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Role of prostaglandin F2α and TGFϒ with polymorphism of IL-1β in calves infected with Babesia

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Abstract

Objective

Babesiosis is caused by *Babesia bovis* in calves. The disease induces strong inflammatory and immunomodulatory responses and is influential in the severity of the disease. The aim of this study was to investigate the serum levels of IgM, IgG, IL-1β, IL-6, TGF-γ and prostaglandin F2α (PGF2α) in naturally infected calves and to study the single nucleotide polymorphism (SNP) rs16944 of the IL-1β gene. In addition, to investigate their potential as markers of immunological and genetic changes associated with infection.

Materials and Methods

A total of 36 Babesia-infected calves were selected. The selection was based on clinical signs (fever, anemia, jaundice, hematuria, and tick infestation) and medical history. Also, 24 healthy calves were selected as the control group. Blood was collected from the animals' veins. Validated enzyme-linked immunosorbent assay (ELISA) kits were used to evaluate and analyze the sera for IgM, IgG, IL-1β, IL-6, TGF-γ, and PGF2α. PCR and Sanger sequencing were used to study the IL-1β rs16944 genotype. t-tests and correlation analysis at a significance level of $P < 0.05$ were used for statistical analysis.

Results

Comparison of infected calves with the control group showed that serum IgM and IgG levels were significantly higher in them than in the control group ($P \leq 0.001$). This indicates that the humoral immune response was strongly activated in them. The proinflammatory cytokines IL-1β and IL-6 were also significantly increased. This also proves that the intense inflammatory response that is characteristic of acute babesiosis occurred. In addition, the level of TGF-γ was also significantly

higher in infected calves. This indicated that regulatory pathways to balance inflammation were effectively activated. Increased PGF2α concentration was also shown to be involved in vascular and inflammatory disorders associated with infection. It was found that in several infected calves the wild-type CC genotype was converted to the TT type. Therefore, it can be said that there is a potential relationship between this SNP and increased susceptibility or increased inflammatory response.

Conclusions

A complex interaction between IL-1β polymorphisms, immunoglobulins, prostaglandin activity, and cytokines was observed in calves infected with Babesiosis. These significant changes in these biomarkers indicate that they have potential diagnostic value. Therefore, they can be used to better understand the immunopathogenesis of *Babesia bovis* infection. The genetic variation observed in rs16944 may be an additional risk factor that can influence the outcome of the disease. These findings can potentially be used to develop improved diagnostic, prognostic, and disease management strategies.

Keywords: Babesia, calves, polymorphism of IL-1β, prostaglandin PGF2α and TGFϒ

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Introduction

Bovine babesiosis is an economically important tick-borne disease of cattle. It is caused by the blood parasite Apicomplexan of the genus Babesia (Jacob et al., 2020). Bovine babesiosis is mainly caused by *Babesia bovis* and *Babesia bygemina*. Studies have reported that more than 500 million cattle in temperate and tropical regions of the world are at risk of contracting the disease (Menshawy, 2020). Acute bovine babesiosis often presents with fever, severe anemia, anorexia, and prostration and can result in deaths or the establishment of persistent infections in calves that

