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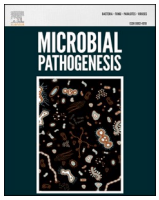

# Cardiac pathology and lipid metabolism alterations in goats infected with *Coxiella burnetii*: Insights into bacterial pathogenesis

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ABSTRACT

*Coxiella burnetii*, a Gram-negative obligate intracellular bacterium and the causative agent of Q fever, is globally distributed and is known for causing abortion and stillbirth in small ruminants. In humans, chronic infection is associated with severe cardiovascular lesions, including endocarditis. This study presents the first evidence of similar cardiac involvement in goats naturally infected with *C. burnetii*. The aim was to investigate histopathological lesions in cardiac tissues along with alterations in lipid profiles and cardiac biomarkers. Twenty Honamli goats were studied and divided into two groups: Coxiella-infected goats (Cox-G, n = 10), which had recently aborted, and healthy controls (CG, n = 10), all PCR- and ELISA-negative. Infection diagnosis was confirmed by PCR and ELISA. Hematological analysis revealed a significantly elevated lymphocyte count in Cox-G ($p < 0.05$). Biochemical analysis showed higher serum levels of CK ($p < 0.01$), CK-MB ($p < 0.01$), LDH ($p < 0.001$), and albumin ($p < 0.01$), while triglycerides were significantly lower ($p < 0.05$). Cardiac histopathology in Cox-G revealed inflammatory cell infiltrates and lesions in the myocardium and endocardium. Uterine and other organs showed findings consistent with normal post-abortion involution. The combination of decreased triglyceride levels, elevated cardiac damage related biochemical parameters, and cardiac lesions may serve as valuable pathological indicators in chronic Coxiellosis. These findings suggest a potential diagnostic role for cardiovascular assessment in caprine Q fever and support the use of goats as a zoonotic model reflecting cardiac pathology observed in humans. In conclusion, evaluating these parameters may enhance understanding of disease pathogenesis and aid in developing new diagnostic and therapeutic strategies.

## 1. Introduction

*Coxiella burnetii*, the Gram-negative obligate intracellular bacterium responsible for causing Q fever, is present worldwide, except in New Zealand. Various hosts, such as humans, ruminants, pets, birds, micromammals and reptiles, are susceptible to *C. burnetii* infection [1–4]. Due to its low infectious dose and high transmissibility, the bacterium is commonly regarded as a significant biothreat [5]. Inhalation of *C. burnetii*-contaminated aerosols from the environment is the primary route of infection. An increased frequency of Q fever was reported in France following the wind and lambing season (Tissot-Dupont et al., 2004; [6]). Less commonly, transmission can occur through the consumption of unpasteurized dairy products [7]. Furthermore, direct transmission between animals and humans has also been reported [8]. On the other hand, ticks are not essential for the life cycle of the agent, but they may contribute to the transmission of infection among farm animals as well as between wild and domestic animals [9]. Infected domestic ruminant animals, primarily through the excretion of *C. burnetii* and the transmission of the bacterium through aborted fetuses, are recognized as the primary contributors to environmental contamination and subsequent human infection [10,11]. On the other hand, in recent years, micromammals such as *Microtus arvalis* and *Rattus rattus* have been reported as sources of human Q fever cases in Europe [3]. Although many investigations have been conducted about the epidemiology and infection roots of *C. burnetii*, the ecology of the agent in wildlife has not been completely understood [12,13].

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Recent serological studies have revealed a significantly high seroprevalence of *C. burnetii* (27 %) in humans living in rural areas [14]. Similarly, in Sardinia, Italy, the seroprevalence of *C. burnetii* in humans was 24 % in 2016 and 27 % overall between 2015 and 2024 [15]. In Ethiopia, the seroprevalence of the agent ranged between 30 and 73 % in goats, 18–66 % in sheep, 55–90 % in camels, and 8–55 % in cattle [16].

Although the agent can cause outbreaks in humans, such as the one in the Netherlands in 2004, human clinical infection with *C. burnetii* typically presents as hepatitis, atypical pneumonia, or a self-limiting flu-like illness. However, if the infection progresses to a chronic form, it may result in fatal endocarditis [4,17,18]. Two cases of Q fever endocarditis have been reported by Mühleman et al. [19] and Dogru et al. [20] have established a significant relationship between obstructive and ectatic coronary artery lesions in people infected with *C. burnetii.* Similarly, Atzpoiden et al. [21] have described valvular endocarditis in immunocompromised mice acutely infected with *C. burnetii*. Moreover, Agerholm et al. [22] have detected the presence of *C. burnetii* in inflamed bovine cardiac valves. However, [58] have reported no significant histopathological findings in the organs of experimentally infected pregnant goats. In contrast, the infection leads to various reproductive disorders and uterine lesions in goats, which are associated with abortion, premature delivery, stillbirth, and weak offspring [23]. On the other hand, Roest et al. [11] reported that pregnant goats might contribute to maintaining Q fever in a goat herd as persistent carriers of infection.

Over the past two decades, multiple studies have suggested that viral and bacterial infections may contribute to atherosclerotic inflammation in humans [24]. Some researchers have reported a potential association between *C. burnetii* infections and atherosclerosis [20,25]. Dogru et al. [20] have observed higher total cholesterol levels in patients with chronic Coxiella infection compared to patients with different types of atherosclerotic lesions. However, our comprehensive literature review has unveiled a scarcity of studies focusing on lipid profiles and general biochemical analysis in Coxiella-infected animals.

Numerous studies have been conducted on the epidemiology, seroprevalence, and pathogenesis of *Coxiella* spp. infections both animals and humans [3,11–13,15]. In studies conducted in humans, it has been determined that chronic Coxiellosis causes changes in the lipid profile, and it is thought that similar changes may occur in goats infected with chronic Coxiellosis. However, further investigation is required to understand the effects of the disease on the cardiovascular system and its impact on serum biochemistry, particularly lipid profiles. This study aimed to examine the potential histopathological abnormalities and lipid profile alterations in the cardiovascular system and uterus of goats affected by chronic Coxiella infection.

## 2. Materials and methods

### 2.1. Statement of animal ethics

The experimental procedures were approved by the Committee of Animal Experiments of Burdur Mehmet Akif Ersoy University. Approval number: 2023/111-11129.

### 2.2. Animals and experimental design

In this study, Honamli goats were used, and twenty female goats between two and three years of age were selected for analysis. These goats were divided into two groups, with ten goats in each group; one group served as a control (CG), while the other group was naturally infected with *C. burnetii* (Cox-G). All the animals in Cox-G had aborted fetuses. However, there were only ten goats in the herd showing clinical and laboratory signs of Coxiella infection. The control group of goats was chosen randomly from the animals in the same herd, which were negative in both ELISA and PCR analyses. None of the control group animals had any history of abortion, unlike the infected group. This study was conducted in September 2023. This herd consisted of 111 goats. There was no previous history of abortion in the herd.

This study was conducted in Gökcebag/Burdur/Turkiye (37°43′N; 30°17′E) and included goats from a herd that gave birth once a year and underwent synchronized estrus and mating. Goats that had an abortion were culled according to farm management rules, and there was no vaccination against Coxiella infection in the herd before. Animal welfare was ensured on the farm. The details of the animals' ration are given in Table 1. Four of the aborted goats gave birth to a single kid, and six gave birth to twins in Cox-G. In the control group, five goats gave birth to a single kid, and five gave birth to twins. All kids in the control group were healthy.

