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RESEARCH ARTICLE

Serum Levels of Mid-Regional Pro-Adrenomedullin and Soluble Triggering Receptor Expressed on Myeloid Cells in Cattle with Pneumonia

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ABSTRACT

This study aimed to determine the serum levels of two inflammatory biomarkers, named, mid-regional pro-adrenomedullin (MR-Pro ADM) and soluble triggering receptor expressed on myeloid cells (sTREM-1), in cattle diagnosed with pneumonia. For this purpose, 40 patient female cattle, which were aged 2-7 years and displayed coughing, dyspnea, nasal discharge, anorexia and abdominal respiration, and 15 healthy female cattle within the same age range, were evaluated. The diseased cattle underwent clinical and radiological examinations and were sampled for blood prior to receiving treatment. The healthy subjects also underwent clinical examination and were sampled for blood once. Blood samples were used for biochemical and hematological measurements. While the diseased group had higher serum levels of MR-Pro ADM (86.38±6.33), compared to the healthy control group (61.81±4.96); the pneumonic cattle had lower levels of sTREM-1 (75.93±1.86), in comparison to the healthy group (96.55±9.13).

In conclusion: MR-Pro ADM and sTREM-1 levels are very important diagnostically in cattle with pneumonia.

Key words: Cattle, MR-Pro ADM, Pneumonia, sTREM-1

Pnömonili Sığırlarda Miyeloid Hücrelerde Eksprese Edilen Mid-regional Pro-Adrenomedullin ve Soluble Tetikleyici Reseptörün Serum Düzeyleri

ÖZ

Bu çalışma, pnömoni tanısı konulan sığırlarda mid-regional pro-adrenomedullin (MR-Pro ADM) ve miyeloid hücrelerde eksprese soluble tetikleyici reseptör olmak üzere iki enflamatuvar biyobelirteç ile bazı biyokimyasal ve hematolojik parametrelerin serum düzeylerinin belirlenmesini amaçladı. Bu amaçla 2-7 yaş arası öksürük, nefes darlığı, burun akıntısı, iştahsızlık ve abdominal solunumu gösteren 40 hasta dişi sığır ve aynı yaş aralığında 15 sağlıklı dişi sığır değerlendirildi. Hasta sığırlar tedavi edilmeden önce klinik ve radyolojik muayenelere tabi tutuldu ve kan örnekleri alındı. Sağlıklı sığırlar ayrıca klinik muayeneye tabi tutuldu ve bir kez kan örnekleri alındı. Kan örnekleri biyokimyasal ve hematolojik ölçümler için kullanıldı. Hasta grupta MR-Pro ADM serum düzeyleri (86,38±6,33) kontrol grubuna (61,81±4,96) göre daha yüksek bulundu. Hasta sığırların sTREM-1 seviyeleri (75,93±1,86) sağlıklı gruba kıyasla (96,55±9,13) karşılaştırıldığında istatistiksel olarak anlamlı düşük bulundu.

Sonuç olarak: MR-Pro ADM ve sTREM-1 seviyeleri pnömonili sığırlarda diagnostik açıdan oldukça önemlidir.

Anahtar kelimeler: Mr-Pro-Adm, Pnömoni, Sığır, sTREM-1

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INTRODUCTION

One of the primary causes of economic loss in cattle production systems across the world and in Turkey is respiratory diseases. Pneumonia is one of the most commonly encountered bovine respiratory diseases (Issi et al. 2015, Durgut and Köse 2017). Pneumonia is described as the inflammation of the pulmonary tissue and is frequently associated with pleuritis (Dörtkardeş 2018)

One of the leading causes of the high prevalence of pneumonia in cattle is the anatomical structure and physiological characteristics of the bovine lungs. The multilobular structure of the bovine lungs reduces their cleansing capacity. Given the normal anatomical flow of pharyngeal fluids towards the lungs, cattle have a high risk of developing pulmonary hypertension. The lungs of cattle are small compared to their body size. Therefore, their pulmonary capacity is low. The ventilation capacity of bovine lungs at both hot and cold temperatures is low. Furthermore, compared to other animal species, cattle are characterized by weak phagocytic activity in the pulmonary tissue (Kurtdede and Kalınbacak 2016).