endure the acute stage of bovine babesiosis. The acute infections caused by *Babesia bovis* may also present with adhesions of infected erythrocytes in liver, brain, or lung capillaries rather than other ٧organs, a condition that is similar to severe malaria, causing high death rates (Zygner et al., 2023). Acaricides to reduce tick infestations and anti-babesicidal drugs, as well as live attenuated *Babesia bovis* and *Babesia bigemina* vaccines, are the currently available control plans used against the disease. Using acaricides can select for populations of resistant ticks and cause toxicities to the environment and animals (Mazuz et al., 2021). Drugs used for therapy are costly and impractical for large cattle herds and may also possibly result in drug-resistant parasite development (Khan & Witola, 2023). It is well recognized that young cattle (less than 6 months) can resist acute bovine babesiosis more than adult ones (more than one year). The high resistance of younger calves to babesiosis is spleen-dependent and related to early activations of the innate immunologic response (Aziz et al., 2025). Moreover, Cells that play a key role in immune and inflammatory responses produce proteins called cytokines. These cytokines participate in these processes by interfering with the regulation of other cells. Cytokines include several groups, although there is considerable overlap between them. These groups include interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), transforming growth factors (TGF), migration inhibitory factors, and smaller chemokines (Khezri et al., 2025). The protection against *Babesia bovis* is specially related to pro-inflammatory phenotypes that are initiated by splenic myeloid cells like dendritic cells and monocytes that induce the lymphocyte to release IFN-γ. In view of splenic immune cell role during babesiosis, delayed production of IFN-γ with concomitant IL-10 expression is related to acute disease progressions (Chen et al., 2023). It is of interest that cattle that endure the acute babesiosis stage caused by *Babesia bovis* develop chronic infection and become a reservoir for acquiring ticks, but they develop protection against clinical diseases when reinfected with the associated parasite's strain (Bastos et al., 2023). Such previous observations collectively show that protective immunities against Babesia can be achieved, and a good understanding of such mechanisms may be helpful in the development of an active vaccine against bovine babesiosis. After sequencing the *Babesia bovis* T2Bo strain's genome (Cuy-Chaparro et al., 2023), a noticeable elevation in understanding the biology of the parasite appeared from studies that used a genetically modified parasite with a highly productive approach (Al-Malki, 2025). Activation of both proinflammatory and regulatory pathways may indicate that babesiosis induces a complex immunopathological response. Interleukin-1β (IL-1β) and interleukin-6 (IL-6) are involved in *Babesia bovis* infection. They induce fever, endothelial activation, and hemolysis during infection and are key mediators of the acute inflammatory response. In contrast, transforming growth factor-gamma (TGF-γ) plays an important regulatory role because it counteracts excessive inflammation and promotes immune homeostasis. Prostaglandin F2α

(PGF2α) is used as an additional marker because it is centrally involved in inflammatory signaling, vasoconstriction, oxidative stress, and leukocyte activation. Previous studies have shown that cytokine secretion in cattle is effectively modulated by prostaglandins. This may influence the severity of parasitic infections (Jeremejeva et al., 2012). A hallmark of acute babesiosis is that it causes vascular permeability, systemic inflammation, and hemodynamic instability. Therefore, PGF2α may act as a critical mediator and link inflammatory cytokine cascades with clinical severity. On the other hand, one of the important economic indicators of most countries is the livestock industry, which is very important and vital (Ahsani et al., 2022). This industry is a suitable means for promoting the economies of countries, because it is very profitable and vital. A high percentage of the world's population is engaged in livestock farming and uses its products (Eghtedari et al., 2024). Food resources, both plant and animal, have been of great interest since the beginning of human creation, and many efforts have been made and are being made to preserve and maintain them. Although humans have made significant progress in different stages of their lives, the issue of preserving and maintaining food resources has always been and is one of the research and vital priorities of humans in terms of economy, treatment, and society. Cattle breeding and its products are one of the most important food sources for humans and provide an important part of their food security. Investigating pathogens and infections that overshadow this important food source and human health is one of the basic goals of researchers in this field (Nejad et al., 2024). Therefore, the aim of this study was to investigate the serum levels of IgM, IgG, IL-1β, IL-6, TGF-γ and prostaglandin F2α (PGF2α) in naturally infected calves and to study the single nucleotide polymorphism (SNP) rs16944 of the IL-1β gene. In addition, to investigate their potential as markers of immunological and genetic changes associated with infection.

Materials and Methods

Blood collection and sample preparation: Blood samples were taken from 50 cows. Of these cows, 36 calves were infected with Babesia and 24 healthy calves were selected as controls. All animals were examined for clinical signs. Clinical signs included fever, anemia, hematuria, pale mucous membranes, atony, weakness, and tick infestation. Two methods were used for the initial diagnosis of Babesia infection. First, they were identified based on clinical signs and then confirmed by microscopic examination of Giemsa-stained blood smears from peripheral blood. 5 ml of blood collected via the jugular vein was transferred to EDTA-containing tubes and another 5 ml to plain tubes. EDTA-containing blood tubes were used for hematology and molecular analyses, and plain blood tubes were used for serum separation. Blood samples were placed on ice for transport to the laboratory. Serum was obtained by centrifugation at 5000 rpm for 5 min.

The separated samples were stored at -20°C until analysis. In addition, animals that were undergoing treatment or had other concomitant diseases were excluded from the study.