### 2.3. Serological and molecular diagnosis

PCR analysis was performed by collecting samples by vaginal swab after abortion in animals with abortion cases. For serological analysis, blood samples were taken from all goats an average of three weeks after the abortion. Other samples were taken on the same day for the control group. Blood was taken for *T. gondii*, *Brucella* spp., *Chlamydia abortus*, and Border disease agents in herd. The Rose Bengal Plate test was performed on goats for Brucella determination.

#### 2.3.1. Serological diagnosis

The goat sera were serologically tested for specific abortion agents, using indirect commercial ELISA kits; for *C. burnetii* (ID Screen® - Cat No: FQS-MS5P), and *Chlamydia abortus* (ID Screen® - Cat No: CHLMS-MS-5P) and Border disease virus (BVDV p80 Ab ELISA, Idexx®- Cat No: P00645-5), Toxoplasma gondii (IgG ELISA Kit, Creative Diagnostics – Cat No: DEIA379) and Rose Bengal Plate Test (ID Screen® Cat No: RSA-RB) for Brucella antibodes.

#### 2.3.2. Molecular diagnosis

DNA was extracted from the vaginal swab sample using the DNeasy Blood &Tissue kit (Qiagen). Real-time PCR for *C. burnetii* was carried out according to Klee et al. [26] using a QuantiNova probe PCR kit (Qiagen). The PCR assay targets a 295 bp fragment of *C. burnetii* IS1111a element.

**Table 1**
Ingredient composition of the diets (as dry matter basis).

| Item | Ingredient |
|---|---|
| Wheat straw, kg | 1 |
| Barley grain, kg | 0.2 |
| Corn grain, kg | 0.2 |
| Wheat bran, kg | 0.09 |
| Cotton seed meal, Solvent, 28 %, kg | 0.15 |
| Soy sauce, Solvent, 44 %, kg | 0.115 |
| Dicalcium Phosphate, kg | 0.015 |
| Salt, kg | 0.005 |
| Vitamin-Mineral Mixture, kg | 0.15 |
| **Nutrients** | **Ration** |
| Dry matter, kg | 1.6 |
| Metabolised energy, Mcal | 3.32 |
| Crude protein, gr | 173.03 |
| Metabolic protein,gr | 121.08 |
| Rumen degradable protein, gr | 135.3 |
| Rumende undegradable protein, gr | 82.2 |
| Ca, gr | 5.59 |
| P,gr | 7.64 |
| Ca/P | 0.73 |
| Vitamin A, IU | 9000 |
| Vitamin D3, IU | 3200 |
| Vitamin E, mg | 45 |
| Vitamin B3, mg | 15 |
| Fe, mg | 450 |
| Mn, mg | 52 |
| Zn, mg | 130 |
| Se, mg | 200 |
| Mg, mg | 2400 |

The Universal Master Mix (Applied Biosystems, Darmstadt, Germany) containing dNUTPs, MgCl2, reaction buffer, and AmpliTaq Gold DNA polymerase, 6.25 l of each primer at 300 nM, and the fluorescence-labeled TaqMan probe at 100 nM made up the real-time PCR reaction mix. For the majority of tests, 1 l of heat-inactivated *C. burnetii* isolates or pure template DNA was used as the template, and water was added to a final volume of 24 l. Water was added to a final volume of 15 l for the measurement of the IS1111 copy numbers in the 75 *C. burnetii* isolates, and 10 l of 10-fold dilutions of the DNA were employed as templates to reduce pipetting mistakes. In a 7700 Sequence Detection System from Applied Biosystems, all real-time PCR reactions were carried out twice, as follows: 2 min at 50 °C, 10 min at 95 °C, and 40 cycles at 15 s at 95 °C and 30 s at 60 °C. Data were analyzed with the corresponding software.

#### 2.3.3. Bacteriological culture for aborted fetus

For the detection of bacterial abortion causes, samples of abomasal content, liver, and lung of aborted fetuses and vaginal swab samples from aborted goats were inoculated onto blood agar, Brucella selective agar with the supplement of SR083A (Oxoid), and MacConkey plates. The plates were incubated in 37 °C aerobic and with 10 % $CO_2$ atmospheres for 7 days [27] (Fig. 1).

### 2.4. Collection of blood samples for biochemical, hematological and blood smear analyses

Blood samples were taken for analysis after an average of three weeks after abortion. To perform hemogram and biochemical tests on all the goats in the study, 10 mL of blood was collected from the jugular vein, both with and without an anticoagulant. On the other hand, the control group's blood sample collection was performed on the same day. The samples were then left at room temperature for 20 min, after which the blood serum was separated by centrifuging at 3000×*g* for 10 min. The resulting sera were stored at −25 °C until analysis.

Biochemical analysis was conducted to measure the levels of High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), total cholesterol, triglycerides, total protein, albumin, lactate dehydrogenase (LDH), creatine kinase (CK), and CK-MB. These measurements were performed using the Abbott Architect Clinical Chemistry Analyzer (model no. C8000, serial number C802239) via the spectrophotometric method. Hematological analysis was also performed to measure red blood cells (RBCs), packed cell volume (PCV), hemoglobin (HGB), mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), white blood cells (WBCs), lymphocytes, neutrophils, monocytes, and eosinophils. These measurements were carried out using the Abacus Junior Vet 5-Diatron hematology analyzer. Blood smears were prepared from EDTA blood samples and were stained using Diff Quick stain (EMD Chemicals, Inc., Gibbstown, New Jersey 08027, USA).

### 2.5. Histopathological examination

Samples were taken for histopathological analysis after an average of three weeks after abortion. After the necropsies of the seropositive animals were performed, the tissue and organ (heart, uterus, liver, spleen, kidney, lung) samples collected from 10 goats were fixed by immersion in 10 % buffered formaldehyde, then the tissues taken into cassettes were passed through routine follow-up procedures in a tissue tracking device (Leica ASP300S, USA), embedded in paraffin, and 5 micron-thick sections were taken (Leica RM2155). The sections were stained with Harris Hematoxylin and Eosin (Merck, Germany) and evaluated under a light microscope. An Olympus DP70 camera (Olympus, Tokyo, Japan) adapted to an Olympus BX51 microscope (Olympus Optical, Tokyo, Japan) was used to photograph the sections.