The main causes of bovine pneumonia include stress factors, seasonal change, transport, high stocking density (overcrowded housing), unfavorable weather conditions (extreme hot and cold temperatures, storm, high humidity), dust-laden air, poor ventilation, poor management and malnourishment, and immunosuppression (Henry et al. 2012, Hilton 2014, Anonymous 2014, Derek 2014, Gülersoy and Şen 2017). Furthermore, microorganisms involved in the etiology of pneumonia include viral pathogens such as *bovine viral diarrhea virus* (BVD), *bovine respiratory syncytial virus* (BRSV), *bovine herpes virus type 1*, *parainfluenza virus type 3* (PI3) and bacteria such as *Pasteurella multocida*, *Mannheimia haemolytica, Mycoplasma spp*. (Hodgins et al. 2002, Radostits et al. 2008, Woolums et al. 2009, Panciera and Confer 2010), *Histophilus somni* (Booker 2005) *Arcanobacterium pyogenes*, staphylococci, streptococci and Gram-negative bacteria belonging to the family *Enterobacteriacea* (Griffin et al. 2010).

Clinical symptoms associated with pneumonia include anorexia, fever, dyspnea, tachypnea, nasal discharge of varying types (Lopez et al. 2017), coughing, pathological breathing sounds at auscultation, lacrimal discharge, mental slowness (Gülersoy and Şen 2017, Dörtkardeş 2018), crepitation at the auscultation of cases with severe exudation in the respiratory system, friction sounds at the auscultation of cases with effects on the pleura (Griffin et al. 2010), and cyanosis (Ives and Richeson 2015).

Soluble triggering receptor-1 expressed on myeloid cells has a molecular weight of 30 kDa and is found on the surface of neutrophils, monocytes, macrophages and endothelial cells (Adly et al. 2014). TREM-1 is involved in the activation of toll-like receptors (TLR-2 and TLR-4) (Jin Jeong et al. 2012) and increases inflammatory signals by means of DAP-12 protein (Zhang et al. 2011). Furthermore, TREM-1 mediates the production of cytokines and chemokines, including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-8 (IL-8) (Smok et al. 2020). The soluble form of triggering receptor-1 expressed on myeloid cells, abbreviated as sTREM 1 (Su et al. 2011), is used for the assessment of the inflammatory response (Gamez-Diaz et al. 2011) and is found in several body fluids, including the cerebrospinal fluid, bronchoalveolar lavage fluid, urine, pleural fluid, and blood plasma (Smok et al. 2020).

One of the precursors of adrenomedullin (ADM) is pro-ADM (Morgenthaler et al. 2005). Adrenomedullin is classified under the family of the calcitonin gene-related peptides (CGRP) (Geven et al. 2018). In the body, ADM is produced in multiple tissues (Valenzulea-Sanchez et al. 2016, Geven et al. 2018), including the pulmonary tissue (Garazzino et al. 2019). ADM has vasodilator (Akpınar et al. 2014), diuretic and natriuretic (Rey et al. 2013), bronchodilator (Önal et al. 2018), antimicrobial (Garazzino et al. 2019), antifungal and anti-inflammatory (Akpınar et al. 2014) effects. ADM is localized to the surface of the epithelium lining the respiratory tract (Valenzulea-Sanchez et al. 2016). In cases of hypoxia, oxidative stress and inflammation, which are induced by lipopolysaccharides (Garayoa et al. 2000) and cytokines such as TNF-α and IL-1 (Ghobrial et al. 2020), ADM synthesis has been determined to increase (Fahmey et al. 2018). It is not possible to measure blood adrenomedullin levels as this peptide hormone rapidly binds to its carrier receptors, has a short half-life and is rapidly metabolized (Geven et al. 2018). Therefore, measurements are targeted at the mid-regional fragment of ADM, referred to as mid-regional pro-adrenomedullin (MR-proADM) (Sönmezer and Tülek 2015, Önal et al. 2018, Garazzino et al. 2019).

This study was aimed at determining alterations in the sTREM-1 and MR-proADM levels of cattle diagnosed with pneumonia, based on clinical and radiographic findings.

