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Investigation of some cytokine levels (IL-4, IL-5, IL-8, IL-12, and IL-33) in the sera of patients with cystic echinococcosis and fasciolosis

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ABSTRACT

Aim: To evaluate serum levels of IL-4, IL-5, IL-8, IL-12p70, and IL-33 in patients with cystic echinococcosis and fascioliasis and to assess their diagnostic potential compared to healthy controls.

Method: A total of 78 serum samples were analyzed, including 26 from patients with cystic echinococcosis, 26 from patients with fascioliasis, and 26 from healthy controls. Cytokine levels were measured using a multiplex ELISA assay, and intergroup comparisons were evaluated using IBM SPSS Statistics.

Results: The echinococcosis group had significantly higher serum levels of IL-4, IL-5, IL-8, and IL-33 than the control group ($p<0.05$). Similarly, the fascioliasis group had significantly higher levels of IL-4, IL-5, and IL-8 than the control group ($p<0.05$), but no significant differences were observed for IL-33 and IL-12p70. Between the helminth groups, the echinococcosis group had significantly higher levels of IL-4 ($p=0.003$), IL-5 ($p<0.001$), and IL-33 ($p=0.015$) than the fascioliasis group.

Conclusions: Cytokine profiles in helminth infections differ significantly from those in healthy controls and between parasite species. Th2-skewed responses, characterized by elevated IL-4 and IL-5 levels, were common, while IL-8 and IL-33 involvement suggests roles for both innate and adaptive immunity in disease pathogenesis. In echinococcosis, IL-33 may serve as a biomarker for early diagnosis, recurrence detection, and therapy monitoring, and it provides insights into the immune response to infections.

Keywords: Cystic echinococcosis, fascioliasis, cytokines, IL-33, diagnosis, biomarker.

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1. Introduction

Caused by *Echinococcus granulosus* (*E. granulosus*), echinococcosis leads to the formation of hydatid cysts in various organs, primarily the liver and lungs. The disease manifests in two primary forms: alveolar echinococcosis and cystic echinococcosis. A significant global health burden, echinococcosis is prevalent in rural areas of developing countries where animal husbandry is widespread, and veterinary public health services are limited [1]. Alveolar echinococcosis typically begins in the liver but

may metastasize to other organs, such as the lungs or brain. Symptoms depend on the cyst's location and size, often remaining asymptomatic for years [2]. Liver involvement may cause weight loss, abdominal pain, and jaundice, characterized by yellowish skin discoloration [3]. Lung involvement can result in shortness of breath, coughing, and chest pain [4]. Transmission occurs when animals or humans ingest food or water contaminated with parasite eggs or through close contact with infected hosts [5]. The parasite promotes immune tolerance and skews the host's immune response toward a T-helper 2 (Th2) profile, reducing the effectiveness of protective inflammatory responses [6].

Caused by the trematode parasites *Fasciola hepatica* (*F. hepatica*) and *Fasciola gigantica* (*F. gigantica*), fascioliasis affects over 81 countries worldwide [7]. *F. hepatica*, a liver fluke, primarily infects the liver and bile ducts of humans and livestock, causing significant economic losses in the livestock sector and posing public health concerns. After ingestion, the parasites migrate through the liver and mature in the bile ducts. Understanding the immune pathogenesis of fascioliasis is critical for developing effective therapeutics and vaccines [8].

The chronic phase of fascioliasis involves immune evasion strategies, including modulation of dendritic cell function, a Th2-biased response, and suppression of T-helper type 1 (Th1)-mediated protective immunity [9]. Both infections represent significant public health and economic burdens, particularly in endemic regions [10]. Immunologically, they trigger a complex interplay between proinflammatory and anti-inflammatory cytokines, influencing disease progression and host-parasite interaction [11]. IL-4, a hallmark of Th2 responses, promotes humoral immunity by stimulating B cell differentiation and immunoglobulin E (IgE) class switching while suppressing. IL-5 drives eosinophil proliferation and activation, contributing to immune defense against helminths and correlating with eosinophilic infiltration in parasitic infections [12, 13]. IL-8, a chemotactic cytokine, attracts neutrophils to sites of inflammation, playing a key role in the early innate immune response. IL-12, a proinflammatory cytokine, promotes Th1 differentiation, interferon-gamma (IFN-γ) production, and macrophage activation, aiding resistance to intracellular pathogens but often downregulated in helminth infections [14, 15]. IL-33, a member of the IL-1 family, acts as an alarming cytokine released during tissue damage, contributing to type 2 immunity, eosinophil responses, and helminth infection pathology [15, 16].