#### 2.5.1. Histopathological examination of the cardiovascular system

Histopathologically, the heart ventricles were evaluated for hemorrhage, myocarditis, endocarditis, thrombosis, necrosis, and vasculitis/perivasculitis; the aorta for fibrinoid necrosis, thrombosis, inflammatory cell infiltrations, and atherosclerosis; and the mitral and tricuspid valves for necrosis, inflammatory cell infiltrations, and valvular endocarditis. Findings were scored from 0 to 3 for each observed parameter (0: none, 1: mild, 2: moderate, and 3: severe). The final lesion degree was determined based on the total scores (1–5; mild, 6–10; moderate, 11–15; severe). In evaluating inflammation scores, we quantified mononuclear cells in the endocardium, myocardium, and perivascular area using cell detection analysis with standard setup parameters in QuPath software

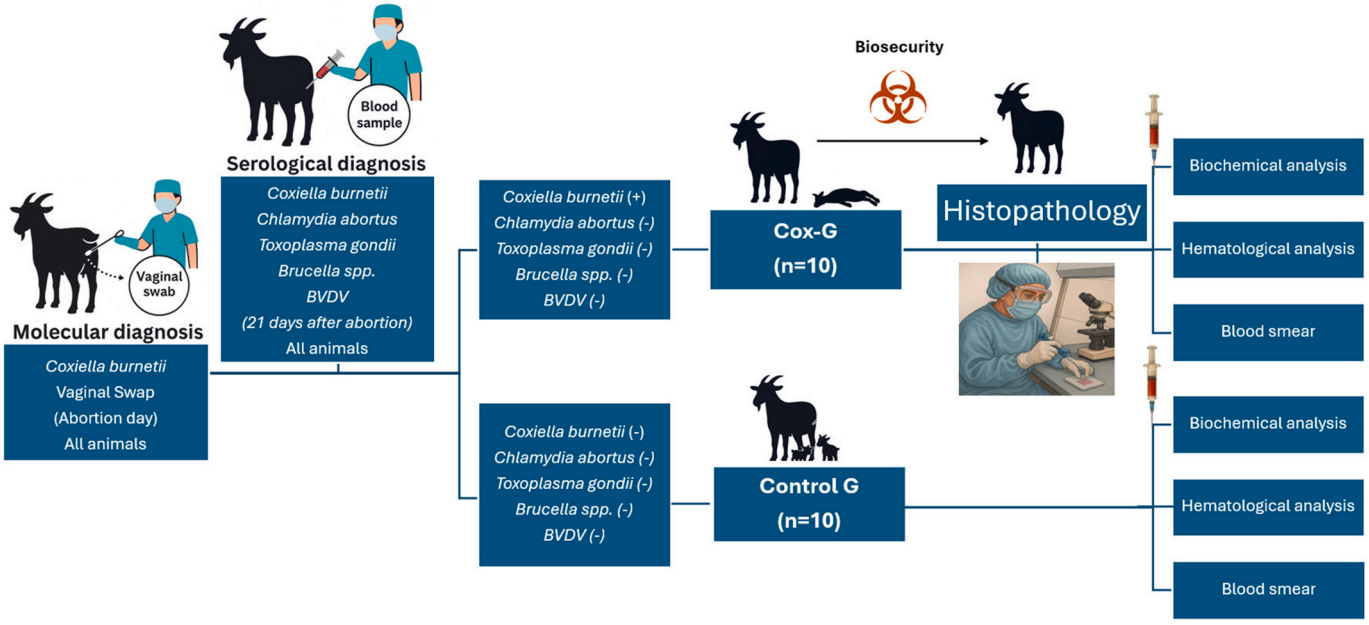


**Fig. 1. Flowchart of the experimental design and diagnostic procedures used in the study.** Molecular diagnosis was performed by vaginal swab sampling on the day of abortion, and serological diagnosis was carried out three weeks later using blood samples. Animals positive for *C. burnetii* (Cox-G, n = 10) and negative controls (Control-G, n = 10) were further evaluated with histopathological, bacteriological, biochemical, hematological, and blood smear analyses.

(Version 0.4.3).

#### 2.5.2. Histopathological examination of the uterine and other organs

Histopathological scorings of uterine were made for the epithelial layer (normal: 0 points, mild destruction: 1 point, multifocal necrosis, and hyperplasia: 2 points), inflammatory infiltration (none: 0 points, mild: 1 point, moderate: 2 points, severe: 3 points), inflammatory cell type (mononuclear: 0 points, segmented: 1 point), glands (normal: 0 points, mild changes [e.g., a small number of clear cells, lumen containing amorphous material: 1 point, moderate changes e.g., hyperplastic epithelium, lumen containing dark pink fluid: 2 points, severe changes e.g., neutrophil and mononuclear cell infiltration, lumen containing amorphous and eosinophilic material]: 3 points), and finally fibrosis (none: 0 points, mild: 1 point, moderate: 2 points, severe: 3 points). The scorings were modified from a previous study in cattle [28]. The final lesion degree was determined based on the total scores (1–4; mild, 5–8; moderate, 9–12; severe) (Table 8). The uterus was also examined for the presence of placental retention and placentitis. Lung, kidney, liver, and spleen samples were also examined for the presence of any pathological lesions.

### 2.6. Biosecurity

All procedures involving suspected or confirmed *C. burnetii* cases and related specimens were conducted under strict biosafety measures. Laboratory work was carried out in a Biosafety Level 2 (BSL-2) facility with enhanced practices consistent with BSL-3 standards. Personnel handling the animals and samples wore appropriate personal protective equipment (PPE), including disposable gloves, laboratory gowns, protective eyewear, and N95/FFP2 respirators. All manipulations of potentially infectious materials were performed in Class II biosafety cabinets to minimize aerosol generation. Serum and tissue samples destined for analysis were heat-inactivated or chemically fixed in 10 % buffered formalin before removal from containment. Waste materials, including disposables and liquid residues, were autoclaved at 121 °C for 30 min before disposal, in compliance with national biosafety regulations. During sample transport, a triple-containment system was used, and packages were labeled according to international standards. An incident response plan was in place, including the use of disinfectants (0.5 % sodium hypochlorite) for surface decontamination in case of spills. No laboratory-acquired infections or biosafety incidents occurred during the course of this study. In addition, farm-level biosecurity measures were applied during the sampling process. Animals were handled in isolation from the main herd, aborted materials were immediately collected and safely disposed of, and equipment used for sampling was disinfected after each procedure. Farm personnel were instructed to use protective clothing, mask, and gloves, and access to the abortion pens was restricted to authorized staff only. These measures minimized the risk of environmental contamination and ensured safe sample collection.

### 2.7. Statistical analyses

The SPSS 25.0 program was used to conduct all statistical analyses. The normality test of the data was performed with the Shapiro-Wilk test. A *t*-test was used for variables with a normal distribution and a Mann-Whitney *U* test for variables with a non-normal distribution while comparing groups. The results were expressed as the mean ± standard error of the mean (SEM). Differences in the $p < 0.05$ value were considered statistically significant. All graphics were prepared using the GraphPad Prism 9.0 program.

## 3. Results

### 3.1. Bacteriological, serological and molecular examination results

Bacteria causing abortion were not isolated in the bacteriological culture of the samples. In serological tests of serum samples, antibodies for *Chlymidia abortus*, *Border disease virus*, and *B. melitensis* were negative. Both real-time PCR in vaginal swab samples and ELISA in serum samples for *C. burnetii* were found positive. The ELISA and PCR analyses of the control group were completely negative.

### 3.2. Biochemical and hematological analyses

The results of biochemical and hematological analyses are given in Tables 2 and 3. As a result of hemogram analysis, a significant difference was found only between lymphocyte levels ($p < 0.05$). As a result of biochemical analyses, significant differences were determined in the levels of triglyceride ($p < 0.05$), albumin ($p < 0.01$), LDH ($p < 0.000$), CK ($p < 0.01$), CK-MB ($p < 0.01$) between the groups. Scatter dot plots graphics of biochemical and hematological analyzes are shown (Graphic 1).

### 3.3. Blood smear examination

The results of the blood smear analysis are described in Table 4.