MATERIAL AND METHOD

The present study was performed pursuant to the approval of the Local Ethics Board for Animal Experiments of Kafkas University (KAU-HADYEK/2022-032). The study material comprised of 40 patient female cattle, which were aged 2-7 years, of different breeds, and referred to the Internal Medicine Clinic of the Animal Health Training, Research and Practice Hospital of Kafkas University Faculty of Veterinary Medicine with complaints of coughing, anorexia and fever. Fifteen healthy female cattle, within the same age range, were maintained for control purposes. The selected diseased animals did not receive any prior treatment. The diseased animals included in the study were selected according to their clinical examination and manifestation of coughing, anorexia, dyspnea, mucosal cyanosis, abdominal respiration, nasal discharge, and pathological sounds such as moist and dry rales and crepitation-friction at auscultation. The body temperature, respiratory rate and pulse of the diseased animals were recorded, and radiographic examinations of pulmones were performed.

Jugular blood samples were collected prior to treatment (at 0 h) from the diseased cattle and only once from the healthy cattle, using a holder and a sterile needle (Vacuette®, Greiner Bio-One GmbH, Austria). Blood samples were drawn into evacuated gel serum tubes (BD Vacutainer®, BD, UK) and evacuated EDTA-coated tubes (BD Vacutainer®, BD, UK). Blood samples in the vacutainers were centrifuged at 3000 rpm for 10 minutes (Hettich Rotina 380R®, Hettich, Germany) for the extraction of serum. The extracted sera were used for the measurement of biochemical parameters, whilst whole-blood samples were used for the measurement of hematological parameters. The sera used for the measurement of sTREM-1 and Mr-Pro-ADM levels were stored at -20 °C until being used for analyses.

With the aid of a fully automated blood cell counter (VG-MS4e®, Melet Schloesing, France), the whole-blood samples were analyzed for the determination of the white blood cell count (WBC), red blood cell count (RBC), hematocrit percentage (HCT), hemoglobin concentration (HGB), and thrombocyte count (THR). Furthermore, with the aid of a fully automated biochemistry analyzer (Mindray BS120®, Mindray Medical Technology, Istanbul, Turkey) the extracted sera were analyzed for alanine aminotransferase (ALT), aspartate amino transferase (AST), glucose, creatinine (CREA), urea (UREA), total protein (TP), albumin (ALB), creatine kinase (CK), and iron (Fe) measurements.

Radiological Evaluation

Radiological evaluations were carried out at the Radiology Unit of the Surgery Department of Kafkas University, Faculty of Veterinary Medicine. Radiographic images were taken using a 35x43 cm cassette, in the right or left laterolateral (L/L) view, at 80-85 kV and 20-25 mAs, using a computerized radiography (CR) system (Fujifilm Türkiye).

ELISA Measurements

In the present study, the serum levels of sTREM-1 and MR-proADM were determined with commercial bovine-specific ELISA kits (Bovine sTREM-1 ELISA kit®, Bovine Mr-Pro-ADM ELISA kit®, BT Lab, China). The ELISA test kits were used according to the manufacturer's instructions, and optical density was measured at a wavelength of 450 nm with an ELISA reader (Thermo Scientific®, USA). The sTREM-1 and MR-proADM values were determined by regression analyses.

Statistical Analysis

Statistical analysis of the data was performed using SPSS® (Version 26.0, Chicago, IL, USA) software. The statistical differences between the groups with normal distribution according to Shapiro-Wilk test were compared by independent sample t-test. The obtained results were given as mean ± standard error of the mean (SEM). $P < 0.05$ was considered significant in the evaluation of the results.

RESULTS

The clinical examination of the diseased cattles included in the study revealed signs of coughing, fever, anorexia, dyspnea, abdominal respiration, nasal discharge of varying types, pathological sounds at pulmonary auscultation, and in cases characterized by severe dyspnea, cyanosis. The vital signs (body temperature, respiratory rate per minute, pulse rate) of the diseased and healthy animals were subjected to comparative statistical evaluation (Table 1). Accordingly, the results demonstrated that values pertaining to the vital signs were significantly higher in the diseased animals, compared to the healthy control subjects ($P<0.05$).

The WBC, RBC, HCT, HGB and THR values of the diseased and healthy animals are presented in Table 1. The indicated hematological parameters were found to be higher in the diseased animals, in comparison to the healthy control group ($P<0.05$).

Radiography revealed increased opacity caused by pulmonary consolidation, particularly in the cranial lobes, but distributed throughout the lungs, due to severe pneumonia (Figure 1). The severity of bronchial consolidation decreased caudally, such that severe opacity was replaced by air-filled radiolucent areas, yet all cases displayed severe pneumonia.

