J. Anim. Sci.		1709-1710	1	Overall liver abscess prevalence not reported by treatment.
Rogers, et al	1995	Journal Article (Experiment 2)	J. Anim. Sci.		48	1	No liver data collected/reported.

Fanning, et al	1999	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		19-20	1	No liver data collected/reported.
Goedeken, et al	1989	Journal Article	Anim. Feed Sci. Technol.	1	54	1	Overall liver abscess prevalence not reported by treatment.
				2	40	1	Overall liver abscess prevalence not reported by treatment.
Heiderscheit, et al	2022	Journal Article	Transl. Anim. Sci.		54	1	Overall liver abscess prevalence not reported by treatment.
Hess, et al	2025	Journal Article	J. Anim. Sci.		125-1434	N/A	Summarizes the results of 7 other papers which have already been individually included in analysis.
Huck, et al	1998	Journal Article	J. Anim. Sci.	1	33-34	1	Overall liver abscess prevalence not reported by treatment.

				2	51	1	Overall liver abscess prevalence not reported by treatment.
Huffman, et al	1992	Journal Article	J. Anim. Sci.	1	33	1	Overall liver abscess prevalence not reported by treatment.
				2	54-55	1	Overall liver abscess prevalence not reported by treatment.
Husz, et al	2023	Journal Article	Appl. Anim. Sci.		939-944	1	Overall liver abscess prevalence not reported by treatment.
Jennings, et al	2021	Journal Article	Livest. Sci.	1	31-32	1	Overall liver abscess prevalence not reported by treatment.
				2	32	1	Overall liver abscess prevalence not reported by treatment.
Johnson, et al	2020	Journal Article	J. Anim. Sci.		1	4	Not a finishing study.
Klinger, et al	2007	Journal Article	Can. J. Anim. Sci.	1	210	4	Not a finishing study.
				2	223-224	4	Not a finishing study.

				3	130	4	Not a finishing study.
Kunkle, et al	1976	Journal Article	J. Anim. Sci.	1	29-41	3	Incomplete ration data.
				2	"3-4"	3	Incomplete ration data.
				3	"10-11"	3	Incomplete ration data.
Mader, et al	1993	Journal Article	Anim. Feed Sci. Technol.		448-512	1	Overall liver abscess prevalence not reported by treatment.
Mader, et al	1991	Journal Article	J. Anim. Sci.	1	28-29	1	Overall liver abscess prevalence not reported by treatment.
				2	25	1	Overall liver abscess prevalence not reported by treatment.
				3	27	1	Overall liver abscess prevalence not reported by treatment.
				4	28-29	1	Overall liver abscess prevalence not reported by treatment.
Meyer, et al	2013	Journal Article	J. Anim. Sci.	1	280	1	Overall liver abscess prevalence not reported by treatment.

		(Experiment 2 & 3)		2	286-287	1	Overall liver abscess prevalence not reported by treatment.
Miller, et al	2023	Report	Nebraska Beef Cattle Reports - University of Nebraska 1-Lincoln		400	1	No liver data collected/reported.
Miller, et al	2013	Journal Article	Bovine Pract.	1	647	1	No liver data collected/reported.
				2	322-323	1	No liver data collected/reported.
Montgomery, et al	2003	Journal Article	J. Anim. Sci.	1	55	4	Not a finishing study.
				2	37-38	4	Not a finishing study.
Sperber, et al	2022	Journal Article	Transl. Anim. Sci.		80	1	No liver data collected/reported.
Sperber, et al	2022	Journal Article	Transl. Anim. Sci.		50	1	No liver data collected/reported.
Stock, et al	1990	Journal Article	Nebraska Agricultural Research Division	1	27	1	Overall liver abscess prevalence not reported by treatment.

			- University of Nebraska - Lincoln	2	42	1	Overall liver abscess prevalence not reported by treatment.
				3	25	1	Overall liver abscess prevalence not reported by treatment.
Strabler, et al	2009	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		12	3	Unable to accurately account for extruded ration nutrition data.
Troyer, et al	2022	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		15	1	No liver data collected/reported.
Van Koevering, et al	1991	Report	Animal Science Research Report - Oklahoma Agricultural Experiment Station		80-216	1	Overall liver abscess prevalence not reported by treatment.
White, et al	1975		J. Anim. Sci.	1	6	3	Incomplete ration data.