Biochemical analysis: Commercially available double antibody sandwich ELISA kits (MyBioSource, Germany) were used to measure serum levels of IgM, IgG, IL-1β and IL-6. The kits were used according to the manufacturer's instructions. Briefly, 100 µl of serum was added to the antibody-coated wells. After adding the serum, they were incubated for 1 h at room temperature. Each well was washed three times. Then, they were incubated for 30 min with enzyme-linked secondary antibody. After this, a final wash was performed. After the addition of substrate solution, the optical density was measured using a microplate reader at a wavelength of 450 nm. The prepared standard curves were used and the cytokine concentrations were calculated according to the kit instructions.

PCR analysis of IL-1β gene: An animal genomic DNA extraction Kit (Tiangen Biotech, Beijing Co LTD, China) was used to extract genomic DNA from EDTA blood samples. The IL-1β gene was amplified using primers previously reported by Im et al. (2016). Final volume for PCR reactions was 25 µL. Each tube contained 1 µL forward primer (10 µM), 1 µL reverse primer (10 µM), 2 µL DNA template, 12.5 µL 2× PCR Master Mix (Taq DNA polymerase, dNTPs, MgCl2, and buffer), and 8.5 µL nuclease-free water. PCR thermocycling conditions contained 3 steps. Step 1 or initial denaturation was performed in 1 cycle at 95°C for 5 minutes. Step 2 was done in 30 cycles. Each cycle had 3 stages including denaturation at 95°C for 30 seconds, annealing at 57°C for 30 seconds, and extension at 72°C for 30 seconds. And then, the step 3 or final extension was performed in 1 cycle at 72°C for 7 minutes. PCR products were electrophoresed on 1.5% agarose gel. Furthermore, PCR products were confirmed by Sanger sequencing.

Statistical analysis:

Student's t-test was used to compare infected and control groups to analyze quantitative data (e.g., serum cytokine levels). Chi-square test or Fisher's exact test, when appropriate, was also used to analyze qualitative data (e.g., presence or absence of specific clinical signs). The statistical significance level used was $P < 0.05$. Results for continuous variables were reported as mean ± standard deviation (SD). However, percentages were used for categorical variables.

Results and discussion

Blood samples were taken from 50 cows. Of these cows, 36 calves were infected with Babesia and 24 healthy calves were selected as controls. In this study, there was no statistically

significant difference between the ages of the two groups of animals studied (P = 0.76). Because the mean age of infected calves was 20.07 ± 2.89 months and the mean age of the control group was 20.5 ± 2.65 months. Examining the distribution of infection among different age groups showed that in infected calves, the age range of 22 to 26 months (63.6%) had the highest infection, followed by the age range of 17 to 21 months (57.9%). However, in the control group, this order was reversed. That is, the age range of 17 to 21 months (42.1%) was at the highest level and the age range of 22 to 26 months (36.4%) was in second place (P = 0.62). There was no significant difference in infection rates between males and females (P = 0.59), although they were not equal. The rates were 62.5% in males and 57.1% in females (Table 1). The results of this study showed that age and sex could not be used as strong predictors of the prevalence of Babesia infection.

Table 1. Demographical properties of infected with Babesia and healthy calves

Properties	Case (n=36)	Control (n=24)	P-value
Age (M ± SD)	20.07 ± 2.89	20.5 ± 2.65	0.76
Age range (17–21 months)	22 (57.9%)	16 (42.1%)	0.62
Age range (22–26 months)	14 (63.6%)	8 (36.4%)	
Sex Male	20 (62.5%)	12 (37.5%)	0.59
Sex Female	16 (57.1%)	12 (42.9%)	

The results of humoral and inflammatory markers showed that there was a significant difference between infected and control calves in terms of these markers. Babesia-infected calves showed significantly higher levels of IgM (2.19 ± 0.21 ng/ml vs. 0.10 ± 0.03 ng/ml, P ≤ 0.001) and IgG (2.19 ± 0.21 ng/ml vs. 0.09 ± 0.03 ng/ml, P ≤ 0.001) than the control group. This could indicate that the adaptive humoral immune response was strongly activated. As shown in Table 2, the proinflammatory cytokines IL-1β and IL-6 were also significantly increased in infected calves compared to the control group (IL-1β: 17.05 ± 1.29 pg/mL vs. 1.64 ± 0.50 pg/mL, P ≤ 0.001; IL-6: 18.23 ± 0.83 pg/mL vs. 0.12 ± 0.03 pg/mL, P ≤ 0.001). This could indicate that an acute inflammatory response was given to parasitology. The results also showed that the regulatory cytokine TGF-γ had a higher level in infected calves compared to the control group (13.01 ± 0.78 pg/mL vs. 1.58 ± 0.48 pg/mL, P ≤ 0.001). This difference could indicate that compensatory anti-inflammatory mechanisms are activated to modulate immune responses (Bastos et al., 2022; da Silva Casa et al., 2023).