### 3.4. Histopathological examination results

#### 3.4.1. Cardiac histopathological examination results

Body weight, heart weight, and body condition scores are detailed in Table 5. While no polymorphonuclear leukocytes were found, numerous mononuclear leukocytes, predominantly lymphocytes, were observed in almost all areas, along with a few plasma cells and macrophages.

Histopathological evaluations revealed hemorrhage in eight goats in Cox-G (3 mild, 2 moderate, and 3 severe). Necrosis was observed in eight goats (5 mild, 1 moderate, 2 severe), as shown in (Table 6). Infiltrated mononuclear cell infiltration results are described in (Table 7). Necrosis, particularly in areas with hemorrhage, was in the form of coagulation necrosis. Lesions associated with mononuclear cell infiltrations in the myocardium, endocardium, and various cardiac areas are depicted in (Figs. 2–3).

The lesion degree based on the final scores was determined to be mild in two goats, moderate in five, and severe in three goats. None of the animals showed histopathological lesions indicative of thrombosis or

**Table 2**
Blood biochemical analysis results of Coxiella infected and non-infected goats.

| Parameters | Group | Result | P |
|---|---|---|---|
| HDL (mg/dL) | Cox-G | 39.2 ± 2.06 | 0.134 |
| | CG | 33.6 ± 2.90 | |
| LDL (mg/dL) | Cox-G | 26.2 ± 2.42 | 0.621 |
| | CG | 24.4 ± 2.6 | |
| Total Cholesterol (mg/dL) | Cox-G | 70.2 ± 3.49 | 0.313 |
| | CG | 64.4 ± 4.35 | |
| Trygliseride (mg/dL) | Cox-G | 25.2 ± 0.98[a] | *0.042** |
| | CG | 30.2 ± 1.99[b] | |
| Total Protein (g/L) | Cox-G | 63.8 ± 2.28 | 0.166 |
| | CG | 58.3 ± 3.05 | |
| Albumin (g/L) | Cox-G | 24.1 ± 0.7[a] | *0.003*** |
| | CG | 20.1 ± 0.94[b] | |
| LDH (U/L) | Cox-G | 773.3 ± 58.18[a] | *0.000**** |
| | CG | 445.7 ± 36.41[b] | |
| CK (U/L) | Cox-G | 183.4 ± 35.25[a] | *0.001*** |
| | CG | 89.0 ± 6.83[b] | |
| CK-MB (U/L) | Cox-G | 177.01 ± 12.25[a] | *0.005*** |
| | CG | 129.5 ± 8.21[b] | |

There are significant differences between groups containing different letters in the same column. *:$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

**Table 3**
Blood hemogram analysis results of Coxiella infected and non-infected goats.

| Parameters | Group | Result | P |
|---|---|---|---|
| WBC | Cox-G | 16.3 ± 1.35 | 0.165 |
| | CG | 13.47 ± 0.96 | |
| Neutrophile | Cox-G | 6.08 ± 0.67 | 0.529 |
| | CG | 5.59 ± 0.38 | |
| Lymphocyte | Cox-G | 8.76 ± 0.86[a] | *0.008*** |
| | CG | 5.68 ± 0.50[b] | |
| Monocyte | Cox-G | 0.59 ± 0.07 | 0.896 |
| | CG | 0.57 ± 0.06 | |
| Eosinophile | Cox-G | 0.83 ± 0.13 | 0.955 |
| | CG | 0.84 ± 0.10 | |
| RBC | Cox-G | 16.52 ± 0.45 | 0.387 |
| | CG | 17.12 ± 0.49 | |
| HGB | Cox-G | 97.1 ± 2.55 | 0.686 |
| | CG | 98.7 ± 2.92 | |
| HCT | Cox-G | 24.84 ± 0.93 | 0.093 |
| | CG | 22.63 ± 0.82 | |
| MCV | Cox-G | 15.01 ± 0.32 | 0.909 |
| | CG | 15.09 ± 0.61 | |
| MCH | Cox-G | 5.88 ± 0.07 | 0.243 |
| | CG | 5.63 ± 0.19 | |

There are significant differences between groups containing different letters in the same column. **p < 0.01.

**Table 4**
Blood smear analysis results of Coxiella infected and non-infected goats.

| Cox-G | | CG | |
|---|---|---|---|
| Parameters | Results | Parameters | Results |
| General Morphology of erithrocytes | | General Morphology of erithrocytes | |
| Normal | %88.8 | Normal | %87.5 |
| Poikilocytosis | %11.1 | Poikilocytosis | %12.5 |
| Morphology of erithrocytes | | Morphology of erithrocytes | |
| Chistocyte | %33.3 | Chistocyte | %37.5 |
| Rarely | %33.3 | Rarely | %37.5 |
| Dacrocyte | %66.6 | Dacrocyte | %100 |
| Rarely | %11.1 | Rarely | %12.5 |
| Mild | %55.5 | Mild | %62.5 |
| | | Common | %25 |
| Elliptocyte | %100 | Elliptocyte | %87.5 |
| Rarely | %11.1 | Rarely | %37.5 |
| Mild | %55.5 | Mild | %37.5 |
| Common | %33.3 | Common | %12.5 |
| Keratocyte | %11.1 | Keratocyte | %25 |
| Rarely | %11.1 | Rarely | %25 |
| Erithrocyte size | | Erithrocyte size | |
| Normal | %22.2 | Normal | %12.5 |
| Anisocytosis + | %66.6 | Anisocytosis + | %62.5 |
| Anisocytosis ++ | %11.1 | Anisocytosis ++ | %25 |

**Table 5**
Body weight, heart weight and body condition score results of Cox-G.

| | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Heart weight | 10 | 186.00 | 300.00 | 222.0000 | 38.43031 |
| Body weight | 10 | 40.00 | 67.00 | 51.1000 | 7.09382 |
| Body condition score | 10 | 2.50 | 3.50 | 2.9750 | 0.24861 |

fibrosis in the coronary arteries. The histopathological analysis of the mitral/tricuspid valves showed no lesions. In the examination of the aorta, mild inflammatory infiltration was observed in three cases. In addition, one of the cases in the infected group had mild lesions in the heart, while two had moderate myocardial lesions.

#### 3.4.2. Uterine histopathological examination results

In our study, only one animal was on the 30th day after abortion, while the others were in the involution process. Endometritis was not observed in this single animal. In other goats, mild to moderate endometrial inflammation was observed. Since the time after abortion varied in each animal, standardization of uterine lesion scores was not achieved as expected, and the scores showed a wide range. However, various degrees of placentitis and neutrophil infiltrations in the uterine lumen were observed in four cases (Fig. 4) (Table 8).

#### 3.4.3. Lung, kidney, spleen, and liver histopathological examination results

As a result of the histopathological evaluations of the lung, kidney, spleen, and liver, cystic echinococcosis was found in two goats, bronchus-associated lymphoid tissue (BALT) hyperplasia in two goats, abscess, inflammatory edema, pleuritis, and bronchitis in one goat's lung, and mild interstitial pneumonia in one goat (Fig. 5). In the kidneys, proliferative glomerulitis was observed in two goats, and capsular hemorrhage was observed in one of them (Fig. 6). No histopathological findings were found in the spleen or liver tissues. The histopathological findings observed in the examination of the lung, kidney, spleen, and liver are given in (Table 9).

## 4. Discussion

Many studies have been conducted on people with chronic Coxiellosis and its cardiovascular effects [4,20,25,29]. There is a lack of research on animals with chronic infections and their cardiovascular and hematological effects. Therefore, additional studies are needed to better understand the pathology of chronic Coxiellosis.