		Journal Article		2	16	3	Incomplete ration data.
				3	8	3	Incomplete ration data.
Williams, et al	2024	Thesis	University of Guelph		"7-8"	4	Not a finishing study.
Zehnder, et al	1997	Report	Minnesota Agripower Project - University of Minnesota		24	3	Unable to sufficiently account for ration alfalfa meal.
Zuvich, et al	2024	Thesis	Colorado State University		620	1, 3	Incomplete ration data & overall liver abscess prevalence not reported by treatment.

Appendix Table A.10 Summary of papers that met inclusion and exclusion criteria to be included in final analysis (n=121). Treatment sizes are included by experiment within paper (n=160).

Authors	Publication Year	Document Type	Publication	Experiment Number	Treatment Size
Adair, et al	2022	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		30
Alvarado-Gilis, et al	2014	Journal Article	J. Anim. Sci.		66
Amat, et al	2014	Journal Article	Can. J. Anim. Sci.		1076-1092
Barajas and Zinn	1998	Journal Article	J. Anim. Sci.		20
Beliveau and McKinnon	2008	Journal Article	Can. J. Anim. Sci.		40
Bittner, et al	2015	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		72
Bowman	2024	Thesis	Texas Tech University		29-41
Bowman-Schnug, et al	2025	Journal Article	Vet. Sci.		725
Brandt	1988	Report	Kansas State University		32
Brandt and Elliott	1991	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		41
Brown, et al	1975	Journal Article	J. Anim. Sci.	1	48-49
				2	101-105

				3	25-26
				4	419-426
Brown, et al	1973	Journal Article	J. Anim. Sci.	1	38-40
				2	19-40
				3	15-34
				4	33-72
Carvalho, et al	2023	Journal Article	Front. Vet. Sci.		50
Casagrande, et al	2024	Journal Article	Anim. Feed Sci. Technol.		40
Ceconi, et al	2022	Journal Article	Transl. Anim. Sci.		48
Clark, et al	2006	Journal Article	PAS		48
Corrigan, et al	2007	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		40
Coulson, et al	2023	Journal Article	J. Anim. Sci.		100
De Aguiar Veloso, et al	2021	Journal Article	Anim. Feed Sci. Technol.		96
DeHaan, et al	2025	Journal Article	J. Anim. Sci.		46-50
Depenbusch, et al	2008	Journal Article	J. Anim. Sci.		59-63
Depenbusch, et al	2009	Journal Article	J. Anim. Sci.		41-44
Depenbusch, et al	2007	Journal Article	PAS		120-124

Dornbach, et al	2025	Journal Article	Front. Microbiol.		225
El-Sabban, et al	1971	Journal Article	J. Anim. Sci.	1	6
				2	"5-6"
Farlin, et al	1971	Journal Article	Can. J. Anim. Sci.		10
Felizari, et al	2025	Journal Article	Vet. Sci.		744-750
Gibb, et al	2008	Journal Article	Can. J. Anim. Sci.		24
Gibb, et al	2005	Journal Article	Can. J. Anim. Sci.		20
Gibb, et al	2004	Journal Article	J. Anim. Sci.	1	"7-10"
				2	20
Gill, et al	1989	Report	Animal Science Research Report - Oklahoma Agricultural Experiment Station		40-80
Greenquist, et al	2004	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		1769-1770
Grimes Francis, et al	2024	Journal Article	Appl. Anim. Sci.		39
Hankins, et al	2005	Journal Article	PAS		4
Harris, et al	2015	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		9

He, et al	2014	Journal Article	Can. J. Anim. Sci.		60
Heinemann and Hanks	1977	Journal Article	J. Anim. Sci.		18
Heinemann, et al	1978	Journal Article	J. Anim. Sci.		20-22
Hess, et al	2025	Journal Article	J. Anim. Sci.		N/A
Hironaka	1988	Journal Article	Can. J. Anim. Sci.		15-16
Horton and Nicholson	1980	Journal Article	Can. J. Anim. Sci.		24
Horton, et al	2020	Journal Article	J. Anim. Sci.		350
Johnson and Johnson	1973	Report	University of Missouri-Columbia College of Agriculture Agricultural Experiment Station	1	12
				2	"11-12"
				3	34-36
Jolly-Breithaupt, et al	2018	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		150
Koch, et al	2020	Journal Article	Appl. Anim. Sci.		55-56
Koenig, et al	2020	Journal Article	J. Anim. Sci.		23-24
LaBrune, et al	2008	Journal Article	J. Anim. Sci.		16
Latack and Buenabad	2019	Journal Article	Appl. Anim. Sci.		30