Table 2. Mean concentrations of IgM, IgG, IL-1β, IL-6, TGF-γ, and Prostaglandin F2α in the infected with Babesia and healthy calves

Parameter	Case (Mean ± SE)	Control (Mean ± SE)	P-value
IgM (ng/mL)	2.19 ± 0.21	0.10 ± 0.03	≤0.001
IgG (ng/mL)	2.19 ± 0.21	0.09 ± 0.03	≤0.001
IL-1β (pg/mL)	17.05 ± 1.29	1.64 ± 0.50	≤0.001
IL-6 (pg/mL)	18.23 ± 0.83	0.12 ± 0.03	≤0.001
TGF-γ (pg/mL)	13.01 ± 0.78	1.58 ± 0.48	≤0.001
Prostaglandin F2α (ng/mL)	356.64 ± 92.66	19.18 ± 1.28	0.001

Based on the results of Pearson correlation analysis, a significant correlation was obtained between immune markers (Table 3). A positive correlation was obtained between IL-1β with IgM ($r = 0.595$, $P < 0.001$), IgG ($r = 0.596$, $P < 0.001$), IL-6 ($r = 0.854$, $P < 0.001$) and TGF-γ ($r = 0.638$, $P < 0.001$). It should be noted that the correlation with prostaglandin F2α ($r = 0.215$, $P = 0.101$) was not statistically significant and should not be interpreted as significant (Moura et al., 2024). As shown in Table 4, prostaglandin F2α had a significant positive correlation with IgM ($r = 0.315$, $P = 0.015$), IgG ($r = 0.315$, $P = 0.015$), IL-6 ($r = 0.370$, $P = 0.004$), and TGF-γ ($r = 0.575$, $P < 0.001$). This finding may indicate that there is a relationship between inflammatory mediators and prostaglandin synthesis during Babesia infection (Pereira de Moraes et al., 2021; Rojas et al., 2024).

Table 3. Correlation analysis of IL-1β with immune markers in **studied calves**

Parameter	r	P-value
IgM	0.595	<0.001
IgG	0.596	<0.001
IL-6	0.854	<0.001
TGF-γ	0.638	<0.001
Prostaglandin F2α	0.215	0.101 (NS)

Amplification of IL-1β gene fragments in the studied samples was performed by PCR and resulted in amplification of a single band. This confirmed the specific amplification of the target gene. The result of SNP analysis of the rs16944 gene was the generation of two genotypes, TT

and TC (Table 5). SNP analysis of the sequencing results for rs16944 of the IL-1β gene are shown in Figure 1.

Table 4. Correlation analysis of Prostaglandin F2α with immune markers in **studied calves**

Parameter	r	P-value
IgM	0.315	0.015
IgG	0.315	0.015
IL-6	0.370	0.004
TGF-γ	0.575	<0.001

Table 5. SNP rs16944 genotypes of IL-1β in studied calves

Sample ID	Genotype	Sample ID	Genotype	Sample ID	Genotype
1	TT	6	No data	11	TT
2	TC	7	TT	12	No data
3	TC	8	TC	13	TC
4	TT	9	TT	14	TT
5	TC	10	TT	15	TT