The hematological analysis results of this study are consistent with previous studies, especially in the control group, as demonstrated by Azab and Abdel-Maksoud [30], Johns and Heller [31], and Tuna [32]. However, our study found significantly higher lymphocyte counts in the Cox-G group than in the CG group. It should be noted that hematological parameters vary significantly between different goat breeds [30]. Previous studies on goats and other ruminants with various chronic infections have reported conflicting results. For instance, Hussain et al. [33] found significantly decreased lymphocyte counts in camels infected with Coxiellosis compared to the healthy group, while Bezos et al. [34] observed reduced lymphocyte counts in goats infected with mycoplasmosis. Conversely, Soffler et al. [35] reported a significantly increased lymphocyte count in goats with *B. mallei* infection. Additionally, Jones and Allison [36] reported that pathologic lymphocytosis in ruminants can be associated with chronic pyogenic conditions. Nor et al. (2023) reported a significant correlation between high levels of IL-10 and infective endocarditis in individuals with persistent Q fever. Nor et al. (2023) reported a significant correlation between high levels of IL-10 and infective endocarditis in individuals with persistent Q fever. On the other hand, chronic Q fever infection does not increase overall lymphocyte counts in humans [37]. In endocarditis cases, several studies have reported reduced counts of conventional T and B cells, while one study demonstrated a correlation between lymphopenia and disease activity [38]. Moreover, increases in regulatory T cells and shifts in $CD8^+$ T cell subsets—with reductions in naïve cells and expansions of central memory cells—indicate alterations in immune balance rather than overall lymphocyte proliferation [37]. Thus, human studies consistently suggest that chronic Q fever is linked to selective lymphocyte depletion rather than total lymphocyte expansion. To the best of our knowledge, no comparable animal studies have been reported to date. Interestingly, our results demonstrated a significant increase in

**Table 6**
Histopathological findings observed in the heart (Cox-G).

| Identity Number | Hemorrhage | Perivasculitis | Endocarditis | Myocarditis | Necrosis | Total Score | Lesion Degree |
|---|---|---|---|---|---|---|---|
| 34 | 2 | 0 | 2 | 2 | 2 | 8 | Medium |
| 532 | 1 | 3 | 3 | 3 | 1 | 11 | Severe |
| 271 | 1 | 3 | 0 | 1 | 0 | 9 | Medium |
| 197 | 0 | 0 | 1 | 3 | 1 | 5 | Mild |
| 81 | 3 | 1 | 1 | 1 | 1 | 7 | Medium |
| 70 | 1 | 2 | 3 | 2 | 1 | 9 | Medium |
| 578 | 0 | 1 | 2 | 1 | 0 | 4 | Mild |
| 29 | 3 | 3 | 2 | 2 | 3 | 13 | Severe |
| 69 | 2 | 3 | 2 | 2 | 1 | 10 | Medium |
| 68 | 3 | 2 | 2 | 1 | 3 | 11 | Severe |

**Table 7**
Infiltrated mononuclear cell counts (Cox-G).

| Identity number | Endocardium ($mm^2$) | Myocardium ($mm^2$) | Perivascular (10 random vessels) |
|---|---|---|---|
| 34 | 180 ± 12 | 443 ± 22 | ND |
| 532 | 409 ± 22 | 818 ± 58 | 11,5 ± 0,9 |
| 271 | ND | 234 ± 17 | 10,6 ± 1,2 |
| 197 | 57 ± 4 | 966 ± 87 | ND |
| 81 | 35 ± 6 | 134 ± 15 | 3,7 ± 0,2 |
| 70 | 437 ± 28 | 670 ± 55 | 7,9 ± 0,3 |
| 578 | 188 ± 9 | 274 ± 7 | 1,5 ± 0,01 |
| 29 | 182 ± 11 | 438 ± 19 | 9 ± 1,1 |
| 69 | 279 ± 21 | 606 ± 45 | 12 ± 0,7 |
| 68 | 152 ± 13 | 396 ± 33 | 7,1 ± 0,3 |

ND: Not determined.

lymphocyte counts in goats with persistent *C. burnetii* infection. This discrepancy may point to species-specific differences in the immunopathogenesis of chronic Q fever. Goats might mount a compensatory proliferative lymphocytic response as part of their defense strategy, whereas humans appear to exhibit an immunoregulatory shift characterized by depletion of certain subsets. From a clinical perspective, this distinction could have practical implications: in goats, lymphocyte expansion may contribute to prolonged inflammatory responses and tissue pathology, potentially affecting fertility and productivity at the herd level. In contrast, the immunoregulatory suppression observed in humans may explain the chronicity and severity of Q fever endocarditis. A deeper understanding of such mechanisms could improve both veterinary strategies for herd health management and zoonotic risk assessment in public health.

Our study also observed poikilocytosis, anisocytosis, and various shapes of erythrocytes in blood smears, which is consistent with previous studies showing that goat erythrocytes are highly pleomorphic [39]. Jain and Kono [40] reported that normal goats often have discocytic, triangular, and pear-shaped red cells, and Johns and Heller [31] noted that certain goat breeds, such as Angora, have significant poikilocytosis naturally. Therefore, our results are in line with previous study.

Mulye et al. [41] reported that using cholesterol supplementation of a cholesterol-free cell model system can reduce the agent growth and may cause a smaller parasitophorous vacuole. Parallel to our findings, Dogru et al. [20] also reported elevated levels of total cholesterol in the Cox-G compared to the CG. Moreover, their study showed higher levels of HDL and LDL in the seropositive group than in the healthy group, but only LDL levels were significantly higher. Similarly, in our study, HDL and LDL levels were elevated in the infected group than in the healthy group, although no significant differences were observed. It can be suggested that the cholesterol level may have increased in order for the organism to gain an advantage in the fight against microorganisms. However, unlike our study, the seropositive group in Dogru et al. [20]