Lee and Laudert	1984	Report	Kansas State University		32
Linneen, et al	2023	Journal Article	Appl. Anim. Sci.	1	560
				2	604
Loe, et al	2005	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		120-124
Loe, et al	2007	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		203-204
Loerch	1990	Journal Article	J. Anim. Sci.	1	40
				2	24
				3	30
Loest, et al	2002	Journal Article	J. Anim. Sci.	1	35
				2	39
Lundy, et al	2015	Journal Article	PAS		245-246
Mader, et al	1999	Journal Article	J. Anim. Sci.		82-83
Mader, et al	1991	Journal Article	J. Anim. Sci.	1	56
				2	40
				3	82
				4	98-99
May, et al	2010	Journal Article	J. Anim. Sci.	1	124-127
				2	91-95

May, et al	2011	Journal Article	J. Anim. Sci.		32
May, et al	2009	Journal Article	PAS		12
McCartor, et al	1972	Journal Article	J. Anim. Sci.		"10-20"
McDermott, et al	2024	Journal Article	Transl. Anim. Sci.		80
Meadows	2022	Thesis	University of Saskatchewan		20
Meyer, et al	2013	Journal Article	J. Anim. Sci.		160
Meyer, et al	2009	Journal Article	J. Anim. Sci.		92-94
Miller, et al	2012	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		62-63
Miller, et al	2013	Report	Kansas Agricultural Experiment Station Research Reports - Kansas State University		219-222
Milton and Klopfenstein	2000	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		46
Mir, et al	2008	Journal Article	J. Anim. Sci.		12

Monteiro	2025	Thesis	Kansas State University		114
Montgomery, et al	2009	Journal Article	J. Anim. Sci.		470
Montgomery, et al	2005	Journal Article	J. Anim. Sci.	1	87-92
				2	220-224
Müller, et al	2018	Journal Article	J. Anim. Sci.		102-104
Müller, et al	2018	Journal Article	J. Anim. Sci.		193-195
Müller, et al	2018	Journal Article	J. Anim. Sci.		196
Nelson, et al	2022	Journal Article	Appl. Anim. Sci.		3826-4431
Parsons, et al	2008	Conference Paper	Kansas State University - Agricultural Experiment Station and Cooperative Extension Service		61-63
Paterson, et al	2024	Journal Article	Appl. Anim. Sci.		90
Pendlum, et al	1978	Journal Article	J. Anim. Sci.		16
Pereira, et al	2021	Journal Article	Transl. Anim. Sci.		90
Poppy, et al	2025	Journal Article	Transl. Anim. Sci.		80
Potter, et al	1985	Journal Article	J. Anim. Sci.	1	21-22
				2	32-36

