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# Effects of bovine respiratory disease on the plasma metabolome of beef steers during the receiving period

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The study aimed to investigate the impact of Bovine Respiratory Disease (BRD) on the metabolism of beef steers during a 35-d receiving period using plasma metabolomics. In this study, 77 newly weaned crossbred (Angus × Hereford) beef steers (BW = 206 ± 12 kg and age = 180 ± 17 days) were categorized into two groups: Healthy and Sick groups. The Sick group comprised beef steers diagnosed with BRD at any time during the 35-day period ( $n = 31$ ), while the Healthy group did not show any signs of BRD ( $n = 46$ ). Blood samples were collected from the coccygeal vessels on day 35, and plasma samples were subjected to targeted metabolomics analysis using Nuclear Magnetic Resonance spectroscopy. Data and statistical analyses, including biomarker and pathway enrichment analyses, were performed using Metaboanalyst 5.0. Results of the growth performance showed that sick steers had lower ( $p \leq 0.05$ ) ADG (1.44 vs. 1.64 kg/d) and higher ( $p = 0.01$ ) feed:gain ratio (3.57 vs. 3.13) compared to healthy steers. A total of 50 metabolites were quantified. The partial least squares discriminant scores plot showed a slight separation between the two groups of steers, indicating some metabolic differences. Furthermore, the plasma concentrations of four metabolites (sarcosine, methionine, dimethyl sulfone, and L-histidine) were greater ( $p \leq 0.05$ ) in healthy steers compared to sick steers. Among these metabolites, sarcosine and methionine qualified as candidate biomarkers associated with BRD infection based on an area under the curve >0.70. Additionally, quantitative enrichment analysis revealed that cysteine and methionine metabolism was enriched in healthy steers compared to sick steers. This suggests that these metabolic pathways may play a role in the response to BRD infection. The findings of this study highlight the altered plasma metabolome in steers with BRD during the receiving period. Understanding these metabolic changes can contribute to the development of effective management strategies and nutritional interventions to mitigate the negative impact of BRD on beef cattle health and immune function.

## KEYWORDS

amino acids, bovine respiratory disease, metabolome, receiving period, beef cattle

## Introduction

Bovine respiratory disease (BRD) is a significant endemic disease that has had a considerable impact on morbidity and mortality rates in feedlots in the United States (1, 2). The complexity of BRD in the feedlot industry arises from various environmental and physiological stress factors that cattle encounter during the critical receiving period (3, 4). These stressors include weaning, dietary changes, mixing of unfamiliar animals, transportation, and exposure to pathogenic agents (4). During the feedlot receiving period, cattle often experience reduced DMI, leading to impaired nutrient metabolism and compromised immune function (5, 6). The combination of these factors creates an environment conducive to the development and progression of BRD.

Vaccination and antibiotic treatments have been integral in the prevention and mitigation of BRD in beef cattle (7–9). These interventions have proven effective in reducing the severity of BRD (10, 11). However, it is essential to address the public concern surrounding the use of antibiotics in food animals, as this issue is likely to persist (1, 13). Therefore, in addition to vaccination and antibiotic treatments, it becomes necessary to implement other management strategies to mitigate the negative impact of BRD on beef cattle health and immune function (14, 15). In recent times, the application of metabolomics has provided a blueprint for the comprehensive analysis of metabolites in biofluids, which has emerged as a powerful tool for understanding disease processes and identifying metabolic alterations associated with various conditions (16–18). By exploring the impact of BRD on overall metabolism, effective strategies for managing and implementing nutritional interventions can be utilized to mitigate the detrimental effects of BRD infection on the nutritional status and performance of beef cattle. Indeed, a recent study (19) demonstrated that dairy calves deliberately infected with BRD causal agents exhibited altered metabolism. However, the metabolism of beef cattle infected with BRD during the receiving period has not been fully described. Therefore, the objective of this study was to determine the effects of BRD infection on the plasma metabolome of beef steers during a 35-d receiving period. We hypothesized that BRD infection would induce alterations in the plasma metabolome of beef steers during this critical period.