Both *F. hepatica* and *E. granulosus* induce a strong Th2-biased immune response, marking elevated IL-4 and IL-5 levels. In fascioliasis, IL-4 suppresses Th1-mediated inflammation, enabling parasite immune evasion. Similarly, in cystic echinococcosis, IL-4 and IL-5 sustain a non-protective Th2 response, promoting the parasite's persistence and cyst development [17]. ~~A~~cute inflammatory stages of fascioliasis may increase IL-8 levels due to neutrophil recruitment to areas of liver damage [18]. IL-12 is typically downregulated in both infections, as *F. hepatica* and *E. granulosus* suppress Th1 responses to ensure survival, leading to reduced IFN-γ production and impaired macrophage-mediated parasite killing [19, 20].

IL-33, increasingly recognized in helminth infections, supports eosinophilic inflammation and tissue regeneration in fascioliasis and maintains the chronic Th2-dominated immune response in cystic echinococcosis, contributing to cyst growth [21, 22]. Current understanding

relies primarily on animal model studies, with limited data on human host-parasite dynamics. Further investigations into cytokine profiles will facilitate the development of immunotherapeutic strategies and biomarkers for disease progression and prognosis [8].

Cystic echinococcosis and fascioliasis are zoonotic helminth infections that can show as acute or chronic conditions, occur sporadically, and may be fatal. Analyzing cytokine profiles plays an essential role in the diagnosis and prognosis of these infections. Specific cytokines, especially IL-33, are valuable for diagnosing Echinococcus and Fasciola infections, determining disease stage (acute or chronic), and predicting outcomes. This study investigates the roles of IL-4, IL-5, IL-8, IL-12, and IL-33 in cystic echinococcosis and fascioliasis.

Understanding the immunological mechanisms of helminth infections is essential for improving diagnostic and therapeutic strategies. This study explores cytokine response patterns in cystic echinococcosis and fascioliasis to identify reliable immunological markers. By evaluating serum levels of IL-4, IL-5, IL-8, IL-12, and IL-33, it aims to enhance early diagnosis, disease monitoring, and understanding of host-parasite immune interactions, with particular emphasis on the diagnostic potential of IL-33 in cystic echinococcosis.

2. Materials and methods

2.1. Study groups: This study included serum samples from individuals who visited the Infectious Diseases and Clinical Microbiology Clinic at Bolu Abant Izzet Baysal University (BAIBU) Training and Research Hospital with suspected helminth infections and provided informed consent. The study was approved by the BAIBU Clinical Research Ethics Committee (protocol no: 2016/27). Participants comprised patients with cystic echinococcosis (17 males/9 females), 26 patients with fascioliasis (16 females/10 males), and 26 healthy controls (19 females/7 males). The mean age was 46 years (range: 16-69 years) for echinococcosis patients, 35 years (range: 1-68 years) for fascioliasis patients, and 64 years (range: 9-85 years) for healthy controls.

2.2. Serum analysis: Serum samples were collected from individuals with suspected parasitic infections. Samples testing positive for *E. granulosus* or *F. hepatica* formed the experimental groups, while samples negative for both parasites served as the control group. Sera were stored at -20°C until analysis. For cystic echinococcosis, the *E. granulosus* indirect hemagglutination (IHA) test (Fumouze Laboratories, France) [23] was used according to the manufacturer's recommendations, and 26 samples with titers of ≥160 were included. Organ involvement in cystic echinococcosis cases was documented from hospital records. For fascioliasis, the *F. hepatica* IgG enzyme-linked immunosorbent assay (ELISA) (DRG International, Inc., USA) [24] was performed according to the manufacturer's recommendations, and 26 samples with positive results were included. The control group (n=26) was randomly selected from samples testing negative for both parasites using the IHA and ELISA assays.