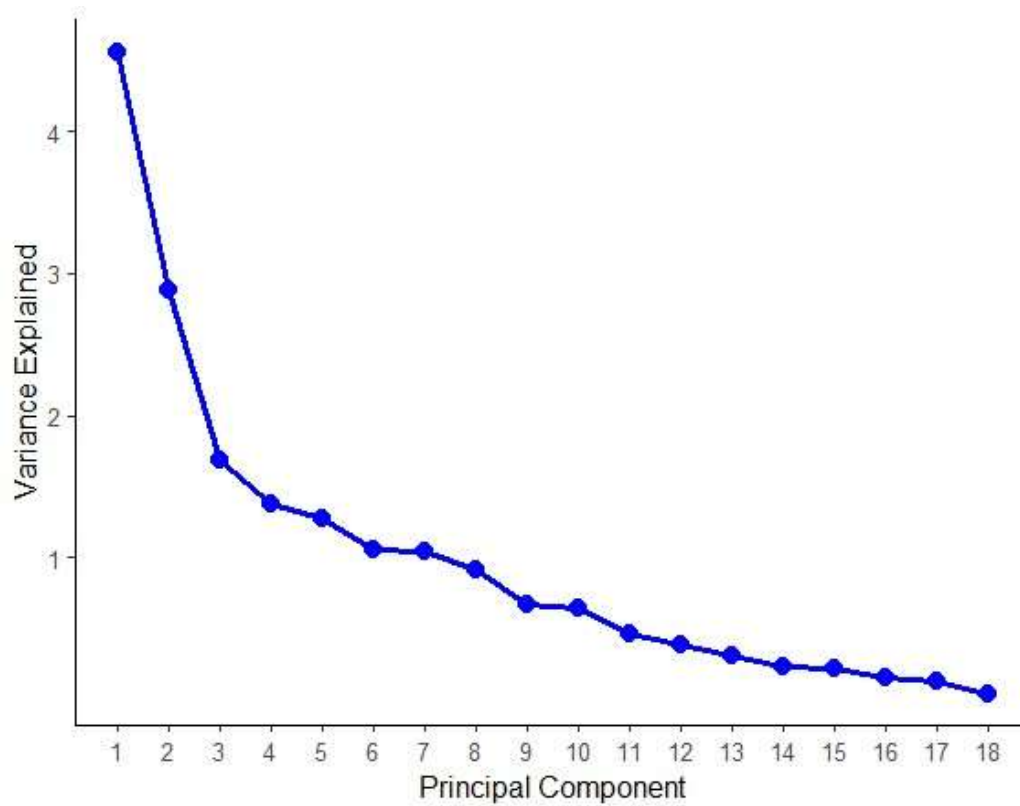
				3	20
				4	46-48
				5	48
				6	20-22
				7	18
				8	20
				9	"10-20"
				10	19-20
				11	24
				12	47-48
				13	45-47
				14	20-30
Preston, et al	1973	Journal Article	J. Anim. Sci.		10
Pritchard	1993	Report	South Dakota Beef Report - South Dakota State University		40
Pukrop, et al	2019	Journal Article	Anim. Feed Sci. Technol.		24
Purevjav, et al	2013	Journal Article	PAS		48
Ribeiro, et al	2023	Journal Article	Transl. Anim. Sci.		79-82
Richeson, et al	2006	Journal Article	PAS		80
Rogers, et al	1995	Journal Article	J. Anim. Sci.	1	5
				2	5
				3	10
				4	10
				5	200

				6	100
Ross, et al	2024	Journal Article	Appl. Anim. Sci.		61-63
Ross, et al	2024	Journal Article	Appl. Anim. Sci.		79-80
Schneider, et al	2012	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		76-77
Schneider, et al	2013	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		98-99
Scott, et al	2000	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		372
Scott, et al	2017	Journal Article	PAS		747-748
Sides, et al	2009	Journal Article	PAS		974-1026
Sindt, et al	2002	Journal Article	J. Anim. Sci.		202-207
Sindt, et al	2003	Journal Article	J. Anim. Sci.		104-106
Stanford, et al	2015	Journal Article	Can. J. Anim. Sci.	1	48
				2	48
Theurer, et al	2024	Journal Article	Appl. Anim. Sci.		672-676
Utley, et al	1972	Journal Article	J. Anim. Sci.		9
Uwituze, et al	2011	Journal Article	J. Anim. Sci.		18-20

Uwituze, et al	2010	Journal Article	J. Anim. Sci.		89-90
Van Cleef, et al	2019	Journal Article	J. Anim. Sci.		71-75
Van Koevering, et al	1993	Report	Animal Science Research Report - Oklahoma Agricultural Experiment Station	1	45783
				2	21
Van Koevering, et al	1994	Journal Article	J. Anim. Sci.		30-32
Vasconcelos, et al	2008	Journal Article	J. Anim. Sci.		35
Veloso	2020	Thesis	Kansas State University	1	112
				2	112
Wagner, et al	2022	Journal Article	J. Anim. Sci.		100
Wallace, et al	2009	Conference Paper	Kansas State University		2096-2103
Wang, et al	2020	Journal Article	Appl. Anim. Sci.		13-14
Williams	2024	Thesis	University of Guelph	1	30
				2	14-15
Williams, et al	2021	Journal Article	Transl. Anim. Sci.		"11-15"
Wilson, et al	2023	Journal Article	J. Anim. Sci.		160
Wilson, et al	2018	Report	Nebraska Beef Cattle Reports - University of Nebraska - Lincoln		200

Word, et al	2024	Journal Article	Appl. Anim. Sci.		814-826
Zinn and Plascencia	1996	Journal Article	J. Anim. Sci.		24
Zinn, et al	1997	Journal Article	J. Anim. Sci.		30
Zinn, et al	1991	Journal Article	J. Anim. Sci.		30

Appendix B - Supplement to Chapter 2



Appendix Figure B.1 Scree plot showing the change in variance with each additional principal component for the histologic measurements in the rumen, small intestine, and spiral colon of feedyard mortalities in the Histologic dataset.