## Materials and methods

### Animals, housing, and feeding

All animal care and use procedures adhered to the guidelines for the use of Animals in Agriculture Teaching and Research at West Virginia University (Protocol #2014-0194). Seventy-seven (77) newly weaned crossbred (Angus × Hereford) beef steers (BW = 204 ± 14 kg; age = 180 ± 17 days) were sourced from a single farm located about 150 miles away from the research station. Following initial vaccination at approximately 60 days of age, the beef steers received booster shots at approximately 7 d prior to weaning. This vaccination protocol involved two separate vaccinations, Pyramid 5 plus preprone sq. and Alpha-7/MB-1 (Boehringer Ingelheim Animal Health, Duluth, GA). Subsequently, the beef steers were transported to the university research farm (over a distance of approximately 150 miles). Upon arrival, the beef steers were weighed and processed. Processing procedures included the application of ear tags for unique

radiofrequency identification purposes, as well as the administration of de-wormers (Valbazen, Zoetis Inc., Kalamazoo, MI). After being grouped according to their body weight on day 0, the steers were stratified into four pens, each pen housing 20 steers. This stratification was implemented to ensure that the starting body weights within each pen were similar. Each pen measured 14.6 by 46.9 m<sup>2</sup> and was equipped with two GrowSafe intake nodes (GrowSafe Systems Ltd., Airdrie, Alberta, Canada) for individual feed intake measurement. The beef steers were fed a total mixed ration (TMR; [Supplementary Table S1](#)) formulated according to the recommendations for growing beef cattle (20) for a duration of 35 days.

### Intake and BW measurement

Individual feed intake was measured using GrowSafe intake nodes (GrowSafe Systems Ltd., Airdrie, Alberta, Canada). A 24-h intake period was defined from 0900 h to 0800 h the following day. Daily samples of the TMR were collected. These samples were weighed and subjected to oven drying at 55°C for a duration of 72 h to determine the dry matter (DM) content. The samples were then ground using a Wiley mill (Arthur H. Thomas Co., Philadelphia, PA) to pass through a 2-mm sieve. These ground subsamples were sent to Dairy One Forage Laboratory (Ithaca, NY) for chemical composition analysis. The BW of the beef steers were recorded prior to the morning feeding on d 0 and 35 of the experiment to calculate the average daily gain (ADG) of the beef steers.

### BRD morbidity and blood collection

The beef steers were subjected to daily visual examinations, and appropriate measures were taken to address sickness when necessary. To qualify for treatment, an animal had to exhibit visible signs of illness, such as lethargy, coughing, or a runny nose, in addition to experiencing BW loss relative to its initial BW and having a rectal temperature exceeding 39.5°C. The treatment administration sequence involved a single subcutaneous injection of Draxxin (Tulathromycin, Pfizer, New York, NY), followed by an injection of Banamine (Flunixin meglumine, Merck Animal Health, Summit, NJ). If any animal did not respond to the initial treatment, second or third treatments were administered accordingly. At the conclusion of the 35-day period, the animals were categorized into two groups: (1) Animals diagnosed with bovine respiratory disease (BRD) at any time during the 35-day period (Sick group) and (2) Animals that did not exhibit any signs of BRD throughout the 35-day period (Healthy group). Prior to the morning feeding on day 35, blood samples (10 mL each) were collected from all beef steers. The blood was drawn from the coccygeal vessels using tubes containing sodium heparin (Fisher Scientific Company). Subsequently, plasma samples were prepared by centrifugation at 2,500 × g for 20 min at 4°C. The plasma samples were then stored at –80°C for subsequent analysis.