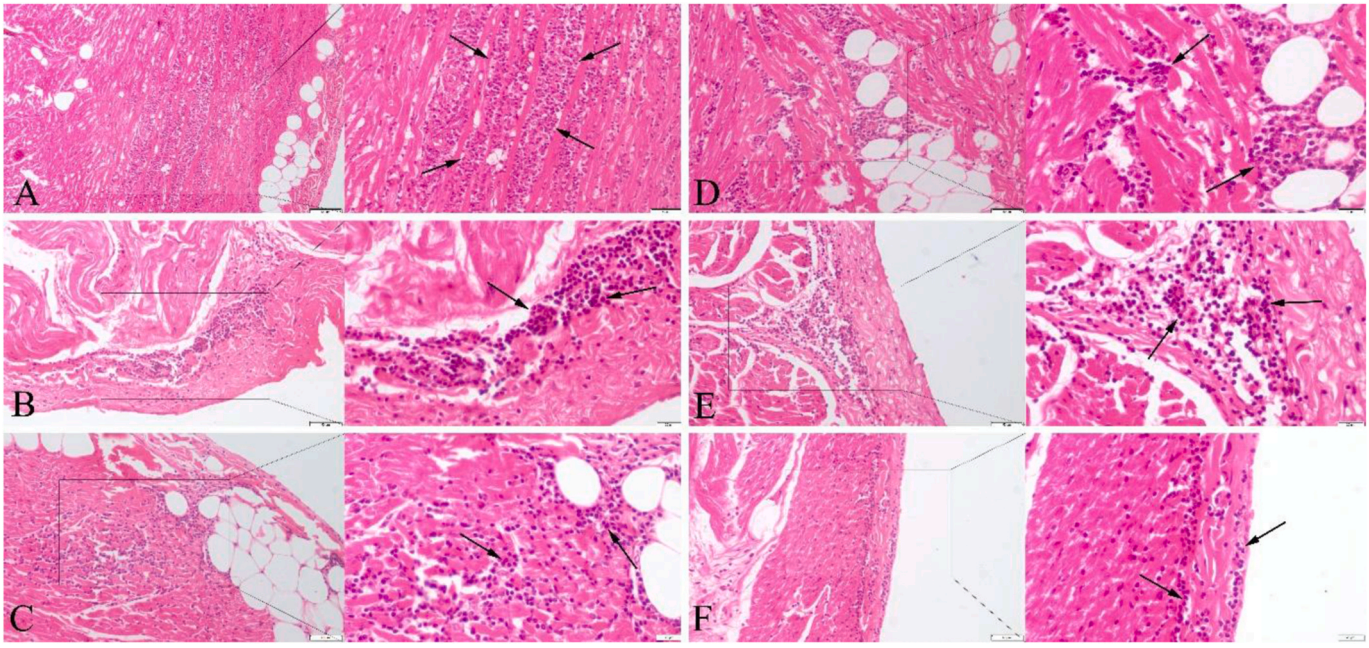


**Fig. 2. Mononuclear Cell Infiltrations in the Myocardium and Endocardium.** This figure presents mononuclear cell infiltrations (arrows) in the myocardium (A, B, C, D) and endocardium (E, F), stained with Hematoxylin and Eosin. Each panel shows a magnified view of the area marked by a rectangle, highlighting the predominance of lymphocytes along with a few plasma cells. Magnification bars for each figure are indicated in the bottom right corner.

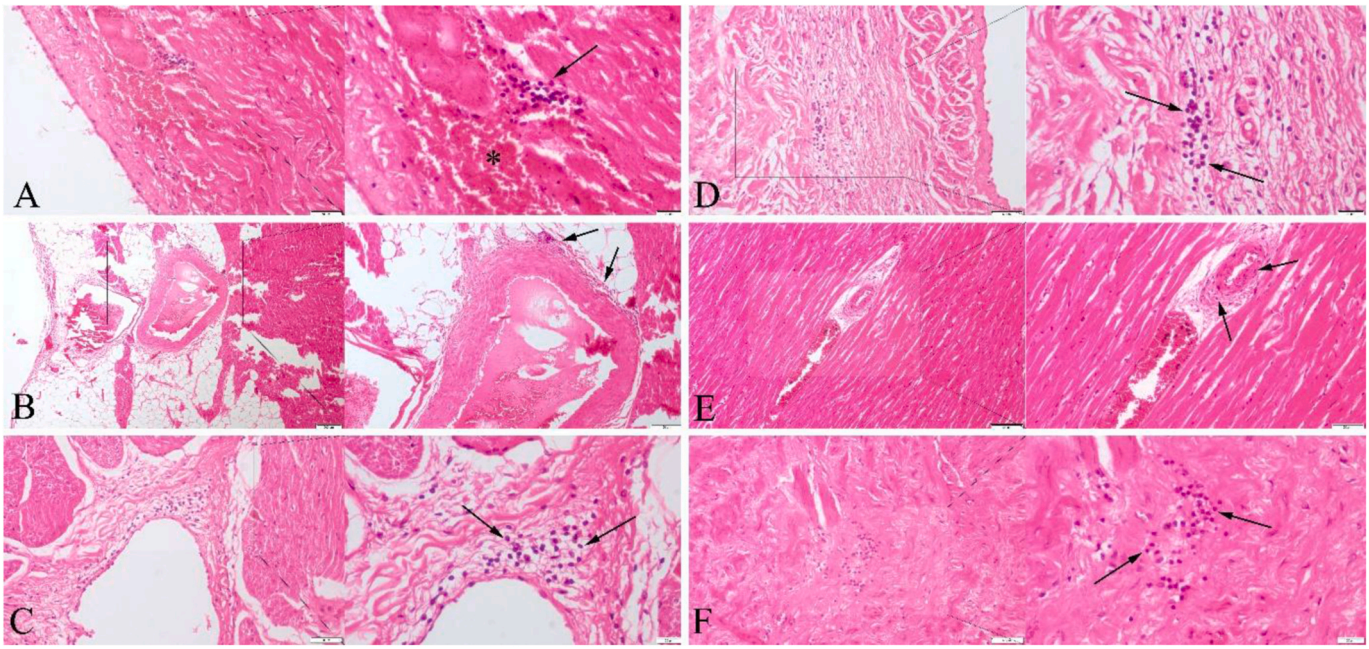


**Fig. 3. Mononuclear Cell Infiltrations in Various Cardiac Areas.** This figure illustrates various instances of mononuclear cell infiltrations: mild mononuclear cell infiltrations (arrows) accompanying hemorrhage (asterisk) in the subendocardial area (A), around the coronary artery (B), surrounding myocardial vessels (C, D, E), and within the wall of the aorta (F), all stained with Hematoxylin and Eosin. Each panel displays a higher magnification view of the area marked by a rectangle. Magnification bars for each figure are located in the bottom right corner.

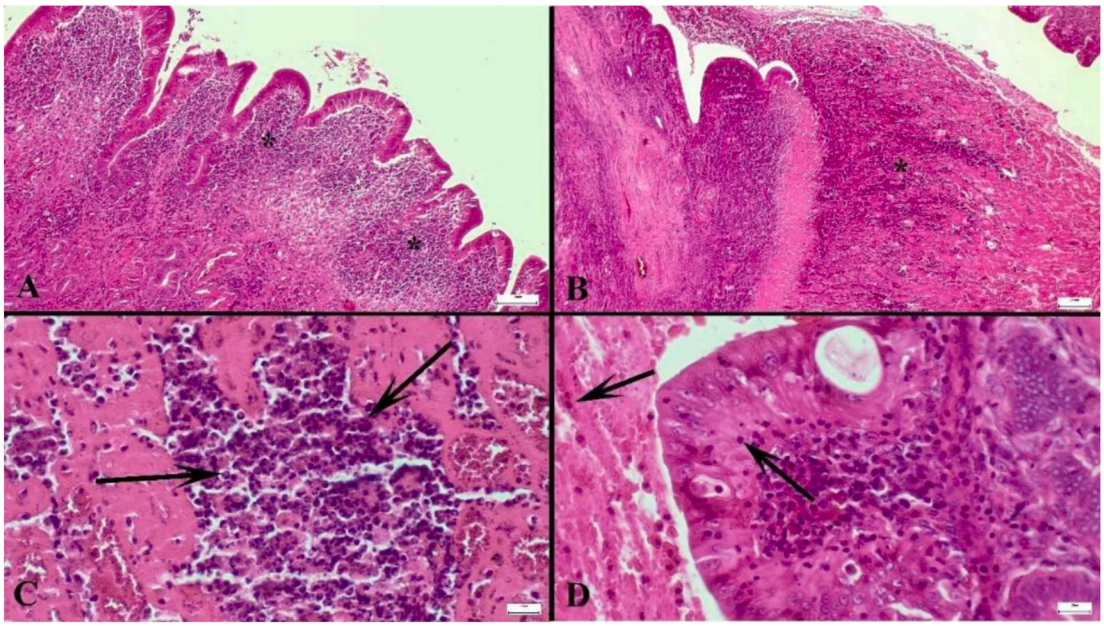


**Fig. 4.** Uterus; mononuclear cell infiltration in the lamina propria (A) (asterisks), placenta retention (B) (asterisk) and placentitis characterized by neutrophil infiltration (C) (arrows), neutrophil infiltration in lumen and lamina propria (D). H&E. Bars: 100 μm for A, 200 μm for B and 50 μm for C and D).