Three groups were: echinococcosis cases, fasciolosis cases, and healthy controls. The sample size (n=26 per group) was determined using regression and variance analysis based on parasite prevalence. All serum samples were tested using ELISA, and IHA assays were performed according to the manufacturer's recommendations. See also Figure 1 for schematic illustration of the study showing the material method.

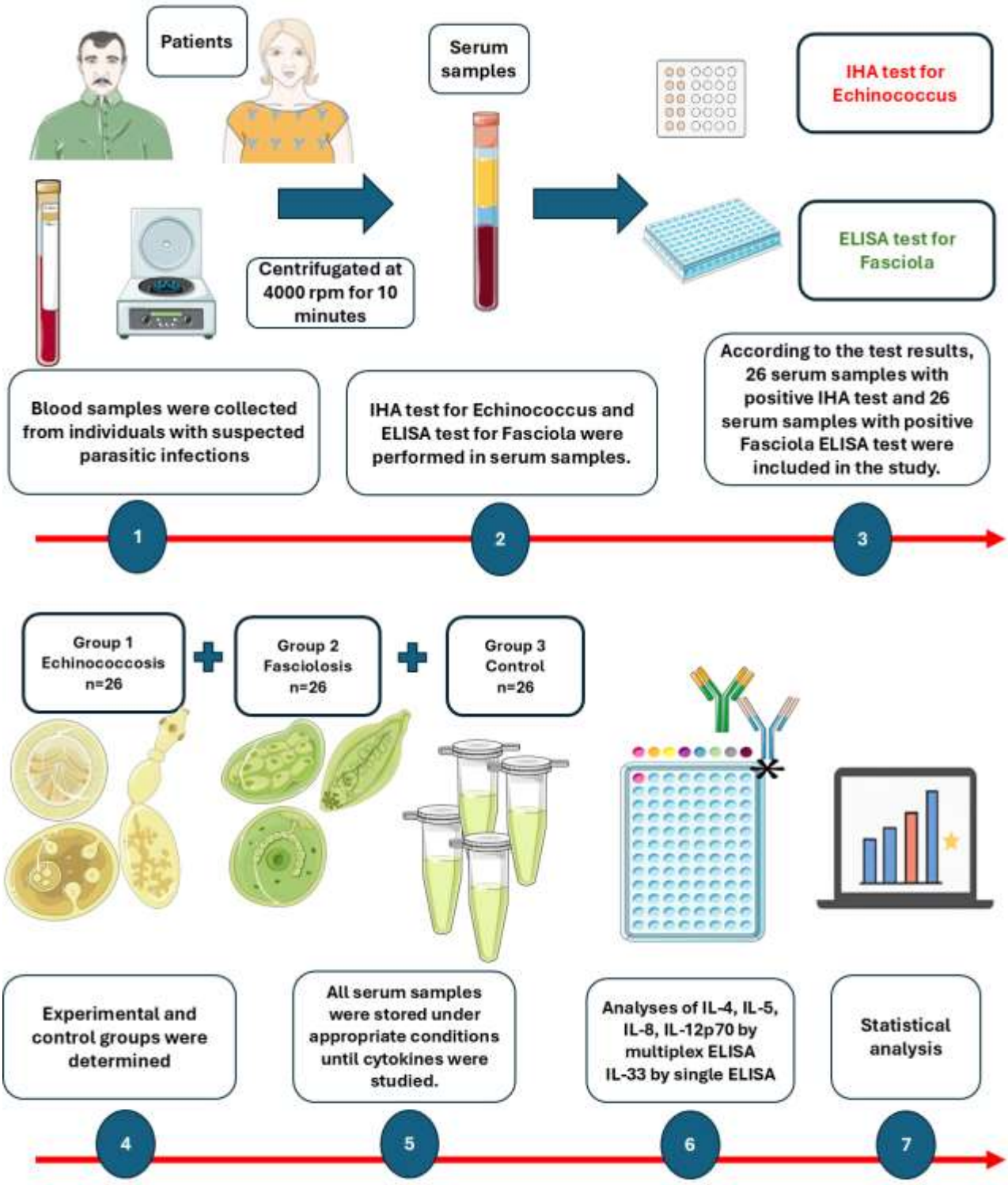

Figure 1. Timeline and graphical abstract of the study showing the material method.