### Targeted metabolomics analysis using nuclear magnetic resonance spectroscopy

To evaluate the metabolic status of the two groups of beef steers, plasma samples collected on day 35 were subjected to metabolome

analysis using Nuclear Magnetic Resonance (NMR) spectroscopy. A total of 50 metabolites, including organic acids, amino acids, hexoses, lipids, and carnitines were quantified using this technique (Supplementary Table S2). The plasma sample preparation and NMR spectral analysis procedures followed the protocols previously published by Ogunade et al. (21). Initially, a deproteinization step was conducted using ultra-filtration, following the method described by Psychogios et al. (22). This step aimed to eliminate macromolecules such as proteins and lipoproteins. Subsequently, 160  $\mu$ L of the sample was combined with 40  $\mu$ L of a standard buffer solution composed of 54% D<sub>2</sub>O and 46% 250 mM KH<sub>2</sub>PO<sub>4</sub> at pH 7.0. The resulting plasma sample (200  $\mu$ L) was then transferred into a 3 mm SampleJet NMR tube to undergo spectral analysis. All <sup>1</sup>H-NMR spectra were acquired utilizing a 700 MHz Avance III spectrometer, which was equipped with a 5 mm HCN Z-gradient pulsed-field gradient cryoprobe. Bayesil, an automated analysis software package enabling qualitative and quantitative analysis (23), was used to process the <sup>1</sup>H-NMR spectra. To minimize potential errors associated with compound identification and quantification, an additional inspection and verification process was conducted by an NMR spectroscopist.

## Statistical analysis

The performance and DMI results were analyzed using the GLIMMIX model of SAS (SAS 9.3, SAS Inst. Inc., Cary, NC) as a randomized block design, using steer as the experimental unit. Metabolome data was analyzed using Metaboanalyst 5.0 software (24). Prior to the statistical analysis, the data were log-transformed and auto-scaled. To identify the differentially abundant metabolites between the two groups of beef steers, a false discovery rate (FDR)-adjusted *p*-values threshold of  $\leq 0.05$  and an area under the curve (AUC) threshold of  $>0.70$  were utilized. The receiver operating characteristic (ROC) curve analysis was performed by the ROCCET web server. To assess the metabolic pathways that were affected by BRD infection, a quantitative enrichment analysis of all the metabolites was conducted using the KEGG database.

## Results

At the end of the experiment, 31 beef steers were diagnosed with BRD at any time during the 35-day period (Sick group) and 46 beef steers did not exhibit any signs of BRD throughout the 35-day period (Healthy group). The results of the growth performance of the healthy and sick beef steers are shown in Table 1. Sick beef steers had lower ( $p=0.01$ ) ADG compared to healthy steers (1.44 vs. 1.64 kg/d). However, DMI was similar for the two groups. Consequently, the sick beef steers had greater ( $p=0.01$ ) feed:gain ratio compared to healthy ones (3.57 vs. 3.13).

A total of 50 metabolites were detected and quantified in the plasma samples of all the beef steers (Supplementary Table S2). The PLS-DA scores plot showed an overlap but with a slight separation of the entire plasma metabolome between the sick and healthy steers. Thus, suggesting that the plasma metabolome was altered by BRD infection (Figure 1). Plasma concentrations of four metabolites (sarcosine, methionine, dimethyl sulfone and L-histidine) were

TABLE 1 Performance of the sick and healthy beef steers during the 35-d receiving period.

	Sick	Healthy	SEM	<i>p</i> -value
ADG, kg/d	1.44	1.64	0.06	0.01
DMI, kg/d	5.13	5.27	0.15	0.33
Feed:gain	3.57	3.13	0.09	0.01

greater (FDR  $\leq 0.05$ ) in the healthy steers compared to the sick steers (Table 2). Out of the four differentially abundant metabolites, only two metabolites (sarcosine and methionine) had AUC values  $>0.70$  (Figure 2). The results of the ROC analysis of the two metabolites revealed an AUC value of 0.773, suggesting that plasma concentrations of methionine and sarcosine could be used as a plasma biomarker panel associated with BRD infection in beef steers (Figure 3). The results of the quantitative enrichment analysis revealed cysteine and methionine metabolism ( $p=0.05$ ) was enriched in healthy, compared to the sick steers (Figure 4). The enriched metabolites associated with this pathway were methionine, cysteine, and pyruvic acid.