Appendix Table B.1 Description of study factors evaluated in the Gross Necropsy and Histopathology models and their respective categories.

Factor Name ¹	Categories
Liver Abscess	Yes
	No
Liver Abscess Score	O
	A
	A+
Breed	Beef-influenced
	Dairy-influenced
Arrival Weight	<272 kg
	272-362 kg
	>362 kg
Current Estimated Weight	<272 kg

	272-362 kg
	>362 kg
Days on Feed at Death	0-50 days
	50-100 days
	100+ days
Number of Pulls	0
	1
	2
	3
	4
	5
	6
	7
	8
	9
	11
Sex	Heifer
	Steer
Autolysis	Slight
	Moderate
SI Serosa	Abnormal
	Within Normal Levels
SI Mucosa	Abnormal
	Within Normal Levels
SI Content	Abnormal
	Within Normal Levels
SI Total	Abnormal
	Within Normal Levels
SC Serosa	Abnormal
	Within Normal Levels
SC Mucosa	Abnormal
	Within Normal Levels
SC Content	Abnormal
	Within Normal Levels
SC Total	Abnormal
	Within Normal Levels
Rumen Mucosa	Abnormal
	Within Normal Levels
Rumen Content	Abnormal
	Within Normal Levels
Rumen Total	Abnormal
	Within Normal Levels
Abomasum Mucosa	Abnormal
	Within Normal Levels
Peritoneal Fluid	Abnormal

	Within Normal Levels
Peritoneal Adhesions	Present
	Absent
Mesenteric Lymph Nodes	Abnormal
	Within Normal Levels
Liver Color	Abnormal
	Within Normal Levels
Kidney	Abnormal
	Within Normal Levels
Spleen	Abnormal
	Within Normal Levels
Other Organs Total	Abnormal
	Within Normal Levels
¹ SI = small intestine; SC = spiral colon	

Appendix Table B.2 Overall performance (mean (sd)) of cattle cohorts from which feedyard mortalities came.

Item	Steers	Heifers	Mixed
No. cohorts	183	399	44
Arrival weight, kg	344 (49)	321 (53)	323 (56)
Final weight, kg	624 (33)	552 (35)	580 (29)
Days on feed	175 (27)	163 (31)	165 (30)
Deads out ADG, kg/d	1.60 (0.19)	1.42 (0.20)	1.56 (0.19)
Dry Matter Intake, kg/d	9.95 (0.97)	9.39 (0.90)	9.40 (0.97)
Gain:feed, kg/kg	0.162 (0.019)	0.153 (0.035)	0.166 (0.019)

Appendix Table B.3 Number of morphologic measurements on gastrointestinal tissue samples collected from liver abscess and time-matched, feedyard-matched cases without liver abscess (Control).

	2022		2023	
Tissue	Liver Abscess Measurements	Control Measurements	Liver Abscess Measurements	Control Measurements
Rumen	(n=21 animals; 105 measurements)	(n=22 animals; 110 measurements)	(n=17 animals; 85 measurements)	(n=18 animals; 90 measurements)
Papilla Width	80/105 (76.2%)	92/110 (83.6%)	22/85 (25.9%)	57/90 (63.3%)
Papilla Length	80/105 (76.2%)	92/110 (83.6%)	22/85 (25.9%)	57/90 (63.3%)
Papilla Area	80/105 (76.2%)	92/110 (83.6%)	22/85 (25.9%)	57/90 (63.3%)
Papilla Keratin	85/105 (81%)	100/110 (90.9%)	22/85 (25.9%)	57/90 (63.3%)
Stratum Corneum	85/105 (81%)	100/110 (90.9%)	53/85 (62.4%)	65/90 (72.2%)