2.3. Cytokine analysis: Serum levels of IL-4, IL-5, IL-8, IL-12p70, and IL-33 were measured in the case and control groups using specific anti-human IL-4, IL-5, IL-8, IL-12p70, and IL-33 antibodies. The ELISA method was used to determine interleukin levels in the study. Milliplex MAP Human Cytokine/Chemokine Magnetic BeadPanel, Millipore Corp. (Cat. No. HCYTOMAG-60K, Billerica, MA) test [25] was used for the analysis of IL-4, IL-5, IL-8, and IL-12p70 cytokines, see also Figure 1. The plate was read by the Luminex MagPix device,

and the collected data were analyzed by Luminex xPONENT® software (v. 4.2).

IL-33 is a newer cytokine compared to the other four cytokines, and there was no test kit compatible with the Milliplex ELISA device. Therefore, IL-33 was studied with the normal ELISA method [26] in line with the company recommendations instead of Milliplex ELISA (Immuno-Biological Laboratories, Inc. (IBL-America). At the end of the study, absorbance values were obtained by reading the plate at a wavelength of 450 nm using a plate microELISA reader (Thermo Fisher Scientific Multiscan Go (Finland). Antibody concentrations from the absorbance data obtained for IL-33 were evaluated by calculating according to the curve drawn according to the concentrations of the standards used during the study. A standard plot curve was drawn according to this evaluation. The lowest IL-33 level that could be detected according to the test was 5 pg/ml. According to the values obtained from the spectrophotometer device, values calculated above 5 pg/ml were evaluated as "Positive", see also Figure 1.

2.4. Statistical analysis: Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26.0. The Shapiro-Wilk test was used to assess the data normality. Results were reported as medians (minimum–maximum) or as frequencies and percentages. The Mann-Whitney U test was used to compare non-normally distributed data between groups. The relationship between IL-33 positivity and group classification was evaluated using Pearson's chi-square test. A p-value <0.05 was considered statistically significant.

3. Results

This study analyzed 78 serum samples, comprising 52 from patients with parasitic infections (26 with cystic echinococcosis and 26 with fascioliasis) and 26 from healthy controls. Participant characteristics are presented in Table. Serum levels of five cytokines (IL-4, IL-5, IL-8, IL-12p70, and IL-33) were measured using ELISA and compared between the echinococcosis and fascioliasis case groups and the healthy control group. For cystic echinococcosis, serum cytokine levels were significantly higher than those in the control group for most cytokines. The median IL-4 level was 180.77 (5.80-890.61) pg/mL) in the echinococcosis group compared to 10.81 (4.97-58.53) pg/mL) in the control group (p=0.034). The median IL-5 serum level was 56.29 (1.11-289.80) pg/mL) in the echinococcosis group versus 4.59 (1.11-16) pg/mL) in the control group (p=0.005). The median IL-8 serum level was 942.61 (18.85-4105.0) pg/mL) in the echinococcosis group compared to 53.26 (2.36-256.27) pg/mL) in the control group (p=0.002). The median IL-33 serum level was 743.04 (1.12-3247.20) pg/mL) in the echinococcosis group versus 65.98 (1.11-337.8) pg/mL) in the control group (p=0.001). No statistically significant difference was observed for IL-12p70 between the echinococcosis group and the control group (p=0.376). All serum cytokine levels between groups are presented in Figure 2.

For Fasciolosis, serum levels of IL-4, IL-5, and IL-8 were significantly higher than those in the control group. The median IL-4 level was 17.06 (5.80-66.20) pg/mL) in the fascioliasis group compared to 10.81 (4.97-58.53) pg/mL) in the control group (p=0.008). The median IL-5 level was 25.75 (0.97-96.88) pg/mL) in the fascioliasis group versus 4.59 (1.11-16) pg/mL) in the control group (p=0.025). The median IL-8 level was 3225.58 (2.70-13253.0) pg/mL) in the fascioliasis group compared to 53.26 (2.36-256.27) pg/mL) in the control group (p=0.007). No statistically significant differences were

observed for IL-12p70 (p=0.276) or IL-33 (p=0.280) between the fascioliasis group and the control group.