## Discussion

The performance parameters of the sick and healthy steers during the receiving period were compared, revealing differences in ADG and feed:gain ratio. Sick steers exhibited lower ADG and higher feed:gain ratio compared to the Healthy steers, indicating that BRD may disrupt the metabolic processes involved in growth and nutrient utilization. Furthermore, though not statistically different, slightly lower DMI in sick steers suggests that BRD may affect satiety and feed intake. Similar effects of BRD on the performance of beef cattle have been reported in previous studies (25–27), suggesting that BRD negatively impacts nutrient absorption and utilization, alters metabolism, and increases energy expenditure due to the immune response and inflammation (28).

Bovine respiratory disease has a profound impact on the overall metabolic homeostasis, causing notable alterations in metabolite levels that reflect the body's response to the infection and its defense mechanisms against the invading pathogens (29). The manifestation of BRD infection in beef cattle can have a significant impact on their metabolism, depending on the degree of pathological condition development (29). The disease disrupts various biological systems within the animal, particularly immune activation and nutrient metabolism (30, 31). The disruptions experienced as a result of these events lead to various biological alterations. One notable change is the upregulation of protein turnover, which is initiated by the production of cytokines in response to the pathogen. This heightened protein turnover necessitates an increased demand for amino acids to facilitate the synthesis of acute-phase proteins in the liver (29).

Metabolomics assessment revealed altered cysteine and methionine metabolism and identified specific plasma metabolites that differed between healthy and sick steers, including sarcosine, methionine, dimethyl sulfone, and L-histidine. These metabolites play crucial roles in biological and metabolic processes related to

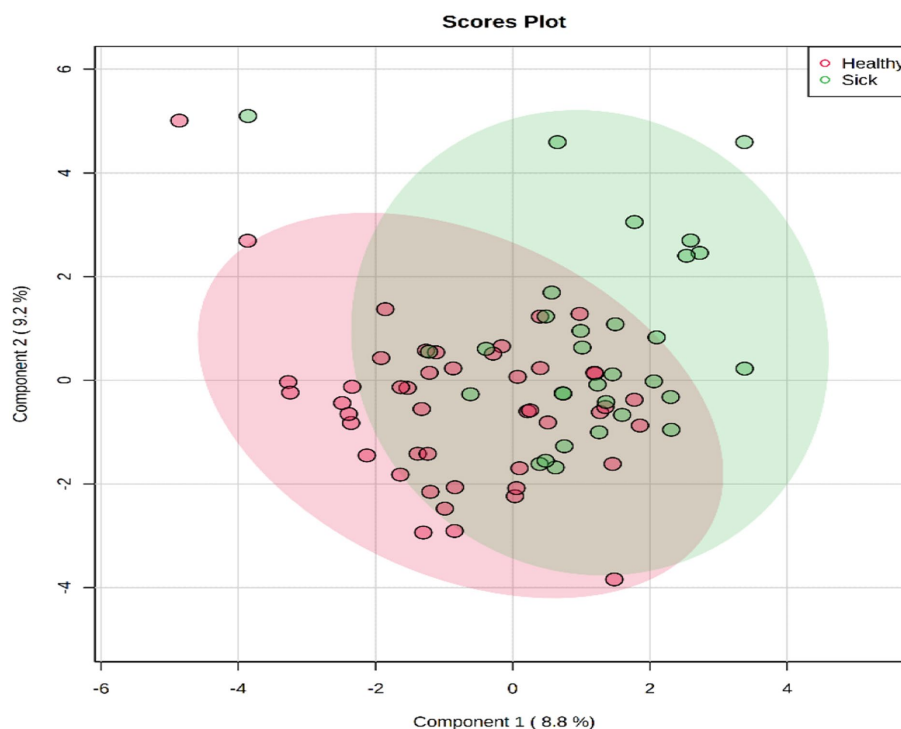


FIGURE 1  
PLS-DA scores plot of plasma metabolome of Healthy and Sick beef steers.