study had significantly higher triglyceride levels. In contrast, Hussain et al. [33] reported lower triglyceride levels in camels with Coxiellosis than in healthy camels, which is consistent with our study. It is noteworthy that lipids play a vital role in the normal functioning of *C. burnetii* by forming the acidic, phagolysosomal-like parasitophorous vacuole (PV) that surrounds the bacteria. Moreover, the microorganism utilizes host cell lipids for membrane biogenesis and as a possible energy source [42]. Thus, it is plausible that the decreased triglyceride levels in infected goats in our study may be due to the microorganism consuming host cell lipids. According to our literature search, no study has directly reported a comprehensive lipid profile in Coxiellosis. Therefore, further studies are needed in this area.

Elevated CK-MB and LDH levels in the blood suggest cellular injury and inflammation, specifically in the heart, as these enzymes are primarily located in the myocardium's cytoplasm. Therefore, they are used as a diagnostic tool for cardiac lesions in goats [43,44]. Joshi et al. [45] reported significantly increased CK-MB and LDH concentrations due to myocardial damage in goats with ruminal acidosis. Similarly, Souza et al. [46] found significantly elevated CK and CK-MB levels in goats suffering from pregnancy toxemia, suggesting that the experimental

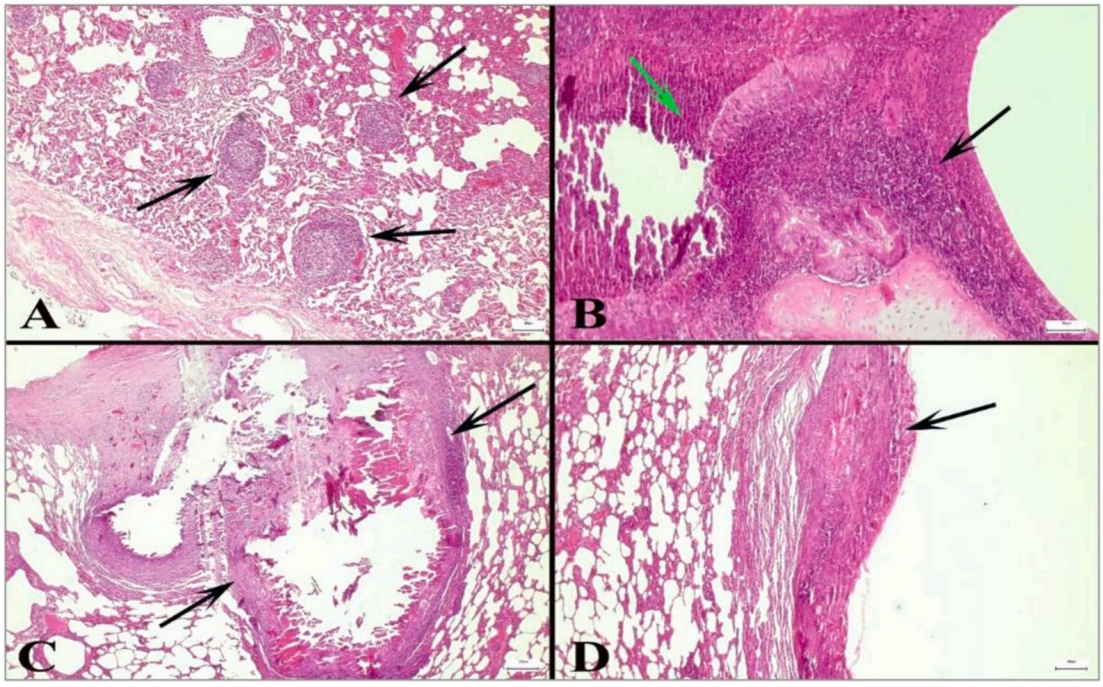


**Fig. 5.** BALT hyperplasia (A), bronchitis (black arrow) and abscess (green arrow) (B) and hydatid cyst (C, D) in the lungs. H&E. Bar: 200 μm (100 μm for B).

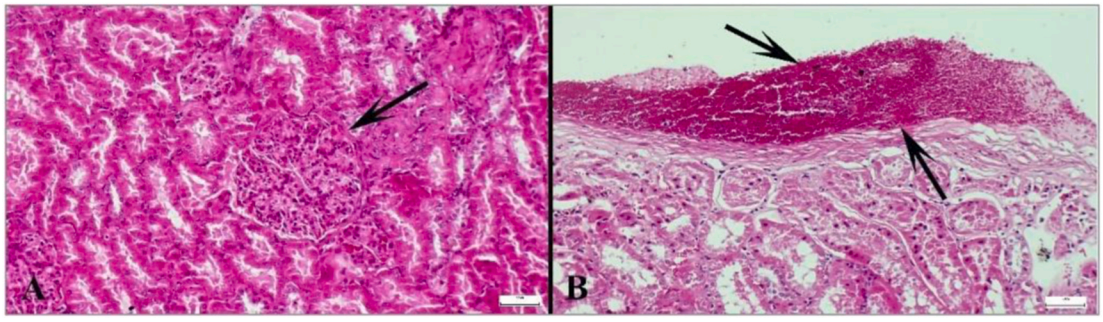


**Fig. 6.** Proliferative glomerulitis (A) and capsular hemorrhage in kidneys (B). H&E. Bars: 50 μm.

**Table 8**
Histopathological findings observed in the uterine (Cox-G).

| Identity Number | Epithelial layer | Inflammation | Inflammatory cell type | Glands | Fibrosis | Placentitis | Total Score | Lesion Degree |
|---|---|---|---|---|---|---|---|---|
| 34 | 0 | 1 | 0 | 0 | 0 | – | 1 | Mild |
| 532 | 0 | 1 | 0 | 0 | 0 | + | 1 | Mild |
| 271 | 2 | 3 | 1 | 3 | 0 | + | 9 | Severe |
| 197 | 0 | 1 | 0 | 0 | 1 | – | 2 | Mild |
| 81 | 2 | 2 | 1 | 3 | 0 | – | 8 | Medium |
| 70 | 0 | 2 | 0 | 2 | 0 | – | 4 | Mild |
| 578 | 2 | 1 | 1 | 3 | 0 | – | 7 | Medium |
| 29 | 0 | 1 | 1 | 1 | 0 | – | 3 | Mild |
| 69 | 0 | 1 | 0 | 0 | 0 | + | 1 | Mild |
| 68 | 0 | 2 | 1 | 0 | 0 | + | 3 | Mild |

group may have suffered a cardiac injury due to increased NEFA concentrations. In our study, prominent cardiac lesions were observed in the Cox-G group, and our cardiac biomarker results are consistent with previous reports.