In fascioliasis, elevated levels of IL-4 and IL-5, which are typically associated with parasitic infections, were statistically significant, consistent with a Th2-biased immune response. Additionally, IL-8 levels were markedly elevated, indicating a robust innate immune response (presented in Table 1).

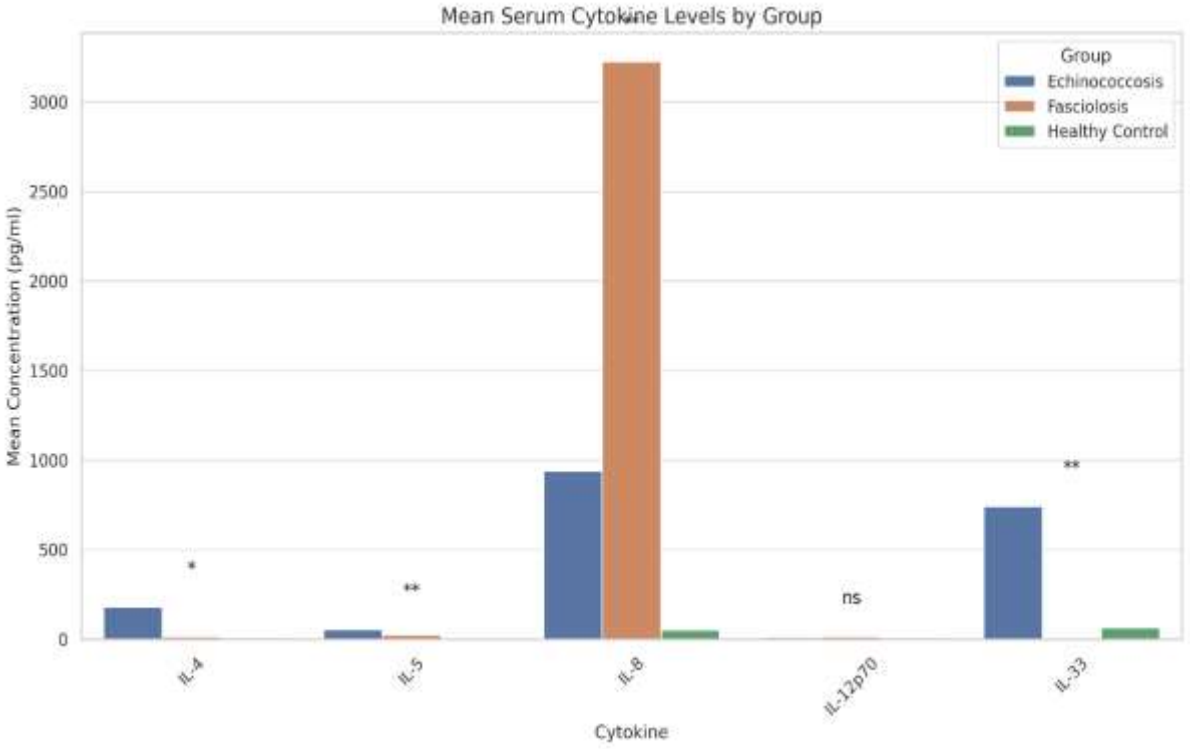

Figure 2. Comparison of mean serum cytokine concentrations (IL-4, IL-5, IL-8, IL-12p70, IL-33) among patients with cystic echinococcosis, fascioliasis, and healthy controls. Data are presented as mean concentration (pg/mL) per group. Asterisks indicate significant differences: p <0.05, and ns = not significant.

Table 1. Demographic data and cytokine levels of case and control groups.