TABLE 2 Differentially abundant plasma metabolites in beef steers with or without bovine respiratory disease.

Metabolites	FC (healthy/sick)	FDR
Sarcosine	1.29	0.01
Methionine	1.13	0.01
Dimethyl sulfone	1.22	0.02
L-Histidine	1.06	0.04

Healthy = healthy beef steers, Sick = sick beef steers.

FC = fold change (healthy/sick).

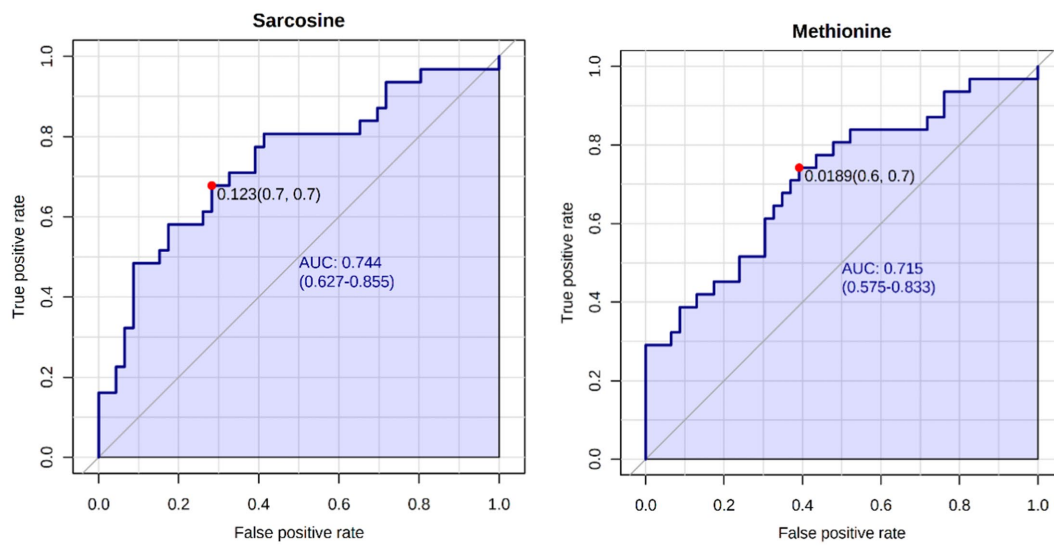
Only metabolites with false discovery rate (FDR)  $\leq 0.05$  are shown.

growth, production, and reproduction in farm animals (32). The decreased plasma concentration of sarcosine and methionine in sick steers suggests potential implications for the growth and energy substrate levels in the blood. Dysregulation in the metabolism of these amino acids may affect protein synthesis, muscle development, energy availability, and utilization, thereby impacting overall growth and body weight gain. Methionine, being an essential amino acid, is involved in various metabolic processes crucial for growth and muscle development. In the context of BRD, decreased methionine levels may compromise protein synthesis, utilization of other amino acids, dietary nutrient utilization, and immune defense mechanisms. Methionine deficiency has been associated with poor growth performance in growing beef cattle fed high forage diet such as the one fed in this study (33). Additionally, decreased methionine availability can compromise antioxidant defense mechanisms,