Albumin is a negative acute-phase protein synthesized primarily in the liver, with additional synthesis in several body tissues [47]. Yang and Niu [48] also reported that albumin synthesizes the uterus origin response to liver mRNA stimulation. However, in contrast to our results, Hussain et al. [33] found significantly decreased albumin levels in camels infected with Coxiella. There is limited information available on the effect of *C. burnetii* on plasma lipid and protein profiles in infected animals.

Brouqui and Raoult [49] and Jaltotage et al. [50] reported that chronic Coxiellosis can cause endocarditis in humans. Raoult et al. [17] reported that 1–5 % of infected humans may develop chronic Coxiellosis, which can lead to lethal endocarditis or vascular infection. In contrast, Fenollar et al. (2001) reported that the incidence of endocarditis following acute Q fever infection reached 40 % percent. In the

**Table 9**
Findings observed in lung and kidney (Cox-G).

| Identity Number | Lung | Kidney |
|---|---|---|
| 34 | Cyst hidatid, BALT hyperplasia | Normal |
| 532 | Normal | Normal |
| 271 | Normal | Normal |
| 197 | Normal | Proliferative glomerulitis, Capsular hemorrhage |
| 81 | Mild intersititial pneumonia | Normal |
| 70 | Normal | Proliferative glomerulitis |
| 578 | BALT hyperplasia | Normal |
| 29 | Abscess, inflammatory edema, pleuritis, bronchitis | Normal |
| 69 | Cyst hidatid | Normal |
| 68 | Normal | Normal |

present study, in the Cox-G, except for one goat, endocarditis was observed in all goats with varying severity. Therefore, it can be suggested that endocarditis might be more common in goats than in humans suffering from chronic Coxiellosis. At this point, our findings are not consistent with previous reports.

Gonzalez-Quijada et al. [25] found a significant association between serological evidence of past *C. burnetii* infection and atherosclerotic cardiovascular disease in patients, while Dogru et al. [20] reported significantly higher Coxiella seropositivity in patients with obstructive and ectatic coronary artery lesions compared to other coronary artery disease groups. Unlike Dogru et al. [20], we found a significantly higher endocarditis prevalence in the Cox G in addition to vasculitis. On the other hand, Agerholm et al. [22] reported the presence of the DNA of the microorganism in inflamed bovine cardiac valves, indicating that both human and bovine endocarditis lesions in Q fever are similar. It was thought that the lymphocytic infiltrates in the coronary artery observed in goats might be one of the changes in the first stages of pathological changes such as ectatic and obstructive coronary artery lesions, endocarditis, and myocardial lesions seen in humans. However, the reasons why the changes observed in infected goats are not the same as the changes observed in infected humans may be due to the shorter lifespan of goats and nutritional differences between species. So, it can be suggested, that there are possible similarities in the pathophysiological mechanisms of the disease in humans and goats with chronic coxiella infection.

Many agents can cause myocarditis in ruminants. Due to the comparable morphology and staining abilities of many bacteria to *T. pyogenes*, which are commonly isolated and identified in endocarditis lesions, the association between *C. burnetii* infection and the observed lesions in endocarditis remains unclear [22]. Watson et al. [51] reported prominently higher WBC counts in a goat suffering from severe endocarditis and suppurative mastitis, unlike our study. Although they observed multiple gram-positive cocci colonies in histopathological examination, no bacterial growth in the blood or vegetative lesion in the aortic or mitral valve was observed, and no diagnostic investigation was performed about concurrent *C. burnetii* infection. Unlike Watson et al. [51], we did not observe any gram-positive cocci colonies or prominently increased WBC count on histopathological examination in our study.

Our study also observed various non-specific inflammatory responses in some goats (bronchitis: one goat; interstitial pneumonia: one goat; glomerulitis: two goats), which is in line with Norina et al. [52] However, in contrast to Norina et al. [52], no histopathological findings were observed in spleen and liver tissues in our study. In goats, it is established that the uterus undergoes complete involution by the 28th day postpartum [53]. In our study, all but one animal were in the involution period, with only one being on the 30th day after abortion. However, information on the effects of Q fever on reproduction in different species is limited. Agerholm [53] suggested that *C. burnetii* may not cause endometritis other than uterine inflammation resulting from abortion. This inflammation is known to resolve spontaneously (Sanchez et al., 2006). Nonetheless, De Biase et al. [54] reported endometritis, uterine vasculitis, and fibrosis associated with *C. burnetii* infection, which is consistent with our results. This condition was considered to be associated with infection, severe inflammation, and/or uterine inertia.

There are various studies on the seroprevalence of *C. burnetii* infection [16,55,56]. Some researchers reported that the infection is more common in cattle from ruminant species, it has been reported that goats have higher seropositivity than sheep [55,56]. However, Robi et al. [16] reported higher seropositivity in goats than in cattle and sheep. Furthermore, Bauer et al. [6] determined that larger quantities of *C. burnetii* DNA were found in goats' nasal swabs and environmental samples compared to ovine ones. These findings may help explain why the seroprevalence of the infection is higher in goats than in sheep. On the other hand, studies conducted in different countries have reported that the seropositivity rate in herds can reach up to 92.9 % [57]; [23]. Consistent with previous reports, this study also observed a prevalence of abortion (9.04 %) and stillbirth and weak offspring (17.14 %) within the goat herd.

The present study has several limitations, and a lack of immunohistochemical assessment of the lesions. The low number of goats inclueded in the study, measurement of the level of important interleukins such as IL-10 and lack of infection dose are another limitations of the study. These limitations may affect the generalizability of the findings and limit the insight into the underlying pathology. However, the study also has several strengths, including blood smear analysis, a detailed histopathological examination of the heart (which is the first report of its kind), a score table of pathological findings in the uterus, lipid profile analysis, and molecular and serological evaluation.

Numerous studies in the literature have investigated the epidemiology of Coxiellosis in small ruminants. However, the impact of chronic Coxiellosis on the heart and lipid profile remains poorly understood. The present study provides clear evidence that goats chronically infected with Coxiellosis develop endocarditis, myocarditis, and vasculitis, mirroring the pathological manifestations observed in humans. These findings not only enhance our understanding of the pathogenesis of *C. burnetii* in small ruminants but also highlight the potential utility of the identified biochemical alterations as supportive diagnostic markers and as targets for the development of more effective therapeutic and preventive interventions. Collectively, the results underscore that *C. burnetii* should not be overlooked in veterinary practice, extending beyond gynecology to internal medicine. Clinician veterinarians should be particularly attentive to this pathogen, given its significant clinical and epidemiological implications in small ruminant populations.

In conclusion, in the case of chronic Coxiellosis, understanding the lipid profile and cardiovascular changes can not only help clarify the disease's pathology but also aid in developing new treatment strategies in animal and human health.

## CRediT authorship contribution statement

**Feyyaz Kaya:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Investigation, Formal analysis, Conceptualization. **Gokhan Bozkurt:** Writing – review & editing, Visualization, Supervision, Investigation, Data curation. **Volkan Ipek:** Writing – review & editing, Investigation, Formal analysis, Data curation. **A. Reha Agaoglu:** Resources, Investigation, Conceptualization. **Busra Gulbenli Turkoglu:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Ismail Akar:** Supervision, Resources, Data curation.

## Declaration of competing interest

The authors declare no competing interests.

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## Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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