Groups		**Echinococcosis**	**Fasciolosis**	**Healthy control**	**p value**
Sample size (n)		26	26	26	
Mean age (min-max)		46 (16-72)	35 (1-68)	64 (9-85)	
Gender (Male/Female)		17/9	10/16	7/19	
Organ location of the body in case*		Liver: 22 Lung: 1 Brain: 1 Spleen: 1 Both liver and lung: 1	-	-	
Cytokines (pg/ml) mean (range)	IL-4	180.77 (5.80-890.61)	17.06 (5.80-66.20)	10.81 (4.97-58.53)	***0.034***
	IL-5	56.29 (1.11-289.80)	25.75 (0.97-96.88)	4.59 (1.11-16)	***0.005***
	IL-8	942.61 (18.85-4105.0)	3225.58 (2.70-13253.0)	53.26 (2.36-256.27)	***0.002***
	IL-12p70	13.05 (3.41-56.67)	17.20 (3.79-72.47)	11.34 (5.39-52.98)	0.376
	IL-33	743.04 (1.12-3247.20)	0.287 (1.09-1.97)	65.98 (1.11-337.8)	***0.001***

**Organ location was determined by reviewing hospital records.*

When the five cytokines included in the study were compared between the two helminths without a control group, the echinococcosis group exhibited significantly higher levels of IL-4 (p=0.003), IL-5 (p<0.001), and IL-33 (p=0.015) compared to the Fasciolosis group. No statistically significant differences were observed for IL-8 or IL-12p70 between the two groups.

4. Discussion

This study compares serum levels of IL-4, IL-5, IL-8, IL-12p70, and IL-33 in patients with cystic echinococcosis and fascioliasis to those in a healthy control group, providing valuable insights into the immunological responses associated with these parasitic infections. The findings reveal distinct immune response profiles in helminth infections, differing from both healthy individuals and each other.

The main findings indicate that serum levels of IL-4, IL-5, IL-8, and IL-33 are significantly elevated in patients with cystic echinococcosis compared to healthy controls, while IL-12p70 levels show significant differences. Similarly, in fascioliasis cases, IL-4, IL-5, and IL-8 levels are significantly higher than in controls, but IL-12p70 and IL-33 levels do not differ significantly. When comparing cytokine levels between the two parasitic infections without a control group, IL-4, IL-5, and IL-33 were notably higher in cystic echinococcosis cases than in fascioliasis cases. IL-33, a member of the IL-1 cytokine family [27], is critical for inducing T helper-2 (Th2) cell-dominant immune responses, such as those involved in host defense against allergic diseases, nematodes, and viral infections [28, 29]. The significantly elevated IL-33 levels in the cystic echinococcosis group suggest that epithelial damage-induced alarmin release may be a feature of this infection [30]. As an alarmin released from epithelial cells, IL-33 plays a key role in initiating Type 2 immune responses [21, 22, 31]. Studies have shown that IL-33 regulates both acute inflammatory responses and chronic infection processes. For example, elevated IL-33 levels in chronic hepatitis B are associated with disease progression, and in chronic schistosomiasis, high IL-33 levels correlate with liver fibrosis, enhancing the Th2 response. Similarly, increased IL-33 levels are reported in inflammatory diseases such as chronic asthma, chronic obstructive pulmonary disease (COPD), and celiac disease, suggesting that alarmin cytokines contribute to chronic inflammation [32, 33, 34, 35, 36]. Although IL-33 levels were not significantly elevated in the fascioliasis group, the increase in the cystic echinococcosis group suggests that IL-33 may contribute to hydatid cyst formation, potentially serving as a specific marker for echinococcus infections.

These findings reveal a significant immune dysregulation in these parasitic infections, characterized by elevated cytokine levels compared to controls. The increased IL-4 and IL-5 levels observed in both cystic echinococcosis and fascioliasis confirm a Th2-biased immune response, a well-documented phenomenon of chronic parasitic infections [19, 37]. IL-4 promotes antibody class switching to IgE, enhancing mast cell degranulation and eosinophilic activity, while IL-5 drives eosinophil recruitment and survival. The significantly higher IL-4 levels in cystic echinococcosis compared to fascioliasis suggest a stronger Th2 dominance, likely due to the prolonged persistence of the parasite in host tissues [6, 11, 12, 38].

IL-8, a potent neutrophil chemotactic cytokine, contributes to inflammatory cell recruitment and tissue remodeling. IL-8 levels were significantly elevated in both cystic

echinococcosis and fascioliasis, with the highest levels observed in fascioliasis cases. The exceptionally high IL-8 levels in fascioliasis patients suggest a stronger innate immune activation, likely due to hepatic tissue damage caused by *Fasciola* migration and feeding activity [14, 15].