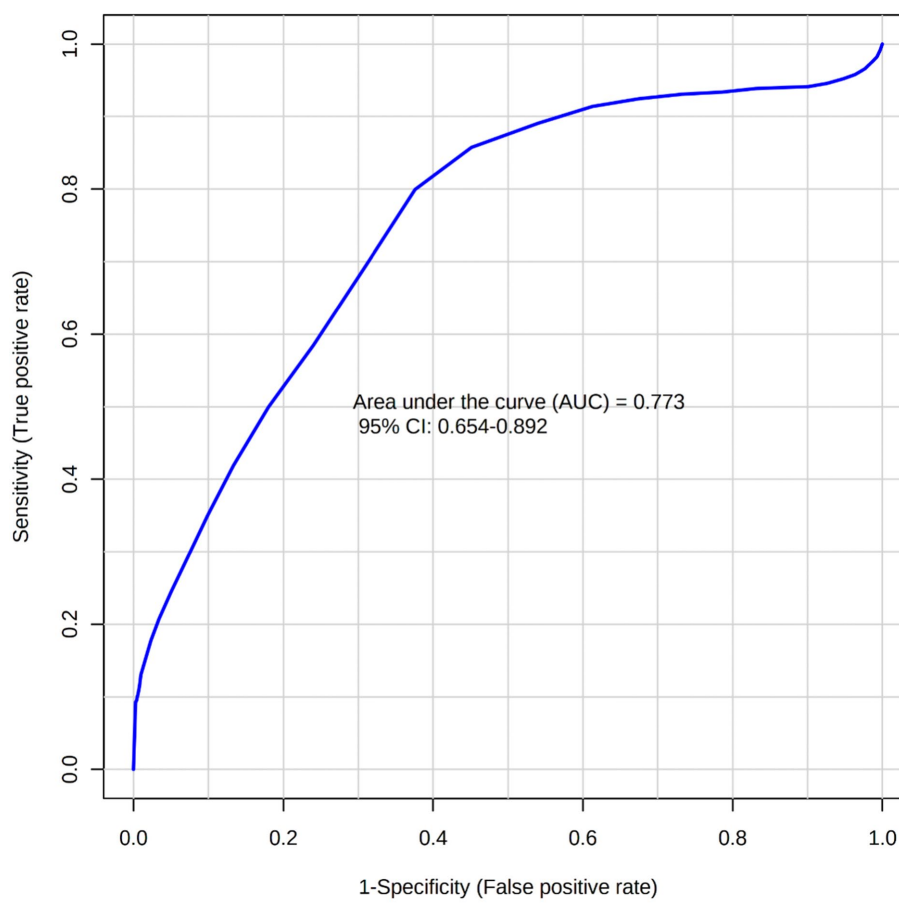
leading to increased oxidative damage, inflammation, and impaired growth. Sarcosine is an intermediate product in the metabolism of glycine and methionine, thus, the reduced plasma concentration of sarcosine in sick beef steers may signify dysregulation in the metabolic pathways of these amino acids, which can have a significant impact on essential processes such as protein synthesis and muscle development which are critical for optimal growth in beef cattle. Furthermore, sarcosine is involved in the one-carbon metabolism pathway, which is crucial for the synthesis of important molecules such as DNA, RNA, and proteins. Disruptions in sarcosine and methionine metabolism can lead to reduced availability of metabolites involved in energy production, which may explain the reduced ADG of the sick steers observed in this study.