The serum biochemical parameters (ALT, AST, glucose, CREA, UREA, TP, ALB, CK, Fe) are presented in Table 2. When compared to the control group, the patient animals had significantly higher ALT, AST and CK activities and CREA, UREA and TP concentrations ($P<0.05$). Also patient animals had significantly lower ALB, glucose and Fe concentrations ($P<0.05$).

The serum sTREM-1 and MR-proADM levels of the diseased and healthy animals are given in Table 3. When compared to the healthy controls, the diseased group presented with significantly higher MR-proADM concentrations ($P<0.05$) and significantly lower sTREM-1 concentrations ($P<0.05$).

Table 1. Mean values and standard error values (SEM) of physical examination findings and hematological parameters in the patient and control groups.

Parameters	**Patient* (n=40)**	**Control (n=15)**	**p**
	Mean ± SEM		
Rectal temperature (°C)	39.47±0.11	38.42±0.11	<0.001
Breaths/min	44.05±1.69	22.53±1.82	<0.001
Heart beats/min	87.70±1.94	66.00±2.13	<0.001
Total leukocytes count (×10^3/µL)	22.29±1.46	9.64±0.99	<0.001
Red blood cell count (x10^6/µL)	12.61±0.59	9.12±0.63	0.002
Hematocrit (%)	48.73±1.65	36.02±2.29	<0.001
Hemoglobin (g/dL)	18.30±0.75	11.05±0.69	<0.001
Platelet count (x10^3/µL)	642.35±38.23	204.53±41.82	<0.001

$p<0.05$: Indicates statistical significance between pneumonia and control groups.
SEM: Standard error of mean.

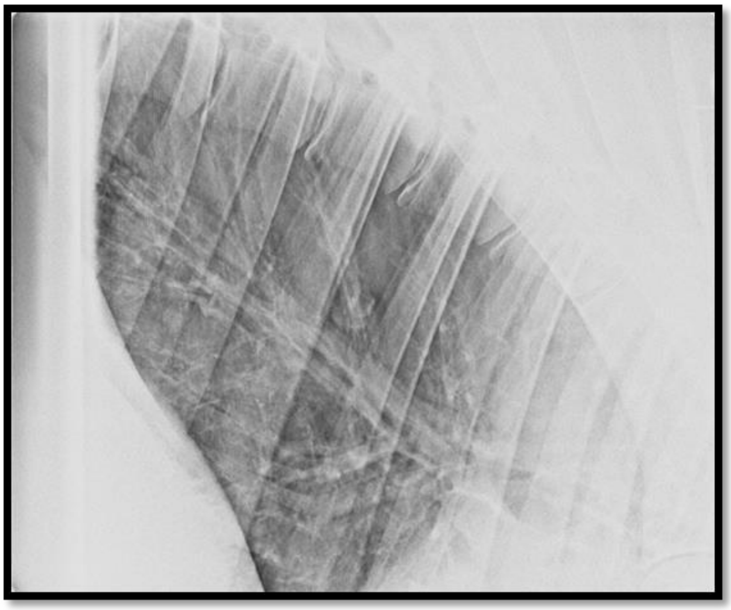

Figure 1: Radiographic image of the lung of one of the cattle in the patient group diagnosed with pneumonia. Radiography revealed increased opacity caused by pulmonary consolidation, particularly in the cranial lobes, but distributed throughout the lungs, due to severe pneumonia. The severity of bronchial consolidation decreased caudally, such that severe opacity was replaced by air-filled radiolucent areas.

Table 2. Mean values and standard error values (SEM) of biochemical parameters in the patient and control groups.

Biochemical Parameters	Patient* (n=40)	Control (n=15)	p
	Mean ± SEM		
Alanine aminotransferase (IU/L)	225.31±22.39	23.20±2.43	<0.001
Aspartate aminotransferase (IU/L)	378.30±28.28	104.73±4.70	<0.001
Creatine (mg/dL)	2.73±0.19	1.20±0.09	<0.001
Urea (mg/dL)	108.53±7.98	31.93±1.68	<0.001
Total protein (g/dL)	8.23±0.40	6.79±0.17	0.002
Albumin (g/dL)	2.78±0.17	3.62±0.15	0.044
Creatine kinase (IU/L)	252.15±17.14	95.13±6.37	<0.001
Glucose (mg/dL)	69.65±5.64	108.73±6.32	<0.001
Iron (mg/dL)	60.27±5.61	105.53±8.00	<0.001

p<0.05: Indicates statistical significance between pneumonia and control groups.
SEM: Standard error of mean.