IL-12, critical for Th1-directed immune response and triggers IFN-γ production, is typically suppressed in helminth infections due to Th2 dominance [14, 39]. Consistent with this, no significant changes were observed in IL-12p70 levels in this study. The low IL-12 levels align with literature indicating that helminths create a Th2-dominant immune response and suppress IL-12 production to escape the host immune system. In addition, the tissue-based nature of these parasites and the chronic stage of infection may contribute to low systemic IL-12 levels, supporting the role of a weak proinflammatory response in the chronicity of these infections [39].

When comparing cystic echinococcosis and fascioliasis, the higher levels of IL-4, IL-5, and IL-33 in the cystic echinococcosis group indicated that *E. granulosus* induces a more pronounced Th2 and alarmin response in its immunopathogenesis. These differences may stem from the Parasite's life cycle, tissue location, and cyst formation processes [5, 12, 21].

Interestingly, while both parasitic infections induce a Th2 response, their cytokine profiles exhibit different patterns of immune activation. Cystic echinococcosis elicits a more controlled Th2 response, whereas fascioliasis triggers a mixed Th2-inflammatory response, potentially contributing to more acute inflammation and liver pathology. These findings align with previous studies highlighting the immunomodulatory nature of cystic echinococcosis, in contrast to the more tissue-invasive nature of *F. hepatica* infections [6, 11, 40]. Overall, this study highlights the distinct immune signatures of cystic echinococcosis and fascioliasis, with cystic echinococcosis showing a predominant Th2 response while fascioliasis exhibiting additional inflammatory components. Further research is required to investigate the long-term immunological consequences of these cytokine changes, particularly in relation to chronic liver injury and secondary infections. Recent literature emphasizes the immunomodulatory effects of helminth infections, particularly their impact on autoimmunity and allergies [11, 41]. This study provides an original contribution by comparatively evaluating cytokine profiles in cystic echinococcosis and fascioliasis, reinforcing that helminth infections induce a Th2-skewed immune response, as evidenced by elevated IL-4 and IL-5 levels. These results are consistent with previous studies [6, 22, 37, 40] showing that IL-4 and IL-5 promote eosinophilia and IgE production, which are characteristic of helminth-induced immune responses. Furthermore, the significant increase in IL-8 levels in both infection groups suggests a strong pro-inflammatory component, potentially linked to neutrophil recruitment and tissue damage. The elevated IL-33 levels in cystic echinococcosis, but not in fascioliasis, raise interesting questions about its specific role in echinococcus-induced pathology, given its involvement in Type 2 immune responses and fibrosis development.

4.1. Limitations of the study: Despite the strengths, this study has some limitations. First, the sample size was relatively small (52 patients and 26 healthy controls), limiting the generalizability of the findings. However, the low or uncertain prevalence of these parasitic infections worldwide constrained the availability of positive clinical case samples. As

sera were collected at the time of the patients' initial hospital admission and confirmed positive by serological tests, cytokine levels were measured at a single time point, limiting our ability to capture dynamic immune responses during infection. Additionally, the study focused solely on seropositive cases for Echinococcus and Fasciola, without separately examining potential co-infections or underlying comorbidities. Future studies with large sample sizes, longitudinal cytokine measurements, and evaluation of immune responses during disease progression and treatment are needed to address these limitations and better understand the temporal dynamics of immune responses in parasitic infections.

4.2. Conclusion: This study enhances our understanding of cytokine responses in cystic echinococcosis and fascioliasis, reinforcing the Th2-biased immune response characteristic of helminthic infections. Notably, the elevated IL-33 levels in cystic echinococcosis highlight its potential role in disease pathogenesis and as a biomarker for disease activity. Further research into the relationship between IL-33 and the pathogenesis of cystic echinococcosis could facilitate the development of novel diagnostic markers and therapeutic strategies. However, further researches are needed to validate these findings, explore other immunological markers, and investigate their clinical diagnostic utility. Addressing these gaps will increase our understanding of helminth-mediated immune responses and support the development of improved diagnostic and therapeutic strategies.

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Conflict of Interest: *The authors declared no conflict of interest.*

Ethical Statement: *The study was approved by the Bolu Abant Izzet Baysal University Clinical Research Ethics Committee (protocol no: 2016/27).*

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