## Conclusion

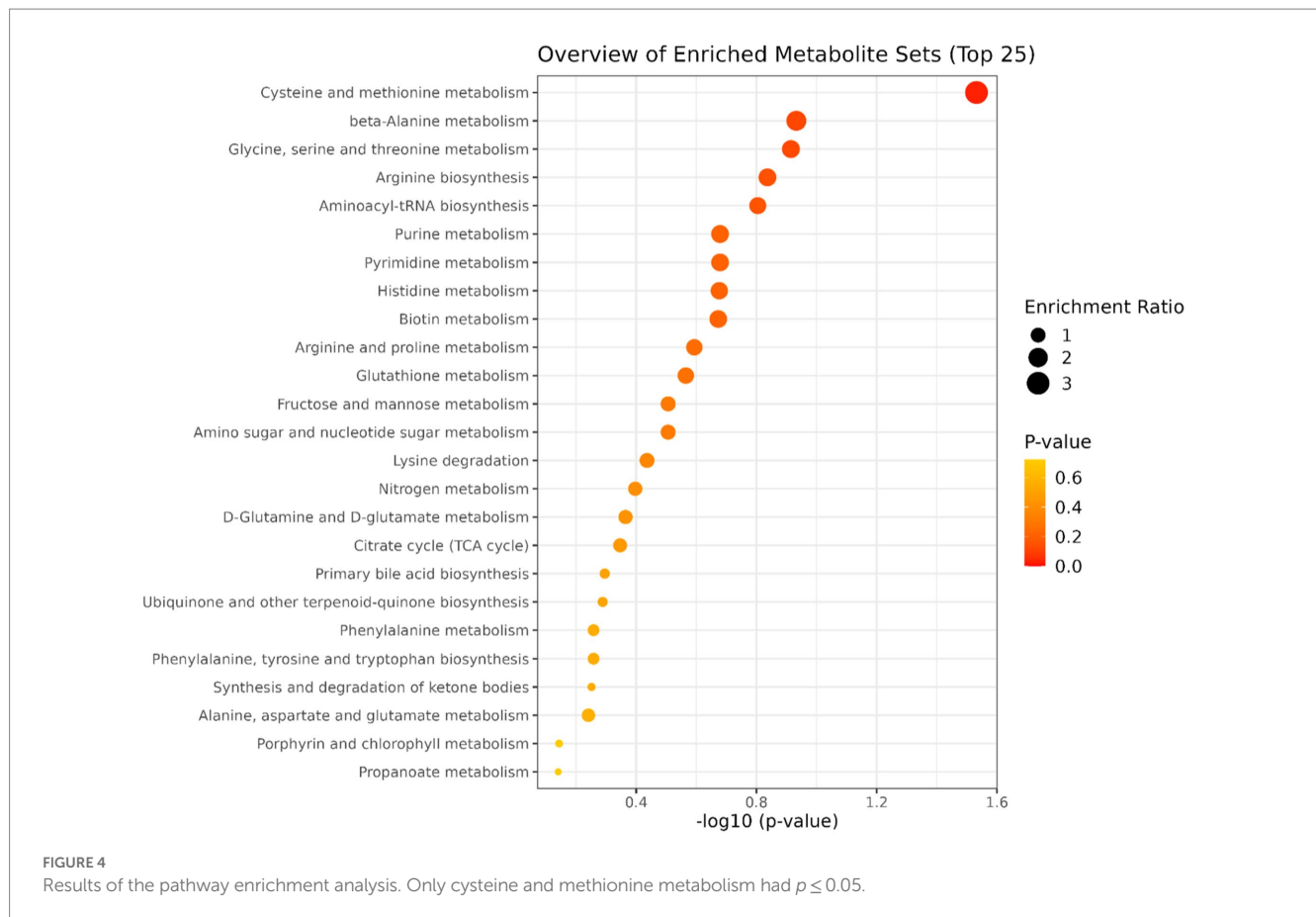
Our findings demonstrate that BRD infection reduced the ADG and increased gain:feed ratio, and altered the plasma metabolome of the beef steers toward reduced concentrations of sarcosine, methionine, dimethyl sulfone and L-histidine. Additionally, quantitative enrichment analysis revealed that cysteine and methionine metabolism was enriched in healthy steers compared to sick steers. Further research is warranted to elucidate the underlying mechanisms and explore targeted interventions, such as nutritional supplementation of methionine, sarcosine, or cysteine, for mitigating the metabolic consequences of BRD in cattle.



**FIGURE 2** Biomarker analysis of plasma metabolome. ROC curve analysis of candidate plasma biomarkers (methionine and sarcosine) associated with BRD infection in the beef steers.



**FIGURE 3** Biomarker analysis using multiple metabolites (Sarcosine and Methionine).



## Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

## Ethics statement

The animal study was reviewed and approved by West Virginia University (Protocol #2014-0194).

## Author contributions

IO designed the experiment. FE, GT, MI, IO, TS, ET, DO, and YL conducted the experiment and analyzed the data. FE drafted the manuscript. IO reviewed the final manuscript together with FE, GT, MI, IO, TS, ET, DO, and YL. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fvets.2023.1239651/full#supplementary-material>

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