Stratum Granulosum	85/105 (81%)	100/110 (90.9%)	53/85 (62.4%)	65/90 (72.2%)
Stratum Spinosum	85/105 (81%)	100/110 (90.9%)	53/85 (62.4%)	65/90 (72.2%)
Stratum Basale	85/105 (81%)	100/110 (90.9%)	53/85 (62.4%)	65/90 (72.2%)
Small Intestine	(n=21 animals; 105 measurements)	(n=22 animals; 110 measurements)	(n=18 animals; 90 measurements)	(n=18 animals; 90 measurements)
Villus Width	93/105 (88.6%)	110/110 (100%)	81/90 (90%)	85/90 (94.4%)
Villus Length	93/105 (88.6%)	110/110 (100%)	81/90 (90%)	85/90 (94.4%)
Crypt Width	95/105 (90.5%)	110/110 (100%)	81/90 (90%)	85/90 (94.4%)
Crypt Depth	95/105 (90.5%)	110/110 (100%)	81/90 (90%)	85/90 (94.4%)
Proprial Thickness	95/105 (90.5%)	110/110 (100%)	81/90 (90%)	85/90 (94.4%)
Goblet Cell Area	100/105 (95.2%)	105/110 (95.5%)	80/90 (88.9%)	90/90 (100%)
Spiral Colon	(n=21 animals; 105 measurements)	(n=22 animals; 110 measurements)	(n=17 animals; 85 measurements)	(n=16 animals; 80 measurements)
Gland Width	105/105 (100%)	105/110 (95.5%)	80/85 (94.1%)	75/80 (93.8%)
Gland Depth	105/105 (100%)	105/110 (95.5%)	80/85 (94.1%)	75/80 (93.8%)
Proprial Thickness	105/105 (100%)	105/110 (95.5%)	80/85 (94.1%)	75/80 (93.8%)
Goblet Cell Area	100/105 (95.2%)	105/110 (95.5%)	80/85 (94.1%)	80/80 (100%)
For each tissue sample collected, a goal of 5 replicates per measurement was attempted. Listed are the tissue measurements able to be collected out of the total number of measurements possible per category (= n x 5). Some tissue measurements were not collected due to autolysis of the sampled tissue after histology preparation or tissues samples not collected at necropsy.				

Appendix Table B.4 Cramer's V and chi-square test for association of liver abscess with cattle demographic and gross pathology variables for Gross Necropsy Dataset.

Variable¹	Cramer's V	Chi-square P-value
Breed	0.06	0.52
Arrival Weight	0.07	0.12
Current Estimated Weight	0.10	0.02
Days on Feed	0.14	< 0.01
Number of Pulls	0.09	0.61
Sex	0.11	< 0.01

Autolysis	0.05	0.26
SI Serosa	0.02	0.74
SI Mucosa	0.01	0.83
SI Content	0.00	1.00
SI Total	0.01	0.97
SC Serosa	0.04	0.40
SC Mucosa	0.02	0.74
SC Content	0.02	0.60
SC Total	0.00	1.00
Rumen Mucosa	0.04	0.31
Rumen Content	0.02	0.66
Rumen Total	0.01	0.76
Abomasum Mucosa	0.05	0.19
Peritoneal Fluid	0.01	0.85
Peritoneal Adhesions	0.15	< 0.01
Mesenteric Lymph Nodes	0.07	0.04
Liver Color	0.04	0.36
Kidney	0.02	0.81
Spleen	0.00	1.00
Other Organs Total	0.02	0.63
¹ SI = small intestine; SC = spiral colon		

Appendix Table B.5 Importance of principal components to explain the variation in the histologic measurements in the rumen, small intestine, and colon in the Histologic dataset.

Principal Component	Proportion of Variance	Cumulative Proportion of Variance
1	0.253	0.253
2	0.160	0.413
3	0.093	0.507
4	0.076	0.583
5	0.071	0.654
6	0.058	0.713
7	0.058	0.771
8	0.051	0.822
9	0.037	0.858
10	0.035	0.894
11	0.025	0.919
12	0.021	0.941
13	0.017	0.958
14	0.013	0.971
15	0.012	0.983
16	0.008	0.991
17	0.007	0.998
18	0.002	1.000

Appendix Table B.6 P-values for potentially confounding variables that were significant in the final statistical models for the rumen tissue morphologic measurements in the Histologic dataset.