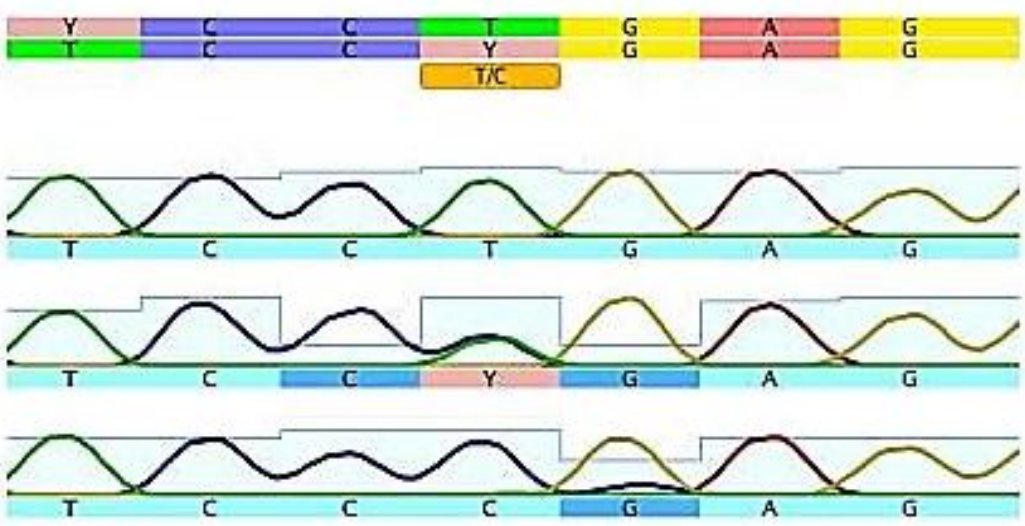

Figure 1. SNP analysis of IL-1β rs16944. Peaks indicate homozygous TT (red), homozygous CC (blue), and heterozygous TC (green) genotypes

The results of the present study showed that strong humoral and proinflammatory immune responses are stimulated by Babesia infection in calves. The increase in IgM and IgG levels could indicate that early and sustained antibody production was achieved. These results are consistent with the results of studies conducted on Babesia bovis infection in cattle (Santamaria et al., 2020; Bastos et al., 2022; da Silva Casa et al., 2023). TGF-γ elevation may represent a regulatory feedback mechanism to prevent excessive inflammation (Moura et al., 2024). Prostaglandin F2α elevation likely reflects both vascular and immunoregulatory effects during infection, potentially contributing to clinical signs such as fever, hemolysis, and anemia (Pereira de Moraes et al., 2021; Rojas et al., 2024; Sipka et al., 2024). The results of the present study showed that there were significant correlations between IL-1β, IL-6, IgM, IgG, and TGF-γ. This correlation could indicate a coordinated interaction between inflammatory and humoral responses. In addition, there was no significant correlation between IL-1β and prostaglandin PGF2α. This could indicate that prostaglandin regulation may involve additional pathways beyond IL-1β-mediated inflammation (Pereira de Moraes et al., 2021; Sajiki et al., 2021; Rojas et al., 2024). The presence of TT genotypes at SNP rs16944 in multiple calves may be associated with higher IL-1β production, in line with previous reports linking this polymorphism to enhanced pro-inflammatory responses and susceptibility to infectious diseases (Wang et al., 2021; Hariyono & Prihandini, 2022; Kloch et al., 2023). Functional studies are required to confirm the mechanistic impact of these SNPs. Our findings align with Rojas et al. (2024), who reported elevated pro-inflammatory cytokines and strong antibody responses in Babesia-infected cattle. Similarly, Attia et al. (2023) observed increases in IL-6 and TNF-α associated with disease severity. Since the present study reported a relationship between cytokine levels, prostaglandin concentrations, and genetic variation in IL-1β, it can be said that the results of this study extend and improve previously reported results. The results suggest that it is better to monitor cytokine profiles and humoral markers, as this may improve early detection and prognosis of Babesia infection. To gain insights into individual susceptibility and guide selective breeding or management strategies, it is better to perform SNP screening for IL-1β variants. This study had a relatively small sample size and was geographically limited. In addition, functional assays were not performed to determine the direct effect of the rs16944 SNPs on cytokine production. Therefore, future research should study larger cohorts and sample from multiple geographic regions to perform functional genomic analyses to better understand host-pathogen interactions.

Conclusions: The results of this study showed that in calves infected with Babesia, the levels of IgM, IgG, IL-1β, IL-6, TGF-γ and prostaglandin F2α were higher than those in healthy calves. The correlation between IL-1β, IL-6, IgM, IgG and TGF-γ was reported to be positive. The results also showed that the TT genotype for SNP rs16944 in IL-1β affects cytokine production.

Therefore, it can be concluded that the findings of this study can probably highlight the complex interaction of humoral, cytokine and genetic factors in the response of calves to Babesia infection.

Author contributions

A. A. H.: Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing original draft preparation, writing review and editing, visualization, supervision, project administration, funding acquisition. The author has read and agreed to the published version of the manuscript.

Data availability statement

All relevant data supporting the findings of this study are included in the article.

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Ethical considerations

This study was approved by the Institute's Scientific-Council of Medical Technology under Administrative Order No. 2/7/27/380B, dated 25/1/2024. It also completed the form designated for obtaining the approval of the Research Ethics Committee, No. 33, authorizing its implementation at the privately owned clinic & the done in the veterinary laboratory services in Al-Khalis District/Diyala. All of the participants were allowed to provide the researcher with the specimens.