Table 3. Mean values and standard error values of biomarkers in the patient and control groups.

Biomarkers	Patient (n=40)	Control (n=15)	p
	Mean ± SEM		
MR-Pro-ADM (ng/L)	86.38±6.33	61.81±4.96	0.004
sTREM-1 (ng/L)	75.93±1.86	96.55±9.13	0.043

p<0.05: Indicates statistical significance between pneumonia and control groups.
SEM: Standard error of mean.

DISCUSSION

Bovine pneumonia is associated with multiple clinical signs, including anorexia, fever, and in advanced cases: dyspnea, tachypnea, nasal discharge of varying types (Lopez et al. 2017), coughing, pathological breathing sounds at auscultation, lacrimal discharge, mental slowness (Gülersoy and Şen 2017, Dörtkardeş 2018), keeping the mouth open, rapid opening and closing of the nostrils, stretching forth of the head, keeping the anterior feet apart from the body, difficulty in laying down and standing up, tachycardia, groaning (Guterbock 2014), crepitation at auscultation in cases associated with severe exudation in the respiratory tract, cyanotic appearance of the mucosae and conjunctivae (Ives and Richeson 2015), sound of friction in cases with impact on the pleura (Griffin et al. 2010), decreased production yields and emaciation (Radostits et al. 2007). In agreement with previous reports, in the present study, the diseased animals were observed to display anorexia, fever, coughing, emaciation, dyspnea, tachypnea, tachycardia, nasolacrimal discharge, pathological breathing sounds at auscultation, and cyanosis.

Bacterial and viral bronchopneumonia cases are associated with leukocytosis or leukopenia. Moreover, due to anorexia and hypoxia, these cases also manifest with polycythemia (Gülersoy and Şen 2017). In the present study, the hematological examination of the diseased animals revealed leukocytosis caused by severe infection, as well as polycythemia caused by anorexia and hypoxia (P<0.05).

In animals, thrombocytosis has been reported to be caused by stress, inflammatory diseases, iron deficiency, drug and corticosteroid use, and polycythemia (Kayar 2013). In the present study, similarly, we considered thrombocytosis to have developed due to the same reasons.

The levels of the hepatic enzymes alanine transferase (ALT) and aspartate transferase (AST) increase in parallel with liver damage, endotoxemia-induced passive congestion, soft tissue damage and tightness of the forestomach (Başer and Civelek 2013, Zeybek 2013). In the present study, the animals diagnosed with pneumonia were also determined to have ALT and AST activities higher than those of the control subjects (P<0.05). We think that the increased activity of these enzymes may be due to soft tissue damage and passive congestion caused by pneumonia-induced endotoxemia.

Renal functions are assessed in view of both serum urea and creatinine levels. Fever caused by severe infection, as well as anorexia, are associated with a dehydration-triggered increase in protein catabolism. In such cases, both blood pressure and the glomerular filtration rate decrease. Eventually, functional kidney disorders occur. Functional disorders of the kidneys are associated with increased serum urea and creatinine levels (Uzlu et al. 2010, Başer and Civelek 2013, Bal 2019, Eroğlu and Kırbaş 2020). Similar to literature reports, in the present study, when compared to the healthy controls, the diseased cattle were found to present with increased serum urea and creatinine levels (P<0.05). We think that urea and creatinine may have increased due to fever, loss of appetite, protein catabolism and dehydration in cattle diagnosed with pneumonia in our study.

In cases of severe infection, soft tissue damage and myopathy occur (Langhans et al. 2014, Rocheteau et al. 2015). This, in return, causes an increase in serum CK activity (Aydın et al. 2018, Akyüz and Gökce 2021). In agreement with literature data, in the present study, the diseased animals displayed an increased CK activity in comparison to the healthy controls (P<0.05).

In the event of dehydration, due to decreased plasma volume, both the total protein level and hemoconcentration increase (Babaç 2014, Eroğlu and Kırbaş 2020). Another cause of an increased total protein level is increased globulin, sialoprotein and fibrinogen levels caused by tissue damage resulting from severe inflammation (Uzlu et al. 2010). The serum levels of albumin, a negative acute-phase protein, decrease under severe inflammatory conditions (Silverstein and Otto 2012). In the present study, in agreement with literature data, the diseased animals were determined to have increased total protein levels and decreased albumin levels, in comparison to the healthy controls (P<0.05).