Factor¹	Papillae Length	Papillae Width	Papillae Area	Papillae Keratin	Stratum Corneum	Stratum Granulosum	Stratum Spinosum	Stratum Basale
Breed	-	-	-	-	< 0.01	-	-	0.02
Arrival Weight	-	-	-	-	-	0.03	-	-
Number of Pulls	< 0.01	0.03	0.03	-	-	-	-	0.04
Autolysis	< 0.01	-	0.03	0.04	-	-	-	-
Rumen Mucosa	0.05	-	-	-	-	-	-	-
Rumen Content	0.07	-	0.09	-	-	-	-	-
Abomasum Mucosa	-	-	0.09	-	-	-	-	-
SI Content	-	-	-	-	-	-	-	0.01
SC Mucosa	-	-	-	0.07	-	-	-	-
SC Total	-	0.01	< 0.01	-	-	-	-	-
Peritoneal Adhesions	-	-	-	-	-	0.05	-	-
Kidney	-	-	-	-	-	-	0.08	0.02
Other Organs Total	-	-	-	-	-	-	-	0.08
¹ Factors that were not included in a model are marked as “-” in that column. Factors that were not included in any rumen histological model include (not included in table): Current Estimated Weight, Days on Feed, Sex, Rumen Total, SI Serosa, SI Mucosa, SI Total, SC Serosa, SC Content, Peritoneal Fluid, Mesenteric Lymph Nodes, Liver Color, Spleen; SI = small intestine; SC = spiral colon								

Appendix Table B.7 P-values for potentially confounding variables that were significant in the final statistical models for the small intestine tissue morphologic measurements in the Histologic dataset.

Factor¹	Villus Height	Villus Width	Crypt Depth	Crypt Width	Proprial Thickness	Goblet Cell Area
Days on Feed	-	-	0.01	-	-	-
Number of Pulls	< 0.01	< 0.01	< 0.01	0.01	-	-
Sex	-	-	-	-	0.02	-
Autolysis	0.01	0.03	-	0.03	-	-
Rumen Mucosa	-	-	-	-	-	0.09
Rumen Content	-	-	< 0.01	0.02	-	-
Abomasum Mucosa	0.02	-	-	-	0.04	-
SI Content	-	-	-	-	-	< 0.01
SC Mucosa	0.02	-	-	-	0.07	-
SC Content	0.05	-	-	-	-	-
Peritoneal Adhesions	-	0.04	0.07	0.05	-	0.02
Mesenteric Lymph Nodes	-	-	0.03	-	-	-
Kidney	-	-	-	-	-	0.02
¹ Factors that were not included in a model are marked as “-” in that column. Factors that were not included in any SI histological model include (not included in table): Breed, Liver Abscess Score, Arrival Weight, Current Estimated Weight, Rumen Total, SI Serosa, SI Mucosa, SI Total, SC Serosa, SC Total, Peritoneal Fluid, Liver Color, Spleen, Other Organs Total; SI = small intestine; SC = spiral colon.						

Appendix Table B.8 P-values for potentially confounding variables that were significant in the final statistical models for the spiral colon tissue morphologic measurements in the Histologic dataset.

Factor¹	Gland Depth	Gland Width	Proprial Thickness	Goblet Cell Area
Days on Feed	-	0.04	-	-
Number of Pulls	-	-	-	0.01
Autolysis	< 0.01	0.04	0.03	< 0.01
Rumen Mucosa	0.10	-	-	-
Rumen Total	-	-	< 0.01	0.03
SI Serosa	< 0.01	-	-	-
SI Total	-	0.03	0.08	0.09
SC Content	0.03	-	0.05	-
Peritoneal Adhesions	0.02	-	-	-
Other Organs Total	-	0.06	0.03	-

¹Factors that were not included in a model are marked as “-” in that column. Factors that were not included in any SC histological model include (not included in table): Breed, Liver Abscess Score, Arrival Weight, Current Estimated Weight, Sex, Rumen Content, Abomasum Mucosa, SI Mucosa, SI Content, SC Serosa, SC Mucosa, SC Total, Peritoneal Fluid, Mesenteric Lymph Nodes, Liver Color, Kidney, Spleen; SI = small intestine; SC = spiral colon