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Conflict of interest

All authors declared no conflict of interest, financial or otherwise.

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نقش پروستاگلاندین F2α و TGFγ همراه با پلی‌مورفیسم IL-1β در گوساله‌های آلوده به بابزیا

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چکیده

هدف: بابزیوز در گوساله‌ها توسط *Babesia bovis* ایجاد می‌شود. این بیماری پاسخ‌های التهابی و ایمنی‌تنظیمی شدیدی را القا می‌کند و در شدت بیماری نقش مؤثری دارد. هدف از این مطالعه بررسی سطوح سرمی IgM، IgG، IL-1β، IL-6، TGF-γ و پروستاگلاندین F2α (PGF2α) در گوساله‌های مبتلا به عفونت طبیعی و همچنین بررسی پلی‌مورفیسم تک‌نوکلئوتیدی (SNP) rs16944در ژن IL-1β بود. علاوه بر این، قابلیت این شاخص‌ها به‌عنوان نشانگرهای تغییرات ایمنی و ژنتیکی مرتبط با عفونت مورد ارزیابی قرار گرفت.

مواد و روش‌ها: در مجموع ۳۶ گوساله آلوده به بابزیا بر اساس علائم بالینی (تب، کم‌خونی، یرقان، هماچوری و آلودگی به کنه) و سابقه بیماری انتخاب شدند. همچنین ۲۴ گوساله سالم به‌عنوان گروه کنترل مورد استفاده قرار گرفتند. نمونه خون از ورید حیوانات جمع‌آوری شد. برای سنجش مقادیر IgM، IgG، IL-1β، IL-6، TGF-γو PGF2α از کیت‌های معتبر الایزا استفاده شد. برای بررسی ژنوتیپ rs16944 ژن IL-1β از روش PCR و توالی‌یابی سانگر بهره گرفته شد. تحلیل آماری با آزمون t و تحلیل همبستگی در سطح معنی‌داری $P < 0.05$ انجام شد.

نتایج: مقایسه گوساله‌های آلوده با گروه کنترل نشان داد که سطوح سرمی IgM و IgG در آنها به‌طور معنی‌داری بالاتر است ($P \leq 0.001$)، که بیانگر فعال‌شدن قوی پاسخ ایمنی هومورال می‌باشد. سیتوکین‌های پیش‌التهابی IL-1β و IL-6 نیز به‌طور معنی‌داری افزایش یافتند که نشان‌دهنده وقوع پاسخ التهابی شدید است که مشخصه بابزیوز حاد است. علاوه بر این، سطح TGF-γ نیز در گوساله‌های آلوده به‌طور معنی‌داری بالاتر بود که نشان‌دهنده فعال شدن مسیرهای تنظیمی برای تعادل التهاب است. افزایش غلظت PGF2α نیز نشان‌دهنده نقش آن در اختلالات عروقی و التهابی مرتبط با عفونت بود. همچنین مشخص شد که در تعدادی از

گوساله‌های آلوده، ژنوتیپ وحشی CC به نوع TT تبدیل شده است؛ بنابراین می‌توان گفت که بین این SNP و افزایش حساسیت یا پاسخ التهابی شدیدتر، ارتباط بالقوه‌ای وجود دارد.

نتیجه‌گیری: یک تعامل پیچیده میان پلی‌مورفیسم IL-1β، ایمونوگلوبولین‌ها، فعالیت پروستاگلاندین و سیتوکین‌ها در گوساله‌های مبتلا به بابزیوز مشاهده شد. تغییرات قابل‌توجه این بیومارکرها نشان می‌دهد که آن‌ها از ارزش تشخیصی بالقوه برخوردارند و می‌توانند برای درک بهتر ایمنی‌زایی بیماری ناشی از *Babesia bovis* مورد استفاده قرار گیرند. تنوع ژنتیکی مشاهده‌شده در rs16944 ممکن است یک عامل خطر افزوده باشد که بر پیامد بیماری تأثیر می‌گذارد. این یافته‌ها می‌توانند در توسعه روش‌های بهتر برای تشخیص، پیش‌آگهی و مدیریت بیماری مورد استفاده قرار گیرند.

کلمات کلیدی: بابزیا، پروستاگلاندین PGF2α و TGFγ، پلی‌مورفیسم IL-1β، گوساله

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