It has been reported that endotoxemia is associated with hypoglycemia (Coşkun and Şen 2012). The underlying reasons of hypoglycemia could be the disruption of the hepatic glucose metabolism (Şen et al. 2009) or infection-induced anorexia (Aydoğdu et al. 2019). In the present study, the blood glucose levels of the diseased group were observed to have significantly decreased (P<0.05). This decrease was attributed to both endotoxemia and anorexia.

Iron (Fe) has several significant functions in the body. Found in the structure of hemoglobin, one of its major functions is maintaining the continuation of oxidation. Iron levels decrease in cases of nutrition disorders, acute and chronic infections and severe inflammatory disorders (Kaneko et al. 2008). The decrease observed in serum Fe levels with the development of disease, result from iron being consumed by pathogens, as well the iron stock of tissue fluids being used by the body defense system to prevent the growth of pathogens (Kuru et al. 2015, Yılmaz and Gökçe 2017, Akyüz et al. 2022). Similarly, in our study, we determined that serum Fe concentrations had decreased in the diseased cattle (P<0.05). This was attributed to both the severity of pneumonia and malnutrition resulting from anorexia.

The soluble triggering receptor expressed on myeloid cells is found in the cerebrospinal fluid, urine, bronchoalveolar lavage fluid, pleural fluid, and plasma (Smok et al. 2020), and is used to assess the intensity of inflammation (Su et al. 2016). Reports indicate that this receptor decreases in the event of severe inflammation and acts as a negative acute phase reactivator. The decrease observed in the level of sTREM results from the physical disrupt of the mucosal barrier by inflammatory mediators, leading to the breakdown of this receptor at tissue level. When inflammation develops in the body, neutrophil leukocytes migrate to the damaged tissues, and mucosal damage occurs. The adhesion of the neutrophils, which migrate to tissues, results in a decrease in the sTREM-1 level (Kutlu et al. 2021, Sezer and Gökce 2021). In agreement with literature reports, in the present study, the animals diagnosed with pneumonia were determined to have decreased sTREM-1 levels.

Adrenomedullin is used for the assessment of the severity of inflammation in cases of sepsis (Abd Elmouttaleb et al. 2016, Geven et al. 2018, Sezer and Gökce 2021), and diseases of the circulatory and respiratory systems. In such cases, ADM levels increase (Morgenthaler et al. 2005, Bernal-Morell et al. 2018) to regulate vascular tonus and maintain perfusion in the visceral organs (Akpınar et al. 2014, Fahmey et al. 2018). In our study, the diseased cattle were also determined to have increased MR-proADM levels. This increase was attributed to circulatory disorder and tissue perfusion deficiency having developed in the pneumonic cattle.

Previous research suggests that ADM levels increase in parallel with the severity of infections (Simon et al. 2016, Geven et al. 2018). In severe inflammatory diseases affecting the lungs, ADM levels increase because of adrenomedullin not being able to be eliminated from the pulmonary circulation (Abd Elmouttaleb et al. 2016). Cases characterized by reduced glomerular filtration and renal failure have also been reported to be associated with increased ADM levels (Jordan et al. 2014). Furthermore, the glucocorticoid hormone, lipopolysaccharides found in the cell wall of Gram-negative bacteria (Garayoa et al. 2000), cytokines (Ghobrial et al. 2020), anoxia, and inflammation-induced oxidative stress also cause increased ADM levels (Fahmey et al. 2018, Garazzino et al. 2019). ADM is known to have antibacterial and anti-inflammatory effects (Akpınar et al. 2014). In agreement with literature data, in our study, we attributed the increased ADM levels of the diseased cattle to the pulmonary damage, anoxia, oxidative stress and anorexia-induced prerenal failure associated with pneumonia, as well as to the antibacterial and anti-inflammatory effects of adrenomedullin.

CONCLUSION

In conclusion, MR-proADM levels increased and sTREM-1 levels decreased in cattle with pneumonia in this study. We think that MR-proADM and sTREM-1 levels may have diagnostic significance in terms of contributing to clinical findings, radiographic imaging and laboratory analysis in cattle with pneumonia.

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Conflict of Interest: The authors declared that there are no actual, potential, or perceived conflicts of interest for this article.

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